SYNTHESIS OF *N*-SUBSTITUTED 3-AMINOMETHYL-2,3-DIHYDROFURO[2,3-*c*]PYRIDINES, POTENT SEROTONINERGIC LIGANDS

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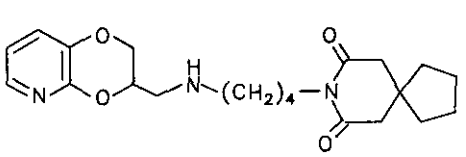
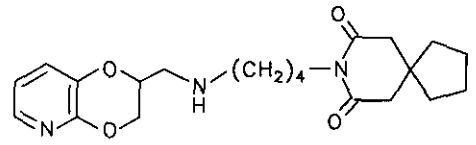
Abstract — Regioselective lithiation of 2-chloro-3-oxiranylmethoxypyridine, followed by intramolecular epoxide ring-opening reaction provided (7-chloro-2,3-dihydrofuro[2,3-*c*]pyridin-3-yl)methanol (**1**). Multistep synthesis from **1** gave a variety of *N*-substituted 3-aminomethyl-2,3-dihydrofuro[2,3-*c*]pyridines as potent serotoninergic ligands.

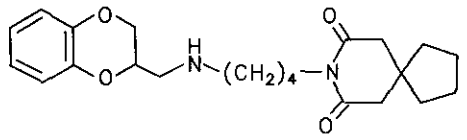
Serotonin (5-hydroxytryptamine, 5-HT) and its receptors[1] are implicated in many physiological or pathophysiological processes in the brain as well in the periphery.[2] The recent advances in the understanding of the 5-HT neurotransmission reflect, in large part, the increasing availability of compounds with selectivity and potency for individual 5-HT receptor subtypes (5-HT_{1A-D}, 5-HT_{2C}, 5-HT_3, 5-HT_4).[3,4] As a part of our ongoing effort to prepare selective ligands of the central nervous system neurotransmitter, we recently reported the synthesis of 2,3-dihydro-1,4-dioxino[2,3-*b*]pyridine analogues **A** and **B**[5-7] of MDL 72382 (selective 5-HT_{1A} ligands).[8] The pharmacological profile showed that incorporating a nitrogen atom in the benzene ring increased (compound **A**) or decreased (compound **B**) the affinity for 5-HT_{1A} receptor according to the *N*-position in the ring.



A *pKi* 5-HT_{1A}= 10.9



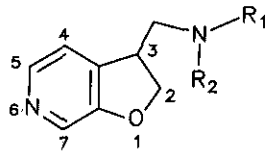
B *pKi* 5-HT_{1A}= 7.4



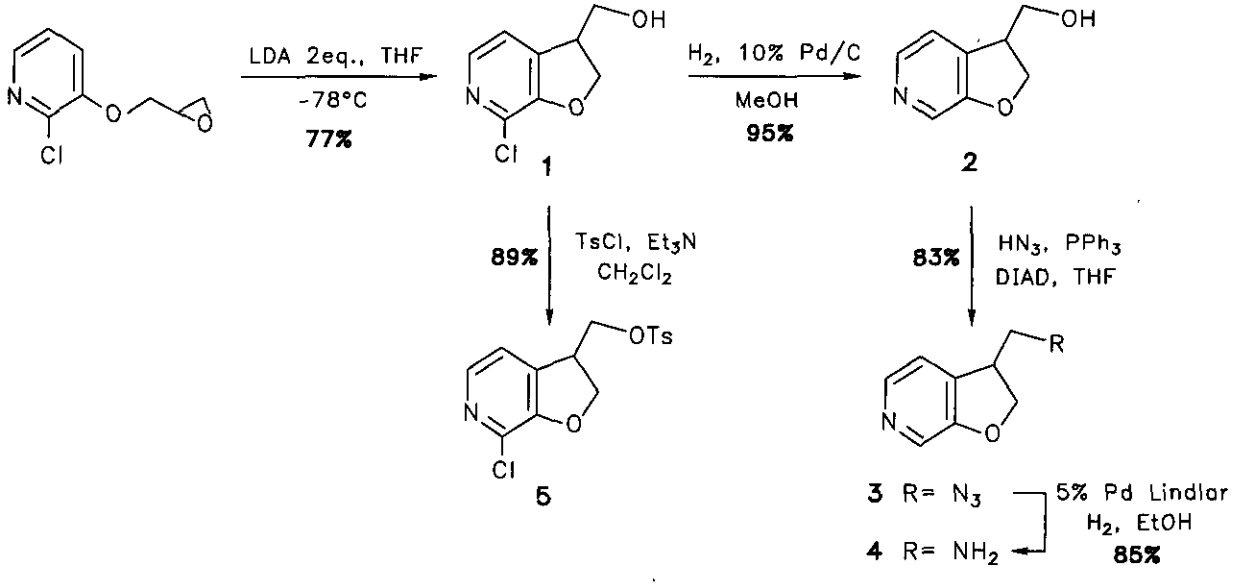
MDL 72382 *pKi* 5-HT_{1A}= 9.1[8]

On the other way, the well known bioisosteric approach has suggested that the 2,3-dihydrobenzofuran nucleus may be useful in the design of serotonin receptor ligands.[9] So, combining this latter observation

and the use of a a pyridine ring instead of a benzene ring, we have speculated that the 2,3-dihydrofuro[2,3-*c*]pyridine nucleus substituted with various functional groups, chosen for their known CNS activity, may afford a new family of compounds with high affinity and selectivity for serotoninergic receptors. Structure-affinity data on a homologous serie have not been previously reported. We, now, report a general and efficient synthetic route to the previously unknown *N*-substituted 3-aminomethyl-2,3-dihydrofuro[2,3-*c*]pyridines.

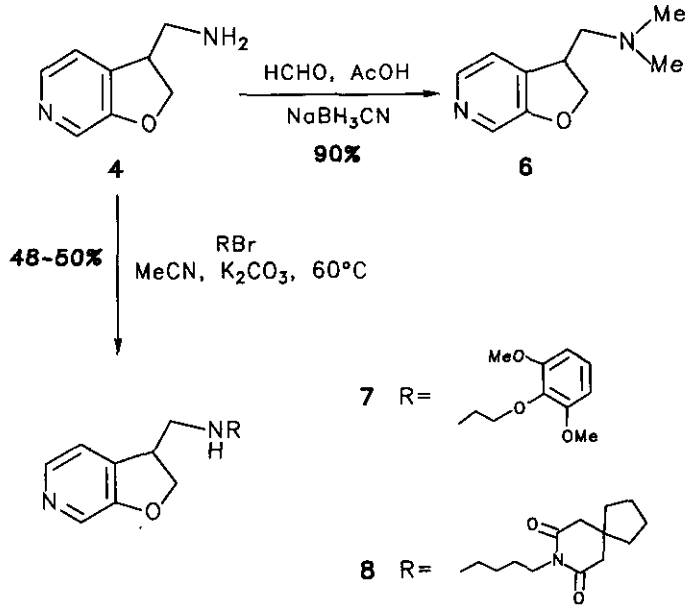


The key intermediates (**4**) and (**5**) were prepared according to Scheme 1. Treatment of 2-chloro-3-oxiranylmethoxypyridine[10] with lithium diisopropylamide in tetrahydrofuran at -78°C results in the regioselective lithiation of the C-4 position,[11,12] followed by an intramolecular epoxide ring-opening reaction[13-15] to give the furopyridine ring (**1**) in moderate yield (77%). Experimentations with 1 or 1.5 eq. of lithium diisopropylamide gave lower yields due to the presence of non consumated starting material. This reaction, performed at -20°C, induced a cleavage of the 2,3-dihydrofuro[2,3-*c*]pyridine ring. Hydrogenolysis of **1** over 10% Pd/C in methanol provided **2** in 95% yield. Mitsunobu reaction (triphenylphosphine, diisopropyl azodicarboxylate, tetrahydrofuran) between alcohol (**2**) and 6% HN_3[16] in chloroform gave the corresponding azido compound (**3**) in 83% yield. The primary amine (**4**) was generated from **3** in good yield (85%) by catalytic hydrogenation in ethanol over 5% Lindlar's palladium. Tosylation of **1** was carried out in the usual way using *p*-toluenesulfonyl chloride in dichloromethane and triethylamine to afford the desired sulfonate (**5**) in 89% yield.



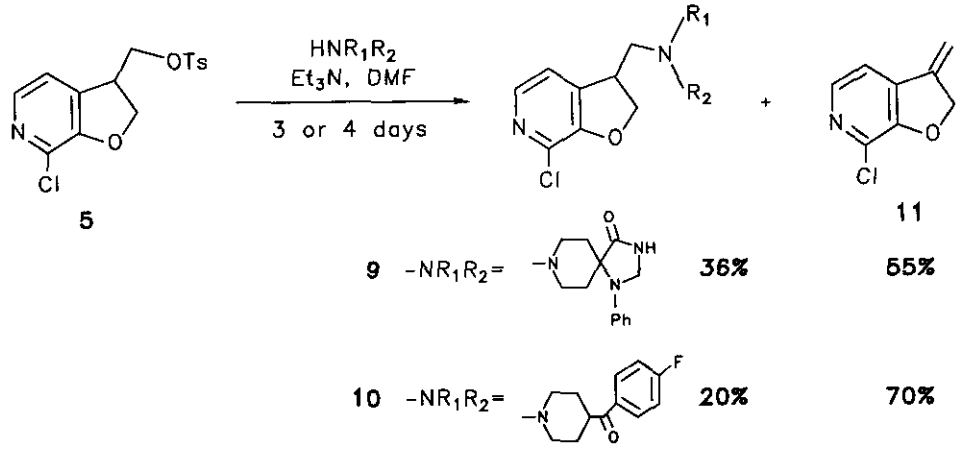
Scheme 1

Compounds (**6**, **7** and **8**) were synthesised as outlined in Scheme 2. *N,N*-Dimethylation of the amino compound (**4**) using classical methodology (sodium cyanoborohydride, formaldehyde, glacial acetic acid) gave **6** in good yield (90%). Direct alkylation of **4**, from either 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione or 2-(2,6-dimethoxyphenoxy)-1-bromoethane in acetonitrile, afforded the corresponding analogue of WB 4101 (**7**) and analogue of MDL 72382 (**8**) respectively in 48% and 50% yields.



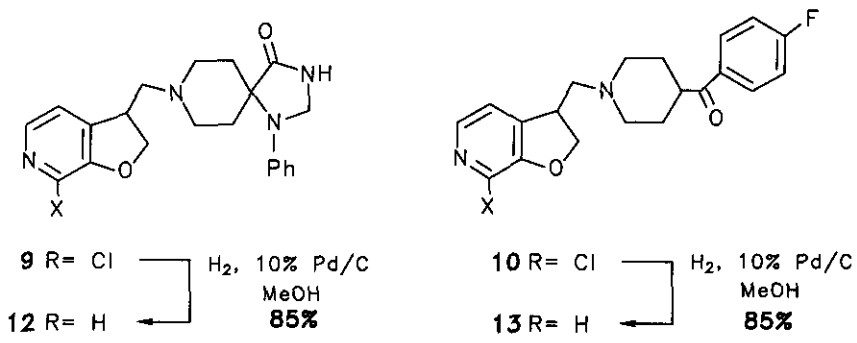
Scheme 2

Similarly, the tosylate (**5**) was alkylated with either 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one or 4-fluorobenzoylpiperidine in DMF, in the presence of triethylamine, for 3 to 4 days at room temperature to give **9** and **10** respectively in 36% and 20% yields (Scheme 3). The low yields of the alkylation were due to the formation of a by-product (**11**) resulting of a β-elimination.[17]



Scheme 3

Finally, catalytic hydrogenolysis of **9** and **10** over 10% Pd/C afforded in 85% yield the desired compound (**12**) (analogue of spiroxatrine) and (**13**) (Scheme 4).



Scheme 4

In summary, this study represents a convenient and effective synthetic pathway to the 2,3-dihydrofuro[2,3-*c*]pyridine ring and 3-substituted 3-aminomethyl derivatives.

EXPERIMENTAL

Analytical thin layer chromatography was performed on Merck $60F_{254}$ silica gel plates. Column chromatography was performed using silica gel 60 (70-230 mesh, E. Merck) and flash chromatography was conducted with silica gel (230-400 mesh, E. Merck). Melting points, determined on a Köfler hot-stage apparatus, are uncorrected. ^{1}H Nmr spectra were run on a Bruker AM 300 WB spectrometer. The coupling constants were recorded in Hertz (Hz) and the chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (TMS) which was used as internal standard. Ir spectra of liquid films or KBr pellets were obtained with a Perkin-Elmer 297 instrument. Mass spectra were registered on a Nermag R-10-10-C apparatus. All air- and moisture-sensitive reactions were conducted under an argon atmosphere in flame-dried glassware. Anhydrous solvents or reactifs were transferred *via* syringe.

(7-Chloro-2,3-dihydrofuro[2,3-*c*]pyridine-3-yl)methanol (**1**). To a stirred solution of 2-chloro-3-oxiranylmethoxypyridine[10] (1.00 g, 5.39 mmol) in THF (10 ml) was added LDA (2 M in THF/heptane, 5.4 ml, 10.8 mmol) diluted in THF (8 ml) over 15 min at -78°C under an argon atmosphere. After 5 min of stirring, water (20 ml) was added to the mixture at -78°C and the solution was brought to room temperature. The solution was concentrated and extracted with CH_2Cl_2 (3 x 20 ml). After drying over $MgSO_4$, the organic layer was evaporated. The crude residue was purified by silica gel chromatography (eluent petroleum ether/Et_2O 1:3) to give 0.77 g (77%) of **1** as a white crystalline compound: mp 110-112°C (EtOAc-petroleum ether); ir (KBr) 3500 to 3000 (OH) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.96 (t, J = 4.1 Hz, 1H, OH), 3.72-3.81 (m, 1H, CH), 3.86-3.88 (m, 2H, CH_2OH), 4.60 (dd, J = 5.9 and J = 8.8 Hz, 1H, OCH_2), 4.78 (t, J = 8.8 Hz, 1H, OCH_2), 7.17 (d, J = 5.1 Hz, 1H, H_{pyr}), 7.93 (d, J = 5.1 Hz, 1H, H_{pyr}); *Anal.* Calcd for $C_8H_8NO_2Cl$: C, 51.77; H, 4.34; N, 7.55. Found: C, 51.85; H, 4.39; N, 7.32.

(2,3-Dihydrofuro[2,3-*c*]pyridin-3-yl)methanol (**2**). A mixture of **1** (2.30 g, 12.5 mmol) and 10% Pd/C (0.23 g) in methanol (30 ml) was shaken in a Parr apparatus under 20 psi of hydrogen at room temperature for 1 h. The catalyst was filtered through Celite and the solvent was removed *in vacuo*. The

crude compound was partitioned between 20% aqueous sodium hydroxyde solution (30 ml) and CH_2Cl_2 (30 ml) and extracted twice. The organic extracts assembled were dried over $MgSO_4$ and evaporated. Flash chromatography of the resulting product, eluting with CH_2Cl_2/MeOH 96:4, gave 1.80 g (95%) of **2** as a white crystalline compound: mp 80°C (EtOAc-petroleum ether); ir (KBr) 3500 to 3000 (OH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.63-3.71 (m, 1H, CH), 3.76-3.86 (m, 2H, CH_2OH), 4.51 (dd, J = 5.9 and J = 9.6 Hz, 1H, OCH_2), 4.67 (t, J = 9.6 Hz, 1H, OCH_2), 7.20 (d, J = 4.4 Hz, 1H, H_{pyr}), 8.04 (d, J = 4.4 Hz, 1H, H_{pyr}), 8.08 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.45; H, 5.85; N, 9.20.

2,3-Dihydrofuro[2,3-*c*]pyridin-3-ylmethyl azide (3). *To a solution of alcohol* (**2**) (1.80 g, 11.9 mmol) and PPh_3 (4.69 g, 17.9 mmol) in anhydrous THF (60 ml) was added a freshly prepared solution of 6% HN_3[16] in $CHCl_3$ (12.8 ml, 17.9 mmol). Diisopropyl azodicarboxylate (3.63 g, 17.9 mmol) was then added dropwise at 0°C. The reaction mixture was stirred during 2 h at room temperature. The solvents were evaporated and the residue was partitioned between CH_2Cl_2 (30 ml) and aqueous 1N HCl (30 ml) and extracted. The acidic aqueous extract was made alkaline with 20% aqueous sodium hydroxyde solution and the azide was extracted into dichloromethane (3 x 30 ml). The organic layer was dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography (eluent Et_2O) to afford 1.73 g (83%) of **3** as a colorless oil; ir (film) 2100 (N_3) cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.50-3.62 (m, 2H, CH_2N_3), 3.63-3.75 (m, 1H, CH), 4.41 (dd, J = 5.2 and J = 9.5 Hz, 1H, OCH_2), 4.67 (t, J = 9.5 Hz, 1H, OCH_2), 7.22 (d, J = 5.2 Hz, 1H, H_{pyr}), 8.20 (d, J = 5.2 Hz, 1H, H_{pyr}), 8.22 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.25; H, 4.34; N, 31.60.

(2,3-Dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)amine (4). To a solution of **3** (1.73 g, 98.2 mmol) in ethanol (15 ml) was added 5% Lindlar palladium (0.18 g). The reaction mixture was stirred overnight under 20 psi of hydrogen at room temperature. The catalyst was filtered through Celite and the solvent was removed *in vacuo*. The desired compound was purified by silica gel chromatography using CH_2Cl_2/MeOH 9:1 then 8:2 as eluent to give 1.25 g (85%) of **4** as a colorless oil; ir (film) 3380 and 3300 (NH_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.31 (bs, 2H, NH_2), 2.92-3.04 (m, 2H, NCH_2), 3.45-3.58 (m, 1H, CH), 4.46 (dd, J = 5.9 and J = 8.9 Hz, 1H, OCH_2), 4.67 (t, J = 8.9 Hz, 1H, OCH_2), 7.19 (d, J = 5.2 Hz, 1H, H_{pyr}), 8.16 (d, J = 5.2 Hz, 1H, H_{pyr}), 8.18 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.80; H, 6.60; N, 18.50.

7-Chloro-2,3-dihydrofuro[2,3-*c*]pyridin-3-ylmethyl 4-toluenesulfonate (5). A solution of *p*-toluenesulfonyl chloride (1.54 g, 8.1 mmol) in CH_2Cl_2 (10 ml) was added dropwise to an ice cold solution of **1** (1.00 g, 5.4 mmol) and triethylamine (1.60 g, 15.8 mmol) in CH_2Cl_2 (50 ml). The solution was stirred for 16 h at room temperature, then the solvents were evaporated. The residue was chromatographied on a silica gel column (eluent petroleum ether/ethyl acetate 3:1) to give 1.59 g (89%) of **5** as a crystalline compound: mp 139-140°C (Et_2O-petroleum ether); ir (KBr) 1364 and 1171 cm^{-1} (OSO_2); ^1H nmr ($CDCl_3$) δ 2.45 (s, 3H, CH_3), 3.88-3.97 (m, 1H, CH), 4.09-4.21 (m, 2H, CH_2OTs), 4.44 (dd, J = 6.0 and J = 9.9 Hz, 1H, OCH_2), 4.71 (t, J = 9.9 Hz, 1H, OCH_2), 7.06 (d, J = 4.9 Hz, 1H, H_{pyr}), 7.34 (d, J = 8.2 Hz, 2H, H_{ar}), 7.71 (d, J = 8.2 Hz, 2H, H_{ar}), 7.75 (d, J = 4.9 Hz, 1H, H_{pyr}); *Anal.* Calcd for $C_{15}H_{14}NO_4ClS$: C, 53.02; H, 4.15; N, 4.12. Found: C, 53.20; H, 4.10; N, 4.05.

(2,3-Dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)dimethylamine (6). A solution of formaldehyde (0.38 ml, 3.6 mmol, 37% in water) in methanol (8 ml) was added to a stirred solution of **4** (200 mg, 1,3 mmol), glacial acetic acid (0.2 ml, 3.6 mmol) and sodium cyanoborohydride (150 mg, 3.6 mmol) in methanol (8 ml) at 0°C such a rate that the temperature of the reaction did not exceed 0°C. The solution was warmed to 25°C and stirred for 2 h before adding saturated K_2CO_3 solution (2 ml). The MeOH was removed *in vacuo* and H_2O (20 ml) and EtOAc (3 x 10 ml) were added to the mixture. After extraction, the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographied on silica gel, elution with CH_2Cl_2/MeOH 96:4, to give 214 mg (90%) of **6** as a colorless oil; ir (film) 1260 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.29 (s, 6H, CH_3), 2.42-2.56 (m, 2H, NCH_2), 3.57-3.68 (m, 1H, CH), 4.40 (dd, J = 6.6 and J = 8.8 Hz, 1H, OCH_2), 4.66 (t, J = 8.8 Hz, 1H, OCH_2), 7.16 (d, J = 5.1 Hz, 1H, H_{pyr}), 8.13 (d, J = 5.1 Hz, 1H, H_{pyr}), 8.16 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.20; H, 8.03; N, 15.66.

(2,3-Dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)-[2-(2,6-dimethoxyphenoxy)ethyl]amine (7). A mixture of **4** (200 mg, 1.33 mmol), 2-(2,6-dimethoxyphenoxy)-1-bromoethane (416 mg, 1.59 mmol), potassium carbonate (550 mg, 3.99 mmol) and potassium iodide (50 mg, 0.3 mmol) in dry acetonitrile (5 ml) was heated at 60°C whilst stirring for 7 h and then cooled to room temperature. After filtration, the solvent was removed under reduced pressure to yield a crude oil which was chromatographied on a silica gel column using CH_2Cl_2/MeOH 96:4 as eluent to afford 210 mg (48%) of **7** as an oil; ir (film) 3310 (NH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.90 (br s, 1H, NH), 2.84-3.03 (m, 4H, CH_2NHCH_2), 3,60-3.70 (m, 1H, CH), 3.80 (s, 6H, OCH_3), 4.05-4.19 (m, 2H, CH_2OAr), 4.48 (dd, J = 6.0 and J = 9.5 Hz, 1H, OCH_2), 4.70 (t, J = 9.5 Hz, 1H, OCH_2), 6.57 (d, J = 8.6 Hz, 2H, H_{ar}), 6.99 (t, J = 8.6 Hz, 1H, H_{ar}), 7.23 (d, J = 5.2 Hz, 1H, H_{pyr}), 8.14 (d, J = 5.2 Hz, 1H, H_{pyr}), 8.18 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.30; H, 6.60; N, 8.52.

8-[4-[(2,3-Dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)amino]butyl]-8-azaspiro[4.5]decane-7,9-dione (8). Following the procedure used for **7** but replacing 2-(2,6-dimethoxyphenoxy)-1-bromoethane by 8-(4-bromobutyl)-8-azaspiro[4.5]decane-7,9-dione (481 mg, 1.60 mmol), purification of the residue by chromatography (eluent CH_2Cl_2/MeOH 96:4) yielded 430 mg (50%) of **8** as an oil; ir (film) 3320 (NH), 1740 and 1660 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.41-1.58 (m, 8H, CH_2), 1.68-1.73 (m, 4H, CH_2), 2.58 (s, 4H, CH_2CO), 2.64 (t, 2H, J = 6.6 Hz, NCH_2), 2.78 (dd, J = 8.1 and J = 11.8 Hz, 1H, NCH_2), 2.90 (dd, J = 5.9 and J = 11.8 Hz, 1H, NCH_2), 3.54-3.60 (m, 1H, CH), 3.76 (t, J = 7.4 Hz, 2H, CH_2NCO), 4.42 (dd, J = 5.9 and J = 9.6 Hz, 1H, OCH_2), 4.65 (t, J = 9.6 Hz, 1H, OCH_2), 7.18 (d, J = 5.1 Hz, 1H, H_{pyr}), 8.13 (d, J = 5.1 Hz, 1H, H_{pyr}), 8.16 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_{21}H_{29}N_3O_3$: C, 67.90; H, 7.87; N, 11.31. Found: C, 67.77; H, 7.96; N, 11.15.

8-(7-Chloro-2,3-dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (9). To a solution of **5** (1 g, 2.94 mmol) and 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (748 mg, 3.23 mmol) in anhydrous DMF (50 ml) was added triethylamine (297 mg, 2.94 mmol). The reaction was stirred at room temperature for 60 h. The solvent was evaporated and the residue was purified by silica gel chromatography (eluent Et_2O, then Et_2O/MeOH 95:5) to give 318 mg (36%) of **9** as a crystalline compound: mp 205-206°C (acetone); ir (KBr) 3200 (NH), 1710 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.75 (br

d, 2H, CH_2), 2.59-2.98 (m, 8H, CH_2), 3,74-3.82 (m, 1H, CH), 4.57 (dd, J = 5.9 and J = 8.8 Hz, 1H, OCH_2), 4.76 (s, 2H, $NHCH_2$), 4.79 (t, J = 8.8 Hz, 1H, OCH_2), 6.75 (br s, 1H, NH), 6.88-6.93 (m, 3H, H_{ar}), 7.19 (d, J = 5.1 Hz, 1H, H_{pyr}), 7.32 (t, J = 8.1 Hz, 2H, H_{ar}), 7.97 (d, J = 5.1 Hz, 1H, H_{pyr}); *Anal.* Calcd for $C_{21}H_{23}N_4O_2Cl$: C, 63.23; H, 5.81; N, 14.05. Found: C, 63.41; H, 5.70; N, 13.99.

4-(4-Fluorobenzoyl)-1-(7-chloro-2,3-dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)piperidine (10). Following the methodology used for **9** but substituting 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one by 4-fluorobenzoylpiperidine (671 mg, 3.24 mmol) in DMF (20 ml), purification of the crude residue by silica gel chromatography (eluent Et_2O/MeOH 99:1, then 98:2) afforded 220 mg (20%) of **10** as an oil; ir (film) 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.80-1.92 (m, 4H, CH_2), 2.15 (m, 1H, CHCO), 2.55 (dd, J = 8.8 and J = 12.5 Hz, 1H, NCH_2), 2.64 (dd, J = 6.6 and J = 12.5 Hz, 1H, NCH_2), 2.93-3.05 (m, 2H, NCH_2), 3.18-3.28 (m, 2H, NCH_2), 3.70-3.81 (m, 1H, CH), 4.49 (dd, J = 5.9 and J = 9.3 Hz, 1H, OCH_2), 4.71 (t, J = 9.3 Hz, 1H, OCH_2), 7.14 (ft, J = 8.8 Hz, 2H, H_{ar}), 7.18 (d, J = 5.1 Hz, 1H, H_{pyr}), 7.93 (d, J = 5.1 Hz, 1H, H_{pyr}), 7.97 (dd, J = 5.9 and 8.8 Hz, 2H, H_{ar}); *Anal.* Calcd for $C_{20}H_{20}N_2O_8ClF$: C, 64.09; H, 5.38; N, 7.47. Found: C, 63.82; H, 5.16; N, 7.60.

7-Chloro-3-methylene-2,3-dihydrofuro[2,3-*c*]pyridine (11). mp 98-100°C (EtOAc-petroleum ether); ir (KBr) 1280 (C-O-C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 5.24 (t, 2H, J = 2.9 Hz, OCH_2), 5.31 (t, J = 2.9 Hz, 1H, $=CH_2$), 5.67 (t, J = 2.9 Hz, 1H, $=CH_2$), 7.24 (d, 1H, J = 5.1 Hz, H_{pyr}), 7.99 (d, 1H, J = 5.1 Hz, H_{pyr}); *Anal.* Calcd for C_8H_6NOCl: C, 57.33; H, 3.61; N, 8.36. Found: C, 57.30; H, 3.57; N, 8.30.

8-(2,3-Dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (12). To a solution of **9** (200 mg, 0.5 mmol) in methanol (20 ml) was added 10% Pd/C (20 mg). The reaction mixture was stirred overnight under 40 psi of hydrogen at 30°C. The catalyst was filtered through Celite and the filtrate was concentrated *in vacuo*. The crude compound is dissolved in 20% aqueous sodium hydroxyde solution (30 ml) and extracted with dichloromethane (3 x 30 ml). The organic layers were assembled, dried over $MgSO_4$ and evaporated. The residue obtained was purified by silica gel chromatography (eluent CH_2Cl_2/MeOH 97:3) to give 153 mg (85%) of **12** as a crystalline compound: mp 217°C (acetone); ir (KBr) 3200 (NH), 1710 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.75 (br d, 2H, CH_2), 2.56-2.94 (m, 8H, CH_2), 3,63-3.75 (m, 1H, CH), 4.46 (dd, J = 6.6 and J = 8.7 Hz, 1H, OCH_2), 4.69 (t, J = 8.7 Hz, 1H, OCH_2), 4.75 (s, 2H, $NHCH_2$), 6.79 (br s, 1H, NH), 6.87-6.93 (m, 3H, H_{ar}), 7.24 (d, J = 5.1 Hz, 1H, H_{pyr}), 7.32 (t, J = 7.9 Hz, 2H, H_{ar}), 8.17 (d, J = 5.1 Hz, 1H, H_{pyr}), 8.18 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_{21}H_{24}N_4O_2$: C, 69.21; H, 6.64; N, 15.37. Found: C, 69.20; H, 6.73; N, 15.16.

4-(4-Fluorobenzoyl)-1-(2,3-dihydrofuro[2,3-*c*]pyridin-3-ylmethyl)piperidine (13). Compound (**13**) was prepared from **10** (200 mg, 0.4 mmol) according to the procedure used for **12**, purification by silica gel chromatography (CH_2Cl_2/MeOH 98:2) gave 161 mg (85%) of **13** as an oil; ir (film) 1670 (C=O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.82-1.92 (m, 4H, CH_2), 2.14-2.30 (m, 1H, CHCO), 2.53 (dd, J = 8.8 Hz and J = 12.5 Hz, 1H, NCH_2), 2.64 (dd, J = 6.6 and J = 12.5 Hz, 1H, NCH_2), 2.96-3.05 (m, 2H, NCH_2), 3.18-3.29 (m, 2H, NCH_2), 3.63-3.74 (m, 1H, CH), 4.40 (dd, J = 9.3 and J = 6.0 Hz, 1H, OCH_2), 4.65 (t, J = 9.3 Hz, 1H, OCH_2), 7.14 (t, 2H, J = 8.8 Hz, H_{ar}), 7.22 (d, 1H, J = 5.1 Hz, H_{pyr}), 7.97 (dd, 2H, J = 8.8 and J = 5.9 Hz, H_{ar}), 8.14 (d, 1H, J = 5.1 Hz, H_{pyr}), 8.16 (s, 1H, H_{pyr}); *Anal.* Calcd for $C_{20}H_{21}N_2O_8F$: C, 70.57; H, 6.22; N, 8.23. Found: C, 70.30; H, 6.02; N, 8.09.

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