4.30 (H, d, J = 12 Hz), 4.75 (H, d, J = 12 Hz), 5.50 (H, m), 5.80 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.0 (2 H, m), 7.32 (2 H, m). Continued elution with methylene chloride–acetone (10:1, v:v) yielded the desilylated **5f** (0.72 g, 1.67 mmol, 13%).

4(*R*)-(*tert*-Butyldimethylsiloxy)-6(*R*)-[2-[8(*S*)-[(4-fluorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-3,4,5,6-tetrahydro-2*H*-pyran-2-one (6f). Solid chromium trioxide (2.22 g, 22.2 mmol) was added at room temperature under a nitrogen atmosphere to a mechanically stirred solution of pyridine (3.51 g, 44.4 mmol) in methylene chloride (130 mL). The resulting mixture was stirred for 0.5 h, then added via a dropping funnel a solution of **5f** (1.87 g, 3.45 mmol) in methylene chloride (20 mL). The resulting mixture was stirred at room temperature for 0.5 h, then quickly filtered through a pad of silica gel on a Buchner filter, washed, and rinsed with portions of methylene chloride–ether. The combined washings and filtrate were washed successively with diluted hydrochloric acid and 5% sodium bicarbonate, dried over $MgSO_4$, and filtered. The filtrate was evaporated to leave a residue which was purified by flash chromatography on a silica gel column. Elution of the column with methylene chloride followed by methylene chloride–acetone (50:1, v:v) provided **6f** (1.16 g, 2.14 mmol; 62%) as a solid: NMR ($CDCl_3$) δ 1.16 (3 H, d, J = 7 Hz), 2.52 (2 H, d, J = 4 Hz), 3.97 (H, m), 4.30 (H, d, J = 12 Hz), 4.72 (H, d, J = 12 Hz), 5.52 (H, m), 5.75 (H, d of d, J = 10, 5 Hz), 6.00 (H, d, J = 10 Hz), 7.0 (2 H, m), 7.3 (2 H, m).

6(*R*)-[2-[8(*S*)-[(4-Fluorobenzyl)oxy]-1,2,6,7,8,8a(*S*)-hexahydro-2(*S*),6(*R*)-dimethyl-1(*S*)-naphthyl]ethyl]-4(*R*)-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (2f). Acetic acid (3.20 mL, 55 mmol) was added to a stirred solution of **6f** (6.8 g, 12.5 mmol) in THF (20 ml) followed by the addition of a solution of tetra-*n*-butylammonium fluoride (1 M in THF, 42 mL, 42 mmol). The resulting mixture was stirred at room temperature for 18 h, poured into cold water, and extracted with ether. The ethereal extract was washed successively with water and 5% sodium bicarbonate, dried, filtered, and evaporated to afford a residue. Purification of the residue on a silica gel column eluted with methylene chloride–acetone (10:1, v:v) provided **2f** (5.3 g, 12.4 mmol, 99%) as a solid. Analytical sample was obtained via recrystallization from ether–hexane: mp 100–103 °C; NMR ($CDCl_3$) δ 0.86 (3 H, d, J = 7 Hz), 1.17 (3 H, d, J = 7 Hz), 2.59 (2 H, m), 3.90 (H, m), 4.30 (H, d, J = 12 Hz), 4.71 (H, d, J = 12 Hz), 5.53 (H, m), 5.76 (H, d of d, J = 10, 5 Hz), 6.01 (H, d, J = 10 Hz), 7.03 (2 H, t), 7.33 (2 H, m). Anal. ($C_{26}H_{33}FO_4$) C, H.

Acknowledgment. We thank Drs. R. F. Hirschmann, P. S. Anderson, and E. H. Cordes for their encouragement during the course of this investigation.

Naphthosultam Derivatives: A New Class of Potent and Selective 5-HT_2 Antagonists

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Départements de Chimie Pharmaceutique et de Biologie, Centre de Recherches de Vitry Alfortville Rhône-Poulenc Rorer, 13 Quai Jules Guesde B.P. 14, F-94403 Vitry-sur-Seine Cédex, France. *Received December 21, 1990*

A series of 2-(aminoalkyl)naphth[1,8-*cd*]isothiazole 1,1-dioxides was synthesized and examined in various receptor binding tests. Most compounds demonstrated high affinity for the 5-HT_2 receptor with moderate to high selectivity. A member of this series, compound 24 (RP 62203), displays high 5-HT_2 receptor affinity (K_i = 0.26 nM), which is respectively more than 100 and 1000 times higher than its affinity for α_1 (K_i = 38 nM) and D_2 (K_i > 1000 nM) receptors. This compound is a potent orally effective and long lasting 5-HT_2 antagonist in the mescaline-induced head-twitches test in mice and rats.

Serotonin (5-HT) may be involved in thermoregulation, appetite, pain, sleep, sexual behavior, and behavioral disorders such as depression and anxiety.[1]

Recent progress in 5-HT research was stimulated by the discovery of multiple 5-HT receptors. The 5-HT_2 subtype has been the most completely characterized due to the availability of more and more selective antagonists.[2]

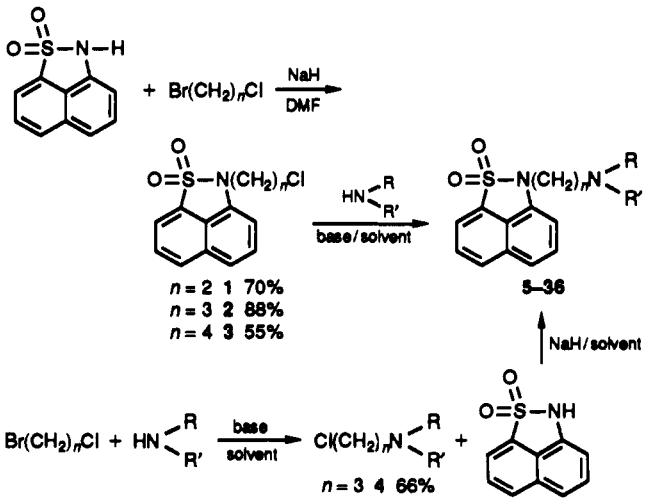
Ritanserin[3] was the first compound identified with a reasonable separation of 5-HT_2 and non 5-HT effects. Clinical studies with ritanserin indicate that this 5-HT_2 antagonist may be effective in anxiety or disthymic disorders.[4]

We describe here a series of naphtho[1,8-*cd*]isothiazole 1,1-dioxide (naphthosultam) derivatives, incidentally discovered and structurally unrelated to ritanserin. These compounds were evaluated in vitro for their binding affinity to rat 5-HT_2, α^1, and D_2 receptors. We describe the structure–activity relationships within this series that led to the discovery of RP 62203 (compound 24). Its pharmacological profile is compared with that of ritanserin.

Chemistry

The synthetic pathway for the preparation of naphthosultam derivatives[5] listed in Tables I–IV is shown in Scheme I. Two methods were used. Naphthosultam was condensed with a ω-bromochloroalkane in the presence

Scheme I

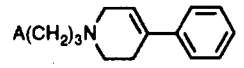


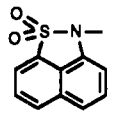
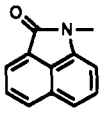
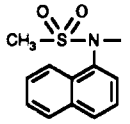
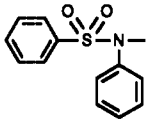
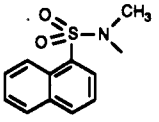
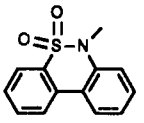
† Département de Chimie.
‡ Département de Biologie.

(1) *Neuropharmacology of Serotonin*; Green, A. R., Ed.; Oxford Univ. Press: Oxford, 1985.
(2) Janssen, P. A. J. "Pharmacology of Potent and Selective S2-Serotoninergic Antagonists", *J. Cardiovasc. Pharmacol.* **1985**, 7 (Suppl. 7), S2–S11.

0022-2623/91/1834-2477$02.50/0

Table I. In Vitro Binding Data of 4-Phenyl-1,2,3,6-tetrahydropyridine Derivatives 5–10 and Ritanserin



compd	A	IC_{50} (nM)[a] 5-HT_2[b]	α_1[b]	D_2[b]
5		1.0	192	1000
6		9.8	580	>100
7		5.1	75	275
8		10	35	80
9		>100		
10		10	10	110
ritanserin		1.7	37	23

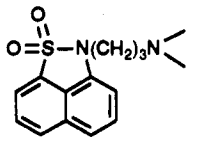
[a] IC_{50} values are the mean of at least 2 determinations each with 6 concentrations of test compounds in triplicate. Standard deviations were always smaller than 10%. [b] See Experimental Section.

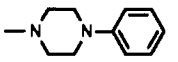
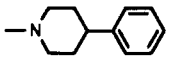
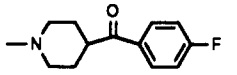
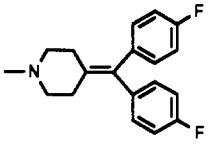
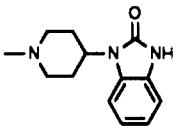
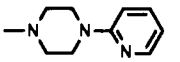
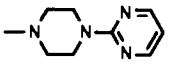
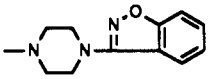
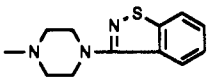
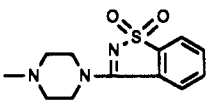
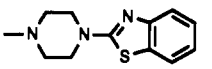
of NaH to give 1–3. These derivatives were reacted with the appropriate amine in the presence of a base ($NaHCO_3$, K_2CO_3, or triethylamine) to give the expected compounds 5 and 11–36. An alternative approach was adopted for the synthesis of compounds 6–10: condensation of 1-bromo-3-chloropropane with 4-phenyl-1,2,3,6-tetrahydropyridine in the presence of potassium carbonate gives 4, which was reacted with an amide or a sulfonamide in the presence of sodium hydride to give 6–10. Yields were moderate but not optimized.

Results and Discussion

In Vitro Studies. Compounds 5–37 and ritanserin were evaluated in vitro in various receptor binding tests using rat brain membranes and suitable [^{3}H] ligands: ketanserin (5-HT_2),[6] prazosin (α_1),[7] spiperone (D_2).[8] IC_{50} values are

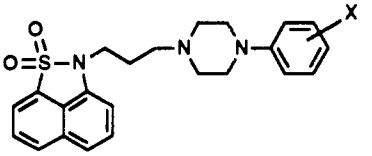
Table II. In Vitro Binding Data of (Aminopropyl)naphthosultam Derivatives 11–21



compd	—N<	IC_{50} (nM)[a] 5-HT_2[b]	α_1[b]	D_2[b]
11		2.6	141	>1000
12		0.2	27	385
13		0.1	7.9	41
14		11	50	603
15		7.0	<10	46
16		6.3	269	>1000
17		32	>1000	>1000
18		2.3	144	990
19		0.4	75	473
20		240	181	>1000
21		540	>1000	>1000

[a] See footnotes to Table I. [b] See Experimental Section.

Table III. In Vitro Binding Data of [(Phenylpiperazinyl)propyl]naphthosultam Derivatives 22–32

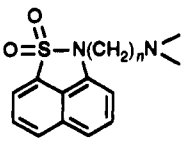


compd	X	IC_{50} (nM)[a] 5-HT_2[b]	α_1[b]	D_2[b]
22	2-F	3.0	52	>1000
23	3-F	18	688	>1000
24	4-F	0.5	103	>1000
25	4-Cl	5.0	>1000	>1000
26	4-Br	7.0	>1000	>1000
27	4-OH	0.3	110	508
28	4-OCH_3	25	>1000	>1000
29	4-CH_3	4.0	700	>1000
30	4-CF_3	275	>1000	>1000
31	4-NO_2	25	>1000	>1000
32	4-$CO_2C_2H_5$	200	>1000	>1000

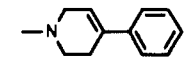
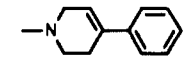
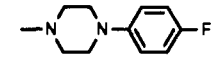
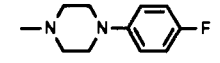
[a] See footnotes to Table I. [b] See Experimental Section.

(3) "Ritanserin", *Drugs of the Future* **1986**, *11*, 391–393.
(4) Reyntgens, A.; Gelderf, Y. F.; Hoppenbrouwers, M.-L. J. A.; Vanden Bussche, G. "Thymosthemic effect of ritanserin (R55667) centrally acting serotonin-S2 receptor blocker", *Drug Dev. Res.* **1986**, *8*, 205–211.
(5) Rhone Poulenc Sante, EP 350403.
(6) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. "[^{3}H]Ketanserin (R41468), a selective ^{3}H-ligand for serotonin 2 receptor binding sites. Binding properties, brain distribution, and functional role", *Mol. Pharmacol.* **1982**, *21*, 301–314.
(7) Greengrass, P.; Bremner, R. "Binding characteristics of ^{3}H-prazosin to rat brain α-adrenergic receptors", *Eur. J. Pharmacol.* **1979**, *55*, 323–326.

Table IV. In Vitro Binding Data of (Aminoalkyl)naphthosultam Derivatives **33–36**



I

compd	—N<	n	IC_{50} (nM)[a] 5-HT_2[b]	α_1[b]	D_2[b]
33		2	6.3	98	>100
34		4	2.1	7.8	55
35		2	1.0	64	
36		4	3.7	11	300

[a] See footnotes to Table I. [b] See Experimental Section.

shown in Tables I–IV. In addition, compound **24** and ritanserin were tested for their 5-HT_{1A} and H_1 receptor binding affinities, using [^{3}H]-8-OH-DPAT[9] and [^{3}H]mepyramine[10] as ligands, respectively. K_i values for **24** and ritanserin are compared in Table V.

Among compounds **5–10**, the naphthosultam derivative **5** was shown to be the most interesting compound with regard to its in vitro potency and selectivity for the 5-HT_2 receptor. In particular, replacement of the sulfonyl group in **5** by a carbonyl group (**6**) resulted in a 10-fold decrease in 5-HT_2 receptor affinity and opening the sultam ring in **5** gave compounds **7–9** with reduced potency and loss of selectivity. Replacement in **5** of the amine moiety 4-phenyl-1,2,3,6-tetrahydropyridine by 4-phenylpiperidine or 4-phenylpiperazine does not substantially affect the selectivity (compounds **11**, **12**). However, affinity for the 5-HT_2 receptor and selectivity are largely determined by the nature of the aromatic group attached to the cyclic amine (compounds **13–21**). Incorporation of the amine moiety present in the structure of ketanserin (**13**), ritanserin (**14**), and benperidol (**15**) resulted in loss of selectivity in comparison with the parent molecules **5**, **11**, and **12**. In the phenylpiperazine series (compounds **22–32**), 4-fluoro (compound **24**) and 4-hydroxy (compound **27**) substituents are optimal. Alternative substituents gave compounds with reduced potency (compounds **25**, **26**, **29–32**) and in some bases reduced selectivity (compounds **11**, **22**, **23**, **28**). In the 4-phenyl-1,2,3,6-tetrahydropyridine as well as in the phenylpiperazine series (compounds **33–36**), the alkylene side chain was optimal with $n = 3$.

In Vivo Studies. For the most potent naphthosultam derivatives found in vitro, central 5-HT_2 antagonistic activity in vivo was assessed by the ability of the compounds to antagonize mescaline-induced head twitches in mice and rats.[11] RP 62203 (compound **24**) was the compound with the optimum combination of selectivity in the in vitro assays and in vivo potency. As shown in Table V, RP 62203 is a potent and long lasting orally active 5-HT_2 antagonist. It displays a higher receptor selectivity than ritanserin with a 5-HT_2 receptor affinity (K_i = 0.26 nM) that is respectively more than 100 and 1000 times higher than its affinity for α_1 (K_i = 38 nM) and D_2 (K_i > 1000 nM) receptors.

Conclusion

RP 62203 (compound **24**) has been identified as a novel potent and selective 5-HT_2 antagonist. It is a member of a series of naphthosultam derivatives of formula I. (See formula in Table IV.)

High affinity was obtained with compounds possessing as a terminal amine moiety one of the following group: 4-phenylpiperazine, 4-phenylpiperidine, or 4-phenyl-1,2,3,6-tetrahydropyridine. Selectivity for the 5-HT_2 receptor versus α_1 and D_2 receptors required a propylene chain (n = 3). In the phenylpiperazine series, 4-fluoro (compound **24**) and 4-hydroxy (compound **28**) substituents led to the optimum combination of in vitro potency and selectivity. Due to its in vivo activity, compound **24** has been selected for clinical evaluation.

Experimental Section

Melting points were recorded on a Köfler apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Brücker WM (250 MHz), a Brücker WP 200 (200 MHz), or a Brücker AM 400 (400 MHz) instrument. IR spectra were taken on a Perkin-Elmer Model 938G or 580B instrument. Mass spectra were recorded on a Finnigan 3300 spectrometer. Unless otherwise noted, where elemental analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. In some cases, crude products were purified by flash column chromatography on silica gel (0.04–0.063 mm supplied by Merck) before recrystallization.

Preparation of the Halogenoalkyl Derivatives 1–4. 2-(2-Chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (1). To 4.8 g (0.10 mol) of sodium hydride (50% dispersion in Vaseline) in 50 mL of DMF, under argon, was slowly added 20.5 g (0.10 mol) of 1,8-naphthosultam in 250 mL of DMF at 25 °C. The reaction mixture was stirred at this temperature for 1 h. To this solution was added 8.8 mL (0.11 mol) of 1-bromo-2-chloroethane, and the mixture was left for 15 h at room temperature. After evaporation to dryness under reduced pressure, the residue was purified by flash chromatography on silica gel, eluting with 7:3 dichloromethane/cyclohexane, to give 20.7 g (77%) of **1** as a solid (mp 96 °C): NMR ($CDCl_3$, 300 MHz) δ 3.92 (t, J = 7 Hz, 2 H, CH_2Cl), 4.18 (t, J = 7 Hz, 2 H, NCH_2), 6.82 (d, J = 7.5 Hz, 1 H, H Ar), 7.44 (d, J = 7.5 Hz, 1 H, H Ar), 7.53 (t, J = 7.5 Hz, 1 H, H Ar), 7.71 (t, J = 7.5 Hz, 1 H, H Ar), 7.94 (d, J = 7.5 Hz, 1 H, H Ar), 8.04 (d, J = 7.5 Hz, 1 H, H Ar); MS, m/z 267 (M^+), 218 ($M^+ - CH_2Cl$), 154 ($C_{11}H_8N^+$).

Compounds **2–4** were prepared in a similar manner.

2-(3-Chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (2) was prepared in 69% yield as a solid (after flash chromatography on silica gel with 6:4 dichloromethane/cyclohexane as eluent, mp 78 °C) from 1,8-naphthosultam, 1-bromo-3-chloropropane, and sodium hydride: NMR ($CDCl_3$, 300 MHz) δ 2.37 (q, J = 6.5 Hz, 2 H, CH_2), 3.74 (t, J = 6.5 Hz, 2 H, CH_2Cl), 4.04 (t, J = 6.5 Hz, 2 H, NCH_2), 6.82 (d, J = 7.5 Hz, 1 H, H Ar), 7.43 (d, J = 7.5 Hz, 1 H, H Ar), 7.52 (t, J = 7.5 Hz, 1 H, H Ar), 7.71 (t, J = 7.5 Hz, 1 H, H Ar), 7.93 (d, J = 7.5 Hz, 1 H, H Ar), 8.04 (d, J = 7.5 Hz, 1 H, H Ar); IR (KBr) 1305 + 1170 + 1140 (SO_2); MS, m/z 281 (M^+), 218 ($M^+ - C_2H_4Cl$), 154 ($C_{11}H_8N^+$).

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Table V. In Vitro and in Vivo Activities of Compound 24 and Ritanserin

	binding[a]: K_i (nM)					mescaline-induced head twitch[b]				
						mice ED_{50} (mg/kg)		duration of	rats ED_{50} (mg/kg)	
compd	5-HT_2	5-HT_{1A}	α_1	D_2	H_1	sc	po	action, h	sc	po
								1	0.65 [0.38–1.12]	0.99 [0.63–1.55]
24	0.26	70	38	>1000	25	0.16 [0.08–0.34]	0.43 [0.08–2.28]	6	0.45 [0.22–0.89]	2.38 [1.08–5.25]
								16	5.91 [3.06–11.43]	14.2 [10.7–18.8]
								1	0.38 [0.24–0.62]	2.55 [1.22–5.33]
ritanserin	0.69	>1000	29	22	6	0.29 [0.08–1.07]	0.09 [0.04–0.23]	6	0.55 [0.34–0.93]	1.54 [0.74–3.20]
								16	>5	18.41 [9.17–36.97]

[a] See footnotes to Table I. [b] ED_{50} values were calculated with 95% confidence limit.

2-(4-Chlorobutyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (3) was prepared in 83% yield as a yellow oil (after flash chromatography on silica gel with 3:7 dichloromethane/cyclohexane as eluent) from 1-bromo-4-chlorobutane, 1,8-naphthosultam, and sodium hydride: NMR ($CDCl_3$, 200 MHz) δ 1.9–2.25 (m, 4 H, CCH_2CH_2C), 3.65 (t, J = 6.5 Hz, 2 H, CH_2Cl), 3.9 (t, J = 7 Hz, 2 H, NCH_2), 6.87 (d, J = 7.5 Hz, 1 H, H Ar), 7.48 (d, J = 8.5 Hz, 1 H, H Ar), 7.57 (dd, J = 8.5 and 7.5 Hz, 1 H, H Ar), 7.77 (dd, J = 8 and 7.5 Hz, 1 H, H Ar), 7.99 (d, J = 7.5 Hz, 1 H, H Ar), 8.1 (d, J = 8 Hz, 1 H, H Ar).

1-(3-Chloropropyl)-4-phenyl-1,2,3,6-tetrahydropyridine (4). A mixture of 6 mL (60.6 mmol) of 1-bromo-3-chloropropane, 5.1 g (32 mmol) of 4-phenyl-1,2,3,6-tetrahydropyridine in 60 mL of acetonitrile, and 97 g of potassium carbonate was stirred for 20 h at 25 °C. After filtration of the precipitate and evaporation under vacuum of the organic phase, the residue was purified by flash chromatography on silica gel with 5:5 cyclohexane/ethyl acetate as eluent to give 5 g (66%) of 4 as an oil: NMR ($CDCl_3$, 250 MHz) δ 2.00 (m, 2 H, CCH_2C), 2.55 (m, 4 H, NCH_2CH_2C=), 2.7 (t, 2 H, CCH_2N), 3.1 (bs, 2 H, NCH_2C=), 3.6 (t, 2 H, $ClCH_2$), 6.00 (bs, 1 H, CH=), 7.18 (bt, 1 H, C_6H_5), 7.28 (bt, 2 H, C_6H_5), 7.35 (bd, 2 H, C_6H_5).

Preparation of 2-(Aminoalkyl)naphth[1,8-*cd*]isothiazole 1,1-Dioxides 5 and 11–35. 2-[3-(4-Phenyl-1,2,3,6-tetrahydropyridyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (5). To 2.8 g (0.01 mol) of 2 and 1.4 mL of triethylamine was added 1.6 g (0.01 mol) of 4-phenyl-1,2,3,6-tetrahydropyridine in 30 mL of toluene. The reaction mixture was stirred 8 h at reflux and then for 15 h at room temperature. After filtration of the precipitate and evaporation to dryness under reduced pressure, the residue was purified by flash chromatography on silica gel with ethyl acetate as eluent. Recrystallization from 2-propanol gave 1.5 g (37%) of 5 as a solid (mp 88 °C): NMR ($CDCl_3$, 200 MHz) δ 2.02 (m, 2 H, CCH_2C), 2.45–2.7 (m, 6 H, NCH_2 and NCH_2CH_2 cycle), 3.1 (m, 2 H, NCH_2 cycle) 3.94 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.17 (m, 1 H, CH=), 7.11–8.28 (m, 11 H, H Ar); IR (KBr) 2815 + 2770 + 2740 (NCH_2), 1310 + 1170 + 1140 (SO_2); MS, m/z 404 (M^+). Anal. ($C_{24}H_{24}N_2O_2S$) C, H, N. S.

Compounds 11–35 were prepared in a similar manner.

2-[3-(4-Phenyl-1-piperazinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (11) was prepared in 54% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 126 °C) from 2 and 1-phenylpiperazine: NMR ($CDCl_3$, 200 MHz) δ 2.16 (q, J = 7 Hz, 2 H, CCH_2C), 2.52 (t, J = 7 Hz, 2 H, NCH_2), 2.56 (m, 4 H, NCH_2 cycle), 3.25 (m, 4 H, $PhNCH_2$), 3.99 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.8–8.09 (m, 11 H, H Ar); IR (KBr) 2825 + 2785 (NCH_2), 1310 + 1175 + 1145 (SO_2); MS, m/z 407 (M^+), 343 ($M^+ - SO_2$). Anal. ($C_{23}H_{25}N_3O_2S$) C, H, N, S.

2-[3-(4-Phenyl-1-piperidinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (12) was prepared in 57% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 125 °C) from 2 and 4-phenylpiperidine: NMR ($CDCl_3$, 200 MHz) δ 1.85 (m, 4 H, CH_2 piperidine), 2–2.3 (m, 4 H, CCH_2C and NCH_2 piperidine), 2.5 (m, 1 H, CCHC), 2.6 (t, J = 7 Hz, 2 H, NCH_2), 3.1 (t, 2 H, NCH_2 piperidine), 3.97 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.9 (m, 11 H, H Ar); IR (KBr) 2810 + 2770 + 2740 (NCH_2), 1310 + 1175 + 1135 (SO_2). Anal. ($C_{24}H_{26}N_2O_2S$) C, H, N. S.

2-[3-[4-(4-Fluorobenzoyl)-1-piperidinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (13) was prepared in 24% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 132 °C) from 2, triethylamine as base, sodium iodide, and (4-fluorobenzoyl)-4-piperidine: NMR ($CDCl_3$, 200 MHz) δ 1.87 (m, 4 H, CH_2 piperidine), 2–2.25 (m, 4 H, CCH_2C and NCH_2 piperidine), 2.54 (t, J = 7 Hz, 2 H, NCH_2), 3.03 (m, 2 H, NCH_2 piperidine), 3.23 (m, 1 H, CHC=O), 3.94 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.87–8.1 (m, 10 H, H Ar); IR (KBr) 2805 + 2870 (NCH_2), 1675 (C=O), 1310 + 1165 + 1135 (SO_2); MS, m/z 452 (M^+), 388 ($M^+ - SO_2$). Anal. ($C_{25}H_{25}FN_2O_3S$) C, H, N, S.

2-[3-[4-[Bis(4-fluorophenyl)methylene]-1-piperidinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (14) was prepared in 67% yield as an oil (after flash chromatography on silica gel with dichloromethane as eluent, hydrochloride, mp 137 °C) from 2, triethylamine as base, and 4-[bis(4-fluorophenyl)-methylene]piperidine: NMR (DMSO, 200 MHz) δ 2.1–2.7 (m, 6 H, CCH_2C and CH_2 piperidine), 2.9–3.6 (m, 6 H, NCH_2 and NCH_2 piperidine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 7.1–8.33 (m, 14 H, H Ar), 10.75 (m, 1 H, NH^+Cl^-); IR (KBr) 2800–2000 (NH^+), 1315 + 1170 + 1140 (SO_2); MS, m/z 530 (M^+), 466 ($M^+ - SO_2$). Anal. ($C_{31}H_{28}F_2N_2O_2S$·HCl) C, H, N, S.

2-[3-[4-(2-Oxo-1-benzimidazolinyl)-1-piperidinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (15) was prepared in 7% yield as a solid (after flash chromatography on silica gel with 95:5 dichloromethane/ethanol as eluent and recrystallization from acetonitrile, mp 253 °C) from 2, triethylamine as base, and 1-(4-piperidinyl)-2-benzimidazolinone: NMR (DMSO, 250 MHz) δ 1.64 (m, 2 H, CH_2 piperidine), 2.0 (m, 4 H, CH_2 piperidine and CCH_2C), 2.33 (m, 2 H, NCH_2 piperidine), 2.5 (m, 2 H, NCH_2), 3.0 (m, 2 H, NCH_2 piperidine), 3.96 (t, J = 7 Hz, 2 H, SO_2NCH_2), 4.15 (m, 1 H, NCH), 6.9–8.32 (m, 10 H, H Ar), 10.86 (m, 1 H, NH); MS, m/z 462 (M^+), 398 ($M^+ - SO_2$). Anal. ($C_{25}H_{26}N_4O_3S$) C, H, N, S. C: calcd, 64.91; found, 63.4.

2-[3-[4-(2-Pyridinyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (16) was prepared in 33% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 101 °C) from 2, triethylamine as base, and 1-(2-pyridyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.17 (q, 2 H, CCH_2C), 2.5–2.7 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.6 (m, 4 H, NCH_2 piperazine), 3.98 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.6–8.12 (m, 10 H, H Ar); IR (KBr) 1590 + 1560 + 1555 + 1480 + 1435 (2-pyridyl), 1310 + 1170 + 1135 (SO_2); MS, m/z 408 (M^+). Anal. ($C_{22}H_{24}N_4O_2S$) C, H, N, S.

2-[3-[4-(2-Pyrimidyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (17) was prepared in 63.5% yield as a solid (after flash chromatography on silica gel with 95:5 ethyl acetate/methanol as eluent and recrystallization from acetonitrile, mp 112 °C) from 2, triethylamine as base, and 1-(2-pyrimidyl)-piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.15 (m, 2 H, CCH_2C), 2.5–2.7 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.86 (t, J = 5.5 Hz,

4 H, NCH_2 piperazine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.5–8.32 (m, 9 H, H Ar); IR (KBr) 1545 + 1510 (pyrimidine), 1310 + 1170 + 1140 (SO_2); MS, m/z 409 (M^+), 345 ($M^+ - SO_2$). Anal. ($C_{21}H_{23}N_5O_2S$) C, H, N. S.

2-[3-[4-(1,2-Benzisoxazol-3-yl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (18) was prepared in 4% yield as a solid (after flash chromatography on silica gel with dichloromethane as eluent and recrystallization from acetonitrile, mp 163 °C) from **2**, triethylamine as base, and 4-(1,2-benzisoxazol-3-yl)-1-piperazine in DMF: NMR ($CDCl_3$, 200 MHz) δ 2.15 (q, J = 7 Hz, 2 H, CCH_2C), 2.63 (t, J = 7 Hz, 2 H, NCH_2), 2.7 (m, 4 H, NCH_2 piperazine), 3.63 (m, 4 H, NCH_2 piperazine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.86–8.09 (m, 10 H, H Ar); IR (KBr) 1610 + 1530 + 1450 (1,2-benzisoxazole); MS, m/z 448 (M^+), 383 ($M^+ - SO_2$). Anal. ($C_{24}H_{24}N_4O_3S$) C, H, N, S.

2-[3-[4-(1,2-Benzisothiazol-3-yl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (19) was prepared in 24% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from methyl ethyl ketone, mp 172–173 °C) from **2**, triethylamine as base, and 4-(1,2-benzisothiazol-3-yl)-1-piperazine in DMF: NMR ($CDCl_3$, 200 MHz) δ 2.16 (q, J = 7 Hz, 2 H, CCH_2C), 2.64 (t, J = 7 Hz, 2 H, NCH_2), 2.72 (m, 4 H, NCH_2 piperazine), 3.6 (m, 4 H, NCH_2 piperazine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.89–8.1 (m, 10 H, H Ar); IR (KBr) 1560 + 1425 (1,2-benzisothiazole), 1310 + 1170 + 1135 (SO_2); MS, m/z 464 (M^+), 432 ($M^+ - SO_2$). Anal. ($C_{24}H_{24}N_4O_2S_2$) C, H, N. S.

2-[3-[4-(1,1-Dioxo-1,2-benzisothiazol-3-yl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (20) was prepared in 51% yield as an oil (after flash chromatography on silica gel with 97:3 dichloromethane/methanol as eluent, dihydrochloride, mp >260 °C) from **2**, triethylamine as base, sodium iodide, and 4-(1,1-dioxo-1,2-benzisothiazol-3-yl)-1-piperazine in DMF: NMR (DMSO, 200 MHz) δ 2.27 (m, 2 H, CCH_2C), 3.2–3.7 (m, 10 H, H and NCH_2 piperazine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 4.7 (m, 1 H, NH^+Cl^-), 7.55–8.4 (m, 10 H, H Ar), 11.2 (m, 1 H, NH^+Cl^-); MS, m/z 496 (M^+), ($M^+ - SO_2$). Anal. ($C_{24}H_{24}N_4O_4S_2 \cdot 2HCl$) C, H, N, S.

2-[3-[4-(2-Benzothiazolyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (21) was prepared in 46% yield as a solid (after flash chromatography on silica gel with 98:2 dichloromethane/methanol as eluent and recrystallization from acetonitrile, mp 195 °C) from **2**, triethylamine as base, and 1-(2-benzothiazolyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.14 (q, J = 7 Hz, 2 H, CCH_2C), 2.5–2.7 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.69 (m, 4 H, NCH_2 piperazine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.85–8.09 (m, 10 H, H Ar); IR (KBr) 1560 + 1535 + 1445 (benzothiazole), 1310 + 1170 + 1135 (SO_2); MS, m/z 464 (M^+). Anal. ($C_{24}H_{24}N_4O_2S_2$) C, H, N, S.

2-[3-[4-(2-Fluorophenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (22) was prepared in 45% yield as a solid (after flash chromatography on silica gel with dichloromethane as eluent and recrystallization from acetonitrile, mp 112 °C) from **2**, triethylamine as base, and 1-(2-fluorophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.13 (q, J = 7 Hz, 2 H, CCH_2C), 2.6 (t, J = 7 Hz, 2 H, NCH_2), 2.67 (m, 4 H, NCH_2 piperazine), 3.15 (m, 4 H, NCH_2 piperazine), 3.97 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.86–7.97 (m, 10 H, H Ar); MS, m/z 425 (M^+), 361 ($M^+ - SO_2$). Anal. ($C_{23}H_{24}FN_3O_2S$) C, H, N, S.

2-[3-[4-(3-Fluorophenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (23) was prepared in 37% yield as a solid (after flash chromatography on silica gel with 5:5 dichloromethane/ethyl acetate as eluent and recrystallization from acetonitrile, mp 103 °C) from **2**, triethylamine as base, and 1-(3-fluorophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.13 (q, J = 7 Hz, 2 H, CCH_2C), 2.6 (t, J = 7 Hz, 2 H, NCH_2), 2.67 (m, 4 H, NCH_2 piperazine), 3.15 (m, 4 H, NCH_2 piperazine), 3.97 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.86–7.97 (m, 10 H, H Ar); MS, m/z 425 (M^+), 361 ($M^+ - SO_2$). Anal. ($C_{23}H_{24}FN_3O_2S$) C, H, N, S.

2-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (24) was prepared in 89% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 95–97 °C) from **2**, triethylamine as base, and 1-(4-fluorophenyl)-piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.17 (q, J = 7 Hz, 2 H, CCH_2C), 2.64 (t, J = 7 Hz, 2 H, NCH_2), 2.67 (m, 4 H, NCH_2 piperazine), 3.19 (m, 4 H, NCH_2 piperazine), 3.99 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.8–8.09 (m, 10 H, H Ar); MS, m/z 425 (M^+), 361 ($M^+ - SO_2$). Anal. ($C_{23}H_{24}FN_3O_2S$) C, H, N, S.

2-[3-[4-(4-Chlorophenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (25) was prepared in 36% yield as a solid (after recrystallization from acetonitrile and then methyl ethyl ketone, mp 120 °C) from **2**, triethylamine as base, sodium iodide, and 1-(4-chlorophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.13 (q, J = 6.5 Hz, 2 H, CCH_2C), 2.5–2.7 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.2 (m, 4 H, NCH_2 piperazine), 3.97 (t, J = 6.5 Hz, 2 H, SO_2NCH_2); MS, m/z 441 (M^+), 377 ($M^+ - SO_2$). Anal. ($C_{23}H_{24}ClN_3O_2S$) C, H, N, S.

2-[3-[4-(4-Bromophenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (26) was prepared in 44% yield as a solid (after flash chromatography with ethyl acetate and recrystallization from acetonitrile, mp 149 °C) from **2**, triethylamine as base, and 1-(4-bromophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.13 (q, J = 6.5 Hz, 2 H, CCH_2C), 2.5–2.7 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.2 (m, 4 H, NCH_2 piperazine), 3.97 (t, J = 6.5 Hz, 2 H, SO_2NCH_2); MS, m/z 485 (M^+), 421 ($M^+ - SO_2$). Anal. ($C_{23}H_{24}BrN_3O_2S$) C, H, N, S.

2-[3-[4-(4-Hydroxyphenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (27) was prepared in 19% yield as a solid (after flash chromatography on silica gel with 50:50 dichloromethane/ethyl acetate as eluent and recrystallization from acetonitrile, mp 185 °C) from **2**, triethylamine as base, and 1-(4-hydroxyphenyl)piperazine dihydrobromide in DMF: NMR (DMSO + ϵCD_3CO_2D, 200 MHz) δ 2.13 (m, 2 H, CCH_2C), 2.7–2.9 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.08 (m, 4 H, NCH_2 piperazine), 3.96 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.68 (m, 10 H, H Ar); IR (KBr) 3200 + 2200 (OH), 1305 + 1170 + 1135 (SO_2); MS, m/z 423 (M^+), 359 ($M^+ - SO_2$). Anal. ($C_{23}H_{25}N_3O_3S$) C, H, N, S.

2-[3-[4-(4-Methoxyphenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (28) was prepared in 64% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 160 °C) from **2**, triethylamine as base, and 1-(4-methoxyphenyl)-piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.14 (q, J = 7 Hz, 2 H, CCH_2C), 2.6 (t, J = 7 Hz, 2 H, NCH_2), 2.65 (m, 4 H, NCH_2 piperazine), 3.14 (m, 4 H, NCH_2 piperazine), 3.78 (s, 3 H, OCH_3), 3.97 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.8–8.08 (m, 10 H, H Ar); IR (KBr) 1300 + 1175 + 1150 + 1140 (SO_2), 1240 (C—O), 2835 + 1035 (OCH_3); MS, m/z 437 (M^+), 373 ($M^+ - SO_2$). Anal. ($C_{24}H_{27}N_3O_3S$) C, H, N, S.

2-[3-[4-(4-Methylphenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (29) was prepared in 43% yield as a solid (after flash chromatography on silica gel with 80:20 dichloromethane/ethyl acetate as eluent and recrystallization from acetonitrile, mp 136 °C) from **2**, triethylamine as base, and 1-(4-methylphenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.14 (q, J = 7 Hz, CCH_2C), 2.29 (s, 3 H, CH_3), 2.6 (t, J = 7 Hz, 2 H, NCH_2), 2.65 (m, 4 H, NCH_2 piperazine), 3.19 (m, 4 H, NCH_2 piperazine), 4.0 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.87–8.08 (m, 10 H, H Ar); MS, m/z 421 (M^+), 357 ($M^+ - SO_2$). Anal. ($C_{24}H_{27}N_3O_2S$) C, H, N, S.

2-[3-[4-[4-(Trifluoromethyl)phenyl]-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1 dioxide (30) was prepared in 39% yield as a solid (after flash chromatography on silica gel with ethyl acetate and recrystallization from acetonitrile, mp 153 °C) from **2**, triethylamine as base, and 1-[4-(trifluoromethyl)phenyl]piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.15 (q, J = 7 Hz, 2 H, CCH_2C) 2.5–2.7 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.82 (m, 4 H, NCH_2 piperazine), 3.98 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.84–8.08 (m, 10 H, H Ar); MS, m/z 475 (M^+), 411 ($M^+ - SO_2$). Anal. ($C_{24}H_{23}F_3N_3O_2S$) C, H, N, S. C: calcd, 60.61; found, 60.1.

2-[3-[4-(4-Nitrophenyl)-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (31) was prepared in 36% yield as a solid (after flash chromatography on silica gel with 80:20 dichloromethane/ethyl acetate as eluent and recrystallization from methyl ethyl ketone, mp 186 °C) from **2**, triethylamine as base, and 1-(4-nitrophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.14 (q, J = 7 Hz, 2 H, CCH_2C), 2.64 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.46 (m, 4 H, NCH_2 piperazine), 3.99 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.85–8.14 (m, 10 H, H Ar); IR (KBr) 1325 (SO_2

+ NO_2), 1175 + 1140 (SO_2); MS, m/z 451 (M^+), 387 ($M^+ - SO_2$). Anal. ($C_{23}H_{24}N_4O_4S$) C, H, N, S.

2-[3-[4-[4-(Ethoxycarbonyl)phenyl]-1-piperazinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (32) was prepared in 33% yield as a solid (after flash chromatography on silica gel with ethyl acetate and recrystallization from acetonitrile, mp 139 °C) from **2**, triethylamine as base, and 1-[4-(ethoxycarbonyl)phenyl]piperazine: NMR ($CDCl_3$, 300 MHz) δ 1.38 (t, J = Hz, 3 H, CH_3), 2.16 (q, J = 6.5 Hz, 2 H, CCH_2C), 2.55–2.75 (m, 6 H, NCH_2 and NCH_2 piperazine), 3.38 (m, 4 H, NCH_2 piperazine), 3.98 (t, J = 6.5 Hz, 2 H, SO_2NCH_2), 4.34 (q, J = 7 Hz, 2 H, CO_2CH_2), 6.85–8.05 (m, 10 H, H Ar); IR (KBr) 1700 (C=O), 1320 + 1170 + 1140 (SO_2), 1285 (OCO); MS, m/z 479 (M^+), 415 ($M^+ - SO_2$). Anal. ($C_{26}H_{29}N_3O_4S$) C, H, N, S. C: calcd, 65.11; found, 64.2.

2-[2-(4-Phenyl-1,2,3,6-tetrahydropyridyl)ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (33) was prepared in 26% yield as a solid (after flash chromatography on silica gel with dichloromethane as eluent and recrystallization from acetonitrile, mp 106 °C) from **1**, triethylamine as base, and 4-phenyl-1,2,3,6-tetrahydropyridine: NMR ($CDCl_3$, 200 MHz) δ 2.64 (m, 2 H, C=CCH_2 cycle), 2.91 (m, 2 H, NCH_2), 3.04 (t, J = 7.5 Hz, 2 H, NCH_2), 3.35 (m, 2 H, NCH_2), 4.1 (t, J = 7.5 Hz, 2 H, SO_2NCH_2), 6.11 (m, 1 H, CH=C), 6.86–8.09 (m, 11 H, H Ar); MS, m/z 390 (M^+). Anal. ($C_{23}H_{22}N_2O_2S$) C, H, N, S.

2-[4-(4-Phenyl-1,2,3,6-tetrahydropyridyl)butyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (34) was prepared in 18% yield as a solid (after flash chromatography on silica gel with ethyl acetate and recrystallization from acetonitrile, mp 101 °C) from **3**, triethylamine as base, and 4-phenyl-1,2,3,6-tetrahydropyridine: NMR ($CDCl_3$, 200 MHz) δ 1.7 (m, 2 H, CCH_2CC), 2.02 (m, 2 H, $CCCH_2C$), 2.5–2.8 (m, 6 H, NCH_2 and C=CCH_2 cycle), 3.2 (m, 2 H, NCH_2), 3.9 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.10 (m, 1 H, CH=C), 6.8–8.07 (m, 11 H, H Ar); MS, m/z 418 (M^+), 354 ($M^+ - SO_2$). Anal. ($C_{25}H_{26}N_2O_2S$) C, H, N, S. C: calcd, 71.74; found, 72.3.

2-[2-[4-(4-Fluorophenyl)-1-piperazinyl]ethyl-2*H*-naphth-[1,8-*cd*]isothiazole 1,1-dioxide (35) was prepared in 23% yield as a solid (after flash chromatography on silica gel with 80:20 dichloromethane/ethyl acetate as eluent and recrystallization from diisopropyl ether, mp 133 °C) from **1**, triethylamine as base, and 1-(4-fluorophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 2.34 (t, J = 7 Hz, 2 H, NCH_2), 2.67 (m, 4 H, NCH_2 piperazine), 3.19 (m, 4 H, NCH_2 piperazine), 4.02 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.8–8.1 (m, 10 H, H Ar); MS, m/z 411 (M^+), 347 ($M^+ - SO_2$). Anal. ($C_{22}H_{22}FN_3O_2S$) C, H, N, S.

2-[4-[4-(4-Fluorophenyl)-1-piperazinyl]butyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide (36) was prepared in 41% yield as a solid (after flash chromatography on silica gel with 50:50 dichloromethane/ethyl acetate and recrystallization from acetonitrile, mp 110 °C) from **3**, triethylamine as base, and 1-(4-fluorophenyl)piperazine: NMR ($CDCl_3$, 200 MHz) δ 1.85 (m, 2 H, CCH_2CC), 2.17 (m, 2 H, $CCCH_2C$), 2.62 (t, J = 7 Hz, 2 H, NCH_2), 2.67 (m, 4 H, NCH_2 piperazine), 3.19 (m, 4 H, NCH_2 piperazine), 3.95 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.8–8.08 (m, 10 H, H Ar); MS, m/z 439 (M^+), 375 ($M^+ - SO_2$). Anal. ($C_{24}H_{26}FN_3O_2S$) C, H, N, S.

Preparation of the 4-Phenyl-1,2,3,6-tetrahydropyridine Alkyl Derivatives 6–10. *N*-[3-(4-Phenyl-1,2,3,6-tetrahydropyridyl)propyl]benz[*cd*]indol-2(1*H*)-one (6). To 1.3 g (27 mmol) of sodium hydride (50% dispersion in Vaseline) in 10 mL of DMF, under argon, was slowly added 4.5 g (26.6 mmol) of benz[*cd*]indol-2(1*H*)-one in 25 mL of DMF at 25 °C. The reaction mixture was stirred at 100 °C for 30 min and then cooled to room temperature. To this solution was added 9.3 g (39.5 mmol) of **4** in 20 mL of DMF. The mixture was stirred at reflux for 2 h. After evaporation to dryness under reduced pressure, the residue was purified by flash chromatography on silica gel with ethyl acetate as eluent to give 7.4 g (75.5%) of **6** (oxalate, mp 138 °C): NMR (DMSO, 250 MHz) δ 2.19 (m, 2 H, CCH_2C), 2.73 (m, 2 H, C=CCH_2 cycle), 3.18 (m, 2 H, NCH_2), 3.32 (m, 2 H, NCH_2 cycle), 3.77 (m, 2 H, NCH_2 cycle), 4.04 (t, J = 6 Hz, $C(O)NCH_2$), 6.18 (m, 1 H, CH=C), 7.30–8.23 (m, 11 H, H Ar); IR (KBr) 1700 (CO); MS, m/z 368 (M^+). Anal. ($C_{25}H_{24}N_2O \cdot C_2H_2O_4$) C, H, N.

***N*-[3-(4-Phenyl-1,2,3,6-tetrahydropyridyl)propyl]-*N*-(1-naphthyl)methanesulfonamide (7)** was prepared in 37% yield as a solid (after flash chromatography on silica gel with 98:2 dichloromethane/ethanol and recrystallization from ethyl acetate, mp 162 °C) from **4**, *N*-(1-naphthyl)methanesulfonamide, and sodium hydride: NMR ($CDCl_3$, 250 MHz) δ 1.86 (m, 2 H, CCH_2C), 2.5–2.7 (m, 6 H, NCH_2 and C=CCH_2 cycle), 3.05 (s, 3 H, SO_2CH_3), 3.12 (m, 2 H, NCH_2 cycle), 3.9 (t, J = 7.5 Hz, 2 H, SO_2NCH_2), 6.02 (m, 1 H, CH=C), 7.2–8.22 (m, 12 H, H Ar); IR (KBr) 1335 + 1145 (SO_2); MS, m/z 420 (M^+). Anal. ($C_{25}H_{28}N_2O_2S$) C, H, N, S. C: calcd, 71.40; found, 70.7.

***N*-[3-(4-Phenyl-1,2,3,6-tetrahydropyridyl)propyl]-*N*-phenylbenzenesulfonamide (8)** was prepared in 56% yield as a solid (after flash chromatography on silica gel with 98:2 dichloromethane/ethanol as eluent and recrystallization from diisopropyl ether, mp 112 °C) from **4**, *N*-phenylbenzenesulfonamide, and sodium hydride: NMR ($CDCl_3$, 250 MHz) δ 1.75 (m, 2 H, CCH_2C), 2.45–2.7 (m, 6 H, $CH_2NCH_2CH_2$), 3.08 (m, 2 H, NCH_2C=C), 3.68 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.03 (m, 1 H, CH=C), 7.05–7.65 (m, 15 H, H Ar). Anal. ($C_{28}H_{28}N_2O_2S$) C, H, N, S.

***N*-Methyl-*N*-[3-(4-phenyl-1,2,3,6-tetrahydropyridyl)propyl]-1-naphthalenesulfonamide (9)** was prepared in 68% yield as an oil (after flash chromatography on silica gel with ethyl acetate, oxalate mp 157 °C) from **4**, *N*-methyl-1-naphthalenesulfonamide, and sodium hydride: NMR (oxalate salt) (DMSO, 250 MHz) δ 1.97 (m, 2 H, CCH_2C), 2.73 (m, 2 H, NCH_2 piperidine), 2.87 (s, 3 H, NCH_3), 3.01 (m, 2 H, NCH_2), 3.3 (m, 4 H, NCH_2 piperidine and SO_2NCH_2), 3.74 (m, 2 H, NCH_2C=C), 6.2 (m, 1 H, CH=C), 7.25–8.75 (m, 13 H, H Ar). Anal. ($C_{25}H_{28}N_2O_2S \cdot C_2H_2O_4$) C, H, N, S.

6-[3-(4-Phenyl-1,2,3,6-pyridyl)propyl]-6*H*-dibenz[*ce*]-1,2-thiazine 5,5-dioxide (10) was prepared in 48% yield as an oil (after flash chromatography on silica gel with 98:2 dichloromethane/ethanol as eluent, oxalate mp 170 °C) from 4, 6*H*-dibenz[*ce*]-1,2-thiazine 5,5-dioxide, and sodium hydride: NMR (oxalate salt) (DMSO, 250 MHz) δ 1.94 (m, 2 H, CCH_2C), 2.63 (m, 2 H, NCH_2 piperidine), 2.90 (m, 2 H, NCH_2), 3.11 (m, 2 H, NCH_2 piperidine), 3.55 (m, 2 H, NCH_2C=C), 3.98 (t, J = 7 Hz, 2 H, SO_2NCH_2), 6.13 (m, 1 H, CH=C), 7.25–8.35 (m, 13 H, H Ar). Anal. ($C_{28}H_{28}N_2O_2S,C_2H_2O_4$) C, H, N, S.

Biological Evaluation. Membrane Preparation. Male Sprague-Dawley rats (200–250 g) were killed by decapitation and their brains rapidly removed on ice. The relevant brain structures were dissected out and homogenized in 10 volumes of ice-cold Tris-HCl buffer (50 mM; pH 7.6). The homogenate was centrifuged for 10 min at 5000*g* at 4 °C and the supernatant discarded. The pellet was washed by resuspension in seven volumes of the same buffer and recentrifugation. The final pellet was then resuspended in five volumes of Tris-HCl buffer, distributed in 1-mL aliquots in plastic vials (Nunc), and frozen at −80 °C until required. For the histamine receptor preparation, cerebellar membranes were prepared in the same way from male guinea pigs (250 g, Dunkey-Hartley). Protein content was measured according to the BCA method[12] using bovine serum albumin as the standard.

5HT_2 Binding Assay. The affinity of the different compounds for 5HT_2 receptors was assessed by using the [^{3}H]ketanserin binding assay described by Leysen et al.[6] Aliquots (1 mL) of cortical membranes at a protein concentration of 0.15 mg mL^{-1} in Tris-HCl buffer containing bovine serum albumin, 2 mg/mL, were incubated for 15 min at 37 °C with the compound of interest or with 10^{-6} M methysergide (to define the nonspecific binding) in the presence of [^{3}H]ketanserin (final concentration 0.4 nm). The binding interaction was terminated by filtration across Whatman GF/B glass fiber filters using a Skatron cell harvester and followed by two washes with 2.5 mL of ice-cold buffer. The radioactivity retained on the filters was determined by liquid scintillometry in 4.5 mL of Ready-Gel scintillant (Beckman).

The specific binding was defined as that displaceable by 10^{-6} M methysergide. The percentage of the specific binding obtained with each concentration of the test compound was calculated and the IC_{50} (concentration that inhibits 50% of the specific binding) determined by nonlinear regression analysis using an iterative

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curve-fitting procedure to a simple Langmuir isotherm performed on an IBM-PC computer.[13]

$5HT_{1A}$ Binding Assay. The $5HT_{1A}$ binding assay was performed by the method described by Hall et al.,[9] using [^{3}H]-8-OH-DPAT as the radioligand and rat hippocampal membranes as the tissue source. Aliquots (0.5 mL) of hippocampal at a protein concentration of 1 mg mL^{-1} in Tris-HCl buffer were incubated at 37 °C with the compound of interest or with 10^{-5} M serotonin. After 5 min, [^{3}H]-8-OH-DPAT (final concentration 1 nM) was added and the incubation continued for a further 10 min. The binding interaction was terminated by filtration as above. The specific binding was defined as that displaceable by 10^{-6} serotonin.

α_1-Adrenoceptor Binding Assay. This assay was carried out according to the method described by Greengrass and Bremner,[7] using [^{3}H]prazosin as the radioligand and rat cerebrocortical membranes as the tissue source. Aliquots (1.2 mL) of cortical membranes at a protein concentration of 0.15 mg mL^{-1} in Tris-HCl buffer containing bovine serum albumin, 2 mg/mL, were incubated for 40 min at 25 °C with the compound of interest or with 10^{-6} M phentolamine in the presence of [^{3}H]prazosin (final concentration 0.065 nM). The binding interaction was terminated by filtration as above. The specific binding was defined as that displaceable by 10^{-6} M phentolamine.

D_2-Dopamine Receptor Binding Assay. Binding to D_2-dopamine receptors was evaluated by using the binding of [^{3}H]spiperone to rat striatal membranes as described by Urwyler and Coward.[8]

Aliquots (1.2 mL) of striatal membranes at a protein concentration of 0.05 mg mL^{-1} in Tris-HCl buffer containing bovine serum albumin, 2 mg/mL, and NaCl (150 nM), cinanserin (10^{-6} M), and 10^{-6} M sulpiride. After 5 min, [^{3}H]spiroperidol (final concentration 0.05 nM) was added and the incubation continued for a further 40 min. The binding interaction was terminated by filtration as above. The specific binding was defined as that displaceable by 10^{-6} M sulpiride.

H_1-Histamine Receptor Binding Assay. The method described by Chang et al.[10] using [^{3}H]mepyramine binding to guinea pig cerebellar membranes was used to assess activity at H_1-histamine receptors.

Aliquots (1.2 mL) of cerebellar membranes at a protein concentration of 0.35 mg mL^{-1} in sodium phosphate buffer (50 mM; pH 7.5) were incubated for 30 min at 25 °C with the compound of interest or with 10^{-6} M promethazine and with [^{3}H]mepyramine (final concentration 0.7 nM). The binding interaction was terminated by filtration as above. The specific binding was defined as that displaceable by 10^{-6} M promethazine.

Mescaline-Induced Head Twitches. In mice,[14] drugs (6 animals/dose) were administered 60 min (sc) or 90 min (po) before 50 mg kg^{-1} ip of mescaline. Fifteen minutes after dosing with mescaline, mice were observed during a 2-min period, and the presence or the absence ("all or none" response) of head twitches was noted. The ED_{50} was defined as the dose of the test compound that protected 50% of mice from head twitches.

In rats, drug activity was studied by using the method described by Niemegers and al.[11] The rats (6 animals/dose) were treated with the test compound and 1 h later received an iv dose (20 mg kg^{-1} of mescaline). Head twitches were counted over a period of 15 min starting immediately after the mescaline injection. The occurrence of less than 3 head twitches was selected as the criterion for drug-induced antagonism. The ED_{50} was defined as the dose of the drug which protected 50% of rats.

The duration of action was assessed in this method, by treating the rats with the compound to be tested 6 and 16 h (both sc and po) before mescaline. The ED_{50} values (50% of protected rats) were calculated at each time point.

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Registry No. **1**, 127625-84-7; **2**, 127625-83-6; **3**, 127625-85-8; **4**, 84404-69-3; **5**, 127625-30-3; **6**, 134133-51-0; **6**·oxalate, 134133-66-7; **7**, 134133-52-1; **8**, 134133-53-2; **9**, 134133-54-3; **9**·oxalate, 134133-68-9; **10**, 134133-55-4; **10**·oxalate, 134133-67-8; **11**, 127625-35-8; **12**, 127625-36-9; **13**, 127625-37-0; **14**, 134133-56-5; **15**, 127625-59-6; **16**, 127625-34-7; **17**, 134133-57-6; **18**, 127648-05-9; **19**, 134133-58-7; **20**, 134133-59-8; **21**, 134133-60-1; **22**, 127625-57-4; **23**, 127625-56-3; **24**, 127625-29-0; **25**, 127625-38-1; **26**, 127625-41-6; **27**, 127648-03-7; **28**, 134133-61-2; **29**, 127625-58-5; **30**, 134133-62-3; **31**, 127625-54-1; **32**, 134133-63-4; **33**, 127625-39-2; **34**, 127625-43-8; **35**, 134133-64-5; **36**, 134133-65-6; 1,8-naphthosultam, 603-72-5; 1-bromo-2-chloroethane, 107-04-0; 1-phenylpiperazine, 92-54-6; 4-phenylpiperazine, 771-99-3; 4-(4-fluorobenzoyl)piperidine, 56346-57-7; 4-[bis(4-fluorophenyl)methylene]piperidine, 58113-36-3; 1-(4-piperidinyl)-2-benzimidazolinone, 20662-53-7; 1-(2-pyridyl)piperazine, 34803-66-2; 1-(2-pyrimidinyl)piperazine, 20980-22-7; 4-(1,2-benzisoxazol-3-yl)-1-piperazine, 87691-89-2; 4-(1,2-benzisothiazol-3-yl)-1-piperazine, 87691-87-0; 4-(1,1-dioxo-1,2-benzisothiazol-3-yl)-1-piperazine, 131540-88-0; 1-(2-benzothiazolyl)piperazine, 55745-83-0; 1-(2-fluorophenyl)-piperazine, 1011-15-0; 1-(3-fluorophenyl)piperazine, 3801-89-6; 1-(4-fluorophenyl)piperazine, 2252-63-3; 1-(4-chlorophenyl)-piperazine, 38212-33-8; 1-(4-bromophenyl)piperazine, 66698-28-0; 1-(4-hydroxyphenyl)piperazine, 56621-48-8; 1-(4-methoxyphenyl)piperazine, 38212-30-5; 1-(4-methylphenyl)piperazine, 39593-08-3; 1-[4-(trifluoromethyl)phenyl]piperazine, 30459-17-7; 1-(4-nitrophenyl)piperazine, 6269-89-2; 1-[4-(ethoxycarbonyl)-phenyl]piperazine, 80518-57-6; 4-phenyl-1,2,3,6-tetrahydropyridine, 10338-69-9; benz[*cd*]indol-2(1*H*)-one, 130-00-7; *N*-(1-naphthyl)methanesulfonamide, 53715-52-9; *N*-phenylbenzenesulfonamide, 1678-25-7; *N*-methyl-1-naphthalenesulfonamide, 71862-34-5; 6*H*-dibenz[*ce*]-1,2-thiazine 5,5-dioxide, 1864-33-1.

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