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Synthesis of arylpiperazines with a terminal naphthothiazole group and their evaluation on 5-HT, DA and α receptors

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Summary — The synthesis, affinities for 5-HT_{1A}, 5-HT_2, D_1, D_2, α_1 and α_2 receptors and structure–activity relationships are described for a series of arylpiperazines substituted on the N-4 atom with an ω-(2-naphthothiazole)alkyl chain. The best affinity for 5-HT_{1A} receptors was obtained for 1-(2-methoxyphenyl)piperazine derivatives with IC_{50} values in the range 3.2–12 nM; however, for all the reported compounds mixed 5-HT_{1A}/D_2/α affinities were observed.

arylpiperazine / naphthothiazole / 5-HT_{1A}/D_2/α ligand / EPS / antipsychotic

Introduction

Classical antipsychotics such as tricyclic and butyrophenone derivatives cause extrapyramidal side effects (EPS) and tardive dyskinesias that have been linked to the blockage of dopamine (DA) receptors in the striatum corpus of the central nervous system (CNS). The development of antipsychotic agents [1] such as clozapine has led to improved antipsychotic treatment with reduced EPS. The clinical use of clozapine, however, has been limited by agranulocytosis and tachycardic phenomena [2, 3].

Improved treatment avoiding EPS and agranulocytosis is the goal of current antipsychotic drug research. Several lines of research have been developed, and recent efforts have been focused on the development of compounds that act on both dopamine and serotonin (5-HT) receptors [4–7]: serotonin interacts with receptors such as the 5-HT_{1A} receptor subtype in the limbic system, where it is thought to play a role in emotional responses such anxiety and depression [8–10]. Furthermore, compounds with 5-HT_{1A} receptor agonist activity reverse the catalepsy produced by antipsychotic agents in rats [11, 12]. The cataleptic response is predictive of EPS in humans, and its reversal suggests that a combination of dopaminergic and 5-HT_{1A} binding affinity may produce an antipsychotic agent with minimal EPS liability; and in particular the 5-HT_{1A} agonist activity could be beneficial in helping to relieve the anxiety that can often trigger psychotic episodes [13–15].

One such class of compound with affinity for both D-2 and 5-HT_{1A} receptors is represented by the arylpiperazine derivatives [16]. The presence of a specific side chain on the basic nitrogen of these compounds results in significantly enhanced affinity for 5-HT_{1A} binding sites.

Different moieties have been linked on the N-4 atom of the piperazine ring (fig 1). Different terminal systems play an important role in the interaction with the respective hydrophobic region of the 5-HT_{1A} receptor [17, 18].

We have recently found a series of arylpiperazines to be atypical potential antipsychotics, having a tetralin group as a new terminal moiety (fig 2), with mixed D_2/5-HT_{1A} receptor affinity [19]. They showed a favourable D_2/5-HT_{1A} ratio with nanomolar affinity for 5-HT_{1A} and moderate affinity for D_2 (being reported as an IC_{50} ratio). Unfortunately, most of them showed remarkable affinity to α-adrenergic receptors and very few compounds showed a high selectivity toward 5-HT_{1A} receptors (IC_{50} α_1/5HT_{1A} > 50).

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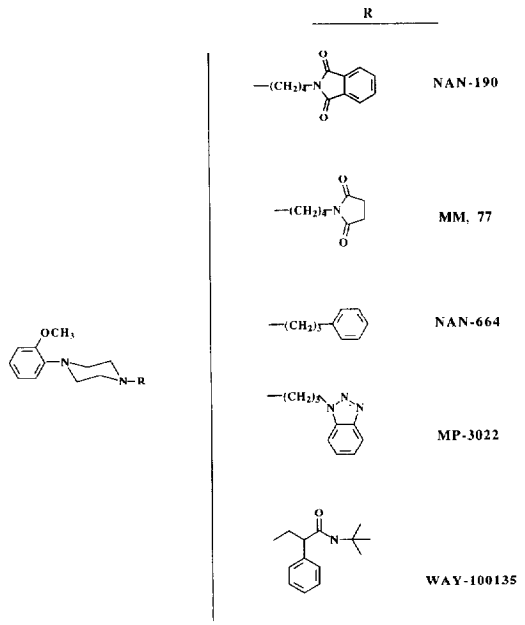


Fig 1. Structures of 5-HT_{1A} ligands.

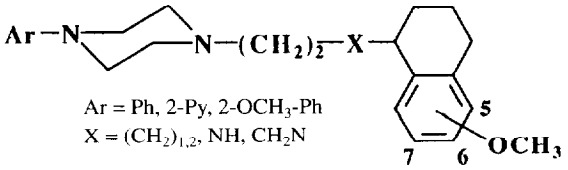


Fig 2. Arylpiperazines with mixed D_2/5-HT_{1A} receptor affinity.

Considering the important role played by the terminal group, in an attempt to: (1) increase the D_2/5-HT_{1A} ratio; and (2) to decrease α receptor affinity [20–22], the tetralin nucleus in the arylpiperazine derivatives studied previously [4, 19, 23, 24] was replaced by a 2-naphthothiazole group because a thiazole substituent appeared to exhibit bioisosteric properties with the carbonyl function present in amide derivatives studied [23].

Herein we describe the synthesis, 5-HT_{1A}, 5-HT_2, D_1, D_2, α_1 and α_2 receptor affinities and structure–activity relationships for a series of arylpiperazines **9–21** N-4-substituted with an ω-(2-napthothiazole)alkyl chain (table I).

The arylpiperazine moieties used are those previously reported displaying the highest affinity for the 5-HT_{1A} receptor, typified by 1-(2-methoxyphenyl)-, 1-phenyl-, 1-(2-pyridyl)piperazine; the polymethylene chain is of variable length and the terminal 2-naphthothiazole nucleus is unsubstituted, or substituted with a methoxy group in different positions.

Chemistry

Final compounds were synthesized as described in scheme 1. Alkylation of the 1-arylpiperazines with the appropriate ω-bromoalkylnitrile yielded nitriles **2c–f** [25, 26], that were submitted, under mild conditions, to a controlled acidic hydrolysis. These afforded amides **3c–f**. Amides **3a,b** were obtained from alkylation of 1-phenylpiperazine with 2-chloroacetamide and 3-chloropropionamide respectively. Sulphonation of the amides **3a–f** with Lawesson's reagent afforded the thioamides **4a–f** that underwent condensation with 2-bromo-1-tetralones **5–8** to give thiazoles **9–21** [27].

Pharmacology

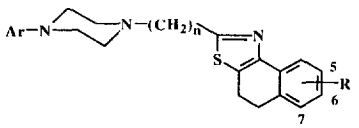
The compounds described in table II were evaluated for in vitro affinity on dopamine D_1 and D_2, serotonin 5-HT_{1A} and 5-HT_2, adrenergic α_1 and α_2 receptors by radioligand binding assays. All the compounds were used as hydrochloride salts and were water-soluble. The following specific radioligands and tissue sources were used: (a) dopamine D_1 receptors, [^{3}H]SCH-23390, rat striatal membranes; (b) dopamine D_2 receptors, [^{3}H]spiperone, rat striatal membranes; (c) serotonin 5-HT_{1A} receptors, [^{3}H]8-OH-DPAT, rat hippocampus membranes; (d) serotonin 5-HT_2 receptors, [^{3}H]ketanserin, rat brain prefrontal cortex membranes; (e) α_1 adrenergic receptors, [^{3}H]prazosin, rat brain cortex membranes; (f) α_2 adrenergic receptors, [^{3}H]yohimbine, rat brain cortex membranes.

Concentrations required to inhibit 50% radioligand specific binding (IC_{50}) were determined using eight or nine different concentrations of the drug studied. The specific binding was defined as described in the *Experimental protocols* under *Pharmacological methods*. In all binding assays, it represents more than 80% of the total binding, except for α_2 (> 60%). The results were analyzed by using the program Ligand to determine the IC_{50} values [28].

Biological results and discussion

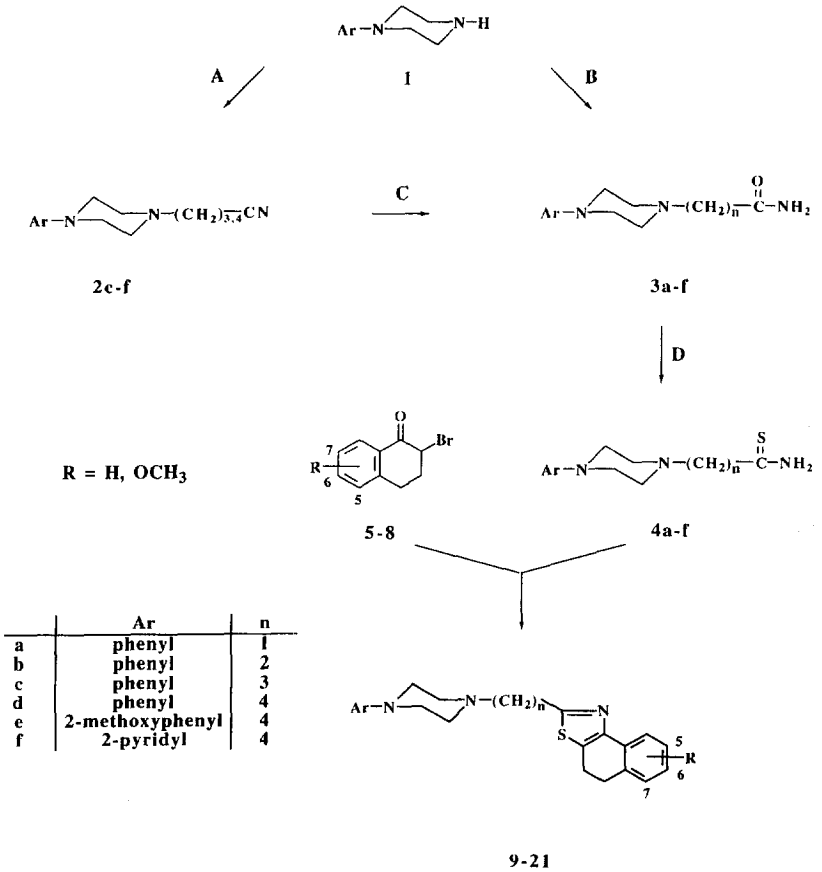
The results of binding assays and selectivities are illustrated in table II. As far as 5-HT_{1A} receptor affinity is concerned, compounds with a chain have been considered in this study. The results indicate that the IC_{50} values are usually higher when the polymethylene chain is shorter than four carbon atoms. For examples see **9** vs **10** (IC_{50} nM = 400 and 42); **11** vs **13** (IC_{50} nM = 170 and 69); **12** vs **14** (IC_{50} nM = 67 and 34). An exception to this rule is **10** vs **11** (IC_{50} nM = 42 and 170). Consequently, structures with a four methylene chain were designed, and the following

Table I. Physical properties of investigated compounds.



Compound	*Ar*	*n*	*R*	*Formula*[a]	*Mp (°C)*	*Recryst solv*
9	Ph	1	H	$C_{22}H_{23}N_3S$·2 HCl	208–210	MeOH/Et_2O
10	Ph	2	H	$C_{23}H_{25}N_3S$·3HCl·2 H_2O	177–178	MeOH/Et_2O
11	Ph	3	H	$C_{24}H_{27}N_3S$·3 HCl	205–206	MeOH/Et_2O
12	Ph	3	7-OCH_3	$C_{25}H_{29}N_3OS$·3 HCl	199–201	MeOH/Et_2O
13	Ph	4	H	$C_{25}H_{29}N_3S$·3 HCl	208–211	MeOH/Et_2O
14	Ph	4	7-OCH_3	$C_{26}H_{31}N_3OS$·3 HCl·H_2O	200–202	$CHCl_3$/petroleum ether
15	Ph	4	6-OCH_3	$C_{26}H_{31}N_3OS$·3 HCl·H_2O	221–222	MeOH/Et_2O
16	Ph	4	5-OCH_3	$C_{26}H_{31}N_3OS$·3 HCl	195–197	$CHCl_3$/petroleum ether
17	2-OCH_3 Ph	4	7-OCH_3	$C_{27}H_{33}N_3O_2S$·3 HCl·H_2O	201–203	MeOH/Et_2O
18	2-OCH_3 Ph	4	6-OCH_3	$C_{27}H_{33}N_3O_2S$·3 HCl·0.5H_2O	223–225	MeOH/Et_2O
19	2-OCH_3 Ph	4	5-OCH_3	$C_{27}H_{33}N_3O_2S$·3 HCl·H_2O	207–269	MeOH/Et_2O
20	2-Py	4	7-OCH_3	$C_{25}H_{30}N_4OS$·3 HCl·H_2O	245–247	MeOH/Et_2O
21	2-Py	4	5-OCH_3	$C_{25}H_{30}N_4OS$·3 HCl·H_2O	219–221	$CHCl_3$/petroleum ether

[a]Analyses for C, H, N; results were within ± 0.4% of the theoretical values for the formulae given.



	Ar	n
a	phenyl	1
b	phenyl	2
c	phenyl	3
d	phenyl	4
e	2-methoxyphenyl	4
f	2-pyridyl	4

Scheme 1. Reagents. A: $Br(CH_2)_{3,4}CN$; B: $Cl(CH_2)_{1,2}CONH_2$; C: conc H_2SO_4; D: Lawesson's reagent.

Table II. Binding affinities and selectivities of investigated compounds.

Compounds	*IC_{50}, nM (± SEM)*					*Selectivity vs 5-HT_{1A} receptor, IC_{50} ratio*			
	5-HT_{1A} [^{3}H]8-OH-DPAT	*5-HT_2 [^{3}H]Ketanserin*	*D_2 [^{3}H]Spiperone*	*α_1 [^{3}H]Prazosin*	*α_2 [^{3}H]Yohimbine*	*5-HT_2*	*D_2*	*α_1*	*α_2*
9	400 ± 52	3180 ± 289	680 ± 74	1140 ± 102	3770 ± 401	8	2	3	9
10	42 ± 4	300 ± 34	120 ± 9	140 ± 12	300 ± 45	7	3	3	7
11	170 ± 15	63 ± 6	210 ± 24	110 ± 10	160 ± 20	0.4	3	0.6	1
12	67 ± 7	66 ± 6	220 ± 18	170 ± 15	260 ± 32	1	3	2.5	4
13	69 ± 7	280 ± 34	76 ± 8	120 ± 14	110 ± 10	4	1	2	2
14	34 ± 4	170 ± 18	110 ± 12	90 ± 9	160 ± 19	5	3	3	5
15	4.1 ± 0.5	55 ± 6	11 ± 2	58 ± 6	20 ± 2	13	3	14	5
16	10 ± 1	66 ± 7	24 ± 3	52 ± 5	18 ± 2	7	2	5	2
17	12 ± 1	870 ± 90	25 ± 3	49 ± 5	500 ± 54	73	2	4	42
18	3.2 ± 0.4	250 ± 29	22 ± 2	52 ± 5	92 ± 9	78	7	16	29
19	3.8 ± 0.4	240 ± 22	8.3 ± 1	35 ± 4	46 ± 5	65	2	10	12
20	7 ± 1	720 ± 68	150 ± 13	200 ± 19	380 ± 46	103	21	28	54
21	8.2 ± 0.8	82 ± 8	61 ± 6	190 ± 21	390 ± 42	10	7	23	48
Buspirone	30 ± 3	>10000	280 ± 31	>10000	>10000				
8-OH-DPAT	2.1 ± 0.2	>10000	5.22 ± 0.60	>10000	810 ± 75				
Ketanserin		3.4 ± 0.3							
Haloperidol			4.8 ± 0.5						
Prazosin				1.4 ± 0.6					
Yohimbine					30 ± 3				

structure–activity relationships will concern these derivatives only. The highest affinity for 5-HT_{1A} receptors were obtained with the *o*-methoxyphenyl derivatives **17–19**, having IC_{50} values in the range 3.7–12 nM. In contrast to tetralin derivatives studied previously [4, 19, 23, 24], the presence and position of the methoxy group in the naphthothiazole system has negligible influence.

The results of this study indicate that the affinity for the 5-HT_2 receptors is usually slightly lower than the affinity for 5-HT_{1A} receptors, with IC_{50} values in the range 55–870 nM. Therefore, all the compounds reported here exhibited an affinity for both serotonergic receptors with a favourable 5-HT_2/5-HT_{1A} ratio.

As far as the dopaminergic components are concerned, the D_1 receptor affinity consistently showed IC_{50} values above 10^{-6} M. The affinity for D_2 receptors was in some cases remarkable, with IC_{50} values in the range 8.3–110 nM and with a D_2/5-HT_{1A} ratio between 1.1 and 6.3. This ratio was higher for 2-pyridylpiperazine derivatives **20** and **21** (7.1 and 21.1 respectively). Therefore, the D_2/5-HT_{1A} ratios were lower than those previously reported for tetralin derivatives.

Affinity toward α_1 and α_2 adrenergic receptors was remarkable, with α_1 or α_2/5-HT_{1A} ratio $\leq$ 50, (the closest values being those of 2-pyridylpiperazine derivatives **20** and **21**). This is in contrast to the arylpiperazines studied previously, which were linked to a tetralin moiety. These results showed that the replacement of the tetralin nucleus with a 2-napthothiazole group did not significantly affect the mixed 5-HT_{1A}/D_2 affinities. Moreover, the undesirable α affinity was retained and the α/5-HT_{1A} ratio was worse.

Experimental protocols

Chemistry

Column chromatography was run with 1:30 ICN silica gel 60A (63–200 mm) as stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses were performed by the microanalytical section of our department on solid samples only. The analytical results (C, H, N) were within ± 0.4% of theoretical values. ^{1}H-NMR spectra were recorded either on a Varian EM-390 (TMS as internal standard) or on a Bruker AM 300 WB instrument. Chemical shifts are reported in parts per million (ppm, δ). Recording of mass spectra was made on an HP 5995C gas chromatograph/mass spectrometer, electron impact 70 eV, equipped with an HP 59970A workstation. All compounds had NMR and mass spectra that were fully consistent with their structure.

*General procedure for preparation of 4-phenyl-1-piperazine-alkanenitrile **2c–f***

A stirred suspension of 1-arylpiperazine (10 mmol), ω-bromoalkylnitrile (15 mmol) and K_2CO_3 (15 mmol) in toluene (50 mL) was refluxed for 1 h. After cooling, the mixture was poured into water and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude residue was chromatographed (ethyl acetate/CH_2Cl_2, 1:1 as eluent) to yield pure **2c–f** (60–70% yield) as a yellow oil.

4-Phenyl-1-piperazinebutanenitrile ***2c***. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.54–2.10 (m, 2H, CH_2CH_2CN), 2.30–2.75 [m, 8H, $(CH_2)_2NCH_2$ and CH_2CN], 3.05–3.32 [m, 4H, $ArN(CH_2)_2$], 6.72–7.42 (m, 5H, aromatic); GC/MS *m/z*: 229 (M^+, 68), 189 (65), 175 (40), 105 (91), 42 (100).

4-Phenyl-1-piperazinepentanenitrile ***2d***. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.52–1.95 (m, 4H, $CH_2CH_2CH_2CH_2CN$), 2.20–2.75 [m, 8H, $(CH_2)_2NCH_2CH_2CH_2CH_2CN$], 3.05–3.35 [m, 4H, $ArN(CH_2)_2$], 6.72–7.50 (m, 5H, aromatic); GC/MS *m/z*: 243 (M^+, 46), 175 (89), 132 (40), 104 (57), 42 (100).

4-(2-Methoxyphenyl)-1-piperazinepentanenitrile ***2e***. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.52–1.95 (m, 4H), 2.20–2.90 (m, 8H), 2.98–3.25 (m, 4H), 3.88 (s, 3H), 6.75–7.22 (m, 4H); GC/MS *m/z*: 273 (M^+, 100), 205 (67), 177 (21), 136 (59), 120 (23).

4-(2-Pyridyl)-1-piperazinepentanenitrile ***2f***. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.60–2.10 (m, 4H), 2.25–2.80 (m, 8H), 3.45–3.80 (m, 4H), 6.52–8.32 (m, 4H); GC/MS *m/z*: 244 (M^+, 6), 150 (8), 119 (13), 107 (100), 79 (17).

4-Phenyl-1-piperazineacetamide ***3a***. A mixture of 1-phenylpiperazine (5.00 g, 31 mmol), 2-chloroacetamide (5.76 g, 62 mmol) in toluene (30 mL) in the presence of K_2CO_3 (8.52 g, 62 mmol) was refluxed overnight. After cooling, the solvent was removed under reduced pressure. The residue was taken up in H_2O and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and the solvent was removed affording **3a** as white solid (5.80 g, 75% yield), mp = 176–178 °C (white powder from CH_2Cl_2/petroleum ether). ^{1}H-NMR (90 MHz, $CDCl_3$): 2.61–2.90 [m, 4H, $(CH_2)_2NCH_2$], 3.01–3.40 [m, 6H, $ArN(CH_2)_2$ and CH_2CO], 6.43 (br s, 2H, NH_2, D_2O exchanged), 6.40–7.42 (m, 5H, aromatic); GC/MS *m/z*: 219 (M^+, 35), 176 (13), 175 (100), 132 (39), 105 (24).

4-Phenyl-1-piperazinepropanamide ***3b***. This compound was prepared in a similar manner as above, starting from 1-phenylpiperazine (5.00 g, 31 mmol) and 3-chloropropionamide (3.30 g, 31 mmol). The crude amide **3b** was chromatographed (ethyl acetate/CH_2Cl_2, 1:1 as eluent) to yield pure **3b** as a white solid (3.30 g, 46% yield), mp = 174–175 °C (white powder from $CHCl_3$/petroleum ether). ^{1}H-NMR (90 MHz, DMSO-d_6): 2.15–2.85 [m, 8H, $(CH_2)_2NCH_2CH_2CO$], 2.90–3.25 [m, 4H, $N(CH_2)_2$], 6.60–7.55 (m, 7H, aromatic and NH_2, D_2O exchanged); GC/MS *m/z*: 233 (M^+, 100), 218 (51), 175 (70), 147 (15), 132 (54).

General procedure for preparation of 4-aryl-1-piperazinealkanamide ***3c–f***

N-substituted piperazinoalkanenitrile **2c–f** (10 mmol) was slowly added under vigorous stirring to conc H_2SO_4 (10 mL) at room temperature. After 30 min in a water-bath at 50 °C, the mixture was kept for 1 h at room temperature, then poured on ice and subsequently basified with Na_2CO_3. The aqueous phase was extracted in a continuous manner with $CHCl_3$, and the solvent was evaporated to yield the amide **3c–f** (70–80% yield) as a white powder (from CH_2Cl_2/petroleum ether).

4-Phenyl-1-piperazinebutanamide ***3c***. Mp = 135–136 °C. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.65–2.05 (m, 2H, CH_2CH_2CO], 2.10–2.80 [m, 8H, $(CH_2)_2NCH_2$ and CH_2CO], 3.00–3.33 [m, 4H, $ArN(CH_2)_2$], 6.10 (br s, 2H, NH_2, D_2O exchanged), 6.70–7.45 (m, 5H, aromatic); GC/MS *m/z*: 247 (M^+, 44), 189 (12), 176 (14), 175 (100), 132 (48), 105 (47).

4-Phenyl-1-piperazinepentanamide ***3d***. Mp = 138–139 °C. ^{1}H-NMR (90 MHz, $CDCl_3$) 1.40–1.88 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.08–2.85 [m, 8H, $(CH_2)_2NCH_2CH_2CH_2CH_2CO$], 3.05–3.40 [m, 4H, $Ar(CH_2)_2$], 5.60–6.35 (br s, 2H, NH_2, D_2O exchanged), 6.75–7.52 (m, 5H, aromatic); GC/MS *m/z*: 261 (M^+, 37), 176 (13), 175 (100), 132 (25), 104 (24), 70 (61).

4-(2-Methoxyphenyl)-1-piperazinepentanamide ***3e***. Mp = 112–115 °C. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.35–1.85 (m, 4H), 2.06–2.80 (m, 8H), 2.88–3.30 (m, 4H), 3.88 (s, 3H), 5.57–6.05 (br s, 2H, D_2O exchanged), 6.70–7.22 (m, 4H); GC/MS *m/z*: 291 (M^+, 45), 205 (100), 177 (16), 138 (14), 134 (12).

4-(2-Pyridyl)-1-piperazinepentanamide ***3f***. Mp = 126–128 °C. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.32–1.87 (m, 4H), 2.05–2.72 (m, 8H), 3.32–3.70 (m, 4H), 5.52–6.05 (br s, 2H, D_2O exchanged), 6.42–8.32 (m, 4H); GC/MS *m/z*: 262 (M^+, 9), 168 (26), 147 (14), 143 (20), 121 (22), 107 (100), 79 (23).

General procedure for preparation of 4-aryl-1-piperazinealkanethioamide ***4a–f***

Lawesson's reagent (10 mmol) was added portionwise to a stirred solution of the amide **3a–f** (10 mmol) in anhydrous toluene (30 mL). The suspension was refluxed for 2 h under nitrogen until it became a yellow solution. After cooling at room temperature, the precipitate was filtered and the solution was evaporated to dryness. The residual oil was treated with 3 N HCl and aqueous solution, repeatedly washed with CH_2Cl_2, alkalized with Na_2CO_3 and extracted with $CHCl_3$. The organic phase was dried (Na_2SO_4) and the solvent removed to give an oil which was chromatographed with $CHCl_3$/MeOH, 19:1 as eluent (60–70% yield, leaflets from CH_2Cl_2/petroleum ether).

4-Phenyl-1-piperazinethioacetamide ***4a***. Mp = 186–187 °C. ^{1}H-NMR (90 MHz, $CDCl_3$): 2.60–2.95 [m, 4H, $(CH_2)_2NCH_2$], 3.10–3.45 [m, 4H, $ArN(CH_2)_2$], 3.53 (s, 2H, CH_2CS), 6.83–7.60 (m, 5H, aromatic), 6.70 and 9.18 (2 br s, 2H, NH_2, D_2O exchanged); GC/MS *m/z*: 235 (M^+, 47), 176 (10), 175 (100), 160 (63), 105 (54), 104 (49).

4-Phenyl-1-piperazinepropanethioamide ***4b***. Mp 139–140 °C. ^{1}H-NMR (90 MHz, DMSO-d_6): 2.42–2.94 [m, 8H, $(CH_2)_2NCH_2CH_2CS$], 3.04–3.32 [m, 4H, $Ar(CH_2)_2$], 6.65–7.53 (m, 5H, aromatic), 9.10 and 9.82 (2 br s, 2H, NH_2, D_2O exchanged); GC/MS *m/z*: 249 (M^+, 89), 215 (31), 175 (91), 120 (97), 105 (57), 70 (100).

4-Phenyl-1-piperazinebutanethioamide ***4c***. Mp = 99–100 °C. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.75–2.10 (m, 2H, $CH_2CH_2CH_2$), 2.40–2.95 [m, 8H, $(CH_2)_2NCH_2CH_2CH_2CS$], 3.05–3.28 [m, 4H, $Ar(CH_2)_2$], 6.70–7.42 (m, 5H, aromatic), 7.85 and 9.00 (2 br s, 2H, NH_2, D_2O exchanged); GC/MS *m/z*: 263 (M^+, 42), 262 (29), 188 (54), 175 (31), 132 (100), 105 (55).

4-Phenyl-1-piperazinepentanethioamide ***4d***. Mp = 134–135 °C. ^{1}H-NMR (90 MHz, DMSO-d_6): 1.20–1.92 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.15–2.85 [m, 8H, $(CH_2)_2NCH_2CH_2CH_2CH_2CS$], 3.05–3.38 [m, 4H, $Ar(CH_2)_2$], 6.58–7.35 (m, 5H, aromatic), 9.20–9.35 (2 br s, 2H, NH_2, D_2O exchanged); GC/MS *m/z*: 277 (M^+, 44), 276 (18), 243 (48), 175 (100), 132 (40), 104 (34).

4-(2-Methoxyphenyl)-1-piperazinepentanethioamide ***4e***. Mp = 140–142 °C. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.38–2.02 (m, 4H), 2.32–2.90 (m, 8H), 3.02–3.35 (m, 4H), 3.88 (s, 3H), 6.76–

7.35 (m, 4H), 7.72 and 8.38 (2 br s, 2H, D_2O exchanged); GC/MS *m/z*: 275 (2), 273 (100), 205 (87), 136 (93), 120 (46), 57 (37).

4-(2-Pyridyl)-1-piperazinepentanethioamide ***4f***. Mp = 146–148 °C. ^{1}H-NMR (90 MHz, DMSO-d_6): 1.27–1.92 (m, 4H), 2.12–2.80 (m, 8H), 3.20–3.75 (m, 4H), 6.52–8.27 (m, 4H), 9.05 and 9.68 (2 br s, 2H, D_2O exchanged); GC/MS *m/z*: 244 (5), 119 (10), 107 (100), 79 (14).

General procedure for thiazole ring closure ***9–21***

A solution of thioamide **4a–f** (10 mmol) and the appropriate α-bromoketone **5–8** (15 mmol) in anhydrous EtOH under nitrogen was refluxed overnight. Evaporation of the solvent afforded an oil, which was treated with 3 N HCl (20 mL) and washed repeatedly with $CHCl_3$. The aqueous layer was then alkalized with Na_2CO_3 and extracted with $CHCl_3$ (3 × 20 mL). The collected extracts, dried (Na_2SO_4) and concentrated under reduced pressure, yielded an oil which was chromatographed ($CHCl_3$/MeOH, 49:1 as eluent) and obtained as oils **4a–f** (60–65% yield).

8,9-Dihydro-2-(4-phenyl-1-piperazinyl)methyl-naphtho[1,2-d]-thiazole ***9***. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.78 [t, 4H, J = 7.4 Hz, $CH_2N(CH_2)_2$], 2.95–3.12 (m, 4H, naphthalenic), 3.25 [t, 4H, J = 4.9 Hz, $(CH_2)_2NAr$], 3.94 (s, 2H, CH_2), 6.80–7.94 (m, 9H, aromatic); GC/MS *m/z*: 361 (M^+, 41), 292 (11), 242 (12), 201 (95), 200 (100), 145 (45).

8,9-Dihydro-2-(4-phenyl-1-piperazinyl)ethyl-naphtho[1,2-d]-thiazole ***10***. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.76–2.88 [m, 4H, $CH_2N(CH_2)_2$], 2.93 (t, 2H, J = 7.3 Hz, CH_2CH_2N), 3.20–3.50 [m, 6H, CH_2CH_2N and $(CH_2)_2NAr$], 6.88–7.95 (m, 9H, aromatic); GC/MS *m/z*: 375 (M^+, 17), 243 (34), 176 (13), 175 (100), 173 (11), 132 (26).

8,9-Dihydro-2-(4-phenyl-1-piperazinyl)propyl-naphtho[1,2-d]-thiazole ***11***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.86–2.15 (m, 2H, $CH_2CH_2CH_2N$), 2.48–2.67 [m, 6H, $CH_2N(CH_2)_2$], 2.92–3.15 (m, 6H, benzylic), 3.22 [t, 4H, J = 4.9 Hz, $(CH_2)_2NAr$], 6.80–7.92 (m, 9H, aromatic); GC/MS *m/z*: 389 (M^+, 16), 257 (34), 228 (14), 202 (18), 201 (100), 189 (13), 161 (14).

8,9-Dihydro-7-methoxy-2-(4-pheny-1-piperazinyl)propyl-naphtho[1,2-d]thiazole ***12***. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.01–2.11 (m, 2H, $CH_2CH_2CH_2N$), 2.54 [t, 2H, J = 7.4 Hz, $CH_2N(CH_2)_2$], 2.55–2.66 [m, 4H, $CH_2N(CH_2)_2$], 2.91–2.97 (m, 2H, $CH_2CH_2CH_2N$), 3.01–3.08 (m, 4H, naphthalenic), 3.21 [t, 4H, J = 4.9 Hz, $(CH_2)_2NAr$], 3.84 (s, 3H, CH_3), 6.78–7.55 (m, 8H, aromatic); GC/MS *m/z*: 419 (M^+, 15), 287 (34), 258 (12), 244 (22), 232 (14), 231 (100).

8,9-Dihydro-2-(4-phenyl-1-piperazinyl)butyl-naphtho[1,2-d]-thiazole ***13***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.64–1.72 (m, 2H, CH_2CH_2N), 1.81–1.91 (m, 2H, $N{=}CCH_2CH_2$), 2.46 [t, 2H, J = 7.6 Hz, $CH_2N(CH_2)_2$], 2.61 [t, 4H, J = 5.0 Hz, $CH_2N(CH_2)_2$], 2.93–3.11 (m, 6H, benzylic), 3.20 [t, 4H, J = 5.0 Hz, $(CH_2)_2N$], 6.81–7.89 (m, 8H, aromatic); GC/MS *m/z*: 403 (M^+, 16), 402 (9), 401 (21), 388 (22), 297 (18), 272 (19), 214 (15), 175 (20), 173 (13).

8,9-Dihydro-7-methoxy-2-(4-phenyl-1-piperazinyl)butyl-naphtho[1,2-d]thiazole ***14***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.61–1.71 (m, 2H), 1.80–1.90 (m, 2H), 2.46 (t, 2H, J = 7.5 Hz), 2.61 (t, 4H, J = 5.0 Hz), 2.91–2.97 (m, 2H, $N{=}CCH_2$), 3.01–3.14 (m, 4H, naphthalenic), 3.20 (t, 4H, J = 5.0 Hz), 3.84 (s, 3H, CH_3), 6.78–7.56 (m, 8H, aromatic); GC/MS *m/z*: 433 (M^+, 12), 431 (15), 327 (24), 315 (10), 302 (20), 301 (100), 272 (39), 244 (15).

8,9-Dihydro-6-methoxy-2-(4-phenyl-1-piperazinyl)butyl-naphtho[1,2-d]thiazole ***15***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.61–1.71 (m, 2H), 1.73–1.90 (m, 2H), 2.45 (t, 2H, J = 7.5 Hz), 2.61 (t, 4H, J = 4.9), 2.91–3.05 (m, 6H), 3.20 (t, 4H, J = 5.0 Hz), 3.80 (s, 3H), 6.75–7.81 (m, 7H); GC/MS *m/z*: 433 (M^+, 11), 432 (8), 431 (20), 327 (4), 302 (20), 301 (100), 272 (42), 244 (18).

8,9-Dihydro-5-methoxy-2-(4-phenyl-1-piperazinyl)butyl-naphtho[1,2-d]thiazole ***16***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.63–1.77 (m, 2H), 1.81–1.91 (m, 2H), 2.47 (t, 2H, J = 7.5 Hz), 2.62 (t, 4H, J = 5.0 Hz), 2.95 (s, 4H), 3.03 (t, 2H, J = 7.5 Hz), 3.21 (t, 4H, J = 5.0 Hz), 3.84 (s, 3H), 6.70–7.12 (m, 8H); GC/MS *m/z*: 433 (M^+, 10), 431 (15), 418 (12), 327 (21), 302 (19), 301 (100), 272 (39), 244 (14), 175 (17).

8,9-Dihydro-7-methoxy-2-[4-(2-methoxyphenyl)-1-piperazinyl]butyl-naphtho[1,2-d]thiazole ***17***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.65–1.73 (m, 2H), 1.83–1.90 (m, 2H), 2.45 (t, 2H, J = 7.6 Hz), 2.67 (s br, 4H), 2.91–3.10 (m, 10H), 3.84 (s, 6H, 2 CH_3), 6.78–7.55 (m, 7H); GC/MS *m/z*: 463 (M^+, 13), 462 (10), 461 (25), 448 (21), 327 (16), 302 (19), 301 (100), 272 (36), 205 (20).

8,9-Dihydro-6-methoxy-2-[4-(2-methoxyphenyl)-1-piperazinyl]butyl-naphtho[1,2-d]thiazole ***18***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.62–1.72 (m, 2H), 1.82–1.89 (m, 2H), 2.47 (t, 2H, J = 7.6 Hz), 2.66 (br s, 4H), 2.90–3.09 (m, 10H), 3.80 and 3.84 (2 s, 6H), 6.74–7.81 (m, 7H); GC/MS *m/z*: 463 (M^+, 15), 462 (9), 461 (21), 301 (100), 272 (38), 243 (14), 205 (18), 190 (16).

8,9-Dihydro-5-methoxy-2-[4-(2-methoxyphenyl)-1-piperazinyl]butyl-naphtho[1,2-d]thiazole ***19***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.62–1.72 (m, 2H), 1.73–1.90 (m, 2H), 2.47 (t, 2H, J = 7.6 Hz), 2.66 (br s, 4H), 2.94 (s, 4H), 3.01–3.09 (m, 6H), 3.84 (s, 6H), 6.70–7.46 (m, 7H); GC/MS *m/z*: 463 (M^+, 16), 462 (10), 461 (21), 315 (14), 302 (20), 301 (100), 272 (39), 244 (17), 231 (13), 205 (23).

8,9-Dihydro-7-methoxy-2-[4-(2-pyridyl)-1-piperazinyl]butyl-naphtho[1,2-d]thiazole ***20***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.61–1.73 (m, 2H), 1.80–1.90 (m, 2H), 2.43 (t, 2H, J = 7.5 Hz), 2.54 (t, 4H, J = 5.1 Hz), 2.90–3.09 (m, 6H), 3.53 (t, 4H, J = 5.0 Hz), 3.83 (s, 3H), 6.57–8.17 (m, 8H); GC/MS *m/z*: 434 (M^+, 40), 432 (30), 340 (57), 327 (52), 272 (100), 270 (27), 244 (25).

8,9-Dihydro-5-methoxy-2-[4-(2-pyridyl)-1-piperazinyl]butyl-naphtho[1,2-d]thiazole ***21***. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.61–1.71 (m, 2H), 1.80–1.90 (m, 2H), 2.44 (t, 2H, J = 7.6 Hz), 2.55 (t, 4H, J = 5.0 Hz), 2.94 (s, 4H), 3.03 (t, 2H, J = 7.6 Hz), 3.53 (t, 4H, J = 5.0 Hz), 3.84 (s, 3H), 6.57–8.17 (m, 7H); GC/MS *m/z*: 434 (M^+, 44), 433 (22), 432 (53), 328 (15), 315 (27), 272 (100), 271 (45), 107 (67).

Hydrochloride salts: general procedure

The hydrochloride salts were prepared by adding an HCl ethereal solution to a methanolic solution of amine. Recrystallization solvents, formulae and melting points are reported in table I. They were obtained as white to sandy yellow crystals or crystalline powders.

Pharmacological methods
The binding studies were performed in rat brain areas. Male Wistar rats weighing 175–200 g, were killed by decapitation under light anesthesia and the various brain regions dissected quickly on an ice-cold plate. Depending on the receptor to be studied the different areas were used following the methods described below.

D_1 dopaminergic binding assay
The binding assay for D_1 dopaminergic receptors was essentially that described by Billard et al [29]. Corpora striata were homogenized in 30 vol (w/v) ice-cold 50 mM Tris–HCl buffer (pH 7.7 at 25 °C) using a Polytron PT10 (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50 000 *g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM ice-cold Tris–HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid and 10 μM pargyline (pH 7.1 at 37 °C). Each assay tube contained 50 μL drug solution, 50 μL [^{3}H]SCH-23390 to achieve a final concentration of 0.4 nM, and 900 μL resuspended membranes (3 mg fresh tissue). The tubes were incubated for 15 min at 37 °C and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL ice-cold 50 mM Tris–HCl buffer (pH 7.7 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]SCH-23390 binding was defined as the difference between binding in the absence or in the presence of 0.1 μM piflutixol.

D_2 dopaminergic binding assay
The procedure used in the radioligand binding assay has been reported in detail by Creese et al [30]. Corpora striata were homogenized in 30 vol (w/v) ice-cold 50 mM Tris–HCl buffer (pH 7.7 at 25 °C) using a Polytron PT10 (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50 000 *g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM ice-cold Tris–HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% ascorbic acid and 10 μM pargyline (pH 7.1 at 37 °C). Each assay tube contained 50 μL drug solution, 50 μL [^{3}H]spiroperidol to achieve a final concentration of 0.4 nM, and 900 μL resuspended membranes (3 mg fresh tissue). The tubes were incubated for 15 min at 37 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL ice-cold 50 mM Tris–HCl buffer (pH 7.7 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]spiroperidol binding was defined as the difference between binding in the absence or in the presence of 1 μM (+)-butaclamol.

5-HT_{1A} serotonergic binding assay
The procedure used in the radioligand binding assay has been reported in detail by Hall et al [31]. The hippocampus was homogenized in 30 vol (w/v) ice-cold 50 mM Tris–HCl buffer (pH 7.2 at 25 °C) using a Polytron PT10 (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50 000 *g* with resuspension of the pellet in fresh buffer. After the second centrifugation, the pellet was resuspended in homogenization buffer and the suspension incubated 10 min at 37 °C. After two further centrifugations and washing, the final pellet was resuspended in 50 mM ice-cold Tris–HCl containing 4 mM $CaCl_2$, 0.1% ascorbic acid and 10 μM pargyline (pH 7.4 at 25 °C). Each assay tube contained 50 μL drug solution, 50 μL [^{3}H]8-OH-DPAT to achieve a final concentration of 0.8 nM, and 900 μL resuspended membranes (10 mg fresh tissue). The tubes were incubated for 30 min at 25 °C and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL ice-cold 50 mM Tris–HCl buffer (pH 7.2 at 25 °C). The radioactivity bound to the filters was measured by liquid scintillation counter. Specific [^{3}H]8-OH-DPAT binding was defined as the difference between binding in the absence or in the presence of 10 μM 5-HT.

5-HT_2 serotonergic binding assay
The procedure used in the radioligand binding assay has been reported in detail by Leysen et al [32]. Prefrontal cortex was homogenized in 30 vol (w/v) ice-cold 50 mM Tris–HCl buffer (pH 7.2 at 25 °C) using a Polytron PT10 (setting 5 for 20 s). Homogenates were centrifuged three times for 10 min at 50 000 *g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM ice-cold Tris–HCl (pH 7.4 at 37 °C). Each assay tube contained 50 μL drug solution, 50 μL [^{3}H]ketanserin to achieve a final concentration of 0.8 nM, and 900 μL resuspended membranes (5 mg fresh tissue). The tubes were incubated for 15 min at 37 °C, and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL ice-cold 50 mM Tris–HCl buffer (pH 7.2 at 25 °C). The radioactivity bound to the filters was measured by liquid scintillation counter. Specific [^{3}H]ketanserin binding was defined as the difference between binding in the absence or in the presence of 1 μM methysergide.

α_1 adrenergic binding assay
The procedure used in the radioligand binding assay has been reported in detail by Greengrass and Bremner [33]. Brain cortex was homogenized in 30 vol (w/v) ice-cold 50 mM Tris–HCl buffer (pH 7.2 at 25 °C) using a Polytron PT10 (setting 5 for 20 s). Homogenates were centrifuged twice for 10 min at 50 000 *g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM ice-cold Tris–HCl (pH 7.4 at 25 °C). Each assay tube contained 50 μL drug solution, 50 μL [^{3}H]prazosin to achieve a final concentration of 0.4 nM, and 900 μL resuspended membranes (10 mg fresh tissue). The tubes were incubated for 30 min at 25 °C and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL ice-cold 50 mM Tris–HCl buffer (pH 7.2 at 25 °C). The radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]prazosin binding was defined as the difference between binding in the absence or in the presence of 1 μM phentolamine.

α_2 adrenergic binding assay
The procedure used in the radioligand binding assay has been reported in detail by Perry and U'Prichard [34]. Brain cortex was homogenized in 30 vol (w/v) ice-cold 5 mM Tris–HCl, 5 mM EDTA buffer (pH 7.3 at 25 °C) using a Polytron PT10 (setting 5 for 20 s). Homogenates were centrifuged three times for 10 min at 50 000 *g* with resuspension of the pellet in fresh buffer. The final pellet was resuspended in 50 mM ice-cold Tris–HCl, 0.5 mM EDTA (pH 7.5 at 25 °C). Each assay tube contained 50 μL drug solution, 50 μL [^{3}H]yohimbine to achieve a final concentration of 1 nM, and 900 μL resuspended membranes (10 mg fresh tissue). The tubes were incubated for 30 min at 25 °C and the incubation was terminated by rapid filtration under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 5 mL ice-cold 50 mM Tris–HCl, 0.5 mM EDTA buffer (pH 7.5 at 25 °C). The

radioactivity bound to the filters was measured by a liquid scintillation counter. Specific [^{3}H]yohimbine binding was defined as the difference between binding in the absence or in the presence of 10 μM phentolamine.

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