Synthesis of aminopyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazine derivatives as serotoninergic 5-HT$_7$ ligands

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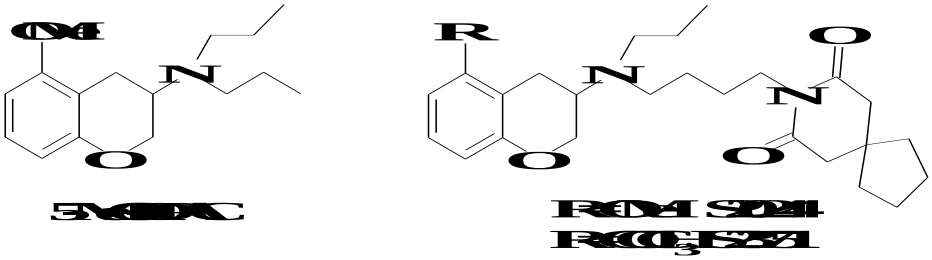
Abstract
A series of piperazinopyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazine derivatives were prepared and evaluated to determine their affinity for the 5-HT$_7$ receptor. Various substitutions on piperazine were explored as well as replacement of the piperazine by other amines.

Keywords: Serotonin, 5-HT$_7$Rs ligands, affinity, aminopyrrolothienopyrazines

Introduction

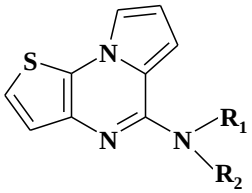
Among the serotoninergic receptors, the 5-HT$_7$ receptor (5-HT$_7$R) is the more recently discovered.[1-3] The 5-HT$_7$R displays a low degree of homology (40%) with other serotonin G-protein-coupled receptors (GPCR$_s$). Recent distribution studies in brain have revealed a high abundance of the 5-HT$_7$R proteins in hippocampus, thalamus, hypothalamus and cerebral cortex.[4] Their distribution in the central nervous system is highly associated with their implication in psychiatric disorders,[5,6] depression, anxiety and mood,[7-9] learning and memory,[10,11] and epilepsy.[12] The 5-HT$_7$ subtype has also been found in smooth muscle cells and in blood vessels of the skull and of other peripheral tissues[13,14] so it is suggested as a putative target for migraine[15] and irritable bowel syndrome[16] treatments. Therefore, this receptor has become an attractive target for drug discovery. Many ligands have been reported to bind with high affinity to 5-HT$_7$ receptors and their number is continuously increasing.[17-19] In the course of a program aimed at the discovery of new serotonine 5-HT$_7$ ligands, we submitted to binding assays a range of *N*-substituted (5-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-yl)amine derivatives previously studied as 5-HT$_{1A}$ receptor ligands.[20-22] We found that two of them (5-

MeO-DPAC and S 20244) displayed significant affinity for 5-HT_7R. Subsequently, we planned some structural modifications on such structures by varying systematically the nature of the substituent at the 5-position of the 2*H*-benzopyran ring to cover further hydrophobic, aromatic ring and H-bond acceptor capacities. The highest affinities in both series were obtained when R = 5-acetyl (S 23751). However, none of the new compounds showed any selectivity for the 5-HT_7 over 5-HT_{1A} receptors.[23]



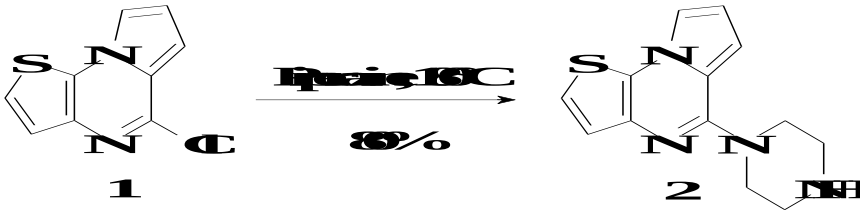
This lack of selectivity has led us to translate the knowledge acquired in the benzopyran series, to aminopyrrolothienopyrazine series, which has been described recently as being the possible support of new 5-HT_7 ligands.[24]

So, in this paper, we report the synthesis of a series of tricyclic aminopyrrolothienopyrazine[25] analogues of benzopyran having the structure key elements previously mentioned.



Results and Discussion

The expected products were prepared from 5-chloropyrrolo[1,2-*a*]thieno[3,2-*e*]pyrazine **1**.
The chloride **1**[26] was triturated with piperazine and then heated at 180°C for 4h to lead to amine **2**[25] in 80% yield (Scheme 1).

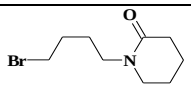
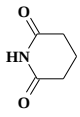
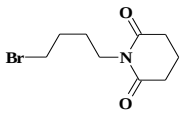
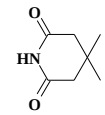
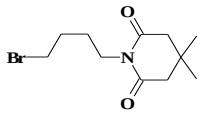
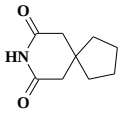
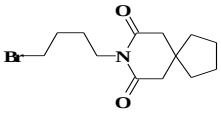
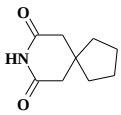
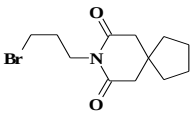


Scheme 1

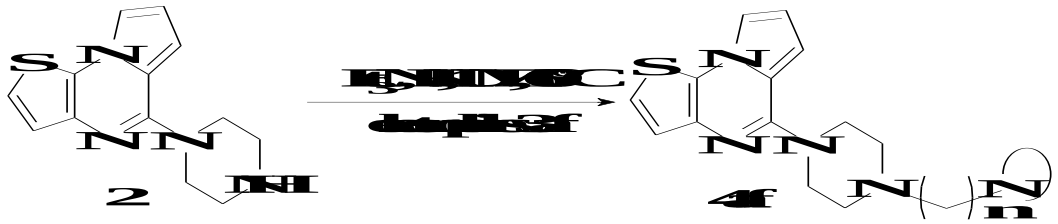
The bromo derivatives **3** could be easily generated by nucleophilic substitution of amides and imides on appropriate dibromoalkanes (Scheme 2). Starting from piperidin-2-one, addition of sodium hydride and 1,4-dibromobutane in DMF gave expected compound **3a** in 46% yield (method A, Table 1). Starting from piperidine-2,6-dione, 3,3-dimethylglutarimide and 3,3-tetramethyleneglutarimide, action of potassium carbonate and 1,4-dibromobutane with a catalytic amount of potassium iodide in refluxing acetonitrile led to compounds **3b-d** in moderate yields (method B). The homologous **3e** was generated in 47% yield starting from 1,3-dibromopropane and 3,3-tetramethyleneglutarimide following method B.

Scheme 2

Table 1

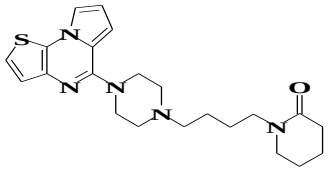
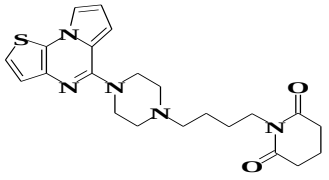
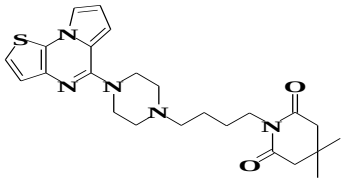
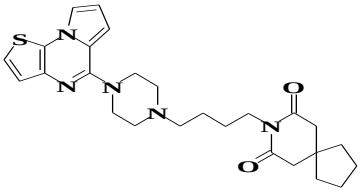
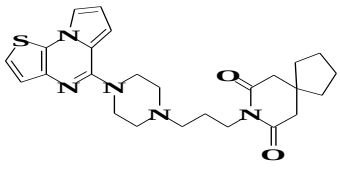
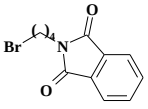
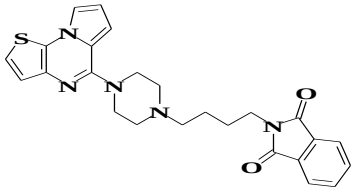
Entry	Methods	n		Products	Yield
1	A	4		 **3a**[27]	46%
2	B	4		 **3b**[28]	53%
3	B	4		 **3c**[28]	60%
4	B	4		 **3d**[21]	64%
5	B	3		 **3e**	47%

Treatment of amine **2** in DMF by bromo derivatives **3a-e** or commercial *N*-(4-bromobutyl)phthalimide **3f** in the presence of triethylamine and catalytic amount of potassium iodide afforded the expected piperazine derivatives **4a-f** in moderate to good yields (Scheme 3, Table 2).

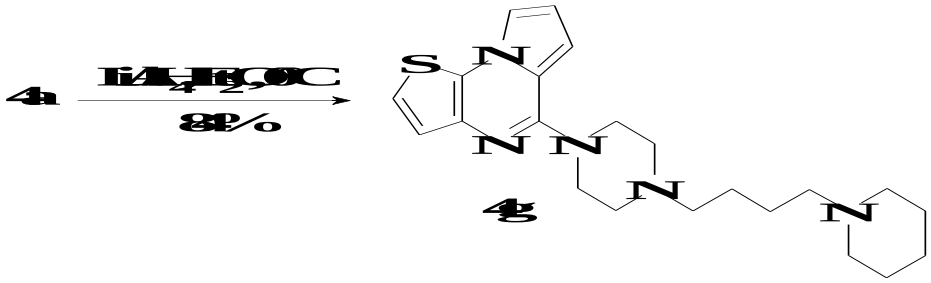


Scheme 3

Table 2

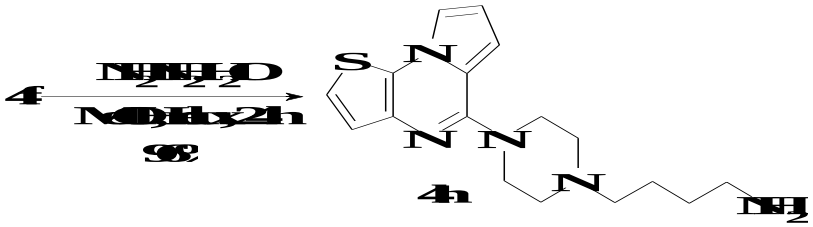
Entry	Electrophiles	Products	Yield
1	**3a**	 **4a**	76%
2	**3b**	 **4b**	82%
3	**3c**	 **4c**	68%
4	**3d**	 **4d**	64%
5	**3e**	 **4e**	55%
6	 **3f**	 **4f**	85%

The piperidine derivative **4g** could be easily generated in 84% yield by reduction of its corresponding compound **4a** with lithium aluminium hydride in diethyl ether (Scheme 4).



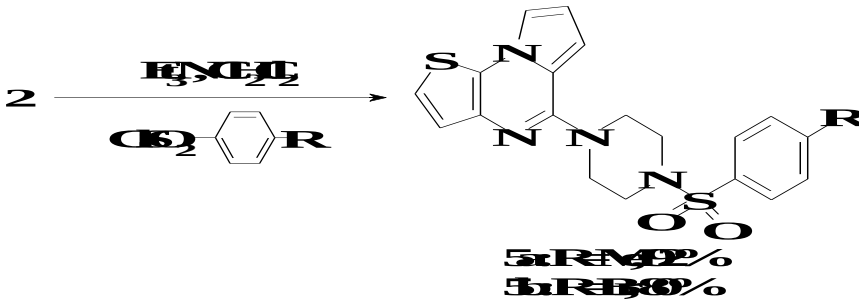
Scheme 4

Starting from the piperazine derivative **4f**, addition of hydrazine hydrate in refluxing methanol afforded the expected compound **4h** in 96% yield (Scheme 5).



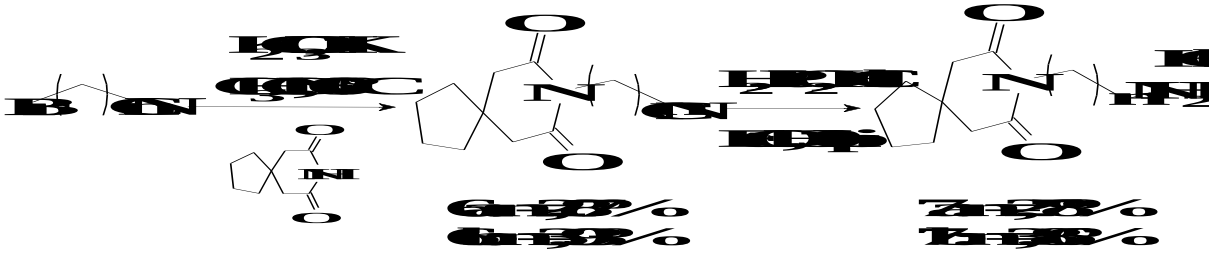
Scheme 5

As described in Scheme 6, sulfonamides **5a** and **5b** were easily obtained by addition of 4-methylbenzenesulfonyl chloride or 4-bromobenzenesulfonyl chloride on amine **2** in 92 and 80% yields, respectively. The reaction was performed in methylene chloride in the presence of triethylamine.



Scheme 6

Amines **7** were obtained in a two steps procedure (Scheme 7). 3-Bromopropionitrile or 4-bromobutyronitrile was added on 3,3-tetramethyleneglutarimide in acetonitrile at 60°C in the presence of potassium carbonate and a catalytic amount of potassium iodide. This reaction furnished compounds **6a** and **6b** in 87 and 93% yield, respectively. Nitrile functions were reduced in their corresponding amines by hydrogenation using platinum oxide in ethanol at 30 psi. Amines **7a** and **7b** were obtained in 78 and 86% yield, respectively. Due to a low stability of such compounds, they were isolated as their corresponding hydrochloride salts.

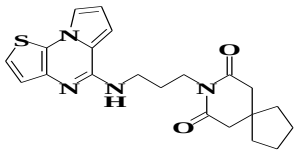
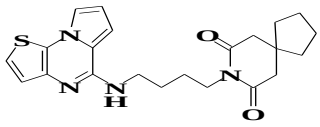
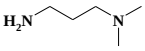
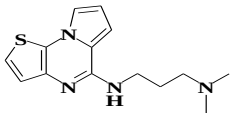


Scheme 7

In literature,[29] a successful technique of cross coupling between the chloride **1** and some amines was already reported using palladium-catalyzed amination. Also, treatment of chloride **1** with several amines (**7a**, **7b** and *N*,*N*-dimethylpropane-1,3-diamine **7c**) in the presence of dibenzylidenacetone palladium II, racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphtyl and sodium *tert*-butoxide in toluene at reflux provided derivatives **8a-c** in 69 to 73% yield (Scheme 8).

Scheme 8

Table 3

Entry	Amines	Products	Yield
1	**7a**	 **8a**	69%
2	**7b**	 **8b**	73%
3	 **7c**	 **8c**	71%

Conclusions

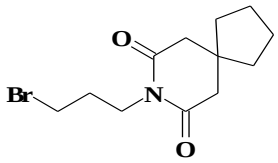
We have reported the successful synthesis of aminopyrrolothienopyrazine derivatives. *In vitro* binding studies show that the compounds **4a-d** have a certain affinity for the 5-HT_7 receptor. However, this affinity is still lower than that observed for the 5-HT_{1A} receptor. Thus, for the interesting compound **4d**, values obtained are the following: 5-HT_{1A} K_i = 15 nM; 5-HT_7 K_i = 165 nM. Further chemical modifications are currently been performed in order to determine the structure activity relationships required for good affinity and good selectivity for the $5HT_7$ receptor over the $5HT_{1A}$ receptor in the light of recent progress in this improvement of selectivity.[30]

Experimental Section

General. All air- and moisture-sensitive reactions were carried out under an argon atmosphere. Anhydrous solvents (Et_2O and THF) were freshly distilled from sodium/benzophenone under nitrogen prior to use. ^1H and ^{13}C NMR spectra were obtained with a Bruker instrument Advance DPX250 at 250.131 and 62.9 MHz, respectively. Chemical shifts (δ values) were reported in parts per million and coupling constants (*J* values) in Hz. Carbon multiplicities have been assigned by distortion-less enhancement by polarization transfer (DEPT) experiments. Infrared spectra were recorded using NaCl film or KBr pellets techniques on a Perkin-Elmer spectrometer FT PARAGON 1000PC. Mass spectra (MS) were recorded on a Perkin-Elmer mass spectrometer SCIEX API 300 by ion spray (IS). Melting points (mp) were determined in open capillary tube and are uncorrected. Analytical thin-layer chromatography was performed on Merck $60F_{254}$ silica gel precoated plates. Flash chromatography was performed using silica gel Merck 40-70 μm

(230-400 mesh). Preparations of compounds **1**[26], **2**[25], **3a**[27], **3b**[28], **3c**[28] and **3d**[20] have been previously described.

8-(3-Bromopropyl)-8-aza-spiro[4.5]decane-7,9-dione (3e)

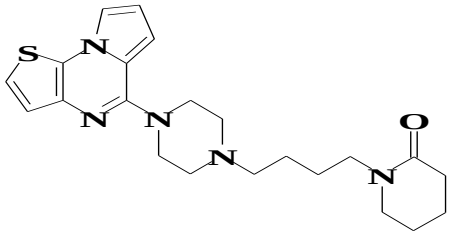


Under an argon atmosphere, to a solution of 3,3-tetramethyleneglutarimide (0.7 g, 4.2 mmol) in dry acetonitrile (7 mL), dry potassium carbonate (3 eq., 1.74 g, 12.6 mmol), 1,3-dibromopropane (1.1 eq., 0.47 mL, 4.6 mmol) and KI(cat.) were added and the solution was refluxed 20 h. The mixture was hydrolyzed, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2) to afford 0.565 g of the bromo derivative **3e** as colourless oil in 47% yield.
IR (NaCl) 1725, 1673 cm^{-1}; MS (IS) *m/z* 286 (^{79}Br, M+1), 288 (^{81}Br, M+1), 309 (^{79}Br, M+23, 311 (^{81}Br, M+23); ^{1}H NMR ($CDCl_3$) δ ppm 1.45-1.90 (m, 10H), 2.60 (s, 4H), 3.41 (t, 2H, *J* = 6.7 Hz), 3.78 (t, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 24.1, 26.6, 33.0, 37.5, 38.4, 39.3, 44.8, 172.1.

General procedure for the synthesis of compounds 4

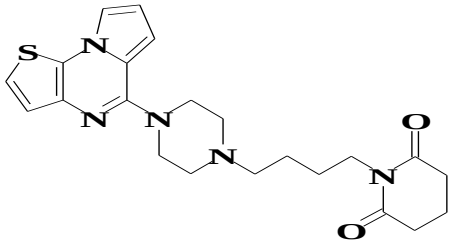
Under an argon atmosphere, to a solution of amine **2** in dry DMF, triethylamine (3 eq.), bromoderivatives 3 or *N*-(4-bromobutyl)phthalimide (1.1 eq.) and KI (cat.) were added. The mixture warmed at 60°C for 6 h, hydrolyzed and the crude product was extracted with AcOEt. The organic layers were dried over $MgSO_4$ and concentrated. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH: 98/2) to afford compounds **4**.

1-{4-[4-(1-Thia-4,8a-diaza-*as*-indacen-5-yl]-butyl}-piperidin-2-one (4a)



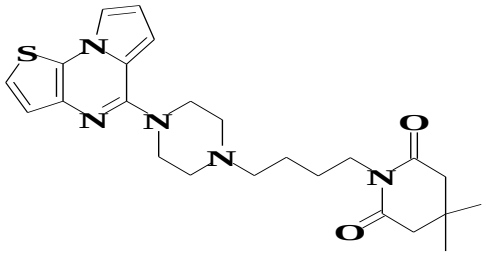
Colourless oil, 76%; IR (NaCl) 1622 cm^{-1}; MS (IS) *m/z* 412.5 $(M+1)^+$; ^{1}H NMR ($CDCl_3$) δ ppm 1.57-1.80 (m, 8H), 2.37 (t, 2H, *J* = 5.5 Hz), 2.45 (t, 2H, *J* = 7.0 Hz), 2.65 (t, 4H, *J* = 4.9 Hz), 3.24-3.32 (m, 2H), 3.39 (t, 2H, *J* = 6.7 Hz), 3.70 (t, 4H, *J* = 4.9 Hz), 6.78 (d, 2H, *J* = 2.1 Hz), 6.99 (d, 1H, *J* = 5.5 Hz), 7.24 (d, 1H, *J* = 5.5 Hz), 7.36 (t, 1H, *J* = 5.5 Hz) ; ^{13}C NMR ($CDCl_3$) δ ppm 21.5, 23.4, 24.2, 25.1, 32.4, 47.0, 47.9, 48.6, 53.3, 58.5, 105.6, 112.8, 114.2, 115.8, 120.8, 123.6, 124.8, 137.7, 152.9, 169.7. Anal. Calcd for $C_{22}H_{29}N_5OS$: C, 64.20; H, 7.10; N, 17.02. Found: C, 64.41; H, 7.15; N, 17.53.

1-{4-[4-(1-Thia-4,8a-diaza-*as*-indacen-5-yl)-piperazin-1-yl]-butyl}-piperidine-2,6-dione (4b)



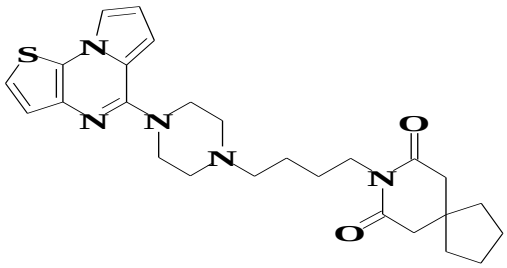
Colourless oil, 82%; IR (NaCl) 1728, 1674 cm^{-1}; MS (IS) *m/z* 426 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.50-1.65 (m, 4H), 1.87-1.98 (m, 2H), 2.44 (t, 2H, *J* = 6.7 Hz), 2.61-2.67 (m, 8H), 3.70 (t, 4H, *J* = 4.9 Hz), 3.77-3.83 (m, 2H), 6.77 (d, 2H, *J* = 2.1 Hz), 6.99 (d, 1H, *J* = 5.5 Hz), 7.24 (d, 1H, *J* = 5.5 Hz), 7.36 (t, 1H, *J* = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 17.3, 24.3, 26.2, 33.0, 39.5, 48.6, 53.3, 58.4, 105.5, 112.8, 114.1, 115.7, 120.7, 123.5, 124.8, 137.7, 152.8, 172.5. Anal. Calcd for $C_{22}H_{27}N_5O_2S$: C, 62.09; H, 6.40; N, 16.46. Found: C, 61.87; H, 6.37; N, 16.53.

4,4-Dimethyl-1-{4-[4-(1-thia-4,8a-diaza-*as*-indacen-5-yl)-piperazin-1-yl]-butyl}-piperidine-2,6-dione (4c)



Colourless oil, 68%; IR (NaCl) 1730, 1671 cm^{-1}; MS (IS) *m/z* 454 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.07 (s, 6H), 1.49-1.62 (m, 4H), 2.41-2.52 (m, 2H), 2.50 (s, 4H), 2.64 (t, 4H, *J* = 4.8 Hz), 3.69 (t, 4H, *J* = 4.8 Hz), 3.76-3.86 (m, 2H), 6.77 (d, 2H, *J* = 1.8 Hz), 6.99 (d, 1H, *J* = 5.5 Hz), 7.24 (d, 1H, *J* = 5.5 Hz), 7.36 (t, 1H, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 24.4, 26.1, 27.8, 29.2, 39.4, 46.5, 48.6, 53.3, 58.4, 105.6, 112.8, 114.2, 115.7, 120.7, 124.8, 137.7, 152.9, 172.1. Anal. Calcd for $C_{24}H_{31}N_5O_2S$: C, 63.55; H, 6.89; N, 15.44. Found: C, 63.87; H, 6.93; N, 15.63.

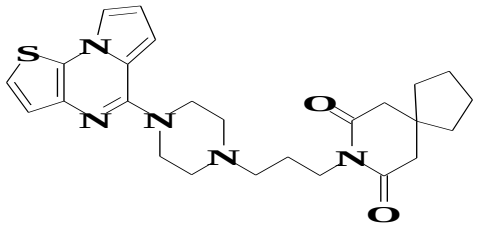
8-{4-[4-(1-Thia-4,8a-diaza-*as*-indacen-5-yl)-piperazin-1-yl]-butyl}-8-aza-spiro[4.5]decane-7,9-dione (4d)



Colourless oil 64%; IR (NaCl) 1726, 1674, cm^{-1}; MS (IS) *m/z* 480 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1,47-1.74 (m, 12H), 2.51-2.60 (m, 2H), 2.59 (s, 4H), 2.76 (t, 4H, *J* = 4.7 Hz), 3.79 (t, 4H, *J* = 4.7 Hz), 6.76-6.80 (m, 2H), 7.00 (d, 1H, *J* = 5.6 Hz), 7.24 (d, 1H, *J* = 7.6 Hz), 7.37 (dd, 1H, *J* = 2.2, 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 24.3, 26.0, 37.7, 39.3, 39.6, 45.0, 48.0, 52.9, 58.1,

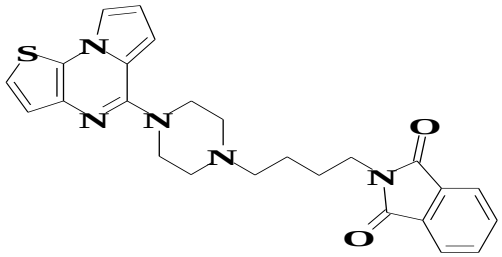
105.5, 113.0, 114.3, 115.8, 120.7, 123.8, 124.8, 126.0, 137.6, 152.4, 172.4. Anal. Calcd for $C_{26}H_{33}N_5O_2S$: C, 65.11; H, 6.93; N, 14.60. Found: C, 65.00; H, 6.78; N, 14.87.

8-{3-[4-(1-Thia-4,8a-diaza-*as*-indacen-5-yl)-piperazin-1-yl]-propyl}-8-aza-spiro[4.5]decane-7,9-dione (4e)



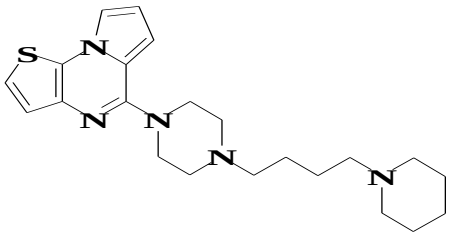
Colourless oil, 55%; IR (NaCl) 1724, 1668 cm^{-1}; MS (IS) *m/z* 466 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.46-1.55 (m, 4H), 1.67-1.83 (m, 6H), 2.46 (t, 2H, *J* = 7.5 Hz), 2.58 (s, 4H), 2.64 (t, 4H, *J* = 4.7 Hz), 3.69 (t, 4H, *J* = 4.7 Hz), 3.84 (t, 2H, *J* = 7.5 Hz), 6.77 (d, 2H, *J* = 1.9 Hz), 6.99 (d, 1H, *J* = 5.6 Hz), 7.24 (d, 1H, *J* = 5.6 Hz), 7.35 (t, 1H, *J* = 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 24.3, 25.2, 37.6, 38.1, 39.6, 45.0, 48.7, 53.2, 56.2, 105.6, 112.8, 114.1, 115.7, 120.7, 123.5, 124.8, 137.7, 152.9, 172.3. Anal. Calcd for $C_{25}H_{31}N_5O_2S$: C, 64.49; H, 6.71; N, 15.04. Found: C, 64.87; H, 6.54; N, 15.12.

2-{4-[4-(1-Thia-4,8a-diaza-*as*-indacen-5-yl)-piperazin-1-yl]-butyl}-isoindole-1,3-dione (4f)



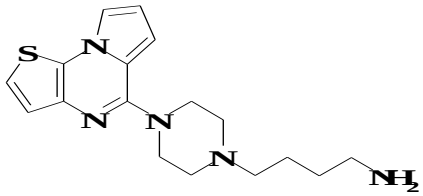
Yellow solid, 85%; mp = 148 °C; IR (KBr) 1771, 1710 cm^{-1}; MS (IS) *m/z* 460 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.55-1.82 (m, 4H), 2.46 (t, 2H, *J* = 7.3 Hz), 2.64 (t, 4H, *J* = 4.9 Hz), 3.67-3.77 (m, 6H), 6.77 (d, 2H, *J* = 2.1 Hz), 6.99 (d, 1H, *J* = 5.5 Hz), 7.24 (d, 1H, *J* = 5.5 Hz), 7.35 (t, 1H, *J* = 2.1 Hz), 7.69-7.73 (m, 2H), 7.81-7.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ ppm 24.3, 26.7, 38.0, 48.6, 53.3, 58.2, 105.6, 112.8, 114.2, 115.7, 120.8, 123.3, 124.9, 132.2, 134.0, 137.7, 152.9, 168.6. Anal. Calcd for $C_{25}H_{25}N_5O_2S$: C, 65.34; H, 5.48; N, 15.24. Found: C, 65.21; H, 5.53; N, 15.33.

5-[4-(4-Piperidin-1-yl-butyl)-piperazin-1-yl]-1-thia-4,8a-diaza-*as*-indacene (4g). Under an argon atmosphere, to a suspension of lithium aluminium hydride (12 mg, 0.30 mmol, 2 eq.) in Et_2O (4 mL) at 0°C was added a solution of compound **4a** (0.06 g, 0.15 mmol) in Et_2O. The reaction mixture was stirred for 3 h at room temperature. A solution of NaOH (10%) (0.3 mL) was added, followed by addition of water (0.3 mL) and concentrated. Water was added and the crude was extracted by CH_2Cl_2, dried over $MgSO_4$, concentrated and purified by flash chromatography (SiO_2; MeOH/Et_3N: 99/1) to afford **4g** as colourless oil in 84% yield.



IR (NaCl) 3000-2800, 1590 cm^{-1}; MS (IS) *m/z* 398 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.40-1.63 (m, 8H), 2.31-2.49 (m, 8H), 2.62 (t, 4H, *J* = 4.9 Hz), 3.70 (t, 4H, *J* = 4.9 Hz), 6.78 (d, 2H, *J* = 2.1 Hz), 6.99 (d, 1H, *J* = 5.8 Hz), 7.24 (d, 1H, *J* = 5.8 Hz), 7.35 (t, 1H, *J* = 2.1 Hz) ; ^{13}C NMR ($CDCl_3$) δ ppm 24.5, 25.0, 25.1, 26.0, 48.7, 53.4, 54.7, 58.8, 105.6, 112.9, 113.0, 114.2, 115.7, 120.9, 124.9, 133.3, 152.9. Anal. Calcd for $C_{22}H_{31}N_5S$: C, 66.46; H, 7.86; N, 17.61. Found: C, 66.34; H, 7.63; N 17.65.

4-[4-(1-Thia-4,8*a*-diaza-*as*-indacen-5-yl)-piperazin-1-yl]-butylamine (4h). To a solution of 0.3 g (0.65 mmol) of compound **4f** in MeOH (10 mL), hydrazine hydrate (1.5 eq., 0.98 mmol) was added and the solution was stirred at reflux for 24 h. The mixture was cooled to room temperature, hydrolyzed by an aqueous solution of NaOH (2.6 N) and extracted by CH_2Cl_2. The organic layers were washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Amine **4h** was obtained in 96% yield as colourless oil.

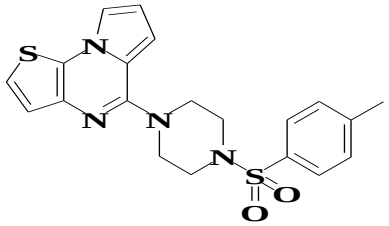


IR (NaCl) 3500-3250 cm^{-1}; MS (IS) *m/z* 331 $(M+1)^+$, 313 $(M-NH_2)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.54-1.93 (m, 6H), 2.41 (t, 2H, *J* = 7.3 Hz), 2.64 (t, 4H, *J* = 4.9 Hz), 3.67-3.77 (m, 6H), 6.77 (d, 2H, *J* = 2.1 Hz), 6.99 (d, 1H, *J* = 5.5 Hz), 7.24 (d, 1H, *J* = 5.5 Hz), 7.35 (t, 1H, *J* = 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ 24.4, 31.5, 42.0, 48.6, 53.3, 58.6, 105.6, 112.8, 114.2, 115.7, 120.7, 123.6, 152.9. Anal. Calcd for $C_{17}H_{23}N_5S$: C, 61.98; H, 7.04; N, 21.26. Found: C, 62.03; H, 7.08; N, 21.48.

General procedure for the synthesis of compounds 5

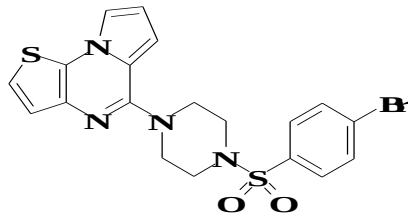
Under an argon atmosphere, to a solution of amine **2** in CH_2Cl_2, Et_3N (3 eq.) and 4-methylbenzenesulfonyl chloride or 4-bromobenzenesulfonyl chloride (1.5 eq.) were added at room temperature. The mixture was stirred for 5 h then hydrolyzed and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH: 98/2) to give sulfonamides **5** as a white foam.

5-[4-*p*-Tolylsulfonyl-piperazin-1-yl)-1-thia-4,8a-diaza-as-indacene (5a)



92%; IR (NaCl) 1311, 1156 cm^{-1}; MS (IS) *m/z* 413 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 2,43 (s, 3H), 3.21 (t, 4H, *J* = 5.2 Hz), 3.74 (t, 4H, *J* = 5.2 Hz), 6.65 (dd, 1H, *J* = 3.9, 1.2 Hz), 6.75 (dd, 1H, *J* = 4.0, 2.4 Hz), 7.00 (d, 1H, *J* = 5.5 Hz), 7.21 (d, 1H, *J* = 5.5 Hz), 7.33 (d, 2H, *J* = 8.2 Hz), 7.34 (t, 1H, *J* = 1.2 Hz), 7.68 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 21.6, 46.1, 48.1, 105.2, 113.1, 114.5, 116.0, 120.4, 124.2, 124.7, 128.0, 129.9, 132.6, 137.4, 143.9, 152.2. Anal. Calcd for $C_{20}H_{20}N_4O_2S_2$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.01; H, 4.78; N, 13.97.

5-[4-(4-Bromophenylsulfonyl)-piperazin-1-yl]-1-thia-4,8a-diaza-*as*-indacene (5b)

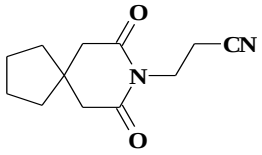


80%; IR (NaCl) 1308, 1172 cm^{-1}; MS (IS) *m/z* 477 (^{79}Br, $M+1)^+$, 479 (^{81}Br, $M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 3.22 (t, 4H, *J* = 4.9 Hz), 3.74 (t, 4H, *J* = 4.9 Hz), 6.65 (dd, 1H, *J* = 4.0, 1.2 Hz), 6.75 (dd, 1H, *J* = 4.3, 2.7 Hz), 6.99 (d, 1H, *J* = 5.5 Hz), 7.20 (d, 1H, *J* = 5.5 Hz), 7.35 (dd, 1H, *J* = 2.4, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 46.0, 48.0, 105.2, 113.1, 114.5, 116.1, 120.3, 124.3, 124.7, 128.2, 129.3, 132.5, 132.6, 134.7, 134.8, 137.3, 152.1. Anal. Calcd for $C_{19}H_{17}BrN_4O_2S_2$: C, 47.80; H, 3.59; N, 11.74. Found: C, 47.64; H, 3.47; N, 11.84.

General procedure for the synthesis of compounds 6

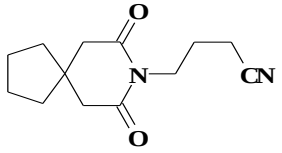
Under an argon atmosphere, to a solution of 3,3-tetramethyleneglutarimide in dry acetonitrile, 3-bromopropionitrile or 4-bromobutyronitrile (1.1 eq.), K_2CO_3 (3 eq.) and a catalytic amount of KI were added at room temperature. The solution was warmed to 60°C and stirred for 20 h. The mixture was concentrated under reduced pressure, hydrolyzed and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography (SiO_2; CH_2Cl_2) to give nitrile derivatives **6**.

3-(7,9-Dioxo-8-aza-spiro[4.5]dec-8-yl)-propionitrile (6a)



White solid, 87%; mp = 61°C; IR (KBr) 2251, 1730, 1688 cm^{-1}; MS (IS) *m/z* 221 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.54-1.73 (m, 8H), 2.64 (s, 4H), 2.67 (t, 2H, *J* = 6.6 Hz), 4.08 (t, 2H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 16.2, 24,1, 34.5, 37.4, 39.2, 44.4, 117.2, 171.8.

4-(7,9-Dioxo-8-aza-spiro[4.5]dec-8-yl)-butyronitrile (6b)

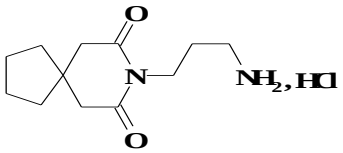


Colourless oil, 93%; IR (NaCl) 2246, 1726, 1668 cm^{-1}; MS (IS) *m/z* 235 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.48-1.53 (m, 4H), 1.69-1.75 (m, 4H), 1.87-1.98 (m, 2H), 2.36 (t, 2H, *J* = 7.3 Hz), 2.63 (s, 4H), 3.91 (t, 2H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 15.5, 24.4, 24.6, 38.0, 38.6, 39.9, 45.1, 119.7, 126.3, 172.8.

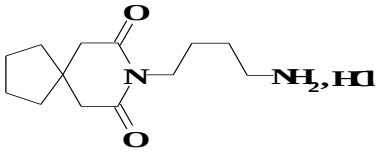
General procedure for the synthesis of compounds 7

To a solution of nitrile **6** in EtOH, 0.4 mL of HCl (12 M) and platinum oxide (0.02 eq.) were added. The mixture was stirred at room temperature under a hydrogen atmosphere (30 psi) for 6 h. The solution was filtered through a Celite pad, concentrated under reduced pressure. Purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH: 9/1) and led to amines **7**, as a hydrochloride salt, as a white solid.

8-(3-Amino-propyl)-8-aza-spiro[4.5]decane-7,9-dione hydrochloride (7a)



78%; mp = 166°C; IR (KBr) 3164, 1724, 1648, cm^{-1}; MS (IS) *m/z* 225 $(M+1)^+$, 208 $(M-NH_2)^+$; ^1H NMR (MeOD) δ ppm 1.36-1.54 (m, 4H), 1.70-1.76 (m, 4H), 1.82-1.93 (m, 2H), 2.67 (s, 4H), 2.89 (t, 2H, *J* = 7.3 Hz), 3.85 (t, 2H, *J* = 6.7 Hz), 4.85 (brs, 3H); ^{13}C NMR (MeOD) δ ppm 25.2, 25.4, 37.7, 38.6, 39.7, 40.1, 45.4, 173.2.



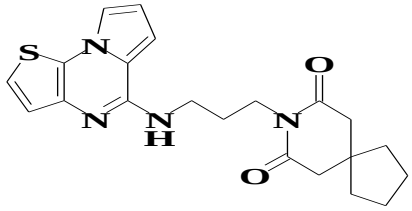
8-(4-Amino-butyl)-8-aza-spiro[4.5]decane-7,9-dione hydrochloride (7b)

86%; mp = 130°C; IR (KBr) 3150, 1715, 1635 cm^{-1}; MS (IS) *m/z* 239 $(M+1)^+$; ^1H NMR (MeOD) δ ppm 1.51-1.73 (m, 12H), 2.63 (s, 4H), 3.05 (t, 2H, *J* = 7.0 Hz), 3.79 (t, 2H, *J* = 7.0 Hz), 6.83 (brs, 3H); ^{13}C NMR (MeOD) δ ppm 24.5, 24.9, 25.1, 37.8, 38.9, 39.8, 40.2, 44.9, 173.2.

General procedure for the synthesis of compounds 8

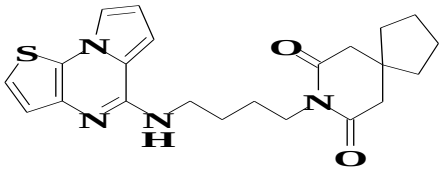
Under an argon atmosphere, to a mixture of chloride **1**, Pd_2dba_3 (0.25 eq.), rac-BINAP (0.75 eq.) and primary amine **7** (1.2 eq.) in degazed toluene was added tBuONa (1.4 eq.). The solution was stirred for 18 h at reflux and concentrated under reduced pressure. The purification was performed by flash chromatography (SiO_2; CH_2Cl_2/MeOH: 98/2) to give imides **8**.

8-[3-(1-Thia-4,8a-diaza-*as*-indacen-5-ylamino)-propyl]-8-aza-spiro[4.5]decane-7,9-dione (8a)



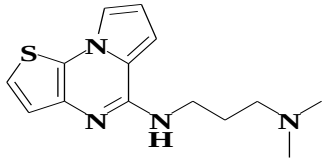
Colourless oil, 69%; IR (NaCl) 3350, 1724, 1672 cm^{-1}; MS (IS) *m/z* 398 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.42-1.54 (m, 4H), 1.66-1.72 (m, 4H), 1.88-1.98 (m, 2H), 2.61 (s, 4H), 3.52-3.62 (m, 2H), 3.93 (t, 2H, *J* = 6.4 Hz), 5.80 (brs, 1H), 6.71 (dd, 1H, *J* = 3.9, 2.4 Hz), 6.81 (dd, 1H, *J* = 3.9, 1.2 Hz), 6.94 (d, 1H, *J* = 5.5 Hz), 7.20 (d, 1H, *J* = 5.5 Hz), 7.31 (dd, 1H, *J* = 2.4, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 24.2, 24.3, 27.7, 37.0, 37.3, 37.6, 39.5, 44.9, 101.8, 112.5, 114.3, 115.1, 119.7, 124.5, 138.3, 149.3, 172.9. Anal. Calcd for $C_{21}H_{24}N_4O_2S$: C, 63.61; H, 6.10; N, 14.13. Found: C, 63.49; H, ; N, 14.15.

8-[4-(1-Thia-4,8a-diaza-*as*-indacen-5-ylamino)-butyl]-8-aza-spiro[4.5]decane-7,9-dione (8b)



Colourless oil, 73%; IR (NaCl) 3369, 1721, 1667 cm^{-1}; MS (IS) *m/z* 412 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.46-1.76 (m, 12H), 2.58 (s, 4H), 3.62-3.69 (m, 2H), 3.84 (t, 2H, *J* = 7.0 Hz), 5.18 (brs, 1H), 6.68-6.75 (m, 2H), 6.95 (d, 1H, *J* = 5.8 Hz), 7.21 (d, 1H, *J* = 5.8 Hz), 7.31 (t, 1H, *J* = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 24.2, 25.7, 26.5, 37.6, 39.1, 39.5, 40.6, 44.9, 101.7, 112.4, 114.3, 115.1, 119.6, 121.2, 124.6, 138.3, 149.4, 172.4. Anal. Calcd for $C_{22}H_{26}N_4O_2S$: C, 64.36; H, 6.38; N, 13.65. Found: C, 64.23; H, 3.27; N, 13.75.

***N,N*-Dimethyl-*N'*-(1-thia-4,8a-diaza-*as*-indacen-5-yl)-propane-1,3-diamine (8c)**



Colourless oil, 71%; IR (NaCl) 3364, 1728, 1663 cm^{-1}; MS (IS) *m/z* 275 $(M+1)^+$; ^1H NMR ($CDCl_3$) δ ppm 1.80-1.89 (m, 2H), 2.31 (s, 6H), 2.51 (t, 2H, *J* = 5.8 Hz), 3.67-3.74 (m, 2H), 6.55 (dd, 1H, *J* = 4.2, 1.2 Hz), 6.69 (dd, 1H, *J* = 3.9, 2.4 Hz), 6.94 (d, 1H, *J* = 5.5 Hz), 7.11 (brs, 1H), 7.22 (d, 1H, *J* = 5.5 Hz), 7.29 (dd, 1H, *J* = 2.4, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ ppm 25.6, 41.8, 45.6, 59.4, 101.6, 112.6, 114.2, 115.0, 120.0, 120.9, 124.6, 138.6, 149.9. Anal. Calcd for $C_{14}H_{18}N_4S$: C, 61.28; H, 6.61; N, 20.42. Found: C, 61.34; N, 6.64; N, 20.58.

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References

1. Ruat, M.; Traiffort, E.; Leurs, R.; Tardivel-Lacombe, J.; Diaz, J.; Arrang, J. M.; Schwartz, J. C. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 8547.
2. Bard, J. A.; Zgombick, J.; Adham, N.; Vaysse, P.; Branchek, T. A.; Weinshank, R. L. *J. Biol. Chem.* **1993**, *268*, 23422.
3. Lovenberg, T. W.; Baron, B. M.; de Lecea, L.; Miller, J. D.; Prosser, R. A.; Rea, M. A.; Foye, P. E.; Racke, M.; Slone, A. L.; Siegel, B. W.; Danielson, P. E.; Sutcliffe, J. G.; Erlander, M. G. *Neuron* **1993**, *11*, 449.
4. Thomas, D. R.; Atkinson, P. J.; Hastie. P. G.; Roberts, J. C.; Middlemiss, D. N.; Price; G. W. *Neuropharmacology* **2002**, *42*, 74.
5. Ikeda, M.; Iwata, N.; Kitajima, T.; Suzuki, T.; Yamanouchi, Y.; Kinoshita, Y.; Ozaki, N. *Neuropsychopharmacology* **2006**, *31*, 866.
6. Purohit, A.; Smith, C.; Herrick-Davis, K.; Teitler, M. *Psychopharmacology (Berl)* **2005**, *179*, 461.
7. Wesolowska, A.; Nikiforuk, A.; Stachowicz, K. *Eur. J. Pharmacol*. **2006**, *553*, 185.
8. A. Wesolowska, A. Nikiforuk, K. Stachowicz, E. Tatarczynska. *Neuropharmacology* **2006**, *51*, 578.
9. Hedlund, P. B.; Huitron-Resendiz, S.; Henriksen, S. J.; Sutcliffe, J. G. *Biol. Psychiatry*. **2005**, *58*, 831.
10. Perez-Garcia, G.; Gonzalez-Espinosa, C.; Meneses, A. *Behav. Brain Res*. **2006**, *169*, 83.
11. Perez-Garcia, G.; Meneses, A. *Behav. Brain Res.* **2008**, *195*, 139.
12. Graf, M.; Jakus, R.; Kantor, S.; Levay, G.; Bagdy, G. *Neurosci. Lett*. **2004**, *359*, 45.
13. Terron, J. A.; Falcon-Neri, A. *Br. J. Pharmacol*. **1999**, *127*, 609.
14. Prins, N. H.; Briejer, M. R.; Van Bergen, P. J.; Akkermans, L. M.; Schuurkes, J. A. *Br. J. Pharmacol.* **1999**, *128*, 849.
15. Terron, J. A. *Eur. J. Pharmacol*. **2002**, *439*, 1.
16. De Ponti, F.; Tonini, M. *Drugs* **2001**, *61*, 317.
17. M. Leopoldo. *Curr. Med. Chem*. **2004**, *11*, 629.
18. Pittala, V.; Salerno, L.; Modica, M.; Siracusa. M. A.; Romeo, G. *Mini Rev. Med. Chem.* **2007**, *7*. 945.
19. Medina, R. A.; Sallander, J.; Benhamü, B.; Porras, E.; Campillo, M.; Pardo, L.; Lopez-Rodríguez, M. L. *J. Med. Chem.* **2009**, *51*, 6259.

20. Podona, T.; Guardiola-Lemaître, B.; Caignard, D. H.; Adam, G.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Med. Chem*. **1994**, *37*, 1779.
21. Comoy, C.; Marot, C.; Podona, T.; Baudin, M. L.; Morin-Allory. L.; Guillaumet, G.; Pfeiffer, B.; Caignard, D. H.; Renard, P ; Rettori, M. C.; Adam, G.; Guardiola-Lemaître, B. *J. Med. Chem.* **1996**, *39*, 4285.
22. Comoy, C.; Guérin, V.; Pfeiffer, B.; Rettori, M. C.; Renard, P.; Guillaumet, G. *Bioorg. Med. Chem.* **2000**, 8, 483.
23. Rezaie, R.; Joseph, B.; Bremner, J. B.; Delagrange, P.; Kopp, C.; Misslin, R.; Pfeiffer, B.; Renard, P.; Guillaumet, G. *J. Pharm. Pharmacol*. **2001**, *53*, 959.
24. Lepailleur, A.; Bureau, R.; Lemaître, S.; Dauphin, F.; Lancelot, J. C.; Contesse, V.; Lenglet, S.; Delarue, C.; Vaudry, H.; Rault, S. *J. Chem. Inf. Comput. Sci*. **2004**, *44*, 1148.
25. Rault, S.; Lancelot, J. C.; Prunier, H.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D. H.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1996**, *39*, 2068.
26. (a) Rault, S.; Cugnon de Sévricourt, M.; Nguyen-Huy, D.; Robba, M. *J. Heterocycl. Chem.* **1981**, 18, 739; (b) Prunier, H.; Besret, L.; Dauphin, F.; Lancelot, J. C.; Bureau, R.; Rault, S. *Pharm. Sci.* **1997**, *3*, 311.
27. Comoy, C.; Benarab, A.; Leinot, M.; Monteil, A.; Guillaumet, G. *II Farmaco*, **1999**, *54*, 791.
28. New, J.; Christopher, W. L.; Yevich, J. P.; Butler, R.; Schlemmer, R. S. Jr.; Vander Maelen, C. P.; Cipollina. J. A. *J. Med. Chem*. **1989**, *32*, 1147.
29. Rouden, J.; Bernard, M. C. *Tetrahedron Lett*. **1999**, *40*, 8109.
30. Lepailleur, A.; Bureau, R.; Paillet-Loilier, M.; Fabis, F.; Saettel, N.; Lemaître, S.; Dauphin, F.; Lesnard, A.; Lancelot, J. C.; Rault, S. *J. Chem. Inf. Model*. **2005**, *45*, 1075.