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1-Substituted-4-[3-(1,2,3,4-tetrahydro-5- or 7-Methoxynaphthalen-1-yl)propyl]piperazines: Influence of the *N*-1 Piperazine Substituent on 5-HT_{1A} Receptor Affinity and Selectivity Versus D_2 and α_1 Receptors. Part 6†

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Abstract—In the present paper, we report the synthesis and the binding profiles on 5-HT_{1A}, D_2, and α_1 receptors of 1-substituted-4-[3-(5- or 7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)propyl]piperazine derivatives **19**–**32** and some related heteroalkyl derivatives **33**–**35**. The results obtained are compared to those previously reported for the 1-phenyl, 1-(2-methoxyphenyl), 1-(2-pyridyl) analogues **2**–**9**. The results pointed out the critical role of the group linked in the *N*-1 position of the piperazine in terms of 5-HT_{1A} binding affinity. In fact, 1-cyclohexyl, 1-(3-benzisoxazolyl), 1-(benzothiazole-2-carbonyl), 1-(2-benzothiazolyl), 1-(2-quinolyl) substituted piperazines **21**–**30** displayed moderate or low 5-HT_{1A} receptor affinity; on the contrary, 1-(3-benzisothiazolyl) and 1-(1-naphthalenyl) substituted piperazines **19**, **20** and **32** displayed high 5-HT_{1A} receptor affinity, the K_i values being in the subnanomolar range. Furthermore, compounds **19**, **20** and **32** demonstrated better selectivity over α_1 receptors than the reference compounds **2**–**9**.

Introduction

During the last decade, the serotonin 5-HT_{1A} receptor subtype has been a major target for neurobiological research[2] because of its involvement in psychiatric disorders such as anxiety and depression.[3–5] Furthermore, some authors suggested that combining dopamine D_2 antagonism with 5-HT_{1A} agonism in a single molecule would give effective antipsychotic compounds with a reduced propensity to induce extrapyramidal side-effects (EPS).[6–8] Besides the therapeutic use in anxiety, depression, and schizophrenia, serotonergic 5-HT_{1A} ligands have been more recently suggested for other therapeutic perspectives. It has been shown that the decrement of 5-HT_{1A} receptor binding is remarkably region-selective in the rat forebrain with increasing age and, particularly, it affects the cholinergic cell groups that innervate the cortex and hippocampus. This phenomenon appeared to be especially significant in relation to the neuronal substrates underlying the age-related alterations of cognition such as Alzheimer's disease.[9,10] For these reasons it has been suggested that 5-HT_{1A} antagonists may have a role in the treatment of some of the cognitive symptoms of dementia.[11,12] Moreover, it has been demonstrated that 5-HT_{1A} receptor agonists show a neuroprotective potency associated with their ability to inhibit ischemia-induced excessive release of glutamate.[13] In the light of the therapeutic perspectives mentioned above, the development of ligands with high affinity and selectivity for the 5-HT_{1A} receptor is still needed. A large number of arylpiperazine derivatives have been identified as ligands at the 5-HT_{1A} receptor: the main shortcoming of this class of compounds is a relatively high affinity at α_1 adrenergic receptors since this may cause unwanted cardiovascular effects.[14] Our research group has already studied the affinity and selectivity at 5-HT_{1A} receptors of some arylpiperazine derivatives of type **1**.[1,15–17] These arylpiperazine derivatives display

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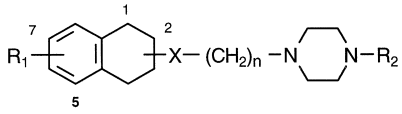
the structural requirements for recognition of the 5-HT_{1A} binding site, i.e., an aromatic ring coupled to a basic nitrogen atom at a suitable distance;[18] this fundamental structure is joined by an alkyl chain to a tetralin group. We studied the effect of some structural modifications on the 5-HT_{1A} binding affinity and selectivity versus α_1 adrenergic and D_2 dopaminergic receptors. The SAFIR studies showed that the highest values of 5-HT_{1A} binding affinity and selectivity were observed for compounds (a) 5-OCH_3 or 7-OCH_3 substituted on the 1-tetralinyl ring; (b) presenting X = CH_2, S, NH, N(CH_3). Moreover, the presence of a heteroatom in the intermediate chain seems mainly to modulate the selectivity. The nature of the aryl group on the piperazine ring seemed to exert a moderate influence, although only three different groups were considered to investigate its effect (phenyl, 2-OCH_3-phenyl, 2-pyridyl). Therefore, in this paper we focus our attention on the effects of *N*-1 piperazine substituents on the 5-HT_{1A} receptor affinity and selectivity for this class of 1-arylpiperazines. Our hypothesis is that specific structural requirements are responsible for 5-HT_{1A} receptor affinity and selectivity for a particular class of long chain arylpiperazines. We chose either substituents that have already been reported for long-chain arylpiperazine 5-HT_{1A} receptor ligands, such as 3-benzisothiazolyl,[19–22] 1-naphthalenyl,[23,24] 2-benzothiazolyl,[25] 2-quinolyl,[26] as well as substituents not yet studied (cyclohexyl, 3-benzisoxazolyl, benzothiazole-2-carbonyl).



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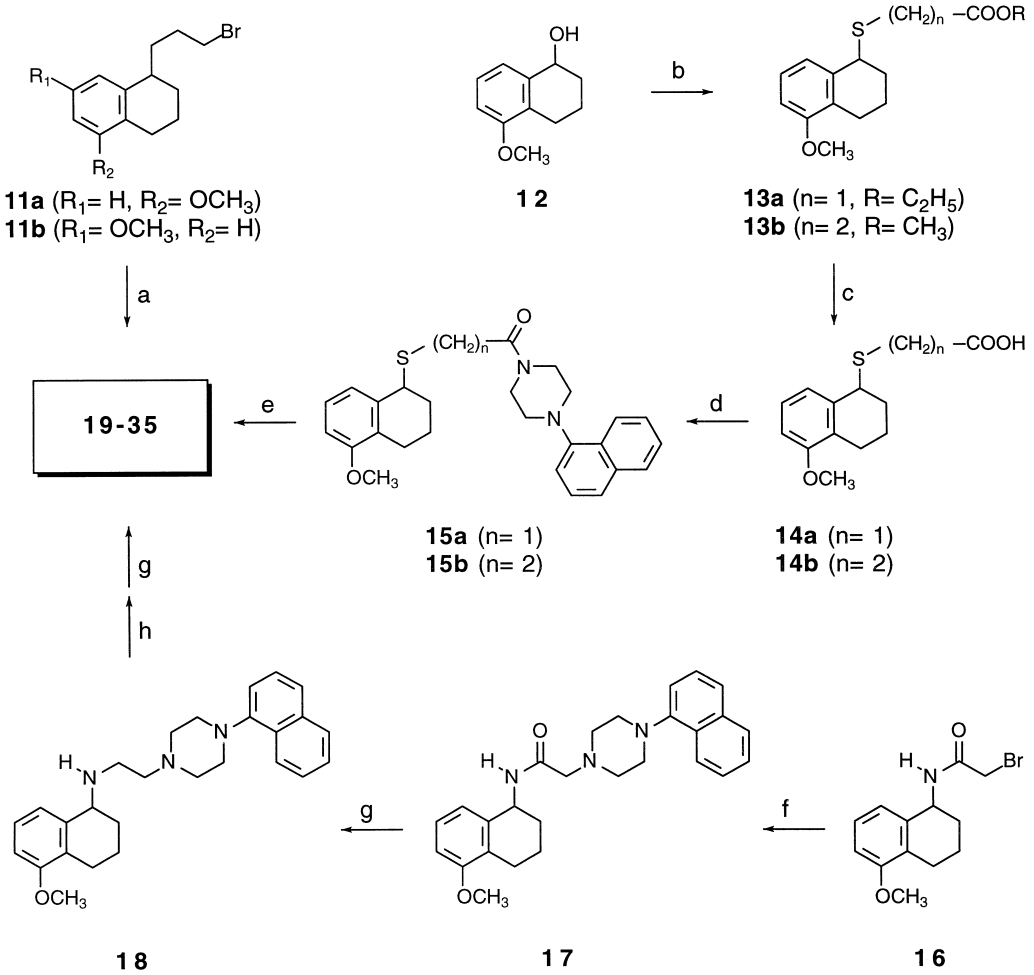
R_1= H, OCH_3; X= CH_2, S, N(CH_3);
n= 2, 3; R_2= Ph, 2-CH_3OPh, 2-Py

Chemistry

The synthesis of target compounds is depicted in Scheme 1. Compounds **19–30** were easily obtained by reacting the appropriate piperazine with bromoalkyl derivatives **11a,b**. Compounds containing a sulfur atom in



Scheme 1. Reagents: (a) 1-substituted piperazines, K_2CO_3, CH_3CN; (b) ethyl 2-mercaptoacetate or methyl 3-mercaptopropionate, ZnI_2, CH_2Cl_2; (c) 10% aq NaOH, THF; (d) 1-(1-naphthalenyl)piperazine, DCC, CH_2Cl_2; (e) $LiAlH_4$, Et_2O; (f) 1-(1-naphthalenyl)piperazine, Et_3N, toluene; (g) $LiAlH_4$, THF; (h) methyl chloroformate, 2.4% aq NaOH, $CHCl_3$.

the spacer were prepared starting from 5-methoxy-1-tetralol (**12**) which was reacted with ethyl 2-mercaptoacetate or methyl 3-mercaptopropionate in the presence of zinc iodide[27] to give esters **13a** and **13b**, respectively. The latter compounds were hydrolyzed in alkaline medium and the resulting acids **14a** and **14b** were condensed, in the presence of 1,3-dicyclohexylcarbodiimide (DCC), with 1-(1-naphthalenyl)piperazine to give amides **15a** and **15b**, respectively. Reduction of these compounds with $LiAlH_4$ afforded target compounds **33** and **34**. Compound **35** was prepared as follows: the bromo derivative **16**[16] was reacted with 1-(1-naphthalenyl)-piperazine to give amide **17** which was reduced with $LiAlH_4$ to give amine **18**. *N*-Methylation was accomplished by treating **18** with methyl chloroformate[28] to yield its carbamate derivative, which was then reduced with $LiAlH_4$ to compound **35**.

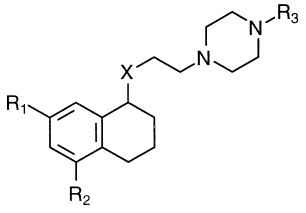
Pharmacology

Target compounds (Table 1) were evaluated for in vitro affinity at serotonin 5-HT_{1A}, dopamine D_2, and adrenergic α_1 receptors by radioligand binding assays. The following specific radioligands and tissue sources were used: (a) serotonin 5-HT_{1A} receptors—[^{3}H]-8-OH-DPAT, rat hippocampal membranes; (b) dopamine D_2 receptors—[^{3}H]spiroperidol, rat striatal membranes; (c) α_1 adrenergic receptors—[^{3}H]prazosin, rat brain cortex membranes. Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by using eight to nine different concentrations of the drug studied. In all binding assays specific binding represented more than 80% of the total. The results were analyzed by using the LIGAND program to determine IC_{50} values which were used to calculate the inhibition constants (K_i) using the Cheng–Prusoff equation.[29]

Results and Discussion

The results of the in vitro binding studies of the target compounds **19–35** are summarized in Table 2. Considering the 5-HT_{1A} receptor affinity of compounds **19–32**, it can be first noted that there was no great difference in affinity between the 5- and 7-methoxy iso-

Table 1. Physical properties



Compound	R_1	R_2	X	R_3	Formula[a]	Recryst. solv.	Mp (°C)
2[b]	H	CH_3O	CH_2	Phenyl	—	—	—
3[b]	CH_3O	H	CH_2	Phenyl	—	—	—
4[b]	H	CH_3O	CH_2	2-CH_3O-phenyl	—	—	—
5[b]	CH_3O	H	CH_2	2-CH_3O-phenyl	—	—	—
6[b]	H	CH_3O	CH_2	2-Pyridyl	—	—	—
7[b]	CH_3O	H	CH_2	2-Pyridyl	—	—	—
8[b]	H	CH_3O	S	2-CH_3O-phenyl	—	—	—
9[c]	H	CH_3O	N(CH_3)	2-CH_3O-phenyl	—	—	—
19	H	CH_3O	CH_2	3-Benzisothiazolyl	$C_{25}H_{31}N_3O_2S{\cdot}HCl{\cdot}1/2H_2O$	MeOH/Et_2O	222–224
20	CH_3O	H	CH_2	3-Benzisothiazolyl	$C_{25}H_{31}N_3O_2S{\cdot}HCl$	MeOH/Et_2O	218–220
21	H	CH_3O	CH_2	2-Benzothiazolyl	$C_{25}H_{31}N_3O_2S{\cdot}3HCl{\cdot}H_2O$	CH_2Cl_2/Et_2O	223–225
22	CH_3O	H	CH_2	2-Benzothiazolyl	$C_{25}H_{31}N_3O_2S{\cdot}3HCl$	CH_2Cl_2/Et_2O	196–198
23	H	CH_3O	CH_2	Benzothiazole-2-carbonyl	$C_{26}H_{31}N_3O_2S{\cdot}HCl$	MeOH/Et_2O	210–212
24	CH_3O	H	CH_2	Benzothiazole-2-carbonyl	$C_{26}H_{31}N_3O_2S{\cdot}HCl$	CH_2Cl_2/Et_2O	226–228
25	H	CH_3O	CH_2	3-Benzisoxazolyl	$C_{25}H_{31}N_3O_2{\cdot}HCl{\cdot}H_2O$	MeOH/Et_2O	220–224
26	CH_3O	H	CH_2	3-Benzisoxazolyl	$C_{25}H_{31}N_3O_2{\cdot}HCl$	MeOH/Et_2O	211–213
27	H	CH_3O	CH_2	2-Quinolyl	$C_{27}H_{33}N_3O{\cdot}2HCl$	MeOH	233–235
28	CH_3O	H	CH_2	2-Quinolyl	$C_{27}H_{33}N_3O{\cdot}2HCl{\cdot}H_2O$	MeOH/Et_2O	229–231
29[d]	H	CH_3O	CH_2	Cyclohexyl	—	—	—
30	CH_3O	H	CH_2	Cyclohexyl	$C_{24}H_{38}N_2O{\cdot}2HCl$	MeOH/Et_2O	>260
31	H	CH_3O	CH_2	1-Naphthalenyl	$C_{28}H_{34}N_2O{\cdot}HCl$	EtOH/Et_2O	245–248
32	CH_3O	H	CH_2	1-Naphthalenyl	$C_{28}H_{34}N_2O{\cdot}2HCl$	MeOH/Et_2O	235–237
33	H	CH_3O	S	1-Naphthalenyl	$C_{27}H_{32}N_2OS{\cdot}HCl{\cdot}H_2O$	MeOH	239–240
34	H	CH_3O	SCH_2	1-Naphthalenyl	$C_{28}H_{34}N_2OS{\cdot}2HCl$	MeOH	198–200
35	H	CH_3O	N(CH_3)	1-Naphthalenyl	$C_{28}H_{35}N_3O_2{\cdot}2HCl{\cdot}H_2O$	MeOH/Et_2O	240

[a]Analyses for C,H,N; results were within ±0.4% of the theoretical values for the formulas given.
[b]See ref 15.
[c]See ref 16.
[d]See ref 34.

Table 2. Binding affinities

Compound	$K_i \pm$ S.E.M., nM[a]			Selectivity (K_i ratio)	
	5-HT_{1A}	D_2	α_1	D_2/5-HT_{1A}	α_1/5-HT_{1A}
2[b]	0.45	92	36	204	80
3[b]	8.32	23	153	3	18
4[b]	0.69	15	5.4	22	8
5[b]	1.4	42.9	36	31	26
6[b]	0.48	117	55	244	115
7[b]	3.07	273	218	89	71
8[b]	0.98	6.53	100	7	102
9[c]	7.9	61	739	8	94
19	0.55 ± 0.02	5.2 ± 0.8	80 ± 9	9	145
20	1.2 ± 0.3	85 ± 7	520 ± 19	71	433
21	500 ± 35	> 850	> 800	—	—
22	755 ± 32	> 850	> 800	—	—
23	827 ± 80	> 850	> 800	—	—
24	> 900	> 850	> 800	—	—
25	49 ± 6	> 850	42 ± 5	—	—
26	345 ± 11	308 ± 21	112 ± 8	—	—
27	80 ± 6	> 850	> 800	—	—
28	718 ± 42	> 850	> 800	—	—
29	258 ± 17	604 ± 24	> 800	—	—
30	718 ± 64	479 ± 13	> 800	—	—
31	30 ± 4	385 ± 18	320 ± 21	13	11
32	6.4 ± 0.6	179 ± 19	> 800	28	125
33	7.3 ± 0.8	427 ± 22	> 800	58	> 100
34	9.1 ± 0.4	> 850	400 ± 20	93	44
35	4.6 ± 0.5	> 850	> 800	185	174
8-OH-DPAT	0.89 ± 0.08	—	—	—	—
Buspirone	52 ± 8.1	—	—	—	—
Spiroperidol	—	0.053 ± 0.002	—	—	—
Prazosin	—	—	0.10 ± 0.08	—	—

[a]Data are the mean of three independent determinations (samples in triplicate).
[b]See ref 15.
[c]See ref 16.

mers. The best results in terms of 5-HT_{1A} receptor affinity were found for the 3-benzisothiazolyl derivatives **19** and **20** ($K_i = 0.55$ and 1.2 nM, respectively) and for the 1-naphthalenyl derivatives **31** and **32** ($K_i = 30$ and 6.4 nM, respectively). All these compounds displayed K_i affinity values at the 5-HT_{1A} receptors in the same range as our reference compounds **2**–**7** and as other compounds bearing the same kind of aryl substituent.[19–22] These data point out that no improvement of 5-HT_{1A} receptor affinity was obtained in comparison with the corresponding compounds **2**–**7** previously studied having R_3 = Ph, 2-Py, 2-OCH_3Ph. On the other hand, the 2-benzothiazolyl (**21** and **22**), benzothiazole-2-carbonyl (**23** and **24**), 3-benzisoxazolyl (**25** and **26**), and quinolyl (**27** and **28**) derivatives displayed moderate or low 5-HT_{1A} binding affinity. Furthermore, it is interesting to note that, when comparing the affinities of the compounds **2** and **3** with those of the corresponding saturated-ring counterparts **29** and **30**, a dramatic loss in affinity was observed. These results point out the importance of the presence and the nature of an aromatic ring in R_3 position for 5-HT_{1A} receptor affinity.

When regarding the D_2 receptor affinity, differently from the reference compounds **2**–**9**, which displayed K_i values ranging between 6.53 and 273 nM, the corresponding compounds **20**–**35** showed D_2 K_i affinity values over 85 nM with the exception of the 3-benzisothiazolyl derivative **19** ($K_i = 5.2$ nM).

Furthermore, the α_1 receptor affinity values of the new compounds **19**–**35** are very low as compared with those of the reference compounds; in particular the most interesting derivatives of the new series which possess high affinities for the 5-HT_{1A} receptor (compounds **19**, **20** and **32**) displayed an α_1/5-HT_{1A} K_i ratio higher than 100. Compound **31** did not display a satisfactory binding profile, so we decided to carry out a strategy previously applied to compound **4**. In fact, the insertion of an S or $N(CH_3)$ group in the alkyl chain of compound **4** gave compounds **8** and **9** which showed a remarkable increase in selectivity versus the α_1 receptor (8-fold for compound **4** and about 100-fold for compounds **8** and **9**, respectively). The same structural modifications have been effected for compound **31**. The new compounds **33** and **35** displayed both a remarkable increase in 5-HT_{1A} receptor affinity and decrease in α_1 receptor affinity, resulting in an increased selectivity for the 5-HT_{1A} over the α_1 receptor; these data confirmed the trend previously observed. We also prepared compound **34** which

displayed similar properties as compared with the lower homologous **33**.

Conclusions

In conclusion, for the long-chain arylpiperazines with structures reported in Table 1, the critical role of the group linked in the *N*-1 position of the piperazine ring seems to be clear: some substituents lead to compounds **21**–**30** displaying moderate or low 5-HT_{1A} receptor affinity, while other substituents can give compounds displaying 5-HT_{1A} receptor affinity (derivatives **19**, **20**, **32**) in the subnanomolar range. Furthermore, the modification herein proposed led to compounds with improved selectivity in comparison with the reference compounds; the most suitable *N*-1 piperazine aromatic substituent was the 3-benzisothiazole (compounds **19** and **20**). The affinity profile of these compounds is very interesting since they show high 5-HT_{1A} receptor affinity values and, in particular, high selectivity versus the α_1 adrenergic receptor in comparison with the previously studied analogues **2**–**9**. An additional increase in selectivity can be achieved by the insertion of an S or N(CH_3) group in the intermediate alkyl chain: in this way the highly selective compounds **33** and **35** were developed from the low selective 1-naphthalenyl derivative **31**.

Experimental

Chemistry

Column chromatography was performed with 1:30 ICN silica gel 60A (63–200 μm) as the stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus. Elemental analyses (C,H,N) were performed on a Carlo Erba model 1106 analyzer; the analytical results were within ± 0.4% of the theoretical values for the formula given. ^{1}H NMR spectra were recorded either on a Varian EM-390 where indicated at 90 MHz (TMS as internal standard) or on a Bruker AM 300 WB instrument, with $CDCl_3$ as solvent; all values are reported in ppm (δ). Recording of mass spectra was done on an HP 5995C gas chromatograph/mass spectrometer, electron impact 70 eV, equipped with an HP59970A workstation; only significant *m*/*z* peaks, with their % relative intensity in parentheses, are reported herein. All spectra were in accordance with the assigned structures. All target compounds were transformed into their hydrochloride or hydrogen oxalate salts in the usual manner.

The following compounds were synthesized by published procedures: 1-(3-bromopropyl)-5-methoxy-1,2,3,4-tetrahydronaphthalene (**11a**),[15] 1-(3-bromopropyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**11b**),[15] 1-(1-naphthalenyl)piperazine,[30] 3-(1-piperazinyl)-1,2-benzisothiazole,[31] 2-(1-piperazinyl)benzothiazole,[32] 3-(1-piperazinyl)-1,2-benzisoxazole,[32] 1-(2-quinolinyl)piperazine,[33] ethyl 2-[(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-thio]acetate (**13a**),[34] *N*-(5-methoxy-1,2,3,4-tetrahydro-naphthalen-1-yl)bromoacetamide (**16**).[16] The spectral properties of compound **29** have already been reported.[35]

2-(1-Piperazinylcarbonyl)benzothiazole (10). A mixture of anhydrous piperazine (1.25 g, 14.5 mmol) and ethyl 2-benzothiazolecarboxylate[36] (1.00 g, 4.8 mmol) was heated at 160 °C for 6 h. Then, the mixture was cooled and chromatographed ($CHCl_3$:MeOH, 19:1, as eluent) to give compound **10** (0.67 g, 56% yield) as a white solid: mp 206–208 °C (from CH_2Cl_2/Et_2O); ^{1}H NMR (90 MHz) 4.05 [br s, 4H, HN(CH_2)$_2$], 4.70 [br s, 4H, (CH_2)$_2$NCO], 7.45–8.30 (m, 5H, aromatic, NH, 1H D_2O exchanged); GC–MS *m*/*z* 247 (M^+, 18), 204 (24), 162 (25), 135 (46), 134 (39), 85 (100).

1-Substituted piperazine derivatives 19–32: general procedure. A stirred suspension of the appropriate alkyl bromide **11a,b** (2.0 mmol), amine (4.0 mmol), and potassium carbonate (2.0 mmol) in acetonitrile was refluxed overnight. After cooling, the mixture was evaporated to dryness and water was added to the residue. The aqueous phase was extracted two times with ethyl acetate. The collected organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was chromatographed, as indicated below, to yield pure compounds **19–32** as pale yellow oils.

3-[4-[3-(1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenyl)-propyl]-1-piperazinyl]-1,2-benzisothiazole (19). Eluted with $CHCl_3$:MeOH, 49:1. ^{1}H NMR 1.58–1.83 [m, 8H, CH(CH_2CH_2)$_2$], 2.48–2.76 [m, 9H, benzylic, CH_2N(CH_2)$_2$], 3.60 [br s, 4H, (CH_2)$_2$NAr], 3.79 (s, 3H, CH_3), 6.62–7.90 (m, 7H, aromatic); GC–MS *m*/*z* 421 (M^+, 40), 285 (31), 258 (100), 232 (24).

3-[4-[3-(1,2,3,4-Tetrahydro-7-methoxy-1-naphthalenyl)-propyl]-1-piperazinyl]-1,2-benzisothiazole (20). Eluted with CH_2Cl_2:ethyl acetate, 7:3; ^{1}H NMR 1.58–1.89 [m, 8H, CH(CH_2CH_2)$_2$], 2.48–2.75 [m, 9H, benzylic, CH_2N(CH_2)$_2$], 3.59 [br t, 4H, (CH_2)$_2$NAr], 3.76 (s, 3H, CH_3), 6.64–7.91 (m, 7H, aromatic); GC–MS *m*/*z* 421 (M^+, 35), 285 (33), 258 (100), 232 (25).

2-[4-[3-(1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenyl)-propyl]-1-piperazinyl]benzothiazole (21). Eluted with $CHCl_3$:MeOH, 49:1; ^{1}H NMR 1.55–1.83 [m, 8H, CH(CH_2CH_2)$_2$], 2.41 [t, 2H, J = 6.3 Hz, CH_2N(CH_2)$_2$], 2.49–2.77 [m, 7H, benzylic, CH_2N(CH_2)$_2$], 3.64 [br t, 4H, (CH_2)$_2$NAr], 3.79 (s, 3H, CH_3), 6.62–7.59 (m, 7H, aromatic); GC–MS *m*/*z* 421 (M^+, 23), 271 (22), 258 (100), 246 (35), 163 (20).

2-[4-[3-(1,2,3,4-Tetrahydro-7-methoxy-1-naphthalenyl)-propyl]-1-piperazinyl]benzothiazole (22). Eluted with $CHCl_3$:MeOH, 49:1; ^{1}H NMR 1.55–1.88 [m, 8H, CH(CH_2CH_2)$_2$], 2.40 [t, 2H, J = 6.9 Hz, CH_2N(CH_2)$_2$], 2.48–2.75 [m, 7H, benzylic, CH_2N(CH_2)$_2$], 3.64 [br t, 4H, (CH_2)$_2$NAr], 3.76 (s, 3H, CH_3), 6.64–7.59 (m, 7H, aromatic); GC–MS *m*/*z* 421 (M^+, 23), 419 (25), 271 (23), 258 (100), 246 (37), 163 (23).

2-[4-[3-(1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenyl)-propyl]-1-piperazinylcarbonyl]benzothiazole (23). Eluted with $CHCl_3$; ^1H NMR 1.53–1.83 [m, 8H, CH(CH_2CH_2)$_2$], 2.40 [t, 2H, $J=6.7$ Hz, $CH_2N(CH_2)_2$], 2.46–2.77 [m, 7H, benzylic, $CH_2N(CH_2)_2$], 3.76 (s, 3H, CH_3), 3.85 and 4.43 [2 br t, 4H, $(CH_2)_2NCO$], 6.62–8.08 (m, 7H, aromatic); GC–MS m/z 449 (M^+, 21), 260 (41), 258 (100).

2-[4-[3-(1,2,3,4-Tetrahydro-7-methoxy-1-naphthalenyl)-propyl]-1-piperazinylcarbonyl]benzothiazole (24). Eluted with $CHCl_3$:MeOH, 49:1; ^1H NMR 1.56–1.88 [m, 8H, CH(CH_2CH_2)$_2$], 2.41 [t, 2H, $J=6.8$ Hz, $CH_2N(CH_2)_2$], 2.51–2.74 [m, 7H, benzylic, $CH_2N(CH_2)_2$], 3.76 (s, 3H, CH_3), 3.86 and 4.44 [2 br t, 4H, $(CH_2)_2NCO$], 6.64–8.08 (m, 7H, aromatic); GC–MS m/z 449 (M^+, 35), 260 (40), 259 (21), 258 (100), 162 (20).

3-[4-[3-(1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenyl)-propyl]-1-piperazinyl]-1,2-benzisoxazole (25). Eluted with CH_2Cl_2:MeOH, 49:1; ^1H NMR 1.55–1.84 [m, 8H, CH(CH_2CH_2)$_2$], 2.41–2.77 [m, 9H, benzylic, $CH_2N(CH_2)_2$], 3.59 [br s, 4H, $(CH_2)_2NAr$], 3.79 (s, 3H, CH_3), 6.62–7.68 (m, 7H, aromatic); GC–MS m/z 288 (65), 246 (36), 99 (100).

3-[4-[3-(1,2,3,4-Tetrahydro-7-methoxy-1-naphthalenyl)-propyl]-1-piperazinyl]-1,2-benzisoxazole (26). Eluted with CH_2Cl_2:ethyl acetate, 1:1; ^1H NMR 1.57–1.86 [m, 8H, CH(CH_2CH_2)$_2$], 2.47–2.74 [m, 9H, benzylic, $CH_2N(CH_2)_2$], 3.59 [br s, 4H, $(CH_2)_2NAr$], 3.76 (s, 3H, CH_3), 6.64–7.68 (m, 7H, aromatic); GC–MS m/z 288 (79), 246 (39), 99 (100).

1-(2-Quinolinyl)-4-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)propyl]piperazine (27). Eluted with CH_2Cl_2:ethyl acetate, 1:1; ^1H NMR 1.58–1.81 [m, 8H, CH(CH_2CH_2)$_2$], 2.44–2.77 [m, 9H, benzylic, $CH_2N(CH_2)_2$], 3.78 [br s, 7H, CH_3, $(CH_2)_2NAr$], 6.62–7.89 (m, 9H, aromatic); GC–MS m/z 415 (M^+, 10), 413 (23), 271 (47), 258 (34), 157 (100), 128 (29).

1-(2-Quinolinyl)-4-[3-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)propyl]piperazine (28). Eluted with CH_2Cl_2:ethyl acetate, 1:1; ^1H NMR 1.54–1.85 [m, 8H, CH(CH_2CH_2)$_2$], 2.44–2.75 [m, 9H, benzylic, $CH_2N(CH_2)_2$], 3.76–3.78 [m + s, 7H, CH_3, $(CH_2)_2NAr$], 6.63–7.89 (m, 9H, aromatic); GC–MS m/z 415 (M^+, 11), 413 (21), 271 (41), 258 (34), 157 (100), 128 (27).

1-Cyclohexyl-4-[3-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)propyl]piperazine (30). Eluted with $CHCl_3$:MeOH, 19:1; ^1H NMR 1.05–1.28 (m, 6H, cyclohexyl), 1.51–1.89 [m, 12H, cyclohexyl NCH(CH_2)$_2$, CH(CH_2CH_2)$_2$], 2.22–2.71 (m, 14H, piperazine, NCH, $CH_2CH_2CH_2N$, benzylic), 3.75 (s, 3H, CH_3), 6.62–7.24 (m, 3H, aromatic); GC–MS m/z 370 (M^+, 67), 327 (26), 260 (32), 181 (100).

1-(1-Naphthalenyl)-4-[3-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)propyl]piperazine (31). Eluted with CH_2Cl_2; ^1H NMR 1.60–1.90 [m, 8H, CH(CH_2CH_2)$_2$], 2.50–2.78 [m, 9H, benzylic, $CH_2N(CH_2)_2$], 3.17 [br s, 4H, $(CH_2)_2NAr$], 3.80 (s, 3H, CH_3), 6.63–8.20 (m, 10H, aromatic); GC–MS m/z 414 (M^+, 75), 225 (100), 212 (33).

1-(1-Naphthalenyl)-4-[3-(1,2,3,4-tetrahydro-7-methoxy-1-naphthalenyl)propyl]piperazine (32). Eluted with $CHCl_3$:MeOH, 19:1; ^1H NMR 1.62–1.90 [m, 8H, CH(CH_2CH_2)$_2$], 2.49–2.82 [m, 9H, benzylic, $CH_2N(CH_2)_2$], 3.15 [br s, 4H, $(CH_2)_2NAr$], 3.77 (s, 3H, CH_3), 6.65–8.21 (m, 10H, aromatic); GC–MS m/z 414 (M^+, 96), 225 (100), 212 (32).

Methyl 3-[(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-thio]propanoate (13b). Anhydrous ZnI_2 (4.44 g, 13.9 mmol) was added to a solution of 5-methoxy-1-tetralol (**12**) (4.96 g, 27.8 mmol) in CH_2Cl_2. Then was added methyl 3-mercaptopropionate (3.8 mL, 33.4 mmol) and the mixture was stirred at room temperature for 40 min. Then the reaction was quenched with H_2O (30 mL). The organic phase was separated, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was chromatographed (CH_2Cl_2 as eluent) to give 7.12 g of compound **13b** as a pale yellow oil (91% yield). ^1H NMR (90 MHz) 1.75–2.20 (m, 4H, *endo* CH_2CH_2), 2.50- 3.00 (m, 6H, CH_2CH_2CO, benzylic CH_2), 3.70 and 3.80 (2 s, 6H, 2 CH_3), 4.13 (br t, 1H, CHS), 6.63–7.33 (m, 3H, aromatic); GC–MS m/z 280 (M^+, 0.3), 161 (100), 160 (63), 115 (21).

2-[(1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenyl)thio]-ethanoic acid (14a). Ethyl 2-[(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)thio]ethanoate (**13a**) (3.57 g, 12.7 mmol) was refluxed overnight in THF in the presence of 10% aqueous NaOH (20 mL). Then the mixture was concentrated under reduced pressure and acidified with 3 N HCl. The aqueous phase was extracted with CH_2Cl_2 and the separated organic layer was dried over Na_2SO_4. The solvent was evaporated in vacuo to give a crude residue which was chromatographed ($CHCl_3$ as eluent) yielding acid **14a** as a pale yellow semisolid (2.2 g, 69% yield). ^1H NMR (90 MHz) 1.75–2.25 (m, 4H, *endo* CH_2CH_2), 2.43–2.85 (m, 2H, benzylic CH_2), 3.25–3.35 (m, 2H, SCH_2), 3.76 (s, 3H, CH_3), 4.33 (br t, 1H, CHS), 6.30–7.30 (m, 3H, aromatic), 10.70 (br s, 1H, OH, D_2O exchanged); GC–MS m/z 252 (M^+, 4), 161 (100), 160 (76), 159 (21), 115 (34).

3-[(1,2,3,4-Tetrahydro-5-methoxy-1-naphthalenyl)thio]-propanoic acid (14b). As above, starting from ester **13b** (7.12 g, 25 mmol) the title compound was obtained as a pale yellow semisolid (4.05 g, 60% yield). ^1H NMR (90 MHz) 1.70–2.20 (m, 4H, *endo* CH_2CH_2), 2.55–2.95 (m, 6H, SCH_2CH_2, benzylic CH_2), 3.80 (s, 3H, CH_3), 4.20 (br t, 1H, CHS), 6.66–7.20 (m, 3H, aromatic), 9.15 (br s, 1H, OH, D_2O exchanged); GC–MS m/z 266 (M^+, 0.3), 161 (100), 160 (61), 115 (20), 90 (19).

1-(1-Naphthalenyl)-4-[[1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)thio]acetyl]piperazine (15a). A solution of 1-(1-naphthalenyl)piperazine (0.62 g, 2.9 mmol), in CH_2Cl_2, was added dropwise to a stirred solution of acid **14a** (0.60 g, 2.4 mmol) and DCC (0.64 g, 3.1 mmol)

in the same solvent. The reaction mixture was stirred overnight at room temperature, then a few milliliters of glacial acetic acid were added to decompose the excess reagent. The insoluble urea was removed by filtration; the filtrate was washed with 2 N NaOH, the organic layer was separated and dried over Na_2SO_4. Evaporation of the solvent in vacuo provided the crude amide which was chromatographed (petroleum ether:ethyl acetate, 19:1, as eluent) to give the expected amide **15a** as a pale yellow semisolid (0.90 g, 83% yield): ^{1}H NMR 1.65–1.89 (m, 2H, *endo* CH_2), 2.00–2.20, 2.44–2.55 and 2.76–2.85 (m, 12H, piperazine, CHCH_2, benzylic CH_2), 3.45 (d, 2H, $J = 3.1$ Hz, SCH_2), 3.79 (s, 3H, CH_3), 4.09–4.33 (m, 1H, CH), 6.66–8.23 (m, 10H, aromatic); GC–MS m/z 446 (M^+, 31), 255 (26), 254 (100), 182 (63), 160 (95).

1-(1-Naphthalenyl)-4-[3-[1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)thio]propanoyl]piperazine (15b). As above, the title compound was obtained in 80% yield starting from acid **14b** (0.96 g, 3.6 mmol) and 1-(1-naphthalenyl)piperazine (0.91 g, 4.3 mmol). ^{1}H NMR (90 MHz) 1.65–2.00 (m, 2H, *endo* CH_2), 2.40–3.20 (m, 12H, piperazine, CHCH_2, benzylic CH_2), 3.55–3.85 (m + s, 7H, SCH_2CH_2, CH_3), 4.05–4.25 (m, 1H, CH), 6.60–8.30 (m, 10H, aromatic); GC–MS m/z 460 (M^+, 23), 300 (28), 299 (100), 239 (35), 182 (39), 169 (39), 161 (49), 160 (47), 154 (27).

1-(1-Naphthalenyl)-4-[2-[(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)thio]ethyl]piperazine (33). Amide **15a** (0.9 g, 2.0 mmol) and $LiAlH_4$ (0.15 g. 4.0 mmol) were placed in a two-necked round bottom flask which was flushed with N_2 and cooled at 0 °C. Then anhydrous Et_2O was slowly added and the resulting suspension was stirred overnight at rt. Then the mixture was cooled and a few drops of H_2O were added to destroy the excess of hydride. The mixture was filtered and the filtrate was dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a crude residue which was chromatographed (CH_2Cl_2:ethyl acetate, 19:1, as eluent) yielding pure **33** as a pale yellow oil (0.57 g, 65% yield). ^{1}H NMR 1.78–1.86 and 2.00–2.17 (m, 4H, *endo* CH_2CH_2), 2.46–2.57 and 2.74–2.83 [m, 10H, $CH_2N(CH_2)_2$, benzylic CH_2, SCH_2], 3.20 [br s, 4H, $(CH_2)_2$NAr], 3.79 (s, 3H, CH_3), 4.18 (br t, 1H, CHS), 6.66–8.17 (m, 10H, aromatic); GC–MS m/z 432 (M^+, 26), 225 (100).

1-(1-Naphthalenyl)-4-[3-[(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)thio]propyl]piperazine (34). As described for **33**, starting from amide **15b** (1.20 g, 2.6 mmol), compound **34** was obtained after elution with petroleum ether:ethyl acetate, 1:1 (0.57 g, 50% yield). ^{1}H NMR 1.70–2.21 (m, 6H, *endo* CH_2CH_2, SCH_2CH_2), 2.46–2.84 [m, 10H, $CH_2N(CH_2)_2$, benzylic CH_2, SCH_2], 3.18 (br s, 4H, CH_2NAr), 3.79 (s, 3H, CH_3), 4.12 (br t, 1H, CHS), 6.66–8.21 (m, 10H, aromatic); GC–MS m/z 446 (M^+, 2), 286 (21), 285 (100), 225 (24).

4-(1-Naphthalenyl)-*N*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-1-piperazineacetamide (17). A solution of 1-(1-naphthalenyl)piperazine (2.6 g, 12.2 mmol), *N*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)bromoacetamide (**16**) (1.31 g, 4.4 mmol), and triethylamine (2 mL) in toluene (40 mL) was refluxed overnight. Then the solution was cooled and washed with 20% aqueous Na_2CO_3. The separated organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was chromatographed ($CHCl_3$:ethyl acetate, 3:2, as eluent) to give compound **17** (1.61 g, 84% yield). ^{1}H NMR (90 MHz) 1.55–2.10 (m, 4H, *endo* CH_2CH_2), 2.50–3.10 (m, 11H, piperazine, benzylic CH_2, NH, 1H D_2O exchanged), 3.20 (s, 2H, $COCH_2$), 3.76 (s, 3H, CH_3), 5.05–5.20 (m, 1H, C*H*NH), 6.65–8.25 (m, 10H, aromatic); GC–MS m/z 429 (M^+, 26), 225 (100), 70 (35).

4-(1-Naphthalenyl)-*N*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-1-piperazineethanamine (18). Amide **17** (1.02 g, 2.4 mmol), in anhydrous THF, was added to a stirred suspension of $LiAlH_4$ (0.18 g, 4.8 mmol) in the same solvent (20 mL). The reaction mixture was refluxed for 2 h. After cooling, a few drops of water were added, the suspension was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with water and extracted twice with CH_2Cl_2. The separated organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude residue which was chromatographed (CH_2Cl_2:MeOH, 19:1, as eluent). Pure **18** was a pale yellow oil (0.45 g, 46% yield). ^{1}H NMR 1.71–2.03 (m, 4H, *endo* CH_2CH_2), 2.51–2.93 [m, 11H, $CH_2CH_2N(CH_2)_2$, benzylic CH_2, NH, 1H D_2O exchanged], 3.12 (br s, 4H, CH_2NAr), 3.79 (s, 3H, CH_3), 3.84–3.87 (m, 1H, NHC*H*), 6.67–8.20 (m, 10H, aromatic); GC–MS m/z 415 (M^+, 9), 226 (46), 225 (100), 197 (20), 195 (33), 182 (30), 161 (60), 154 (27).

***N*-Methyl-4-(1-naphthalenyl)-*N*-(1,2,3,4-tetrahydro-5-methoxy-1-naphthalenyl)-1-piperazineethanamine (35).** 2.4% aqueous NaOH (8.7 mL, 5.2 mmol) was added to a solution of amine **18** (0.92 g, 2.2 mmol) in $CHCl_3$ (50 mL). Then methyl chloroformate (0.4 mL, 5.2 mmol) in $CHCl_3$ (5 mL) was added dropwise to the ice-cooled mixture, under vigorous stirring. The cold mixture was stirred for 1 h, then acidified with 6 N HCl, and stirred for 0.5 h at 25 °C. The separated aqueous phase was extracted with $CHCl_3$. The combined organic layers were washed first with aqueous $NaHCO_3$, then with water, dried over Na_2SO_4 and concentrated under reduced pressure to yield the oily carbamate derivative. To a stirred suspension of $LiAlH_4$ (0.17 g, 4.4 mmol) in anhydrous THF was added a solution of the carbamate derivative in the same solvent. The mixture was refluxed for 24 h, then it was cooled, and the excess of reagent was decomposed with a few drops of water. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with $CHCl_3$ and washed with water. The separated organic layer was dried over Na_2SO_4 and evaporated in vacuo to afford the *N*-methylated derivative **35** (0.40 g, 42% yield). ^{1}H NMR 1.59–1.68 and 1.98–2.10 (m, 4H, *endo* CH_2CH_2), 2.37 (s, 3H, NCH_3), 2.45–3.00 [m, 10H, $CH_2CH_2N(CH_2)_2$, benzylic CH_2], 3.22 (br s, 4H, CH_2Ar), 3.79 (s, 3H, OCH_3), 4.03 (br s, 1H, C*H*NH), 6.68–8.16 (m, 10H,

aromatic); GC–MS m/z 429 (M^+, 2), 204, (38), 161 (100).

Pharmacological methods

5-HT$_{1A}$ serotonergic binding assay. Binding experiments were performed according to Borsini et al.[37] with minor modifications. Each tube received in a final volume of 1 mL of 50 mM Tris·HCl (pH 7.6) hippocampus membranes suspension and 1 nM [^{3}H]-8-OH-DPAT. For competitive inhibition experiments various concentrations of drugs studied were incubated. Nonspecific binding was defined using 1 μM 8-OH-DPAT. Samples were incubated at 37 °C for 20 min and then filtered on Whatman GF/B glass microfiber filters. The K_d value determined for 8-OH-DPAT was 8.8 nM.

D$_2$ dopaminergic binding assay. Binding experiments were performed according to Creese and co-workers[38] with minor modifications. Each tube received in a final volume of 3 mL of 50 mM Tris·HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$ and 5.7 mM ascorbic acid (pH 7.4), rat striatal membranes suspension, and 0.2 nM [^{3}H]spiroperidol. For competitive inhibition experiments various concentrations of drugs studied were incubated. Non-specific binding was defined using 1 μM haloperidol. Samples were incubated at 37 °C for 20 min and then filtered on Whatman GF/B glass microfiber filters. The K_d value determined for spiroperidol was 0.05 nM.

α_1 Adrenergic binding assay. Binding experiments were performed according to Glossman and Hornung[39] with minor modifications. Each tube received in a final volume of 1 mL of 50 mM Tris·HCl (pH 7.4) rat cerebral cortical membranes suspension and 1 nM [^{3}H]prazosin. For competitive inhibition experiments various concentrations of drugs studied were incubated. Nonspecific binding was defined using 1 μM prazosin. Samples were incubated at 25 °C for 50 min and then filtered on Whatman GF/B glass microfiber filters. The filters were presoaked for 50 min in Tris·HCl-polyethylenimine 0.5%. The K_d value determined for prazosin was 0.5 nM.

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