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SYNTHESIS AND CONVERSION OF 3-(2-HYDROXYTHIOBENZAMIDO)BENZO[*b*]FURANS

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Abstract - A simple method for the introduction of a 2-aroylbenzofuran-3-yl residue at the nitrogen atom of 2-hydroxythiobenzamide is described. Thereby *N*-(2-aroylbenzofuran-3-yl)-2-hydroxythiobenzamides (**4**) were obtained which undergo an oxygen-sulfur position exchange when they were heated in acetic acid yielding the isomeric *N*-(2-thioaroylbenzofuran-3-yl)-2-hydroxybenzamides (**6**).

INTRODUCTION

A large number of substituted *N*-aryl-2-hydroxy(thio)benzamide derivatives are used as drugs with different indications (e.g. as antipyretic, antiinflammatory or antibacterial drugs).[1] In contrast thereto the pharmacological actions of *N*-benzofuryl-2-hydroxy(thio)benzamide derivatives are previously unknown. On the other hand, a number of 2-aroyl-3-aminobenzo[*b*]furans are known to be active as analgesic,[2] antiinflammatory[3] and antiallergic[4] compounds; 2-aroyl-3-thiocarbonylbenzo[*b*]furanes were described to have antiinflammatory properties.[3] These facts lead one to suppose that the previously unknown 2-aroyl-3-(2-hydroxythiobenzamido)benzo-[*b*]furans may be a class of pharmacologically relevant compounds.

RESULTS AND DISCUSSION

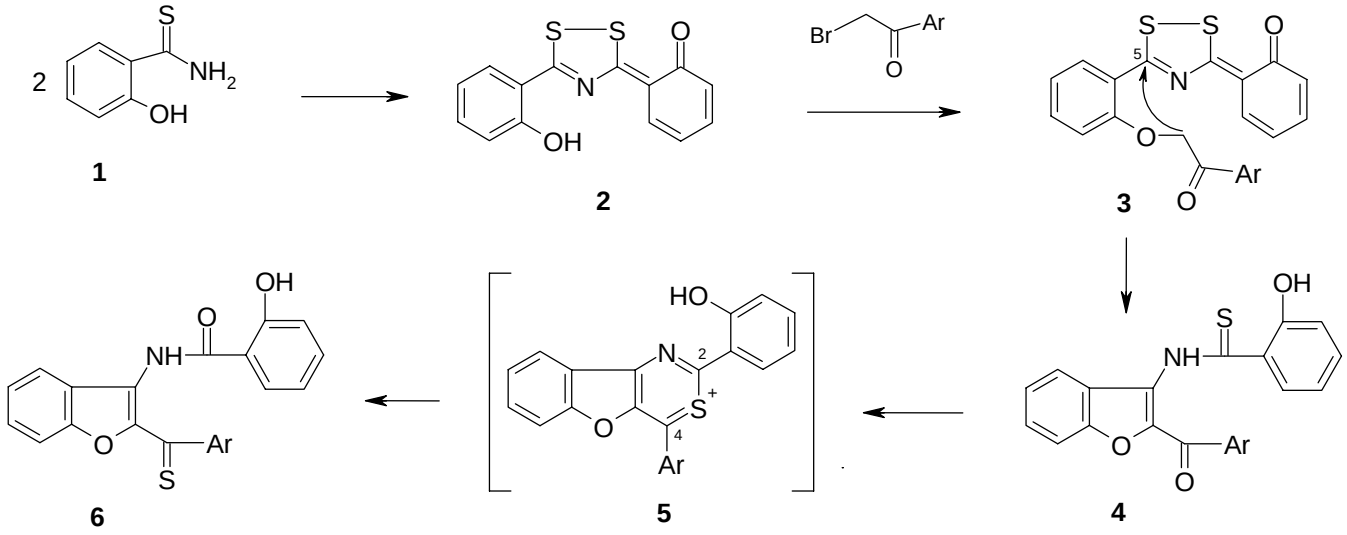
The dithiazole (**2**) which is prepared by oxidation of 2-hydroxythiobenzamide (**1**)[5,6] can be alkylated at the phenolic hydroxyl group.[7] Using bromoacetylaryl derivatives ($BrCH_2COAr$) with Et_3N in DMF the alkylation leads to the formation of the phenolic ethers (**3**) (Scheme 1) which were obtained in yields of 73-96% as dark violet crystals, only slightly soluble in the common solvents.

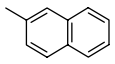
When the suspension of **3** in sodium methoxide/MeOH was refluxed for a few minutes a clear

solution resulted from which the hydroxythiobenzamidobenzofurans (**4**) precipitated after acidification. This reaction can be explained as a nucleophilic attack of the lateral acidic methylene moiety at the electrophilic dithiazole-C5-atom of **3**. After ring opening and extrusion of one sulfur atom the products (**4**) are formed.

Alternatively an attack of sodium methoxide is possibly the first step of the ring opening reaction, however no evidence is given for this course of the reaction.

A possible role of the benzoxazines (**7**) (isomeres of **4**) as intermediates or reaction products[8] could be excluded by the spectroscopic data that indicated no appearence of **7**.



3 - 6	Ar
a	C_6H_5
b	C_6H_4-4-Cl
c	C_6H_4-3-NO_2
d	
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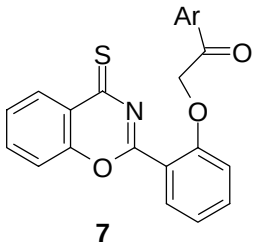


Scheme 1

The type of the synthesis belongs to those benzo[b]furan preparations in which an *ortho*-carbofunctionalized phenol is reacting with an acceptor-substituted halomethane ($HalCH_2CY$).[9] Thereby an *O*-alkylation is the first step of the reaction. The resulting aryl ether possesses an activated nucleophilic methylene group that attacks the *ortho*-carbon substituent leading to the formation of the C2-C3 bond of the resulting benzofuran (Figure 1). Benzofurans prepared by this way always bear an acceptor group (CY) at the C2. The substituent at the C3 atom can be

determined by the choice of the *ortho*-carbo function of the phenolic educt.[9-11] When a nitrile (2-hydroxybenzonitrile) is used, for example, benzofurans with an amino function (Z = NH_2) are obtained.[12,13,19]

In the syntheses described in this report the *ortho*-carbo function is a part of a dithiazole cycle. The benzofuran is formed as the product of a ring transformation during the course of which the 2-hydroxythiobenzamido substituent at the C3 is generated.

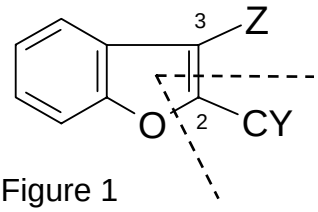
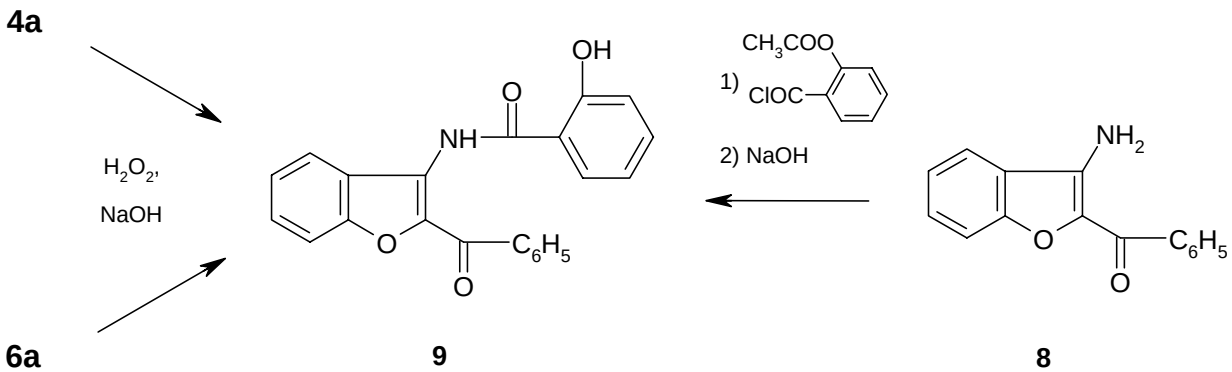


Figure 1

The yellow hydroxythiobenzamidobenzofurans (**4**) were converted into the isomeric dark brown thioaroylbenzofurans (**6**) by refluxing in acetic acid. A possible intermediate of this conversion could be the thiazinium salt (**5**) that may undergo a ring opening to form **6** after addition of water at the C2. Considering the reactivity of other 1,3-thiazinium salts, the attack of nucleophiles at the thiazine-C2-atom[14] as well as at the thiazine-C4-atom[15-17] is probable. Possibly, the products of a nucleophilic reaction at the C2 are formed as thermodynamically stable final compounds. Thereby the phenolic hydroxy group may have an influence on the course of the reaction.

The structures of **4a** and **6a** were confirmed by the ^{1}H NMR (H-COSY) and ^{13}C NMR spectra (HMQC, HMBC). For an additional structural proof **4a** and **6a** were treated with H_2O_2/NaOH**.** Thereby the sulphur atom of the respective thioamide or thioketone group was replaced by oxygen. In both cases the benzofuran (**9**) was the resulting product (Scheme 2). Compound (**9**)



Scheme 2

was also obtained by an alternative synthesis. Therefore the benzofuran (**8**) was prepared according to Gewald and Jänsch[19] followed by subsequent conversion with 2-acetoxybenzoyl-chloride/ NaOH.

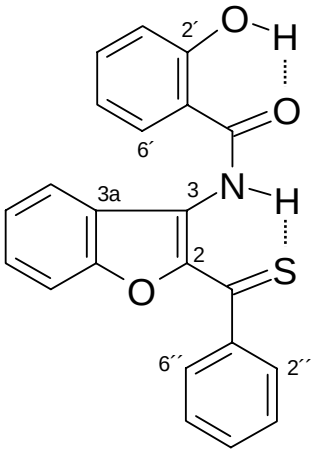
The comparison of the NMR signals of the compounds listed in Table 1 reveal the following results: The peaks of the acylamide-C-atoms of **6a** (164.96) and **9** (165.75) have almost the same chemical shifts. The analogous peak of the 2-hydroxybenzamide (**11**) has a shift of 172.42 ppm. The chemical shifts of the thioacylamide-C-atoms of **4a** (196.94) and the 2-hydroxythiobenzamide (**10**) (196.90) are identical. As well, the signals of the ketone-C-atoms of **4a**, **9** and **8** have nearly the same chemical shifts.

Table 1. Chemical shifts of the carbonyl- and thiocarbonyl-C-atoms of **4a**, **6a**, **8**, **9**, **10** and **11**

	-NH-CO-	-NH-CS-	-CO-C_6H_5	-CS-C_6H_5
4a		196.94	183.86	
6a	164.96			213.25
8			180.78	
9	165.75		183.24	
2-hydroxythiobenzamide (**10**)		196.90		
2-hydroxybenzamide (**11**)	172.42			

The identity of the thioketone-atom of **6a** (213.25) was checked by the respective cross peaks (correlation with C-H2`` and C-H6``: 7.72; HMBC). The acylamide-C-atom of **6a** (164.96) is characterized by a correlation with the CH-6` (7.98) and a weak correlation with NH (12.31).

In the ^{1}H NMR spectra of **6a** the position of the peaks of the NH and the OH group at 11.64 and

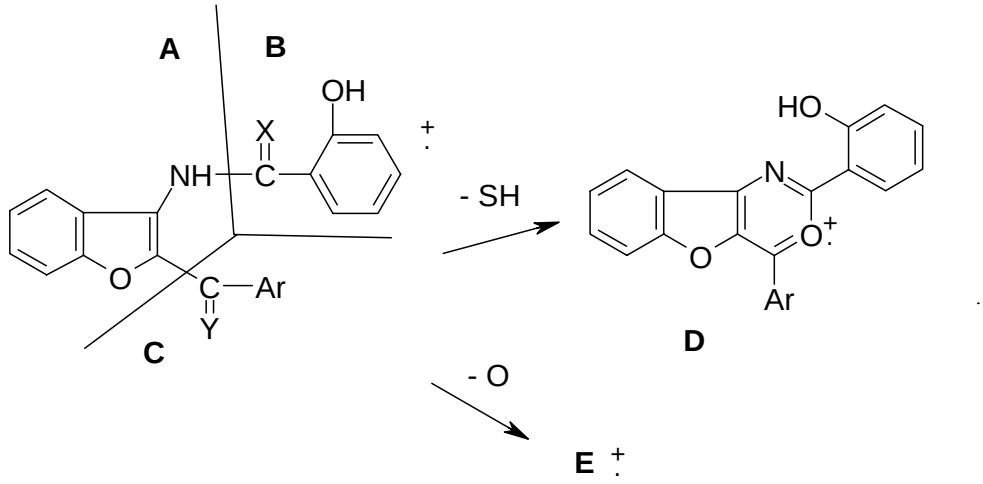


6a

Figure 2

12.31 is an indication for the appearance of hydrogen bridge linkages. Dissolution experiments provided evidence that these hydrogen bonds are intramolecular (Figure 2).

The MS spectra of the benzofurans (**4**) and (**6**) exhibit the molecular peaks with an intensity of 10-73 % (Table 2).The main process of the fragmentation is the α-cleavage of the compounds into an aminothioaroylbenzofuran ion (**AC**, Y=S, 40-100 %; Scheme 3) and a 2-hydroxybenzoyl fragment ion (**B**, X=O, 41-100 %). This fragmentation is observerd in the case of hydroxy-benzoylbenzofurans (**6**) as well as in the case of the hydroxythiobenzoylbenzofurans (**4**)



Scheme 3

Table 2. MS spectral fragmentation of the hydroxy(thio)benzoylbenzofurans (**4**) and (**6**) [% rel.int.]

				AC	**B**	**AC**+H[(a)]	**B**	**C**	**C**	**D**	**E**
	X	Y	$M^{+\cdot}$	(Y=S)	(X=O)	(Y=O)	(X=S)	(Y=O)	(Y=S)		
4a	S	O	32	100	50	18	-	44	-	48	17
4b	S	O	28	100	93	21	-	13	8	47	7
4c	S	O	20	62	100	20	-	11	-	19	9
4d	S	O	20	100	41	10	-	5	8	34	10
4e	S	O	73	53	33	4	-	100	-	20	20[(b)]
6a	O	S	27	100	52	4	-	-	-	48	2
6b	O	S	10	47	100	15	-	5	7	19	7
6c	O	S	27	40	100	21	-	5	-	28	7
6d	O	S	25	100	43	9	-	-	7	37	8
6e	O	S	37	100	55	5	-	8	8	19	5

[(a)] no appearence of an **AC** fragment

[(b)] $M^{+\cdot}$-OH instead of $M^{+\cdot}$-O

leading to the supposition that under MS conditions a conversion of **4** into **6** is induced.
The appearence of an isomeric fragmentation in the case of **4a** and **6a** under formation of **AB** (X=O) and **C** (Y=S) could be excluded by highly resolution MS spectra. A cleave-off of hydroxythiobenzoyl radical with formation of an aminoaroylbenzofuran ion (**AC**+H, Y=O), which could be expected in the case of the hydroxythiobenzoylbenzofurans (**4**)**,** was detected in only small amounts. This fragment was also observed with a low intensity in the MS spectra of **6** (4-21 %) indicating that under MS conditions a slight conversion of **6** into **4** seems to take place.
All the compounds (**4**) generate aroyl fragment ions (**C**, Y=O, 5-100 %). The intensity of this fragmentation is higher in the case of **4** than in the case of the compounds (**6**) and proves to be the striking difference between the MS spectra of these isomers. In contrast, thereto the formation of a thioaroyl fragment ion (**C**, Y=S) was observed to an only small extend.
Another fragmental ion - [($M^{+\cdot}$)-HS] (19-48 %) - is also visible in all the MS spectra of **4** and **6**. This is possibly due to the formation of an oxazinium cation (**D**).
A remarkable observation in all the spectra of **4** and **6** is the release of oxygen leading to the formation of the fragment ion [($M^{+\cdot}$)-O] (E, 5-17 %; high resolution MS spectrum in the case of **4a** and **6a**; M-OH in the case of **4e**, 20 %, high resolution). This fragmentation is known from substances that are able to release oxygen (e.g. nitro compounds or sulfoxides).[18] For compounds with keto or carbonamide stuctures it is rather exceptional.
To suppress thermally induced conversions during the MS spectrometry additional spectra of **4a** and **6a** were recorded using a cold ionization source. However, no differences to the usual spectra of these compounds could be found.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured with a Perkin Elmer 16 PC FTIR spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian Gemini 300 operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C and a Bruker DRX-600 Avance operating at 600,13 MHz and 150,91 MHz for ^{13}C. MS spectra were recorded on a JEOL JMS-D 100 spectrometer (EI, 70eV), resp. Finnigen MAT 8230. The temperature of the ion source was 250 °C; in measurements with a cold ionization source the temperature was 130 °C. ESI-HRMS spectra were recorded on a Bruker Daltonics 7T Apex II FT-ICR-MS.

Substituted 6-[5-(2-hydroxyphenyl)-1,2,4-dithiazol-3-ylidene]-2,4-cyclohexadien-1-one (3) General procedure

To a stirred solution of Et_3N (1 mL, 7.2 mmol) in DMF (10 mL) **2**[5,6] (1.0 g, 3.5 mmol) was

added. After stirring for 2 min at rt powdered $BrCH_2COAr$ (7 mmol) was added in one portion. The mixture was stirred for further 5 min and the precipitated product was filtered off by suction. The collected crystals were washed with MeOH. (All the resulting compounds were only very slightly soluble in the common solvents. For this reason it was not possible to record NMR-spectra).

6-[5-(2-Phenacyloxyphenyl)-1,2,4-dithiazol-3-ylidene]-2,4-cyclohexadien-1-one (3a)

Starting from $BrCH_2COC_6H_5$ (1.4 g; 7 mmol). Yield 1.31 g (92%). dark violet crystals (AcOH); mp 165-170 ^oC (lit.,[7] 158-165 ^oC). IR (KBr): υ = 3060, 2925, 1692, 1609 cm^{-1}. MS (EI): *m/z* (%)= 405 ($M^{+\cdot}$, 1), 287 (37), 105 (100). MS (EI-HRMS): *m/z* (%) = 405.05039(7)($M^{+\cdot}$) ($C_{22}H_{15}NO_3S_2$ requires 405.04928). Anal. Calcd for $C_{22}H_{15}NO_3S_2$: C, 65.17; H, 3.73; N, 3.45; S, 15.82. Found: C, 65.21; H, 3.74; N, 3.26, S, 16.01.

6-{5-[2-(4-Chlorophenacyloxy)phenyl]-1,2,4-dithiazol-3-ylidene}-2,4-cyclohexadien-1-one (3b)

Starting from $BrCH_2COC_6H_4$-4-Cl (1.63 g; 7 mmol). Yield 1.39 g (90%). dark violet crystals (after boiling with AcOH and subsequent separation by filtration); mp 238-240 ^oC. IR (KBr): υ = 2924, 2854, 1696, 1609 cm^{-1}. MS (EI): *m/z* (%)= 439 ($M^{+\cdot}$, 3), 287 (80), 139 (100). Anal. Calcd for $C_{22}H_{14}NO_3ClS_2$: C, 60.06; H, 3.21; N, 3.18, S, 14.58. Found: C, 60.36; H, 3.15; N, 3.11, S, 14.39.

6-{5-[2-(3-Nitrophenacyloxy)phenyl]-1,2,4-dithiazol-3-ylidene}-2,4-cyclohexadien-1-one (3c)

Starting from $BrCH_2COC_6H_4$-3-NO_2 (1.71 g; 7 mmol). Yield 1.51 g (96%). dark violet crystals (AcOH); mp 178-183 ^oC (lit.,[7] 178-183 ^oC). IR (KBr): υ = 3086, 2925, 1699, 1609 cm^{-1}. MS (EI): *m/z* (%)= 450 ($M^{+\cdot}$, 2), 298 (76), 287 (65), 150 (63). Anal. Calcd for $C_{22}H_{14}N_2O_5S_2$: C, 58.66; H, 3.13; N, 6.22, S, 14.24. Found: C, 58.69; H, 3.19, N, 6.16; S, 14.36.

6-{5-[2-(2-Naphth-2-yl-2-oxoethoxy)phenyl]-1,2,4-dithiazol-3-ylidene}-2,4-cyclohexadien-1-one (3d)

Starting from $BrCH_2COC_{10}H_7$ (1.74 g; 7 mmol). Yield 1.39 g (87%). dark violet crystals (AcOH); mp 229-232 ^oC. IR (KBr): υ = 3057, 2924, 1683, 1609 cm^{-1}. MS (EI): *m/z* (%)= 455 ($M^{+\cdot}$, 5), 302

(40), 287 (100), 155 (82). Anal. Calcd for $C_{26}H_{17}NO_3S_2$: C, 68.55; H, 3.76; N, 3.07; S, 14.08. Found: C, 68.37; H, 3.72; N, 2.96; S, 14.27.

6-{5-[2-(2-Thien-2-yl-2-oxoethoxy)phenyl]-1,2,4-dithiazol-3-ylidene}-2,4-cyclohexadien-1-one (3e)

Starting from $BrCH_2COC_4H_3S$ (1.44 g; 7 mmol). Yield 1.05 g (73%). dark violet crystals (AcOH); mp 201-203 ^oC. IR (KBr): υ = 3072, 2924, 1671, 1609 cm^{-1}. MS (EI): *m/z* (%)= 411 ($M^{+\cdot}$, 14), 287 (61), 111 (100). Anal. Calcd for $C_{20}H_{13}NO_3S_3$: C, 58.37; H, 3.18, N, 3.40; S, 23.38. Found: C, 58.39; H, 3.22; N, 3.30; S, 23.40.

***N*-(2-Aroylbenzo[*b*]furan-3-yl)-2-hydroxythiobenzamides (4)**

General Procedure

3 (1.0 g; crude product) was added to a 5M NaOMe-solution in MeOH (5 mL). The mixture was refluxed for 5 min. After cooling to rt the solution was acidified with 1M HCl. The oily precipitate was repeatedly rubbed with water until the substances began to crystallize.

***N*-(2-Benzoylbenzo[*b*]furan-3-yl)-2-hydroxythiobenzamide (4a)**

Starting from **3a** (1.0 g, 2.5 mmol). Yield 0.68 g (73%). yellow needles (benzene); mp 156-160 ^oC. IR (KBr): υ = 1610 cm^{-1}. ^1H NMR (DMSO-d_6, H-COSY): δ = 6.87 (br dd, 1H, CH-5´), 6.97 (br d, 1H, CH-3´), 7.33 (br dd, 1H, CH-4´), 7.41 (br dd, 1H, CH-5), 7,54 (br dd, 2H, CH-3´´,CH-5´´), 7.59 (br dd, 1H, CH-6), 7.66 (m, 2H, CH-6´, CH-4´´), 7.79 (br d, 1H, CH-4), 7.79 (br d, 1H, CH-7), 7.98 (br d, 2H, CH-2´´, CH-6´´), 10.89 (br s, 1H, NH), 12.02 (br s, 1H, OH). Broad signals because of tautomerism, the giving of coupling constants is therefore not possible. ^{13}C NMR (DMSO-d_6, HMQC, HMBC): δ = 112.68 (C-7), 116.95 (C-3´), 118.88 (C-5´), 123.43 (C-4), 123.57 (C-5), 126.69, 127.58, 143.82 (C-2, C-3, C-3a, C1´), 128.40 (C-3´´, C-5´´), 128.57 (C-6), 129.08 (C-2´´, C-6´´), 131.25 (C-6´), 132.20 (C-4´), 133.15 (C4´´). 136.72 (C-1´´), 153.39, 153.97 (C-2´, C7a), 183.86 (CO), 196.94 (CS). MS (EI-HRMS): *m/z* (%) = 373.0806 (32)($M^{+\cdot}$) ($C_{22}H_{15}NO_3S$ requires 373.07725), 357.08849 (17)$(M-O)^+$($C_{22}H_{15}NO_2S$ requires 357.08234), 340.10064 (48)$(M-SH)^+$ ($C_{22}H_{14}NO_3$ requires 340.09735), 280.04343 (8)$(M-C_6H_5O)^+$ ($C_{16}H_{10}NO_2S$ requires 280.04321), 268.04332 (6)$(M-C_7H_5O)^+$ ($C_{15}H_{10}NO_2S$ requires 268.04321), 252.04807 (100)$(M-C_7H_5O_2)^+$ ($C_{15}H_{10}NOS$ requires 252.0483) ($C_{15}H_{10}NO_3$ requires 252.06605), 237.07734 (18)$(M-C_7H_4OS)^+$ ($C_{15}H_{11}NO_2$ requires 237.07896) ($C_{15}H_9OS$ requires 237.0374), 220.07489 (4),121.0285 (50)($C_7H_5O_2$ requires 121.02895)(C_7H_5S requires

121.0112), 105.0351 (44)(C_7H_5O requires 105.03404), 93.03454 (12)(C_6H_5O requires 93.03404). MS (ESI-HRMS)(positive): *m/z* = 396.06650 $(M+Na)^+$ ($C_{22}H_{15}NO_3NaS$ requires 396.06703). Anal. Calcd for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.75. Found: C, 70.72; H, 4.07, N, 3.68.

***N*-[2-(4-Chlorobenzoyl)benzo[*b*]furan-3-yl]-2-hydroxythiobenzamide (4b)**

Starting from **3b** (1.0 g, 2.3 mmol). Yield 0.75 g (80%). yellow needles (benzene); mp 118 ^oC (decomp). IR (KBr): υ = 1611 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.88-7.96 (m, 12H, aromat.), 11.0-12.3 (very br, NH, OH). ^{13}C NMR (DMSO-d_6): δ = 113.40, 117.45, 119.43, 124.25, 124.36, 129.20, 131.45, 132.95, 136.71, 154.22, 173.59 (CO), 197.41 (CS). MS (EI): *m/z* (%)= 407 ($M^{+\cdot}$, 28), 391 $(M-O)^+$ (7), 374 $(M-SH)^+$ (47), 286 $(M-C_7H_5O_2)^+$ (100), 271 $(M-C_7H_4OS)^+$ (21), 155 $(C_7H_4ClS)^+$ (8), 139 $(C_7H_4ClO)^+$ (13), 121 $(C_7H_5O_2)^+$ (93), 93 $(C_6H_5O)^+$ (20). Anal. Calcd for $C_{22}H_{14}NO_3ClS$: C, 64.79; H, 3.46, N, 3.43. Found: C, 64.69; H, 3.51, N, 3.43.

***N*-[2-(3-Nitrobenzoyl)benzo[*b*]furan-3-yl]-2-hydroxythiobenzamide (4c)**

Starting from **3c** (1.0 g, 2.2 mmol). Yield 0.56 g (61%). yellow needles (benzene); mp 116-119 ^oC (decomp). IR (KBr): υ = 1611 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.87-8.61 (m, 12H, aromat.), 10.5-12.3 (very br, NH,OH). ^{13}C NMR (DMSO-d_6): δ = 112.62, 116.62, 118.68, 123.04, 123.50, 123.75, 126.80, 128.28, 128.94, 130.05, 131.42, 132.18, 134.87, 147.54, 153.60, 154.46, 177.40 (CO), 196.67 (CS). MS (EI): *m/z* (%)= 418 ($M^{+\cdot}$, 20), 402 $(M-O)^+$ (9), 385 $(M-SH)^+$ (19), 298 $(M-C_7H_4O_2)^+$ (32), 297 $(M-C_7H_5O_2)^+$ (62), 282 $(M-C_7H_4OS)^+$ (20), 251 (15), 121 $(C_7H_5O_2)^+$ (100), 150 $(C_7H_4NO_3)^+$ (11), 93 $(C_6H_5O)^+$ (21). Anal. Calcd for $C_{22}H_{14}N_2O_5S$. C, 63.15; H, 3.37; N, 6.69. Found: C, 62.88; H, 3.40; N, 6.70.

***N*-[2-(Naphth-2-oyl)benzo[*b*]furan-3-yl]-2-hydroxythiobenzamide (4d)**

Starting from **3d** (1.0 g, 2.2 mmol). Yield 0.88 g (95%). yellow needles (benzene); mp beginning at 150 ^oC (decomp). IR (KBr): υ = 1605 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.70-8.72 (m, 15H, aromat.), 10.5-12.4 (very br, NH,OH). ^{13}C NMR (DMSO-d_6): δ = 112.63, 116.52, 118.29, 123.14, 123.41, 123.58, 124.58, 126.74, 127.57, 127.98, 128.28, 128.48, 128.97, 129.65, 130.92, 131.87, 134.41, 134.47, 134.84, 153.52, 155.15, 183.76 (CO), 196.05 (CS). MS (EI): *m/z* (%)= 423 ($M^{+\cdot}$, 20), 407 $(M-O)^+$ (10), 390 $(M-SH)^+$ (34), 302 $(M-C_7H_5O_2)^+$ (100), 287 $(M-C_7H_4OS)^+$ (10), 270 (13), 171 $(C_{11}H_7S)^+$ (8), 160 (7), 155 $(C_{11}H_7O)^+$ (5), 139 (7), 121

$(C_7H_5O_2)^+$ (41), 93 $(C_6H_5O)^+$ (13). Anal. Calcd for $C_{26}H_{17}NO_3S$: C, 73.74, H, 4.05; N, 3.31. Found: C, 73.69; H, 4.07, N, 3.33.

***N*-[2-(Then-2-oyl)benzo[*b*]furan-3-yl]-2-hydroxythiobenzamide (4e)**

Starting from **3e** (1.0 g, 2.4 mmol). Yield 0.69 g (76%). yellow needles (benzene); mp beginning at 130 ^oC (decomp). IR (KBr): υ = 1612 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.98-8.43 (m, 11H, aromat.), 10.5-12.7 (br, NH, OH). ^{13}C NMR (DMSO-d_6): δ = 112.89, 116.86, 119.13, 123.20, 123.56, 123.98, 125.95, 128.67, 128.84, 129.21, 132.08, 132.69, 135.06, 136.58, 142.09, 142.77, 153.25, 154.49, 174.65 (CO), 196.42 (CS). MS (EI-HRMS): *m/z* (%)= 379.03252 (73)($M^{+\cdot}$), ($C_{20}H_{13}NO_3S_2$ requires 379.03368), 362.02695 (20)$(M-OH)^+$ ($C_{20}H_{12}NO_2S_2$ requires 362.03095), 346.05379 (20)$(M-HS)^+$ ($C_{20}H_{12}NO_3S$ requires 346.0493), 268.0405 (87)$(M-C_5H_3OS)^+$ ($C_{15}H_{10}NO_2S$ requires 268.04323), 257.99859 (53)$(M-C_7H_5O_2)^+$ ($C_{13}H_8NOS_2$ requires 258.00473), 243 (4)$(M-C_7H_4OS)^+$, 242 (13), 226 (7), 121.02743 (33)$(C_7H_5O_2)^+$ (requires 121.02895), 110.98942 (100)$(C_5H_3OS)^+$ (requires 110.99046). Anal. Calcd for $C_{20}H_{13}NO_3S_2$: C, 63.31, H, 3.45, N, 3.69. Found. C, 63.39; H, 3.41; N, 3.65.

***N*-(2-Thioaroylbenzo[*b*]furan-3-yl)- 2-hydroxybenzamide (6)**

General Procedure

Powdered **4** (100 mg) was added to acetic acid (2 mL). The mixture was refluxed for 10 min and the solvent was evaporated i.vac.. After cooling to rt the precipitate was collected.

***N*-(2-Thiobenzoylbenzo[*b*]furan-3-yl)-2-hydroxybenzamide (6a)**

Starting from **4a** (100 mg, 0.268 mmol). Yield 93 mg (93%). dark brown crystals (AcOH); mp 178-180 ^oC. IR (KBr): υ = 1658, 1593 cm^{-1}. ^1H NMR (DMSO-d_6, H-COSY): δ = 7.01 (dd, J = 7.8, 7.8 Hz, 1H, CH-5´), 7.07 (d, J = 8.4 Hz, 1H, CH-3´), 7.38 (dd, J = 7.8, 7.7 Hz, 1H, CH-5), 7,47 (dd, J = 7.8, 7.7 Hz, 2H, CH-3´´, CH-5´´), 7.50 (dd, J = 7.8, 7.8 Hz, 1H, CH-4´), 7.57 (m, 1H, CH-4´´), 7.62 (d, J = 8.4 Hz, 1H, CH-7), 7.67 (dd, J = 7.3, 7.1 Hz, 1H, CH-6), 7.72 (d, J = 7.8 Hz, 2H, CH-2´´,CH-6´´), 7.98 (m, 1H, CH-6´), 8.12 (d, J = 8.4 Hz, 1H, CH-4), 11.64 (br s, 1H, OH), 12.31 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, HMQC, HMBC): δ = 112.44 (C-7), 117.13 (C-3´), 117.54 (C-1´), 119.66 (C-5´), 123.19 (C-3a), 123.42 (C-5), 126.41 (C-4), 128.02 (C-3´´, C-5´´), 128.55 (C-2´´, C-6´´), 130.94 (C-6´), 131.12 (C-6), 131.42 (C-4´´), 131.91 (C-3), 134.59 (C-4´), 146.13, 146.58 (C-2, C-1´´), 152.68 (C-7a), 157.04 (C2´), 164.96 (CO), 213.25 (CS). MS (EI-HRMS): *m/z* (%) = 373.08025 (27) ($M^{+\cdot}$)($C_{22}H_{15}NO_3S$ requires 373.07725), 357.08539 (2)$(M-O)^+$($C_{22}H_{15}NO_2S$ requires 357.08234), 340.09878 (48)$(M-SH)^+$ ($C_{22}H_{14}NO_3$ requires

340.09735), 252.05146 (100)(M-$C_7H_5O_2$)$^+$ ($C_{15}H_{10}NOS$ requires 252.0483) ($C_{15}H_{10}NO_3$ requires 252.06605), 237.07804 (4)(M-C_7H_4OS)$^+$ ($C_{15}H_{11}NO_2$ requires 237.07896) ($C_{15}H_9OS$ requires 237.0374), 220.07348 (4), 121.02781 (52)($C_7H_5O_2$ requires 121.02895)(C_7H_5S requires 121.0112), 93.03464 (11)(C_6H_5O requires 93.03404). MS (ESI-HRMS)(positive): *m/z* = 374.08442 (M+H)$^+$ ($C_{22}H_{16}NO_3S$ requires 374.08509). Anal. Calcd for $C_{22}H_{15}NO_3S$: C, 70.76; H, 4.05; N, 3.75. Found: C, 70.68; H, 4.11, N, 3.88.

_N_-[2-(4-Chlorothiobenzoyl)benzo[*b*]furan-3-yl]-2-hydroxybenzamide (6b)

Starting from **4b** (100 mg, 0.246 mmol). Yield 64 mg (64%). dark brown crystals (AcOH); mp 186-190 ^{o}C. IR (KBr): υ = 1655, 1592 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.03-8.14 (m, 12H, aromat.), 11.70 (s, 1H, OH), 12.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 113.19, 117.86, 118.24, 120.39, 123.86, 124.21, 128.81, 131.02, 131.64, 132.04, 135.34, 137.04, 145.32, 147.27, 153.53, 157.73, 165.96 (CO), 213.67 (CS). MS (EI): *m/z* (%)= 407 (M$^{+\cdot}$, 10), 391 (M-O)$^+$ (7), 374 (M-SH)$^+$ (19), 286 (M-$C_7H_5O_2$)$^+$ (47), 271 (M-C_7H_4OS)$^+$ (15), 155 (C_7H_4ClS)$^+$ (7), 139 (C_7H_4ClO)$^+$ (5), 121 ($C_7H_5O_2$)$^+$ (100), 93 (C_6H_5O)$^+$ (26). Anal. Calcd for $C_{22}H_{14}NO_3ClS$: C, 64.79; H, 3.46, N, 3.43. Found: C, 64.66; H, 3.50, N, 3.56.

_N_-[2-(3-Nitrothiobenzoyl)benzo[*b*]furan-3-yl]-2-hydroxybenzamide (6c)

Starting from **4c** (100 mg, 0.239 mmol). Yield 53 mg (53%). dark brown crystals (AcOH); mp 235-237 ^{o}C. IR (KBr): υ = 1660, 1594 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.03-8.51 (m, 12H, aromat.), 11.70 (s, 1H, OH), 12.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 112.48, 117.06, 117.35, 119.62, 122.75, 123.57, 125.15, 126.61, 129.57, 130.85, 131.68, 134.29, 134.65, 146.67, 147.35, 153.17, 156.92, 164.87, 208.80. MS (EI): *m/z* (%)= 418 (M$^{+\cdot}$, 27), 402 (M-O)$^+$ (7), 385 (M-SH)$^+$ (28), 298 (M-$C_7H_4O_2$)$^+$ (80), 297 (M-$C_7H_5O_2$)$^+$ (40), 282 (M-C_7H_4OS)$^+$ (21), 251 (16), 121 ($C_7H_5O_2$)$^+$ (100), 150 ($C_7H_4NO_3$)$^+$ (5), 93 (C_6H_5O)$^+$ (17). Anal. Calcd for $C_{22}H_{14}N_2O_5S$: C, 63.15; H, 3.37; N, 6.69. Found: C, 63.13; H, 3.42; N, 6.57.

_N_-[2-(Naphthalene-2-carbothioyl)benzo[*b*]furan-3-yl]-2-hydroxybenzamide (6d)

Starting from **4d** (100 mg, 0.236 mmol). Yield 72 mg (72%). dark brown crystals (AcOH); mp 190-192 ^{o}C. IR (KBr): υ = 1655, 1592 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.00-8.37 (m, 15H, aromat.), 11.73 (s, 1H, OH), 12.35 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 113.21, 117.82, 118.22, 120.33, 124.06, 124.15, 126.70, 127.03, 127.73, 128.18, 128.34, 128.94, 129.48,

130.26, 131.58, 131.70, 132.40, 132.62, 134.82, 135.25, 144.08, 147.61, 153.46, 157.78, 165.73 (CO), 213.61 (CS). MS (EI): *m/z* (%)= 423 ($M^{+\cdot}$, 25), 407 $(M\text{-}O)^+$ (8), 390 $(M\text{-}SH)^+$ (37), 302 $(M\text{-}C_7H_5O_2)^+$ (100), 287 $(M\text{-}C_7H_4OS)^+$ (9), 286 $(M\text{-}C_7H_5OS)^+$ (9), 270 (13), 269 (13), 171 $(C_{11}H_7S)^+$ (7), 121 $(C_7H_5O_2)^+$ (43), 93 $(C_6H_5O)^+$ (15). Anal. Calcd for $C_{26}H_{17}NO_3S$: C, 73.74, H, 4.05; N, 3.31. Found: C, 73.70; H, 4.03, N, 3.33.

N-[2-(Thiophene-2-carbothioyl)benzo[*b*]furan-3-yl]-2-hydroxybenzamide (6e)

Starting from **4e** (100 mg, 0.264 mmol). In exception from the general procedure the mixture was refluxed for 20 min. Yield 73 mg (73%). dark brown crystals (AcOH); mp 145-154 ^oC. IR (KBr): υ = 1654, 1594 cm^{-1}. ^1H NMR (DMSO-d_6): δ = 6.98-8.23 (m, 11H, aromat.), 11.72 (s, 1H, OH), 12.37 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): δ = 113.13, 117.88, 119.91, 120.43, 124.14, 124.29, 126.91, 129.59, 131.54, 131.72, 133.18, 135.27, 135.82, 137.34, 140.51, 145.16, 152.85, 157.77, 165.37 (CO), 196.90 (CS). MS (EI-HRMS): *m/z* (%)= 379.03252 (37)($M^{+\cdot}$) ($C_{20}H_{13}NO_3S_2$ requires 379.03368), 363 $(M\text{-}O)^+$ (5), 346.05135 (19)$(M\text{-}SH)^+$ ($C_{20}H_{12}NO_3S$ requires 346.0493), 258.00084 (100)$(M\text{-}C_7H_5O_2)^+$ ($C_{13}H_8NOS_2$ requires 258.00473), 243 (5) $(M\text{-}C_7H_4OS)^+$, 226 (8), 126.96498 (8)$(C_5H_3S_2)^+$, ($C_5H_3NS_2$ requires 126.96762), 121.02518 (55)$(C_7H_5O_2)^+$ (requires 121.02895), 110.98733 (8)$(C_5H_3OS)^+$ (requires 110.99046), 93 $(C_6H_5O)^+$ (17). Anal. Calcd for $C_{20}H_{13}NO_3S_2$: C, 63.31, H, 3.45, N, 3.69. Found. C, 63.31; H, 3.42; N, 3.71.

(3-Aminobenzo[*b*]furan-2-yl)phenylmethanone (8)

The preparation was carried out as described in the literature.[19] light yellow crystals (EtOH); mp 124-126 ^oC (lit.,[19] 125-126 ^oC). IR (KBr): υ = 3380, 3275, 1620 cm^{-1}. ^{13}C NMR (DMSO-d_6): δ = 112.30, 120.91, 122.22, 128.31, 128.71, 130.21, 131.47, 133.63, 138.06, 143.56, 154.22, 180.78 (CO). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.93; H, 4.58, N, 5.81.

N-(2-Benzoylbenzo[*b*]furan-3-yl)-2-hydroxybenzamide (9)

A) To a stirred solution of **4a** (100 mg, 0.268 mmol) in a mixture of MeOH (1 mL) and 5M NaOH (1 mL) was added H_2O_2-solution (30%)(1 mL). After cooling to rt the solution was concentrated and acidified with 5M HCl. The precipitate was purified by PLC (Merck, PLC plates 20x20 mm, silica gel 60 F254, 2 mm, toluene). Yield 70 mg (73%).

B) Analogous to method A, starting from **6a** (100 mg, 0.268 mmol). Yield 77 mg (80%).
C) To a stirred solution of **8** (100mg, 0.42 mmol) in pyridine (1 mL) 2-acetoxybenzoylchloride (0.33 g, 1.66 mmol) was added. After stirring for 2 h at rt the mixture was poured into water (3mL) and the solution was brought to a pH of 9 by addition of 1M NaOH. The mixture was heated up to 90 ^{o}C for 2 min. After cooling to rt the oily precipitate was dissolved in a 0.5 M NaOMe-solution in MeOH (1 mL). The product was precipitated again by addition of water and was purified by PLC according to method A. Yield 65 mg (68%). yellow needles (MeCN); mp 173-175 ^{o}C. IR (KBr): υ = 1645, 1600 cm^{-1}. ^{1}H NMR (DMSO-*d*$_6$, H-COSY): δ = 6.30 (br dd, J = 7.2, 7.2 Hz, 1H, CH-5´), 6.64 (br d, J = 7.8 Hz, 1H, CH-3´), 7.06 (br dd, J = 7.2, 7.2 Hz, 1H, CH-4´), 7.32 (dd, J = 7.2, 7.2 Hz, 1H, CH-5), 7,54 (m, 3H, CH-3´´, CH-5´´, CH-6), 7.61 (m, 2H, CH-7, CH-4´´), 7.77 (br m, 1H, CH-6´), 8.05 (d, J = 7.2 Hz, 2H, CH-2´´, CH-6´´), 8.33 (d, J = 7.4 Hz, 1H, CH-4). The signals of OH and NH do not appear. This seems to be due to tautomerism connected with an H/D-exchange. ^{13}C NMR (DMSO-*d*$_6$, HMQC, HMBC): δ = 110.73 (br, C-5´), 111.90 (C-7), 117.87 (br, C-1´), 121.12 (br, C-3´), 122.29 (C-5), 123.50 (C-3a), 126.51 (C-4), 128.19 (C-6, C-3´´, C-5´´), 128.59 (C-3), 129.10 (C-2´´, C-6´´), 129.69 (C-6´), 132.09 (C-4´´), 132.31 (C-4´), 137.85 (C-1´´), 139.14 (C-2), 153.74 (C-7a), 165.75 (NHCO), 169.67 (br, C-2´), 183.24 (C_6H_5-$\underline{C}$O). MS (EI): *m/z* (%)= 357 ($M^{+\cdot}$, 24), 237 $(M-C_7H_4O_2)^+$ (100), 121 $(C_7H_5O_2)^+$ (64), 105 $(C_7H_5O)^+$ (15), 93 $(C_6H_5O)^+$ (22). Anal. Calcd for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23, N, 3.92. Found: C, 73.78; H, 4.30, N, 4.00.

2-Hydroxythiobenzamide (10)

The preparation was carried out as described in the literature.[20] light yellow crystals (EtOH); mp 119-120 ^{o}C (lit.,[20] 119-120 ^{o}C). IR (KBr): υ = 3406, 3300, 3203, 1640 cm^{-1}. ^{13}C NMR (DMSO-*d*$_6$): δ = 117.38, 118.67, 122.87, 129.98, 132.87, 156.24, 196.90 (CS). Anal. Calcd for C_7H_7NS: C, 61.28; H, 5.14, N, 10.21. Found: C, 61.43; H, 5.19, N, 10.18.

2-Hydroxybenzamide (11)

Commercially available product, purchased from Acros Organics; B 2440 Gel, Belgium. IR (KBr): υ = 3396, 3190, 1674 cm^{-1}. ^{13}C NMR (DMSO-*d*$_6$): δ = 114.56, 117.61, 118.05, 128.29, 134.42, 161.35, 172.42 (CO).

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