(Phenylpiperazinyl-butyl)oxindoles as Selective 5-HT$_7$ Receptor Antagonists

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A series of potent 5-hydroxytryptamine$_7$ (5-HT$_7$) ligands has been synthesized that contain a 1,3-dihydro-2*H*-indol-2-one (oxindole) skeleton. The binding of these compounds to the 5-HT$_7$ and 5-HT$_{1A}$ receptors was measured. Despite the structural similarity of these two serotonin receptor subtypes, several derivatives exhibited a high selectivity to the 5-HT$_7$ receptor. According to the structure–activity relationship observations, compounds unsubstituted at the oxindole nitrogen atom and containing a tetramethylene spacer between the oxindole skeleton and the basic nitrogen atom are the most potent ligands. Concerning the basic group, besides the moieties of the 4-phenylpiperazine type, halophenyl-1,2,3,6-tetrahydropyridines also proved to be 5-HT$_7$ receptor–ligands. Because of halogen substitution on the aromatic rings, good metabolic stability could be achieved. A representative of the family, 3-{4-[4-(4-chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-6-fluoro-1,3-dihydro-2*H*-indol-2-one (**9e′**) exhibited selective 5-HT$_7$ antagonist activity (K_i = 0.79 nM). The in vivo pharmacological potencies of these 5-HT$_7$ receptor–ligands were estimated by the conflict drinking (Vogel) and the light−dark anxiolytic tests.

Introduction

The 5-HT$_7$ receptor is the last addition to the serotonin subfamily of G-protein coupled receptors.[1,2] Although the functional significance of this receptor is largely unknown, several reports have associated the human 5-HT$_7$ receptor with a variety of CNS[a] functions and disorders such as schizophrenia,[3] depression,[4–7] epilepsy,[8] migraine,[9,10] and control of circadian rhythm.[11,12] Therefore, the 5-HT$_7$ receptor may be a novel and valuable drug target, so the development of its potent ligands is of key importance.

In recent years, some selective 5-HT$_7$ receptor antagonists have been reported.[13–18] Also, papers have been published on selective[15,19] and nonselective agonists[20,21] and partial agonists at the 5-HT$_7$ receptor.[15,19,22] However, the number of compounds reported in the literature is still quite low. Additionally, some of the potent compounds caused strong side-effects (e.g., blood pressure and heart rate changes[20]) or showed poor metabolic stability in animal experiments.

Kikuchi et al. have achieved remarkable success during the study of the tetrahydrobenzindole family and patented these compounds as agents against depression and anxiety.[23] The first representatives of this family of compounds showed high affinity for the 5-HT$_7$ and also for the 5-HT$_2$ receptors.[23] Later on, the (2-methoxyphenyl)piperazinyl derivative (**1**, Figure 1) proved to be a selective 5-HT$_7$ antagonist (pK_i = 8.67).[24] The selectivity over 5-HT$_2$ and other 5-HT receptors was further increased with fused ring analogues **2** (DR4365) and **3** (DR4446).[25,26] After serious problems with the oral bioavailability of these compounds had been realized, the authors synthesized halogen-substituted derivatives, e.g., **4** (DR4485), with increased in vitro metabolic stability.[27] However, the measured value of bioavailability (18% in rats for **4**) was still quite low.

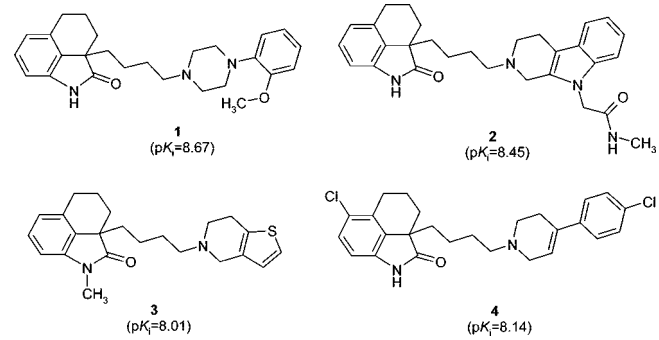

Figure 1. Tetrahydrobenzindole 5-HT$_7$ antagonists.

Chemistry

We aimed at elaborating an efficient synthesis of new compounds containing an oxindole skeleton, which can be formally deduced from the tetrahydrobenzindoles by opening the saturated carbocycle. It was assumed that the replacement of the carbocycle by simple alkyl groups at position 3 of the oxindole scaffold or the complete omission of this carbocycle would result in less rigid and less lipophilic compounds (in order to fulfill the requirements of the Lipinski's Rule), hopefully with strong 5-HT$_7$ receptor affinity and good selectivity over other receptors. We expected to achieve satisfactory metabolic stability in addition to the required receptor binding profile by introducing various substituents to both aromatic rings. Therefore, our aim was to synthesize such substituted derivatives as well.

Despite the structural similarity of oxindoles with tetrahydrobenzindoles, a new synthetic approach was needed. The planned synthetic route to the title compounds made the preparation of 3-alkyloxindole intermediates necessary. We succeeded in elaborating a novel, practical synthesis of these

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[a] Abbreviations: CNS, central nervous system; *n*-BuLi, *n*-butyllithium; Ra−Ni, Raney nickel; cAMP, cyclic adenosine monophosphate; CHO, Chinese hamster ovary; 5-CT, 5-carboxytryptamine; TMS tetramethylsilane; 8-OH-DPAT, 8-hydroxy-2-(di-*n*-propylamino)-tetralin; DMEM, Dulbecco's modified Eagle's medium with Ham's F-12; EIA, enzyme immunoassay; BCA, bicinchoninic acid; Tris, tris(hydroxymethyl)aminomethane.

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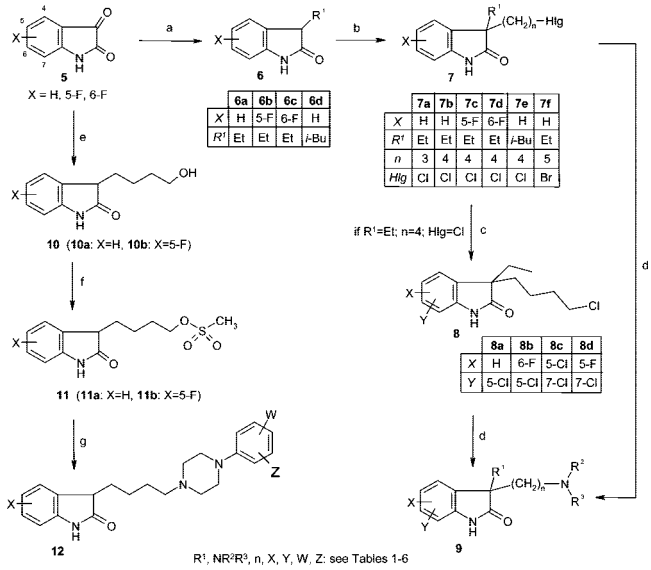
Scheme 1[a]



	6a	6b	6c	6d
X	H	5-F	6-F	H
R1	Et	Et	Et	i-Bu

	7a	7b	7c	7d	7e	7f
X	H	H	5-F	6-F	H	H
R1	Et	Et	Et	Et	i-Bu	Et
n	3	4	4	4	4	5
Hlg	Cl	Cl	Cl	Cl	Cl	Br

	8a	8b	8c	8d
X	H	6-F	5-Cl	5-F
Y	5-Cl	5-Cl	7-Cl	7-Cl

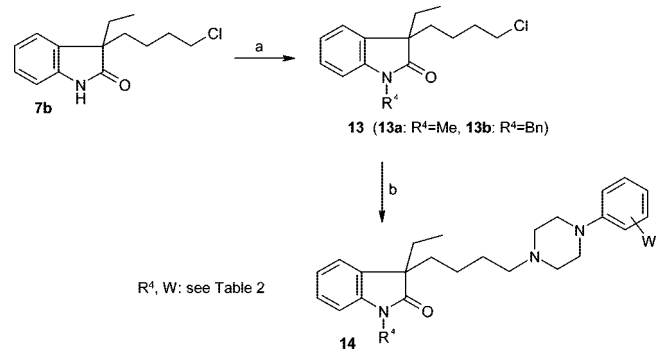
[a] Reagents and conditions: (a) R^{1}OH, Ra−Ni, 15 bar H_2, 180–210 °C, 3–5 h, 71–91%; (b) *n*-BuLi, Br-(CH$_2$)$_n$-Hlg, THF, from −78 °C to rt, 4 h, 82–94%; (c) Chlorination at position 5: SO_2Cl_2, cc. AcOH, 16–18 °C, 2 h, 86–91%; 7-chlorination or 5,7-dichlorination: SO_2Cl_2, cc. AcOH, 60 °C, 3 h, 67–79%; (d) HNR^{2}R^3, Na_2CO_3, in melt, 180 °C, 1–2 h, 32–88%; (e) HO-(CH$_2$)$_4$-OH, Ra−Ni, 15 bar H_2, 190 °C, 4–5 h, 75–81%; (f) $MeSO_2Cl$, Et_3N, THF, from −78 °C to rt, 1–2 h, 81–93%; (g) subst. phenylpiperazine, Na_2CO_3, in melt, 120 °C, 1 h, 52–87%.

compounds, starting from isatins,[28–30] which circumvents the usual problem of *N*-alkylation and *C*(3)-dialkylation of oxindoles.[31–33] By means of this new method, it was possible to synthesize a wide variety of the desired compounds.

The synthetic procedures to the 3-mono and 3,3-disubstituted target compounds are illustrated in Scheme 1. Isatin (**5**, X = H) is commercially available, the substituted isatins (**5**, X = 5-F, 6-F) were synthesized, starting from anilines, by the classical Sandmeyer procedure.[34] The one-pot reductive alkylation of these starting materials (with alcohols, in the presence of Raney nickel) to the corresponding 3-alkyloxindoles (**6**) was performed by the method elaborated at our laboratory.[29] Selective *C*(3)-alkylation of compounds **6** was carried out using ω-dihaloalkanes after deprotonation with *n*-BuLi,[33] resulting in 3-alkyl-3-(ω-haloalkyl)oxindole intermediates (**7**). Chlorination of compounds **7** afforded the corresponding mono and dichloro derivatives **8**. Reaction of **7b** and **7d** with sulfuryl chloride (3 equiv) in glacial acetic acid at 16–18 °C yielded selectively the 5-chloro derivatives (**8a** and **8b**), while at 60 °C, position 7 was also affected, thus 7-chloro-5-fluoro (**7c** → **8d**) or 5,7-dichloro (**7b** → **8c**) analogues were obtained. Finally, replacement of the side-chain halogen atom with various secondary amines led to the target compounds **9**. When necessary, the product was purified by column chromatography. In cases where the base was not a crystalline compound, the oily products were converted into their hydrochloride or oxalate salts.

A different route was applied for the synthesis of the 3-monosubstituted derivatives (Scheme 1). Isatins (**5**) were reductively hydroxyalkylated with butane-1,4-diol in the presence of Raney nickel to afford 3-(4-hydroxybutyl)oxindoles (**10**).[29] Mesylation of compounds **10** with methanesulfonyl chloride to derivatives **11**, followed by treatment with the appropriate arylpiperazines led to the desired compounds **12**. Finally, the crude products were purified by column chromatography and, if necessary, they were converted into their hydrochloric salts.

Scheme 2[a]



[a] Reagents and conditions: (a) NaH, MeI or BnCl, DMF, from 0 °C to rt, 1 h; 76–86%; (b) subst. phenylpiperazine, Na_2CO_3, in melt, 180 °C, 1.5 h, 56–71%.

The corresponding *N*-alkylated derivatives were synthesized by the alkylation of 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) with methyl iodide or benzyl chloride after deprotonation with sodium hydride (Scheme 2). The *N*-alkyl derivatives **13** were then treated with the appropriate arylpiperazines, resulting in compounds **14**.

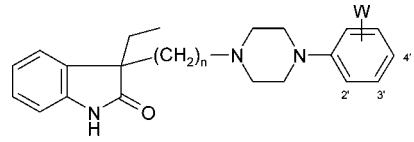
Results and Discussion

The examination of the 5-HT$_7$ receptor binding site revealed its close similarities to that of the 5-HT$_{1A}$ receptor,[35] which can explain dual activity and difficulties in developing selective ligands for the 5-HT$_7$ receptor. Therefore, all the synthesized compounds were primarily evaluated for their binding affinities for human 5-HT$_7$ and rat 5-HT$_{1A}$ receptors, in vitro. The pharmacological activity of the compounds was also determined in two anxiolytic tests, the conflict drinking (Vogel) test[36] in rats and the light−dark test[37] in mice. The minimal effective doses (MED, mg/kg ip.) calculated in these anxiolytic tests are listed in Tables 1−7.

First of all, experiments were performed for the determination of the optimal spacer length. The results in Table 1 led us to the conclusion that among the (3-chlorophenyl)piperazine derivatives, the one with a tetramethylene spacer (n = 4) between the oxindole skeleton and the basic group (**9b**) was superior to other spacer lengths in terms of 5-HT$_7$ receptor affinity and selectivity over 5-HT$_{1A}$ receptor. The derivative with a C_5 alkyl chain (**9c**) demonstrated slightly lower 5-HT$_7$ affinity, while compound **9a**, containing a C_3 spacer, showed very strong undesired binding to the 5-HT$_{1A}$ receptor and was not further evaluated. The corresponding (4-chlorophenyl)piperazine derivatives (**9d**, **9e**) also exhibited high 5-HT$_7$ affinity and confirmed the supremacy of the C_4 spacer. In case of **9d**, strong 5-HT$_7$ receptor binding was accompanied by good in vivo efficacy (Vogel: 10 mg/kg). Concerning the distance between the carbonyl group and the piperazine moiety, our results are in accordance with the observations of Perrone and co-workers:[21] in a structurally related family of compounds, the authors found the same spacer length ideal in terms of selectivity over 5-HT$_{1A}$ receptor.

A short study was conducted regarding the impact of the substitution of the oxindole nitrogen atom on 5-HT$_7$ and 5-HT$_{1A}$ receptor affinities. Considering the affinity data of the two compounds bearing a substituent at the oxindole nitrogen atom (**14a**, **14b**, Table 2), it was demonstrated that substitution at the oxindole nitrogen atom was detrimental: it reduced 5-HT$_7$ affinity and enhanced 5-HT$_{1A}$ receptor binding at the same time. This observation is particularly interesting in comparison with

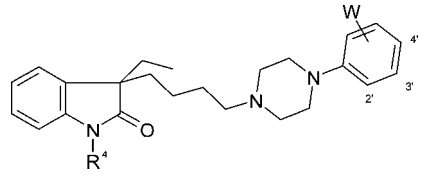
Table 1. Human Recombinant 5-HT$_7$ and Rat 5-HT$_{1A}$ Receptor Affinities of Compounds **9**: The Effect of Spacer Length



compound	*n*	*W*	5-HT$_7$[a] K_i (nM)	5-HT$_{1A}$ % inhibition[a] 10^{-7} M	5-HT$_{1A}$ % inhibition[a] 10^{-8} M	conflict drinking test[b] MED (mg/kg ip)	light−dark test[c] MED (mg/kg ip)
9a	3	3′-Cl	21	91	57	>20	3
9b	4	3′-Cl	0.41	42	11	>20	>10
9c	5	3′-Cl	1.45	43	12	>10	>10
9d	4	4′-Cl	0.38	11	2	10	>10
9e	5	4′-Cl	1.24	11	0	>20	ND[d]

[a] Receptors and radioligands used in binding assays and data analysis: see Experimental Section. [b] A modification of the Vogel[36] method was used for the conflict drinking test in rats, drugs were administered intraperitoneally. For details, see Experimental Section. [c] Testing of drugs in the light−dark test was carried out in mice as described by Costall[37] after intraperitoneal administration of the drugs. For details, see Experimental Section. [d] Not determined.

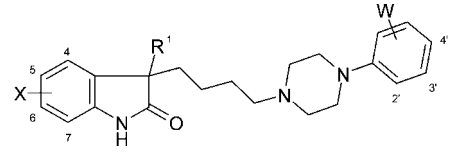
Table 2. Human Recombinant 5-HT$_7$ and Rat 5-HT$_{1A}$ Receptor Affinities of Compounds **9** and **14**: The Effect of Oxindole Nitrogen Substitution



compound	R^4	*W*	5-HT$_7$[a] K_i (nM)	5-HT$_{1A}$ % inhibition[a] 10^{-7} M	5-HT$_{1A}$ % inhibition[a] 10^{-8} M	conflict drinking test[a] MED (mg/kg ip)	light−dark test[a] MED (mg/kg ip)
9f	H	H	2.07	26	6	10	ND[a]
14a	Me	H	33.38	42	12	20	ND
9g	H	2′-MeO	5.38	79	28	10	ND
14b	Bn	2′-MeO	6.57	86	32	>20	ND

[a] See Table 1 for details,

Table 3. Human Recombinant 5-HT$_7$ and Rat 5-HT$_{1A}$ Receptor Affinities of Compounds **9** and **12**: Role of the Substituent at Position 3



compound	R^1	*X*	*W*	5-HT$_7$[a] K_i (nM)	5-HT$_{1A}$ % inhibition[a] 10^{-7} M	5-HT$_{1A}$ % inhibition[a] 10^{-8} M	conflict drinking test[a] MED (mg/kg ip)	light−dark test[a] MED (mg/kg ip)
9h	Et	5-F	3′-Cl	2.11	24	ND[a]	<5	>10
12a	H	5-F	3′-Cl	1.96	43	ND	>20	ND
9i	Et	5-F	4′-F	1.5	7	ND	>20	ND
12b	H	5-F	4′-F	3.4	6	ND	>10	ND
9j	*i*-Bu	H	3′-Cl	1.80	12	ND	10	>10
9b	Et	H	3′-Cl	0.41	42	11	>20	>10
12c	H	H	3′-Cl	0.49	40	9	<5	>10
9d	Et	H	4′-Cl	0.38	11	2	10	>10
12d	H	H	4′-Cl	7.0	10	ND	<2.5	<1
12e	H	5-F	H	44	33	5	<10	ND

[a] See Table 1 for details.

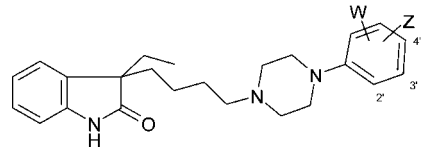
the previous findings in the tetrahydrobenzindole family in which small *N*-alkyl groups increased 5-HT$_7$ receptor binding (see **3**, Figure 1).[26]

In the following experiments, we inquired into the influence of various substituents (R^1 = H, Et, *i*-Bu) at position 3 on 5-HT$_7$ receptor affinity (Table 3). Thus, an answer was sought to the question of how the replacement of the third ring of the tetrahydrobenzindole derivatives (e.g., **1**−**4**) by simple alkyl groups or a hydrogen atom influence 5-HT$_7$ receptor affinity. It was demonstrated that the 3-ethyl derivatives (R^1 = Et) exhibited a slightly more favorable binding profile than the 3-monosubstituted (R^1 = H) analogues. On the other hand, several 3-monosubstituted derivatives (**12c**−**e**) were efficacious in the conflict drinking test. Nevertheless, because of higher metabolic stability, 3,3-disubstituted compounds proved to be more favorable for further development.

When compared with the corresponding 3-isobutyl analogue **9j**, the 3-ethyl compound **9b** proved to be more potent at the 5-HT$_7$ receptor, however, with lower selectivity over the 5-HT$_{1A}$ receptor. The exceedingly high efficacy of several compounds in this series (e.g., **9d**: pK_i = 9.42) showed that the saturated carbocycle of tetrahydrobenzindoles[23−27] is not indispensable for the 5-HT$_7$ receptor binding.

By keeping the spacer length (n = 4) and the alkyl group at position 3 (R^1 = Et) fixed, and by keeping the oxindole nitrogen atom unsubstituted (R^4 = H), further derivatives have been synthesized for the investigation of the role of various substitution patterns at the phenylpiperazine moiety (Table 4). The

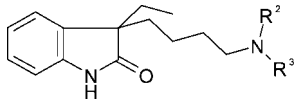
Table 4. Human Recombinant 5-HT$_7$ and Rat 5-HT$_{1A}$ Receptor Affinities of Compounds **9**: The Effects of Various Phenylpiperazine Basic Groups

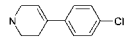
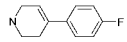
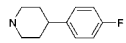
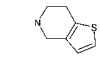
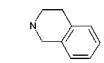
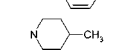


compound	*W*, *Z*	5-HT$_7$[a] K_i (nM)	5-HT$_{1A}$ % inhibition[a] 10^{-7} M	5-HT$_{1A}$ % inhibition[a] 10^{-8} M	conflict drinking test[a] MED (mg/kg ip)	light−dark test[a] MED (mg/kg ip)
9f	H	2.07	26	6	10	ND[a]
9g	2′-MeO	5.38	79	28	10	ND
9k	3′-MeO	2.55	33	6	>20	ND
9l	4′-MeO	25.40	24	3	>20	ND
9m	2′-Cl	5.11	51	9	>20	ND
9b	3′-Cl	0.41	42	11	>20	>10
9d	4′-Cl	0.38	11	2	10	>10
9n	4′-F	0.43	10	12	10	<1
9o	3′,4′-di-Cl	0.63	11	0	>20	ND
9p	3′-Cl-4′-F	0.60	14	0	>20	ND
9q	3′-Cl-4′-Me	0.66	11	0	>20	ND

[a] See Table 1 for details.

Table 5. Human Recombinant 5-HT$_7$ and Rat 5-HT$_{1A}$ Receptor Affinities of Compounds **9**: The Effects of Other Basic Groups



Compound	NR^2R^3	5-HT$_7$[a] K_i (nM)	5-HT$_{1A}$ % inhibition[a] 10^{-7} M	5-HT$_{1A}$ % inhibition[a] 10^{-8} M	Conflict drinking test[b] MED (mg/kg ip.)	Light-dark test[c] MED (mg/kg ip.)
9r		1.02	10	ND[d]	>20	ND
9s		1.19	19	ND	20	ND
9t		5.30	11	ND	20	>10
9u		4.31	29	ND	>20	>10
9v		7.65	52	ND	>20	ND
9w		ND	0	ND	ND	ND

[a] See Table 1 for details. [b] See Table 1 for details. [c] See Table 1 for details. [d] See Table 1 for details.

introduction of a methoxy substituent at position 2 (**9g**) leads to high 5-HT$_7$ receptor affinity, as described for other 5-HT$_7$ ligands containing a 2-methoxyphenylpiperazine (2-MPP) unit.[38] Nevertheless, **9g** exhibits a strong 5-HT$_{1A}$ binding as well. A shift of the methoxy group from position 2 to position 3 resulted in a promising derivative (**9 h**), although 3-methoxyphenylpiperazine was described in the literature as a basic group leading to poor 5-HT$_7$ receptor binding.[39] The introduction of a (4-methoxyphenyl)piperazine moiety (**9l**) was detrimental to 5-HT$_7$ receptor affinity. This tendency is in perfect accordance with previous findings.[19,25] On the other hand, contrary to literature data,[25] we have found that not only the monosubstituted derivatives (e.g., **9b**, **9d**) but also some disubstituted analogues (**9o**, **9p**) exhibited high 5-HT$_7$ receptor binding potency in this series. Para-halogenated phenylpiperazine derivatives (**9d**, **9n**) showed very strong 5-HT$_7$ receptor affinity and good activity in vivo. In summary, phenylpiperazines bearing a substituent at the meta or para position were superior to the ortho-substituted analogues, which was not the case in a structurally related family of compounds, described recently.[40]

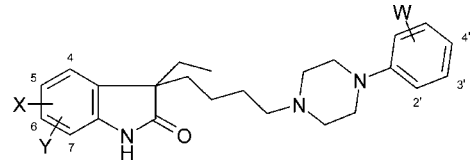
In addition to phenylpiperazine-type basic groups, some piperidine derivatives have also been investigated (Table 5), which facilitated 5-HT$_7$ receptor binding previously in other laboratories. Halophenyl-1,2,3,6-tetrahydropyridines (**9r**, **9s**),[27] 4-fluorophenylpiperidine (**9t**), tetrahydrothienopyridine (**9u**),[26] and tetrahydroisoquinoline (**9v**)[26] have proved to be efficient in our hands as well. The omission of the aromatic ring at this position and its replacement by a methyl group (**9w**)[16] resulted in a significant reduction in the 5-HT$_7$ affinity in accordance with former results.[21,24,38,41] Nonetheless, the increased rigidity of the structure, caused by fused rings (**9u**, **9v**) or the extension of the conjugated π-electron system (**9r**, **9s**), which led to an enhanced potency among the tetrahydrobenzindoles,[25,26] was not superior to simple phenylpiperazines in our case.

With the above information in hand, 3- and 4-chlorophenylpiperazine moieties were used in the studies to evaluate the effect of further substitution patterns at the oxindole benzene ring on the receptor binding. The introduction of halogen substituents at the oxindole carbocycle (Table 6) was expected to maintain 5-HT$_7$ receptor affinity and at the same time to increase the in vitro metabolic stability in rats, which was not satisfactory in the case of the unsubstituted analogues (e.g., **9b**: 4%, **9d**: 9%). Indeed, several substituted derivatives demonstrated improved stability: e.g. **12b**: 40%, **9h′**: 76%.

Among the several compounds exhibiting high 5-HT$_7$ receptor affinity, combined with good selectivity over the 5-HT$_{1A}$ receptor, **9e′**, **12d**, and **12e** were selected for further evaluation. The detailed study showed that **9e′** had high selectivity over a series of other receptors (Table 7). Despite the strong 5-HT$_7$ receptor binding, **9e′** was inactive in both anxiolytic tests. Nevertheless, **12d** and **12e** exhibited lower 5-HT$_7$ affinities, but demonstrated outstanding in vivo activity. The remarkable anxiolytic potency observed for **12d** and **12e** may be due to a multireceptorial action involving not only 5-HT$_7$ but also 5-HT$_{2A}$ receptor and α_1 adrenoceptor. In fact, several lines of evidence suggest the importance of these receptors or their interaction in the mediation of anxiety.[42,43] Receptor binding affinities of **9e′**, **12d**, and **12e** were also determined on α_2- and β-adrenoceptors and other G-protein coupled receptors, however, these compounds exhibited only unsubstantially low displacement when applied in a concentration of 1 μmol/L.

The effects of 9 EGIS compounds, including **9e′**, **12d**, and **12e**, on the intracellular cAMP levels have been studied in CHO cells stably expressing the human 5-HT$_{7A}$ receptor. The drugs

Table 6. Human Recombinant 5-HT_7 and Rat 5-HT_{1A} Receptor Affinities of Compounds **9**: The Effects of Various Substitution Patterns on the Oxindole Carbocycle



compound	X	Y	W	5-HT_7[a] K_i (nM)	5-HT_{1A} % inhibition[a] 10^{-7} M	5-HT_{1A} % inhibition[a] 10^{-8} M	conflict drinking test[a] MED (mg/kg ip)	light−dark test[a] MED (mg/kg ip)
9x	5-Cl	H	3′-Cl	8.27	18	ND[a]	>20	ND
9y	6-F	H	3′-Cl	0.67	37	11	>20	ND
9z	5-Cl	6-F	3′-Cl	9.07	16	ND	20	ND
9a′	5-F	7-Cl	3′-Cl	4.75	31	ND	>20	>10
9b′	5-Cl	7-Cl	3′-Cl	9.46	7	ND	>20	ND
9c′	5-F	H	4′-Cl	2.81	9	ND	>20	>10
9d′	5-Cl	H	4′-Cl	3.72	0	ND	>20	ND
9e′	6-F	H	4′-Cl	0.79	9	0	>20	>10
9f′	5-Cl	6-F	4′-Cl	6.99	0	ND	ND	ND
9g′	5-F	7-Cl	4′-Cl	5.97	0	ND	>20	ND
9h′	5-Cl	7-Cl	4′-Cl	10.13	5	ND	<5	<1

[a] See Table 1 for details.

Table 7. Receptor Binding Profile and Anxiolytic Effects of **9e′**, **12d**, and **12e**

receptor/in vivo test	K_i[a] (nM) or MED (mg/kg ip) **9e′**	**12d**	**12e**
5-HT_{1A}	1610	1800	150
5-HT_{2A}	19.4	17.5	55
5-HT_{2C}	358	690	1500
5-HT_6	186.5	580	1800
5-HT_7	0.79	7.0	44
α_1	71.3	42	20
D_1	3360	2400	1900
D_2	950	960	330
conflict drinking test[a]	>20	<2.5	<10
light−dark test[a]	>10	<1	>10

[a] See Table 1 for details.

were added at 10 nM or 1 μM concentrations in the presence of 10 nM 5-CT, or at 1 μM in the absence of 5-CT and cAMP levels, were measured. On its own, 10 nM 5-CT produced an approximately 30-fold elevation in cAMP levels (Figure 2). None of the compounds produced a significant change in the cAMP levels at 1 μM concentration when they were incubated in the absence of 5-CT. However, all EGIS compounds and the reference SB-269970[44] antagonized the effect of 10 nM 5-CT by more than 95%. The EGIS compounds behaved differently when incubated at 10 nM concentration prior to treatment with 10 nM 5-CT. At 10 nM concentration, SB-269970 and **12c**−**d** inhibited the 5-CT-induced elevation in cAMP level by approximately 80%. **12e**, **9e′**, **9q**, and **9b** inhibited cAMP level elevation by 40−65%, and **9c** by 20%. **9j** and **9r** were ineffective. Overall, it can be stated that all the compounds studied are antagonists at the human 5-HT_{7A} receptor, with the following order of potency: **12d** = **12c** > **12e** > **9e′** ≈ **9b** > **9c** > **9r** ≈ **9j**.

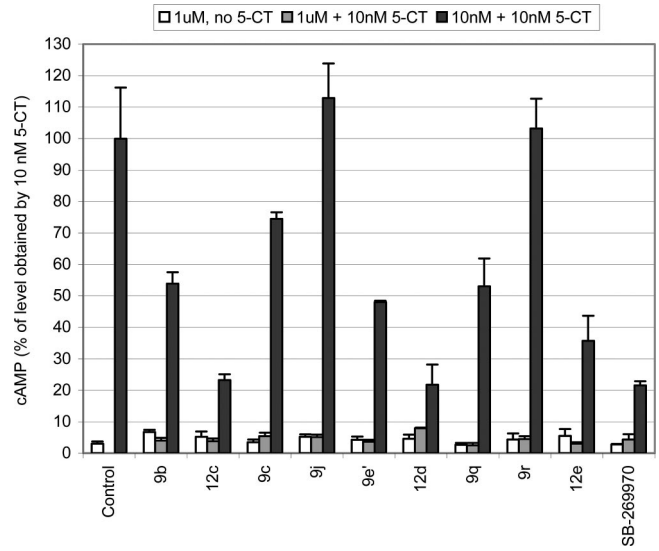


Figure 2. Effect of incubation with 1 μM EGIS compounds on cAMP levels in uninduced CHO cells stably expressing the human 5-HT_{7A} receptor, and the effect of a preincubation with 1 μM or 10 nM EGIS compounds on cAMP levels induced by an incubation with 10 nM 5-CT. The average cAMP level of control cells was 20 ± 8 fmol/μg protein, the average cAMP level of cells induced by 10 nM 5-CT was 592 ± 232 fmol/μg protein (taken as 100%) in six independent experiments. For methodological details, see Experimental Section.

Conclusion

The present study describes the identification of new, potent 5-HT_7 receptor–ligands, which contain an oxindole skeleton. Besides the compounds presented here, more than 200 other representatives of this family have also been synthesized.[45] The binding of these compounds to the 5-HT_7 and 5-HT_{1A} receptors was measured, and their in vivo pharmacological activity was studied in two anxiolytic tests. Several members of this family proved to be highly potent 5-HT_7 receptor antagonists (e.g., **9d**: $pK_i = 9.42$), some of them also with good selectivity over other receptors. While possessing an oxindole scaffold, the most potent representatives can be considered long-chain arylpiperazines at the same time, which is a family of high importance among 5-HT_7 receptor–ligands.[19,21,46–49] The 5-HT_7 receptor affinity of the compounds also made certain conclusions possible in terms of structure−affinity relationships. Nonetheless, only a limited correlation was found between the affinity of the compounds for the 5-HT_7 receptor and their in vivo activity. Further studies on the enantiomeric separation and on more detailed in vivo effects of the above compounds are in progress.

Experimental Section

Chemistry. All melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on

a Varian Unity Inova 400 (400 and 101 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or 500 (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively) spectrometer using TMS as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer. All reactions were followed by analytical thin layer chromatography (TLC) on silica gel 60 F_{254}. Degussa's activated Raney nickel catalyst in water was used in the reactions.

General Procedure A: Preparation of 3-Alkyl-3-(ω-haloalkyl)-oxindoles (7). To a mixture of n-BuLi in hexane (2.5 M, 200 mL, 0.50 mol) and THF (200 mL), the solution of the appropriate 3-alkyloxindole[29] (**6**, 0.20 mol) in THF (250 mL) was added dropwise at –78 °C, under argon atmosphere. Then the appropriate α,ω-dihaloalkane (0.50 mol) was added dropwise, and the reaction mixture was allowed to warm to room temperature. The stirring was continued for 3 additional hours, the mixture was quenched with ethanol (20 mL), and the solvents were evaporated. The residue was taken up in ethyl acetate and extracted with water. The organic layer was dried over Na_2SO_4 and evaporated. The oily residue crystallized upon trituration with hexane (200 mL). The white solid was filtered, washed with hexane, and dried. The products were used without further purification. Analytical samples were obtained by recrystallization from the indicated sovents.

3-(3-Chloropropyl)-3-ethyl-1,3-dihydro-2*H*-indol-2-one (7a). The title compound was prepared according to the general procedure A, starting from 3-ethyloxindole (**6a**) and 1-bromo-3-chloropropane. Yield: 86%, mp 91–93 °C (hexane). IR (KBr): 3183, 1701, 751 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (br, 1H, NH), 7.23 (dt, 1H, J = 7.7, 1.3 Hz, H-6), 7.14 (d, 1H, J = 6.8 Hz, H-4), 7.06 (dt, 1H, J = 7.4, 0.9 Hz, H-5), 6.95 (d, 1H, J = 7.7 Hz, H-7), 3.48–3.36 (m, 2H, CH_2Cl), 2.02–1.93 (m, 3H), 1.85–1.78 (m, 1H), 1.66–1.54 (m, 1H), 1.44–1.30 (m, 1H), 0.65 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 182.6, 141.3, 132.0, 127.9, 123.0, 122.6, 109.8, 53.7, 44.8, 34.8, 31.0, 27.5, 8.5. Anal. ($C_{13}H_{16}ClNO$) C, H, N, Cl.

3-(4-Chlorobutyl)-3-ethyl-1,3-dihydro-2*H*-indol-2-one (7b). The title compound was prepared according to the general procedure A, starting from 3-ethyloxindole (**6a**) and 1-bromo-4-chlorobutane. Yield: 94%, mp 104–105 °C (hexane−ethyl acetate). IR (KBr): 3181, 2941, 1700, 1306, 755 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.57 (br, 1H, NH), 7.21 (dt, 1H, J = 7.6, 1.5 Hz, H-6), 7.12 (d, 1H, J = 7.4 Hz, H-4), 7.06 (dt, 1H, J = 7.5, 1.0 Hz, H-5), 6.92 (d, 1H, J = 7.7 Hz, H-7), 3.39 (t, 2H, J = 6.7 Hz, CH_2Cl), 1.96–1.84 (m, 2H, CH_2), 1.83–1.74 (m, 2H, CH_2), 1.74–1.60 (m, 2H, CH_2), 1.24–1.18 (m, 1H), 1.08–1.03 (m, 1H), 0.64 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 182.4, 141.2, 132.3, 127.7, 123.0, 122.5, 109.6, 54.1, 44.4, 36.8, 32.7, 31.0, 21.8, 8.5. Anal. ($C_{14}H_{18}ClNO$) C, H, N, Cl.

General Procedure B: 1-Alkylation of 3-(4-Chlorobutyl)-3-ethyloxindole (7b). NaH (55% suspension; 0.79 g, 18.0 mmol) was suspended in DMF (20 mL) under argon atmosphere. To the ice-cooled suspension, the solution of 3-(4-chlorobutyl)-3-ethyloxindole (**7b**, 3.78 g, 15.0 mmol) in DMF (15 mL) was added dropwise over a period of 15 min. Then the solution of the alkylating agent (methyl iodide or benzyl chloride, 18.0 mmol) was added dropwise. After the addition, the solution was allowed to room temperature, stirred for 1 h, and poured onto ice. After extraction with diethyl ether (30 mL), the organic layer was washed with water (30 mL), dried over Na_2SO_4, and evaporated. The white crystalline compounds were used without further purification. Analytical samples were obtained after a recrystallization from hexane.

3-(4-Chlorobutyl)-3-ethyl-1-methyl-1,3-dihydro-2*H*-indol-2-one (13a). The title compound was prepared according to the general procedure B, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and methyl iodide. Yield: 76%, mp 62–63 °C (hexane). IR (KBr): 3385, 2959, 1700, 763 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.28 (dt, 1H, J = 7.7, 1.3 Hz, H-6), 7.14 (dd, 1H, J = 7.3, 0.8 Hz, H-4), 7.08 (dt, 1H, J = 7.5, 0.9 Hz, H-5), 6.86 (d, 1H, J = 7.8 Hz, H-7), 3.38 (m, 2H, CH_2Cl), 1.91 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 1.64 (m, 2H), 1.09 (m, 1H), 0.99 (m, 1H), 0.55 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 179.9, 144.1, 131.9, 127.7, 122.6, 122.5, 107.8, 53.5, 44.5, 36.8, 32.7, 31.0, 25.6, 21.8, 8.5. Anal. ($C_{15}H_{20}ClNO$) C, H, N, Cl.

General Procedure C: 5-Chlorination of 3-Alkyl-3-(ω-haloalkyl)oxindoles (7). The corresponding 3-alkyl-3-(ω-haloalkyl)oxindole (**7**, 5.0 mmol) was dissolved in glacial acetic acid (15 mL), the solution was cooled to 16–18 °C, then the solution of sulfuryl chloride (0.5 mL, 5.7 mmol) in glacial acetic acid (85 mL) was added dropwise, maintaining the temperature below 20 °C. The reaction mixture was stirred for a further 2 h at this temperature, then it was poured onto ice under stirring. The white solid was filtered, washed with water and hexane, and dried. The products were used without further purification. Analytical samples were obtained by recrystallization from the indicated solvents.

5-Chloro-3-(4-chlorobutyl)-3-ethyl-1,3-dihydro-2*H*-indol-2-one (8a). The title compound was prepared according to the general procedure C, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**). Yield: 86%, mp 116–117 °C (hexane−ethyl acetate). IR (KBr): 3285, 1717, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.72 (br, 1H, NH), 7.15 (dd, 1H, J = 8.2, 2.1 Hz, H-6), 7.12 (d, 1H, J = 2.1 Hz, H-4), 6.86 (d, 1H, J = 8.2 Hz, H-7), 3.41 (t, 2H, J = 6.7 Hz, CH_2Cl), 2.00–1.86 (m, 2H, CH_2), 1.84–1.74 (m, 2H, CH_2), 1.74–1.60 (m, 2H), 1.29–1.15 (m, 1H), 1.12–0.95 (m, 1H), 0.65 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 182.0, 139.8, 134.2, 127.9, 127.8, 123.4, 110.7, 54.5, 44.4, 36.8, 32.5, 31.0, 21.7, 8.5. Anal. ($C_{14}H_{17}Cl_2NO$) C, H, N, Cl.

5,7-Dichloro-3-(4-chlorobutyl)-3-ethyl-1,3-dihydro-2*H*-indol-2-one (8c). 3-(4-Chlorobutyl)-3-ethyloxindole (**7b**, 10.06 g, 40 mmol) was dissolved in glacial acetic acid (80 mL). Sulfuryl chloride (9.6 mL, 120 mmol) was added dropwise at ambient temperature, then the solution was stirred at 60 °C for 3 h. The reaction mixture was allowed to cool to room temperature, poured onto ice, and extracted with diethyl ether. The organic layer was extracted twice with 10% NaOH solution, dried over Na_2SO_4, and evaporated. The residue crystallized upon treatment with hexane. It was triturated in hexane, filtered, washed with hexane, and dried. The product was used without further purification. An analytical sample was obtained by recrystallization from hexane. Yield: 67%, mp 65–67 °C (hexane). IR (KBr): 3165, 2964, 1713, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.38 (br, 1H, NH), 7.20 (d, 1H, J = 1.9 Hz, H-6), 6.97 (d, 1H, J = 1.8 Hz, H-4), 3.38 (t, 2H, J = 6.7 Hz, CH_2Cl), 1.95–1.84 (m, 2H, CH_2), 1.76–1.60 (m, 4H, 2 × CH_2), 1.19–1.16 (m, 1H), 1.04–0.96 (m, 1H), 0.62 (t, 3H, J = 7.4 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 180.5, 137.7, 135.1, 128.3, 127.6, 121.9, 115.7, 55.7, 44.3, 36.8, 32.5, 31.0, 21.7, 8.5. Anal. ($C_{14}H_{16}Cl_3NO$) C, H, N, Cl.

General Procedure D: Mesylation of 3-(4-Hydroxybutyl)oxindoles (10). The corresponding 3-(4-hydroxybutyl)oxindole[28,29] (**10**, 55 mmol) was dissolved in THF (150 mL). Triethyl amine (15.2 mL, 110 mmol) was added, and the solution was cooled to –78 °C. Methanesulfonyl chloride (8.5 mL, 110 mmol) was added dropwise. After the addition, the reaction mixture was allowed to warm to room temperature and stirred for further 1 h. The white precipitate was filtered off, and the filtrate was evaporated. The residual oil was dissolved in ethyl acetate and extracted with 10 wt % aqueous hydrochloric acid until pH = 5. The organic layer was dried over Na_2SO_4 and evaporated. The brown oily residue crystallized upon treatment with diisopropyl ether. It was triturated with diisopropyl ether (100 mL), filtered, washed with hexane, and dried. The beige solid was recrystallized from the indicated solvent, resulting in white crystals.

Methanesulfonic acid 4-(2-oxo-2,3-dihydro-1*H*-indol-3-yl)-butyl ester (11a). The title compound was prepared according to the general procedure D, starting from 3-(4-hydroxybutyl)oxindole (**10a**). Yield: 93%, mp 84–85 °C (heptane−ethyl acetate). IR (KBr): 3180, 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.33 (1H, s), 7.22 (1H, d, J = 7.1 Hz), 7.21 (1H, t, J = 7.0 Hz), 7.03 (1H, t, J = 7.5 Hz), 6.93 (1H, d, J = 7.6 Hz), 4.19 (2H, t, J = 6.5 Hz), 3.49 (1H, t, J = 6.0 Hz), 2.97 (3H, s), 2.05–1.98 (2H, m), 1.82–1.72 (2H, m) 1.58–1.40 (2H, m). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 180.5,

141.6, 129.1, 127.9, 123.9, 122.3, 109.9, 69.5, 45.7, 37.2, 29.6, 28.9, 21.6. Anal. ($C_{13}H_{17}NO_4S$) C, H, N, S.

General Procedure E: Coupling Reaction of the 3-Alkyl-3-(ω-haloalkyl)oxindole Intermediates (7, 8) or 1,3-Dialkyl-3-(ω-haloalkyl)oxindole Intermediates (13) with the Appropriate Secondary Amines. The melt of the secondary amine (12 mmol) was heated to 180 °C under slow stirring. The appropriate 3-alkyl-3-(ω-haloalkyl)oxindole (**7**, **8**, or **13**; 12 mmol) and sodium carbonate (1.36 g, 12 mmol) were added. After 1 h reaction time, the brown melt was cooled to ambient temperature. Ethyl acetate and water were added, and the layers were separated. The organic layer was dried over $MgSO_4$ and evaporated. The residual oil or solid was purified by column chromatography using ethyl acetate as eluent.

General Procedure E/1. In case the product of the chromatographic purification crystallized upon treatment with diethyl ether, it was triturated in this solvent, filtered, and the solid was recrystallized from the solvent indicated below and dried to give a white crystalline product.

General Procedure E/2. In case the product of the chromatographic purification did not crystallize upon treatment with diethyl ether, it was dissolved in diethyl ether (200 mL), the solid residue was removed by filtration, and a calculated amount (1 equiv) of hydrogen chloride (saturated solution of HCl gas in diethyl ether) was added dropwise, under vigorous stirring. The white precipitate was filtered, washed with diethyl ether and hexane, and dried in vacuo at ambient temperature for 3 h. Where indicated, the obtained hydrochloric salt was recrystallized.

General Procedure E/3. In case the product of the chromatographic purification did not crystallize upon treatment with diethyl ether and it did not give a crystalline hydrochloric acid salt in diethyl ether, it was dissolved in ethyl acetate (100 mL) at 60–65 °C and the solution of oxalic acid dihydrate (1 equiv) in ethyl acetate (50 mL) was added dropwise, keeping the temperature at 60–65 °C during the addition. After the addition, the suspension was cooled to ambient temperature, the white oxalic acid salt was filtered, washed with ethyl acetate, and dried.

3-{4-[4-(3-Chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-1,3-dihydro-2*H*-indol-2-one−H_2O−HCl−Isopropyl Alcohol (1:1:1:1) (9b). The coupling reaction was carried out according to the general procedure E, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 1-(3,4-dichlorophenyl)-piperazine. After cooling the reaction mixture to room temperature, ethyl acetate and aqueous hydrochloric acid (10 wt %, 50 mL) were added and the layers were separated. The organic layer was dried over Na_2SO_4, evaporated, and the beige solid was recrystallized from isopropyl alcohol; mp 109–111 °C (isopropyl alcohol). IR (KBr): 1701, 1180 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.14 (1H, br), 10.44 (1H, s), 7.25 (1H, t, J = 8.2 Hz), 7.22 (1H, d, J = 7.9 Hz), 7.18 (1H, dt, J = 1.2, 7.7 Hz), 7.03 (1H, t, J = 2.1 Hz), 6.99 (1H, dt, J = 0.9, 7.6 Hz), 6.94 (1H, dd, J = 1.9, 8.3 Hz), 6.86 (1H, d, J = 7.8 Hz), 6.86 (1H, d, J = 7.9 Hz), 4.37 (1H, br), 3.84 (2H, br), 3.83–3.75 (1H, m), 3.5–3.3 (4H, br), 3.21 (2H, t), 3.10–2.85 (4H, m), 1–85–1.65 (4H, m), 1.65–1.55 (2H, m), 1.04 (2H, d, J = 6.1 Hz), 1.01–0.94 (1H, m), 0.9–0.7 (1H, m), 0.51 (3H, t, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 180.8, 151.0, 142.7, 134.1, 132.1, 130.8, 127.8, 123.2, 121.8, 119.3, 115.4, 114.3, 109.4, 62.2, 55.1, 53.2, 50.3, 44.9, 36.6, 30.3, 25.7, 23.2, 21.4, 8.6. Anal. ($C_{27}H_{41}Cl_2N_3O_3$) C, H, N, Cl.

3-{5-[4-(3-Chlorophenyl)-piperazin-1-yl]-pentyl}-3-ethyl-1,3-dihydro-2*H*-indol-2-one oxalate (9c). The title compound was prepared according to the general procedure E/3, starting from 3-(5-bromopentyl)-3-ethyloxindole (**7f**) and 1-(3-chlorophenyl)-piperazine. Yield: 57%, mp 127–129 °C. IR (KBr): 3187, 1705, 754 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.35 (1H, s), 8.8–7.4 (2H, m), 7.24 (1H, dt, J = 8.1 Hz), 7.20 (1H, d, J = 7.6 Hz), 7.16 (1H, dt, J = 1.1, 7.7 Hz), 7.00 (1H, t, J = 2.3 Hz), 6.98 (1H, dt, J = 0.9, 7.6 Hz), 6.93 (1H, dd, J = 2.0, 8.4 Hz), 6.84 (2H, d, J = 8.4 Hz), 3.38 (4H, br), 3.07 (4H, br), 2.81 (2H, t, J = 7.9 Hz), 1.80–1.64 (4H, m), 1.50 (2H, quintet, J = 7.5 Hz), 1.15 (2H, quintet, J = 6.8 Hz), 1.04–0.90 (1H, m), 0.90–0.76 (1H, m), 0.50 (3H, t, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 180.9, 164.3, 151.3, 142.7, 134.1, 132.4, 130.7, 127.7, 123.1, 121.6, 119.1, 115.2, 114.2, 109.3, 55.9, 53.2, 50.9, 45.6, 36.9, 30.5, 26.6, 23.8, 23.6, 8.6. Anal. ($C_{27}H_{34}ClN_3O_5$) C: calcd, 62.84; found, 62.43; H, N, Cl.

3-{4-[4-(4-Chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-1,3-dihydro-2*H*-indol-2-one (9d). The title compound was prepared according to the general procedure E/1, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 1-(4-chlorophenyl)-piperazine. Yield: 88%, mp 145–146 °C (hexane−ethyl acetate). IR (KBr): 3163, 1712 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.92 (1H, s), 7.20 (1H, dt, J = 1.4, 7.6 Hz), 7.18 (2H, d, J = 9.2 Hz), 7.12 (1H, dt, J = 0.7, 7.4 Hz), 7.05 (1H, dt, J = 1.0, 7.5 Hz), 6.88 (1H, dt, J = 0.7, 7.7 Hz), 6.80 (2H, d, J = 9.0 Hz), 3.10 (4H, t, J = 5.0 Hz), 2.49 (4H, t, J = 5.0 Hz), 2.24 (2H, t, J = 7.8 Hz), 1.96–1.73 (4H, m), 1.50–1.36 (2H, m), 1.18–1.06 (1H, m), 0.98–0.84 (1H, m), 0.63 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 182.6, 149.9, 141.3, 132.6, 128.9, 127.6, 124.4, 123.0, 122.3, 117.1, 109.5, 58.1, 54.2, 52.9, 49.0, 37.5, 31.0, 26.9, 22.2, 8.5. Anal. ($C_{24}H_{30}ClN_3O$). C: calcd, 69.97; found, 69.49; H, N, Cl.

3-{5-[4-(4-Chlorophenyl)-piperazin-1-yl]-pentyl}-3-ethyl-1,3-dihydro-2*H*-indol-2-one (9e). The title compound was prepared according to the general procedure E/1, starting from 3-(5-bromopentyl)-3-ethyloxindole (**7f**) and 1-(4-chlorophenyl)-piperazine. Yield: 61%, mp 143–144 °C (hexane−ethyl acetate). IR (KBr): 2939, 1700, 1497, 1236 cm^{-1}. ^1H NMR (DMSO-d_6, 500 MHz) δ: 10.32 (1H, s), 7.22–7.14 (4H, m), 6.99–6.96 (1H, m), 6.92–6.89 (2H, m), 6.83 (1H, d, J = 7.7 Hz), 3.06 (4H, t, J = 4.9 Hz), 2.39 (4H, t, J = 4.8 Hz), 2.16 (2H, t, J = 7.3 Hz), 1.74–1.67 (4H, m), 1.31–1.27 (2H, m), 1.16–1.11 (2H, m), 0.97–0.94 (1H, m), 0.81–0.78 (1H, m), 0.50 (3H, t, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 181.0, 150.0, 142.6, 132.5, 128.7, 127.6, 123.1, 122.3, 121.6, 116.8, 109.2, 57.8, 53.3, 52.7, 48.1, 37.1, 30.5, 27.3, 26.1, 23.9, 8.6. Anal. ($C_{25}H_{32}ClN_3O$) C, H, N, Cl.

3-[4-(4-Phenylpiperazin-1-yl)-butyl]-3-ethyl-1,3-dihydro-2*H*-indol-2-one oxalate (9f). The title compound was prepared according to the general procedure E/3, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 1-phenyl-piperazine. Yield: 71%, mp 121–123 °C. IR (KBr): 3245, 1710, 1620 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.77 (2H, br), 10.46 (1H, s), 7.30–7.16 (4H, m), 7.02–6.91 (3H, m), 6.89 (1H, d, J = 7.7 Hz), 6.84 (1H, t, J = 7.3 Hz), 3.37 (4H, br), 3.20 (4H, br), 2.93, 2.90 (2H, d, J = 6.0 Hz), 2.00–1.72 (4H, m), 1.56 (2H, m), 0.98 (1H, m), 0.83 (1H, m), 0.51 (3H, t, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 180.9, 149.9, 142.7, 132.2, 129.3, 127.6, 123.2, 121.8, 120.1, 116.1, 109.4, 55.4, 53.2, 50.8, 45.7, 36.8, 30.4, 23.5, 21.5, 8.6. Anal. ($C_{26}H_{33}N_3O_5$) C: calcd, 66.79; found, 66.29; H, N.

3-Ethyl-3-{4-[4-(2-methoxyphenyl)-piperazin-1-yl]-butyl}-1,3-dihydro-2*H*-indol-2-one oxalate (9g). The title compound was prepared according to the general procedure E/3, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 1-(2-methoxyphenyl)-piperazine. Yield: 74%, mp 180–183 °C. IR (KBr): 3201, 1707 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 10.4 (1H, br), 9.10 (2H, m), 7.21 (1H, d, J = 7.9 Hz), 7.18 (1H, dt, J = 7.7, 1.1 Hz), 7.02–6.94 (3H, m), 6.91–6.87 (2H, m), 6.86 (1H, d, J = 7.7 Hz), 3.78 (3H, s), 3.15 (8H, br), 2.88 (2H, t, J = 7.8 Hz), 1.78–1.68 (4H, m), 1.53 (2H, m), 0.99–0.94 (1H, m), 0.83–0.77 (1H, m), 0.51 (3H, t, J = 7.3 Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 180.8, 164.6, 152.0, 142.7, 139.8, 132.2, 127.8, 123.5, 123.2, 121.7, 121.0, 118.4, 112.1, 109.3, 55.5, 55.5, 53.2, 51.4, 47.4, 36.6, 30.4, 23.7, 21.5, 8.6. Anal. ($C_{27}H_{35}N_3O_6$) C, H, N.

3-{4-[4-(3-Chlorophenyl)-piperazin-1-yl]-butyl}-3-isobutyl-1,3-dihydro-2*H*-indol-2-one hydrochloride (9j). The title compound was prepared according to the general procedure E/2, starting from 3-(4-chlorobutyl)-3-isobutyloxindole (**7e**) and 1-(3-chlorophenyl)-piperazine. Yield: 32%, mp 214–216 °C. IR (KBr): 3166, 2411, 1701 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz) δ: 11.1 (1H, br), 10.4 (1H, s), 7.25 (1H, t, J = 8.1 Hz), 7.22 (1H, d, J = 7.7 Hz), 7.17 (1H, dt, J = 1.2, 7.7 Hz), 7.03 (1H, t, J = 2.1 Hz), 6.98 (1H, dt, J = 0.9, 7.5 Hz), 6.93 (1H, dd, J = 1.9, 8.4 Hz), 6.86 (1H, dd, J = 2.0, 7.8 Hz), 6.86 (1H, d, J = 7.9 Hz), 3.44–3.35 (4H, m), 3.18 (2H, t, J = 11.9 Hz), 2.94 (4H, br), 1.80–1.55 (6H, m), 1.25–1.15 (1H, m), 1.03–0.91 (1H, m), 0.79–0.72 (1H, m), 0.67 (3H, d, J =

6.7 Hz), 0.56 (3H, d, $J = 6.7$ Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 181.2, 151.0, 142.4, 134.1, 132.4, 130.8, 127.7, 123.5, 121.6, 119.3, 115.4, 114.3, 109.4, 55.0, 52.1, 50.3, 45.7, 44.9, 38.9, 25.7, 25.1, 24.2, 23.2, 20.8. Anal. ($C_{26}H_{35}Cl_2N_3O$) C: calcd, 65.54; found, 65.05; H, N, Cl: calcd, 14.88; found, 14.45.

3-Ethyl-3-{4-[4-(4-fluorophenyl)-piperazin-1-yl]-butyl}-1,3-dihydro-2*H*-indol-2-one (9n). The title compound was prepared according to the general procedure E/1, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 1-(4-fluoro-phenyl)-piperazine. Yield: 66%, mp 118–119 °C (hexane−ethyl acetate). IR (KBr): 3161, 1713 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.06 (1H, s), 7.19 (1H, dt, $J = 1.3$, 7.6 Hz), 7.11 (1H, d, $J = 6.6$ Hz), 7.04 (1H, dt, $J = 0.8$, 7.5 Hz), 6.93 (2H, t, $J = 9.1$ Hz), 6.90 (1H, d, $J = 8.0$ Hz), 6.82 (2H, dd, $J = 4.7$, 9.3 Hz), 3.06 (4H, t, $J = 4.9$ Hz), 2.50 (4H, t, $J = 4.9$ Hz), 2.24 (2H, t, $J = 7.8$ Hz), 1.97–1.88 (2H, m), 1.84–1.74 (2H, m), 1.47–1.35 (2H, m), 1.14–1.10 (1H, m), 0.94–0.88 (1H, m), 0.63 (3H, t, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 182.8, 157.0 (d, $J = 238.8$ Hz), 147.9 (d, $J = 1.9$ Hz), 141.4, 132.6, 127.6, 123.0, 122.3, 117.6 (d, $J = 7.6$ Hz), 115.4 (d, $J = 22.1$ Hz), 109.5, 58.1, 54.2, 53.1, 50.0, 37.5, 31.0, 26.9, 22.2, 8.5. Anal. ($C_{24}H_{30}FN_3O$) C, H, N.

3-{4-[4-(3,4-Dichlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-1,3-dihydro-2*H*-indol-2-one−H$_2$O−HCl−Isopropyl Alcohol (1:1:1:1) (9o). The coupling reaction was carried out according to the general procedure E, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 1-(3,4-dichlorophenyl)-piperazine. After cooling the reaction mixture to room temperature, ethyl acetate, and aqueous hydrochloric acid (10 wt %, 50 mL) were added and the layers were separated. The organic layer was dried over $MgSO_4$, evaporated, and the beige solid was recrystallized from a mixture of ethyl acetate and isopropyl alcohol. Yield: 67%, mp 224–226 °C (ethyl acetate−isopropyl alcohol). IR (KBr): 3385, 1708, 946 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.1 (1H, br), 10.4 (1H, s), 7.44 (1H, d, $J = 9.0$ Hz), 7.23–7.16 (3H, m), 7.02–6.97 (2H, m), 6.87 (1H, d, $J = 7.6$ Hz), 4.38 (1H, br), 3.83 (2H, br), 3.78 (1H, m), 3.42 (2H, m), 3.21 (2H, m), 2.97–2.95 (4H, m), 1.82–1.62 (6H, m), 1.04 (6H, d, $J = 6.1$ Hz), 1.01–0.95 (1H, m), 0.81–0.77 (1H, m), 0.51 (3H, t, $J = 7.3$ Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 180.8, 149.5, 142.7, 132.1, 131.8, 130.8, 127.8, 123.2, 121.7, 120.9, 117.1, 116.0, 109.4, 55.1, 53.2, 50.2, 44.9, 36.6, 30.3, 23.3, 21.4, 8.6. Anal. ($C_{27}H_{40}Cl_3N_3O_3$) C: calcd, 57.81; found, 58.46; H, N, Cl.

3-Ethyl-3-{4-[4-(4-fluorophenyl)-1,2,3,6-tetrahydro-pyridin-1-yl]-butyl}-1,3-dihydro-2*H*-indol-2-one hydrochloride (9s). The title compound was prepared according to the general procedure E/2, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 4-(4-fluoro-phenyl)-1,2,3,6-tetrahydropyridine. Yield: 44%, mp 108–111 °C. IR (KBr): 3426, 1705 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.9 (1H, br), 10.45 (1H, s), 7.52 (2H, m), 7.23–7.15 (4H, m), 7.00 (1H, dt, $J = 0.9$, 7.5 Hz), 6.87 (1H, d, $J = 7.7$ Hz), 6.12 (1H, s), 3.80–2.86 (6H, m), 2.98 (2H, t, $J = 8.1$ Hz), 1.83–1.64 (6H, m), 1.02–0.94 (1H, m), 0.88–0.78 (1H, m), 0.51 (3H, t, $J = 7.4$ Hz). ^{13}C NMR (DMSO-d_6, 400 MHz) δ: 180.8, 162.0 (d, $J = 244.9$ Hz), 142.7, 134.9 (d, $J = 3.1$ Hz), 133.3, 132.1, 127.8, 127.0 (d, $J = 8.0$ Hz), 123.2, 121.7, 116.5, 115.5 (d, $J = 21.4$ Hz), 109.3, 54.6, 53.2, 49.4, 48.0, 36.6, 30.4, 23.8, 23.6, 21.5, 8.6. Anal. ($C_{25}H_{30}ClFN_2O$) C, H, N, Cl.

3-Ethyl-3-{4-[4-(4-fluorophenyl)-piperidin-1-yl]-butyl}-1,3-dihydro-2*H*-indol-2-one hydrochloride (9t). The title compound was prepared according to the general procedure E/2, starting from 3-(4-chlorobutyl)-3-ethyloxindole (**7b**) and 4-(4-fluorophenyl)-piperidine, and the obtained hydrochloric salt was recrystallized from a mixture of ethyl acetate and isopropyl alcohol. Yield: 40%, mp 199–201 °C (ethyl acetate−isopropyl alcohol). IR (KBr): 3123, 3086, 2510, 1698 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 10.9 (1H, br), 10.49 (1H, s), 7.27–7.17 (4H, m), 7.15 (2H, t, $J = 8.9$ Hz), 7.00 (1H, dt, $J = 0.9$, 7.6 Hz), 6.89 (1H, d, $J = 7.6$ Hz), 3.43–3.35 (2H, m), 2.91–2.77 (5H, m), 2.10–1.63 (10H, m), 1.00–0.80 (2H, m), 0.51 (3H, t, $J = 7.3$ Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 180.8, 161.0 (d, $J = 241.9$ Hz), 142.7, 140.6, 132.1, 128.5 (d, $J = 7.6$ Hz), 127.7, 123.2, 121.7, 115.4 (d, $J = 21.0$ Hz), 109.4, 55.6, 53.2, 51.8, 38.2, 36.6, 30.4, 29.9, 23.4, 21.5, 8.6. Anal. ($C_{25}H_{32}ClFN_2O$) C, H, N, Cl.

3-[4-(6,7-Dihydro-4*H*-thieno[3,2-c]pyridin-5-yl)-butyl]-3-ethyl-1,3-dihydro-2*H*-indol-2-one hydrochloride (9u). The title compound was prepared according to the general procedure E/2, starting from 3-(4-chlorobutyl)-3-isobutyloxindole (**7e**) and 6,7-dihydro-4*H*-thieno[3,2-c]pyridine. Yield: 57%, mp 143–144 °C. IR (KBr): 3427, 1706 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.2 (1H, br), 10.5 (1H, s), 7.48 (1H, d, $J = 5.1$ Hz), 7.25 (1H, d, $J = 7.2$ Hz), 7.21 (1H, dt, $J = 1.2$, 7.6 Hz), 7.03 (1H, dt, $J = 1.0$, 7.5 Hz), 6.91 (1H, d, $J = 5.3$ Hz), 6.90 (1H, d, $J = 7.8$ Hz), 4.37 (1H, br), 4.11 (1H, br), 3.63 (1H, br), 3.25 (1H, sz), 3.20 (1H, m), 3.07 (3H, br), 1.83–1.72 (6H, m), 1.01 (1H, m), 0.85 (1H, m), 0.54 (3H, t, $J = 7.4$ Hz). ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 180.7, 142.7, 132.1, 131.5, 128.2, 127.7, 125.3, 123.2, 121.6, 109.3, 54.6, 53.1, 49.9, 49.0, 36.5, 30.3, 23.6, 21.7, 21.4, 8.5. Anal. ($C_{21}H_{27}ClN_2OS$) C, H, N, Cl, S.

3-{4-[4-(3-Chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-6-fluoro-1,3-dihydro-2*H*-indol-2-one (9y). The title compound was prepared according to the general procedure E/1, starting from 3-(4-chlorobutyl)-3-ethyl-6-fluorooxindole (**7d**) and 1-(3-chlorophenyl)-piperazine. Yield: 81%, mp 116–117 °C (hexane−ethyl acetate). IR (KBr): 3163, 1717 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.34 (1H, s), 7.13 (1H, t, $J = 8.0$ Hz), 7.03 (1H, dd, $J = 5.4$, 8.1 Hz), 6.83 (1H, t. $J = 2.1$ Hz), 6.78 (1H, ddd, 0.8, 1.9, 8.0 Hz), 6.76–6.70 (2H, m), 6.67 (1H, dd, $J = 2.3$, 8.8 Hz), 3.13 (4H, t, $J = 5.0$ Hz), 2.48 (4H, t, $J = 5.0$ Hz), 2.24 (2H, t, $J = 7.8$ Hz), 1.95–1.87 (2H, m), 1.80–1.72 (2H, m), 1.50–1.34 (2H, m), 1.16–1.04 (1H, m), 0.98–0.84 (1H, m), 0.62 (3H, t, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 183.2, 162.4 (d, $J = 244.1$ Hz), 152.2, 142.6 (d, $J = 11.8$ Hz), 134.8, 129.9, 127.8 (d, $J = 3.1$ Hz), 123.8 (d, $J = 9.5$ Hz), 119.1, 115.6, 113.7, 108.6 (d, $J = 22.1$ Hz), 98.3 (d, $J = 26.7$ Hz), 58.1, 53.9, 52.9, 48.5, 37.5, 31.0, 26.8, 22.2, 8.5. Anal. ($C_{24}H_{29}ClFN_3O$) C, H, N, Cl.

5-Chloro-3-{4-[4-(3-chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-6-fluoro-1,3-dihydro-2*H*-indol-2-one hydrochloride (9z). The title compound was prepared according to the general procedure E/2, starting from 5-chloro-3-(4-chlorobutyl)-3-ethyl-6-fluorooxindole (**8b**) and 1-(3-chlorophenyl)-piperazine. Yield: 53%, mp 237–239 °C. IR (KBr): 3133, 2446, 1710, 1150, 946 cm^{-1}. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.15 (1H, br), 10.79 (1H, s), 7.52 (1H, d, $J = 7.4$ Hz), 7.25 (1H, t, $J = 8.2$ Hz), 7.03 (1H, t, $J = 2.0$ Hz), 6.94 (1H, dd, $J = 2.0$, 8.2 Hz), 6.90 (1H, d, $J = 9.4$ Hz), 6.86 (1H, dd, $J = 1.4$, 7.8 Hz), 3.83 (2H, d, $J = 12.5$ Hz), 3.48–3.42 (2H, m), 3.20 (2H, t, $J = 11.8$ Hz), 2.98 (4H, br), 1.87–1.63 (6H, m), 0.96–0.78 (2H, m), 0.51 (3H, t, $J = 7.3$ Hz). ^{13}C NMR (DMSO-d_6, 101 MHz) δ: 180.6, 156.9 (d, $J = 243.8$ Hz), 151.0, 143.0 (d, $J = 11.5$ Hz), 134.1, 130.8, 129.4 (d, $J = 3.4$ Hz), 125.1, 119.3, 115.4, 114.3, 111.7 (d, $J = 18.3$ Hz), 99.0 (d, $J = 26.3$ Hz), 55.0, 53.4, 50.3, 44.9, 36.4, 30.2, 23.2, 21.4, 8.5. Anal. ($C_{24}H_{29}Cl_3FN_3O$) C: calcd, 57.55; found, 57.08; H, N, Cl: calcd, 21.23; found, 20,76.

3-{4-[4-(4-Chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-6-fluoro-1,3-dihydro-2*H*-indol-2-one (9e′). The title compound was prepared according to the general procedure E/1, starting from 3-(4-chlorobutyl)-3-ethyl-6-fluorooxindole (**7d**) and 1-(4-chlorophenyl)-piperazine. Yield: 68%, mp 145–147 °C (hexane−ethyl acetate). IR (KBr): 3284, 1716, 1088 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.28 (1H, s), 7.18 (2H, d, $J = 8.9$ Hz), 7.04 (1H, dd, $J = 5.3$, 8.2 Hz), 6.81 (2H, d, $J = 9.0$ Hz), 6.75 (1H, ddd, $J = 2.4$, 8.2, 9.7 Hz), 6.64 (1H, dd, $J = 2.4$, 8.7 Hz), 3.11 (4H, t, $J = 5.0$ Hz), 2.50 (4H, t, $J = 5.0$ Hz), 2.25 (2H, t, $J = 7.8$ Hz), 1.95–1.81 (2H, m), 1.80–1.71 (2H, m), 1.48–1.35 (2H, m), 1.12–1.04 (1H, m), 0.96–0.84 (1H, m), 0.63 (3H, t, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 182.6, 162.4 (d, $J = 244.2$ Hz), 149.9, 142.4 (d, $J = 11.4$ Hz), 128.9, 127.8 (d, $J = 2.7$ Hz), 124.4, 123.9 (d, $J = 9.9$ Hz), 117.1, 108.7 (d, $J = 22.1$ Hz), 98.2 (d, $J = 27.1$ Hz), 58.1, 53.8, 53.0, 49.0, 37.6, 31.1, 26.9, 22.2, 8.5. Anal. ($C_{24}H_{29}ClFN_3O$) C, H, N, Cl.

5,7-Dichloro-3-{4-[4-(4-chlorophenyl)-piperazin-1-yl]-butyl}-3-ethyl-1,3-dihydro-2*H*-indol-2-one (9h′). The title compound was prepared according to the general procedure E/1 starting from 5,7-dichloro-3-(4-chlorobutyl)-3-ethyloxindole (**8c**) and 1-(4-chlorophenyl)-piperazine. Yield: 60%, mp 152–154 °C (heptane−ethyl acetate). IR (KBr): 3137, 1719, 826 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.15 (1H, s), 7.23 (1H, d, $J = 1.8$ Hz), 7.18 (2H, d, $J = 9.1$ Hz), 7.01 (1H, d, $J = 1.8$ Hz), 6.81 (2H, d, $J = 9.1$ Hz), 3.12 (4H, t, $J = 5.0$ Hz), 2.51 (4H, t, $J = 5.0$ Hz), 2.27 (2H, t, $J = 7.8$ Hz), 1.98–1.88 (2H, m), 1.80–1.70 (2H, m), 1.50–1.36 (2H, m), 1.16–1.04 (1H, m), 0.98–0.86 (1H, m), 0.65 (3H, t, $J = 7.4$ Hz). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 180.3, 149.9, 137.7, 135.3, 128.9, 128.2, 127.5, 124.4, 122.0, 117.1, 115.7, 57.9, 55.8, 53.0, 49.1, 37.5, 31.1, 26.7, 22.2, 8.5. Anal. ($C_{24}H_{28}Cl_3N_3O$) C, H, N, Cl.

General Procedure F: Coupling Reaction between the 3-[4-(Methanesulfonyloxy)-butyl]oxindole Intermediates (11) and the Appropriately Substituted 4-Phenylpiperazines. The melt of the secondary amine (12 mmol) was heated to 120 °C under slow stirring. The appropriate 3-[4-(methanesulfonyloxy)-butyl]oxindole (**11**, 12 mmol) and sodium carbonate (1.36 g, 12 mmol) were added. After 1 h reaction time, the brown melt was cooled to ambient temperature. Ethyl acetate and water were added and the layers were separated. The organic layer was dried over $MgSO_4$ and evaporated. The residual oil or solid was purified by column chromatography using ethyl acetate as eluent.

General Procedure F/1. In case the product of the chromatographic purification crystallized upon treatment with diethyl ether, it was triturated in this solvent, filtered, and the solid was recrystallized from the solvent indicated below and dried to give a white crystalline product.

General Procedure F/2. In case the product of the chromatographic purification did not crystallize upon treatment with diethyl ether, it was dissolved in diethyl ether (200 mL), the solid residue was removed by filtration, and a calculated amount (1 equiv) of hydrogen chloride (saturated solution of HCl gas in diethyl ether) was added dropwise, under vigorous stirring. The white precipitate was filtered, washed with diethyl ether and hexane, and dried in vacuo at ambient temperature for 3 h.

3-{4-[4-(4-Chloro-phenyl)-piperazin-1-yl]-butyl}-1,3-dihydro-2*H*-indol-2-one (12d). The title compound was prepared according to the general procedure F/1, starting from 3-[4-(methanesulfonyloxy)-butyl]oxindole (**11a**) and (4-chlorophenyl)-piperazine. Yield: 74%, mp 135–136 °C (hexane−ethyl acetate). IR (KBR): 3203, 1718, 754 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 8.60 (1H, s), 7.24–7.15 (2H, m), 7.18 (2H, d, $J = 9.1$ Hz), 7.02 (1H, dt, $J = 0.9$, 7.6 Hz), 6.88 (1H, d, $J = 7.7$ Hz), 6.81 (2H, d, $J = 9.2$ Hz), 3.48 (1H, t, $J = 6.0$ Hz), 3.13 (4H, t, $J = 5.0$ Hz), 2.55 (4H, t, $J = 5.0$ Hz), 2.36 (2H, t, $J = 7.5$ Hz), 2.05–1.96 (2H, m), 1.58–1.36 (4H, m). ^{13}C NMR ($CDCl_3$, 101 MHz) δ: 180.3, 149.9, 141.5, 129.7, 128.9, 127.8, 124.4, 124.1, 122.2, 117.1, 109.6, 58.2, 53.0, 49.1, 45.9, 30.3, 26.8, 23.7. Anal. ($C_{22}H_{26}ClN_3O$) C, H, N, Cl.

5-Fluoro-3-[4-(4-phenyl-piperazin-1-il)-butyl]-1,3-dihydro-2*H*-indol-2-one (12e). The title compound was prepared according to the general procedure F/1, starting from 5-fluoro-3-[4-(methanesulfonyloxy)-butyl]oxindole (**11b**) and phenylpiperazine. Yield: 61%, mp 142–144 °C (hexane−ethyl acetate). IR (KBr): 3188, 1705 cm^{-1}. ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ: 9.52 (1H, s), 7.24 (2H, dd, $J = 7.3$, 8.8 Hz), 6.97 (1H, dd, $J = 1.8$, 8.1 Hz), 6.92–6.87 (3H, m), 6.84 (1H, t, $J = 7.3$ Hz), 6.80 (1H, dd, $J = 4.3$, 8.4 Hz), 3.47 (1H, t, $J = 6.0$ Hz), 3.17 (4H, t, $J = 5.0$ Hz), 2.57 (4H, t, $J = 5.0$ Hz), 2.36 (2H, t, $J = 7.7$ Hz), 1.99–1.95 (2H, m), 1.57–1.52 (2H, m), 1.45–1.34 (2H, m). ^{13}C NMR ($CDCl_3$, TMS, 125 MHz) δ: 180.7, 158.9, 151.2, 137.6 (d, $J = 2.1$ Hz), 131.2 (d, $J = 8.1$ Hz), 129.0, 119.6, 115.9, 114.1 (d, $J = 23.5$ Hz), 112.0 (d, $J = 24.8$ Hz), 110.1 (d, $J = 8.1$ Hz), 58.1, 53.1, 49.0, 46.5 (d, $J = 1.7$ Hz), 30.2, 26.6, 23.6. Anal. ($C_{22}H_{26}FN_3O$) C, H, N.

Pharmacology. Cell Culture. CHO cells stably expressing the 5-HT_{7A} receptor were cultured in 1:1 F12:DMEM (Sigma) supplemented with 1% (v/v) penicillin−streptomycin (Sigma), 5% fetal calf serum (Gibco BRL), and 2 mM L-glutamine (Sigma) at 37 °C in a humidified atmosphere with 5% CO_2. Cells were seeded at 30000 cells per well in a 96-well plate 24 h before treatment with compounds.

Compound Preparation and Treatment. The compounds were dissolved in DMSO at a concentration of 1 mM. The final concentration of DMSO in the experiments was 0.1% (v/v). In the absence of 5-CT, the cells were incubated with 1 μM or 10 nM compounds for 20 min at 37 °C in order to investigate their effect on the resting cAMP level. To examine antagonist behavior, the cells were preincubated with 1 μM or 10 nM compounds for 10 min, immediately before a 20 min incubation with 10 nM 5-CT at 37 °C.

cAMP Measurement. The cells were lysed and the cAMP levels were detected using the BioTrak Direct cAMP EIA kit (Amersham). Protein determination was made by the BCA assay (Sigma).

Radioligand Binding Assay and Data Analysis. In the case of 5-HT_7 assays, we used cloned human serotonin receptor subtype 7 (h5-HT_7) produced in CHO cells (PerkinElmer), following the recommended assay conditions using [^{3}H]LSD (NEN) as radioligand. Nonspecific binding was determined in the presence of 25 μM clozapine (Sigma). Binding assays were terminated by filtration over Whatman GF/C glass-fiber filter (presoaked in 0.3% polyethylenimine for 30 min) using a Brandel cell harvester, and bound radioactivity was measured with a Packard TopCount scintillation spectrometer.

5-HT_{1A} receptor binding assays were performed according to the method of Peroutka and Snyder[50] with minor modifications. 5-HT_{1A} membrane was prepared from adult rat frontal cortex obtained immediately following decapitation. The wet weight was measured and the tissue was homogenized (Potter-Elvehjem) in 50 volumes of 50 mM Tris-HCl buffer (pH 7.7 at 25 °C). The tissue homogenate was centrifuged at 40000*g* for 15 min at 4 °C, and the pellet was resuspended in the same volume of the above buffer. The homogenate was incubated in a shaking water bath for 10 min at 37 °C. After a quick chilling on ice, the homogenate was centrifuged (40000*g*, 15 min, 4 °C), resuspended, and centrifuged again (40000*g*, 15 min, 4 °C). The membrane was finally resuspended in 30 volumes of 50 mM Tris-HCl buffer (pH 7.7). The incubation buffer contained 50 mM Tris-HCl (pH 7.7), 6.66 mM $CaCl_2$, 16.66 μM pargyline, and 0.166% ascorbic acid. 5-HT_{1A} sites were labeled with 1.5 nM [^{3}H]8-OH-DPAT (Amersham). Nonspecific binding was determined in the presence of 10 μM 5-hydroxytryptamine creatinine sulfate complex (5-HT, Sigma). The samples were incubated for 45 min at 25 °C. Following the incubation, the samples were rapidly filtered over Whatman GF/B glass fiber filter (presoaked in 0.05% polyethylenimine for 30 min) and washed. Individual filters were inserted into vials, equilibrated for 6 h with Opti-Fluor scintillation fluid (PerkinElmer), and counted with a Packard TopCount scintillation spectrometer.

Membranes, radioligands, and varying concentrations of competitive ligands were incubated in triplicates. Competition binding data were fit to a single-site binding model using Prism GraphPad for K_i determination. K_i values were calculated from two displacement curves (nine concentrations) in triplicate.

Conflict Drinking (Vogel) Test. Experiments were performed in a computer-operated system (LIIKOSYS, Experimetria, Hungary) consisting of 8 test chambers (20 cm × 20 cm × 20 cm Plexiglas boxes), each of which was equipped with a drinking spout mounted at appropriate height on the wall of the chamber and a metal grid floor for delivering electric shocks. Male Wistar rats, weighing 160–180 g, were deprived of drinking water for 48 h and fasted for 24 h prior to test. Test and reference compounds or vehicle were administered ip 30 min prior to test. All procedures were carried out in a quiet, air-conditioned room between 07:30 and 13:00 h at an ambient temperature of 23 °C. At the beginning of the experiment, the animals were placed in the test chamber where they had free access to drinking water for a 30 s grace period. After that, electric shocks (600 μA, 0.6 s) were applied through the drinking spout following every 20 licks during a 5 min test period.[36] Number of punished licks was recorded and stored in a computer. Means ± SEM of numbers of tolerated shocks were calculated in

each group, statistical analysis of data was performed by one-way ANOVA, followed by the Duncan's test.

Light−Dark Test. Test was performed in a room illuminated with a 2 lx light source. An animal activity monitor equipped with six two-compartment automated test chambers (Omnitech, Digiscan, model RXYZCM16) was used for all experiments. Each box consisted of one dark and one lit compartment. Both areas measured 39 cm × 20 cm × 29 cm. Access between the two compartments was provided by an 8 cm × 8 cm passage way. A 60 W white tungsten light bulb was used to illuminate the lit area. Interruptions of the 32 infrared beams (16 at 2 cm and 16 at 8 cm height above the box floor) in both compartments were automatically recorded by the Digiscan analyzer and transmitted to a computer. Male NMRI mice, weighing 25–33 g, were used for the test. Mice were kept in a dark room, treated ip 30 min prior to test, and were placed individually in the center of the lit area. Behavioral activity was detected for 5 min. Time spent in each area, number of transitions, and horizontal and vertical activities were recorded.[37] Means ± SEM values were calculated and the statistical analysis of data was performed by one-way ANOVA, followed by the Duncan's test.

Supporting Information Available: Elemental analysis data for all new compounds, characterization and preparation of compounds **7c−f**, **8b**, **8d**, **9a**, **9h−i**, **9k−m**, **9p−r**, **9v−x**, **9a′−d′**, **9f′−g′**, **11b**, **12a−c**, **13b**, **14a−b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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