New Indole Derivatives as Potent and Selective Serotonin Uptake Inhibitors

Jean-Luc Malleron,*,† Claude Guérémy,† Serge Mignani,† Jean-François Peyronel,† Alain Truchon,† Jean-Charles Blanchard,‡ Adam Doble,‡ Pierre Laduron,‡ Odile Piot,‡ Jean-Luc Zundel,‡ Josette Betschart,‡ Hélène Canard,‡ Pascal Chaillou,‡ Odette Ferris,‡ Christian Huon,† Bernard Just,† Roselyne Kerphirique,† Brigitte Martin,† Pierre Mouton,† and Alain Renaudon†

Départements de Chimie Pharmaceutique et de Biologie, Centre de Recherches de Vitry-Alfortville, Rhone-Poulenc Rorer, 13 quai Jules Guesde, B.P. 14, F.94403 Vitry-sur-Seine Cedex, France

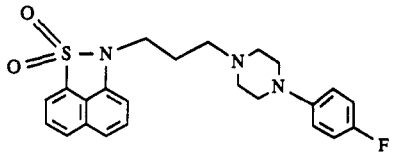
Received November 16, 1992

A series of new indole derivatives (2–28) has been prepared in the search for novel 5-HT uptake inhibitors. These compounds were obtained by the condensation of *N*-(chloroalkyl) naphthalenesultam derivatives with the appropriate amine in presence of a base, at reflux of DMF or THF. The yields were moderate (12–56%), except for the piperazine derivative **20** (85%). The affinity of the compounds for uptake site and 5-HT_2, α_1, and D_2 receptors was measured. Some compounds were studied in vivo by their potentiating effect of 5-HTP-induced symptomatology. The most potent and selective (uptake, 5-HT_2 versus α_1, D_2 sites) compounds contain a 3-[(4-piperidinyl)-methyl]indole moiety. 5-Fluoro-3-[(4-piperidinyl)methyl]indole itself (compound **1**) displayed a high affinity for the uptake site but was devoided of in vivo activity. N-Methylation of this compound abolished the affinity. In contrast N-substitution by a two-carbon chain linked to a naphthalenesultam or related heterocycle led to compounds exhibiting high affinity for the uptake site. One of them, 1-[2-[4-((5-fluoro-1*H*-indol-3-yl)methyl)-1-piperidinyl]ethyl]-5,6-dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline 2,2-dioxide (compound **24**), was found as active as fluoxetine in vivo.

Since the first paper on fluoxetine was published in 1975[1] and on indalpine in 1977,[2] many compounds have been described as selective inhibitors of the presynaptic reuptake of serotonin (5-hydroxytryptamine, 5-HT). A number of them, including fluoxetine, fluvoxamine, and paroxetine, have been studied in humans. The efficacy of these compounds is comparable to the widely used tricyclic antidepressants, but they are better tolerated.[3] In particular they do not produce the anticholinergic and cardiovascular side effects observed with tricyclic antidepressants.

A good correlation exists between the capacities of a variety of drugs to inhibit [^{3}H]paroxetine binding and [^{3}H]-5-HT uptake in rat cortex,[4] thus allowing this binding test to be used in screening for new 5-HT uptake inhibitors.

In a previous paper[5] we described a series of naphthalenesultam derivatives exhibiting 5-HT_2 antagonist activity. RP 62203 (**29**) was selected from this series as one of the most potent and selective 5-HT_2 antagonists.



29 RP62203

When exploring the binding profile of analogs of this compound, we discovered that in RP 62203 replacement of the phenylpiperazine moiety by a 4-(indol-3-yl)-1,2,3,6-tetrahydropyridinyl group led to a compound (**3** in Table I) which exhibited a high affinity not only for the 5-HT_2 receptor but also for the 5-HT uptake site. Unfortunately this compound displayed a substantial affinity for α_1 and D_2 receptors.

These results prompted us to undertake the synthesis of analogs of the naphthalenesultam derivative (compound **3**) in order to find more selective compounds which possess a nanomolar affinity for the 5-HT uptake site and are devoided of significant affinity for α_1 and D_2 receptors.

Chemistry

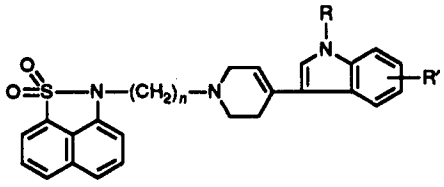
The synthetic pathway for the preparation of naphthalenesultam derivatives (**3–8** and **11–22**), listed in Tables I and II, is shown in Scheme I. *N*-(Chloroalkyl)naphthalenesultam derivatives[5] were reacted at reflux with the appropriate amine in the presence of sodium bicarbonate in a 1:1 dilution of DMF and THF. Yields were moderate (12–56%), except for piperazine derivative (compound **20**) (85%). The N-substituted derivatives of **3** (**9** and **10**) were obtained from **3** by treatment with sodium hydride followed by reaction of the anion thus formed by methyl iodide (**9**) or acetyl chloride (**10**), respectively.

Unsubstituted 3-(1,2,3,6-tetrahydro-4-pyridinyl)indole as well as its 5-methoxy, 5-hydroxy, and 5-chloro derivatives were prepared by condensation of piperidone hydrochloride on the corresponding indoles in acidic medium, according to the literature,[6] and this procedure was extended to the synthesis of the new 5-bromo and 5-fluoro analogs. Other starting piperidine derivatives have already previously published, including 3-(4-piperidinyl)indole[7] and 4-[(inden-1-yl)methyl]piperidine.[8] Here we adapted literature processes to synthesize 5-fluoro-3-[2-(4-piperidinyl)ethyl]indole,[9] 5-fluoro-3-[(4-piperazinyl)methyl]indole,[10] and 5-fluoro-2-[(4-piperidinyl)methyl]indole.[11] Other indolic intermediates, 5-fluoro-3-[(4-piperidinyl)methyl]indole (**1**) and analogs, were synthesized according to the routes described in Scheme II. An appropriate indolylmagnesium halide was condensed with nicotinoyl chloride to give an (indol-3-yl)(4-pyridinyl)-methanone. Reduction of this ketone with $NaBH_4$ gave a 3-[(4-pyridinyl)methyl]indole which can be converted

† Département de Chimie Pharmaceutique.
‡ Département de Biologie.

0022-2623/93/1836-1194$04.00/0

Table I. In Vitro Binding Data for [3-(4-(1*H*-Indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl)propyl]-naphthalenesultam Derivatives 3–12



compd	R	R′	*n*	IC$_{50}$ (nM)[a] 5-HT uptake[b]	5-HT$_2$[b]	α_1[b]	D$_2$[b]
3	H	H	3	0.2	0.7	11	30
4	H	5-OCH$_3$	3	10	45	33	>100
5	H	5-OH	3	25	11	11	10
6	H	5-Cl	3	1.4	25	71	24
7	H	5-Br	3	10	>100	>100	22
8	H	5-F	3	0.3	6	75	13
9	CH$_3$	H	3	0.6	1.3	>100	>100
10	COCH$_3$	H	3	10	6	>100	>100
11	H	H	2	0.6	4.3	8	81
12	H	H	4	0.8	4.0	0.7	<30

[a] IC$_{50}$ (nM) values are the mean of at least two determinations each with six concentrations of test compounds in triplicate. Standard deviations were always smaller than 10%. [b] See Experimental Section.

into conventional sequences to the desired piperidine or tetrahydropyridine derivatives.

Compounds 23–28 listed in Table III were prepared by reacting 1 with the appropriate chloroalkyl derivatives according to Scheme III. Yields were in the same range as in the naphthalenesultam series. The reaction of 1 with ethyl formate afforded the corresponding formyl derivative which was subsequently reduced by LiAlH$_4$ to give the *N*-methylpiperidine derivative (compound 2) (Scheme II).

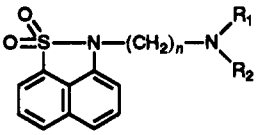
Biology

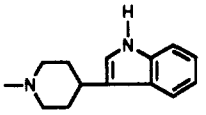
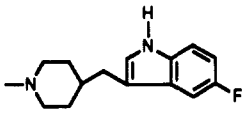
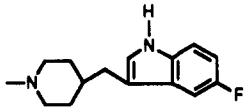
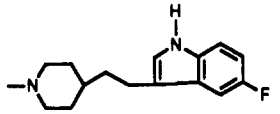
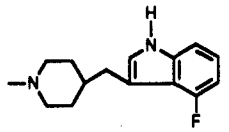
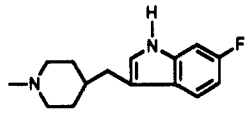
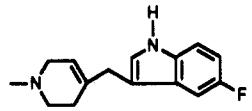
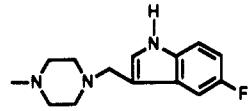
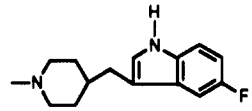
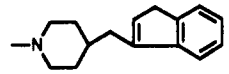
The indole derivatives shown in Tables I–IV were tested as 5-HT uptake inhibitors by measuring their ability to inhibit [^{3}H]paroxetine binding to rat cortical membranes.[4] Potentiation of 5-hydroxytryptophan (5-HTP)-induced behavioral symptomatology in mice[12] was used to measure the in vivo activity of several compounds (Table V). Affinities for brain 5-HT$_2$, α_1, and D$_2$ receptors were measured by the inhibition of binding to [^{3}H]ketanserin,[13] [^{3}H]prazosin,[14] and [^{3}H]spiperone,[15] respectively. Rat cortical membranes were used for 5-HT$_2$ and α_1 binding assays whereas D$_2$ binding was measured in rat striatal membranes. The activity of the test compounds was compared to that of the standard fluoxetine.

Results and Discussion

As already mentioned, 3 had been incidentally found to display high affinity for paroxetine binding sites (IC$_{50}$ = 0.2 nM) and for 5-HT$_2$ receptors (IC$_{50}$ = 0.7 nM). This compound also displayed a significant affinity for α_1 and D$_2$ receptors. Interestingly N-methylation of the indole ring in 3 (compound 9) did not substantially affect affinities for the uptake site or for 5-HT2 receptor, but D$_2$ and α_1 affinities were dramatically dropped. On the other hand, N-acetylation of the indole ring (compound 10) lowered affinities for both 5-HT$_2$ and uptake sites. Compounds with a substituent in the 5-position of indole such as OMe (4), OH (5), and Br (7) exhibited moderate affinity for the uptake site. In contrast the 5-Cl (6) and the 5-F (8) derivatives as well as compounds with shorter (n = 2) or longer (n = 4) alkyl chains (11, 12) were almost as potent as 3 at the uptake site, but selectivity, namely regarding D$_2$ receptors, did not improve. Replacement in 3 of the tetrahydropyridine moiety by a piperidine gave 13 which displayed an extremely high 5-HT$_2$ affinity (IC$_{50}$ = 0.05 nM) but showed a moderate affinity for the uptake site. Other structural modifications are shown in Table II (compounds 14–22). It is interesting to note that incorporation of a methylene group between the indole ring and the piperidine moiety led to very selective compounds regarding the ratio of uptake to α_1 or to D$_2$. The most potent and selective compounds were obtained with a two-carbon alkyl chain between the naphthalenesultam ring and the piperidine nitrogen. Increasing the length from one carbon (compound 14) to two (compound 16) in the chain linking the piperidine moiety to the indole ring increased affinity for α_1 receptors. In terms of selectivity and potency at the uptake site, the 5-fluoro derivative 14 was better than the 4-fluoro (17) and the 6-fluoro (18) isomers. The binding profile was not affected by incorporation of a double bond in the piperidine ring of 14 (19), and neither did the replacement in 14 of the piperidine by a piperazine (20) or the shift in the chain on the indole ring of 14 from the 3- to the 2-position (21). The indene analog of 14 (22) exhibited about the same binding profile as 14 but was less potent at the uptake site. Among the compounds listed in Tables I and II, compound 14 was considered to be the closest to our target with an affinity for the uptake site higher than that of fluoxetine, combined with a moderate affinity for the 5-HT$_2$ receptor and no affinity for α_1 and D$_2$ receptors. Starting from this compound, we decided to replace the naphthalenesultam ring by other heterocycle moieties, in order to explore the role of the "head-part" in such molecules. Table III shows some examples of these molecules. Replacement of the naphthalenesultam ring by its carbonyl analog (23) or by the related thiadiazoloquinoline (24) or imidazoquinoline (25) retained the same binding profile. Alternative heterocyclic moieties gave compounds with reduced potency at the uptake site (26–28). The intermediate 5-fluoro-3-[(4-piperidinyl)methyl]indole (1) and its *N*-methyl derivative 2 were also tested as 5-HT uptake inhibitors (Table IV). Compound 1 (as compounds 9 and 14) was found very active in vitro but inactive in vivo (Table V). Compound 1 was previously studied[9b] and found to be moderately active in vitro as a 5-HT uptake inhibitor in rat brain synaptosomes and poorly active in potentiating 5-HTP in mice. Interestingly N-methylation of 1 which led to 2 completely abolished the affinity of 2 for the uptake site. To explain the high affinity of most of the compounds listed in Tables I–III, it may be assumed that the naphthalenesultam moiety or a related heterocycle has a critical role in the binding of the molecule to the 5-HT transporter complex. This "head-part" is also responsible for bioavailability since compounds such as 24, in contrast to 1, 9, and 14, were very active in vivo (Table V). 24 was active by the oral route as fluoxetine in potentiating 5-HTP syndrome despite a significant 5-HT$_2$ antagonist activity. The ability of 24 to inhibit the 5-HT uptake selectively was confirmed by directly measuring its affinity for the uptake of 5-HT (IC$_{50}$ = 2 nM), noradrenaline, and dopamine (IC$_{50}$ higher than 10 μM) in rat brain synaptosomes. This study confirmed that 24 was a very potent and selective 5-HT uptake inhibitor. Residual 5-HT$_2$ antagonist activity could be of interest for the therapeutic profile of the drug because there is some evidence that 5-HT$_2$ antagonists may be effective in

Table II. In Vitro Binding Data for (Aminoalkyl)naphthalenesultam Derivatives 13–22



compd	n	$-N(R_1)(R_2)$	IC_{50} (nM)[a] 5-HT uptake	5-HT_2	α_1	D_2
13	3		11	0.05	3.4	4.6
14	2		0.4	16	>100	>100
15	3		2	>100	70	>100
16	2		1.4	>100	8	>100
17	2		6	23	>100	>100
18	2		0.3	2.8	>100	31
19	2		1.1	72	>100	>100
20	2		5	>100	>100	>100
21	2		4	>100	>100	>100
22	2		5	4	>100	>100

[a] See footnotes Table I.

disthymic disorders.[16] This profile makes **24** an interesting candidate for clinical investigation as an antidepressant.

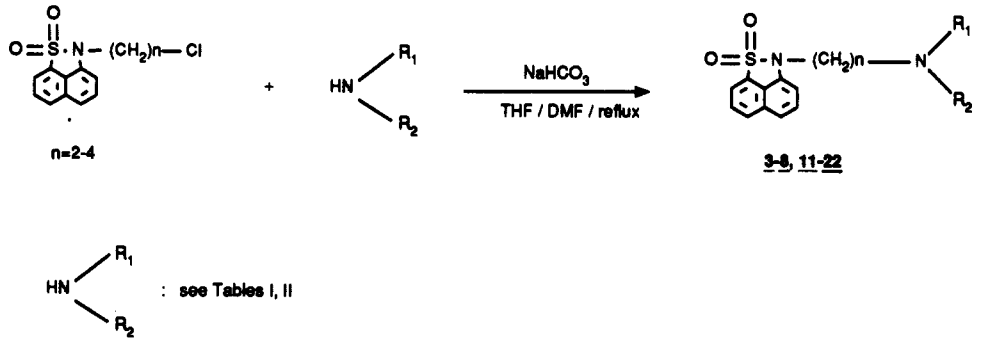
Experimental Section

Melting points were recorded on a Köfler apparatus and were uncorrected. ^1H 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. Mass spectra were recorded on a Finnigan 3300 spectrometer. Unless otherwise indicated 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.

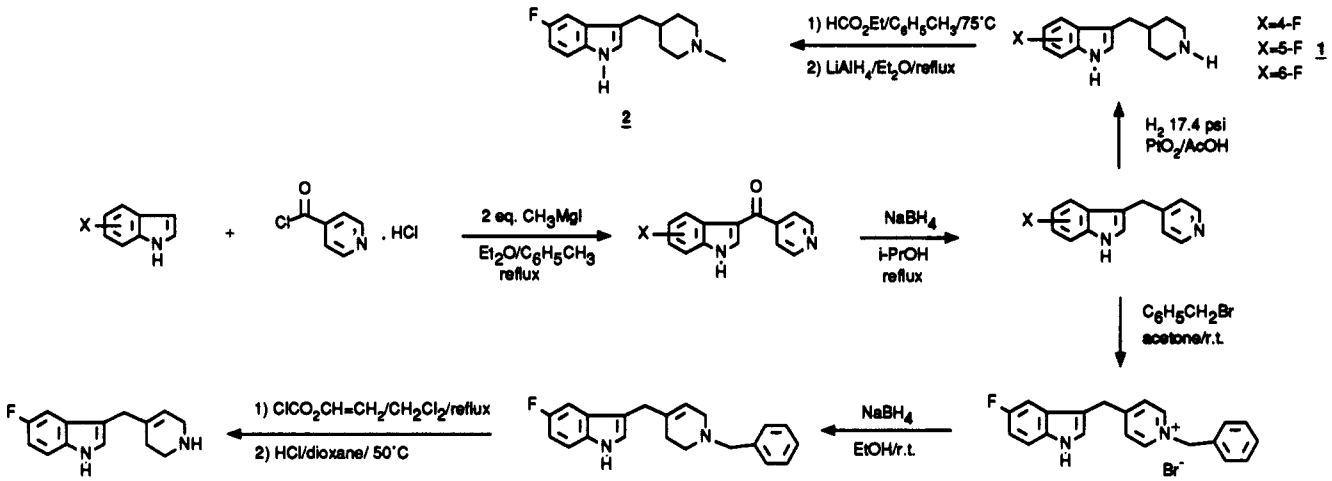
Preparation of Fluoro-3-[(4-piperidinyl)methyl]-1*H*-indoles. (5-Fluoro-1*H*-indol-3-yl)(4-pyridinyl)methanone. A mixture of 70 g (0.52 mol) of 5-fluoroindole in 250 mL of diethyl ether was added at room temperature under argon to 1 mol of methylmagnesium iodide (prepared from 142 g of methyl iodide and 24 g of magnesium in 500 mL of diethyl ether). The solution was refluxed 2 h and then cooled to 5 °C. A 172-g (0.72-mol) portion of isonicotinoyl chloride hydrochloride in 500 mL of toluene was added, and the reaction mixture was stirred for 15 h at room temperature. After acidification of the solution with 1000 mL of 2 N HCl, the precipitate formed is collected by filtration to give 105 g (73%) as the hydrochloride of (5-fluoro-1*H*-indol-3-yl)(4-pyridinyl)methanone (mp >250 °C): NMR (DMSO, 200 MHz), δ 7.3 (ddd, 1 H, H indole), 7.6 (dd, 1 H, H indole), 7.9 (dd, 1 H, H indole), 8.1 (bs, 1 H, H indole), 8.2 (m, 2 H, H pyridine), 9.0 (m, 2 H, H pyridine), 12.5 (bs, 1 H, NH).

5-Fluoro-3-[(4-pyridinyl)methyl]-1*H*-indole. To 105 g (0.38 mol) of (5-fluoro-1*H*-indol-3-yl)(4-pyridinyl)methanone hydrochloride in 2000 mL of 2-propanol, under argon, was slowly added 145 g (3.8 mol) of sodium borohydride at 25 °C. The reaction

Scheme I



Scheme II



mixture was stirred under reflux for 2 h, cooled to 15 °C, and poured into 2500 mL of ice and 1000 mL of dichloromethane, and the mixture was left for 15 h at room temperature. After addition of 3000 mL of water, the organic layer was extracted twice with 1000 mL of dichloromethane, washed three times with 2000 mL of water, dried over Na_2SO_4, and concentrated. Purification by flash chromatography on silica gel eluting with dichloromethane and then ethyl acetate and recrystallization from ethyl acetate afforded 25.5 g (26%) of 5-fluoro-3-(4-pyridinylmethyl)-1*H*-indole as a white solid (mp 149 °C): NMR ($CDCl_3$, 200 MHz), δ 4.1 (s, 2 H, CH_2), 6.8–7.4 (m, 6 H, H indole and pyridine), 8.5 (bd, 2 H, H pyridine), 9.0 (bs, 1 H, NH); MS *m/z* 226 (M^+).

5-Fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole[9b] (1). A stirred mixture of 25.5 g (113 mmole) of 5-fluoro-3-(4-pyridinylmethyl)-1*H*-indole and 1.5 g of PtO_2 in 450 mL of AcOH were hydrogenated under 17.4 psi at room temperature during 20 h. After filtration of the catalyst and concentration of the filtrate, the oil was taken up with 400 mL of water and basified to pH 9 with NaOH. The organic phase was extracted twice with 300 mL of dichloromethane, dried over Na_2SO_4, and concentrated to give 9.4 g of 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole (1) (82% yield, mp 163 °C).

4-Fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole. This compound was prepared in 20% (overall yield) as a solid (mp >260 °C) following the same procedure as for 1, from 4-fluoro-1*H*-indole[17] and isonicotinoyl chloride hydrochloride.

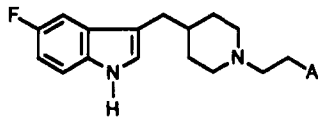
6-Fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole. This compound was prepared in 21% (overall yield) as a solid (mp 161 °C) following the same procedure as for 1, from 6-fluoro-1*H*-indole[18] and isonicotinoyl chloride hydrochloride.

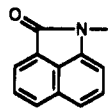
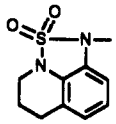
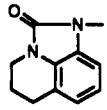
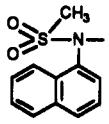
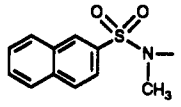
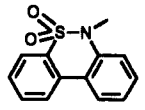
Preparation of 5-Fluoro-3-[(1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole. 1-Benzyl-4-[(5-fluoro-1*H*-indol-3-yl)methyl]pyridinium Bromide. To 7 g (31 mmol) of 5-fluoro-3-[(4-pyridinyl)methyl]-1*H*-indole in 40 mL of acetone was slowly added 3.7 mL (31 mmol) of benzyl bromide at room temperature. The reaction mixture was stirred for 15 h; the precipitate formed was collected by filtration and washed with diisopropyl ether to afford 12 g (98%) of 1-benzyl-4-[(5-fluoro-1*H*-indol-3-yl)methyl]-pyridinium bromide as a yellow solid (mp 100 °C, dec): NMR (DMSO, 250 MHz) δ 4.40 (s, 2 H, CH_2), 5.75 (s, 2 H, CH_2N), 7.0 (ddd, 1 H, H indole), 7.20–7.45 (m, 8 H, H indole and pyridine), 8.05 (bd, 2 H, H pyridine), 9.7 (bd, 2 H, H pyridine), 11.25 (bs, 1 H, NH).

5-Fluoro-3-[(1-benzyl-1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole. To 12 g (30 mmol) of 1-benzyl-4-[(5-fluoro-1*H*-indol-3-yl)methyl]pyridinium bromide in 200 mL of ethanol, under argon, was slowly added 1.4 g (37.8 mmol) of sodium borohydride at room temperature. The mixture was left for 15 h and then taken up with 100 mL of water. The organic layer was extracted four times with 50 mL of dichloroethane, washed with 50 mL of water, dried over $MgSO_4$, and concentrated to afford 9 g (94%) of 5-fluoro-3-[(1-benzyl-1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole as a yellow oil: NMR ($CDCl_3$, 300 MHz), δ 2.1 (bt, 2 H, CH_2), 2.6 (bt, 2 H, CH_2), 3.0 (bs, 2 H, CH_2), 3.3 (s, 2 H, CH_2), 3.6 (s, 2 H, CH_2N), 5.4 (bs, 1 H, CH=C), 6.8 (m, 2 H, H indole and phenyl), 7.1–7.3 (m, 7 H, H indole and phenyl), 8.5 (bs, 1 H, NH).

5-Fluoro-3-[(1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole. To 9 g (28 mmol) of 5-fluoro-3-[(1-benzyl-1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole in 150 mL of dichloromethane, under argon, was slowly added 3.8 mL (40 mmol) of vinyl chloroformate at room temperature. The reaction mixture was stirred under reflux for 8 h, cooled to 20 °C, and concentrated. The residue (11 g) was stirred for 1 h, at room temperature, with 100 mL of a 6.3 N solution of hydrochloric acid in dioxane. The mixture was concentrated, taken up with 40 mL of ethanol, and heated at 50 °C for 90 min. After concentration, the residue was taken up with 50 mL of diisopropyl ether and the precipitate formed collected by filtration. Purification by flash chromatography on silica gel eluting with dichloromethane and ethanol (9:1 then 8:2) afforded 3.3 g (50.5%) of 5-fluoro-3-[(1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole NMR ($CDCl_3$, 200 MHz) δ 2.2 (t, 2 H, CH_2), 3.10 (t, 2 H, CH_2), 3.15 (s, 2 H, CH_2), 3.40 (s, 2 H, CH_2N), 5.45 (bs, 1 H, CH=C), 6.90 (ddd, 1 H, H indole), 7.22 (dd, 1 H, H indole), 7.28 (bs 1 H, H indole), 7.35 (dd, 1 H, H indole), 11.2 (bs, 1 H, NH); MS *m/z* 230 (M^+).

Table III. In Vitro Binding Data for 2-[4-((5-Fluoro-1*H*-indol-3-yl)methyl)piperidinyl]ethyl Derivatives 23–28



compd	A	IC_{50} (nM)[a] 5-HT uptake	5-HT_2	α_1	D_2
23		1.7	27	>100	>100
24		1.2	30	>100	>100
25		0.4	14	85	56
26		100	>100	5	>100
27		22	>100	>100	20
28		35	100	>100	>100

[a] See footnotes Table I.

Preparation of 5-Fluoro-3-[(1-methyl-4-piperidinyl)methyl]-1*H*-indole (2). To 2.3 g (0.01 mole) of 1 in 20 mL of toluene was added 1.8 mL (0.02 mol) of ethyl formate at room temperature. The reaction mixture was stirred under reflux for 14 h and then cooled to room temperature; the precipitate, as a white solid (1.9 g), was separated by filtration and then added by portions to a mixture of 0.42 g (0.011 mol) of lithium aluminum hydride in 50 mL of diethyl ether, at room temperature, under argon. The reaction mixture was stirred under reflux for 2 h and then cooled to 0 °C. After addition of 10 mL of water and alcalinization with NaOH to pH = 8, the precipitate formed was separated by filtration and recrystallized in 40 mL of methyl ethyl ketone to give 0.64 g (35.5%) of **2** as a white solid (mp 203 °C): NMR (DMSO, 200 MHz) δ 1.2 (m, 2 H, 2 H_a piperidine), 1.4 (m, 1 H, C—CH—C), 1.6 (bd, 2 H, 2 H_e piperidine), 1.8 (bt, 2 H, NCH_2), 2.1 (s, 3 H, CH_3N), 2.6 (d, 2 H, CH_2) 2.7 (bd, 2 H, NCH_2), 6.9 (m, 1 H, H indole), 7.2–7.4 (m, 3 H, H indole), 10.9 (bs, 1 H, NH). Anal. ($C_{15}H_{19}N_2F$) C, H, N.

5-Hydroxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole. This compound was prepared in 73% yield as a solid (mp 185 °C) following the literature procedure,[6] from 5-hydroxy-1*H*-indole and piperidone hydrochloride.

5-Bromo-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole. This compound was prepared in 90% yield as a solid (mp 213 °C) following the literature procedure,[6] from 5-bromo-1*H*-indole and piperidone hydrochloride.

5-Fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole. This compound was prepared in 77% yield as a solid (mp 155 °C) following the literature procedure,[6] from 5-fluoro-1*H*-indole and piperidone hydrochloride.

5-Fluoro-3-[2-(4-piperidinyl)ethyl]-1*H*-indole. This compound was prepared in 45% yield as a solid (mp 163 °C) following the literature procedure,[9b] from 5-fluoro-1*H*-indole and 4-vinylpyridine.

5-Fluoro-3-[(4-piperazinyl)methyl]-1*H*-indole. This compound was prepared in 46% (overall yield) as an oil following the literature procedure,[10] from 5-fluoro-1*H*-indole.

5-Fluoro-2-[(4-piperidinyl)methyl]-1*H*-indole. This compound was prepared in 6% (overall yield) as a solid (mp 120 °C) following the literature procedure,[11] from 5-fluoro-1*H*-indole-2-carboxylic acid.

Preparation of 2-(Aminoalkyl)naphth[1,8-*cd*]isothiazole 1,1-Dioxides 3–8, 11–22. 2-[3-(4-(1*H*-Indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (3). To 9.3 g (33 mmol) of 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 2.7 g (33 mmol) of sodium bicarbonate in 100 mL of DMF and 100 mL of THF was added at room temperature, 6.5 g (33 mmol) of 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole.[6] The reaction mixture was stirred for 5 h under reflux. After evaporation to dryness under reduced pressure, the residue was flash chromatographed on silica gel with 9:1 dichloromethane/MeOH as eluent and recrystallized from acetonitrile to afford 2.9 g (14%) of **3** as a solid (mp 226 °C): NMR (DMSO, 200 MHz) δ 2.00 (m, 2 H, CH_2), 2.60 (m, 6 H, 3 CH_2), 3.15 (bs, 2 H, CH_2N), 4.00 (t, 2 H, CH_2N), 6.15 (bs, 1 H, CH=C), 7.10–8.30 (m, 1 OH, H indole and arom), 11.15 (bs, 1 H, NH); MS *m/z* 443 (M^+). Anal. ($C_{26}H_{25}N_3O_2S$) C, H, N, S.

Compounds 4–8 and 11–22 were prepared in a similar manner.

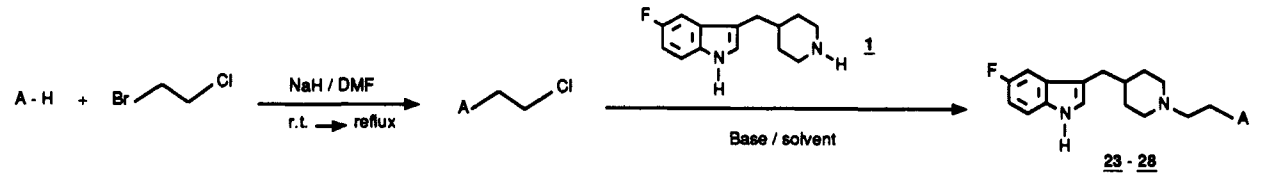
2-[3-(4-(5-Methoxy-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (4). This compound was prepared in 45% yield as a solid (after recrystallization from acetone/EtOH, mp 204 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide,[5] and 5-methoxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole: NMR (DMSO, 200 MHz), δ 2.1 (m, 2 H, CH_2), 2.6 (m, 6 H, CH_2 and 2 CH_2N), 3.15 (bs, 2 H, CH_2N), 3.80 (s, 3 H, CH_3), 3.90 (t, 2 H, CH_2N), 6.10 (bs, 1 H, CH=C), 6.75 (dd, 1 H, H indole), 7.10 (d, 1 H, H arom), 7.30 (m, 2 H, H indole), 7.40 (bs, 1 H, H indole), 7.65 (m, 2 H, H arom), 7.90 (t, 1 H, H arom) 8.30 (m, 2 H, H arom), 11.0 (bs, 1 H, NH); MS *m/z* 473 (M^+). Anal. ($C_{27}H_{27}N_3O_3S$) C, H, N, S.

2-[3-(4-(5-Hydroxy-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (5). This compound was prepared in 45% yield as a solid (after crystallization from water and recrystallization from acetone/EtOH, mp 214 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-hydroxy-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole: NMR (DMSO, 200 MHz) δ 2.05 (m, 2 H, CH_2), 2.60 (m, 6 H, CH_2 and 2 CH_2N), 3.15 (bs, 2 H, CH_2N), 3.90 (t, 2 H, NCH_2), 6.00 (bs, 1 H, CH=C), 6.60 (dd, 1 H, H indole), 7.10 (bd, 1 H, H arom), 7.15 (m, 2 H, H arom), 7.30 (bs, 1 H, H indole), 7.60 (m, 2 H, H arom), 7.90 (t, 1 H, H arom), 8.25 (m, 2 H, H arom), 8.70 (bs, 1 H, OH), 10.8 (bs, 1 H, NH); MS *m/z* 459 (M^+). Anal. ($C_{26}H_{25}N_3O_3S$) C, H, N, S.

2-[3-(4-(5-Chloro-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (6). This compound was prepared in 52% yield as a solid (after crystallization from water and recrystallization from acetonitrile, mp 189 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-chloro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole:[6] NMR (DMSO, 200 MHz) δ 2.05 (m, 2 H, CH_2), 2.60 (m, 6 H, CH_2 and 2 CH_2N), 3.15 (bs, 2 H, CH_2N), 3.95 (t, 2 H, NCH_2), 6.10 (bs, 1 H, CH=C), 7.10 (m, 2 H, H indole and arom), 7.40 (d, 1 H, H indole), 7.50 (bd, 1 H, H indole), 7.60 (m, 2 H, H arom), 7.80 (bd, 1 H, H indole), 7.90 (t, 1 H, H arom), 8.30 (m, 2 H, H arom), 11.3 (bs, 1 H, NH); MS *m/z* 477 (M^+). Anal. ($C_{26}H_{24}ClN_3O_2S$) C, H, N, S.

2-[3-(4-(5-Bromo-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl)propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (7). This compound was prepared in 29% yield as a solid (after crystallization from water and recrystallization from acetone, mp 184 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-bromo-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole: NMR (DMSO, 200 MHz) δ 2.00 (m, 2 H, CH_2), 2.60 (m, 6 H, CH_2 and 2 CH_2N), 3.10 (bd, 2 H, CH_2N), 3.90 (t, 2 H, CH_2N), 6.10 (bs, 1 H, CH=C), 7.10 (dd, 1 H, H arom), 7.25 (dd, 1 H, H indole), 7.35 (d, 1 H, H indole), 7.50 (bs, 1 H, H indole), 7.60 (m, 2 H, H arom), 7.80 (t, 1, H arom), 7.90 (bd, 1 H, H indole), 8.30 (m, 2 H, H arom), 11.4 (bs, 1 H, NH); MS *m/z* 521 (M^+). Anal. ($C_{26}H_{24}BrN_3O_2S$) C, H, N, S.

Scheme III



A-H : see Table III

Table IV. In Vitro Binding Data of Compounds 1, 2, and Fluoxetine

compd	IC_{50} (nM)[a] 5-HT uptake	5-HT_2	α_1	D_2
1	1.6	>100	>100	>100
2	>100	>100	>100	>100
fluoxetine	15.0	>100	>100	>100

[a] See footnotes Table I.

Table V. In Vivo Activities of Compounds 1, 24, and Fluoxetine

compd	5-HTP potentialisation in mice: time before 5-HTP administration	ED_{50} (mg/kg)[a] sc	po
1	1 h 30 min		in 40
	1 h	5.11 [2.65–9.87]	
24	1 h 30 min		2.89 [1.22–6.83]
	6 h	2.64 [1.41–4.95]	4.32 [2.43–7.67]
	1 h	6.31 [3.29–12.10]	
fluoxetine	1 h 30 min		7.47 [3.64–15.31]
	6 h	4.96 [2.57–9.60]	2.69 [1.46–4.97]

[a] ED_{50} values were calculated with 95% confidence limit.

2-[3-[4-(5-Fluoro-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (8). This compound was prepared in 52% yield as a solid (after crystallization from water and recrystallization from acetone/EtOH, mp 224 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-fluoro-3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole: NMR (DMSO, 200 MHz) δ 2.10 (m, 2 H, CH_2), 2.60 (m, 6 H, CH_2 and 2 NCH_2), 3.15 (bs, 2 H, CH_2N), 3.90 (t, 2 H, CH_2N), 6.10 (bs, 1 H, CH=C), 6.95 (ddd, 1 H, H indole), 7.10 (bd, 1 H, H arom), 7.40 (dd, 1 H, H indole), 7.50 (dd, 1 H, H indole), 7.60 (m, 3 H, H arom and indole), 7.90 (t, 1 H, H arom), 8.30 (m, 2 H, H arom), 11.2 (bs, 1 H, NH); MS *m/z* 461 (M^+). Anal. ($C_{26}H_{24}FN_3O_2S$) C, H, N, S.

2-[2-[4-(1*H*-Indole-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (11). This compound was prepared in 12% yield as a solid (crystallization from acetonitrile and recrystallization from methyl ethyl ketone, mp 208 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole:[6] NMR (DMSO, 200 MHz) δ 2.6 (m, 2 H, CH_2), 2.9 (m, 4 H, 2 CH_2N), 3.3 (bs, 2 H, CH_2N), 4.1 (t, 2 H, CH_2N), 6.2 (bs, 1 H, CH=C), 7.1–7.65 (m, 7 H, H arom), 8.3 (m, 2 H, H arom) 11.2 (bs, 1 H, NH); MS *m/z* 429 (M^+). Anal. ($C_{25}H_{23}N_3O_2S$) C, H, N, S; C: calcd, 69.91; found, 69.5.

2-[4-[4-(1*H*-Indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]butyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (12). This compound was prepared in 33% yield as a solid (after flash chromatography on silica gel with dichloromethane then ethyl acetate as eluent and recrystallization from methyl ketone, mp 203 °C), from 2-(4-chlorobutyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1*H*-indole:[6] NMR ($CDCl_3$, 250 MHz) δ 1.8 (m, 2 H, CH_2), 2.0 (m, 2 H, CH_2), 2.6 (m, 4 H, CH_2 and CH_2N), 2.8 (t, 2 H, CH_2N), 3.25 (bd, 2 H, CH_2N), 3.9 (t, 2 H, CH_2N), 6.2 (bs, 1 H, CH=C), 6.8 (d, 1 H, H arom), 7.10–7.55 (m, 6 H, H arom and indole), 7.75–8.10 (4 H, H arom and indole), 8.75 (bs, 1 H, NH); MS *m/z* 458 (M^+). Anal. ($C_{27}H_{27}N_3O_2S$) C, H, N, S.

2-[3-(4-(1*H*-Indol-3-yl)-1-piperidinyl)propyl]-2*H*-naphth-[1,8-*cd*]isothiazole 1,1-Dioxide (13). This compound was prepared in 20% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from methyl ethyl ketone, mp 162 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 3-(4-[piperidinyl)-1*H*-indole:[7] NMR ($CDCl_3$, 200 MHz) δ 1.9 (m, 2 H, CCH_2C), 2.1 (m, 6 H, 2 H_a piperidine and 2 CH_2), 2.6 (t, 2 H, CH_2N), 2.9 (m, 1 H, 1 H_a piperidine), 3.1 (bd, 2 H, 2 H_e piperidine), 4.0 (t, 2 H, CH_2N), 6.9 (d, 1 H, H arom), 7.0 (bs, 1 H, H indole), 7.1–7.7 (m, 6 H, H arom and indole), 7.75 (t, 1 H, H arom), 7.9 (m, 2 H, H arom and NH), 8.1 (d, 1 H, H arom); MS *m/z* 445 (M^+). Anal. ($C_{26}H_{27}N_3O_2S$) C, H, N, S.

2-[2-[4-((5-Fluoro-1*H*-3-yl)methyl)-1-piperidinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (14). This compound was prepared in 38% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole (1): NMR ($CDCl_3$, 300 MHz) δ 1.4–1.8 (m, 5 H, H piperidine), 2.15 (bt, 2 H, 2 H_a piperidine), 2.7 (d, 2 H, CH_2), 2.9 (bt, 2 H, CH_2N), 3.1 (bd, 2 H, 2 H_e piperidine), 4.0 (bt, 2 H, CH_2N), 6.85 (bd, 1 H, H arom), 6.9 (ddd, 1 H, H indole), 7.0 (bs, 1 H, H indole), 7.2 (dd, 1 H, H indole), 7.3 (dd, 1 H, H indole), 7.4 (d, 1 H, H arom), 7.5 (t, 1 H, H arom), 7.7 (t, 1 H, H arom), 7.9 (d, 1 H, H arom), 8.0 (bs, 1 H, NH), 8.1 (d, 1 H, H arom); MS *m/z* 463 (M^+). Anal. ($C_{26}H_{26}FN_3O_2S$) C, H, N, S.

2-[3-[4-((5-Fluoro-1*H*-indol-3-yl)methyl)-1-piperidinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (15). This compound was prepared in 44% yield as a solid (after flash chromatography on silica gel with ethyl acetate and recrystallization from acetonitrile, mp 100 °C) from 2-(3-chloropropyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 1: NMR ($CDCl_3$, 200 MHz) δ 1.4–1.8 (m, 5 H, CH_2 piperidine), 2.0 (bt, 2 H, 2 H_a piperidine), 2.10 (m, 2 H, CH_2), 2.7 (d, 2 H, CH_2), 3.0 (bd, 2 H, 2 H_e piperidine), 4.0 (t, 2 H, CH_2N), 6.9 (d, 1 H, H arom), 7.0 (ddd, 1 H, H indole), 7.05 (bs, 1 H, H indole), 7.3 (m, 2 H, H indole), 7.5 (m, 2 H, H arom), 7.7 (t, 1 H, H arom), 7.9 (d, 1 H, H arom), 8.0 (m, 2 H, NH and H arom); MS *m/z* 477 (M^+). Anal. ($C_{27}H_{28}FN_3O_2S$) C, H, N, S.

2-[2-[4-(2-(5-Fluoro-1*H*-indol-3-yl)ethyl)-1-piperidinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (16). This compound was prepared in 35% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 164 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-fluoro-3-[2-(4-piperidinyl)ethyl]-1*H*-indole: NMR (DMSO, 300 MHz) δ 1.1–1.9 (m, 7 H, CH_2), 2.0 (bt, 2 H, 2 H_a piperidine), 2.7 (m, 4 H, CH_2 and CH_2N), 3.0 (bd, 2 H, 2 H_e piperidine), 3.9 (t, 2 H, CH_2N), 6.9 (ddd, 1 H, H indole), 7.1 (bd, 1 H, H arom), 7.18 (bs, 1 H, H indole), 7.2 (dd, 1 H, H indole), 7.3 (dd, 1 H, H indole), 7.6 (m, 2 H, H arom), 7.9 (bt, 1 H, H arom), 8.25 (bd, 1 H, H arom), 8.3 (bd, 1 H, H arom), 10.85 (bs, 1 H, NH); MS *m/z* 477 (M^+). Anal. ($C_{27}H_{28}FN_3O_2S$) C, H, N, S.

2-[2-[4-((4-Fluoro-1*H*-indol-3-yl)methyl)-1-piperidinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (17). This compound was prepared in 36% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from diisopropyl ether, mp 123 °C) from 2-(2-

chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 4-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole: NMR ($CDCl_3$, 200 MHz) 1.4–1.8 (m, 5 H, H piperidine), 2.1 (bt, 2 H, 2 H_a piperidine), 2.8 (m, 4 H, CH_2N and CH_2), 3.0 (bd, 2 H, 2 H_e piperidine), 4.0 (t, 2 H, CH_2N), 6.8 (m, 2 H, H indole and arom), 6.9 (bs, 1 H, H indole), 7.1 (m, 2 H, H indole), 7.5 (m, 2 H, H arom), 7.9 (t, 1 H, H arom), 8.0 (d, 1 H, H arom), 8.1 (d, 1 H, H arom), 8.15 (bs, 1 H, NH); MS *m/z* 463 (M^+). Anal. ($C_{26}H_{26}FN_3O_2S$) C, H, N, S.; C: calcd, 67.37; found, 67.8.

2-[2-[4-((6-Fluoro-1*H*-indol-3-yl)methyl)-1-piperidinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (18). This compound was prepared in 17% yield as a solid (after flash chromatography on silica gel with dichloromethane then ethyl acetate as eluent and recrystallization from acetonitrile, mp 177 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 6-fluoro-3-[(4-piperidinyl)methyl]-1*H*-indole: NMR ($CDCl_3$, 200 MHz) δ 1.4–1.8 (m, 5 H, H piperidine), 2.15 (bt, 2 H, 2 H_a piperidine), 2.65 (d, 2 H, CH_2), 2.9 (t, 2 H, CH_2N), 3.1 (bd, 2 H, H_e piperidine), 4.0 (t, 2 H, CH_2N), 6.9 (m, 3 H, H indole), 7.05 (dd, 1 H, H arom), 7.25 (bs, 1 H, H indole), 7.50 (m, 2 H, H arom), 7.75 (t, 1 H, H arom), 7.95 (d, 1 H, H arom), 8.0 (bs, 1 H, NH), 8.1 (d, 1 H, H arom); MS *m/z* 463 (M^+). Anal. ($C_{26}H_{26}FN_3O_2S$) C, H, N, S.; C: calcd, 67.37; found, 67.8.

2-[2-[4-((5-Fluoro-1*H*-indol-3-yl)methyl)-1,2,3,6-tetrahydro-1-pyridinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (19). This compound was prepared in 12% yield as an oil (after flash chromatography on silica gel, oxalate salt mp 128 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-fluoro-3-[(1,2,3,6-tetrahydro-4-pyridinyl)methyl]-1*H*-indole: NMR (DMSO, 300 MHz) (oxalate salt of **19**) δ 2.30 (bs, 2 H, CH_2), 3.15 (bs, 2 H, CH_2N), 3.3 (bt, 2 H, CH_2N), 3.45 (bs, 2 H, CH_2), 3.6 (bs, 2 H, CH_2N), 4.2 (bt, 2 H, CH_2N), 5.5 (bs, 1 H, CH=C), 6.9 (ddd, 1 H, H indole), 7.2–7.4 (m, 4 H, H arom and indole), 7.7 (m, 2 H, H arom), 7.95 (t, 1 H, H arom), 8.9 (2d, 2 H, H arom), 11.5 (bs, 1 H, NH); MS *m/z* 461 (M^+). Anal. ($C_{26}H_{24}FN_3O_2S \cdot C_2H_2O_4$) C, H, N, S.

2-[2-[4-((5-Fluoro-1*H*-indol-3-yl)methyl)-1-piperazinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (20). This compound was prepared in 85% yield as a solid (after flash chromatography on silica gel with 9:1 ethyl acetate/MeOH as eluent and recrystallization from acetonitrile, mp 85 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-fluoro-3-[(4-piperazinyl)methyl]-1*H*-indole: NMR (DMSO, 200 MHz) δ 2.3–2.6 (bs, 8 H, CH_2N piperazine), 2.7 (bt, 2 H, CH_2N), 3.6 (bs, 2 H, CH_2), 3.9 (t, 2 H, CH_2N), 6.9 (ddd, 1 H, H indole), 7.1 (dd, 1 H, H arom), 7.3 (m, 3 H, H indole), 7.6 (m, 2 H, H arom), 7.8 (t, 1 H, H arom), 8.3 (m, 2 H, H arom), 11.0 (bs, 1 H, NH); MS *m/z* 465 (M^+). Anal. ($C_{25}H_{25}FN_4O_2S$) C, H, N, S.; C: calcd, 64.64; found, 63.9.

2-[2-[4-((5-Fluoro-1*H*-indol-2-yl)methyl)-1-piperidinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (21). This compound was prepared in 38% as a solid (after flash chromatography on silica gel with 1:1 cyclohexane/ethyl acetate, mp 154 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]isothiazole 1,1-dioxide[5] and 5-fluoro-2-[(4-piperidinyl)methyl]-1*H*-indole: NMR (DMSO, 200 MHz) δ 1.2–1.6 (m, 5 H, H piperidine), 2.0 (bt, 2 H, 2 H_a piperidine), 2.6 (d, 2 H, CH_2), 2.7 (t, 2 H, CH_2N), 3.0 (bd, 2 H, 2 H_e piperidine), 3.95 (t, 2 H, CH_2N), 6.1 (bs, 1 H, H indole), 6.8 (ddd, 1 H, H indole), 7.1 (dd, 1 H, H indole), 7.15 (dd, 1 H, H arom), 7.25 (dd, 1 H, H indole), 7.6 (m, 2 H, H arom), 7.9 (t, 1 H, H arom), 8.1 (m, 2 H, H arom), 11.0 (bs, 1 H, NH); MS *m/z* 463 (M^+). Anal. ($C_{26}H_{26}FN_3O_2S$) C, H, N, S.

2-[2-[4-((1*H*-Inden-3-yl)methyl)-1-piperidinyl]ethyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (22). This compound was prepared in 56% as an oil (after flash chromatography on silica gel with 99:1 dichloromethane/MeOH as eluent, oxalate salt mp 166 °C) from 2-(2-chloroethyl)-2*H*-naphth[1,8-*cd*]-isothiazole 1,1-dioxide[5] and 4-[(1*H*-inden-1-yl)methyl]piperidine:[8] NMR (DMSO, 200 MHz) (oxalate salt of **22**) δ 1.4–1.9 (m, 5 H, H piperidine), 2.8 (bt, 2 H, H_a piperidine), 3.2–3.6 (m, 6 H, CH_2, CH_2N, 2 H_e piperidine), 4.2 (t, 2 H, CH_2N), 6.3 (bs, 1 H, CH=C), 7.25 (m, 3 H, H arom), 7.45 (m, 2 H, H arom), 7.7 (m, 2 H, H arom), 7.9 (t, 1 H, H arom), 8.3 (m, 2 H, H atom); MS *m/z* 444 (M^+). Anal. ($C_{27}H_{28}N_2O_2S \cdot C_2H_2O_4$) C, H, N, S.

Preparation of Compounds 9–10. 2-[3-[4-(1-Methyl-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (9). To 1.3 g (27 mmol) of sodium hydride (50% dispersion in vaselin) in 50 mL of DMF, under argon, was slowly added 11 g (24.8 mmol) of **3** in 100 mL of DMF at room temperature. The mixture was stirred at this temperature for 2 h. To this solution was added 3.9 g (27.5 mmol) of methyl iodide in 50 mL of dioxane. The mixture was left for 15 h at room temperature and then taken up with 250 mL of water; the organic layer was extracted four times with dichloroethane, washed with 400 mL of water, dried over $MgSO_4$, and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel with dichloroethane as eluant and recrystallized from methyl ethyl ketone to afford 3.3 g (29%) of **9** as a solid (mp 161 °C): NMR ($CDCl_3$, 200 MHz) δ 2.05 (m, 2 H, CH_2), 2.60 (m, 6 H, 2 CH_2N and CH_2), 3.15 (bs, 2 H, CH_2), 3.75 (s, 3 H, CH_3), 3.9 (t, 2 H, CH_2N), 6.15 (bs, 1 H, CH=C), 7.15 (m, 3 H, H arom and indole), 7.40 (m, 2 H, H indole), 7.60 (m, 2 H, H arom), 8.0 (d, 1 H, H indole), 7.9 (t, 1 H, H arom), 8.3 (m, 2 H, H arom); MS *m/z* 457 (M^+). Anal. ($C_{27}H_{27}N_3O_2S0$ C, H, N, S.

Compound **10** was prepared in a similar manner.

2-[3-[4-(1-Acetyl-1*H*-indol-3-yl)-1,2,3,6-tetrahydro-1-pyridinyl]propyl]-2*H*-naphth[1,8-*cd*]isothiazole 1,1-Dioxide (10). This compound was prepared in 11% yield as a solid (after flash chromatography on silica gel with dichloromethane then ethyl acetate as eluent and recrystallization from acetonitrile, mp 163 °C) from **3** and acetyl chloride: NMR ($CDCl_3$, 200 MHz) δ 2.2 (m, 2 H, CH_2), 2.6–2.8 (m, 9 H, 2 CH_2N, CH_2 and CH_3), 3.3 (bd, 2 H, CH_2N), 4.0 (t, 2 H, CH_2N), 6.3 (bs, 1 H, CH=C), 6.9 (d, 1 H, H arom), 7.2–7.6 (m, 5 H, H arom and indole), 7.7 (t, 1 H, H arom), 7.8 (d, 1 H, H indole), 8.0 (d, 1 H, H arom), 8.1 (d, 1 H, H arom), 8.5 (bd, 1 H, H indole); MS *m/z* 485 (M^+). Anal. ($C_{28}H_{27}N_3O_3S$) C, H, N, S.

Preparation of Chloroalkyl Derivatives ACH_2CH_2Cl. 1-(2-Chloroethyl)benz[*cd*]indol-2(1*H*)-one. To 1.1 g (22.9 mmol) of sodium hydride (50% dispersion in Vaseline) in 50 mL of DMF, under argon, was slowly added 4.1 g (24.3 mmol) of benz[*cd*]indol-2(1*H*)-one in 65 mL of DMF at room temperature. The reaction mixture was stirred at this temperature for 1 h. To this solution was added 1.9 mL (22.9 mmol) of 1-bromo-2-chloroethane, and the mixture was left for 18 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 ethyl acetate/cyclohexane to give 1.4 g (27%) of 1-(2-chloroethyl)benz[*cd*]indol-2(1*H*)-one as a solid (mp 136 °C): NMR ($CDCl_3$, 200 MHz) δ 3.9 (t, 2 H, CH_2), 4.3 (t, 2 H, CH_2), 7.0 (d, 1 H, H arom), 7.5 (m, 2 H, H arom), 7.75 (t, 1 H, H arom), 8.1 (m, 2 H, H arom).

Other derivatives were prepared in a similar manner.

1-(2-Chloroethyl)-5,6-dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline 2,2-Dioxide. This compound was prepared in 94% yield as an oil (after extraction of the organic layer with dichloromethane) from 5,6-dihydro-1*H*,4*H*-1,2,5-thiadiazolo[4,3,2-*ij*]quinoline 2,2-dioxide,[19] 1-bromo-2-chloroethane, and sodium hydride: NMR ($CDCl_3$, 250 MHz) δ 2.2 (m, 2 H, CH_2), 2.8 (t, 2 H, CH_2), 3.8 (t, 2 H, CH_2N), 3.9 (t, 2 H, CH_2Cl), 4.1 (t, 2 H, CH_2N), 6.7 (d, 1 H, H arom), 6.8 (d, 1 H, H arom), 6.9 (t, 1 H, H arom); MS *m/z* 272 (M^+).

1-(2-Chloroethyl)-2-oxo-1,2,5,6-tetrahydro-4*H*-imidazo[4,5,1-*ij*]quinoline. This compound was prepared in 55% as an oil (after flash chromatography on silica gel with ethyl acetate as eluent) from 2-oxo-1,2,5,6-tetrahydro-4*H*-imidazo[4,5,1-*ij*]-quinoline,[20] 1-bromo-2-chloroethane, and sodium hydride: NMR ($CDCl_3$, 200 MHz) δ 2.1 (m, 2 H, CH_2), 2.9 (t, 2 H, CH_2), 3.8 (m, 4 H, CH_2N and CH_2Cl), 4.2 (t, 2 H, CH_2N), 6.8–7.1 (m, 3 H, H arom); MS *m/z* 236 (M^+).

***N*-(2-Chloroethyl)-*N*-(1-naphthyl)methanesulfonamide.** This compound was prepared in 32% yield (after flash chromatography on silica gel with 1:1 cyclohexane/ethyl acetate as eluent, mp 120 °C) from *N*-(1-naphthyl)methanesulfonamide, 1-bromo-2-chloroethane, and sodium hydride: NMR (DMSO, 200 MHz) δ 3.2 (s, 3 H, CH_3), 3.5 (m, 2 H, CH_2Cl), 4.1 (m, 2 H, CH_2N), 7.6 (m, 3 H, H arom), 7.8 (d, 1 H, H arom), 8.0 (m, 2 H, H arom), 8.3 (bd, 1 H, H arom); MS *m/z* 283 (M^+).

N-(2-Chloroethyl)-N-methyl-2-naphthalenesulfonamide. This compound was prepared in 37% yield as a solid (after flash chromatography on silica gel with 8:2 cyclohexane/ethyl acetate, mp 101 °C) from N-methyl-2-naphthalenesulfonamide, 1-bromo-2-chloroethane, and sodium hydride: NMR (DMSO, 200 MHz) δ 2.8 (s, 3 H, CH_3), 3.4 (t, 2 H, CH_2), 3.8 (t, 2 H, CH_2), 7.7–8.3 (m, 6 H, H arom), 8.5 (bs, 1 H, H arom); MS m/z 283 (M^+).

6-(2-Chloroethyl)-6H-dibenz[ce]-1,2-thiazine 5,5-Dioxide. This compound was prepared in 57% as an oil (after flash chromatography on silica gel with 7:3 dichloroethane/cyclohexane as eluent) from 6H-dibenz[ce]-1,2-thiazine 5,5-dioxide,[21] 1-bromo-2-chloroethane, and sodium hydride: NMR, (DMSO, 400 MHz) δ 3.6 (t, 2 H, CH_2Cl), 4.4 (t, 2 H, CH_2N), 7.5 (t, 1 H, H arom), 7.6 (t, 1 H, H arom), 7.7 (m, 2 H, H arom), 7.9 (t, 1 H, H arom), 8.0 (d, 1 H, H arom), 8.3 (m, 2 H, H arom).

2-(2-Chloroethyl)-1,2-benzisothiazole 1,1-Dioxide. This compound was prepared in 52% as a solid (after flash chromatography on silica gel with dichloroethane, mp 85 °C) from 1,2-benzisothiazole 1,1-dioxide, 1-bromo-2-chloroethane, and sodium hydride. MS m/z 231 (M^+).

Compounds **23–29** were prepared in a similar manner to compounds **3–8** and **11–22**.

1-[2-[4-((5-Fluoro-1H-indol-3-yl)methyl)-1-piperidinyl]ethyl]benz[cd]indol-2(1H)-one (23). This compound was prepared in 40% yield (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from cyclohexane/ethyl acetate, mp 156 °C) from 1-(2-chloroethyl)benz[cd]indol-2(1H)-one and 1: NMR (DMSO, 300 MHz) δ 1.1–1.6 (m, 5 H, CH piperidine), 1.9 (bt, 2 H, 2 H_a piperidine), 2.55 (m, 4 H, CH_2N and CH_2), 2.9 (bd, 2 H, 2 H_e piperidine), 4.0 (t, 2 H, CH_2N), 6.85 (ddd, 1 H, H indole), 7.15 (m, 3 H, H indole), 7.3 (dd, 1 H, H indole), 7.5 bt, 1 H, H arom), 7.65 (bd, 1 H, H arom), 7.8 (bt, 1 H, H arom), 8.05 (bd, 1 H, H arom), 8.2 (bd, 1 H, H arom), 10.9 (bs, 1 H, NH); MS m/z 427 (M^+). Anal. ($C_{27}H_{26}FN_3O$) C, H, N.

1-[2-[4-((5-Fluoro-1H-indol-3-yl)methyl)-1-piperidinyl]ethyl]-5,6-dihydro-1H,4H-1,2,5-thiadiazolo[4,3,2-ij]quinoline 2,2-Dioxide (24). This compound was prepared in 13% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 149 °C) from 1-(2-chloroethyl)-5,6-dihydro-1H,4H-1,2,5-thiadiazolo[4,3,2-ij]quinoline 2,2-dioxide and 1: NMR (DMSO, 300 MHz) δ 1.2–1.6 (m, 5 H, CH piperidine), 1.95 (bt, 2 H, 2 H_a piperidine), 2.1 (m, 2 H, CH_2), 2.6 (m, 4 H, 2 CH_2), 2.7 (bt, 2 H, CH_2N), 2.9 (bd, 2 H, 2 H_e piperidine), 3.6 (bt, 2 H, CH_2N), 3.8 (bt, 2 H, CH_2N), 6.7–6.9 (m, 4 H, H arom and indole), 7.2 (bs, 1 H, H indole), 7.25 (dd, 1 H, H arom), 7.35 (dd, 1 H, H indole), 10.9 (bs, 1 H, NH); MS m/z 468 (M^+). Anal. ($C_{25}H_{29}FN_4O_2S$) C, H, N, S.

1-[2-[4-((5-Fluoro-1H-indol-3-yl)methyl)-1-piperidinyl]ethyl]-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]quinoline (25). This compound was prepared in 28% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from acetonitrile, mp 177 °C) from 1-(2-chloroethyl)-2-oxo-1,2,5,6-tetrahydro-4H-imidazo[4,5,1-ij]-quinoline and 1: NMR ($CDCl_3$, 200 MHz) δ 1.3–1.7 (m, 5 H, CH piperidine), 2.1 (m, 4 H, 2 CH_2), 2.65 (m, 4 H, 2 CH_2), 2.8 (t, 2 H, CH_2N), 3.0 (bd, 2 H, 2 H_e piperidine), 3.8 (t, 2 H, CH_2N), 4.05 (t, 2 H, CH_2N), 6.9 (m, 4 H, H indole and arom), 7.25 (m, 3 H, H indole and arom), 8.25 (bs, 1 H, NH); MS m/z 432 (M^+). Anal. ($C_{26}H_{29}FN_4O$) C, H, N.

N-[2-[4-((5-Fluoro-1H-indol-3-yl)methyl)-1-piperidinyl]ethyl]-N-(1-naphthyl)methanesulfonamide (26). This compound was prepared in 26% yield as a solid (after flash chromatography on silica gel with ethyl acetate as eluent and recrystallization from 2-propanol, mp 163 °C) from N-(2-chloroethyl)-N-(1-naphthyl)methanesulfonamide and 1: NMR ($CDCl_3$, 200 MHz) δ 1.4–1.8 (m, 5 H, CH piperidine), 2.0 (m, 2 H, 2 H_a piperidine), 2.5 (m, 2 H, CH_2N), 2.7 (d, 2 H, CH_2), 2.9 (bd, 2 H, 2 H_e piperidine), 3.2 (s, 3 H, CH_3), 3.7 (m, 1 H, CH_2N), 4.2 (m, 1 H, CH_2N), 7.0 (m, 2 H, H indole), 7.2 (m, 2 H, H indole), 7.5 (m, 4 H, H arom), 7.9 (m, 2 H, H arom), 8.0 (bs, 1 H, NH), 8.2 (bd, 1 H, H arom); MS m/z 479 (M^+). Anal. ($C_{27}H_{30}FN_3O_2S$) C, H, N, S; C: calcd, 67.62; found, 68.1.

N-[2-[4-((5-Fluoro-1H-indol-3-yl)methyl)-1-piperidinyl]ethyl]-N-methyl-2-naphthalenesulfonamide (27). This compound was prepared in 26% yield as a solid (after flash chromatography on silica gel with ethyl acetate and recrystallization from acetonitrile, mp 146 °C) from N-(2-chloroethyl)-N-methyl-2-naphthalenesulfonamide and 1: NMR ($CDCl_3$, 300 MHz) δ 1.3–1.7 (m, 5 H, CH piperidine), 2.0 (bt, 2 H, 2 H_a piperidine), 2.6 (t, 2 H, CH_2N), 2.65 (d, 2 H, CH_2), 2.9 (m, 5 H, CH_3 and 2 H_e piperidine), 3.3 (t, 2 H, CH_2N), 6.95 (ddd, 1 H, H indole), 7.0 (bs, 1 H, H indole), 7.2–8.0 (m, 9 H, H arom and indole), 8.4 (bs, 1 H, NH); MS m/z 479 (M^+). Anal. ($C_{27}H_{30}FN_3O_2S$) C, H, N, S.

6-[2-[4-((5-Fluoro-1H-indol-3-yl)methyl)-1-piperidinyl]ethyl]-6H-dibenz[ce]-1,2-thiazine 5,5-Dioxide (28). This compound was prepared in 67% yield as an oil (after flash chromatography on silica gel with 9:1 dichloromethane/MeOH as eluent, oxalate salt mp 130 °C) from 6-(2-chloroethyl)-6H-dibenz[ce]-1,2-thiazine 5,5-dioxide and 1: NMR (DMSO, 300 MHz) (oxalate salt) δ 0.8 (bs, 2 H, CH piperidine), 1.5 (bd, 3 H, CH piperidine), 2.2 (bs, 2 H, CH_2), 2.5–2.8 (m, 4 H, 2 CH_2N), 4.1 (bt, 2 H, CH_2N), 6.8 (ddd, 1 H, H indole), 7.1 (bs, 1 H, H indole), 7.15 (dd, 1 H, H arom) 7.3 (m, 2 H, H indole and arom), 7.5 (m, 3 H, H indole and arom), 7.7 (t, 1 H, H arom) 7.8 (d, 1 H, H arom), 8.1 (m, 2 H, H arom), 10.9 (bs, 1 H, NH); MS m/z 489 (M^+). Anal. ($C_{28}H_{28}FN_3O_2S \cdot C_2H_2O_4$) C, H, N, S.

Biological Methods. Membrane Preparation. Male Sprague–Dawley rats (200–250 g) were killed by decapitation and their brains rapidly removed onto 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 50000g 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. Protein content was measured according to the BCA method[22] using bovine serum albumin as the standard.

[3H]Paroxetine Binding Assay. The affinity of the different compounds for the 5HT uptake site was assessed using the [3H]-paroxetine binding assay described by Habert et al.[4] Aliquots (1 mL) of cortical membranes at a protein concentration of 0.07 mg mL^{-1} in Tris-HCl buffer containing 120 mM NaCl and 5 mM KCl were incubated for 90 min at 25 °C with the compound of interest or with 10^{-6} M indalpine (to define the nonspecific binding) in the presence of [3H]paroxetine (final concentration 0.2 nM). The binding interaction was terminated by filtration across Whatman GF/C glass fibre filters using a Skatron cell harvester and followed by three 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 indalpine. 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 curve-fitting procedure to a simple Langmuir isotherm performed on an IBM-PC computer.[23]

5HT$_2$ binding assay. The affinity of the different compound for 5-HT_2 receptors was assessed using the [3H]ketanserin binding assay described by Leysen et al.[13] Aliquots (1 mL) of cortical membranes at a protein concentration of 0.15 mg mL^{-1} in Tris-HCl buffer 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 [3H]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 scintilland (Beckman).

The specific binding was defined as that displaceable by 10^{-6} 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 curve-fitting procedure to a simple Langmuir isotherm performed on an IBM-PC computer.[23]

α_1-Adrenoceptor Binding Assay. This assay was carried out according to the method described by Greengrass and Bremner,[14] 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 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 using the binding of [^{3}H]-spiperone to rat striatal membranes as described by Urwyler and Coward.[15] Aliquots (1.2 mL) of striatal membranes at a protein concentration of 0.05 mg mL^{-1} in Tris-HCl buffer containing NaCl (150 mM), cinanserin (10^{-6} M), and prazosin (10^{-6} M) were incubated at 25 °C with the compound of interest or with 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.

Potentiation of DL-5-HTP-Induced Head Twitches in Mice. The procedure was adapted from that described by Corne et al. (1963).[12] Male and female mice (CD_1, Crl. CD^{TH} (1CR), Charles River, France), weighing 20.24 g, were used. At t = 0, the compound to be studied or its vehicle was orally or subcutaneously administrated (25 mL/kg; six animals per dose level). At t = 1 h for subcutaneous administration, or 1 h 30 min for oral administration, the mice received an intraperitoneal injection of DL-5-HTP (100 mg/kg; 50 mL/kg). The mice were then placed in individual observation chambers (13 × 13 × 12.5 cm) immediately following DL-5-HTP injection, and 15 min later the number of mice exhibiting at least one head twitch over a 2-min period was recorded.

The ED_{50} value (dose which induced head twitches in 50% of animals) was calculated by the Litchfield and Wilcoxon's method (1949).[24]

Acknowledgment. We were indebted to M. Vuilhorgne and colleagues for analysis assistance.

References

(1) Wong, D. T.; Bymaster, F. P.; Horng, J. S.; Molloy, B. B. A new selective inhibitor for uptake of serotonin into synaptosomes of rat brain: (p-Trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. *J. Pharmacol. Exp. Ther.* **1975**, *193*, 804–811.

(2) Le Fur, G.; Uzan, A. Effects of 4-(3-indolylalkyl)piperidine derivatives on uptake and release of noradrenaline, dopamine and 5-hydroxytryptamine in rat brain synaptosomes, rat heart and human blood platelets. *Biochem. Pharmacol.* **1977**, *26*, 497–503.

(3) (a) Heel, R. C.; Morley, P. A.; Carmine, R. N.; Speight, T. M.; Avery, G. S. Zimelidine: A review of its pharmacological properties and therapeutic efficacity in depressive illness. *Drugs* **1982**, *24*, 169–206. (b) Penfield, P.; Ward, A. Fluvoxamine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacity in depressive illness. *Drugs* **1986**, *32*, 313–334. (c) Shopsin, B.; Cassano, G. B.; Conti, L. An overview of new "second generation" antidepressant compounds: Research and treatment implications. In *Antidepressants: Neurochemical and Clinical Perspectives*; Enna, S. J., Malik, J. B., Richelson, E., eds.; New York: Raven Press, 1981; pp 219–251.

(4) Habert, E.; Graham, D.; Tahrahoui, L.; Claustre, Y.; Langer, S. Z. Characterization of [^{3}H] paroxetine binding to rat cortical membranes. *Eur. J. Pharmacol.* **1985**, *118*, 107–114.

(5) Malleron, J.-L.; Comte, M.-T.; Gueremy, C.; Peyronel, J.-F.; Truchon, A.; Blanchard, J.-C.; Doble, A.; Piot, O.; Zundel, J.-L. Naphtosultam Derivatives: a New Class of Potent and Selective 5-HT_2 Antagonists. *J. Med. Chem.* **1991**, *34*, 2477–2483.

(6) Guillaume, J.; Dumont, C.; Laurent, J.; Nedelec, L. *Eur. J. Med. Chem.* **1987**, *22*, 33–43.

(7) Bergmann, J. The Reaction of N-Acylpyridinium Salts with Indole. *J. Heterocycl. Chem.* **1970**, 1071–1076.

(8) Rhône-Poulenc Santé, EP 42322.

(9) (a) Gray, A. P.; Kraus, H. The catalytic hydrogenation of indolylethylpyridines. 4-(Indolylethyl)-1-aralkylpiperidine as potent analgesics. *J. Org. Chem.* **1961**, *26*, 3368–3373. (b) Gueremy, C.; Audiau, F.; Champseix, A.; Uzan, A.; Le Fur G.; Rataud, J. 3-(4-Piperidinylalkyl)indoles, selective inhibitors of neuronal 5-hydroxytryptamine uptake. *J. Med. Chem.* **1980**, *23*, 1306–1310.

(10) (a) Runti, C. S. *Gazz. Chim. Ital.* **1951**, *81*, 613–620. (b) Stoppani, A. O. M. Synthetic trypanocides: growth-inhibiting properties of new 1,2,3,4-tetrahydrocarbazoles on Trypanosoma cruzi. *Rev. Argent. Microbiol.* **1987**, *19*, 121–124.

(11) Eenkhoorn, J. A.; Osmonde da Silva, S.; Snieckus, V. The Wittig reaction of indole-2-methyltriphenylphosphonium iodide, with 4-piperidone derivatives and aromatic aldehydes. *Can. J. Chem.* **1973**, *51*, 792–810.

(12) Corne, S. J.; Pickering, R. W.; Warner, B. T. A method for assessing the effects of drugs on the central actions of 5-hydroxytryptamine. *Br. J. Pharmacol.* **1963**, *20*, 106–120.

(13) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. [^{3}H]-Ketanserin (R 41468), a selective [^{3}H]-ligand for serotonin 2 receptor binding sites. Binding properties, brain distribution and functional role. *Mol. Pharmacol.* **1982**, *21*, 301–314.

(14) Greengrass, P.; Bremner, R. Binding characteristics of [^{3}H]-prazosin to rat brain α-adrenergic receptors. *Eur. J. Pharmacol.* **1979**, *55*, 323–326.

(15) Urwyler, S.; Coward, D. Binding of [^{3}H] spiperone and [^{3}H]-(−)-sulpiride to dopamine D_2 receptors in rat striatal membranes: methodological considerations and demonstration of the identical nature of the binding sites for the two ligands. *Naunyn-Schmiedeberg'ss Arch. Pharmacol.* **1987**, *335*, 115–122.

(16) Reyntgens, A.; Gelderf, Y. F.; Hoppenbrouwers, M.-L. J. A.; Vanden-Bussche, G. Thymosthenic effect of ritanserin (R55667) centrally acting serotonin-S2 receptor blocker. *G. Drug Dev. Res.* **1986**, *8*, 205–211.

(17) Kawase, M.; Sinhababu, A. K.; Borchardt, R. T. Silica Gel Assisted Reductive Cyclization of 2-Nitro-β-piperidinostyrenes, Derived from 2-Nitrotoluenes to Indoles. *J. Heterocycl. Chem.* **1987**, *24*, 1499–1501.

(18) Batcho, A. D.; Leimgruber, W. Indoles from 2-methylnitrobenzenes by condensation with formamide acetals followed by reduction: 4-benzyloxyindole (1H-indole, 4-(phenylmethoxy)-). *Org. Synth.* **1963**, 214–225.

(19) Mignani, S.; Gueremy, Cl.; Malleron, J.-L.; Peyronel, J.-F.; Truchon, A.; Bastart, J.-P.; Leconte, J.-P. 5,6-dihydro-1H,4H-1,2,5-thiadiazolo[4,3,2-ij] quinoline-2,2-dioxide: a New N,N'-Cyclic Sulfamide. *Heterocycles* **1992**, *34*, 907–910.

(20) Poludnenko, V. G.; Simonov, A. M. Derivatives of 5,6-dihydro-4,4-imidazo[4,5,1-ij]quinoline. I. Synthesis and reactions of 2-amino derivatives. *Khim. Geterotsikl.* **1970**, *10*, 1410–1413; *Chem. Abstr.* **1970**, *74*, 53657d.

(21) Ullmann, F.; Gross, C. *Chem. Ber.* **1910**, *43*, 2694–2704.

(22) Smith, P. K.; Krohn, R. I.; Hermanson, G. T.; Mallia, A. K.; Gartner, F. H.; Provenzano, M. D.; Fujimoto, E. K.; Gocke, N. M.; Olson, B. J.; Klenck, D. C. Measurement of protein with bicinchoninic acid. *Anal. Biochem.* **1985**, *150*, 76–85.

(23) McPherson, G. A. Analysis of radioligand binding experiments. A collection of computer programs for the IBM PC. *J. Pharmacol. Meth.* **1985**, *14*, 213–228.

(24) Litchfield, J. T.; Wilcoxon, F. A simplified method of evaluating dose-effect experiments. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99–113.