Medicinal Chemistry Driven Approaches Toward Novel and Selective Serotonin 5-HT$_6$ Receptor Ligands

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Based on a medicinal chemistry guided hypothetical pharmacophore model, novel series of indolyl sulfonamides have been designed and prepared as selective and high-affinity serotonin 5-HT$_6$ receptor ligands. Furthermore, based on a screening approach of a discovery library, a series of benzoxazinepiperidinyl sulfonamides were identified as selective 5-HT$_6$ ligands. Many of the compounds described in this paper possess excellent affinities, displaying pK_i values greater than 8 (some even >9) and high selectivities against a wide range (>50) of other CNS relevant receptors. First, structure−affinity relationships of these ligands are discussed. In terms of functionality, high-affinity antagonists, as well as agonists and even partial agonists, were prepared. Compounds **19c** and **19g** represent the highest-affinity 5-HT$_6$ agonists ever reported in the literature. These valuable tool compounds should allow for the detailed study of the role of the 5-HT$_6$ receptor in relevant animal models of disorders such as cognition deficits, depression, anxiety, or obesity.

Introduction

It is estimated that about 90% of actual patent applications citing CNS diseases claim serotonergic agents.[1] At least 14 distinct serotonin (5-HT) receptor subclasses are expressed in the mammalian CNS.[2] These receptors are assembled into seven main classes (5-HT$_{1-7}$)[3] 5-HT$_6$ being the most recently discovered and cloned member of the family. Rat[4] and mouse[5] 5-HT$_6$ receptors were described in 1993 and 1994, respectively, and the human 5-HT$_6$ (h5-HT$_6$) receptor was first reported in 1996.[6] The cloned rat receptor was initially found to consist of a polypeptide chain of 437 amino acids with little homology to other 5-HT receptors.[7] Afterward, the discovery of an additional guanine base in the rat sequence led to a corrected sequence comprising 438 amino acids.[6] The cloned h5-HT$_6$ receptor contains 440 amino acids and shares 96% homology with the rat receptor within the transmembrane region. The cloned mouse 5-HT$_6$ receptor is a 440 amino acid peptide with a 97% and 89% identity as compared with the rat and human receptor, respectively. Expression of the 5-HT$_6$ receptor mRNA and the 5-HT$_6$ receptor localization and distribution has been described using several methods in rat and human.[4,7,8] The 5-HT$_6$ receptor has been mainly localized in olfactory tubercles, striatum, nucleus accumbens, and hippocampus. Lower levels have been found in amygdala, hypothalamus, substantia nigra, cerebellum, or cerebral cortex. No 5-HT$_6$ mRNA has been detected in several human peripheral tissues,[8g] whereas other authors have reported some expression of the 5-HT$_6$ receptor mRNA in the peripheral nervous system of rats[8a,8c,9] and in other rat organs and tissues.[7,10] Interestingly, Hirst et al.[8g] found that even though there is a sequence homology between rat and mouse 5-HT$_6$ receptors, the mouse receptor has a much lower level of expression as compared to rats or humans, especially in the basal ganglia. Thus, the pharmacological profile of mice is, with respect to the 5-HT$_6$ receptor, quite different from that of rats and humans. These results should be kept in mind when analyzing data obtained with different animal species.

Being positively coupled to adenylyl cyclase,[6,7,11] 5-HT$_6$ receptor is a member of the G-protein family, which also includes the 5-HT$_4$ and 5-HT$_7$ receptors. A constitutive activity of the mouse receptor has been proposed,[12] and due to the high degree of conservation of the sequence responsible for such activity in the rat and human receptor, the same constitutive activity is likely. In fact, a constitutively active mutant of the human receptor has been created recently.[13] The 5-HT$_6$ receptor appears to regulate several neurotransmitter systems including dopamine, noradrenaline, glutamate, aspartate, or acetylcholine. This has been demonstrated by microdialysis,[14] in situ hybridization,[15] or electrophysiology.[16] Its unique distribution in the brain and high affinity for therapeutic antipsychotics[17] and antidepressants[4] suggests a possible role of the 5-HT$_6$ receptor in CNS disorders. Along with this, several studies have been published reporting an association of 5-HT$_6$ receptor variants with schizophrenia,[18] bipolar affective disorders,[19] Parkinson's disease,[20] or Alzheimer's disease.[18b,21] In 1995, the importance of the 5-HT$_6$ receptor in memory and learning was postulated using antisense oligonucleotides in rats.[22] The behavioral syndrome induced by this treatment suggests that one function of the receptor could be the control of cholin-

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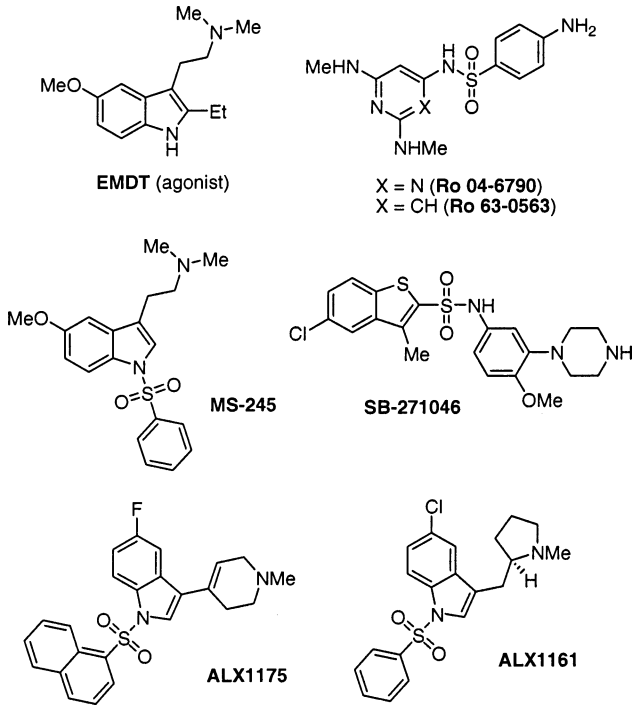


Figure 1. Selection of 5-HT$_6$ reference ligands.

ergic neurotransmission. Following studies using selective antagonists of the receptor, an involvement of the cholinergic system in the role of the 5-HT$_6$ receptor[23] can be deduced, leading to the proposal of 5-HT$_6$ as a therapeutic target for those pathologies where the cholinergic function is altered, such as Alzheimer's disease and other dementias. Since then, great effort has been done trying to elucidate the role and therapeutic possibilities of this receptor in these pathologies. Controversial results have been obtained with either positive[24] or negative[25] conclusions. Much work has been performed to elucidate the involvement of 5-HT$_6$ receptors in disorders such as anxiety, depression, psychosis, obesity, or convulsions.[26] Nevertheless, the exact (functional) role of the receptor in these indications has yet to be ascertained. The use of knockout mice for the receptor[27] should help to understand the receptor in more detail.

Potent and selective ligands with defined functionality are important tools to further elucidate the functional role of the 5-HT$_6$ receptor. During the past few years, the synthesis of a series of novel ligands has been reported, introducing various new classes of compounds as potent and selective binders for this serotonin receptor.[1] Agents that bind at the h5-HT$_6$ receptor with K_i values <50 nM include 5-methoxytryptamine, bromocriptine, octoclothepin, and the neuroleptics, clozapine, olanzapine, loxapine, chlorpromazine, and fluphenazine. 2-Ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (EMDT) represents the first selective 5-HT$_6$ agonist. As selective antagonists, the benzenesulfonamides Ro 04-6790 and Ro 63-0563,[23a] the benzo[*b*]thiophenesulfonamide SB-271046,[28] and the sulfonylindoles ALX1161, ALX1175,[29] and MS-245[30] (Figure 1) have been reported among others.

To further study the 5-HT$_6$ receptor and its physiological function, different series of indolyl sulfonamides were prepared based on a medicinal chemistry guided conceptual framework model. These potent ligands of 5-HT$_6$ were investigated in terms of their structure−affinity relationships (SAFIR), as well as their functionalities.[31] Furthermore, as a result of a screening of Esteve's discovery library against the cloned h5-HT$_6$ receptor, a series of benzoxazinepiperidinyl sulfonamide derivatives was identified as selective 5-HT$_6$ agents.[32] In the following, these approaches will be discussed in detail.

Chemistry

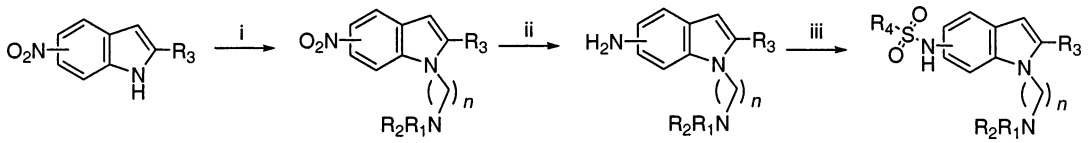
Novel series of sulfonamides of indoles with different substitution patterns were developed as potential 5-HT$_6$ ligands and can be grouped into four classes based on their common scaffolds: *N*-aminoalkylindoles, 3-aminoalkylindoles, 3-glyoxamidoindoles, and 3-piperidinylindoles. The synthesis of all these series was carried out starting from the suitable commercial nitroindoles **1**−**3** (Schemes 1−3). These were reacted with β-chloroalkylamines[33] as depicted in Scheme 1 to afford *N*-aminoalkyl-nitroindoles **4**−**6**. Tryptamine-like compounds were prepared by previously reported procedures[34] using oxalyl chloride[35,36] and a secondary amine, followed by reduction of the glyoxamide intermediates **7a**−**f** with borane to afford **8a**−**f** (Scheme 2). 3-Tetrahydropiperidinyl-5-nitroindole **9** was synthesized by reaction of 5-nitroindole **2a** with *N*-methyl-4-piperidone[37] (Scheme 3). In the next step, all functionalized nitroindole derivatives obtained before (**4**−**9**) were hydrogenated over palladium to yield the corresponding amines **10**, **11a**−**f** and **12a**−**c** (Scheme 1), **13a**−**f**[34] and **14a,b** (Scheme 2), and **15** (Scheme 3). These were treated with the corresponding sulfonyl chloride to afford the final compounds **16**−**20**. Furthermore, a series of *N*-(3-glyoxamidoindolyl)sulfonamide derivatives (**21a**−**e**) was prepared starting from the 5-nitro-3-glyoxamidoindole intermediates **7a**−**b** (Scheme 2).

1-Piperidin-4-yl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one **22a** was synthesized as shown in Scheme 4 according to the method described by Bell et al.[38] from 2-aminobenzyl alcohol, by reductive amination with *N*-(*tert*-butyloxycarbonyl)-4-piperidone, followed by cyclization using triphosgene. The cleavage of the protective group is carried out by treatment with acidic media. 8-Methyl-1-piperidin-4-yl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one **22b** was obtained using the same procedure from commercially available 2-amino-3-methylbenzyl alcohol. The piperidine derivatives were treated with the appropriate sulfonyl chlorides to afford the final compounds **23a**−**j**.

Results and Discussion

Analysis of the structures of different 5-HT$_6$ reference ligands (cf. Figure 1) allowed for the construction of a hypothetical framework model, which is depicted in Figure 2. In total, four important parts within the molecules were identified for obtaining good affinities against the 5-HT$_6$ receptor: these structural requirements within the framework comprise two hydrophobic regions separated by a double electron acceptor functional group (commonly a sulfone amide) and a proton donor area (represented by an amino group that is protonated at physiological pH). This model could now be used to find novel lead structures. Thus, by fitting

Scheme 1[a]



1 4-nitro, R_3 = H
2a 5-nitro, R_3 = H
2b 5-nitro, R_3 = Me
3a 6-nitro, R_3 = H
3b 6-nitro, R_3 = Me

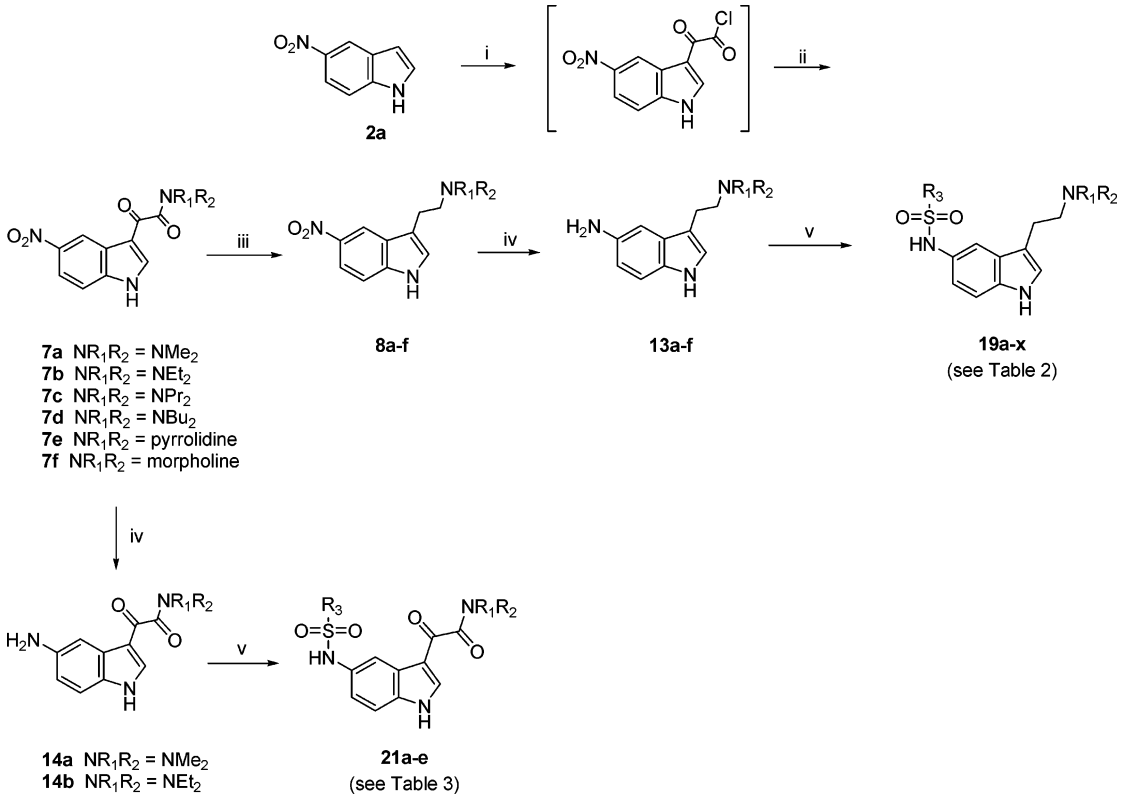
4 4-nitro, R_1, R_2 = Me, R_3 = H, n =2
5a 5-nitro, R_1, R_2 = Me, R_3 = H, n = 2
5b 5-nitro, R_1, R_2 = Me, R_3 = Me, n = 2
5c 5-nitro, R_1, R_2 = Et, R_3 = H, n = 2
5d 5-nitro, R_1, R_2 = pyrrolidine, R_3 = H, n = 2
5e 5-nitro, R_1, R_2 = piperidine, R_3 = H, n = 2
5f 5-nitro, R_1, R_2 = piperidine, R_3 = H, n = 3
6a 6-nitro, R_1, R_2 = Me, R_3 = H, n = 2
6b 6-nitro, R_1, R_2 = Me, R_3 = Me, n = 2
6c 6-nitro, R_1, R_2 = pyrrolidine, R_3 = H, n = 2

10, 11a-f, 12a-c

16a-c, 17a-n, 18a-k
(see Table 1)

[a] (i) $Cl(CH_2)_nNR_1R_2$, NaH, DMF, 80 °C; (ii) H_2, Pd/C, EtOH; (iii) R_4SO_2Cl, pyridine.

Scheme 2[a]



2a

7a NR_1R_2 = NMe_2
7b NR_1R_2 = NEt_2
7c NR_1R_2 = NPr_2
7d NR_1R_2 = NBu_2
7e NR_1R_2 = pyrrolidine
7f NR_1R_2 = morpholine

8a-f

13a-f

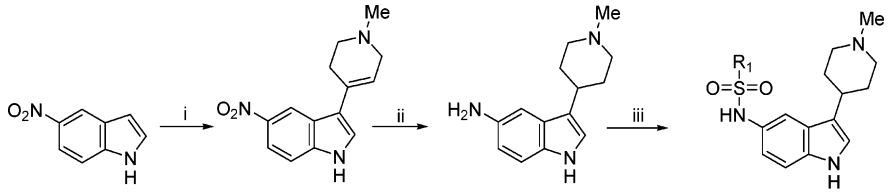
19a-x
(see Table 2)

14a NR_1R_2 = NMe_2
14b NR_1R_2 = NEt_2

21a-e
(see Table 3)

[a] (i) Oxalyl chloride, Et_2O, phthalimide, rt, 72 h; (ii) NHR_1R_2, Et_2O, rt, 1 h; (iii) BH_3-THF, rt, 16 h; (iv) H_2, Pd/C, EtOH, rt; (v) R_3SO_2Cl, pyridine.

Scheme 3[a]



2a

9

15

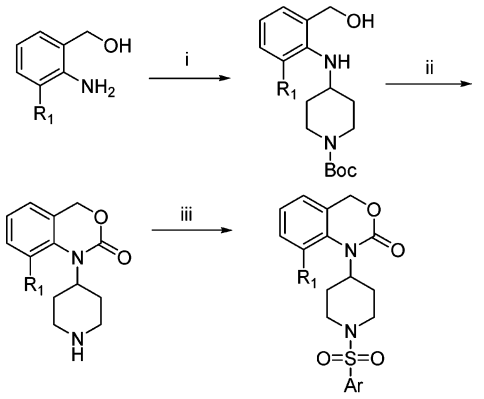
20a-f
(see Table 4)

[a] (i) *N*-Methyl-4-piperidone, NaOMe, MeOH, 48 h, reflux; (ii) H_2, Pd/C, EtOH; (iii) R_1SO_2Cl, pyridine.

different hypothetical structures in this framework, the likeliness of obtaining good binding affinities could be estimated.

Based on this approach, in total four novel indole-based series were selected and their synthesis was developed, namely, *N*-aminoalkylindoles (**16a**−**c**, **17a**−**n**,

Scheme 4[a]



22a R_1 = H
22b R_1 = Me

23a-j
(see Table 5)

[a] (i) (a) *N*-Boc-4-piperidone, AcOH, toluene, reflux; (b) $NaBH_3CN$, AcOH, toluene, THF; (ii) (a) triphosgene, DIEA, THF; (b) HCl, EtOAc; (iii) $ArSO_2Cl$, DIEA, CH_2Cl_2.

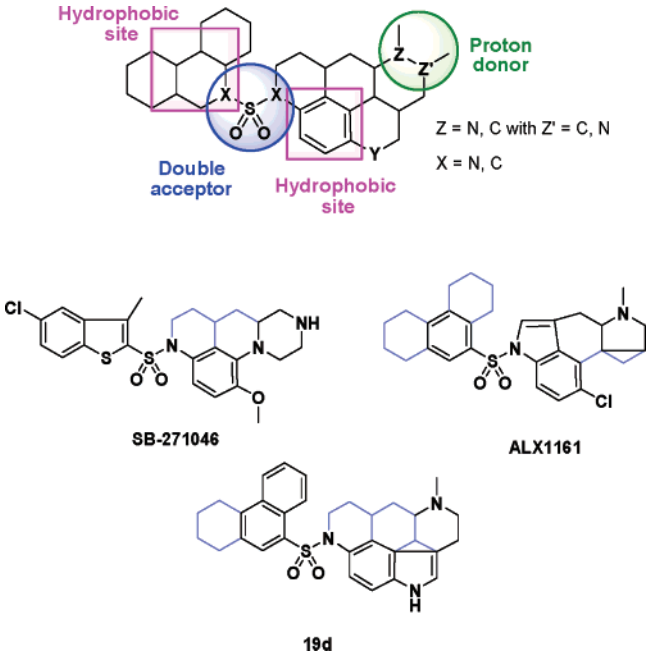


Figure 2. Hypothetical framework model for 5-HT_6 ligands.

18a−**k**), 3-aminoalkylindoles (**19a**−**x**), 3-piperidinylindoles (**20a**−**f**), and 3-glyoxamidoindoles (**21a**−**e**). Furthermore, as a result of a screening campaign of Esteve's proprietary compound library, a new series of selective 5-HT_6 ligands (benzoxazinepiperidinyl sulfonamides **23a**−**j**) has been identified and preliminarily investigated in terms of its structure−affinity relationships.

The binding affinities at the human 5-HT_6 receptor were determined in a filter binding assay using [^{3}H]-LSD. The activity of the compounds as putative agonists or antagonists was studied in an in vitro system using C6 cells overexpressing the receptor. The 5-HT_6 receptor is known to be positively coupled to the adenylyl cyclase system, so agonists of the receptor would increase in a significant way the levels of intracellular cyclic AMP (cAMP). Figure 3 shows two typical examples of concentration−response curves to 5-HT in the presence of different concentrations of compounds **19e** and **23d**, which behave as clear antagonists. In addition, the agonistic activity of compound **19g** is displayed. Besides,

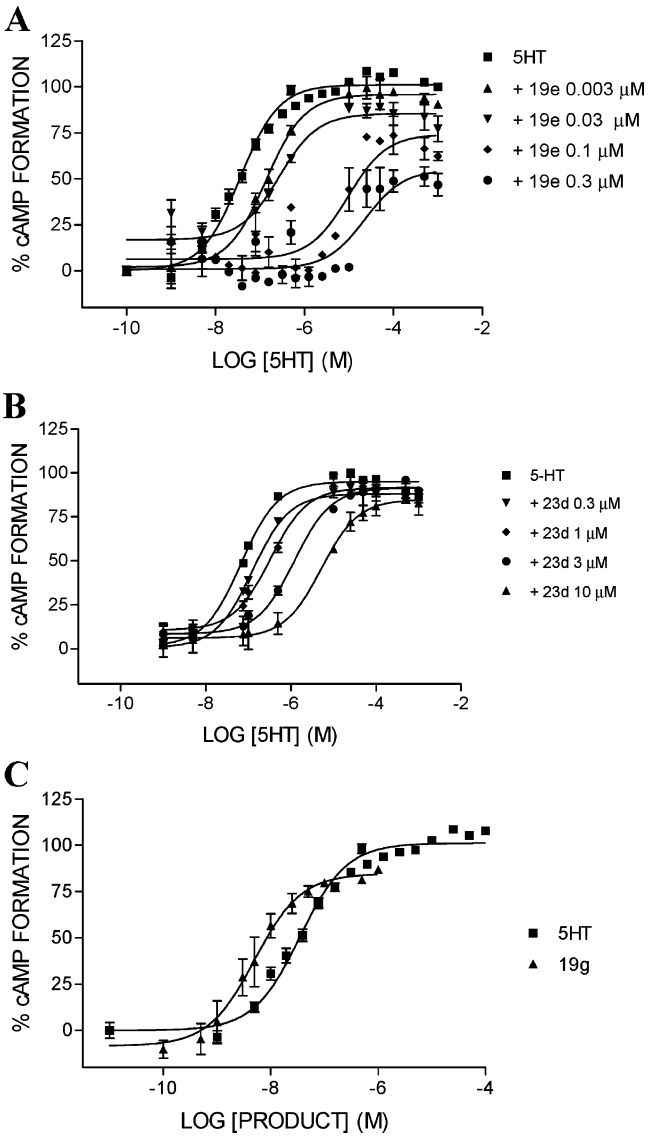
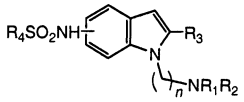


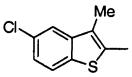
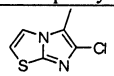
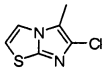
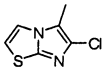
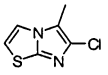
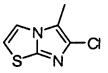
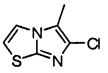
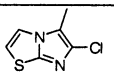
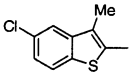
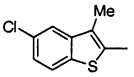
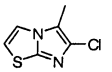
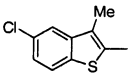
Figure 3. Stimulation of cyclic AMP accumulation in C6 cells stably expressing the human 5-HT_6 receptor by either 5-HT alone or 5-HT in the presence of (A) **19e** (0.003, 0.03, 0.1m or 0.3 μM) or (B) **23d** (0.3, 1, 3, or 10 μM). Panel C shows the effect of 5-HT and **19g** on cyclic AMP accumulation in C6 cells. All data points represent the means of at least three separate experiments.

compounds displaying agonist properties in *some* degree have been found to antagonize the serotonin-induced cAMP formation, being defined as partial agonists. Selected compounds with high affinity were profiled in a commercially available panel of more than 50 radioligand binding assays (MSD, Taiwan). These comprise the characterization of potential interactions at the ligand binding site of a wide range of mainly G-protein-coupled receptors (GPCRs) and ligand-gated ion channels, plus a limited number of modulatory sites on voltage-gated ion channels.

The binding and functionality results of selected compounds are illustrated in Tables 1−5. Within the N-aminoalkylindole series (Table 1), in total 28 representatives have been prepared covering a wide range of affinities reaching down to the nanomolar level (e.g., **17a**, K_i = 1.9 nM). In comparison, the reference compounds SB-271046, Ro 04-6790, and Ro 63-0563 have been reported[23a,26b] to possess binding affinities (K_i) of

Table 1. 5-HT$_6$ Binding Affinity and Functionality of *N*-Aminoalkylindolyl Sulfonamides

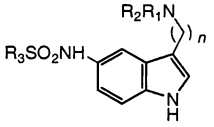


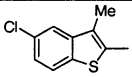
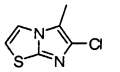
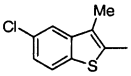
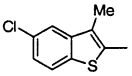
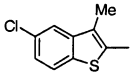
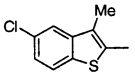
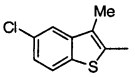
	Cpd	*n*	NR_1R_2	R_3	R_4	K_i (nM)	cAMP formation[a]
4-sulfonamides	**16a**	2	NMe_2	H		57.7	ANT
	16b	2	NMe_2	H	1-Naphthyl	64.7	ANT
	16c	2	NMe_2	H	2-Naphthyl	14.9	ANT
5-sulfonamides	**17a**	2	NMe_2	H		1.9	ANT
	17b	2	NMe_2	H	1-Naphthyl	94.2	ANT
	17c	2	NMe_2	H	2-Naphthyl	57.7	ANT
	17d	2	NMe_2	H	Benzyl	> 1000	--
	17e	2	NMe_2	Me		74.6	ANT
	17f	2	NMe_2	Me	1-Naphthyl	123.6	ANT
	17g	2	NMe_2	Me	2-Naphthyl	85.8	ANT
	17h	2	NEt_2	H		97.3	ANT
	17i	2	NEt_2	H	1-Naphthyl	116.2	ANT
	17j	2	NEt_2	H	2-Naphthyl	140.5	ANT
	17k	2	NEt_2	H	*p*-Biphenyl	> 1000	--
	17l	2		H		9.8	ANT
	17m	2		H		31.4	ANT
	17n	3		H		> 1000	--
6-sulfonamides	**18a**	2	NMe_2	H		55.2	--
	18b	2	NMe_2	H		90.2	pAGO
	18c	2	NMe_2	H	1-Naphthyl	19.8	--
	18d	2	NMe_2	H	2-Naphthyl	41.2	ANT
	18e	2	NMe_2	H		74.5	--
	18f	2	NMe_2	Me		> 1000	--
	18g	2		H		52.2	ANT
	18h	2		H		108.8	ANT
	18i	2		H	1-Naphthyl	18.6	ANT
	18j	2		H	2-Naphthyl	100.8	ANT
	18k	2		H		194.8	ANT

[a] ANT = antagonist; pAGO = partial agonist.

0.8, 44.7, and 14.8 nM against h5-HT$_6$, respectively. In terms of functionalities, the majority of compounds of this series behave as antagonists, with the exception of **18b**, being a partial agonist. SAFIR showed that the methyl group is the most appropriate alkyl group for R_1 and R_2 to obtain highest affinities: **17a** (K_i = 1.9 nM)

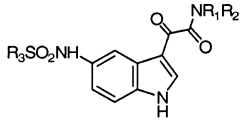
Table 2. 5-HT_6 Binding Affinity and Functionality of 3-Aminoalkylindolyl Sulfonamides

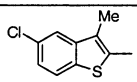
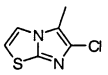
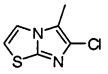


Cpd	*n*	NR_1R_2	R_3	K_i (nM)	cAMP formation[a]
19a	1	NMe_2		5.3	ANT
19b	2	NMe_2		2.2	pAGO
19c	2	NMe_2		0.1	AGO
19d	2	NMe_2	1-Naphthyl	0.8	pAGO
19e	2	NMe_2	5-Cl-2-Naphthyl	0.2	ANT
19f	2	NMe_2	*p*-Biphenyl	0.4	AGO
19g	2	NEt_2		0.3	AGO
19h	2	NEt_2	1-Naphthyl	3.5	AGO
19i	2	NEt_2	2-Naphthyl	5.3	AGO
19j	2	NEt_2	5-Cl-1-Naphthyl	3.3	pAGO
19k	2	NEt_2	3,5-diCl-phenyl	9.3	pAGO
19l	2	NEt_2	*p*-Biphenyl	1.0	AGO
19m[b]	2	NEt_2	2-Naphthyl	40.8	ANT
19n	3	NEt_2	2-Naphthyl	163.0	ANT
19o	2	NPr_2		0.5	pAGO
19p	2	NPr_2	2-Naphthyl	3.9	pAGO
19q	2	NBu_2	1-Naphthyl	7.2	ANT
19r	2			4.0	pAGO
19s	2		1-Naphthyl	4.5	ANT
19t	2		2-Naphthyl	4.3	pAGO
19u	2			15.1	ANT
19v	2		1-Naphthyl	163.5	ANT
19w	2		2-Naphthyl	132.0	ANT
19x	2		8-Quinolyl	117.0	ANT

[a] ANT = antagonist; AGO = agonist; pAGO = partial agonist. [b] *N*-Methylindole derivative.

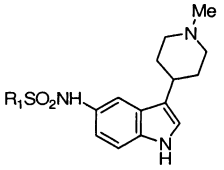
Table 3. 5-HT_6 Binding Affinity and Functionality of *N*-(3-Glyoxamidoindolyl) Sulfonamides

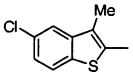


Cpd	NR_1R_2	R_3	K_i (nM)	cAMP formation[a]
21a	NMe_2		> 1000	--
21b	NMe_2		18.4	ANT
21c	NEt_2		224.4	ANT
21d	NEt_2	1-Naphthyl	> 1000	--
21e	NEt_2	8-Quinolyl	> 1000	--

[a] ANT = antagonist.

Table 4. 5-HT_6 Binding Affinity and Functionality of 3-Piperidinylindolyl Sulfonamides

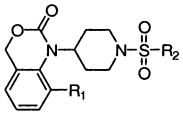


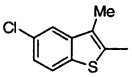
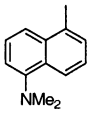
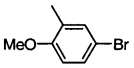
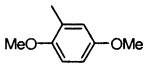
Cpd	R_1	K_i (nM)	cAMP formation[a]
20a		1.0	ANT
20b	1-Naphthyl	4.7	ANT
20c	5-Cl-1-Naphthyl	9.6	ANT
20d	2-Cl-5-thienyl	24.3	--
20e	8-Quinolyl	21.2	ANT
20f	*p*-Biphenyl	6.8	ANT

[a] ANT = antagonist.

> **17h** (K_i = 97.3 nM) and **17c** (K_i = 57.7 nM) > **17j** (K_i = 140.5). Interestingly, replacement of the dimethylamino group with pyrrolidine results in only slightly weaker to similar affinities (cf. **17l**, K_i = 9.8 nM, with **17a**, K_i = 1.9 nM, or **18i**, K_i = 18.6 nM, with **18c**, K_i = 19.8 nM), whereas replacement with the six-membered homologue piperidine shows a decrease in affinity (**17m**, K_i = 31.4 nM, vs **17a**, K_i = 1.9 nM). Further homologation of the alkylamino chain from ethylenamine (**17m**, K_i = 31.4 nM) to propylenamine (**17n**, K_i > 1000 nM) results in a loss of affinity. Although alkyl substitution in position 2 of the indole with a methyl group is tolerated, a tendency toward lower affinities is displayed: **17e** (K_i = 74.6 nM) < **17a** (K_i = 1.9 nM), **17f** (K_i = 123.6 nM) ≤ **17b** (K_i = 94.2 nM), **17g** (K_i = 85.8 nM) ≤ **17c** (K_i = 57.7 nM), and **18f** (K_i > 1000 nM) < **18b** (K_i = 90.2 nM). There is not a general (true for all sulfonamides) correlation between the sulfonamide position within the indole moiety and the corresponding affinity: in naphthyl-substituted systems, for instance, the affinity ranking is 6- (**18c**) > 4- (**16b**) > 5-substitu-

Table 5. 5-HT$_6$ Binding Affinity and Functionality of Benzoxazinepiperidinyl Sulfonamides



Cpd	R_1	R_2	K_i (nM)	cAMP formation[a]
23a	H	3-Benzothienyl	125.8	ANT
23b	Me	3-Benzothienyl	124.5	ANT
23c	H		107.4	--
23d	H	1-Naphthyl	51.7	ANT
23e	Me	1-Naphthyl	246.2	ANT
23f	Me		336.0	ANT
23g	H	8-Quinolyl	151.9	ANT
23h	Me	8-Quinolyl	165.9	ANT
23i	Me		> 1000	--
23j	Me		131.3	ANT

[a] ANT = antagonist.

tion (**17b**) for a 1-naphthyl substitution, whereas it is 4- (**16c**) > 6- (**18d**) > 5-substitution (**17c**) for 2-naphthyl sulfonamides. There is a tendency toward higher affinities achieved with 5-substitution pattern (5-sulfonamides) even though more representatives of the 4-sulfonamides need to be prepared to prove this trend. In agreement to that, the 6-chloroimidazothiazol-5-sulfonamides **17a** and **17l** are the highest-affinity compounds of the whole *N*-aminoalkylindole series. Alkylaryl sulfonamides (**18e** or **18k**) seem to possess less pronounced binding affinity within this series.

Representatives of the 5-sulfonamidotryptamine series (Table 2) display the highest affinities of all series described within this paper, reaching below the nanomolar range (e.g., **19c** 0.1 nM), thus being superior to most compounds known in the literature. In terms of functionality, this series comprises antagonists as well as agonists and partial agonists. Affinities (K_i) under 0.5 nM were obtained by compounds **19c**, **19e**, **19f**, **19g**, and **19o**. Again, the NMe_2 group has a beneficial influence on affinity with longer alkyl substituents having slightly decreased affinities (e.g., **19d** vs **19h**, **19q**), but the introduction of heterocylic moieties such as morpholine (**19v**, K_i = 163.5 nM vs **19d**, K_i = 0.8 nM) or pyrrolidine (**19r**, K_i = 4.0 nM vs **19g**, K_i = 0.3 nM) reduces the affinity significantly. The ideal length for the alkyl chain that connects the indole moiety with the NR_1R_2 group seems again to be two carbon atoms. The gramine pattern (n = 1) reduces the affinity (**19a**, K_i = 5.3 nM vs **19c**, K_i = 0.1 nM), and longer chains (n = 3) decrease the affinity (**19n**, K_i = 163.0 nM vs **19i**, K_i = 5.3 nM). Especially aromatic sulfonamide substituents bearing the 5-chloro-3-methylbenzothiazole motif (**19c**, **19g**, **19o**) lead to low K_i values. *N*-Methyl substitution results in lower affinities (**19m**, K_i = 40.8 nM).

Recently, a new series, the N-(3-glyoxamidoindolyl)-sulfonamides (Table 3), has been prepared to make use of synthetic opportunities along with the elaborated chemical pathways (see Scheme 2). Five representatives have been prepared so far to have a first insight into the potential of this class. Interestingly, already two compounds reached remarkable affinities (**21b**, K_i = 18.4 nM and **21c**, K_i = 224.4 nM) suggesting potential for further optimization. Both compounds behave as antagonists. As within the series described before, it seems that the NMe_2 substitution pattern and the 6-chloroimidazothiazol-5-sulfonamide are favorable for good binding in this class as well. On the other side, **21b** reaches a slightly weaker affinity as compared to its "alkyl chain" analogue **19b** (cf. Table 2).

Within the 3-piperidinylindoles series (Table 4), six representatives have been synthesized, nearly all of them displaying excellent affinities reaching into the nanomolar range. The 5-sulfonamido-3-methyl-5-chlorobenzothiazole substituted compound **20a** has a K_i value of 1 nM. Other substitutions, for example, 5-chlorothiophene (**20d**, K_i = 24.3 nM) or 8-quinolyl (**20e**, K_i = 21.2 nM), lead to slightly reduced affinities. Five compounds have been proven to display antagonistic properties. Formally, these compounds can be regarded as cyclic analogues of 5-sulfonamido-3-aminoalkylindoles with n = 3 (cf. Table 3). Even though only one representative of the latter class has been prepared (**19n**, K_i = 163.0 nM), it can be concluded, that the cyclic orientation of the proton donor group (i.e., the amino function) has a beneficial influence on binding as compared to the rotationally not hindered propyl group in **19n**.

As a result of a screening performed with a series of more than 700 compounds containing a benzoxazinepiperidinyl sulfonamide scaffold, belonging to a more general discovery library, several compounds (depicted in Table 5) showed affinities for the 5-HT$_6$ receptor with a high degree of selectivity. Among a large number of aromatic group substituents at R_2, 3-benzothienyl (**23a,b**), 5-chloro-3-methyl-2-benzothienyl (**23c**), 1-naphthyl (**23d,e**), 8-quinolyl (**23g,h**), and 2,5-dimethoxyphenyl (**23j**) displayed the best affinities (e.g., **23d** K_i = 51.7 nM). Substitution on the phenyl ring of the benzoxazinone moiety with a methyl group seems not to affect affinity in a significant manner. Thus, methyl substitution at R_1 led to similar results for compounds **23a** vs **23b** and **23g** vs **23h**. A bigger difference was observed for compound **23d** (K_i = 51.7 nM) vs **23e** (K_i = 246.2 nM). In terms of functionality, antagonist behavior was observed within all tested compounds. This series is currently undergoing a further lead optimization phase.

Conclusions

New series of 5-HT$_6$ receptor ligands with high affinity and selectivity have been synthesized. The affinities for the 5-HT$_6$ receptor are comparable or in some cases even superior to 5-HT$_6$ ligands reported in

the literature. In terms of functionality, high-affinity antagonists, as well as agonists and even partial agonists, were prepared and could function as potent and selective tool compounds to further elucidate the role of the 5-HT_6 receptor in many possible indications, for example, cognition enhancement, depression, anxiety, or obesity. Compound **19e** (K_i = 0.2 nM) represents an excellent tool compound for in vivo studies of 5-HT_6 antagonist properties, whereas **19c** (K_i = 0.1 nM) and **19g** (K_i = 0.3 nM) represent the highest-affinity 5-HT_6 agonists ever reported in the literature to our knowledge. Having these valuable tools in hands, we are currently performing in vivo studies to elucidate the role of the 5-HT_6 receptor in the above-mentioned therapeutic indications. In addition, to further optimize and to understand the structure−affinity relationships within the different lead scaffolds in more detail as well as to confirm the trends described above, more representatives of the different classes are currently being synthesized.

Experimental Section

General Methods. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and are uncorrected. Proton NMR spectra were obtained on a Varian Unity 300 spectrometer. Elemental analysis for carbon, hydrogen, and nitrogen for target compounds that are critical for the interpretation of the relationship between structure and affinity (SAFIR) were performed by Servei de Microanàlisi in the Consejo Superior de Investigaciones Científicas of Barcelona (CSIC) and were within ±0.4% of theory for the formulas given unless otherwise indicated. Furthermore, for critical compounds, the purity was determined by HPLC and found to be >95% for all these compounds (see Supporting Information), using the following conditions: Waters Alliance 2690 and 2695 (Software Millenium 3.20) and Agilent 1100 (software Chemstation A.06.03) equipment with Waters Symmetry C8 3.9 μm p.s. 150 mm × 3.9 mm eluted with a mixture of acetonitrile and water containing 10 mM heptanesulfonate and 25 mM K_3PO_4 at pH 2.5; Waters Xterra MS-C8 5 μm p.s. 150 mm × 3.9 mm or 100 mm × 3.5 mm eluted with a mixture of acetonitrile containing 0.05% TFA and water containing 0.05% TFA; Waters Xterra MS-C8 3.5 μm p.s. 100 mm × 3 mm eluted with a mixture of acetonitrile and water containing 10 mM phosphate buffer at pH 7.0 and Waters Xterra RP8 5 μm p.s. 150 mm × 3.9 mm eluted with a mixture acetonitrile and water containing 10 mM ammonium acetate buffer, pH 7.0. Analytical thin-layer chromatography (TLC) was conducted on precoated silica gel 60 F_{254} plates (Merck). Silica gel 60, 220−400 mesh was used for flash chromatography purification. All starting materials were obtained from commercial sources and used as received.

General Procedure for Preparation of *N*-Aminoalkylaminoindoles (10, 11a−f, 12a−c). 5-Amino-1-(2-diethylaminoethyl)-1*H*-indole Dihydrochloride (11c). A solution of 5-nitroindole (**2a**) (6.5 g, 40 mmol) in anhydrous DMF (25 mL) was added dropwise to a solution of NaH (50%, suspension in mineral oil, 4.0 g, 85.2 mmol) in anhydrous DMF (150 mL) at room temperature. After being stirred for 30 min, the mixture was cooled to 0 °C, and 2-chloro-*N,N*-diethylethanamine hydrochloride (10.8 g, 80 mmol) was added dropwise. Then, the solution was heated at 80 °C for 3 h. After the solution was cooled (0 °C), H_2O (50 mL) was added slowly. The mixture was extracted with $CHCl_3$, and the organic extract was washed with water, dried with Na_2SO_4, and evaporated to give a brown colored oil. This oil was dissolved in EtOH (50 mL), cooled to 0 °C, and treated with a solution of 5 N HCl in EtOH (10 mL). The yellow colored amorphous solid was filtered off, washed with precooled EtOH, and dried at 60 °C to afford 9.87 g (83%) of 5-nitro-1-(2-diethylaminoethyl)-1*H*-indole hydrochloride **5c**. ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 6H, J = 7.1 Hz), 3.14 (m, 4H), 3.43 (m, 2H), 4.78 (t, 2H, J = 7.3 Hz), 6.80 (d, 1H, J = 3.2 Hz), 7.78 (d, 1H, J = 3.2 Hz), 7.89 (d, 1H, J = 9.1 Hz), 8.06 (dd, 1H, J = 9.1, 2.3 Hz), 8.58 (d, 1H, J = 2.3 Hz), 11.1 (br s, 1H).

Compounds **4**, **5a**−**f**, and **6a**−**c** were prepared analogously.

To a solution of **5c** (4.15 g, 13.95 mmol) in EtOH/H_2O (2:1), 1 g (5%) of Pd/C moistened with water (50%) was added. The mixture was hydrogenated under 20 psi at room temperature for 20 h and filtered through a pad of Celite. The EtOH was evaporated, and the aqueous solution was treated with 20% aqueous NaOH. After extraction with $CHCl_3$, the organic phase was dried with Na_2SO_4 and evaporated to afford a brown colored oil. This oil was dissolved in EtOH (10 mL), cooled to 0 °C, and treated with a solution of 4.2 N HCl in EtOH (10 mL). The violet colored amorphous solid obtained was filtered off, washed with precooled EtOH, and dried at 60 °C to afford 2.71 g (64%) of **11c**. Mp 245−246 °C. ^{1}H NMR (DMSO-d_6) δ 1.17 (t, 6H, J = 7.2 Hz), 3.13 (q, 4H, J = 7.2 Hz), 3.41 (m, 2H), 4.67 (t, 2H, J = 7.0 Hz), 6.59 (d, 1H, J = 3.1 Hz), 7.16 (dd, 1H, J = 8.8, 2.0 Hz), 7.58 (d, 1H, J = 2.0 Hz), 7.60 (d, 1H, J = 3.1 Hz), 7.76 (d, 1H, J = 8.8 Hz).

Compounds **10**, **11a**−**f**, and **12a**−**c** were prepared analogously.

General Procedure for the Preparation of (5-Amino-1*H*-indol-3-yl)-2-oxoacetamides (14). 2-(5-Amino-1*H*-indol-3-yl)-*N,N*-diethyl-2-oxoacetamide Hydrochloride (14b). To a solution of 2-(5-Nitro-1*H*-indol-3-yl)-*N,N*-diethyl-2-oxoacetamide (**7b**)[34] (4.0 g, 13.8 mmol) in DMF (100 mL), 800 mg (5%) of Pd/C moistened with water (50%) were added. The mixture was hydrogenated under 20 psi at room temperature for 20 h. The resulting mixture was filtered through a pad of Celite. The solvent was evaporated to afford an oil that was dissolved in EtOH (25 mL), cooled to 0 °C, and treated with a solution of 5 N HCl in EtOH (3 mL). The suspension was filtered, and the yellow colored amorphous solid obtained was washed with precooled Et_2O and dried at 60 °C to afford 3.9 g (98%) of **14b**. Mp 210−213 °C. ^{1}H NMR (DMSO-d_6) δ 1.05 (m, 3H), 1.16 (m, 3H), 3.22 (m, 2H), 3.41 (m, 2H), 7.26 (dd, 1H, J = 8.6, 1.9 Hz), 7.62 (d, 1H, J = 8.6 Hz), 8.11 (d, 1H, J = 1.9 Hz), 8.15 (d, 1H, J = 3.3 Hz), 10.18 (br s, 2H), 12.57 (s, 1H).

Compound **14a** was prepared analogously.

Preparation of 5-Amino-3-(1-methylpiperidin-4-yl)-1*H*-indole (15). To a solution of 5-nitro-3-(1,2,3,6-tetrahydro-1-methyl-4-pyridinyl)-1*H*-indole[39] (**9**) (11.3 g, 44 mmol) in DMF (500 mL), 4 g (5%) of Pd/C moistened with water (50%) were added. The mixture was hydrogenated under 20 psi at room temperature for 20 h. The resulting mixture was filtered through a pad of Celite. The solvent was evaporated to afford an oil that was triturated with Et_2O (3 mL) to obtain a dark colored amorphous solid. The solid was filtered off, washed with cooled Et_2O, and dried at 60 °C to afford 7.3 g (73%) of **15** as a brown colored amorphous solid. ^{1}H NMR ($CDCl_3$) δ 1.80−1.90 (m, 2H), 2.00−2.14 (m, 4H), 2.34 (m, 3H), 2.71 (m, 1H), 2.98 (d, 2H, J = 11.9 Hz), 3.49 (m, 2H), 6.64 (dd, 1H, J = 8.4, 2.1 Hz), 6.90 (d, 1H, J = 2.1 Hz), 6.95 (d, 1H, J = 1.6 Hz), 7.15 (d, 1H, J = 8.4 Hz), 7.86 (br s, 1H).

General Procedure for the Synthesis of Indolylsulfonamido Compounds (16−21). To a solution of 1.5 mmol of the corresponding amino-1*H*-indole in 10 mL of pyridine, a solution of 1.5 mmol of the corresponding sulfonyl chloride in 2 mL of pyridine was added dropwise at room temperature. The reaction mixture was monitored by TLC until completion, then evaporated to dryness, dissolved in EtOAc, and slightly alkalized with aqueous diluted NH_3. The organic phase was separated and washed with water and a saturated solution of $NaHCO_3$. The organic layer was separated, dried with anhydrous Na_2SO_4, and evaporated. The products were further purified using SiO_2 column chromatography with $CHCl_3$/MeOH mixtures as eluents.

The following compounds were prepared analogously from the properly substitued aminoindoles.

***N*-[1-(2-Dimethylaminoethyl)-2-methyl-1*H*-indol-4-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (16a).** Cream colored amorphous solid. Yield 41%. Mp 78−80 °C. ^{1}H

NMR (DMSO-d_6) δ 2.10 (s, 6H), 2.28 (s, 3H), 2.50 (m, 2H), 4.14 (t, 2H, J = 6.3 Hz), 6.43 (d, 1H, J = 2.0 Hz), 6.92 (d, 1H, J = 7.5 Hz), 7.00 (t, 1H, J = 7.7 Hz), 7.17 (d, 1H, J = 2.2 Hz), 7.25 (d, 1H, J = 7.5 Hz), 7.49 (d, 1H, J = 8.4 Hz), 7.85 (s, 1H), 7.99 (d, 1H, J = 8.5 Hz).

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-4-yl]naphthalene-1-sulfonamide (16b).** Cream colored amorphous solid. Yield 55%. Mp 169−172 °C. ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 6H), 2.48 (m, 2H), 4.10 (t, 2H, J = 6.6 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.85−6.96 (m, 2H), 7.15 (d, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 3.1 Hz), 7.54−7.68 (m, J = 2 Hz), 7.83 (dd, 1H, J = 8.6, 1.8 Hz), 7.94 (d, 1H, J = 8.1 Hz). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-4-yl]naphthalene-2-sulfonamide (16c).** Cream colored amorphous solid. Yield 51%. Mp 156−158 °C. ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 6H), 2.48 (m, 2H), 4.10 (t, 2H, J = 6.6 Hz), 6.58 (d, 1H, J = 3.1 Hz), 6.85−6.96 (m, 2H), 7.15 (d, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 3.1 Hz), 7.54−7.68 (m, J = 2 Hz), 7.83 (dd, 1H, J = 8.6, 1.8 Hz), 7.94 (d, 1H, J = 8.1 Hz). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (17a).** Cream colored amorphous solid. Yield 24%. Mp 50−52 °C. ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6H), 2.64 (t, 2H, J = 6.4 Hz), 4.16 (t, 2H, J = 6.4 Hz), 6.39 (m, 1H), 6.78 (d, 1H, J = 4.0 Hz), 6.94 (d, 1H, J = 8.4 Hz), 7.15 (m, 2H), 7.39 (s, 1H), 7.55 (d, 1H, J = 4.0 Hz).

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]naphthalene-1-sulfonamide (17b).** Orange colored amorphous solid. Yield 54%. Mp 179−181 °C. ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 6H), 2.63 (t, 2H, J = 7.0 Hz), 4.11 (t, 2H, J = 7.0 Hz), 6.28 (d, 1H, J = 3.1 Hz), 6.68 (dd, 1H, J = 8.6, 2.0 Hz), 7.03−7.11 (m, 3H), 7.37 (m, 1H), 7.58−7.70 (m, 2H), 7.94 (d, 1H, J = 8.7 Hz), 8.00 (d, 1H, J = 7.9 Hz), 8.06 (d, 1H, J = 7.3 Hz), 8.73 (d, 1H, J = 8.7 Hz). Anal. ($C_{22}H_{23}N_3O_2S$) H, N, C: calcd, 67.15; found, 66.71.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]naphthalene-2-sulfonamide (17c).** Grey colored solid. Yield 48%. Mp 54−57 °C. ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6H), 2.63 (t, 2H, J = 7.1 Hz), 4.14 (t, 2H, J = 7.1 Hz), 6.35 (d, 1H, J = 3.1 Hz), 6.88 (dd, 1H, J = 8.6, 2.0 Hz), 7.10 (d, 1H, J = 3.1 Hz), 7.15 (d, 1H, J = 8.6 Hz), 7.31 (d, 1H, J = 2.0 Hz), 7.50−7.63 (m, 2H), 7.69 (dd, 1H, J = 8.7, 1.8 Hz), 7.84 (m, 3H), 8.29 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2S$) H, N, C: calcd, 67.15; found, 66.73.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-1-phenylmethanesulfonamide (17d).** Cream colored amorphous solid. Yield 34%. Mp 163−166 °C. ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 6H), 2.70 (t, 2H, J = 7.1 Hz), 4.22 (t, 2H, J = 7.1 Hz), 4.29 (s, 2H), 6.48 (d, 1H, J = 3.1 Hz), 7.04 (dd, 1H, J = 8.8, 2.2 Hz), 7.19 (d, 1H, J = 3.1 Hz), 7.31 (d, 1H, J = 8.8 Hz), 7.33−7.40 (m, 5H), 7.49 (d, 1H, J = 2.2 Hz).

***N*-[1-(2-Dimethylaminoethyl)-2-methyl-1*H*-indol-5-yl]-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (17e).** Colorless amorphous solid. Yield 24%. Mp 182−183 °C. ^{1}H NMR (DMSO-d_6) δ 2.14 (s, 6H), 2.34 (s, 3H), 2.39 (m, 2H), 4.01 (m, 2H), 6.09 (s, 1H), 6.70 (dd, 1H, J = 8.5, 1.8 Hz), 7.08 (d, 1H, J = 1.8 Hz), 7.21 (d, 1H, J = 8.5 Hz), 7.51 (d, 1H, J = 4.5 Hz), 7.80 (d, 1H, J = 4.5 Hz). Anal. ($C_{18}H_{20}ClN_5O_2S_2$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-2-methyl-1*H*-indol-5-yl]-naphthalene-1-sulfonamide (17f).** Colorless amorphous solid. Yield 33%. Mp 183−184 °C. ^{1}H NMR (DMSO-d_6) δ 2.12 (s, 6H), 2.29 (s, 3H), 2.35 (t, 2H, J = 7.0 Hz), 4.01 (t, 2H, J = 7.0 Hz), 5.98 (s, 1H), 6.62 (dd, 1H, J = 8.7, 1.9 Hz), 6.98 (d, 1H, J = 2.0 Hz), 7.07 (d, 1H, J = 8.6 Hz), 7.49 (m, 1H), 7.63 (m, 1H), 7.70 (m, 1H), 8.02 (d, 2H, J = 7.5 Hz), 8.12 (d, 1H, J = 8.0 Hz), 8.75 (d, 1H, J = 8.4 Hz), 10.15 (s, 1H). Anal. ($C_{23}H_{25}N_3O_2S$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-2-methyl-1*H*-indol-5-yl]-naphthalene-2-sulfonamide (17g).** Colorless amorphous solid. Yield 58%. Mp 199−200 °C. ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 6H), 2.30 (s, 3H), 2.35 (t, 2H, J = 7.0 Hz), 4.03 (t, 2H, J = 7.0 Hz), 6.03 (s, 1H), 6.75 (dd, 1H, J = 8.6, 2.0 Hz), 7.10 (d, 1H, J = 2.0 Hz), 7.13 (d, 1H, J = 8.6 Hz), 7.54−7.67 (m, 2H), 7.73 (dd, 1H, J = 8.6, 1.8 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.02 (d, 2H, J = 8.6 Hz), 8.27 (d, 1H, J = 1.5 Hz), 9.89 (s, 1H). Anal. ($C_{23}H_{25}N_3O_2S$) C, H, N.

***N*-[1-(2-Diethylaminoethyl)-1*H*-indol-5-yl]-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (17h).** Beige colored amorphous solid. Yield 44%. Mp 68−70 °C. ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 6H, J = 7.0 Hz), 2.60 (q, 4H, J = 7.0 Hz), 2.81 (t, 2H, J = 6.7 Hz), 4.21 (t, 2H, J = 6.7 Hz), 6.38 (d, 1H, J = 3.0 Hz), 6.79 (d, 1H, J = 4.5 Hz), 6.96 (dd, 1H, J = 8.6, 1.7 Hz), 7.14 (d, 1H, J = 3.0 Hz), 7.19 (d, 1H, J = 8.8 Hz), 7.40 (d, 1H, J = 1.5 Hz), 7.59 (d, 1H, J = 4.4 Hz). Anal. ($C_{19}H_{22}ClN_5O_2S_2$) C, H, N.

***N*-[1-(2-Diethylaminoethyl)-1*H*-indol-5-yl]naphthalene-1-sulfonamide (17i).** Cream colored amorphous solid. Yield 63%. Mp 133−135 °C. ^{1}H NMR (DMSO-d_6) δ 0.87 (m, 6H), 2.58 (m, 4H), 2.76 (m, 2H), 4.14 (m, 2H), 6.24 (s, 1H), 6.73 (d, 1H, J = 8.8 Hz), 7.11 (s, 1H), 7.21 (d, 1H, J = 8.0 Hz), 7.29 (s, 1H), 7.50 (t, 1H, J = 7.8 Hz), 7.63−7.71 (m, 2H), 8.04 (d, 2H, J = 7.5 Hz), 8.13 (d, 1H, J = 8.2 Hz), 8.76 (d, 1H, J = 8.2 Hz), 10.21 (s, 1H).

***N*-[1-(2-Diethylaminoethyl)-1*H*-indol-5-yl]naphthalene-2-sulfonamide (17j).** Cream colored amorphous solid. Yield 46%. Mp 97−104 °C. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 6H, J = 7.1 Hz), 2.54 (q, 4H, J = 7.0 Hz), 2.76 (t, 2H, J = 6.7 Hz), 4.07 (t, 2H, J = 6.7 Hz), 6.66 (dd, 1H, J = 8.5, 1.7 Hz), 6.91 (s, 1H), 6.97 (s, 1H), 7.01 (d, 1H, J = 8.8 Hz), 7.22 (dd, 1H, J = 8.6, 1.6 Hz), 7.26 (s, 1H), 7.42−7.55 (m, 3H), 7.63 (d, 1H, J = 8.1 Hz), 7.70 (d, 1H, J = 8.2 Hz), 8.03 (s, 1H), 9.95 (s, 1H). Anal. ($C_{24}H_{27}N_3O_2S$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-4-phenylbenzenesulfonamide (17k).** Yellow colored oil. Yield 68%. ^{1}H NMR (DMSO-d_6) δ 0.83 (m, 6H), 2.50 (m, 4H), 2.70 (m, 2H), 4.13 (m, 2H), 6.30 (d, 1H, J = 2.6 Hz), 6.87 (d, 1H, J = 8.6 Hz), 7.24 (s, 1H), 7.30 (m, 2H), 7.44 (m, 3H), 7.66 (d, 2H, J = 7.2 Hz), 7.72 (AB sys, 2H, J = 8.5 Hz), 7.78 (AB sys, 2H, J = 8.5 Hz), 9.91 (s, 1H).

***N*-{1-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-5-yl}-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (17l).** Colorless amorphous solid. Yield 54%. Mp 81−84 °C. ^{1}H NMR ($CDCl_3$) δ 1.85 (m, 6H), 2.68 (m, 4H), 3.00 (m, 2H), 4.38 (m, 2H), 6.40 (d, 1H, J = 3.1 Hz), 6.82 (d, 1H, J = 4.5 Hz), 6.96 (d, 1H, J = 8.6 Hz), 7.19 (d, 1H, J = 2.7 Hz), 7.22 (m, 1H), 7.41 (m, 1H), 7.64 (d, 1H, J = 4.5 Hz). Anal. ($C_{19}H_{20}ClN_5O_2S_2 \cdot {}^1/_3H_2O$) C, H, N.

***N*-{1-[2-(Piperidin-1-yl)ethyl]-1*H*-indol-5-yl}-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (17m).** Colorless amorphous solid. Yield 61%. Mp 74−80 °C. ^{1}H NMR (DMSO-d_6) δ 1.37−1.44 (m, 6H), 2.36 (m, 4H), 2.57 (m, 2H), 4.20 (t, 2H, J = 6.6 Hz), 6.34 (d, 1H, J = 2.7 Hz), 6.83 (d, 1H, J = 8.7 Hz), 7.24 (s, 1H), 7.35−7.38 (m, 2H), 7.57 (d, 1H, J = 4.2 Hz), 7.88 (d, 1H, J = 4.5 Hz), 10.48 (br s, 1H). Anal. ($C_{20}H_{22}ClN_5O_2S_2$) C, H, N.

***N*-{1-[3-(Piperidin-1-yl)propyl]-1*H*-indol-5-yl}-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (17n).** Colorless amorphous solid. Yield 30%. Mp 85−86 °C. ^{1}H NMR (DMSO-d_6) δ 1.36 (m, 2H), 1.49 (m, 4H), 1.86 (m, 2H), 2.15−2.44 (m, 6H), 4.10 (t, 2H, J = 6.7 Hz), 6.33 (d, 1H, J = 3.1 Hz), 6.79 (dd, 1H, J = 8.7, 2.0 Hz), 7.21 (d, 1H, J = 2.0 Hz), 7.30−7.36 (m, 2H), 7.52 (d, 1H, J = 4.4 Hz), 7.83 (d, 1H, J = 4.4 Hz), 10.25 (br s, 1H). Anal. ($C_{21}H_{24}ClN_5O_2S_2 \cdot {}^2/_3H_2O$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-6-yl]-6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (18a).** Cream colored amorphous solid. Yield 67%. ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 6H), 2.61 (t, 2H, J = 7.0 Hz), 4.14 (t, 2H, J = 7.0 Hz), 6.41 (d, 1H, J = 3.1 Hz), 6.81 (m, 2H), 7.12 (d, 1H, J = 3.1 Hz), 7.19 (m, 1H), 7.42 (d, 1H, J = 8.2 Hz,), 7.56 (d, 1H, J = 4.6 Hz).

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-6-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (18b).** Colorless amorphous solid. Yield 67%. ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 9H), 2.55 (t, 2H, J = 6.7 Hz), 4.13 (t, 2H, J = 6.7 Hz), 6.42 (d, 1H, J = 3.1 Hz), 6.69 (dd, 1H, J = 8.3, 1.9 Hz), 7.13 (d, 1H,

J = 3.1 Hz), 7.23 (m, 1H), 7.45−7.37 (m, 2H), 7.63 (d, 1H, J = 2.0 Hz), 7.69 (d, 1H, J = 8.6 Hz). Anal. ($C_{21}H_{22}ClN_3O_2S_2$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-6-yl]naphthalene-1-sulfonamide (18c).** Cream colored amorphous solid. Yield 67%. Mp 139−142 °C. ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 6H), 2.50 (t, 2H, J = 7.0 Hz), 4.03 (t, 2H, J = 7.0 Hz), 6.35 (d, 1H, J = 3.1 Hz), 6.48 (dd, 1H, J = 8.4, 1.7 Hz), 7.00 (s, 1H), 7.05 (d, 1H, J = 3.1 Hz), 7.29 (m, 1H), 7.37 (t, 1H, J = 7.8 Hz), 7.60 (m, 1H), 7.67 (m, 1H), 7.92 (d, 1H, J = 8.1 Hz), 7.98 (d, 1H, J = 8.1 Hz), 8.10 (d, 1H, J = 7.3 Hz), 8.73 (d, 1H, J = 8.8 Hz). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N: calcd, 10.68; found, 11.30.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-6-yl]naphthalene-2-sulfonamide (18d).** Cream colored amorphous solid. Yield 80%. Mp 140−143 °C. ^{1}H NMR (DMSO-d_6) δ 2.19 (s, 6H), 2.55 (t, 2H, J = 7.0 Hz), 4.11 (t, 2H, J = 7.0 Hz), 6.39 (d, 1H, J = 3.1 Hz), 6.67 (dd, 1H, J = 8.3, 1.4 Hz), 7.10 (d, 1H, J = 3.1 Hz), 7.19 (s, 1H), 7.39 (d, 1H, J = 8.4 Hz), 7.49−7.65 (m, 2H), 7.69 (dd, 1H, J = 8.9, 1.6 Hz), 7.81−7.88 (m, 3H), 8.29 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2S$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-1*H*-indol-6-yl]-2-(naphthalen-1-yl)-ethanesulfonamide (18e).** Yellow colored amorphous solid. Yield 40%. ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 6H), 2.62 (t, 2H, J = 7.1 Hz), 3.38 (m, 2H), 3.49 (m, 2H), 4.22 (t, 2H, J = 7.1 Hz), 6.47 (d, 1H, J = 2.8 Hz), 7.04 (m, 2H), 7.23 (d, 1H, J = 3.1 Hz), 7.26−7.45 (m, 5H), 7.56 (d, 1H, J = 8.4 Hz), 7.68 (dd, 1H, J = 7.5, 1.5 Hz), 7.77 (d, 1H, J = 8.3 Hz). Anal. ($C_{24}H_{27}N_3O_2S$) C, H, N.

***N*-[1-(2-Dimethylaminoethyl)-2-methyl-1*H*-indol-5-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (18f).** Colorless amorphous solid. Yield 46%. Mp 203−205 °C. ^{1}H NMR (DMSO-d_6) δ 2.13 (s, 6H), 2.33 (s, 6H), 2.39 (t, 2H, J = 7.0 Hz), 4.07 (t, 2H, J = 6.8 Hz), 6.08 (s, 1H), 6.76 (dd, 1H, J = 8.6, 2.0 Hz), 7.13 (d, 1H, J = 2.0 Hz), 7.20 (d, 1H, J = 8.6 Hz), 7.51 (dd, 1H, J = 8.7, 2.0 Hz), 7.93 (d, 1H, J = 2.0 Hz), 8.00 (d, 1H, J = 8.8 Hz), 10.20 (s, 1H). Anal. ($C_{22}H_{24}ClN_3O_2S_2$) C, H, N.

***N*-{1-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-6-yl}-6-chloro-imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (18g).** Yellow colored amorphous solid. Yield 59%. Mp 53−57 °C. ^{1}H NMR (DMSO-d_6) δ 1.64 (m, 4H), 2.50 (m, 4H), 2.70 (m, 2H), 4.14 (m, 2H), 6.31 (d, 1H, J = 2.8 Hz), 6.71 (d, 1H, J = 8.8 Hz), 7.11 (s, 1H), 7.31 (d, 1H, J = 2.9 Hz), 7.37 (d, 1H, J = 8.6 Hz), 7.56 (d, 1H, J = 4.4 Hz), 7.91 (d, 1H, J = 4.5 Hz), 10.63 (br s, 1H).

***N*-{1-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-6-yl}-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (18h).** Yellow colored amorphous solid. Yield 58%. Mp 69−71 °C. ^{1}H NMR (DMSO-d_6) δ 1.58 (m, 4H), 2.31 (m, 4H), 2.36 (s, 3H), 2.59 (m, 2H), 4,11 (m, 2H), 6.31 (s, 1H), 6.79 (d, 1H, J = 8.4 Hz), 7.09 (s, 1H), 7,29 (d, 1H, J = 2.3 Hz), 7.38 (d, 1H, J = 8.5 Hz), 7.51 (d, 1H, J = 8.6 Hz), 7.94 (d, 1H, J = 1.0 Hz), 8.00 (d, 1H, J = 8.35 Hz), 10.39 (br s, 1H).

***N*-{1-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-6-yl}naphthalene-1-sulfonamide (18i).** Cream colored amorphous solid. Yield 66%. Mp 160−165 °C. ^{1}H NMR (DMSO-d_6) δ 1.74 (m, 4H), 2.71 (m, 4H), 2.94 (m, 2H), 4.24 (m, 2H), 6.27 (d, 1H, J = 2.8 Hz), 6.61 (d, 1H, J = 8.6 Hz), 7.09 (s, 1H), 7.24 (d, 1H, J = 8.5 Hz), 7.28 (d, 1H, J = 2.8 Hz), 7.54 (t, 1H, J = 7.9 Hz), 7.63 (m, 1H), 7.71 (m 1H), 8.03 (d, 1H, J = 7.6 Hz), 8.11−8.23 (m. 2H), 8.77 (d, 1H, J = 8.2 Hz), 10.46 (br s, 1H). Anal. ($C_{24}H_{25}N_3O_2S\cdot{}^1/_3CHCl_3$) C, H, N.

***N*-{1-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-6-yl}naphthalene-2-sulfonamide (18j).** Beige colored amorphous solid. Yield 57%. Mp 54−60 °C. ^{1}H NMR (DMSO-d_6) δ 1.54 (m, 4H), 2.24 (m, 4H), 2.50 (m, 2H), 4.06 (m, 2H), 6.25 (s, 1H), 6.77 (d, 1H, J = 8.4 Hz), 7.07 (s, 1H), 7.23 (m, 1H), 7.32 (d, 1H, J = 8.1 Hz), 7.61 (m, 2H), 7.75 (d, 1H, J = 8.8 Hz), 7.95 (d, 1H, J = 7.6 Hz), 8.03 (m, 2H), 8.34 (s, 1H), 10.11 (br s, 1H).

***N*-{1-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-6-yl}-2-(naphthalen-1-yl)-ethanesulfonamide (18k).** Yellow colored amorphous solid. Yield 68%. ^{1}H NMR (DMSO-d_6) δ 1.49 (m, 4H), 2.31 (m, 4H), 2.66 (t, 2H, J = 6.5 Hz), 3.3 (m, 4H), 4.16 (t, 2H, J = 6.5 Hz), 6.40 (dd, 1H, J = 3.1, 0.7 Hz), 7.04 (dd, 1H, J = 8.4, 1.8 Hz), 7.13 (m, 1H), 7.33−7.44 (m, 5H), 7.48 (d, 1H, J = 8.6 Hz), 7.52 (d, 1H, J = 8.4 Hz), 7.75 (t, 1H, J = 4.8 Hz), 7.85 (d, 1H, J = 8.1 Hz), 9.84 (s, 1H). Anal. ($C_{26}H_{29}N_3O_2S\cdot 1.75\ H_2O$) C, H, N.

***N*-[3-Dimethylaminomethyl-1*H*-indol-5-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (19a).** Cream colored amorphous solid. Yield 33%. Mp 148−152 °C. ^{1}H NMR (DMSO-d_6) δ 1.89 (m, 6H), 2.29 (s, 3H), 2.48 (s, 2H), 6.83 (m, 1H), 7.18 (m, 3H), 7.50 (m, 1H), 7.91 (m, 1H), 8.00 (m, 1H), 10.13 (br s, 1H), 10.92 (s, 1H). Anal. ($C_{20}H_{20}ClN_3O_2S_2$) C, H, N.

***N*-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-6-chloro-imidazo[2,1-*b*][1,3]thiazole-5-sulfonamide (19b).** Cream colored amorphous solid. Yield 36%. Mp 215 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 6H), 2.36 (m, 2H), 2.65 (m, 2H), 6.77 (dd, 1H, J = 8.6, 1.7 Hz), 7.07 (s, 1H), 7.09 (s, 1H), 7.18 (d, 1H, J = 8.6 Hz), 7.51 (d, 1H, J = 4.5 Hz), 7.81 (d, 1H, J = 4.5 Hz), 10.80 (s, 1H).

***N*-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (19c)**. Cream colored amorphous solid. Yield 82%. Mp 226−227 °C. ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 6H), 2.23 (m, 2H), 2.28 (s, 3H), 2.59 (m, 2H), 6.83 (dd, 1H, J = 8.4, 1.5 Hz), 7.09 (s, 2H), 7.19 (d, 1H, J = 8.4 Hz), 7.49 (dd, 1H, J = 8.7, 1.6 Hz), 7.91 (d, 1H, J = 1.6 Hz), 7.99 (d, 1H, J = 8.7 Hz), 10.13 (br s, 1H), 10.79 (s, 1H). Anal. ($C_{21}H_{22}ClN_3O_2S_2\cdot{}^1/_4H_2O$) C, H, N.

***N*-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]naphthalene-1-sulfonamide (19d).** Cream colored amorphous solid. Yield 66%. Mp 203−205 °C. ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 6H), 2.21 (m, 2H), 2.54 (m, 2H), 6.69 (dd, 1H, J = 8.6, 1.7 Hz), 6.94 (s, 1H), 7.03 (s, 1H), 7.06 (d, 1H, J = 8.1 Hz), 7.49 (t, 1H, J = 7.8 Hz), 7.64 (m, 1H), 7.71 (m, 1H), 8.02 (m, 2H), 8.13 (d, 1H, J = 8.1 Hz), 8.79 (d, 1H, J = 8.4 Hz), 10.10 (br s, 1H), 10.68 (s, 1H). Anal. ($C_{22}H_{23}N_3O_2S$) H, N, C: calcd, 67.15; found, 66.71.

***N*-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-5-chloro-naphthalene-2-sulfonamide (19e).** Cream colored amorphous solid. Yield 55%. Mp 230−240 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 6H), 2.18 (m, 2H), 2.57 (m, 2H), 6.81 (dd, 1H, J = 8.6, 1.7 Hz), 7.02 (s, 1H), 7.05 (d, 1H, J = 1.7 Hz), 7.15 (d, 1H, J = 8.6 Hz), 7.57 (m, 1H), 7.82 (d, 1H, J = 7.5 Hz), 7.91 (d, 1H, J = 8.9 Hz), 8.06 (d, 1H, J = 8.2 Hz), 8.29 (d, 1H, J = 8.9 Hz), 8.35 (s, 1H), 9.94 (br s, 1H), 10.74 (s, 1H). Anal. ($C_{22}H_{22}ClN_3O_2S\cdot{}^1/_4H_2O$) C, H, N.

***N*-[3-(2-Dimethylaminoethyl)-1*H*-indol-5-yl]-4-phenyl-benzenesulfonamide (19f).** Colorless amorphous solid. Yield 69%. Mp 184−186 °C. ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 6H), 2.32 (m, 2H), 2.64 (m, 2H), 6.83 (dd, 1H, J = 8.6, 1.9 Hz), 7.08 (d, 1H, J = 2.0 Hz), 7.11 (d, 1H, J = 1.9 Hz), 7.17 (d, 1H, J = 8.6 Hz), 7.34−7.50 (m, 3H), 7.66 (d, 2H, J = 7.5 Hz), 7.72 (AB sys, 2H, J = 8.6 Hz), 7.79 (AB sys, 2H, J = 8.6 Hz), 9.79 (s, 1H), 10.75 (s, 1H). Anal. ($C_{24}H_{25}N_3O_2S$) C, H, N.

***N*-[3-(2-Diethylaminoethyl)-1*H*-indol-5-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (19 g).** Cream colored amorphous solid. Yield 62%. Mp 170−173 °C. ^{1}H NMR (DMSO-d_6) δ 0.88 (t, 6H, J = 7.1 Hz), 2.28 (s, 3H), 2.30−2.46 (m, 6H), 2.58 (m, 2H), 6.85 (dd, 1H, J = 8.6, 2.0 Hz), 7.10 (m, 2H), 7.20 (d, 1H, J = 8.6 Hz), 7.50 (dd, 1H, J = 8.7, 2.0 Hz), 7.90 (d, 1H, J = 2.0 Hz), 7.98 (d, 1H, J = 8.7 Hz), 10.10 (br s, 1H), 10.80 (s, 1H). Anal. ($C_{23}H_{26}ClN_3O_2S_2$) C, H, N.

***N*-[3-(2-Diethylaminoethyl)-1*H*-indol-5-yl]naphthalene-1-sulfonamide (19h).** Cream colored amorphous solid. Yield 67%. Mp 174−175.5 °C. ^{1}H NMR (DMSO-d_6) δ 0.90 (t, 6H, J = 6.9 Hz), 2.35−2.43 (m, 8H), 6.69 (dd, 1H, J = 8.4, 1.8 Hz), 6.95 (d, 1H, J = 1.8 Hz), 7.02 (d, 1H, J = 2.4 Hz), 7.05 (d, 1H, J = 8.7 Hz), 7.47 (t, 1H, J = 8.1 Hz), 7.66 (m, 2H), 8.01 (m, 2H), 8.12 (d, 1H, J = 8.4 Hz), 8.78 (d, 1H, J = 7.8 Hz), 10.10 (br s, 1H), 10.67 (s, 1H). Anal. ($C_{24}H_{27}N_3O_2S$) C, H, N: calcd, 9.97; found, 10.40.

***N*-[3-(2-Diethylaminoethyl)-1*H*-indol-5-yl]naphthalene-2-sulfonamide (19i).** Cream colored amorphous solid. Yield 70%. Mp 172−173 °C. ^{1}H NMR (DMSO-d_6) δ 0.87 (t, 6H, J = 7.1 Hz), 2.39 (m, 6H), 2.55 (m, 2H), 6.82 (d, 1H, J = 8.6 Hz), 7.05 (s, 1H), 7.09 (s, 1H), 7.13 (d, 1H, J = 8.6 Hz), 7.60 (m,

2H), 7.73 (d, 1H, J = 8.6 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.01 (m, 2H), 8.26 (s, 1H), 9.86 (br s, 1H), 10.71 (s, 1H). Anal. ($C_{24}H_{27}N_3O_2S$) C, H, N.

***N*-[3-(2-Diethylaminoethyl)-1*H*-indol-5-yl]-5-chloronaphthalene-1-sulfonamide (19j).** Cream colored amorphous solid. Yield 56%. Mp 154−156 °C. ^{1}H NMR (DMSO-d_6) δ 0.88 (t, 6H, J = 6.7 Hz), 2.41 (m, 6H), 2.49 (m, 2H), 6.71 (d, 1H, J = 8.1 Hz), 6.88 (s, 1H), 7.07 (m, 2H), 7.66 (m, 2H), 7.84 (d, 1H, J = 7.0 Hz), 8.09 (d, 1H, J = 7.0 Hz), 8.41 (d, 1H, J = 8.2 Hz), 8.79 (d, 1H, J = 8.6 Hz), 10.17 (br s, 1H), 10.71 (s, 1H).

***N*-[3-(2-Diethylaminoethyl)-1*H*-indol-5-yl]-3,5-dichlorobenzenesulfonamide (19k).** Cream colored amorphous solid. Yield 67%. Mp 168−170 °C. ^{1}H NMR (DMSO-d_6) δ 0.95 (t, 6H, J = 7.1 Hz), 2.44−2.58 (m, 6H), 2.66 (m, 2H), 6.79 (dd, 1H, J = 8.6, 1.7 Hz), 7.08 (d, 1H, J = 0.9 Hz), 7.13 (d, 1H, J = 1.7 Hz), 7.23 (d, 1H, J = 8.6 Hz), 7.58 (m, 2H), 7.87 (m, 1H), 9.95 (br s, 1H), 10.82 (s, 1H).

***N*-[3-(2-Diethylaminoethyl)-1*H*-indol-5-yl]-4-phenylbenzenesulfonamide (19l).** Cream colored amorphous solid. Yield 68%. Mp 161−163 °C. ^{1}H NMR (DMSO-d_6) δ 0.89 (t, 6H, J = 7.1 Hz), 2.32−2.55 (m, 6H), 2.62 (m, 2H), 6.85 (d, 1H, J = 8.6 Hz), 7.08 (d, 1H, J = 2.0 Hz), 7.13 (s, 1H), 7.18 (d, 1H, J = 8.6 Hz), 7.33−7.50 (m, 3H), 7.64 (d, 2H, J = 7.5 Hz), 7.72 (sys AB, 2H, J = 8.6 Hz), 7.78 (sys AB, 2H, J = 8.6 Hz), 9.80 (br s, 1H), 10.75 (s, 1H).

***N*-[3-(2-Diethylaminoethyl)-1-methyl-1*H*-indol-5-yl]-naphthalene-2-sulfonamide (19m).** Cream colored amorphous solid. Yield 13%. Mp 134−136 °C. ^{1}H NMR (DMSO-d_6) δ 0.98 (t, 6H, J = 7.1 Hz), 2.55 (m, 6H), 2.70 (m, 2H), 3.67 (s, 3H), 6.84 (s, 1H), 6.93 (dd, 1H, J = 8.6, 2.0 Hz), 7.10 (d, 1H, J = 8.7 Hz), 7.18 (d, 1H, J = 1.7 Hz), 7.26 (s, 1H), 7.57 (m, 2H), 7.67 (dd, 1H, J = 8.7, 1.8 Hz), 7.84 (m, 3H), 8.27 (d, 1H, J = 1.7 Hz). Anal. ($C_{25}H_{29}N_3O_2S\cdot{}^1/_4H_2O$) C, H, N.

***N*-[3-(2-Dipropylaminoethyl)-1*H*-indol-5-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (19o).** Yellow colored amorphous solid. Yield 82%. Mp 90−95 °C. ^{1}H NMR (DMSO-d_6) δ 0.80 (t, 6H, J = 7.3 Hz), 1.31 (q, 4H, J = 7.3 Hz), 2.26 (m, 7H), 2.38 (m, 2H), 2.56 (m, 2H), 6.83 (dd, 1H, J = 8.4, 1.8 Hz), 7.08 (s, 2H), 7.20 (d, 1H, J = 8.6 Hz), 7.50 (dd, 1H, J = 8.6, 2.0 Hz), 7.90 (d, 1H, J = 2.0 Hz), 7.99 (d, 1H, J = 8.6 Hz), 10.12 (br s, 1H), 10.79 (s, 1H). Anal. ($C_{25}H_{30}ClN_3O_2S_2\cdot{}^1/_2H_2O$) C, H, N.

***N*-[3-(2-Dipropylaminoethyl)-1*H*-indol-5-yl]naphthalene-2-sulfonamide (19p).** Cream colored amorphous solid. Yield 50%. Mp 58−64 °C (dec). ^{1}H NMR (DMSO-d_6) δ 0.79 (t, 6H, J = 7.3 Hz), 1.31 (q, 4H, J = 7.3 Hz), 2.28 (t, 4H, J = 7.3 Hz), 2.42 (m, 2H), 2.57 (m, 2H), 6.80 (dd, 1H, J = 8.6, 1.7 Hz), 7.04 (d, 1H, J = 1.7 Hz), 7.12 (m 2H), 7.60 (m, 2H), 7.72 (dd, 1H, J = 8.6, 1.7 Hz), 7.98 (m, 3H), 8.25 (s, 1H), 9.87 (br s, 1H), 10.70 (s, 1H).

***N*-[3-(2-Dibutylaminoethyl)-1*H*-indol-5-yl]naphthalene-1-sulfonamide (19q).** Cream colored amorphous solid. Yield 71%. Mp 111−113 °C. ^{1}H NMR (DMSO-d_6) δ 0.86 (t, 6H, J = 7.0 Hz), 1.29 (m, 8H), 2.35 (m, 4H), 2.41 (m, 2H), 2.53 (m, 2H), 6.67 (dd, 1H, J = 8.5, 1.9 Hz), 7.09 (m, 3H), 7.48 (t, 1H, J = 7.9 Hz), 7.68 (m, 2H), 8.01 (s, 1H), 8.04 (s, 1H), 8.12 (d, 1H, J = 8.2 Hz), 8.78 (d, 1H, J = 8.2 Hz), 10.13 (s, 1H), 10.67 (s, 1H). Anal. ($C_{28}H_{35}N_3O_2S\cdot{}^1/_4H_2O$) C, H, N.

***N*-{3-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-5-yl}-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (19r).** Colorless amorphous solid. Yield 35%. Mp 201−203 °C. ^{1}H NMR (DMSO-d_6) δ 1.62 (m, 4H), 2.29 (s, 3H), 2.30 (m, 4H), 2.36 (m, 2H), 2.63 (m, 2H), 6.86 (d, 1H, J = 8.6 Hz), 7.05 (s, 1H), 7.09 (s, 1H), 7.21 (dd, 1H, J = 8.6, 2.2 Hz), 7.50 (dd, 1H, J = 8.7, 2.0 Hz), 7.92 (s, 1H), 7.99 (dd, 1H, J = 8.7, 2.2 Hz), 10.10 (br s, 1H), 10.81 (s, 1H). Anal. ($C_{23}H_{24}ClN_3O_2S_2\cdot{}^1/_2H_2O$) C, H, N.

***N*-{3-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-5-yl}naphthalene-1-sulfonamide (19s).** Cream colored amorphous solid. Yield 66%. Mp 212−214 °C. ^{1}H NMR (DMSO-d_6) δ 1.66 (m, 4H), 2.36 (m, 6H), 2.58 (m, 2H), 6.71 (d, 1H, J = 8.6 Hz), 6.93 (s, 1H), 7.02 (s, 1H), 7.07 (d, 1H, J = 8.6 Hz), 7.48 (m, 1H), 7.68 (m, 2H), 8.02 (dd, 2H, J = 7.2, 1.2 Hz), 8.12 (d, 1H, J = 8.2 Hz), 8.79 (d, 1H, J = 8.6 Hz), 10.10 (br s, 1H), 10.68 (s, 1H).

***N*-{3-[2-(Pyrrolidin-1-yl)ethyl]-1*H*-indol-5-yl}naphthalene-2-sulfonamide (19t).** Cream colored amorphous solid. Yield 52%. Mp 180−182 °C. ^{1}H NMR (DMSO-d_6) δ 1.60 (m, 4H), 2.26 (m, 4H), 2.35 (m, 2H), 2.61 (m, 2H), 6.82 (dd, 1H, J = 8.6, 2.0 Hz), 7.05 (m, 2H), 7.14 (d, 1H, J = 8.6 Hz), 7.61 (m, 2H), 7.74 (dd, 1H, J = 8.6, 1.8 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.02 (m, 2H), 8.27 (s, 1H), 9.86 (br s, 1H), 10.72 (s, 1H).

***N*-{3-[2-(Morpholin-4-yl)ethyl]-1*H*-indol-5-yl}-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (19u).** Cream colored amorphous solid. Yield 91%. Mp 200−201 °C. ^{1}H NMR (DMSO-d_6) δ 2.25 (m, 6H), 2.27 (s, 3H), 2.62 (t, 2H, J = 7.9 Hz), 3.52 (m, 4H), 6.84 (d, 1H, J = 8.2 Hz), 7.06 (s, 1H), 7.10 (s, 1H), 7.20 (d, 1H, J = 8.6 Hz), 7.50 (d, 1H, J = 8.6 Hz), 7.92 (s, 1H), 8.00 (d, 1H, J = 8.6 Hz), 10.13 (s, 1H), 10.80 (s, 1H).

***N*-{3-[2-(Morpholin-4-yl)ethyl]-1*H*-indol-5-yl}naphthalene-1-sulfonamide (19v).** Cream colored amorphous solid. Yield 94%. Mp 218−220 °C. ^{1}H NMR (DMSO-d_6) δ 2.30 (m, 6H), 2.56 (m, 2H), 3.56 (m, 4H), 6.69 (d, 1H, J = 8.4 Hz), 6.93 (s, 1H), 7.06 (m, 2H), 7.48 (t, 1H, J = 7.3 Hz), 7.67 (m, 2H), 8.02 (m, 2H), 8.13 (d, 1H, J = 8.1 Hz), 8.78 (d, 1H, J = 8.1 Hz), 10.10 (s, 1H), 10.68 (s, 1H). Anal. ($C_{24}H_{25}N_3O_3S\cdot{}^2/_3$-HCl) C, H, N.

***N*-{3-[2-(Morpholin-4-yl)ethyl]-1*H*-indol-5-yl}naphthalene-2-sulfonamide (19w).** Cream colored amorphous solid. Yield 92%. Mp 85−90 °C. ^{1}H NMR (DMSO-d_6) δ 2.27 (m, 6H), 2.61 (t, 2H, J = 7.9 Hz), 3.52 (t, 4H, J = 4.6 Hz), 6.82 (dd, 1H, J = 8.6, 2.0 Hz), 7.06 (s, 1H), 7.07 (s, 1H), 7.15 (d, 1H, J = 8.6 Hz), 7.61 (m, 2H), 7.74 (dd, 1H, J = 8.8, 1.8 Hz), 7.96 (d, 1H, J = 8.1 Hz), 8.03 (m, 2H), 8.27 (s, 1H), 9.87 (s, 1H), 10.74 (s, 1H).

***N*-{3-[2-(Morpholin-4-yl)ethyl]-1*H*-indol-5-yl}quinolyl-8-sulfonamide (19x).** Brown colored amorphous solid. Yield 48%. Mp 234−235 °C. ^{1}H NMR (DMSO-d_6) δ 2.29 (m, 6H), 2.66 (m, 2H), 3.47 (m, 4H), 6.84 (d, 1H, J = 8.6 Hz), 7.07 (s, 1H), 7.09 (s, 1H), 7.18 (d, 1H, J = 8.4 Hz), 7.45 (m, 3H), 7.70 (m, 4H), 7.79 (m, 2H), 9.79 (s, 1H), 10.77 (s, 1H).

***N*-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]-5-chloro-3-methyl-benzo[*b*]thiophene-2-sulfonamide (20a).** Colorless amorphous solid. Yield 51%. Mp 239−241 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.53−1.80 (m, 4H), 2.26 (s, 3H), 2.39−2.71 (m, 6H), 3.02 (d, 2H, J = 8.8 Hz), 6.76 (d, 1H, J = 8.8 Hz), 7.05 (s, 1H), 7.11 (s, 1H), 7.19 (d, 1H, J = 8.8 Hz), 7.51 (d, 1H, J = 8.7 Hz), 7.91 (s, 1H), 8.00 (d, 1H, J = 8.7 Hz), 10.10 (br s, 1H), 10.90 (s, 1H). Anal. ($C_{23}H_{24}ClN_3O_2S_2$) C, H, N.

***N*-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]naphthalene-1-sulfonamide Hydrochloride (20b).** Colorless amorphous solid. Yield 69%. Mp 212 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.80 (m, 4H), 2.74 (m, 4H), 3.04 (m, 2H), 3.39 (m, 2H), 6.63 (d, J = 8.6 Hz, 1H), 7.00 (s, 2H), 7.08 (d, J = 8.6 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.60−7.77 (m, 2H), 8.04 (d, J = 7.5 Hz, 2H), 8.13 (d, J = 8.2 Hz, 1H), 8.79 (d, J = 8.2 Hz, 1H), 10.16 (s, 1H), 10.66 (br s, 1H), 10.88 (s, 1H).

***N*-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]-5-chlorothiophene-1-sulfonamide (20c).** Cream colored amorphous solid. Yield 59%. Mp 246−249 °C. ^{1}H NMR (DMSO-d_6) δ 1.35−1.47 (m, 4H), 1.86 (m, 2H), 2.17 (s, 3H), 2.28 (m, 1H), 2.76 (d, 2H, J = 10.6 Hz), 6.68 (d, 1H, J = 8.8 Hz), 6.75 (s, 1H), 6.94 (s, 1H), 7.08 (d, 1H, J = 9.0 Hz), 7.60−7.73 (m, 2H), 7.85 (d, 1H, J = 7.1 Hz), 8.06 (d, 1H, J = 7.1 Hz), 8.40 (d, 1H, J = 7.9 Hz), 8.79 (d, 1H, J = 9.0 Hz), 10.20 (br s, 1H), 10.68 (s, 1H).

***N*-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]-5-chlorothiophene-2-sulfonamide (20d).** Cream colored amorphous solid. Yield 18%. Mp 284 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.62 (m, 2H), 1.78 (d, 2H, J = 11.7 Hz), 1.99 (m, 2H), 2.18 (s, 3H), 2.55 (m, 1H), 2.84 (d, 2H, J = 10.6 Hz), 6.81 (d, 1H, J = 8.6 Hz), 7.07 (s, 1H), 7.13 (m 1H), 7.16 (s, 1H), 7.20−7.26 (m, 1H), 9.90 (br s, 1H), 10.83 (s, 1H).

***N*-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]quinolyl-2-sulfonamide (20e).** Cream colored amorphous solid. Yield 71%. Mp 280 °C (dec). ^{1}H NMR (DMSO-d_6) δ 1.25−1.52 (m, 4H), 1.85 (m, 2H), 2.18 (s, 3H), 2.27 (m, 1H), 2.74 (d, 2H, J = 11.4 Hz), 6.72 (dd, 1H, J = 8.6, 2.0 Hz), 6.83 (d, 1H, J = 1.5

Hz), 6.90 (d, 1H, J = 2.0 Hz), 7.02 (d, 1H, J = 8.6 Hz), 7.57 (m, 1H), 7.74 (dd, 1H, J = 8.4, 4.3 Hz), 8.12 (dd, 1H, J = 7.3, 1.3 Hz), 8.19 (dd, 1H, J = 8.2, 1.3 Hz), 8.52 (dd, 1H, J = 8.4, 1.7 Hz), 9.21 (dd, 1H, J = 4.3, 1.7 Hz), 9.36 (s, 1H), 10.64 (s, 1H). Anal. ($C_{23}H_{24}N_4O_2S \cdot {}^1/_2H_2O$) C, H, N.

***N*-[3-(1-Methylpiperidin-4-yl)-1*H*-indol-5-yl]-4-phenylbenzenesulfonamide (20f).** Cream colored amorphous solid. Yield 70%. Mp 247−248 °C. ^{1}H NMR (DMSO-d_6) δ 1.52 (s, 2H), 1.67 (m, 2H), 1.85 (m, 2H), 2.08 (s, 3H), 2.44 (m, 1H), 2.67 (d, 2H, J = 10.25 Hz), 6.83 (d, 1H, J = 8.4 Hz), 7.01 (s, 1H), 7.03 (s, 1H), 7.19 (d, 1H, J = 8.4 Hz), 7.35−7.50 (m, 3H), 7.63−7.73 (m, 4H), 7.79 (sys AB, 2H, J = 7.6 Hz), 9.71 (br s, 1H), 10.76 (s, 1H).

2-[5-(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonylamino)-1*H*-indol-3-yl]-*N,N*-dimethyl-2-oxoacetamide (21a). Cream colored amorphous solid. Yield 42%. Mp 272 °C. ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 2.80 (s, 3H), 2.93 (s, 3H), 7.06 (dd, 1H, J = 8.7, 1.9 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.50 (dd, 1H, J = 8.8, 2.0 Hz), 7.85 (s, 1H), 7.94 (d, 1H, J = 1.7 Hz), 8.00 (d, 1H, J = 8.5 Hz), 8.05 (d, 1H, J = 3.1 Hz), 10.53 (s, 1H), 12.30 (s, 1H).

2-[5-(6-Chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonylamino)-1*H*-indol-3-yl]-*N,N*-dimethyl-2-oxoacetamide (21b). Cream colored amorphous solid. Yield 41%. Mp 161−164 °C. ^{1}H NMR (DMSO-d_6) δ 2.84 (s, 3H), 2.94 (s, 3H), 7.02 (d, 1H, J = 7.6 Hz), 7.39 (d, 1H, J = 8.5 Hz), 7.56 (d, 1H, J = 4.4 Hz), 7.79 (s, 1H), 7.88 (d, 1H, J = 4.4 Hz), 8.06 (s, 1H), 10.68 (s, 1H), 12.29 (s, 1H). Anal. ($C_{17}H_{14}ClN_5O_4S_2 \cdot {}^1/_2H_2O$) C, H, N.

2-[5-(6-Chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonylamino)-1*H*-indol-3-yl]-*N,N*-diethyl-2-oxoacetamide (21c). Colorless amorphous solid. Yield 37%. Mp 249−251 °C. ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 3H, J = 7.0 Hz), 1.14 (t, 3H, J = 7.0 Hz), 3.17 (m, 2H), 3.39 (m, 2H), 7.02 (dd, 1H, J = 8.8, 2.0 Hz), 7.39 (d, 1H, J = 8.8 Hz), 7.56 (d, 1H, J = 4.4 Hz), 7.79 (d, 1H, J = 1.6 Hz), 7.87 (d, 1H, J = 4.4 Hz), 7.99 (d, 1H, J = 2.5 Hz), 10.67 (s, 1H), 12.24 (s, 1H). Anal. ($C_{19}H_{18}ClN_5O_4S_2$) C, H, N.

***N,N*-Diethyl-2-[5-(naphthalene-1-sulfonylamino)-1*H*-indol-3-yl]-2-oxoacetamide (21d).** Cream colored amorphous solid. Yield 56%. Mp 275−277 °C. ^{1}H NMR (DMSO-d_6) δ 0.99 (t, 3H, J = 7.0 Hz), 1.12 (t, 3H, J = 7.0 Hz), 3.14 (m, 2H), 3.36 (m, 2H), 6.94 (dd, 1H, J = 8.6, 2.0 Hz), 7.27 (d, 1H, J = 9.0 Hz), 7.54 (t, 1H, J = 7.7 Hz), 7.63 (m, 1H), 7.70 (m, 2H), 7.92 (s, 1H), 8.03 (d, 1H, J = 7.3 Hz), 8.13 (m, 2H), 8.76 (d, 1H, J = 8.8 Hz), 10.49 (s, 1H), 12.14 (s, 1H).

***N,N*-Diethyl-2-oxo-2-[5-(quinoline-8-sulfonylamino)-1*H*-indol-3-yl]-acetamide (21e).** Cream colored amorphous solid. Yield 42%. Mp 227−232 °C. ^{1}H NMR (DMSO-d_6) δ 0.99 (t, 3H, J = 6.9 Hz), 1.13 (t, 3H, J = 6.9 Hz), 3.13 (m, 2H), 3.36 (m, 2H), 6.92 (dd, 1H, J = 8.8, 1.8 Hz), 7.21 (d, 1H, J = 8.6 Hz), 7.63 (t, 1H, J = 7.6 Hz), 7.72 (m, 2H), 7.88 (s, 1H), 8.23 (m, 2H), 8.49 (d, 1H, J = 7.4 Hz), 9.18 (dd, 1H, J = 7.4, 1.4 Hz), 9.9 (s, 1H), 12.10 (s, 1H).

***N*-[3-(3-Diethylaminopropyl)-1*H*-indol-5-yl]naphthalene-2-sulfonamide (19n).** To a stirred mixture of **2a** (6.7 g, 41.3 mmol) and phthalimide (2.7 g, 18.4 mmol) in anhydrous Et_2O (150 mL), malonyldichloride (18.1 g, 128 mmol) was added dropwise. The reaction mixture was stirred at room temperature under nitrogen for 72 h. The resulting reaction mixture was cooled to 4 °C, and dimethylamine (67 mL) was added. The resulting mixture was stirred at room temperature for 1 h. Water (100 mL) was added, and the pH was adjusted to pH 3 using concentrated aqueous HCl. The mixture was extracted with EtOAc. The organic layer was separated, dried, and evaporated to obtain an orange colored amorphous solid that was purified using SiO_2 flash chromatography with $CHCl_3$/MeOH (9:1) as solvent to yield 3.0 g (24%) of *N,N*-diethyl-3-(5-nitro-1*H*-indol-3-yl)-3-oxopropanamide as a yellow colored amorphous solid. ^{1}H NMR (DMSO-d_6) δ 1.02 (t, 3H, J = 7.1 Hz), 1.11 (t, 3H, J = 7.1 Hz), 3.20−3.40 (m, 4H), 4.02 (s, 2H), 7.68 (d, 1H, J = 9.0 Hz), 8.11 (dd, 1H, J = 9.0, 2.3 Hz), 8.59 (d, 1H, J = 2.0 Hz), 9.00 (d, 1H, J = 2.3 Hz), 12.59 (br s, 1H).

To a stirred solution of *N,N*-diethyl-3-(5-nitro-1*H*-indol-3-yl)-3-oxopropanamide (1.0 g, 3.3 mmol) in anhydrous THF (30 mL), borane in THF (12.5 mL, 1.0 M, 12.5 mmol, 3.8 equiv) was added dropwise. The reaction mixture was stirred at room temperature under N_2 atmosphere for 20 h. A saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with Et_2O. The organic extracts were combined, dried, and evaporated to dryness to afford 1.8 g of the borane complex as an orange colored amorphous solid that was treated with CsF (1.8 g) and Na_2CO_3 (1.8 g) in absolute EtOH (50 mL). The mixture was heated at reflux under N_2 atmosphere for 16 h. The resulting reaction mixture was filtered through Decalite, and the filtrate was dried with Na_2SO_4 and evaporated to dryness. The obtained solid was purified using SiO_2 flash chromatography with CH_2Cl_2/MeOH/NH_4OH (9:1:0.01) as solvent to afford 0.5 g (55%) of *N,N*-diethyl-3-(5-nitro-1*H*-indol-3-yl)propanamine as an orange colored oil. ^{1}H NMR (DMSO-d_6) δ 0.91 (t, 6H, J = 7.1 Hz), 1.74 (m, 2H), 2.40−2.50 (m, 6H), 2.73 (m, 2H), 7.38 (s, 1H), 7.47 (d, 1H, J = 9.0 Hz), 7.95 (dd, 1H, J = 9.0, 2.0 Hz), 8.47 (d, 1H, J = 2.0 Hz), 11.54 (br s, 1H).

To a solution of *N,N*-diethyl-3-(5-nitro-1*H*-indol-3-yl)propanamine (0.5 g, 1.8 mmol) in absolute EtOH (20 mL), 100 mg (5%) of Pd/C moistened with water (50%) were added. The mixture was hydrogenated under 20 psi at room temperature for 20 h. The resulting mixture was filtered through a pad of Celite, and the filtrate was evaporated to dryness to afford 0.44 g (98%) of 3-[3-(diethylamino)propyl]-1*H*-indol-5-amine as a red colored oil. ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 6H, J = 7.1 Hz), 1.86 (m, 2H), 2.50−2.60 (m, 6H), 2.67 (m, 2H), 6.64 (dd, 1H, J = 8.4, 2.1 Hz), 6.90 (m, 2H), 7.16 (d, 1H, J = 8.4 Hz), 7.78 (br s, 1H).

From 3-[3-(diethylamino)propyl]-1*H*-indol-5-amine, following the general methodology for the synthesis of indolylsulfonamido compounds, **19n** was obtained as a colorless amorphous solid. Yield 47%. Mp 128−130 °C. ^{1}H NMR (DMSO-d_6) δ 0.86 (t, 6H, J = 7.0 Hz), 1.51 (t, 2H, J = 6.9 Hz), 2.27 (t, J = 6.9 Hz), 2.35 (q, 4H, J = 7.0 Hz), 2.46 (m, 2H), 6.77 (d, 1H, J = 8.6 Hz), 7.00 (s, 1H), 7.10 (m, 2H), 7.60 (m, 2H), 7.72 (d, 1H, J = 8.8 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.02 (m, 2H), 8.26 (s, 1H), 9.86 (br s, 1H), 10.67 (s, 1H). Anal. ($C_{25}H_{29}N_3O_2S$) C, H, N.

8-Methyl-1-piperidin-4-yl-1,4-dihydro-benzo[*d*][1,3]-oxazin-2-one Hydrochloride (22b). 1-(*tert*-Butyloxycarbonyl)-4-piperidone (9.96 g, 50 mmol), 2-amino-3-methyl-benzyl alcohol (7.54 g, 55 mmol), and AcOH (6.3 mL, 110 mmol) were dissolved in dry toluene (200 mL). The solution was refluxed with azeotropic removal of water for 6 h, then evaporated to half of the original volume. To the solution, $NaBH_3CN$ (10.37 g, 165 mmol) in dry THF (150 mL) was added. Then, AcOH (4.9 mL, 85 mmol) was added dropwise. The reaction was stirred at room temperature for 24 h and concentrated under reduced pressure, and the residue was dissolved in EtOAc (350 mL). The solution was washed with saturated aqueous $NaHCO_3$ (4 × 125 mL) and brine (125 mL). The combined EtOAc layers were separated and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using 30% EtOAc in hexane. 1-(*tert*-Butyloxycarbonyl)-4-(2-hydroxymethyl-6-methyl-phenylamine)-piperidine was obtained as a brown viscuous oil (14.70 g, 92%). ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 2H), 1.45 (s, 9H), 1.87 (d, 2H, J = 12.4 Hz), 2.26 (s, 3H), 2.69 (t, 2H, J = 12.4 Hz), 3.08 (m, 1H), 3.59 (br s, 2H), 4.10 (m, 2H), 4.67 (s, 2H), 6.87 (m, 1H), 7.00 (d, 1H, J = 7.3 Hz), 7.07 (d, 1H, J = 7.5 Hz). This intermediate (14.60 g, 47 mmol) was dissolved in dry THF (150 mL) and cooled to 0 °C. To the solution, *N,N*-diisopropylethylamine (26 mL, 150 mmol) and triphosgene (5.04 g, 17 mmol) were added. The reaction was stirred at 0 °C for 1 h and then at room temperature for 72 h. Et_2O (150 mL) was added, the mixture was cooled to 0 °C for 2 h, and the hydrochloride salt of *N,N*-diisopropylethylamine was removed by filtration. The filtrates were evaporated to dryness, and the residue was dissolved in EtOAc (300 mL). The EtOAc solution was washed with 5% aqueous citric acid (2 × 250 mL), water (100 mL), and saturated aqueous $NaHCO_3$ (2 × 200 mL). The EtOAc layer was dried with Na_2SO_4, and the solvent was removed under

reduced pressure to give 1-(*tert*-butyloxycarbonyl)-4-(piperidinyl)-8-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (15.63 g, 96%) of a crude yellow colored oil. ^{1}H NMR ($CDCl_3$) δ 1.33 (m, 2H), 1.45 (s, 9H), 1.87 (d, 2H, J = 12.4 Hz), 2.26 (s, 3H), 2.69 (t, 2H, J = 12.4 Hz), 3.08 (m, 1H), 3.59 (br s, 2H), 4.10 (m, 2H), 4.67 (s, 2H), 6.87 (m, 1H), 7.00 (d, 1H, J = 7.3 Hz), 7.07 (d, 1H, J = 7.5 Hz).

To a stirred solution of the crude 1-(*tert*-butyloxycarbonyl)-4-(piperidinyl)-8-methyl-1,4-dihydrobenz[*d*][1,3]oxazin-2-one (15.25 g, 44 mmol) in EtOAc (200 mL), a 5 M solution of HCl in Et_2O (500 mL) was added at 0 °C, and the resulting mixture was stirred for 4 h at 0 °C. The precipitate formed was collected by filtration, washed with Et_2O, and dried, giving **22b** as a colorless amorphous solid (9.58 g, 77%). Mp 257−262 °C. ^{1}H NMR (DMSO-d_6) δ 2.04 (d, 2H, J = 13.6 Hz), 2.38 (s, 3H), 2.65 (m, 2H, J = 12.9, 3.5 Hz), 2.98 (m, 2H), 3.28 (d, 2H, J = 12.1 Hz), 3.76 (ddd, 1H, J = 11.5, 8.3, 3.5 Hz), 5.06 (s, 2H), 7.11 (m, 2H), 7.23 (dd, 1H, J = 7.2, 1.4 Hz), 8.50 (s, 1H), 9.48 (s, 1H).

General Procedure for the Synthesis of Piperidin-4-yl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one Sulfonamides (23a−j). The corresponding benzoxazinone hydrochloride (0.1 mmol) was suspended in dry CH_2Cl_2 (10 mL). *N,N*-Diisopropylethylamine (0.25 mmol) was added, and the reaction mixture was stirred at room temperature for 15 min. The appropriate sulfonyl chloride (0.11 mmol) was then added, and the mixture was stirred at room temperature until complete conversion (TLC). The solution was washed with water, dried with Na_2SO_4, evaporated, and crystallized as described for each compound.

The following compounds were prepared according to the procedures described above from the corresponding substituted benzoxazinones.

1-[1-(Benzo[*b*]thiophene-3-sulfonyl)-piperidin-4-yl]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23a). The reaction product was purified by crystallization with EtOH to provide **23a** in 76% yield as a colorless amorphous solid. Mp 166−168 °C. ^{1}H NMR (DMSO-d_6) δ 1.81 (d, 2H, J = 11.1 Hz), 2.48 (m, 2H), 2.64 (t, 2H, J = 11.6 Hz), 3.83−3.95 (m, 3H), 5.08 (s, 2H), 7.01−7.12 (m, 2H), 7.20−7.25 (m, 2H), 7.49−7.58 (m, 2H), 8.15−8.23 (m, 2H), 8.60 (s, 1H). Anal. ($C_{21}H_{20}N_2O_4S_2$) C, H, N.

1-[1-(Benzo[*b*]thiophene-3-sulfonyl)-piperidin-4-yl]-8-methyl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23b). The reaction product was purified by crystallization with EtOH to provide **23b** in 70% yield as a colorless amorphous solid. Mp 179−181 °C. ^{1}H NMR (DMSO-d_6) δ 1.93 (d, 2H, J = 12 Hz), 2.23 (s, 3H), 2.43 (m, 2H), 2.59 (t, 2H, J = 12 Hz), 3.49 (t, 1H, J = 10.9 Hz), 3.82 (d, 2H, J = 10.8 Hz), 4.99 (s, 2H), 7.06 (m, 3H), 7.51 (m, 2H), 8.15 (m, 2H), 8.56 (s, 1H). Anal. ($C_{22}H_{22}N_2O_4S_2$) C, H, N.

1-[1-(5-Chloro-3-methyl-benzo[*b*]thiophene-2-sulfonyl)-piperidin-4-yl]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23c). The reaction product was purified by crystallization with EtOH to provide **23c** in 84% yield as a colorless amorphous solid. Mp 204−206 °C. ^{1}H NMR (DMSO-d_6) δ 1.8 (d, 2H, J = 10.8 Hz), 2.5 (m, 2H), 2.7 (s, 3H), 2.8 (t, 2H, J = 11.4 Hz), 3.8 (d, 2H, J = 11.4 Hz), 3.9 (m, 1H), 5.1 (s, 2H), 7.0 (t, 1H, J = 7.2 Hz), 7.2 (d, 1H, J = 8.1 Hz), 7.2 (m, 2H), 7.6 (dd, 1H, J = 8.6, 2.0 Hz), 8.1 (d, 1H, J = 2.0 Hz), 8.2 (d, 1H, J = 8.6 Hz). Anal. ($C_{22}H_{21}ClN_2O_4S_2$) C, H, N.

1-[1-(Naphthalene-1-sulfonyl)-piperidin-4-yl]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23d) The reaction product was purified by crystallization with EtOH to provide **23d** in 82% yield as a colorless amorphous solid. Mp 147−149 °C. ^{1}H NMR (DMSO-d_6) δ 1.8 (d, 2H, J = 10.5 Hz), 2.4 (m, 2H), 2.7 (t, 2H, J = 11.6 Hz), 3.9 (n, 3H), 5.1 (s, 2H), 7.1 (m, 2H), 7.2 (m, 2H), 7.7 (m, 3H), 8.1 (d, 1H, J = 8.1 Hz), 8.2 (d, 1H, J = 7.8 Hz), 8.3 (d, 1H, J = 8.1 Hz), 8.7 (d, 1H, J = 8.3 Hz). Anal. ($C_{23}H_{22}N_2O_4S$) C, H, N.

8-Methyl-1-[1-(naphthalene-1-sulfonyl)-piperidin-4-yl]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23e). The reaction product was purified by crystallization with EtOH to provide **23e** in 72% yield as a colorless amorphous solid. Mp 203−204 °C. ^{1}H NMR ($CDCl_3$) δ 1.9 (d, 2H, J = 12.5 Hz), 2.3 (s, 3H), 2.7 (m, 4H), 3.3 (m, 1H), 4.0 (d, 2H, J = 11.2 Hz), 4.9 (s, 2H), 7.0 (m, 2H), 7.1 (d, 1H, J = 7.0 Hz), 7.6 (m, 3H), 7.9 (m, 1H), 8.1 (d, 1H, J = 8.2 Hz), 8.2 (dd, 1H, J = 7.3, 1.1 Hz), 8.7 (d, 1H, J = 8.8 Hz). Anal. ($C_{24}H_{24}N_2O_4S$) C, H, N.

1-[1-(5-Dimethylaminonaphthalene-1-sulfonyl)-piperidin-4-yl]-8-methyl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23f). The reaction product was purified by crystallization with EtOH to provide **23f** in 72% yield as a colorless amorphous solid. Mp 202−203 °C. ^{1}H NMR ($CDCl_3$) δ 1.9 (d, 2H, J = 11.9 Hz), 2.3 (s, 3H), 2.7 (m, 4H), 2.9 (s, 6H), 3.3 (m, 1H), 4.0 (d, 2H, J = 9.9 Hz), 4.9 (s, 2H), 7.0 (m, 2H), 7.2 (m, 2H, J = 7.3 Hz), 7.5 (m, 2H), 8.2 (dd, 1H, J = 7.3, 1.1 Hz), 8.4 (d, 1H, J = 8.6 Hz,), 8.6 (d, 1H, J = 8.4 Hz). Anal. ($C_{26}H_{29}N_3O_4S$) C, H, N.

1-[1-(Quinoline-8-sulfonyl)-piperidin-4-yl]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23g). The reaction product was purified by crystallization with EtOH to provide **23g** in 96% yield as a colorless amorphous solid. Mp 169−171 °C. ^{1}H NMR ($CDCl_3$) δ 1.8 (d, 2H, J = 9.5 Hz), 2.6 (qd, 2H, J = 12.6, 4.4 Hz), 3.0 (td, 2H, J = 12.8, 2.5 Hz), 4.1 (tt, 1H, J = 12.5, 3.8 Hz), 4.3 (ddd, 2H, J = 13.0, 2.3 Hz), 5.0 (s, 2H), 7.1 (m, 3H), 7.3 (m, 1H), 7.6 (dd, 1H, J = 8.4, 4.2 Hz), 7.6 (m, 1H), 8.1 (dd, 1H, J = 8.2, 1.3 Hz), 8.3 (dd, 1H, J = 8.3, 1.7 Hz), 8.5 (dd, 1H, J = 7.3, 1.5 Hz), 9.1 (dd, 1H, J = 4.2, 1.8 Hz). Anal. ($C_{22}H_{21}N_3O_4S$) C, H, N.

8-Methyl-1-[1-(quinoline-8-sulfonyl)-piperidin-4-yl]-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23h). The reaction product was purified by crystallization with EtOH to provide **23h** in 71% yield as a colorless amorphous solid. Mp 202−207 °C. ^{1}H NMR ($CDCl_3$) δ 1.9 (d, 2H, J = 12.6 Hz), 2.3 (s, 3H), 2.7 (qd, 2H, J = 12.2, 3.9 Hz), 2.9 (m, 2H), 3.3 (tt, 1H, J = 11.7, 3.4 Hz), 4.3 (d, 2H, J = 12.8 Hz), 4.9 (s, 2H), 7.0 (m, 2H), 7.1 (d, 1H, J = 7.3 Hz), 7.5 (dd, 1H, J = 8.3, 4.1 Hz), 7.6 (m, 1H), 8.0 (dd, 1H, J = 8.2, 1.3 Hz), 8.2 (dd, 1H, J = 8.3, 1.7 Hz), 8.5 (dd, 1H, J = 7.3, 1.5 Hz), 9.1 (dd, 1H, J = 4.2, 1.8 Hz). Anal. ($C_{23}H_{23}N_3O_4S$) C, H, N.

1-[1-(5-Bromo-2-methoxybenzenesulfonyl)-piperidin-4-yl]-8-methyl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23i). The reaction product was purified by crystallization with EtOH to provide **23i** in 68% yield as a colorless amorphous solid. Mp 213-216 °C. ^{1}H NMR ($CDCl_3$) δ 1.90 (d, 2H, J = 11.9 Hz), 2.36 (s, 3H), 2.64 (m, 2H), 2.80 (m, 2H), 3.97 (s, 3H), 4.01 (m, 3H), 4.95 (s, 2H), 6.93 (d, 1H, J = 8.8 Hz), 7.02 (m, 2H), 7.17 (d, 1H, J = 7.3 Hz), 7.62 (dd, 1H, J = 8.9, 2.5 Hz), 8.04 (d, 1H, J = 2.6 Hz). Anal. ($C_{21}H_{23}BrN_2O_5S$) C, H, N.

1-[1-(2,5-Dimethoxybenzenesulfonyl)-piperidin-4-yl]-8-methyl-1,4-dihydro-benzo[*d*][1,3]oxazin-2-one (23j). The reaction product was purified by crystallization with 2-propanol to provide **23j** in 68% yield as a colorless amorphous solid. Mp 100−102 °C. ^{1}H NMR ($CDCl_3$) δ 1.89 (d, 2H, J = 12.45 Hz), 2.35 (s, 3H), 2.72 (m, 4H), 3.37 (m, 1H), 3.80 (s, 3H), 3.92 (s, 3H), 4.01 (d, 2H, J = 10.6 Hz), 4.95 (s, 2H), 7.02 (m, 4H), 7.17 (d, 1H, J = 7.8 Hz), 7.46 (d, 1H, J = 3.1 Hz). Anal. ($C_{22}H_{26}N_2O_6S$) C, H, N.

In Vitro 5-HT$_6$ Membrane Binding Assays. Membranes from HEK-293 with human 5-HT$_6$ serotonin receptor expressed were supplied by Receptor Biology. The binding assays were performed as described by Roth et al.[17] with slight modifications. The radioligand used was [^{3}H]-LSD at 2.7 nM, and the final volume was 200 μL. The incubation was initiated by addition of 100 μL of membrane (22.9 μg of protein), and the incubation time was 60 min at 37 °C. After incubation, the membranes were collected onto polyethylenimine-pretreated glass fiber filters (Schleicher & Schnell 3362). The filters were washed with buffer (50 mM Tris Cl, pH = 7.4). Then, filter sections were transferred to vials, and liquid scintillation cocktail was added to each vial. Nonspecific binding was determined with 100 μM serotonin. Competition binding data were analyzed by using the LIGAND program,[40] and assays were performed in triplicate determinations for each point.

Adenylyl Cyclase Activity Assay. The activation or inhibition of adenylyl cyclase activity was studied by measuring levels of cAMP in 96-well plates by the FlashPlate method (PerkinElmer). C6 cells overexpressing the 5-HT$_6$ receptor

were grown to 80% confluence in Dulbecco's modified Eagle's medium with L-glutamine, penicillin, and streptomycin without fetal bovine serum. Two hours prior to the assay, the medium was removed, and cells were dissociated with trypsin and centrifuged, and the resulting resuspended pellets were added to the wells (50 000 cells/well, approximately). Test compounds were added (either in the presence or absence of forskolin), and after 30 min, the reactions were stopped by the addition of detection solution (^{125}I−succinyl cAMP tracer). The plates were measured after 2 h. Results are expressed as percentages of the cAMP amounts formed over basal levels.

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Supporting Information Available: Two HPLC-system charts for key target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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