
# The Alkaloids

## Volume 61

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*Numbers in parentheses indicate the pages on which the authors' contributions begin.*

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# PREFACE

In this volume of *The Alkaloids: Chemistry and Biology* the recent progress on two classes of alkaloids, the *Lycopodium* alkaloids and the dibromotyrosine alkaloids, is presented.

The first chapter, by Kobayashi and Morita, is a superb extension of the chapter that was published in Volume 45 of the series. It is a comprehensive review of the *Lycopodium* alkaloids in terms of their structural classification, distribution, and occurrence, followed by detailed discussions of their spectroscopic aspects, the determination of stereochemistry, and their biological activities. The substantial efforts made in the past few years to effect the synthesis of the diverse skeleta of this group of alkaloids from the club mosses are also presented, together with a detailed overview of their complex biogenetic interrelationships.

In the second chapter, Hamann, Peng and Li present a new topic to the series, the marine dibromotyrosine alkaloids. These alkaloids have grown enormously in number in the recent past as the marine environment has been explored for its chemical and biological diversity. The alkaloids are thoroughly and excellently reviewed from the perspectives of isolation, structure determination, and synthesis, with a detailed discussion of their biological properties and biogenetic pathways.

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—Chapter 1—

# THE *LYCOPODIUM* ALKALOIDS

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## I. Introduction

*Lycopodium* species produce a number of structurally diverse alkaloids, which often possess unusual skeletons, and many of them continue to be of interest from the biogenetic and biological points of view, as well as providing challenging targets for total synthesis. There are over 500 species in the genus *Lycopodium* (family Lycopodiaceae), but the alkaloid content has been studied in fewer than 40 species (*1–5*). Most of the species are low, evergreen, coarsely moss-like plants, which are commonly known as club mosses. They are non-flowering plants which reproduce by means of spores rather than seeds. In many species, the spore-bearing bodies, known as strobili, appear as club-shaped growths at the tips of the moss like branches, hence the name club mosses. The taxonomy of the genus and the family is still in a state of flux. Some botanists have subdivided the genus into four genera (*Lycopodium*, *Diphasiastrum*, *Lycopodiella*, and *Huperzia*), and some have placed *Huperzia* in a separate family (*6,7*). We prefer to retain the single genus name, since this allows us to use a name which is familiar to most and typifies plants that can be easily recognized as being closely related.

Huperzine A (**1**) has been shown to be a potent, reversible inhibitor of acetylcholine esterase and shows promise in the treatment of Alzheimer's disease and myasthenia gravis (*8–10*). This alkaloid has provided the focus for a good portion of the synthetic work in the period under review. The biosynthesis of the alkaloids is still not

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completely understood, and only limited biosynthetic studies have been reported. Plants of the genus *Lycopodium* have not been cultivated, and labeling experiments must be carried out in the field. Because the club mosses often are not easily accessible, very few feeding studies have been conducted. This is an area where plant tissue culture may prove extremely useful in future biosynthetic studies.

There are some reviews of the chemistry of *Lycopodium* alkaloids (*1–5*), and of the biology and chemistry of huperzine A (**1**) (*8–10*). Since the last review by Ayer in Volume 45 (*4*) of this treatise, a number of new *Lycopodium* alkaloids have been discovered. As a result, the number of known *Lycopodium* alkaloids has grown markedly in recent years to a present count of *ca*. 200. These alkaloids, isolated chiefly by Manske and Ayer *et al*., are classified into different frameworks of $C_{16}N$, $C_{16}N_2$, and $C_{27}N_3$ types (*1–4*). These unusual ring systems have attracted great interest as challenging targets for total synthesis or biosynthetic studies. This chapter covers the reports on *Lycopodium* alkaloids that have been published between 1993 to 2003, and provides an update of the previous review by Ayer in 1994 (*4*). The natural *Lycopodium* alkaloids published between 1993 to 2003 (compounds **1**–**82**) are listed in Table I. Classification of the alkaloids basically follows that of the previous reviews (*1–4*), but sections on the newly found skeletons have been added.

This review describes the recent studies on *Lycopodium* alkaloids isolated from the genus *Lycopodium* and *Huperzia*, the proposed biogenetic pathway, and the syntheses of *Lycopodium* alkaloids based on these biogenetic proposals. In section II, all of the *Lycopodium* alkaloids isolated so far, and including our recent work, are surveyed, while sections III and IV mainly deal with the biogenetic pathways and the total syntheses of the *Lycopodium* alkaloids, respectively. In sections V, VI, and VII, pharmacology, total synthesis, and SAR studies, respectively of huperzine A (**1**) are briefly surveyed.

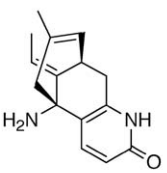
## II. Structures of Representative Alkaloids

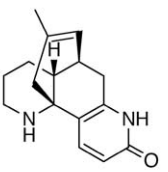
### A. HUPERZINES

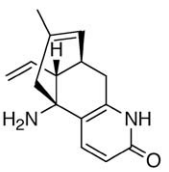
In 1986, Liu isolated two new *Lycopodium* alkaloids, huperzines A (**1**) and B (**2**) (*11*) from *Huperzia serrata* (*Lycopodium serratum*), which is a Chinese traditional medicine. They exhibited potent anticholinesterase activity in pharmacological studies and markedly increased the efficiency for learning and memory in animals (*12*). Presently, the use of huperzine A (**1**) in the treatment of myasthenia gravis (*17*), Alzheimer's dementia (*13–16*), and for the improvement of senile memory loss are under clinical investigation. In the 1990s, a series of huperzines was isolated (*18–29*). The absolute stereochemistry of huperzines C (**3**) and D (**4**) isolated from *Lycopodiastrum casuarinoides* was assigned, and **3** exhibited an inhibitory activity close to that of huperzine A (**1**), whereas **4** did not (*18*). Huperzines E (**5**), F (**6**) (*19,20*), G (**7**) (*21*), and O (**13**) (*25*) with the lycopodane skeleton were isolated from *Huperzia serrata*. Huperzine H (**8**), with a novel skeleton, was also isolated from *H. serrata* (*22*). Structures of new irregular fawcettimine-type *Lycopodium* alkaloids, huperzines I (**9**) (*23*), P (**14**) (*26*), and Q (**15**) (*27*), and *N*-oxyhuperzine Q (*27*) isolated from *H. serrata* were elucidated by spectroscopic data and X-ray analysis. The relative stereochemistry

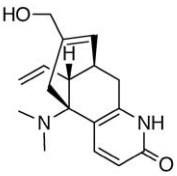
TABLE I.
New *Lycopodium* Alkaloids.

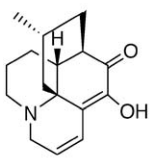
A. Huperzine Alkaloids

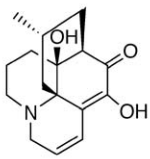

huperzine A (**1**)[11]
$C_{15}H_{18}N_2O$

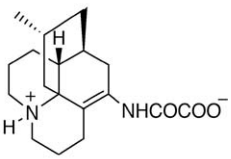

huperzine B (**2**)[11]
$C_{16}H_{20}N_2O$

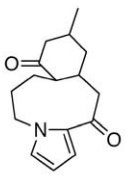

huperzine C (**3**)[18]
$C_{15}H_{18}N_2O$


huperzine D (**4**)[18]
$C_{17}H_{22}N_2O_2$


huperzine E (**5**)[19,20]
$C_{16}H_{21}NO_2$


huperzine F (**6**)[19,20]
$C_{16}H_{21}NO_3$


huperzine G (**7**)[21]
$C_{18}H_{26}N_2O_3$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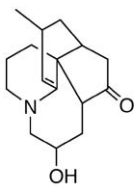
huperzine I (**9**)[23]
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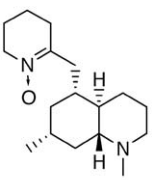
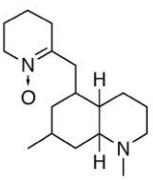
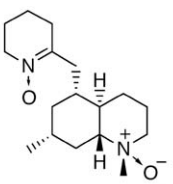
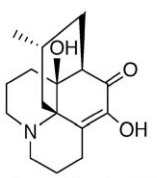
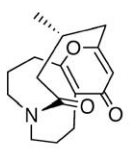
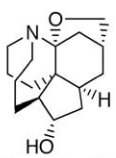

huperzine J (**10**)[24]
$C_{17}H_{30}N_2O$

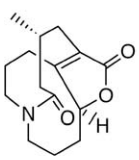

huperzine K (**11**)[24]
$C_{17}H_{30}N_2O$

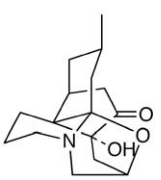

huperzine L (**12**)[24]
$C_{17}H_{30}N_2O_2$

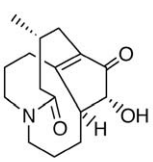

huperzine O (**13**)[25]
$C_{16}H_{23}NO_3$

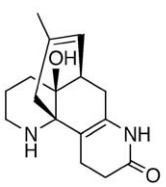

huperzine P (**14**)[26]
$C_{16}H_{21}NO_3$

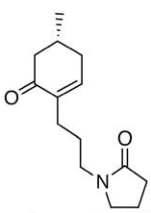

huperzine Q (**15**)[27]
$C_{16}H_{25}NO_2$


huperzine R (**16**)[28]
$C_{15}H_{21}NO_3$


huperzine S (**17**)[29]
$C_{16}H_{23}NO_3$


huperzine T (**18**)[29]
$C_{16}H_{23}NO_3$

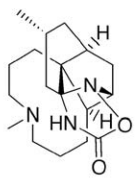

huperzine U (**19**)[29]
$C_{16}H_{22}N_2O_2$


huperzine W (**20**)[30]
$C_{14}H_{21}NO_2$

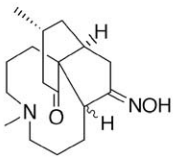
(*continued*)

TABLE I.
Continued.

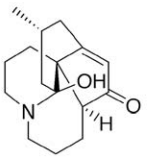
B. Lycoposerramines



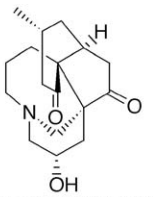

lycoposerramine-A (**21**)[31,32]
$C_{18}H_{29}N_3O_2$



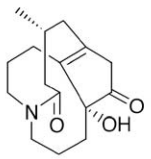

lycoposerramine-B (**22**)[33]
$C_{17}H_{28}N_2O_2$




lycoposerramine-C (**23**)[33]
$C_{16}H_{23}NO_2$




lycoposerramine-D (**24**)[33]
$C_{17}H_{25}NO_3$




lycoposerramine-E (**25**)[33]
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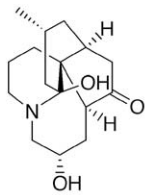
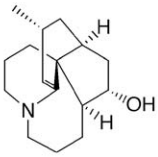
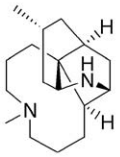


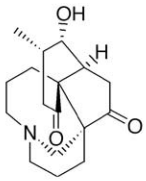

lycoposerramine-P (**26**)[33]
$C_{16}H_{25}NO_3$




lycoposerramine-Q (**27**)[33]
$C_{16}H_{25}NO$




lycoposerramine-S (**28**)[33]
$C_{17}H_{30}N_2$




lycoposerramine-U (**29**)[33]
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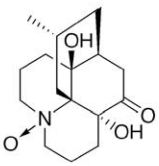
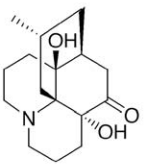
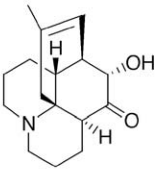


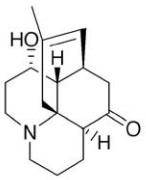

lycoposerramine-F (**30**)[34]
$C_{16}H_{25}NO_4$(=miyoshianine A)



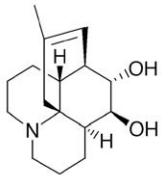

lycoposerramine-G (**31**)[34]
$C_{16}H_{25}NO_3$



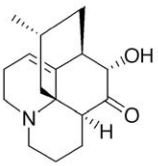

lycoposerramine-H (**32**)[34]
$C_{16}H_{23}NO_2$



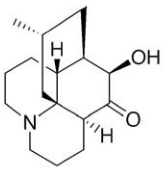

lycoposerramine-I (**33**)[33]
$C_{16}H_{23}NO_2$



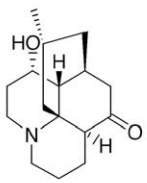

lycoposerramine-J (**34**)[34]
$C_{16}H_{25}NO_2$(=miyoshianine B)



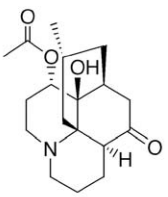

lycoposerramine-K (**35**)[34]
$C_{16}H_{23}NO_2$



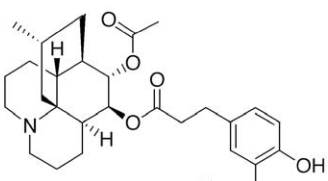

lycoposerramine-L (**36**)[34]
$C_{16}H_{25}NO_2$




lycoposerramine-M (**37**)[33]
$C_{16}H_{23}NO_2$




lycoposerramine-N (**38**)[34]
$C_{18}H_{27}NO_4$

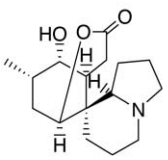



lycoposerramine-O (**39**)[34]
$C_{28}H_{39}NO_6$

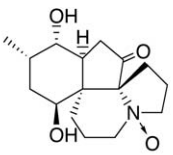
(*continued*)

TABLE I.
Continued.

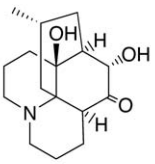
C. Serratezomines



serratezomine A (**40**)[35]
$C_{16}H_{25}NO_3$

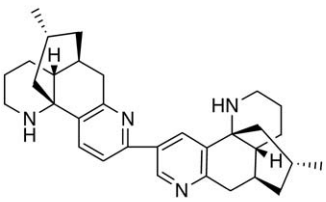


serratezomine B (**41**)[35]
$C_{16}H_{25}NO_4$

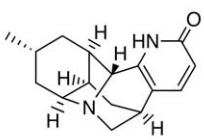


serratezomine C (**42**)[35]
$C_{16}H_{25}NO_3$

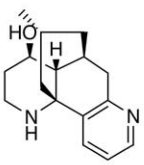
D and E. Complanadine A and Lyconadin A



complanadine A (**43**)[36]
$C_{32}H_{42}N_4$

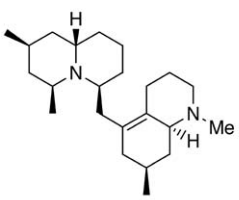


lyconadin A (**44**)[37]
$C_{16}H_{20}N_2O$

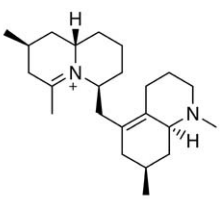


11-hydroxy lycodine (**45**)[37]
$C_{16}H_{22}N_2O$

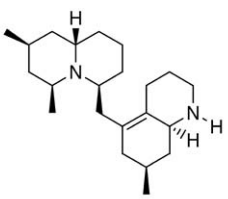
F. Senepodines



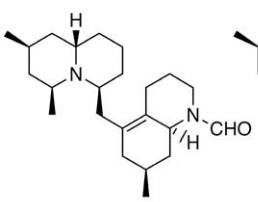
senepodine A (**46**)[38,39]
$C_{23}H_{40}N_2$



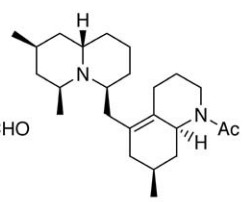
senepodine B (**47**)[39]
$C_{23}H_{39}N_2^+$



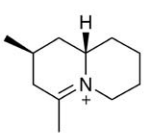
senepodine C (**48**)[39]
$C_{22}H_{38}N_2$



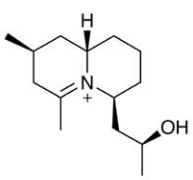
senepodine D (**49**)[39]
$C_{23}H_{38}N_2O$



senepodine E (**50**)[39]
$C_{24}H_{40}N_2O$



senepodine G (**51**)[40]
$C_{11}H_{20}N^+$

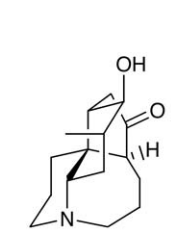


senepodine H (**52**)[40]
$C_{14}H_{26}NO^+$

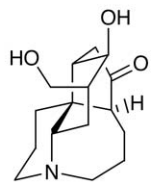
(*continued*)

TABLE I.
Continued.

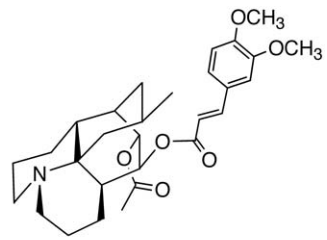
G, H, and I. Lyconesidines, Himeradine A, and Sieboldine A



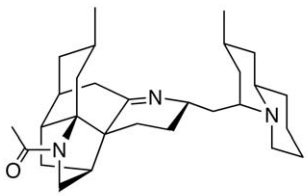
lyconesidine A (**53**)[41]
$C_{16}H_{25}NO_2$



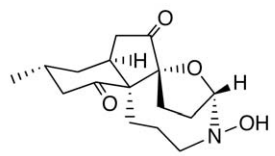
lyconesidine B (**54**)[41]
$C_{16}H_{25}NO_3$



lyconesidine C (**55**)[41]
$C_{30}H_{43}NO_6$

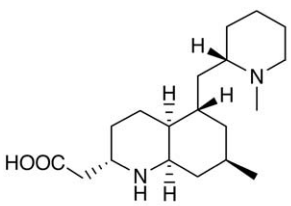


himeradine A (**56**)[42]
$C_{29}H_{45}N_3O$

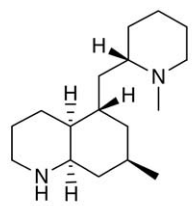


sieboldine A (**57**)[43]
$C_{16}H_{23}NO_4$

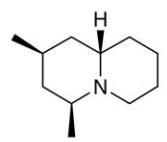
J. Cermizines



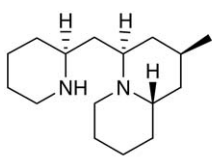
cermizine A (**58**)[40]
$C_{19}H_{34}N_2O_2$



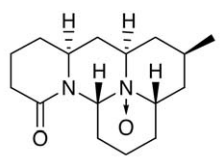
cermizine B (**59**)[40]
$C_{17}H_{32}N_2$



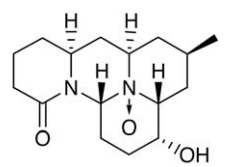
cermizine C (**60**)[40]
$C_{11}H_{21}N$



cermizine D (**61**)[40]
$C_{16}H_{30}N_2$



cernuine N-oxide (**62**)[40]
$C_{16}H_{26}N_2O_2$

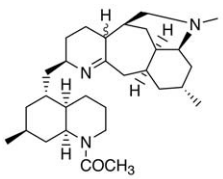


lycocernuine *N*-oxide (**63**)[40]
$C_{16}H_{26}N_2O_3$

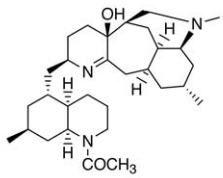
(*continued*)

TABLE I.
Continued.

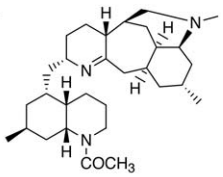
K. Lucidines



lucidine A (**64**)[44,45]
$C_{30}H_{49}N_3O$

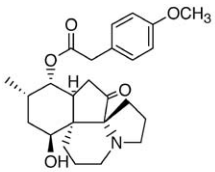


oxolucidine A (**65**)[45]
$C_{30}H_{49}N_3O_2$

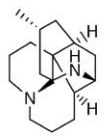


lucidine B (**66**)[45]
$C_{30}H_{49}N_3O$

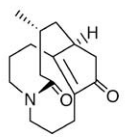
L. Other Alkaloids



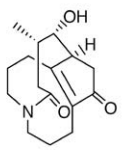
huperserratinine (**67**)[46]
$C_{25}H_{33}NO_5$



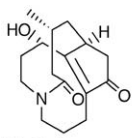
macleanine (**68**)[47]
$C_{16}H_{26}N_2$



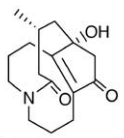
phlegmariurine B (**69**)[26]
$C_{16}H_{23}NO_2$



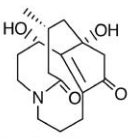
8α-hydroxy
phlegmariurine B (**70**)[48]
$C_{16}H_{23}NO_3$



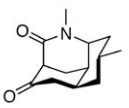
11α-hydroxy
phlegmariurine B (**71**)[49]
$C_{16}H_{23}NO_3$



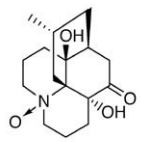
7α-hydroxy
phlegmariurine B (**72**)[49]
$C_{16}H_{23}NO_3$



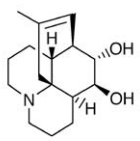
7α,11α-dihydroxy
phlegmariurine B (**73**)[49]
$C_{16}H_{23}NO_4$



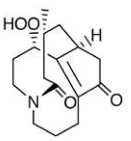
lucidulinone (**74**)[45]
$C_{13}H_{19}NO_2$



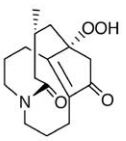
miyoshianine A (**75**)[50]
$C_{16}H_{25}NO_4$



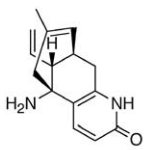
miyoshianine B (**76**)[50]
$C_{16}H_{25}NO_2$



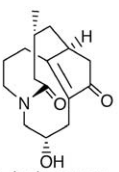
11α-hydroperoxy
phlegmariurine B (**77**)[51]
$C_{16}H_{23}NO_4$



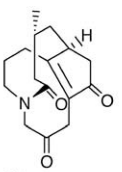
7-hydroperoxy
phlegmariurine B (**78**)[51]
$C_{16}H_{23}NO_4$



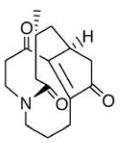
isofordine (**79**)[52]
$C_{15}H_{18}N_2O$



2α-hydroperoxy
phlegmariurine B (**80**)[53]
$C_{16}H_{23}NO_3$



2-oxo
phlegmariurine B (**81**)[53]
$C_{16}H_{21}NO_3$



11-oxo
phlegmariurine B (**82**)[53]
$C_{16}H_{21}NO_3$

of huperzine R (**16**), a novel $C_{15}$ *Lycopodium* alkaloid from *H. serrata*, was established by X-ray crystallography (*28*). Recently, three new alkaloids, huperzines S (**17**), T (**18**), and U (**19**) of the fawcettimine-, phlegmariurine B-, and lycodine-types, respectively, were isolated from *H. serrata* (*29*). A novel $C_{14}$ *Lycopodium* alkaloid, huperzine W (**20**), was isolated together with alopecuridine from *H. serrata* (*30*). The structures and molecular formulae of these alkaloids are listed in Table I.

## B. LYCOPOSERRAMINES

A series of lycoposerramines isolated by Takayama *et al.* were fawcettimane-type and fawcettidane-type alkaloids from the same species *Lycopodium serratum* in Japan which contains huperzines in China. The structure of lycoposerramine-A (**21**), which has a 1,2,4-oxadiazolidin-5-one residue in the molecule, was elucidated through spectroscopic data and X-ray analysis (*31*,*32*). Seven new alkaloids, lycoposerramines B (**22**), C (**23**), D (**24**), E (**25**), P (**26**), Q (**27**), S (**28**), and U (**29**), with novel, fawcettimine-related structures were isolated from the club moss *Lycopodium serratum* in Japan (*33*). Their relative and absolute stereochemistries were analyzed by spectroscopic data, X-ray analysis, and chemical correlations. The skeleton of lycoposerramine A (**21**) may be constructed by the incorporation of $NH_3$, $NH_2OH$, and a $C_1$ unit into a fawcettimine-type skeleton.

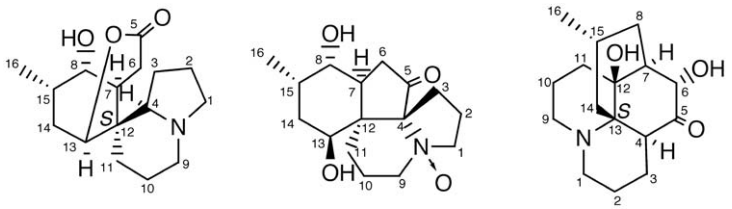
Furthermore, ten new alkaloids, lycoposerramines F (**30**), G (**31**), H (**32**), I (**33**), J (**34**), K (**35**), L (**36**), M (**37**), N (**38**), and -O (**39**), having lycopodine-related structures, were isolated from the club moss *Lycopodium serratum* and their structures were elucidated on the basis of spectroscopic analysis and/or chemical transformation (*34*). Lycoposerramines F (**30**) and J (**34**) were the same structures as miyoshianines A and B, respectively, isolated from *Huperzia miyoshiana* (*50*).

## C. SERRATEZOMINES

*Lycopodium* alkaloids are a class of natural products with unique ring systems, which have attracted great interest from a biogenetic point of view. These unique skeletons have prompted extensive phytochemical work and a project was initiated on the alkaloids of the club moss *Lycopodium serratum* var. *serratum*. Three new alkaloids, serratezomines A (**40**), B (**41**), and C (**42**), with a seco-serratinine-type, a serratinine-type, and a lycodoline-type skeleton, respectively, were isolated from the club moss *L. serratum* var. *serratum* (*35*). All of the structures are listed in Table I.

Samples of the club moss *L. serratum* var. *serratum* collected in Sapporo were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted to pH 10 with sat. $Na_2CO_3$, were partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to a $C_{18}$ column ($CH_3CN$/0.1% $CF_3CO_2H$, 1:4 → 4:1), in which a fraction eluted with $CH_3CN$/0.1% $CF_3CO_2H$ (1:4) was purified by an amino silica gel column ($CHCl_3$/MeOH, 1:0 → 1:1) followed by $C_{18}$ HPLC ($CH_3CN$/0.1% $CF_3CO_2H$, 13:87) to afford serratezomines A (**40**, 0.0002% yield), B (**41**, 0.002%), and C (**42**: 0.0002%) as colorless solids, together with the known related alkaloids, serratinine (**83**, 0.02%) (*54*), lycodoline

(0.004%) (*55*), and L20 (0.004%) (*56*).



**40** **41** **42**

The molecular formula, $C_{16}H_{25}NO_3$, of serratezomine A (**40**) was established by HRFABMS. IR absorptions implied the presence of hydroxyl (3400 $cm^{-1}$) and ester carbonyl (1730 $cm^{-1}$) functionalities. $^1H$ and $^{13}C$ NMR data disclosed the existence of one ester carbonyl, one $sp^3$ quaternary carbon, five $sp^3$ methines, eight $sp^3$ methylenes, and one secondary methyl. Among them, two methines ($\delta_c$ 76.2; $\delta$H 3.77 and $\delta_c$ 83.6; $\delta_H$ 4.32) were ascribed to those bearing an oxygen, while one methine ($\delta_c$ 66.8; $\delta_H$ 3.81) and two methylenes ($\delta_c$ 56.0; $\delta_H$ 3.35 and 3.54 and $\delta_c$ 48.8; $\delta_H$ 2.98 and 3.26) were ascribed to those attached to a nitrogen. Since one of the five unsaturations was accounted for, **40** was inferred to possess four rings. The gross structure of **40** was elucidated by analysis of the 2D NMR data, including $^1H$–$^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in $CD_3OD$, and the presence of a 2-oxabicyclo[3.3.1]nonan-3-one ring system connected to the indolizine ring through the spiro carbon at C-12 was disclosed.

The relative stereostructure of **40**, as shown in a computer-generated 3D drawing (Fig. 1), was deduced from the cross-peaks observed in the phase sensitive NOESY spectrum. The proton coupling constants ($J_{7,8}$ = 3.4 Hz and $J_{8,15}$ = 3.4 Hz) in the cyclohexane ring and a **W**-type long-range coupling between H-7 and H-13, which were both equatorial, supported the proposed relative stereochemistry, and a chair form for the cyclohexane ring in the 2-oxabicyclo[3.3.1]nonan-3-one system (Fig. 1). The *cis*-fused ring

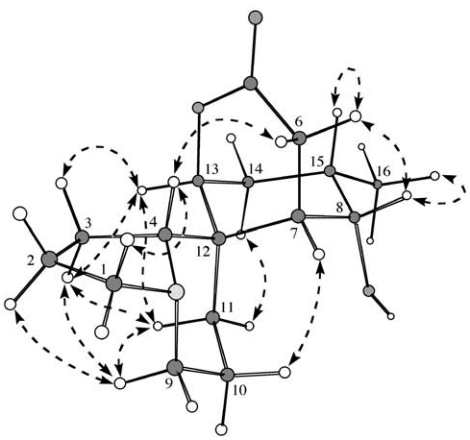


Figure 1. Selected NOESY correlations (dotted arrows) and relative configurations for serratezomine A (**40**) (*35*).

junction in the indolizidine ring, and a chair form for the piperidine ring, were also deduced from the NOESY correlations.

Furthermore, the relative configuration at C-12 was estimated by the floating chirality method (*57*), which allows the distance constraints to guide the molecule into configurations consistent with its NOE data (Fig. 2). For molecules possessing complex ring systems, high-temperature dynamics alone may fail to invert certain chiral centers

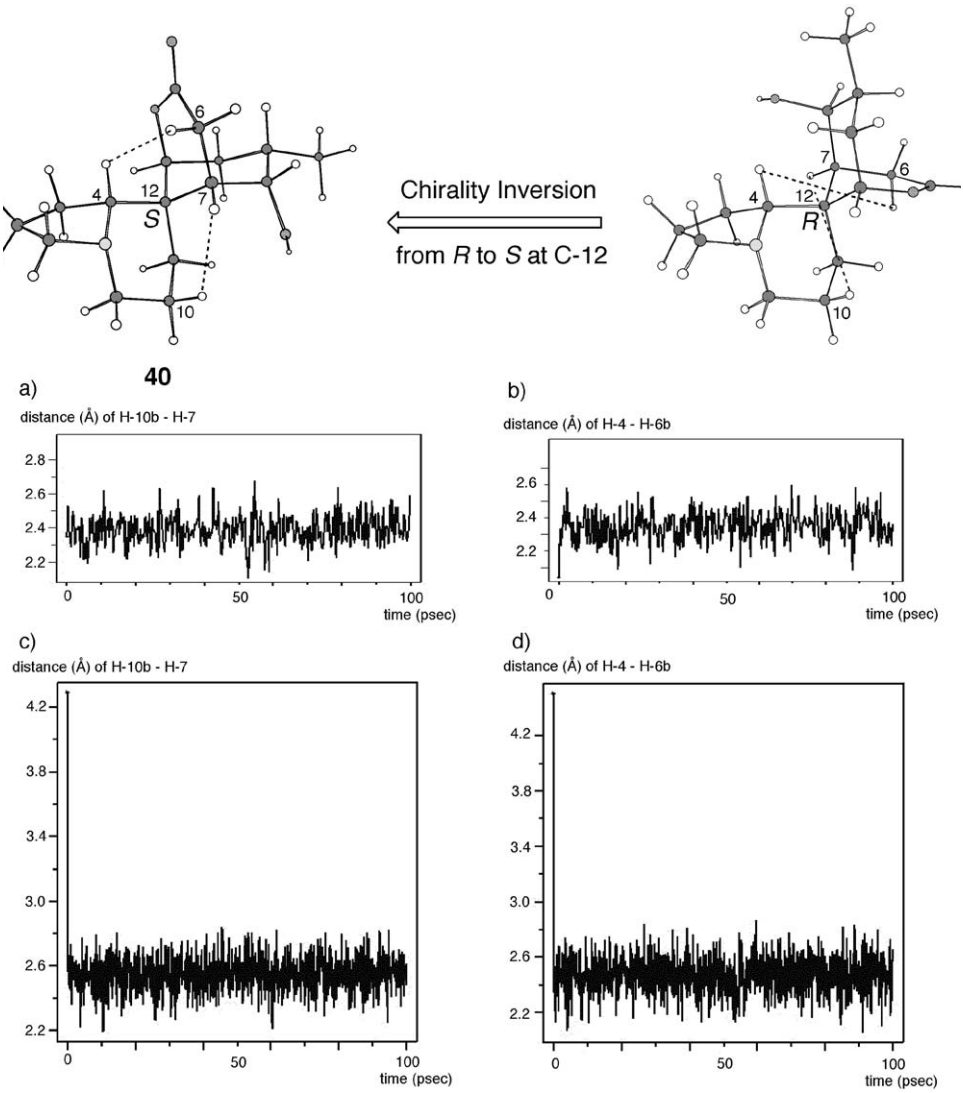



Figure 2. Inversion of chirality at C-12 from *R* to *S* during MD simulation *in vacuo* (*35*). Charts a) and b) represent distances from $H_b$-10 to H-7, and from H-4 to $H_b$-6, respectively, when started from serratezomine A (**40**) (*S* at C-12). Charts c) and d) represent those started from the isomer (*R* at C-12).

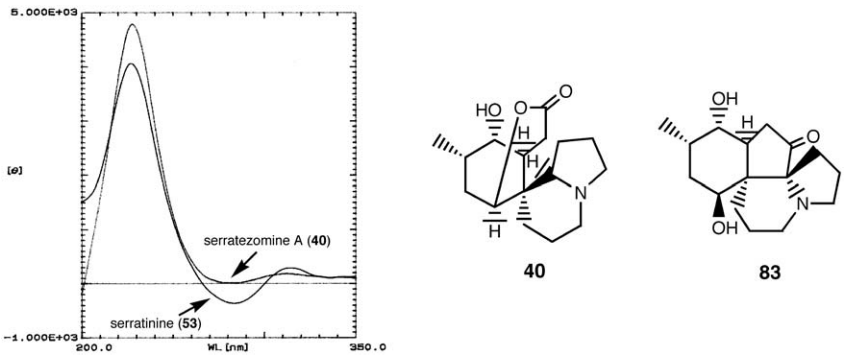



Figure 3. CD spectra of serratezomine A (**40**) and serratinine (**83**) (*35*).

with sufficient frequency. This chiral inversion is caused by the application of NOE constraints. Inversion of chirality about C-12 could be detected by monitoring the distances of H-10b–H-7 and H-4–H-6b. A significant change in these interproton distances would indicate that an inversion about this chiral center has occurred. When initiated with an *S** configuration at C-12 of **40**, no inversion of the chiral center at C-12 was observed at any time during the course of the simulation, whereas a simulation starting from the *R** isomer at C-12 led to conversion into the *S** configuration. These results provided additional corroborating evidence of the relative stereochemistry and the stable conformer of **40** in $CD_3OD$. The CD spectra (Fig. 3) of **40** showed a similar CD curve ($[\theta]_{230}+4800$, and $[\theta]_{312}+200$) to that of serratinine (**83**: $[\theta]_{230}+4050$, $[\theta]_{303}-400$, and $[\theta]_{313}+350$), whose absolute stereochemistry was established by X-ray analysis (*75*). Therefore, the absolute configurations of **40** were assigned as 4*R*, 7*S*, 8*S*, 12*S*, 13*S*, and 15*S*.

To confirm the absolute configuration at C-8, alkaloid **40** was treated with 3-cyanocarbonyl-3′-methoxycarbonyl-2,2′;-binaphthalene to yield the 8-*O*-binaphthyl ester of **40**, to which an induced exciton chirality method (*78*) was applied (*80*). In the CD spectrum, a split CD curve having a negative exciton chirality at 256 nm and a positive one at 234 nm was observed (Fig. 4). Calculated screw sense of the 2-naphthyl group in the energetically more stable conformer (**A**) rather than the alternative conformer (**B**) was coincident with that expected from its exciton chirality (Fig. 5). Thus, the configuration at C-8 of **40** was assigned as *S*. This assignment was also confirmed by application of a modified Mosher method (*65*) for a derivative of **40**.

Serratezomine A (**40**) is a novel structural type of alkaloid consisting of a 2-oxabicyclo[3.3.1]nonan-3-one and an indolizidine ring connected through a spiro carbon.

The HRFABMS data of serratezomine B (**41**) indicated the molecular formula, $C_{16}H_{25}NO_4$, which was larger than that of **83** by one oxygen unit. Detailed analyses of the 2D NMR spectra of **41**, and comparison of the $^{13}C$ chemical shifts of C-1, C-4, and C-9 ($\delta$ 68.6, 87.4, and 63.2, respectively) in **41** with those ($\delta$ 53.2, 79.4, and 51.3, respectively) of serratinine (**83**), indicated the presence of an *N*-oxide functionality in **41**. Oxidation of **83** with *m*-chloroperbenzoic acid (*m*-CPBA) afforded the *N*-oxide

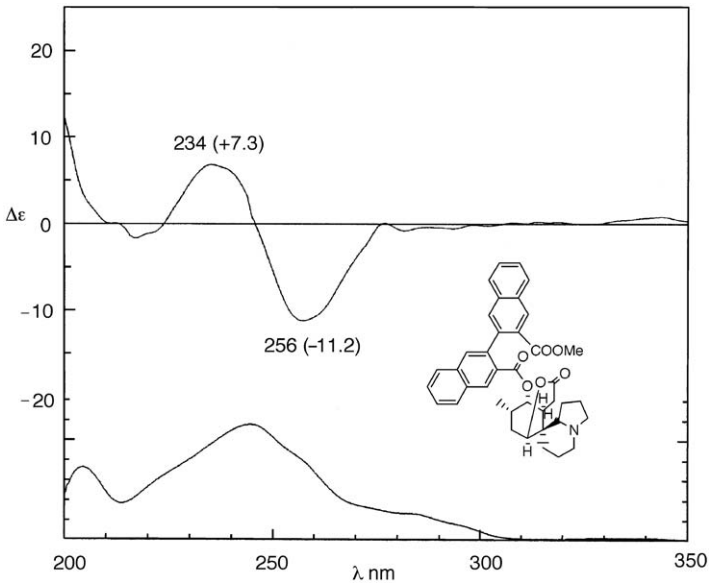



Figure 4. CD and UV spectra of 8-*O*-binaphthyl ester of serratezomine A (**40**) (*76*).

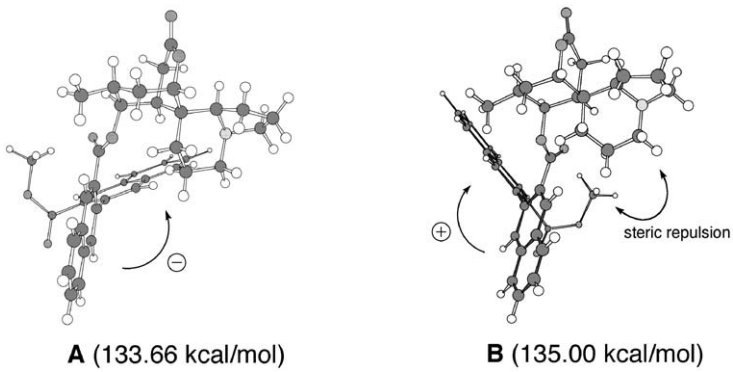
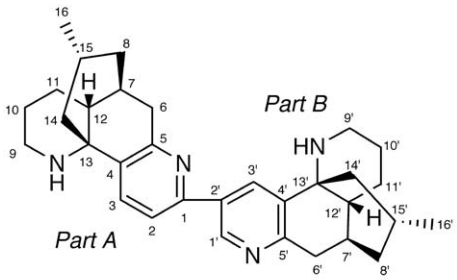



Figure 5. Two representative stable conformers (**A** and **B**) of the 8-*O*-binaphthyl ester of serratezomine A (**40**) analyzed by Monte Carlo simulation followed by minimization and clustering analysis (*76*).

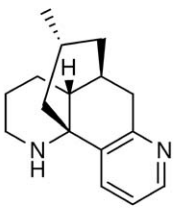
derivative, whose spectral data and $[\alpha]_D$ value were identical with those of natural serratezomine B (**41**). Thus, serratezomine B (**41**) was concluded to be the *N*-oxide of serratinine (**83**).

The HRESIMS data of serratezomine C (**42**) revealed the same molecular formula, $C_{16}H_{25}NO_3$, as that of **40**. The structure of alkaloid **42** was elucidated to be the 6-hydroxy derivative of lycodoline through analysis of the 2D NMR data.

## D. COMPLANADINE A




**43**




**84**

Samples of the club moss *L. complanatum* collected in Hokkaido were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, adjusted to pH 10 with sat. $Na_2CO_3$, were partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column, in which a fraction eluted with $CHCl_3$/MeOH (1:1) was purified by a silica gel column to afford complanadine A (**43**, 0.003% yield) (*36*), together with the known, related alkaloid, lycodine (**84**, 0.0005%) (*58*).

The molecular formula, $C_{32}H_{42}N_4$, of complanadine A (**43**) {$[\alpha]_D^{24} + 14^\circ$ (*c* 0.3, MeOH)} was established by HRFABMS. $^1H$ and $^{13}C$ NMR data disclosed the existence of ten olefinic carbons, two $sp^3$ quaternary carbons, six $sp^3$ methines, twelve $sp^3$ methylenes, and two secondary methyls. Among them, four olefinic carbons [$\delta_c$ 147.2 (d), 154.2 (s), 160.1 (s), and 160.3 (s)] assignable to nitrogen-bearing carbons were elucidated to form two tri-substituted pyridine rings together with the remaining six olefinic carbons [$\delta_c$ 120.5 (d), 132.7 (s), 133.1 (d), 134.2 (s), 134.8 (s), and 135.3 (d)]. Two quaternary carbons ($\delta_c$ 60.2 and 60.5) and two methylenes ($\delta_c$ 42.1; $\delta_H$ 2.73 and 3.05, and $\delta_c$ 42.1; $\delta_H$ 2.73 and 3.07) were ascribed to carbons attached to a nitrogen. UV absorptions [290 ($\varepsilon$ 14000) and 251 nm (12000)] also supported the presence of the pyridine ring. Since eight out of the fourteen unsaturations were accounted for, alkaloid **43** was inferred to possess six more rings. The gross structure of **43** was elucidated by analysis of the 2D NMR data, including the $^1H$–$^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in $CD_3OD$. Each pair of these $^1H$ and $^{13}C$ NMR signals seemed to be due to each half moiety (parts A and B) of a dimer. The linkage between the pyridine rings in parts A and B was provided by the HMBC correlation of H-3′ ($\delta$H 8.61) to C-1 ($\delta_c$ 154.2), thus giving rise to the connectivity of C-1 to C-2′. NOESY correlations of H-2/H-3′ and H-2/H-1′ (Fig. 6) also supported the connectivity between parts A and B. Thus, the gross structure of complanadine A (**43**) was assigned as a dimer of lycodine (**84**), in which C-1 in part A was connected to C-2′ in part B.

The phase sensitive NOESY spectrum of **43** showed cross-peaks as shown in the computer-generated 3D drawing (Fig. 6). The relative configurations at C-7, C-12, C-13, and C-15 in part A were based on the NOESY correlations of H-6b/H-15, H-12/H-10b and H-3/H-14b, while the piperidine and cyclohexane (C-7, C-8, and C-12 ~ C-15) rings both adopted chair conformations. On the other hand, the corresponding NOESY

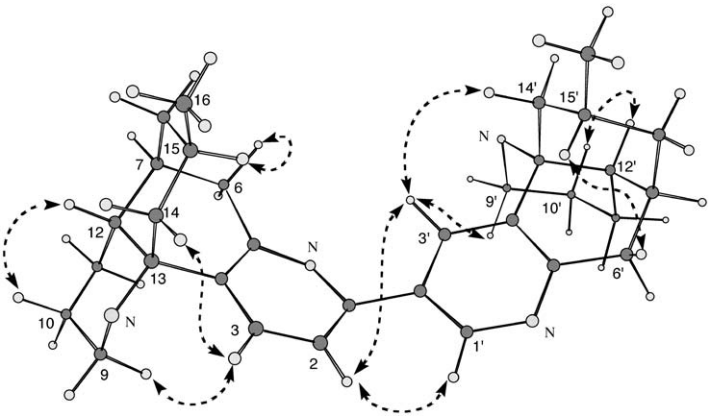


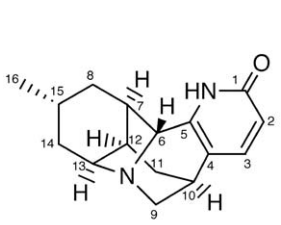

Figure 6. Selected NOESY correlations (dotted arrows) and relative stereochemistry for complanadine A (**43**) (*36*).

correlations were also observed for part B. The CD spectrum of **43** in MeOH showed similar CD curves ($[\theta]_{260}+4500$, $[\theta]_{285}+1500$), $[\theta]_{295}+2000$, and $[\theta]_{315}+3000$) to those ($[\theta]_{250}+5000$), $[\theta]_{280}+3000$, and $[\theta]_{325}+3000$) of lycodine (**84**), indicating the same absolute stereochemistry for parts A and B of **43** as that of lycodine (**84**).

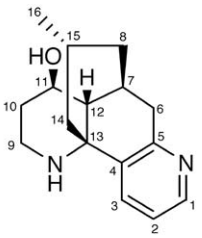
Complanadine A (**43**) is the first dimeric alkaloid containing a lycodine-type $C_{16}N_2$ skeleton among the many *Lycopodium* alkaloids reported so far.

## E. LYCONADIN A

Further chromatographic purification of the $CHCl_3$-soluble materials prepared from the club moss *L. complanatum* afforded lyconadin A (**44**, 0.0003% yield) and 11-hydroxy lycodine (**45**, 0.0003% yield) (*37*).




**44**




**45**

The molecular formula, $C_{16}H_{20}N_2O$, of lyconadin A (**44**) was established by HRFABMS and the IR absorption implied the presence of a conjugated carbonyl (1660 $cm^{-1}$) functionality. $^1H$ and $^{13}C$ NMR data disclosed the existence of an amide carbonyl, a di-substituted olefin, a tetra-substituted olefin, four $sp^3$ methylenes, six $sp^3$ methines, and a methyl group. Among them, the signals due to two methines ($\delta_C$ 64.6; $\delta_H$ 4.19 and $\delta_C$ 73.1; $\delta_H$ 3.54) and one methylene ($\delta_C$ 61.4; $\delta_H$ 2.88 and 3.55) were ascribed to those bearing a nitrogen, while those due to an amide carbonyl ($\delta_C$ 165.3), a di-substituted

olefin ($\delta_C$ 116.6 and 141.6), and a tetra-substituted olefin ($\delta_C$ 126.2 and 148.8) indicated the presence of a 4,5-disubstituted pyridone ring. Since three out of eight unsaturations were accounted for, **44** was inferred to possess five rings. The gross structure of **44** was elucidated by analysis of the 2D NMR data, including $^1H$–$^1H$ COSY, HOHAHA, HMQC, and HMBC spectra in $CD_3OD$.

The connectivity of C-7 to C-8, C-9 ~ C-16, C-7 to C-12, and C-8 to C-15 was revealed by the $^1H$–$^1H$ COSY and HOHAHA spectra. The HMBC cross-peak of H-9a to C-13 indicated the connection between C-9 ($\delta_C$ 61.4) and C-13 ($\delta_C$ 73.1) through a nitrogen. On the other hand, the presence of a 4,5-disubstituted pyridone ring was inferred by the mutually coupled olefinic protons ($\delta_H$ 6.35 and 7.42, $J = 8.9$ Hz) whose attached carbon resonances were observed at $\delta_C$ 116.6 and 141.6, respectively. HMBC correlations from H-3 to C-10 ($\delta_C$ 33.6) and from H-9b to C-4 ($\delta_C$ 126.2) established the connection between C-4 and C-10. HMBC correlations of both H-9b and H-13 to C-6 ($\delta_C$ 64.6) indicated that C-6 was attached to C-9 and C-13 through N-9, while the HMBC correlations of H-6 to C-4 and C-5 suggested the C-5 to C-6 linkage. The final connectivity between C-6 and C-7 was supported by the HMBC correlations of H-8a and H-12 to C-6. Thus, the gross structure of lyconadin A was assigned as **44**.

The relative stereostructure of **44** as shown in a computer-generated 3D drawing (Fig. 7), was deduced from the cross-peaks observed in the phase sensitive NOESY spectrum and from $^3J$ proton coupling constants. NOESY correlations of H-12/H-8a and H-12/H-14a, and the large $^1H$–$^1H$ couplings of H-8a/H-15 ($J = 13.0$ Hz) and H-14a/H-15 ($J = 12.1$ Hz), and the small ones of H-12/H-13 ($J = 2.7$ Hz) and H-7/H-12 ($J = ca.$ 2 Hz), indicated that H-8a, H-12, and H-14a had a 1,3-diaxial relationship. It was found that the cyclohexane ring (C-7 ~ C-8 and C-12 ~ C-15) assumed a chair form, which was consistent with a **W**-type long-range coupling between H-7 and H-13, both equatorial. On the other hand, the NOESY cross-peaks of H-9a/H-13, H-9a/H-11a, and H-11a/H-13 indicated that the piperidine ring also assumed a chair form. Both of the 6-membered rings were *cis* fused to form the decahydroquinoline ring system from the NOESY correlation of H-12/H-13 and their small coupling constant ($J = 2.7$ Hz). The relative stereochemistry at C-10 was elucidated by the NOESY correlation of H-3/H-10, and the small coupling of H-10

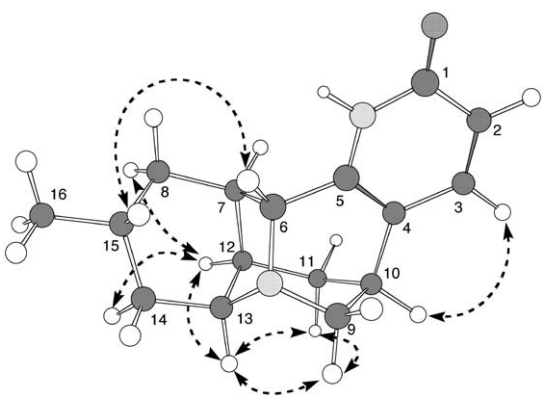


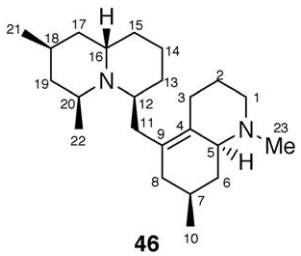

Figure 7. Selected NOESY correlations (dotted arrows) and relative configurations for lyconadin A (**44**) (*37*).

($J < 1$ Hz), which was equatorial. A small coupling constant of less than 1 Hz between H-6 and H-7, together with the NOESY correlation of H-6/H-15, indicated that the angle between H-6 and H-7 was near 90°, and that H-6 and H-15 were on the $\beta$ face of the molecule. On the basis of the above arguments, the relative stereochemistry of lyconadin A (**44**) was assigned as 6*R**, 7*R**, 10*S**, 12*R**, 13*S**, and 15*R**.

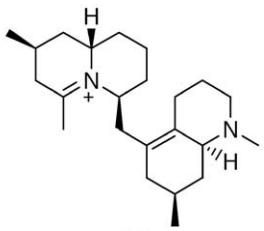
The gross structure of **45** was elucidated by analysis of the 2D NMR data, including $^1$H–$^1$H COSY, HOHAHA, HMQC, and HMBC spectra in $CDCl_3$, to be 11-hydroxy lycodine. The relative stereochemistry of **45** was deduced from NOESY correlations, indicating the same stereochemistry as that of lycodine **84**. To determine the absolute configuration at C-11, **45** was converted into its (*S*)- and (*R*)-$\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenylacetic acid (MTPA) esters (*65*). The values of $\Delta\delta$ [$\delta$(*S*-MTPA ester) – $\delta$(*R*-MTPA ester)] for H-12, H-15, $H_2$-14, $H_3$-16, and $H_2$-6 were negative, while positive $\Delta\delta$ values were observed for $H_2$-9 and $H_2$-10, indicating that the absolute configuration at C-11 was *R*. Thus the absolute stereostructure of 11-hydroxy lycodine (**45**) was assigned as shown.

## F. SENEPODINES

A new class of $C_{22}N_2$ *Lycopodium* alkaloids consisting of an octahydroquinoline and a quinolizidine ring, senepodines A (**46**, 0.003% yield), B (**47**), C (**48**), D (**49**), and E (**50**) (*38,39*), were isolated from the club moss *Lycopodium chinense*, together with a known $C_{16}N_2$ alkaloid, cernuine (*59–61*).




**46**

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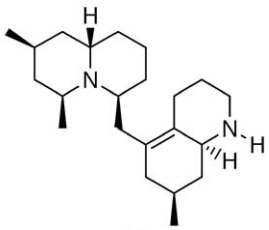
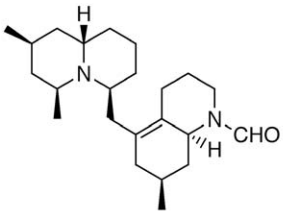



**48**

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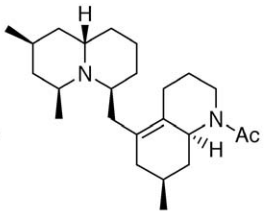
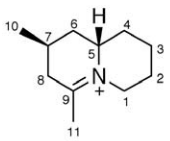
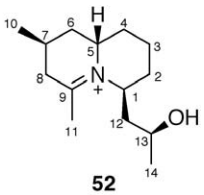



**50**




**51**



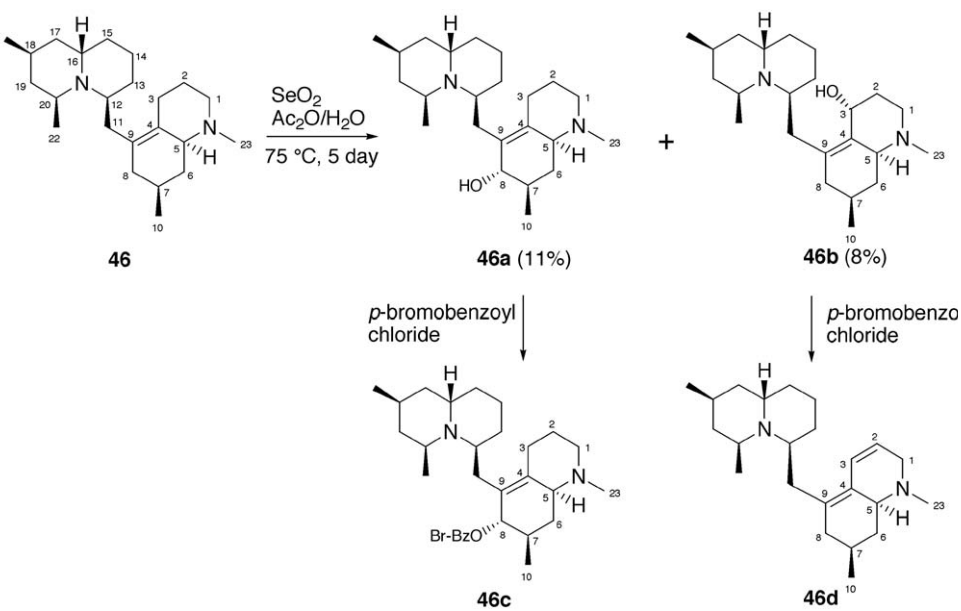

**52**

Senepodine A (**46**), colorless solid, $[\alpha]_D^{25}$ −33° (*c* 0.6, MeOH), was shown to have the molecular formula of $C_{23}H_{41}N_2$. The $^1$H NMR spectrum of **46** in $CDCl_3$ showed broad signals, while the $^1$H and $^{13}$C NMR spectra in $CD_3OD$ showed relatively well-resolved signals and disclosed the existence of a tetra-substituted olefin, eleven $sp^3$ methylenes, six $sp^3$ methines, and four methyls. Interpretation of the 2D NMR data, including the $^1$H–$^1$H COSY, HOHAHA, HMQC, and HMBC spectra in $CD_3OD$,

revealed the presence of an octahydroquinoline moiety, a tetra-substituted olefin, an N–$CH_3$, a quinolizidine moiety, and a nitrogen atom. The carbon–carbon connectivity of the above units was elucidated by HMBC correlations and the gross structure of senepodine A was assigned as **46**. The relative stereochemistry was deduced from NOESY data and proton–proton couplings.

The absolute stereochemistry of **46** was elucidated by applying the exciton chirality method (*62*) after oxidation of the allylic position at C-3 or C-8 with selenium dioxide, followed by introduction of a *p*-bromobenzoyl group into the hydroxyl group at C-3 or C-8 as follows. Treatment of **46** with selenium dioxide in acetic anhydride and $H_2O$ at 75°C for 5 days gave two oxidized products (**46a**, 11% yield; **46b**, 8%) (Scheme 1) (*39*). The location of the oxidation and the relative stereochemistry of the introduced hydroxy group in **46a** and **46b** was elucidated by NOESY correlations (Fig. 8) to be 8$\alpha$ and 3$\alpha$, respectively. Inspection of molecular models gave the same results as those obtained by Monte Carlo simulation (*63*) using the MMFF force field method (*64*). Treatment of **46a** with *p*-bromobenzoyl chloride afforded the corresponding *p*-bromobenzoyl ester (**46c**), whereas in the case of **46b**, with the axially oriented hydroxyl at C-3, the same treatment resulted in dehydration to give the diene **46d** (Scheme 1). The sign of the first Cotton effect [$\lambda_{max}$ 244 nm ($\Delta\varepsilon$−9.2)] for **46c** was negative (Fig. 9), indicating that the chirality between the *p*-bromobenzoyl group at C-8 and the olefin at C-4–C-9 was as shown in Fig. 9 (left-handed screw). Thus, the absolute configuration at C-8 of the hydroxylated compound **46a** was assigned as *S*, indicating that the absolute structure of senepodine A (**46**) was as shown in Scheme 1.

Senepodine B (**47**) was shown to have the molecular formula of $C_{23}H_{39}N_2$, and the IR spectrum was indicative of the presence of an imine (1680 $cm^{-1}$) functionality. The 2D




Scheme 1. (*39*)

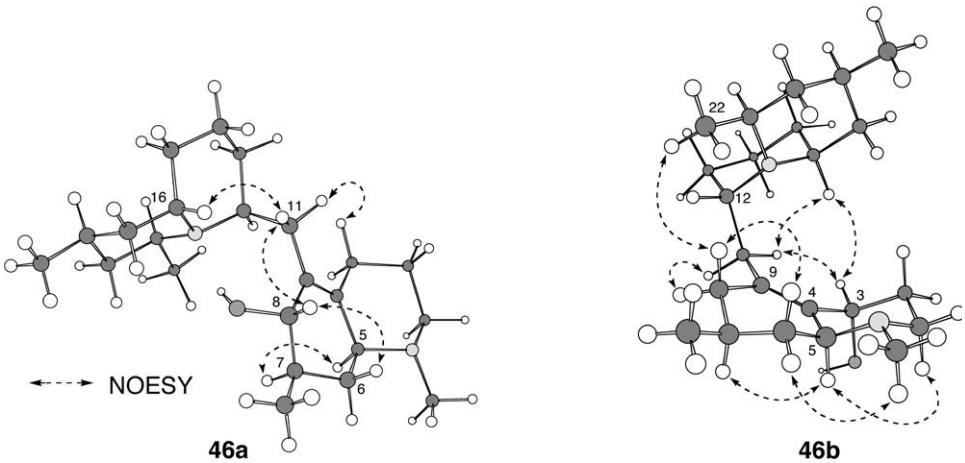



Figure 8. Selected NOESY correlations for 8-hydroxysenepodine A (**46a**) and 3-hydrosxy-senepodine A (**46b**) (*39*).

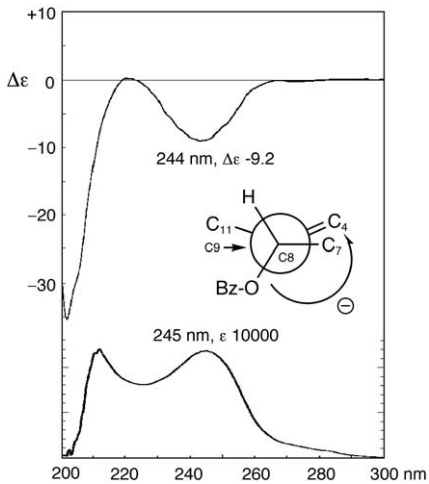
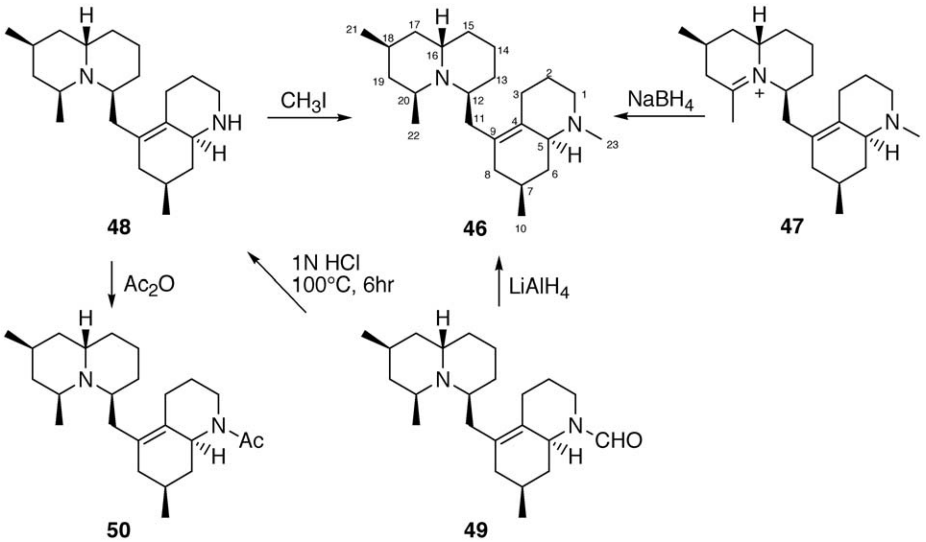



Figure 9. CD and UV spectra of *p*-bromobenzoate (**46c**) of 8-hydroxysenepodine A (**46a**) and rotation model for the C8–C9 bond (*39*).

NMR data of **47**, including the $^{1}H$–$^{1}H$ COSY, HOHAHA, HMQC, and HMBC spectra, and the FABMS/MS fragmentation, corroborated well with those of the imine (C-20 and N) form of **46**. The treatment of **47** with $NaBH_4$ afforded senepodine A (**46**) by stereoselective attack of a hydride outside the cage form of **46**.

Analysis of senepodine C (**48**) established the molecular formula to be $C_{22}H_{38}N_2$, which was less than that of senepodine A (**46**) by a $CH_2$ unit. The gross structure of **48** was elucidated by the 2D NMR data. Treatment of **48** with $CH_3I$ gave senepodine A (**46**). Thus, the structure of senepodine C was assigned as **48**. The IR spectrum of senepodine D (**49**) was indicative of the presence of an amide carbonyl (1667 $cm^{-1}$). Treatment of **49**



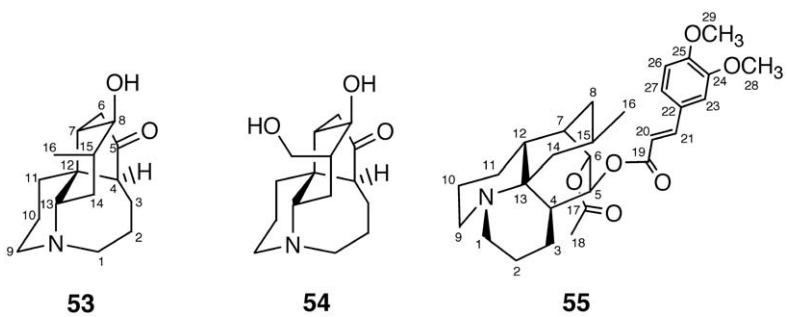

Scheme 2. (*39*)

with $LiAlH_4$ afforded senepodine A (**46**), while hydrolysis of **49** with 1 N HCl at 100°C for 6 h gave senepodine C (**48**) (Scheme 2) (*39*). Thus, senepodine D (**49**) was concluded to be the *N*-formyl form at C-23 of senepodine A (**46**). Acetylation of senepodine C (**48**) afforded senepodine E (**50**) (Scheme 2) (*39*). Thus, senepodine E was concluded to be the *N*-acetyl form at C-23 of senepodine A (**46**).

Two new quinolizidine alkaloids, senepodines G (**51**) and H (**52**) were also isolated (*40*) and their structures were assigned by a combination of the 2D NMR data and a modified Mosher's method (*65*).

## G. LYCONESIDINES

The continuing search for biogenetically interesting alkaloids from *L. chinense* led to the isolation of three new $C_{16}N$ alkaloids, lyconesidines A (**53**, 0.002% yield), B (**54**, 0.005%), and C (**55**, 0.003 %) (*41*), together with a known $C_{16}N$ type alkaloid, lycodoline (*55*).



The IR absorptions of lyconesidine A {**53**, $[\alpha]_D^{25}$ –53° (*c* 1.0, MeOH)}, $C_{16}H_{25}NO_2$ implied the presence of hydroxyl (3370 $cm^{-1}$) and carbonyl (1730 $cm^{-1}$) groups. $^1H$–$^1H$ COSY and HOHAHA experiments on **53** clearly revealed the two structural units **a** (C-1 ~ C-4) and **c** (C-9 ~ C-11). Connections among these three units **a** ~ **c**, C-5 ($\delta_C$ 219.9), and C-12 ($\delta_C$ 46.6) were suggested by the HMBC correlations, and the gross structure of lyconesidine A was elucidated to be **53**. The phase-sensitive NOESY spectrum displayed the correlations shown in the computer-generated 3D drawing (Fig. 10). The absolute stereochemistry of lyconesidine A (**53**) was elucidated by applying a modified Mosher's method (*65*). To determine the absolute configuration at C-8, **53** was converted into its (*S*)- and (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) esters of the hydroxy group at C-8. The values of $\Delta\delta$ [$\delta$(*S*-MTPA ester) – $\delta$(*R*-MTPA ester)] obtained from the $^1H$ NMR spectra of the MTPA esters suggested that the absolute configuration at C-8 was *S*.

IR absorptions of lyconesidine B {**54**, $[\alpha]_D^{25}$ −71° (*c* 1.8, MeOH)}, $C_{16}H_{25}NO_3$, implied the presence of both hydroxyl (3430 $cm^{-1}$) and ketone (1730 $cm^{-1}$) functionalities. The $^1H$ and $^{13}C$ NMR spectra suggested that **54** had the same tetracyclic backbone framework as that of **53**, except for the presence of a hydroxy group at C-16 ($\delta_C$ 60.5, $\delta_H$ 3.71 and 3.90). The relative stereochemistry of lyconesidine B (**54**) was deduced by an X-ray crystallographic analysis (Fig. 11) of a crystal of **54** obtained from MeOH–$H_2O$.

The absolute stereochemistry of lyconesidine B (**54**) was elucidated by applying a modified Mosher's method (*65*) as follows. The hydroxy group at C-16 of **54** was protected with a triphenyl methyl (trityl) group and then esterified with its (*S*)- and (*R*)-MTPA chlorides, followed by hydrolysis of the trityl ester with formic acid to give its (*S*)- and (*R*)-MTPA esters. The values of $\Delta\delta$ [$\delta$(*S*-MTPA ester) – $\delta$(*R*-MTPA ester)]

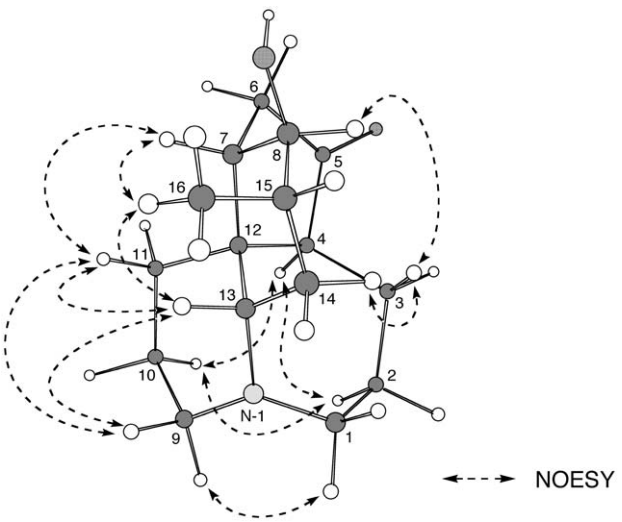



Figure 10. Selected NOESY correlations and relative stereochemistry for lyconesidine A (**53**) (*41*).

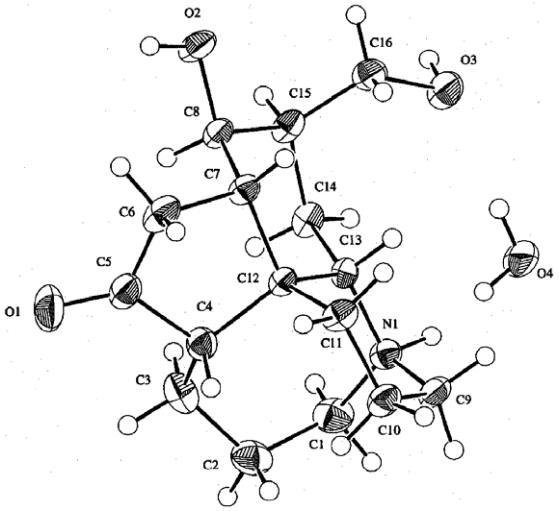


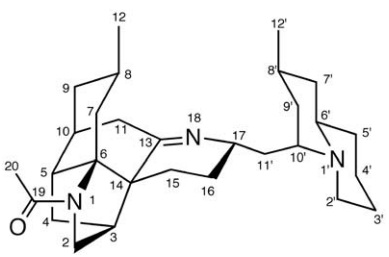

Figure 11. Molecular structure of lyconesidine B (**54**) containing one molecule of $H_2O$ obtained by X-ray analysis (ORTEP drawing; ellipsoids are drawn at the 30% probability level) (*41*).

obtained from the $^1$H NMR spectra of the MTPA esters suggested that the absolute configuration at C-8 of **54** was *R*.

Detailed spectroscopic analysis of lyconesidine C (**55**) revealed that **55** had a similar backbone skeleton to that of lycodoline. The presence of an acetoxy at C-6 and a 3,4-dimethoxy cinnamoyl ester at C-5 was revealed by the HMBC correlations of H-6 and $H_3$-18 to C-17, and H-5 and H-20 to C-19. The relative stereochemistry of **55** was deduced from NOESY correlations.

## H. HIMERADINE A

Further investigation of the extracts of *L. chinense* resulted in the isolation of himeradine A (**56**, 0.001% yield) (*42*), a novel $C_{27}N_3$ type alkaloid consisting of a fastigiatine-type skeleton ($C_{16}N_2$) and a quinolizidine moiety ($C_{11}N$), together with a known related alkaloid, lucidine B (**66**, 0.001%) (*44,45,66*).




**56**

IR absorptions of himeradine A (**56**), $C_{29}H_{45}N_3O$, implied the presence of amide carbonyl and/or imine (1640 $cm^{-1}$) functionalities. Analysis of the $^1H$ and $^{13}C$ NMR data and the HMQC spectrum revealed the presence of two $sp^2$ and two $sp^3$ quaternary carbons, eight $sp^3$ methines, fourteen $sp^3$ methylenes, and three methyl groups. Among them, two $sp^3$ methylene ($\delta_C$ 57.5; $\delta_H$ 3.34 and 3.80; $\delta_C$ 52.9; $\delta_H$ 3.19 and 3.33), three $sp^3$ methines ($\delta_C$ 56.6; $\delta_H$ 4.09; $\delta_C$ 58.4; $\delta_H$ 3.24; $\delta_C$ 60.0; $\delta_H$ 3.77), and one $sp^3$ quaternary carbon ($\delta_C$ 76.1) were ascribed to those bearing a nitrogen. The remaining carbons were assigned as an amide carbonyl carbon ($\delta_c$ 174.3) and an $sp^2$ iminium carbon ($\delta_C$ 196.7).

Detailed NMR analysis in $CD_3OD$ and pyridine-$d_5$ revealed that the gross structure of himeradine A was elucidated to be **56** possessing a fused-pentacyclic fastigiatine-type ring system (*67*) consisting of a tetrahydropyridine ring (N-18, C-13 ~ C-17), a bicyclo[3.3.1]nonane ring (C-5 ~ C-11, C-13, and C-14) with a methyl group at C-8, and a 2-aza-bicyclo[2.2.1]heptane ring (N-1, C-2 ~ C-6, and C-14) with an acetyl group at N-1, which was further connected through C-11′ to a quinolizidine ring (N-1′ and C-2′ ~ C-10′) with a methyl group at C-8′. Additional evidence supporting the proposed structure of **56** was provided by tandem mass spectrometry through examination of the collision-induced dissociation (CID) mass spectrum of the $(M+H)^+$ ion. The positive ion FABMS/MS spectrum of **56** showed product ion peaks generated by fissions at the bonds between C-10′ and C-11′, and between C-11′ and C-17 (Fig. 12).

The relative stereochemistry of **56** was elucidated by NOESY correlations and $^3J_{H-H}$ coupling as depicted in the computer-generated 3D drawing (Fig. 13). Conformations of the quinolizidine ring (N-1′, C-2′ ~ C-10′) and the bicyclo[3.3.1]nonane ring (C-5 ~ C-11, C-13, and C-14), in which all of the six-membered rings took chair forms, were deduced from NOESY correlations as shown in Fig. 13, except for the stereochemistry at C-17 and C-10′. The large $^3J$ coupling constant ($J = 12.9$ Hz) between H-8 and H-7b indicated the configuration of methyl group at C-8 as shown in Fig. 13. NOESY correlations for H-17/H-10′, H-11′a/H-8′ and H-6′, and H-11′b/H-2′a were observed for the free base of **56** (Fig. 14), indicating that H-17 and H-10′ both had a $\beta$ configuration. The large vicinal coupling constant ($J = 11.8$ Hz) for H-11′b/H-17 and H-11′b/H-10′ indicated that the two heterocyclic ring systems were almost fixed through C-11′. The conformational space for **56** searched by Monte Carlo simulation (*63,64*) followed by minimization was consistent with the NOESY data and

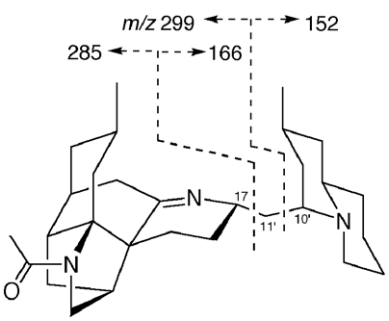



Figure 12. Fragmentation patterns observed in positive ion FABMS/MS spectrum of himeradine A (**56**) (precursor ion $m/z$ 452) (*42*).

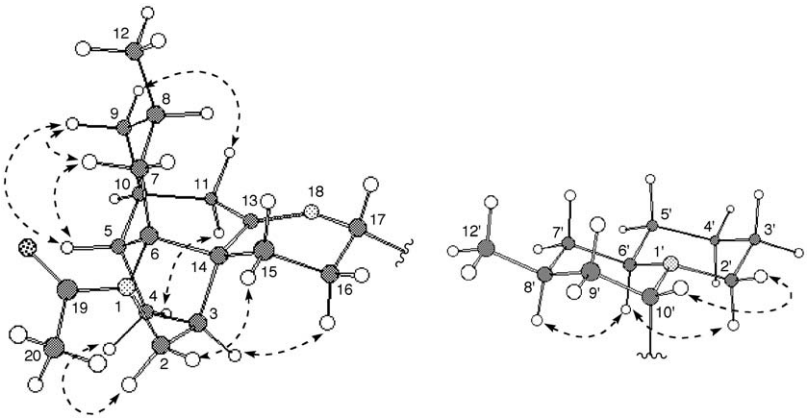



Figure 13. Selected NOESY correlations (dotted arrows) and relative stereochemistry for himeradine A (**56**) (*42*).

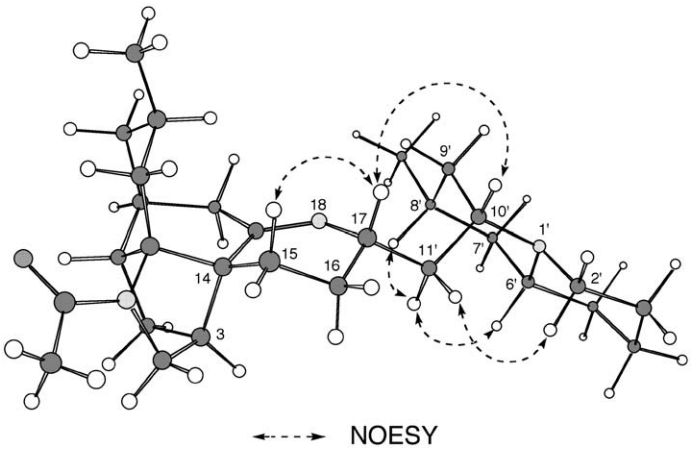
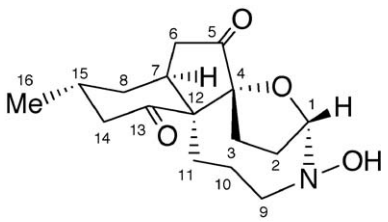



Figure 14. Stable conformer analyzed by Monte Carlo simulation followed by minimization and selected NOESY correlations for himeradine A (**56**) (*42*).

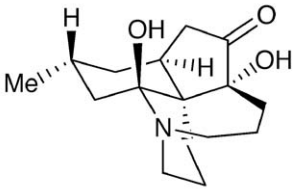
the proton vicinal coupling constants. Thus, the relative stereochemistry of **56** was assigned as shown in Fig. 14.

## I. SIEBOLDINE A

Samples of the club moss *L. sieboldii* collected in Kagoshima were extracted with MeOH, and the basic $CHCl_3$-soluble materials were subjected to an LH-20 column ($CHCl_3$/MeOH, 1:1), followed by a silica gel column ($CHCl_3$/MeOH, 80:1), to afford sieboldine A (**57**, 0.003% yield) (*43*), together with a known related alkaloid, alopecuridine (**85**, 0.03%) (*69*).




**57**




**85**

The molecular formula, $C_{16}H_{23}NO_4$, of sieboldine A (**57**) was established by HRFABMS. IR absorptions implied the presence of hydroxyl (3400 $cm^{-1}$), and cyclopentanone and cyclohexanone (1750 and 1695 $cm^{-1}$, respectively) functionalities. $^{13}C$ NMR data revealed sixteen carbon signals due to two carbonyls, two $sp^3$ quaternary carbons, three $sp^3$ methines, eight $sp^3$ methylenes, and one methyl. Among them, one quaternary carbon ($\delta_C$ 92.8) was ascribed to that bearing an oxygen atom, while one methine ($\delta_C$ 98.5; $\delta_H$ 4.89) was ascribed to that bearing both an oxygen and a nitrogen atom.

The $^1H$–$^1H$ COSY and HOHAHA spectra revealed connectivities of three partial structures **a** (C-6 to C-8, C-8 to C-15, and C-14 to C-16), **b** (C-9 to C-11), and **c** (C-1–C-3) as shown in Fig. 15. HMBC correlations were observed for H-6b and H-8a to C-12 ($\delta_C$ 62.3) and H-11b to C-7 ($\delta_C$ 38.7), suggesting that C-7 and C-11 were connected to each other through C-12. The connectivity of C-4 to C-12 was implied by an HMBC correlation for H-11b to C-4 ($\delta_C$ 92.8). HMBC cross-peaks for $H_2$-6 to C-5 ($\delta_C$ 212.6) and $H_2$-14 to C-13 ($\delta_C$ 216.5) indicated that two carbonyls were attached to C-6 and C-14, respectively. Since the $^1H$ and $^{13}C$ NMR signals at C-2, 3, 10, and 11 were broadened, further connections could not be clarified by the NMR data.

The X-ray crystal structure (Fig. 16) of sieboldine A (**57**) revealed a unique, fused-tetracyclic ring system consisting of an aza-cyclononane ring (C-1 ~ C-4, C-9 ~ C-12, and N-1) having an *N*-hydroxy group, and a tetrahydrofuran ring (C-1 ~ C-4 and O-1) connected to a *cis*-5,13-dioxo-octahydroindene ring (C-4 ~ C-8 and C-12 ~ C-15) with a methyl (C-16) group at C-15 through the spiro carbon at C-4 (*43*).

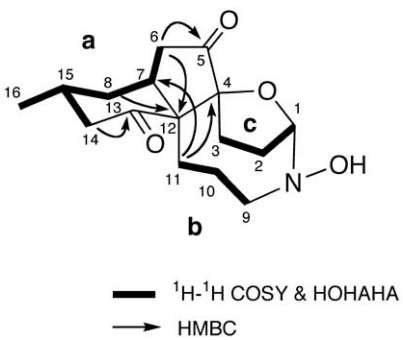



Figure 15. Selected 2D NMR correlations for sieboldine A(**57**).

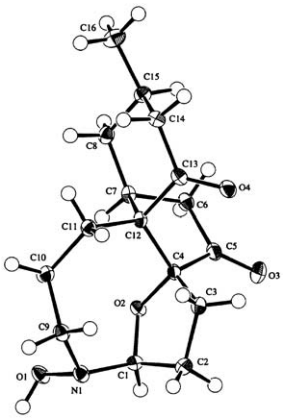
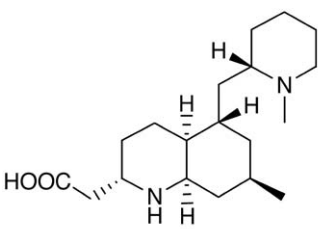



Figure 16. X-ray structure of sieboldine A (**57**).

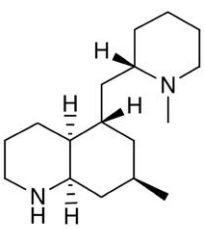
Sieboldine A (**57**) inhibited acetylcholinesterase (from electric eel) with an $IC_{50}$ value of 2.0 μM, which was comparable to that ($IC_{50}$, 1.6 μM) of (±)-huperzine A (**1**), and sieboldine A (**57**) exhibited cytotoxicity against murine lymphoma L1210 cells ($IC_{50}$, 5.1 μg/mL) *in vitro*, whereas alopecuridine (**85**) did not show such activity ($IC_{50} > 10$ μg/ml) (*43*).

## J. CERMIZINES

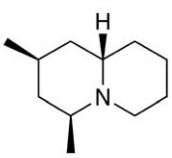
Samples of the club moss of *L. cernuum* collected in Okinawa were extracted with MeOH, and the basic $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 1:0 → 0:1, and then $CHCl_3$/MeOH, 1:0 → 0:1), in which a fraction eluted with MeOH was purified by a silica gel column ($CHCl_3$ → MeOH) to afford cermizines B (**59**, 0.00005%), C (**60**, 0.00008%), and D (**61**, 0.0002%) (*40*) together with cernuine (**86**, 0.01%) (*70*) and lycocernuine (**87**, 0.004%) (*70*). Basic BuOH-soluble materials were subjected to an ODS column ($H_2O$ → MeOH) followed by an amino silica gel column ($CHCl_3$/MeOH, 15:1) and then a silica gel column ($CHCl_3$/MeOH, 10:1→0:1) to give cermizine A (**58**, 0.0002%), cernuine *N*-oxide (**62**, 0.002%), and lycocernuine *N*-oxide (**63**, 0.003%) (*40*).



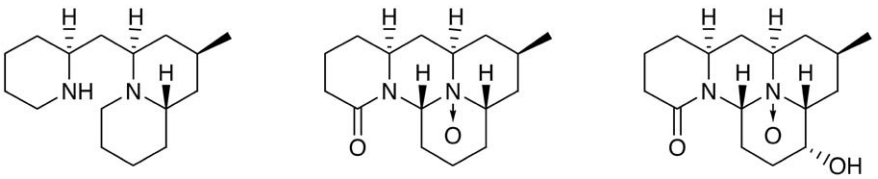

**58**




**59**




**60**



61 62 63

The molecular formula, $C_{19}H_{34}N_2O_2$, of cermizine A (**58**) was established by HRFABMS. IR absorptions implied the presence of a carboxylate (1580 $cm^{-1}$) functionality. $^1H$ and $^{13}C$ NMR data revealed nineteen carbon signals due to one $sp^2$ quaternary carbon, six $sp^3$ methines, ten $sp^3$ methylenes, and two methyl groups. Among them, three methines ($\delta_C$ 63.7; $\delta_H$ 2.08, $\delta_C$ 49.6; $\delta_H$ 3.44, and $\delta_C$ 52.8; $\delta_H$ 3.62), one methylene ($\delta_C$ 57.6; $\delta_H$ 2.29 and 2.91), and one methyl ($\delta_C$ 42.5; $\delta_H$ 2.33) were ascribed to those bearing a nitrogen. Since one out of four elements of unsaturation was accounted for, alkaloid **58** was inferred to possess three rings. A partial structure (C-1 ~ C-17) was deduced from detailed analysis of the 2D NMR data ($^1H$–$^1H$ COSY and HOHAHA). HMBC correlations verified alkaloid **58** to have a phlegmarane-type skeleton consisting of a decahydroquinoline ring (C-7 ~ C-15 and N-9) with a methyl group (C-16) at C-15 and a carboxymethyl group (C-17 and C-18) at C-9 and a piperidine ring (C-1 ~ C-5 and N-1) with an *N*-methyl group (C-19) through a methylene bridge (C-6). The relative stereochemistry of **58** was elucidated from NOESY correlations as shown in a computer-generated 3D drawing (Fig. 17). The *cis* junction of the decahydroquinoline ring with a chair-form and the presence of an $\alpha$-oriented $C_2$ unit at C-9 were elucidated by the NOESY correlation of H-9/H14a, although known phlegmarane-type alkaloids possess a *trans* junction for that ring (*71,72*). In addition, NOESY correlations of H-6a/H-13 and H-5/H-8b and $^3J$ coupling constants ($J_{5/6b} = 9.6$ and $J_{6b/7} = 3.7$Hz) indicated that the two heterocyclic ring systems did not rotate freely. Thus, the relative stereochemistry of cermizine A (**58**) was assigned as shown (*40*).

HRFABMS data of cermizine B (**59**) established the molecular formula to be $C_{17}H_{32}N_2$, which was less than that of cermizine A (**58**) by a $C_2H_2O_2$ unit. $^1H$ and $^{13}C$

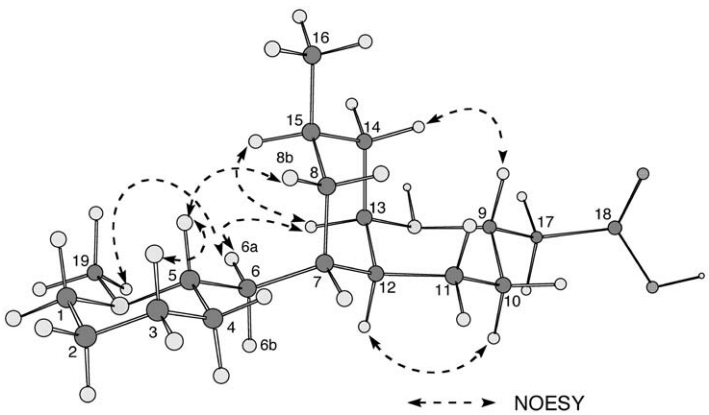



Figure 17. Selected NOESY correlations and relative stereochemistry for cermizine A (**58**).

NMR data of **59** were analogous to those of **58**, although the $^{1}H$ and $^{13}C$ signals of a $C_2$ unit ($\delta_H$ 2.37 and 2.42, $\delta_C$ 41.2 and 178.2) at C-9 observed for **58** were absent for **59**. Cermizine B (**59**) was elucidated to be a decarboxymethyl form at C-9 of **58** by 2D NMR ($^{1}H$–$^{1}H$ COSY, HOHAHA, HMQC, and HMBC) data. The relative stereochemistry of **59** was deduced from the same NOESY correlations as those of **58** (*40*).

Cermizine C (**60**) was revealed to have the molecular formula, $C_{11}H_{21}N$, by HRESIMS. $^{1}H$ and $^{13}C$ NMR data for **60** suggested the presence of three $sp^3$ methines, six $sp^3$ methylenes, and two methyl groups. Among them, two methines ($\delta_c$ 61.4 and 51.1) and one methylene ($\delta_c$ 49.9) were ascribed to those bearing a nitrogen. The $^{1}H$–$^{1}H$ COSY and HOHAHA spectra revealed the presence of a quinolizidine ring (C-1–C-9) with two methyl groups (C-10 and C-11) at C-7 and C-9, respectively. Connections among C-1 ($\delta_C$ 49.9), C-5 ($\delta_C$ 61.4), and C-9 ($\delta_C$ 51.1) through a nitrogen were suggested by HMBC correlations for H-1b of C-5, H-1a of C-9, and H-5 of C-9. Thus, cermizine C (**60**) was elucidated to be a 1,3-dimethyl quinolizidine. The relative stereochemistry was deduced from cross-peaks observed in the phase sensitive NOESY spectrum as shown in a computer-generated 3D drawing (Fig. 18).

$^{1}H$ and $^{13}C$ NMR data of cermizine D (**61**) were analogous to those of cermizine C (**60**), except for an additional piperidine unit (C-1 ~ C-5) at C-6. The 2D NMR data revealed the presence of a quinolizidine ring (C-7–C-8, C-9–C-15, and N-7) with a methyl group (C-16) at C-15 and a piperidine ring (C-1–C-5 and N-1) through a methylene bridge (C-6). The relative stereochemistry was deduced from cross-peaks observed in the phase sensitive NOESY spectrum as shown in a computer-generated 3D drawing (Fig. 19).

Compounds **62** {$[\alpha]_D$ –38° (*c* 0.2, MeOH)} and **63** {$[\alpha]_D$ –23° (*c* 1.0, MeOH)} were revealed to have the molecular formula, $C_{16}H_{26}N_2O_2$ and $C_{16}H_{26}N_2O_3$, respectively, by HRFABMS. 2D NMR data of **62** clearly revealed the presence of a cernuane-type skeleton (*70*) consisting of a fused tetracyclic ring system containing two nitrogen atoms, with a methyl group at C-15. Oxidation of cernuine with hydrogen peroxide afforded the *N*-oxide derivative, whose spectral data and $[\alpha]_D$ value were identical with those of alkaloid **62**. Thus, **62** was concluded to be an *N*-oxide form of cernuine. Compound **63** was also elucidated to be the *N*-oxide derivative of lycocernuine by detailed analysis of the NMR data and comparison with those of lycocernuine (*70*). Chemical transformation of lycocernuine into alkaloid **63** by oxidation with hydrogen peroxide led to the conclusion that **63** was an *N*-oxide form of lycocernuine.

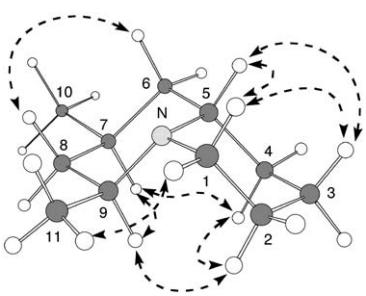



Figure 18. Selected NOESY correlations and stereochemistry for cermizine C (**60**).

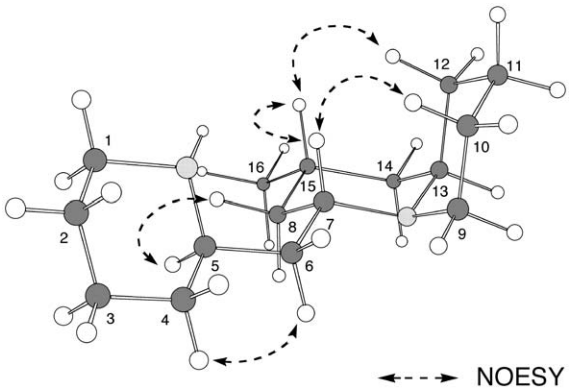
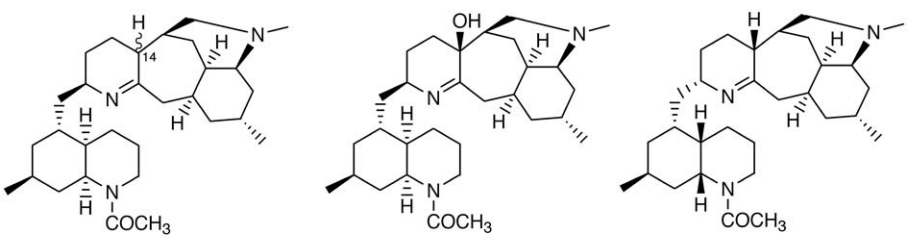



Figure 19. Selected NOESY correlations and relative stereochemistry for cermizine D (**61**).

## K. LUCIDINES




**64** **65** **66**

The structures of three $C_{27}N_3$ type alkaloids isolated from *Lycopodium lucidulum* were established by X-ray and 2D NMR spectroscopic analyses (*44,45*). Although these alkaloids had been previouly isolated by Ayer *et al*. (*66*), a part of the stereostructures remained unsolved. Lucidines A (**64**) and B (**66**) are converted to oxolucidines A (**65**) and B, respectively, on exposure to air. This occurs due to the readily oxidizable imino group present in the molecules. Furthermore, it is not easy to analyze the NMR spectrum of **66** at room temperature because of the line broadening. Therefore, tetrahydrodeoxyoxolucidine B, which was derived from **66** by $LiAlH_4$, was converted to the dibenzoate, a crystal of which was used for X-ray analysis (*66*). However, the stereochemistry at C-14 of lucidine B (**66**) was not known yet. The 2D NMR spectra of tetrahydrodeoxylucidine B derived from lucidine B (**66**) were analyzed to establish the complete structure of lucidine B (**66**), and the hitherto unknown stereochemistry at the C-14 position was established as $\beta$-H. The dihydro-derivative of oxolucidine A, which was obtained by $NaBH_4$ reduction of oxolucidine A (**65**), was treated with *p*-bromobenzoyl chloride to afford crystals **86**, whose X-ray crystallographic analysis established the stereostructure, including the absolute configuration (*44*) (Fig. 20). However, the stereochemistry at C-14 in lucidine A (**64**) remains unsolved.

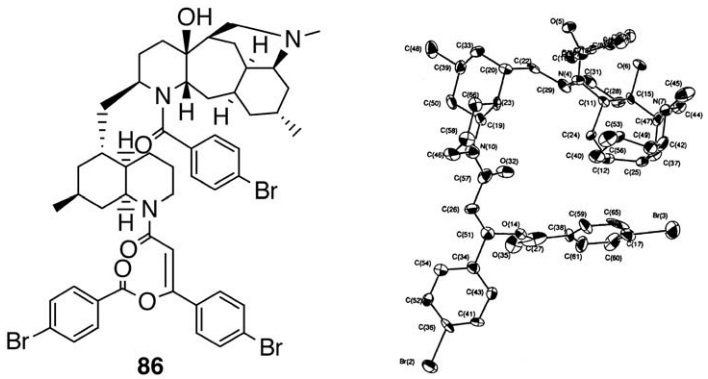
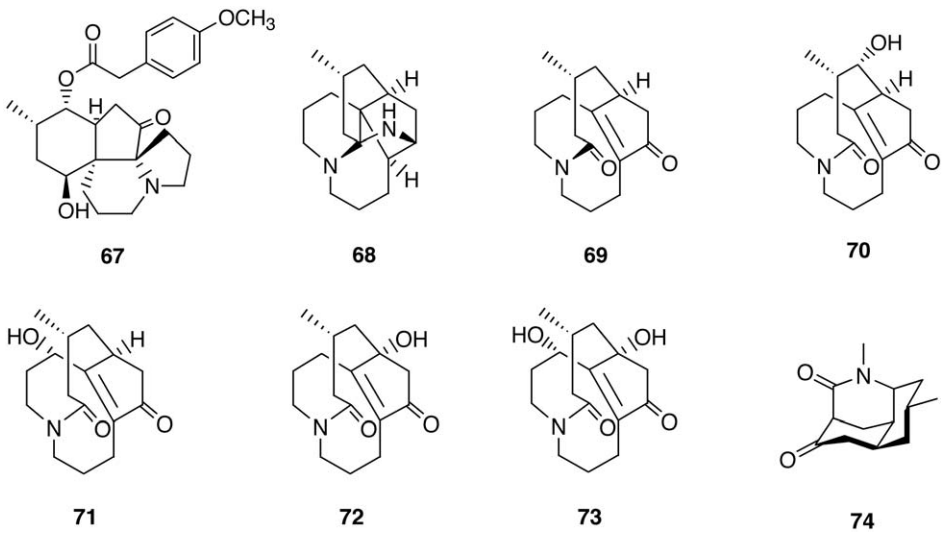
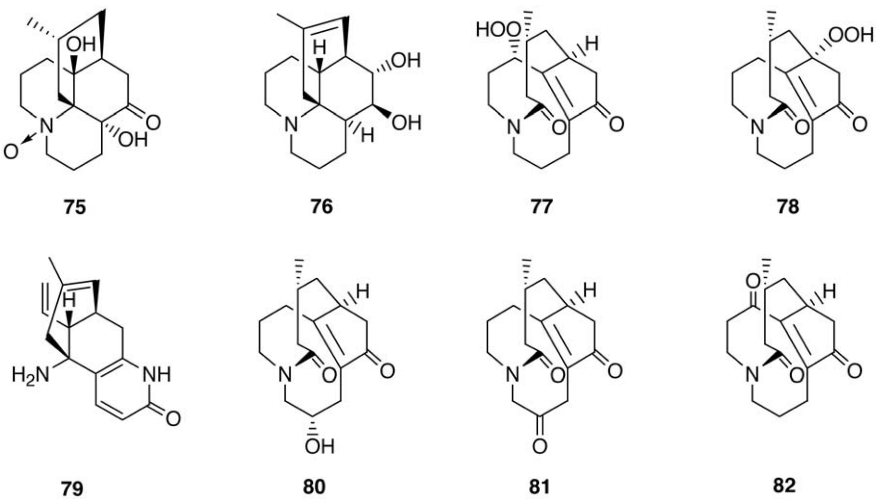



Figure 20. Structure and the ORTEP drawing of the tribenzoate derivative **86** of dihydrolucideine A (*44*).

## L. MISCELLANEOUS




Huperserratinine (**67**) with a serratinane skeleton was isolated from *Huperzia serrata* and its structure was assigned by a combination of NMR experiments and computer modeling calculations (*46*). Five alkaloids (**68**, **70**–**73**) (*47–49*) belonging to the fawcettidane skeleton were isolated from *H. serrata*, together with phlegmariurine B (**69**) (*26*). The structure of macleanine (**68**) named in honor of MacLean, a pioneer in the field of *Lycopodium* alkaloids, was verified by an X-ray crystallographic study of the hydroperchlorate (*47*). The structures of four phlegmariurine B related alkaloids (**70**–**73**) were elucidated by spectroscopic studies (*48,49*). Lucidulinone (**74**) (*45*) isolated from *Lycopodium lucidulum* was determined to be luciduline lactam by spectroscopic analysis (*68*).

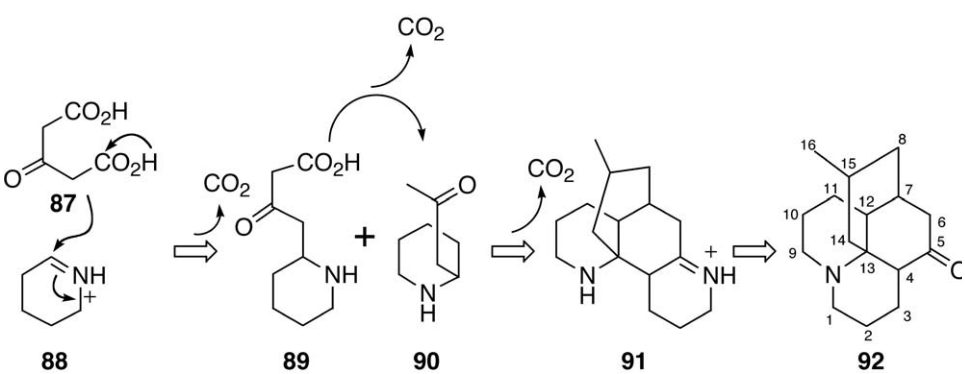



Miyoshianines A (**75**) and B (**76**) with a lycopodane skeleton were isolated from *Huperzia miyoshiana* and their structures were determined by means of spectroscopic techniques (*50*). Five new alkaloids (**77**–**78**, **80**–**82**) belonging to the phlegmarane skeleton were isolated from *Huperzia serrata* (*51,53*). The structure of isofordine (**79**), which is the isomer of huperzine A (**1**), was isolated from *Phlegmariurus fordii* (*52*).

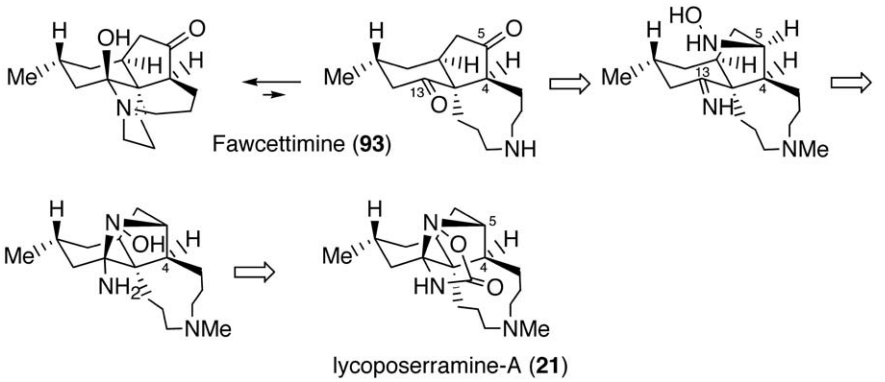
## III. Biosynthesis and Biogenesis

### A. BIOSYNTHESIS OF *LYCOPODIUM* ALKALOIDS

Hemscheidt and Spenser conducted feeding experiments on the *Lycopodium* alkaloids using the club moss *Lycopodium tristachyum* (*73,74*). The acetate-derived C3 fragments, C-6–C-8 and C-14–C-16, of lycopodine (**92**) were introduced into the alkaloid *via* acetonedicarboxylic acid (**87**). Therefore, lycopodine (**92**) was generated through an intermediate **91** produced by condensation of 4-(2-piperidyl)acetoacetic acid (**89**) and pelletierine (**90**), in which both units were derived from the condensation




Scheme 3. Biosynthesis of lycopodine (**92**) (*74*).




Scheme 4. Biogenesis of lycoposerramine-A (**21**) (*31,32*).

of $\Delta^1$-piperideine (**88**) and acetonedicarboxylic acid (**87**). This was the first experimental evidence that acetonedicarboxylic acid (**87**) served as an intermediate in the biosynthesis of lycopodine (**92**) (*74*).

## B. BIOGENESIS OF LYCOPOSERRAMINES

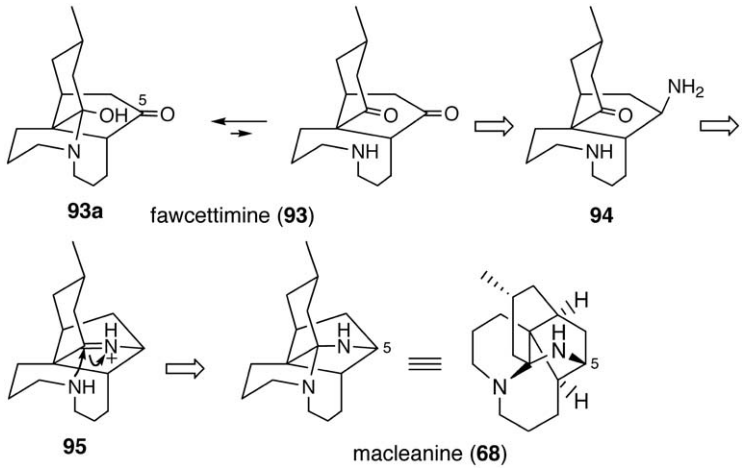
Lycoposerramine-A (**21**), isolated from *Lycopodium serratum* by Takayama *et al*. (*31,32*), was biogenetically derived from fawcettimine (**93**) *via* the hypothetical route as shown in Scheme 4. The carbonyl functions at C-5 and C-13 in fawcettimine (**93**) were converted into hydroxylamine and imine, respectively. *N*-Methylation and diaminoacetal formation at C-13, followed by formation of cyclic carbamate, afforded lycoposerramine-A (**21**).

## C. BIOGENESIS OF MACLEANINE

Ayer *et al*. proposed the pathway for the biogenesis of macleanine (**68**) (*47*). Most of the *Lycopodium* alkaloids known to date possess functionality at C-5. Fawcettimine (**93**) readily forms a transannular carbinolamine **93a**. Macleanine (**68**) might be derived from fawcettimine (**93**) through reductive amination to generate **94**, formation of the internal immonium ion **95**, and subsequent transannular cyclization (*47*).

## D. BIOGENESIS OF SERRATEZOMINES

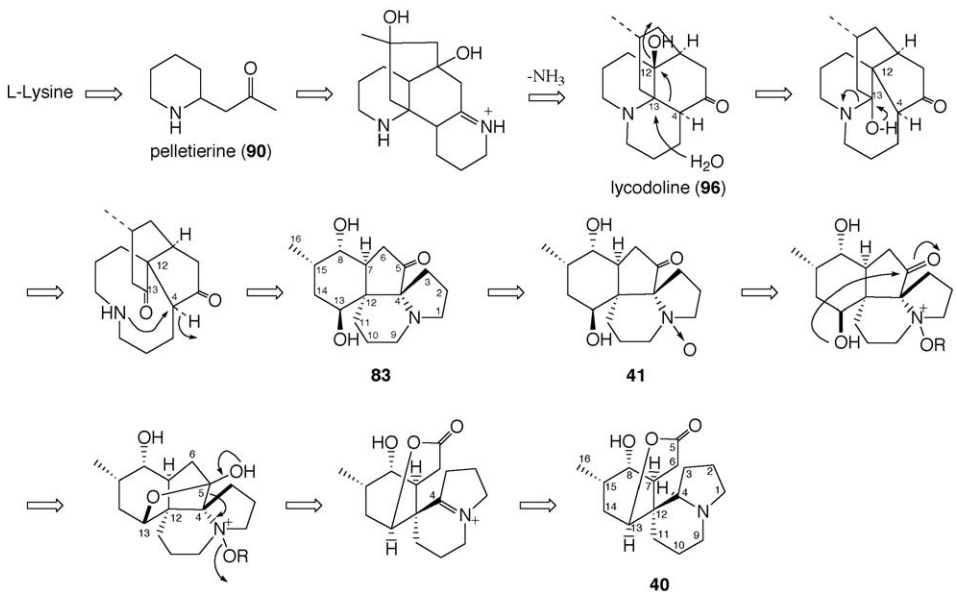
Serratezomine A (**40**) is a novel alkaloid structure type consisting of a 2-oxabicyclo[3.3.1]nonan-3-one and an indolizidine ring connected through a spiro carbon, while serratezomine B (**41**) is the first example of the *N*-oxide of a serratinine-type alkaloid. A plausible biogenetic pathway for serratezomine A (**40**) is proposed as shown in Scheme 6 (*35*). It is known that the lycodoline-type skeleton, as represented by serratezomine C (**42**) and lycodoline (**96**), is biosynthesized from L-lysine *via* pelletierine (**90**), in which the acetate-derived $C_3$ fragments are introduced *via* acetonedicarboxylic acid (**87**) (*74*). Furthermore, biogenesis of lycodoline (**96**) to serratinine (**83**) has been



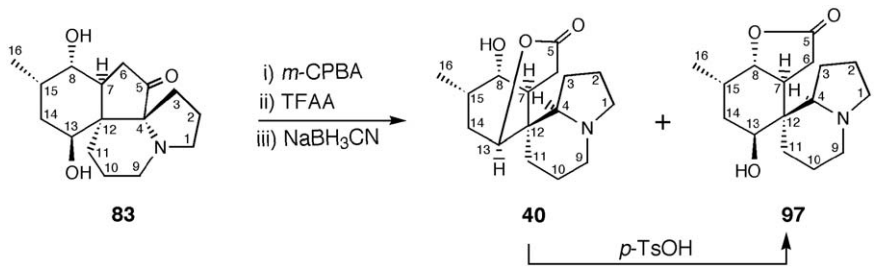

Scheme 5. Biogenesis of macleanine (**68**) (*47*).

proposed by Inubushi *et al*. (Scheme 6) (*76*). Serratezomine A (**40**) might be derived from serratinine (**83**) through *N*-oxidation to generate serratezomine B (**41**), formation of a hemiacetal linkage between the hydroxyl at C-13 and the ketone at C-5, and subsequent cleavage of the C-4–C-5 bond.

In order to substantiate the proposal shown in Scheme 6, a modified Polonovski reaction (*79*) was applied to serratinine (**83**) as follows (Scheme 7) (*80*). Sequential treatment of **83** with *m*-chloroperbenzoic acid (*m*-CPBA), trifluoroacetic anhydride




Scheme 6. Biogenesis of serratezomine A (**40**) (*35*).




Scheme 7. Conversion of serratinine (**83**) to serratezomina A (**40**) (*80*).

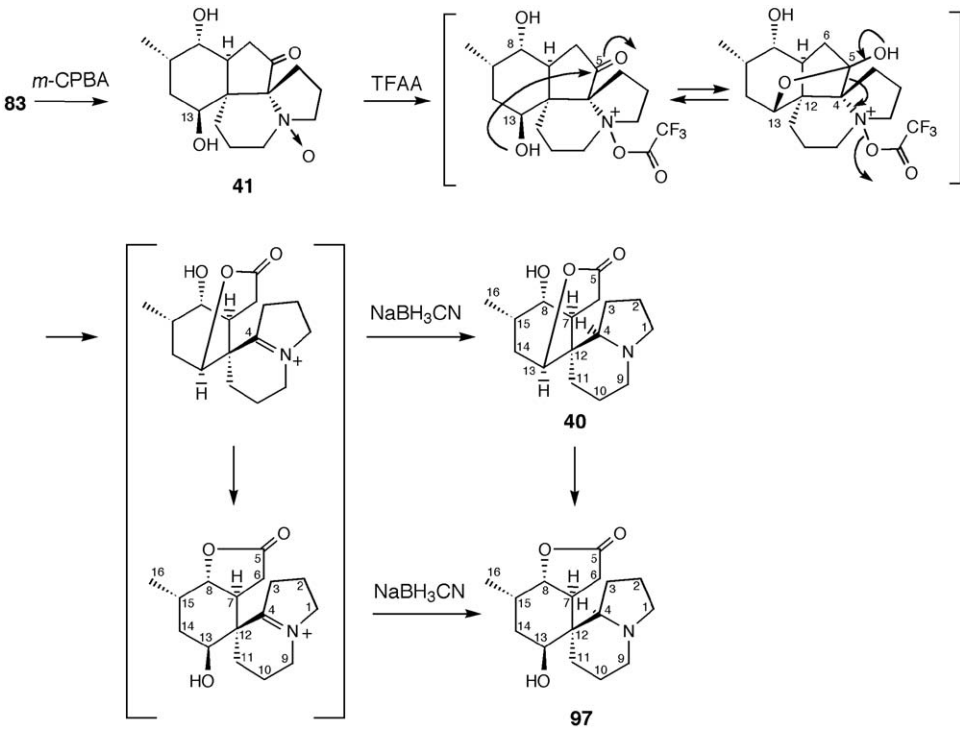
(TFAA), and sodium cyanotrihydroborate ($NaBH_3CN$) gave two compounds **40** and **97** (Scheme 7). In this one-pot reaction, compound **40**, which was identified as serratezomine A by comparison of spectral data, was predominant at lower temperatures (−50 and −20 °C), while the level of compound **97**, which was also obtained by treatment of **83** with *p*-TsOH, increased with increasing temperature (0 and 20°C) (Table II). A possible mechanism of the one-pot reaction is proposed in Scheme 8. Trifluoroacetylation of the *N*-oxide (**41**) could be followed by attack of the hydroxy group at C-13 to the ketone at C-5 to yield a hemiketal, which is accompanied by cleavage of the C-4–C-5 bond to form the lactone ring in **40** between C-5 and C-13. Formation of the alternative lactone ring in **97** might occur through migration of the ester linkage. Compounds **40** and **97** were obtained in $CH_2Cl_2$, $CHCl_3$, or $CH_3CN$, but not in THF or toluene (Table II). The increasing amount of **97** with elevating temperature after addition of TFAA (Table II) indicated an acid-catalyzed cleavage of the $\delta$-lactone ring of serratezomine A (**40**) followed by the formation of a $\gamma$-lactone ring with a hydroxy group at C-8 after conformational change of a cyclohexane ring (C-7 ~ C-8 and C-12 ~ C-15). The rigid conformation of serratinine (**83**) consisting of a fused tetracyclic ring system was expected to induce fragmentation through a Polonovski reaction, since the C(4)–C(5) bond in the *N*-oxide **41** was synperiplanar to the N–O bond (Fig. 21). A molecular model

TABLE II.

Effect of solvents and temperature on generation of serratezomine A (**40**) and **97** from serratinine (**83**) through a modified Polonovski reaction (*80*).

| Entry | Solvent | Temp. °C | Time | Yield (%) | | Recovered (%) |
|---|---|---|---|---|---|---|
| | | | | **40** | **97** | **83** |
| 1 | $CH_2Cl_2$ | −50 | 2h | 30 | 6 | – |
| 2 | $CH_2Cl_2$ | −20 | 1h | 48 | 27 | – |
| 3 | $CH_2Cl_2$ | 0 | 1h | 17 | 38 | – |
| 4 | $CH_2Cl_2$ | 20 | 1h | – | 65 | – |
| 5 | $CHCl_3$ | −20 | 1h | 27 | 13 | – |
| 6 | $CH_3CN$ | −20 | 1h | 17 | 6 | – |
| 7 | THF | −20 | 1h | 0 | 0 | 66 |
| 8 | toluene | −20 | 1h | 0 | 0 | 54 |

Temperature was elevated after addition of TFAA




Scheme 8. Mechanism of formation of serratezomine A (**40**) (*80*).

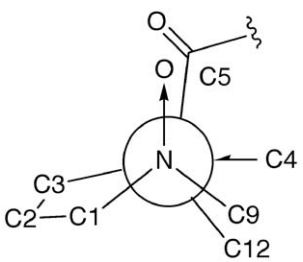



Figure 21. Rotational model for the N–C-4 bond of serratezomine B (**41**) (*80*).

and the X-ray crystal structure of **83** (Fig. 22) indicated that in the $NaBH_3CN$ reduction of an unstable iminium intermediate, the hydride must enter from the $\alpha$ face of the molecule due to steric hindrance, thereby generating the *R* configuration at C-4. Compound **97**, with an energetically more stable $\gamma$-lactone ring, seems to be produced from **40** by acid catalyzed cleavage of its unstable $\delta$-lactone ring, followed by recyclization with the hydroxyl group at C-8.

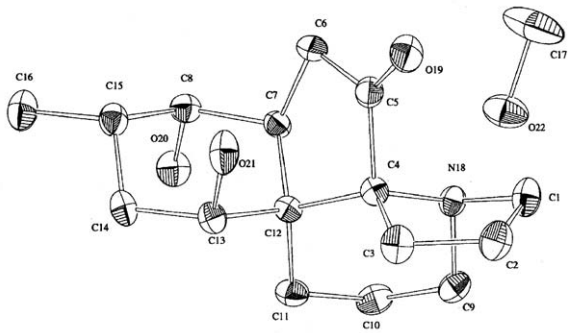
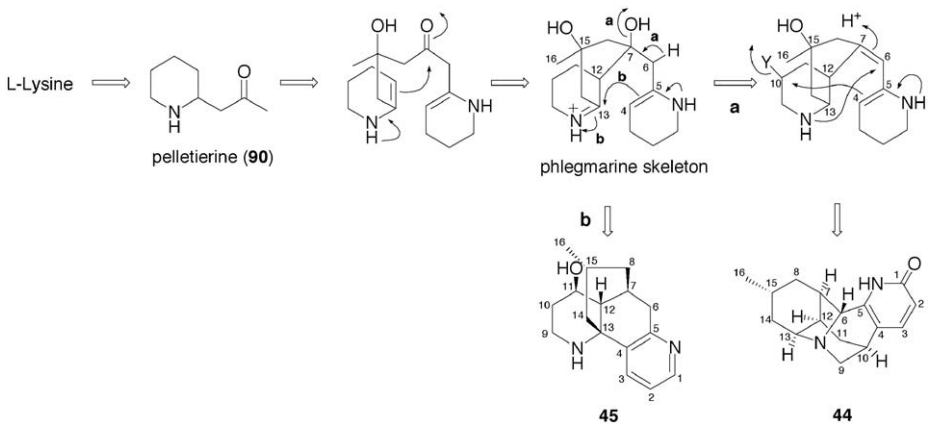



Figure 22. Molecular structure of serratinine (**83**) obtained by X-ray analysis (ORTEP drawing; ellipsoids are drawn at the 30% probability level). One molecule of MeOH is contained in the crystal and the hydrogen atoms are omitted for clarity (*80*).



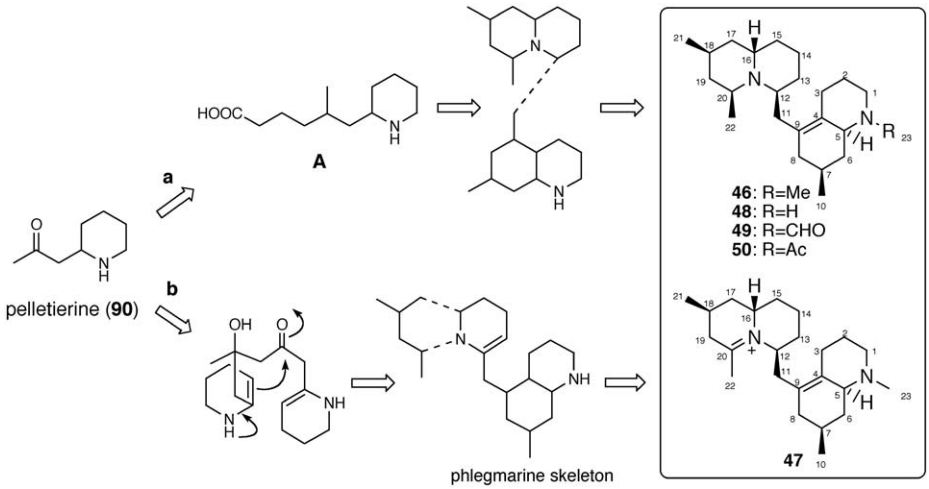

Scheme 9. Biogenesis of lyconadin A (**44**) (*37*).

## E. BIOGENESIS OF LYCONADIN A

Lyconadin A (**44**) is a novel type of alkaloid consisting of five fused rings (one 5-membered and four 6-membered rings), while alkaloid **45** is the first lycodine analog with a hydroxy group at C-11 (*37*). A plausible biogenetic path for **44** and **45** is shown in Scheme 9 (*37*). Both alkaloids may be derived from L-lysine *via* pelletierine, followed by further cyclization of the phlegmarine skeleton (*74,77*).

## F. BIOGENESIS OF SENEPODINES

Senepodines A–E (**46**–**50**) are new class of $C_{22}N_2$ *Lycopodium* alkaloids, consisting of an octahydroquinoline ring and a quinolizidine ring. A plausible biogenetic pathway for the senepodines is proposed as shown in Scheme 10 (*38,39*). Biogenetically, the decahydroquinoline and quinolizidine units in **46**–**50** may be derived from an intermediate




Scheme 10. Biogenesis of the senepodines A–E (**46**–**50**) (*38*,*39*).

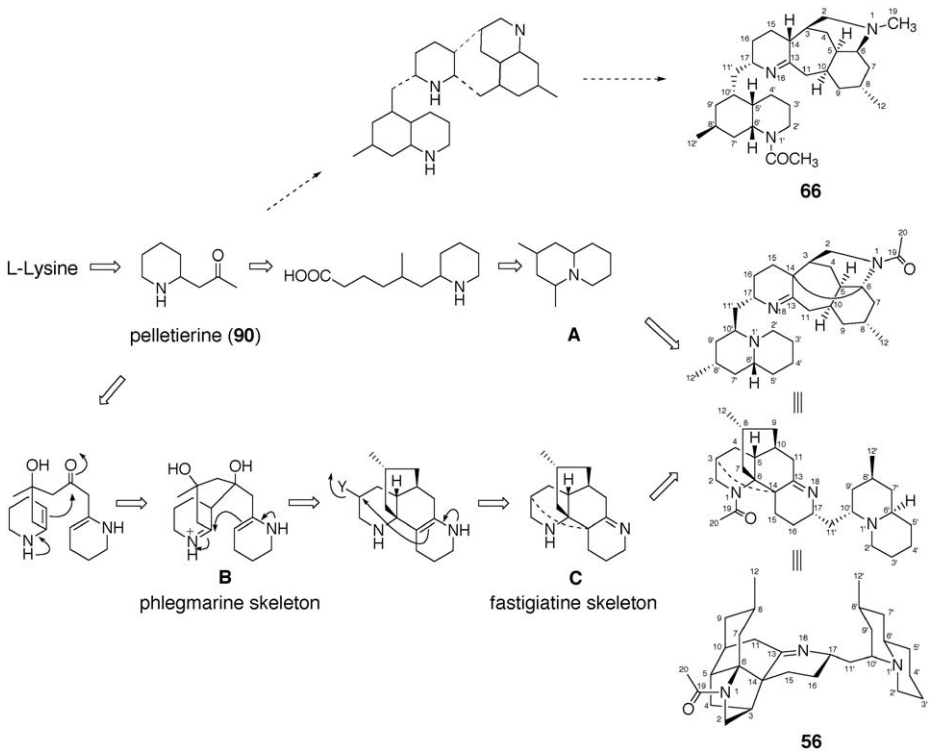
**A** with decarboxylation (path **a**), although an alternative path **b**, which forms the C-20–N and C-17–C-16 connectivities of senepodines A–E (**46**–**50**) with a $C_6$ unit, is also possible.

## G. BIOGENESIS OF HIMERADINE A

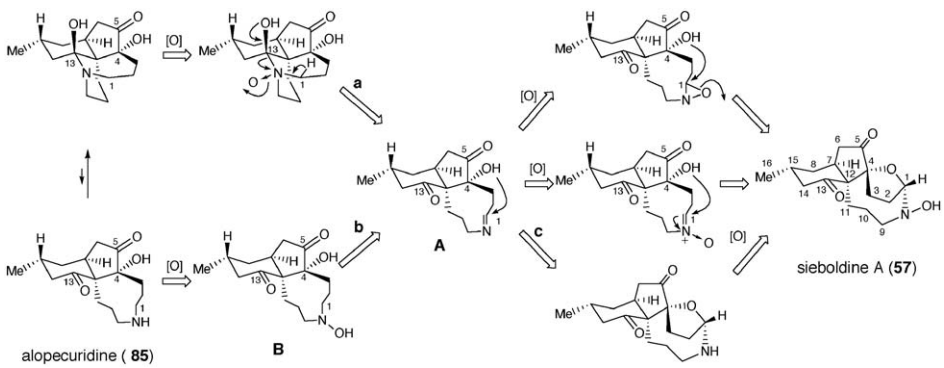
A plausible biogenetic pathway for himeradine A (**56**) is proposed as shown in Scheme 11 (*42*). Himeradine A (**56**) might be generated from a quinolizidine unit (**A**) and fastigiatine skeleton (**C**), through the phlegmarine skeleton (**B**) derived from L-lysine *via* pelletierine (**90**). The fastigiatine skeleton (**C**) has been found only in the structure of fastigiatine isolated from *L. fastigiatum* (*67*). Ayer's proposal (*66*) for lucidine B (**66**) is also shown in Scheme 11, in which **66** is generated from two (enantiomeric) $C_{11}N$ units and a piperidine ring. Isolation of himeradine A (**56**) and lucidine B (**66**) from the same plant suggests that **66** might be also derived from $C_{16}N_2$ and $C_{11}N$ units like **56**.

## H. BIOGENESIS OF SIEBOLDINE A

A plausible biogenetic pathway for sieboldine A (**57**) is proposed as shown in Scheme 12 (*43*). Alopecuridine (**85**) (*69*) which might be derived from the lycopodane skeleton, as well as fawcettimine (*81*) may exist in either an aminoacetal form or an amino ketone form. The aminoacetal form of **85** was confirmed directly by X-ray analysis (*43*). Sieboldine A (**57**) might be generated from a fawcettimine-type alkaloid such as alopecuridine (**85**) as follows. Cleavage of the C-13–N-1 bond of an *N*-oxidative product of **85**, followed by Polonovski-type reaction (*79*) (path **a**) might result in an iminium intermediate **A** with a nine-membered ring system, although an alternative path through a hydroxyl amine derivative **B** is also possible (path **b**). Oxidation of the imine **A** to produce an oxaziridine ring or a nitrone followed by attack of the hydroxy group at C-4 to C-1 will give sieboldine A (**57**) with a hydroxyl amine and a tetrahydrofuran ring, although an alternative path (path **c**) is also possible.



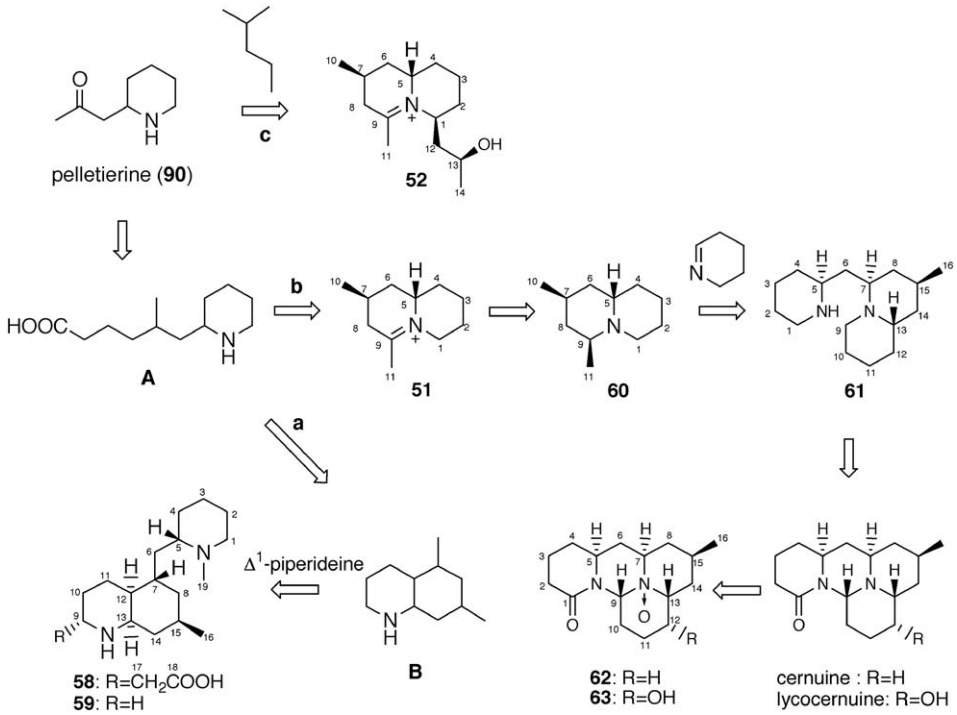

Scheme 11. Biogenesis of himeradine A (**56**) and lucidine B (**66**) (*42*).




Scheme 12. Biogenesis of sieboldine A (**57**) (*43*).

## I. BIOGENESIS OF CERMIZINES

Biogenetically, cermizines A (**58**) and B (**59**), a new type of phlegmarane alkaloid with a *cis* decahydroquinoline ring, may be generated from pelletierine through intermediates **A** and **B** (path **a**) (*77*) followed by coupling with $\Delta^1$-piperideine, while cermizine C (**60**) and senepodine G (**51**) may be derived from the intermediate **A** (path **b**)




Scheme 13. Biogenesis of cermizines (**58**–**63**) and senepodines G (**51**) and H (**52**) (*40*).

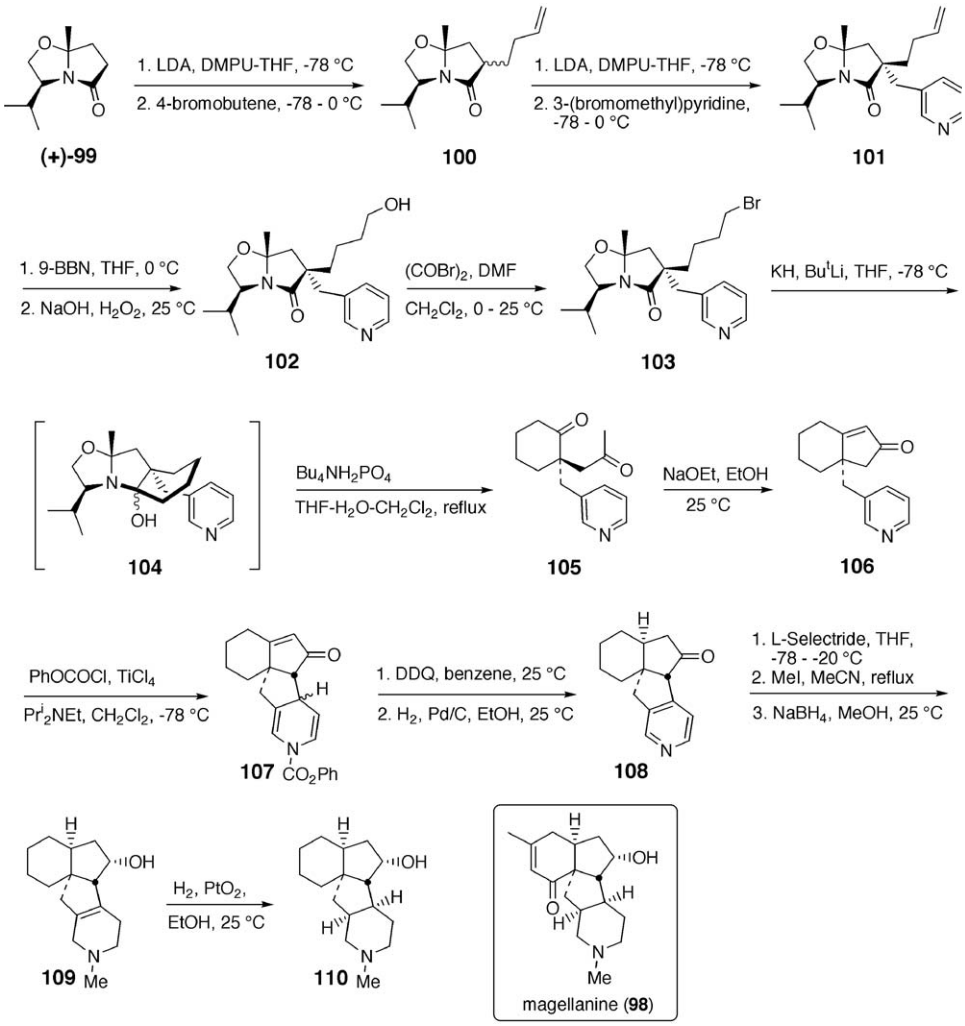
(*40*). On the other hand, senepodine H (**52**) might be generated from pelletierine through coupling with a $C_6$ unit derived from two moles of acetone dicarboxylic acid (*73,74*) (path **c**). Cernuane-type alkaloids such as **62** and **63** might be generated from cermizine C (**60**) through coupling with $\Delta^1$-piperideine to form cermizine D (**61**) followed by coupling between N-1 and C-9.

## IV. Total Synthesis

### A. MAGELLANINE (98)

Magellanine (**98**) isolated from *L. magellanicum*, possesses a highly condensed tetracyclic nucleus with six adjacent stereogenic centers (*82*). The structural novelty of the magellanine skeleton has evoked a great deal of attention from the synthetic community, and several studies have been directed toward its total synthesis (*83–85*). Asymmetric synthesis of the framework of magellanine (**98**) was achieved in 13 steps starting from the commercially available bicyclic lactam **99** (Scheme 14) (*86*). The key reactions employed include the asymmetric synthesis of an angularly substituted hydrinden-2-one.

Recently, the efficient total synthesis of magellanine (**98**) was achieved by Yen and Liao (Scheme 15) (*87*). The key reactions employed include a Diels-Alder reaction of a

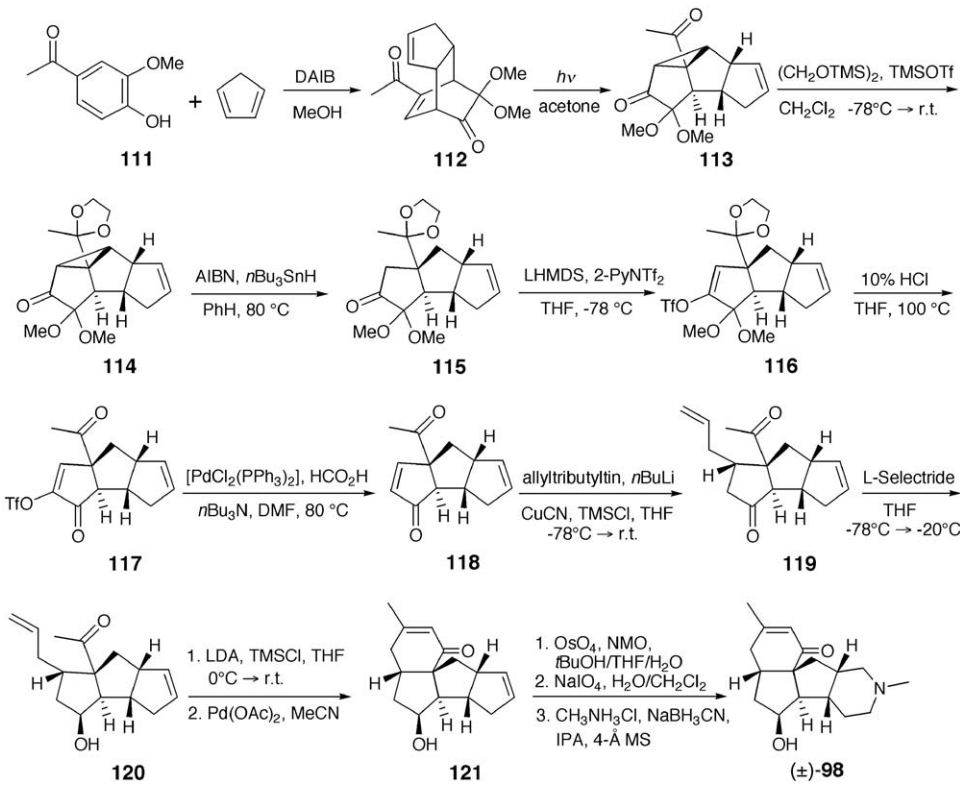



Scheme 14. Synthesis of magellanine framework (**110**) (*86*).

masked *o*-benzoquinone followed by the oxa-di-$\pi$-methane (ODPM) rearrangement (Scheme 15). The total synthesis was completed in 14 steps in 9% overall yield, which is much higher than that of the earlier reported routes (*83–85*).

## B. LYCOPODINE (**92**)

A new strategy for the synthesis of (±)-lycopodine (**92**) has been developed which is based on a sequential dipolar cycloaddition-*N*-acyliminium ion cyclization (Scheme 16) (*88*). Synthesis of the required $\alpha$-diazo imide precursor **126** involved treating 5-methyl-cyclohex-2-en-1-one (**122**) with the organocopper reagent derived from 3-methoxybenzyl

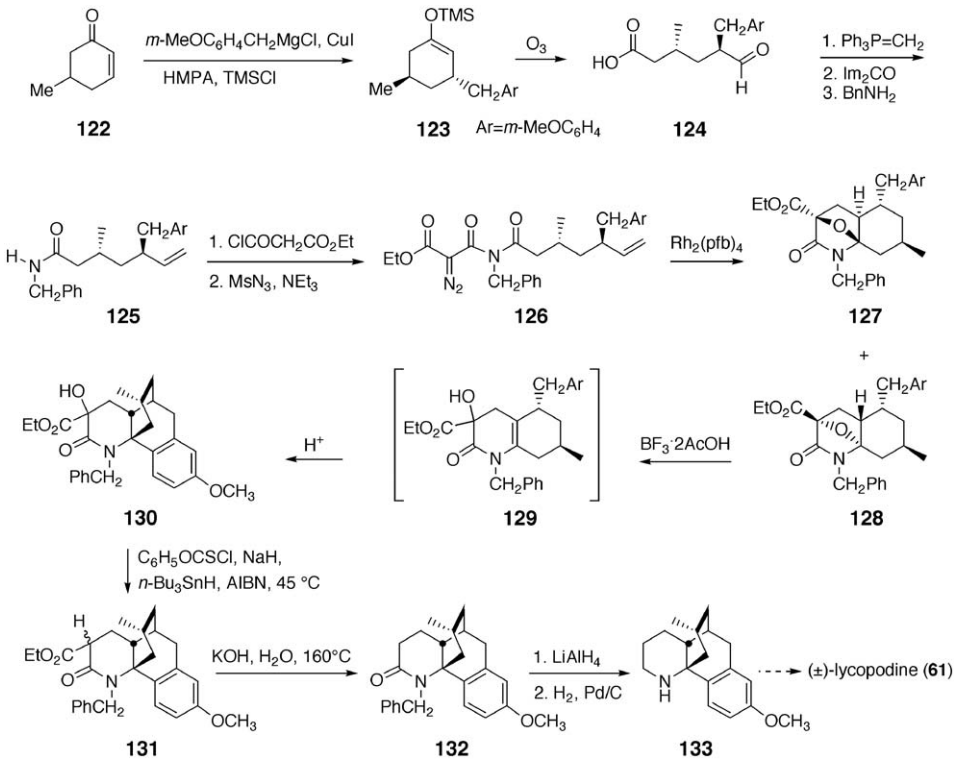



Scheme 15. Synthesis of magellanine (**98**) (*87*).

chloride in the presence of chlorotrimethylsilane. Ozonolysis of the resulting silyl enol ether **123**, followed by a Wittig reaction and conversion into the desired $\alpha$-diazo imide **126**, was carried out using standard malonylacylation and diazotization procedures. Treatment of the $\alpha$-diazo imide **126** with rhodium(II) perfluorobutyrate afforded a transient 1,3-dipole which subsequently underwent cycloaddition across the tethered $\pi$-bond. The resulting cycloadduct **128** was treated with $BF_3 \cdot 2AcOH$ to give a rearranged tetracyclic compound **130** derived from the Pictet–Spengler-type cyclization of an *N*-acyliminium ion. The rearranged product **130** was subsequently converted into a key intermediate **133** previously used for the synthesis of (±)-lycopodine (**92**) (*88*).

## C. HUPERZINE B (2)

Huperzine B (**2**) exhibits a memory facilitating effect in mice and may be useful as an acetylcholinesterase inhibitor for the treatment of Alzheimer's disease (*90–92*). An efficient synthetic approach to huperzine B (**2**) has been established successfully. The tetracyclic intermediate **140** is constructed by means of a tandem Michael addition and an intramolecular Mannich cyclization using **139** and 6-methyl-3,4-dihydropyridin-2-one as the two reactants. Racemic huperzine B (**2**) is obtained *via* a reaction sequence of 12 steps in 6.6% overall yield (Scheme 17) (*89*).



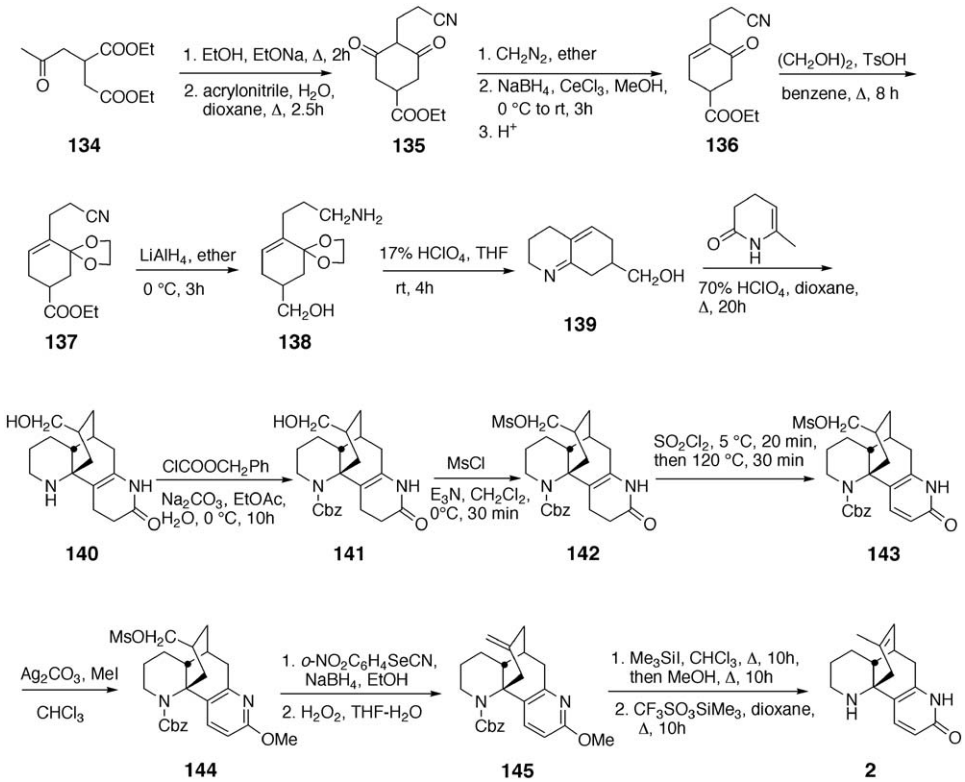

Scheme 16. Synthesis of (±)-lycopodine (**92**) (*88*).

## D. PANICULATINE (**146**)

In 1994, the total syntheses of magellanine (**98**) and magellaninone were accomplished independently by Overman *via* a Prins pinacol rearrangement (*83*) and by Paquette via a tandem Michael–Michael addition (*84,85*). In 1999, Sha *et al*. developed an efficient $\alpha$-carbonyl radical-initiated tandem cyclization reaction for the synthesis of angularly fused tricyclic ketones. Application of this methodology to the first total synthesis of (+)-paniculatine (**146**) has been achieved (Scheme 18) (*93*).

## E. LUCIDULINE (**160**)

The first, chiral auxiliary mediated, asymmetric synthesis of (+)-luciduline (**160**) has been accomplished from readily available materials in 14 steps (10% overall) with a high degree of stereocontrol (*94*). Key steps include an intramolecular Diels-Alder reaction of a chiral dihydropyridine, a subsequent retro-Mannich ring opening, and a novel cationic reductive cyclization reaction. The enantiopure dihydropyridone **164**, prepared from the chiral 1-acylpyridinium salt **161**, was converted to the 1,2-dihydropyridine **166**. Intramolecular Diels-Alder reaction and subsequent reduction leads to **168**, which, after retro-Mannich ring opening, is converted into the enecarbamate **171**. The

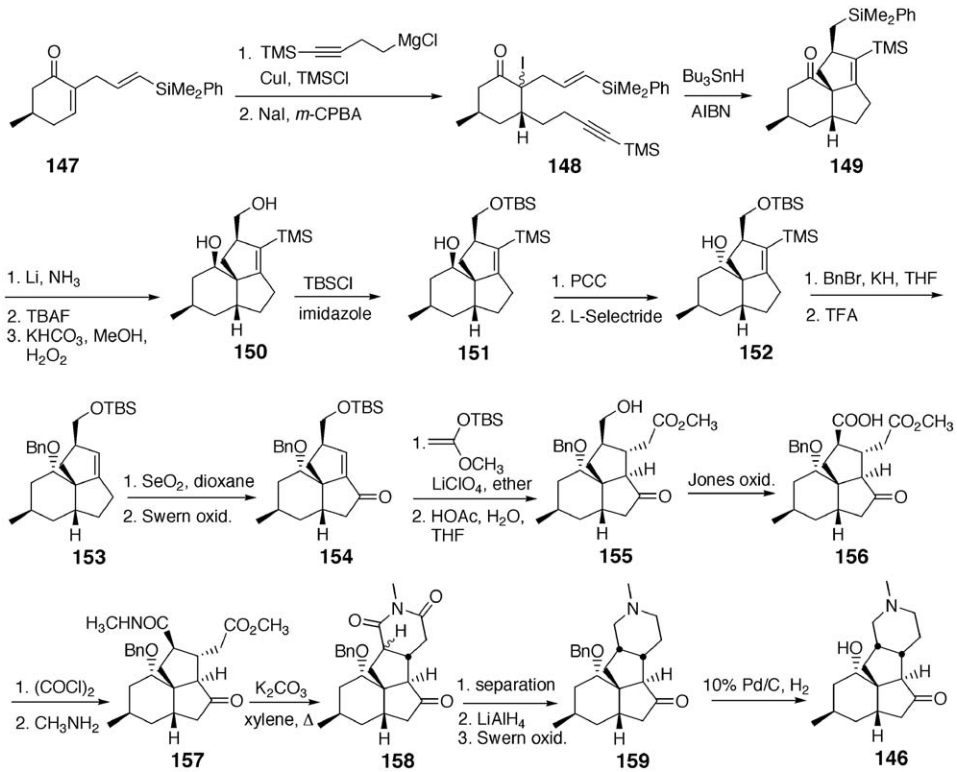



Scheme 17. Synthesis of (±)-huperzine B (**2**) (*89*).

desired ring closure to luciduline (**160**) was obtained *via* a cationic reductive cyclization reaction with $SnCl_4$ in the presence of triethylsilane, followed by oxidation and deprotection (Scheme 19).

## F. $N_a$-ACETYL-$N_b$-METHYLPHLEGMARINE (**174**)

The phlegmarines are a $C_{16}N_2$ skeletal group of *Lycopodium* alkaloids discovered by Braekman and co-workers in 1978 (*96*). Unlike most other perhydroquinoline containing *Lycopodium* alkaloids, the phlegmarines possess a *trans*-decahydroquinoline unit in their skeleton rather than the usual *cis* arrangement. Racemic $N_a$-methyl-$N_b$-acetylphlegmarine was synthesized by MacLean and coworkers (*97,98*). Comins and co-workers accomplished the first asymmetric synthesis of (−)-$N_a$-Acetyl-$N_b$-methylphlegmarine (**174**) (*95*). Their strategy involved enantioselective preparation of the key fragment **187**, which, after conversion to an organometallic, is added to the chiral 1-acylpyridinium salt **175** to give the phlegmarine precursor **189** with control of stereochemistry at C-2′. The first asymmetric synthesis was accomplished in 18 steps with a high degree of stereocontrol and established the absolute stereochemistry of phlegmarine (Scheme 20) (*95*).



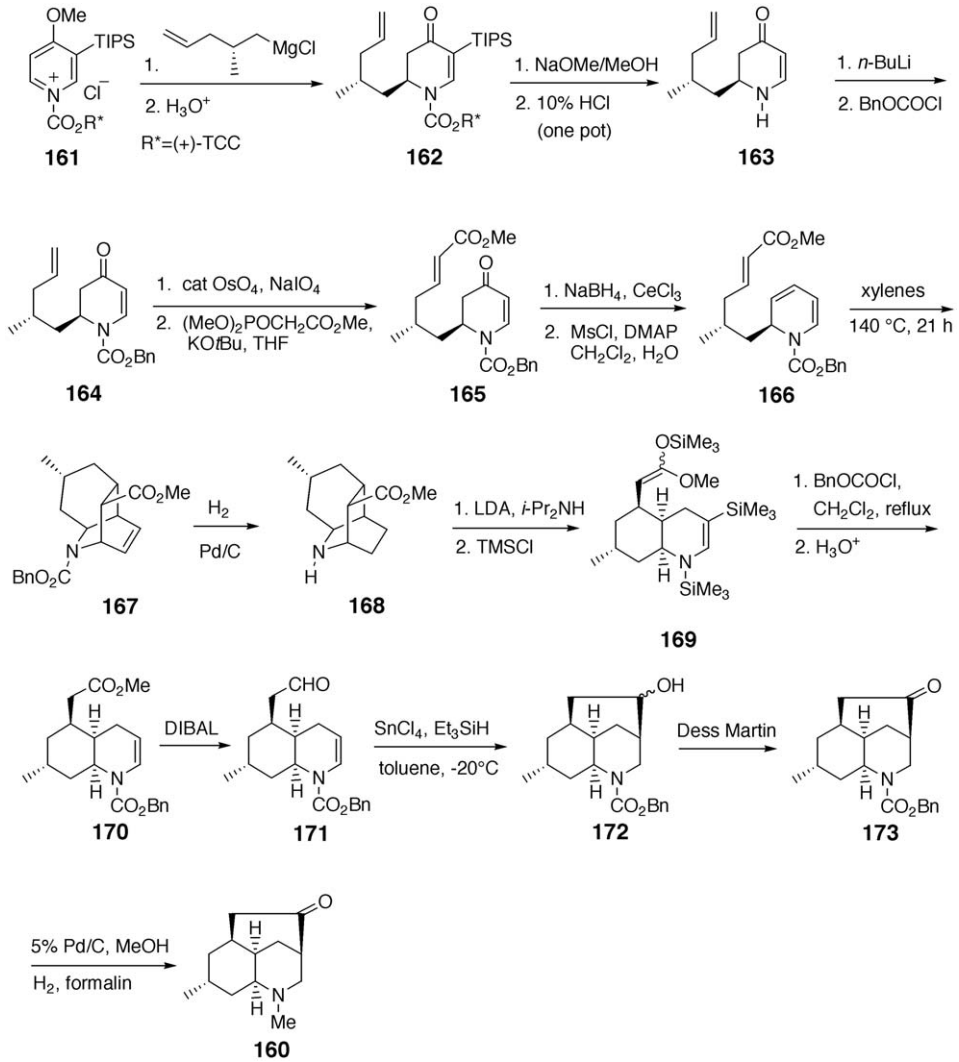

Scheme 18. Synthesis of (+)-paniculatine (**146**) (*93*).

## G. SPIROLUCIDINE (**193**)

The relative stereochemistry of spirolucidine (**193**) isolated from *Lycopodium lucidulum* by Ayer and coworkers was determined by chemical, spectroscopic, and X-ray studies (*99*). A strategy for the synthesis of the spirocyclic core of spirolucidine (**193**) was explored through a model study (*100*). Their route to spirolucidine (**193**) involves the preparation and cyclobutane ring opening of the intermediate **194**, which would arise from an intramolecular [2+2] photocyclization of dihydropyridone **195** (Scheme 21). The diene **200b** was prepared and photolyzed to give the desired [2+2] photoadduct **202** containing the correct relative stereochemistry corresponding to spirolucidine (**193**) (*100*).

## H. (±)-13-DEOXYSERRATINE (**203**)

A concise (10 steps) and efficient (12% overall yield) synthesis of (±)-13-deoxyserratine (**203**) has been achieved starting from an amidyl radical (*101*). The key reactions employed include the stereocontrolled introduction of the four stereogenic centers at C-4, C-7, C-12, and C-15. A diastereoselective Pauson–Khand reaction (*102*)

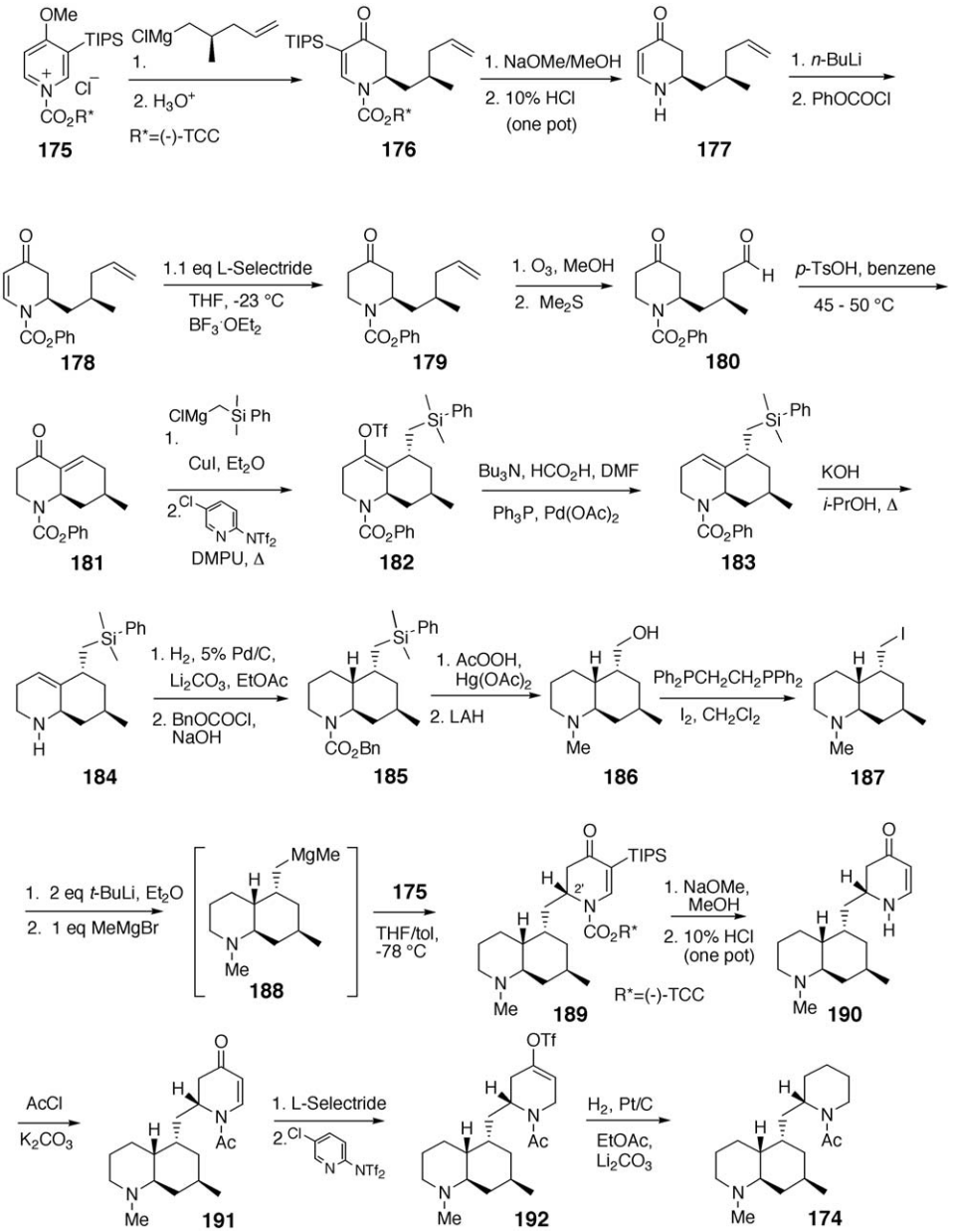



Scheme 19. Synthesis of (+)-luciduline (**160**) (*94*).

would allow easy access to the key bicyclo[4.3.0]nonenone intermediate **208**. The use of an amidyl radical intermediate, generated from the radical precursor **209**, allowed the creation of the two adjacent quaternary centers at C-4 and C-12 in one step, with the correct relative stereochemistry (*101*).

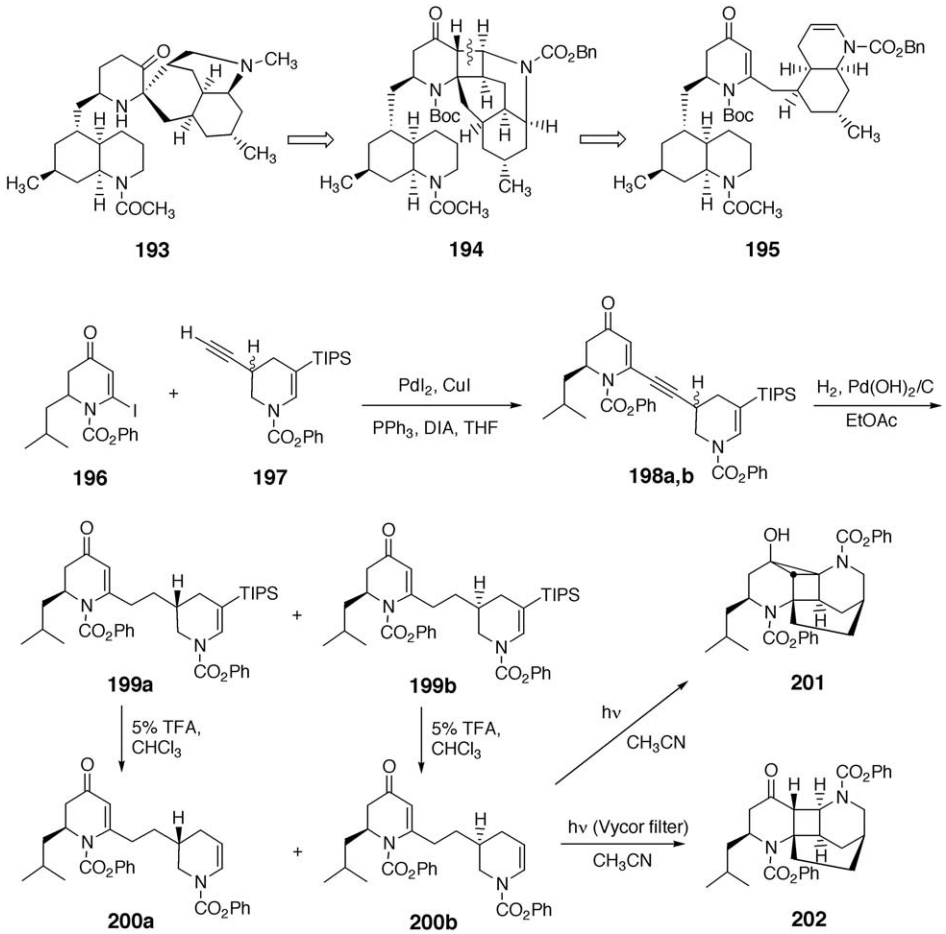
## V. Pharmacology of Huperzine A (1)

Huperzine A (**1**), isolated from the club moss *Huperzia serrata* (syn. *Lycopodium serratum*), has been used in the treatment of Alzheimer's disease (AD). The club moss



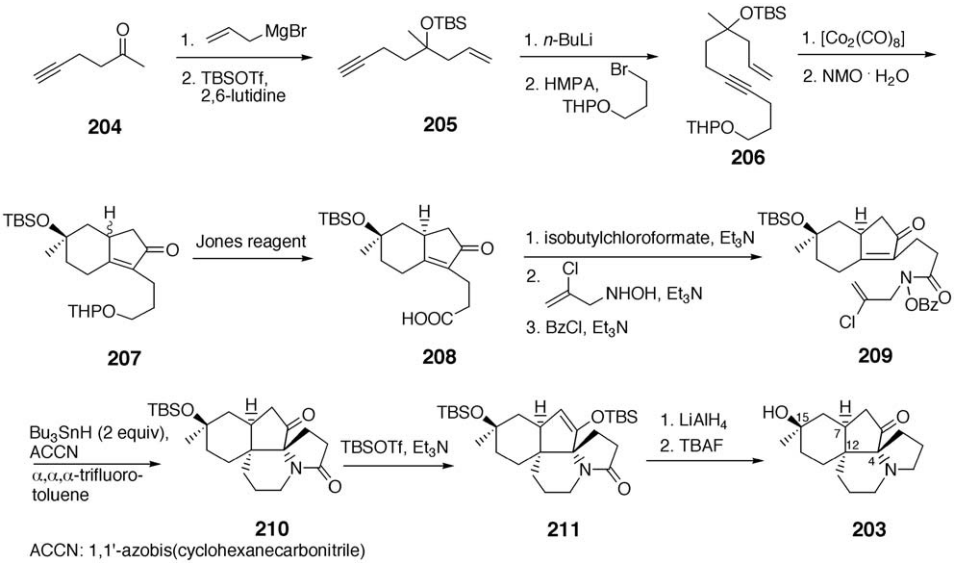

Scheme 20. Synthesis of (−)-$N_a$-acetyl-$N_b$-methylphlegmarine (**174**) (*95*).

grows in southern China and has been used in traditional medicines. Huperzine A (**1**) is a potent inhibitor of acetylcholinesterase (AChE), the key brain enzyme responsible for the rapid degradation of the neurotransmitter acetylcholine (*11,12*). Huperzine A (**1**) is also used as a dietary supplement in the USA for the correction of memory impairment (*8*). Huperzine A (**1**) also shows insecticidal and antifeedant activities (*103*). On the other



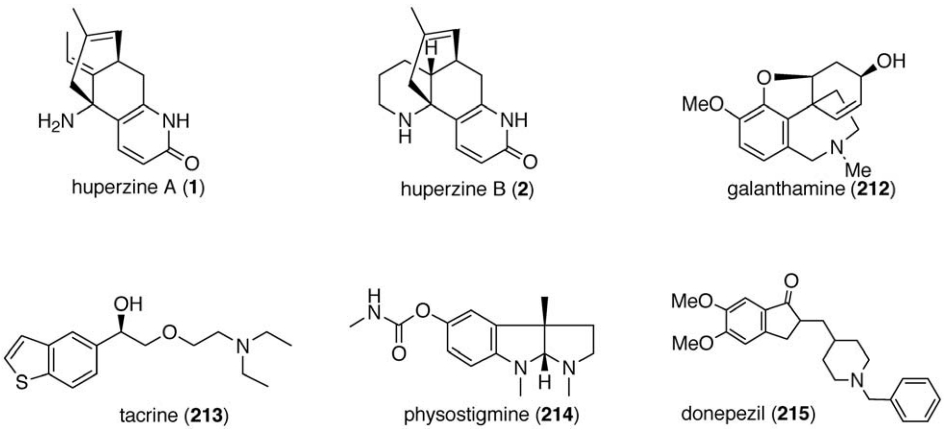

Scheme 21. Model studies toward the synthesis of spirolucidine (**193**) (*100*).

hand, huperzine B (**2**), a congener of huperzine A (**1**), showed a lower AChE inhibitory potency (*90*). The activity was specific, not for butyrylcholinesterase (BuChE) but for AChE, and its potency was more than that of galanthamine (**212**), from *Lycoris* or *Galanthus* species, and tacrine (**213**) (*104*). Although the activity of huperzine B (**2**) is less potent as an inhibitor of AChE than tacrine (**213**), its selectivity is higher. Extensive studies on the inhibition of AChE have been carried out for the development of more effective drugs. Huperzines A (**1**) and B (**2**) facilitated memory retention and retrieval in mice and improved impaired memory (*105,106*). At the same time, **1** exhibited less peripheral side effects than galanthamine (**212**) and physostigmine (**214**). The inhibition of AChE activity induced by huperzine A (**1**) was less pronounced than that of donepezil (**215**) *in vitro*. In contrast, huperzine A (**1**) inhibited BuChE at a much higher concentration than that needed for the inhibition of AChE compared with donepezil (**215**). The AChE activity of huperzine A (**1**) was shown to be reversible and **1** preferentially inhibited tetrameric AChE (*107*).




Scheme 22. Synthesis of (±)-13-deoxyserratine (**203**) (*101*).

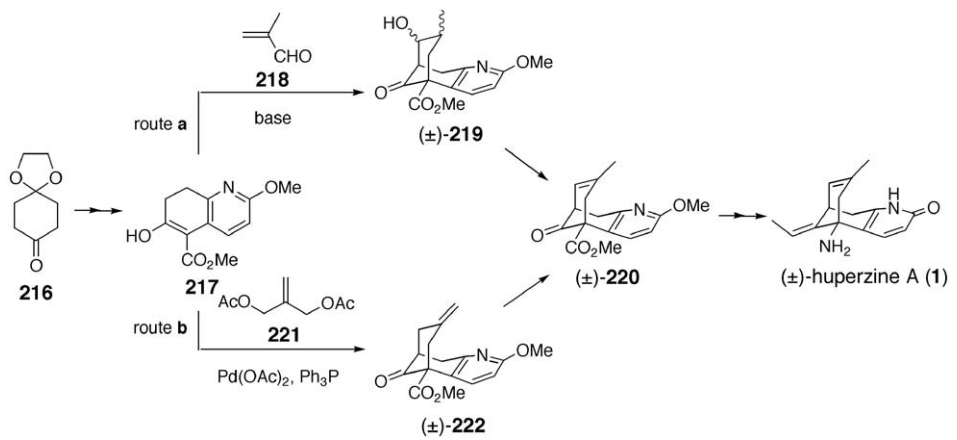
These pharmacological features might provide a promising candidate for AD therapy. Both huperzines A (**1**) and B (**2**) were shown to exert an antagonist effect on the *N*-methyl-D-aspartate receptor, and thus could reduce neuronal cell death caused by glutamate (*108,109*). Pretreating the neurons with huperzine A (**1**) improved neuronal survival (*110*). Significant protection against hypoxic-ischemic brain injury on behavior and neurophthology was produced by huperzine A (**1**) (*111*). Huperzine A (**1**) also exhibits impressive beneficial effects for the pretreatment of organophosphate poisoning (*112*). Huperzine B (**2**) is a potential agent for AD, and may be beneficial in vascular dementia and other neurodegenerative disorders with an ischemic component (*113*). These actions may increase the value of huperzines A (**1**) and B (**2**) as therapeutic agents for the treatment of AD and other neurodegenerative diseases.



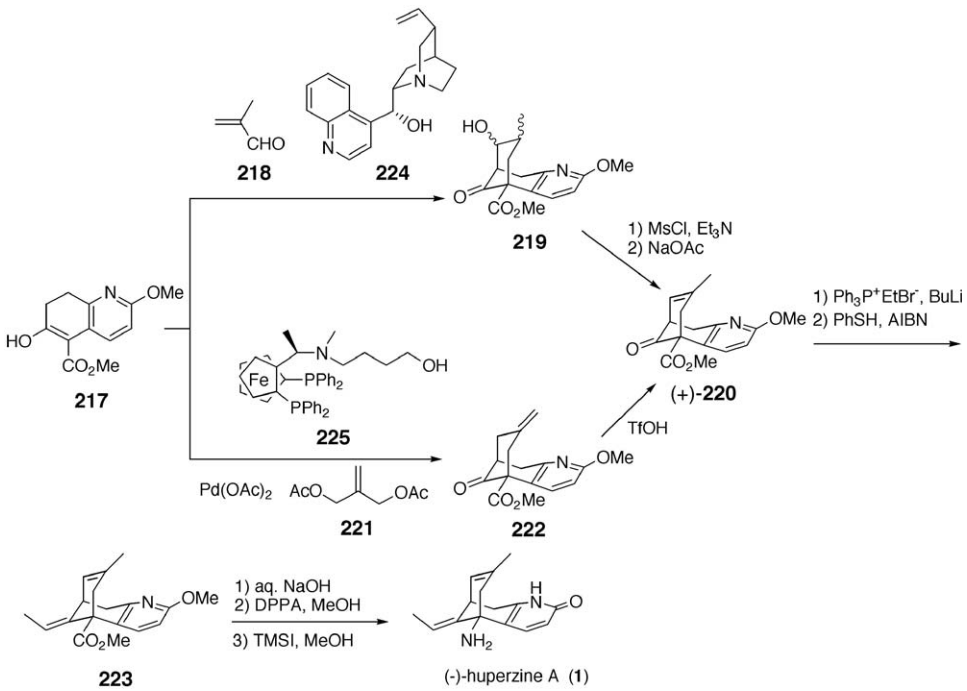
## VI. Total Synthesis of Huperzine A (1)

(−)-Huperzine A (**1**), from the club moss *Huperzia serrata*, has been shown to be a potent reversible acetylcholinesterase inhibitor (*11,114*). This alkaloid is anticipated to be a promising agent for the treatment of Alzheimer's disease, and is now being investigated in clinical trials (*11,114*). Both Kozikowski (*115–117*) and Qian (*118*) *et al*. in 1989 accomplished the first total synthesis of racemic huperzine A (**1**) by the method employing the tandem Michael addition/aldol reaction of the $\beta$-keto ester **217** with methacrolein **218** as the key step to construct the 5,9-methanocyclocta[*b*]-pyridine system (Scheme 23). The first total synthesis of natural (−)-huperzine A (**1**) was achieved by Kozikowski and coworkers in 1991 using (−)-8-phenylmenthol as a chiral auxiliary agent (*119*), and an improved synthetic route to huperzine A (**1**), employing the palladium-catalyzed bicycloannulation of **217** with 2-methylene-1,3-propanediol diacetate (**221**), was reported in 1993 (Scheme 23) (*120,121*).

Recently, new enantioselective synthetic methods which are more efficient and practical were reported by Terashima *et al*. (Scheme 24) (*122–124*). Some chiral amines, such as the *Cinchona* alkaloid **224**, promote the tandem asymmetric Michael addition/aldol reaction of **217** with **218** with good enantioselectivity, and the palladium catalysts bearing a chiral ferrocenylphosphine ligand **225** effectively modulate the asymmetric bicycloannulation of **217** with **221**. Recrystallization of the partially optically active tricycles (+)- and (−)-**220** derived from the products of the asymmetric syntheses provided the corresponding optically pure samples. The conversion from (+)- and (−)-**220** into huperzine A [(−)- and (+)-**1**], respectively, was carried out according to Kozikowski's protocol. Wittig reaction of **220** with ethylidenetriphenylphosphorane and subsequent isomerization of the ethylidene moiety provided the desired (*E*)-ester **223** in two steps. Alkaline hydrolysis of **223** followed by a modified Curtius rearrangement and subsequent deprotection furnished natural huperzine A [(−)-**1**]. Unnatural (+)-**1** was similarly prepared from (−)-**220**. Taking into account the chemical yield as well as operational simplicity, the method utilizing chiral palladium catalysts seems to be more efficient and




Scheme 23. Synthetic routes to huperzine A (**1**) by Kozikowski (route **a** and **b**) and Qian *et al*. (route **a**) (*115–118,120,121*).




Scheme 24. Synthesis of (−)-huperzine A (**1**) (*122–124*).

practical. Chen (*125*) and He (*126*) *et al*. explored almost the same synthetic pathway as that reported by Terashima *et al*.

## VII. SAR Studies of Huperzine A (1)

### A. ANALOGUES OF HUPERZINE A AND INHIBITORY ACTIVITIES OF AChE

Natural (−)-huperzine A (**1**) inhibits acetylcholinesterase (AChE) 30 times more potently than its enantiomer (+)-huperzine A, and the racemic form is about two times less potent than the natural form (*127,128*). In the past ten years, major efforts have been devoted to the preparation of both structurally simplified analogues and derivatives with the tricyclic skeleton of huperzine A (**1**) as a promising lead compound (Fig. 23).

Several types of simplified analogues were designed. Neither of the conformationally more flexible aminomethyl substituted pyridones **226** and **227** showed AChE inhibition (*129*). A series of 5-amino-5,6,7,8-tetrahydro-quinolinones **228**, related to huperzine A (**1**), was synthesized and they inhibit AChE *in vitro* (*130*). Many of them are active *in vivo* in reversing a scopolamine-induced impairment of 24 h memory in a passive avoidance paradigm. Although these compounds were designed as partial structures of huperzine A (**1**), it is unlikely that they bind to the enzyme in a similar fashion. The poor activity of **229** and graphical overlay of huperzine A (**1**) with acetylcholine would suggest that its three-carbon bridge in presenting the required

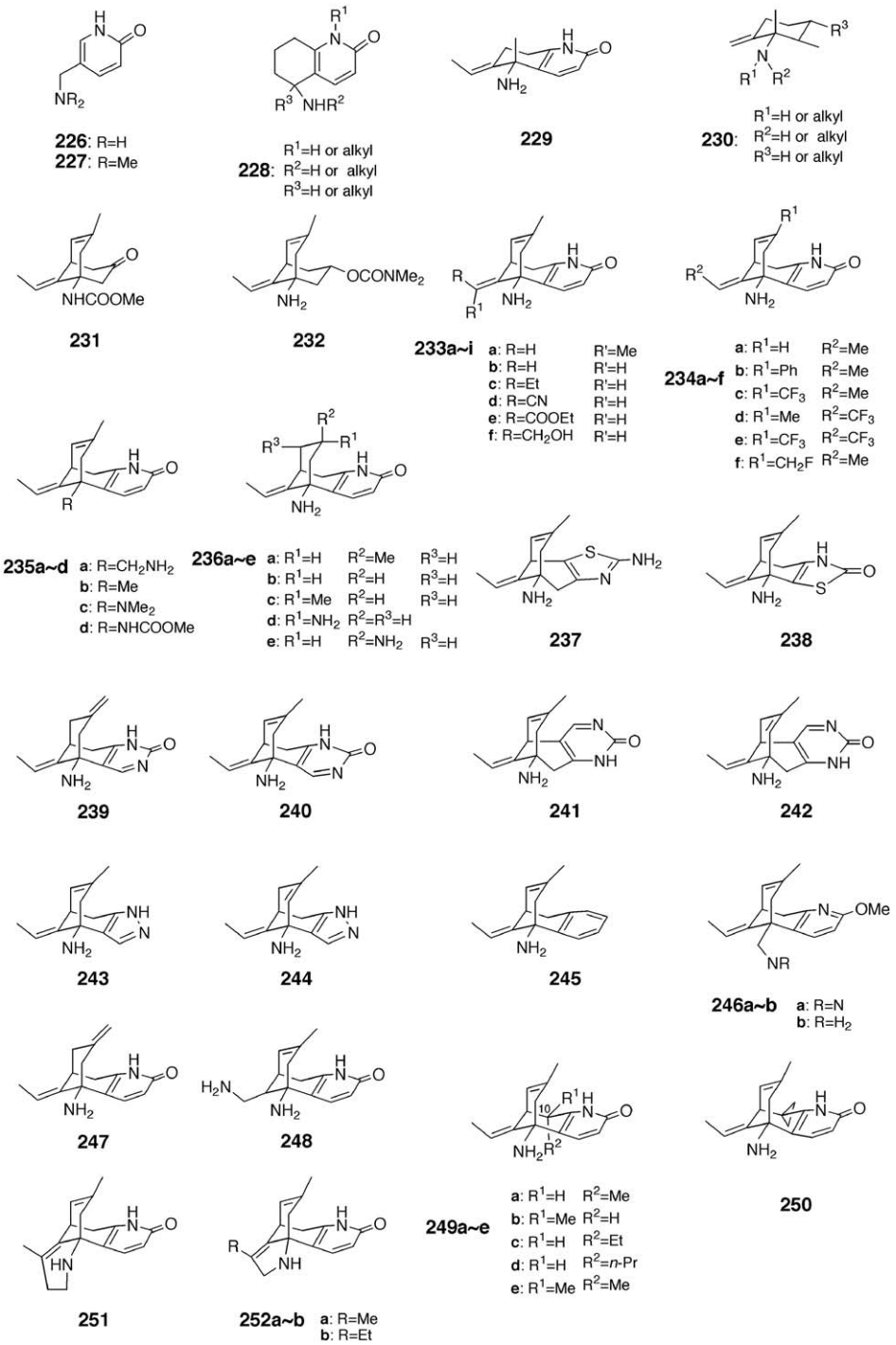



Figure 23. Structures of synthetic huperzine A (**1**) analogues.

electrostatic field to the AChE enzyme may be superfluous to its AChE inhibitory activity (*129*). The single ring analogues **230** derived from huperzine A (**1**) by removal of the bridge and the opening of pyridone ring, and by the replacement of amide group with the isosteric ester group showed less activity than (−)-huperzine A (**1**) (*131*). The dimethyl-carbamoyloxy analogue **232** was synthesized through the keto urethane analogue **231** with a bicyclo[3.3.1]nonane ring (*132*).

The synthesis of (±)-*Z*-huperzine A (**233a**), which showed inhibition of AChE comparable to that of huperzine B (**2**), was accomplished (*133*). To evaluate the contribution of the ethylidene group, both the methylene analogue **233b** and the propylidene analogue **233c** were synthesized (*117*). The analogues **233d** and **233e** bearing an ester function or a cyano group, respectively, in place of the C-14 methyl group were synthesized, and DIBALH reduction of the ethoxycarbonyl group **233e** furnished the hydroxyethylidene analogue **233f** in 82% yield (*121*). Removing or adding at the exocyclic double bond resulted in loss of activity. The compound norhuperzine A (**234a**) is 30 times less potent than (−)-huperzine A (**1**) (*134*). Analogue **234b** containing a phenyl substituent at C-15 in place of the methyl group was synthesized to probe the ability of the unsaturated carbon bridge to accommodate additional functionality (*117*). Four types of the new fluorinated huperzine A analogues **234c**∼**234f** were synthesized by Terashima *et al.* (*135–138*). All of these analogues had inhibitory activities inferior to that of huperzine A (**1**). The one-carbon homologue **235a** was synthesized (*117*). In addition, the *N*,*N*-dimethylated derivative **235c** and partially protected carbamate analogue **235d** were prepared from huperzine A (**1**) by reaction with formic acid and formaldehyde (*117*). Another series of analogues **236a**∼**c** were derived from huperzine A (**1**) by deleting the 7,8-double bond (*129*). Both the axial and equatorial amines **236d** and **236e**, respectively, were prepared (*121*). All of these compounds were significantly less active than huperzine A (**1**).

Compound **237** exhibited weak AChE activity. The analogue **238** in which the pyridinone moiety of huperzine A (**1**) is replaced with a thiazolone moiety was ineffective in the AChE inhibition assay in concentrations up to 14 μM (*139*). The pyrimidone analogues **239**–**242** of huperzine A (**1**) were obtained starting from cyclohexane-1,4-dione monoethylene ketal by first annealing this to a pyrimidine ring, and then constructing the unsaturated three-carbon bridge using the palladium-catalyzed, bicycloannulation methodology (*140*), together with the pyrazole analogues **243** and **244**. While none of these new analogues were found to rival huperzine A (**1**) in its ability to act as a reversible inhibitor of AChE, the pyrimidone analogues **241** and **242** of isohuperzine were more active than the pyrimidone analogues **239** and **240** of huperzine A (**1**) (*140*). The pyrimidone **240** was also synthesized by Li *et al.* (*141*). The derivative **245** with a benzene ring in place of the pyridone ring was at least 1000-times less active than huperzine A (**1**) (*117,142*). Methoxypyridine analogues **246a** and **246b** failed to inhibit AChE at the highest concentrations (*117*). The pyridone **247**, a positional isomer of huperzine A (**1**), and the analogue **248** bearing an aminomethyl group in place of ethylidene group were not able to rival the activity of huperzine A (**1**) (*121*).

It thus appears that the structure of huperzine A (**1**) tolerates little modification without lack of biological activity. Neither heteroatoms or $\pi$-bonds could be omitted, nor could the olefinic methyl substituents be removed or modified without significantly reducing activity.

The 10,10-dimethyl analogue, **249e**, of huperzine A (**1**) was comparable in activity to (±)-huperzine A (**1**), and the off-rate of this dimethyl analogue from AChE was slightly slower than huperzine A (**1**) (*143*). The important finding was made that introduction of an axial methyl group into the C-10 position of huperzine A (**1**), as in **249a**, increased the potency for AChE inhibition 8-fold. Whereas the corresponding equatorial isomer was about 1.5-fold less active than huperzine A (**1**) (*144*). The introduction of substituents larger than methyl resulted in a drop in activity. Through the use of molecular modeling methods involving the docking of these analogues to the reported X-ray crystal structure of *Torpedo californica* AChE, it is clearly evident that the C-10 axial methyl group points into a hydrophobic region of the enzyme, while the equatorial methyl group is directed to a less favorable hydrophilic region. Substituents larger than methyl were found to result in a conformational energy penalty (*144*). The spirocyclic analog **250** of huperzine A (**1**) that bears a cyclopropane ring at its 10-position was achieved in an enantioselective manner using a diastereoselective Michael-aldol reaction and was found to be nearly as active as huperzine A (**1**) (*145*).

Huperzine B (**2**), a congener of huperzine A (**1**), shows lower AChE inhibitory potency (*90*). Interestingly, huperzine B (**2**) exhibits a higher therapeutic index due to its longer duration of action in comparison with huperzine A (**1**) (*146*). The synthesis of a new hybrid analog **251** of huperzines A (**1**) and B (**2**), showing a potency that is comparable to that of huperzine B (**2**), was accomplished (*147*). The new huperzine B analog **252** possessing a better AChE inhibitory activity than the natural huperzine B (**2**) was also synthesized (*148*).

## B. MOLECULAR MODELING AND X-RAY STUDIES

Extensive molecular modeling studies to define the binding site of huperzine A in *Torpedo californica* AChE, for which the X-ray structure has been determined by Sussman and coworkers, were carried out (*149,150*). The binding site is nearly identical to that determined from the X-ray study as shown below. The crystal structure of the complex of AChE with (−)-huperzine A (**1**) at 2.5 Å resolution showed an unexpected orientation for the inhibitor with surprisingly few strong direct interactions with protein residues to explain its high affinity (*149*). This structure was compared to the native structure of AChE devoid of any inhibitor as determined at the same resolution. An analysis of the affinities of the structural analogues of huperzine A (**1**), correlated with their interactions with the protein, and showed the importance of the individual hydrophobic interactions between huperzine A (**1**) and the aromatic residues in the active-site gorge of AChE (*151*). These studies provide a solid structural foundation for designing other huperzine analogues likely to be of therapeutic interest.

The X-ray structures of the complexes of (+)-huperzine A (**1**) and (−)-huperzine B (**2**) with *Torpedo californica* AChE were determined at 2.1 and 2.35 Å resolution, respectively (*152*), and compared to the previously determined structure of the (−)-huperzine A complex. Recently, alkylene-linked dimers of 5-amino-5,6,7,8-tetrahydro-quinolinone (hupyridone, **254a**), a fragment of huperzine A (**1**), were shown to serve as more potent inhibitors of AChE than (−)-huperzine A (**1**) and monomeric **253a**. Two dimers, (*S*,*S*)-(−)-bis(10)-hupyridone [(*S*,*S*)-(−)-**254a**] and (*S*,*S*)-(−)-bis(12)hupyridone [(*S*,*S*)-(−)-**254b**] containing, respectively, 10 and 12 methylenes in

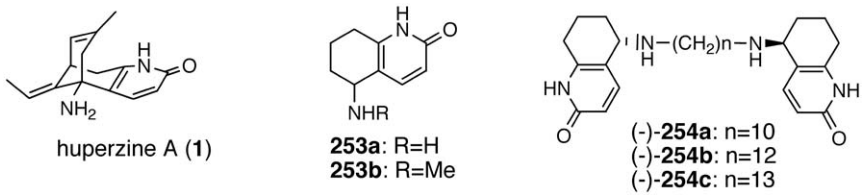



Figure 24. Chemical structures of the principal AChE inhibitors (*153*).

the spacer, were introduced into trigonal *Torpedo californica* AChE crystals, and the X-ray structures of the resulting complexes solved using the difference Fourier technique, both to 2.15 Å resolution (Fig. 24) (*153*). The crystallographic data shows that the huperzine A-like bivalent dimers, (−)-**254a** and (−)-**254b**, indeed bind within the gorge of *Torpedo californica* AChE in a bivalent fashion, with one **253a** unit bound to the catalytic anionic site and the other to the peripheral anionic site. Their enhanced affinity for *Torpedo californica* AChE relative to (−)-huperzine A (**1**) is conferred by dual-site binding and operation of the chelate effect (*153*). These results offer new insights into the factors affecting protein–ligand complementarity within the gorge and should assist the further development of improved AChE inhibitors (*153*). The entering and leaving processes of huperzine A (**1**) binding with the long active-site gorge of *Torpedo californica* AChE was also investigated by using steered molecular dynamic simulations (*154*).

## VIII. Conclusions

Studies on the *Lycopodium* alkaloids from 1994 to 2003 have been reviewed, particularly focusing on recent developments in the synthesis of these alkaloids, the structures of the new types of alkaloids, such as the huperzines, lycoposerramines, serratezomines, complanadine A, lyconadin A, senepodines, lyconesidines, himeradine A, sieboldine A, cermizines, and lucidines, and huperzine A (**1**), which has become available to numerous individuals for the treatment of memory problems in China and USA. There are currently more than two hundred *Lycopodium* alkaloids of known structure. Further phytochemical investigations will bring increasing structural variation to this alkaloid group. Although the total syntheses of some of the $C_{16}N$ and $C_{16}N_2$ type skeletons have been accomplished, the other skeletal variants remain attractive targets.

Huperzine A (**1**) has undergone clinical trials in China in patients suffering from various memory disorders, including Alzheimer's disease. Significant effects of huperzine A (**1**) were noted in these patients in terms of their quality of life and it has become available to numerous individuals for the treatment of memory problems. Since the other pharmacological activities of the various types of *Lycopodium* alkaloids have been poorly studied, this area should also be developed. Similarly, the biosynthesis of *Lycopodium* alkaloids has been only preliminarily studied, and the pathways have not been characterized with respect to the intermediates and the relevant enzymes. It will further be of value to elucidate the structural and pharmacological features of more *Lycopodium* alkaloids.

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—CHAPTER 2—

# THE MARINE BROMOTYROSINE DERIVATIVES

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## I. Introduction

The isolation of bromotyrosine secondary metabolites from marine organisms can be traced back to 1913, when Morner reported the isolation of dibromotyrosine from two coral species (*1*). There were no reports provided for these secondary metabolites again until 1967, when Sharma and Burkholder isolated 2,6-dibromo-4-acetamide-4-hydroxy-cyclohexadienone (**1**) and the dimethoxyketal **2** from two marine sponges *Verongia fistularis* and *V. cauliformis* (*2–4*). Since then, driven by the diverse bioactivities, more and more bromotyrosine-derived marine natural products have been reported. To date, there are over 280 bromotyrosine-derived alkaloids reported from marine invertebrates with a variety of biological activities including: antimicrobial, anticancer, antifouling, antiviral, ATPase regulator, calcium channel modulator, etc.

In this review, we discuss the isolation, structure, physicochemical and spectral data of all bromotyrosine derivatives isolated from marine organisms. The biosynthesis, total synthesis, and bioactivity of the bromotyrosine derivatives are also reviewed. Neither tyrosine derivatives without halogenation, nor indole alkaloids (with or without halogenation), are included in this review. Proteins or peptides containing bromotyrosine units are not included in this review since they are considered as primary metabolites. Cyclopeptides containing halogenated tyrosine units are, however, discussed in this review.

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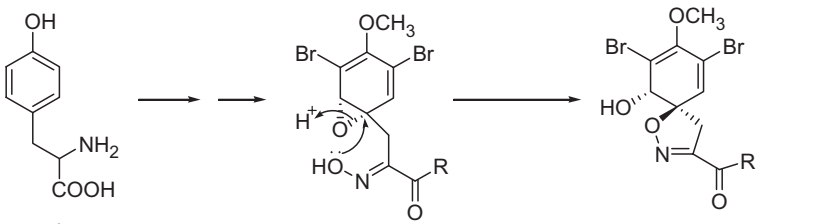
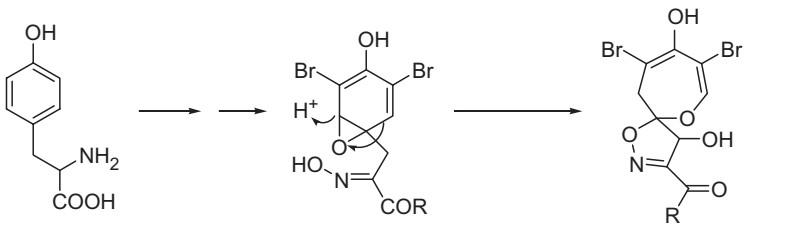
For convenience, the bromotyrosine derivatives are divided into six categories: simple bromotyrosine derivatives, spirocyclohexadienylisoxazolines, spirooxepinisoxazolines, oximes, bastadins, and other structural classes. The simple bromotyrosine derivatives are products of one bromotyrosine undergoing degradation, reduction, hydroxylation, alkylation, or esterification with simple functional groups. In spirocyclohexadienylisoxazoline bromotyrosine derivatives, one or two bromotyrosine units are transformed into a spirocyclohexadienylisoxazoline undergoing an arene oxide biosynthetic pathway. This class of alkaloids generally consists of one to three bromotyrosine-derived units, as well as other functional groups, such as histamine.



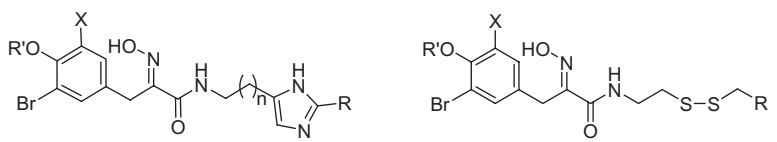

tyrosine spirocyclohexadienylisoxazoline

In the spirooxepinisoxazoline bromotyrosine derivatives, one bromotyrosine is transferred into a spirooxepinisoxazoline. There are only eight alkaloids in this class reported to date.

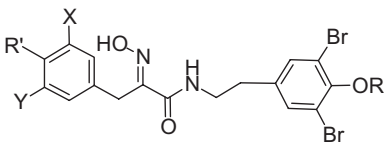



tyrosine spirooxepinisoxazoline

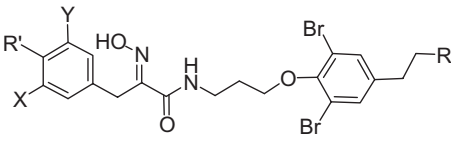
The amine functionality is transferred into an oxime in the oxime class of bromotyrosine derivatives. The geometries of the oxime functionalities were determined to be *E* in almost every case of this class of compounds. Although the geometries of some alkaloids in this class were not reported, it is easy to assign the *E* geometries for most of them from the $^{13}C$ NMR data. There are basically three structural groups in this class of bromotyrosine derivatives. The first group of alkaloids consists of a bromotyrosine oxime and a histamine moiety. The second group of alkaloids has one or two bromotyrosine oximes connected with a disulfide chain, cysteine. The third group of alkaloids has a bromotyrosine oxime connected to a bromotyramine directly or through a three carbon chain.




oxime-histamine oxime-disulfide

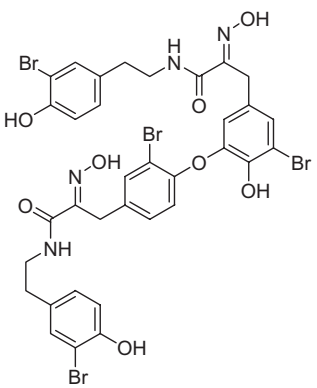


oxime-tyrosine

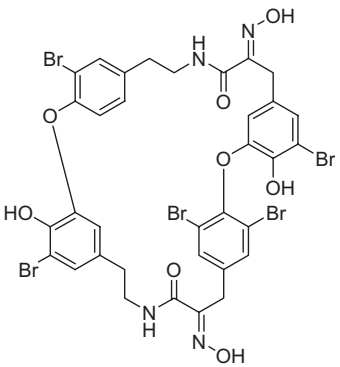


oxime-tyrosine

The bastadins are a series of predominantly macrocyclic bromotyrosine derivatives, which are biogenetically derivable from four bromotyrosines by the oxidative phenolic coupling of two tyramine–tyrosine units connected through an amide bond. Until now, there are four acyclic, twenty cyclic bastadins, and sixteen hemibastadins isolated from marine sponges and ascidians. Examples of this class of alkaloids are bastadins-1 (**204**) and -5 (**209**).



bastadin-1 (**204**)



bastadin-5 (**209**)

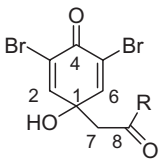
There are a number bromotyrosine derived compounds not belonging to any of the above structure classes. Geodiamolides, a series of cyclic depsipeptides, are included in this review since they contain halogenated tyrosine. Polycitones and polycitrins are condensation products of substituted bromotyrosine molecules, isolated from ascidians, and are also included in this review. Similar structures including lamellarins are not included due to the absence of halogenation. For the same reason, polyandrocarpamides A-C (**253**–**255**), chelonin B (**256**), and 5-bromochelonin B (**257**) are included.

## II. Isolation and Structure Elucidation

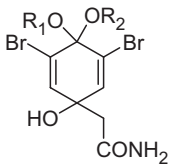
### A. SIMPLE BROMOTYROSINE DERIVATIVES

The first two members of this series, 2,6-dibromo-4-acetamide-4-hydroxycyclohexadienone (**1**) and the dimethoxyketal **2**, were isolated from the methanolic extracts of *Verongia fistularis* and *V. cauliformis* by Sharma and Burkholder in 1967 (*2–4*). Anderson and Faulkner isolated a mixed methoxy–ethoxy ketal **3** from *Verongia* sp. in 1973. Since the $^{1}$H NMR spectrum of **3** showed two methoxy signals, indicating that **3** is a mixture of two diastereoisomers, **2** and **3** were considered as artifacts generated during the extraction process (*5*). Faulkner *et al.* also reported the dienone **4** from *Tylodina fungina* (*6*).

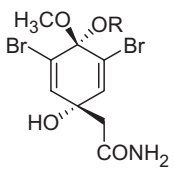
Two additional mixed ketals, aplysinketal A (**5**) and aplysinketal B (**6**), along with **7** and **8**, were obtained from the Mexican sponge *Aplysina (Verongia) thiona* (*7*). Unlike **2** and **3**, the structure of aplysinketal A (**5**) was shown to be only one of the two diastereoisomers by X-ray and NMR data. Furthermore, the mixed ketals **5** and **6** would not be expected to be formed without simultaneous formation of the dimethoxy ketal **2**, which was never detected. According to these results, aplysinketal A (**5**) and aplysinketal B (**6**) are very likely to be natural products. The diethyl ketal **9** was obtained from a Turkish sponge *V. aerophoba* (*8*).



**1**: R= $NH_2$
**7**: R =OMe
**8**: R =OH
**4**: R =OEt

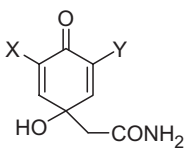


**2**: $R_1$=$R_2$=$CH_3$
**3**: $R_1$= Me $R_2$=Et
**9**: $R_1$=$R_2$=Et

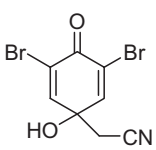


aplysinketal A (**5**): R=butyl
aplysinketal B (**6**): R=pentyl

Monobromo- (**10**), bromochloro- (**11**), and dichloro- (**12**) dienones were isolated from *Aplysina cavernicola* (*9,10*). Both **10** and **11** were isolated as racemic mixtures. The dienone **13** was first obtained as a synthetic product after treatment of aeroplysinin-1 (**14**) with trifluoroacetic acid (*11*). Our group isolated **13** from the Jamaican sponge *Verongula gigantea* as a natural product (*12*).

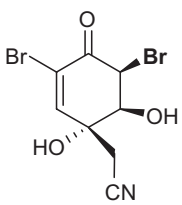


3-bromoverongiaquinol (**10**): X = Br Y = H
3-bromo-5-chloroverongiaquinol (**11**): X = Br Y =Cl
dichloroverongiaquinol (**12**): X = Y =Cl

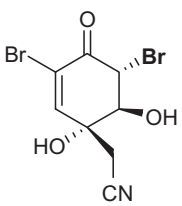


**13**

A 3:1 mixture of the two epimeric dibromonitriles, **15** and **16**, was isolated from an Australian sponge *Aplysina laevis* (*11*). Attempts to resolve the mixture by either normal or reverse-phase HPLC, as well as GC, proved unsuccessful. Treatment of (+)-aeroplysinin-1 (**14**) with neat trifluoroacetic acid resulted in a good yield of **15** and **16** (3:1 mixture) with a small optical rotation value, which permitted the assignment of the absolute stereochemistries of **15** and **16** as shown. Molecular modeling calculations suggested that the *cis* isomer **15** was the thermodynamically more stable isomer.

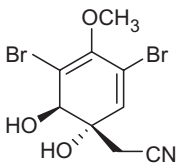


**15**

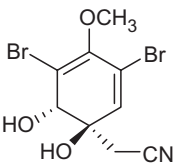


**16**

Aeroplysinin-1 (**14**), the first naturally occurring 1,2-dihydroarene-1,2-diol (*13*), was initially isolated as a dextrorotatory isomer from *V. aerophoba* [the species name was later revised to *V. cavernicola* (*72*)] (*14,15*). Fulmor *et al.* isolated the laevorotatory antipode of aeroplysinin-1 from a closely related sponge *Ianthella ardis*, for which the absolute configuration was proposed as shown in **17** on the basis of chemical, CD and NMR data (*16*). The absolute stereochemistries of both antipodes, as shown in **14** and **17**, were firmly established by X-ray diffraction analysis (*17,18*).

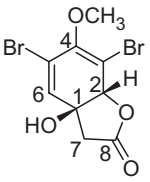



(+)-aeroplysinin-1 (**14**)

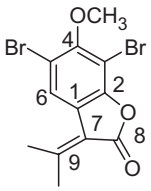



(–)-aeroplysinin-1 (**17**)

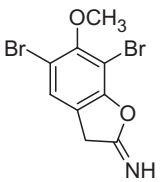
Aeroplysinin-2 (**18**), the first bromotyrosine derivative with a lactone functionality, was isolated from *V. aerophoba* in 1972 [the species name was later revised to *V. cavernicola* (*69*)] (*19*), and its structure was established on the basis of proton NMR and chemical methods. The small coupling (0.7 Hz) between the olefinic and methine protons suggested a W relationship for these two protons, indicating a quasi-equatorial orientation for the methine proton and accordingly, a quasi-diaxial orientation for the hydroxyl- and acyloxy-groups. The circular dichroism curve indicated a right-handed helicity for the diene, and therefore confirmed the absolute configuration as depicted in **18**. Aplysinolide (**19**) and aplysinimine (**20**) were obtained from *Aplysina (Verongia) thiona* (*7*).




aeroplysinin-2 (**18**)

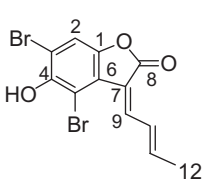



aplysinolide (**19**)

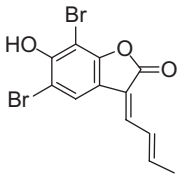



aplysinimine (**20**)

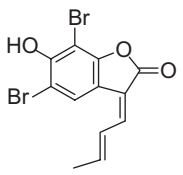
The isolation of aplysinimine (**20**) is remarkable because this alkaloid could be considered as a possible precursor of other bromo compounds obtained from *Aplysina* sponges. Aplysinolide (**19**) has an unusual $\alpha,\beta$-unsaturated side chain. Another bromotyrosine derivative containing an $\alpha,\beta$-unsaturated side chain is aplysinadiene (**21**), isolated from *Aplysina aerophoba* (*20*). The structure was determined by comparison of the NMR data with the synthesized isomers **21a** and **21b**. Structure **21c** was precluded due to the interaction of the bromine atom with the butenylide side chain (*21*).



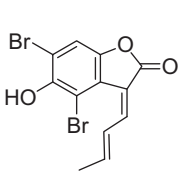

**21**




**21a**

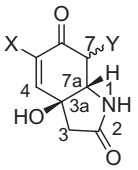



**21b**

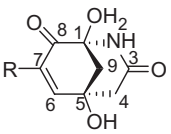



**21c**

Eight lactams, including cavernicolin-1 (**22**), cavernicolin-2 (**23**), 5-bromocavernicolin (**24**), 5-chlorocavernicolin (**25**), 7$\beta$-bromo-5-chlorocavernicolin (**26**), 7$\alpha$-bromo-5-chlorocavernicolin (**27**), 5-bromo-7$\beta$-chlorocavernicolin (**28**), and 5-bromo-7$\alpha$-chlorocavernicolin (**29**), were identified from *V. cavernicola* (*9,22,23*). 5-Bromocavernicolin (**24**) and 5-chlorocavernicolin (**25**) were the first examples of marine products with low enantiomeric purity. Cavernicolin-1 (**22**) and cavernicolin-2 (**23**), 7$\beta$-bromo-5-chlorocavernicolin (**26**) and 7$\alpha$-bromo-5-chlorocavernicolin (**27**), 5-bromo-7$\beta$-chlorocavernicolin (**28**) and 5-bromo-7$\alpha$-chlorocavernicolin (**29**), could be separated by HPLC, but they quickly equilibrate as a 3:1 mixture (*9*).



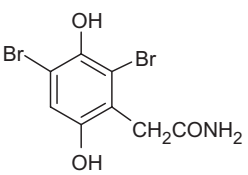

cavernicolin-1 (**22**): X = Br Y = β-Br
cavernicolin-2 (**23**): X = Br Y = α-Br
5-bromocavernicolin (**24**): X = Br Y = H
5-chlorocavernicolin (**25**): X = Cl Y = H
7β-Bromo-5-chlorocavernicolin (**26**): X = Cl Y = β-Br
7α-Bromo-5-chlorocavernicolin (**27**): X = Cl Y = α-Br
5-Bromo-7β-chlorocavernicolin (**28**): X = Br Y = β-Cl
5-Bromo-7α-chlorocavernicolin (**29**): X = Br Y = α-Cl



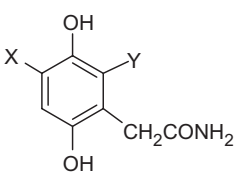

7-bromocarvernicolenone (**30**): R = Br
7-chlorocarvernicolenone(**31**): R = Cl

Two $\delta$-lactams, 7-bromocarvernicolenone (**30**) and 7-chlorocarvernicolenone (**31**), were also isolated from *V. cavernicola* (*24, 25*) and exhibited mild antibacterial activities. The structure and relative stereochemistry of 7-bromocarvernicolenone (**30**) was confirmed by X-ray diffraction analysis. 7-Bromocarvernicolenone (**30**) and 7-chlorocarvernicolenone (**31**) are additional examples of marine natural products having low enantiomeric purity.

The first, skeletally rearranged dibromotyrosine metabolite, and also the first hydroquinone in this family of marine natural products, **32**, whose structure was determined by X-ray crystallography, was isolated from *Verongia aurea*, along with **33** or **34,** as detected by gas chromatography–mass spectrometry of the ether extract (*26*). It represented a major departure from the normal dibromotyrosine metabolites, in which the aliphatic side chain remained in the *para* position relative to the hydroxyl group flanked by bromine atoms. An analogy for such a rearrangement of the tyrosine skeleton is available, however, in the conversion of 4-hydroxyphenylpyruvic acid into 2,5-dihydroxyphenylacetic (homogentisic acid), catalyzed by an enzyme classified as a mono-oxygenase (*27*).

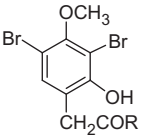



**32**

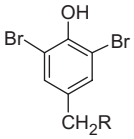



**33**: X=H Y=Br
**34**: X=Br Y=H

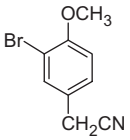
Additional aromatic bromotyrosine derivatives, **35**–**41**, were isolated from *Psammaplysilla purpurea*, *Verongia aerophoba*, *V. archeri*, and *Pseudoceratina crassa*, respectively (*28*–*33*).



**35**: R=$NH_2$
**36**: R=OMe
**37**: R=OH

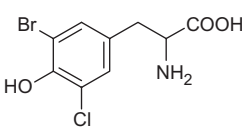


**38**: R=$CONH_2$
**39**: R=CN
**40**: R=COOH

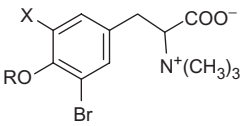


**41**

3′-Chloro-5′-bromotyrosine (**42**) was identified from hydrolysates of a sclero-protein constituting the operculum of the gastropod mollusk *Baccinum undatum* in 1971 (*34*). *N*,*N*,*N*-Trimethyl halogenated tyrosines, **43**, **44**, **45**, and **46** were isolated from the Caribbean sponge *Pseudoceratina crassa* by Fattorusso's group (*35*). The absolute stereochemistries of **43** and **44** were determined to be *L* by Gao and Hamann (*36*).

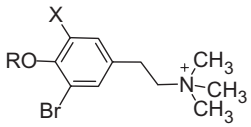


**42**

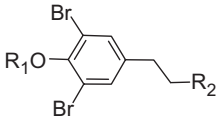


**43**: R = Me X = H
**44**: R = H X = H
**45**: R = Me X = Br
**46**: R = H X = Br

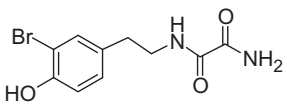
The first tyramine derivative, *N*,*N*,*N*-trimethyl-dibromotyramine (**47**), was identified from the sponge *Verongia fistularis* as a dual adrenergic compound in 1978 (*37*). Compound **48** was obtained as a natural and major bromo compound (1.7% dry weight) from a Caribbean sponge *Verongula* sp. (*38*). *N*,*N*,*N*-Trimethyl-3′-bromotyramine (**49**) and *N*,*N*-dimethyl-3′,5′-dibromotyramine (**50**) were isolated from the marine sponge *Verongula gigantea* (*39*). An undescribed ascidian *Eudistoma* sp. was found to contain 3′,5′-dibromo-4′-methoxyphenethylamine (**51**), tryptamine and 4-hydroxyphenylaceta-mide (*40*). The 3′-bromotyramine amide of oxalic acid amide (**207**) was obtained from the Papua New Guinea sponge *Ianthella basta* (*41*).



**47**: R=H X=Br
**48**: R= Me X=Br
**49**: R=X=H



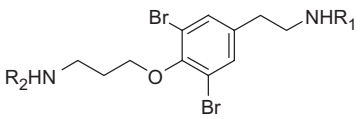
**50**: $R_1$=H $R_2$=$NMe_2$
**51**: $R_1$=Me $R_2$=$NH_2$



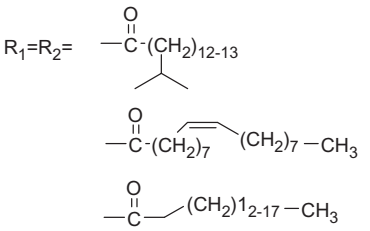
**207**

Moloka'iamine (**52**), which is often represented as a substructure of many bromotyrosine derivatives, was reported as an independent entity from an undescribed Hawaiian Verongid sponge by Hamann and Scheuer (*42*). Mololipids (**53**) are a mixture of bisamides of moloka'iamine with long chain fatty acids and were isolated as an anti-HIV agent from this sponge more recently (*43*). The fatty acids of the mololipid mixture (**53**) are a homologous series of saturated linear and methyl branched fatty acids ranging

from $C_{14}$ to $C_{20}$. Included is at least one monounsaturated fatty acid of 18 carbon atoms, with a double bond at C-9. There were no fatty acids with more than one double bond detected. There are also mono-, di-, and trimethyl, internally branched, fatty acids containing 15, 17, and 19 carbons. The positions of the methyl substituents vary in the carbon chain. The $^{13}C$ NMR data clearly showed that the internal branching of the most abundant fatty acids did not occur at positions $\alpha$, $\beta$, or $\gamma$ from the carbonyl carbon or the terminal methyl group. There were no data to support or dismiss the possibility that the individual acids may occur randomly on either nitrogen of the core moloka'iamine nucleus.

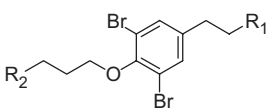



moloka'iamine (**52**): $R_1=R_2=H_2$

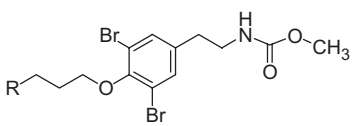



mololipids (**53**): principal fatty acid composition

Different *N*-methylation derivatives of moloka'iamine, aplysamine 1 (**54**) (*44*), purealidin F (**55**), and G (**56**) (*45*), were obtained from an Australian sponge *Aplysina* sp. and the Okinawan sponge *Psammaplysilla purea*, respectively. 3,5-Dibromo-4-(3-dimethylaminopropoxy)phenethyl carbamic acid methyl ester (**57**) and its salt **58** were obtained as the first bromotyrosine derivatives containing a carbamate group from an Indian sample of *Psammaplysilla purpurea* (*46*), along with **59** (*47,48*).



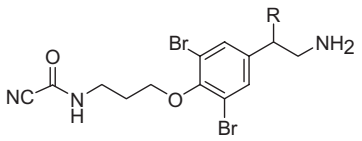

aplysamine 1 (**54**): $R_1=NHMe_2^+$ $R_2=NHMe_2^+$
purealidin F (**55**): $R_1=NHMe_2^+$ $R_2=NH_2Me^+$
purealidin G (**56**): $R_1=NH_2Me^+$ $R_2=NHMe_2^+$
**59**: $R_1=NH_2$ $R_2=NMe_2H^+X^-$
**59a**: $R_1=NHAc$ $R_2=NMe_2H^+X^-$



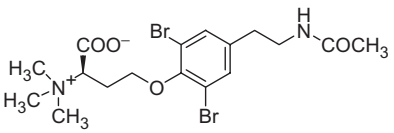

**57**: $R=NMe_2$
**58**: $R=NMe2H^+X^-$

An unprecedented cyanoformyl derivative, ceratinamine (**60**), was reported from the marine sponge *Pseudoceratina purpurea* by Fusetani's group in 1996 (*49*). Ceratinamine (**60**) was the first report of a cyanoformamide metabolite in natural products. It exhibited antifouling activity against *Balanus amphitrite* cyprides and cytotoxicity against P388 murine leukemia cells. The second example of a naturally occurring cyanoformamide metabolite, 7-hydroxyceratinamine (**61**), was isolated from a Micronesian sponge *Aplysinella* sp. by Fu and Schmitz (*50*). Nakirodin A (**62**) was isolated from an Okinawan marine Verongid sponge (*51*). The absolute configuration was determined to be *R* by the CD spectrum, of which *N*,*N*,*N*-trimethylhomoserine hydrolyzed from nakirodin A (**62**) showed a positive Cotton effect at 203.5 nm ($\Delta\varepsilon$ +2.0) that was identical to that of the authentic sample of *N*,*N*,*N*-trimethyl-*D*-homoserine. Although many bromotyrosine alkaloids possess one or more aminopropanol units (*52*), bromotyrosine alkaloids having an *N*,*N*,*N*-trimethylhomoserine residue, such as nakirodin A (**62**), are very rare (*35,36*). The structure of **62** indicated that the aminopropanol units found in

many bromotyrosine alkaloids may be biogenetically derived from a homoserine through decarboxylation.

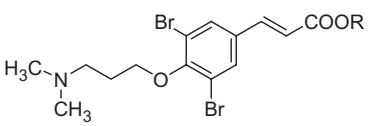


ceratinamine (**60**): R=H
7-hydroxyceratinamine (**61**): R=OH

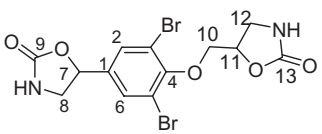


nakirodin A (**62**)

3,5-Dibromo-4-(3′-*N*,*N*-dimethylaminopropyloxy)cinnamic acid (**63**) and its ethyl ester (**64**) were identified from the Caribbean sponge *Pseudoceratina crassa* by spectroscopic methods and total synthesis (*53*). LL-PPA216 (**65**) was first isolated as dextrorotatory ($[\alpha]_D$ +8.9°) from the sponge *Verongia lacunosa* collected off the coast of Puerto Rico by Borders *et al*. in 1977 (*54*), and appeared to be the first bromine compound containing 2-oxazolidone rings isolated from a sponge. Makarieva *et al*. later reported the isolation of the (−)-enantiomer of LL-PPA216 (**66**, $[\alpha]_D = -6.5°$) from *Aplisina* sp. collected in Cuba (*55*). Another isomer **67** was identified from the marine sponge *Aplysina aerophoba* by Norte *et al*. in 1988 and its absolute configuration was determined as *R*, *R* by X-ray analysis (*21*). The optical rotation of **67** ($[\alpha]_D = -33°$) is significantly different from that of **65** and **66**, indicating that it is a new diastereomer of **65** and **66**.



**63**: R=H
**64**: R=Et



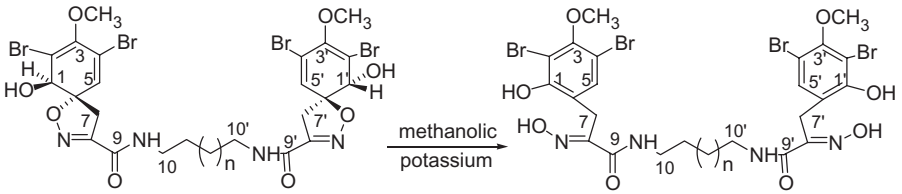
(+)-LL-PPA216 (**65**)
(–)-LL-PPA216 (**66**)
**67**: 7,11-*R,R*

## B. SPIROCYCLOHEXADIENYLISOXAZOLINE BROMOTYROSINE DERIVATIVES

### *1. Bis-Spirocyclohexadienylisoxazolines*

The first spirocyclohexadienylisoxazoline type bromotyrosine derivatives were aerothionin (**68**) and homoaerothionin (**69**), which were initially isolated from the marine sponge *Verongia aerophoba* [the species name was later revised to *V. cavernicola* (*69*)] and *V. thiona* by Fattorusso *et al*. in 1970 (*56–58*). The structure of aerothionin, the major component of both sponges (*ca*. 10% in *V. aerophoba*), was a result of a collaborative effort between Minale's laboratory and Thomson's laboratory based on proton NMR and chemical methods (*59*). Treatment of aerothionin with aqueous methanolic potassium converted it quantitatively into the oxime **68a**. This reaction was used to identify the spirocyclohexadienylisoxazoline structure. It must be noted that since aerothionin is optically active ($[\alpha]_D$ +252°), the asymmetric end units must be identical and not in a mirror-image relationship. The structures of aerothionin and related bis-spirocyclohexadienylisoxazoline derivatives were mistakenly drawn as mirror-image relationships in many later publications. 3′,5′-Dibromotyrosine is the probable precursor of the spirocyclohexadienylisoxazoline, and the $C_4N_2$ and $C_5N_2$ chains are derived from ornithine and lysine, respectively. The absolute stereochemistry was determined by

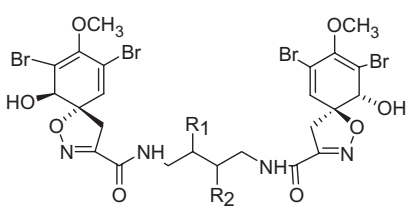
X-ray crystallographic analysis and circular dichroism (*60*). The $^{13}C$ NMR chemical shift assignments of C-2 and C-4 were inverted based on the correlation peaks between H-1/H-1′ with C-2/C-2′ and between H-5/H-5′ and C-4/C-4′ in the COLOC NMR experiment (*61*).



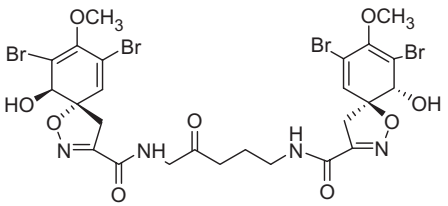

aerothionin (**68**): n=1
homoaerothionin (**69**): n=2

**68a**: n=1
**69a**: n=2

Dihydroxyaerothionin (**70**) was isolated from the sponge *Verongula rigida* collected from Sweetings Cay, Bahamas at a depth of 228 feet using an untethered manned submersible. Its structure was determined based on the NMR data and the stereochemistry of the hydroxy group in the central chain was not determined (*62*). 11-Hydroxyaerothionin (**71**) was identified from the sponge *Pseudoceratina durissima*, collected from the Great Barrier Reef, Australia, as an antimicrobial component against *Staphylococcus aureus* at 100 μg/disk, *Bacillus subtilis* at 50 μg/disk, and *Candida albicans* at 50 μg/disk. The relative stereochemistry of the 11-hydroxyl group was not determined (*63*). 11-Oxoaerothionin (**72**) was isolated from a Caribbean sponge *Aplysina lacunosa* (*64*). It showed pronounced selective cytotoxicity toward the human colon HCT-116 cell line within a limited concentration range (0.01–0.1 μg/mL), in addition to moderate antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Two epimeric 11-oxo-12-hydroxyaerothionins, **73** and **74**, were isolated from the Caribbean sponge *Aplysina fistularis* forma *fulva* (Pallas) by Fattorusso's group (*61*). Their $^{13}C$ NMR, UV, and IR spectra are identical. However, their $^{1}H$ NMR spectra have minor differences, suggesting that they differ only in some stereochemical details. Because their CD spectra, which are sensitive to the configuration of the spirocyclohexadiene chromophore, are superimposable, **73** and **74** were concluded to be epimers at C-12. The configurations of 12-hydroxyl groups were determined as 12*S* for **73** and 12*R* for **74** using the modified Mosher's method. Oxohomoaerothionin (**75**) was reported from the sponge *Aplysina cavernicola* (*65*).

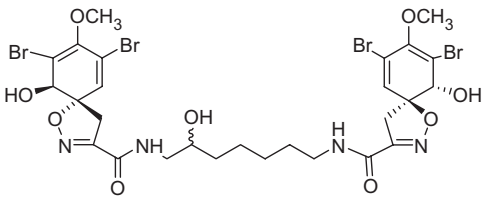


dihydroxyaerothionin (**70**): $R_1$=$R_2$=OH
11-hydroxyaerothionin (**71**): $R_1$=OH $R_2$=H
11-oxoaerothionin (**72**): $R_1$=oxo $R_2$=H
12(*S*)-hydroxy-11-oxoaerothionin (**73**): $R_1$=oxo $R_2$=*S*-OH
12(*R*)-hydroxy-11-oxoaerothionin (**74**): $R_1$=oxo $R_2$=*R*-OH



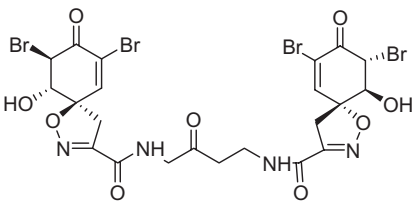
oxohomoaerothionin (**75**)

Structurally related to aerothionin and homoaerothionin, caissarine B (**76**), recently isolated from the Brazilian sponge *Aplysina caissara*, is the only bromotyrosine-derived alkaloid bearing a 1,7-diamino-3-hydroxyheptane chain, a diamine moiety that has no precedent among natural products (*66*).



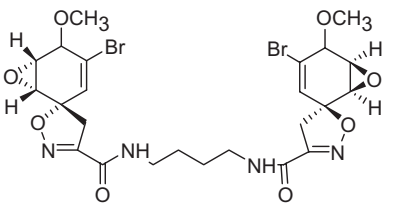
caissarine B (**76**)

Modification of the spirocyclohexadienylisoxazoline is very rare, which includes compound **77** and calafianin (**78**). Alkaloid **77**, isolated from the sponge *Aplysina archeri*, was the second example of a bromotyrosine derivative with a spirocyclohexenonyl-isoxazole ring. Its structure was assigned on the basis of spectroscopic evidence, including 2D-NMR experiments, and the absolute configuration shown in the structure has been suggested using the helicity rule (*67*).



**77**

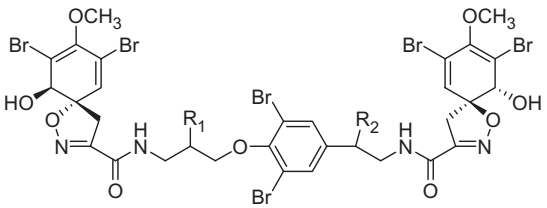
Calafianin (**78**), isolated from the Mexican sponge *Aplysina gerardogreeni*, is the only bromotyrosine derivative containing an epoxy group (*30*).



calafianin (**78**)

Fistularin-3 (**79**) was isolated from *Aplysina fistularis* forma *fulva* as a cytotoxic component by Gopichand and Schmitz in 1979 (*68*). Its planar structure was determined as two spirocyclohexadienylisoxazolines connected by a bromotyramine central chain based on proton NMR and alkaline hydrolysis. The relative stereochemistry of the spirocyclohexadienylisoxazoline was the same as aerothionin, based on the proton chemical shifts and coupling constants of H-1/1′ and H-7/7′. The absolute stereochemistry was also determined to be the same as aerothionin based on comparable CD spectrum (*36*). The configuration of the two chiral centers at C-11 and C-17 remain to be determined. Three stereoisomers of fistularin-3 were reported later. Cimino *et al.* argued that isofistularin-3 (**80**), which was isolated from *Verongia aerophoba* with practically identical UV, IR and optical rotation, was different from fistularin-3 in the stereochemistry at one (or more) of the chiral centers based on minor differences when the proton NMR spectra of the acetates of both isofistularin-3 and fistularin-3 were directly compared (*69*).

König and Wright reported a C-11 stereoisomer of fistularin-3, 11-*epi*-fistularin-3 (**81**), from the tropical sponge *Agelas oroides* (*70*). Comparison of the $^{13}C$ and $^{1}H$ NMR of **81** with those for fistularin-3 revealed small, but significant, differences, notably at C-11 (70.7 ppm in **81** and 69.5 ppm in fistularin-3). All other differences between the two sets of $^{13}C$ NMR data were in the range of 0.1 to 0.2 ppm. The optical rotation of **81** is $+66^{\circ}$ compared to $+104^{\circ}$ (*68*) and $+102^{\circ}$ (*71*) for fistularin-3. The stereochemistry of the spiroisoxazole moiety was deduced as 1*R*, 1′*R*, 6*S*, and 6′*S* by CD analysis, leaving the configuration of the hydroxyl groups at C-11 and C-17 undetermined. 11-*epi*-Fistularin-3 was not cytotoxic towards KB-cells ($IC_{50} > 20$ μg/mL) in contrast to fistularin-3 ($IC_{50} > 4.1$ μg/mL) (*68*) and isofistularin-3 ($IC_{50} > 4$ μg/mL) (*69*). Aydogmus *et al.* claimed another stereoisomer of fistularin-3, 1-*epi*-fistularin-3, based on the minor differences (less than 0.03ppm) of the proton chemical shifts of H-1,1′ and H-7,7′ for 1-*epi*-fistularin-3 tetraacetate compared to isofistularin-3 tetraacetate (*69*) and fistularin-3 (*68*), and an optical rotation of $+51.6^{\circ}$ (*8*).

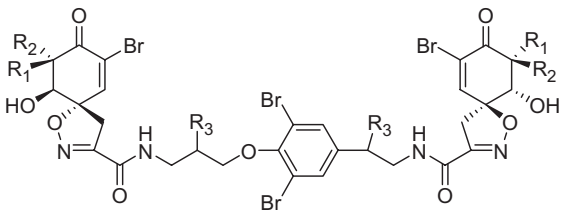



fistularin-3 (**79**): $R_1$=$R_2$=OH
11-*epi*-fistularin-3 (**81**): $R_1$=*epi*-OH $R_2$=OH
11-ketofistularin-3 (**82**): $R_1$=oxo $R_2$=OH
11,19-dideoxyfistularin-3 (**83**): $R_1$=$R_2$=H
19-deoxyfistularin-3 (**84**): $R_1$=OH $R_2$=H
19-deoxy-11-oxofistularin-3 (**85**): $R_1$=oxo $R_2$=H
11-dehydroxyfistularin-3 (**86**): $R_1$=H $R_2$=*S*-OH

11-Ketofistularin-3 (**82**) and fistularin-3 were obtained from the sponge *Aplysina archeri* (*71*). Both compounds exhibited antiviral activity against feline leukemia virus with $ED_{50}$ values of 42 μM and 22 μM, respectively. 11,19-Dideoxyfistularin-3 (**83**) was reported as an antibiotic from the sponge *Pseudoceratina durissima*, which is more active than aerothionin (**68**) and homoaerothionin (**69**) (*63*). 19-Deoxyfistularin 3 (**84**) and

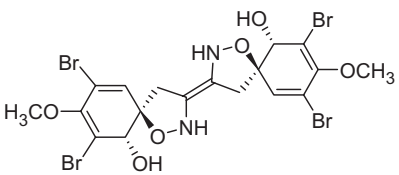
19-deoxy-11-oxofistularin 3 (**85**) were isolated from an undescribed Italian sponge *Verongia* sp. by Mancini *et al*. in 1993 (*72*). 19-Dehydroxyaerothion (**86**) was isolated from the sponges *Aplysina cavernicola* (*65*) and *Aplysina fistularis* (*73*). The absolute stereochemistry of the spirocyclohexadienylisoxazole moieties were determined to be the same as aerothionin by the CD spectrum, and the configuration of C-19 was deduced as *S* by the modified Mosher's method (*65*).

Agelorins A and B (**87** and **88**) were isolated from the marine sponge *Agelas oroides* (Agelasidae, Axinellida) (*70*). The structures contain two units quite similar to the usual spirocyclohexadienylisoxazole fragments differing only by the presence of a cyclohexenone instead of a cyclohexadienyl ring. This structural feature is unique among the bromotyrosine derivatives. The relative stereochemistry of the spirocyclohexenonylisoxazole was determined from the proton NMR and NOESY spectra. A collection of the marine sponge *Suberea* aff. *praetensa* from the Gulf of Thailand furnished the bromotyrosine derivatives fistularin-3, agelorin A and B, and the new 11,17-dideoxyagelorin A (**89**) and B (**90**) (*74*).



agelorin A (**87**): $R_1$= H $R_2$=Br $R_3$=OH
agelorin B (**88**): $R_1$= Br $R_2$=H $R_3$=OH
11,17-dideoxyagelorin A (**89**): $R_1$= H $R_2$=Br $R_3$=H
11,17-dideoxyagelorin B (**90**): $R_1$= Br $R_2$=H $R_3$=H

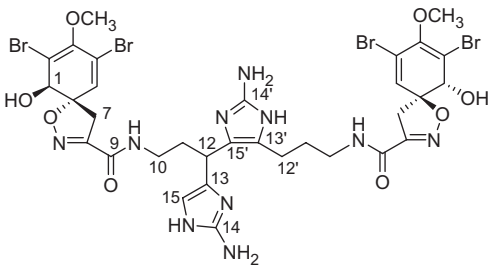
Zamamistatin (**91**) was isolated from the sponge *Pseudoceratina purpurea* with significant antibacterial activity against *Rhodospirillum salexigens*, which has adhering properties, and may be a valuable candidate for novel antifouling agents (*75,76*). It was determined to be an optically active dimer of spirocyclohexadienylisoxazoline by the careful analysis of the 1D and 2D NMR spectra and its absolute stereochemistry was determined by the modified Mosher's method.



zamamistatin (**91**)

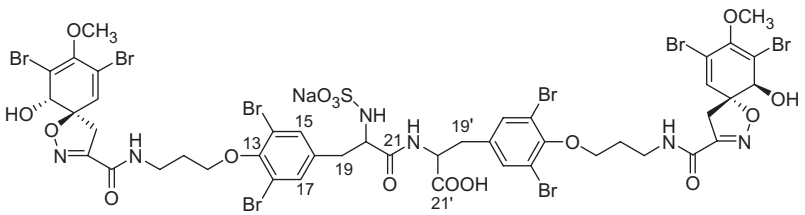
Archerine (**92**), a novel anti-histaminic bromotyrosine derivative, was identified from the Caribbean marine sponge *Aplysina archeri* by Fattorusso's group in 2001 (*77*). Its structure is novel in having the central chain formed by two 2-amino-homohistamine residues through a carbon–carbon bond. The configuration of C-12 remains to be assigned. Histamine or homohistamine are not unusual in bromotyrosine derivatives. However, archerine (**92**) is the only example having two homohistamine residues. The structure of archerine (**92**) suggests a biogenetic origin from a [1 + 1] intermolecular

oxidative coupling of two molecules of aerophobin-2 (**114**), which also exists in this sponge.



archerine (**92**)

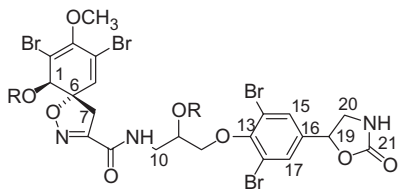
Ianthesine C (**93**) was isolated as a 3:2 mixture of diastereomers from an Australian marine sponge of the genus *Ianthella* sp. by Okamoto *et al*. in 2000 (*78*). It is a tetrameric bromotyrosine derivative having two spirocyclohexadienylisoxazoline ring systems linked by two bromotyrosines and two C3 units. The configurations of C-20 and C-20′ of these diastereomers are unclear.



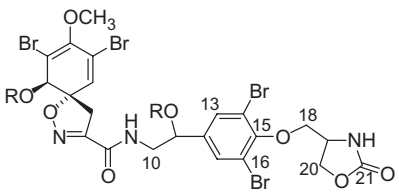
ianthesine C (**93**)

*2. Mono-spirocyclohexadienylisoxazolines*

This class of bromotyrosine derivatives contains one spirocyclohexadienylisoxazoline ring system. The first two alkaloids in this class are fistularin-1 (**94**) and fistularin-2 (**95**) isolated from the marine sponge *Aplysina fistularis* forma *fulva* by Gopichand and Schmitz in 1979 (*68*). Both compounds contain a spirocyclohexadienylisoxazoline, a bromotyramine, and a C3 unit.



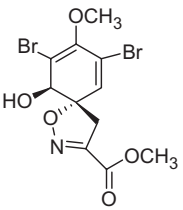
fistularin-1 (**94**): R=H
fistularin-1 acetate (**94a**): R= $COCH_3$



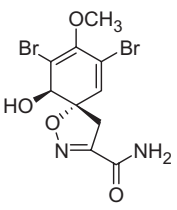
fistularin-2 (**95**): R=H
fistularin-2 acetate (**95a**): R= $COCH_3$

*a. Simple Mono-spirocyclohexadienylisoxazolines*. There are only three alkaloids in this group. Alkaloids **96** and **97** were reported by Ciminiello *et al*. from the Caribbean sponge *Verongula* sp. (*38*). Alkaloid **97** was also isolated from the Okinawan sponge

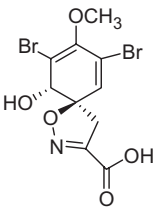
*Psammaplysilla purea* and was named as purealidin R (*79*). Alkaloid **98** was isolated from a Caribbean sponge *Pseudoceratina* sp. as a major brominated metabolite (*80*).




**96**

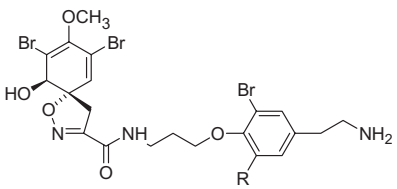



purealidin R (**97**)

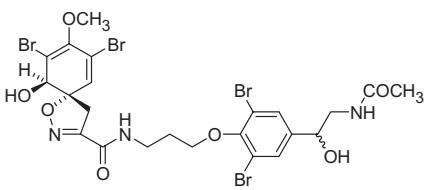



**98**

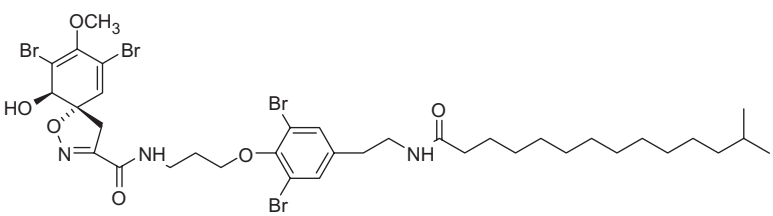
*b*. *Bromotyrosine Mono-spirocyclohexadienylisoxazoline*. Araplysillins-I (**99**) and -II (**100**) were isolated from the sponge *Psammaplysilla arabica* and were established to be inhibitors of Na,K-ATPase and have antimicrobial activity (*81*). Two closely related alkaloids, 14-debromoaraplysillin-I (**101**) and aplysinamisin III (**102**) were isolated from *P. purpurea* (*82*) and *Aplysina cauliformis* (*83*), respectively.




araplysillin-I (**99**): R=Br
14-debromoaraplysillin-I (**101**): R=H

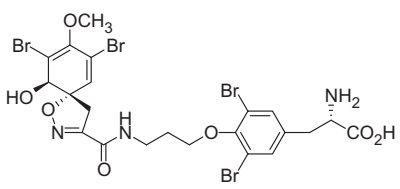



aplysinamisin-III (**102**)

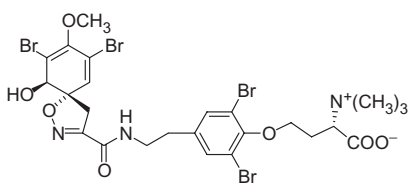



araplysillin-II (**100**)

Gao *et al*. reported araplysillin-III (**103**) and hexadellin C (**104**) from the sponge *Aiolochroia crassa* (*36*). The absolute configuration of the spiroisoxazoline of both alkaloids was determined by CD spectra. The absolute configuration at C-18 of araplysillin-III (**103**) was shown to be L by HPLC analysis according to Marfey's procedure. The configuration of the *N*,*N*,*N*-trimethylhomoserine moiety was deduced as L by comparison of the optical rotation with the D- and L- standards.

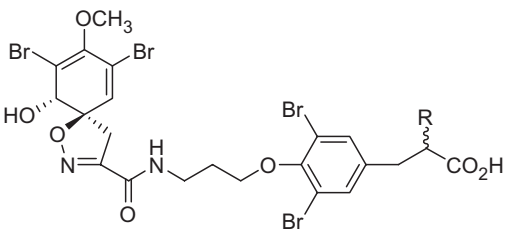



araplysillin-III (**103**)

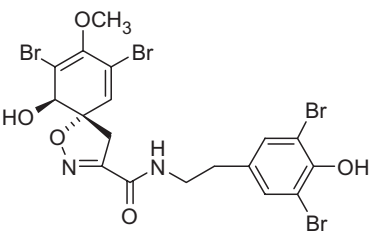



hexadellin C (**104**)

Ianthesines A (**105**), B (**106**), and D (**107**) were isolated from the Australian marine sponge *Ianthella* sp. as Na,K-ATPase inhibitors with an active range of 50–440 μM (*78*). The 1*S*, 6*R* configuration of the ianthesines was deduced by the negative optical rotation and Cotton effects at 248 and 285 nm. The dibromo-*N*,*N*-dimethyltyrosine moiety of ianthesine A (**105**) was determined as D by chiral HPLC analysis of the hydrobromic acid hydrolysis product of **105**. The configuration of the dibromotyrosine moiety of ianthesine B (**106**) was found to be a mixture of L- and D-forms in the ratio of 7:3, using the same method. Chiral HPLC analysis revealed that ianthesine B (**106**) is a 7:3 mixture of two diastereomers, 1*S*, 6*R*, 20*S* and 1*S*, 6*R*, 20*R*. The minor diastereomer is an enantiomer of araplysillin-III (**103**). Hemifistularin-3 (**108**), which is the right-side portion of 11-oxofistularin-3 (**82**), was isolated from a new species of sponge in the family Aplysinellidae Bergquist, order Verongida, collected in the Coral Sea (*72*). Hemifistularin-3 (**108**) can be obtained by treatment of 11-oxofistularin-3 with methanolic KOH. Since both hemifistularin-3 (**108**) and 11-oxofistularin-3 (**82**) were found to exist in the same sponge, it is possible that hemifistularin-3 is a product of the degradation of 11-oxofistularin-3 or an elaborated biogenetic precursor.

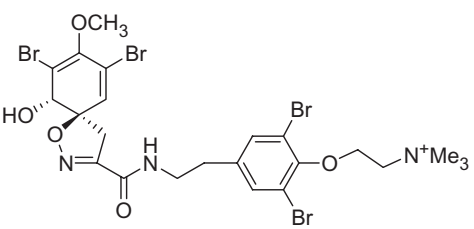


ianthesine A (**105**): R= β-$NMe_2$
ianthesine B (**106**): R= α-$NH_2$
ianthesine D (**107**): R= $NHSO_3Na$

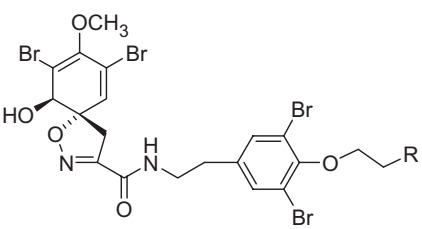


hemifistularin-3 (**108**)

Purealidins B (**109**), P (**110**), and Q (**111**) were isolated from two different collections of an Okinawan sponge *Psammaplysilla purea* by Kobayashi *et al*. (*79*,*84*,*85*). The absolute stereochemistry of the spirocyclohexadienylisoxazoline in purealidin B (**109**) (*84*), as determined by the CD spectrum, was opposite of that in purealidin P (**110**) and Q (**111**) (*79*). Purealidin S (**112**) was isolated from the Fijian sponge *Druinella* sp. (*86*).



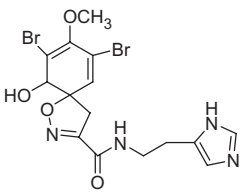
purealidin B (**109**)



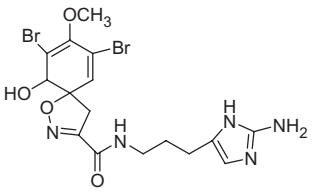
purealidin P (**110**): R=$NMe_2$
purealidin Q (**111**): R=$CH_2NMe_2$
purealidin S (**112**): R=$CH_2NHMe$

*c*. *Histamine Mono-spirocyclohexadienylisoxazolines*. Aerophobin-1 (**113**) and aerophobin-2 (**114**) were isolated from the sponge *Verongia aerophoba* by Cimino *et al*. in 1983 (*69*). Their structures consisted of a spirocyclohexadienylisoxazoline and a histamine or 2-amino-homohistamine and were determined by NMR spectroscopy and hydrolysis.

A methylation derivative of aerophoin-2, *N*-methyl-aerophobin-2 (**115**), was isolated from a Caribbean sponge specimen of *Aiolochroia crassa* (*87*).

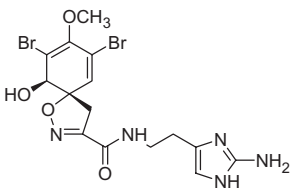


aerophobin-1 (**113**)

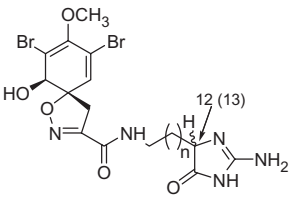


aerophobin-2 (**114**): R=H
N-methyl-aerophobin-2 (**115**): R=Me

Purealidins J (**116**) and K (**117**) were isolated from the Okinawan sponge *Psammaplysilla purea* by Kobayashi *et al*. (*79*). The absolute stereochemistry of the spirocyclohexadienylisoxazoline was determined by the positive Cotton effects at 248 and 184 nm in the CD spectra. Purealidin K was subjected to ozonolysis, followed by oxidation with $H_2O_2$, and subsequently acid hydrolysis. Chiral HPLC analysis of the hydrolysate revealed D- and L-2,4-diaminobutyric acids in the ratio of 1:1, suggesting that C-12 of purealidin K is racemic. A similar alkaloid, 14-oxo-aerophobin-2 (**118**), was identified from the Caribbean sponge *Aplysina insularis* (*88*). The stereochemistry of C-13 was not determined.

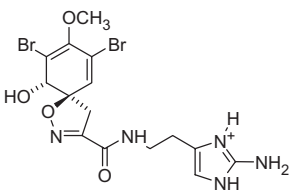


purealidin J (**116**)

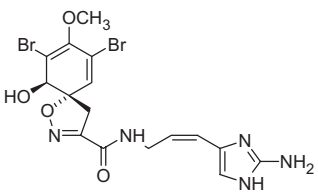


purealidin K (**117**): n=1
14-oxo-aerophobin-2 (**118**): n=2

The enantiomer of purealidin J, pseudoceratinine A (**119**), was reported one year later from *Pseudoceratina verrucosa* (*89*). Pseudoceratinine A showed a negative optical rotation and Cotton effects near 250 and 290 nm, which is opposite to that of aerothionin (**68**), whose absolute stereochemistry was determined by X-ray and CD spectra (*60*). Aplysinamisine I (**120**), which can be considered as a 11,12-dehydro product of aerophobin-2 (**114**), was isolated from the Caribbean sponge *Aplysina cauliformis* (*83*).



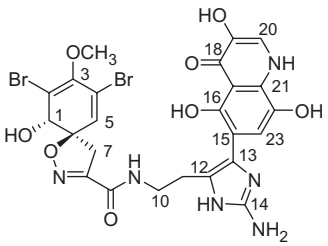
pseudoceratinine A (**119**)



aplysinamisin I (**120**)

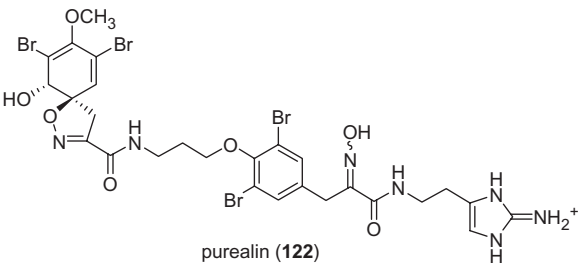
Alkaloid **121** was isolated from an Australian, non-verongid sponge *Oceanapia* sp. by Bewley's group in 2001 (*90*). Its structure was elucidated as an unprecedented imidazolyl-quinolinone substructure attached to a spirocyclohexadienylisoxazoline by 1D and 2D NMR, and its absolute configuration was determined to be 1-(*S*), 6-(*R*)

by comparison of its specific rotation and CD spectrum with those of pseudoceratinine A (**119**) and purealidin J (**116**). Bromotyrosine-derived metabolites were initially limited exclusively to sponges of the order Verongida. While a voucher specimen corresponding to the sponge from which **121** was obtained was re-identified as *Oceanapia* sp., it remains possible that a sample of a verongid sponge was present in the actual collection. Alkaloid **121** was the first example of a natural product that inhibits an enzyme central to a mycothiol-dependent detoxification pathway found in mycobacteria.

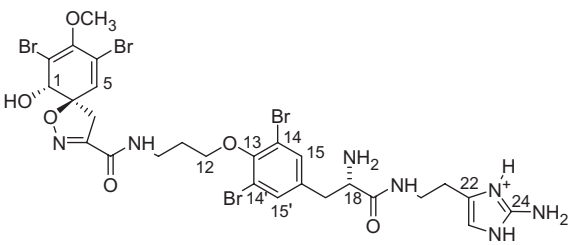


**121**

Purealin (**122**) and pseudoceratinine C (**123**) are two spirocyclohexadienylisoxazoline derivatives containing both bromotyrosine and 2-amino-histamine in the side chain. Purealin (**122**) was first isolated from *Psammaplysilla purea* by Nakamura *et al.* in 1985 (*91*). Both alkaloids were reported from *Pseudoceratina verrucosa* by Benharref and Païs in 1996 (*89*). The absolute configurations of 1-(*S*) and 6-(*R*) of both compounds were deduced by the negative specific rotation and the Cotton effects near 250 and 290 nm. The 18-(*S*) configuration of pseudoceratinine C (**123**) was also determined by a positive Cotton effect at 215 nm, corresponding to the *S*-configuration of the tyrosine residue (*89*).

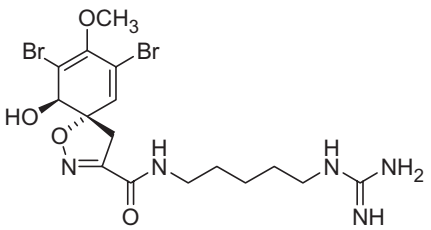


purealin (**122**)

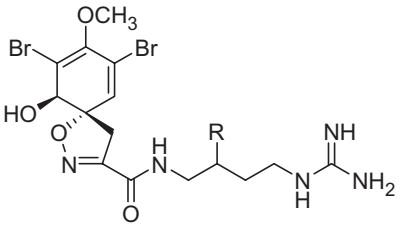


pseudoceratinine C (**123**)

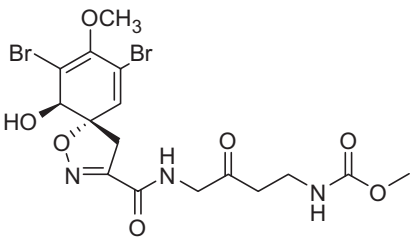
*d. Linear Side Chain Mono-spirocyclohexadienylisoxazolines*. Alkaloids in this class include aplysinamisin II (**124**) from the Caribbean sponge *Aplysina cauliformis* (*83*), purealidin L (**125**) from *Psammaplysilla purea* (*79*), caissarine A (**126**) from *Aplysina caissara* (*66*), and **127** and **128** from *Aplysina cauliformis* collected in the Bahamas (*92*).



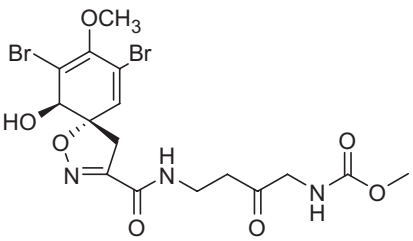
aplysinamisin II (**124**)



purealidin L (**125**): R=H
caissarine A (**126**): R=OH



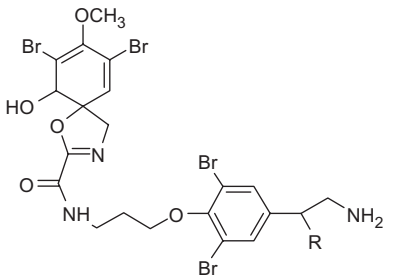
**127**



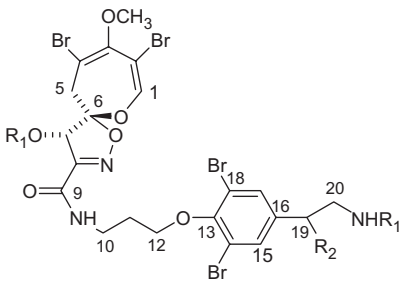
**128**

## C. SPIROOXEPINISOXAZOLINE (OXEPIN) BROMOTYROSINE DERIVATIVES

Prompted by the antibiotic activity of the MeOH extract of *Psammaplysilla purpurea* collected from the southern part of the Gulf of Eilat (off the Red Sea), two spirooxepinisoxazoline type dibromotyrosine derivatives, psammaplysins A and B were first isolated by Kashman's group from *P. purpurea* in 1982 (*93*). The freeze-dried sponge was extracted with methanol and the extract was chromatographed on a Sephadex LH-20 column eluted with $CHCl_3$–MeOH 1:1 to yield psammaplysin A and a mixture of psammaplysin A and B. After acetylation, psammaplysins A and B were separated by silica gel column chromatography and eluted with 2% and 6% EtOH in $CHCl_3$. The structures were proposed as having a spiro[4.5]oxazadecane skeleton (**129a** and **130a)** based mainly on the $^1H$ and $^{13}C$ NMR spectra data and the alkaline degradation of psammaplysin A, which is different from that of aerothionin (*58*). In 1985, Scheuer's group isolated psammaplysins A and B from the sponge *P. purpurea* collected in Palau and revised the structures of spiro[4.5]oxazadecane skeleton to a spiro[4.6]dioxazundecane (**129**) on the basis of two-dimensional $^{13}C$–$^{13}C$ connectivity and single-crystal X-ray diffraction studies on psammaplysin A acetamide acetate (**129b**) (*94*).

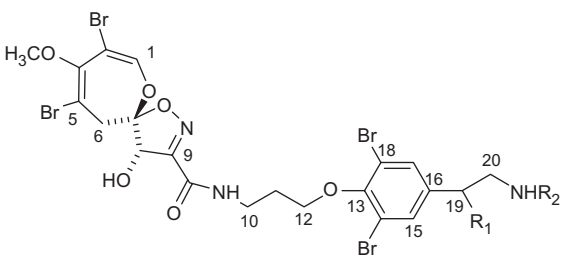


**129a**: R=H
**130a**: R=OH

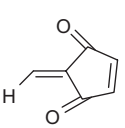


psammaplysin A (**129**): $R_1$=H $R_2$=H
(**129b**): $R_1$=Ac $R_2$=H
psammaplysin B (**130**): $R_1$=H $R_2$=OH
(**130b**): $R_1$=Ac $R_2$=OAc

Psammaplysin C (**131**) was isolated from *P. purpurea* collected off Makaluva Island in Fiji in 1992, it exhibited *in vitro* cytotoxicity towards the human colon tumor cell-line HCT 116 with an $IC_{50}$ of 3 μg/mL (*95*). Psammaplysin D (**132**) and E (**133**) were identified from a new species of *Aplysinella* (order Verongida) collected from Pingelap Atoll, Micronesia in 1993 (*96*). Psammaplysin D is the isopentadecanoyl of psammaplysin B, while psammaplysin E has an unprecedented cyclopentenedione, which was not previously encountered in compounds from natural sources. Psammaplysin D displays anti-HIV activity against the Haitian RF strain of HIV-I with a 51% inhibition at 0.1 μg/mL. Psammaplysin E exhibits cytotoxicity against KB and LOVO cells at 5 μg/mL. Psammaplysin F (**134**) was isolated from an undescribed species of *Aplysinella* sponge, collected from Chuuk, Micronesia (*97*). Ceratinamides A (**135**) and B (**136**) were isolated from *P. purpurea* collected from Hachijo-jima in 1996 and were found to exhibit antifouling activity with $EC_{50}$ values of 0.10 and 2.4 μg/mL (*98*).



psammaplysin C (**131**): $R_1$=OH $R_2$=Me
psammaplysin D (**132**): $R_1$=OH $R_2$=$CO(CH_2)_{11}CHMe_2$

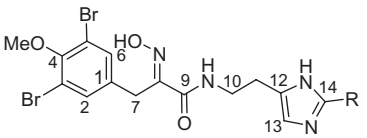
psammaplysin E (**133**): $R_1$=H $R_2$= 

psammaplysin F (**134**): $R_1$=H $R_2$=Me
ceratinamide A (**135**): $R_1$=H $R_2$=CHO
ceratinamide B (**136**): $R_1$=H $R_2$=$CO(CH_2)_{11}CHMe_2$

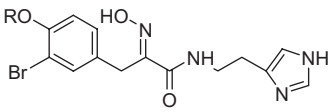
## D. OXIMES

### *1. Oxime-histamines*

Ianthellin (**137**) was isolated from the sponge *Ianthella ardis*, collected in the Bahamas, and was determined to be the major antibiotic and antifungal component (*99*). 5-Bromoverongamine (**138**), a novel antifouling tyrosine alkaloid has been isolated from the Caribbean sponge *Pseudoceratina* sp. (*100*). Verongamine (**139**), a specific histamine-H3 antagonist at concentrations as low as 1.0 μg/mL, was isolated from *Verongula gigantea* (*101*). Alkaloid **140** was isolated from the Caribbean sponge *Pseudoceratina crassa* (*33*).

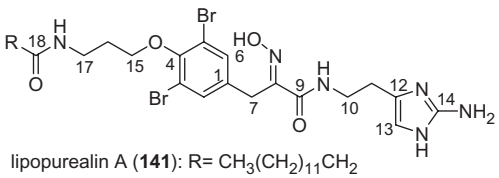


ianthellin (**137**): R=$NH_2$
5-bromoverongamine (**138**): R=H



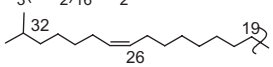
verongamine (**139**): R=$CH_3$
**140**: R=H

Lipopurealins A (**141**), B (**142**), and C (**143**) are unique metabolites with a long alkyl chain, isolated from the marine sponge *Psammaplysilla purea* by Kobayashi's group in 1986 (*102*). Lipopurealins are inhibitors of Na,K-ATPase, and lipopurealin B is most active. Two additional lipopurealins, lipopurealins D (**144**) and E (**145**) were isolated from the same sponge in 1995 (*103*).

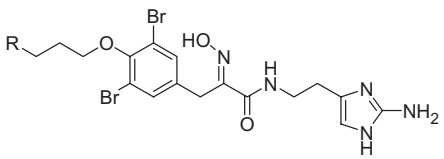


lipopurealin A (**141**): R= $CH_3(CH_2)_{11}CH_2$
lipopurealin B (**142**): R= $Me_2CH(CH_2)_{10}CH_2$
lipopurealin C (**143**): R= $CH_3(CH_2)_{13}CH_2$
lipopurealin E (**145**): R= $CH_3(CH_2)_{16}CH_2$

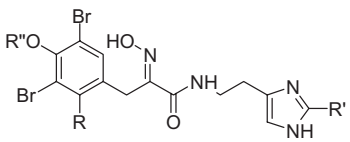
lipopurealin D (**144**): R=



Additional oxime bromotyrosine derivatives containing a histamine group were reported by Kobayashi's group from *Psammaplysilla purea*, including purealidins A (**146**), D (**147**), H (**148**), M (**149**), and N (**150**) (*79,103-105*). The *E*-geometries of the oxime in lipopurealins A (**141**), B (**142**), C (**143**), purealidins A (**146**), and D (**147**) were assigned based on the chemical shifts of C-7 around $\delta$ 28 ppm, which were not assigned in the original literature.

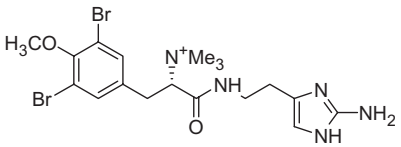


purealindin A (**146**): R= $NH_2$
purealindin D (**147**): R= 1-pyridine



purealidin H (**148**): R=H R'=$NH_2$ R"=H
purealidin M (**149**): R=OH R'=$NH_2$ R"=$CH_3$
purealidin N (**150**): R=OH R'=H R"=$CH_3$

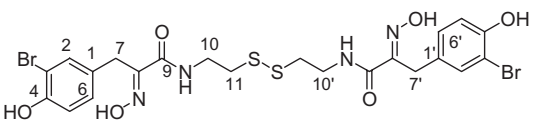
Pseudoceratinine B (**151**), in which the oxime is reduced and tri-methylated, was isolated from *Pseudoceratina verrucosa* (*89*). The absolute configuration of tyrosine was deduced from the positive Cotton effect at 212 nm, corresponding to an *S*-configuration (*106*). Pseudoceratinine B (**151**) is the second bromotyrosine alkaloid containing a non-oxidized amino group.



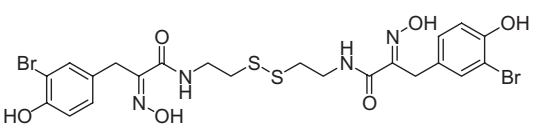
pseudoceratinine B (**151**)

*2. Oxime-Disulfides*

Alkaloids **152** and **153** were the first bromotyrosine derivatives characterized containing a disulfide moiety, and were isolated from an unidentified Verongida sponge by Arabshahi and Schmitz in 1987 (*107*). Almost at the same time, Quinoa and Crews reported the isolation of **152** from a marine sponge *Psammaplysilla* sp. collected from Tonga and gave the compound a trivial name of psammaplin A (*108*). The geometry of the oxime was determined by the carbon chemical shift of the methylene group (C-7) $\alpha$ to the oxime. The chemical shift of C-7 is about 28 ppm for an *E*-geometry and 35 ppm for a *Z*-geometry (*107*).

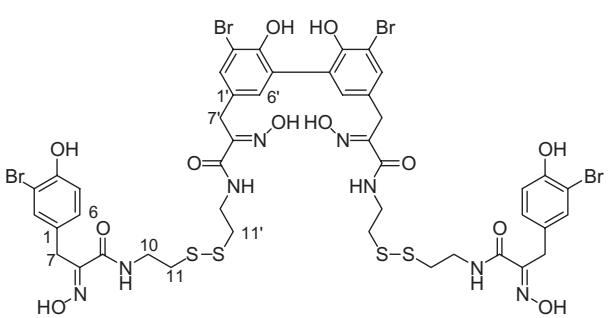


(*E*,*E*)-psammaplin A (**152**)



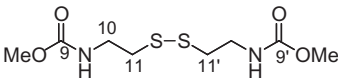
(*E*,*Z*)-psammaplin A (**153**)

Scheuer *et al*. later reported the psammaplin A (**152**) and the psammaplin A dimer, bisaprasin (**154**), from the Guam sponge *Thorectopsamma xana* (*109*).

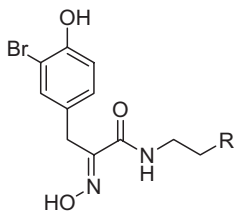


bisaprasin (**154**)

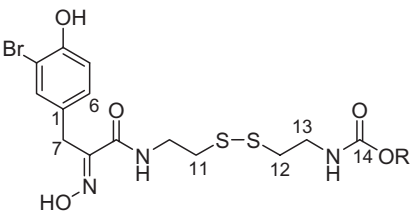
Prepsammaplin A (**155**) and psammaplins B (**156**), C (**157**), and D (**158**) were isolated from the marine sponge *Psammaplysilla purpurea* by Jimenez and Crews (*110*). The isolation of prepsammaplin A (**155**), a cysteine dimer, indicated that cysteine might be the precursor of the central part of psammaplin A. Interestingly, the R functional groups of psammaplin B (**156**) and C (**157**) are unique and do not appear to have counterparts among any known marine sponge amino acid derivatives (*110*). Additionally, the only precedent of the thiocyanate group, as found in psammaplin B (**156**), is the sesquiterpene thiocyanate isolated from the sponge *Trachyopsis aplysinoides* (*111*).



prepsammaplin A (**155**)

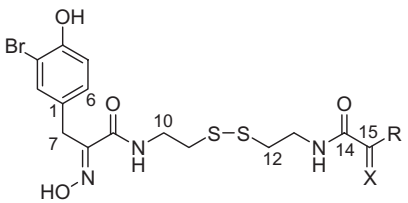


psammaplin B (**156**): R=-SCN
psammaplin C (**157**): R=-$SO_2NH_2$
psammaplin I (**163**): R=-$SO_2CH_3$

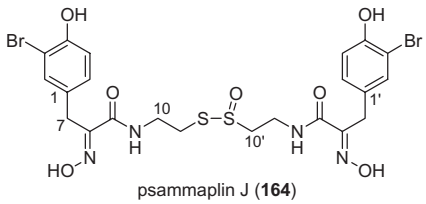


psammaplin D (**158**): R=$CH_3$
psammaplin H (**162**): R=$CH_2CH_3$

Additional disulfide bromotyrosine derivatives, psammaplin E (**159**), F (**160**), G (**161**), H (**162**), I (**163**), and J (**164**) were isolated from the sponge *Psammaplysilla purpurea* collected from Papua New Guinea by Crews' group in 2003 (*112*). Psammaplin D (**158**) and H (**162**) possess a methyl or ethyl carbamate moiety, respectively. The unprecedented functional groups in psammaplin E (**159**), F (**160**), G (**161**), and J (**164**) were identified by detailed spectroscopic analysis. The *N*-substituted oxalamide functionality of psammaplin E (**159**) is rare among marine natural products. The only known marine natural products that possess an oxalamide functional group are igzamide, isolated from the marine sponge *Plocamissa igzo* (*113*), and 3-bromotyramine amide, isolated from *Ianthella basta* (*41*). Psammaplin F (**160**) is the first marine natural product containing an oxalamic functionality. The functionality in psammaplin G (**161**) has no precedent in the natural products literature. Psammaplin A (**152**), F (**160**), and bisaprasin (**154**) are potent histone deacetylase inhibitors with mild cytotoxicity. Psammaplin A (**152**), G (**161**), and bisaprasin (**154**) are potent DNA methyltransferase inhibitors.

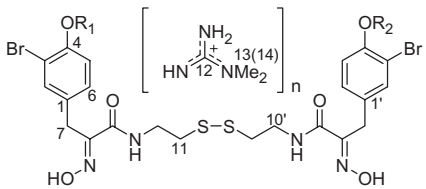


psammaplin E (**159**): R=$NH_2$ X=O
psammaplin F (**160**): R=OH X=O
psammaplin G (**161**): R=OH X=N-$NH_2$

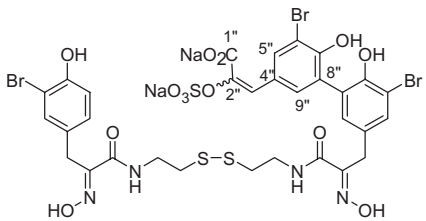


psammaplin J (**164**)

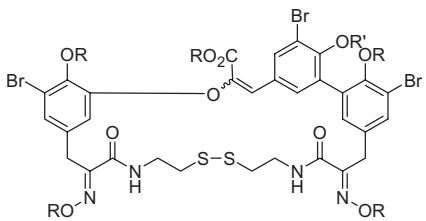
Shin and Paul reported four new psammaplin A analogs, psammaplins $A_1$ (**165**), $A_2$ (**166**), aplysinellin A (**167**), and B (**168**), from the marine sponge *Aplysinella rhax* collected from Guam, Palau, and Pohnpei Micronesia (*114*). Psammaplins $A_1$ (**165**) and $A_2$ (**166**) are mono- or bis-*N*,*N*-dimethylguanidinium salts of psammaplin A (**152**) mono- or dualsulfate. Organic sulfates with *N*,*N*-dimethylguanidinium as counter ions are very rare among sponge metabolites. Suvanine and sulfircin, both sesterterpenoid sulfates from the sponge *Ircinia* sp., are two examples (*115,116*). Aplysinellin A (**167**) possesses a bromotyrosine-derived $C_9$-unit of the cinnamic acid type attached to psammaplin A by a biphenyl linkage, while aplysinellin B (**168**) is the corresponding cyclic enol ether. Treatment of aplysinellin B (**168**) afforded compound **168a**. Alkaloids **165**–**168** exhibited inhibitory activity against the growth of the K562 cell-line and against farnesyl protein transferase.



psammaplin $A_1$ (**165**): $R_1$= H $R_2$=$SO_3^-$ n=1
psammaplin $A_2$ (**166**): $R_1$= $R_2$=$SO_3^-$ n=2

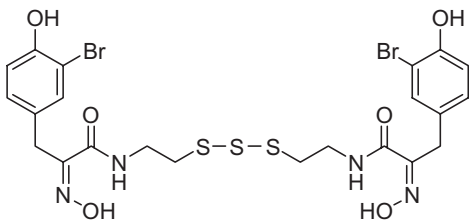


aplysinellin A (**167**)

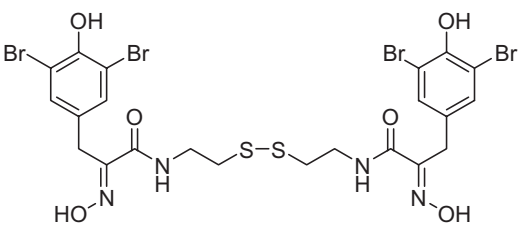


aplysinellin B (**168**): R=H R'=$SO_3Na$
**168a**: R=$CH_3$ R'=H

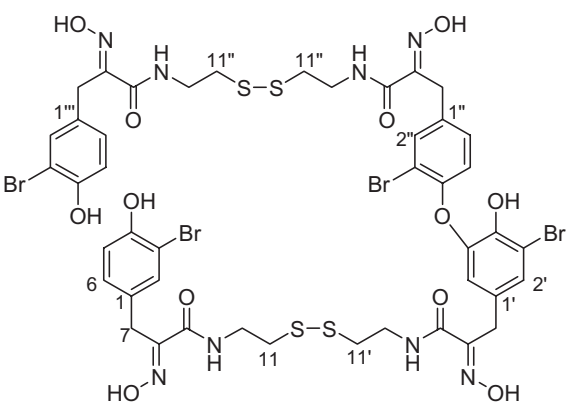
Jung's group reported the isolation of three new psammaplin analogs, **169**, (*E*,*E*)-bromopsammaplin A (**170**), and bispsammaplin A (**171**), along with the known alkaloids (*E*,*E*)-psammaplin A (**152**), (*E*,*Z*)-psammaplin A (**153**), psammaplin D (**158**), and bisaprasin (**154**), from an association of two sponges, *Jaspis wondoensis* and *Poecillastra wondoensis* collected from Korea (*117*). Alkaloid **169** is the only bromotyrosine derivative containing a trisulfide moiety. This is the second report of bromotyrosine derivatives isolated from sponges not belonging to the order Verongida. The first example described the isolation of three bromotyrosine derivatives from a non-verongid sponge *Oceanapia* sp., but it remains possible that a sample of verongid sponge was present in the actual sample analyzed (*90*).



**169**



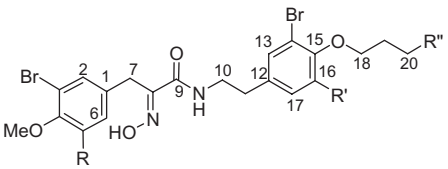
bromopsammaplin A (**170**)



bispsammaplin A (**171**)

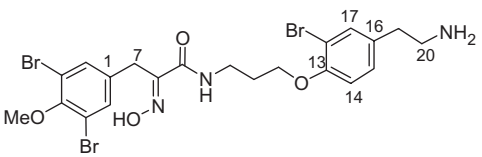
*3. Oxime-Bromotyramines*

Xynas and Capon reported aplysamine 2 (**172**) from an Australian marine sponge *Aplysina* sp. in 1989 (*44*). Aplysamines 3 (**173**), 4 (**174**), and 5 (**175**) were isolated from the Hawaiian sponge *Psammaplysilla purpurea* by Scheuer's group (*118*). All of these alkaloids exhibited cytotoxic activity, while aplysamine 3 and 4 showed mild antibacterial activity against *Staphylococcus aureus*. Alkaloids **176** and **177** were isolated from the sponge *P. purpurea* collected in Okinawa by an Indian group (*119,120*).



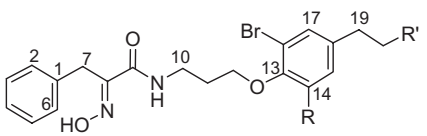
aplysamine 2 (**172**): R=H R'=Br R"=$NHMe_2^+$
aplysamine 3 (**173**): R=H R'=Br R"=$NH_3^+$
aplysamine 4 (**174**): R=Br R'=Br R"=$NH_3^+$
aplysamine 5 (**175**): R=H R'=Br R"= $NHCO(CH_2)_{11}CH(CH_3)_2$
**176**: R=R'=H R"=$NH_2$
**177**: R=Br R'=H R"=$NH_2$

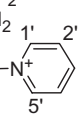
Alkaloid **178** was isolated from *P. purpurea* collected in the Seychelles by Faulkner's group (*82*). Since it is the presumed biogenetic precursor of 14-debromoaraplysillin-I (**101**), the name 14-debromoprearaplysillin I was given. The isolation of spiroisoxazoline **101** and the oxime **178** from the same sponge was the first reported instance in which a spiroisoxazoline has been isolated together with its proposed precursor.

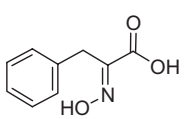


14-debromoprearaplysillin I (**178**)

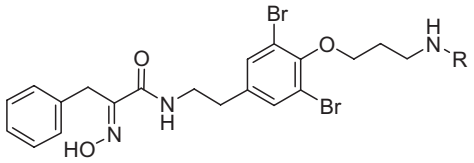
Fusetani *et al.* reported nine new bromotyrosine-derived metabolites, purpuramines A-I (**179**–**187**), from *P. purpurea* (*121*). The carboxylic acid oxime units present in the bromotyrosine-derived metabolites were exclusively derived from bromotyrosines, while the oxime function in purpuramines A-I (**179**–**183**) is part of a phenylalanine moiety, which is a new variant among verongid metabolites. Phenylpyruvic acid oxime (**188**), which is a building block for **179**–**183**, was also isolated from the sponge.



purpuramine A (**179**): R=Br R'=$NH_2$
purpuramine B (**180**): R=H R'=$NH_2$
purpuramine C (**181**): R=Br R'= 

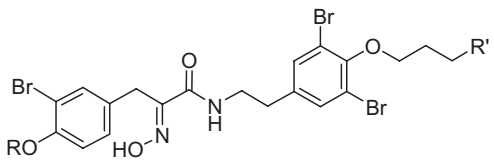


phenylpyruvic acid oxime (**188**)



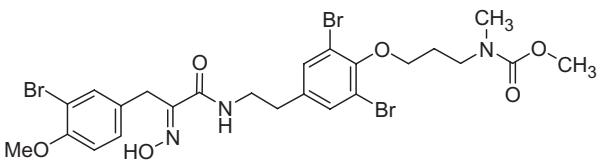
purpuramine D (**182**): R=H
purpuramine E (**183**): R=$CH_3$

Purpuramines A-I (**179**–**187**) exhibited antibacterial activity against *Staphylococcus aureus*, but phenylpyruvic acid oxime (**188**) was not active. Purpuramine J (**189**) was isolated from the Fijian sponge *Psammaplysilla* (*Druinella*) sp., along with purpuramine I (**187**), aplysamine 2 (**172**), and eight other bromotyrosine derivatives (*86*). Purpuramine J (**189**) is the first bromotyrosine derivative containing an *N*-oxide functionality, which is considered rare in marine natural products.

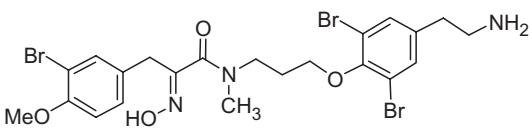


purpuramine F (**184**): R=H R'=$NH_2$
purpuramine G (**185**): R=H R'=$NHCH_3$
purpuramine H (**186**): R=$CH_3$ R'=$NH_2$
purpuramine I (**187**): R=$CH_3$ R'=$NHCH_3$
purpuramine J (**189**): R=$CH_3$ R'=$N^+Me2O^-$

Purpuramines K (**190**) and L (**191**), isolated from the Indian sponge *Psammaplysilla purpurea*, exhibited antimicrobial activity against both Gram positive and Gram negative bacteria (*122*).



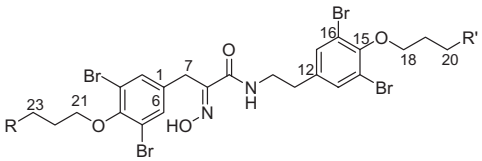
purpuramine K (**190**)



purpuramine L (**191**)

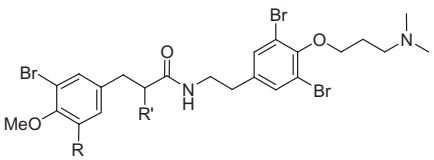
Purealidin C (**192**) was isolated from the Okinawan sponge *P. purea*, which exhibited cytotoxic, antifungal, and antimicrobial activities (*84*). Tokaradines A (**193**) and B (**194**), isolated from *Pseudoceratina purpurea*, are rare examples of marine bromotyrosine-derived metabolites containing an *N*-substituted pyridinium group.

Another example is purpureamine C (**181**) (*123*). Tokaradines A (**193**) and B (**194**) were seen to be lethal to the crab *Hemigrapsus sanguineus* (*123*).



purealidin C (**192**): R=R'=$NH_2$
tokaradine A (**193**): R=$NH_2$ R'=
tokaradine B (**194**): R'=$NH_2$ R=

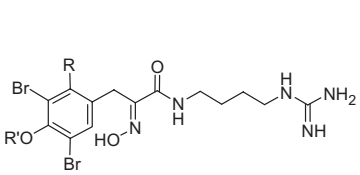
Anomoian A (**195**) was isolated from an Australian sponge *Anomoianthella popeae*, belonging to a new genus of the family Ianthellidae (*124*). Anomoian A is the first bromotyrosine-derived metabolite with a non-oxidized amino group and exhibited strong antimicrobial activity. Aplyzanzine A (**196**) was isolated from the sponge *Aplysina* sp. collected from Zanzibar (*125*). The stereochemistry at C-8 was not determined. Suberedamines A (**197**) and B (**198**) were isolated from an undescribed sponge of the genus *Suberea* (*126*). The absolute configurations at C-8 of both alkaloids were assigned as *S* by chiral HPLC analysis of the hydrobromic acid hydrolysate of each compound. Both suberedamines A (**197**) and B (**198**) exhibited moderate cytotoxic and antibacterial activity.



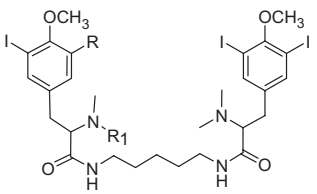
anomoian A (**195**): R=Br R'=NHMe
aplyzanzine A (**196**): R=Br R'=$NMe_2$
suberedamine A (**197**): R=H R'=α-$NH_2$
suberedamine B (**198**): R=H R'=α-NHMe

*4. Other Oxime Structures*

Compound **199** and purealidin O (**200**) are two oxime-type bromotyrosine-derived metabolites containing an agmatine moiety, isolated from *Psammaplysilla purea* and *Oceanapia* sp., respectively (*79,90*). Alkaloids **201**, **202**, and **203** were iodinated tyrosine derivatives isolated from the ascidian *Aplidium* sp. (*127*).



**199**: R=H R'=$CH_2CH_2CH_2NH_2$
purealidin O (**200**): R=OH R'=$CH_3$

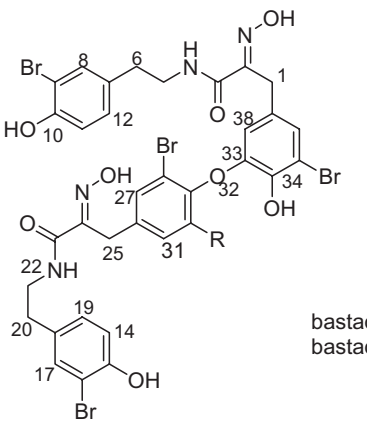


**201**: R=H $R_1$=Me
**202**: R=I $R_1$=Me
**203**: R=H $R_1$=H

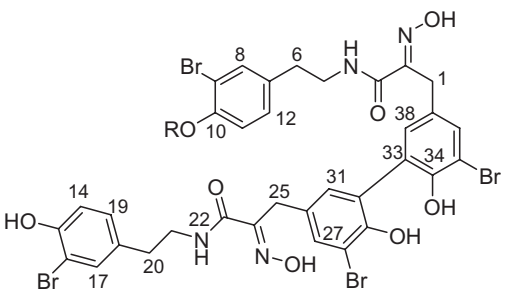
## E. BASTADINS

### *1. Bastadins*

The bastadins are a series of predominantly macrocyclic sponge metabolites, which are biogenetically derivable from four bromotyrosines by oxidative phenolic coupling of two tyramine–tyrosine units connected through an amide bond. To date, there are 24 bastadins isolated from marine sponges. The pioneering studies of Wells and colleagues in the late 1970s led to the isolation and identification of bastadins 1–7 from *Ianthella basta* collected from Queensland, Australia (*128,129*). Bastadins-1 (**204**), 2 (**205**), and 3 (**206**), and 10-*O*-sulfatobastadin-3 (**227**) (*130*), are the only known acyclic bastadins. Bastadin-3 (**206**) and its sulfate (**227**) (*130*) both have a biaryl bond connecting two tyramine–tyrosine units, other than the ether bridge present in the remaining bastadins (*129*).

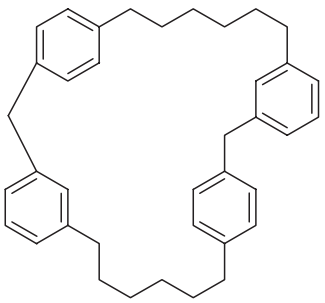



bastadin-1 (**204**): R=H
bastadin-2 (**205**): R=Br

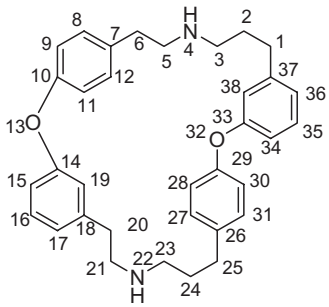



bastadin-3 (**206**): R=H
10-*O*-sulfatobastadin-3 (**227**): R=$SO_3Na$

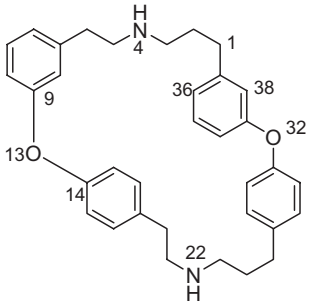
The remaining 20 bastadins possess a macrocyclic system, which was given a name bastarane and numbered as shown (*129*). According to the oxidative cyclization, there are two structural classes, i.e. 13,23-dioxa-4,22-diazabastarane and 13,32-dioxa-4,22-diazaisobastarane (*131*).



bastarane

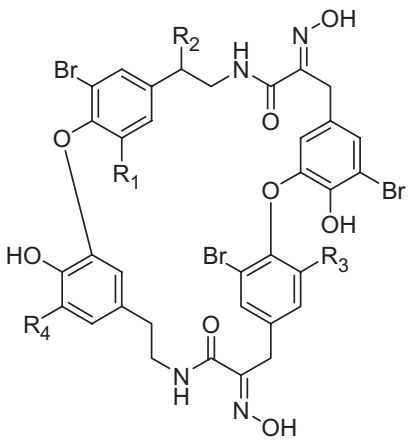


13,32-dioxa-4,22-diazabastarane

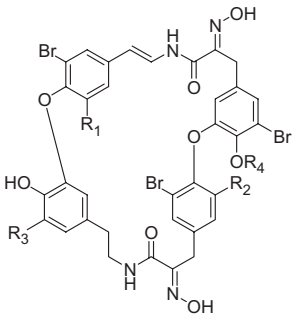


13,32-dioxa-4,22-diazaisobastarane

Most of the bastadins are of the 13,23-dioxa-4,22-diazabastarane type, including bastadins-4 (**208**), -5 (**209**), -6 (**210**), -7 (**211**) (*129*), -8 (**212**), -9 (**213**), -10 (**214**), -11 (**215**) (*132*), -12 (**216**), -14 (**218**) (*133*), -15 (**219**) (*134*), -16 (**220**), -17 (**221**) (*135–137*), -18 (**222**) (*138*), and 15,34-*O*-disulfatobstadin-7 (**228**) (*130*).

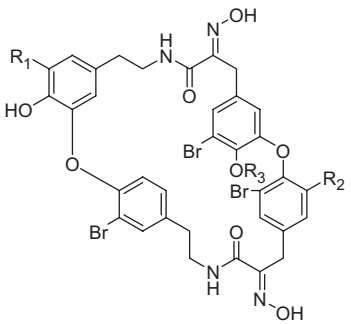


bastadin-5 (**209**): $R_1$=H $R_2$=H $R_3$=Br $R_4$=Br
bastadin-6 (**210**): $R_1$=Br $R_2$=H $R_3$=Br $R_4$=Br
bastadin-8 (**212**): $R_1$=H $R_2$=OH $R_3$=Br $R_4$=Br
bastadin-9 (**213**): $R_1$=H $R_2$=H $R_3$=Br $R_4$=H
bastadin-10 (**214**): $R_1$=H $R_2$=OH $R_3$=H $R_4$=Br
bastadin-12 (**216**): $R_1$=H $R_2$=OH $R_3$=Br $R_4$=Br
bastadin-15 (**219**): $R_1$=Br $R_2$=H $R_3$=H $R_4$=Br
bastadin-16 (**220**): $R_1$=Br $R_2$=H $R_3$=Br $R_4$=H
bastadin-17 (**221**): $R_1$=H $R_2$=OH $R_3$=Br $R_4$=H
bastadin-18 (**222**): $R_1$=H $R_2$=H $R_3$=H $R_4$=Br



bastadin-4 (**208**):$R_1$=H $R_2$=$R_3$=Br $R_4$=H
bastadin-7 (**211**): $R_1$=H $R_2$=H $R_3$=Br $R_4$=H
bastadin-11 (**215**): $R_1$=$R_2$=$R_3$=$R_4$=H
bastadin-14 (**218**): $R_1$=Br $R_2$=H $R_3$=Br $R_4$=H
15,34-*O*-disulfatobastadin-7 (**228**): $R_1$=$R_2$=H $R_3$=Br $R_4$=$SO_3Na$

Five bastadins contain the 13,32-dioxa-4,22-diazaisobastarane ring pattern, including bastadins-13 (**217**) (*131*), -19 (**223**) (*139*), -21 (**225**) (*140*), and 34-*O*-sulfatobastadin-13 (**226**) (*141*).



bastadin-13 (**217**): $R_1$=H $R_2$=Br $R_3$=H
bastadin-19 (**223**): $R_1$=Br $R_2$=Br $R_3$=H
bastadin-20 (**224**): $R_1$=Br $R_2$=$R_3$=H
bastadin-21 (**225**): $R_1$=$R_2$=$R_3$=H
34-*O*-sulfatobastadin-13 (**226**): $R_1$=H $R_2$=Br $R_3$=$SO_3Na$

The majority of the bastadins were isolated from the marine sponge *Ianthella basta* (class Demospongiae, order Verongida, family Inthellidae) with several obtained from *I. flabelliformis*, *I. quadrangulata*, *Ianthella* sp., and *Psammaplysilla purpurea*. Bastadins 1–7 (**204**–**211**) were isolated from the Australian sponge *I. basta*, as antimicrobial agents against Gram positive organisms in 1980 (*128,129*). Their structures were determined by spectroscopic methods and alcoholic KOH hydrolysis. X-ray diffraction analyses were performed on a single crystal of bastadin-4 (**208**) and bastadin-5 permethylate. The X-ray structure showed that the conformations of bastadin-4 and bastadin-5 permethylate are considerably different. The macrocyclic ring of bastadin-5 permethylate appears to be open, whereas the ring of bastadin-4 is more elongated.

The studies of bastadins 8–13 were published simultaneously, unfortunately leading to the assignment of the same number to different bastadins. Scheuer *et al.* suggested that these alkaloids be renamed in the order of when they were received for publication. Thus, bastadins-8 to -11 of Pordesimo and Schmitz (*132*) retained their original numbering, bastadin-9 of Miao *et al.* (*142*) was renumbered as bastadin-12 (bastadin-8 from Miao *et al.* coincidentally has the same structure as bastadin-8 of Pordesimo and Schmitz), and bastadin-12 of Butler *et al.* (*131*) became bastadin-13.

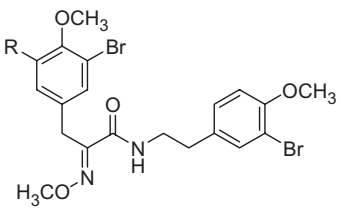
Bastadins-8 to -11 (**212**–**215**) were isolated from the sponge *I. basta* collected in Guam by Pordesimo and Schmitz in 1990 (*132*). Bastadin-4 (**208**), -8 (**212**), and -9 (**213**) exhibited cytotoxic and anti-inflammatory activities. Bastadins-8 and -12 were isolated from the Papua New Guinean sponge *I. basta* by Miao *et al*. (*142*).

The structure of bastadin-13 (**217**) was elucidated as a novel alternative oxidative cyclization of bastarane, which was proposed for nomenclature purposes as 13,32-dioxa-4,22-diazaisobastarane, based on detailed spectroscopic analyses and derivatization (*131*). The co-occurrence of bastadin-13 and bastadin-9 (**213**) in a single specimen of *I. basta* collected from Australia introduced another dimension to the structure elucidation of the bastadins, therefore it can no longer be assumed on biosynthetic grounds that all cyclic bastadins possess the same 13,32-dioxa-4,22-diazabastarane ring system (*131*). Bastadin-14 (**218**), isolated from *Psammaplysilla purpurea* collected in Pohnpei, Micronesia, is the only bastadin isolated from a sponge that does not belong to the genus *Ianthella*. Bastadin-15 was identified from an undescribed marine sponge of the genus *Ianthella* collected from Australia (*134*). Bastadin-16 (**220**) and -17 (**221**) were isolated from an Indonesian collection of *I. basta* (*135–137*). Bastadin-18, along with bastadins-1, -2, -5, -6, -8, and -10, were isolated from the marine sponge *I. basta* collected in Papua New Guinea (*138*). In addition, a mixture of bastadins-2 and -5 were also isolated from *I. flabelliformis*.

Bastadins-8 and -10 were found to be moderate inhibitors of inosine 5′-phosphate dehydrogenase (*138*). Molinski *et al*. reported bastadins-19 (**223**), -20 (**224**), 15,34-*O*-disulfatobastadin-7 (**228**), and 10-*O*-sulfatobastadin-3 (**227**) from *I. basta*, as novel modulators of the skeletal isoform of the ryanodine-sensitive sarcoplasmic reticulum calcium channel by a novel mechanism involving the FKBP12/RyR-1 complex (*130,139*). Bastadin-21 (**225**) was isolated from an Australian marine sponge *I. quadrangulata* (*140*). Bastadins-6 and -16 were also reported from the Indian sponge *Psammaplysilla purpurea*, along with other bromotyrosine derivatives (*46*). The absolute stereochemistry of the C-6 hydroxyl group in bastadins-8 (**212**), -10 (**214**), and -12 (**216**) were determined as *S* by Pettit *et al*. using the Mosher–Trost method (*143*).

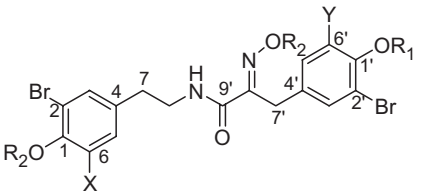
### *2. Hemibastadins*

Two dimers of bromotyrosine, trimethylhemibastadin-1 (**229**) and trimethylhemibastadin-2 (**230**), were isolated as their methyl ethers, along with bastadin-9 and bastadin-12 from the sponge *I. basta* (*131*). Although trimethylhemibastadin-1 (**229**) and trimethylhemibastadin-2 (**230**) were obtained from a methylated fraction, it is not clear whether the natural products themselves were methylated to any extent.

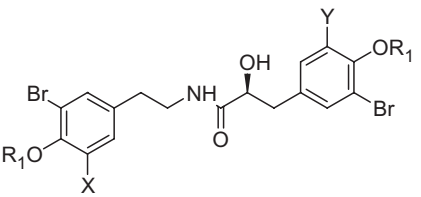



trimethylhemibastadin-1 (**229**): R=H
trimethylhemibastadin-2 (**230**): R=Br

Eight hemibastadins were identified from a scale-up (160 kg wet weight) collection of the sponge *I. basta*, including hemibastadins 1 (**231**), 2 (**232**), and 3 (**233**), hemibastadinols 1 (**234**), 2 (**235**) and 3 (**236**), and 1′-methoxyhemibastadin 1 (**237**) and 2 (**238**) (*41*). Hemibastadin 2 (**232**) and 3 (**233**) were obtained as a mixture (3:1), while hemibastadinol 2 (**235**) and 3 (**236**) were an optically active oily mixture (19:1) that effectively resisted separation. The absolute stereochemistry of hemibastadinols 1 (**234**), 2 (**235**), and 3 (**236**) was determined as *S* using Trost's modification of the Mosher's method (*144*).

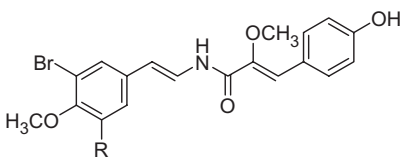



hemibastadin 1 (**231**): X=Y=$R_1$=$R_2$=H
hemibastadin 2 (**232**): X=$R_1$=$R_2$=H Y=Br
hemibastadin 3 (**233**): X=Br Y=$R_1$=$R_2$=H
trimethoxyhemibastadin 3 (**233b**): X=Br Y=H $R_1$=$R_2$=Me
1'-methoxyhemibastadin 1 (**237**): X=Y=$R_2$=H $R_1$=Me
1'-methoxyhemibastadin 2 (**238**): X=$R_1$=$R_2$=H Y=Br

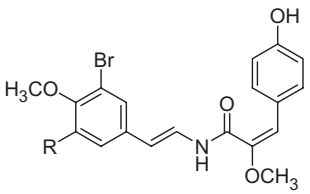



hemibastadinol 1 (**234**): X=Y=$R_1$=H
1,1'-dimethoxyhemibastadinol 1 (**234a**): X=Y=H $R_1$=Me
hemibastadinol 2 (**235**): X=$R_1$=H Y=Br
hemibastadinol 3 (**236**): X=Br Y=$R_1$=H
1,1'-dimethoxyhemibastadinol 2 (**235a**): X=H Y=Br $R_1$=Me
1,1'-dimethoxyhemibastadinol 3 (**236a**): X=Br Y=H $R_1$=Me

Botryllamides A–D (**239–242**), which have similar structures as the hemibastadins, but with two additional double bonds, were isolated from the Philippine ascidian *Botryllus* sp. and the Australian ascidian *Botryllus schlosseri* (*145*).



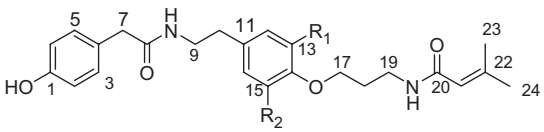

botryllamide A (**239**): R=Br
botryllamide C (**241**): R=H




botryllamide B (**240**): R=Br
botryllamide D (**242**): R=H

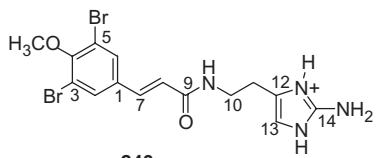
## F. OTHER STRUCTURAL CLASSES

Three novel halogenated metabolites (**243**–**245**) were isolated from the Caribbean sponge *Iotrochota birotulata*, which is taxonomically far removed from the order Verongida (*146*). Bromotyrosine-derived metabolites have been considered to be characteristic of the sponges in the order of Verongida (*147*). *I. birotulata* is the first sponge that elaborates such metabolites which does not belong to the order Verongida. The presence of iodine atoms in alkaloids **244** and **245** is interesting. Iodo-compounds are relatively rare in marine chemistry, and particularly in sponges, even if all known haloperoxidases are effective in oxidizing iodide (*148*). The biosynthesis of iodinated metabolites seems to be related to the ability of the organism to concentrate iodide from sea water, rather than the presence of a specific peroxidase. Most iodo-metabolites have been isolated from red algae, which are known to contain as high as 0.5% of iodine by wet weight. Significant amounts of iodine (0.12–1.21%), together with comparable quantities of bromine (0.16–2.66%), were reported to exist in the spicule tracts of *I. birotulata* (*149*), further supporting the relationship between the presence of iodo-metabolites and high concentrations of iodine in sponge tissues.

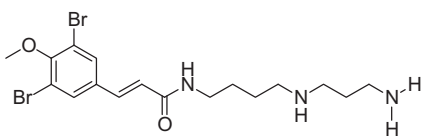


**243**: $R_1$=Br $R_2$=Br
**244**: $R_1$=I $R_2$=Br
**245**: $R_1$=I $R_2$=I

Alkaloid **246** was isolated from the Caribbean sponge *Verongula* sp. (*38*). Tokaradine C (**247**) was isolated from the marine sponge *Pseudoceratina purpurea* as a toxic constituent against the crab *Hemigrapsus sanguineus* (*123*).

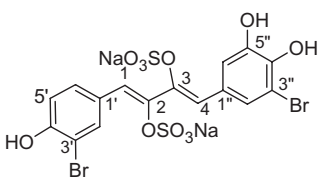


**246**



tokaradine C(**247**)

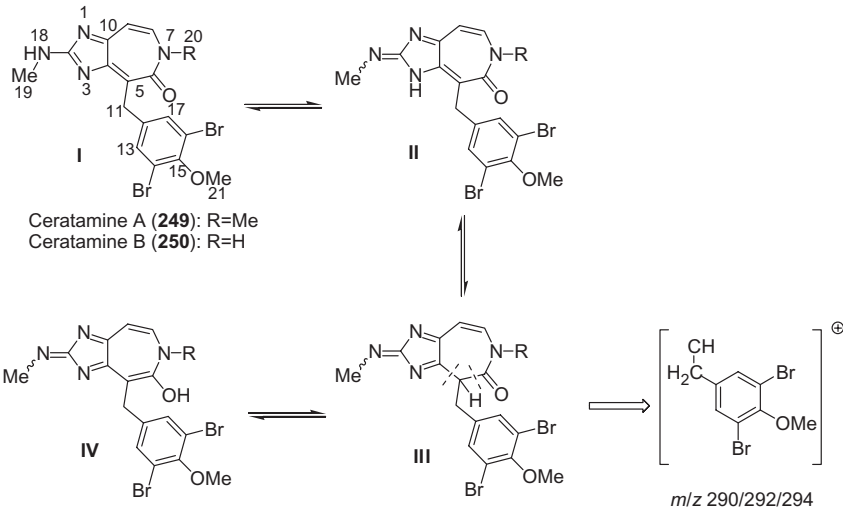
An unusual disulfate ester of a 1,4-diphenyl-1,3-butadiene, aplysillin A (**248**), was isolated from the sponge *Aplysina fistularis fulva*, collected at a depth of 369 feet off Sweetings Cay, Grand Bahama Island (*150*). Aplysillin A weakly inhibited the binding of thrombin to platelet membranes with an $IC_{50}$ value of 20 μM.



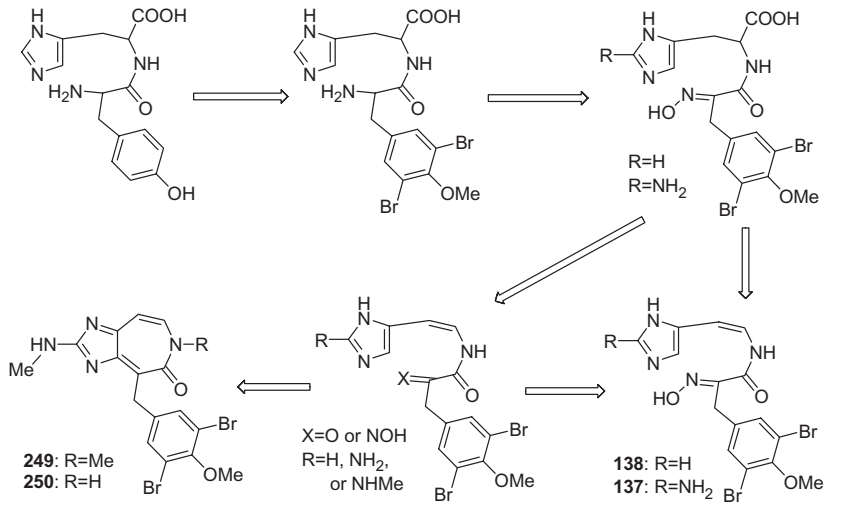
aplysillin A (**248**)

Two novel antimitotic heterocyclic alkaloids, ceratamines A (**249**) and B (**250**), were isolated from the marine sponge *Pseudoceratina* sp. collected in Papua New Guinea

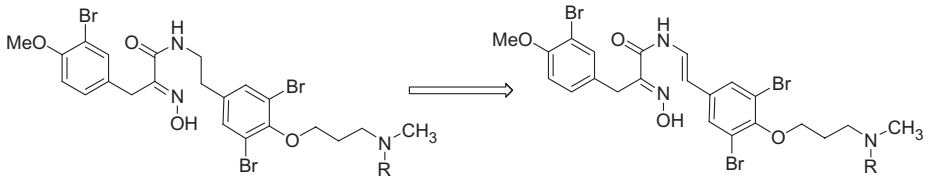
(*151*). Their structures were elucidated by analysis of the spectroscopic data. A number of possible tautomers exist for ceratamine A as shown below. Each of the constitutional isomers **II**, **III**, and **IV** can exist as the *E* and *Z* stereoisomers about the C-2/N-18 imine bond. Both $^{1}H$ and $^{13}C$ NMR spectra showed evidence for two forms. Scalar coupling observed between the Me-19 and NH-18 resonances provided evidence that the major tautomer observed in the $^{1}H$ NMR spectrum was **I**. A significant fragment peak cluster at *m*/*z* 290/292/294 (1:2:1) in the EIMS of ceratamine A could formally arise from tautomer(s) **III** via an $\alpha$ cleavage next to the carbonyl accompanied by cleavage of the bond linking the substituted phenethyl fragment to the imidazole ring carbon as shown (*151*).



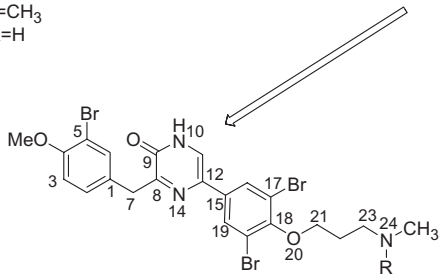

The obvious biogenetic relationship of ceratamines A and B to 5-bromoverogamine (**138**) (*100*), also isolated from a *Pseudoceratina* sp., and ianthelline (**137**) (*99*) supports the proposed structures **249** and **250**. The putative biogenetic precursors to these alkaloids are histidine and tyrosine as shown.



Two new cytotoxic bromotyrosine alkaloids, ma'edamines A (**251**) and B (**252**), with a unique 2(1*H*)pyrazinone ring were isolated from the Okinawan marine sponge *Suberea* sp., along with aplysamine 2 (**172**), purpuramine H (**186**), and purpuramine I (**187**) (*152*). Biogenetically, ma'edamines A (**251**) and B (**252**) may be generated from the 11,12-dehydro form of aplysamine-2 (**172**) and purpuramine I (**187**) through the formation of a six-membered ring and dehydroxylation.

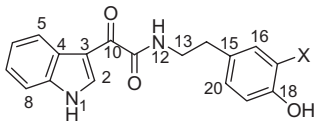


aplysamine 2 (**172**): R=$CH_3$
purpuramine I (**187**): R=H

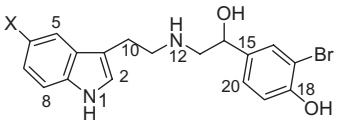


ma'edamine A (**251**): R=$CH_3$
ma'edamine B (**252**): R=H

Polyandrocarpamides A–C (**253**–**255**), which are derived from tryptophan and tyrosine subunits, were isolated from the marine ascidian *Polyandrocarpa* sp. (*153*). Structurally related alkaloids, the chelonins, were reported from the marine sponge *Chelonaplysilla* sp., of which chelonin B (**256**) and 5-bromochelonin B (**257**) contain a bromotyrosine (*154*).

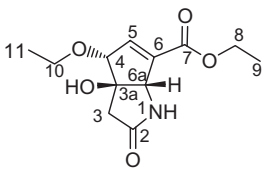


polyandrocarpamide A (**253**): X=Br
polyandrocarpamide B (**254**): X=I
polyandrocarpamide C (**255**): X=H



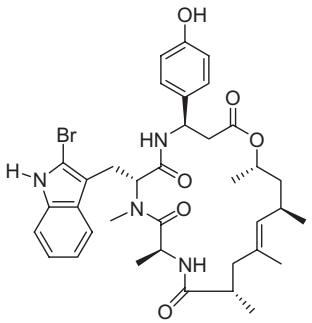
chelonin B (**256**): X=H
bromochelonin B (**257**): X=Br

Examination of the marine sponge *Suberea* aff. *praetensa* (Row) from the Gulf of Thailand furnished, in addition to the known cavernicolins, an unusual rearranged tyrosine metabolite subereatensin (**258**) (*155*).



subereatensin (**258**)

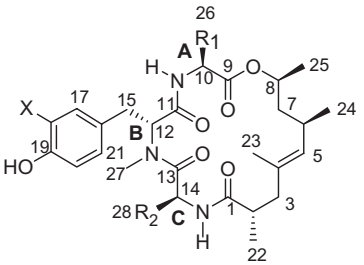
Geodiamolides and jaspamides are closely related cyclic depsipeptides isolated from a variety of tropical marine sponges. Jaspamide (**259**), also named jasplakinolide, obtained independently from *Jaspis* sp. collected in Palau (*156*) and Fiji (*157*), was the first member of this group of depsipeptides to be reported.



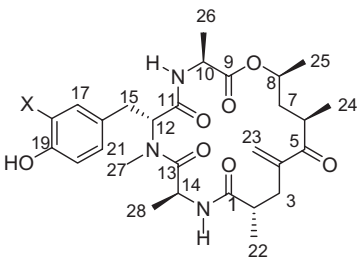

jaspamide (**259**)

Shortly thereafter, geodiamolides A (**260**) and B (**261**) were isolated from the Caribbean sponge *Geodia* sp. (*158*). Subsequently, geodiamolides C–G (**262–265, 266**) were reported from the sponge *Cymbastela (Pseudaxinyssa)* sp. collected in Papua New Guinea (*159,160*); geodiamolides H (**267**) and I (**268**) were reported from a *Geodia* sp. (*161*); geodiamolide TA (**269**) was reported from the South African sponge *Hemiastrella minor* (*162*); neosiphoniamolide A (**270**) was reported from the New Caledonian sponge *Neosiphonia superstes* (*163*); and geodiamolides J–P (**271–277**) and R (**279**) were isolated from a recollection of the sponge *Cymbastela* sp. from Papua New Guinea (*164*). Although no chloro analogue of geodiamolide O (**276**) was isolated, it is likely to exist as a natural product, and therefore Andersen *et al*. reserved the name geodiamolide Q (**278**) for the hypothetical structure in anticipation of its future discovery (*164*).

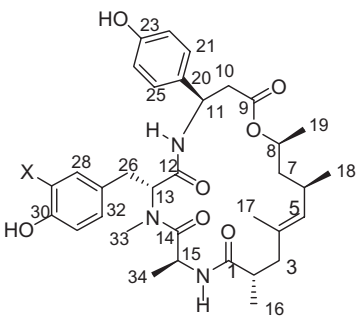
The structures of the geodiamolides were determined by 1D and 2D NMR spectroscopy, and the absolute stereochemistries of geodiamolides A (**260**) and H (**267**) were determined by X-ray crystallography (*158,161*). There are now 19 known members of the geodiamolide family of cyclic depsipeptides. Variations have been observed in all three amino acid positions, as well as the polyketide portion of the molecule. Amino acid A variants include alanine (**260, 261, 262–265, 276, 277**), serine (**273–275, 267**), $\beta$-tyrosine (**267, 268**), and valine (**269, 270**); amino acid B variants include only the C-18 halogen atom, with iodine (**260, 263, 266, 267, 273, 276, 278, 270**), bromine (**261, 264, 268, 271, 274, 277**), and chlorine (**262, 264, 272, 275, 269**) all being observed; amino acid C variants include alanine (**260, 261, 262, 267, 268, 273–275, 269**), glycine (**263–265**), and serine (**276, 277**). The jaspamide/geodiamolide family of metabolites occurs across a taxonomically distant group of sponge species (*156,158–160,162,163*). To account for this observation, it has been suggested that microorganisms associated with the sponges produce these metabolites (*162*). The chondramides, which are jaspamide analogues from cultures of various strains of *Chondromyces myxobacteria* (*165,166*), strongly support the hypothesis of a microbial origin for the jaspamide/geodiamolides.



geodiamolide A (**260**): $R_1$=Me $R_2$=Me X=I
geodiamolide B (**261**): $R_1$=Me $R_2$=Me X=Br
geodiamolide C (**262**): $R_1$=Me $R_2$=Me X=Cl
geodiamolide D (**263**): $R_1$=Me $R_2$=H X=I
geodiamolide E (**264**): $R_1$=Me $R_2$=H X=Br
geodiamolide F (**265**): $R_1$=Me $R_2$=H X=Cl
geodiamolide L (**273**): $R_1$=$CH_2OH$ $R_2$=Me X=I
geodiamolide M (**274**): $R_1$=$CH_2OH$ $R_2$=Me X=Br
geodiamolide N (**275**): $R_1$=$CH_2OH$ $R_2$=Me X=Cl
geodiamolide O (**276**): $R_1$=Me $R_2$=$CH_2OH$ X=I
geodiamolide P (**277**): R1=Me $R_2$=$CH_2OH$ X=Br
geodiamolide Q(**278**): $R_1$=Me $R_2$=$CH_2OH$ X=Cl
geodiamolide R (**279**): $R_1$=$CH_2OH$ $R_2$=H X=I
geodiamolide TA (**269**): $R_1$=*i*-pr $R_2$=Me X=Cl
neosiphoniamolide (**270**): $R_1$=*i*-pr $R_2$=H X=I



geodiamolide G (**266**): X=I
geodiamolide J (**271**): X=Br
geodiamolide K (**272**): X=Cl

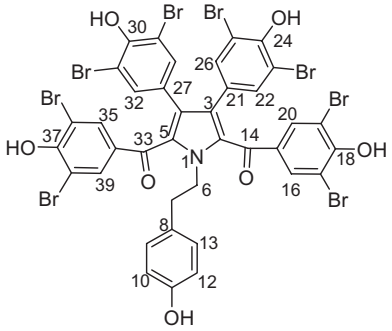


geodiamolide H (**267**): X=I
geodiamolide I (**268**): X=Br

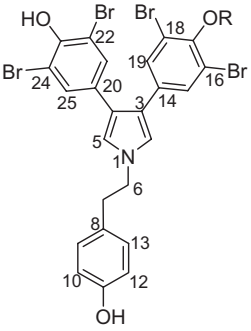
Polycitone A (**280**) and B (**281**), polycitrin A (**282**) and B (**283**), and prepolycitrin A (**284**) were reported from the Indo-Pacific ascidians *Polycitor* sp. and *P. africanus* by Kashman's group (*167,168*). Their structures were established by spectroscopic and chemical methods. The structure of polycitone A (**280**) was confirmed by X-ray crystallography (*167*).

The structures of polycitone A (**280**) and B (**281**) and polycitrin A (**282**) and B (**283**) were close to the lamellarins isolated from the mollusk *Lamellaria* sp. (*169*) and an ascidian of the genus *Didemnum* (*170,171*). Lammellarins are not included in this review because of the absence of a halogen in their structures. A possible biogenetic

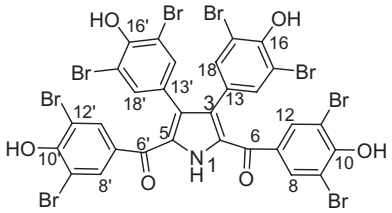
relationship between the lamellarins, polycitone A (**280**), and polycitrin A (**282**) and B (**283**) is shown below. The lamellarins may be derived from a precursor **285**, which is a condensation product of three, suitably substituted tyrosine molecules.



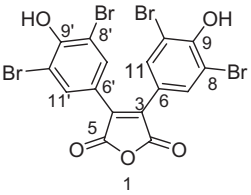
polycitone A (**280**)



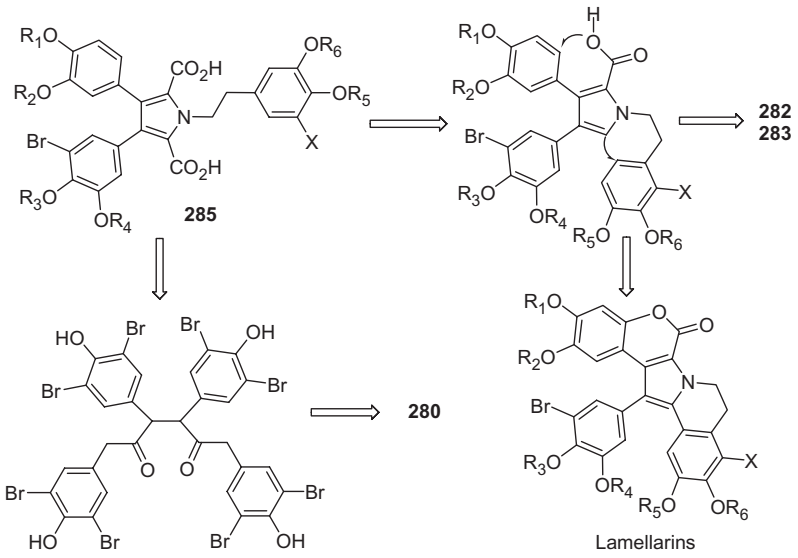
polycitrin A (**282**): R=H
polycitrin B (**283**): R=Me



polycitone B (**281**)



prepolycitrin A (**284**)



### III. Spectroscopic Data

As seen from the previous section, bromotyrosine derivatives exhibit a variety of chemical structures. The structure elucidation of bromotyrosine derivatives was based on chemical methods and the contemporary spectroscopic methods, which include 1D proton and carbon NMR, 2D homo- and heteronuclear correlations, as well as different mass spectroscopic methods. Some of the structures were verified by X-ray diffraction analysis. The physicochemical properties are listed in Table I, including appearance, molecular formula, MS, MP, $[\alpha]_D$, UV, IR, and CD. The proton and carbon NMR data are collected in Table II. All of the $^{13}$C-NMR resonance assignments for C-2 and C-4 of the spirocyclohexadienylisoxazoline type of compounds were revised based on Fattorusso's (*61*) COLOC NMR experiment, and our HMQC and HMBC experiment on a number of mono- and bis-spirocyclohexadienylisoxazoline bromotyrosine derivatives (*12*). The chemical shift of C-2 is at around 114 ppm and that of C-4 is around 122 ppm. The relative stereochemistry of the hydroxyl group at C-1 and the oxygen atom in the spirocyclohexadienylisoxazoline ring can be determined by comparison of the chemical shifts of H-1 and H-7 with synthesized *cis* and *trans* isomers (*217*). For the *trans* configuration, H-1 resonances at 4.2 ppm, H-7 resonances at 3.1 (d, $J = 18$ Hz) and 3.8 (d, $J = 18$ Hz) while in *cis* configuration $\delta$ 4.5 (H-1) and 3.42 (2H, H-7) were observed. The absolute configuration of aerothionin (**68**) was determined by X-ray crystallographic analysis and the CD spectrum (*60*). The stereochemistry of the spirocyclohexadienylisoxazoline ring in other alkaloids can be conventionally deduced by comparison of the CD spectrum with that of aerothionin.

The $^1$H and $^{13}$C NMR spectra of the spirooxepinisoxazoline type of alkaloids are significantly different from those of the spirocyclohexadieneisoxazoline type of alkaloids. The chemical shift of H-1 of the spirooxepinisoxazoline type at 7.3 ppm is 1.0 ppm lower than that of the corresponding proton (H-5) in the spirocyclohexadieneisoxazolines. The carbon-13 chemical shifts of C-1 and C-6 (the spiro-carbon) for the spirooxepinisoxazoline type are at 145 and 102 ppm, which are 15 and 12 ppm lower than those of the corresponding carbons (C-5, C-6) in the spirocyclohexadieneisoxazoline type of bromotyrosine derivatives.

The geometry of the oxime can be determined by the chemical shift of C-7, where 25.3–27.0 ppm indicated an *E*-geometry, while 35 ppm indicated a *Z*-geometry (*107*).

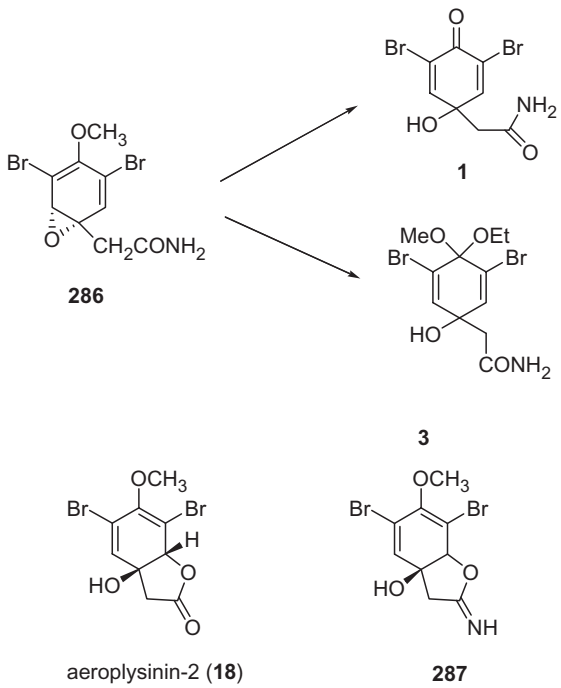
Bastadins are often spectroscopically similar to one another. $^1$H and $^{13}$C NMR alone are insufficient to discriminate bastarane and isobastarane isomers (*130*). For example, the structure of bastadin 5 (**209**) is almost impossible to distinguish from bastadin 19 (**223**) by 1D NMR, without recourse to 2D heteronuclear experiments. Molinski *et al*. reported that using "fingerprinting" of the MeO $^1$H NMR signals of the permethyl derivatives of bastadins provided a partial solution to the problem (*130*). The chemical shift pattern of the MeO signals measured in $CDCl_3$ can be matched reliably against those of previously reported bastadins tetra-*O*-methyl ethers (see Table III). For example, the $^1$H NMR of the three isomers, bastadin 5, bastadin 15, and bastadin 19, are very similar in $CD_3OD$ or DMSO-$d_6$. However, the $^1$H NMR signals of the MeO of the corresponding tetramethyl ethers are readily distinguishable in $CDCl_3$.

## IV. Biosynthesis of Bromotyrosine Derivatives

When the first bromotyrosine derivative, the dienone **1**, was isolated (*3*), the biogenetic precursor of this antibiotic was easily envisioned from tyrosine, which, after bromination, may be transformed into 3,5-dibromo-4-hydroxy-phenylacetaldehyde through a pathway already suggested in the literature (*172*). From the inspection of the structures, Minale *et al*. (*19*) and Moddy *et al*. (*58*) suggested that the Verongia bromo-metabolites are most likely biogenetically derived from 3,5-dibromo-tyrosine and, presumably, the central $C_4N_2$ and $C_5N_2$ chains of aerothionin (**68**) and homoaerothionin (**69**) are derived from ornithine and lysine, respectively.

### A. BIOGENESIS OF ISOSPIROXAZOLINE

Based on the acid-catalyzed addition of methanol to 1,4-dimethylbenzene oxide which gave 4-methoxy-1,4-dimethyl-2,5-cyclohexadienol (*173*), Anderson and Faulkner (*5*) proposed that an analogous 1,4-addition of solvent to an arene oxide **286** could result in the formation of dienone **1** or the corresponding ketal **3** (*5*). Although arene oxides have been proposed as intermediates in the biosynthetic oxidation of aromatic compounds, there is no evidence of their existence as natural products. The coexistence of the lactone aeroplysinin-2 (**18**) with dienone **1** and the ketal **3** suggested that the imino-ether **287** should also be considered as a possible precursor of these alkaloids.




The spiro systems could arise in various ways, including nucleophilic attack by an oxime function on an arene oxide as shown in **288** (*59*). Following suggestions that nitriles may be derived *in vivo* from $\alpha$-amino acids (*174*), the oxime **288** could be speculated as a precursor of the nitrile (±)-aeroplysinin-1 (**14** and **17**).

TABLE I.
Physical-Chemical Properties of Bromotyrosine Derivatives.

| | **1** (*3*) | **5** (*7*) | **6** (*7*) | **14** (*15*) | **17** (*16*) |
|---|---|---|---|---|---|
| Appearance | Crystal | Colorless crystals | Colorless crystals | Crystal | Crystal |
| Molecular formula | $C_8H_7Br_2NO_3$ | | | $C_9H_9Br_2NO_3$ | $C_9H_9Br_2NO_3$ |
| MS *m/z* | | 380, 382, 384 $[M–MeO]^+$ (8, 14, 8), 338, 340, 342, $[M–BuO]^+$ (40, 78, 39), 306, 308, 310 $[M–MeOH–BuO]^+$ (14, 27, 18) | 394, 396, 398 $[M–MeO]^+$ (1, 1.5, 1), 338, 340, 342 $[M–PenO]^+$ (21, 40, 20), 306, 308, 310$[M–MeOH–PenO]^+$ (12.5, 25, 13) | 341, 339, 337 $[M]^+$, 323, 321, 319 $[M–H_2O]^+$, 240, 242 $[M–H_2O–Br]^+$ | |
| MP (°C) | 193–195 | 194–195 | 166–168 | 120–121 | 112–116 |
| $[\alpha]_D$ | | | | +186° (MeOH) | −189° (*c* 0.5, acetone) |
| UV $\lambda_{max}$ (MeOH) nm | 257 (8000) | 204 (9912) | 203 (12134) | 231 (3220), 284 (4915) | |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3445, 3420, 3125, 1700, 1675, 1660, 1650 | 3410, 3200, 1660 | 3390, 3185, 1668 | 3380, 2265, 1635, 1585 | |

| | **15**:**16** 3:1(*11*) | **18** (*19*) | **19** (*7*) | **20** (*7*) | **21** (*20*) |
|---|---|---|---|---|---|
| Appearance | Oil | | Yellow crystals | | |
| Molecular formula | $C_8H_7Br_2NO_3$ | $C_9H_8Br_2O_4$ | $C_{12}H_{10}Br_2O_3$ | $C_{24}H_{24}Br_4N_4O_{10}$ | $C_{24}H_{24}Br_4N_4O_{10}$ |
| MS *m/z* | 323, 325, 327 $[M]^+$, 306, 308, 310 (2), 278, 280, 282 (3), 201, 203, 205 (100) | | 360, 362, 364 (49, 100, 48), 345, 347, 349 (M–Me, 15, 25, 14), 331, 333, 335 (M-29, 5, 9, 4), 317, 319, 321 (M-43, 36, 70, 35). | | |
| MP (°C) | | 106–108 | 142–144 | | |
| $[\alpha]_D$ | +30° (*c* 5.7, MeOH) | +22° (*c* 3, MeOH) | | +152.5° (*c* 0.92, MeOH) | +160.7° (*c* 0.92, MeOH) |

| | | | | | |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | 254 (4100), 249 (4000) | 281 (4900) | 207 (6717), 327 (3732) | 280 (10600), 231 (17400) | 281 (10500), 230 (17500) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3443, 2263, 1710, 1611 | 3400, 1785 | $CHCl_3$ 1780 | 3402, 1728, 1665 | 3350, 1732, 1662 |

| | **22**:**23** (3:1 mixture) (*22*) | **24** (*23*) | **25** (*9*) | **26**, **27**, **28**, **29** mixture (*9*) | **31** (*25*) | **30** (*24*) |
|---|---|---|---|---|---|---|
| Appearance | Oily mixture | | Sticky semi-solid | Sticky semi-solid | | Colorless needles |
| Molecular formula | $C_8H_7Br_2NO_3$ | $C_8H_8BrNO_3$ | $C_8H_8ClNO_3$ | $C_8H_7BrClNO_3$ | | |
| MS *m*/*z* | VG-ZAB, EI 328 (2), 326 (4), 324 (2) (M+1), 327 (6), 325 (12), 323 (6) (M) [calcd for $C_8H_7{}^{79}Br_2NO_3$ 322.8790; found 322.8766 ± 0.005], 246 (52) (M–Br), 229 (5), 227 (6) (244-OH), 218 (7), 216 (7) (244-CO), 204 (40), 202 (42) (244-ketone), 176 (24), 174 (24) (202-CO), 95 (17) (174-Br), 43 (100) (O=C=NH) | EIMS: 245 (2), 175 (5), 174 (6) | EIMS 203 (3), 201 (9, $M^+$), 186 (1), 184 (3, $M^+-17$), 161 (15), 159 (46, $M^+$–$CH_2CO$), 134 (5), 132 (15), 133 (5), 131 (15, $M^+$–$C_2H_2O_2$), 96 (21), 70 (95), 43 (100, $OCNH^+$) | EIMS 283 (4), 281 (14), 279 (11) (four $M^+$) | EIMS 219 (1), 217 (3, $M^+$), 203 (12), 201 (35), 191 (2), 189 (7), 174 (4), 172 (11), 159 (33), 157 (100), 182 (13), 136 (15), 123 (19), 59 (52), 44 (46), 43 (35), 39 (40) | MS 264, 262 (2.7 each, $(M+1)^+$), 263, 261 (1.4 each, $M^+$), 247, 245 (7 each, $((M+1)-17)^+$), 246, 244 (1.5 each, $M^+-17$), 235, 223 (23 each, $M^+-28$), 218, 216 (19 each HR: 215.9613 ±0.01 $C_7H_7BrNO_2$), 204, 205 (5 each, 244–42), 203, 201 (16 each, 244–243) 182 (70 HR: 182.0480 ±0.01 $C_7H_6NO_2$), 59 (100), 53 (48), 44 (61), 43 (59) |
| MP (°C) | | 183–185 | | | | 165–170 |
| $[\alpha]_D$ | | +0.036° (*c* 0.084, MeOH) | | | | |
| UV $\lambda_{max}$ (MeOH) nm | 255 (4000), 315 sh (100) | 250 (6000), 315 (35) | 238 (4100) | 250 (2500), 312 (60) | 242 (2200) | 254 (2600) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Nujol) 3400–3200, 1700, 1620 | (Nujol) 3300, 1680, 1605 | | | | |

(*continued*)

TABLE I.
Continued.

| | **43** (*35*) | **44** (*35*) | **45** (*35*) | **46** (*35*) | **67** (*21*) | **51** (*40*) |
|---|---|---|---|---|---|---|
| Appearance | Amorphous white solid | Amorphous solid | Amorphous solid | Amorphous solid | Solid | Colorless solid |
| Molecular formula | $C_{12}H_{15}Br_2O_3N$ | $C_{13}H_{17}Br_2O_3N$ | $C_{13}H_{18}BrO_3N$ | $C_{12}H_{16}BrO_3N$ | $C_{13}H_{12}Br_2N_2O_5$ | $C_9H_{11}Br_2NO$ |
| MS *m/z* | HRMS 378.9406 | HRMS 333.8839 [$M^+$–$NMe_3$] | HRMS 255.9720 [$M^+$–$NMe_3$] | HRMS 301.0323 | HRMS 433.9094 MS 434, 436, 438 ($M^+$) 348, 350, 352 ($M^+$–$C_3H_4O_3N$), 318, 320, 322 ($M^+$–$C_4H_6O_3N$) | HRFAB: 307.9279 |
| MP (°C) | | | | | 220–222 | |
| $[\alpha]_D$ | −1.35° | −8.33° | −9.00° | −15.00° | −33° (*c* 1.1, MeOH) | |
| UV $\lambda_{max}$ (MeOH) nm | ($H_2O$) 287 (1260), 307 (1995), 281 (1250) | ($H_2O$) 277 (1263) | ($H_2O$) 277 (1260) | ($H_2O$) 287 (1257), 307 (1994), 281 (1254) | (EtOH) 274 (524), 282 (491) | 224 (3.91), 284 (3.08) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (KBr matrix) 3446, 1576 | (KBr matrix) 3446, 1576 | (KBr matrix) 3446, 1576 | (KBr matrix) 3446, 1576 | $(CHCl)_3$ 3670, 3000, 1760, 1595 | |

| | **48** (*38*) | **207** (*41*) | **52** (*42*) | **54** (*44*) | **55** (*45*) |
|---|---|---|---|---|---|
| Appearance | Amorphous solid | Colorless amorphous solid | Off-white powder | Pale yellow semicrystalline solid | Colorless oil |
| Molecular formula | $C_{12}H_{18}NBr_2O$ | $C_{10}H_{11}BrN_2O_3$ | $C_{11}H_{17}Br_2N_2O$ | $C_{15}H_{24}Br_2N_2O$ | $C_{14}H_{22}N_2OBr_2$ |
| MS *m/z* | FABMS 350, 352, 354 | EI 288 (6), 286 (6), 200 (99), 199 (13), 198 (100), 187 (32), 185 (32), 120 (20), 101 (10), 77 (11) HREIMS 287.9935 | EIMS 354.9 ($M^+$+H+4,1), 352.9 ($M^+$+H+2,3), 350.9752 ($M^+$+H, 2), 324.9 (57), 322.9 (100), 320.9 (61), 294.9 (18), 292.9 (16), 273.0 (88), 271.0 (91), 264.8 (30), 262.8 (16), 81.9 (66), 80.9 (27), 79.9 (68), 78.9 (28) | EI 406, 408, 410 ($M^+$–2HCl, 3%; found: 406.025; $C_{15}H_{24}{}^{79}Br_2N_2O$ requires 406.0255), 165 (5), 121 (54; found: 121.065; $C_8H_9O$ requires 121.0653), 85 (64), 58 (100) FAB 407, 409, 411 ([$M^+$−2HCl]+1) | EIMS 396, 394, 392 (1:2:1), 352, 349, 347 (1:2:1), 324, 322, 320 (1:2:1), 95, 89, 69, 53, 51, 44 HREIMS 392.0081 |

| | | | | | |
|---|---|---|---|---|---|
| MP (°C) | | | | 122–123 | |
| $[\alpha]_D$ | | | | | |
| UV $\lambda_{max}$ (MeOH) nm | (EtOH) 277 (1260) | ($CH_3OH$) 212 (7762), 281 (1380), 205 (18900) | 206 (28000), 284 (600) | 293 (400), 448 (440) | (MeOH, HCl salt) 218 (12000), 274 (800), 285 (1000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Dry film) 2578, 1635 | (NaCl film) 3387, 3310, 1651 | (NaCl) 3000, 1592, 1473, 1459, 1385, 1261, 865, 739 | 3000, 2940, 1632, 1454, 1256, 1043 | (KBr, HCl salt) 3420, 2950, 1635, 1455, 1260, 1035 |

| | **56** (*45*) | **57** (*46*) | **58** (*46*) | **60** (*49*) | **59a** (*47*) |
|---|---|---|---|---|---|
| Appearance | Colorless oil | Brown solid | White solid | Colorless solid | Colorless crystalline compound |
| Molecular formula | $C_{14}H_{22}N_2OBr_2$ | $C_{15}H_{23}Br_2N_2O_3$ | $C_{15}H_{23}Br_2N_2O_3$ | $C_{13}H_{15}Br_2N_3O_2$ | $C_{15}H_{22}N_2O_2Br_2$ |
| MS *m/z* (int) | EIMS 396, 394, 392 (1:2:1), 353, 351, 349 (1:2:1), 315, 313 (1:1), 87, 69, 58, 44 HREIMS 394.0053 | FABMS 437, 439, 441 (1:2:1) HRFABMS 437.0083 | FABMS 437, 439, 441 (1:2:1) HRFABMS 437.0090 | FAB 404, 406, 408 (1:2:1) (Δ −1.6 mmu) | FABMS 421, 423, 425 (1:2:1) HRFABMS 421.010534 |
| MP (°C) | | 160–162 | 170–173 | | 148 |
| $[\alpha]_D$ | | | | | |
| UV $\lambda_{max}$ (MeOH) nm | (MeOH, HCl salt) 214 (14000), 276 (8000), 288 (1100) | | | 207 (37800), 220 (12600), 276 (850 | (MeOH, HCl salt) 280 (944), 275 (950), 223 (5769) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (KBr, HCl salt) 3420, 2950, 1635, 1455, 1260, 1035 | 3300, 2720, 1720, 1620, 1480 | 3350, 2700, 1725, 1610 | (Film) 3200, 3040, 2950, 1680, 1450, 1200, 1130 | 3328, 2700, 1680, 1580, 1480, |

(*continued*)

TABLE I.
Continued.

| | **61** (*50*) | **62** (*51*) | **63** (*53*) | **64** (*53*) | **65** (*54*) | **67** (*21*) |
|---|---|---|---|---|---|---|
| Appearance | Amorphous solid | Colorless oil | Colorless flakes | White crystals | Colorless crystals | Solid |
| Molecular formula | $C_{13}H_{16}$ $Br_2N_3O_3$ | $C_{17}H_{25}$ $N_2O_4Br_2$ | $C_{16}H_{21}$ $Br_2NO_3$ | $C_{14}H_{18}$ $Br_2NO_3$ | $C_{13}H_{12}$ $N_2O_5Br_2$ | $C_{13}H_{12}Br_2N_2O_5$ |
| MS *m/z* | FABMS 420, 422, 424 (1:2:1) HRFABS 419.9568 | ESIMS 479, 481, 483 (1:2:1, $[M+H]^+$), 501, 503, 505 (1:2:1, $[M+Na]^+$) HRFABMS 479.0176 | EIMS 437 (0.7), 435 (1.4), 356 (1), 354 (1), 167 (1), 149 (1), 86 (8), 84 (2), 73 (3), 71 (3), 58 (100) HREIMS 432.9860 | FABMS 410 (46), 408 (94), 406 (61), 325 (11), 323 (24), 321 (14), 307 (8), 305 (19), 303 (10), 244 (12), 58 (100) HRFABMS 407.9641 | 433.9109 | HRMS 433.9094 MS 434, 436, 438 ($M^+$) 348, 350, 352 ($M^+$–$C_3H_4O_3N$), 318, 320, 322 ($M^+$–$C_4H_6O_3N$) |
| MP (°C) | | | 67 | 193–194 | 222–225 | 220–222 |
| $[\alpha]_D$ | +3.0° (*c* 0.8, MeOH) | +35° (*c* 0.1, MeOH) | | | +8.9° (*c* 0.87, MeOH) | −33° (*c* 1.1, MeOH) |
| UV $\lambda_{max}$ (MeOH) nm | | 283 (880) | 230 (11200), 282 (9500) | 223 (13700), 267 (11000) | 275 (480) | (EtOH) 274 (524), 282 (491) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (neat) 3365, 3280, 1675, 1453, 1206, 1138 | 3411, 1630, 1057 | (Neat, NaCl) 2920, 2840, 2805, 2758, 1712, 1635, 1195, 950 | (Neat, NaCl) 3700–2900, 2940, 2870, 1635, 1565, 930 | 1748 (sh. 1722, 1703) | ($CHCl_3$) 3670, 3000, 1760, 1595 |

| | **68** (*58*) | **70** (*62*) | **71** (*63*) | **72** (*64*) | **73** (*61*) | **74** (*61*) | **75** (*65*) |
|---|---|---|---|---|---|---|---|
| Appearance | Plates | White powder | Colorless glass | White powder | | | |
| Molecular formula | $C_{24}H_{26}Br_4N_4O_8$ | $C_{24}H_{27}Br_4N_4O_{10}$ | $C_{24}H_{26}Br_4N_4O_9$ | $C_{24}H_{24}Br_4N_4O_9$ | $C_{24}H_{24}Br_4N_4O_{10}$ | $C_{24}H_{24}Br_4N_4O_{10}$ | $C_{25}H_{26}Br_4N_4O_9$ |
| MS *m/z* | | HRFABMS 850.84 13 (Δ 1.9 mmu) | | HRFABMS 831.8235 (Δ 0.1 mmu) | | | FABMS 841, 843, 845, 847, 849 |
| MP (°C) | 134–137 (dec.) | 162–164 | | 174.6–176.6 (dec) | | | |
| $[\alpha]_D$ | +252° (acetone) | −64.2° (*c* 0.1, MeOH) | +189° (*c* 0.15) | +181.15° (*c* 2.17, DMSO) | +152.5° | +160.7° | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | (EtOH) 234 (4.16), 284 (4.13) | 282 (9400), 225 (19000), 202 (34000) | 284 (11100), 233 (19750), 205 (18900) | (DMSO) 284 (11500), 262 (11600) | 280.5 (10600), 231 (17400) | 281 (10500), 230.5 (17500) | 284 (10500), 232 (19000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3335, 3160, 1675, 1660, 1580, 1550 | 3600–3000, 1660, 1600, 1530 | 3400, 3350 (OH, NH), 1650 (CONH) | 3600–3000, 1713, 1665, 1558, 1552, 1435, 1293, 1271, 1131, 1100, 1025 | 3402, 1728, 1665 | 3350, 1732, 1662 | (KBr matrix) 3450, 1715, 1665 |
| CD | NA | NA | NA | NA | NA | NA | 285, +52000 250, +60,200 |

| | **76** (*66*) | **77** (*67*) | **78** (*30*) | **79** (*25*) | **81** (*70*) |
|---|---|---|---|---|---|
| Appearance | Colorless glassy solid | NA | Colorless solid | Amorphous white solid | Amorphous white solid |
| Molecular formula | $C_{27}H_{32}Br_4N_4O_9$ | $C_{22}H_{20}Br_4N_4O_9$ | $C_{22}H_{20}Br_2N_4O_8$ | $C_{31}H_{30}Br_6N_4O_{11}$ | $C_{31}H_{30}Br_6N_4O_{11}$ |
| MS *m/z* | FABMS (thioglycerol+MeOH) 875 (1), 873 (2), 871 (4) $[M]^+$, 869 (2), 867 (1), 861 (1.5), 859 (3.5), 857 (5), 855 (3.5), 853 (1.5), 322 (1.5), 320 (2.5), 318 (1.5), 297 (2.5), 295 (4.5). 293 (2.5), 281 (18), 279 (37), 277 (18), 70 (100) HRFABMS 871.97028, found 871.97930 [M]+ | FABMS 801, 803, 805, 807, 809 | FABMS 629 | NA | FABMS 1141, 1139, 1137, 1133 ($[M+Na]^+$, 39, 64, 100, 80, 48) |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | +104° (*c* 1.67, MeOH) | +65.2° (*c*, 1.04, acetone) |
| UV $\lambda_{max}$ (MeOH) nm | 234 (9000), 283 (4300) | 250 (7850) | 260 (0.63), 230 (0.78), 210 (0.90) | 283 (10387), 223 (26545) | (EtOH) 233 (13500), 283 (2650) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3382, 2357, 1665, 1549, 1106, 603 | (KBr matrix) 3360, 1713, 1705, 1660, 1600 | NA | 3395, 1655, 1602, 1550 | 3350, 2920, 1655, 1545 |
| CD | NA | 252, +1.6 | 344.1 (2.5), 270.3 (13.8), 233.6 (24.1), 199.0 (−25.0) | NA | NA |

(*continued*)

TABLE I.
Continued.

| | **82** (*71*) | **83** (*63*) | **84** (*72*) | **85** (*72*) | **86** (*65*) |
|---|---|---|---|---|---|
| Appearance | Pale yellow gummy solid | Unstable yellow power | | Powder | NA |
| Molecular formula | $C_{31}H_{29}Br_6N_4O_{11}$ | $C_{31}H_{30}Br_6N_4O_9$ | | $C_{31}H_{28}Br_6N_4O_{10}$ | $C_{31}H_{30}Br_6N_4O_{10}$ |
| MS *m/z* | HRFABMS 1112.6897 (Δ 0.6 mmu) | | | EIMS 351 (2), 349 (4), 347 (2), 336 (2), 334 (4), 332 (2), 323 (4), 321 (9), 319, (5), 308 (6), 306 (12), 304 (6), 267 (6), 265 (12), 263 (6) | FABMS 1091, 1093, 1095, 1097, 1099, 1101, 1103 |
| MP (°C) | NA | NA | | NA | NA |
| $[\alpha]_D$ | +130° (*c* 0.1, MeOH) | +98.5° (*c* 0.10, MeOH) | | +136° (*c* 0.2, acetone) | NA |
| UV $\lambda_{max}$ (MeOH) nm | 283 (9900), 242(14000), 225 (27000) | 284(10400), 257(16000), 224(26000) | | 280 (3400), 205 (18500) | 284 (11000), 232 (19000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3600–3200, 1720, 1660, 1590, 1525, | 3450, 3350 (OH, NH), 1645 (CONH) | | (Nujol) 3400 br, 1725, 1650, 1590, 1530 | (KBr matrix) 3450, 1715, 1665 |
| CD | NA | NA | | NA | 285, +56500 250, +65200 |

| | **87** (*70*) | **88** (*70*) | **89:90** (*74*) | **91**(*75*) |
|---|---|---|---|---|
| Appearance | Amorphous off-white powder | Amorphous white powder | Noncrystalline mixture | |
| Molecular formula | $C_{29}H_{26}N_4O_{11}Br_6$ | $C_{29}H_{26}N_4O_{11}Br_6$ | $C_{29}H_{26}N_4O_9Br_6$ | $C_{18}H_{18}Br_4N_2O_6$ |
| MS *m/z* | FABMS 1092, 1090, 1088, 1086, 1084, 1082, (1, 1.8, 1.8, 2, 1.8, 1.8, 1) [M+], 707 (0.8), 705 (1), 703 (0.8), 427 (10), 425 (18), 423 (10) | FABMS 1092, 1090, 1088, 1086, 1084, 1082 (< 1) [$M^+$], 707 (1), 705 (1), 703 (1), 427 (6), 425 (10), 423 (6) | FABMS 1054.68209 $[M+H]^+$ | ESIMS 696.7766 $[M+Na]^+$ |

| | | | |
|---|---|---|---|
| MP (°C) | NA | NA | NA |
| $[\alpha]_D$ | −17.1° (*c* 1.26, acetone) | +50.0° (*c* 0.27, acetone) | +248° (*c* 0.012, $CHCl_3$) |
| UV $\lambda_{max}$ (MeOH) nm | (EtOH) 220 (12600), 250 (7740) | (EtOH) 215 (12570), 250 (7940) | |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3360, 2930, 1750, 1660, 1600, 1540, 1260, 1095 | 3350, 2920, 1700, 1665, 1605, 1540, 1255, 1095, 910 | |

| | **92** (*77*) | **93** (*78*) | **94** (*68*) | **95** (*68*) |
|---|---|---|---|---|
| Appearance | Brown amorphous solid | Yellow powder | Amorphous white solid | Crystalline |
| Molecular formula | $C_{32}H_{36}Br_4N_{10}O_8$ | $C_{44}H_{43}Br_8N_6NaO_{16}S$ | $C_{22}H_{21}Br_4N_3O_8$ | $C_{26}H_{25}Br_4N_3O_{10}$ |
| MS *m/z* | FABMS 1005, 1007, 1009, 1011, 1013 HRFABMS 1008.9488 | FABMS 1583 $[M–Na]^+$, 1503 $[M–SO_3Na]$ | NA | NA |
| MP (°C) | NA | 200 (dec.) | NA | 168–171 |
| $[\alpha]_D$ | +111.4° (*c* 0.07, MeOH) | −96° (*c* 0.86, DMSO) | +93.5° (*c* 1.2, MeOH) | +122.7° (*c* 0.44, $CHCl_3$) |
| UV $\lambda_{max}$ (MeOH) nm | 221 (19600, 279 (9500) | 231 (2690), 283 (11900) | 284 (5681), 230 (15217) | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (KBr matrix) 3450, 1665 | 3700–2500, 1660, 1584, 1541, 1257, 1218, 1183, 1047, 990 | 3360, 1750, 1660, 1600, 1545 | 3360, 1750, 1740, 1660, 1600, 1545 |
| CD | 245, +60000 285, +50000 | 252 (−16.0), 289 (−16.9) | | |

| | **97** (*79*) | **98** (*80*) | **99** (*81*) | **101** (*82*) |
|---|---|---|---|---|
| Appearance | Colorless oil | Amorphous white solid | White solid | Glass |
| Molecular formula | $C_{10}H_{10}Br_2N_2O_4$ | $C_{10}H_9Br_2NO_5$ | $C_{21}H_{23}Br_4N_3O_5$ | $C_{21}H_{24}Br_3N_3O_5$ |
| MS *m/z* | EI: 380, 382, 384 (1:2:1) | FABMS 938, 940, 942, 944, 946 (1:4:6:4:1) $[M+H]^+$ | FABMS 714, 716, 718, 720, 722 (1:4:6:4:1) $[M+H]^+$ | HRFABMS 635.9360 |

(*continued*)

TABLE I.
Continued.

| | **97** (*79*) | **98** (*80*) | **99** (*81*) | **101** (*82*) |
|---|---|---|---|---|
| MP (°C) | | 40–42 | 140–142 | NA |
| $[\alpha]_D$ | + 86° | −38° (*c* 0.73, $CHCl_3$) | −70° (*c* 0.7, MeOH) | +21° (*c* 0.47, $CHCl_3$–MeOH 1:1) |
| UV $\lambda_{max}$ (MeOH) nm | 228 (8000), 290 (2000) | 270 (11650) | 283 (9392) | ($CHCl_3$) 240 (23000), 287 (16700) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3400, 2940, 1675, 1135, 1120 | NA | NA | ($CHCl_3$–MeOH 1:1) 3690, 3630, 3420, 3020, 2945, 1600, 1570, 1535, 1500, 1465, 1255, 1015 |
| CD | 248 (+4.0), 284 (+4.0) | | | |

| | **102** (*83*) | **100** (*81*) | **102** (*36*) | **104**(*36*) | **105** (*78*) |
|---|---|---|---|---|---|
| Appearance | Colorless semisolid | Amorphous white solid | Colorless solid | Colorless solid | Colorless fine crystals |
| Molecular formula | $C_{23}H_{25}Br_4N_3O_7$ | $C_{36}H_{51}Br_4N_3O_6$ | $C_{22}H_{24}Br_4N_3O_7$ | $C_{25}H_{29}Br_4N_3O_7$ | $C_{24}H_{27}Br_4N_3O_7$ |
| MS *m/z* | HRFABMS 797.82940 FABMS 802 (19), 800 (67), 798 (95), 796 (67), 794 (21), 776 (28), 700 (9), 681 (14), 661 (4), 612 (33), 532 (38), 510 (100), 482 (85), 464 (42), 437 (65), 413 (48) | FABMS 938, 940, 942, 944, 946 (1:4:6:4:1) $[M+H]^+$ | ESI-FTMS 761.8307 (Δ +10.3 mmu) | ESI-FTMS 803.8777 (Δ −27.3 mmu) $[M+H]^+$ | FABMS (Thiogylcerol matrix) 786, 788, 790, 792, 794 (1:4:6:4:1) [M+H] HRFABMS 785.8661, found 785.8649 [M+H] |
| MP (°C) | NA | 40–42 | NA | NA | 154–156 |
| $[\alpha]_D$ | +69.0° (*c* 6.4, MeOH) | −38° (*c* 0.73, $CHCl_3$) | +96.3° (*c* 0.19, MeOH) | +102° (*c* 0.067, MeOH) | −118° (*c* 1.02, MeOH) |

| | | | | | |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | 282 (5200), 208 (145000) | 270 (11650) | (EtOH) 208 (8100), 284 (1200) | (EtOH) 207 (8300), 284 (1200) | 210 (29500), 283 (7390) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3692–3026, 2933, 2853, 1649, 1643, 1545, 1400, 1384, 1281, 1095, 1044, 988, 918, 868, 765, 739, 704 | NA | (NaCl) 3251 br, 2935, 1658, 1543, 1456, 1257, 989 | (NaCl) 3255 br, 3058, 2933, 1771, 1631, 1542, 1456, 1257, 1024, 987 | 3700–2300, 1660, 1630, 1540, 1260, 1045 |

| | **106** (*78*) | **107** (*78*) | **108** (*72*) | **109** (*85*) | **110** (*79*) |
|---|---|---|---|---|---|
| Appearance | Colorless fine crystals | Colorless powder | Powder | Colorless amorphous solid | Colorless oil |
| Molecular formula | $C_{22}H_{23}Br_4N_3O_7$ | $C_{22}H_{22}Br_4N_3O_7S$ | $C_{18}H_{16}Br_4N_2O_6$ | $C_{24}H_{30}Br_4N_3O_5$ | $C_{23}H_{27}Br_4N_3O_5$ |
| MS *m/z* | FABMS (Glycerol matrix) 758, 760, 762, 764, 766 (1:4:6:4:1) [M+H] HRFABMS 757.8348, found 757.8359 [M+H] | FABMS (Glycerol matrix) 836, 838, 840, 842, 844 (1:4:6:4:1) $[M-Na]^-$ | FABMS (Glycerol–MeOH–$H^+$) 676.8 (0.2%, as the centre of a cluster of ions) $[MH^+]$ FABMS (3-nitrobenzyl alcohol) 698.6 (1.0% as the centre of a cluster of ions) $[MNa^+]$, 658.6 (1.1% as a quintet) $[MH^+–H_2O]$ | FABMS 764, 762, 760, 758, 756 $[M^+]$, 748, 746, 742, 740, 684, 682, 680, 678, 602, 600, 658 HRFABMS 759.8892 | FABMS 742, 744, 746, 748, 750 (1:4:6:4:1) $[M^+$+H] HRFABMS 745.8721 $[M+4+H]^+$, found 745.8776 |
| MP (°C) | 154–157 | 190 | 73–75 | NA | NA |
| $[\alpha]_D$ | −97° (*c* 0.58, MeOH) | −69° (*c* 0.19, MeOH) | +110° (*c* 0.2, acetone) | −4.5° (*c* 1.3, MeOH) | +6.6° (*c* 0.75, MeOH) |
| UV $\lambda_{max}$ (MeOH) nm | 207 (45400), 283 (7300) | 206 (53200), 220 (25000 sh), 282 (6760) | 281 (6900), 207 (39200) | 220 (10000), 284 (1000) | 277 (1700), 284 (1400) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3700–2300, 1660, 1635, 1540, 1260, 1045 | 3700–2500, 1662, 1596, 1541, 1258, 1217, 1046 | (Nujol) 3350 br, 1660, 1590, 1540, 1270, 1220, 1095 | 3450, 2980, 2880, 1690, 1470, 1400, 1220, 1150 | 3400, 2940, 2845, 1670, 1520, 1470, 1135, 1120 |

(*continued*)

TABLE I.
Continued.

| | **111** (*79*) | **112** (*86*) | **113** (*69*) | **114** (*69*) | **116** (*79*) | **117**(*79*) |
|---|---|---|---|---|---|---|
| Appearance | Colorless oil | Colorless oil | NA | NA | Colorless oil | Colorless oil |
| Molecular formula | $C_{23}H_{27}Br_4N_3O_5$ | $C_{22}H_{25}Br_4N_3O_5$ | $C_{15}H_{16}Br_2N_4O_4$ | $C_{16}H_{19}Br_2N_5O_4$ | $C_{15}H_{17}Br_2N_5O_4$ | $C_{15}H_{17}Br_2N_5O_5$ |
| MS $m/z$ | FABMS 742, 744, 746, 748, 750 (1:4:6:4:1) $[M^+ + H]$ HRFABMS 745.8721 $[M+4+H]^+$, found 745.8729 | ESIMS 726.85, 728.85, 730.85, 732.86, 734.85 $[M+H]^+$ HRESIMS 728.8676 ($\Delta$ 0.8 mmu) $[M+H]^+$ | FABMS 475, 477, 479 $[MH^+]$ | FABMS 504, 506, 508 $[MH^+]$ | FABMS 490, 492, 494 (1:2:1) $[M^+ + H]$ HRFABMS 491.9705 $[M+2+H]^+$, found 491.9682 | FABMS 506, 508, 510 (1:2:1) $[M^+ + H]$ HRFABMS 507.9654 $[M+2+H]^+$, found 507.9672 |
| MP (°C) | NA | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | +9.1° (*c* 0.39, MeOH) | NA | +187° (*c* 2.0, MeOH) | +139° (*c* 1.9, MeOH) | +24° (*c* 0.98, MeOH) | +26° (*c* 0.38, MeOH) |
| UV $\lambda_{max}$ (MeOH) nm | 277 (1700), 284 (1400) | 280 (3.28) | NA | NA | 277 (1700), 284 (1400) | 231 (6300), 284 (2400) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3400, 2940, 2850, 1675, 1470, 1200, 1135, 1120 | 1736, 1655, 1591, 1542, 1458, 1390, 1257, 1044, 737 | NA | NA | 3400, 2930, 2845, 1680, 1540, 1430, 1200, 1135 | 3400, 2920, 2850, 1670, 1540, 1430, 1200, 1135, 1125 |

| | **119** (*89*) | **120** (*83*) | **121** (*90*) | **122** (*91*) | **123** (*89*) |
|---|---|---|---|---|---|
| Appearance | NA | Colorless oil | NA | Colorless amorphous solid | NA |
| Molecular formula | $C_{15}H_{18}Br_2N_5O_4$ | $C_{16}H_{18}Br_2N_5O_4$ | $C_{24}H_{22}O_8N_6Br_2$ | $C_{27}H_{29}Br_4N_7O_7 \cdot HCl$ | $C_{27}H_{32}Br_4N_7O_6$ |

| | | | | | |
|---|---|---|---|---|---|
| MS $m/z$ | FABMS 490, 492 494 [$MH^+$] | HRFABMS 503.97073 FABMS 506 (53), 504 (100), 502 (55), 307 (5), 154 (50) | FABMS 681, 683, 685 (1:2:1) HRFABMS 680.9940 | FDMS 880, 882, 884, 886, 888 (1:4:6:4:1) | FABMS 866, 868, 870, 872, 874 [$MH^+$] |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | −158° (*c* 1.0, MeOH) | +121.9° (*c* 5.7, MeOH) | NA | −85° (*c* 2.10, MeOH) | −10° (*c* 1.0, MeOH) |
| UV $\lambda_{max}$ (MeOH) nm | 220 (4.47), 284 (4.08) | 266 (13100), 226 (13700) | NA | NA | 220 (4.54), 228 (4.11) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3400, 1680, 1543, 1437, 1381, 1250 | 3654–3000, 2937, 1660, 1595, 1543, 1435, 1273, 1219, 1047, 1025, 997, 824, 765 | NA | NA | 3375, 1680, 1543, 1456, 1387, 1250 |

| | **124** (*83*) | **125** (*79*) | **126** (*66*) | **127** (*92*) | **128**(*92*) |
|---|---|---|---|---|---|
| Appearance | Colorless semisolid | Colorless oil | Colorless glassy solid | NA | NA |
| Molecular formula | $C_{16}H_{24}Br_2N_5O_4$ | $C_{15}H_{21}Br_2N_5O_4$ | $C_{15}H_7D_7\ Br_2N_5O_5$ | $C_{16}H_{19}Br_2N_3O_7$ | $C_{16}H_{19}Br_2N_3O_7$ |
| MS $m/z$ | HRFABMS 510.01640 FABMS 512 (25), 510 (50), 508 (25), 451 (7), 273 (22), 219 (12), 154 (100) | FABMS 494, 496, 498 (1:2:1) [$M^+$+H] HRFABMS 496.0018 [M+4+H]$^+$, found 496.0035 | FABMS (Thioglycerol) 518 [M+7D−7H]$^+$ (13), 513 [M+2D−2H]$^+$ (4), 496 (8), 478 (6), 295 (23), 279 (22), 157 (60), 71 (100) HRFABMS 518.20911 [M+7D−7H]$^+$ | ESIMS 524, 526, 528 (1:2:1) [M+H]$^+$ | ESIMS 524, 526, 528 [M+H]$^+$ |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | +47.0° (*c* 7.9, MeOH) | +27° (*c* 0.18, MeOH) | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 284 (2500), 218 (4600) | 228 (8600), 290 (3400) | 232 (9100), 283 (4250) | 229 (18500), 280 (10600) | 227 (19000), 281(10500) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3588–3050, 3024, 2782, 1658, 1402, 1024, 992 | 3400, 2920, 1660, 1520, 1470, 1210 | 3500–3000, 2928, 2860, 1690–1630, 1405, 1100, 605 | 3450, 1730, 1715, 1665 | 3450, 1730, 1715, 1665 |

(*continued*)

TABLE I.
Continued.

| | **129** (*94*) | **130** (*94*) | **131** (*95*) | **132** (*96*) |
|---|---|---|---|---|
| Appearance | Colorless glass | Colorless glass | Glass | Colorless oil |
| Molecular formula | $C_{21}H_{23}Br_4N_3O_6$ | $C_{21}H_{23}Br_4N_3O_7$ | $C_{22}H_{25}Br_4N_3O_7$ | $C_{36}H_{51}Br_4N_3O_8$ |
| MS $m/z$ | EIMS 406 (0.4), 404 (0.4), 402 (0.4), 3.62 (1), 360 (2), 358 (2), 356 (1), 323 (1), 321 (2), 319 (2), 281 (2), 280 (7), 279 (6), 278 (17), 277 (4), 276 (4), 268 (1), 267 (4), 266 (2), 265 (6), 264 (1), 263 (7), 248 (5), 246 (3), 200 (6), 198 (4), 58 (100). CIMS 407, 405, 403, 361, 359, 281, 279, 277, 275, 249, 247, 233, 231, 221, 219, 193, 191, 166, 164, 125, 123, 121 | EIMS 523 (9), 521 (27), 519 (26), 517 (8) overlapping 2 Br clusters, 477 (3), 475 (4), 473 (2) 2 Br cluster, 441 (6), 439 (13), 437 (6) 2 Br cluster, 423 (5), 421 (11), 419 (4) 2 Br cluster, 407 (3), 405 (4), 403 (2) 2 Br cluster, 393 (11), 391 (39), 358 (2), 356 (6), 354 (2), 283 (8), 281 (16), 279 (12), 278 (9), 276 (20), 274 (18), 272 (8) 2 Br cluster, 249 (94), 247 (97) 1 Br cluster, 235 (16), 233 (14) 1 Br cluster, 221 (24), 219 (27) 1 Br cluster, 207 (11), 205 (24), 203 (16) 2 Br cluster, 196 (9), 194 (100), 192 (17), 179 (9), 177 (18), 175 (8), 169 (4), 167 (19), 155 (45), 127 (38), 125 (43), 113 (9), 111 (12). CIMS 441, 439, 437 (2 Br), 407, 405, 403 (2 Br), 340, 338, 336 (2 Br), 249, 247 (1 Br), 221, 219 (1 Br). HRFDMS 749.8308 (M+H, $C_{21}H_{24}{}^{79}Br_2{}^{81}Br_2N_3O_7$, calcd 749.83068) | HRFABMS 763.8499 | HRFABMS 974.0468 [M+H] |
| $[\alpha]_D$ | −65.2° (*c* 0.52, MeOH) | −60.2° (*c* 0.63, MeOH) | −57.1° (*c* 0.014, MeOH) | −71.4° (*c* 2.8, acetone) |
| UV $\lambda_{max}$ (MeOH) nm | 229 (12700), 262 (7100 sh), 276 (4650 sh), 283 (3200 sh) | 218 (28600), 256 (7000 sh), 262 (6400 sh), 277 (4000 sh), 282 (3000) | 218 (17600), 255 (6700 sh), 279 (3000 sh) | 210 (50900), 224 (27600 sh), 258 (10400 sh) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | ($CHCl_3$) 3420, 2950, 1675 s, 1660, 1540–1530, 1460, 1260, 1150, 1120, 910 | ($CHCl_3$) 3420, 2940, 1670 s, 1620, 1590, 1530 s, 1450, 1250, 1140, 1110, 900 | (KBr smear) 3362, 2925, 2851, 1668, 1652, 1558, 1540, 1456, 1258, 1197, 1146, 1118, 1044, 1024 | ($CHCl_3$) 3430, 3390, 2910, 2830, 1660, 1570, 1445, 1135, 1105, 1030, 980, 950, 890 |

| | **133** (*96*) | **134** (*97*) | **135** (*98*) | **136** (*98*) |
|---|---|---|---|---|
| Appearance | Bright yellow oil | NA | Colorless solid | Colorless solid |
| Molecular formula | $C_{27}H_{25}Br_4O_8$ | $C_{22}H_{25}O_6Br_4N_3$ | $C_{22}H_{23}Br_4N_3O_7$ | $C_{35}H_{51}Br_4N_3O_7$ |
| MS *m/z* | FABMS 994.4 [M+H+$C_4H_{10}O_2S_2$], 840.0 [M+H]. HRFABMS 993.8563 [M+H+$C_4H_{10}O_2S_2$] | FABMS $[M+H]^+$ 752 (22), 750 (57), 748 (100), 746 (71), 744 (23), 393 (26) | FABMS (positive, glycerol matrix) 758, 760, 762, 764, 766 [M+H]+, 780, 782, 784, 786, 788 [M+Na]+ HRFABMS 783.8152 (calcd for $C_{22}H_{23}{}^{79}Br_2{}^{81}Br_2N_3O_7Na$, Δ +2.6 mmu) | FABMS (Positive, NBA matrix) 954, 956, 958, 960, 962 [M+H]+, 976, 977, 980, 982, 984 [M+Na]+ HRFABMS 980.0320 (calcd for $C_{36}H_{51}{}^{79}Br_2{}^{81}Br_2N_3O_7Na$, Δ −0.4 mmu) |
| MP (°C) | | NA | NA | NA |
| $[\alpha]_D$ | −80.3° (*c* 0.3, acetone) | −62.3° (*c* 1.2, MeOH–$CH_2Cl_2$) | −89.7° (*c* 0.146, MeOH) | −53.5° (*c* 0.263, acetone) |
| UV $\lambda_{max}$ (MeOH) nm | 208 (53400), 224 (33300 sh), 298 (25000) | NA | (EtOH) 207 (64200), 218 (28900 sh), 255 (11000 sh) | (EtOH) 207 (51100), 219 (22700 sh), 255 (9000 sh) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | ($CHCl_3$) 3380, 2910, 1700, 1640, 1610, 1445, 1145, 1105, 1035, 985, 950, 880 | (Neat) 3450, 3300, 1660 s, 1620, 1590, 1260 | (Film) 3300, 2930, 1660, 1530, 1450, 1380, 1260, 1110, 760 | (Film) 3320, 2920, 2850, 1650, 1540, 1450, 1250, 1120 |

| | **137** (*99*) | **138** (*100*) | **139** (*101*) | **140** (*33*) | **141** (*102*) |
|---|---|---|---|---|---|
| Appearance | NA | Oil | Yellow semisolid, oil | NA | Colorless amorphous solid |
| Molecular formula | $C_{15}H_{17}N_5O_3Br_2$ | $C_{15}H_{16}N_4O_3Br_2$ | $C_{15}H_{18}N_4O_3Br$ | $C_{14}H_{15}BrN_4O_3$ | $C_{31}H_{48}N_6O_4Br_2$ |
| MS *m/z* | EIMS 477, 475, 473 | EIMS 351, 149, 247 (2.5, 5, 2.5), 335, 333, 331 (2.5, 5, 2.5), 307, 305, 303 (50, 100, 50), 292, 290, 288 (20, 40, 20), 195 (22), 181 (31), 137 (30), 81 (80) | FABMS 381 (92), 383 (100) $[M+H]^+$, 403 (36), 405 (38) $[M+Na]^+$ HRFABMS 381.0573 | FAMS 367, 369 | SIMS 727, 729, 731 (1:2:1) |

(*continued*)

TABLE I.
Continued.

| | **137** (*99*) | **138** (*100*) | **139** (*101*) | **140** (*33*) | **141** (*102*) |
|---|---|---|---|---|---|
| MP (°C) | 113–115 | NA | NA | NA | 94–95 |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | 207.5 (44140) | 388 (630), 289 (sh 2660), 280 (3040), 206 (33600) | 387 (620), 289 (2600), 278 (3020), 207 (31000) | 284 (970) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 1538, 1372, 1107 | 3271, 1652, 1471, 1260 | 3390 br, 3231 br, 2936, 2837, 1655, 1495, 1254, 1054 | 3151, 1675 | 2930, 2850, 1675, 1520, 1450, 1250 |

| | **142** (*102*) | **143** (*102*) | **144** (*103*) | **145** (*103*) |
|---|---|---|---|---|
| Appearance | Colorless amorphous solid | Colorless amorphous solid | Colorless amorphous solid | Colorless amorphous solid |
| Molecular formula | $C_{32}H_{50}N_6O_4Br_2$ | $C_{33}H_{52}N_6O_4Br_2$ | $C_{34}H_{53}N_6O_4Br_2$ | $C_{36}H_{59}N_6O_4Br_2$ |
| MS *m/z* | SIMS 741, 743, 745 (1:2:1) | SIMS 755, 757, 759 (1:2:1) | FABMS 767, 769, 771 (1:2:1) $[M+H]^+$ HRFABMS 767.2540 | FABMS 797, 799, 801 (1:2:1) $[M+H]^+$ HRFABMS 767.2956 |
| MP (°C) | 93–95 | 108–110 | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 284 (930) | 284 (910) | 284 (1100), 274 (1400) | 284 (710), 274 (1000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 2930, 2850, 1675, 1540, 1455, 1260 | 2930, 2860, 1675, 1520, 1450 | 3400, 2910, 1675, 1625, 1535, 1450, 1250, 1120 | 3400, 2840, 1675, 1620, 1535, 1450, 1200, 1130 |

| | **146** (*104*) | **147** (*105*) | **148** (*103*) | **149** (*79*) | **150** (*79*) |
|---|---|---|---|---|---|
| Appearance | Colorless amorphous solid | NA | Colorless oil | Colorless oil | Colorless oil |
| Molecular formula | $C_{17}H_{23}O_3N_6Br_2$ | $C_{22}H_{25}N_6O_3Br_2$ | $C_{14}H_{15}Br_2N_6O_3$ | $C_{15}H_{18}Br_2N_5O_4$ | $C_{15}H_{17}Br_2N_4O_4$ |

| | | | | | |
|---|---|---|---|---|---|
| MS *m/z* | FABMS (Positive glycerol matrix) 559, 557, 555 (1:2:1) $[M+K]^+$, 521, 519, 517 (1:2:1) $[M+H]^+$, 505, 503, 501 (1:2:1) $[M+H-NH_2]^+$, 441, 439 (1:2:1) $[M-Br]^+$ HRFABMS 517.0241 | FABMS 579, 581, 583 (1:2:1) HRFABMS 581.0366 (Δ 3.1 mmu) | 459.9631 | FABMS 490, 492, 494 ($M^+$+H, 1:2:1) HRFABMS 491.9705 | FABMS 475, 477, 479 ($M^+$+H, 1:2:1) HRFABMS 476.9596 |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 277 (520) | 286 (800), 269 (shoulder), 260 (2900), 217 (15300) | 277 (1700), 284 (1400) | 277 (1700), 284 (1400) | 235 (2600), 290 (2800) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Film) 3400, 1680, 1540, 1435, 1200, 1140 | 3400, 1680, 1200, 1140 | 3400, 2920, 2845, 1680, 1520, 1470, 1200, 1135, 1120 | 3400, 2920, 1680, 1520, 1470, 1200, 1135, 1120 | 3400, 2920, 2845, 1680, 1520, 1135, 1120 |

| | **151** (*89*) | **152** (*107*) | **153** (*107*) | **154** (*109*) | **155** (*110*) |
|---|---|---|---|---|---|
| Appearance | NA | White powder | White powder | Colorless foam | Oil |
| Molecular formula | $C_{18}H_{26}Br_2N_5O_2$ | $C_{22}H_{24}Br_2N_4O_6S_2$ | $C_{22}H_{24}Br_2N_4O_6S_2$ | $C_{44}H_{46}Br_4N_8O_{12}S_4$ | $C_8H_{17}N_2O_4S_2$ |
| MS *m/z* | 502.0432 | FABMS 689 (5), 687 (15), 685 (7) $[M^+$+Na], 667 (62), 665 (100), 663 (50) $[M^+$+H] HRFABMS 664.9560 | NA | NA | EIMS 268 (18) $[M^+]$, 193 (60), 134 (60) $[M^+-SCH_2CH_2NHCOOMe]$, 102 (100) $[M^+-SSCH_2CH_2NHCOOMe]$ CIMS (isobutane) 269 (100) $[M^+$+H], 237 (18), 197 (5), 134 (80), 102 (8) HRFABMS 269.0626 (Δ 0.4 mmu) |
| MP (°C) | NA | 172–174 | NA | NA | NA |
| $[\alpha]_D$ | +17° (*c* 1.0, MeOH) | NA | NA | 0° (*c* 1.0, MeOH) | NA |

(*continued*)

TABLE I.
Continued.

| | **151** (*89*) | **152** (*107*) | **153** (*107*) | **154** (*109*) | **155** (*110*) |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | 285 (3.17), 330 (2.69) | (EtOH) 277 (4875) | NA | 212 (110,000), 290 (14,100) | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3406, 1680, 1556, 1475, 1262 | 3348, 1657, 1637, 1536, 1025, 679 | 3300 br, 1670, 1540 | 3400–3100 br, 2900, 1670, 1570, 1450, 1200, 1025 | 3630, 3547, 2960, 1724, 1630, 1525, 1255, 1052 |

| | **156** (*110*) | **157** (*110*) | **158** (*110*) | **159** (*112*) | **160** (*112*) |
|---|---|---|---|---|---|
| Appearance | Oil | Oil | Oil | NA | NA |
| Molecular formula | $C_{12}H_{13}N_3O_3BrS$ | $C_{11}H_{15}N_3O_5BrS$ | $C_{15}H_{20}N_3O_5BrS_2$ | $C_{15}H_{19}N_4O_5S_2Br$ | $C_{15}H_{18}N_3O_6S_2Br$ |
| MS *m/z* | EIMS 357/359 (3) [$M^+$], 328/330 (5) [$M^+$–HCN–2H], 298/300 (5) [$M^+$–HSCN], 281/283 (7), 211/213 (100) [$C_8H_6NOBr$], 59 (30) [HSCN]. CIMS (isobutane) 358/360 (21) [$M^+$+H], 329/331 (29) [$M^+$–HCN–H], 299/301 (35) [$M^+$−HSCN+H], 283/285 (25). HRFABMS 357.9856 (Δ 0.5 mmu) | EIMS 379/381 (4) [$M^+$], 363/365 (2) [$M^+$–$NH_2$], 211/213 (100) [$C_8H_6NOBr$]. CIMS (isobutane) 380/382 (32) [$M^+$+H], 364/366 (20) [$M^+$−$NH_2$+H], 301/303 (15) [$M^+$−$SO_2NH_2$+2H]. HRFABMS 379.9913 (Δ 0.3 mmu) | EIMS 465/467 (5) [$M^+$], 390/392 (1) [$M^+$–NHCOOMe–H], 331/333 (22) [$M^+$–$SCH_2CH_2NHCOOMe$], 299/301 (37) [$M^+$–$SSCH_2CH_2NHCOOMe$], 226/230 (40), 211/213 (31) [$C_8H_6NOBr$]. CIMS (isobutane) 466/468 (10) [$M^+$+H], 375/377 (3), 333/335 (8), 299/301 (35). HREIMS 465.0030 (Δ 0.2 mmu) | HRFABMS 479.0094 [M+H]$^+$ (Δ−3.5 mmu) | HRFABMS 501.9724 [M+H]$^+$ (Δ 0.6 mmu) |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |

| | | | | | |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | 280 (5450) | NA | NA | 206 (18070), 284 (1858) | 206 (25935), 280 (2057) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3627, 3541, 2257, 2157, 1678, 1634, 1442, 1378, 1040 | 3300 br, 1670, 1540 | 3630, 3547, 2960, 1724, 1630, 1525, 1255, 1052 | (Film) 3500–3100 br, 3327, 1668, 1539, 1420, 1358, 1287, 1221, 1010, 985 | (Film) 3600–2600 br, 1647, 1527, 1424, 1390, 1287, 1219, 1047, 1019, 985 |

| | **161** (*112*) | **162** (*112*) | **163** (*112*) | **164** (*112*) | **165** (*114*) |
|---|---|---|---|---|---|
| Appearance | NA | NA | NA | NA | Pale yellow amorphous solid |
| Molecular formula | $C_{15}H_{20}N_5O_5S_2Br$ | $C_{16}H_{22}N_3O_5S_2BrNa$ | $C_{12}H_{15}N_2O_5S_2Br$ | $C_{22}H_{24}N_4O_7S_2Br_2$ | $C_{25}H_{34}Br_2N_7O_6S_2$ |
| MS $m/z$ | HRFABMS 494.0055 $[M+H]^+$ ($\Delta$ 3.4 mmu) | HRFABMS 502.0102 $[M+Na]^+$ ($\Delta$ 2.0 mmu) | HRFABMS 400.9795 $[M+Na]^+$ ($\Delta$ 1.2 mmu) | HRFABMS 700.9396 $[M+Na]^+$ ($\Delta$ 4.5 mmu) | (+)-HRFABMS 752.0381 for $C_{25}H_{34}Br_2N_7O_6S_2$ ($\Delta$ −2.3 mmu) (−)-HRFABMS 742.8976 for $C_{22}H_{23}Br_2N_4O_9S_2$ ($\Delta$ −0.3 mmu) ESIMS 743 |
| MP (°C) | NA | NA | NA | NA | 76–80 |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | NA | NA | NA | 204 (4.73), 281 (3.88) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Film) 3600–2600 br, 1666, 1631, 1596, 1531, 1437, 1408, 1354, 1290, 1220, 1145, 1043. 1025, 996 | (Film) 3500–3000 br, 1660, 1531, 1419, 1384, 1360, 1260, 1231, 1037, 985 | (Film) 3600–3000 br, 1654, 1531, 1501, 1420, 1361, 1284, 1043, 973 | 3600–2900 br, 1660, 1625, 1531, 1502, 1449, 1425, 1361, 1287, 1284, 1213, 1149, 1044 | 3400 br, 2925, 1655, 1530, 1485, 1250, 1230, 1040 |

(*continued*)

TABLE I.
Continued.

| | **166** (*114*) | **167** (*114*) | **168** (*114*) | **168a** (*114*) | **169** (*117*) |
|---|---|---|---|---|---|
| Appearance | Pale yellow amorphous solid | Yellow amorphous solid | Yellow amorphous solid | White solid | White amorphous solid |
| Molecular formula | $C_{25}H_{32}Br_2N_7O_{12}S_4$ | $C_{31}H_{27}Br_3N_4O_{13}S_3$ | $C_{31}H_{26}Br_3N_4O_{13}S_3$ | $C_{36}H_{37}Br_3N_4O_{10}S_2$ | $C_{22}H_{24}N_4O_6S_3Br_2$ |
| MS *m/z* | HRFABMS 909.9285 | (+)−FABMS 1068.8/1066.8, 1046.8/1044.8, 944.8/942.8 $[M\text{-}SO_3+Na+2H]^+$ (−)-FABMS 1044.9/1042.9 $[M+2Na-H]^-$, 1022.9/1020.9 $[M+Na\}^-$ (+)−HRFABMS 1068.7794 $[M+3Na]^+$, 1046.8165 $[M+2Na+H]^+$ | (+)−FABMS 1044.7/1042.7, 1022.6/1020.6 $[M+Na+H]^+$, 942.8/940.8 $[M-SO_3+Na+H]^+$ (−)-FABMS 998.7/996.8 ESIMS 998.7/996.8 (+)−HRFABMS 1044.8008 $[M+2Na]^+$ | HRFABMS 990.9545 $[M+H]^+$ | ESIMS 695 (*46*), 697 (100), 699 (60) $[M+H]^+$, 717 (35), 719 (74), 721 (45) $[M+Na]^+$, 466 (19), 468 (20), 363 (19), 365 (22) MALDI-TOFMS 718.9037 $[M+Na]^+$ |
| MP (°C) | 155–160 | 191–194 | 236–239 | 136–138 | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 204 (4.60), 281 (3.98) | 204 (4.83), 291 (4.11) | 205 (4.88), 280 (3.93) | NA | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3400 br, 2930, 1660, 1530, 1485, 1230, 1040 | 3400 br, 2925, 1660, 1565, 1270, 1230, 1040 | 3400 br, 2925, 1655, 1540, 1385, 1270, 1235, 1045 | NA | NA |

| | **170** (*117*) | **171** (*117*) | **172** (*44*) | **173** (*118*) | **174** (*118*) |
|---|---|---|---|---|---|
| Appearance | White amorphous solid | Yellow oil | Pale tan semicrystalline solid | White semicrystalline solid | White semicrystalline solid |
| Molecular formula | $C_{22}H_{23}N_4O_6S_2Br_3$ | $C_{44}H_{46}N_8O_{12}S_4Br_4$ | $C_{23}H_{28}Br_3N_3O_4$ | $C_{21}H_{24}Br_3N_3O_4$ | $C_{21}H_{23}Br_4N_3O_4$ |

| | | | | | |
|---|---|---|---|---|---|
| MS *m/z* | ESIMS 741 (25), 743 (81), 745 (100), 747 (35) $[M+H]^+$ MALDI–TOFMS 766.8495 $[M+Na]^+$ | ESIMS 1323 (8), 1325 (38), 1327 (52), 1329 (43), 1331 (15) $[M+H]^+$, 1345 (13), 1347 (54), 1349 (100), 1351 (77), 1353 (25) $[M+Na]^+$ MALDI-TOFMS 1348.9407 $[M+Na]^+$ | EIMS 647, 649, 651, 653, ($M^+$–HCl. 5%), 631, 633, 635, 637 (4), 562, 564, 566, 568 (9), 484, 486, 488 (5), 404, 406 (2), 225, 227 (35), 58 (100) FABMS 648, 650, 652, 654 ([$M^+$–HCl]+1) | FABMS 619.9380 $[M+H]^+$ | FABMS 699.8480 $[M+H]^+$ |
| MP (°C) | NA | NA | 87–88.5 | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | NA | 294 (3286), 266 (3850), 260 (4000), 250 (8300), 215 (26100) | 222 (16700), 280 (3100) | 222 (17400), 274 (2100) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | NA | 3369, 1655, 1534, 1490, 1426, 1228, 1016, 669 | 3427, 2922, 1632, 1454, 1256, 1053 | 3350, 2940, 1655, 1620, 1530, 1490, 1455 | 3400, 2990, 1670, 1630, 1530, 1460 |

| | **175** (*118*) | **176** Acetate (*119*) | **177** Acetate (*119*) | **178** (*82*) | **179** (*121*) |
|---|---|---|---|---|---|
| Appearance | Colorless gum | NA | NA | Glass | NA |
| Molecular formula | $C_{36}H_{52}Br_3N_3O_5$ | $C_{21}H_{25}Br_2N_3O_4$ | $C_{21}H_{24}Br_3N_3O_4$ | $C_{21}H_{24}Br_3N_3O_4$ | $C_{20}H_{23}Br_2N_3O_3$ |
| MS *m/z* | HRFABMS 844.1459 $[M+H]^+$ | FABMS 588 (4), 586 (7), 584 (4) $[M+H]^+$, 572 (5), 570 (8), 568 (5), 492 (4), 490 (4), 343 (11), 341 (10), 301 (9), 299 (9), 228 (19), 226 (21), 201 (47), 199 (57) | FABMS 668 (2), 666 (4), 664 (4), 662 (2) $[M+H]^+$, 652 (2), 650 (4), 648 (4), 646 (2), 586 (2), 584 (1), 572 (3), 570 (4), 568 (3), 492 (1), 490 (1), 343 (8), 341 (7), 308 (2), 306 (2), 304 (3), 281 (8), 279 (13), 277 (7) | EIMS 409 (13), 407 (33), 405 (13), 307 (20), 305 (45), 303 (23), 292 (18), 290 (29), 288 (16), 187 (40), 185 (54), 183 (38), 181 (32) HRFABMS 619.9377 | HRFABMS 514.0178 $[M+H]^+$ |

(*continued*)

TABLE I.
Continued.

| | **175** (*118*) | **176** Acetate (*119*) | **177** Acetate (*119*) | **178** (*82*) | **179** (*121*) |
|---|---|---|---|---|---|
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 214 (18500), 222 (17200), 282 (2700) | NA | NA | ($CHCl_3$) 240 (6750), 280 (3500) | 280 (834) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3400, 2910, 1660, 1645, 1490, 1445 | NA | NA | [$CHCl_3$–MeOH (1:1)] 3410, 3015, 2930, 1670, 1605, 1530, 1495, 1470, 1420 | (Film) 1658, 1540, 1458, 1420, 1258, 1200, 1010 |

| | **180** (*121*) | **181** (*121*) | **182** (*121*) | **182** (*121*) | **183** (*121*) |
|---|---|---|---|---|---|
| Appearance | NA | NA | NA | NA | NA |
| Molecular formula | $C_{20}H_{24}BrN_3O_3$ | $C_{25}H_{26}Br_2N_3O_3$ | $C_{20}H_{23}Br_2N_3O_3$ | $C_{21}H_{25}Br_2N_3O_3$ | $C_{20}H_{22}Br_3N_3O_4$ |
| MS *m/z* | HRFABMS 434.1086 $[M+H]^+$ | HRFABMS 578.0306 $[M]^+$ | HRFABMS 512.0141 $[M+H]^+$ | HRFABMS 526.0292 $[M+H]^+$ | HRFABMS 609.9254 $[M+H]^+$ |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 280 (641) | 250 (5600) | 282 (512) | 282 (600) | 282 (2600) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Film) 1680, 1540, 1498, 1458, 1200, 1138, 840, 800 | (Film) 1670, 1200, 1130, 800 | (Film) 1678, 1200, 1138, 840, 800 | 1678, 1204, 1140, 840, 800 | 1678, 1204, 1140, 800 |

| | **185** (*121*) | **186** (*121*) | **187** (*121*) | **188** (*121*) | **189** (*86*) | **190** (*122*) |
|---|---|---|---|---|---|---|
| Appearance | NA | NA | NA | White powder | Colorless oil | White solid |
| Molecular formula | $C_{21}H_{24}Br_3N_3O_4$ | $C_{21}H_{24}Br_3N_3O_4$ | $C_{22}H_{26}Br_3N_3O_4$ | $C_9H_9NO_3$ | $C_{23}H_{28}Br_3N_3O_5$ | $C_{24}H_{28}N_3O_6Br_3$ |

| | | | | | | |
|---|---|---|---|---|---|---|
| MS *m/z* | HRFABMS 619.9391 $[M+H]^+$ | HRFABMS 619.9349 $[M+H]^+$ | HRFABMS 639.9457 $[M+H]^+$ | NA | ESIMS 663.97, 665.96, 667.98, 669.96 $[M+H]^+$ HRESIMS 663.9763 $[M+H]^+$ ($\Delta$ 2.3 mmu) | FABMS 692, 694, 696, 698, (1:2:2:1) $[M+H]^+$ HRFABMS 694.2150 $[M+H]^+$ ($\Delta$ −2.2 mmu) |
| MP (°C) | NA | NA | NA | | NA | 190–195 |
| $[\alpha]_D$ | NA | NA | NA | | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 282 (2800) | 280 (2000) | 280 (1800) | | 280 (3.26) | 217 (3.65), 280 (4.78) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 1680, 1400, 1200, 800 | 1678, 1202, 1138, 842, 800, 722 | 1670, 1200, 1135, 838, 798, 721 | 1694, 1650, 1600, 1480, 1452, 1430, 1282, 1200, 1132, 1120, 1072, 1020, 920, 890, 740, 688 | 2937, 2852, 1743, 1656, 1533, 1493, 1452, 1253, 1047, 739 | 3404, 2926, 1675, 1494 |

| | **191** (*122*) | **192** (*84*) | **192** (*123*) | **194** (*123*) | **195** (*124*) |
|---|---|---|---|---|---|
| Appearance | White solid | Colorless amorphous solid | Yellow amorphous solid | Yellow amorphous solid | White powder |
| Molecular formula | $C_{22}H_{26}N_3O_4Br_3$ | $C_{23}H_{29}O_4N_4Br_4$ | $C_{28}H_{31}Br_4N_4O_4$ | $C_{28}H_{31}Br_4N_4O_4$ | $C_{24}H_{31}N_3Br_4O_3 \cdot HCl$ |
| MS *m/z* | FABMS 633, 635, 637, 639 (1:2:2:1) $[M+H]^+$. HRFABMS 635.7964 ($\Delta$ −2.8 mmu) | FABMS 771, 769, 767, 765, 763 $[M+Na]^+$, 749, 747, 745, 743, 741 $[M+H]^+$, 669, 667, 665, 663 HRFABMS 744.8868 | FABMS (glycerol matrix) 803, 805, 807, 809, 811 $[M]^+$; 645, 647, 649; 466, 468, 470; 426. 428. 430; 409, 411, 413, 415; 347, 349, 351 HRFABMS 806.9037 $[M]^+$ ($\Delta$ 0.0 mmu) | FABMS 803, 805, 807, 809, 811 $[M]^+$; 645, 647, 649; 466, 468, 470; 426. 428. 430; 409, 411, 413 HRFABMS 806.9007 $[M]^+$ ($\Delta$ −3.1 mmu) | DEIMS 726, 728, 730, 732, 734 (1.7); 448, 450, 452 (25:50:25); 403, 405, 407 (10:15:10); 320, 322, 324 (50:100:50) |
| MP (°C) | 175–178 | NA | NA | NA | 200 |
| $[\alpha]_D$ | NA | NA | NA | NA | +5.1° (*c* 0.013, MeOH) |

(*continued*)

TABLE I.
Continued.

| | **191** (*122*) | **192** (*84*) | **192** (*123*) | **194** (*123*) | **195** (*124*) |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | 214.5 (5.12), 280.0 (4.02) | 210 (23000), 285 (1600) | 216 (21800), 258 (4000 sh) | 214 (20600), 258 (3800 sh) | 283 (7800), 276 (9400), 245 (12300) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3350, 1670, 1200, 1137, 720 | 3400, 3100, 1680, 1400, 1200, 1130 | NA | NA | ($CHCl_3$) 3350, 1645, 1535, 1515, 1470, 1450, 1240, 980 |

| | **196** (*125*) | **197** (*125*) | **198** (*125*) | **199** (*90*) |
|---|---|---|---|---|
| Appearance | Pale orange oil | Colorless amorphous solid | Colorless, amorphous solid | NA |
| Molecular formula | $C_{25}H_{33}Br_4N_3O_3$ | $C_{23}H_{31}N_3O_3Br_3$ | $C_{24}H_{33}N_3O_3Br_3$ | $C_{17}H_{26}N_6O_3Br_2$ |
| MS *m/z* | CIMS 740 (22), 742 (70), 744 (100), 746 (64), 748 (20) [$MH^+$]; 696 (1), 698 (5), 700 (7), 702 (4), 704 (1) [$MH^+$–$NMe_2$]; 662 (4), 664 (10), 666 (8), 668 (2) [$MH^+$–Br]; 582 (3), 584 (6), 586 (3) [$MH^+$–$Br_2$]; 462 (3), 464 (12), 466 (12), 468 (3), 334 (15), 336 (26), 338 (15) [$C_{11}H_{14}Br_2NO^+$]; 309 (12), 311 (21), 313 (8), 118 (22). EIMS 696 (1), 698 (3), 700 (7), 702 (3), 704 (1) [$MH^+$–$NMe_2$]; 462 (4), 464 (9), 466 (7), [$C_{17}H_{26}Br_2N_3O_2^+$]; 377 (5), 379 (6), 381 (3) [$C_{12}H_{15}Br_2N_2O_2^+$]; 334 (52), 336 (99), 338 (50) [$C_{11}H_{14}Br_2NO^+$]; 256 (20), 258 (15) [$C_{11}H_{14}BrNO^+$]; 84 (17), 58 (100) [$CH_2NMe_2^+$] | FABMS 634, 636, 638, 640 (1:3:3:1) $[M+H]^+$ HRFABMS 633.9944 | FABMS 648, 650, 652, 654 (1:3:3:1) $[M+H]^+$ HRFABMS 648.0092 | FABMS 521, 523, 525 (1:2:1) HRFABMS [$MH^+$] 521.0501 |
| MP (°C) | NA | 64–67 | 79–81 | NA |
| $[\alpha]_D$ | 0° (*c* 5.0, $CHCl_3$) | +21° (*c* 1.0, MeOH) | +16° (*c* 1.0 MeOH) | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | 281 (2400) | 281 (2900) | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 1036, 1211, 1221, 1259, 1473, 1545, 1678, 2450, 2969, 3023, 3222 | 3425, 1655 | 3425, 1655 | NA |

| | **200** (*79*) | **201** (*127*) | **202** (*127*) | **203** (*127*) |
|---|---|---|---|---|
| Appearance | Colorless oil | White needles | White needles | Colorless gum |
| Molecular formula | $C_{15}H_{22}$ $Br_2N_5O_4$ | $C_{29}H_{41}I_3N_4O_4$ | $C_{29}H_{40}I_4N_4O_4$ | $C_{28}H_{39}I_3N_4O_4$ |
| MS *m/z* | FABMS 494, 496, 498 (1:2:1) $[M^+ + H]$ HRFABMS 496.0018 | FABMS 891 (100) [MH $^+$], 643 (18), 517 (10), 430 (93), 391 (12), 304 (93). EIMS 890 (Not observed) [M], 643 (10), 517 (10), 430 (25), 304 (35), 254 (56), 142 (100), 127 (92) | FABMS 1017 (87) [MH $^+$], 643 (18), 430 (100), 391 (12), 307 (45). EIMS 1016 (Not observed) [M], 643 (30), 430 (50), 304 (100), 254 (10) | FABMS 877 (100) [MH $^+$], 629 (13), 503 (17), 430 (100), 329 (10), 290 (37). EIMS 876 (Not observed) [M], 629 (45), 503 (15), 430 (100), 304 (12), 290 (11), 142 (40), 127 (15) |
| MP (°C) | NA | 135–137 | 114–116 | NA |
| $[\alpha]_D$ | NA | −0.23° (*c* 0.51) | −0.20° (*c* 0.35) | −0.74° (*c* 0.24) |
| UV $\lambda_{max}$ (MeOH) nm | 235 (2600), 287 (700) | 211 (25000), 223 (24000), 273 (5400) | 207 (32000), 221 (35000), 275 (8400) | 210 (40000), 222 (39000), 278 (9200) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3400, 2920, 2850, 1680, 1635, 1135, | ($CHCl_3$) 3368, 2935, 2883, 2855, 1672, 1600, 1518, 1500, 1491, 1479, 1463, 1447, 1441, 1416, 1278, 1272, 1254, 1050, 1020, 996 | ($CHCl_3$) 3368, 2938, 2882, 2855, 1674, 1614, 1602, 1522, 1464, 1416, 1264, 996 | ($CHCl_3$) 3367, 2940, 2861, 1671, 1522, 1492, 1463, 1264, 1260, 1255, 1050, 996, 925 |

| | **204** (*129*) | **205** (*129*) | **206** (*129*) | **227** (*129*) | **208** (*129*) |
|---|---|---|---|---|---|
| Appearance | Colorless foam | Colorless foam | Pale yellow foam | White powder | Yellow needles |
| Molecular formula | $C_{34}H_{30}Br_4N_4O_8$ | $C_{34}H_{29}Br_5N_4O_8$ | $C_{34}H_{30}Br_4N_4O_8$ | $C_{34}H_{29}Br_4N_4O_{11}Sna$ | $C_{34}H_{25}Br_5N_4O_8$ |
| MS *m/z* | 424 (23), 423 (11), 422 (48), 421 (6), 420 (24), 398 (24), 397 (10), 396 (13), 3959 (11), 394 (8), 316 (26), 314 (25), 303 (27), 301 (25), 262 (16), 243 (9), 241 (9), 201 (17), 200 (68), 199 (19), 198 (70), 188 (26), 187 (100), 186 (31), 185 (95), 120 (25), 119 (10), 107 (19), 105 (21), 103 (15), 102 (12), 91 (18), 89 (22), 88 (10), 82 (49), 81 (17), 80 (43), 79 (16), 78 (28), 77 (76), 76 (27), 75 (25), 74 (10), 65 (15), 64 (17), 63 (43), 62 (20), 58 (11), 53 (29), 52 (21), 51 (82), 50 (33) | No molecular ion; 504 (3), 502 (10), 500 (10), 498 (3), 200 (100), 198 (100), 187 (87), 185 (87) | 426 (2), 425 (6), 424 (11), 423 (10), 422 (18), 421 (4), 420 (8), 399 (6), 398 (8), 397 13), 396 (8), 395 (9), 243 (10), 201 (24), 200 (84), 199 (26), 198 (80), 189 (12), 188 (54), 187 (100), 186 (54), 185 (100), 120 (20), 108 (12), 107 (30), 105 (14), 91 (12), 89 (10), 82 (56), 81 (27), 80 (62), 79 (22), 78 (28), 77 (64), 51 (60) | MALDI FTMS $[M+Na_2^+]$ 1062.8130 | 504 (4), 502 (11), 500 (11), 498 (4), 424 (2), 422 (6), 420 (7), 418 (2), 396 (6), 394 (7), 392 (3), 342 (12), 340 (12), 82 (100), 81 (27), 80 (100), 79 (27) Found: 497.8219, $C_{16}H_9{}^{79}Br_3N_2O_2$ requires 497.8214 |

(*continued*)

TABLE I.
Continued.

| | **204** (*129*) | **205** (*129*) | **206** (*129*) | **227** (*129*) | **208** (*129*) |
|---|---|---|---|---|---|
| MP (°C) | NA | NA | NA | NA | 250 (dec) |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 220 (4.80) 282 (4.30), 288 sh (3.93) | 220 sh (4.70), 280 (3.93), 193 sh (3.87) | 220 (4.77), 285 (3.94) | 209 (84400), 279 (5550) | 210 (4.84), 288 (4.00), 315 (4.00) |
| IR $\upsilon_{max}$ (KBr) $cm^{-1}$ | NA | NA | NA | (ZnSe film) 3400–3000, 2921, 2852, 1660, 1531, 1486, 1424, 1262, 1234, 1180, 989 | (KBr disc) 3600, 2800, 1657, 1633, 1490, 1250 |

| | **209** Tetramethyl ether (*129*) | **210** (*129*) | **211** (*129*) | **228** (*130*) | **212** (*132*) |
|---|---|---|---|---|---|
| Appearance | Colorless prisms | White powder | Off-white foam | Yellow solid | White film |
| Molecular formula | $C_{38}H_{35}Br_5N_4O_8$ | $C_{34}H_{26}Br_6N_4O_8$ | $C_{34}H_{26}Br_4N_4O_8$ | $C_{34}H_{25}Br_4N_4O_{14}S_2Na_2$ | $C_{34}H_{27}Br_5N_4O_9$ |
| HR-MS $m/z$ | 1073.8310 | NA | NA | MALDI FTMS $[M+K_3^+]$ 1208.6481 | EIMS 504 (7.0), 502 (18.7), 500 (18.7), 498 (5.8), 342 (15.8), 340 (21.1), 199 (7.6), 199 (7.0) |
| MP (°C) | 262–264 | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 220 sh, 275 | 220 sh (4.69), 281 (3.47) | 290 (4.18), 315 (4.19) | 207 (82300), 321 (12400) | 208 (5.1), 280 (3.9) |
| IR $\upsilon_{max}$ (KBr) $cm^{-1}$ | 1670, 1565, 1520, 1495, 1455, 1043 | 3500–2800, 1665, 1658, 1630, 1500, 1450, 1420, 1280, 1245, 1020, 980 | 3600–2900, 1663, 1635, 1490, 1455, 1430, 1250, 1015, 1000, 990 | (ZnSe film) 3300–2860, 1670, 1653, 1571, 1523, 1482, 1418, 1277, 1240, 1051, 1026, 1005 | (Film on NaCl plate) 3340, 1700, 1660, 1590, 1530, 1490, 1450, 1420, 1360, 1280, 1240, 990 |

| | **212** Tetramethyl ether (*132*) | **213** (*132*) | **213** Tetramethyl ether (*132*) | **214** (*132*) | **215** (*132*) |
|---|---|---|---|---|---|
| Appearance | White powder | White powder | NA | Colorless oil | Whitish film |
| Molecular formula | $C_{37}H_{33}Br_5N_4O_9$ | $C_{34}H_{28}O_8N_4Br_4$ | NA | $C_{34}H_{28}O_9N_4Br_4$ | $C_{34}H_{26}O_8N_4Br_4$ |
| MS *m/z* | FABMS [*p*-nitrobenzyl alcohol/magic bullet (dithiothreitol/dithioerythritol) matrix] 1076.9 (33.2), 1074.9 (52.5), 1072.8 (24.7), 1070.8 (19.9). HRFABMS 1110.8194 ($C_{38}H_{35}N_4O_9{}^{79}Br_4{}^{81}BrNa$ requires 1110.8198), 1112.8194 ($C_{38}H_{35}N_4O_9{}^{79}Br_3{}^{81}Br_2Na$ requires 1112.8178), 1114.8035 ($C_{38}H_{35}N_4O_9{}^{79}Br_2{}^{81}Br_3Na$ requires 1114.8157), 1116.7491 ($C_{38}H_{35}N_4O_9{}^{79}Br{}^{81}Br_4Na$ requires 1116.8137) | FABMS (Magic bullet matrix) 942 (1), 940 (2), 938 (2), 936 (1) [$M^+$] | FABMS 1014 (7.1) [$M+Na]^+$, 1016 (21.1), 1018 (28.3), 1020 (26.3), 1022 (1.2). HREIMS 511.8354 (34.4), 513.8460 (95.8), 515.88416 (100), 517.8290 (37.5) | NA | NA |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | 208 (5.1), 280 (4.0) | NA | 210 (4.7), 277 (3.7) | 208 (4.3), 285 (3.4), 331 (3.5) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | NA | (Film) 3420–3200, 1710, 1660, 1620, 1585, 1450, 1420, 1360, 1230 | NA | (Film) 3340 br, 1698, 1662, 1590, 1545, 1483, 1421, 1290, 1240 | (Film) 3300 br, 1718, 1662, 1646, 1544, 1495, 1479, 1447, 1418, 1284, 1243 |

(*continued*)

TABLE I.
Continued.

| | **216** Methyl ether (*142*) | **217** (*131*) | **217** Methyl ether (*131*) | **226** (*141*) |
|---|---|---|---|---|
| Appearance | White amorphous solid | White powder | White powder | NA |
| Molecular formula | $C_{38}H_{35}N_4O_9Br_5$ | $C_{34}H_{28}Br_4N_4O_8$ | $C_{38}H_{36}Br_4N_4O_8$ | $C_{34}H_{27}Br_4N_4O_{11}S$ |
| MS $m/z$ | 1096 (0.5), 1094 (2.0), 1092 (4.1), 1090 (4.2), 1088 (2.4), 1086 (0.7), 1078 (1.0), 1076 (3.7), 1074 (7.2), 1072 (6.5), 1070 (3.4), 1068 (0.8), 1065 (1.1), 1063 (2.3), 1061 (5.6), 1059 (5.3), 1057 (3.0), 1055 (0.8), 1047 (1.1), 1045 (3.2), 1043 (5.6), 1041 (5.0), 1039 (2.9), 1037 (0.7), 1015 (1.3), 1013 (2.2), 1011 (2.7), 1009 (2.1), 1007 (0.9), 648 (0.4 ), 632 (0.8), 630 (0.6), 602 (3.1), 600 (5.7), 598 (2.8), 592 (1.2), 590 (1.6), 571 (8.0), 569 (13.9), 567 (7.6), 551 (2.0), 549 (5.1), 547 (4.9), 545 (2.3), 536 (2.5), 534 (3.6), 532 (4.6), 530 (3.3), 438 (21.1), 436 (40.4), 434 (20.8), 412 (12.9), 411 (14.1), 410 (19.6), 409 (14.0), 408 (10.0), 342 (20.5), 340 (18.3), 318 (5.6), 316 (13.8), 314 (10.4), 276 (22.5), 261 (8.8), 169 (9.2), 115 (9.4), 82 (41.5), 80 (42.1), 31 (73.6), 29 (100.0). HREIMS 1089.8312. CIMS (Showed one extra Br) $[M+Br]^+$ 1178 (122.7), 1176 (37.3), 1174 (72.2), 1172 (92.9), 1170 (56.4), 1168 (21.8), 1166 (1.2), 1096 (21.0), 1094 (52.0), 1092 (74.2), 1090 (54.0), 1088 (22.6), 1086 (2.4) | EI: 520 (4), 518 (4), 516 (3), 396 (9), 394 (16), 392 (8), 342 (23), 340 (24), 317 (8), 316 (7), 315 (10), 57 (100) | EI: 1000 (4), 998 (14), 996 (20), 994 (13), 992 (4), 969 (4), 967 (10), 965 (14), 963 (9), 518 (20), 516 (530, 514 (54), 512 (18420 (16), 419 (16), 417 (21), 376 (33), 375 (53), 73 (52), 333 (31), 332 (97), 331 (31), 330 (100) | HRFABMS: 1018.8064 $[M–Na]^-$ |
| MP (°C) | NA | 177–179 | 107–109 | NA |
| $[\alpha]_D$ | +2.7° ($c$ 0.77, $CH_2Cl_2$) | | 0.0° ($c$ 1.52, $CH_2Cl_2$) | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | 209 (81100), 283 (6200) | 209 (76400), 276 (7450) | 280 (4800), 204 (74000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Film) 3327, 2932, 2857, 1669, 1487 | | 3413, 1666 | NA |

| | **218** (*133*) | **219** (*134*) | **220** (*135*) | **221** (*135*) |
|---|---|---|---|---|
| Appearance | NA | White amorphous solid | NA | NA |
| Molecular formula | $C_{38}H_{25}Br_5N_4O_8$ | $C_{34}H_{27}N_4O_8Br_5$ | $C_{34}H_{27}Br_5N_4O_8$ | $C_{34}H_{28}Br_4N_4O_9$ |
| MS *m/z* | EIMS 424 (2.4), 422 (4.5), 420 (2.5), 316 (3.4), 314 (2.6), 303 (2.7), 301 (3.1) HREIMS 421.9089 | HRFABMS 1016.7785 $[M+H]^+$ | HRFABMS 1018.7792 $[M+H]^+$ | HRFABMS 956.8606 $[M+H]^+$ |
| MP (°C) | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | Negative, too small to be measured | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 284 (4.3), 292 (4.3), 314 (4.4) | NA | (Nujol) 280 (3.6) | (Nujol) 278 (4.1) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Nujol) 3500–3300, 1655, 1580, 1530, 1500, 1455, 1425, 1280, 1245, 1230, 1180 | NA | 3500–3300, 1650, 1630, 1480, 1240, 1225 | 3600–3100, 1660, 1640, 1490, 1470, 1285, 1220 |

| | **222** (*138*) | **223** (*139*) | **224** (*130*) | **225** (*140*) | **225** Tetramethyl ether (*140*) |
|---|---|---|---|---|---|
| Appearance | Colorless amorphous solid | Colorless amorphous powder | Colorless solid | Amorphous white solid | Pale yellow gum |
| Molecular formula | $C_{34}H_{28}Br_4N_4O_8$ | $C_{34}H_{27}Br_5N_4O_8$ | $C_{34}H_{28}Br_4N_4O_8$ | $C_{34}H_{29}N_4O_8Br_3$ | $C_{38}H_{37}N_4O_8Br_3$ |
| MS *m/z* | FABMS $[M^+ +1]$ 613 (4.9), 581 (1.8), 461 (5.3), 427 (1.5) HRFABMS 940.8705 | FABMS 1018.8 | MALDI FTMS $[M+Na^+]$ 958.8588 | ESIMS $[M+Na]^+$ 887 (40), 885 (100), 883 (96), 881 (32) HRESIMS 886.9394, 884.9406, 882.9412, 880.9431 | HRESI: 920 (24), |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |

(*continued*)

TABLE I.
Continued.

| | **222** (*138*) | **223** (*139*) | **224** (*130*) | **225** (*140*) | **225** Tetramethyl ether (*140*) |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | NA | NA | 209 (84400), 279 (5550) | 279 (3.4), 3.83 (2.99) | 205 (4.71) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | NA | NA | (ZnSe film) 3400–3000, 2921, 2852, 1660, 1531, 1486, 1424, 1262, 1234, 1180, 989 | 3422, 2925, 1743, 1654, 1697, 1490, 1380, 1235, 1044 | 3054, 2970, 2954, 2854, 1735, 1676, 1376, |

| | **231** (*41*) | **237** (*41*) | **232:233** 3:1 (*41*) | **238** (*41*) |
|---|---|---|---|---|
| Appearance | Colorless oil | Colorless oil | | Colorless solid |
| Molecular formula | $C_{17}H_{16}Br_2N_2O_4$ | $C_{18}H_{18}Br_2N_2O_4$ | $C_{17}H_{15}Br_3N_2O_4$ | $C_{18}H_{18}Br_3N_2O_4$ |
| MS *m/z* | EIMS 474 (10), 472 (19), 470 (10), 458 (7), 456 (16), 454 (7), 256 (9), 214 (23), 213 (91), 212 (33), 211 (84), 201 (26), 200 (97), 199 (27), 198 (98), 188 (13), 187 (95), 186 (15), 185 (100), 132 (43), 120 (31), 77 (42). HREIMS 469.9437 ($C_{17}H_{16}{}^{81}Br_2N_2O_4$ calcd 473.9430), 471.9445 ($C_{17}H_{16}{}^{79}Br^{81}BrN_2O_4$ calcd 471.9457), 469.9467 ($C_{17}H_{16}{}^{79}Br_2N_2O_4$ calcd 473.9477) | EIMS 488 (6), 486 (13), 484 (6), 472 (6), 470 (11), 468 (6), 288 (12), 286 (12), 228 (21), 227 (97), 226 (20), 225 (100), 201 (38), 200 (30), 199 (38), 198 (27), 187 (50), 185 (53), 146 (52), 120 (18), 103 (33), 77 (38). HREIMS 487.9615 ($C_{18}H_{18}{}^{81}Br_2N_2O_4$ calcd 487.9593), 485.9609 ($C_{18}H_{18}{}^{79}Br^{81}BrN_2O_4$ calcd 485.9614), 483.9633 ($C_{18}H_{18}{}^{79}Br_2N_2O_4$ calcd 485.9634) | EIMS 554 (4), 552 (14), 550 (14), 548 (5), 293 (33), 291 (67), 289 (34), 267 (24), 265 (50), 263 (24), 213 (41), 212 (51), 211 (24), 198 (76), 187 (91), 185 (100), 132 (28), 120 (25), 77 (49). HREIMS 553.8549 ($C_{17}H_{15}{}^{81}Br_3N_2O_4$ calcd 553.8522), 551.8536 ($C_{17}H_{15}{}^{79}Br^{81}Br_2N_2O_4$ calcd 551.8542), 549.8562 ($C_{17}H_{15}{}^{79}Br_2{}^{81}BrN_2O_4$ calcd 549.8562), 547.8570 ($C_{17}H_{15}{}^{79}Br_3N_2O_4$, calcd 547.8582) | EIMS 568 (2), 566 (6), 564 (7), 562 (2), 552 (2), 550 (7), 548 (8), 546 (2), 307 (30), 305 (61), 303 (30), 292 (14), 290 (25), 288 (13), 281 (10), 279 (17), 277 (9), 271 (7), 269 (23), 267 (10), 201 (15), 200 (96), 199 (18), 198 (100), 187 (44), 185 (48), 183 (17), 181 (15), 143 (18), 120 (18), 77 (17). HREIMS 567.8672 ($C_{18}H_{18}{}^{81}Br_3N_2O_4$ calcd 567.8679), 565.8701 ($C_{18}H_{18}{}^{79}Br^{81}Br_2N_2O_4$ calcd 565.8699), 563.8715 ($C_{18}H_{18}{}^{79}Br_2{}^{81}BrN_2O_4$ calcd 563.8719), 561.8716 ($C_{18}H_{18}{}^{79}Br_3N_2O_4$ calcd 561.8739) |

| | | | | |
|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | 210 (4.53), 281 (3.88) | 213 (4.53), 280 (3.87) | NA | 213 (4.50), 281 (3.87) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (NaCl film) 3383, 3000, 1659, 1537, 1495, 1422, 1283, 1256 | (NaCl film) 3385, 3283, 1657, 1537, 1497, 1283, 1256 | (NaCl film) 3393, 1657, 1476 | (NaCl film) 3300, 1661, 1537, 1497, 1472, 1422, 1260, 993 |

| | **234** (*41*) | **234a** (*41*) | **235** (*41*) | **235a:236a** (*41*) |
|---|---|---|---|---|
| Appearance | Colorless solid | Colorless solid | Mixture with hemibastadinol-3 | Colorless solid |
| Molecular formula | $C_{17}H_{17}Br_2NO_4$ | $C_{19}H_{21}Br_2NO_4$ | $C_{17}H_{16}Br_3NO_4$ | $C_{19}H_{20}Br_3NO_4$ |
| MS *m/z* | EIMS 461 (>1), 459 (0.3), 457 (>1), 443 (6), 441 (13), 439 (6), 244 (30), 242 (35), 241 (18), 227 (14), 225 (15), 201 (19), 200 (98), 199 (21), 198 (100), 187 (28), 185 (28), 120 (20), 107 (23), 77 (18) HREIMS 460.9477 ($C_{17}H_{17}{}^{81}Br_2NO_4$ calcd 460.9494), 458.9483 ($C_{17}H_{17}{}^{79}Br^{81}BrNO_4$ calcd 458.9514), 456.9507 ($C_{17}H_{17}{}^{79}Br_2NO_4$ calcd 456.9534) | HRFABMS [M+H] 485.9897 ($C_{19}H_{22}{}^{79}Br_2NO_4$, calcd 485.9915) | EIMS 541 (<1), 539 (<1), 537 (<1), 535 (<1), [$M^+$–$H_2O$] 523 (2), 521 (7), 519 (6), 517 (2), 244 (9), 242 (10), 201 (15), 200 (100), 199 (16), 198 (100), 187 (16), 185 (17), 120 (20), 77 (13). HREIMS 540.8558 ($C_{17}H_{16}{}^{81}Br_3NO_4$ calcd 540.8572), 538.8586 ($C_{17}H_{16}{}^{79}Br^{81}Br_2NO_4$ calcd 538.8593), 536.8631 ($C_{17}H_{16}{}^{79}Br_2{}^{81}BrNO_4$ calcd 536.8612), 534.8605 ($C_{17}H_{16}{}^{79}Br_3NO_4$ calcd 534.8633), [$M^+$–$H_2O$] 522.8446 ($C_{17}H_{14}{}^{81}Br_3NO_3$ calcd 522.8464), 518.8497 ($C_{17}H_{14}{}^{79}Br_2{}^{81}BrNO_3$ calcd 518.8504), 516.8509 ($C_{17}H_{14}{}^{79}Br_3NO_3$ calcd 516.8524) | HRFABMS [M+H], 563.9019 ($C_{19}H_{20}{}^{79}Br_3NO_4$, calcd 563.9020) |
| MP (°C) | NA | NA | NA | NA |
| $[\alpha]_D$ | −31° (*c* 1.83, MeOH) | −23° (*c* 0.66, MeOH) | −24° (*c* 0.10, MeOH) | NA |
| UV $\lambda_{max}$ (MeOH) nm | 208 (4.43), 281 (3.69) | 208 (4.45), 281 (3.60) | NA | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Film) 3381, 1643, 1541, 1495, 1420, 1289 | (Film) 3387, 1651, 1497, 1279, 1256, 1057 | (Film) 3381, 1643, 1539, 1478, 1279 | 3393, 2930, 1651, 1537, 1497, 1472, 1258 |

(*continued*)

TABLE I.
Continued.

| | **236** (*41*) | **239** (*145*) | **240** (*145*) | **241** (*145*) |
|---|---|---|---|---|
| Appearance | Mixture with hemibastadinol-2 | White needles | Colorless gum | White needles |
| Molecular formula | $C_{17}H_{16}Br_3NO_4$ | $C_{19}H_{17}Br_2NO_4$ | $C_{19}H_{17}Br_2NO_4$ | $C_{19}H_{18}BrNO_4$ |
| MS *m*/*z* | EIMS 541 (< 1), 539 (< 1), 537 (< 1), 535 (< 1), [$M^+$–$H_2O$] 523 (2), 521 (7), 519 (6), 517 (2), 244 (9), 242 (10), 201 (15), 200 (100), 199 (16), 198 (100), 187 (16), 185 (17), 120 (20), 77 (13) HREIMS 540.8558 ($C_{17}H_{16}{}^{81}Br_3NO_4$ calcd 540.8572), 538.8586 ($C_{17}H_{16}{}^{79}Br^{81}Br_2NO_4$ calcd 538.8593), 536.8631 ($C_{17}H_{16}{}^{79}Br_2{}^{81}BrNO_4$ calcd 536.8612), 534.8605 ($C_{17}H_{16}{}^{79}Br_3NO_4$ calcd 534.8633), [$M^+$–$H_2O$] 522.8446 ($C_{17}H_{14}{}^{81}Br_3NO_3$ calcd 522.8464), 518.8497 ($C_{17}H_{14}{}^{79}Br_2{}^{81}BrNO_3$ calcd 518.8504), 516.8509 ($C_{17}H_{14}{}^{79}Br_3NO_3$ calcd 516.8524) | EIMS 484.9 (3), 482.9 (6), 480.9 (3), 177 (17), 149 (20), 134 (100), 106 (25), 78 (15), 77 (13) HREIMS 480.9526 | EIMS 484.9 (4), 482.9 (8), 480.9 (4), 177 (21), 149 (21), 134 (100), 106 (19), 78 (10), 77 (9) HREIMS 480.9526 | EIMS 405 (7), 403 (6), 229 (7), 227 (7), 177 (11), 149 (16), 78 (13), 77 (15) HREIMS 403.418 |
| MP (°C) | NA | 169–171 | NA | 173–175 |
| $[\alpha]_D$ | −24° (*c* 0.10, MeOH) | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | (EtOH) 205 (10900), 220 (10300), 225 sh (9900), 325 (15900) | (EtOH) 206 (10800), 214 (9600), 230 sh (9400), 328 (14100) | (EtOH) 204 (13200), 227 sh (10600), 329 (14100) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (NaCl film) 3381, 1643, 1539, 1478, 1279 | ($CHCl_3$) 3410, 3018, 2927, 2855, 1735, 1650, 1607, 1513, 1496, 1468, 1423, 1265, 1171, 1087, 909 | ($CHCl_3$) 3409, 3018, 1700, 1650, 1607, 1513, 1468, 1423, 1250, 1171, 1087, 1001, 949 | ($CHCl_3$) 3409, 3018, 2927, 2855, 1730, 1693, 1653, 1607, 1513, 1486, 1463, 1441, 1259, 1171, 1089, 1054, 1019 |

| | **242** (*145*) | **243** (*146*) | **244** (*146*) | **245** (*146*) | **247** (*123*) |
|---|---|---|---|---|---|
| Appearance | Colorless gum | NA | NA | NA | Yellow amorphous solid |
| Molecular formula | $C_{19}H_{18}BrNO_4$ | $C_{24}H_{28}Br_2N_2O_4$ | $C_{24}H_{28}BrIN_2O_4$ | $C_{24}H_{28}I_2N_2O_4$ | $C_{17}H_{25}Br_2N_3O_2$ |
| MS *m/z* | EIMS 405 (8), 403 (7), 229 (8), 227 (7), 177 (12), 149 (18), 135 (9), 134 (100), 106 (21), 78 (13), 77 (16)<br>HREIMS 403.0418 | FABMS 571, 569, 567 $[M+H]^+$ | FABMS 617, 615 $[M+H]^+$ | FABMS 663 $[M+H]^+$ | FABMS 803, 805, 807, 809, 811 $[M]^+$, 466, 468, 470, 426, 428, 430, 409, 411, 413<br>HRFABMS 806.9007 $[M]^+$ |
| MP (°C) | NA | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | (EtOH) 203 (11100), 224 sh (9100), 326 (11700) | NA | NA | NA | 214 (20600), 258 sh (3800) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | ($CHCl_3$) 3413, 3018, 2935, 1710, 1650, 1607, 1513, 1466, 1425, 1248, 1168, 1087, 1001, 949 | (Neat) 3286, 1635, 1542, 1515, 1455, 1256 | (Neat) 3283, 1628, 1537, 1514, 1443, 1260 | (Neat) 3276, 1629, 1538, 1514, 1435, 1256 | NA |

| | **246** (*38*) | **248** (*150*) | **249** (*151*) | **250** (*151*) | **251** (*152*) | **252** (*152*) |
|---|---|---|---|---|---|---|
| Appearance | Amorphous solid | NA | Small yellow crystals | Small yellow crystals | Yellow amorphous solid | Yellow amorphous solid |
| Molecular formula | $C_{15}H_{17}N_4O_2Br_2$ | $C_{14}H_{10}O_{11}S_2Br_2$ | $C_{17}H_{16}Br_2N_4O_2$ | $C_{16}H_{14}Br_2N_4O_2$ | $C_{23}H_{24}N_3O_3Br_3$ | $C_{22}H_{22}N_3O_3Br_3$ |
| MS *m/z* | FABMS 443, 445, 447 | NA | HREIMS 467.9624 $[M^+]$ | HREIMS 453.9460 $[M^+]$ | FABMS 628, 630, 632, 634 (1:3:3:1) $[M+H]^+$<br>HRFABMS 631.9403 $[M+H]^+$<br>($\Delta$ −0.2 mmu) | FABMS 614, 616, 618, 620 (1:3:3:1) $[M+H]^+$<br>HRFABMS 615.9280 $(M+H)^+$<br>($\Delta$ +1.8 mmu) |

(*continued*)

TABLE I.
Continued.

| | **246** (*38*) | **248** (*150*) | **249** (*151*) | **250** (*151*) | **251** (*152*) | **252** (*152*) |
|---|---|---|---|---|---|---|
| MP (°C) | NA | NA | 236 | 242 | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | (EtOH) 226 (12200), 298 (32000) | NA | NA | NA | 285 (4000), 350 (1000) | 285 (5000), 350 (1200) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Dry film) 1690 | (Film) 3454 (br d), 1631, 1257 (br d), 1059, 1018 | NA | NA | 3422, 1680 | 3422, 1680 |

| | **253** (*153*) | **254** (*153*) | **255** (*153*) | **256** (*154*) | **257** (*154*) |
|---|---|---|---|---|---|
| Appearance | Needles | White amorphous solid | White amorphous solid | White solid | White gum |
| Molecular formula | $C_{18}H_{15}N_2O_3Br$ | $C_{18}H_{15}N_2O_3I$ | $C_{18}H_{16}N_2O_3$ | $C_{19}H_{21}N_2O_2Br$ | $C_{19}H_{20}N_2O_2Br_2$ |
| MS *m/z* | HRFABMS $[M^+ + H]$ 387.0313 | HREIMS 434.0146 | HREIMS 308.1159 | HREIMS 370.0681 $[M-H_2O]^+$ | HREIMS 465.9891 $[M^+]$ |
| MP (°C) | 178–179 | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | (MeOH) 324 (8400), 290 (5000), 274 (9600), 267 (9900), 255 (10300), 205 (41400) (MeOH+NaOH), 309 (9800), 272 (8600), 266 (9900), 247 (1600), 207 (58500) | (MeOH) 325 (6600), 274 (8200), 267 (sh), 254 (9100), 230 (sh), 205 (50000) (MeOH+NaOH), 311 (8200), 274 (7600), 267 (sh), 247 (13200), 203 (79100) | (MeOH) 324 (4600), 285 (sh), 272 (5700), 266 (6100), 254 (6400), 205 (19200) (MeOH+NaOH), 218 (4600), 272 (5300), 266 (6100), 246 (8300), 205 (21400) | 288 (sh), 280 (6400), 221 (30600), 208 (29000) | (DMSO) 299 (sh), 287 (2500), 279 (sh), 221 (30600), 208 (29000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | ($CHCl_3$) 3010, 1680, 1635, 1500, 1420, 1215, 1120 | (neat NaCl) 2930, 1680, 1640, 1505, 1420 | NA | ($CHCl_3$) 3470, 3330 br, 1605, 1500, 1460, 1445, 1420, 1285, 1260, 1055 | ($CHCl_3$) 3470, 3330 br, 1605, 1500, 1460, 1445, 1420, 1285, 1260, 1055 |

| | **258** (*155*) | **259** (*164*) | **260** (*158*) | **261** (*158*) | **262** (*159*) |
|---|---|---|---|---|---|
| Appearance | Gum | NA | Colorless prisms | Colorless crystals | Colorless glass |
| Molecular formula | $C_{12}H_{17}NO_5$ | $C_{36}H_{45}I\ N_4O_6Br$ | $C_{28}H_{40}I\ N_3O_6$ | $C_{28}H_{40}BrN_3O_6$ | $C_{28}H_{40}N_3O_6Cl$ |
| MS *m/z* | FABMS 256 ($M+H^+$, 100) HRFABMS 256.11858, 256.11850 | NA | FABMS 642 (100) [$MH^+$], 516 (50), 393 (15), 276 (30), 217 (50), 150 (50) | FABMS 594 (95) [$MH^+$], 516 (60), 345 (30), 267 (30), 228 (80), 150 (100) | HREIMS 549.2603, 551.2562 ($\Delta$ −0.2, −1.4 mmu) |
| MP (°C) | NA | NA | 217–218 | 203–204 | NA |
| $[\alpha]_D$ | +25.51° (*c* 0.002, MeOH) | +35° (*c* 3.62, $CHCl_3$) | +53° (*c* 0.04, $CHCl_3$) | +101° (*c* 0.04, $CHCl_3$) | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | 281 (5400), 290 (4100) | 219 (13800), 284 (3200), 292 (3000) | 214 (15400), 281 (2700), 290 (2500) | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | NA | ($CDCl_3$) 3400–3100, 1710, 1660, 1630 | ($CHCl_3$) 1725, 1670, 1655, 1630 | ($CHCl_3$) 3510, 3410, 1725, 1670, 1655 (sh), 1630 | NA |

| | **263** (*159*) | **264** (*159*) | **265** (*159*) | **266** (*164*) | **267** (*161*) |
|---|---|---|---|---|---|
| Appearance | Colorless glass | NA | NA | Colorless glass | NA |
| Molecular formula | $C_{27}H_{38}N_3O_6I$ | $C_{27}H_{38}N_3O_6Br$ | $C_{27}H_{38}N_3O_6Cl$ | $C_{28}H_{38}N_3O_7I$ | $C_{34}H_{44}O_7N_3I$ |
| MS *m/z* | HREIMS 627.1798 ($\Delta$ −0.9 mmu) | HREIMS 579.1955, 581.1909 ($\Delta$ +1.1, −1.6 mmu) | HREIMS 535.2449, 537.2442 ($\Delta$ 0.0, +2.2 mmu) | HREIMS 655.1760 ($\Delta$M, 0.6 mmu) | EIMS 773 (48) [$M]^+$, 706 (10), 608 (15), 552 (5), 460 (54), 413 (17), 321 (24), 276 (100), 250 (19), 162 (73), 109 (46), HREIMS 733.2199 |
| MP (°C) | NA | NA | NA | NA | 186–189 |
| $[\alpha]_D$ | NA | NA | NA | NA | +19.1° (*c* 0.17, $CHCl_3$) |

(*continued*)

TABLE I.
Continued.

| | **263** (*159*) | **264** (*159*) | **265** (*159*) | **266** (*164*) | **267** (*161*) |
|---|---|---|---|---|---|
| UV $\lambda_{max}$ (MeOH) nm | NA | NA | NA | NA | 215 (12500), 280 (2800) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | NA | NA | NA | 3313, 1732, 1675, 1635 | 3495, 1724, 1670 |

| | **268** (*161*) | **271** (*164*) | **272** (*164*) | **273** (*164*) | **274** (*164*) |
|---|---|---|---|---|---|
| Appearance | NA | Colorless glass | Colorless glass | Colorless glass | Colorless glass |
| Molecular formula | $C_{34}H_{44}O_7N_3Br$ | $C_{28}H_{39}N_3O_7Br$ | $C_{28}H_{39}N_3O_7Cl$ | $C_{28}H_{40}N_3O_7I$ | $C_{28}H_{39}N_3O_7Br$ |
| MS *m/z* | EIMS 685 (38) $[M]^+$, 657 (10), 460 (52), 413 (24), 273 (26), 228 (100), 162 (87), 109 (59) HREIMS 685.2374 | HRDCIMS 610.19509, 608.19713 ($C_{28}H_{39}N_3O_7{}^{81}Br$, $C_{28}H_{39}N_3O_7{}^{79}Br$); found 610.19431, 608.19508 ($\Delta$ −1.49, −3.38 ppm) | HRDCIMS 565.23688, 563.23981 ($C_{28}H_{39}N_3O_7{}^{37}Cl$, $C_{28}H_{39}N_3O_7{}^{35}Cl$); found 565.23956, 563.24011 ($\Delta$ −4.7, −0.5 ppm) | HREIMS 658.19892, found 658.19767 ($\Delta$ −1.91 ppm) | HREIMS 611.20294, 609.20496 ($C_{28}H_{40}N_3O_7{}^{81}Br$, $C_{28}H_{40}N_3O_7{}^{79}Br$); found 611.20371, 609.20519 ($\Delta$ −1.3, −0.4 ppm) |
| MP (°C) | 168–170 | NA | NA | NA | NA |
| $[\alpha]_D$ | +39.3° (*c* 0.17, $CHCl_3$) | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | 214 (14000), 280 (3000) | NA | NA | NA | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | ($CHCl_3$) 3500, 1725, 1670 | NA | NA | NA | NA |

| | **275** (*164*) | **276** (*164*) | **277** (*164*) | **278** (*164*) |
|---|---|---|---|---|
| Appearance | Colorless glass | Colorless glass | Colorless glass | Colorless glass |
| Molecular formula | $C_{28}H_{39}N_3O_7Cl$ | $C_{28}H_{40}O_7N_3I$ | $C_{28}H_{39}N_3O_7Br$ | $C_{27}H_{38}O_7N_3I$ |

| | | | | | |
|---|---|---|---|---|---|
| MS *m/z* | HREIMS 567.25250, 265.25549 ($C_{28}H_{40}N_3O_7{}^{37}Cl$, $C_{28}H_{40}N_3O_7{}^{735}Cl$); found 567.25184, 565.25403 (Δ 1.2, 2.6 ppm) | HREIMS 658.19892, found 658.19880 (Δ −0.19 ppm) | HREIMS 611.20294, 609.20496 ($C_{28}H_{40}N_3O_7{}^{81}Br$, $C_{28}H_{40}N_3O_7{}^{779}Br$); found 611.20374, 609.20515 (Δ −1.3, −0.3 ppm) | HREIMS 643.17548, found 643.17539 (Δ 0.1 ppm) | |
| MP (°C) | NA | NA | NA | NA | |
| $[\alpha]_D$ | NA | NA | NA | NA | |
| UV $\lambda_{max}$ (MeOH) nm | NA | NA | NA | NA | |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | NA | NA | NA | NA | |

| | **269**(*164*) | **270** (*164*) | **280** (*167*) | **281** (*168*) | **282** (*167*) |
|---|---|---|---|---|---|
| Appearance | Colorless glass | Colorless amorphous solid | Yellowish needles | Yellow oil | Yellowish, fluorescent oil |
| Molecular formula | $C_{30}H_{44}N_3O_6I$ | | $C_{38}H_{21}Br_8NO_7 \cdot (CH_3)_2CO$ | $C_{30}H_{13}Br_8NO_6$ | $C_{24}H_{15}Br_4NO_5$ |
| MS *m/z* | HRMS 670.2335 [$MH^+$] | FABMS 656 [M+H]$^+$ | NA | EIMS 1123 (20) [M+], 596 (55), 526 (55), 448 (15), 337 (20), 279 (55) | HRMS 719.0348 |
| MP (°C) | NA | NA | 285 | NA | NA |
| $[\alpha]_D$ | +30° (*c* 0.027, $CHCl_3$) | +5.2° | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | NA | 219 (13270), 284 (4000), 292 (3000) | 36 (17000), 300s (11700) | NA | 400 (2000), 280 (5250) (MeOH/KOH) 515 (2800), 400 (2800), 300 (5000) |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | (Neat) 3420, 1720, 1670, 1655, 1630 | NA | ($CHCl_3$) 3500, 2900, 1645, 1580, 1514, 1300 | (Neat) 3500, 1645, 1582, 1515 | 3500, 2919, 1699, 1400 |

(*continued*)

TABLE I.
Continued.

| | **283** (*167*) | **284** (*168*) | **229** (*41*) | **230** (*41*) |
|---|---|---|---|---|
| Appearance | Yellowish fluorescent oil | Yellow oil | White solid | White solid |
| Molecular formula | $C_{25}H_{17}Br_4NO_5$ | $C_{16}H_6Br_4O_5$ | $C_{20}H_{22}Br_2N_2O_4$ | $C_{20}H_{21}Br_3N_2O_4$ |
| MS *m/z* | HRMS 732.0619 $[M+H]^+$ | HREIMS 597.6915 | EIMS 516 (*1*), 514 (2), 512 (1), 258 (2), 257 (2), 256 (3), 255 (9), 228 (10), 227 (64), 226 (14), 225 (65), 215 (10), 214 (38), 213 (11), 212 (46), 201 (61), 199 (65), 149 (48), 146 (40), 57 (100) HREIMS 511.9948 | EIMS 596 (0.4), 594 (2), 592 (2), 590 (0.4), 565 ($\ll$1), 563 (1), 561 (1), 559 ($\ll$1), 366 (0.3), 364 (1), 362 (0.4), 338 (0.6), 336 (2), 334 (0.7), 308 (1), 307 (10), 306 (4), 305 (20), 304 (4), 303 (10), 302 (1), 292 (5), 290 (10), 288 (5), 281 (6), 279 (14), 277 (7), 257 (2), 255 (2), 224 (2), 223 (3), 222 (3), 221 (2), 215 (15), 214 (97), 213 (16), 212 (100), 201 (30), 199 (34), 185 (4), 183 (11), 181 (8), 134 (16), 105 (17), 77 (39) HREIMS 589.9049 |
| MP (°C) | NA | NA | NA | NA |
| $[\alpha]_D$ | NA | NA | NA | NA |
| UV $\lambda_{max}$ (MeOH) nm | | | NA | NA |
| IR $\nu_{max}$ (KBr) $cm^{-1}$ | 3500, 1702, 1698, 1400 | (Neat) 3460, 1761, 1721, 1475 | NA | NA |

TABLE II.
$^{1}H$ and $^{13}C$ NMR Data of Bromotyrosine Derivatives.

| | **1** (*176*) | | **5** (*7*) | **6** (*7*) | **14** (*14*) | | **15** (*11*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}H$ acetone-$d_6$ | $^{13}C$ acetone-$d_6$ | $^{1}H$ acetone-$d_6$ | $^{1}H$ acetone-$d_6$ | $^{1}H$ $CD_3CN$ | $^{13}C$ (12) acetone-$d_6$ | $^{1}H$ acetone-$d_6$ | $^{13}C$ acetone-$d_6$ |
| 1 | | 72.8 | | | | 75.8 | | 74.2 |
| 2 | 7.59 s | 121.5 | 7.20 s | 7.14 s | 4.10 br | 87.8 | 7.30 d, 2.2 | 146.6 |
| 3 | | 153.2 | | | | 106.4 | | 123.7 |
| 4 | | 174.5 | | | | 150.1 | | 183.0 |
| 5 | | 153.2 | | | | 118.1 | 5.72 d, 2.2 | 57.1 |
| 6 | 7.59 | 121.5 | 7.20 s | 7.14 s | 6.34 | 134.9 | 4.44 ddd, 2.2, 2.2, 5.6 | 78.9 |
| 7 | 2.75 | 46.0 | 2.58 s | 2.57 s | 2.74 s | 41.7 | 3.11 s | 28.4 |
| 8 | | 173.0 | | | | 171.9 | | 116.9 |
| NH | 2.97 | | 6.68, 6.77 s | 6.65, 6.76 s | | | | |
| OMe | | | 3.07 s | 3.10 s | 3.70 s | 60.0 | | |
| OH | | | 5.88 s | 5.85 s | 2.28 | | 5.96 d, 5.6, 5.93 s | |
| 1′ | | | 3.25 t | 3.22 t | | | | |
| 2′ | | | 1.55 m | 1.50 m | | | | |
| 3′ | | | 1.41 m | 1.50 m | | | | |
| 4′ | | | 0.98 t | 1.50 m | | | | |
| 5′ | | | | 0.98 t | | | | |

| | **16** (*11*) | | **18** (*19*) | | **19** (*7*) | | **20** (*7*) |
|---|---|---|---|---|---|---|---|
| | $^{1}H$ acetone-$d_6$ | $^{13}C$ acetone-$d_6$ | $^{1}H$ $CDCl_3$ | $^{13}C$ (12) acetone-$d_6$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ |
| 1 | | 75.5 | | 78.2 | | 122.4 | |
| 2 | 7.52 s | 151.7 | 5.20 d, 0.7 | 113.4 | | 162.0 | |
| 3 | | 122.7 | | 147.9 | | 111.8 | |

(*continued*)

TABLE II.
Continued.

| | **16** (*11*) | | **18** (*12*, *19*) | | **19** (*7*) | | **20** (*7*) |
|---|---|---|---|---|---|---|---|
| | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C acetone-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ |
| 4 | | 183.0 | | 120.4 | | 150.8 | |
| 5 | 5.04 d, 11.2 | 56.1 | | 133.2 | | 117.5 | |
| 6 | 4.28 dd, 11.2, 5.0 | 78.4 | 6.36 d, 0.7 | 73.9 | 7.65 s | 125.8 | 7.48 s |
| 7 | 3.15 dq, 14.0 | 28.4 | 2.88 d, 18 | 26.3 | | 100.7 | 3.67 s |
| 8 | | 116.9 | | 117.5 | | 165.2 | |
| 9 | | | | | | 154.3 | |
| NH | | | | | | | 5.82 s |
| 10 | | | | | 2.39 s | 23.7 | |
| 11 | | | | | 2.59 s | 25.2 | |
| OMe | | | 3.79 s | 59.6 | 3.92 s | | 3.85 s |
| OH | 5.98 d, 5.0, 5.70 s | | 3.38 | | | | |

| | **21** (*20*) | | **22** (*22*) | | **23** (*22*) | | **24** (*23*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H acetone-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | | 147.2 | 7.6 br | | 7.6 br | | | 7.1 br |
| 2 | 7.30 s | 109.1 | | | 173.9 | 173.5 | | 172.4 |
| 3 | | 113.7 | 2.92 d, 16.8 | 42.3 | 2.75 d, 16.8 | 44.1 | 2.60 d, 16.8 | 43.4 |
| | | | 2.48 d, 16.8 | | 2.58 d, 16.8 | | 2.69 d, 16.8 | |
| 3a | | | | 75.5 | | 74.2 | | 73.9 |
| 4 | | 146.4 | 7.44 s | 150.4 | 7.33 d, 0.6 | 149.2 | 7.28 br | 149.7 |
| 5 | | NA | | 119.0 | | 119.2 | | 122.2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6 | | NA | | 183.7 | | 183.9 | | 188.6 |
| 7 | | 103.8 | 5.16 d, 9.8 | 57.4 | 5.28 d, 4.2 | 52.7 | 2.82 dd, 16.4, 4.9<br>3.06 dd, 16.4, 4.9 | 39.5 |
| 7a | | | 4.22 dd, 9.8, 1.6 | 68.3 | 4.46 brd, 4.2 | 63.4 | 4.14 brt | 58.4 |
| 8 | | 165.9 | | | | | | |
| 9 | 8.21 d, 11.4 | 148.9 | | | | | | |
| 10 | 7.74 ddq, 14.3, 11.4, 1.6 | 144.7 | | | | | | |
| 11 | 6.59 dq, 14.3, 7.4 | 128.1 | | | | | | |
| 12 | 2.07 dd, 7.4, 1.6 | 19.8 | | | | | | |
| OH | | | 5.5 br | | 5.6 br | | | 5.4 br |

NA: not reported

| | **25** (*9*) | | **26** (*9*) | | **27** (*9*) | **28** (*9*) | **29** (*9*) |
|---|---|---|---|---|---|---|---|
| | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H acetone-$d_6$ | $^{1}$H acetone-$d_6$ | $^{1}$H acetone-$d_6$ |
| 1 | | | 5.5 br | | 5.5 br | 5.6 br | 5.6 br |
| 2 | | 176.3 | | 173.6 | | | |
| 3 | 2.70 s | 45.0 | 2.90 d, 16.9<br>2.50 d, 16.9 | 42.4 | 2.74 d, 16.9<br>2.59 d, 16.9 | 2.90 d, 16.9<br>2.48 d, 16.9 | 2.74 d, 16.9<br>2.56 d, 16.9 |
| 3a | | 74.8 | | 74.4 | | | |
| 4 | 7.03 d, 0.9 | 145.4 | 7.21 s | 146.3 | 7.07 br | 7.43 s | 7.32 br |
| 5 | | 133.0 | | 127.4 | | | |
| 6 | | 183.1 | | 183.4 | | | |
| 7 | 3.04, 2.80 d, 16.4 | 41.0 | 5.15 d, 9.8 | 58.0 | 5.24 d, 4.1 | 5.06 d, 10.4 | 5.26 d, 3.8 |
| 7a | 4.14 ddd, 6.0, 5.1, 0.9 | 60.8 | 4.19 brd, 9.8 | 67.9 | 4.8 brd, 4.1 | 4.03 brd, 10.4 | 4.48 brd, 3.8 |

(*continued*)

TABLE II.
Continued.

| | **30** (*24*) | | **31** (*25*) | | **43** (*35*) | | **44** (*35*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 80.9 | | 82.7 | | 128.8 | | 136.4 |
| 2 | | | | | 7.46 s | 134.2 | 7.30 s | 135.1 |
| 3 | | 168.3 | | 171.4 | | 113.0 | | 119.0 |
| 4 | 2.64 br | 43.1 | 2.66 dd, 18.0, 1.7<br>2.55 dd, 18.0, 1.7 | 44.0 | | 153.4 | | 154.8 |
| 5 | | 69.5 | | 69.5 | | 113.0 | | 119.0 |
| 6 | 7.43 d, 2.2 | 156.9 | 7.16 d, 2.2 | 153.2 | 7.46 s, 3.12 t, 12.0 | 134.2 | 7.0 s, 3.12 t, 12.0 | 135.1 |
| 7 | | 118.8 | | 129.5 | 3.29 | 32.8 | 3.29 | 32.9 |
| 8 | | 187.8 | | 188.9 | 8.73 dd, 12.0, 3.5 | 81.3 | 3.74 dd, 12.0, 3.5 | 81.0 |
| 9 | 2.43 d, 12.5<br>2.31 dd, 12.5, 2.2 | 46.6 | 2.44 dd, 12.4, 1.7<br>2.32 dd, 12.4, 2.2 | 47.6 | | 170.6 | | 170.6 |
| OMe | | | | | | | 3.81 s | 61.0 |
| $N(Me)_3$ | | | | | 3.28 | 52.7 | 3.30 s | 52.7 |

| | **45** (*35*) | | **46** (*35*) | | **51** (*40*) | |
|---|---|---|---|---|---|---|
| | $^{1}$H $D_2O$ | $^{13}$C $CD_3OD$ | $^{1}$H $D_2O$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | | 130.5 | | 128.0 | | 136.7 |
| 2 | 7.22 d, 2.0 | 135.3 | 7.20 | 134.9 | 7.58 s | 133.1 |
| 3 | | 112.8 | | 111.4 | | 117.6 |
| 4 | | 156.8 | | 155.8 | | 152.2 |
| 5 | 6.66 d, 8.5 | 113.9 | 6.65 d, 8.5 | 117.8 | | 117.6 |
| 6 | 6.95 dd, 8.5, 2.0; 2.80 t, 12.0 | 131.0 | 6.89 dd, 8.5, 2.0; 2.80 t, 12.0 | 130.7 | 7.58 s | 133.1 |
| 7 | 2.95[a] | 33.7 | 3.01[a] | 33.2 | 2.82 t, 7.4 | 31.4 |
| 8 | 3.42 dd, 12.0, 3.7 | 81.9 | 3.52 dd, 12.0, 3.7 | 81.6 | 3.06 t, 7.4 | 39.4 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 9 | | 170.5 | | | 170.9 | |
| OMe | 3.54 s | 57.0 | | | | 3.76 | 60.3 |
| $N(Me)_3$ | 2.96 s | 53.2 | 3.02 s | | 52.7 | |

| | **48** (*38*) | | **207** (*41*) | | **52** (*42*) | | **54** (*44*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^1H$ $CD_3OD$ | $^{13}C$ DMSO-$d_6$ | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ |
| 1 | | 136.4 | | 132.8 | | 137.1 | | |
| 2 | 7.69 s | 134.84 | 7.01 dd, 2.0, 8.2 | 130.0 | 7.30 s | 133.1 | 7.62 s | 134.4 |
| 3 | | 119.21 | 6.81 d, 8.2 | 117.3 | | 117.5 | | |
| 4 | | 154.46 | | 154.0 | | 150.8 | | |
| 5 | | 119.21 | | 110.8 | | 117.5 | | |
| 6 | 7.69 s | 134.84 | 7.33 d, 2.0 | 134.3 | 7.30 s | 133.1 | 7.62 s | |
| 7 | 3.17 ddd, 17.5, 12.5, 5.5 | 29.04 | 2.72 t, 7.4 | 35.0 | 2.70 t | 31.3 | 3.02 t, 8.0 | 35.2 |
| 8 | 3.67 ddd, 17.5, 12.5, 5.5 | 67.54 | 3.41 t, 7.4 | 42.2 | 2.92 t | 39.6 | 3.50 t, 8.0 | 41.3 |
| 9 | | | | 161.8 | 3.84 t | 70.4 | 4.12 t, 5.5 | 71.7 |
| 10 | | | | 164.0 | 1.97 m | 27.6 | 2.30 tt, 5.5, 5.5 | 26.4 |
| 11 | | | | | 3.07 t | 36.4 | 3.22 t, 5.5 | 56.9 |
| OMe | 3.85 s | 61.42 | | | | | | |
| $N(Me)_3$ | 3.32 s | 54.11 | | | | | | |
| $NH(Me)_2$ | | | | | | | 2.91, 2.96 s | 43.7, 43.6 |

| | **55** HCl salt (*45*) | | **56** HCl salt (*45*) | | **59a** (*47*) | | **57** (*46*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1H$ $CD_3OD$ | $^{13}C$ NA | $^1H$ $CD_3OD$ | $^{13}C$ NA | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^1H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ |
| 1 | | | | | | 140.4 | | 137.6 |
| 2 | 7.62 s | | 7.59 s | | 7.40 s | 134.3 | 7.35 s | 132.9 |
| 3 | | | | | | 118.7 | | 118.2 |

(*continued*)

TABLE II.
Continued.

| | **55** HCl salt (*45*) | | **56** HCl salt (*45*) | | **59a** (*47*) | | **57** (*46*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C NA | $^{1}$H $CD_3OD$ | $^{13}$C NA | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 4 | | | | | | 152.2 | | 151.6 |
| 5 | | | | | | 118.7 | | 118.2 |
| 6 | 7.62 s | | 7.59 s | | 7.40 s | 134.3 | 7.35 s | 132.9 |
| 7 | 3.01 t, 8.1 | | 3.23 t, 8.1 | | 2.72 t, 7.5 | 35.1 | 2.65 t, 7.0 | 35.0 |
| 8 | 3.25 t, 8.1 | | 2.94 t, 8.1 | | 3.35 t, 7.5 | 41.4 | 3.40 q, 6.8 | 41.9 |
| 9 | 4.13 t, 5.5 | | 4.12 t, 5.5 | | 4.12 t, 7.5 | 71.1 | 4.05 t, 6.5 | 71.1 |
| NH | | | | | | | 4.70 brt | |
| 10 | 2.24 tt, 5.5, 8.4 | | 2.30 tt, 5.5, 8.4 | | 2.38 m | 26.4 | 2.05 m | 27.1 |
| 11 | 3.34 t, 8.4 | | 3.52 t, 8.4 | | 3.51 t, 7.5 | 57.0 | 2.75 t, 7.0 | 56.0 |
| OMe | | | | | | | 3.70 s | 52.1 |
| $N(Me)_2$ | 2.93 s | | 2.96 s | | 3.0 s | 43.7 2C | 2.32 s | 44.4 |
| $NH_2(Me)$ | 2.77 s | | 2.72 s | | | | | |
| NHAc | | | | | 2.01 s | 22.6 | | |
| CO | | | | | | 173.3 | | 156.8 |

| | **58** (*46*) | | **60** (*49*) | | **61** (*50*) | | **62** (*51*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$-TFA | $^{13}$C $CD_3OD$ |
| 1 | | 140.4 | | 136.8 | | 141.8 | | 141.2 |
| 2 | 7.38 s | 134.3 | 7.59 s | 133.2 | 7.66 s | 131.6 | 7.50 s | 135.2[a] |
| 3 | | 118.7 | | 117.5 | | 119.4 | | 119.6 |
| 4 | | 152.1 | | 151.1 | | 154.0 | | 153.3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5 | | 118.7 | | 117.5 | | 119.4 | | 119.6 |
| 6 | 7.38 s | 134.3 | 7.59 s | 133.2 | 7.66 s | 131.6 | 7.50 s | 135.3[a] |
| 7 | 2.70 t, 7.0 | 34.9 | 7.82 t, 7.2 | 31.4 | 4.86 1H, m | 69.2 | 2.65 t, 7.0 | 31.6 |
| 8 | 3.20 q, 6.8 | 42.8 | 3.07 t, 7.2 | 39.3 | 3.16 dd, 3.5, 13 | 46.9 | 3.32 m | 42.8 |
| 9 | 4.05 t, 6.5 | 71.1 | 3.95 t, 5.7 | 70.6 | 4.04 t, 6 | 71.6 | 3.98, 4.07, m | 71.1 |
| NH | | | 9.92 br | | | | | |
| 10 | 2.30 m | 26.4 | 1.99 tt, 6.1, 5.7 | 28.6 | 2.09 m | 30.1 | 2.35, 2.70, m | 30.3 |
| 11 | 3.50 t, 7.0 | 57.1 | 3.43 t, 6.1 | 36.8 | 3.56 t, 7 | 38.4 | 4.35 dd, 2.1, 2.7 | 77 |
| 12 | | | | 143.0 | | 145.2 | | 165[b] |
| 13 | | | | 112.4 | | 113.1 | | 174.1 |
| 14 | | | | | | | 1.79 s | 23.8 |
| OMe | 3.65 s | 52.5 | | | | | | |
| $N(Me)_3$ | | | | | | | 3.25 s | 53.6 |
| $NH(Me)_2$ | 3.00 s | 44.0 | | | | | | |
| CO | | 159.5 | | | | | | |
| $NH_3$ | | | 7.79 br | | | | | |

[a]Interchangeable
[b]Broad signal

| | **63** (*53*) | | **64** (*53*) | | **65** (*54*) | | **67** (*21*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^1H$ DMSO-$d_6$ | $^{13}C$ DMSO-$d_6$ | $^1H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ |
| 1 | | 133.0 | | 136.6 | | 140.6 | | 140.0 |
| 2 | 7.63 s | 132.0 | 7.70 s | 132.7 | 7.75 s | 131.9 | 7.75 s | 130.8 |
| 3 | | 118.9 | | 119.4 | | 119.3 | | 118.2 |
| 4 | | 154.0 | | 154.0 | | 153.5 | | 142.3 |
| 5 | | 118.9 | | 119.4 | | 119.3 | | 118.2 |
| 6 | 7.63 s | 132.0 | 7.70 s | 132.7 | 7.75 s | 131.9 | 7.75 s | 130.8 |
| 7 | 7.46 d, 16.0 | 141.0 | 7.21 d, 15.9 | 128.1 | 5.60 dd, 8.7, 4.5 | | 5.65 dd, 8.7, 9.2 | 53.6[a] |

(*continued*)

TABLE II.
Continued.

| | **63** (*53*) | | **64** (*53*) | | **65** (*54*) | | **67** (*21*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 8 | 6.04 d, 16.0 | 120.1 | 6.44 d, 15.9 | 137.8 | 3.38 d, 9.3<br>3.89 d, 9.0 | | 3.71 dd, 9.3, 11.5<br>4.30 dd, 7.1, 8.5 | 41.5 |
| 9 | | 166.3 | | 174.0 | | 160.2[c] | | 158.4[b] |
| 10 | 4.06 t, 6.2 | 72.2 | 4.10 t, 5.6 | 71.4 | 4.16 d, 7.1 | | 4.15 dd, 4.5, 4.2 | 53.0 |
| 11 | 2.12 tt, 7.1, 6.2 | 28.2 | 2.25 tt, 7.8, 6.5 | 26.7 | 4.96 d, 8.7 | | 4.96 dd, 7.1, 7.1 | 54.1[a] |
| 12 | 2.72 t, 7.1 | 56.1 | 3.40 t, 7.8 | 56.8 | 3.61 d, 7.1 | | 3.52 dd, 9.0, 8.5<br>3.65 dd, 8.7, 8.5 | 47.0 |
| 13 | | | | 43.8 | | 159.8[c] | | 157.8[b] |
| 14 | | | | 43.8 | | | | |
| $NMe_2$ | 2.38 s | 45.5 | 2.83 s | | | | | |
| OEt | 4.23 d, 7.1 | 60.7 | | | | | | |
| OEt | 1.30 t, 7.1 | 14.3 | | | | | | |

[a,b,c] Exchangeable.

| | **68** (*58*) | | **69** (*58*) | | **70** (*62*) | | **71** (*63*) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H (*820*) acetone-$d_6$ | $^{13}$C (*6485*) $CD_3OD$ | $^{1}$H $CDCl_3$ + DMSO-$d_6$ | $^{1}$H 1%TFA-D in DMSO-$d_6$ | $^{13}$C 1%TFA in DMSO-$d_6$ | $^{1}$H $CDCl_3$ + $CD_3OD$ 4:1 | $^{1}$H acetone-$d_6$ | $^{13}$C $CDCl_3$ + $CD_3OD$ 4:1 | $^{13}$C $CDCl_3$ |
| 1,1′ | 4.18 d, 8 | 75.5 | 4.16 s | 3.92 s | 73.6 | 4.10 s 4.11 s | 4.16 d, 7 | 73.9 | 73.8 |
| 2,2′ | | 114.2 | | | 113.1 | | | 113.5 | 113.1 |
| 3,3′ | | 149.3 | | | 147.2 | | | 147.9 | 147.7 |
| 4,4′ | | 122.7 | | | 120.8 | | | 121.8, 121.7 | 121.4, 121.3 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 5,5′ | 6.50 s | 133.2 | 6.28 s | 6.56 s | 131.3 | 6.17 s | 6.51 s | 130.8 | 130.6 |
| 6,6′ | | 92.6 | | | 90.3 | | | 91.9, 91.8 | 91.9, 91.8 |
| 7,7′ | 3.84 d, 18<br>3.14 d, 18 | 40.1 | 3.87 d, 18.5<br>3.02 d, 18.5 | 3.61 d, 17.8<br>3.19 d, 17.8 | 42.5 | 3.70, 3.71 d, 18<br>2.85 d, 18 | 3.82, 3.83, d,<br>18, 3.12 d, 18 | 39.7 | 38.7 |
| 8,8′ | | 155.5 | | | 154.5 | | | 154.1 | 153.9 |
| 9,9′ | | 161.6 | | | 159.0 | | | 160.3 | 160.0 |
| NH | 7.58 bt | | 7.60 b | 8.10, 2H t,<br>6.9 | | | 7.56 brt, 6<br>7.81 brt, 6 | | |
| 10 | 3.34 m | 38.4 | 3.35 m | 3.48 m<br>3.14 m | 39.0 | 3.46 dd,14, 3<br>3.32 dd,14, 7 | 3.29 m, 3.52 m | 36.4 | 36.2 |
| 11 | 1.60 m | 26.1 | 1.69 m | 3.43 m | 71.0 | 3.60 m | 3.79 m | 68.1 | 68.0 |
| 12 | | 26.1 | | | | 1.73, 1.61 m | 1.97, 1.60 m | 45.3 | 45.0 |
| 13 | | 38.4 | | | | 3.55, 3.37 m | 3.43 2H m | 33.8 | 33.6 |
| OMe | 3.72 s | 60.4 | 3.73 s | 3.63 s | 59.6 | 3.59 s | 3.71 s | 60.3 | 60.0 |
| OH | 5.37 d, 8 | | | | | | 5.46, 5.47 d, 7 | | |

| | **72** (*64*) | | **74** (*61*) | | **73** (*61*) | | **75** (*65*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H<br>DMSO-$d_6$ | $^{13}$C<br>DMSO-$d_6$ | $^{1}$H<br>$CD_3OD$ | $^{13}$C<br>$CD_3OD$ | $^{1}$H<br>$CD_3OD$ | $^{13}$C<br>$CD_3OD$ | $^{1}$H<br>$CD_3OD$ | $^{13}$C<br>$CD_3OD$ |
| 1,1′ | 3.94 d, 8.5<br>3.88 d, 8.5 | 73.6 | 4.15 d, 0.9<br>4.13 d, 0.9 | 75.5 | 4.14 d, 0.9<br>4.13 d, 0.9 | 75.5 | 4.16 s<br>4.14 s | 75.5 |
| 2,2′ | | 113.1 | | 114.1 | | 114.1 | | 114.2 |
| 3,3′ | | 147.1 | | 149.3 | | 149.3 | | 149.3 |
| 4,4′ | | 120.9 120.8 | | 122.8 | | 122.8 | | 122.8 |
| 5,5′ | 6.60 s<br>6.57 s | 131.2 | 6.46 d, 0.9<br>6.47 d, 0.9 | 132.2<br>133.2 | 6.47 d, 0.9<br>6.45 d, 0.9 | 132.2<br>133.2 | 6.46 s<br>6.47 s | 132.3 |
| 6,6′ | | 90.5, 90.2 | | 92.6, 92.5 | | 92.6, 92.5 | | 92.6, 92.4 |
| 7,7′ | 3.60 d,18.2<br>3.19 d,18.2 | 39.7<br>39.5 | 3.14, 3.13 d, 18.3<br>3.82, 3.81 d, 18.3 | 40.1<br>40.0 | 3.15, 3.12 d, 18.3<br>3.82, 3.81 d, 18.3 | 40.1<br>40.0 | 3.15, 3.13 d, 18<br>3.82, 3.80 d, 18 | 40.2<br>40.0 |

(*continued*)

TABLE II.
Continued.

| | **72** (*64*) | | **74** (*61*) | | **73** (*61*) | | **75** (*65*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 8,8′ | | 154.4, 154.1 | | 155.1, 154.9 | | 155.1 154.9 | | 155.3, 154.9 |
| 9,9′ | | 159.1, 158.9 | | 161.9, 161.8 | | 161.9 161.8 | | 161.8 |
| NH | 8.66, 8.48 t, 5.5 | | | | | | | |
| 10 | 4.02 d, 5.7 | 48.5 | 4.43, 4.42 d, 18.8 | 49.9 | 4.43, 4.43 d, 18.8 | 49.9 | 4.12 s | 49.2 |
| 11 | | 204.4 | | 207.8 | | 207.8 | | 206.2 |
| 12 | 2.70 2H t, 6.8 | 38.6 | 4.41 dd, 6.3, 4.9 | 75.7 | 4.40 dd, 6.3, 4.9 | 75.7 | 2.60 t, 7 | 37.57 |
| 13 | 3.34 2H m | 33.8 | 3.66 dd, 13.9, 4.9<br>3.63 dd, 13.9, 6.3 | 43.4 | 3.66 dd, 13.9, 4.9<br>3.63 dd, 13.9, 6.3 | 43.4 | 1.88 dt, 7, 7 | 24.1 |
| 14 | | | | | | | 3.32 t, 7 | 39.6 |
| OMe | 3.63, 3.60 3H s | 59.6 | 3.76 3H s | 60.4 | 3.76 3H s | 60.4 | 3.75 3H s | 60.4 |
| OH | 6.41, 6.35 d, 8.5 | | | | | | | |

| | **76** (*66*) | | **77** (*67*) | | **78** (*30*) | |
|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1,1′ | 3.93 s | 74.1 | 4.38 dd, 5, 12<br>4.40 dd, 5, 12 | 74.7 74.8 | 4.13 dd, 2.6[b], 3.7 | 56.9 |
| 2,2′ | | 113.5 | 5.08 d, 12; 5.06 d, 12 | 57.1 | 3.93 d, 3.5 | 53.0 |
| 3,3′ | | 147.6 | | 183.5 | | 186.0 |
| 4,4′ | | 121.2 | | 122.5, 122.4 | | 122.7 |
| 5,5′ | 6.57 s | 131.7 | 7.63 s; 7.67 s | 149.1, 149.2 | 7.49 d, 2.6 | 143.7 |
| 6,6′ | 7.47 dd, 8.6, 1.5 | 90.7 | | 91.7, 91.4 | | 84.0 |
| 7,7′ | 3.12 d, 18<br>3.62 d, 18 | 40.0 | 3.31, 3.29 d, 18<br>3.85, 3.86 d, 18 | 38.2<br>38.1 | 3.68 d, 17.8<br>3.61 d, 17.9 | 43.6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 8,8′ | | 155.0 | | 154.5, 154.3 | | 154.9 |
| 9,9′ | | 159.3 | | 159.8, 159.6 | | 158.3 |
| 10 | 3.08 m, 3.15 m | 45.7 | 4.22 d, 6 | 49.2 | 3.19 br | 38.6 |
| 11 | 3.55 m, 3.61 m | 67.4, 68.9 | | 204.7 | 1.50 br | 26.4 |
| 12 | 1.28 m, 1.40 m | 32.3 | 2.87 t, 6 | 39.6 | | |
| 13 | 1.50 m, 1.60 m | 25.5 | 3.58 dt, 6, 6 | 34.8 | | |
| 14 | 3.28 m, 3.22 m | 36.6 | | | | |
| 15 | 1.45 m, 1.65 m | 34.4 | | | | |
| 16 | 3.15 m | 39.4 | | | | |
| OMe | 3.65 m | 60.1 | | | | |
| NH | 8.41 t, 6, 8.45 t, 5 | | 7.90 t, 6 | | 8.63 t, 5.7 | |
| NH | 8.27 t, 6; 8.21 t, 5 | | 7.66 t, 6 | | | |
| OH | 6.36 s | | 6.03 d, 5; 6.08 d, 5 | | | |

| | **79** (*71*) | | | | **81** (*70*) | | **82** (*71*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H pyridine-$d_5$ | $^{13}$C | $^{1}$H DMSO-$d_6$ (*36*) | $^{13}$C | $^{1}$H acetone-$d_6$ | $^{13}$C | $^{1}$H pyridine-$d_5$ | $^{13}$C |
| 1,1′ | 4.61, 4.58 d, 7.9 | 74.7 | 3.93, 3.91 d, 7.9 | 73.6 | 4.19 m | 75.0 | 4.65, 4.64 s | 74.7 |
| 2,2′ | | 115.2 | | 113.2 | | 113.7 | | 115.2 |
| 3,3′ | | 148.1 | | 147.2 | | 148.6 | | 148.1 |
| 4,4′ | | 121.8 | | 121.1 | | 122.0 | | 121.9 |
| 5,5′ | 6.62, 6.63 s | 132.4 | 6.58, 6.56 s | 131.3 | 6.49, 6.51 d, 1.0 | 132.0 | 6.62, 6.58 s | 132.3 |
| | | | | 131.2 | | 132.1 | | |
| 6,6′ | | 91.9 | | 90.4 | | 91.8 | | 91.9 |
| 7,7′ | 3.47, 3.44 d, 18.2 | 40.3 | 3.61, 3.59d, 18.8 | 39.4 | 3.16, 3.19 d, 18.5 | 39.839.9 | 3.40, 3.47 d, 18.2 | 40.3 40.2 |
| | 4.40, 4.43 d, 18.2 | | 3.24, 3.19 d, 18.8 | | 3.85, 3.83 d, 18.5 | | 4.44, 4.45 d, 18.2 | |
| 8,8′ | | 155.2, 155.3 | | 154.5 | | 154.9, 155.0 | | 155.2, 155.8 |
| 9,9′ | | 160.5 | | 159.2, 159.1 | | 160.4, 160.5 | | 160.5, 160.6 |
| NH | 9.34, 9.71 t,5.8 | | 8.43, 8.39, d 5.8 | | 7.66, 7.71 t, 5.9 | | 9.80, 9.71 t, 5.8 | |

(*continued*)

TABLE II.
Continued.

| | **79** (*71*) | | | | **81** (*70*) | | **82** (*71*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H pyridine-$d_5$ | $^{13}$C | $^1$H DMSO-$d_6$ (*36*) | $^{13}$C | $^1$H acetone-$d_6$ | $^{13}$C | $^1$H pyridine-$d_5$ | $^{13}$C |
| 10 | 4.25, 3.98 m | 44.0 | 3.47, 3.29 m | 42.6 | 3.55, 3.76 m | 43.4 | 4.97 dd, 18.0, 5.8 | 47.49 |
| 11 | 4.76 m | 69.5 | 4.06 m | 68.1 | 4.25 m | 69.7 | | 201.3 |
| 12 | 4.34 dd, 8.8, 5.5; 4.26 m | 76.1 | 3.89, 3.82 m | 75.4 | 4.05 m | 75.7 | 4.82s | 76.1 |
| 13 | | 152.3 | | 151.3 | | 152.5 | | 152.2 |
| 14 | | 118.4 | | 117.3 | | 118.3 | | 118.1 |
| 15 | 7.92s | 131.1 | 7.57 s | 130.5 | 7.65 s | 131.3 | 7.91s | 131.1 |
| 16 | | 143.5 | | 142.7 | | 142.9 | | 144.2 |
| 17 | 7.92s | 131.1 | 7.57 s | 130.5 | 7.65 s | 131.3 | 7.91s | 131.1 |
| 18 | | 118.4 | | 117.3 | | 118.3 | | 118.1 |
| 19 | 5.29 dd, 4.3, 5.8 | 69.5 | 4.68 m, 5.2 | 69.4 | 4.90 dd, 4.3, 7.5 | 71.3 | 5.30 dd, 7.5, 4.6 | 70.7 |
| 20 | 3.97 m<br>3.81 ddd, 15.3, 5.8, 4.3 | 48.2 | 3.33 d, 5.3 | 46.4 | 3.48 m 3.61 m | 47.5 | 3.97 ddd, 5.8, 13.3, 4.6<br>3.81 ddd, 5.8, 13.3, 7.5 | 48.0 |
| OMe | 3.63 s | 59.9 | 3.64 s | 59.7 | 3.71, 3.71 s | 60.2 | 3.63 s | |
| 11-OH | 7.23 d, 5.2 | | 5.29 d, 5.4 | | 5.41 br s | | | |
| 1,1′-OH | 8.62, 8.61 d, 7.9 | | 6.39, 6.37 d, 7.9 | | | | 8.60 br s | |
| 17-OH | 7.77 d, 4.3 | | 5.75 d, 4.6 | | 5.43 br s | | | |

| | **83** (*63*) | | **84** (*72*) | | **85** (*72*) | | **86** (*65*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $(CD_3)_2CO$ | $^{13}$C $CDCl_3$ | $^1$H $(CD_3)_2CO$ | $^{13}$C $(CD_3)_2CO$ | $^1$H $(CD_3)_2CO$ | $^{13}$C $(CD_3)_2CO$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1,1′ | 4.15 d, 6<br>4.16 d, 6 | 73.9 73.8 | 4.23 dd, 8.1, 0.9<br>4.18 dd, 8.1, 0.9 | 75.1, 75.2 | 4.23, 4.18 dd,<br>8.1, 0.9 | 75.1,<br>75.2 | 4.12 s<br>4.11 s | 75.4 |
| 2,2′ | | 112.7 | | 113.8 | | 113.9 | | 114.2 |
| 3,3′ | | 147.9 | | 148.8 | | 148.7 | | 149.3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4,4′ | | 121.4 | | 122.1 | | 122.1 | | 122.7 |
| 5,5′ | 6.50, 6.51 d, 1 | 130.9 | 6.56, 6.52 d, 0.9 | 132.3 | 6.57, 6.52 d, 0.9 | 132.3 | 6.46, 6.44 s | 132.2 |
| 6,6′ | | 91.8, 91.6 | | 91.6, 91.8 | | 92.0, 91.6 | | 92.5 |
| 7,7′ | 3.83, 3.18 d, 18 | 38.9 | 3.86, 3.22 d, 18.1 | 40.0 | 3.86, 3.22 d, 18.1 | 40.0 40.1 | 3.81, 3.14 d, 18 | 40.1, 40.0 |
| | 3.81, 3.15 d, 18 | 38.8 | 3.84, 3.18 d, 18.1 | 40.1 | 3.84, 3.16 d, 18.1 | | 3.79, 3.09 d, 18 | |
| 8,8′ | | 154.1, 154.0 | | 155.1, 155.2 | | 154.8, 155.2 | | 155.3, 155.1 |
| 9,9′ | | 159.3 | | 160.0, 160.4 | | 160.2, 160.0 | | 161.7, 161.6 |
| NH | 7.78, 7.73 t, 6 | | | | | | | |
| 10 | 3.53 q, 6 | 37.2 | 3.50, 3.70 m | 43.5 | 4.60 d, 6.0 | 47.5 | 3.62 t, 6.5 | 37.9 |
| 11 | 2.11 m | 29.2 | 4.25 m | 69.7 | | 200.9 | 2.15 t, 6.5 | 30.6 |
| 12 | 4.07 t, 6 | 71.7 | 4.03 m | 75.8 | 4.75 s | 76.5 | 4.10 t, 6.5 | 71.6 |
| 13 | | 151.3 | | 152.0 | | 151.2 | | 153.6 |
| 14 | | 118.1 | | 118.3 | | 118.1 | | 119.0 |
| 15 | 7.50 s | 132.9 | 7.53 s | 134.1 | 7.57 s | 134.2 | 7.64 s | 131.7 |
| 16 | | 137.4 | | 139.9 | | 140.5 | | 143.1 |
| 17 | 7.50 s | 132.9 | 7.53 s | 134.1 | | 134.2 | 7.64 s | 131.7 |
| 18 | | 118.1 | | 118.3 | | 118.1 | | 119.0 |
| 19 | 2.86 t, 7 | 34.2 | 2.88 t, 7.0 | 34.7 | 2.91 t, 7.0 | 34.7 | 4.79 dd, 4.5, 7.5 | 72.2 |
| 20 | 3.60 td, 7, 6 | 40.4 | 3.58 td, 7.0, 6.0 | 40.9 | 3.58 q, 6.9 | 40.9 | 3.51, 3.46 | 47.6 |
| OMe | 3.71 s, 6H | 60.1 | 3.78, 3.73 s | 60.2 | 3.74, 3.72 s | 60.2 | 3.76 s | 60.4 |
| OH | 5.46, 5.45 d, 6 | | | | | | | |

| | **87** (*70*) | | **88** (*70*) | | **89** (*74*) | | **90** (*74*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H acetone-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1,1′ | 4.39, 4.40 d, 11.3 | 74.6 | 4.56 2H m | 72.3 | 4.18 d, 11.4 | 73.3 | 4.29 br | 72.01 |
| 2,2′ | 5.06, 5.07 d, 11.3 | 57.0, 57.1 | 5.27 2H m | 54.8 | 5.19 d, 11.3 | 57.8 | 5.35 | 55.84 |
| 3,3′ | | 183.7 | | 183.6 | | 183.8 | | 183.39 |
| 4,4′ | | 122.6 | | 124.9 | | 121.3 | | 122.75 |
| 5,5′ | 7.61 s | 149.2 149.3 | 7.46 d, 1.0 | 146.2 | 7.68 s | 149.1 | 7.54 s | 145.35 |
| | 7.64 s | | 7.49 d, 0.9 | 146.4 | 7.65 s | 149.0 | | |

(*continued*)

TABLE II.
Continued.

| | **87** (*70*) | | **88** (*70*) | | **89** (*74*) | | **90** (*74*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H acetone-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 6,6′ | | 91.7 | | 90.8 | | 90.5 | | 89.38 |
| 7,7′ | 3.26, 3.30 d, 18.2 | 38.4 | 3.38, 3.35 d, 18.2 | 41.4 | 3,65, 3.63 d, 18 | 38.0 | 3.65, 3.63 d, 18 | 38.03 |
| | 3.88, 3.86 d, 18.2 | | 3.87, 3.90 d, 18.2 | | 3.13, 3.10 d, 18 | | 3.33, 3.30 d, 18 | 39.79 |
| 8,8′ | | 154.6, 154.7 | | 155.4, 155.5 | | 153.9, 153.9 | | 154.57, 153.92 |
| 9,9′ | | 160.2 | | 160.2 | | 158.9 | | 158.78 |
| NH | 7.65 br | | 7.66 br | | 8.67 dd, 11.8, 5.7 | | 8.67 | |
| | 7.67 br | | 7.68 br | | 8.64 dd, 11.8, 5.7 | | 8.64 | |
| 10 | 3.53, 3.81 m | 43.4 | 3.53, 3.80 m | 43.6 | 3.42 m | 36.3 | 3.42 m | 36.31 |
| 11 | 4.26 m | 69.7 | 4.25 m | 69.9 | 2.00 q, 6 | 29.6 | 2.00 q, 6 | 29.62 |
| 12 | 4.04, 4.08 m | 75.8 | 4.04, 4.08 m | 76.0 | 3.95 dd, 6, 4 | 71.2 | 3.95 dd, 6, 4 | 71.24 |
| 13 | | 152.6 | | 152.7 | | 150.8 | | 150.75 |
| 14,18 | | 118.4 | | 118.4 | | 117.4 | | 117.38 |
| 15,17 | 7.67 s | 131.4 | 7.67 s | 131.5 | 7.53 s | 133.0 | 7.53 s | 133.04 |
| 16 | | 143.1 | | 143.3 | | 133.9 | | 133.88 |
| 19 | 4.91 dd, 4.4, 7.5 | 71.0 | 4.91 ddd, 4.2, 4.2, 7.5 | 71.4 | 2.76 t, 7 | 33.2 | 2.76 t, 7 | 33.20 |
| 20 | 3.48, 3.65 m | 47.4 | 3.51, 3.62 m | 47.4 | 3.42 m | 34.0 | 3.42 m | 39.79 |
| OH | 5.97 d, 5.6 | | 4.45 d, 5.2; 5.00 d, 4.2 | | 6.77 br | | 6.77 br | |
| | 5.99 d, 5.6 | | 5.92 d, 5.6; 5.92 d, 5.6 | | | | | |

| | **91** (*75*) | | **92** (*77*) | | | **93** (3:2 diastereomeric mixture ) (*78*) | |
|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1,1′ | 4.44 d, 5.1 | 77.4 | 4.13, 4.14 s | 75.4, 75.5 | 1,1′ | 3.96 br | 73.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2,2′ | | 112.3 | | 114.2 | 2,2′ | | 113.0 |
| 3,3′ | | 148.1 | | 149.3 | 3,3′ | | 147.1 |
| 4,4′ | | 121.3 | | 122.8 | 4,4′ | | 120.6 |
| 5,5′ | 6.42 | 131.6 | 6.46 s | 132.3 | 5,5′ | 6.54 s | 131.3 |
| 6,6′ | | 74.3 | | 92.4, 92.5 | 6,6′ | | 90.3 |
| 7,7′ | 2.81 d, 16 | 25.5 | 3.11, 3.14 d, 18.4 | 40.3 | 7,7′ | 3.64 d, 17.5 | 39.4 |
| | 2.85 d, 16 | | 3.79, 3.83 d, 18.4 | | | 3.17 d, 17.5 | |
| 8,8′ | | 116.6 | | 155.3, 155.4 | 8,8′ | | 154.3 |
| 9,9′ | | | | 161.4, 161.6 | 9,9′ | | 158.9 |
| NH | 2.52 br | | | | NH | 8.35 m, 7.90 brd, 6.4; 8.06 br | |
| 10,10′ | | | 3.28, 3.29 m | 39.1, 40.0 | 10,10′ | 3.40 q, 6.6 | 36.2 |
| 11,11′ | | | 2.07, 2.23 m; 1.80 q, 6.8 | 33.9, 30.1 | 11,11′ | 2.00 q, 6.6 | 29.4 |
| 12,12′ | | | 3.96 t, 7.4; 2.48 t, 6.8 | 33.5, 23.1 | 12,12′ | 3.96 m | 71.2 |
| 13,13′ | | | | 135.9, 126.1 | 13,13′ | | 150.6, 150.7, 150.8 |
| 14,14′ | | | | 150.7, 149.5 | 14,14′, 18,18′ | | 116.7, 116.8, 116.9 |
| 15,15′ | | | 6.36 s | 111.3, 126.7 | 15,17 | 7.52 s, 7.44 s | 133.5 |
| OH | 2.45 d, 5.1 | | | | 16 | | 138.0, 138.2 |
| OMe | 3.77 s, 3H | 60.3 | 3.75 s | 60.4 | 19a | 2.94 m, 2.79 m | 36.7, 37.0 |
| | | | | | 19b | 2.79 m, 3.01 dd, 4.7, 13.6 | |
| | | | | | 20 | 3.87 m, 3.89 m | 57.9, 57.3 |
| | | | | | 21 | | 171.8, 172.5 |
| | | | | | OH | 6.24 br | |
| | | | | | 20-NH | 4.91 br, 4.52 br | |
| | | | | | OMe | 3.66 s | 59.5 |
| | | | | | 15′, 17′ | 7.38 s, 7.47 s | 133.5 |
| | | | | | 19′a | 2.95 m, 2.64 dd, 7.5, 14 | 36.7, 36.2 |
| | | | | | 19′b | 2.86 dd, 6.2, 13.4; 2.81 m | |
| | | | | | 20′ | 4.26 m, 4.24 m | 54.5, 54.5 |
| | | | | | 21′ | | 172.0, 172.3 |

(*continued*)

TABLE II.
Continued.

| | **94** (*68*) | **94a** (*68*) | **95a** (*68*) | **97** (*79*) | | **99** (*81*) | | **101** (*82*) | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 1 | 4.21 s | 5.87 s | 5.86 s | 3.92 d, 6.2 | 75.5 | 4.12 s | 74.1 | 4.32 s | 60.1 |
| 2 | | | | | 114.2 | | 113.5 | | 113.4 |
| 3 | | | | | 149.3 | | 148.1 | | 147.7 |
| 4 | | | | | 122.7 | | 121.9 | | 121.1 |
| 5 | 6.57 s | 6.34 s | 6.32 s | 6.58 s | 132.3 | 6.34 s | 130.9 | 6.30 s | 131.1 |
| 6 | | | | | 92.6 | | 91.9 | | 91.7 |
| 7 | 3.23 d, 18.2<br>3.87 d, 18 | 3.08 d, 18<br>3.47 d, 18 | 3.06 d, 18<br>3.45 d, 18 | 3.18 d, 18.2<br>3.60 d, 18.2 | 40.0 | 3.03 d, 18.3<br>3.80 d, 18.3 | 39.3 | 3.86 d, 18.5<br>2.94 d, 18.5 | 38.7 |
| 8 | | | | | 155.2 | | 154.2 | | 154.0 |
| 9 | | | | | 163.6 | | 159.9 | | 159.4 |
| 10 | 3.40–3.60 m | 3.80 m<br>3.96 m | 3.57 m<br>3.70–3.95 m | | | 3.59 t | 37.7 | 3.55 m | 38.0 |
| 11 | 4.27 m | 5.28 q, 4 | 5.76 dd, 7, 4 | | | 2.10 tt | 29.5 | 2.10 m | 28.9 |
| 12 | 4.11 m | 4.19 dd, 10, 4<br>4.24 dd, 10, 4 | | | | 4. 06 t | 71.3 | 4.12 t, 5.7 | 73.4 |
| 13 | | | 7.50 s | | | | 151.6 | | 153.4 |
| 14 | | | | | | | 118.5 | | 134.4 |
| 15 | 7.72 m | 7.54 s | | | | 7.43 s | 133.3 | 7.39 d, 2 | 133.4 |
| 16 | | | 4.22 d, 4.5 | | | | 137.0 | | 112.2 |
| 17 | 5.68 t, 8 | 5.54 t, 8 | 5.03 m | | | 7.43 s | 133.3 | 7.09 dd, 8.4, 2 | 128.8 |
| 18 | 3.56, 4.08 t, 8 | 3.50, 4.00 t, 8 | 3.70–3.95 m | | | | 118.5 | 6.83 d, 8.4 | 113.3 |
| 19 | | | | | | 2.74 t | 35.9 t | 2.67 t, 6.8 | 37.3 |
| 20 | | | | | | 2.95 bt | 42.2 t | 2.94 t, 7.2 | 42.9 |
| OMe | 3.74 s, 3H | 3.74 s, 3H | 3.77 s, 3H | 3.65 s | 59.6 | 3.71 s | 60.2 | 3.74 s | |
| 1-OH | | | | 6.35 d, 6.2 | | | | | |
| NH | | 7.10 t, 6.5<br>5.80 br | 6.84 brt<br>5.33 br | 7.58 br<br>7.82 br | | 7.33 t | | 7.00 brt | |

| | **102** (*83*) | | **100** (*81*) | | **103** (*36*) | | **104** (*36*) |
|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 4.08 s | 75.4 | 4.08 s | 3.95 s | 73.7 | 3.93 d, 8.3 | 73.7 |
| 2 | | 114.1 | | | 113.4 | | 113.3 |
| 3 | | 149.2 | | | 147.2 | | 147.3 |
| 4 | | 122.7 | | | 121.0 | | 121.1 |
| 5 | 6.37 s | 132.1 | 6.41 s | 6.55 s | 131.4 | 6.56 s | 131.3 |
| 6 | | 92.6 | | | 90.4 | | 90.4 |
| 7 | 3.74, 3.03 d, 18.0 | 40.1 | 3.78, 3.08 d, 18.3 | 3.21, 3.67 d, 18.2 | 39.5 | 3.17, 3.60 d, 18.1 | 39.5 |
| 8 | | 155.1 | | | 154.6 | | 154.5 |
| 9 | | 161.6 | | | 159.2 | | 159.1 |
| 10 | 3.48 m | 37.9 | 3.58 t | 3.41 bdd | 36.4 | 3.36 m | 39.9 |
| 11 | 2.02 tt, 6.9, 13.8 | 30.8 | 2.12 tt | 1.99 q, 6.6 | 29.5 | 2.74 t, 6.9 | 33.3 |
| 12 | 4.01 t, 6 | 72.3 | 4.04 t | 3.93 m | 71.3 | | 139.0 |
| 13 | | 153.6 | | | 151.2 | 7.49 s | 133.2 |
| 14 | | 118.9 | | | 117.5 | | 117.3 |
| 15 | 7.57 s | 131.7 | 7.44 s | 7.55 s | 133.9 | | 151.1 |
| 16 | | 142.8 | | | 136.8 | | 117.3 |
| 17 | 7.57 s | 131.7 | 7.44 s | 7.55 s | 133.9 | 7.49 s | 133.2 |
| 18 | | 118.9 | | | 117.5 | 3.94, 4.08 m | 71.3 |
| 19 | 4.75 t | 71.64 | 2.73 t | 2.90 m; 3.08 bd | 35.3 | 2.23, 2.38 m | 27.8 |
| 20 | 3.42 brt, 7.8 | 47.62 | 3.37 dt | 3.56 m | 55.0 | 3.56 m | 74.8 |
| 21 | | 173.3 | 2.12 m | | 169.9 | | 167.1 |
| 22 | 1.93 s | 22.7 | 1.25 s | | | | |
| 23-32 | | | 1.25 s | | | | |
| 33 | | | 1.54 m | | | | |
| OMe | 3.69 s | 60.4 | 3.72 s | 3.63 s | 59.8 | 3.63 s | 59.8 |
| $Me_2$ | | | 0.87 d | | | | |
| NH | | | 7.31 t, 5.67 t | 8.57 t, 5.6 | | 8.57 t, 5.8 | |
| $^{+}NMe_3$ | | | | | | 3.15 s | 51.0 |

(*continued*)

TABLE II.
Continued.

| | **105** (*78*) | | **106** (*78*) | | **107** (*78*) | | **108** (*72*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C |
| 1 | 4.10 s | 75.4 | 4.07 s | 75.5 | 3.94 br | 73.7 | 4.18 dd, 7.8, 0.9 | 75.2 |
| 2 | | 114.2 | | 114.2 | | 113.1 | | 113.9 |
| 3 | | 149.2 | | 149.3 | | 147.2 | | 148.8 |
| 4 | | 122.7 | | 122.8 | | 120.7 | | 122.2 |
| 5 | 6.40 s | 132.3 | 6.41 s | 132.3 | 6.56 s | 131.4 | 6.52 d, 0.9 | 132.3 |
| 6 | | 92.4 | | 92.4 | | 90.3 | | 91.8 |
| 7 | 3.09, 3.79 d, 18.2 | 40.2 | 3.09, 3.77 d, 18.2 | 40.2 | 3.63, 3.20 d, 18.2 | 39.4 | 3.83, 3.17 d, 18.2 | 40.1 |
| 8 | | 155.3 | | 155.3 | | 154.5 | | 155.1 |
| 9 | | 161.4 | | 161.6 | | 159.0 | | 160.4 |
| 10 | 3.57 t, 7.0 | 38.0 | 3.58 t, 7.0 | 38.0 | 3.40 dt, 5.8, 6.5 | 36.3 | 3.58 ddd, 13.5, 6.4, 5.8<br>3.45 ddd, 13.5, 7.3, 5.8 | 47.7 |
| 11 | 2.09 m | 30.6 | 2.11 m | 30.6 | 1.99 quint, 6.5 | 29.5 | 4.84 ddd, 7.3, 6.4, 3.8 | 71.4 |
| 12 | 4.02 t, 6.0 | 72.2 | 4.07 t, 6.0 | 72.2 | 3.95 m | 71.2 | | 138.5 |
| 13 | | 153.3 | | 153.7 | | 150.4 | 7.57 s | 130.9 |
| 14 | | 119.1 | | 119.4 | | 116.5 | | 111.4 |
| 15 | 7.57 s | 134.9 | 7.55 s | 135.0 | 7.53 s | 134.0 | | 150.7 |
| 16 | | 136.9 | | 136.6 | | 138.8 | | 111.4 |
| 17 | 7.57 s | 134.9 | 7.55 s | 135.0 | 7.53 s | 134.0 | 7.57 s | 130.9 |
| 18 | | 119.1 | | 119.4 | | 116.5 | | |
| 19 | 3.09 dd, 8.8, 13.9<br>3.17 dd, 5.2, 13.9 | 33.7 | 2.98 dd, 8.1, 14.7<br>3.20 dd, 4.7, 14.7 | 36.8 | 2.98 dd, 4.0, 13.0<br>2.86 dd, 4.0, 13.0 | 36.3 | | |
| 20 | 3.74 dd, 5.2, 8.8 | 72.6 | 3.75 dd, 4.7, 8.1 | 57.1 | 3.82 br | 57.2 | | |
| 21 | | 171.4 | | 173.0 | | 174.3 | | |
| OMe | | | 3.72 s | 60.4 | 3.65 s | 59.6 | 3.72 s | 60.2 |
| NH-20 | | | | | Not detected | | 7.69 brt, 5.8 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| OH-1 | | | | 6.32 br | | 5.48 d, 7.8 | | |
| OH-11 | | | | | | 5.02 d, 3.8 | | |
| OH-15 | | | | | | 3.79 s | | |
| NH-9 | | | | 8.46 t, 5.8 | | | | |

| | **109** (*84*) | | **110** (*79*) | | **111** (*79*) | | **112** (*86*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | 3.91 s | 73.5 | 3.92 d, 8.1 | 75.5 | 3.92 d, 8.2 | 75.5 | 4.04 s | 75.2 |
| 2 | | 113.0 | | 114.2 | | 114.2 | | 113.8 |
| 3 | | 147.1 | | 149.4 | | 149.3 | | 148.9 |
| 4 | | 120.8 | | 122.8 | | 122.8 | | 122.5 |
| 5 | 6.58 s | 131.2 | 6.59 s | 132.3 | 6.57 s | 132.3 | 6.36 s | 132.0 |
| 6 | | 90.2 | | 92.5 | | 92.4 | | 92.0 |
| 7 | 3.20 d, 18.1 | 39.1 | 3.23 d, 18.0 | 40.1 | 3.18 d, 18.2 | 41.4 | 3.73 d, 18.2 | 39.0 |
| | 3.62 d, 18.1 | | 3.62 d, 18.0 | | 3.60 d, 18.2 | | 3.01 d, 18.2 | |
| 8 | | 154.4 | | 155.3 | | 155.2 | | 154.8 |
| 9 | | 158.9 | | 161.6 | | 161.6 | | 161.2 |
| 10 | 3.38 m | 36.1 | 3.41 m | 37.9 | 3.36 m | 40.1 | 3.42 t, 7.6 | 40.1 |
| 11 | 1.99 m | 29.3 | 2.01 m | 30.6 | 2.76 t, 6.9 | 35.1 | 2.76 t, 7.6 | 34.7 |
| 12 | 3.95 t, 6.3 | 71.3 | 3.97 t, 6.3 | 72.3 | | 140.3 | | 139.8 |
| 13 | | 151.3 | | 153.7 | 7.54 s | 134.5 | 7.45 s | 134.1 |
| 14 | | 117.5 | | 119.5 | | 118.8 | | 118.4 |
| 15 | 7.68 s | 132.9 | 7.64 s | 134.4 | | 152.5 | | 151.9 |
| 16 | | 135.8 | | 136.5 | | 118.8 | | 118.4 |
| 17 | 7.68 s | 132.9 | 7.64 s | 134.5 | 7.54 s | 134.6 | 7.45 s | 134.1 |
| 18 | | 117.5 | | 153.7 | | 71.2 | 4.08 t, 5.6 | 71.4 |
| 19 | 3.05 m | 26.9 | 2.93 t, 8.1 | 30.3 | 2.15 m | 26.4 | 2.14 t, 6.0 | 28.0 |
| 20 | 3.50 m | 64.2 | 3.35 m | 59.2 | 3.40 m | 57.2 | 3.30 t, 6.6 | 48.8 |

(*continued*)

TABLE II.
Continued.

| | **109** (*84*) | | **110** (*79*) | | **111** (*79*) | | **112** (*86*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| OMe | 3.64 s | 59.5 | 3.65 s | 60.4 | 3.64 s | 60.4 | 3.69 s | 60.1 |
| OH-1 | 6.36 m | | 6.36 d, 8.1 | | 6.34 d, 8.2 | | | |
| NMe | | | | | | | 2.69 s | 32.0 |
| NH-9 | 8.57 t, 5.8 | | 8.57 t, 5.8 | | 8.58 t, 5.7 | | | |
| $NMe_3$-18 | 3.09 s | 52.3 | 2.78 s | 43.6 | 2.83 s | 43.7 | | |

| | **113** (*69*) | **113** acetate (*69*) | **114** (*69*) | **114** acetate (*69*) | **115** (*87*) | | **116** (*79*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD/CDCl_3$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD/CDCl_3$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 4.26 s | 74.7 | 4.14 s | 73.4 | 4.13 d, 0.8 | 75.5 | 3.91 d, 6.4 | 73.6 |
| 2 | | 108.5 | | 107.5 | | 114.1 | | 113.0 |
| 3 | | 151.5 | | 148.9 | | 149.3 | | 147.1 |
| 4 | | 122.4 | | 121.8 | | 122.8 | | 120.8 |
| 5 | 6.35 s | 132.3 | 6.35 s | 130.5 | 6.45 d, 0.9 | 132.2 | 6.58 s | 131.2 |
| 6 | | 90.6 | | 89.7 | | 92.4 | | 90.2 |
| 7 | 3.77 d, 17.5 | 40.7 | 3.20 d, 17.5 | 40.0 | 3.12 d, 18.3 | 40.1 | 3.19 d, 18.6 | 39.2 |
| | 3.93 d, 17.5 | | 3.85 d, 17.5 | | 3.82 d, 18.3 | | 3.61 d, 18.6 | |
| 8 | | 155.5 | | 153.9 | | 155.2 | | 154.3 |
| 9 | | 160.9 | | 159.4 | | 161.7 | | 158.9 |
| 10 | 3.67 t, 7 | 40.3 | 3.43 t, 7 | 38.6 | 3.38 t, 6.8 | 39.5 | 3.37 brt, 6.4 | 37.3 |
| 11 | 2.99 t, 7 | 27.4 | 2.01 t, 7 | 21.9 | 1.90 q, 7.1 | 22.9 | 2.61 t, 6.4 | 24.2 |
| 12 | | 134.6 | 2.67 t, 7 | 27.8 | 2.60 t, 7.1 | 28.9 | | 124.1 |
| 13 | 6.85 s | 117.7 | | 130.8 | | 128.5 | 6.62 br | 109.4 |
| 14 | 7.59 s | 135.9 | 6.47 s | 108.4 | 6.62 s | 110.3 | | 146.9 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 15 | | | | 146.9 | | 149.5 | | |
| OMe | 3.86 s | 60.6 | 3.79 s | 60.3 | 3.77 s | 60.4 | 3.64 s | 59.6 |
| OH-1 | | | | | | | 6.37 d, 6.4 | |
| NMe | | | | | 2.98 s | 29.5 | | |
| $OCOCH_3$ | NA | 171.1, 20.5 | NA | 170.0, 20.7 | | | | |
| NH-9 | | | | | | | 8.63 t, 5.6 | |
| NH-12 | | | | | | | 11.71 br | |
| NH-13 | | | | | | | 12.13 br | |
| NH-14 | | | | | | | 7.40 s | |

| | **117** (*79*) | | **118** (*88*) | | **119** (*89*) | | **120** (*83*) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{13}$C $CD_3OD$ |
| 1 | 3.92 d, 6.3 | 73.6 | 4.13 s | 75.5 | 4.08 s | 75.6 | 3.92 br | 73.5 | 75.5 |
| 2 | | 113.1 | | 114.1 | | 114.5 | | 113.0 | 114.1 |
| 3 | | 147.2 | | 149.3 | | 149.0 | | 147.0 | 149.2 |
| 4 | | 120.9 | | 122.8 | | 123.1 | | 120.6 | 122.7 |
| 5 | 6.58 s | 131.3 | 6.46 s | 132.3 | 6.40 s | 132.6 | 6.56 s | 131.2 | 132.2 |
| 6 | | 90.4 | | 92.3 | | 92.9 | | 90.1 | 92.4 |
| 7 | 3.19 d, 18.0 | 39.5 | 3.13 d, 18.3 | 40.2 | 3.09 d, 18.0 | 39.5 | 3.62 Abq, 18.0 | 39.3 | 40.2 |
| | 3.62 d, 18.0 | | 3.81 d, 18.3 | | 3.75 d, 18.0 | | 3.20 Abq, 18.0 | | |
| 8 | | 154.3 | | 155.3 | | 155.6 | | 154.5 | 155.3 |
| 9 | | 157.9 | | 161.6 | | 162.1 | | 158.4 | 161.3 |
| 10 | 3.35 m | 35.0 | 3.34-3.37 m | 39.9 | 3.51 t, 7.0 | 40.5 | 4.16 brt, 5.1 | 37.9 | 39.5 |
| 11 | 1.86, 1.96 m | 30.2 | 1.65 m | 29.8 | 2.76 t, 7.0 | 26.1 | 5.24 dt[b] | 121.0 | 123.5 |
| 12 | 4.30 dd, 4.9, 7.8 | 56.9 | 1.87, 1.65 m | 25.6 | | 126.3 | 6.06 d, 11.4 | 121.8 | 122.3 |
| 13 | | 174.8 | 4.09 dd, 5.2, 5.2 | 61.9 | 6.55 s | 111.3 | | 115.1 | 130.8 |
| 14 | | 159.2 | | 190.6 | | 149.7 | | 150.0 | 151.5 |
| 15 | | | | 171.4 | | | 6.52 s | 131.2 | 118.1 |

(*continued*)

TABLE II.
Continued.

| | **117** (*79*) | | **118** (*88*) | | **119** (*89*) | | **120** (*83*) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{13}$C $CD_3OD$ |
| OMe | 3.65 s | 59.7 | 3.77 s | 60.4 | 3.72 s | 59.6 | 3.63 s | 29.5 | 60.4 |
| OH-1 | 6.36 d, 6.3 | | | | 6.55 br | | 6.56 | | |
| NH-15 | | | | | | | 5.28 br, | | |
| $NH_2$ | | | | | | | 5.28 br, | | |
| NH-9 | 8.63 t, 5.1 | | | | 8.75 br | | 9.01 t, 5.4 | | |
| NH-12 | 12.5 br | | | | 11.70 s | | | | |
| NH-13 | 9.64 br | | | | 12.30 s | | | | |
| NH-14 | 8.96 s | | | | 7.45 s | | | | |

| | **121** (*90*) | | **122** (*91*) | | **123** (*89*) | | **124** (*83*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H[a] $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 3.89 d, 0.6 | 73.5 | 3.98 br | 73.5 | 4.10 s | 75.4 | 3.88 br | 73.4 |
| 2 | | 113.1 | | 113.0 | | 114.1 | | 113.0 |
| 3 | | 147.1 | | 147.0 | | 149.3 | | 147.1 |
| 4 | | 120.8 | | 120.7 | | 122.7 | | 120.6 |
| 5 | 6.56 d, 0.6 | 131.2 | 6.58 br | 131.2 | 6.40 s | 132.3 | 6.53 s | 131.2 |
| 6 | | 90.1 | | 90.2 | | 92.5 | | 90.1 |
| 7 | 3.12 d, 18.0 | 39.4 | 3.24 d, 18 | 39.4 | 3.10 d, 18.0 | 40.2 | 3.62 d, 18.0 | 39.5 |
| | 3.60 overlapped | | 3.71 d, 18 | | 3.78 d, 18.0 | | 3.20 d, 18.0 | |
| 8 | | 154.4 | | 154.4 | | 155.3 | | 154.4 |
| 9 | | 158.9 | | 158.9 | | 161.1 | | 158.8 |
| 10 | 3.40 overlapped | 38.1 | 3.43 dt, 6, 7 | 36.1 | 3.60 t, 7.0 | 38.3 | 3.10 m | 38.5 |
| 11 | 2.75 m | 24.6 | 2.02 tt, 7 | 29.3 | 2.12 m | 30.6 | 1.42 m | 28.2[c] |
| 12 | | 120.4 | 3.97 t, 7 | 71.2 | 4.02 t, 7.0 | 72.3 | 1.24 m | 23.3 |
| 13 | | 118.7 | | 150.7 | | 154.1 | 1.42 m | 28.0[c] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 14,14′ | | 146.2 | | 117.1 | | 119.2 | 3.10 m | 40.7 |
| 15,15′ | | 103.1 | 7.46 s | 132.8 | 7.52 s | 135.0 | | 157.2 |
| 16 | | 149.32 | | 136.1 | | 136.0 | | |
| 17 | | 112.2 | 3.78 s | 27.8 | 3.07, m | 38.0 | | |
| 18 | | 173.2 | | 150.7 | 4.07 m | 56.0 | | |
| 19 | | 137.7 | | 163.1 | | 170.1 | | |
| 20 | 7.70 s | 124.2 | 3.42 dt, 6, 7 | 37.3 | 3.45 m | 39.3 | | |
| 21 | | 128.9 | 2.66 t, 7 | 24.3 | 2.65 m | 25.7 | | |
| 22 | | 137.0 | | 124.1 | | 125.9 | | |
| 23 | 6.96 | 113.8 | 6.59 s | 109.0 | 6.55 s | 110.6 | | |
| 24 | | | | 146.7 | | 149.9 | | |
| OMe | 3.69 | 59.6 | 3.67 s | 59.5 | 3.72 s | 60.4 | 3.58 s | 59.6 |
| OH-1 | 6.42 br | | 6.48 br | | 6.50 br | | 6.56 br | |
| OH | 10.4, 11.8, 14.4 br | | | | | | | |
| $NH_2$-18 | | | | | 4.18 br | | | |
| NH | 11.95, 9.0 br | | | | | | 7.85 brt (NH-14) | |
| NH | | | | | | | 7.35 br (NH-15) | |
| $NH_2$ | 7.27 br | | 7.38 br | | 7.35 br | | 7.35 br | |
| NH-9 | 8.62 t, 5.7 | | 8.57 t, 6 | | 8.60 t, 6.0 | | 8.46 brt, 5.4 | |
| NH-19 | | | 8.15 t, 6 | | 8.70 t, 6.0 | | | |
| NH-22 | | | 11.74 br | | 11.80 s | | | |
| NH-23 | | | 12.16 br | | 12.35 s | | | |

| | **125** (*79*) | | **126** (*66*) | | **127** (*92*) | | **128** (*92*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | 1H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 3.91 d, 7.9 | 76.3 | 4.10 s | 76.4 | 3.93 d, 8.6 | 73.6 | 3.91 d, 8.2 | 73.6 |
| 2 | | 114.9 | | 115.1 | | 113.1 | | 113.0 |
| 3 | | 150.1 | | 150.2 | | 147.2 | | 147.1 |
| 4 | | 123.5 | | 123.7 | | 120.9 | | 120.8 |
| 5 | 6.57 s | 133.0 | 6.40 s | 133.2 | 6.60 s | 131.2 | 6.57 s | 131.2 |

(*continued*)

TABLE II.
Continued.

| | **125** (*79*) | | **126** (*66*) | | **127** (*92*) | | **128** (*92*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 6 | | 93.2 | | 93.4 | | 90.5 | | 90.2 |
| 7 | 3.19 d, 18.2<br>3.62 d, 18.2 | 40.1 | 3.11 d, 18<br>3.78 d, 18 | 41.0 | 3.21 d, 18.4<br>3.62 d, 18.4 | 39.3 | 3.18 d, 18.3<br>3.61 d, 18.3 | 39.5 |
| 8 | | 159.5 | | 156.0 | | 154.1 | | 154.3 |
| 9 | | 162.5 | | 162.8 | | 159.1 | | 158.9 |
| 10 | 3.16 m | 40.5 | 3.54 d, 4 | 44.7 | 3.99 d, 5.5 | 48.6 | 3.34 dt, 6.5, 5.9 | 33.8 |
| 11 | 1.47 m | 28.3 | 4.45 m | 78.4 | | 205.8 | 2.67 t, 6.5 | 38.3 |
| 12 | 1.45 m | 28.0 | 1.78, 2.05 m | 25.7 | 2.61 t, 6.8 | 39.8 | | 205.7 |
| 13 | 3.09 m | 42.9 | 3.35 m | 40.2 | 3.16 dt, 6.8, 4.8 | 35.2 | 3.83 d, 6.2 | 49.9 |
| 14 | | 156.1 | | 157.5 | | 157.0 | | 157.0 |
| OMe | 3.64 s | 61.2 | 3.72 s | 61.3 | 3.64 s | 59.8 | 3.65 s | 59.6 |
| OH-1 | 6.34 d, 7.9 | | | | 6.42 d, 8.6 | | 6.33 d, 8.2 | |
| OMe-14 | | | | | 3.50 s | 51.3 | 3.55 s | 51.5 |
| NH-9 | 8.54 t, 5.8 | | | | 8.64 t, 5.5 | | 8.43 t, 5.9 | |
| NH-13 | 7.44 br | | | | 7.09 t, 4.8 | | 7.34 t, 6.2 | |
| NH-14 | 7.1–7.3 4H, br | | | | | | | |

| | **131** (*95*) | | **132** (*96*) | | **133** (*96*) | | **129** (*94*) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H $CD_3OD$ | $^{1}$H $CD_2Cl_2$ | $^{13}$C DMSO-$d_6$ |
| 1 | 7.13 s | 146.7 | 7.17 s | 146.4 | 7.17 s | 147.3 | 7.13 s | 7.01 s | 146.3 |
| 2 | | 104.5 | | 103.6 | | 103.5 | | | 104.3 |
| 3 | | 149.9 | | 149.3 | | 149.3 | | | 149.4 |
| 4 | | 104.4 | | 104.1 | | 104.1 | | | 103.9 |
| 5 | 3.38 d, 16.0<br>3.06 d, 16.0 | 38.3 | 3.45 d, 16.0<br>3.15 d, 16.5 | 37.5 | 3.44 d, 16.2<br>3.13 d, 16.2 | 37.4 | 3.38 d, 16<br>3.05 d, 16 | 3.37 d, 16<br>3.08 d, 16 | 38.2 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | | 120.9 | | 119.9 | | 119.9 | | | 120.4 |
| 7 | 4.98 s | 80.4 | 5.07 d,7.0 | 80.2 | 5.07 d, 7.2 | 80.1 | 4.97 s | 5.05 s | 80.2 |
| 8 | | 158.7 | | 158.5 | | 158.4 | | | 158.2 |
| 9 | | 160.7 | | 159.1 | | 159.1 | | | 160.2 |
| CONH | | | 7.84 t, 5.8 | | 8.64 br | | 5.48 s | 7.15 brt, 6 | |
| NH | | | 7.26 brt, 5.3 | | 6.02 d,7.2 | | | 5.40 br | |
| 10 | 3.61 t, 6.0 | 38.0 | 3.64 q, 6.5 | 37.5 | 3.63 q, 6.6 | 37.9 | 3.61 t, 7.0 | 3.68 t, 6.0 | 39.7 |
| 11 | 2.14 dd, 6.0, 6.5 | 30.5 | 2.15 q, 6.0 | 30.4 | 2.14 q, 6.6 | 30.4 | 2.13 dd, 6.0, 7.0 | 2.10 2H | 29.9 |
| 12 | 4. 08 t, 6.0 | 72.2 | 4.10 t, 6.3 | 72.0 | 4.08 t, 6.2 | 72.0 | 4. 06 t, 6.0 | 4.08 t, 6.0 | 71.9 |
| 13 | | 154.2 | | 152.6 | | 152.5 | | | 153.0 |
| 14 | | 119.4 | | 118.4 | | 118.6 | | | 119.1 |
| 15 | 7.67 s | 1316 | 7.60 d,0.5 | 131.4 | 7.55 s | 134.3 | 7.48 s | 7.38 s | 134.1 |
| 16 | | 141.5 | | 143.6 | | 138.6 | | | 136.9 |
| 17 | 7.67 s | 131.6 | 7.60 d,0.5 | 131.4 | 7.55 s | 134.3 | 7.48 s | 7.38 s | 134.1 |
| 18 | | 119.4 | | 118.4 | | 118.6 | | | 119.1 |
| 19 | 4.92 dd, 3.0, 10 | 68.6 | 4.78 q, 5.3 | 72.3 | 3.01 t, 7.2 | 32.4 | 2.76 dd, 7.5, 7.0 | 2.66 t, 7.0 | 32.9 |
| 20 | 3.21 dd, 3.0, 13<br>3.09 dd, 10, 13 | 56.4 | 3.49 dt, 13.8, 5.1<br>3.37 dt, 14.0, 6.0 | 47.9 | 3.75 q, 7.0 | 51.2 | 2.96 dd, 7.5, 7.0 | 2.90 t, 7.0 | 41.5 |
| 21 | | | | 174.8 | 7.34 d, 14.4 | 149.8 | | | |
| 22 | | | 2.14 t, 7.0 | 39.7 | | 99.4 | | | |
| 23 | | | | 26.6 | | 197.4 | | | |
| 24 | | | | | 6.64 d, 6.3 | 142.6 | | | |
| 25 | | | 1.28 br($H_{23}$-$H_{32}$) | 27.8 ($C_{24}$-$C_{31}$) | 6.73 d, 6.3 | 142.4 | | | |
| 26 | | | | | | 194.1 | | | |
| 32 | | | | 28.6 | | | | | |
| 33 | | | 1.55 m | 28.1 | | | | | |
| 34,35 | | | 0.85 d, 6.5 | 22.9 | | | | | |
| OMe | 3.64 s | 59.3 | 3.64 s | 59.0 | 3.65 s | 60.0 | 3.64 s | 3.66 s | 59.3 |
| NMe | 2.73 s | 33.9 | | | | | | | |
| 7-OH | | | 5.99 d, 7.0 | | 7.86 brt, 5.4 | | | | |
| 19-OH | | | 5.19 dd ,4.5 | | | | | | |

(*continued*)

TABLE II.
Continued.

| | **130** (*94*) | | **135** (*98*) | | **136** (*98*) | | **134** (*97*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}H^{a}$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ acetone-$d_6$ | $^{13}C$ acetone-$d_6$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ |
| 1 | 7.13 s | 146.7 | 7.14 s | 146.8 | 7.17 s | 147.3 | 7.00 s | 145.4 |
| 2 | | 104.3 | | 104.4 | | 103.5 | | 103.5 |
| 3 | | 149.8 | | 149.9 | | 149.3 | | 148.5 |
| 4 | | 104.5 | | 104.6 | | 104.1 | | 104.6 |
| 5 | 3.38, 3.07 d | 38.2 | 3.39, 3.07 d, 16.1 | 38.3 | 3.44, 3.13 d, 16.2 | 37.4 | 3.38, 3.09 d, 16 | 37.1 |
| 6 | | 120.8 | | 120.9 | | 119.9 | | 121.3 |
| 7 | 4.97 s | 80.4 | 4.99 s | 80.4 | 5.07 d,7.2 | 80.1 | 5.03 s | 78.8 |
| 8 | | 158.7 | | 158.8 | | 158.4 | | 156.7 |
| 9 | | 160.6 | | 160.7 | | 159.1 | | 158.8 |
| CONH | | | | | 8.64 br | | 7.26 s | |
| NH | | | | | 6.02 d, 7.2 | | 3.68 | |
| 10 | 3.62 t | 38.0 | 3.62 t, 6.8 | 38.0 | 3.63 q, 6.6 | 37.9 | 3.68 m | 37.0 |
| 11 | 2.10 pentet | 30.5 | 2.13 tt, 6.0, 6.8 | 30.6 | 2.14 q, 6.6 | 30.4 | 2.08 m | 29.3 |
| 12 | 4.07 t | 72.1 | 4.07 t, 6.0 | 72.1 | 4.08 t, 6.2 | 72.0 | 4.05 t, 5.5 | 70.8 |
| 13 | | 153.6 | | 152.9 | | 152.5 | | 151.0 |
| 14 | | 119.2 | | 119.0 | | 118.6 | | 118.0 |
| 15 | 7.62s | 134.3 | 7.48s | 134.3 | 7.55 s | 134.3 | 7.34 s | 132.8 |
| 16 | | 143.2 | | 139.7 | | 138.6 | | 138.6 |
| 17 | 7.62 s | 131.5 | 7.48 s | 134.3 | 7.55 s | 134.3 | 7.34 s | 132.8 |
| 18 | | 119.4 | | 119.0 | | 118.6 | | 118.0 |
| 19 | 2.83 dd | 72.7 | 2.77 t, 7.1 | 35.0 | 3.01 t, 7.2 | 32.4 | 2.73 t, 7.0 | 34.3 |
| 20 | 2.97 dd | 18.4 | 3.44 t, 7.1 | 40.0 | 3.75 q, 7.0 | 51.2 | 2.82 t, 7.0 | 52.1 |
| 21 | | | 7.80 s | 163.8 | 7.34 d, 14.4 | 149.8 | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 22 | | | | | | 99.4 | | |
| 23 | | | | | | 197.4 | | |
| 24 | | | | | 6.64 d, 6.3 | 142.6 | | |
| 25 | | | | | 6.73 d, 6.3 | 142.4 | | |
| 26 | | | | | | 194.1 | | |
| $NCH_3$ | | | | | | | 2.44 s | 35.8 |
| OMe | 3.65 s | 59.3 | 3.65 s | 59.3 | 3.65 s | 60.0 | 3.67 s | 59.0 |
| 7-OH | | | | | 7.86 brt, 5.4 | | 4.1 s | |

[a]Coupling constants were not reported in original paper.

| | **137** (*99*) | | | **138** (*100*) | | **139** (*101*) | | | **140** (*33*) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $^1H$ $CD_3OD$ | $^1H$ DMSO-$d_6$ | $^{13}C$ $CD_3OD$ | $^1H$ 0.2% TFA-H in $CD_3OD$ | $^{13}C$ | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{13}C$ $CD_3OD + 5\%$ $CD_3CO_2D$ | $^1H$ 0.2% TFA-H in $CD_3OD$ | $^{13}C$ |
| 1 | | | 126.0 | | 137.7 | | 112.1 | 112.1 | | 130.6 |
| 2 | 7.46 s | 7.44 s | 134.4 | 7.46 s | 134.8 | 7.42 d, 2.1 | 134.8 | 134.7 | 7.45 d, 2.2 | 134.3 |
| 3 | | | 118.5 | | 118.8 | | 131.8 | 131.7 | | 110.4 |
| 4 | | | 148.6 | | 154.2 | | 155.9 | 155.9 | | 153.6 |
| 5 | | | 118.5 | | 118.8 | 6.89 d, 8.4 | 113.1 | 113.1 | 6.81 d, 8.5 | 117.1 |
| 6 | 7.46 s | 7.44 s | 134.4 | 7.46 s | 134.8 | 7.17 dd, 8.4, 2.1 | 130.5 | 130.4 | 7.06 dd, 8.5, 2.2 | 130.4 |
| 7 | 3.81 s | 3.75 s | 28.8 | 3.82 | 29.1 | 3.79 2YH, s | 28.7 | 28.7 | 3.78 s | 28.7 |
| 8 | | | 152.1 | | 152.4 | | 153.0 | 152.9 | | 153.1 |
| 9 | | | 165.6 | | 165.6 | | 165.7 | 165.9 | | 166.1 |
| 10 | | | 38.9 | 3.49 t, 7 | 40.6 | 3.47 t, 7.1 | 40.3 | 39.2 | 3.57 t, 7.0 | 39.0 |
| 11 | | | 25.7 | 2.79 t, 7 | 27.9 | 2.77 t, 7.1 | 27.8 | 26.1 | 2.94 t, 7.0 | 25.7 |
| 12 | 3.47 t | 3.36 m | 137.2 | | 134.0 | | NA | 133.4 | | 132.8 |
| 13 | 2.69 t | 2.58 t | 110.7 | 6.84 br | 118.0 | 6.80 br | NA | 117.6 | 7.25 br | 117.5 |
| 14 | | | 153.8 | 7.62 br | 136.2 | 7.55 br | 136.1 | 135.0 | 8.70 br | 134.6 |
| OMe | 3.81 s | 3.75 s | 61.0 | 3.80 s | 61.3 | 3.80 s | 56.7 | 56.7 | | |
| NH | 6.50 s | 6.50 s | | | | | | | | |

(*continued*)

TABLE II.
Continued.

| | **141** (*102*) | **142** (*102*) | | **143** (*102*) | **144** (*103*) | | **145** (*103*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | | 137.2 | | | 138.2 | | 138.1 |
| 2 | 7.48 s | 7.48 s | 134.4 | 7.48 s | 7.46 s | 135.3 | 7.46 s | 135.3 |
| 3 | | | 118.7 | | | 119.6 | | 119.6 |
| 4 | | | 152.8 | | | 153.7 | | 153.6 |
| 5 | | | 118.7 | | | 119.6 | | 119.6 |
| 6 | 7.48 s | 7.48 s | 134.4 | 7.48 s | 7.46 s | 135.3 | 7.46 s | 135.3 |
| 7 | 3.83 br | 3.82 br | 28.8 | 3.83 br | 3.82 s | 28.9 | 3.82 s | 28.9 |
| 8 | | | 151.9 | | | 152.9 | | 152.9 |
| 9 | | | 165.4 | | | 166.3 | | 166.4 |
| 10 | 3.47 t, 7 | 3.48 t, 7 | 38.9 | 3.47 t, 7 | 3.45 t, 6.8 | 40.2 | 3.45 t, 6.8 | 39.9 |
| 11 | 2.70 t, 7 | 2.71 t, 7 | 25.8 | 2.71 t, 7 | 2.66 t, 6.8 | 24.5 | 2.67 t, 6.8 | 24.5 |
| 12 | | | 126.0 | | | 126.2 | | 126.4 |
| 13 | 6.51 s | 6.51 s | 110.7 | 6.51 s | 6.41 s | 112.0 | 6.46 s | 111.7 |
| 14 | | | 148.5 | | | 148.3 | | 148.5 |
| 15 | 4.01 t, 7 | 4.01 t, 7 | 72.3 | 4.02 t, 7 | 4.00 t, 6.1 | 73.1 | 4.00 t, 6.1 | 73.1 |
| 16 | 2.04 quin, 7 | 2.04 quin, 7 | 30.9 | 2.04 quin, 7 | 2.03 m | 31.1 | 2.03 tt, 6.1, 6.8 | 31.1 |
| 17 | 3.44 t, 7 | 3.44 t, 7 | 37.7 | 3.44 t, 7 | 3.43 t, 7.3 | 38.5 | 3.43 t, 66.8 | 39.0 |
| 18 | | | 176.3 | | | 177.2 | | 177.2 |
| 19 | 2.19 t, 7 | 2.20 t, 7 | 37.2 | 2.19 t, 7 | 2.18 t, 7.3 | 38.0 | 2.18 t, 7.6 | 38.0 |
| 20 | 1.61 quin, 7 | 1.61 quin, 7 | 27.1 | 1.61 quin, 7 | 1.60 m | 27.4 | 1.60 m | 34.7–31.2 |
| 21–24 | 1.28 m | 1.28 m | 30.2 | 1.28 m | 1.35–1.27 m | 31.9–31.1 | 1.33–1.26 m | 34.7–31.2 |
| 25 | 1.28 m | 1.28 m | 30.7 | 1.28 m | 2.03 m | 27.9 | 1.33–1.26 m | 34.7–31.2 |
| 26 | 1.28 m | 1.28 m | 30.7 | 1.28 m | 5.33 t, 5.4 | 131.7 | 1.33–1.26 m | 34.7–31.2 |
| 27 | 1.28 m | 1.28 m | 31.0 | 1.28 m | 5.33 t, 5.4 | 131.6 | 1.33–1.26 m | 34.7–31.2 |
| 28 | 1.28 m | 1.28 m | 28.5 | 1.28 m | 2.03 m | 27.9 | 1.33–1.26 m | 34.7–31.2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 29 | 1.28 m | 1.28 m | 40.2 | 1.28 m | 1.35–1.27 m | 31.9–31.1 | 1.33–1.26 m | 34.7–31.2 |
| 30 | 1.28 m | 1.51 m | 29.0 | 1.28 m | 1.35–1.27 m | 31.9–31.1 | 1.33–1.26 m | 34.7–31.2 |
| 31 | 0.90 t, 7 | 0.87 d, 7 | 23.1 | 1.28 m | 1.35–1.27 m | 31.9–31.1 | 1.33–1.26 m | 34.7–31.2 |
| 32 | | 0.87 d, 7 | 23.1 | 1.28 m | 1.51 m, 6.8 | 30.0 | 1.33–1.26 m | 34.7–31.2 |
| 33 | | | | 0.88 t, 7 | 0.86 d, 6.8 | 23.8 | 1.33–1.26 m | 34.7–31.2 |
| 34 | | | | | 0.86 d, 6.8 | 23.8 | 1.33–1.26 m | 29.6 |
| 35 | | | | | | | 1.33–1.26 m | 27.9 |
| 36 | | | | | | | 0.89 t, 6.8 | 15.2 |

| | **146** (*104*) | | **147** (*105*) | | **148** (*103*) | | **149** (*79*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ + 1 d 1N HCl |
| 1 | | 136.4 | | 136.5 | | 131.4 | | 122.0 |
| 2 | 7.45 s | 132.9 | 7.45 s | 132.8 | 7.32 s | 132.5 | | 152.8 |
| 3 | | 117.4 | | 117.0 | | 111.9 | | 107.6 |
| 4 | | 150.5 | | 150.5 | | 149.2 | | 152.7 |
| 5 | | 117.4 | | 117.0 | | 111.9 | | 105.5 |
| 6 | 7.45 s | 132.9 | 7.45 s | 132.8 | 7.32 s | 132.5 | 7.26 s | 132.2 |
| 7 | 3.75 s | 27.7 | 3.75 s | 27.9 | 3.69 s | 27.7 | 3.70 s | 27.0 |
| 8 | | 150.9 | | 150.8 | | 151.5 | | 150.3 |
| 9 | | 163.1 | | 163.1 | | 163.4 | | 164.7 |
| CONH | | | | | 8.13 t, 5.9 | | 8.55 t, 5.9 | |
| NOH | 12.03 s | | 12.09 s | | 11.93 s | | 12.19 s | |
| NH-9 | 8.15 t, 6 | | 8.17 t, 5.4 | | | | | |
| NH-12 | | | | | 11.56 br | | 11.55 br | |
| NH-13 | 11.77 br | | 11.96 br | | 11.98 br | | 11.19 br | |
| NH-14 | 12.16 br | | 12.33 br | | 7.33s | | 7.33 s | |
| $NH_2$ | 7.83 br | | 7.49 s | | | | | |
| 10 | 3.36 dt, 6 | 37.3 | 3.36 dt, 5.4, 6.4 | 37.3 | 3.36 dt, 5.9, 6.8 | 37.5 | 3.40 dt, 5.9, 6.9 | 37.6 |

(*continued*)

TABLE II.
Continued.

| | **146** (*104*) | | **147** (*105*) | | **148** (*103*) | | **149** (*79*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ + 1 d 1N HCl |
| 11 | 2.59 t, 6 | 24.4 | 2.61 t, 6.4 | 24.4 | 2.59 t, 6.8 | 24.6 | 2.63 t, 6.9 | 24.7 |
| 12 | | 124.3 | | 124.2 | | 124.5 | | 124.2 |
| 13 | 6.57 s | 109.2 | 6.58 br | 109.2 | 6.57 s | 109.4 | 6.60 s | 109.3 |
| 14 | | 146.9 | | 147.1 | | 147.0 | | 146.7 |
| 15 | 3.98 t, 6 | 70.4 | 4.01 5.9 | 70.1 | | | | |
| 16 | 2.02 m | 27.9 | 2.50 2H overlapped | 31.0 | | | | |
| 17 | 3.06 m | 36.5 | 4.89 t, 7.3 | 58.5 | | | | |
| 1′,5′ | | | 9.20 d, 5.9 | 145.1 | | | | |
| 2′,4′ | | | 8.18 dt, 5.9, 7.8 | 128.0 | | | | |
| 3′ | | | 8.61 t, 7.8 | 145.6 | | | | |
| OMe | | | | | | | 3.74 s | 60.0 |
| OH | | | | | 9.77 br | | 10.48 br | |

| | **150** (*79*) | | **151** (*89*) | |
|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ + 1 d 1N HCl |
| 1 | | 122.7 | | 134.0 |
| 2 | | 155.0 | 7.55 s | 135.2 |
| 3 | | 108.8 | | 118.9 |
| 4 | | 154.3 | | 154.8 |
| 5 | | 107.4 | | 118.9 |
| 6 | 7.26 s | 134.6 | 7.55 s | 132.5 |

| | | | | | |
|---|---|---|---|---|---|
| 7 | 3.70 s | 25.5 | 3.30 m | 32.0 |
| 8 | | 151.5 | 4.25 dd, 12.0, 4.0 | 75.8 |
| 9 | | 167.3 | | 166.2 |
| CONH | 8.59 t, 5.9 | | 9.20 t, 6.0 | |
| NOH | 12.20 s | | | |
| NH-12 | | | 11.70 s | |
| NH-13 | 14.1 br | | 12.25 s | |
| NH-14 | | | 7.25 br | |
| 10 | 3.48 dt, 5.9, 6.7 | 39.2 | 3.30 m | 38.7 |
| 11 | 2.85 t, 6.7 | 25.8 | 2.45 m | 25.2 |
| 12 | | 132.2 | | 125.3 |
| 13 | 7.40 s | 117.7 | 6.42 s | 110.5 |
| 14 | | 134.9 | | 148.5 |
| OMe | 3.74 s | 60.8 | 3.82 s | 61.0 |
| NMe | | | 3.32 s | 53.2 |
| OH | 10.45 br | | | |

| | **152** (*107*) | | | | **153** (*107*) | | **154** (*109*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$/ $CD_3OD$ | $^{1}$H pyridine-$d_5$ | $^{13}$C $CD_3OD$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CDCl_3$/ $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ |
| 1,1′ | | | 132.1 | 128.8 | | 128.2 | Signals were not assigned | |
| 2,2′ | 7.62 d, 2 | 7.76 d, 2 | 136.0 | 132.9 | 7.40 d, 2<br>7.48 d, 2 | 132.5, 139.7 | 8.08 t, 6; 805, t, 6; 7.29, d, 2; | 166.1, 165.8, 154.7, 153.6, |
| 3,3′ | | | 112.1 | 108.8 | | 108.8, 108.9 | 7.00, dd, 8.3, 2; | 153.5, 153.0, |
| 4,4′ | | | 155.4 | 152.3 | | 152.6, 152.9 | 6.83, d, 8.3; | 134.4, 133.1, |
| 5,5′ | 6.85 d, 8 | 6.84 d, 8 | 118.7 | 116.2 | 6.83 d, 8 6.87 d, 8 | 115.9 | 6.73, d, 1.9;<br>6.65, d, 1.9; | 132.1, 130.6, |
| 6,6′ | 7.15 dd, 8, 2 | 7.26 dd, 8, 2 | 131.9 | 129.1 | 7.10 dd, 8, 2<br>7.17 dd, 8, 2 | 128.9, 129.1 | 3.67, s; 3.61, s;<br>3.44 dt, 7, 6; | 117.0, 114.4, 110.5, 39.7 |

(*continued*)

TABLE II.
Continued.

| | **152** (*107*) | | | | **153** (*107*) | | **154** (*109*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CDCl_3$/ $CD_3OD$ | $^1$H pyridine-$d_5$ | $^{13}$C $CD_3OD$ | $^{13}$C DMSO-$d_6$ | $^1$H DMSO-$d_6$ | $^{13}$C $CDCl_3$/ $CD_3OD$ | $^1$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ |
| 7,7′ | 3.87 s | 4.01 s | 30.3 | 26.7 | 3.68, 3.87 s | 27.5, 35.7 | 3.41 dt, 7, 6; | 39.6, 38.5, |
| 8,8′ | | | 154.7 | 151.8 | | 151.1, 151.6 | 2.81 t, 7; 2.79 t, | 28.9, 28.7 |
| 9,9′ | | | 167.5 | | | 161.9, 163.1 | 7 | |
| 10,10′ | 3.63 t, 7 | 3.48 q, 7 | 41.2 | 38.1 | 3.50, 3.65 m | 37.6, 38.0 | | |
| 11,11′ | 2.87 t, 7 | 2.65 t, 7 | 40.1 | 37.0 | 2.95 m | 36.6, 36.7 | | |
| OH | | 12, 14 br | | | | | | |
| NH | | 8.56 t, 7 | | | | | 8.08, 8.05 t, 6 | |

| | **155** (*110*) | | **156** (*110*) | | **157** (*110*) | | **158** (*110*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3CN$ | $^{13}$C $CD_3CN$ | $^1$H $CD_3CN$ | $^{13}$C $CD_3CN$ | $^1$H $CD_3CN$ | $^{13}$C $CD_3CN$ | $^1$H $CD_3CN$ | $^{13}$C $CD_3CN$ |
| 1 | | | | 130.9 | | 130.8 | | 130.9 |
| 2 | | | 7.08 dd, 2.1, 8.4 | 130.4 | 7.07 dd, 1.8, 8.4 | 130.4 | 7.07 dd, 1.8, 8.4 | 130.4 |
| 3 | | | 6.83 d, 8.4 | 117.2 | 6.82 d, 8, 4 | 117.1 | 6.82 d, 8.4 | 117.1 |
| 4 | | | | 153.0 | | 152.8 | | 152.8 |
| 5 | | | | 109.1 | | 109.9 | | 109.9 |
| 6 | | | 7.36 d, 2.1 | 134.1 | 7.35 d, 1.8 | 134.0 | 7.35 d, 2.1 | 134.1 |
| 7 | | | 3.76 s | 28.5 | 3.75 s | 28.5 | 3.76 d, 2.1 | 28.5 |
| 8 | | | | 153.4 | | 153.2 | | 153.4 |
| 9 | | 154.2 | | 164.5 | | 164.2 | | 164.1 |
| 10 | 3.35 q, 6.3 | 40.7 | 3.57 q, 6.3 | 39.7 | 3.65 q, 6.3 | 35.1 | 3.50 q, 6.6 | 39.1 |
| 11 | 2.77 t, 6.6 | 38.9 | 3.10 t, 6.6 | 34.1 | 3.21 t, 6.3 | 54.5 | 2.79 t, 6.6 | 39.0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12 | | | | | 2.76 t, 6.3 | 38.2 |
| 13 | | | | | 3.33 q, 6.3 | 40.6 |
| 14 | | | | | | 158.2 |
| OMe | 3.57 s | 52.4 | | | 3.56 s | 52.4 |
| NH-9 | 5.77 br | | 7.37 br | 7.47 t, 5.4 | 7.29 t, 5.4 | |
| NH-13 | 5.77 br | | | | 5.82 br | |
| CN | | 111.9 | | | | |
| $NH_2$ | | | | 5.49 br | | |

| | **159** (*112*) | | **160** (*112*) | | **161** (*112*) | | **162** (*112*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 130.2 | | 130.7 | | 130.7 | | 130.6 |
| 2 | 7.06 dd, 8.0, 2.0 | 130.5 | 7.05 dd, 8.0, 2.0 | 130.5 | 7.01 dd, 8.0, 2.0 | 130.5 | 7.06 dd, 8.0, 2.5 | 130.5 |
| 3 | 6.75 d, 8.0 | 117.4 | 6.75 d, 8.0 | 117.2 | 6.83 d, 8.0 | 117.2 | 6.75 d, 8.5 | 117.2 |
| 4 | | 154.5 | | 153.9 | | 153.8 | | 153.9 |
| 5 | | 111.0 | | 110.6 | | 110.6 | | 110.6 |
| 6 | 7.35 d, 2.0 | 134.6 | 7.35 d, 2.0 | 134.6 | 7.28 d, 2.5 | 134.6 | 7.36 d, 2.5 | 134.6 |
| 7 | 3.78 s | 28.8 | 3.78 s | 28.8 | 3.69 s | 28.2 | 3.78 s | 28.8 |
| 8 | | 153.4 | | 153.3 | | 153.2 | | 153.2 |
| 9 | | 166.0 | | 166.0 | | 166.0 | | 166.0 |
| 10 | 3.54 t, 6.0 | 39.9 | 3.54 t, 6.0 | 39.8 | 3.42 t, 6.5 | 39.7 | 3.54 t, 7.0 | 39.8 |
| 11 | 2.84 t, 6.0 | 38.8 | 2.84 t, 6.0 | 38.6 | 2.83 t, 6.5 | 38.6 | 2..82 t, 7.0 | 39.4 |
| 12 | 2.84 t, 6.0 | 38.2 | 2.84 t, 6.0 | 37.9 | 2.83 t, 6.5 | 37.9 | 2.78 t, 7.0 | 38.5 |
| 13 | 3.53 t, 6.0 | 39.8 | 3.54 t, 6.0 | 40.1 | 3.42 t, 6.5 | 40.1 | 3.36 t, 7.0 | 41.0 |
| 14 | | 162.1 | | 161.9 | | 161.9 | | 159.2 |
| 15 | | 164.0 | | 159.2 | | 159.2 | | |
| $OCH_2CH_3$ | | | | | | | 4.05 q, 7.0, 1.21 t, 7.0, | 61.9, 15.1 |

(*continued*)

TABLE II.
Continued.

| | **164** (*112*) | | **165** (*114*) | | **166** (*114*) | | **167** (*114*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 129.2 | | 130.6 | | 136.1 | | 130.0 |
| 2 | 7.35 d, 2.0 | 133.0 | 7.36 d, 2.0 | 134.4 | 7.49 d, 2.0 | 134.6 | 7.34 d, 2.0 | 134.4 |
| 3 | | 109.0 | | 110.4 | | 116.5 | | 110.8 |
| 4 | | 152.3 | | 153.7 | | 149.5 | | 154.3 |
| 5 | 6.75 d, 8.5 | 115.6 | 6.75 d, 8.3 | 117.0 | 7.47 d, 8.3 | 123.3 | 6.73 d, 8.3 | 117.3 |
| 6 | 7.05 dd, 8.5, 2.0 | 129.0 | 7.06 dd, 8.3, 2.0 | 130.3 | 7.21 dd, 8.3, 2.0 | 130.0 | 7.03 dd, 8.3, 2.0 | 130.3 |
| 7 | 3.78 s | 27.2 | 3.78 s | 28.7 | 3.86 s | 29.0 | 3.77 s | 28.7 |
| 8 | | 151.6 | | 153.0 | | 152.5 | | 153.0 |
| 9 | | 164.6 | | 165.8 | | 165.6 | | 165.9 |
| 10 | 3.62 m | 33.5 | 3.51 t, 6.8 | 39.7[b] | 3.52 t, 6.8 | 39.6 | 3.49 t, 6.8 | 39.7[c] |
| 11 | 3.51 m | 39.3 | 2.80 t, 6.8 | 38.6[a] | 2.80 t, 6.8 | 38.5 | 2.78 t, 6.8[a] | 38.6[b] |
| 12 | | | | 158.6 | | 158.6 | | |
| 13 | | | 3.02 s | 38.3 | 3.01 s | 38.3 | | |
| 14 | | | 3.02 s | 38.3 | 3.01 s | 38.3 | | |
| 1′ | | 129.2 | | 130.6 | | 136.1 | | 127.9 |
| 2′ | 7.35 d, 2.0 | 133.0 | 7.49 d, 2.0 | 134.6 | 7.49 d, 2.0 | 134.6 | 7.31 d, 2.0 | 132.5 |
| 3′ | | 109.0 | | 116.5 | | 116.5 | | 114.6 |
| 4′ | | 152.3 | | 149.6 | | 149.5 | | 155.0 |
| 5′ | 6.75 d, 8.5 | 115.6 | 7.47 d, 8.8 | 123.3 | 7.47 d, 8.3 | 123.3 | | 131.7 |
| 6′ | 7.05 dd, 8.5, 2.0 | 129.0 | 7.21 dd, 8.3, 2.0 | 130.0 | 7.21 dd, 8.3, 2.0 | 130.0 | 7.35 d, 2.0 | 132.2 |
| 7′ | 3.78 s | 27.2 | 3.86 s | 29.0 | 3.86 s | 29.0 | 3.86 s | 29.0 |
| 8′ | | 151.6 | | 152.5 | | 152.5 | | 153.8 |
| 9′ | | 164.6 | | 165.6 | | 165.6 | | 166.1 |
| 10′ | 3.22, 3.32 m | 55.0 | 3.51 t, 6.8 | 39.6[b] | 3.52 t, 6.8 | 39.6 | 3.51 t, 6.8 | 39.6[c] |
| 11′ | 3.29 m | 32.2 | 2.80 t, 6.8 | 38.5[a] | 2.80 t, 6.8 | 38.5 | 2.77 t, 6.8[a] | 38.5[b] |
| 1″ | | | | | | | | 172.7 |

| | | |
|---|---|---|
| 2″ | | 142.5 |
| 3″ | 6.93 s | 123.8 |
| 4″ | | 124.1 |
| 5″ | 8.22 d, 2.2 | 134.3 |
| 6″ | | 116.4 |
| 7″ | | 160.2 |
| 8″ | | 130.8 |
| 9″ | 7.65 d, 2.2 | 134.2 |

[a,b,c]Interchangeable signals.

| | **168** (*114*) | | **168a** (*114*) | | **169** (*117*) | | **170** (*117*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 129.6 | | 133.1 | | 130.3 | | 130.8 |
| 2 | 6.81 d, 2.0 | 126.3 | 6.96 d, 1.4 | 126.0 | 7.35 d, 2.0 | 134.6 | 7.36 d, 2.0 | 134.5 |
| 3 | | 110.5 | | 117.6 | | 110.0 | | 110.2 |
| 4 | | 143.7 | | 144.3 | | 153.2 | | 153.7 |
| 5 | | 147.5 | | 151.2 | 6.74 d, 8.5 | 116.8 | 6.74 d, 8.5 | 117.0 |
| 6 | 6.18 d, 2.0 | 115.0 | 6.17 d, 1.4 | 114.3 | 7.05 dd, 8.5, 2.0 | 130.0 | 7.06 dd, 8.0, 2.0 | 130.6 |
| 7 | 3.72 s | 28.3 | 3.71 s | 25.6 | 3.79 s | 28.0 | 3.76 s | 28.7 |
| 8 | | 153.1 | | 151.7 | | 152.8 | | 152.8 |
| 9 | | 166.2 | | 163.1 | | 165.8 | | 166.0 |
| 10 | 3.51 m[d] | 40.0 | 3.48 br | 38.7 | 3.60 t, 7.0 | 39.0 | 3.51 t, 7.0[b] | 39.6 |
| 11 | 2.87 m[d] | 41.1 | 2.48 br | 38.8 | 2.99 7.0 | 37.8 | 2.81 7.0[c] | 38.5 |
| 1′ | | 130.3 | | 132.9 | | 130.3 | | 128.3 |
| 2′ | 7.32 d, 2.0 | 134.6 | 7.43 d, 1.8 | 134.7 | 7.35 d, 2.0 | 134.6 | 7.35 s | 133.0 |
| 3′ | | 113.1 | | 117.1 | | 110.0 | | 112.0 |
| 4′ | | 151.2 | | 153.1 | | 153.2 | | 151.0 |
| 5′ | | 128.4 | | 132.0 | 6.74 d, 8.5 | 116.8 | | 112.0 |

(*continued*)

TABLE II.
Continued.

| | **168** (*114*) | | **168a** (*114*) | | **169** (*117*) | | **170** (*117*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 6′ | 6.78, d, 2.0 | 131.3 | 6.65 d, 1.8 | 129.6 | 7.05 dd, 8.5, 2.0 | 130.0 | 7.35 s | 133.0 |
| 7′ | 3.68 br s[d] | 28.7 | 3.63 s | 28.6 | 3.79 s | 28.0 | 3.78 s | 28.7 |
| 8′ | | 152.9 | | 151.1 | | 152.8 | | 153.3 |
| 9′ | | 165.4 | | 162.7 | | 165.8 | | 166.0 |
| 10′ | 3.43 t, 6.8 | 39.6 | 3.54 t, 6.1 | 39.0 | 3.60 t, 7.0 | 39.0 | 3.50 t, 7.0[b] | 39.6 |
| 11′ | 2.87 t, 6.8 | 38.4 | 3.48 br | 38.8 | 2.99 7.0 | 37.8 | 2.80 7.0[c] | 38.5 |
| 1″ | | 171.4 | | 166.2 | | | | |
| 2″ | | 146.8 | | 140.0 | | | | |
| 3″ | 6.96 s | 120.9 | 6.50 s | 108.5 | | | | |
| 4″ | | 134.5 | | 132.6 | | | | |
| 5″ | 8.42 d, 2.0 | 135.7 | 8.12 d, 1.8 | 134.6 | | | | |
| 6″ | | 118.2 | | 117.9 | | | | |
| 7″ | | 150.4 | | 148.1 | | | | |
| 8″ | | 135.5 | | 133.8 | | | | |
| 9″ | 7.59 d, 2.0 | 134.1 | 7.67 d, 1.9 | 132.1 | | | | |
| 1″-Me | | | 3.92 s | 53.5 | | | | |
| 8,8′-Me | | | 3.91 s, 3.85 s | 63.0, 62.9 | | | | |
| 4,4′-Me | | | 3.61 s, 3.58 s | 61.1, 60.5 | | | | |
| NH | | | 7.71 br; 7.23 t, 6.3 | | | | | |

[a,b,c]Interchangeable signals.
[d]Shape of signal was changed in temperature-variable experiment in DMSO-$d_6$.

| | **171** (*117*) | | | | | | | | **163** (*112*) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3OD$ | $^{13}$C | | $^1$H $CD_3OD$ | $^{13}$C | | $^1$H $CD_3OD$ | $^{13}$C | | $^1$H $CD_3OD$ | $^{13}$C |
| 1 | | 130.8 | 1′ | | 128.7 | 1″ | | 129.3 | 1‴ | | 130.8 | | 129.1 |
| 2 | 7.35 d, 2.0 | 133.3 | 2′ | 7.14 d, 2.0 | 128.2 | 2″ | 7.54 d, 2.0 | 134.0 | 2‴ | 7.35 d, 2.0 | 133.3 | 7.05 dd, 8.5, 2.0 | 129.0 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | | 109.5 | 3′ | | 110.9 | 3″ | | 113.6 | 3‴ | | 109.5 | 6.75 d, 8.5 | 115.6 |
| 4 | | 152.8 | 4′ | | 145.3 | 4″ | | 152.3 | 4‴ | | 152.8 | | 152.4 |
| 5 | 6.74 d, 8.5 | 116.0 | 5′ | | 145.3 | 5″ | 6.75 d, 8.5 | 119.6 | 5‴ | 6.74 d, 8.5 | 116.0 | | 109.0 |
| 6 | 7.05 dd, 8.5, 2.0 | 129.2 | 6′ | 6.75 d, 2.0 | 118.3 | 6″ | 7.20 dd, 8.5, 2.0 | 129.6 | 6‴ | 7.05 dd, 8.5, 2.0 | 129.2 | 7.35 d, 2.0 | 133.0 |
| 7 | 3.78 s | 27.5 | 7′ | 3.70 s | 27.6 | 7″ | 3.88 s | 27.9 | 7‴ | 3.78 s | 27.5 | 3.78 s | 27.2 |
| 8 | | 152.0 | 8′ | | 151.7 | 8″ | | 151.5 | 8‴ | | 152.0 | | 151.6 |
| 9 | | 164.7 | 9′ | | 164.6 | 9″ | | 164.6 | 9‴ | | 164.7 | | 164.5 |
| 10 | 3.51 t, 7.0 | 38.5 | 10′ | 3.54 t, 7.0[a] | 38.5 | 10″ | 3.47 t, 7.0[a] | 38.5 | 10‴ | 3.51 t, 7.0 | 38.5 | 3.62 dt, 6.5, 2.0 | 31.9 |
| 11 | 2.80 t, 7.0 | 37.4 | 11′ | 2.81 t, 7.0[b] | 37.4 | 11″ | 2.76 t, 7.0[a] | 37.4 | 11‴ | 2.80 t, 7.0 | 37.4 | 2.96 m | 55.8 |
| 12 | | | | | | | | | | | | 3.75 s | 54.1 |

[a,b,c]May be interchanged

| | **172** (*44*) | | **173** (*118*) | | **174** (*118*) | | **175** (*118*) |
|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ |
| 1 | | 113.1 | | 112.2 | | 137.4 | |
| 2 | 7.43 d, 2.2 | 134.7 | 7.17 dd, 2.2, 8.5 | 130.4 | 7.47 s | 134.5 | 7.14 dd, 2.0, 8.5 |
| 3 | | 130.3 | 6.88 d, 8.5 | 113.2 | | 113.2 | 6.88 d, 8.5 |
| 4 | | 155.8 | | 155.9 | | 152.1 | |
| 5 | 6.88 d, 8.5 | 112.1 | | 131.8 | | 118.6 | |
| 6 | 7.17 dd, 2.2, 8.5 | 131.1 | 7.42 d, 2.0 | 134.7 | 7.47 s | 134.5 | 7.47 d, 2.0 |
| 7 | 3.79 s | 28.7 | 3.79 s | 28.7 | 3.81 s | 28.8 | 3.79 s |
| 8 | | 152.9 | | 153.0 | | 152.2 | |
| 9 | | 165.8 | | 165.8 | | 165.5 | |
| 10 | 3.41 t, 7.0 | 41.3 | 3.42 t, 7.3 | 41.3 | 3.43 t, 7.2 | 41.3 | 3.42 t, 7.2 |
| 11 | 2.73 t, 7.0 | 35.2 | 2.75 t, 7.3 | 35.2 | 2.75 t, 7.2 | 35.2 | 2.73 t, 7.2 |
| 12 | | 140.3 | | 140.3 | | 140.3 | |
| 13,17 | 7.42 s | 134.4 | 7.43 s | 134.4 | 7.44 s | 134.4 | 7.41 s |
| 14,16 | | 118.7 | | 118.7 | | 118.7 | |
| 15 | | 152.1 | | 152.2 | | 152.1 | |

(*continued*)

TABLE II.
Continued.

| | **172** (*44*) | | **173** (*118*) | | **174** (*118*) | | **175** (*118*) |
|---|---|---|---|---|---|---|---|
| | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ |
| 18 | 4.05 t, 5.5 | 71.7 | 4.08 t, 5.7 | 71.6 | 4.06 t, 5.8 | 71.6 | 3.99 t, 6.2 |
| 19 | 2.25 tt, 5.5, 7.6 | 26.4 | 2.19 tt, 5.5, 7.5 | 29.0 | 2.18 tt, 5.8, 7.8 | 29.0 | 2.03 tt, 6.2, 6.5 |
| 20 | 3.46 t, 7.6 | 56.9 | 3.29 t, 7.5 | 39.0 | 3.29 t, 7.8 | 39.0 | 3.41 t, 6.5 |
| 22 | | | | | | | 2.17 t, 7.3 |
| 23 | | | | | | | 1.60 m |
| 24–32 | | | | | | | 1.28 16H, m 1.16 m |
| 33 | | | | | | | 1.51 m |
| 34,35 | | | | | | | 0.86 d, 6.5 |
| Ome | 3.81 s | 56.7 | 3.82 s | 56.7 | 3.81 s | 61.0 | 3.82 s |
| $NH(CH_3)_2$ | 2.93 s | 43.7 | | | | | |

| | **176** acetate (*119*) | **177** acetate (*119*) | | **178** (*82*) | | **179** (*121*) | |
|---|---|---|---|---|---|---|---|
| | $^{1}H$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CD_3OD$ | $^{13}H$ $CD_3OD$ |
| 1 | | | 132.6 | | 135.6 | | 138.2 |
| 2 | 7.56 d, 2 | 7.50 s | 133.5 | 7.48 s | 133.4 | 7.25 d, 7.5 | 130.1 |
| 3 | | | 117.8 | | 117.7 | 7.20 dd, 7.3, 7.5 | 129.3 |
| 4 | | | 153.1 | | 153.8 | 7.12 t, 7.3 | 127.2 |
| 5 | 6.80 d, 8 | | 117.8 | | 117.7 | 7.20 dd, 7.3, 7.5 | 129.3 |
| 6 | 7.2–7.5 m | 7.50 s | 133.5 | 7.48 s | 133.4 | 7.25 d, 7.5 | 130.1 |
| 7 | 3.85 s | 3.84 s | 27.9 | 3.84 s | 28.0 | 3.91 s | 29.9 |
| 8 | | | 152.5 | | 150.9 | | 153.2 |
| 9 | | | 162.8 | | 163.4 | | 166.0 |
| 10 | 3.4–3.7 m | 3.4–3.6 m | 39.9 | 3.60 dt, 6.1, 5.8 | 37.3 | 2.60 t, 6.7 | 37.7 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 | 2.76 t, 7 | 2.74 t, 6 | 34.0 | 2.06 m | 28.4 | 2.05 tt, 6.2, 6.7 | 30.7 |
| 12 | | | 135.3 | 4.06 t, 5.8 | 67.9 | 4.10 t, 6.2 | 72.2 |
| 13 | 7.2–7.5 m | 7.38 d, 2 | | | 152.4 | | 153.6 |
| 14 | | | 111.9 | | 114.0 | | 119.5 |
| 15 | | | 151.2 | 7.32 d, 1.8 | 133.3 | 7.51 s | 134.4 |
| 16 | 6.80 d, 8 | 6.76 d, 8 | 113.0 | | 111.5 | | 137.3 |
| 17 | 7.02 dd, 8, 2 | 7.02 dd, 8, 2 | 129.2 | 7.02 dd, 8.3, 1.8 | 128.8 | 7.51 s | 134.4 |
| 18 | 4.20 t, 6 | 4.14 t, 6 | 68.4 | 6.78 d, 8.6 | 133.2 | | 119.5 |
| 19 | 1.9–2.2 m | 1.9–2.2 m | 28.1 | 2.68 t, 6.5 | 37.0 | 2.88 t, 7.5 | 33.3 |
| 20 | 3.4–3.7 m | 3.4–3.6 m | 38.6 | 2.96 t, 6.5 | 42.5 | 3.13 t, 7.5 | 41.5 |
| Ome | 3.86 s | 3.86 s | 60.6 | 3.82 s | 60.5 | | |
| $NH(CH_3)_2$ | | | | | | | |
| NH | 6.60 brt, 6 | 6.64 t, 6 | | 7.10 brt, 6.1 | | | |
| NH | 6.32 m | 6.44 m | | | | | |
| NOH | 9.80 br | 10.64 br | | | | | |
| $OCOCH_3$ | 1.94 s | 1.94 s | 23.1 | | | | |
| $NHCOCH_3$ | | | 171.3 | | | | |

| | **180** (*121*) | | **181** (*121*) | | **182** (*121*) | | | **183** (*121*) | |
|---|---|---|---|---|---|---|---|---|---|
| | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^1H$ $CD_3OD$ | $^1H$ DMSO-$d_6$ | $^{13}C$ $CD_3OD$ | $^1H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ |
| 1 | | 138.1 | | 138.1 | | | 138.1 | | 137.1 |
| 2 | 7.25 d, 7.5 | 130.0 | 7.25 d, 7.5 | 130.0 | 7.21 m | 7.23 m | 130.0 | 7.21 m | 130.0 |
| 3 | 7.20 dd, 7.3, 7.5 | 129.3 | 7.20 dd, 7.3, 7.5 | 129.3 | 7.21 m | 7.14 m | 129.3 | 7.21 m | 129.3 |
| 4 | 7.15 t, 7.3 | 127.2 | 7.12 t, 7.3 | 127.2 | 7.13 m | 7.14 m | 127.2 | 7.14 m | 127.2 |
| 5 | 7.20 dd, 7.3, 7.5 | 129.3 | 7.20 dd, 7.3, 7.5 | 129.3 | 7.21 m | 7.14 m | 129.3 | 7.21 m | 129.3 |
| 6 | 7.25 d, 7.5 | 130.0 | 7.25 d, 7.5 | 130.0 | 7.21 m | 7.23 m | 130.0 | 7.21 m | 130.0 |
| 7 | 3.90 s | 30.2 | 3.91 s | 29.9 | 3.88 s | 3.78 s | 29.9 | 3.88 s | 29.9 |
| 8 | | 153.4 | | 153.3 | | | 153.2 | | 153.2 |
| 9 | | 166.1 | | 166.0 | | | 166.0 | | 166.0 |

(*continued*)

TABLE II.
Continued.

| | **180** (*121*) | | **181** (*121*) | | **182** (*121*) | | | **183** (*121*) | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 10 | 3.43 t, 6.7 | 37.7 | 3.51, t, 6.8 | 37.7 | 3.42 t, 7.2 | 3.32 m | 41.3 | 3.42 t, 7.1 | 41.4 |
| 11 | 2.00 tt, 6.1, 6.7 | 30.0 | 2.04 tt, 6.1, 6.8 | 30.7 | 2.73 t, 7.2 | 2.73 t, 6.8 | 35.2 | 2.74 t, 7.1 | 35.2 |
| 12 | 4.02 t, 6.1 | 68.3 | 3.99 t, 6.1 | 72.3 | | | 140.3 | | 139.1 |
| 13 | | 155.9 | | 153.9 | 7.45 s | 7.48 s | 134.4 | 7.45 s | 134.4 |
| 14 | | 113.4 | | 119.6 | | | 118.7 | | 118.7 |
| 15 | 7.47 d, 1.8 | 134.4 | 7.44 s | 134.4 | | | 152.2 | | 152.2 |
| 16 | | 131.6 | | 136.1 | | | 118.7 | | 118.7 |
| 17 | 7.18 d, 1.8, 8.4 | 130.0 | 7.44 s | 134.4 | 7.45 s | 7.48 s | 134.4 | 7.45 s | 134.4 |
| 18 | 6.95 d, 8.4 | 115.0 | | 119.6 | 4.09 t, 5.7 | 3.98 t, 5.9 | 71.6 | 4.10 t, 5.7 | 71.4 |
| 19 | 2.88 t, 7.6 | 33.3 | 3.27 t, 7.3 | 36.6 | 2.19 tt, 5.7, 7.3 | 2.06 m | 29.0 | 2.22 tt, 5.7, 7.2 | 33.8 |
| 20 | 3.13 t, 7.6 | 41.9 | 4.83 t, 7.3 | 63.3 | 3.30 t, 7.3 | 3. 60 m | 38.9 | 3.32 t, 7.2 | 48.2 |
| 21,25 | | | 8.88 t, 5.6 | 146.2 | | | | | |
| 22,24 | | | 8.08 t, 5.6, 7.1 | 129.5 | | | | | |
| 23 | | | 8.59 t, 7.1 | 147.2 | | | | | |
| NH-9 | | | | | | 8.00 t, 5.8 | | | |
| NOH-8 | | | | | | 11.77 s | | | |
| NMe-20 | | | | | | | | 2.76 s | 27.1 |

| | **184** (*121*) | | **185** (*121*) | | **186** (*121*) | | **187** (*121*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 130.3 | | 130.6 | | 131.8 | | 131.8 |
| 2 | 7.04 dd, 2.0, 8.3 | 130.6 | 7.03 dd, 1.7, 8.3 | 130.3 | 7.18 dd, 1.8, 8.5 | 130.4 | 7.17 dd, 2.0, 8.4 | 130.4 |
| 3 | 6.75 d, 8.3 | 117.1 | 6.75 d, 8.3 | 117.1 | 6.90 d, 8.5 | 113.2 | 6.89 d, 8.4 | 113.2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4 | | 153.7 | | 153.7 | | 155.9 | | 155.9 |
| 5 | | 110.5 | | 110.5 | | 112.2 | | 112.2 |
| 6 | 7.43 d, 2.0 | 134.4 | 7.34 d, 1.7 | 134.4 | 7.42 d, 1.8 | 134.4 | 7.42 d, 2.0 | 134.7 |
| 7 | 3.76 s | 28.7 | 3.75 s | 28.7 | 3.79 s | 28.7 | 3.79 s | 28.7 |
| 8 | | 153.2 | | 153.1 | | 153.0 | | 153.0 |
| 9 | | 166.2 | | 165.8 | | 165.8 | | 165.8 |
| NMe-20 | | | 2.76 s | 27.7 | | | 2.76 s | 27.7 |
| 10 | 3.41 t, 7.1 | 41.4 | 3.42 t, 7.0 | 41.3 | 3.43 t, 7.2 | 41.3 | 3.42 t, 7.1 | 41.3 |
| 11 | 2.74 t, 7.1 | 35.2 | 2.73 t, 7.0 | 35.2 | 2.75 t, 7.2 | 35.2 | 2.74 t, 7.1 | 35.2 |
| 12 | | 140.3 | | 140.3 | | 140.3 | | 140.3 |
| 13 | 7.43 s | 134.4 | 7.43 s | 134.4 | 7.43 s | 134.4 | 7.43 s | 134.4 |
| 14 | | 118.7 | | 118.7 | | 118.7 | | 118.7 |
| 15 | | 152.2 | | 152.1 | | 152.2 | | 152.2 |
| 16 | | 118.7 | | 118.7 | | 118.7 | | 118.7 |
| 17 | 7.43 s | 134.4 | 7.43 s | 134.4 | 7.44 s | 134.4 | 7.43 s | 134.4 |
| 18 | 4.07 t, 5.7 | 71.6 | 4.06 t, 5.7 | 71.5 | 4.08 t, 5.7 | 71.6 | 4.05 t, 5.6 | 71.6 |
| 19 | 2.18 tt, 5.7, 7.2 | 29.0 | 2.21 tt, 5.7, 7.2 | 33.8 | 2.18 tt, 5.7, 7.6 | 29.0 | 2.21 tt, 5.6, 7.6 | 33.8 |
| 20 | 3.30 t, 7.2 | 39.0 | 3.34 t, 7.2 | 48.2 | 3.30 t, 7.6 | 38.9 | 3.30 t, 7.6 | 38.2 |
| OMe | | | | | 3.82 s | 56.7 | 3.82 s | 56.7 |

| | **188** (*121*) | | **189** (*86*) | | **190** (*122*) | | **191** (*122*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 138.0 | | 131.4 | | 130.4 | | 131.7 |
| 2 | 7.23 m | 130.0 | 7.40 d, 2.0 | 134.4 | 7.38 d, 2.0 | 133.0 | | 7.44 d. 2.0 |
| 3 | 7.23 m | 129.3 | | 111.8 | | 110.2 | | 112.5 |
| 4 | 7.16 m | 127.3 | | 155.4 | | 153.8 | | 155.7 |
| 5 | 7.23 m | 129.3 | 6.85 d, 8.0 | 112.8 | 6.97 d, 8.0 | 112.6 | 6.78 d, 8.0 | 113.2 |
| 6 | 7.23 m | 130.0 | 7.13 dd, 2.4, 8.5 | 130.0 | 7.12 dd, 2.0, 8.0 | 129.1 | 7.02 dd, 2.0, 8.0 | 130.4 |
| 7 | 3.91 s | 31.0 | 3.76 s | 28.2 | 3.72 s | 27.8 | 3.76 s | 28.1 |

(*continued*)

TABLE II.
Continued.

| | **188** (*121*) | | **189** (*86*) | | **190** (*122*) | | **191** (*122*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 8 | | 152.2 | | 152.6 | | 151.8 | | 152.7 |
| 9 | | 166.9 | | 165.4 | | 163.2 | | 165.5 |
| 10 | | | 3.39 t, 7.2 | 41.0 | 3.35 t, 7.0 | 41.1 | 3.15 t, 7.2 | 48.7 |
| 11 | | | 2.70 t, 6.9 | 34.8 | 2.73 t, 7.0 | 34.0 | 2.15 t, 7.2 | 29.0 |
| 12 | | | | 139.8 | | 139.0 | 4.08 t, 6.0 | 71.5 |
| 13 | | | 7.39 s | 134.0 | 7.46 s | 132.9 | | 152.2 |
| 14 | | | | 118.4 | | 117.2 | | 118.9 |
| 15 | | | | 152.0 | | 150.7 | 7.36 s | 134.3 |
| 16 | | | | 118.0 | | 117.2 | | 139.9 |
| 17 | | | 7.39 s | 134.0 | 7.46 | 132.9 | 7.36 s | 134.3 |
| 18 | | | 4.03 t, 5.7 | 70.9 | 3.91 t, 6.0 | 71.0 | | 118.9 |
| 19 | | | 2.37 q, 6.4 | 25.1 | 2.03 t, m | 28.0 | 2.72 t, 7.8 | 35.5 |
| 20 | | | 3.61 dt, 8.4, 7.6 | 69.0 | 3.38 t, 6.8 | 40.6 | 3.45 t, 7.8 | 41.5 |
| 21 | | | | | | 156.5 | | |
| 22 | | | | | 3.57 s | 52.3 | | |
| 23 | | | | | | | | |
| OMe | | | 3.79 br | 56.0 | 3.79 s | 56.2 | 3.79 s | 57.0 |
| $NOMe_2$ | | | 3.24 br | 58.0 | | | | |
| NH | | | | | 7.99 t, 6.0 | | | |
| NMe | | | | | 2.83 s | 41.4 | 2.60 s | 34.4 |

| | **192** (*84*) | | **193** (*123*) | | **194** (*123*) | | **195** (*124*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ + TFA | $^{13}$C | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 1 | | 136.4 | | 137.9 | | 138.0 | | 135.7 |
| 2 | 7.48 s | 132.9 | 7.49 s | 134.4 | 7.47 s | 134.6 | 7.41 br | 134.2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | | 117.2 | | 117.8 | | 118.5 | | 118.6 |
| 4 | | 150.5 | | 152.2 | | 152.3 | | 152.6 |
| 5 | | 117.2 | | 117.8 | | 118.5 | | 118.6 |
| 6 | 7.48 s | 132.9 | 7.49 s | 134.4 | 7.47 s | 134.6 | 7.41 br | 134.2 |
| 7 | 3.74 s | 27.7 | 3.82 s | 30.7 | 3.81 s | 30.7 | 3.07 dd, 13, 6, 2.95 dd, 13, 9 | 37.2 |
| 8 | | 150.8 | | 151.9 | | 151.9 | 3.70 dd, 9, 6 | 63.9 |
| 9 | | 163.0 | | 165.5 | | 165.4 | | 169.4 |
| 10 | 3.34 m | 49.7 | 3.41 t, 7.1 | 41.5 | 3.42 t, 7.1 | 41.5 | 3.53 ddd, 14, 8, 6, 3.40 dt, 14, 7 | 36.7 |
| 11 | 2.27 t | 33.3 | 2.74 t, 7.1 | 35.2 | 2.74 t, 7.1 | 35.2 | 1.90 m | 30.0 |
| 12 | | 139.1 | | 140.3 | | 140.2 | 3.91, 3.89 m | 71.1 |
| 13 | 7.45 s | 132.9 | 7.43 s | 134.6 | 7.43 s | 134.4 | | 153.9 |
| 14 | | 117.1 | | 118.7 | | 118.7 | | 118.9 |
| 15 | | 150.4 | | 152.4 | | 152.3 | 7.46 br | 133.6 |
| 16 | | 117.1 | | 118.7 | | 118.7 | | 134.7 |
| 17 | 7.45 s | 132.9 | 7.43 s | 134.6 | 7.43 s | 134.4 | 7.46 br | 133.6 |
| 18 | 3.97 t | 70.3 | 4.10 t, 5.4 | 70.8 | 4.08 t, 5.8 | 71.6 | | 118.9 |
| 19 | 2.07 m | 27.7 | 2.60 tt, 5.4, 6.9 | 32.5 | 2.20 tt, 5.8, 7.7 | 29.0 | 3.01 m | 30.2 |
| 20 | 3.04 m | 36.5 | 4.99 t, 6.9 | 60.9 | 3.29 t, 7.7 | 38.9 | 3.20 m | 58.9 |
| 21 | 3.97 t | 70.4 | 4.80 t, 5.7 | 71.6 | 4.10 t, 5.6 | 70.9 | | |
| 22 | 2.07 m | 27.7 | 2.19 tt, 5.7, 7.7 | 29.0 | 2.60 tt, 5.6, 7.1 | 32.5 | | |
| 23 | 3.04 m | 36.5 | 3.28 t, 7.7 | 38.9 | 4.98 t, 7.1 | 60.8 | | |
| NOH | 12.05 s | | | | | | | |
| 1′,5′ | | | 9.13 d, 5.8 | 146.4 | 9.13 d, 5.8 | 146.4 | | |
| 2′,4′ | | | 8.14 dd, 5.8, 7.7 | 129.5 | 8.13 dd, 5.8, 7.7 | 129.5 | | |
| 3′ | | | 8.60 t, 7.7 | 147.1 | 8.59 t, 7.7 | 147.1 | | |
| NH | 8.12 t | | | | | | | |
| $NH_2$ | 7.86 br | | | | | | | |
| NMe | | | | | | | 2.82 s | 43.4 |
| $NMe_2$ | | | | | | | 2.52 s | 33.1 |
| OMe | | | | | | | 3.77 s | 60.9 |

(*continued*)

TABLE II.
Continued.

| | **196** (*125*) | | **197** (*126*) | | **198** (*126*) | | **199** (*90*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3OD + CDCl_3$ | $^{13}$C | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 137.7 | | 129.8 | | 129.4 | | 136.5 |
| 2 | 7.31 s | 133.2 | 7.47 d, 1.9 | 136.1 | 7.44 d, 1.1 | 136.1 | 7.49 s | 132.9 |
| 3 | | 117.6 | | 113.6 | | 113.6 | | 117.2 |
| 4 | | 152.3 | | 157.9 | | 157.9 | | 150.5 |
| 5 | | 117.6 | 7.04 d, 8.5 | 114.5 | 7.04 d, 8.4 | 114.4 | | 117.2 |
| 6 | 7.31 s | 133.2 | 7.20 dd, 1.9, 8.5 | 131.7 | 7.18 dd, 1.1, 8.4 | 131.8 | 7.49 s | 132.9 |
| 7 | 2.71 dd, 4.5, 13.8<br>2.94 dd, 8.8, 13.5 | 31.6 | 3.08 dd, 7.8, 14.0<br>2.98 dd, 7.3, 14.0 | 38.3 | 3.12 dd, 5.7, 13.6<br>3.05 dd, 8.6, 13.6 | 37.4 | 3.82 s | 28.1 |
| 8 | 3.14 dd, 4.5, 8.8 | 69.8 | 4.00 t, 7.3 | 56.5 | 3.90 m | 64.9 | | 151.0 |
| 9 | | 170.8 | | 170.3 | | 168.9 | | 165.7 |
| 10 | 3.29 dt, 2.8, 7.0 | 39.8 | 3.56 m<br>3.32 dd, 6.6, 13.2 | 42.3 | 3.47 m<br>3.38 m | 42.1 | 3.27 m | 38.9 |
| 11 | 2.57, 2.54 m | 34.2 | 2.74 t, 7.2 | 35.8 | 2.73, 2.63 m | 35.8 | 1.56 m | 27.1 |
| 12 | | 137.9 | | 140.9 | | 140.8 | 1.56 m | 27.2 |
| 13 | 7.23 s | 132.8 | 7.51 s | 135.1 | 7.47 s | 135.1 | 3.17 m | 41.8 |
| 14 | | 117.7 | | 119.7 | | 119.7 | | 156.8 |
| 15 | | 150.9 | | 153.2 | | 153.2 | 4.09 t, 5.5 | 70.7 |
| 16 | | 117.7 | | 119.7 | | 119.7 | 1.26 m | 33.6 |
| 17 | 7.23 s | 132.8 | 7.51 s | 135.1 | 7.47 s | 135.1 | 3.25 m | 39.5 |
| 18 | 3.96 t, 5.5 | 69.7 | 4.13 t, 5.6 | 71.9 | 4.12 t, 5.5 | 71.9 | | |
| 19 | 2.18 m | 25.4 | 2.32 tt, 5.6, 7.9 | 27.2 | 2.32 tt, 5.5, 7.5 | 27.2 | | |
| 20 | 3.16 m | 55.4 | 3.54 t, 7.9 | 57.8 | 3.54 t, 7.4 | 57.6 | | |
| 21 | 3.74 s | 60.4 | | | | | | |
| 22,23 | 2.26 s | 41.5 | | | | | | |
| 24,25 | 2.67 s | 42.9 | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| NH | 8.67 brt | | | | | |
| OMe | | 3.91 s | 57.6 | 3.90 s | 57.6 | |
| $NMe_2$ | | 3.00 s | 44.5 | 3.00 s | 44.4 | |
| NMe | | | | 2.62 s | 33.3 | |

| | **200** (*79*) | | **201** (*127*) | | **202** (*127*) | | **203** (*127*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1H$ DMSO-$d_6$ | $^{13}C$ DMSO-$d_6$ | $^1H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^1H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^1H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ |
| 1 | | 123.7 | | 133.7 | | 139.1 | | 130.9 |
| 2 | | 155.2 | 7.63 d, 2.1 | 139.8 | 7.65 s | 140.5 | 7.61 d, 2.1 | 140.0 |
| 3 | | 108.2 | | 85.7 | | 90.3 | | 86.1 |
| 4 | | 153.6 | | 156.4 | | 157.2 | | 157.2 |
| 5 | | 108.2 | 6.72 d, 8.3 | 110.7 | | 90.3 | 6.76 d, 8.3 | 111.0 |
| 6 | 7.31 s | 135.4 | 7.22 dd, 2.1, 8.3 | 130.4 | 7.65 s | 140.5 | 7.14 dd, 2.1, 8.3 | 130.3 |
| 7 | 3.70 | 26.7 | 2.78 dd, 4.9, 13.5 | 31.5 | 2.73 dd, 4.6, 13.8 | 31.0 | 2.63 dd, 8.7, 13.5 | 37.1 |
| | | | 3.05 dd, 7.5, 13.5 | | 3.02 dd, 7.9, 13.8 | | 3.05 dd, 4.3, 13.5 | |
| 8 | | 152.6 | 3.13 dd, 4.9, 7.5 | 70.9 | 3.14 dd, 4.6, 7.9 | 69.8 | 3.13, dd, 8.7, 4.3 | 65.1 |
| 9 | | 167.8 | | 171.5 | | 170.3 | | 171.6 |
| 10 | 3.18 m | 40.7 | 3.18 q, 6.6 | 38.8 | 3.20 q, 6.6 | 39.0 | 3.22 quin, 7.2 | 38.7 |
| 11 | 1.44 m | 29.0 | 1.44 m | 29.2 | 1.45 m | 29.0 | 1.46 m | 28.9 |
| 12 | 1.42 m | 28.4 | 1.22 m | 24.1 | 1.22 quin, 7.2 | 24.1 | 1.24 m | 24.0 |
| 13 | 3.09 m | 42.9 | 1.44 m | 29.2 | 1.45 m | 29.0 | 1.46 m | 28.9 |
| 14 | | 156.4 | 3.18 q, 6.6 | 38.9 | 3.20 q, 6.6 | 39.0 | 3.22 quin, 7.2 | 38.9 |
| 15 | | | | 171.2 | | 170.3 | | 170.2 |
| 16 | | | 3.14 dd, 4.6, 7.8 | 70.4 | 3.14 dd, 4.6, 7.9 | 69.8 | 3.14 dd, 4.4, 7.9 | 69.6 |
| 17 | | | 2.72 dd, 4.6, 13.7 | 30.5 | 2.73 dd, 4.6, 13.8 | 31.0 | 2.73 dd, 4.4, 13.8 | 31.0 |
| | | | 3.01 dd, 7.8, 13.7 | | 3.02 dd, 7.9, 13.8 | | 3.02 dd, 7.9, 13.8 | |
| 18 | | | | 139.9 | | 139.1 | | 139.0 |
| 19,23 | | | 7.65 s | 140.4 | 7.65 s | 140.5 | 7.65 s | 140.5 |

(*continued*)

TABLE II.
Continued.

| | **200** (*79*) | | **201** (*127*) | | **202** (*127*) | | **203** (*127*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 20,22 | | | | 90.1 | | 90.3 | | 90.2 |
| 21 | | | | 157.0 | | 157.2 | | 157.3 |
| 4-OMe | 3.74 | 61.7 | 3.81 s | 56.3 | 3.82 s | 60.7 | 3.81 s | 56.4 |
| 21-OMe | | | 3.84 s | 60.6 | 3.82 s | 60.7 | 3.86 s | 60.7 |
| 8-NMe | | | 2.33 s | 42.1 | 2.30 s | 41.9 | 2.28 s | 34.6 |
| 18-NMe | | | 2.30 s | 42.2 | 2.30 s | 41.9 | 2.30 s | 41.8 |
| $NH_2$ | 7.1–7.3 br | | | | | | | |
| 9-NH 13-NH | 7.56 t, 5.9, 7.43 br | | | | | | | |
| OH | 10.68, 10.12 br | | | | | | | |

| | **204** (*129*) | **205** (*129*) | **206** (*129*) |
|---|---|---|---|
| | $^{1}$H acetone-$d_6$ | $^{1}$H acetone-$d_6$ | $^{1}$H acetone-$d_6$ |
| 1 | 3.65 s[H] | 3.54 s[G] | 3.72 s |
| 4 | 7.96 t[F] | 7.89 t, 6[E] | 8.00 t, 7 |
| 5 | 3.32 q[E] | 3.25 dt, 6, 7[D] | 3.29 q, 7 |
| 6 | 2.62 t[D] | 2.67 t, 7[C] | 2.62 t, 7 |
| 8 | 7.29 d, 1.9[A] | 7.28 d, 1.9[A] | 7.32 d, 1.9[A] |
| 11 | 6.86 d, 8.2[B] | 6.85 d, 8 | 6.85 d, 8.2 |
| 12 | 6.96 dd, 1.9, 8.2[C] | 6.96 dd, 1.9, 8[B] | 6.98 dd, 1.9, 8.2 |
| 16 | 6.87 d, 8.2[B] | 6.85 d, 8 | 6.85 d, 8.2 |
| 17 | 6.99 dd, 1.9, 8.2[C] | 6.99 dd, 1.9, 8[B] | 6.98 dd, 1.9, 8.2 |
| 19 | 7.31 d, 1.9[A] | 7.30 d, 1.9[A] | 7.32 d, 1.9[A] |

| | | | |
|---|---|---|---|
| 20 | 2.65 t[D] | 2.60 t, 7[C] | 2.62 t, 7 |
| 21 | 3.27 q[E] | 3.33 dt, 6, 7[D] | 3.29 q, 7 |
| 22 | 8.01 t[F] | 8.11 t, 6[E] | 8.00 t, 7 |
| 25 | 3.76 s[H] | 3.83 s[G] | 3.72 s |
| 27 | 7.51 d, 1.7 | 7.57 s | 7.29 d, 1.9[A] |
| 30 | 6.75 d, 8.5 | | |
| 31 | 7.15 dd, 1.7, 8.5 | 7.57 s | 6.93 d, 1.9 |
| 36 | 7.13 d, 1.7 | 6.97 d, 1.9 | 7.29 d, 1.9[A] |
| 38 | 6.64 d, 1.7 | 6.21 d, 1.9 | 6.93 d, 1.9 |
| OH-15 | 10.02 s | 10.02 s | 10.02 s |
| OH-10 | 10.02 s | 10.02 s | 10.02 s |
| OH-29 | | | 8.94 s |
| OH-34 | 9.85 s | 10.02 s | 8.94 s |
| NOH-24 | 11.94 s[G] | 11.75 s[F] | 11.84 s |
| NOH-2 | 11.83 s[G] | 12.08 s[F] | 11.84 s |

[A,B,C,D,E,F,G,H] May be interchanged.

| | **208** (*129*) | **208** Tetramethyl ether (*129*) | **210** (*129*) | **211** (*129*) |
|---|---|---|---|---|
| | $^1$H acetone-$d_6$ | $^1$H acetone-$d_6$ | $^1$H acetone-$d_6$ | $^1$H acetone-$d_6$ |
| 1 | 3.52 s[C] | signals were not | 3.57 s[E] | 3.50 s[D] |
| 4 | 10.24 d, 10.2 | assigned | 8.00 t, 6[C] | 10.29 d, 10 |
| 5 | 7.31 dd, 10.2, 14.5 | 7.50 2H s | 3.30 m | 7.34 dd, 10, 15 |
| 6 | 6.44 d, 14.5 | 7.45 d, 2 | 2.72 m | 6.42 d, 15 |
| 8 | 7.63 d, 1.9 | 7.16 d, 2 | 7.65 s[F] | 7.67 d, 1.9 |
| 11 | 6.92 d, 8.5 | 7.10 d, 2 | | 6.99 d, 8.8 |
| 12 | 7.48 dd, 1.9, 8.5 | 6.80 d, 2 | 7.65 s[F] | 7.45 dd, 1.9, 8.8 |
| 17[1] | 6.55 d, 1.9 | 6.24 d, 2 | 6.23 d, 1.7[BA] | 6.43 d, 2.0[AB] |
| 19[1] | 7.13 d, 1.9[A] | Other aromatic | 7.08 d, 1.7[AB] | 7.20 d, 2.0[AB] |
| 20 | 2.73 m | signals are | 2.72 m | 2.64 t, 6 |
| 21 | 3.35 m | overlapped. | 3.30 m | 3.24 q, 6 |

(*continued*)

TABLE II.
Continued.

| | **208** (*129*) | **208** Tetramethyl ether (*129*) | **210** (*129*) | **211** (*129*) |
|---|---|---|---|---|
| | $^1$H acetone-$d_6$ | $^1$H acetone-$d_6$ | $^1$H acetone-$d_6$ | $^1$H acetone-$d_6$ |
| 22 | 7.85 t, 6 | 4.02, 3.98, | 8.13 t, 6[C] | 7.85, 6 |
| 25 | 3.64 s[C] | 3.94, 3.52, | 3.66 s[E] | 3.71 s[D] |
| 27 | 7.51 s | 3H each, s, | 7.64 s[F] | 7.44 d, 1.9 |
| 30 | | $OCH_3$ | | 6.66 d, 8.3 |
| 31 | 7.51 s | | 7.64 s[F] | 7.10 dd, 1.9, 8.3 |
| 36 | 7.08 d, 1.9[A] | | 7.04 d, 1.9[AB] | 7.09 d, 1.5[BA] |
| 38 | 6.09 d, 1.9 | | 6.16 d, 1.9[BA] | 6.40 d, 1.5[BA] |
| OH | 9.85 s[B] | | 10.00 s | 9.89 s |
| OH-34 | 10.10 s[B] | | 10.00 s | 9.89 s |
| NOH | 12.00 s | | 11.92 s[D] | 12.09 s[C] |
| NOH-2 | 12.00 s | | 11.71 s[D] | 11.99 s[C] |

[A,B,C,D,E,F,G,H,AB,BA]May be interchanged.

| | **228** (*130*) | | **212** (*132*) | | **212** Tetramethyl ether (*132*) | | **213** (*132*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^1$H $CDCl_3$ | $^{13}$C NA | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 3.74 s | 27.8 | 3.57 br | 27.3 | 3.79 br | | 3.54 br | 27.6 |
| 2 | | 151.2[e] | | 150.9 | | | | 151.4 |
| 3 | | 161.2 | | 162.8 | | | | 162.9 |
| 4 | 10.26 d, 10 | | | | | | | |
| 5 | 7.32 dd, 10, 14 | 124.1 | 3.40, 3.00 m | 47.3 | 3.72, 3.38 m | | 3.18 q | 40.9 |
| 6 | 6.40 d, 14 | 111.4 | 4.63 m | 70.4 | 4.88 m | | 2.62 t | 34.0 |
| 7 | | 134.6 | | 140.6 | | | | 135.4 |
| 8 | 7.62 d, 2 | 129.6 | 7.69 d, 2.0 | 130.2 | 7.69 d, 2.0 | | 7.49 d, 2.1 | 132.8 |
| 9 | | 114.9 | | 112.0 | | | | 111.8 |
| 10 | | 151.3[e] | | 151.8 | | | | 152.4 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 | 7.01 d, 8.5 | 122.7 | 6.94 d, 8.4 | 119.5 | 6.97 d, 8.0 | 6.75 d, 8.4 | 120.3 |
| 12 | 7.42 dd, 8.5, 2 | 125.6 | 7.27 dd, 8.4, 2.0 | 126.5 | 7.28 dd, 8.0, 2.0 | 7.10 dd, 8.4, 2.1 | 125.7 |
| 14 | | 151.4 | | 144.7 | | | 148.0 |
| 15 | | 139.6 | | 143.8 | | | 143.0 |
| 16 | | 118.8 | | 110.6 | | 6.85 d, 8.1 | 116.5 |
| 17 | 7.12 d, 2 | 127.2 | 7.13 d, 2.0 | 128.1 | 7.14 d, 2.0 | 6.81 dd, 8.1, 1.8 | 128.9 |
| 18 | | 137.1 | | 131.4 | | | 130.6 |
| 19 | 6.39 d, 2 | 116.6 | 6.60 d, 2.0 | 118.0 | 6.65 d, 2.0 | 6.73 d, 1.8 | 118.0 |
| 20 | 2.71 t, 6 | 33.0 | 2.68 t, 6.0 | 33.4 | 2.75 m | 2.67 t, 5.7 | 34.0 |
| 21 | 3.27 m | 38.7 | 3.40 q | 39.2 | 3.46, 3.55 | 3.41 q | 39.4 |
| 22 | 7.85 t, 6.0 | | | | 6.76 t, 6.0 | | |
| 23 | | 163.2 | | 163.2 | | | 163.0 |
| 24 | | 151.0 | | 150.4 | | | 150.4 |
| 25 | 3.43 s | 29.0 | 3.62 br | 28.7 | 3.78 br | 3.52 br | 28.8 |
| 26 | | 133.9 | | 137.6 | | | 137.7 |
| 27 | 7.38 d, 2 | 132.6 | 7.56 s | 133.5 | 7.52 s | 7.59 s | 133.1 |
| 28 | | 112.8 | | 117.1 | | | 117.2 |
| 29 | | 151.5 | | 145.9 | | | 145.9 |
| 30 | 6.70 d, 8.5 | 120.2 | | 117.1 | | | 117.2 |
| 31 | 7.02 dd, 2, 8.5 | 129.8 | 7.56 s | 133.5 | 7.52 s | 7.59 s | 133.1 |
| 33 | | 151.4 | | 144.7 | | | 144.8 |
| 34 | | 140.5 | | 141.9 | | | 141.9 |
| 35 | | 119.0 | | 109.7 | | | 109.8 |
| 36 | 7.23 d, 2 | 128.1 | 7.07 d, 2.0 | 126.8 | 7.16 d, 2.0 | 7.05 d, 1.8 | 126.8 |
| 37 | | 133.6 | | 127.9 | | | 128.1 |
| 38 | 6.40 d, 2 | 117.9 | 6.24 d, 2.0 | 112.9 | 6.28 d, 2.0 | 6.22 d, 1.8 | 112.8 |
| OMe | | | | | 4.02 s, 4.01 s, 3.97 s, 3.70 s | | |
| OH | | | 5.62 d, 4.2 | | 6.87 t, 6.0 | | |
| NH-4 | | | 7.77 t, 6.0 | | | 7.97 t, 6.0 | |
| NH | | | 8.00 t, 6.0 | | | 8.03 t, 5.7 | |
| NOH | 11.94, 12.13 s | | 11.83 br, 12.0 br | | | 11.73, 11.96 br | |
| ArOH | | | 9.8 br | | | 10.02 br | |

(*continued*)

TABLE II.
Continued.

| | **213** Tetramethyl ether(*132*) | **214** (*132*) | | **215** (*132*) | | **215** Tetramethyl ether(*132*) |
|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{1}$H (*132*) DMSO-$d_6$ | $^{13}$C (*143*) DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CDCl_3$ |
| 1 | 3.67 br | 3.61 br | 27.6 | 3.64 br | 27.3 | |
| 2 | | | 151.2 | | 151.3 | |
| 3 | | | 162.9 | | 161.4 | |
| 4 | | | | | | |
| 5 | | 3.30 q | 47.0 | 7.25 dd, 14.6, 10.3 | 123.6 | 7.34 dd[a] |
| 6 | | 4.62 m | 70.2 | 6.39 d, 14.6 | 110.9 | 6.17 d, 14.7 |
| 7 | | | 141.0 | | 133.3 | |
| 8 | 7.44 d, 2.0 | 7.64 d, 1.7 | 130.6 | 7.52 d, sm | 130.5 | 7.54 d, 2.7 |
| 9 | | | 113.3 | | 112.5 | |
| 10 | | | 151.7 | | 152.3 | |
| 11 | 6.85 d, 8.0 | 6.91 d, 8.5 | 120.0 | 6.73 d, 8.7 | 119.9 | 6.90 d, 8.4 |
| 12 | 7.03 dd, 8.3, 2.0 | 7.21 dd, 8.0, 2.0 | 126.8 | 7.43 dd, 8.7, 2.1 | 124.1 | 7.38 dd[a] |
| 14 | | | 145.0 | | 146.7 | |
| 15 | | | 143.4 | | 143.0 | |
| 16 | 6.97 d, 8.3 | | 110.7 | 6.87 d, 8.0 | 116.7 | 6.96 d, 8.4 |
| 17 | 6.91 dd, 8.3, 2.0 | 7.12 d, 2.1 | 127.7 | 6.82 dd, 8.0, sm | 125.8 | 6.90 dd[a] |
| 18 | | | 131.7 | | 130.6 | |
| 19 | 6.66 d, 2.0 | 6.45 d, 1.8 | 117.4 | 6.72 d, sm | 119.1 | 6.71 d, 2.1 |
| 20 | | 2.61 t, 6.0 | 33.5 | 2.70 bt | 33.5 | |
| 21 | | 3.38 q | 40.6 | 3.43 q | 38.5 | |
| 23 | | | 163.1 | | 162.7 | |
| 24 | | | 150.8 | | 150.1 | |
| 25 | 3.86 br | 3.61 br | 28.5 | 3.53 br | 28.9 | |
| 26 | | | 134.5 | | 137.6 | |
| 27 | 7.53 s | 7.49 d, 2.0 | 133.5 | 7.51 s | 133.5 | 7.46 s |
| 28 | | | 113.3 | | 116.9 | |
| 29 | | | 151.2 | | 145.9 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 30 | | 6.78 d, 8.5 | 119.9 | | 116.9 | |
| 31 | 7.53 s | 7.07 dd, 8.5, sm | 129.6 | 7.51 s | 133.5 | 7.46 s |
| 33 | | | 145.0 | | 144.8 | |
| 34 | | | 143.4 | | 141.9 | |
| 35 | | | 110.5 | | 110.1 | |
| 36 | 7.19 d, 2.0 | 7.15 d, 1.9 | 126.8 | 7.07 d, 1.9 | 126.8 | 7.12 d, 2.0 |
| 37 | | | | | 127.6 | |
| 38 | 6.27 d, 2.0 | 6.47 d, 1.9 | 117.4 | 6.14 d, 1.9 | 112.4 | 6.25 d, 2.0 |
| OMe | 3.90, 3.49, 4.05, 4.00, Each s | | | | | 4.01 s; 3.93 s; 3.92 s |
| OH | | 5.64 d, 4.4 | | | | |
| NH-4 | 6.79 t, 6.0 | 7.78 t, 6.0 | | 10.2 d, 10.3 | | 8.30 d, 11.4 |
| NH-22 | 6.61 t, 6.0 | 7.94 t, 5.8 | | 7.78 t, 6.0 | | 6.58 t, 5.4 |
| NOH | | 11.87 br, 11.86 br | | 11.98 br, 11.97 br | | |
| ArOH | | 9.78 br | | 10.04 br, 9.38 br | | |
| $CH_2$ | 3.53 q, 6.3; 3.46 q; 2.75 t; 2.73 t | | | | | 3.73 br; 3.65 br; 3.58 q, 5.4; 2.82 t, 5.4 |

[a]Coupling constants were not reported.

| | **216** (*142*) | **216** Tetramethyl ether (*142*) | | **227** (*130*) | | **217** (*131*) | |
|---|---|---|---|---|---|---|---|
| | $^1$H $CDCl_3$ | $^1$H $CDCl_3$ | $^1$H $CDCl_3/C_6D_6$ 1:2 | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 3.72 d, 12.9<br>3.78 d, 12.9 | 3.80 s | 3.73 s | 3.69 s | 27.8 | 3.40 s | 27.8 |
| 2 | | | | | 152.0 | | 151.2 |
| 3 | | | | | 163.1 | | 162.8 |
| 4 | 7.08 t, 6.1[b] | 6.73 t, 6.1[b] | 6.26 t, 6.1[b] | 7.89 t, 5.5 | | | |
| 5 | 3.41 m 3.63 m | 3.38 m | 2.94 m 3.32 m | 3.30 m | 39.9 | 3.20 dt, 6.6, 6.6 | 40.5 |

(*continued*)

TABLE II.
Continued.

| | **216** (*142*) | **216** Tetramethyl ether (*142*) | | **227** (*130*) | | **217** (*131*) | |
|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3/C_6D_6$ 1:2 | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 6 | 4.80 t, 6.1 | 4.86 dd, 3.2, 7.5 | 4.37 brd, 7.3 | 2.68 t, 7 | 33.7 | 2.54 t, 6.6 | 34.0 |
| 7 | | | | | 135.4 | | 130.8 |
| 8 | 7.58 br | 7.65 br | 7.30–7.60 br | 7.36 d, 2 | 132.3 | 6.53 d, 1.8 | 120.4 |
| 9 | | | | | 113.8 | | 143.0 |
| 10 | | | | | 148.9 | | 146.9 |
| 11 | | | | 7.47 d, 8.5 | 121.2 | 6.86 d, 8.1 | 117.2 |
| 12 | 7.58 br | 7.65 br | 7.30–7.60 br | 7.09 dd, 2, 8.5 | 128.6 | 6.81 dd, 1.8, 8.1 | 125.2 |
| 14 | | | | | 109.0 | | 152.4 |
| 15 | | | | | 152.1 | | 111.9 |
| 16 | | | | 6.76 d, 8 | 116.2 | 7.48 d, 1.8 | 133.3 |
| 17 | 6.13 d, 1.8[c] | 7.08 d, 1.9[c] | 6.86 d, 1.9[c] | 6.88 dd, 2, 8 | 128.7 | | 135.4 |
| 18 | | | | | 131.4 | 7.02 dd, 1.8, 8.4 | 129.4 |
| 19 | 7.03 d, 1.8[c] | 6.15 d, 1.9[c] | 6.30 d, 1.9[c] | 7.25 d, 2 | 132.5 | 6.58 d, 8.4 | 117.7 |
| 20 | 2.66 m | 2.69 m | 2.19 m | 2.62 t, 7 | 33.5 | 2.68 t, 6.6 | 33.9 |
| 21 | 3.36 m | 3.38 m | 3.10, 2.94 m | 3.30 m | 39.8 | 3.37 obscured | 39.9 |
| 22 | 7.14 t, 6.1[b] | 7.07 t, 6.1[b] | 6.70 t, 6.0[b] | 7.87 t, 5.5 | | | |
| 23 | | | | | 163.0 | | 163.3 |
| 24 | | | | | 152.0 | | 151.3 |
| 25 | 3.89 d, 13.0<br>3.81 d, 13.0 | 3.84 d, 13.0<br>3.78 d, 13.0 | 3.69 s | 3.69 s | 27.8 | 3.70 s | 28.5 |
| 26 | | | | | 131.4 | | 138.0 |
| 27 | 7.52 d, 1.8 | 7.52 d, 2.0 | 7.60 d, 2.0 | 7.22 br | 132.3 | 7.46 s | 133.2 |
| 28 | | | | | 112.4 | | 117.3 |
| 29 | | | | | 152.2 | | 146.2 |
| 30 | 6.78 d, 8.4 | 6.65 d, 8.4 | 6.64 d, 8.4 | | 128.2 | | 117.3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 31 | 7.14 dd, 2.0, 8.4 | 7.14 dd, 2.0, 8.4 | 7.13 dd, 2.0, 8.4 | 6.96 d, 2 | 130.7 | 7.46 s | 133.2 |
| 33 | | | | | 128.2 | | 144.6 |
| 34 | | | | | 152.2 | | 141.9 |
| 35 | | | | | 112.3 | | 110.1 |
| 36 | 7.26 d, 1.8[a] | 7.29 d, 2.0[a] | 7.28 d, 2.0[a] | 7.22 br | 132.3 | 6.93 d, 2.0 | 126.2 |
| 37 | | | | | 131.4 | | 128.4 |
| 38 | 6.64 d, 1.8[a] | 6.70 d, 2.0[a] | 6.78 d, 2.0[a] | 6.97 d, 2 | 130.7 | 6.02 d, 2.0 | 113.2 |
| OMe-10 | | 4.05 s | 4.00 s | | | | |
| | | 4.01 s | 3.80 s | | | | |
| | | 3.89 s | 3.65 s | | | | |
| | | 3.87 s | 3.58 s | | | | |
| OH | | 3.21 br | 2.70 br | 10.00 s | | | |
| OH-10 | | | | | | 9.39 s | |
| OH-24 | | | | 8.90 br | | | |
| OH-34 | | | | 8.90 br | | 9.97 s | |
| NH-4 | | | | | | 7.82 brt, 6.6 | |
| NH-22 | | | | | | 8.16 brt, 6.6 | |
| NOH-24 | | | | 11.75 s | | 11.93 s | |
| NOH-2 | | | | 11.69 s | | 11.66 s | |
| ArOH | 10.73 br | | | | | | |
| OMe-34 | 11.27 br | | | | | | |

[a–c]may be interchanged.

| | **217** Methyl ether(*131*) | | **226** (*141*) | | **218** (*133*) | | **218a** (*133*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ |
| | $CDCl_3$ | | DMSO-$d_6$ | | DMSO-$d_6$ | | $CDCl_3$ | |
| 1 | 3.48 s | 29.0 | 3.41 | 27.9 | 3.70 s | 27.5 | 3.85 br | 28.3 |
| 2 | | 150.7 | | 150.7 | | 151.5 | | 150.9 |
| 3 | | 161.9 | | 162.6 | | 161.4 | | 159.6 |

(*continued*)

TABLE II.
Continued.

| | **217** Methyl ether(*131*) | | **226** (*141*) | | **218** (*133*) | | **218a** (*133*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H | $^{13}$C | $^{1}$H | $^{13}$C | $^{1}$H | $^{13}$C | $^{1}$H | $^{13}$C |
| | $CDCl_3$ | | DMSO-$d_6$ | | DMSO-$d_6$ | | $CDCl_3$ | |
| 4 | 6.58 brt, 6.1 | | 7.72 t, 5.8 | | 10.31 d, 10.2 | | 8.44 d, 8.4 | |
| 5 | 3.47 obscured | 40.8 | 3.22 dt, 5.8, 7.0 | 40.3 | 7.45 dd, 14.3, 10.2 | 126.0 | 7.46 dd, 14.6, 8.4 | 124.8 |
| 6 | 2.71 brt, 6.0 | 34.5 | 2.54 t, 7.0 | 33.8 | 6.41 d, 14.3 | 110.0 | 6.11 d, 14.6 | 110.0 |
| 7 | | 132.1 | | 130.7 | | 137.6 | | 136.9 |
| 8 | 6.68 d, 1.5 | 121.2 | 6.50 d, 2. | 120.1 | 7.77 s | 129.5 | 7.57 s | 129.8 |
| 9 | | 144.3 | | 143.0 | | 118.1 | | 118.5 |
| 10 | | 149.5 | | 146.7 | | 145.6 | | 146.4 |
| 11 | 6.96 m | 113.6 | 6.85 d, 8.5 | 117.0 | | 118.1 | | 118.5 |
| 12 | 6.96 m | 125.2 | 6.81 dd, 2.0, 8.5 | 125.0 | 7.77 s | 129.5 | 7.57 s | 129.8 |
| 14 | | 153.1 | | 152.3 | | 145.0 | | 150.4 |
| 15 | | 112.9 | | 111.9 | | 141.6 | | 144.3 |
| 16 | 7.45 d, 2.2 | 134.4 | 7.47 d, 2.0 | 133.1 | | 110.1 | | 118.1 |
| 17 | | 133.7 | | 135.4 | 7.00 d, 1.5 | 126.4 | 7.03 d, 2.0 | 126.7 |
| 18 | 6.94 dd, 2.2, 8.4 | 128.6 | 7.00 dd, 2.0, 8.3 | 129.3 | | 130.8 | | 135.5 |
| 19 | 6.64 d, 8.4 | 117.8 | 6.57 d, 8.3 | 117.9 | 6.18 d, 1.5 | 111.7 | 6.15 d, 2.0 | 112.5 |
| 20 | 2.78 brt, 6.0 | 34.5 | 2.66 t, 6.5 | 33.9 | 2.67 t, 6.5 | 32.8 | 2.72 t, 6.5 | 34.5 |
| 21 | 3.55 dt, 5.8, 6.0 | 40.5 | 3.37 dt, 6.5, 6.3 | 39.8 | 3.19 q, 6.3 | 38.3 | 3.36 bq, 6.5 | 39.4 |
| 22 | 6.76 brt, 5.8 | | 8.10 t, 6.3 | | 7.80 t, 5.7 | | 6.71 t, 6.5 | |
| 23 | | 162.0 | | 163.1 | | 162.9 | | 162.3 |
| 24 | | 150.8 | | 151.3 | | 150.9 | | 150.4 |
| 25 | 3.89 s | 28.7 | 3.69 s | 28.4 | 3.59 s | 28.4 | 3.75 br | 29.2 |
| 26 | | | | 137.4 | | 134.4 | | 132.5 |
| 27 | 7.51 s | 136.6 | 7.42 s | 133.1 | 7.46 br | 133.7 | 7.47 d, 2.2 | 134.1 |
| 28 | | 118.1 | | 117.2 | | 112.8 | | 112.3 |
| 29 | | 146.8 | | 146.6 | | 150.9 | | 152.1 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 30 | | 118.1 | | 117.2 | 6.64 d, 8.3 | 119.1 | 6.47 d, 8.4 | 117.1 |
| 31 | 7.51 s | 136.6 | 7.42 | 113.1 | 7.14 dd, 8.3, 1.9 | 130.3 | 7.12 dd, 8.4, 2.2 | 129.9 |
| 33 | | 149.6 | | 150.3 | | 144.8 | | 148.9 |
| 34 | | 144.2 | | 138.6 | | 143.8 | | 147.5 |
| 35 | | 117.9 | | 119.1 | | 110.9 | | 117.9 |
| 36 | 7.16 d, 2.0 | 127.3 | 6.93 s | 125.9 | 7.20 d, 1.9 | 126.0 | 7.32 d, 2.2 | 129.9 |
| 37 | | 133.0 | | 133.6 | | 128.3 | | 133.0 |
| 38 | 6.09 d, 2.0 | 114.7 | 5.98 s | 113.5 | 6.40 br | 117.3 | 6.86 d, 2.0 | 121.3 |
| OMe-10 | 3.81 s | 56.3 | | | | | | |
| C=NOH | 3.48 s | 62.4 | 11.68, 11.88 | | | | | |
| OMe-34 | 4.01 s | 63.3 | | | | | 3.83 s | 61.1 |
| NOMe-2 | 4.04 s | 61.0 | | | | | 4.05 s | 61.0 |
| NOMe-24 | | | | | | | 4.10 s | 63.7 |
| OMe-15 | | | | | | | 4.03 s | 63.1 |
| 10-OH | | | 9.35 | | | | | |

| | **219** (*134*) | **220** (*135*) | | **221** (*135*) | | **222** (*138*) | |
|---|---|---|---|---|---|---|---|
| | $^1$H $CDCl_3$ + 1 drop DMSO-$d_6$ | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | 3.71 s | 3.55 s | 27.4 | 3.52 s | 27.4 | 3.67 s | 28.7 |
| 2 | | 11.65 s | 151.4 | 11.77 s | 151.0 | | 153.3 |
| 3 | | | 163.0 | | 162.9 | | 166.0 |
| 4 | 6.76 t, 6.2 | 8.06 t, 6.0 | | 7.77 t, 6.3 | | | |
| 5 | 3.51 m | 3.28 m | 40.4 | 2.92, 3.38 m | 47.7 | 3.30 m | 41.5 |
| 6 | 2.82 m | 2.71 t, 6.6 | 33.9 | 4.58 m, 5.53 d, 4.4 | 70.5 | 2.55 t, 7 | 35.4 |
| 7 | | | 139.8 | | 139.3 | | 138.6 |
| 8 | 7.38 s | 7.59 s | 133.2 | 7.62 d, 1.9 | 129.8 | 7.39 d, 2.0 | 135.1 |
| 9 | | | 117.7 | | 111.4 | | 115.6 |
| 10 | | | 146.6 | | 153.1 | | 152.4 |
| 11 | | | 117.7 | 6.73 d, 8.5 | 117.4 | 6.82 d, 8.3 | 122.2 |

(*continued*)

TABLE II.
Continued.

| | **219** (*134*) | **220** (*135*) | | **221** (*135*) | | **222** (*138*) | |
|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ + 1 drop DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 12 | 7.38 s | 7.59 s | 133.2 | 7.13 dd, 8.5, 1.9 | 126.2 | 7.06 dd, 8.3, 2.1 | 130.9 |
| 14 | | | 144.1 | | 142.5 | | 145.3 |
| 15 | | | 144.3 | | 146.9 | | 146.6 |
| 16 | | 6.81 d, 8.2 | 116.6 | 6.83 d, 8.2 | 116.5 | | 111.6 |
| 17 | 7.04 d, 1.9 | 6.67 dd, 8.2. 1.8 | 122.9 | 6.81 dd, 8.2, 1.9 | 126.1 | 7.04 d, 2.0 | 128.5 |
| 18 | | | 129.5 | | 130.6 | | 132.7 |
| 19 | 6.14 d, 1.9 | 6.17 d, 1.8 | 112.5 | 6.76 d, 1.9 | 112.5 | 6.35 d, 2.0 | 118.0 |
| 20 | 2.67 m | 2.67, 6.6 | 33.3 | 2.65 t, 6.3 | 34.1 | 2.66 t, 6.5 | 35.5 |
| 21 | 3.34 m | 3.29 m | 38.8 | 3.40 m | 39.2 | 3.34 m, 7 | 41.7 |
| 22 | 7.16 t, 6.4 | 7.94 t, 6.0 | | 7.95 t, 6.3 | | | |
| 23 | | | 163.3 | | 163.0 | | 166.6 |
| 24 | | 11.86 s | 150.7 | 11.91 s | 150.4 | | 152.6 |
| 25 | 3.88 s | 3.68 s | 28.7 | 3.51 d, 12.9<br>3.56 d, 12.9 | 28.7 | 3.72 s | 29.3 |
| 26 | | | 137.8 | | 137.6 | | 135.8 |
| 27 | 7.49 d, 2.0 | 7.63 s | 133.7 | 7.58 s | 133.6 | 7.42 d, 2.0 | 135.1 |
| 28 | | | 117.2 | | 117.2 | | 115.2 |
| 29 | | | 146.1 | | 146.0 | | 153.0 |
| 30 | 6.87 d, 8.3 | | 117.2 | | 117.2 | 6.67 d, 8.4 | 121.2 |
| 31 | 7.14 dd, 2.0, 8.3 | 7.63 s | 133.7 | 7.58 s | 133.6 | 6.94 dd, 8.5, 2.1 | 130.3 |
| 33 | | | 144.8 | | 144.6 | | 145.1 |
| 34 | | | 142.0 | | 141.8 | | 147.0 |
| 35 | | | 109.8 | | 109.7 | | 111.7 |
| 36 | 7.22 d, 2.0 | 7.07 d, 1.6 | 127.0 | 7.03 d, 1.9 | 126.8 | 7.13 d, 1.9 | 129.5 |
| 37 | | | 128.2 | | 128.0 | | 129.7 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 38 | 6.52 d, 2.0 | | 6.15 d, 1.6 | 112.8 | 6.24 d, 1.9 | 113.1 | 6.46 d, 1.9 | 118.6 |
| OH-15 | | | 9.25 s | | 9.36 s | | | |
| OH-34 | | | 9.99 s | | 9.98 s | | | |
| NOHe | 11.48 br | | | | | | | |
| Ar-OH | 10.17 br | | | | | | | |

| | **223a** (*139*) | | **224** (*130*) | | **225** (*140*) | | **225** Tetramethyl ether(*140*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 1 | 3.72 s | 28.3 | 3.63 s | 28.1 | 3.58 br | 27.8 | 3.62 br | 29.1 |
| 2 | | 150.9 | | 151.3 | | 151.4 | | 151.0 |
| 3 | | 163.0 | | 162.9 | | 162.8 | | 162.0 |
| 4 | 7.78 t, 6.8 | | 6.75 t, 6 | | 7.92 brt | | 6.62 brt | |
| 5 | 3.36 m | 39.6 | 3.39 m | 40.4 | 3.31 m | 39.7 | 3.47 q, 6 | 40.9 |
| 6 | 2.68 t, 6.8 | 34.0 | 2.62 t, 6.5 | 34.4 | 2.61 m | 33.9 | 2.72 6 | 34.6 |
| 7 | | 136.8 | | 131.6 | | 130.6 | | 132.0 |
| 8 | 6.76 d, 1.9 | 133.3 | 7.06 d, 2 | 127.5 | 6.62 d, 2 | 120.0 | 6.69 d, 2 | 121.1 |
| 9 | | 113.2 | | 110.3 | | 142.9 | | 145.0 |
| 10 | | 151.2 | | 144.7 | | 146.7 | | 149.5 |
| 11 | | 119.9 | | 143.2 | 6.96 d, 8 | 116.9 | 6.93 d, 8 | 125.0 |
| 12 | 7.09 dd, 8.3, 1.9 | 129.5 | 6.44 d, 2 | 117.2 | 6.89 dd, 8, 2 | 124.9 | 6.93 dd, 2, 8 | 113.5 |
| 14 | | 145.1 | | 151.4 | | 152.2 | | 153.2 |
| 15 | | 143.4 | | 114.1 | | 111.9 | | 113.0 |
| 16 | | | 7.41 d, 2 | 133.7 | 7.58 d, 2 | 133.1 | 7.43 d, 2 | 133.6 |
| 17 | 7.10 d, 1.9 | 127.4 | | 136.8 | | 135.5 | | 135.0 |
| 18 | | 131.8 | 7.06 dd, 2, 8 | 129.3 | 7.10 dd, 8, 2 | 129.2 | 6.94 dd, 2, 8 | 128.8 |
| 19 | 7.50 d, 1.9 | 117.4 | 6.84 d, 8 | 120.4 | 6.69 d, 8 | 117.8 | 6.66 d, 8 | 118.0 |
| 20 | 2.49 t, 6.8 | 33.2 | 2.77 t, 6.5 | 34.6 | 2.79 m | 33.6 | 2.78 t, 6 | 34.5 |
| 21 | 3.16 m | 40.0 | 3.54 m | 40.2 | 3.50 m | 39.5 | 3.58 q, 6 | 40.5 |
| 22 | 8.19 t, 6.8 | | 6.97 t, 6 | | 8.09 brt | | 6.67 brt | |

(*continued*)

TABLE II.
Continued.

| | **223a** (*139*) | | **224** (*130*) | | **225** (*140*) | | **225** Tetramethyl ether(*140*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 23 | | 162.7 | | 163.4 | | 163.3 | | 162.5 |
| 24 | | 151.1 | | 151.9 | | 151.7 | | 151.5 |
| 25 | 3.36 s | 27.6 | 3.88 s | 28.3 | 3.79 br | 28.4 | 3.87 br | 28.7 |
| 26 | | 128.3 | | 134.5 | | 134.5 | | 135.0 |
| 27 | 6.89 d, 1.9 | 125.8 | 7.54 d, 2 | 134.2 | 7.17 dd, 8, 2 | 129.5 | 7.11 dd, 2, 8 | 129.4 |
| 28 | | 110.0 | | 114.1 | 6.92 d, 8 | 120.2 | 6.77 8 | 120.9 |
| 29 | | 141.7 | | 151.1 | | 150.9 | | 151.2 |
| 30 | | 144.5 | 6.83 d, 8.5 | 120.2 | | 113.3 | | 114.2 |
| 31 | 5.94 d, 1.9 | 112.9 | 7.13 dd, 2, 8.5 | 129.3[c] | 7.53 d, 2 | 133.4 | 7.54 d, 2 | 134.5 |
| 32 | | | | | | | | |
| 33 | | 117.0 | | 142.8 | | 145.1 | | 153.5 |
| 34 | | 146.1 | | 144.6 | | 143.4 | | 146.1 |
| 35 | | 117.0 | | 109.8 | | 110.6 | | 114.5 |
| 36 | 7.46 s | 133.0 | 7.20 d, 2 | 128.1 | 7.14 d, 2 | 127.2 | 7.21 d, 2 | 128.3 |
| 37 | | 137.7 | | 129.3 | | 128.9 | | 133.2 |
| 38 | 7.46 s | 133.0 | 6.53 d, 2 | 117.8 | 6.44 2 | 117.2 | 6.48 d, 2 | 119.0 |
| OMe-10 | | | | | | | 3.83 s | 56.3 |
| OH-10 | 11.91, 11.68 s | | 6.70 br | | 9.41 s | | | |
| OH-24 | | | | | 11.87 s | | | |
| OH-34 | | | 7.65 br | | 9.89 s | | | |
| NOH-24 | | | 11.24 s[d] | | | | | |

| | | | | |
|---|---|---|---|---|
| NOH | 9.8 br | 10.89 s[d] | 11.77 s | |
| OMe-34 | | | 3.92 s | 61.0 |
| NOMe-2 | | | 3.65 s | 62.8 |
| NOMe-24 | | | 3.99 s | 63.0 |

| | **231** (*41*) | | | | **237** (*41*) | | **232** (*41*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{1}$H pyridine-$d_5$ | $^{13}$C $CD_3OD$ | $^{13}$C pyridine-$d_5$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | | 153.9 | 154.1 | | 153.8 | | 154.1 |
| 2 | | | 110.7 | 111.0 | | 110.7 | | 110.9 |
| 3 | 7.29 d, 2.0 | 7.53 s | 134.3 | 133.8 | 7.29 d, 2.0 | 134.2 | 7.30 d, 2.0 | 134.5 |
| 4 | | | 133.1 | 132.2 | | 133.0 | | 133.3 |
| 5 | 6.95 dd, 2.0, 8.3 | 7.05 br | 130.1 | 129.6 | 6.95 dd, 2.0, 8.3 | 130.0 | 6.96 dd, 2.0, 8.3 | 130.2 |
| 6 | 6.77 d, 8.3 | 7.05 br | 117.3 | 117.2 | 6.77 d, 8.3 | 117.2 | 6.78 d, 8.3 | 117.5 |
| 7 | 2.67 t | 2.87 t, 6.5 | 35.3 | 35.0 | 2.67 t, 7.2 | 35.3 | 2.68 t, 7.3 | 35.1 |
| 8 | 3.38 t, 7.3 | 3.67 dt, 6.5, 6.5 | 42.0 | 41.5 | 3.40 t, 7.2 | 41.9 | 3.39 t, 7.3 | 42.0 |
| 1′ | | | 153.8 | 154.2 | | 155.9 | | 151.0 |
| 2′ | | | 110.5 | 111.1 | | 112.2 | | 112.2 |
| 3′ | 7.35 d, 2.0 | 8.06 d, 2.1 | 134.5 | 134.5 | 7.43 d, 2.3 | 134.8 | 7.38 s | 134.2 |
| 4′ | | | 130.7 | 130.4 | | 131.6 | | 132.6 |
| 5′ | 7.03 dd, 2.0, 8.3 | 7.55 dd, 2.1, 8.3 | 130.4 | 130.3 | 7.14 dd, 2.3, 8.4 | 130.4 | 7.38 s | 134.2 |
| 6′ | 6.76 d, 8.3 | 7.12 d, 8.3 | 117.1 | 117.2 | 6.89 d, 8.4 | 113.2 | | 112.2 |
| 7′ | 3.77 s | 4.32 s | 28.7 | 28.9 | 3.80 s | 28.7 | 3.77 s | 28.3 |
| 8′ | | | 153.3 | 153.1 | | 153.1 | | 152.9 |
| 9′ | | | 165.8 | 164.6 | | 165.7 | | 165.9 |
| NH | | 8.60 t, 6.5 | | | | | | |
| OMe-1′ | | | | | 3.82 s | 56.7 | | |

(*continued*)

TABLE II.
Continued.

| | **238** (*41*) | | **233** (*41*) | | **233b** (*41*) | | **234** (*41*) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^{1}$H $CDCl_3$ | $^{1}$H $CD_3OD$ | $^{1}$H pyridine-$d_5$ | $^{13}$C $CD_3OD$ | $^{13}$C $CD_3OD$ |
| 1 | | 153.9 | | 154.0 | | | | 153.9 | 154.1 |
| 2 | | 110.7 | | 112.3 | | | | 110.7 | 111.0 |
| 3 | 7.30 d, 2.0 | 134.2 | 7.31 s | 133.9 | 7.42 s | 7.28 d, 1.9 | 7.56 obscured | 134.2 | 133.8 |
| 4 | | 133.0 | | 135.0 | | | | 133.0 | 132.2 |
| 5 | 6.97 dd, 2.0, 8.3 | 130.0 | 7.31 s | 133.9 | 7.42 s | 6.92 dd, 1.9, 8.3 | 7.08 br | 130.0 | 129.4 |
| 6 | 6.79 d, 8.3 | 117.2 | | 112.3 | | 6.79 d, 8.3 | 7.08 br | 117.3 | 117.2 |
| 7 | 2.68 t, 7.3 | 35.2 | 2.68 t, 7.3 | 34.8 | 2.76 t, 7.0 | 2.57 m | 2.82 m | 35.4 | 35.2 |
| 8 | 3.40 t, 7.3 | 42.0 | 3.39 t, 7.3 | 41.7 | 3.51 dt, 7.0, 7.0 | 3.26 m, 3.38 m | 3.69 m | 41.5 | 40.9 |
| 1′ | | 153.8 | | 151.0 | | | | 154.0 | 154.1 |
| 2′ | | 118.6 | | 110.7 | | | | 110.4 | 110.7 |
| 3′ | 7.47 s | 134.5 | 7.36 d, 2.0 | 134.8 | 7.38 d, 2.2 | 7.34 d, 1.9 | 7.82 d, 1.9 | 135.2 | 134.8 |
| 4′ | | 137.4 | | 130.9 | | | | 131.6 | 131.7 |
| 5′ | 7.47 s | 134.5 | 7.04 dd, 2.0, 8.3 | 130.5 | 7.08 dd, 2.2, 8.4 | 7.02 dd, 1.9, 8.3 | 7.32 dd, 1.9, 8.3 | 131.0 | 130.6 |
| 6′ | | 118.6 | 6.76 d, 8.3 | 117.3 | 6.83 d, 8.4 | 6.79 d, 8.3 | 7.12 d, 8.3 | 116.9 | 116.8 |
| 7′ | 3.82 s | 28.8 | 3.77 s | 28.6 | 3.81 s | 2.72 dd, 7.2, 14.0<br>2.90 dd, 4.0, 14.0 | 3.18 dd, 7.8, 13.5<br>3.47 dd, 3.5, 13.5 | 40.6 | 40.6 |
| 8′ | | 152.1 | | 153.5 | | 4.13 dd, 4.0, 7.2 | 4.73 dd, 3.5, 7.8 | 73.7 | 73.4 |
| 9′ | | 165.3 | | 166.2 | | | | 176.2 | 174.3 |
| NH | | | | | 6.76 brt, 7.0 | | 8.39 t, 5.6 | | |
| NOMe | | | | | 3.99 s | | | | |
| OMe-1 | | | | | 3.84 s | | | | |
| OMe-1′ | 3.80 s | 61.0 | | | 3.87 s | | | | |

| | **234a** (*41*) | **235** (*41*) | | **235a** (*41*) | **236** (*41*) | |
|---|---|---|---|---|---|---|
| | $^{1}H$ $CDCl_3$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ |
| 1 | | | 153.8 | | | 150.8 |
| 2 | | | 110.7 | | | 112.2 |
| 3 | 7.35 d, 2.1 | 7.28 d, 2.0 | 134.2 | 7.36 d, 2.0 | 7.31 s | 133.6 |
| 4 | | | 133.1 | | | 131.9 |
| 5 | 7.04 dd, 2.1, 8.4 | 6.92 dd, 2.0, 8.0 | 129.9 | 7.05 dd, 2.0, 8.3 | 7.31 s | 133.6 |
| 6 | 6.92 d, 8.4 | 6.80 d, 8.0 | 117.3 | | | 112.2 |
| 7 | 2.60 m | 2.53 ddd, 7.0, 8.0, 14.0<br>2.60 ddd, 6.5, 8.5, 14.0 | 35.5 | 2.59 m | | 35.1 |
| 8 | 3.25 ddd, 7.4, 7.4, 15.0<br>3.41 ddd, 6.5, 7.9, 13.3 | 3.23 ddd, 6.5, 8.0, 15.0<br>3.40 ddd, 7.0, 8.5, 15.0 | 41.5 | 3.24 ddd, 6.9, 8.0, 14.6<br>3.42 ddd, 6.3, 8.3, 14.6 | | 41.2 |
| 1′ | | | 150.9 | | | 153.9 |
| 2′ | | | 111.8 | | | 110.4 |
| 3′ | 7.42 d, 2.1 | 7.34 s | 134.6 | 7.45 s | 7.34 d, 2.0 | 135.2 |
| 4′ | | | 132.9 | | | 131.6 |
| 5′ | 7.15 dd, 2.1, 8.4 | 7.34 s | 134.6 | 7.45 s | 7.02 dd, 2.0, 8.0 | 130.9 |
| 6′ | 6.92 d, 8.4 | | 111.8 | 6.92 d, 8.3 | 6.80 d, 8.0 | 116.9 |
| 7′ | 2.77 dd, 6.9, 14.0<br>2.93 dd, 4.1, 14.0 | 2.75 dd, 4.0, 14.0<br>2.88 dd, 7.0, 14.0 | 41.5 | 2.80 dd, 6.8, 14.0<br>2.93 dd, 4.1, 14.0 | | 40.6 |
| 8′ | 4.15 dd, 4.1, 6.9 | 4.14 dd, 4.0, 7.0 | 73.3 | 4.17 dd, 4.1, 6.8 | | 73.7 |
| 9′ | | | 175.8 | | | 176.2 |
| OMe-1 | 3.82 s | | | 3.80 s | | |
| OMe-1′ | 3.83 s | | | 3.83 s | | |

(*continued*)

TABLE II.
Continued.

| | **236a** (*41*) | | **239** (*145*) | | **240** (*145*) | | **241** (*145*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{13}$C NA | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H acetone-$d_6$ | $^{13}$C acetone-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 1 | | | | 152.5 | | 152.8 | | 155.0 |
| 2 | | | | 118.3 | | 118.8 | | 112.3 |
| 3 | 7.40 s | | 7.48 s | 129.4 | 7.42 s | 130.1 | 7.55 d, 2.0 | 130.7 |
| 4 | | | | 135.0 | | 137.3 | | 132.5 |
| 5 | 7.40 s | | 7.48 s | 129.4 | 7.42 s | 130.1 | 7.27 dd, 8.4, 2.0 | 126.4 |
| 6 | | | | 118.3 | | 118.8 | 6.85 d, 8.4 | 112.3 |
| 7 | 2.59 m | | 6.08 d, 14.6 | 110.7 | 5.95 d, 14.6 | 110.5 | 6.14 d, 14.6 | 113.5 |
| 8 | 3.24 ddd, 6.9, 8.0, 14.6<br>3.42 ddd, 6.3, 8.3, 14.6 | | 7.53 dd, 11.1, 14.6 | 124.0 | 7.46 dd, 11.6, 14.6 | 125.9 | 7.49 dd, 11.4, 14.6 | 123.8 |
| 1′ | | | | 156.9 | | 157.2 | | 158.9 |
| 2′ | | | 6.88 d, 8.4 | 115.8 | 6.78 d, 8.7 | 115.4 | 6.86 d, 8.6 | 116.4 |
| 3′ | 7.42 d, 2.0 | | 7.59 d, 8.4 | 132.0 | 7.29 d, 8.7 | 131.3 | 7.60 d, 8.6 | 132.5 |
| 4′ | | | | 125.2 | | 126.4 | | 125.8 |
| 5′ | 7.16 dd, 2.0, 8.3 | | 7.59 d, 8.4 | 132.0 | 7.29 d, 8.7 | 131.3 | 7.60 d, 8.6 | 132.5 |
| 6′ | 6.92 d, 8.3 | | 6.88 d, 8.4 | 115.8 | 6.78 d, 8.7 | 115.4 | 6.86 d, 8.6 | 116.4 |
| 7′ | 2.80 dd, 6.8, 14.0<br>2.93 dd, 4.1, 14.0 | | 7.13 s | 122.3 | 6.14 s | 109.9 | 7.12 s | 121.3 |
| 8′ | 4.14 dd, 4.1, 6.8 | | | 145.3 | | 148.2 | | 147.8 |
| 9′ | | | | 162.0 | | 162.0 | | 162.4 |
| NH | | | 8.45 d, 11.1 | | 8.23 d, 11.6 | | 8.37 d, 11.4 | |
| OMe-1 | 3.83 s | | 3.87 s | 60.7 | 3.85 s | 60.9 | 3.89 s | 56.6 |
| OMe-1′ | 3.82 s | | | | | | | |
| OMe-8′ | | | 3.68 s | 59.5 | 3.78 s | 56.1 | 3.68 s | 59.7 |
| OH-1′ | | | 5.85 br | | 5.75 br | | 5.95 br | |

| | **242** (*145*) | | | | **243** (*146*) | | | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{1}$H acetone-$d_6$ | $^{13}$C DMSO-$d_6$ | | $^{1}$H $CDCl_3$ | $^{1}$H acetone-$d_6$ | $^{13}$C $CDCl_3$ | $^{13}$C acetone-$d_6$ |
| 1 | | | 153.9 | 1 | | | 156.4 | 157.1 |
| 2 | | | 111.0 | 2 | 6.77 d, 8.1 | 6.75 d, 8.5 | 115.9 | 116.1 |
| 3 | 7.55 d, 2.0 | 7.49 d, 2.0 | 129.5 | 3 | 6.92 d, 8.1 | 7.04 d, 8.5 | 130.7 | 130.9 |
| 4 | | | 130.6 | 4 | | | 124.6 | 127.5 |
| 5 | 7.34 m | 7.23 dd, 8.6, 2.1 | 125.7 | 5 | 6.92 d, 8.1 | 7.04 d, 8.5 | 130.7 | 130.9 |
| 6 | 7.01 d, 8.7 | 6.81 d, 8.6 | 112.9 | 6 | 6.77 d, 8.1 | 6.75 d, 8.5 | 115.9 | 116.1 |
| 7 | 6.21 d, 14.8 | 6.04 d, 14.6 | 111.8 | 7 | 3.47 s | 3.33 s | 42.9 | 43.1 |
| 8 | 7.34 m | 7.41 dd, 14.6, 11.7 | 122.5 | 8 | | | 171.7 | 171.5 |
| 1′ | | | 156.0 | NH-9 | 5.01 br | 6.94 br | | |
| 2′ | 6.64 d, 8.5 | 6.74 d, 8.6 | 114.9 | 10 | 3.39 q, 6.2 | 3.42 t, 6.5 | 40.0 | 40.8 |
| 3′ | 7.11 d, 8.5 | 7.26 d, 8.6 | 129.4 | 11 | 2.68 t, 6.2 | 2.74 t, 6.5 | 33.6 | 34.8 |
| 4′ | | | 124.9 | 12 | | | 137.5 | 139.9 |
| 5′ | 7.11 d, 8.5 | 7.26 d, 8.6 | 129.4 | 13 | 7.18 s | 7.42 s | 133.0 | 134.1 |
| 6′ | 6.64 d, 8.5 | 6.74 d, 8.6 | 114.9 | 14 | | | 124.8 | 118.4 |
| 7′ | 5.93 s | 6.13 s | 105.9 | 15 | | | 151.8 | 152.3 |
| 8′ | | | 148.4 | 16 | | | 124.8 | 118.4 |
| 9′ | | | 161.7 | 17 | 7.18 s | 7.42 s | 133.0 | 134.1 |
| NH | 10.40 d, 10.0 | 8.22 d, 11.7 | | 18 | 4.04 t, 7.5 | 4.04 t, 6.4 | 71.9 | 72.3 |
| OMe-1 | 3.82 s | 3.87 s | 56.2 | 19 | 2.13 m | 2.06 submerged | 31.9 | 32.2 |
| OMe-8′ | 3.66 s | 3.78 s | 55.6 | 20 | 3.54 q, 6.2 | 3.45 t, 6.5 | 36.1 | 36.6 |
| OH-1′ | 9.38 br | 5.75 br | | 21 | 5.80 br | 7.10 br | | |
| | | | | 22 | | | 167.9 | 167.5 |
| | | | | 23 | 5.62 br | 5.70 br | 124.8 | 119.9 |
| | | | | 24 | | | 151.8 | 149.8 |
| | | | | 25 | 1.85 br | 1.96 br | 27.2 | 26.5 |
| | | | | 26 | 2.13 br | 2.13 br | 20.1 | 19.6 |
| | | | | OH-1 | | 8.37 s | | |

(*continued*)

TABLE II.
Continued.

| | **244** (*146*) | **245** (*146*) | **247** (*123*) | | **246** (*38*) | |
|---|---|---|---|---|---|---|
| | $^{1}H$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{1}H$ $CD_3OD$ + TFA | $^{13}C$ $CD_3OD$ + TFA | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ |
| 1 | | | | 135.3 | | 136.4 |
| 2 | 6.77 d, 8.1 | 6.77 d, 8.1 | 7.78 s | 132.9 | 7.82 s | 133.0 |
| 3 | 6.92 d, 8.1 | 6.92 d, 8.1 | | 119.5 | | 119.5 |
| 4 | | | | 156.3 | | 154.5 |
| 5 | 6.92 d, 8.1 | 6.92 d, 8.1 | | 119.5 | | 119.5 |
| 6 | 6.77 d, 8.1 | 6.77 d, 8.1 | 7.78 s | 132.9 | 7.82 s | 133.0 |
| 7 | 3.47 s | 3.47 s | 7.38 d, 15.8 | 138.2 | 7.42 d, 15.5 | 138.4 |
| 8 | | | 6.56 d, 15.8 | 123.8 | 6.57 d, 15.5 | 124.0 |
| 9 | 3.39 q, 6.2 | 3.39 q, 6.2 | | 168.0 | | 167.5 |
| 10 | 2.67 t, 6.2 | 2.65 t, 6.2 | 3.34 t, 7.7 | 39.5 | 3.56 t, 6.6 | 39.3 |
| 11 | | | 1.65 tt, 6.9, 7.7 | 27.5 | 2.77 t, 6.6 | 25.9 |
| 12 | 7.42 d, 1.8 | 7.45 s | 1.75 tt, 6.9, 8.1 | 24.4 | | 125.9 |
| 13 | | | 3.06 t, 8.1 | 48.5 | 6.59 s | 110.9 |
| 14 | | | 3.12 t, 7.7 | 45.7 | | 146.4 |
| 15 | | | 2.07 tt, 7.7, 8.1 | 25.3 | | |
| 16 | 7.21 d, 1.8 | 7.45 s | 3.05 t, 8.1 | 37.8 | | |
| 17 | 4.02 t, 7.5 | 4.00 t, 7.5 | | | | |
| 18 | 2.15 m | 2.16 m | | | | |
| 19 | 3.55 q, 6.2 | 3.56 2H | | | | |
| 21 | 5.63 br | 5.64 br | | | | |
| 23 | 1.85 s | 1.85 s | | | | |
| 24 | 2.13 s | 2.13 s | | | | |
| OMe | | | 3.87 s | 61.2 | 3.91 s | 61.3 |
| NH-8 | 5.01 br | 5.01 br | | | | |
| NH-19 | 5.81 br | 5.82 br | | | | |

| | **248** (*150*) | | | | **249** (*151*) | | **250** (*151*) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CD_3OD$ | $^{1}$H DMSO-$d_6$ | $^{13}$C $CD_3OD$ | $^{13}$C DMSO-$d_6$ | | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | 6.71 s | 6.66 s | 118.3 | 115.5 | 1 | | | | |
| 2 | | | 144.3 | 144.7 | 2 | | 175.6 | | 175.3 |
| 3 | | | 144.3 | 144.5 | 3 | | | | |
| 4 | 6.65 s | 6.60 s | 118.6 | 116.1 | 4 | | 160.5 | | 161.2 |
| 1′ | | | 129.7 | 128.3 | 5 | | 121.3 | | 121.3 |
| 2′ | 7.94 d, 2.1 | 7.90 d, 1.9 | 135.7 | 133.6 | 6 | | 164.1 | | 164.7 |
| 3′ | | | 110.4 | 108.8 | 7 | | | 10.55 br | |
| 4′ | | | 154.6 | 152.4 | 8 | 7.73 d, 10.0 | 142.9 | 7.14 t, 9.5 | 137.9 |
| 5′ | 6.83 d, 8.4 | 6.83 d, 8.7 | 116.7 | 115.5 | 9 | 6.42 d, 10.0 | 100.4 | 6.42 d, 9.5 | 101.2 |
| 6′ | 7.72 dd, 8.4, 2.1 | 7.55 dd, 8.7, 1.9 | 131.5 | 130.0 | 10 | | 169.7 | | 170.8 |
| 1″ | | | 129.1 | 128.9 | 11 | 4.23 s | 35.0 | 4.17 s | 33.9 |
| 2″ | 7.32 d, 1.7 | 7.55 d, 1.7 | 127.0 | 124.3 | 12 | | 140.2 | | 140.1 |
| 3″ | | | 110.0 | 109.4 | 13 | 7.67 s | 133.2 | 7.66 s | 133.1 |
| 4″ | | | 143.9 | 141.9 | 14 | | 116.7 | | 116.7 |
| 5″ | | | 146.5 | 145.1 | 15 | | 151.4 | | 151.4 |
| 6″ | 7.48 d, 1.7 | 7.04 d, 1.7 | 116.5 | 116.4 | 16 | | 116.7 | | 116.7 |
| OH-4′ | | 10.12 br | | | 17 | 7.67 s | 133.2 | 7.66 s | 133.1 |
| OH-4″ | | 9.00 br | | | 18 | 8.69 | | 8.69 | |
| OH-5″ | | 9.52 br | | | 19 | 3.07 d, 3.7 | 29.2 | 3.07 d, 3.7 | 28.9 |
| | | | | | 20 | 3.56 s | 43.7 | | |
| | | | | | 21 | 3.71 s | 60.3 | 3.72 s | 60.3 |

(*continued*)

TABLE II.
Continued.

| | **251** (*152*) | | **252** (*152*) | | **253** (*153*) | |
|---|---|---|---|---|---|---|
| | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ | $^{1}H$ $CD_3OD$ | $^{13}C$ $CD_3OD$ |
| 1 | | 133.0 | | 133.0 | | |
| 2 | 7.60 d, 1.7 | 136.0 | 7.61 d, 1.7 | 136.1 | 8.67 s | 139.5 |
| 3 | | 113.6 | | 114.0 | | 114.0 |
| 4 | | 157.0 | | 157.1 | | 127.9 |
| 5 | 7.00 d, 7.0 | 114.0 | 7.00 d, 7.0 | 114.1 | 8.29 m | 122.9 |
| 6 | 7.33 dd, 1.7, 7.0 | 131.5 | 7.34 dd, 1.7, 7.0 | 131.6 | 7.25 m | 123.8 |
| 7 | 4.10 s | 39.8 | 4.20 s | 39.9 | 7.25 m | 124.8 |
| 8 | | 160.8 | | 160.8 | 7.47 m | 113.1 |
| 9 | | 157.7 | | 157.8 | | 138.0 |
| 10 | | | | | | 183.3 |
| 11 | 7.83 s | 124.4 | 7.86 s | 124.5 | | 165.8 |
| 12 | | 131.5 | | 131.6 | | |
| 13 | | | | | 3.51 t, 7.1 | 41.8 |
| 14 | | 137.5 | | 137.6 | 2.79 t, 7.1 | 35.2 |
| 15 | 8.07 s | 130.9 | 8.12 s | 131.7 | | 132.9 |
| 16 | | 120.2 | | 120.3 | 7.38 d, 2.0 | 134.3 |
| 17 | | 153.7 | | 153.7 | | 110.8 |
| 18 | | 120.2 | | 120.3 | | 154.0 |
| 19 | 8.07 s | 131.0 | 8.12 s | 131.7 | 6.82 dd, 8.2 | 117.3 |
| 20 | | | | | 7.06 dd, 8.2, 2.0 | 130.1 |
| 21 | 4.19 s, 5.6 | 72.1 | 4.21 s, 5.6 | 72.5 | | |
| 22 | 2.35 tt, 5.6, 7.9 | 27.2 | 2.30 tt, 5.6, 7.4 | 34.7 | | |
| 23 | 3.57 t, 7.9 | 57.9 | 3.43 t, 7.4 | 49.4 | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 38 | 3.88 s | 57.5 | 3.88 s | 57.6 | | |
| OMe | | | | | | |
| $NMe_2$ | 3.02 s | 44.5 | | | | |
| NMe | | | 2.83 s | 28.6 | | |

| | **254** (*153*) | | **255** (*153*) | | **256** (*154*) | | **257** (*154*) | |
|---|---|---|---|---|---|---|---|---|
| | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H $CD_3OD$ | $^{13}$C $CD_3OD$ | $^1$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | | | | | Signals were not assigned | | Signals were not assigned | |
| 2 | 8.65 s | 139.6 | 8.67 s | 139.5 | 2.75 d, 5.7; 2.76 | 26.0 50.5 | 2.63 br d, 5.9; | 24.7 |
| 3 | | 114.0 | | No | d, 7.3; 2.96 4H, | 50.5 | 2.79 4H, br; 3.81 | 49.4 |
| 4 | | 127.9 | | 127.8 | br; 3.82 s; 4.66 | 56.7 | s; 5.25 br; 6.98 | 56.1 |
| 5 | 8.28 m | 122.9 | 8.29 m | 123.0 | dd, 7.3, 5.7; 6.86 | 57.5 | d, 8.4; 7.13 dd, | 56.7 |
| 6 | 7.25 m | 123.8 | 7.25 s | 123.8 | d, 8.5; 8.5; 6.98 | 72.0 | 8.5, 1.6; 7.14 br; | 69.9 |
| 7 | 7.25 m | 124.8 | 7.25 m | 124.8 | ddd, 7.3, 7.1, 1.0; | 112.3 | 7.23 dd, 8.4, 1.7; | 110.2 |
| 8 | 7.45 m | 113.1 | 7.46 m | 113.1 | 7.04 ddd, 7.7, 7.3, | 112.4 | 7.18 d, 8.5; 7.48 | 110.9 |
| 9 | | 138.0 | | 138.0 | 1.1; 7.14 dd, 8.5, | 113.0 | d, 1.7; 7.66 d, | 112.0 |
| 10 | | 183.3 | | 182.9 | 2.0; 7.32 dd 7.7, | 113.0 | 1.6; 11.04 br. | 112.1 |
| 11 | | 166.0 | | 165.7 | 1.1; 7.48 d, 2.0; | 119.2 | | 113.3 |
| 13 | 3.49 t, 7.2 | 41.8 | 3.51 t, 7.7 | 42.1 | 7.52 dd, 7.1, 1.1. | 119.6 | | 120.6 |
| 14 | 2.76 t, 7.2 | 35.2 | 2.80 t, 7.7 | 35.6 | | 122.4 | | 123.2 |
| 15 | | 131.0 | | 131.0 | | 123.6 | | 124.4 |
| 16 | 7.59 d, 2.0 | 140.5 | 7.08 d, 2.0 | 130.8 | | 127.4 | | 126.4 |
| 17 | | 84.9 | 6.72 d, 8.5 | 116.3 | | 128.6 | | 129.1 |
| 18 | | 157.1 | | 157.0 | | 131.8 | | 130.3 |
| 19 | 7.07 dd, 8.1 | 115.7 | 6.72 dd, 8.5 | 116.3 | | 138.9 | | 134.9 |
| 20 | 7.07 dd, 8.1, 2.0 | 133.3 | 7.08 dd, 8.5 | 130.8 | | 138.2 | | 137.9 |
| | | | | | | 156.7 | | 154.2 |

(*continued*)

TABLE II.
Continued.

| | **258** (*155*) | | **259** (*164*) | | **260** (*158*) | | **261** (*158*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 1 | | | | 175.1[a] | | 170.9 | | 170.7 |
| 2 | | 174.2 | 2.50 m | 40.1 | 2.32 m | 42.4 | 2.32 m | 42.4 |
| 3 | 2.37 d, 17.4<br>2.19 d, 17.4 | 43.4 | 2.38 dd, 15.7,<br>10.8 1.89 d, 15.7 | 40.7 | 2.04 dd, 15, 4<br>2.16 d, 15 | 43.3 | 2.03 dd, 14,<br>4 2.16 d, 14 | 43.4 |
| 3a | | 81.6 | | | | | | |
| 4 | 4.1–4.2 m | 83.2 | | 131.1 | | 129.6 | | 129.9 |
| 5 | 6.75 d, 2.5 | 142.0 | 4.75 d, 7.1 | 127.8 | 4.93 d, 8 | 131.6 | 4.94 d, 8 | 131.7 |
| 6 | | 137.8 | 2.23 m | 29.2 | 2.16 m | 29.0 | 2.16 m | 29.0 |
| 6a | | 67.4 | | | | | | |
| 7 | | 163.4 | 1.32 m | 43.3 | 1.34 m, 1.59 m | 43.7 | 1.35 m, 1.60 m | 43.8 |
| 8 | 4.1–4.2 m | 60.6 | 4.62 m | 70.8 | 4.91 m | 71.0 | 4.88 m | 71.0 |
| 9 | 1.24 t, 7 | 14.0 | | 174.4[a] | | 168.8 | | 168.8 |
| 10 | 3.69 dq, 9.2, 7<br>3.55 dq, 9.2, 7 | 65.9 | 2.65 dd, 4.7, 15.0 | 39.7 | 4.75 dq, 8, 6.5 | 49.0 | 4.73 dq, 8, 6.5 | 49.0 |
| 11 | 1.13 t, 7 | 15.4 | 5.26 dd, 4.7, 8.4 | 49.0 | | 175.1 | | 175.1 |
| 12 | | | | 170.5[a] | 5.21 dd, 9, 8 | 56.7 | 5.20 dd, 9, 8 | 56.7 |
| 13 | | | 5.85 dd, 6.4, 10.2 | 55.5 | | 174.4 | | 174.4 |
| 14 | | | | 168.9 | 4.46 dq, 8, 7 | 45.9 | 4.47 dq, 8, 7 | 45.9 |
| 15 | | | 4.75 m | 45.8 | 2.95 dd, 15, 9<br>3.15 dd, 15, 8 | 32.7 | 2.95 dd, 15,<br>93.18 dd, 15, 8 | 32.5 |
| 16 | | | 1.12 d, 6.8 | 20.3 | | 133.0 | | 133.1 |
| 17 | | | 1.56 s | 18.5 | 7.29 d, 2 | 132.2 | 7.30 d, 2.0 | 132.1 |
| 18 | | | 0.81 d, 6.5 | 21.9 | | 85.1 | | 110.0 |
| 19 | | | 1.05 d, 6.3 | 19.0 | | 154.5 | | 151.4 |
| 20 | | | | 133.6 | 6.87 d, 9 | 116.1 | 6.95 d, 9 | 116.0 |
| 21 | | | 6.94 d, 8.3 | 127.1 | 7.05 dd, 9, 2 | 129.4 | 7.07 dd, 9, 2 | 129.5 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 22 | | 6.66 d, 8.3 | 115.6 | 1.14 d, 6.5 | 20.4 | 1.13 d, 6.5 | 20.4 |
| 23 | | | 155.7 | 1.49 s | 17.7 | 1.49 s | 17.7 |
| 24 | | 6.66 d, 8.3 | 115.6 | 0.86 d, 6.5 | 18.2 | 0.84 d, 6.5 | 18.2 |
| 25 | | 6.94 d, 8.3 | 127.1 | 1.24 d, 6.5 | 20.6 | 1.22 d, 6 | 20.5 |
| 26 | | 3.38 dd, 6.3, 15.2<br>3.24 dd, 10.5, 15.2 | 23.2 | 1.02 d, 6.5 | 18.7 | 1.02 d, 6.5 | 18.8 |
| 27 | | | 109.0 | 2.97 s | 30.7 | 2.96 s | 30.6 |
| 28 | | | 111.1 | 1.34 d, 7 | 18.8 | 1.33 d, 7 | 18.8 |
| 29 | | | 131.3 | | | | |
| 30 | | 7.24 d, 7.3 | 118.1 | | | | |
| 31 | | 7.13 dd, 7.3, 7.7 | 122.3 | | | | |
| 32 | | 7.10 dd, 7.3, 7.7 | 120.9 | | | | |
| 33 | | 7.56 brd, 7.3 | 110.6 | | | | |
| 34 | | | 136.1 | | | | |
| 35 | | 2.98 s | 30.8 | | | | |
| 36 | | 0.70 d, 6.9 | 17.8 | | | | |
| OH | 5.36 br | | | 6.27 s | | 6.29 s | |
| NH | 8.14 br | 6.63, 8.70 br | | 6.59 d, 8 | | 6.59 d, 8 | |
| NH | | 7.65 d, 8.4 | | 6.52 d, 8 | | 6.50 d, 8 | |

| | **262** (*159*) | | **263** (*159*) | | **264** (*159*) | | **265** (*159*) |
|---|---|---|---|---|---|---|---|
| | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ |
| 1 | | 170.8 | | 170.5 | | 170.5 | |
| 2 | 2.32 m | 42.3 | 2.42 m | 42.3 | 2.42 m | 42.3 | 2.4 m |
| 3 | 2.03 dd, 13.8, 3.6, 2.16 | 43.2 | 2.1 m | 43.2 | 2.1 m | 43.2 | 2.1 m |
| 4 | | 129.0 | | 130.6 | | no[a] | |
| 5 | 4.93 d, 8.8 | 129.5 | 4.99 d, 8.3 | 131.5 | 4.99 d, 8.7 | 131.4 | 4.99 d, 8.7 |
| 6 | 2.16 m | 28.9 | 2.21 m | 29.1 | 2.21 m | 29.1 | 2.21 m |

(*continued*)

TABLE II.
Continued.

| | **262** (*159*) | | **263** (*159*) | | **264** (*159*) | | **265** (*159*) |
|---|---|---|---|---|---|---|---|
| | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ |
| 7 | 1.36 m, 1.60 m | 43.6 | 1.40 m, 1.69 m | 43.5 | 1.40 m, 1.69 m | 43.5 | 1.40 m, 1.69 m |
| 8 | 4.88 m | 70.9 | 4.86 m | 71.4 | 4.86 m | 71.4 | 4.86 m |
| 9 | | 168.7 | | 168.2 | | no[a] | |
| 10 | 4.48 dq, 7.7, 7.1 | 49.0 | 4.51 dq, 8.0, 7.1 | 48.9 | 4.52 dq, 8.0, 7.1 | 48.9 | 4.52 dq, 8.0, 7.1 |
| 11 | | 175.1 | | 175.8 | | no[a] | |
| 12 | 5.21 dd, 9.0, 7.3 | 56.6 | 5.08 dd, 9.0, 6.8 | 57.6 | 5.09 dd, 9.0, 6.8 | 57.5 | 5.11 dd, 9.0, 6.8 |
| 13 | | 174.5 | | 169.9 | | 169.9 | |
| 14 | 4.75 dq, 6.3, 6.3 | 45.8 | 3.77 dd, 17.6, 3.8 4.16 dq, 17.6, 1 | 42.2 | 3.77 dd, 17.9, 3.2 4.16 dq, 17.9, 4.2 | 42.0 | 3.77 dd, 18, 3.24.16 dq, 18, 4.2 |
| 15 | 2.92 dd, 14.7, 9.0 3.17 dd, 14.7, 7.3 | 32.7 | 2.81 dd, 14, 6.8 3.25 dd, 14, 9 | 32.2 | 2.83 dd, 14, 6.8 3.26 dd, 14, 9 | 32.4 | 2.84 dd, 14, 6.7 3.26 dd, 14, 9 |
| 16 | | 133.0 | | 133.4 | | NA | |
| 17 | 7.15 d, 1.7 | 131.5 | 7.15 d, 1.7 | 138.4 | 7.32 d, 2.0 | 132.2 | 7.18 d, 2.0 |
| 18 | | 119.8 | | no[a] | | no[a] | |
| 19 | | 150.2 | | no[a] | | no[a] | |
| 20 | 6.93 d, 8.3 | 116.3 | 6.90 d, 8.3 | 115.1 | 6.94 d, 8.3 | 116.2 | 6.93 d, 8.3 |
| 21 | 7.01 dd, 8.3, 1.7 | 128.8 | 7.08 dd, 8.3, 1.7 | 130.7 | 7.06 dd, 8.3, 2 | 129.7 | 7.01 dd, 8.3, 2 |
| 22 | 1.15 d, 6.7 | 18.7 | 1.16 d, 6.7 | 18.5 | 1.16 d, 6.7 | 18.5 | 1.16 d, 6.7 |
| 23 | 1.51 3H | 17.6 | 1.53 d, 1 | 18.2 | 1.54 d, 1.2 | 18.2 | 1.5 d, 1.0 |
| 24 | 0.88 d, 6.6 | 20.4 | 0.90 d, 6.6 | 20.4 | 0.90 d, 6.7 | 20.4 | 0.91 d, 6.7 |
| 25 | 1.24 d, 6.3 | 20.5 | 1.25 d, 6.2 | 20.8 | 1.25 d, 6.2 | 20.7 | 1.25 d, 6.2 |
| 26 | 1.35 d, 7.1 | 18.2 | 1.30 d, 7.1 | 18.2 | 1.30 d, 7.1 | 18.2 | 1.30 d, 7.1 |
| 27 | 2.97 s | 30.5 | 2.94 s | 29.8 | 2.97 s | 29.7 | 2.93 s |
| 28 | 1.09 d, 6.7 | 18.7 | | | | | |
| OH | 5.5 s | | 5.3 s | | 5.46 s | | 5.46 s |

[a] not observed due to limited sample size

| | | | | |
|---|---|---|---|---|
| NH | 6.56 d, 7.7 | 6.60 d, 8 | 6.60 d, 8 | 6.60 d, 8 |
| NH | 6.46 d, 6.3 | 6.45 dd, 3.8, 1 | 6.44 dd, 3.8, 1 | 6.44 dd, 3.8, 1 |

| | **266** (*164*) | **267** (*161*) | | **268** (*161*) | | **271** (*164*) |
|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ + 5% DMSO-$d_6$ | $^{13}$C $CDCl_3$ + 5% DMSO-$d_6$ | $^{1}$H $CDCl_3$ + 5% DMSO-$d_6$ | $^{13}$C $CDCl_3$ + 5% DMSO-$d_6$ | $^{1}$H $CDCl_3$ |
| 1 | | | 175.0 | | 174.9 | |
| 2 | 2.46 m | 2.55 m | 40.1 | 2.56 m | 40.1 | 2.45 m |
| 3 | 2.55 dd, 4, 12<br>2.14 t, 12 | 2.36, 15.2, 11.4<br>1.95, 15.2, 2.0 | 40.9 | 2.35, 15.2, 11.4<br>1.94, 15.2, 2.0 | 40.9 | 2.54 dd, 4, 13<br>2.14, 12 |
| 4 | | | 133.6 | | 133.6 | |
| 5 | | 4.82, 9.6 | 128.4 | 4.82 9.6 | 128.3 | |
| 6 | 2.95 | 2.28 m | 29.2 | 2.28 m | 29.2 | ns[a] |
| 7 | 1.82 ddd, 3, 9, 15<br>1.61 ddd, 3, 11, 15 | 1.39, 13.6, 11.1, 4.7<br>1.18, 13.5, 9.4, 4.5 | 43.4 | 1.38, 13.6, 11.1, 4.7<br>1.19, 13.5, 9.4, 4.5 | 43.4 | 1.82 m, 1.60 m |
| 8 | 5.11 m | 4.64 m | 70.4 | 4.64 m | 70.4 | 5.11 m |
| 9 | | | 170.5 | | 170.5 | |
| 10 | 4.51 dq, 7, 7 | 2.68, 15.5, 4.5<br>2.59, 15.5, 6.6 | 40.2 | 2.69, 15.5, 4.5<br>2.60, 15.5, 6.6 | 40.0 | 4.50 dq, 7, 7 |
| 11 | | 5.25 m | 48.8 | 5.24 m | 48.8 | |
| 12 | 5.06 dd, 8, 9 | | 168.4 | | 168.4 | 5.06 dd, 8, 9 |
| 13 | | 5.38, 9.8, 6.7 | 56.8 | 5.40, 9.8, 6.7 | 56.7 | |
| 14 | 4.72 dq, 7 | | 174.1 | | 174.1 | 4.71 dq, 7, 8 |
| 15 | 3.12 dd, 8,<br>15 2.90 dd, 9, 15 | 4.75 m | 46.0 | 4.24 m | 45.0 | 3.13 dd, 8, 15<br>2.90 dd, 9, 15 |
| 16 | | 1.16, 7.0 | 20.2 | 1.16, 7.0 | 20.2 | |
| 17 | 7.45 d, 1 s | 1.60, 1.0 | 18.5 | 1.60, 1.0 | 18.5 | 7.25 d, 2 |
| 18 | | 0.86, 7.0 | 21.9 | 0.86, 7.0 | 21.9 | |
| 19 | | 1.09, 7.0 | 19.1 | 1.08, 7.0 | 19.1 | |

(*continued*)

TABLE II.
Continued.

| | **266** (*164*) | **267** (*161*) | | **268** (*161*) | | **271** (*164*) |
|---|---|---|---|---|---|---|
| | $^1$H $CDCl_3$ | $^1$H $CDCl_3$ + 5% DMSO-$d_6$ | $^{13}$C $CDCl_3$ + 5% DMSO-$d_6$ | $^1$H $CDCl_3$ + 5% DMSO-$d_6$ | $^{13}$C $CDCl_3$ + 5% DMSO-$d_6$ | $^1$H $CDCl_3$ |
| 20 | 6.88 d, 8 | | 130.8 | | 130.7 | 6.91 d, 8 |
| 21 | 7.04 dd, 1, 8 | 7.00, 8.5 | 127.1 | 7.01, 8.5 | 127.1 | 7.02 dd, 2, 8 |
| 22 | 1.15 d, 6 | 6.77, 8.5 | 115.6 | 6.87, 8.5 | 115.6 | 1.14 d, 7 |
| 23 | 5.90 s | | 156.6 | | 156.6 | 5.90 s |
| | 5.78 s | | | | | 5.78 s |
| 24 | 1.09 d, 7 | 6.77, 8.5 | 115.6 | 6.87, 8.5 | 115.6 | 1.09 d, 7 |
| 25 | 1.28 d, 6 | 7.00, 8.5 | 127.1 | 7.01, 8.5 | 127.1 | 1.28 d, 6 |
| 26 | 1.32 d, 7 | 3.18, 14.5, 5.7 | 31.7 | 3.19, 14.5, 5.7 | 31.9 | 1.31 d, 7 |
| | | 2.86, 14.5, 9.9 | | 2.88, 14.5, 9.9 | | |
| 27 | 2.97 s | | 129.6 | | 129.2 | 2.96 s |
| 28 | 1.04 d, 7 | 7.48, 2.3 | 138.7 | 7.26, 2.3 | 132.7 | 1.03 d, 7 |
| 29 | | | 84.2 | | 109.7 | |
| 30 | | | 155.2 | | 152.6 | |
| 31 | | 6.79, 8.5 | 115.1 | 6.85, 8.5 | 116.4 | |
| 32 | | 6.96, 8.5, 2.3 | 129.8 | 6.93, 8.5, 2.3 | 128.8 | |
| 33 | | 2.94 s | 30.3 | 2.92 s | 30.3 | |
| 34 | | 1.08, 7.0 | 18.2 | 1.06, 7.0 | 18.1 | |
| OH | | 9.12 s | | 8.85 s | | |
| OH | | 8.68 s | | 8.69 s | | |
| NH-10 | 6.35 d, 7 | 7.46, 8.3 | | 7.47, 8.3 | | 6.21 d, 7 |
| NH-14 | 6.19 d, 7 | 6.78, 8.5 | | 6.77, 8.5 | | 6.36 d, 8 |

| | **272** (*164*) | **273** (*164*) | | **274** (*164*) | **275** (*164*) | **276** (*164*) | |
|---|---|---|---|---|---|---|---|
| | $^{1}H$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{1}H$ $CDCl_3$ | $^{13}C$ $CDCl_3$ |
| 1 | | | 175.5 | | | | 177.6 |
| 2 | 2.46 m | 2.26 m | 42.4 | 2.28 m | 2.27 m | 2.40 m | 42.2 |
| 3 | 2.54 d, 12 | 2.17 m | 42.3 | 2.17 m | 2.16 m | 2.14 m | 43.2 |
| | NA | 1.98 dd, 3, 14 | | 1.98 dd, 3, 14 | 1.98 dd, 2, 12 | 2.04 m | |
| 4 | | | 132.9 | | | | 147 |
| 5 | | 4.87 d, 9 | 131.3 | 4.87 d, 9 | 4.87 d, 9 | 4.93 d, 9 | 131.2 |
| 6 | NA | 2.18 m | 29.3 | 2.18 m | 2.16 m | 2.16 m | 28.7 |
| 7 | NA | 1.63 ddd, 6, 8, 14 | 43.7 | 1.64 m | ns[b] | 1.56 m | 43.9 |
| | NA | 1.39 ddd, 4, 8, 14 | | 1.37 m | 1.37 m | 1.37 m | |
| 8 | 5.11 m | 4.94 m | 71.9 | 4.94 m | 4.93 m | 4.87 m | 70.6 |
| 9 | | | 169.8 | | | | 170.4 |
| 10 | 4.51 m | 4.43 dq, 7, 7 | 53.3 | 4.43 m | 4.43 m | 4.5 dq, 7, 8 | 48.8 |
| 11 | | | 168.9 | | | | 168.4 |
| 12 | 5.06 m | 5.26 dd, 7, 9 | 56.9 | 5.27 dd, 7, 9 | 5.28 dd, 7, 9 | 5.16 dd, 8, 9 | 57.1 |
| 13 | | | 174.6 | | | | 171.3 |
| 14 | 4.71 m | 4.71 dq, 4, 9 | 45.8 | 4.71 quint, 7 | 4.72 quint, 6 | 4.71 m | 52.8 |
| 15 | 3.14 m | 3.19 dd, 7, 15 | 32.5 | 3.22 dd, 7, 15 | 3.22 dd, 7, 15 | 3.17 dd, 8, 15 | 32.2 |
| | 2.90 m | 2.89 dd, 9, 15 | | 2.91 dd, 9, 15 | 2.93 dd, 9, 15 | 2.88 dd, 9, 15 | |
| 16 | | | 130.3 | | | | 130.1 |
| 17 | 7.12 s | 7.46 d, 2 | 138.2 | 7.27 d, 2 | 7.13 d, 2 | 7.46 d, 2 | 138 |
| 18 | | | 85 | | | | 85.3 |
| 19 | | | 154.0 | | | | 154.1 |
| 20 | 6.91 d, 8 | 6.86 d, 8 | 115.1 | 6.91 d, 8 | 6.91 d, 8 | 6.88 d, 8 | 114.9 |
| 21 | 6.98 d, 8 | 7.03 dd, 2, 8 | 130.4 | 7.03 dd, 2, 8 | 7.03 dd, 2, 8 | 7.05 dd, 2, 8 | 130.1 |
| 22 | 1.14 d, 7 | 1.12 d, 7 | 19 | 1.12 d, 7 | 1.13 d, 7 | 1.16 d, 7 | 18.8 |
| 23 | 5.90 s 5.79 s | 1.45 s | 17.8 | 1.45 s | 1.45 s | 1.49 s | 17.7 |

(*continued*)

TABLE II.
Continued.

| | **272** (*164*) | **273** (*164*) | | **274** (*164*) | **275** (*164*) | **276** (*164*) | |
|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ |
| 24 | 1.09 d, 7 | 0.86 d, 7 | 20.5 | 0.86 d, 7 | 0.87 d, 7 | 0.88 d, 7 | 20.4 |
| 25 | 1.28 d, 6 | 1.24 d, 6 | 20.8 | 1.23 d, 6 | 1.23 d, 6 | 1.23 d, 6 | 20.5 |
| 26 | 1.31 d, 7 | 3.97 dd, 4, 11<br>3.81 dd, 4, 11 | 63.1 | 3.97 dd, 4, 11<br>3.82 dm, 4, 11 | 3.97 dd, 4, 11<br>3.82 dm, 4, 11 | 1.32 d, 7 | 18.1 |
| 27 | 2.96 s | 2.97 | 30.7 | 2.97 s | 2.97 s | 3.03 s | 30.9 |
| 28 | 1.03 d, 7 | 1.08 d, 7 | 18.5 | 1.09 d, 7 | 1.09 d, 7 | 3.54 br | 65.2 |
| NH-10 | 4.51 m | 7.00 d, 8 | | 6.99 d, 8 | 6.98 d, 7 | 6.45 d, 7 | |
| NH-14 | 6.37 d, 8 | 6.44 d, 6 | | 6.43 d, 6 | 6.44 d, 6 | 6.67 br | |

| | **277** (*164*) | **278** (*164*) | **269** (*162*) | | **270** (*163*) | | **280** (*167*) | |
|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H DMSO-$d_6$ | $^{13}$C DMSO-$d_6$ |
| 1 | | | | 175.2 | | 169.7 | | |
| 2 | 2.41 m | 2.39 m | 2.23 m | 42.1 | 2.47 m | 42.0 | | 132.0 |
| 3 | 2.10 m, 2.04 m | 2.10 m, 2.05 m | 1.98 m, 2.06 m | 42.5 | 2.10 m | 43.3 | | 136.3 |
| 4 | | | | 133.5 | | 130.5 | | 136.3 |
| 5 | 4.93 d, 9 | 4.97 d, 9 | 4.86 d, 8.5 | 132.0 | 4.99 d, 8.5 | 131.6 | | 132.0 |
| 6 | 2.15 m | 2.19 m | 2.06 m | 29.0 | 2.21 m | 29.1 | 4.57 t, 6.0 | 47.2 |
| 7 | 1.56 m, 1.37 m | 1.70 m, 1.41 m | 1.30 m, 1.60 m | 43.6 | 1.78 m, 1.40 m | 43.3 | 2.97 t, 6.0 | 37.1 |
| 8 | 4.87 m | 4.88 m | 4.78 sextet, 7 | 71.7 | 4.84 sextet, 6.4 | 71.5 | | 132.8 |
| 9 | | | | 170.0 | | 168.5 | 6.89 d, 8.0 | 134.7 |
| 10 | 4.45 m | 4.53 dq, 7, 8 | 4.25 dd, 6, 9 | 58.6 | 4.43 dd, 8.7, 7.0 | 58.4 | 6.58 d, 8.0 | 120.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 11 | | | | 169.5 | | 175.9 | | 161.2 |
| 12 | 5.17 dd, 7, 10 | 5.11 dd, 7, 9 | 5.18 t, 7 | 57.2 | 5.13 dd, 9.8, 6.4 | 57.8 | 6.58 d, 8.0 | 120.4 |
| 13 | | | | 174.7 | | 169.5 | 6.89 d, 8.0 | 134.7 |
| 14 | 4.79 m | 4.15 dd, 4, 18 | 4.67 quin, 6.5 | 46.8 | 4.15 dd, 18.3, 4.1 | 41.9 | | 189.7 |
| | | | | | 3.19 dd, 18.3, 3.4 | | | |
| 15 | 3.18 dd, 7, 15 | 3.24 dd, 9, 14 | 2.82 dd, 14.5, 8 | 32.2 | 3.25 dd, 13.2, 9.0 | 32.7 | | 132.8 |
| | 2.91 dd, 10, 15 | 2.81 dd, 7, 14 | 3.08 dd, 14.5, 8 | | 2.80 dd, 13.2, 6.1 | | | |
| 16 | | | | 130.5 | | 133.2 | 7.62 4H, s | 138.9 |
| 17 | 7.27 d, 2 | 7.50 d, 2 | 7.42 d, 2 | 138.8 | 7.53 d, 2.0 | 138.6 | | 116.1 |
| 18 | | | | 86.2 | | 85.5 | | 159.9 |
| 19 | | | | 154.5 | | 154.0 | | 116.1 |
| 20 | 6.92 d, 8 | 6.89 d, 8 | 6.82 d, 8 | 115.1 | 6.90 d, 8.5 | 115.2 | 7.62 4H, s | 138.9 |
| 21 | 7.03 dd, 2, 8 | 7.07 dd, 2, 8 | 7.01 d, 8 | 131.0 | 7.10 dd, 8.5, 2.0 | 130.9 | | 136.0 |
| 22 | 1.16 d, 7 | 1.14 d, 7 | 1.09 d, 6.5 | 18.5 | 1.17 d, 6.8 | 18.8 | 7.00 4H, s | 139.3 |
| 23 | 1.49 s | 1.49 s | 1.46 s | 17.7 | 1.56 s | 17.8 | | 116.2 |
| 24 | 0.86 d, 6 | 0.89 d, 7 | 0.79 d, 6.5 | 20.5 | 0.90 d, 6.8 | 20.5 | | 154.6 |
| 25 | 1.23 d, 6 | 1.26 d, 6 | 1.16 d, 6.5 | 20.6 | 1.25 d, 6.4 | 20.8 | | 116.2 |
| 26 | 1.32 d, 7 | 3.91 dm, 8, 3.75 m | 1.98 m | 32.0 | 1.99 m | 31.5 | 7.00 4H, s | 139.3 |
| 27 | 3.03 s | 2.93 s | 2.97 s | 30.5 | 2.96 s | 29.7 | | 136.0 |
| 28 | 3.54 br | | 1.04 d, 6.5 | 18.8 | 0.79 d, 6.5 | 18.1 | 7.00 4H, s | 139.3 |
| 29 | | | 0.75 d, 6.5 | 17.8 | 0.75 d, 6.5 | 18.1 | | 116.2 |
| 30 | | | 0.77 d, 6.5 | | | | | 154.6 |
| 31 | | | | | | | | 116.2 |
| 32 | | | | | | | 7.00 4H, s | 139.3 |
| 33 | | | | | | | | 189.7 |
| 34 | | | | | | | | 132.8 |
| 35,39 | | | | | | | 7.62 4H, s | 138.9 |
| 36,38 | | | | | | | | 116.1 |
| 37 | | | | | | | | 159.9 |
| NH-10 | 6.46 d, 8 | 6.6 d, 8 | | | 6.42 d, 8.8 | | | |
| NH-14 | 6.68 br | 6.45 dd, 4, 1 | | | 6.64 t, 3.4 | | | |

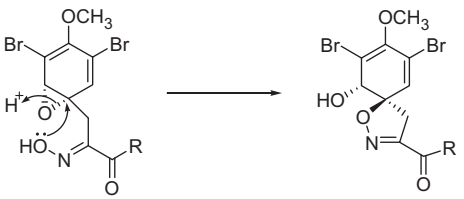
(*continued*)

TABLE II.
Continued.

| | **282** (*167*) | | **283** (*167*) | | | **281** (*168*) | | **284** (*168*) | |
|---|---|---|---|---|---|---|---|---|---|
| | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3$ | $^{13}$C $CDCl_3$ | | $^{1}$H $CD_3OD$ | $^{13}$C $CDCl_3$ | $^{1}$H $CDCl_3 + CD_3OD$ | $^{13}$C |
| 2 | | 170.0 | | 170.0 | 2,5 | | 131.2 | | 166.6 |
| 3 | | 122.6 | | 122.6 | 3,4 | | 128.0 | | 135.2 |
| 4 | | 122.6 | | 122.4 | 6,6′ | | 186.0 | | 124.9 |
| 5 | | 170.0 | | 170.0 | 7,7′ | | 129.0 | 7.75 | 136.2 |
| 6 | 3.58 t, 6 | 40.0 | 3.85 t, 6 | 40.0 | 8,8′ | 8.00 s | 136.1 | | 114.2 |
| 7 | 2.90 t, 6 | 34.0 | 2.90 t, 6 | 34.0 | 9,9′ | | 114.0 | | 153.7 |
| 8 | | 129.5 | | 129.5 | 10,10′ | | 162.6 | | 114.2 |
| 9,13 | 7.10 d, 8 | 130.0 | 7.10 d, 8 | 128.9 | 11,11′ | | 114.0 | 7.75 | 136.2 |
| 10,12 | 6.85 d, 8 | 115.5 | 6.85 d, 8 | 115.0 | 12,12′ | 8.00 s | 136.1 | | |
| 11 | | 155.0 | | 153.1 | 13,13′ | | 131.2 | | |
| 14 | | 132.9 | | 132.5 | 14,14′ | 7.40 | 135.9 | | |
| 15,19 | 7.60 s | 133.3 | 7.63 | 133.0 | 15,15′ | | 112.2 | | |
| 16,18 | | 110.2 | | 109.0 | 16,16′ | | 153.5 | | |
| 17 | | 152.8 | | 154.0 | 17,17′ | | 112.2 | | |
| 20 | | 132.9 | | 132.5 | 18,18′ | 7.40 | 135.9 | | |
| 21,25 | 7.60 s | 133.3 | 7.62 | 132.8 | NH | 8.31 s | | | |
| 22,24 | | 110.2 | | 118.2 | | | | | |
| 23 | | 152.8 | | 156.2 | | | | | |
| 26 | | | 3.94 s | 61.0 | | | | | |

TABLE III.
Selected $^1$H-NMR Data of Bastadin Tetra-*O*-methyl Ethers (*130*).

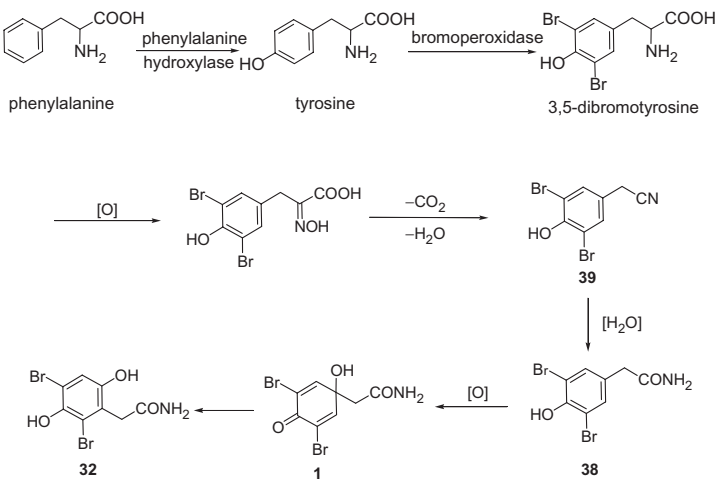
| Parent bastadins | -4 (**208**) | -5 (**209**) | -6 (**210**) | "Isobastadin 6" | -8 (**212**) | -9 (**213**) | -11 (**215**) | -12 (**216**) | -13 (**217**) | -14 (**218**) | 15 (**219**) | 19 (**223**) | 20 (**224**) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $\delta$ of MeO | 4.01 | 4.02 | 4.06 | 4.08 | 4.02 | 4.05 | 4.01 | 4.05 | 4.04 | 4.10 | 4.03 | 4.04 | 4.00 |
| groups | 4.01 | 3.98 | 4.03 | 4.04 | 4.01 | 4.00 | 4.01 | 4.01 | 4.01 | 4.05 | 4.01 | 4.01 | 3.92 |
| ($CDCl_3$) | 4.01 | 3.94 | 4.02 | 4.02 | 3.97 | 3.90 | 3.93 | 3.89 | 3.81 | 4.03 | 3.89 | 3.91 | 3.91 |
| | 4.01 | 3.52 | 3.61 | 3.92 | 3.70 | 3.49 | 3.92 | 3.87 | 3.48 | 3.83 | 3.73 | 3.61 | 3.72 |




**288**

Quite surprisingly, the first attempt to demonstrate the conversion of tyrosine into bromotyrosine derivatives was unsuccessful (*175*). In that experiment, *Verongia aerophoba* failed to incorporate radioactivity from {U–$^{14}$C}-L-tyrosine into aerothionin (**68**), aeroplysinin-1 (**14**) and the dienone **1.** Inactive aerothionin (**68**) was also isolated when the sponge was fed with {U–$^{14}$C}-L-ornithine and {$CH_3$–$^{14}$C}methionine. However, the sponge utilized these amino acids for the synthesis of fatty acids. A very slow rate of biosynthesis might account for these results.

By using liposome-enclosed precursors and modified culture conditions, which allowed the sponge to survive in the laboratory for as long as 2 weeks, Rinehart's group demonstrated the conversion of phenylalanine and tyrosine to the dienone **1**, as well as the rearranged product dibromohomogetisamide (**32**), by the sponge *Aplysina fistularis* in 1981 (*176*). In addition to implying that the sponge can convert phenylalanine to tyrosine (*177*), the comparable radioactivity found in **1** and **32** supports the hypothesis (*26*) that **32** is formed from **1** via a skeletal rearrangement analogous to the mammalian catabolism of tyrosine to homogentisic acid. Although the enzymatic mechanism of the side chain migration is still unclear (*178*), the conversion of 4-hydroxy-2,5-cyclohexadienone-4-acetic acid to homogentisic acid in aqueous alkali has been demonstrated (*179*). Double labeling studies also revealed that the sponge can convert the side chain in phenylalanine to the acetamide side chain in **32** without deamination. In addition to corroborating the known occurrence of bromophenol nitriles and oximes in Verongid sponges, this work supported the following biosynthetic pathway:

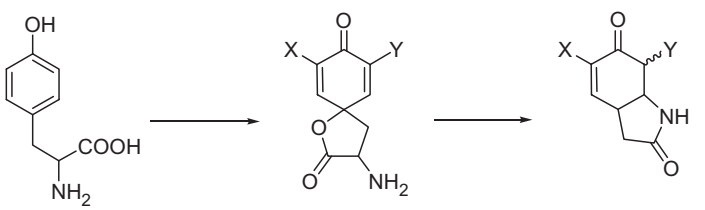



Moreover, it has been demonstrated that α-oximino acids undergo facile dehydration/decarboxylation to give nitriles *in vitro* (*180*) and *in vivo* (*181*),

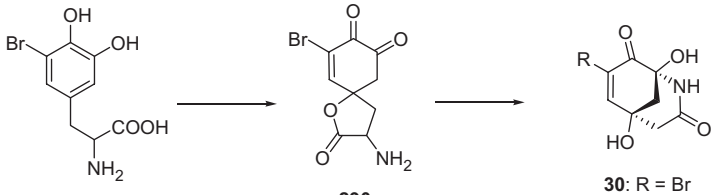
that **1** was converted to **32** (*182*), and that (4-hydroxyphenyl)pyruvic acid oxime was isolated from *Hymeniacidon sanguinea* (*183*), further supporting the proposed mechanism.

Carney and Rinehart reported the results of additional feeding experiments in the marine sponge *Aplysina fistularis* in 1995 (*184*). {U–$^{14}$C}-L-tyrosine, {U–$^{14}$C}-L-3-bromotyrosine, and {U–$^{14}$C}-L-3,5-dibromotyrosine were incorporated into both the dienone **1** and aeroplysinin-1 (**14**), and {methyl-$^{14}$C}-methionine was specifically incorporated into the *O*-methyl group of aeroplysinin-1. In contrast to expectations, tyrosine was incorporated more efficiently than 3-bromotyrosine, which is in turn incorporated more efficiently than 3,5-dibromotyrosine. This may result from the bulky bromines interfering with the permeability of the precursors across cell membranes. It was surprising that {methyl-$^{14}$C}-L-methyltyrosine, {methyl-$^{14}$C}-L-3,5-dibromo-*O*-methyltyrosine, 3-bromo-4-hydroxybenzyl cyanide, and 3,5-dibromo-4-hydroxybenzyl cyanide were not incorporated into the dienone **1** and aeroplysinin-1 (**14**). Both 3-bromo-4-hydroxybenzyl cyanide and 3,5-dibromo-4-hydroxybenzyl cyanide have been identified as metabolites of *A. fistularis* (*185*), and their involvement as a potential precursor to the dienone **1** seems reasonable. The possible reasons for the lack of incorporation into **1** and **14**, aside from the possibility of their not being part at the biosynthetic path, are poor transport of the halogenated nitriles across cell membranes, or poor solubility of the nitriles in sea water (*184*).

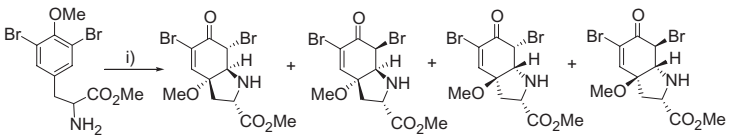
Although, from the above feeding experiments, it is clear that the Verongida bromotyrosine derivatives are biogenetically derived from tyrosine, it is still a matter of debate whether these alkaloids are produced via an arene oxide, or through phenol oxidative coupling (*186*). Based on the isolation of the racemic verongiaquinols, (±)-3-bromoverongiaquinol (**10**) and (±)-3-bromo-5-chloroverongiaquinol (**11**), and the low enantiomeric pure cavernicolins, 5-bromocavernicolin (**24**) (*23*) and 5-chlorocavernicolin (**25**), D'Ambrosio *et al*. (*9*) proposed a phenol oxidative (*187*) route based upon tyrosine precursors for their formation, since the proposal of an arene epoxide as a biogenetic precursor demands enantiomerically pure **11** and **10**. In fact, natural products derived from phenol oxidations occur in nature in both optically active forms or as racemates, or even in nearly racemic forms (*188*). One way to rationalize the formation of the cavernicolins in full respect of the classical *ortho–para* orientation rules for the oxidative coupling of phenolic compounds (*188*) is to postulate a racemic or nearly racemic spirolactone **289** as the intermediate derived from the halotyrosine precursor (*9*). There is, in fact, ample precedent for cyclohexadienone spirolactone in oxidative couplings of phenols (*188*). Hydrolysis of the lactone, followed by conjugate attack of the amino acid *N*-atom and decarboxylative oxidation may then be seen to lead to the cavernicolins (*9*).




7-Bromocavernicolenone (**30**) and 7-chlorocavernicolenone (**31**) may be biogenetically derived from 5-bromodopa undergoing a similar pathway (*24,25*).



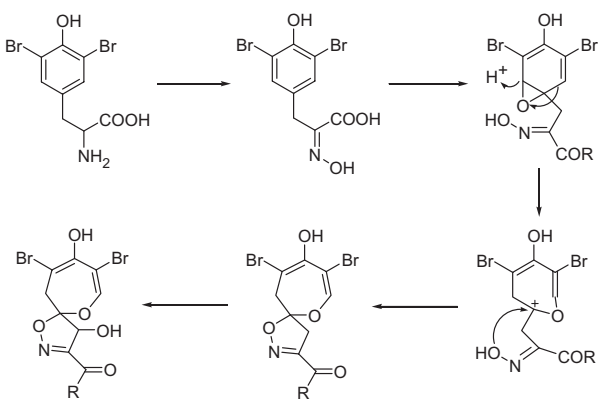

Anodic oxidation of 3′,5′-dibromo-4′-methoxyphenylalanine methyl ester led to the cavernicolin model compounds as four possible stereoisomers (*189,190*). This may constitute a new model for the biogenesis of the carvernicolins as an alternative to a spirolactone route from oxidation of amino-protected tyrosines




i) 0.1 mol dm-3 $LiClO_4$ in MeOH, 10 V, 25–30 mA, 3 hr, r.m. 25% yield.

## B. BIOGENESIS OF THE PSAMMAPLYSINS

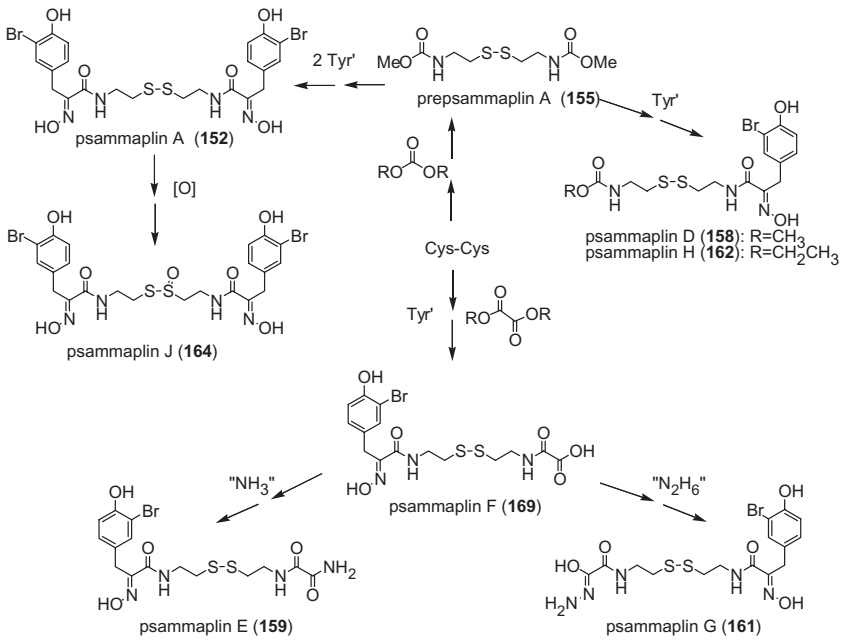
Biogenesis of the psammaplysins may proceed through an oximino epoxide as shown in the scheme below (*94*). The epoxide ring opening leads to ring enlargement and results in the spiro[4.6]dioxazundecane. The benzene oxide-oxepin pathway, first adumbrated on theoretical grounds by Vogel and Günther, (*191*) was experimentally demonstrated through the biosynthesis of aranotin by Neuss *et al.* (*192,193*).



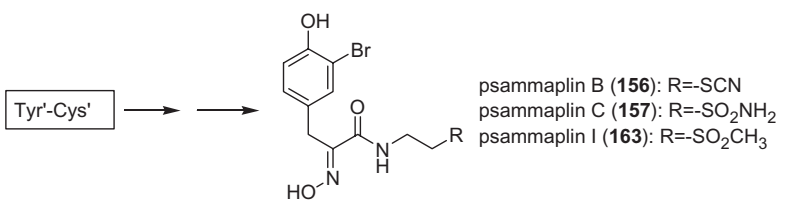

## C. BIOSYNTHESIS OF PSAMMAPLIN TYPE OF COMPOUNDS

Crews *et al.* proposed a biogenetic pathway, based on the isolation of prepsammaplin A (**155**), to rationalize the formation of psammaplin A (**152**) and other bromotyrosine derivatives isolated from *Pseudoceratina purea* by his group (*110, 112*). A straightforward dimerization of a rearranged cysteine (Cys′ = HS–$CH_2$–$CH_2$–NHCOOMe) could generate prepsammaplin A (**155**). Condensation of the dimer

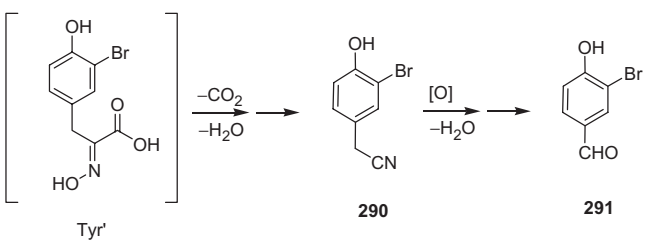
**155** with either one or two functionalized tyrosine groups (Tyr′ = the bromo oxime derivative) could rationalize the formation of psammaplins A (**152**), D (**158**), and H (**162**), respectively. Likewise, cysteine can lead to psammaplin F (**160**), which is envisioned to be the precursor of psammaplin E (**159**) and psammaplin G (**161**). Oxidation of psammaplin A (**152**) (possibly by a cytochrome P450 reaction) provides a connection to psammaplin J (**164**). The two esterified psammaplins D (**158**) and H (**162**) may be artifacts of the isolation derived from the acid formed via condensation of cysteine and tyrosine.




Similarly, condensation of the functional tyrosine (Tyr′) and the rearranged cysteine (Cys′) could generate psammaplins B (**156**), C (**157**), and I (**163**).




Modified tyrosine (Tyr′) is also the logical precursor of alkaloids **290** and **291.**

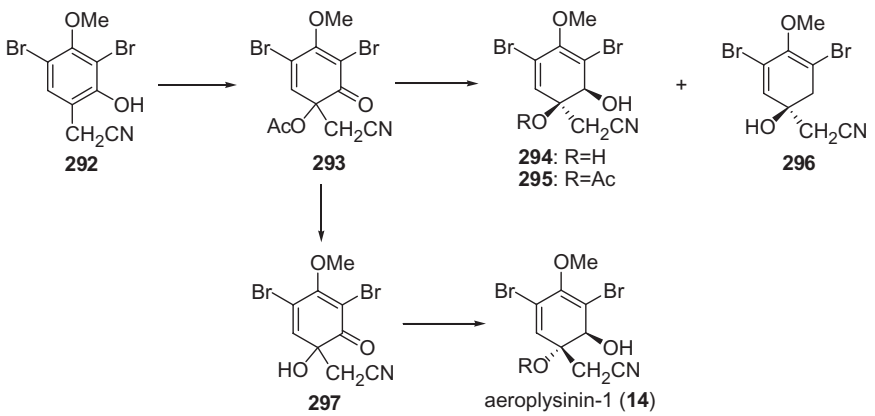


## V. Synthesis

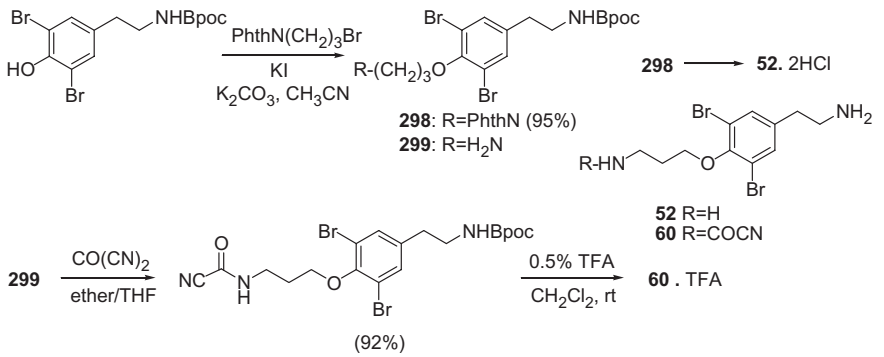
The diverse and unique chemical structures, and the variety of biological activities of bromotyrosine derivatives, make them ideal synthetic targets for synthetic and natural products chemists. Studies on the synthesis of bromotyrosine can be traced back to 1912 (*194*). In former studies, degradation, chemical transformation to known compounds, or even total synthesis were conducted for the purpose of verifying the structures. Later studies were focused on the total synthesis of more complex structures, such as the spirocyclohexadienylisoxazoline and bastadin ring systems.

### A. SYNTHESIS OF SMALL BROMOTYROSINE DERIVATIVES

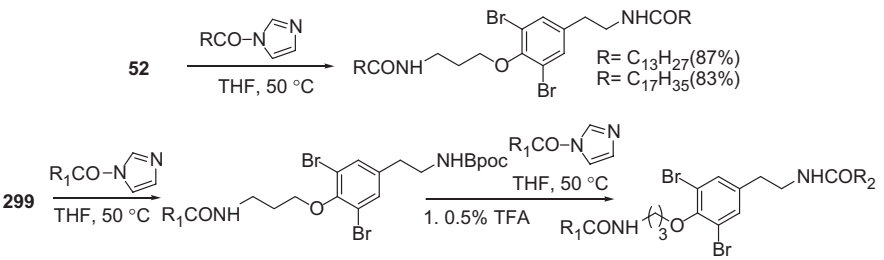
Synthesis of functionalized cyclohexadienones, dienols, and dienediols was studied, which may be useful for the synthesis of some bromotyrosine derived dienones or ketals (*195*). Andersen and Faulkner reported the synthesis of aeroplysinin-1 (**14**). 3,5-Dibromo-2-hydroxy-4-methoxyphenylacetonitrile (**292**) was oxidized with excess lead tetraacetate in acetic acid at 25°C for 18 h to obtain the dienone **293** in 35% yield. Reduction of **293** with sodium borohydride in absolute ethanol at 0°C gave three products: isoaeroplysinin-1 (**294**) (40%), the corresponding monoacetate **295** (18%), and 2-deoxyaeroplysinin-1 (**296**) (22%). The failure to obtain a *trans*-diol was attributed to the influence of the acetoxy function. The dienone **293** was therefore transformed to the corresponding keto alcohol **297** by transesterification in methanol containing *p*-toluenesulfonic acid. Reduction of the keto alcohol **297** with sodium borohydride in absolute ethanol at 0°C for 10 min gave aeroplysinin-1 in 60% yield (**14**). This synthesis of aeroplysinin-1 (**14**) and isoaeroplysinin-1 (**294**) constitutes a novel approach to the synthesis of arene glycols and has the added advantage in that both *cis*- and *trans*- glycols can be prepared stereospecifically (*196*).



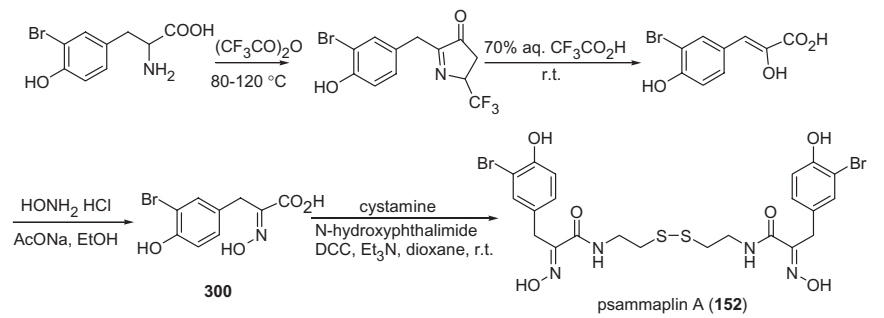

Ganem *et al*. synthesized ceratinamine (**60**), moloka'iamine (**52**), and mololipids (**53**), together with several analogues, for antifouling, anti-HIV and cytotoxicity studies (*197–199*).




Mololipids can be produced smoothly by the direct dualacylation of moloka'i-amine (**52**) with myristoyl, stearoyl, and oleoyl imidazoles or the step-wise acylation of a protected precursor with different fatty acyl groups (*198*).

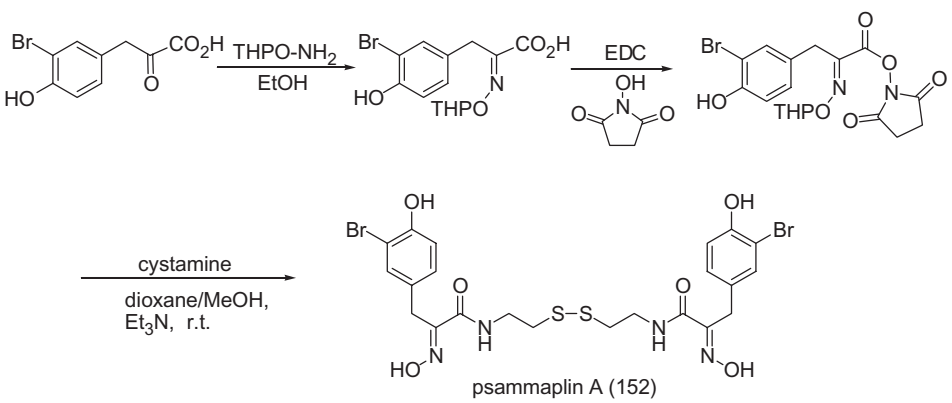



Hoshino *et al.* reported a convenient method to synthesize psammaplin A (**152**) (*200*). As for a synthetic strategy, direct coupling of the phenolic oxime-acid **300** with cystamine was considered, because **300** could be readily prepared from 3′-bromotyrosine. After several attempts to couple **300** directly with cystamine, a mixture of **300** (1.0 eq.) and free cystamine (0.5 eq.) in dioxane containing one equivalent of $Et_3N$, DCC and *N*-hydroxyphthalimide was stirred at room temperature for 12 h to afford, after purification using column chromatography, psammaplin A (**152**) in 67% yield.

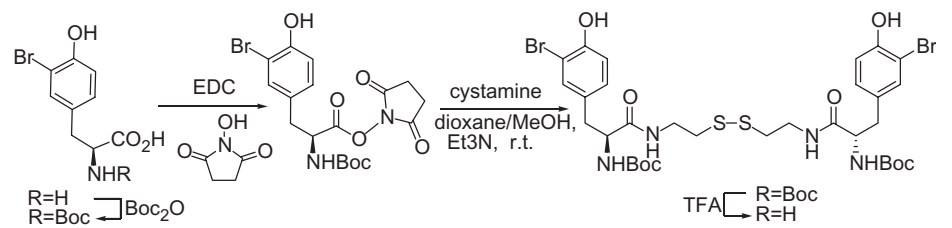



Inspired by the structure of psammaplin A (**152**), a combinatorial scrambling strategy for the construction of heterodimeric disulfide analogues was developed and applied to the construction of a 3828-membered library starting from 88 homodimeric disulfides (*201*). The disulfide motif was utilized as a readily exchangeable linkage (*202*),

which would allow rapid construction of a heterodimeric analogue library suitable for defining structure–activity relationships (*203*). It is well-precedented that disulfide bonds will readily undergo facile exchange reactions with other disulfides in high yield under mild conditions (*204*). For example, if two homodimeric disulfides, A-SS-A and B-SS-B, are mixed under basic conditions in the presence of a suitable catalyst they will undergo rapid exchange reactions to afford a statistical mixture of three disulfides: A-SS-A, A-SS-B, and B-SS-B in a ratio of 1:2:1, respectively. Hoshino's synthesis of psammaplin A (*200*) was modified as shown in the following scheme to synthesize 44 homodimeric psammaplin A analogues.



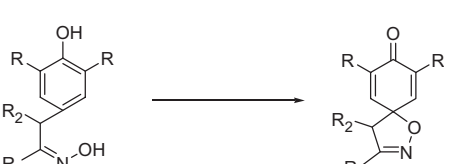

Amino acid homodimeric disulfide analogues were prepared using the following scheme.




Additional sulfonamide analogues and amide analogues were synthesized by standard techniques. Finally, 43 homodimeric disulfide building blocks were obtained from commercial sources in order to enhance the library's structural diversity. The disulfide exchange reaction in $DMSO/H_2O$ (3:1) by adding catalytic amounts of dithiothreitol was reproducible and led to a statistical mixture. Solution phase combinatorial synthesis of the psammaplin A (**152**) analogue library was conducted in 88 96-well plates. The disulfide products could be screened directly from the reaction mixture since the catalyst, dithiothreitol, and the byproduct *trans*-1,2-dithiane-4,5-diol did not show any detectable antibacterial activity at a concentration which was 50-fold greater than the concentration at which either of these compounds would be in the screen mixture. After screening, six structurally distinct psammaplin analogues from this library demonstrated higher antibacterial activity than psammaplin A (*201*).

## B. SYNTHESIS OF SPIROCYCLOHEXADIENYLISOXAZOLINE

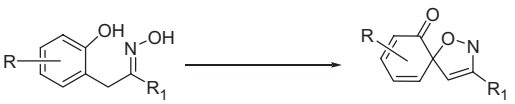
The unique spirocyclohexadienylisoxazoline ring system of the bromotyrosine derivatives, such as aerothionin (**68**), aerophobin-1 (**69**), and fistularin 3 (**79**), and their wide range of bioactivities make them attractive targets for synthesis. A number of studies on the formation of the spiroisoxazoline through intramolecular oxidative cyclization of a phenolic oxime have been reported (*205*). Forrester *et al*. examined the reactions of oxime **301** with different oxidizing reagents including lead tetra-acetate, potassium ferricyanide, silver oxide, sodium periodate, Fremy's salt, and manganese tris(acetylacetonate) (*206, 207*). Of these, the manganese reagent was found to be the most effective oxidant, and gave the spiroisoxazoline **302** in fair yields of 19–62%. Oxidation with lead tetra-acetate did give the corresponding spiroisoxazolines, but in a much lower yield of 10%, while potassium ferricyanide, silver oxide, sodium periodate, and Fremy's salt failed to effect cyclization of the phenolic oximes. In a subsequent study, the same researchers showed that oxidation of **301** (R = H, $R_1 = CO_2Me$) with bromine water resulted in both electrophilic bromination and spirocyclization to give **302** (R = Br, $R_1 = CO_2Me$) in 65% yield, while use of NBS with **301** (R = *t*-Bu, $R_1$ = Me) gave **302** (R = *t*-Bu, $R_1$ = Me) in 72% yield (*208*). Similarly, Boehlow *et al*. reported that addition of one equivalent of NBA to the oxime **301** (R = H, $R_1 = CO_2Et$) in THF at −60°C gave the monobromide **301** (R = 3-mono-Br, $R_1 = CO_2Et$, 60%). Addition of two equivalents of NBA to the oxime **301** (R = H, $R_1 = CO_2Et$) in THF or DMF at 0°C gave the dibromide **301** (R = 3,5-di-Br, $R_1 = CO_2Et$, 69%), and three equivalents at 0°C cleanly produced the spiroisoxazoline **302** (R = 3,5-di-Br, $R_1 = CO_2Et$, 74%) (*209*). Treatment of the oxime **301** (R = H, $R_1 = CO_2Et$) with Furia's bromoperoxidase enzyme mimic (*210*) of $NH_4VO_3$, $H_2O_2$, and KBr in water/chloroform resulted in the formation of both the monobromide **301** (R = 3-mono-Br, $R_1 = CO_2Et$) and dibromide **301** (R = 3,5-di-Br, $R_1 = CO_2Et$) without forming the spiroisoxazoline (*209*). Yamamura reported that oxidation of **301** (R = Br, $R_1 = CO_2Me$) with thallium (III) nitrate in methanol gave a mixture of products, which included 7–11% of **302** (R = Br, $R_1 = CO_2Me$) (*211*). Intriguingly, the same transformation could be carried out in quantitative yield by anodic oxidation (*211*). Kacan *et al*. reported phenyliodine (III) bis(trifluoroacetate) as an efficient reagent for the intramolecular oxidative cyclization. A series of oximes **301** (R = H, Br, $R_1$ = Me, Et, $CMe_3$, $C_6H_5$, $CO_2Et$, 4-$BrC_6H_4$) reacted with phenyliodine (III) bis(trifluoroacetate) in acetonitrile at 0 °C smoothly and rapidly to give the corresponding isoxazolines **302** in good to excellent yield (*212*). Application of this procedure to an *ortho*-phenolic oxime resulted in the formation of the [4 + 2] dimer of the initially formed spiroisoxazoline.




**301** **302**

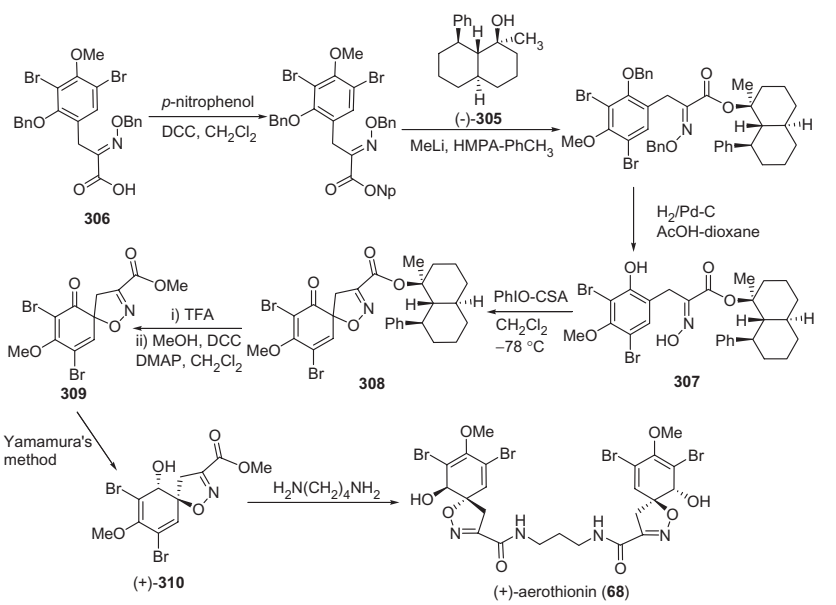
Cyclization of the *ortho*-phenolic oxime has also been studied. Forrester *et al*. found that of all the oxidants they examined, only tetrabromocyclohexa-2,5-dienone would convert **303** (R = 2,4-di-*t*Bu, $R_1$ = Me) into **304** (R = 2,4-di-*t*Bu, $R_1$ = Me) in 20%

yield (*208*). An equally low yield of 27% was obtained by Yamamura, on oxidation of **303** (R = 2,4-di-Br, 3-OMe, $R_1$ = COOMe) to **304** (R = 2,4-di-Br, 3-OMe, $R_1$ = COOMe) with thallium trifluoroacetate in trifluoroacetic acid (*213*). Application of the above phenyliodine (III) bis(trifluoroacetate) to the *ortho*-phenolic oxime resulted in the direct formation of the [4 + 2] dimer of the initially formed spiroisoxazoline (*212*). Independently, Murakata *et al.* found that the hypervalent iodine compound phenyliodium diacetate (PIDA) was an efficient cyclization reagent of *o*-phenolic oxime-esters and oxime-amides (*214*). The cyclization of various oximes **303** (R = mono-, di-bromo, H, OMe, $R_1$ = OMe, O$^t$Bu, NH$(CH_2)_3$OMe) in acetonitrile at 0°C proceeded smoothly to afford the spiroisoxazoline in good yield.



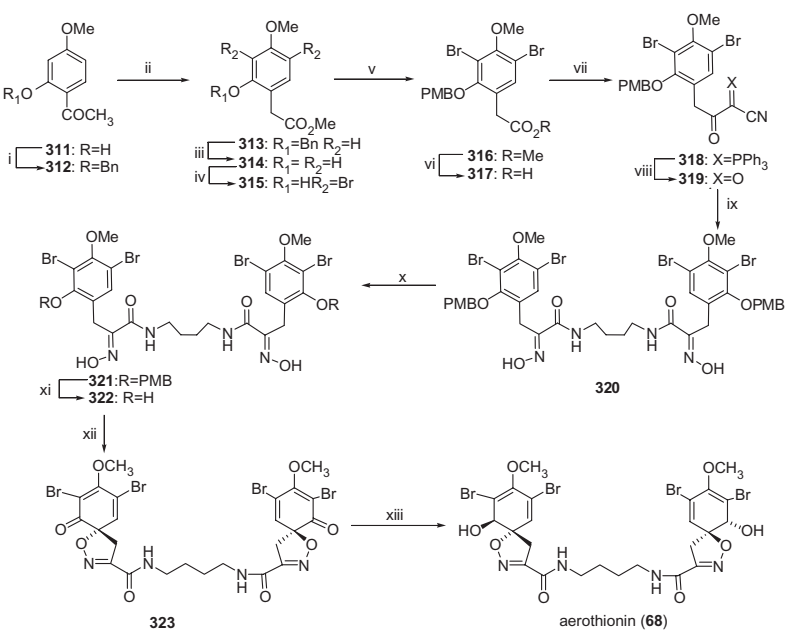

**303** **304**

Asymmetric oxidative cyclization of *o*-phenolic oxime-esters was also studied by Murakata *et al.* (*215*). A novel, optically active tertiary alcohol (−)-**305** was synthesized as a chiral auxiliary. The *ortho*-phenolic oxime **306** was first transformed to the oxime ester **307** in three steps (see the following scheme). The reaction of **307** with PhIO in the presence of camphor sulfonic acid (CSA) in $CH_2Cl_2$ at −78°C proceeded smoothly to afford the spiroisoxazoline **308** in 83% yield with 70–80% estimated diastereomeric excess by the $^1$H NMR spectrum. The chiral auxiliary in **308** was removed by treatment with TFA at room temperature. Methylation using DCC and MeOH gave methyl ester (−)-**309** ($[\alpha]_D$ −56.4°) in 74% *ee* with the *S*-configuration. Optically active spiroisoxazoline **309** was reduced with $Zn(BH_4)_2$ to give cyclohexadienylisoxazoline (+)-**310**, amidation of which with butanediamine afforded (+)-aerothionin ($[\alpha]_D$ + 166°) with the *S*-configuration.



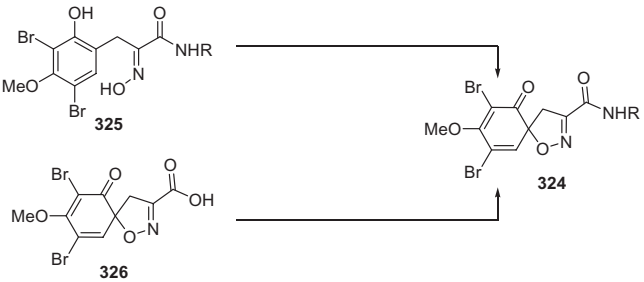
With the key spiroisoxazoline synthon in hand, total synthesis of some spirocyclohexadienylisoxazoline bromotyrosine derivatives was achieved. Forrester *et al*. reported that reducing tetradehydroaerothionin using $NaBH_4$ did not yield the natural *trans*, *trans*-aerothionin, but *cis*,*cis*-aerothionin (*216*). Yamamura *et al*. reduced the spiroisoxazoline **309** using excess $Zn(BH_4)_2$ in $CH_2Cl_2$–$Et_2O$ (3:2) to give the corresponding *cis*- and *trans*-isomers **310** in 29% and 40% yields, which were easily separated on preparative TLC (*217, 213*). Mixing *trans*- **310** with 1,4-butanediamine, 1,5-pentanediamine, or histamine, at room temperature overnight afforded aerothionin (**68**), homoaerothionin (**69**), and aerophobin-1 (**113**) in 18, 4.4, and 82% yields, respectively.

Wasserman *et al*. developed an efficient methodology for the formation of key $\alpha$-keto amido residues common to many members of this family of natural products (*218–221*). Using this method, the $\alpha,\beta$-diketo nitrile **319** was synthesized from the oxidation of the ylide **318** (*222*). The generation of **318** from 2-hydroxy-4-methoxyacetophenone (**311**) was accomplished according to the sequence outlined in the following scheme by protecting the phenolic hydroxyl as the benzyl ether **312**, rearrangement with $Ti(NO_3)_3$ to **313**, deprotection to **314**, and bromination to form dibromide **315**. Following reprotection to **316** and hydrolysis of the ester to the acid **317**, coupling with $Ph_3P{=}CHCN$ in the presence of EDCI yielded **318**. After the ylide **318** was oxidized by $O_3$ to the labile diketonitrile **319**, generation of the bis-$\alpha$-ketoamide **320** took place on treatment of **319** with 1,4-diaminobutane in $CH_2Cl_2$. Conversion of **320** to the oxime **321** and deprotection provided the substrate **322**, which underwent the oxidative cyclization with tetrabromocyclohexadienone to afford **323** in 71% yield. Reduction of **323** with $NaCNBH_3$ in TFA gave the desired *trans*,*trans*-aerothionin (**68**) (*222*).

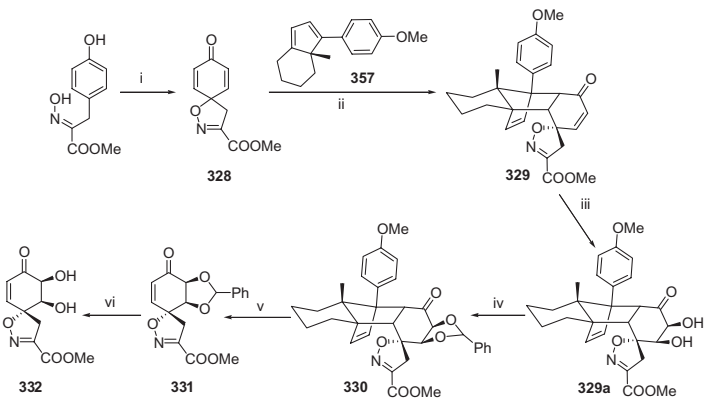



(i) BnBr, $K_2CO_3$, acetone; (ii) $Tl(NO_3)_3$, MeOH, 76%; (iii) $H_2$, Pd/C, MeOH, 96%;(iv) $Br_2$, pyr. 90%; (v) PMBCl,$K_2CO3$, acetone, 93%; (vi) 2N NaOH, MeOH, 94%; (vii) $Ph_3P{=}CHCN$, EDCI, $CH_2Cl_2$, 88%; (viii) $O_3$, $CH_2Cl_2$; (ix) 1,4-diaminobutane, $CH_2Cl_2$, 64% (two steps); (x) $NH_2OHHCl$, NaOAc, EtOH, 95%;(xi) TFA, $CH_2Cl_2$, 92%;(xii) tetrabromocyclohexadienone, $CH_3CN$, 70%; (xiii) $NaCNBH_3$, TFA, 25%.

Murakata *et al*. synthesized the cyclohexadienonespiroisoxazoline amides **324**, which could be useful as intermediates for the synthesis of araplysillin I (**99**) and II (**100**) (*223*). The synthesis of these metabolites was efficiently achieved using two routes. The first route is direct cyclization of *o*-phenolic oxime-amide **325** with phenyliodonium diacetate (PIDA) to produce **324**. The second is the amidation of the cyclohexadienonespiroisoxazoline-acid **326** to afford **324**.




Based on the enantioselective cycloaddition of the optically pure cyclopentadiene (**4**) with spirolactone (*224*,*225*), Winterfeldt *et al*. synthesized enantiomerically pure spiroxazoline **332**, which is the crucial intermediate en route to the agelorins (**87**, **88**) and their analogues (*226*). Face selectivity was successfully achieved in the cycloaddition of cyclopentadiene **327** and spiroxazoline **328** to form the enantiopure **329**. This may be due to the lower spatial demand of an oxygen atom than a methylene group. Flash-hydroxylation of **329** with ruthenium tetraoxide afforded *cis*-diol **329a**, which underwent pyrolysis after it was transformed into the acetal **330** to generate the spirocyclohexenone **331**. Subsequently, hydrolysis afforded the enantiopure intermediate **332**, representing the agelorins (**87**, **88**) chromophore (*226*).



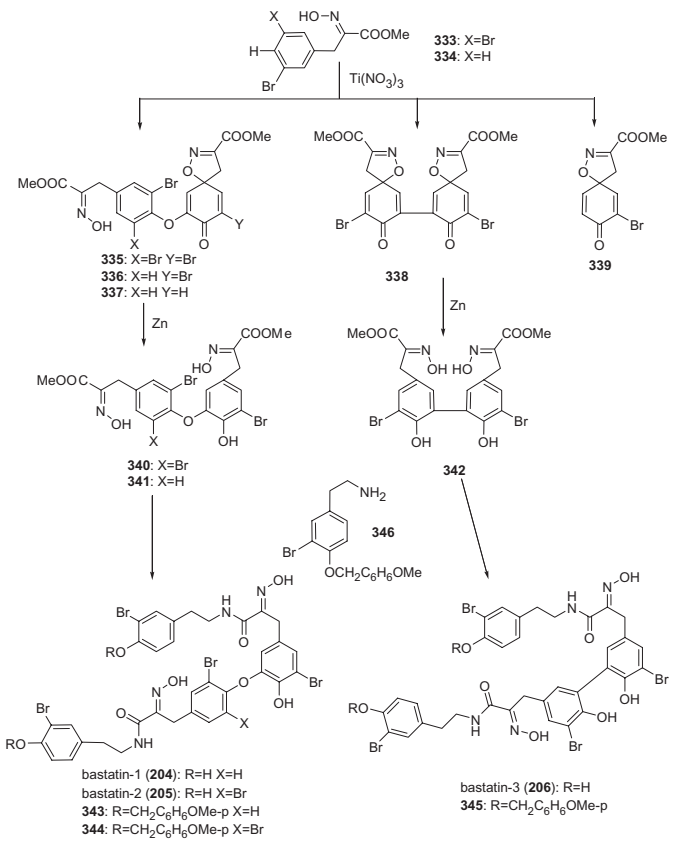

i) PIFA, $CH_3CN$; ii) 6.5 kbar, $CH_2Cl_2$ (78%); iii) $RuCl_3$, NaIO4, $EtOAc/CH_3CN/H_2O$, 0 °C (89%); iv) α,α'-dimethoxytoluene, *p*-TsOH, $CH_3CN$ (90%); v) 300 °C, $1x10^{-2}$mbar (69%);vi) 2 N HCl, aq. acetone (72%).

In a continuing report, several enantiopure spiroisoxazoline amides were prepared using the above method and tested on an isoxazoline-splitting enzyme, which is involved in an injury-induced defense reaction of the sponge *Aplysina cauliformis* (*227*). The results indicated that the bromoatoms in the cyclohexenone moiety are important for enzyme binding, while the presence of the N–H bond of a monoalkylamide turned out to be mandatory for ring fission.

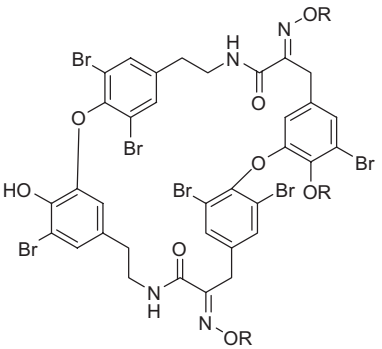
Boehlow *et al.* summarized the approach to the synthesis of some spirocyclohexadienylisoxazoline and oxime bromotyrosine derivatives and synthesized two oxime bromotyrosine derivatives verongamine (**139**) and purealidin N (**150**) (*205*).

## C. SYNTHESIS OF BASTADINS

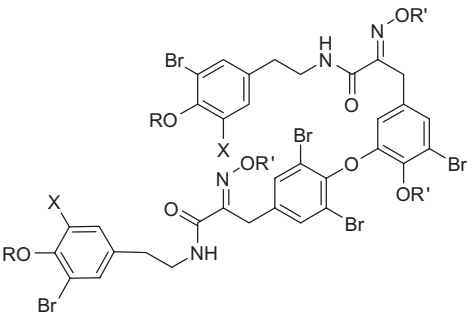
Yamamura's group reported the total synthesis of bastadins 1, 2, 3, and 6 (*228,229,230*). Biomimetic oxidation of methyl 3,5-dibromo-4-hydroxyphenylpyruvate oxime (**333**) was carried out using $Ti(NO_3)_3$ to afford 7–11% of spiroisoxazole **339** and 37–44% of the dimeric spiroisoxazole **335**. Reduction of **335** gave the biphenyl ether **340**, as a key intermediate for bastadins-2 synthesis, in almost quantitative yield (*228*). Similarly, on oxidation with thallium trifluoroacetate in trifluoroacetic acid containing a small amount of $CH_2Cl_2$, methyl 3-bromo-4-hydroxyphenylpyruvate oxime (**334**) was converted into three spiroisoxazoles [**339** (7%), **336** (6%), and **337** (5%)] and a plausible compound **338**, which was directly reduced with Zn powder to the biphenyl compound **342** in 8% overall yield. Zn reduction of **336** afforded the biphenyl ether **341** in 48% yield. The biphenyl ether (**341**, **340**, and **342**) was reacted with excess amounts of 3-bromotyramine *p*-methoxybenzyl ether **346** (60°, 3–4 days) to give the desirable diamide (**343**, **344**, and, **345**), which gave the corresponding bastadins-1, -2, and -3 after deprotection (*230*).



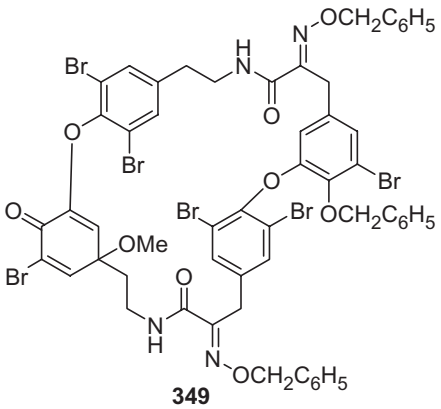
Bastadin-6 can be produced by phenolic oxidation of the corresponding acyclic precursor, bastadin-2 (*229*). Bis-*p*-methoxybenzyl bastadin-2 (**344**) was converted to tribenzyl bastadin-2 (**347**), which was further treated with $Br_2$ to afford dibromobastadin-2 tribenzyl ether (**348**). Under the same procedure, **348** was oxidized with $Ti(NO_3)_3$ to afford two macrocyclic dienones (**349** and **350**). Compound **349** was reduced with Zn to give the tribenzyl ether **351**. Finally, **351** was subjected to hydrogenlysis, using Pd black to afford bastadin-6 (*229*). Bastadin-6 trimethyl ether was produced in a similar procedure (*231*).



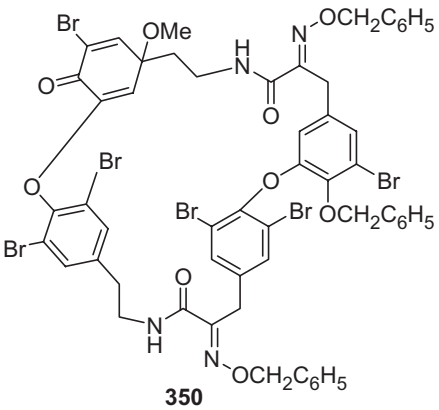
bastadin-6 (**210**): R=H
**351**: R=$CH_2C_6H_5$



**344**: R=$CH_2C_6H_6$OMe-p R'=H X=H
**347**: R=H R'=$CH_2C_6H_6$OMe-p X=H
**348**: R=H R'=$CH_2C_6H_6$OMe-p X=Br



**349**

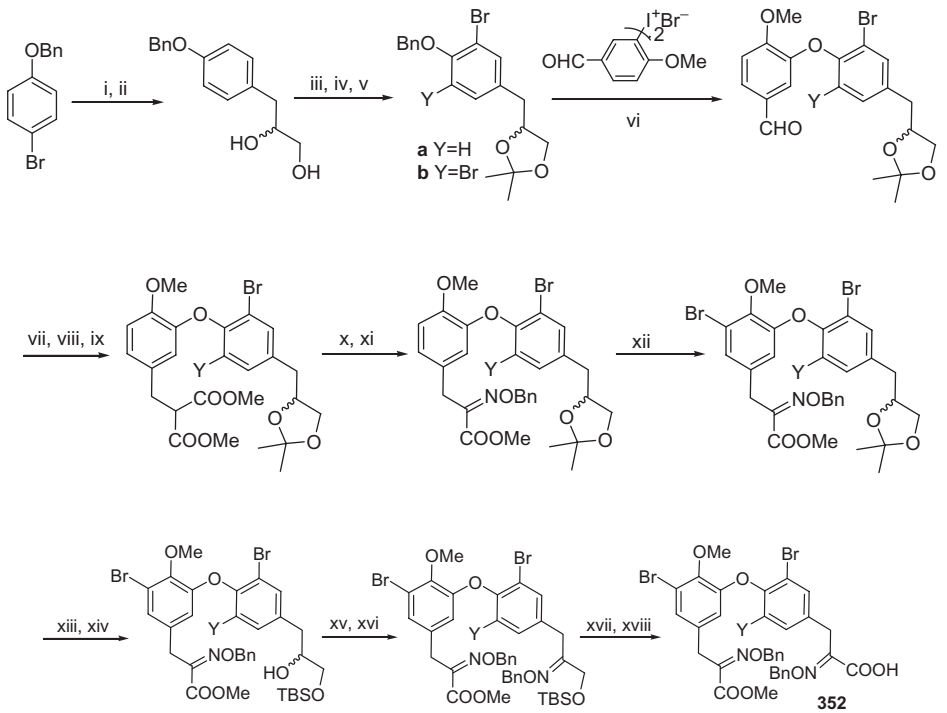


**350**

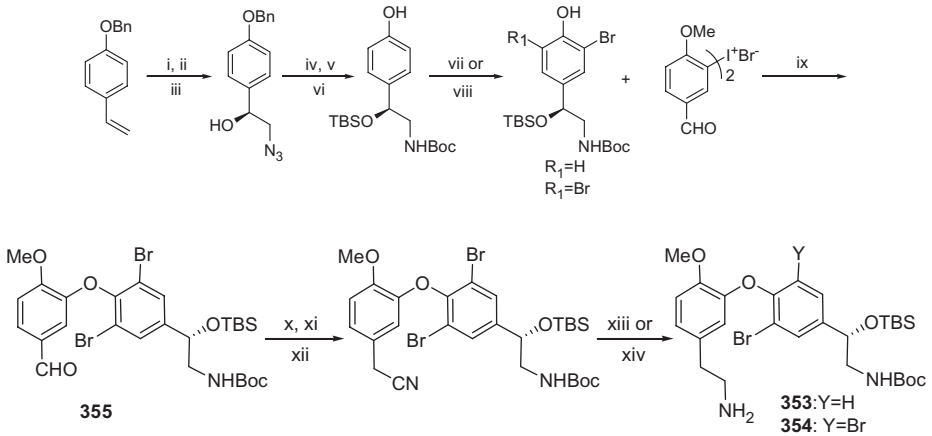
Guo *et al*. developed a chemoenzymatic strategy for the synthesis of bastadins-2, -3, and -6 (*232*). The requisite dimeric dityrosine and isodityrosine were successfully prepared by C–C and C–O oxidative phenolic coupling of mono- and dihalogenated derivatives of tyrosine and tyramine using horseradish (*233*) and soybean peroxidases.

By carefully controlling the experimental conditions, the required synthons were prepared in synthetically useful yields without the exhaustive protection and deprotection of the sensitive functional groups. This mode of oxidative coupling may represent the biogenetic synthetic route for bastadins, which is, the isodityrosine and isodityromine are formed via the coupling of dihalogenated tyrosine and tyramine derivatives.

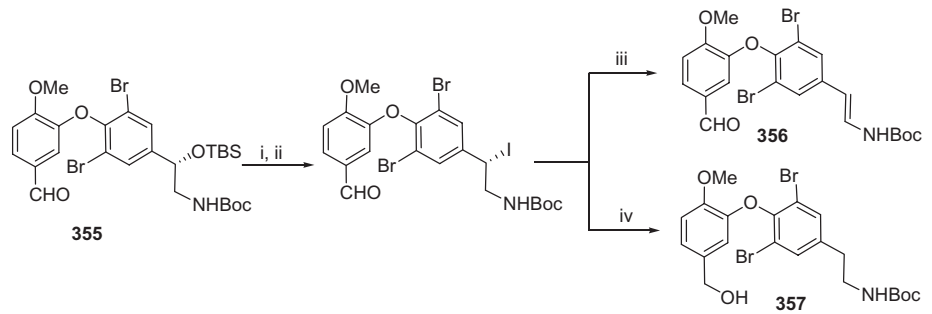
Couladouros and Moutsos reported a general synthetic route for the synthesis of the eastern and western parts of bastadins, which can be used for construction of bastadins 4–16 (*234–236*). The brominated biaryl ethers are synthesized using the iodonium salt method. The eastern segment **352** was synthesized within 18 steps in 15.5% overall yield. The western segment **353** and **354**, which can be used to construct bastadins-8 (**212**), -10 (**214**), -12 (**216**), and -17 (**221**), was synthesized in 13 steps (see the following scheme).




(i) Mg, THF, reflux, allyl bromide 93%; (ii) $K_2OsO_2(OH)_2$, *tert*-BuOH/$H_2O$, $K_3Fe(CN)_6$, $K_2CO_3$, rt, 99%; (iii) 2.2-dimethoxypropane, acetone, PPTS, rt, 95%; (iv) $H_2$, AcOEt, 10% Pd/C, rt, 99%; (v) NBS, DMF, rt, 87% for **a**, 92% for **b**; (vi) NaH, DMF, 90 oC, 76% from **a**, 78% from **b**; (vii) NaBH4, MeOH/THF, rt, 95%; (viii) I2, $Ph_3P$, imidazole, rt, 90%; (ix) $NaCH(COOMe)_2$, $Et_2O$, rt, 85%; (x) BuONO, MeONa, MeOH, 0 °C, 85%; (xi) BnBr, NaH, DMF, rt, 87%; (xii) NBS, $CH_3CN$, 50 °C, 85%; (xiii) HCl 1N, THF, rt, 100%; (xiv) TBSCl, imidazole, DMF, rt, 97%; (xv) TEMPO, NaOCl, acetone, KBr, NaHCO3, 0 °C, 85%; (xvi) $BnONH_2HCl$, pyridine/EtOH, 100 °C, 92%; (xvii) TBAF, THF, rt, 100%; (xviii) TEMPO, NaOCl, acetone, KBr, $NaHCO_3$, 0 °C, 78%.

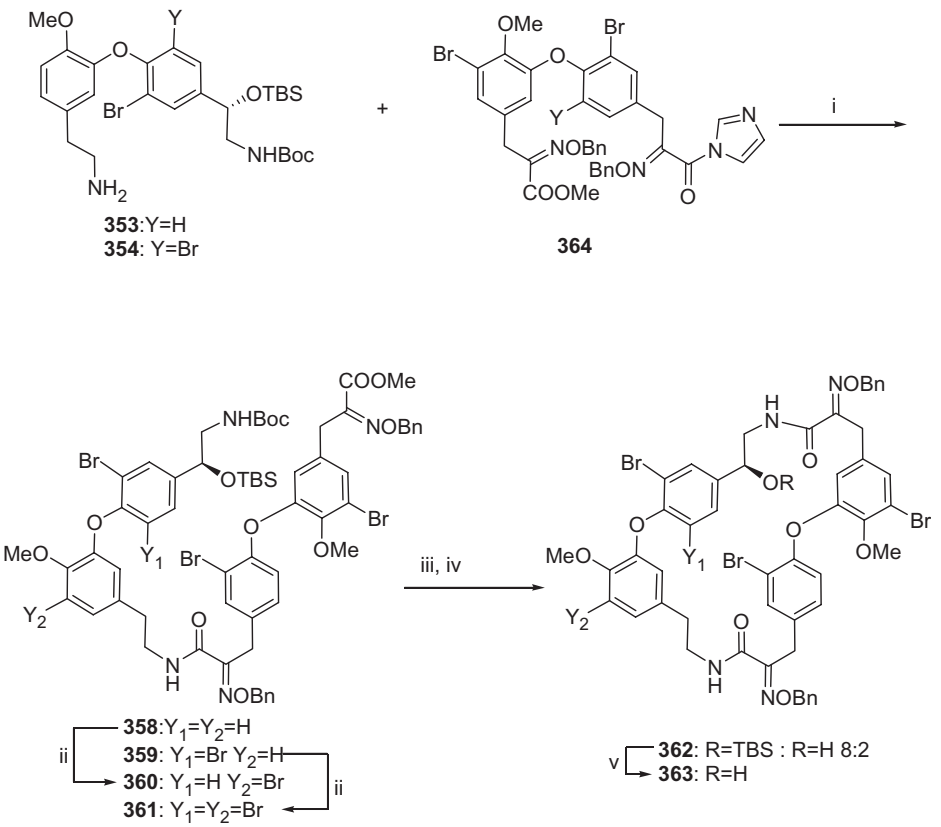



In order to utilize the hydroxyl group as a general precursor for all functionalities present at C-5 and C-6 of the bastadins, **355** was transformed after desilylation either to alkene **356** or alkane **357** using DBU or $NaBH_4$, respectively, providing the necessary intermediates for the construction of bastadins-4 to -7 (**208**–**211**), -9 (**213**), -11 (**215**), and -14 to -16 (**218**–**220**).



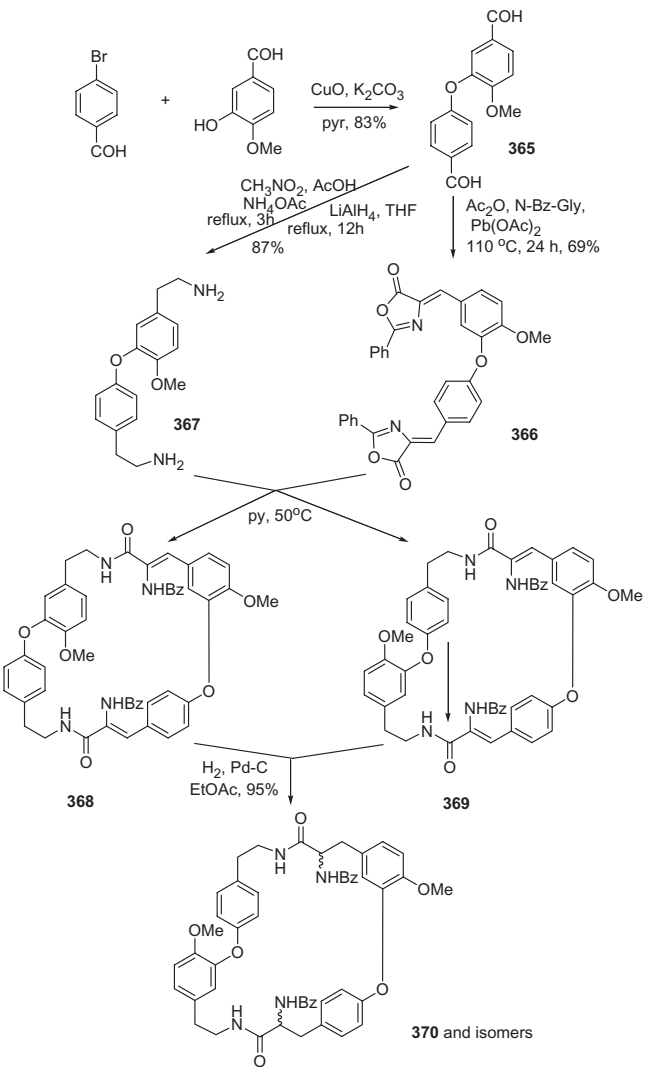

(i) TBAF, THF, rt, 98%; (ii) $I_2$, $Ph_3P$, imidazole, THF, rt, 90%; (iii) DBU, THF, rt, 85%;(iv)NaBH4, THF/MeOH, rt, 62%.

Having the western and eastern parts of the molecule, the synthesis of the cyclic skeleton of bastadins was attempted. In order to study the efficiency of macrolactamization, four protected amino acids (**358**, **359**, **360**, and **361**) were used as advanced intermediates. Several experiments revealed that these amino acids could be synthesized in good yields through the coupling of imidazolide **364** with primary amines **353** or **354**. Subsequently, these open bastadin precursors could be selectively brominated at $Y_2$ position with TBS (*237*). The terminal amino and carboxylic acid were unmasked followed by *in situ* cyclization using EDC and *N*-hydroxybenzotriazole to afford a mixture of bastadin precursor **362** and its desilylated analog **363**. The mixture was treated with TBAF providing compound **393** in 67% yield from the precursor **361**. Compound **363** is protected bastadin-12, which possesses the unsymmetrical bromination pattern and asymmetric hydroxyl group.

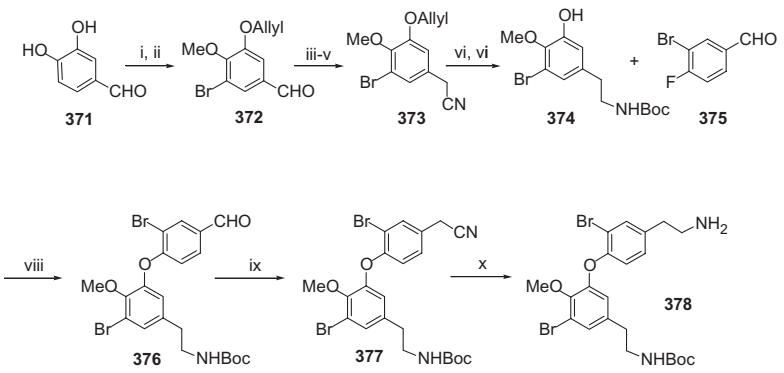



Scheme Synthesis of fully protected bastadin-12. (i) THF, 65% (**358**), 67% (**359**); (ii) NBS, $CH_3CN$, 80 °C, 75% (**360**), 78% (**361**); (iii) LiOH. 3N/MeOH/THF, rt, 95%; (iv) TFA/CH2Cl2, rt, 30 min then EDC, HOBt, DMF, 67%; (v) TBAF, THF, rt, 98%.

Bailey and Molinski presented a convergent strategy that allows the rapid assembly of isodityrosine-isodityrosine cyclic analogues of bastadin-5 in four steps from a common precursor, dialdehyde **365**, by exploiting a tandem Erlenmeyer condensation – macrolactamization (*238*). Dialdehyde **365**, prepared by Ullmann coupling of commercially available 3-hydroxy-4-methoxybenzaldehyde with 4-bromobenzaldehyde, was treated with *N*-benzoylglycine to obtain **366**. Diamine **367** was readily prepared from **365** by double Henry condensation-elimination followed by reduction of the resultant bis-$\beta$-nitrostyrene. Heating **366** and **367** in pyridine (50°C) resulted in the regioisomeric 28-membered macrocycles bastarane **368** and isobastarane **369** as a 1:1 mixture with a 30% combined yield. Hydrogenation of the mixture of **368** and **369** provides the isodityrosine cyclic peptide **370** as a mixture of isomers in 20–26% overall yield.

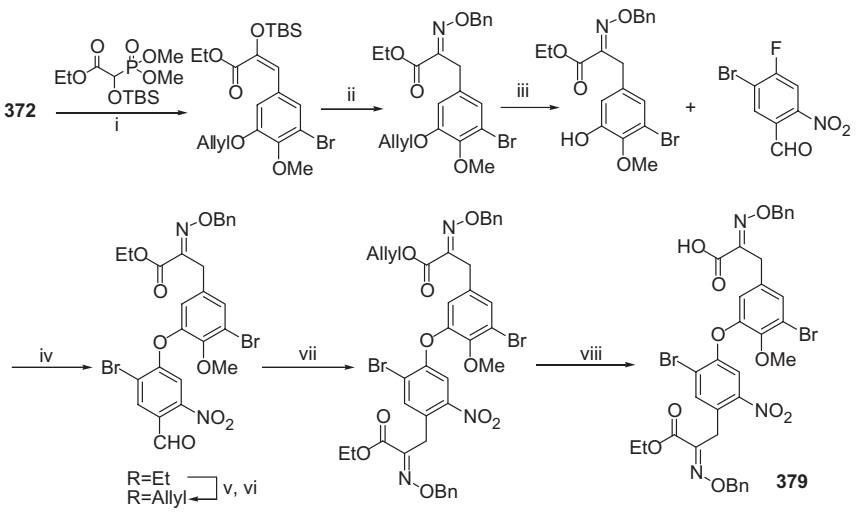



In order to gain control of the regiochemistry of the ring closure, Bailey and Molinski proposed an intermolecular $S_NAr$ strategy to synthesize the unsymmetrical bastadin-5 analog **382** (*239*). Bromination of catechol **371** followed by two sequential directed alkylations gave the differentially protected benzaldehyde **372**, which was converted into phenylacetonitrile **373** in three steps. Reduction of **373** and simultaneous removal of the *O*-allyl protecting group was achieved in one step to give the expected phenethylamine, which was immediately protected as the *N*-Boc compound **374**. Intermolecular $S_NAr$ substitution of **374** with 3-bromo-4-fluorobenzaldehyde (**375**) afforded aldehyde **376** in high yield (88%). Repetition of the homologation sequence on **376** (reduction-halide displacement-cyanide displacement) afforded **377** followed by nitrile reduction to give the monoprotected western diamine **378** (55% from **375**).

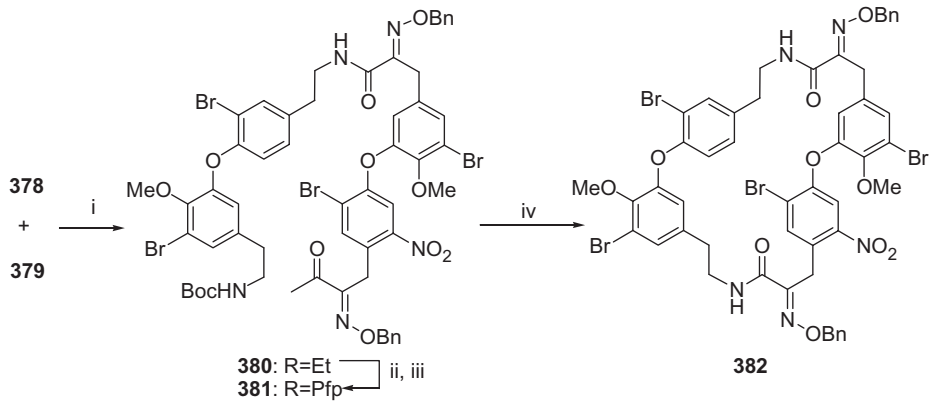



i) $Br_2$, HOAc, 92%; ii) MeI, $Li_2CO_3$, DMF, 4h, then allyl Br, $K_2CO_3$, 2h, 82%; iii) $NaBH_4$, MeOH, 0 °C, 30 min; iv) *n*-$Bu_3P$, $CCl_4$, 0 °C; v) $Bu_4NCl$, NaCN, $CH_2Cl_2$:$H_2O$ (10:1 v/v), 89%; vi) $BH_3$·THF, THF, reflex, 6h then HCl/MeOH, reflux, 2h; vii) $Et_3N$, pH 8, $(BOC)_2O$, MeCN, 4h, 78%; viii) $K_2CO_3$, DMF, 5h, 88%; ix) repeat iii), iv), v) 91%; x) $BH_3$·THF, THF, 0 °C, 10h, 98%.

The eastern hemisphere intermediate **379** was also prepared from **372**, using a Horner–Emmons strategy for step-wise extension of each carboxyaldehyde group to the corresponding $\alpha$-ketoxime (see the following scheme). The western diamine **378** and the eastern acid **379** were coupled to give the protected teracycle **380** in 78% yield. Compound **380** was transformed to the activated pentafluorophenol (Pfp) ester **381**, which underwent the macrolactamization upon removal of the *N*-Boc group to give the product **382**. The overall yield of **382** from **371** was 16% (16 steps).



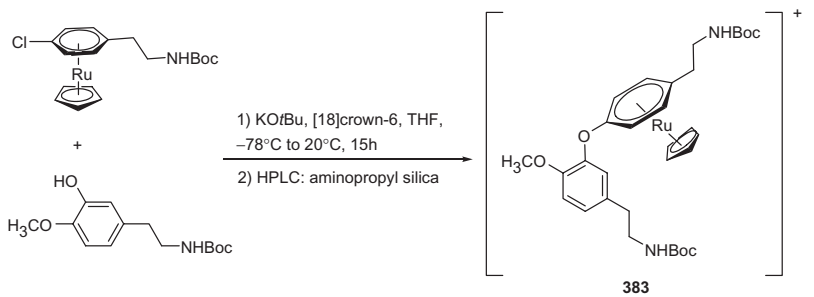

i) –78°C to rt, 30 min, 82% (1:1 *E*/*Z*); ii) HF-pyr, HCl·$H_2$NOBn, rt, 10h, 89%; iii) $RhCl_3$·$H_2O$ 4% w/v), EtOH, reflux,12 h, 76%; iv) $K_2CO_3$, DMF, 4 h, 91%; v) LiOH, THF:MeOH:$H_2O$ (4:1:1 v/v/v); vi) AllylBr, $K_2CO_3$, 83%; vii) repeat i) and ii), 73%; viii) $Pd(OAc)_2$, $PPH_3$, $Et_3N$, $HCO_2H$, THF, 3 h , 90%

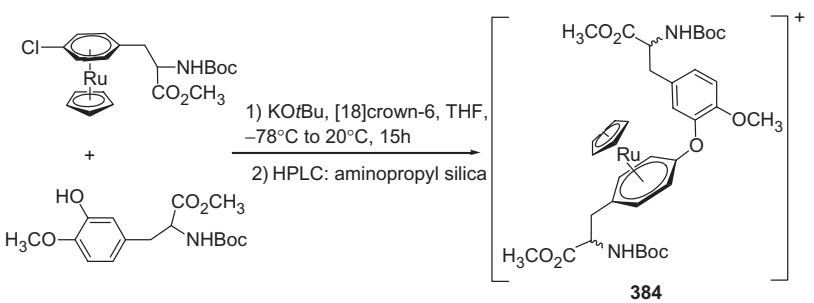



i) DCC, HOBT, $CH_2Cl_2$, 10 h, 78%; ii) LiOH, THF:MeOH:$H_2O$ (4:1:1); iii) $C_6F_5OH$, DCC, $CH_2Cl_2$, 10 h, 81%; iv) HCl, $CH_2Cl_2$, pH 2, 4 h, dilute to 0.005 M in $CH_2Cl_2$, $Et_3N$, pH 8, rt 3days, 60%.

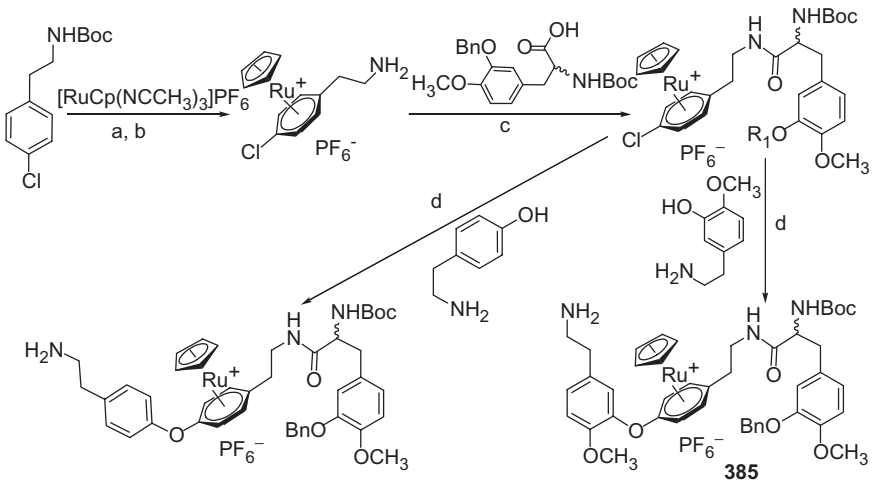
Molinski *et al.* also reported the reduction of bastadin-4 (**208**) to bastadin-5 (**209**) using cationic hydrogenation ($Et_3SiH$, TFA, 60%) (*240*). Specific deuteration at H-5 of bastadin-5 was conducted following this method.

Leone-Stumpf and Lindel synthesized the ruthenium labeled western (**383**) and eastern (**384**) diaryl ether and tripeptide (**385**) of bastadin-5, and for the first time established an HPLC method using aminopropyl-functionalized silica to purify the $[CpRu]^+$ complexes (*241,242*).



The free amino group of 4-*O*-methyldopamine and 4-*O*-methyltyramine react as nucleophiles in a chemoselective manner with $[RuCp]^+$-complexed *p*-substituted chloroarenes. As a consequence, it is not necessary to use protecting groups for the synthesis of peptides with alternating amide and diaryl ether bonds.




a: 1,2-dichloroethane, 4H, reflux; b: 4N HCl/MeOH, 3h, room temp.; c: THF/MeOH (1:1), EDCI, HOBt, DIEA, room temp., 34h; d: KO*t*Bu, [18]crown-6, THF/MeCN (1:1), –78°C to 0°C.

The total synthesis of polycitone A (**280**) and B (**281**) (*243*), and the cyclodepsipeptides, jaspamide (**259**) (*244*), geodiamolide A (**260**) (*245*), and geodiamolide B (**261**) (*246*) were also reported. Since these are not typical bromotyrosine derivatives, the details of the syntheses are not included here.

## VI. Bioactivity

Bromotyrosine alkaloids provide a unique diversity in chemical structure and in bioactivity. Since the first bromotyrosine derivative, the dienone **1**, was isolated as an antibiotic, a large number of bromotyrosine derivatives have been found to have diverse activities, which include antibacterial, antifungal, anticancer, antiviral, antifouling, Na,K-ATPase inhibitor, etc. The majority of the dibromotyrosine-derived natural products from Verongida have been reported to possess significant antimicrobial and cytotoxic activity (*247*). The presence of antibacterial compounds in marine sponges has been reported as a general phenomenon (*248*), and has been suggested to reflect a defensive strategy of these sedentary, filter-feeding animals (*249*).

### A. ANTIMICROBIAL ACTIVITY

Bromotyrosine derivatives were first isolated in the process of searching for antibiotics from marine sources. The dienone **1**, aeroplysinin-1 (**14**), and aerothionin (**68**) are the earliest antimicrobial bromotyrosine derivatives (*2,14,58*). The antibacterial and antifungal activities of the bromotyrosine alkaloids are summarized in Table IV and

Table V. Bromotyrosine derivatives exhibited a broad antimicrobial spectrum, which include Gram-positive bacteria such as *Streptococcus faecalis*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Sarcina lutea*, Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Neisseria gonorrhoeae*, and *Alcaligena faecalis*, and fungi such as *Candida albicans*.

The active compounds distribute in all of the structural subclasses. The simple bromotyrosine derivatives that were reported to possess antibacterial activity include the dienone **1**, aeroplysinin-1 (**14**), aeroplysinin-2 (**18**), 3-bromoverongiaquinol (**10**), 3-bromo-5-chloroverongiaquinol (**11**), aplysamine 1 (**54**), moloka'iamine (**52**), ceratinamine (**60**), 7-bromocavernicolenone (**30**), **38**, and **51**. The first bromotyrosine derivative, the dienone **1**, was reported as a broad-spectrum antibiotic (*2*). Both dextrorotatory and levorotary aeroplysinin-1 are active against Gram-positive and Gram-negative bacteria (*14,16*). The MICs (MBCs) of the dienone **1** and aeroplysinin-1 (**14**) ranged from 12.5–25 μg/mL against *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli* (*250*). (+)-Aeroplysinin-1 showed greater than 65% inhibition of the growth of phytopathogenic fungus *Phytophthora infestans* (potatoes late blight) (*251*).

Although the bis-spirocyclohexadienylisoxazoline bromotyrosine derivatives, aerothionin (**68**), homoaerothionin (**69**), 11-hydroxyaerothionin (**71**), and 11,19-dideoxyfistularin 3 (**83**), all had *in vitro* antimicrobial activity, 11,19-dideoxyfistularin 3 is the most active. Aerothionin (**68**), homoaerothionin (**69**), and 11-hydroxyaerothionin (**71**) all inhibited the growth of *Staphylococcus aureus* at 100 μg/disk, *Bacillus subtilis* at 50 μg/disk, and *Candida albicans* at 50 μg/disk, whereas 11,19-dideoxyfistularin 3 (**83**) inhibited the growth of *S. aureus* at 25 μg/disk, *B. subtilis* at 10 μg/disk, and *C. albicans* at 25 μg/disk (*63*). Aerothionin (**68**) was reported to be active against a group of monoresistant variants of *Mycobacterium tuberculosis* H37Rv at 12.5 μg/mL (*252*). It was also active against a group of multidrug resistant TB clinical isolates with MIC values between 6.5 and 25 μg/mL and active against three of nine nontuberculosis mycobacteria (*252*).

Both 11-oxo-12-hydroxyaerothionin (**73**) and 11-hydroxyaerothionin (**71**) induced 60 and 70% inhibition, respectively, of *Mycobacterium tuberculosis* growth at 12.5 μg/mL, while 11-oxoaerothionin (**72**) induced no inhibition at all (*253*). Single spirocyclohexadienylisoxazoline bromotyrosine derivatives, aplysinamisine I (**120**), aplysinamisine Π (**124**), aplysinamisine III (**102**), purealidin B (**109**), araplysillin-I (**99**), and araplysillin-II (**100**), showed moderate antimicrobial activity (*81,83,84*). Some of the oxime type bromotyrosine derivatives showed potent antimicrobial activity. Anomoian A (**195**), a reduced oxime, exhibited strong antimicrobial activity against *Staphylococcus aureus* at 10 μg/disk, *Bacillus subtilis* at 5 μg/disk, and *Candida albicans* at 25 μg/disk.

Purpuramine L (**191**) is highly active against *Staphylococcus aureus*, *Bacillus subtilis*, and *Chromobacterium violaceum*, moderately against *Bacillus sphaericus, K. aerogenes*, and *P. aeruginosa* (*122*). Purpuramine K (**190**) is moderately active against all the organisms. Interestingly, Gram-positive bacteria are highly susceptible to purpuramine L when compared to the positive control kanamycin (*122*). Psammaplin A (**152**) was found to possess antimicrobial activity (*109,254,255*). It also selectively inhibited the growth of methicillin-resistant *Staphylococcus aureus* (MRSA) (*256*). The minimal inhibitory concentration of psammaplin A against twenty-one MRSAs ranged from 0.78 to 6.25 μg/mL while that of ciprofloxacin was 0.39–3.13 μg/mL. Psammaplin A

TABLE IV.
Antibacterial Activity of Bromotyrosine Derivatives.

| Alkaloids | Antimicrobial activity[a] | Ref. |
|---|---|---|
| 3-Bromoverongiaquinol (**10**) | Active against *S. f.*, *B. s.*; not active against *A. f.*, *P. v.* | *9* |
| 3-Bromo-5-chloroverongiaquinol (**11**) | Active against *S. l.*, *A. f.*, *P. v.* | *9* |
| (−)-Aeroplysinin-1 (**17**) | MIC 20–100 μg/mL against *S. a.*, *B. s.*, *M. l.*, *E. c.*, *P. a.* | *16* |
| (+)-Aeroplysinin-1 (**14**) | MIC 20–100 μg/mL against *S. a.*, *B. s.*, *M. l.*, *E. c.*, *P. a.* | *16*<br>*31* |
| 7-Bromocavernicolenone (**30**) | Active against *P. c.*; not active against *B. s.* | *24* |
| **38** | 3000 μg/disk shows inhibition zone against *E. c.*18–22 mm | *31* |
| Aeroplysinin-2 (**18**) | 3000 μg/disk shows inhibition zone against *E. c.* < 15 mm | *31* |
| Moloka'iamine (**52**) | Inhibit the growth of *B. m.*, *P. n.*, *A. m.*, *V. a.*, *F. m.*at 10 μg /disk | *49* |
| Aplysamine-1 (**54**) | Not active against *S. a.*, *B. s.*, *S. l.*, *E. c.*, *S.* sp. | *44* |
| Aplysamine 2 (**172**) | Not active against *S. a.*, *B. s.*, *S. l.*, *E. c.*, *S.* sp. | *44* |
| Ceratinamine (**60**) | Inhibit the growth of *B. m.*, *P. n.*, *A. m.*, *V. a.*, *F. m.*at 10 μg/disk | *49* |
| Aerothionin (**68**) | Inhibit the growth of *S. a.* at 100 μg/disk, *B. s.* at 50 μg/disk | *63* |
| Homoaerothionin (**69**) | Inhibit the growth of *S. a.* at 100 μg/disk, *B. s.* at 50 μg/disk | *63* |
| 11,19-Dideoxy-fistularin 3 (**83**) | Inhibit the growth of *S. a.* at 25 μg/disk, *B. s.* at 10 μg/disk | *63* |
| 11-Hydroxyaerothionin (**71**) | Inhibit the growth of *S. a.* at 100 μg/disk, *B. s.* at 50 μg/disk | *63* |
| 11-Oxoaerothionin (**72**) | MIC 30 μg/mL against *S. a.*, *P. a.*; 10 μg/mL against *E. c.* | *64* |
| 11-*Epi*-fistularin-3 (**81**) | Active against *B. s.*, *M. l.*; not active against *E. c.* | *70* |
| Agelorin A (**87**) | Active against *B. s.*, *M. l.*; not active against *E. c.* | *70* |
| Agelorin B (**88**) | Active against *B. s.*, *M. l.*; not active against *E. c.* | *70* |
| Zamamistatin (**91**) | Active against *R. s.* | *75* |
| Aplysinamisine I (**120**) | Inhibit the growth of *S. a.*, *E. c.*, *P. a.* at 50–100 μg/disk | *83* |
| Aplysinamisine II (**124**) | Inhibit the growth of *S. a.*, *E. c.*, *P. a.* at 50–100 μg/disk | *83* |
| Aplysinamisine III (**102**) | Inhibit the growth of *S. a.*, *E. c.*, *P. a.* at 50–100 μg/disk | *83* |
| Purealidin B (**109**) | MIC 62.5 μg/mL against *S. a.*, 15.6 μg/mL against *B. s.*, 3.9 μg/mL against *S. l.* | *84* |

(*continued*)

TABLE IV.
Continued.

| Alkaloids | Antimicrobial activity[a] | Ref. |
|---|---|---|
| Purealidin C (**192**) | MIC 62.5 μg/mL against *S. a.*, 15.6 μg/mL against *S. l.* | *84* |
| Araplysillin-I (**99**) | 250 μg/disk shows inhibition zone against *S. a.* 12 mm | *81* |
| Araplysillin-II (**100**) | 250 μg/disk shows inhibition zone against *S. a.* 7 mm | *81* |
| Anomoian A (**195**) | Inhibit the growth of *S. a.* at 10 μg/disk, *B. s.* at 5 μg/disk | *124* |
| Bromochelonin B (**257**) | Inhibit the growth of *B. s.* at 100 μg/disk | *154* |
| Purpuramine K (**190**) | 25 μg/disk shows inhibition zone against *S. a.* 10, *P. a.* 10; *B. s.* 8; *C. v.* 7; *K. a.* 10 mm | *122* |
| Purpuramine L (**191**) | 25 μg/disk shows inhibition zone against *S. a.*, *B. s.* 14; *P. a.* 16; *B. sp* 12 mm | *122* |
| Psammaplin A (**152**) | Active against *S. a.*, *B. s.* | *109* |
| Bisaprasin (**154**) | Active against *S. a.*, *B. s.* | *109* |
| Psammaplin D (**158**) | Inhibit the growth of *S. a.*, *T. m.* at 100 μg/disk. | *110* |
| Bastadin-1 (**204**) | MIC: *S. a.* 6.25–12.5, *E. c.* 100, *N. g.* 50–100, *E. f.* 12.5–25 μg/disk | *41* |
| Bastadin-2 (**205**) | MIC: *S. a.* 6.25–12.5, *N. g.* 50–100, *E. f.* 50–100 μg/disk | *41* |
| Bastadin-3 (**206**) | MIC: *S. a.* 1.56–3.12, *N. g.* 0.78–1.56, *E. f.* 3.12–6.25 μg/disk | *41* |
| Bastadin-4 (**208**) | MIC: *S. a.* 12.5–25, *N. g.* 12.5–25, *E. f.* 50–100 μg/disk | *41* |
| Bastadin-5 (**209**) | MIC: *S. a.* 12.5–25, *N. g.* 50–100, *E. f.* 50–100 μg/disk | *41* |
| Bastadin-6 (**210**) | MIC: *S. a.* 6.25–12.5, *E. f.* 12.5–25 μg/disk | *41* |
| **207** | MIC: *N. g.* 50-100 μg/disk | *41* |
| Hemibastadin 1 (**231**) | MIC: *S. a.* 1.56–3.12, *N. g.* 12.5–25, *E. f.* 50–100 μg/disk | *41* |
| 1′-(Methyloxy) hemibastadins 1 (**237**) | MIC: *S. a.* 6.25–12.5, *N. g.* 6.25–12.5 μg/disk | *41* |
| Hemibastadins 2 and 3 (**232**, **233**) | MIC: *S. a.* 6.25–12.5, *N. g.* 6.25–12.5, *E. f.* 50–100 μg/disk | *41* |
| Hemibastadinol 1 (**234**) | MIC: *N. g.* 50–100 μg/disk | *41* |
| Hemibastadinols 2 and 3 (**235**, **236**) | MIC: *N. g.* 50–100 μg/disk | *41* |
| Bastadin-13 (**217**) | MIC 6 μg/mL against *B. s.* | *41* |

[a]*Streptococcus faecalis* (*S. f.*); *Staphylococcus aureus* (*S. a.*); *Bacillus subtilis* (*B. s.*); *Micrococcus luteus* (*M. l.*); *Sarcina lutea* (*S. l.*); *Bacillus marinus* (*B. m.*); *Bacillus sphaericus* (*B. sp.*). *Escherichia coli* (*E. c.*); *Pseudomonas aeruginosa* (*P. a.*); *Neisseria gonorrhoeae* (*N. g.*); *Alcaligena faecalis* (*A. f.*); *Chromobacterium violaceum* (*C. v.*); *Klebsiella aerogenes* (*K. a.*); *Proteus vulgaris* (*P. v.*); *Vibrio alginolyticus* (*V. a.*); *Pseudomonas cichorii* (*P. c.*); *Pseudomonas nautical* (*P. n.*); *Alteromonas macleodii* (*A. m.*); *Flavobacterium marinotypicum* (*F. m.*); *Rhodospirillum salexigens* (*R. s.*); *Serratia sp.* (*S. sp.*); *Escherichia faecalis* (*E. f.*).

TABLE V.
Antifungal activity of Bromotyrosine Derivatives.

| Alkaloids | Antifungal activity | Ref. |
|---|---|---|
| Aplysamine-1 (**54**) | No activity | *44* |
| Aplysamine-2 (**172**) | | |
| Ceratinamine (**60**) | No activity against *Candida albicans*, *Penicillium chrysogenum*, *Mortierelia ramanniana* at 10 μg/ disk | *49* |
| Aerothionin (**68**) | Active against *C. albicans* at 50 μg/ disk | *63* |
| Homoaerothionin (**69**) | Active against *C. albicans* at 50 μg/ disk | *63* |
| 11-Hydroxyaerothionin (**71**) | Active against *C. albicans* at 50 μg/ disk | *63* |
| 11,19-Dideoxyfistularin-3 (**83**) | Active against *C. albicans* at 25 μg/ disk | *63* |
| **77** | MIC 64 μg/ml on *Criptococcus neoformans* ATCC90113 | *67* |
| 11-*Epi*-fistularin-3 (**81**) | Not active toward *Penicillium oxalicum* | *70* |
| Agelorin A (**87**) | Not active toward *Penicillium oxalicum* | *70* |
| Agelorin B (**88**) | Not active toward *Penicillium oxalicum* | *70* |
| Purealidin C (**192**) | Modest activity against *C. albicans*, *Crypotococcus neoformans*, and *Paecilomyces variotii* | *84* |
| Anomoian A (**195**) | Inhibit the growth of *C. albicans* at 25 μg/disk | *124* |
| Geodiamolide A (**260**) | Active against *C. albicans* (MIC: 31.3 μg/ml) | *158* |
| Geodiamolide B (**261**) | Active against *C. albicans* (MIC: 31.3 μg/ml) | *158* |
| Psammaplin D (**158**) | Inhibit the growth of *Trichopyhton mentagrophytes* at 100 μg/disk. | *110* |

(**152**) could not bind to the penicillin binding protein, but inhibited the DNA synthesis and the DNA gyrase activity with the respective 50% (DNA synthesis) and 100% (DNA gyrase) inhibitory concentrations of 2.83 and 100 μg/mL. These results indicated that psammaplin A inhibited the growth of bacteria probably by inhibiting DNA gyrase (*256*). Since the significant antimicrobial activity of psammaplin A (**152**) was disclosed, the antibacterial activities against 40 drug-resistant *Staphylococcus aureus* strains were determined for psammaplin D (**158**), **169**, bromopsammaplin A (**170**), bispsammaplin A (**171**), and bisaprasin (**154**) (*117*). Alkaloid **169** showed the highest potency, which is higher than that of meropenem against several strains (see Table VI.) (*117*). Bromopsammaplin A (**170**) and bisaprasin (**154**) exhibited strong to moderate activity against all these strains, while psammaplin D (**158**) and bispsammaplin A (**171**) did not show significant activity against all strains.

Bastadins-1 to- 7 (**204**–**211**) were isolated because of the potent activity against Gram-positive and Gram-negative bacteria, but data were not provided (*129*). Bastadin-13 showed a minimum inhibitory concentration of 6 μg/mL against *Bacillus subtilis*, while 34-sulfatobastadin-13 showed no activity at 50 μg/mL, suggesting the free phenolic group at C-34 is required for the antimicrobial activity (*141*). Pettit *et al*. evaluated the ability of bastadins-1 to 6 (**204**–**210**), hemibastadins (**231**–**233**, **237**), hemibastadinols (**234**, **235**, **236**), and amide **51** to inhibit growth of Gram-positive bacteria, Gram-negative bacteria,

TABLE VI.
Antibacterial Activity against Different *Staphylococcus* Strains[a] (MIC, μg/mL).

| Strains | **158** | **169** | **170** | **171** | **154** | Meropenem |
|---|---|---|---|---|---|---|
| *S. aureus* KIST 1[b] | > 25.0 | 3.1 | 12.5 | > 50.0 | 12.5 | 25.0 |
| *S. aureus* KIST 2[b] | > 25.0 | 3.1 | 12.5 | > 50.0 | 6.3 | 3.1 |
| *S. aureus* KIST 3[b] | > 25.0 | 6.3 | 12.5 | > 50.0 | 6.3 | 50.0 |
| *S. aureus* KIST 4[b] | > 25.0 | 3.1 | 12.5 | > 50.0 | 6.3 | 50.0 |
| *S. aureus* 003[c] | > 25.0 | 3.1 | 12.5 | > 50.0 | 12.5 | 3.1 |
| *S. aureus* 004[c] | > 25.0 | 3.1 | 12.5 | > 50.0 | 6.3 | 3.1 |
| *S. aureus* Y-80-12-1109[d] | > 25.0 | 6.3 | 12.5 | > 50.0 | 50.0 | 50.0 |
| *S. aureus* Y-80-12-1999[d] | > 25.0 | 6.3 | 12.5 | > 50.0 | 50.0 | 50.0 |
| *S. aureus* Y-80-12-844[d] | > 25.0 | 25.0 | 25.0 | > 50.0 | 25.0 | 50.0 |
| *S. epidermidis* 178[e] | > 25.0 | 0.8 | 3.2 | > 50.0 | 6.3 | 0.8 |
| *S. epidermidis* 291[e] | > 25.0 | 0.8 | 3.2 | > 50.0 | 12.5 | 1.6 |

[a] A total of 40 strains were employed for testing, and only the strains to which **169** exhibited equipotency to or higher potency than meropenem were registered. [b] Strains were obtained from KIST (Korea Institute of Science and Technology). [c] Strains were obtained from LG Chemical, Korea. [d] Strains were obtained from Yon-Sei Medical Center, Korea. [e] Ofloxacin-resistant strains.

and two fungi (Table IV) (*41*). Except for bastadin-6, all of these alkaloids inhibited the growth of the Gram-negative pathogen *Neisseria gonorrhoeae*. Most of the compounds also inhibited the growth of the Gram-positive opportunists *Enterococcus faecalis* and *Staphylococcus aureus*. At up to 100 μg/disk, these alkaloids exhibited no antimicrobial activity against *Escherichia coli* or the fungi *Candida albicans* and *Cryptococcus neoformans* (*41*).

Antibiotic activity of sponge metabolites has frequently been demonstrated in the past (*257–259*). However, most of these studies were conducted with terrestrial rather than marine bacteria. For example, antibiotic activity of aeroplysinin-1 (**14**) and dienone **1** was proven using terrestrial Gram-positive and Gram-negative bacteria (*250*). Proksch *et al.* confirmed this activity using several marine bacteria such as *Alteromonas*, *Moraxella*, or *Vibrio* sp. (see Table VII) (*260*). The $EC_{50}$ values of aeroplysinin-1 (**14**) and the dienone **1** towards *Photobacterium phophoreum*, which is a well-established model for the analysis of water-borne toxins (*261,262*), are comparable to those of pentachlorophenol ($EC_{50}$: 1.3 μM), lead ($EC_{50}$: 1.9 μM) or cadmium ions ($EC_{50}$: 71 μM) which are known for their pronounced toxicity. At the same time, aeroplysinin-1 and the dienone **1** are also active against microalgae (*260*).

## B. ANTICANCER ACTIVITY

Anticancer active bromotyrosine derivatives are summarized in Table VIII. Many of the bromotyrosine derivatives exhibited cytotoxicity, emphasizing the ecological relevance of this type of compounds in the sponge's chemical defense. The small molecules, aeroplysinin-1 (**14**) and the dienone **1**, which are from the enzymatic

TABLE VII.
Antibiotic Activity against Several Marine Bacteria.

| Compounds | Diameter of inhibitory zone (mm) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Isofistularin-3 (**80**) | Aerophobin-2 (**114**) | Aeroplysinin-1 (**14**) | | | Dienone (**1**) | | |
| Dose (μg/disk) | 100 | 100 | 100 | 50 | 5 | 100 | 50 | 5 |
| *Alteromonas* sp.* NCIMB 224 | – | – | 11 | 7 | – | 10 | 9 | – |
| *Cytophage/Flexibacter* sp.* NCIMB 251 | – | – | 30 | n.d. | n.d. | 28 | n.d. | n.d. |
| *Moraxella* sp.* NCIMB 308 | – | – | 22 | 20 | – | 19 | 16 | 7 |
| *Pseudomonas fluorescens** NCIMB 129 | – | – | 8 | – | – | 9 | 7 | 7 |
| *Serratia plymuthica** | – | – | 11 | 8 | – | 14 | 11 | 7 |
| *Vibrio* sp.* | – | – | 28 | 24 | 12 | 24 | 21 | 8 |
| *Vibrioanguillarum** NCIMB 407 | – | – | 27 | 24 | 11 | 34 | 21 | 7 |
| *Plancoccus citraus*+ NCIMB 1495 | – | – | 14 | n.d. | n.d. | 14 | n.d. | n.d. |

n.d.: not determined; +Gram positive bacteria; *Gram negative bacteria.

degradation of larger bromotyrosine derivatives such as isofistularin-3 (**80**), aerophobin-2 (**114**), fistularin-1 (**94**), and other alkaloids, are more toxic than the parent compounds, suggesting a wound defense reaction (*250,263,264*).

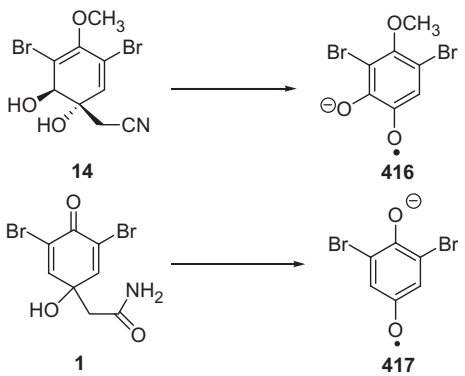
The anticancer activity of aeroplysinin-1 (**14**) was the most studied among all bromotyrosine derivatives. Kreuter *et al.* evaluated the *in vitro* and *in vivo* anticancer activity of (+)-aeroplysinin-1 (**14**) (*265,266*). Aeroplysinin-1 displayed pronounced cytostatic activity against L5178y mouse lymphoma cells ($ED_{50}$: 0.5 μM), Friend erythroleukemia cells ($ED_{50}$: 0.7 μM), human breast carcinoma cells ($ED_{50}$: 0.3 μM), and human colon carcinoma cells ($ED_{50}$: 5.0 μM), but not against the related normal cells *in vitro*. The $ED_{50}$ values of aeroplysinin-1 for these cell lines are significantly lower than those obtained in cultures with non-transformed lymphocytes. The inhibitory activity of aeroplysinin-1 in the L5178y cell system is higher than other cytostatic agents including 9-β-D-arabinofuranosyladenine, $ED_{50}$ 29 μM (*267*), 1-β-D-arabinofuranosylthymine, $ED_{50}$ 9.8 μM (*268*), bleomycin, $ED_{50}$ 0.9 μM (*269*), and distamycin, $ED_{50}$ 13.1 μM (*270*). Aerothionin caused a preferential inhibition of [$^3$H]thymidine incorporation rates in L5178y mouse lymphoma cells when compared with murine spleen lymphocytes *in vitro*. These results showed that a higher concentration of the alkaloid is required to influence the incorporation rates in lymphocytes than in L5178y cells; e.g., at a concentration of 2.9 μM the incorporation rates in lymphocytes are reduced only by 40–50%, while those in L5178y cells are diminished by almost 100%. The same differential effect *in vitro* was found with the following epithelial cells: 14.7 μM of the compound was required to inhibit normal human fibroblasts to 50%, but only 2.9 μM in the assays with human malignant keratinocytes or malignant melanoma cells was needed to observe the same inhibitory effect.

Aeroplysinin-1 (**14**) also displayed antileukemic activity *in vivo* using the L5178y cell/NMRI mouse system. Administration of a dose of 50 mg/kg for five consecutive days, the life span T/C (%) value was determined to be 338. Preliminary toxicology studies revealed an acute $LD_{50}$ of 202 mg/kg, a subacute $LD_{50}$ of 150 mg/kg, and a subacute $LD_{10}$ 133.3 mg/kg. A daily dose of 30 mg/kg for 30 consecutive days neither caused any toxicity nor a change of body weight compared to the controls. The animals were sacrificed for autopsy 40 days after the last injection. In no case were any morphological abnormalities detected in the peritoneal cavity. Using the *umu*-test system, which has been demonstrated to detect many types of DNA-damaging agents, such as base change mutagens, frameshift mutagens or oxidative mutagens (*271*), aeroplysinin-1 turned out to be neither a direct nor an indirect mutagen. The excellent T/C value of aeroplysinin-1 is the combined result of the antitumor effect and low toxicity. Following the arbitrary activity rating proposed (*272*), aeroplysin-1 was classified to the markedly active (+ + → + + +) to highly active anticancer agents (+ + +).

In the continuing paper, Kreuter *et al.* reported the inhibition of intrinsic protein tyrosine kinase activity of the EGF-receptor kinase complex from human breast cancer cells by (+)-aeroplysinin-1 (**14**) (*273*). Aeroplysinin-1, which possesses a close structure-relationship to tyrosine, blocks the epidermal growth factor (EGF) dependent proliferation of both MCF-7 and ZR-75-1 human breast cancer cells, and inhibited the ligand-induced endocytosis of the EGF receptor *in vitro*. Aeroplysinin-1 was found to inhibit the tyrosine-specific phosphorylation of lipocortin-like proteins, which have been established as major substrates of the EGF receptor-associated protein–tyrosine kinase

(*274*), by a highly purified preparation of the EGF receptor protein–tyrosine kinase complex, isolated from MCF-7 cells. Treatment of aeroplysinin-1 in the concentration range of 0.25–0.5 μM resulted in MCF-7 cells losing their ability for EGF-mediated cell response and cell death occurred within 36–72 h. At a 10-fold higher concentration, aeroplysinin-1 did not reveal cytostatic activity in normal human fibroblasts. From these data, aeroplysinin-1 was concluded to be a promising compound in a rational chemotherapy (*273*). Based on the potent anticancer activity, production of aeroplysinin-1 by the *in vitro* culturing of the sponge *Verongia aerophoba* was also studied (*275*).

In other studies, aeroplysinin-1 (**14**) and the related dienone **1** exhibited cytotoxicity against Ehrlich ascites tumor (EAT) cells and HeLa tumor cells in the microculture tetrazolium (MTT) and clonogenic assays (*276*). Both alkaloids were able to cause growth inhibition, as well as cell death, in these cell lines. When the cells were depleted of glutathione by pretreatment with buthionine sulfoximine, they were significantly more sensitive toward aeroplysinin-1 (**14**) and the dienone **1** in the MTT assay. A dose-enhancement factor as high as 11.8 was found in EAT cells after a 2-h incubation with the dienone **1**. These results suggested that in both tumor cell lines, glutathione may play an important role in the defense against the cytotoxic action of aeroplysinin-1 (**14**) and the dienone **1**, and a free-radical mechanism might be involved in the cytotoxicity of both compounds (*277*,*278*). Using electron paramagnetic resonance, the formation of free radicals from aeroplysinin-1 (**14**) and the dienone **1** were measured in a culture medium with tumor cells. When dissolved in pure $H_2O$, **1** yielded an EPR spectrum, but **14** failed to do so. Thus, metabolic activation by living cells may be required to obtain free radicals from aeroplysinin-1 (**14**). Structures **416** and **417** are possibilities for the semiquinone radicals that originate from **14** and **1**. Semiquinone radicals are known to be very toxic (*279*).




From the above results it may be concluded that free radicals are, at least in part, responsible for the cytotoxic effects of aeroplysinin-1 (**14**) and the dienone **1** *in vitro*. Although aeroplysinin-1 (**14**) and the dienone **1** were less effective than the clinically used anticancer drug cisplatin, their chemical structures may be of interest as leads for future drug development. The different reactivity of aeroplysinin-1 (**14**) and the dienone **1** fits very well in the defensive role of these alkaloids for *Aplysina aerophoba*, when the following hypothesis is used. As soon as a predator attacks this sponge, aeroplysinin-1 (**14**) is formed due to enzymatic degradation of the larger precursors. Aeroplysinin-1 will generate free radicals after metabolic activation by the predator's cell, which results in an

antifeedant effect. Simultaneously, the dienone **1** is released, which immediately yields free radicals in the water surrounding the sponge, thereby shielding the sponge from further predation or attack (*276*).

Recent studies revealed that (+)-aeroplysinin-1 (**14**) has a strong inhibitory antiangiogenic activity (*280,281*). Since the earliest hypothesis that tumor growth was dependent on angiogenesis (*282*), it has become clear that interfering with and/or preventing angiogenesis is an attractive therapeutic approach to the treatment of angiogenesis-dependent diseases (*283,284*). In a variety of experimental systems, representing the sequential events of the angiogenic process, aeroplysinin-1 treatment of endothelial cells resulted in strong inhibitory effects. Aeroplysinin-1 inhibited the growth of endothelial cells in culture with an $IC_{50}$ of 2.1 μM and induced endothelial cell apoptosis. Capillary tube formation on Matrigel was completely abrogated by addition of aeroplysinin-1 at the low micromolar range. Aeroplysinin-1 also exhibited a clear inhibitory effect on the migration capabilities of endothelial cells. Zymographic assays showed that aeroplysinin-1 treatment produced a decrease in the concentration of matrix metalloproteinase-2 and urokinase in conditioned medium from endothelial cells. Finally, aeroplysinin-1 exhibited a dose-dependent inhibitory effect on the *in vivo* chorioallantoic membrane assay, showing potent apoptosis-inducing activity in the developing endothelium. The *in vivo* inhibition of angiogenesis by aeroplysinin-1 was confirmed by the Matrigel plug assay. Together, all of these data indicate that aeroplysinin-1 is a compound that interferes with key events in angiogenesis, making it a promising drug for further evaluation in the treatment of angiogenesis-related pathologies (*280*).

Most of the bis-spirocyclohexadienylisoxazoline type of bromotyrosine derivatives tested exhibited moderate cytotoxicity against different cancer cell lines. These include fistularin-3 (**79**) (*68*), 11-oxoaerothionin (**72**) (*64*), 11-*epi*-fistularin-3 (**81**) (*70*), 11-oxofistularin (**82**) (*72*), isofistularin-3 (**80**) (*72*), and 11-deoxyfistularin-3 (**86**) (*73*). 11-Oxoaerothionin (**72**) is the most potent agent and showed pronounced selective cytotoxic activity toward the human colon HCT cell line at a limited concentration range of 0.01–0.1 μg/mL (*64*).

Purealidins, which are single spirocyclohexadienylisoxazoline or oxime type of bromotyrosine derivatives, exhibited moderate to strong cytotoxicity, among which purealidin N (**150**) is very potent against K1210 and KB cells with $IC_{50}$ values of 0.07 and 0.074 μg/mL, respectively (*79,84,104*).

The oxime disulfides, psammaplin A (**152**), psammaplin D (**158**), bromopsammaplin A (**170**), bispsammaplin A (**171**), and bisaprasin (**154**), were reported to have significant cytotoxicity against human lung A549, ovarian SK-OV-3, skin SK-MEL-2, CNS XF498, and colon HCT15 solid tumor cell lines (Table VIII). Psammaplin A (**152**) exhibited the highest potency among the five compounds (*117*). Inspired by its HDAC and DNMT enzyme inhibitory actions and unique structural features, the antiproliferative properties of psammaplin A (**152**) were thoroughly explored (*112*). Encouraging *in vitro* results were found as **152** inhibited cells grown in monolayer and in soft agar at the following levels ($IC_{50}$ values in μM): A549 lung tumor at 1.35 and 2.5, and MDA-MB-435 breast tumor at 1.15 and 2.0, respectively. These positive results were also observed *in vivo*, as psammaplin A (**152**) inhibited tumor growth in the A549 lung xenograph mouse model, while also maintaining low toxicity (*285*). Very recently, psammaplin A (**152**) was found to

TABLE VIII
Cytotoxicity of Bromotyrosine Derivatives

| Alkaloids | Cytotoxicity | Ref. |
|---|---|---|
| Psammaplin A (**152**) | $IC_{50}$: K562 0.4 mM. | *114* |
| | $IC_{50}$: P388 0.3 μg/mL; | *108* |
| | $ED_{50}$: A549 0.57; SK-OV-3 0.14; SK-MEL-2 0.13; XF498 0.57; HCT15 0.68 μg/mL | *117* |
| Psammaplin D (**158**) | $ED_{50}$: A549 0.80; SK-OV-3 0.17; SK-MEL-2 0.20; XF498 0.60; HCT15 1.23 μg/mL | *117* |
| Bromopsammaplin A (**170**) | $ED_{50}$: A549 1.34; SK-OV-3 1.38; SK-MEL-2 0.90; XF498 0.92; HCT15 3.31 μg/mL | *117* |
| Bispsammaplin A (**171**) | $ED_{50}$: A549 1.53; SK-OV-3 1.52; SK-MEL-2 1.02; XF498 1.10; HCT15 3.35 μg/mL | *117* |
| Bisaprasin (**154**) | $ED_{50}$: A549 3.40; SK-OV-3 2.78; SK-MEL-2 2.94; XF498 2.44; HCT15 6.0 μg/mL | *117* |
| Psammaplin $A_1$ (**165**) | K562: $LC_{50}$ 1.9 mM | *114* |
| Psammaplin $A_2$ (**166**) | K562: $LC_{50}$ 4.2 mM | *114* |
| Aplysinellin A (**167**) | K562: $LC_{50}$ 10.7 mM | *114* |
| Aplysinellin B (**168**) | K562: $LC_{50}$ 7.1 mM | *114* |
| Moloka'iamine (**52**) | MIC: KB 50 μg/mL; LOVO 10 μg/mL; | *42* |
| | $IC_{50}$: P-388 5 μg/mL; A-549 10 μg/mL; HT-29 5 μg/mL; CV-1 10 μg/mL | *49* |
| Mololipids (**53**) | >100 μM (−) | *43* |
| Ceratinamine (**60**) | P388 $IC_{50}$ 3.4 μg/mL | *49*,*98* |
| *N*,*N*,*N*-Trimethyl-dibromotyramine (**47**) | P388 $ED_{50}$ 20 μg/mL | *37* |
| 11-Oxoaerothionin (**72**) | HCT 116 (0.01-0.1 μg/mL) | *64* |
| 11-*Epi*-fistularin-3 (**81**) | $IC_{50}$: KB >20; BCI 5.9; ZR-75-1 4.5 μg/mL | *70* |
| 11-Oxofistularin-3 (**82**) | 100% inhibition of KB in culture at 7 μg/mL | *72* |
| Isofistularin-3 (**80**) | KB: 4 μg/mL active | *69* |
| Fistularin-3 (**79**) | $ED_{50}$: KB 4.1; PS 4.3; LE 1.3 μg/mL | *68* |
| 11-Deoxyfistularin-3 (**86**) | $LD_{50}$: CF-7 17 μg/mL; X-17, Hela, Hep-2, RD, Lovo >50 μg/mL | *73* |
| Aplysinamisine I (**120**) | $IC_{50}$: MCF-7 >50; CCRF-CEM >50 μg/mL; HCT116 (-). | *83* |
| Aplysinamisine II (**124**) | $IC_{50}$: MCF-7 >50; CCRF-CEM >50; HCT116 10 μg/mL. | *83* |
| Aplysinamisine III (**102**) | $IC_{50}$: MCF-7 30; CCRF-CEM 6; HCT116 10 μg/mL | *83* |
| Purealidin N (**150**) | $IC_{50}$: K1210 0.07; KB cells 0.074 μg/mL | *79* |
| Purealidin P **110** | $IC_{50}$: K1210 2.8; KB: 7.6 μg/mL | *79* |
| Purealidin Q (**111**) | $IC_{50}$: K1210 0.95; KB 1.2 μg/mL | *79* |
| Purealidin J (**116**) | >10 μg/mL. | *79* |
| Purealidin K (**117**) | >10 μg/mL | *79* |
| Purealidin L (**125**) | >10 μg/mL | *79* |
| Purealidin M (**149**) | >10 μg/mL | *79* |

(*continued*)

TABLE VIII.
Continued.

| Alkaloids | Cytotoxicity | Ref. |
|---|---|---|
| Purealidin O (**200**) | > 10 μg/mL | *79* |
| Purealidin R (**97**) | > 10 μg/mL | *79* |
| Aerophobin-1 (**113**) | > 10 μg/mL | *79* |
| Purealidin C (**192**) | $IC_{50}$: KB 3.2; K1210 2.4 μg/mL | *84* |
| Purealidin B (**109**) | – | *84* |
| Purealidin A (**146**) | $IC_{50}$: L1210 1.1 μg/mL | *104* |
| Fistularin-1 (**94**) | $ED_{50}$: 21-35 μg/ml against KB, PS, LE | *68* |
| **128** | $IC_{50}$: HeLa 50 μg/mL | *92* |
| Jaspamide (**259**) | $ED_{50}$: larynx epithelial carcinoma 0.32 μg/mL, human embryonic lung 0.01 μg/mL | *157* |
| Geodiamolide A (**260**) | L1210: 0.0032 ($ED_{50}$). $ED_{50}$: U373 0.016, HEY 0.043 μg/mL | *158,159,169* |
| Geodiamolide B (**261**) | L1210: 0.0026 ($ED_{50}$). | *158,159* |
| Geodiamolide C (**262**) | L1210: 0.0025 ($ED_{50}$). | *159* |
| Geodiamolide D (**263**) | L1210: 0.0039 ($ED_{50}$). | *159* |
| Geodiamolide E (**264**) | L1210: 0.014 ($ED_{50}$). | *159* |
| Geodiamolide F (**265**) | L1210: 0.006 ($ED_{50}$). | *159* |
| Geodiamolide G (**266**) | $ED_{50}$: U373 7.7, HEY 8.6 μg/mL | *160* |
| Geodiamolide H (**267**) | TGI: HOP92 0.118, SF-268 0.153, OV Car-4 0.0186, A498 0.0948, UO-31 0.185, MDA-MB-23/ATCC 0.433 μM | *161* |
| Geodiamolide I (**268**) | not active | *161* |
| Bastadin-4 (**208**) | P-388 $ED_{50}$: 2.0 μg/mL | *132* |
| Bastadin-8 (**212**) | P-388 $ED_{50}$: 3.6 μg/mL, L1210 $ED_{50}$: 5 μg/mL | *132, 142* |
| Bastadin-9 (**213**) | P-388 $ED_{50}$: 2.7 μg/mL | *132* |
| Bastadin-12 (**216**) | L1210 $ED_{50}$: 5 μg/mL | *142* |
| Bastadin-14 (**218**) | $IC_{50}$ 2 μg/mL against A-549, HT-29, P-388 | *133* |
| Botryllamide D (**242**) | HCT116: 17 μg/mL | *145* |
| Ma'edamine A (**251**) | $IC_{50}$: L1210 4.3 μg/mL; KB 5.2 μg/mL | *152* |
| Ma'edamine A (**252**) | $IC_{50}$: L1210 3.9 μg/mL; KB 4.5 μg/mL | *152* |
| Psammaplysin A (**129**) | HCT116 $IC_{50}$ 6 μg/mL | *95* |
| Psammaplysin B (**130**) | HCT116 $IC_{50}$ 6 μg/mL | *95* |
| Psammaplysin C (**131**) | HCT116 $IC_{50}$ 3 μg/Ml | *95* |
| Psammaplysin E (**133**) | active at 5 μg/mL against KB and LoVo cells | *96* |

inhibit mammalian aminopeptidase N (APN) that plays a key role in tumor cell invasion and angiogenesis, with an $IC_{50}$ value of 18 μM in a noncompetitive manner (*286*). Interestingly, psammaplin A potently inhibited the proliferation of several cancer and endothelial cells and this effect was dependent on the cellular amount of APN expression. Finally, psammaplin A suppressed the invasion and tube formation of endothelial cells

stimulated by basic fibroblast growth factor. These data demonstrated that psammaplin A is a new inhibitor of APN and might be developed as a novel anti-angiogenic agent (*286*).

Geodiamolides are a group of depsipeptides with very strong cytotoxicity. Geodiamolides A (**260**), B (**261**), C (**262**), D (**263**), E (**264**), and F (**265**) exhibited very potent cytotoxicity against L1210 cell line with an $ED_{50}$ range of 0.0025–0.039 μg/mL (*159*). Comparison of the cytotoxicities of jaspamide (**259**) (*157*) and geodiamolide A (**260**) to F (**265**) (*158,159*) shows that significant variation in the three amino acid residues causes only minor changes in the levels of cytotoxicity exhibited by the peptides. By contrast, geodiamolide G (**266**), with a modified polyketide fragment, is significantly less cytotoxic than the analogue geodiamolide A (**260**) (*160*). Surprisingly, geodiamolide I (**268**) was completely devoid of activity (*161*).

Oxepin-type bromotyrosine derivatives, including psammaplysin A (**129**), B (**130**), and C (**131**) and bastadins-4 (**208**), -8 (**212**), -9 (**213**), -12 (**216**), and -14 (**218**) showed moderate cytotoxicities (*95,132,133,142*).

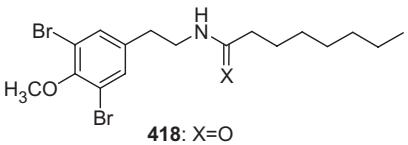
## C. ANTIFOULING

Biofouling causes serious problems in the shipping business, in aquaculture and in the cooling systems of power stations. The biofouling of ship hulls increases drag, and consequently increases fuel costs. The biofouling of fishing nets in marine aquaculture prevents a smooth flow of sea water, followed by a serious decline in the number of fish due to an insufficient oxygen supply. Metallic compounds, such as copper (I) oxide and bis(tributyltin)oxide (TBTO), have previously been used as antifouling agents. Today, however, the use of TBTO in antifouling paints is restricted in order to prevent environmental pollution. Therefore, the development of environmentally benign antifouling agents is essential for resolving this global problem (*287*). Soft-bodied benthic invertebrates are believed to have chemical defenses against predators and the overgrowth of other benthic organisms (*288*). Therefore, metabolites of these invertebrates are potential ''environmentally-friendly'' antifouling agents (*289*).

The Verongida sponges provide excellent examples for the use of metabolites in chemical defense (*260,290*). The marine sponge *Verongia aerophoba* represents an example for a wound-induced chemical defense that relies on an enzymatic conversion of inactive storage compounds into an active defense metabolite (*260*). Following disrupture of the compartmentation (e.g. by wounding) both major components, isofistularin-3 (**80**) and aerophobin-2 (**114**), are enzymatically converted into aeroplysin-1 (**14**), which in turn gives rise to the dienone **1** (*291*). Aeroplysin-1 (**14**) and dienone **1** were shown to have pronounced inhibitory activity against a number of marine organisms (bacteria, microalgae, and molluscs), which may be associated with biofouling (*260*). This may account for the remarkably clean surfaces of the Verongida sponges.

A bioassay system suitable for screening crude extracts against biofilm formation was developed by Yamada *et al.* (*292*). Interestingly, most sponges examined using this method contained anti-biofilm compounds, among which aeroplysin-1 (**14**) exhibited activity with an $IC_{50}$ value of 0.66 μg/$cm^2$.

Ceratinamide A (**135**), ceratinamide B (**136**), psammaplysin A (**129**), psammaplysin E (**133**), ceratinamine (**60**), and moloka'iamine (**52**) isolated from the marine sponge *Pseudoceratina purpurea*, were found to have antifouling activity (settlement and metamorphosis inhibitory activity) against cyprid larvae of the barnacle *Balanus amphitrite* with $ED_{50}$ values of 0.10, 2.4, 0.27, 4.8, 5.0, and 4.3 μg/mL, respectively (*49,98*). Ceratinamide A (**135**) and psammaplysin A (**129**) were particularly potent in the assay. Ceratinamide B (**136**), psammaplysin A (**129**), and ceratinamine (**60**) were lethal to the larvae at a concentration of 30 μg/mL, while other metabolites were not toxic at this concentration. Thus, ceratinamide A (**135**) is a promising antifouling agent. Interestingly, psammaplysin A (**129**) induced larval metamorphosis of the ascidian *Halocynthia roretzi* (*98*). Ceratinamine (**60**) and moloka'iamine (**52**), and 3,5-dibromo-4-methoxy-$\beta$-phenethylamine (**51**), together with several analogues, have been synthesized (*197,199*). 3,5-Dibromo-4-methoxy-$\beta$-phenethylamine (**51**) and its two analogues, octanoic amide (**418**) and octylamine (**419**) strongly inhibited the settlement of barnacle cyprids, with $IC_{50}$ values of 0.07, 0.2, and 0.008 μg/mL, respectively.




**418**: X=O
**419**: X=H

*Rhodospirillum salexigens* is a marine bacterium, which has adhering properties to form bacteria biofilm. Zamamistatin (**91**) exhibited significant antibacterial activity against *R. salexigens* with an inhibition zone of 21 mm at 1.6 μg/disk, and may be a valuable candidate for novel antifouling agents (*75,76*). 5-Bromoverongamine (**138**) was also reported to exhibit antifouling activity (*100*).

Due to the noteworthy absence of fouling observed on sponges of the order Verongida, a number of natural and synthetic dibromotyramine derivatives, including moloka'iamine, were selected as potential zebra mussel (*Dreissena polymorpha*) antifoulants in our laboratory (*293*). The zebra mussel (ZM) re-attachment assays yielded an antifouling activity with an $EC_{50}$ value of 10.4 μM for moloka'iamine (**52**). Hemifistularin-3 (**108**) had significant activity in a preliminary study against ZM attachment at a single high point concentration of 30 μM, while fistularin-3 (**79**) and aerophobin-2 (**114**) showed no antifouling activity against ZMs.

## D. ENZYME ACTIVITY

Purealin (**122**) inhibited the activity of myosin Ca-ATPase and Na,K-ATPase (see Table IX) (*91*). However, the activity of myosin K,EDTA-ATPase was enhanced by purealin. Purealin is the first natural product which activates myosin K,EDTA-ATPase (*91*). A number of papers have been published about the activity of purealin (**122**) on ATPase in different modes (*294–299*). Purealin (**122**) modulates the ATPase activities of dephosphorylated gizzard myosin by enhancing the stability of myosin filaments against the disassembling action of ATP (*294*). Purealin blocks the sliding movement of sea urchin flagellar axonemes by selective inhibition of half the ATPase activity of axonemal dyneins. Purealin-sensitive APTase activity of the dynein arms plays an essential role in generating the sliding movement of flagellar axonemes (*295*). Purealin activates skeletal muscle

TABLE IX.
Enzyme Activity of Some Bromotyrosine Derivatives.

| Alkaloids | Activity ($IC_{50}$) | | | | | Ref. |
|---|---|---|---|---|---|---|
| | Tyrosine kinase (mM) | Na,K-ATPase | Myosin K,EDTA-ATPase | Farnesyl protein transferase | AP-N (mM) | |
| Psammaplin D (**158**) | 2.8 | | | | | *110* |
| Purealidin A (**146**) | | 22% Inhibition at $10^{-4}$M | – | | | *104* |
| Purealin (**122**) | | | Activate | | | *91* |
| Lipopurealin-A (**141**) | | 30 M (brain)<br>20 M (kidney)<br>100 M (heart) | | | | *102* |
| Lipopurealin-B (**142**) | | 6 M (brain)<br>10 M (kidney)<br>> 100 M (heart) | Inhibit | | | *102* |
| Lipopurealin-C (**143**) | | 60 M (brain)<br>20 M (kidney)<br>> 100 M (heart) | | | | *102* |
| Araplysillin-I (**99**) | | 0.5 mM (brain) | | | | *81* |
| Araplysillin-II (**100**) | | 1 mM (brain) | | | | *81* |
| Psammaplin A (**152**) | | | | 7.0 mM | 70.9 | *114* |
| Bisaprasin (**154**) | | | | 4.2 mM | 30.2 | *114* |
| Psammaplin $A_1$ (**165**) | | | | 3.0 mM | | *114* |
| Psammaplin $A_2$ (**166**) | | | | 4.4 mM | | *114* |
| Aplysinellin A (**167**) | | | | 85.2 mM | 2.4 | *114* |
| Aplysinellin B (**168**) | | | | 25.1 mM | | *114* |

actomyosin ATPase and myosin EDTA-ATPase that enhanced the superprecipitation of actomyosin (*296*). Purealin binds to the myosin portion involved in actin–myosin interaction and increases the actin-activated ATPase activity of myosin (*298*). Purealin acts as a calmodulin antagonist in reconstituted actomyosin from chicken gizzard, resulting in the inhibition of light chain phosphorylation and the actin-activated ATPase activity of myosin (*299*).

Lipopurealin-A (**141**), lipopurealin-B (**142**), and lipopurealin-C (**143**) exhibited inhibitory activities on Na,K-ATPase from porcine brain and dog kidney, lipopurealin-B being the most potent inhibitor. In cardiac Na,K-ATPase all three alkaloids showed only weak activity. In addition, myosin K,EDTA-ATPase was markedly activated by purealin, whereas the enzyme was inhibited by lipopurealin-B (*102*). Purealidin A (**146**) showed weak inhibitory activity (22% inhibition at $10^{-4}$ M) on Na,K-ATPase, and had no effect on myosin K,EDTA-ATPase. These results suggest that the acryl part of purealin (**122**), lacking in purealidin A (**146**), is important for the activity of these ATPase inhibitors (*104*). Ianthesines B (**106**), C (**93**), and D (**107**) exhibited inhibitory activity against dog kidney Na,K-ATPase with $IC_{50}$ values of 440, 50, and 280 μM,

respectively, while ianthesine A (**105**) was inactive (> 2.5 mM) (*78*). The amino group of the terminal $\alpha$-amino acid (in **105**, **106,** and **93**) or the dipeptide moiety (in **93**) seems to be important for the activity, because the activity decreased in the order, $-NHSO_3^-$ (**93**), $-NHSO_3^-$ (**107**), $NH_2$ (**105**), and $NMe_2$ (**105**). Araplysillins-I (**99**) and -II (**100**) inhibited the purified porcine brain Na,K-ATPase with $IC_{50}$ values of 0.5 mM and 1 mM, respectively, which is more significant than the parent alkaloids purealin (**122**) and lipopurealins (**142**) (*81*).

Psammaplin A (**152**)**,** bisaprasin (**154**), psammaplin $A_1$ (**165**), psammaplin $A_2$ (**166**), aplysinellin A (**167**), and aplysinellin B (**168**) exhibited inhibitory activity against farnesyl protein transferase with $IC_{50}$ values of 7.0, 4.2, 3.0, 4.4, 85.2, and 25.1 mM, respectively. In addition, alkaloids **152**, **154**, and **167** exhibited inhibitory activity against leucine aminopeptidase (AP-N) with $IC_{50}$ values of 70.9, 30.2, and 2.4 mM, respectively, while other derivatives tested were inactive ($IC_{50}$ > 100 mM).

Recently, psammaplins were reported as potent histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors (see Table X) (*112*). Eleven psammaplins (see Table X), isolated from the sponge *Pseudoceratina purpurea*, were tested in the histone deacetylase (HDAC) enzyme assay at concentrations ranging from 16 nM to 10 μM, and the data obtained were compared to that of two standards, trichostatin A (*300*) and trapoxin A (*301*). There were three psammaplin derivatives whose $IC_{50}$ values were in a

TABLE X.

Enzyme-Based Histone Deacetylase (HDAC) and DNA Methyltransferase (DNMT) Inhibition Data, and Cell-Based p21 Promoter Activity Data, for the Psammaplins (*112*).

| Alkaloids | HDAC enzyme inhibition $IC_{50}$ (nM)[a] | cell-based fold induction activity $AC_{50}$ (μM)[b] | max fold induction (22 MFI is produced at 0.5 μM) | DNMT enzyme inhibition $IC_{50}$ (nM) |
|---|---|---|---|---|
| Psammaplin A (**152**) | 4.2 ± 2.4 | 7.5 | 15 | 18.6 |
| Psammaplin B (**156**) | 48 ± 12 | 15.0 | 7 | nt |
| Psammaplin C (**157**) | nt | nt | nt | nt |
| Psammaplin D (**158**) | 44 ± 10 | > 15.0 | 5 | > 30.0 |
| Psammaplin E (**159**) | 327 ± 39 | > 15.0 | 2 | > 30.0 |
| Psammaplin F (**160**) | 2.1 ± .4 | 0.7 | 18 | > 30.0 |
| Psammaplin G (**161**) | 18 ± 8 | 7.5 | 7 | 12.8 |
| Psammaplin H (**162**) | 79 ± 22 | 3.8 | 7 | > 30.0 |
| Psammaplin I (**163**) | 299 ± 70 | 2.6 | 9 | > 30.0 |
| Psammaplin J (**164**) | 20 ± 17 | 3.6 | 8 | nt |
| Bisaprasin (**154**) | 9 ± 5 | 0.7 | 9 | 3.4 |
| Trichostatin A | 14 ± 1 | 0.2 | 7.2 | nt |
| Trapoxin A | 9 ± 3 | 0.005 | 28.5 | nt |

[a] Compounds were titrated in a 1:5 dilution series (10 μM, 2 μM, 400 nM, 80 nM, and 16 nM); averages from duplicate trials are shown, except for known HDAC inhibitors, trichostatin A and trapoxin A. [b] Concentration of compound required to produce 50% p21 promoter activity by psammaplin A (**152**).

range of very potent activity (≤10 nM) and these included the following: psammaplin A (**152**) $IC_{50}$ = 4.2 nM, bisaprasin (**154**) $IC_{50}$ = 10.7 nM, and psammaplin F (**160**) $IC_{50}$ = 8.6 nM. In contrast, psammaplins B (**156**), C (**157**), D (**158**), G (**161**), H (**162**), and J (**164**) were only considered moderately active ($IC_{50}$ values >40 nM), while the other two psammaplins E (**159**) and I (**163**) were weakly active ($IC_{50}$ values >100 nM). These trends are mirrored in the activation of p21 promoter regions in cell-based assays (see Table X). The factors responsible for the structure–activity relationship (SAR) variations based on potency are clearly complex. It would appear that the structural features required for the best HDAC inhibition activity include the disulfide spacer linked to a hydroxyimino amide capped on each end by modified tyrosine residues. Deletion of one of the tyrosine end groups was not tolerated, but in one case it could be replaced by an oxalamic acid group (i.e. **160**).

Eight psammaplin analogues were then assessed in the DNA methyltransferase assay and the results are presented in Table X. Unfortunately, scarcity of material prevented the testing of three of the analogues, psammaplins B (**156**), C (**157**), and J (**164**). Only one alkaloid, bisaprasin (**154**), was observed to be very potent (≤10 nM) and two other alkaloids, psammaplin A (**152**) and G (**161**), were also potent. Interestingly, two of these, psammaplin A (**152**) and bisaprasin (**154**), were also potent HDAC inhibitors. Although the data set is limited, it would appear that the unifying feature for dual activity against both HDAC and DNMT is the presence of the disulfide spacer linked to a hydroxyimino amide capped on each end by aromatic moieties.

Recent findings implicate an interesting relationship between DNMT and HDAC as epigenetic modifiers in the silencing of tumor supressor genes, but to date no single compound has been shown to exhibit dual activity for both of these distinct targets. Psammaplin A (**152**) and bisaprasin (**154**) are the first single compounds to inhibit both of these enzymes. Furthermore, while psammaplin F (**160**) is selective for HDAC, psammaplin G (**161**) is selective for DNMT. The unique structural differences between these various psammaplins make them relevant for further SAR studies. In summary, psammaplin A (**152**) and bisaprasin (**154**), are micromolar inhibitors of both HDAC and DNMT and may be useful as biomolecular probes of epigenetic gene regulation pathways. Finally, the logical next step has been taken by the Novartis group to design a synthetic compound, NVP-LAQ824 (*302*), based in part on the trichostatin A, tripoxin B, and psammaplin A (**152**) pharmacophores, and this HDAC inhibitor has been advanced into a Phase I anticancer clinical trial (*303*).

## E. ANTIVIRAL ACTIVITY

Several bromotyrosine alkaloids have been reported to possess antiviral activities (see Table XI). These include moloka'iamine (**52**), mololipids (**53**), fistularin-3 (**79**) 11-ketofistularin-3 (**82**), and psammaplysin D (**132**).

Moloka'iamine (**52**) and the naturally occurring mixture mololipids (**53**) showed moderate anti-HIV activity. Moloka'iamine (**52**) showed an inhibition of 90% at 10 μg/mL against HSV-II (*42*). Mololipids (**53**) exhibited selective activity against HIV-1 with an $ED_{50}$ of 52.2 μM without cytotoxicity against human peripheral blood mononuclear cells ($IC_{50}$ > 100 μg/mL), suggesting that this series of anti-HIV activity lipids has potential for future studies (*43*). A series of pure synthetic mololipids was screened for gp120 binding

TABLE XI
Antiviral Activity of Bromotyrosine Derivatives

| Alkaloids | Antiviral activity | Ref. |
|---|---|---|
| Moloka'iamine (**52**) | Mv 1 Lu/HSV II: 10 μg/mL 92% reduced; CV-1/HSV-1 and BHK/VSV not active | *42* |
| Mololipids (**53**) | HIV-1 ED50 52.2 μM | *43* |
| Fistularin-3 (**79**) | Feline leukemia [$ED_{50}$: 22 μM (4.8 μg/200 μl)]. $ED_{50}$: AZT 0.10 μM, $ED_{50}$: ddCyd 15 μM. Not active against FeLV at 100 μg/200 μl | *71* |
| 11-Ketofistularin-3 (**82**) | Feline leukemia [$ED_{50}$: 42 μM (9.3 μg/200 μl)]. $ED_{50}$: AZT 0.10 μM, $ED_{50}$: ddCyd 15 μM. Not active against FeLV at 100 μg/200 μl | *71* |
| Psammaplysin D (**132**) | 51% inhibition at 0.1 μg/mL against Haitian RF stran of HIV-1 | *96* |

by analyzing the interaction of mololipid monolayers with recombinant gp120 at an air–water interface (*198*). None of these interacted significantly with gp120, suggesting that the action of mololipids seems unlikely by impairing HIV–glycolipid interactions on the plasma cell membrane.

Fistularin-3 (**79**) and 11-ketofistularin (**82**) showed activity against feline leukemia virus with an $ED_{50}$ value of 22 μM (4.8 μg/200 μl) and 42 μM (9.3 μg/200 μl), respectively (*71*). The highest concentrations tested for cytotoxicity against FeLV were 100 μg/200 μl, and neither compound was toxic at this dosage. The alkaloids were less active than 3′-azido-3′-deoxythymidine (AZT, $ED_{50}$ 0.10 μM), but were comparable to 2′,3′-dideoxycytidine (ddCyd ,$ED_{50}$ 15 μM) in these assays. Fistularin-3 (**79**) also exhibited anti-HIV-1 activity with an $EC_{50}$ value of 6.9 μM (*311*).

Reverse transcriptase (RT) plays a critical role in the early steps of the life of human immunodeficiency virus (HIV) (*304* ), and for over a decade has been one of the major targets of AIDS therapy. Polycitone A (**280**) was found to be a potent general inhibitor of retroviral reverse transcriptases and cellular DNA polymerases (*305*). Polycitone A exhibited potent inhibitory capacity of both RNA- and DNA-directed DNA polymerases. It inhibits retroviral reverse transcriptases (RTs) of human immunodeficiency virus type 1 (HIV), murine leukemia virus (MLV) and mouse mammary tumor virus (MMTV)] as efficiently as cellular DNA polymerases of both DNA polymerases $\alpha$ and $\beta$ and the prokaryotic Klenow fragment of *Escherichia coli* DNA polymerase I. The mode and mechanism of inhibition of the DNA-polymerase activity associated with HIV-1 RT by polycitone A (**280**) have been studied. The results suggest that the inhibitory capacity of the DNA polymerase activity is independent of the template-primer used. The RNase H function is hardly affected by this inhibitor. Polycitone A has been shown to interfere with DNA primer extension, as well as with the formation of the RT-DNA complex. Steady-state kinetic studies demonstrate that this inhibitor can be considered as an allosteric inhibitor of HIV-1 RT. The target site on the enzyme may be also spatially related to the

substrate binding site, since this inhibitor behaves competitively with respect to dTTP with poly(rA)·oligo(dT) as a template primer. Chemical transformation of the five phenol groups of polycitone A by methoxy groups decreased the ability to inhibit the DNA polymerase function by 40-fold. Furthermore, this analog lacks the ability to inhibit DNA primer extension as well as the formation of the RT-DNA complex (*305*).

## F. CALCIUM CHANNEL REGULATOR

Bastadins were found to be modulators of skeletal muscle FKBP12/calcium channel complex, which selectively modulated the skeletal isoform of the ryanodine-sensitive sarcoplasmic reticulum (SR) calcium channel by a novel mechanism involving the FK506 binding protein (FKBP12)/ryanodine receptor skeletal isoform (RyR-1) complex (*139*). Bastadins-5 (**209**), -7 (**211**), and -19 (**223**) showed marked differences in potency and efficacy toward activation of the binding of [$^3$H]ryanodine. In physiological salt, bastadin-5 (5 μM) increases the [$^3$H]ryanodine binding capacity of SR membranes 5-fold, by stabilizing the high affinity conformation of RyR-1 for ryanodine without shifting the affinity of the activator site for $Ca^{2+}$ or altering the response to caffeine or adenine nucleotides. Bastadin-5 decreases the inhibitory potency of $Mg^{2+}$ 7-fold and high concentrations of ($>100$ μM) $Ca^{2+}$ nearly 5-fold. Bastadin-5 inhibits $Ca^{2+}$ uptake into SR vesicles and enhances $Ca^{2+}$-induced $Ca^{2+}$ release 8-fold. Bastadin-5 increases single-channel open dwell time, $\tau_1$ and $\tau_2$, 65- and 92-fold, respectively, without changing unitary conductance for $Cs^+$ (450 picosiemens) or open probability. The most significant finding is that the unique actions of bastadin-5 on [$^3$H]ryanodine binding and $Ca^{2+}$ transport are antagonized by the immunosuppressant FK506. FK506 alone weakly enhances the binding of [$^3$H]ryanodine, compared to bastadin-5. However, FK506 diminishes bastadin 5-induced changes in [$^3$H]ryanodine binding and $Ca^{2+}$ transport without altering the efficacy of adenine nucleotides. Unlike FK506, bastadin-5 does not directly promote the dissociation of FKBP12 from the RyR-1 membrane complex. However, it markedly enhances the release of FKBP12 induced by FK506. These results suggest that the bastadin-5 effector site is a novel modulatory domain on FKBP12. Bastadins represent a new class of compounds that will allow insight into the functional interactions between FKBP12 and RyR-1 (*139*).

Utilizing single channel analysis and measurements of $Ca^{2+}$ flux across the sarcoplasmic reticulum, bastadin-10 (**214**) was identified as the structural congener responsible for dramatically stabilizing the open conformation of the RyR channel, possibly by reducing the free energy associated with closed to open channel transitions ($\Delta G^*c \rightarrow o$) (*306*). The stability of the channel open state induced by bastadin-10 sensitized the channel to activation by $Ca^{2+}$ to such an extent that it essentially obviated regulation by physiological concentrations of $Ca^{2+}$ and relieved inhibition by physiological $Mg^{2+}$. These actions of bastadin-10 were produced only on the cytoplasmic face of the channel, were selectively eliminated by pretreatment of channels with FK506 or rapamycin, and were reconstituted by human recombinant FKBP12. The actions of bastadin-10 were found to be reversible. A structure–activity model is proposed by which substitutions on the Eastern and Western hemispheres of the bastarane macrocycle may confer specificity toward the RyR1–FKBP12 complex to stabilize either the closed or open channel conformation. These results indicate that RyR1–FKBP12 complexes possess a novel binding domain for phenoxycatechols and raise the possibility of molecular recognition of

an endogenous ligand (*306*). Bastadins are now used as tools to study the calcium channel (*307*,*308*).

## G. OTHER ACTIVITIES

Searching for a selective histamine-$H_3$ antagonist led to the isolation of verongamine (**139**) (*101*). Verongamine binds with an $IC_{50}$ of 0.5 μM to the $H_3$-receptor isolated from guinea pig brain membranes (*309*). Verongamine also demonstrated $H_3$-antagonist activity in the electrical field stimulated (EFS) contracted guinea pig ileum. (*310*). In this assay, EFS-induced contractions are inhibited by the H-receptor agonist (*R*)-α-methyl histamine (RAM), and the effect of RAM can be blocked by $H_3$-antagonists. Verongamine at 1 μg/ml blocked the effect of RAM. For comparison, aerophobin-1 (**113**) gave an $H_3$-receptor binding $IC_{50}$ of 9.0 μM, and showed no activity in the guinea pig ileum assay. Additionally, verongamine at 1 μg/ml has no effect against the inhibition of EFS-induced ileum contractions by the $\alpha_2$-adrenoceptor agonist clonidine. These results indicate verongamine (**139**) is a specific $H_3$-receptor antagonist (*101*). Although bromotyrosine derivatives have been reported to possess a variety of bioactivities, the detection of histamine-$H_3$ activity is unprecedented among sponge metabolites and marine natural products in general.

Archerine (**92**) was assessed for antihistaminic activity on histamine-induced contractions of guinea pig isolated ileum. The histamine agonist ($10^{-8}$–$10^{-4}$ M) caused a concentration-dependent contraction of the isolated organ. Archerine (**92**) at the concentration of $1.2\times10^{-4}$ M completely abolished the 1 μM response of histamine, while a milder effect was observed at the concentrations $1.2\times10^{-5}$ M and $1.2\times10^{-6}$ M. This inhibition was removed by washing the tissue with fresh medium, indicating that the antagonism produced by archerine (**92**) is reversible. This result is particularly interesting if we consider that archerine (**92**) appears not to possess all the structural features which are currently used as guidelines for the synthesis of antihistamine drugs (*77*).

Intravenous injection of 100 mcg/kg of *N*,*N*,*N*-trimethyl-dibromotyramine (**47**) in an anesthetized dog caused a small, transient hypertensive response (20 mm, 25 s), followed by a similar short-lived hypotensive reaction (20mm, 30 s). Large doses of **47** (1 mg/kg) caused a marked and relatively sustained rise in blood pressure (120 mm, 4.8 min), typical of that induced by 1 μg/kg of epinephrine. This pressor effect was blocked by an *alpha* adrenergic antagonist, tolfazoline (12 mg/kg), thus characterizing **47** as an *alpha* adrenergic agent (*37*). When the pressor effect of **47** was blocked by tolazoline, a fall in blood pressure was observed, indicating a *beta*-adrenoreceptor mediated response. This depressive effect was blocked by propanolol (2 mg/kg), a beta-adrenergic blocker, thereby identifying a dual adrenergic effect of **47** on blood pressure. Synthetic and natural **47** caused identical responses when administered consecutively in identical doses to the same dog. Thus the possibility that the dual adrenergic activity might be due to a trace impurity seems to be ruled out (*37*).

*N*,*N*,*N*-Trimethyl-dibromotyramine (**47**) had stimulant properties on the central nervous system. Spontaneous motor activity in mice was increased 41% at a 1 mg/kg i.p. dose. A preliminary study on the smooth muscle preparations indicated that **47** had a non-specific spasmogenic response at 10 μg/mL bath concentrations. Both atropine

and antihistamine could partially antagonize this response. Although the mechanism of this action is difficult to explain at present, the quaternary structural features of **47** may possibly contribute to its spasmogenic activity in smooth muscles (*37*).

Ceratamines A (**249**) and B (**250**) both had $IC_{50}$ values of 10 μg/ml in the cell-based antimitotic assay. They are the first two representatives of a novel family of antimitotic heterocyclic alkaloids. The imidazo[4,5,d]azepine core heterocycle in the ceratamines appears to have no precedent at any oxidation level among known natural products or synthetic compounds (*151*).

Aplysillin A (*248*) weakly inhibited the binding of [$^{125}$I]-thrombin to platelet membranes with an $IC_{50}$ value of 20 μM (*150*).

## VII. Conclusions

The abundance of metabolites involving the halogenation of tyrosine is an occurrence which is highly unique to the marine environment. Both the broad range of structural classes, as well as the diversity of bioactivity associated with this structural group, suggests that this group of molecules will continue to find their way into clinical applications. From the point of view of the development of novel drug leads, these molecules have a unique potential for the introduction of new drug leads and scaffolds for the generation of new drugs. This is clearly due, in part, to the good drug-like properties for this group of secondary metabolites, which, combined with the unique and abundant structural variations, suggests that the opportunites for applying these molecules to issues associated with human health has just begun.

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