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64 *Current Bioactive Compounds* **2013**, *9*, 64-100

Small Molecule 5-HT_6R Ligands: A Comprehensive Insight into their Selectivity and Activity

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Abstract: In recent years, considerable research efforts have focused on the role of serotonin in various pathological states, as well as on the identification of the respective serotonin receptors involved. Among serotonin receptors, 5-HT_6R is the most recently discovered sub-class. Despite the development of multiple selective ligands, the functional role of this receptor has thus far remained elusive. Available *in vitro* and *in vivo* evidence indicates that 5-HT_6 receptor antagonists can produce promnesic or antiamnesic effects in a variety of contexts, including memory formation, age-related cognitive impairments, and memory deficits associated with conditions such as schizophrenia, Parkinson's disease, and Alzheimer's disease. Recent progress in the understanding of the 5-HT_6 receptor and its ligands includes a suggested constitutive activity for the receptor, development of a number of multimodal small molecule ligands, and re-classification of many selective antagonists as pseudo-selective compounds. In light of these findings, the observed pharmacological effects produced by 5-HT_6R ligands are now properly assigned to a spectrum of related biological targets, rather than to an individual receptor.

Keywords: Serotonin receptors, 5-HT_6R ligands, selectivity, depression, schizophrenia, Alzheimer's disease, Huntington's disease, obesity.

INTRODUCTION

The endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) produces its physiological action by interacting with a highly diverse family of plasma membrane receptors found widely distributed throughout the brain and peripheral tissues. To date, 14 different 5-HT receptors (5-HTRs) have been identified. They have been classified into families designated 5-HT_1R through 5-HT_7R on the basis of radioligand binding, second messenger activation, and amino acid sequence homology. In addition, there are multiple splice variants and isoforms that further enhance the molecular diversity of the 5-HTR subtypes. Thirteen of the 5-HTRs are G protein-coupled receptors (GPCRs) and one, 5-HT_3R, is a ligand-gated ion channel. All known homologues have 7 transmembrane (7-TM) domains that form 3 cytoplasmic and 3 extracellular loops. 5-HTRs coupled to four different families of G proteins: G_s, $G_{i/0}$, $G_{q/11}$ and $G_{12/13}$. Within a given 5-HTR family the overall amino acid sequence homology ranges from 40–63%, while the sequence homology between different families of 5-HTRs is lower and ranges from 25–39%. The human and mouse 5-HT_6Rs are glycoproteins consisting of 440 amino acids; in rats, the proteins have 438 amino acids. 5-HTRs are targets for many different classes of drugs currently prescribed for treating anxiety, depression, schizophrenia, migraine, eating disorders, emesis, irritable bowel syndrome, Parkinson's disease and Alzheimer's disease. It is therefore of great importance to understand the molecular mechanisms involved in 5-HTR activation. Among the discovered subtypes, 5-HT_6R has attracted particular attention in the scientific community, due to its versatile therapeutic potential.

5-HT_6Rs were originally discovered in 1993 (rats) [1], 1994 (mice) [2] and 1996 (humans) [3], and form a unique sub-class within the serotonin receptor family. The native endogenous ligand serotonin—as well as several small molecule compounds—has been found to activate this receptor pathway. 5-HT_6Rs are G-protein coupled receptors (GPCRs), linked to the adenylate cyclase (AC) signal transduction pathway. Ligand binding leads to activation of AC, which subsequently catalyses the cyclisation of ATP into the key second messenger cATP. This represents one of the canonical molecular mechanisms of GPCR-related signaling [4]. 5-HT_6Rs are abundantly distributed within the CNS, predominantly in areas that play a pivotal role in cognitive processes. Elevated receptor levels have been revealed in the striatum, nucleus accumbens (NAcc, accumbens nucleus), islands of Calleja (ISC) and olfactory bulb using autoradiographic mapping [5] and RT-PCR [6]. This CNS-predominant expression pattern may explain the low rate of peripheral side effects noted for several promising selective 5-HT_6R antagonists [5-7]. It has also been demonstrated that 5-HT_6Rs can modify other neuronal signaling routes, including the cholinergic, noradrenergic, glutamatergic and dopaminergic pathways [7]. Considering the fundamental significance of these systems in human cognitive machinery, the vital importance of 5-HT_6Rs in normal and pathologic condi-

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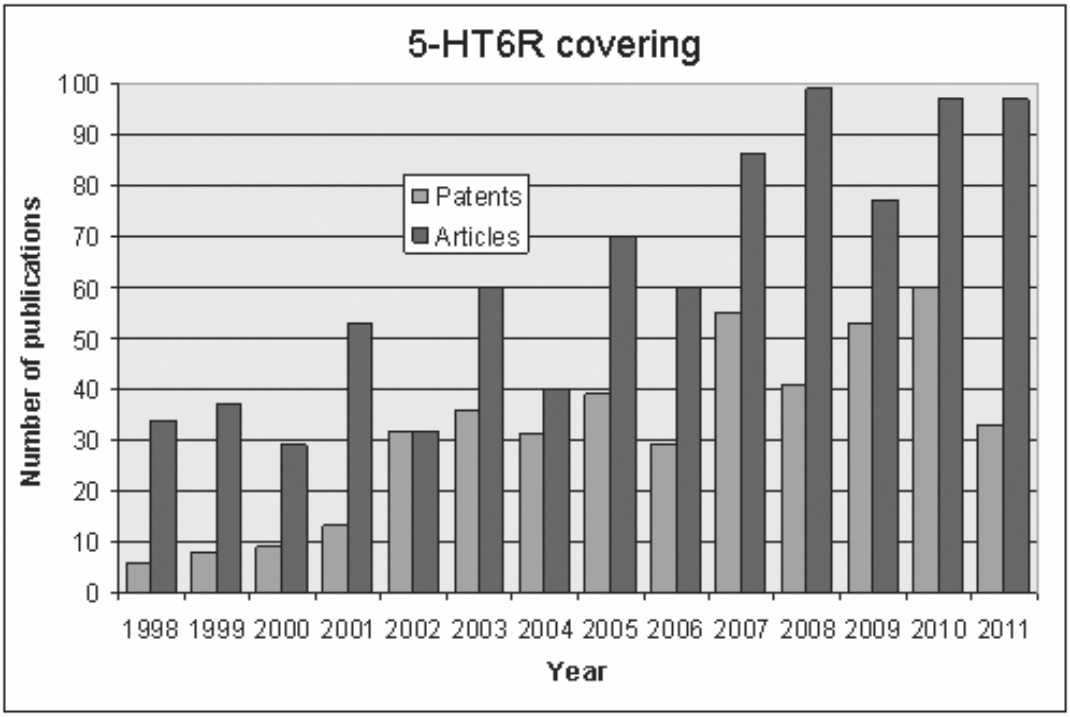


Fig. (1). Number of scientific papers in the field of 5-HT$_6$Rs published from 1998 to 2011. The data were obtained from the SciFinder database using the key word "5-HT$_6$R" (December 01, 2011).

tions has become glaringly obvious. Therefore, these receptors represent an incredibly attractive biological target for the development of novel drug candidates against various CNS-related diseases [8-10]. Considerable growth in the number of scientific publications and patents directly dedicated to 5-HT$_6$Rs is clearly observed in both industrial and academic areas (Fig. **1**).

It should be noted that during the last five years, a significant number of comprehensive reviews and focused book chapters that describe the medicinal chemistry profile and pharmacology of 5-HT$_6$R ligands have been published [10-35]. The present work specifically focuses on the selectivity of 5-HT$_6$R ligands. These are commonly classified into three key categories: *multimodal* (multi-target or polyfunctional, "magic shotgun" particularly), *pseudo-selective* and *selective ligands*:

- the first class includes ligands with a comparative or very similar activity (*in vitro* or/and *in vivo*) against a range of biological targets within the scope of the same pharmacological profile (PhPr);
- the second group, in our opinion, is filled by various 5-HT$_6$R ligands with a comparative or the same activity against a single other target in the same PhPr; or ligands with specific 5-HT$_6$R activity <250-fold higher as compared to other targets from the PhPr;
- the final category includes selective ligands with >250-fold higher activity toward 5-HT$_6$Rs than toward other biological targets assigned to the common PhPr.

Sufficient evidence has accumulated to suggest that the etiology of CNS diseases is extremely complex, with an array of potential drug targets found in a number of biochemical pathways. Therefore, it is unlikely that the complex pathological cascade leading to disease initiation or progression will be mitigated by any one drug acting on a single pathway or target. In accordance with this, two drug therapy strategies are currently in development. The first is wholly based on multimodal ligands. In contrast, the second strategy aims at the development of "*combined drugs;*" such formulations contain several ligands enclosed in one capsule with specific activity and selectivity, or selective and multimodal ligands with pre-defined doses for the achievement of optimal therapeutic effect [36-38]. However, the clinical use of multimodal and pseudo-selective ligands is frequently accompanied by undesired side effects.

1. MULTIMODAL 5-HT$_6$R LIGANDS

1.1. Typical and Atypical Antipsychotics

Multimodal 5-HT$_6$R ligands are associated with several neuronal systems. Typical and atypical antipsychotics with activity against dopaminergic, serotonergic (including 5-HT$_6$Rs), noradrenergic, cholinergic and histaminergic systems are prime examples (Fig. **2**). Many typical and atypical antipsychotics (Tables **1** and **2**) are promising 5-HT$_6$R antagonists with nanomolar activity [39-41]. For instance, this group includes substituted 3-thioxanthen-9-ylidene-propylamines **1** and **2**, 10*H*-phenothiazine **3-10**, dibenzo[a,d]cycloheptene **11**, dibenzo[b,f]thiepine **12**, dibenzo[b,f]thiepines, dibenzo[b,f][1,4]oxazepines, dibenzo[b,f][1,4]thiazepines, 5*H*-Dibenzo[b,e][1,4]diazepine **13-18**, 4*H*-3-thia-4,10-diazabenzo[f]azulene **19** and several other heterocyclic compounds **20-26** (see Table **1**).

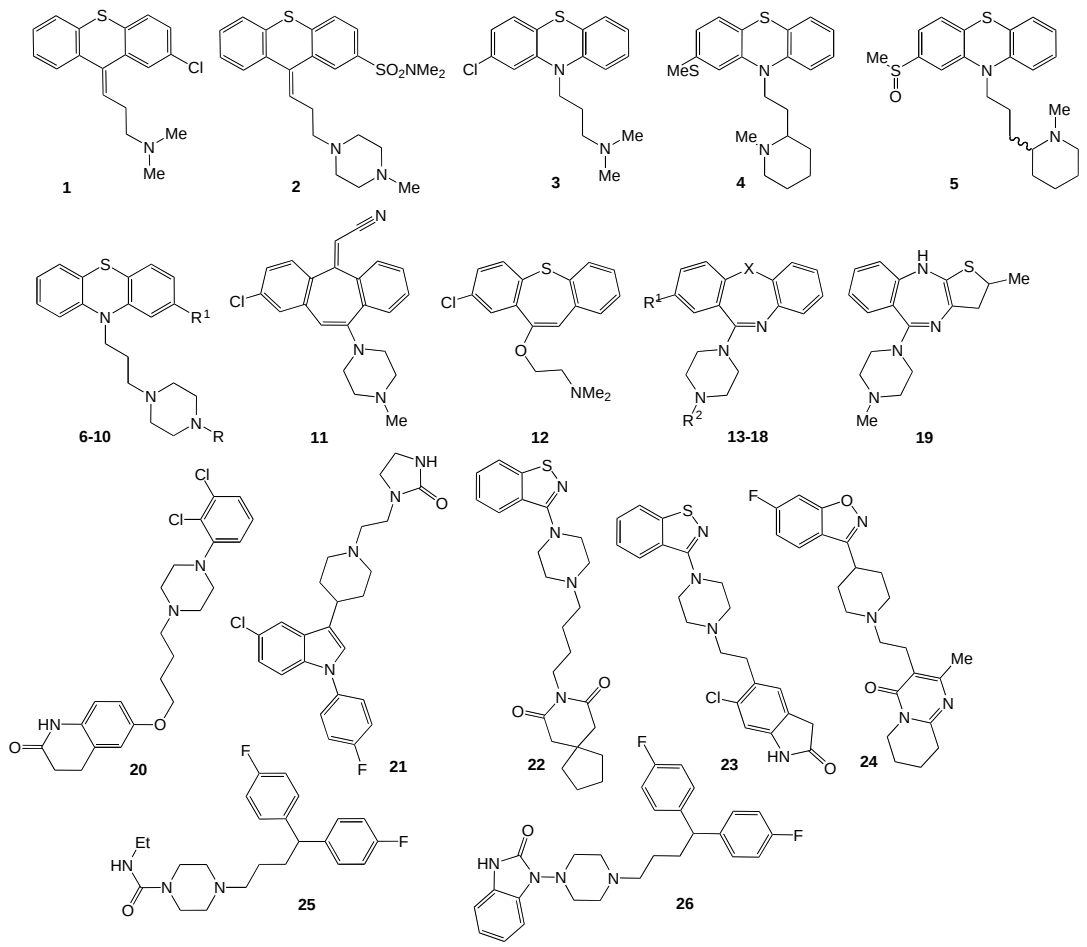


Fig. (2). Typical and atypical antipsychotics (**6**: R^1 = Cl, R^2 = Me. **7**: R^1 = Cl, R^2 = CH_2CH_2OH. **8**: R^1 = CF_3, R^2 = Me. **9**: R^1 = CF_3, R^2 = CH_2CH_2OH. **10**: R^1 = $COCH_3$, R^2 = CH_2CH_2OH. **13**: X = CH_2, R^1 = H, R^2 = Me. **14**: X = CH_2, R^1 = F, R^2 = Me. **15**: X = O, R^1 = Cl, R^2 = H. **16**: X = O, R^1 = Cl, R^2 = Me. **17**: X = S, R^1 = Cl, R^2 = Me. **18**: X = NH, R^1 = Cl, R^2 = Me).

Table 1. Activity of typical and atypical antipsychotics toward 5-HT_6, 5-HT_7, 5-HT_2, 5-HT_{1C} and dopamine D_2 receptors [40]

Compound number	Drug (A = Atypical, T = Typical)	Annotated binding affinity					
		5-HT_6		5-HT_7	5-HT_2	5-HT_{1C}	D_2
		K_i[b], nM*	pK_i, nM				
1	Chlorprothixene (T)	3.0	8.5	8.3	9.4	ND	ND
2	Thiothixene (T)	45.0	7.4	7.9	7.3	5.8	9.2
3	Chlorpromazine (T)	4.0	8.4	7.6	8.6	7.6	8.9
4	Thioridazine (T)	6.6	8.2	7.2	8.2	7.1	8.1
5	Mesoridazine (T)	159		-	-	-	-
6	Prochlorperazine (T)	148	6.8	6.7	8.2	7.1	8.3
7	Perphenazine (T)	17	7.8	7.6	8.6	7.3	9.2
8	Trifluoperazine (T)	66	7.2	7.1	8.4	7.0	9.7
9	Fluphenazine (T)	17	7.8	8.1	8.7	6.2	9.3
10	Acetophenazine (T)	72	7.1	8.6	ND	6.0	ND
11	Rilapine (A)	6.95	8.2	8.6	9.2	7.6	7.4

Table (1). Contd…

12	Zetepine (A)	1.17		-	-	-	-
13	Perlapine (A)	70	7.2	7.6	7.9	ND	6.3
14	Fluperlapine (A)	16.5	7.8	-	-	-	-
15	Amozapine (T)	6.0	8.2	-	-	-	-
16	Loxapine (T)	15	7.8	-	-	-	-
17	Clothiapine (T)	16	7.8	-	-	-	-
18	Clozapine (A)	4.0	8.4	8.2	8.2	8.4	7.25
19	Olanzapine (A)	2.5	8.6	7.0	ND	ND	ND
20	Aripiprazole (A)*	574	-	-	-	-	10
21	Sertindole (A)*	5.4	-	-	-	-	28
22	Tiospirone (A)	74	7.6	9.2	10.2	8.0	9.3
23	Ziprasidone (A)*	61	-	-	-	-	6
24	Risperidone (A)	426	6.4	8.9	9.6	7.5	8.8
25	Amperozide (A)	67	7.2	6.3	7.9	5.9	6.3
26	Pimozide (T)	7.15	-	-	-	-	-

* - here and below *K* means constant, 'i' means the inhibition of agonist binding, 'b' means binding assay, not functional – 'f'; * data from [41]; ND – not detected

Table 2. Activity of typical and atypical antipsychotics against a panel of serotonin and dopamine receptors [41]

Compound number	**K_i^b, nM**													
	Dopamine D$_x$ receptors							**Serotonin 5-HT$_x$ receptors**						
	x													
	1	**2**	**3**	**4**	**4.2**	**4.4**	**5**	**1A**	**1B**	**2A**	**2B**	**2C**	**6**	**7**
2	51	1.4	185	6.4	548	-	261	410	151	50	-	1356	208	15
3	112	2.0	5.0	10.8	26.2	15.9	133	3115	1489	3.32	-	15.55	12	21
4	89	10	53	10.65	-	-	216	108	109	21.5	-	53	57	99
5	-	4.3	2.6	9.1	-	-	-	-	-	-	-	157	380	-
7	-	0.56	0.43	28.5	-	-	-	421	-	5.6	-	132	17	23
8	-	1.12	0.45	38	178	-	-	950	-	74	-	378	144	291
9	24	0.54	3	35	-	-	12	145	334	21	-	983	28	8
16	54	10	30	10.9	14	5.9	75	2456	388	4.38	-	13.3	33	88
18	189	431	646	22.5	45.2	30	235	105	398	9.15	7.38	14.9	17	18
19	58	72	63	17.1	44.2	40.5	90	2063	509	4.90	11.8	14.2	6.0	105
21	-	4.44	5.76	9.29	17.67	-	-	280	60	0.387	-	0.9	5.4	28
23	30	4.0	17	500.8	35.3	-	152	76	4	0.73	-	13	61	6
26	-	2.51	2.84	1.8	-	-	-	650	-	48.35	-	2112	71	0.5

Among the listed examples, typical antipsychotic Chlorprothixene (**1**) with K_i = 3 nM, atypical antipsychotic Zetepine (**12**) with K_i = 1.17 nM and Olanzepine (**19**) with K_i = 2.5 nM are the most potent 5-HT_6R antagonists, whereas typical antipsychotic Mesoridazine (**5**) with K_i = 159 nM and atypical antipsychotic Risperidone (**24**) with K_i = 426 nM possess a relatively weak (sub-nanomolar) activity (Table **1**). Activities of several typical and atypical antipsychotics listed above against a panel of serotonin and dopamine receptors are presented in (Table **2**).

It should be particularly noted that a novel multimodal atypical antipsychotic, the serotonin/dopamine antagonist (3a*R*12b*R*)-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1*H*-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole-(2Z)-2-butenedioate (Asenapine maleate, **27**) (Fig. **3**) [42-44] represents the best example of a "*magic shotgun*" [39].

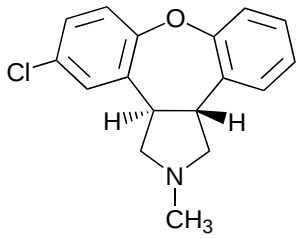


Fig. (3). Asenapine (**27**), launched in 2009 by Merck & Co. to treat schizophrenia and acute mania.

Asenapine maleate holds potential for the treatment of a variety of neurological and psychiatric disorders. Pfizer had been developing the drug candidate in collaboration with Organon; however, Pfizer discontinued development in November 2006 based upon a commercial analysis of the compound. In 2009, Schering-Plough (now Merck & Co.) received FDA approval of the drug for the acute treatment and maintenance of schizophrenia, and for the treatment of acute mania or mixed episodes associated with bipolar I disorder, in a fast-dissolving tablet formulation. In 2010, the product was licensed to Lundbeck by Merck & Co. for worldwide commercialization with the exception of the U.S., China and Japan for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. The same year, E.U. approval was assigned for the latter indication. The first E.U. launch took place in Germany in 2010. The U.K. launch took place in 2012. Phase III clinical trials are ongoing in Japan for the treatment of schizophrenia.

Asenapine exhibits nanomolar activity against a panel of α-adrenergic receptors (pK_i^b=8.9 for α_1, pK_i^b=8.9 for α_{2A}, pK_i^b=9.5 for α_{2B}, and pK_i^b=8.9 for α_{2C} isoform) in competitive radioligand binding assays (CRBA). These receptors play important roles in a variety of psychiatric diseases, migraine, schizophrenia, sleep disorders [45], as well as in controlling benign prostatic hyperplasia [46], coronary stenosis [47,48] and cerebellum-dependent neurological diseases [49]. It has also been shown that stimulation of α_2-adrenergic receptors improved memory and cognition in aged monkeys [50].

Asenapine also interacts with several dopaminergic receptors (pK_i^b=8.9 for D_1, pK_i^b=8.9 for D_2, pK_i^b=9.5 for D_3, and pK_i^b=9.0 for D_4 isoform), which are well recognized and comprehensively described targets associated with psychotropic drugs such as antipsychotics and psychostimulants [51]. These receptors are widely distributed in the brain and participate in controlling neural signaling. Dysfunction of dopaminergic neurotransmission in the CNS has been implicated in a variety of neuropsychiatric disorders, including social phobia [52], Tourette's syndrome [53], Parkinson's disease [54], schizophrenia [55], neuroleptic malignant syndrome [56], attention deficit hyperactivity disorder (ADHD) [57], and drug and alcohol dependence [58,53]. The receptors are also present in non-CNS tissues such as the cardiopulmonary [59] and renal systems [60]. Agonists of D_1-like and D_2-like receptors could therefore be beneficial for patients with high blood pressure [60], although chronic use of the receptor antagonists could potentially lead to hypertension due to reduced dopamine activity in the cardiovascular and renal systems.

Asenapine readily binds to a broad class of serotonergic receptors: pK_i^b=8.6 for 5-HT_{1A}, pK_i^b=8.4 for 5-HT_{1B}, pK_i^b=10.2 for 5-HT_{2A}, pK_i^b=9.8 for 5-HT_{2B}, pK_i^b=10.5 for 5-HT_{2C}, pK_i^b=8.8 for 5-HT_5, pK_i^b=9.6 for 5-HT_6, and pK_i^b=9.9 for 5-HT_7 receptors. The 5-HT_{1A} and 5-HT_{1B} receptors are, in turn, well recognized targets for many psychotropic drugs such as antidepressants [61-63], anxiolytics [64-68], non-opioid analgesics [69], agents targeting generalized anxiety disorder (GAD) [70,71], generalized psychosis [62,67,68], cognitive disorders [62], and other indications [72-74]. Polymorphisms of the 5-HT_{2A} and 5-HT_{2C} receptors (T102C and C23S, respectively) are thought to be associated with different neuropsychiatric symptoms, including hallucinations and depression in patients with Alzheimer's disease [75-77] and may be responsible for antipsychotic treatment responses [78]. Inverse agonists of 5-$HT_{2A/2C}$ receptors have been shown to elicit antipsychotic and antidyskinetic behavior in an *in vivo* animal study [79].

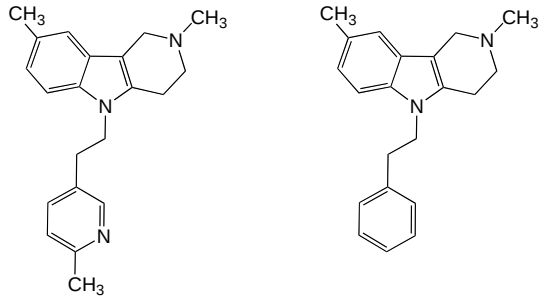
Many typical and atypical antipsychotic agents show high affinities for 5-HT_6 and 5-HT_7 receptors [80-82]. This makes them very attractive targets for antipsychotic intervention [83]. 5-HT_6 and 5-HT_7 receptor antagonists have been shown to play a significant role in memory formation and in improving learning consolidation as well as memory retention [84]. The blockade of 5-HT_6 receptors is suggested to lead to the improvement of cognitive performance in a wide variety of learning and memory paradigms, and also to produce anxiolytic and antidepressant-like activity. Recent reports show that 5-HT_6 receptor antagonists demonstrate cognition enhancing properties [85], improvement of spatial recognition memory and reversal of age-related consolidation deficits of episodic-like memory [86].

Finally, Asenapine does not strongly interact with the muscarinic receptors ($pK_i^b \leq 5$). However, a relatively high activity against histamine H_1 (pK_i^b=9) and H_2 (pK_i^b=8.2) receptors in some cases leads to several undesired side effects, including somnolence (up to 24%), extrapyramidal symptoms excluding akathisia (up to 12%), headache (up to 12%), dizziness (up to 11%), increased weight (up to 5%), fatigue (up to 4%), and others [87].

1.2. Saturated γ-Carbonyls and their Analogues

Saturated γ-carbonyls, including the well known antihistamine agent Dimebon (Latrepirdine) **28** [88-90], and the

promising drug candidate AVN-101 **29** (Fig. **4**, Table **3**) [91-95], are typical examples of 5-HT$_6$R-targeted multimodal ligands [96]. Dimebon was originally synthesized and described in 1962 by Alexey N. Kost (Prof., D. Sc.) and colleagues [97]. In 2001, Bachurin and co-workers clearly demonstrated that Dimebon could be readily used as a novel neuroprotector and cognition enhancer [98]. Dimebon successfully passed Phase II clinical trials for Alzheimer's [99] and Huntington's [100] diseases. As a result, Pfizer and Medivation signed an agreement to co-develop and market Dimebon for drug therapy in Alzheimer's and Huntington's Diseases [101]. Since then, many research projects targeting the synthesis and biological evaluation of related analogues have been conducted. Unfortunately, Phase III evaluation of Dimebon did not provide the desired outcome against the therapeutic indications listed above [102,103]. Therefore, the Pfizer and Medivation alliance abruptly discontinued further clinical trials and development [104,105].



28 (Dimebon, Latrepirdine) **29** (AVN-101)

Fig. (4). Multimodal 5-HT$_6$R ligands with high similarity in structure: 2,8-dimethyl-5-(6-methylpyridin-3-yl)-1*H*-pyrido[4,3-b]indole **28** (Dimebon) and 2,8-dimethyl-5-phenethyl-1*H*-pyrido[4,3-b]indole **29** (AVN-101).

Despite this outcome, it is still important to describe the pharmacological and pharmacokinetic profile of Dimebon, as it remains a potential candidate for the treatment of other diseases such as schizophrenia and depression. The pharmacological profile of Dimebon has been described using a broad panel of 70 therapeutic targets that includes enzymes, ion channels, neurotransmitter transporters, and GPCRs [96]. Dimebon has demonstrated interaction with butyrylcholinesterase and histaminergic H_1 and H_2 receptors with relatively low affinities (~50% radioligand displacement at 10 μM), with several types of ion channels (benzothiazepine site of L-type Ca^{2+} channel, site 2 of sodium channel, and hERG potassium channel), as well as with the transporter for norepinephrine. While it exhibits no interaction with adenosine A_1 and A_{2A} receptors, Dimebon binds to α-adrenergic (including imidazoline I_2 receptor) but not to β-adrenergic receptors. Dimebon also effectively competes with specific radiolabeled ligands for dopaminergic and serotonergic receptors. AVN-101 **29** (Table **3**), a close structural analogue of Dimebon, has a similar pharmacological profile (Fig. **5**) [92,93].

Diazolin (Mebhydrolin, Fabahistin) **30** (Fig. **6**) [106], initially developed as an anti-histamine drug, has demonstrated a broad pharmacological profile; it includes adrenergic receptors (α_{1A}, α_{1B}, α_{1D}, α_{1A}, α_{2A}, β_2), dopamine receptors (D_1, D_{2l}, D_{2S}, D_3), serotonin receptors (5-HT$_{1B}$, 5-HT$_{2B}$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_6$, 5-HT$_7$), sigma σ_1 and σ_2 receptors, calcium and sodium channels, and norepinephrine (NET) and dopamine (DAT) transporters [107,108]. This range of activities has generated speculation that Diazolin holds promise for the therapy of several CNS diseases [109]. Regrettably, this broad range of activities is responsible for some of the harmful side effects produced by Diazolin, including anxiety, irritation of the gastrointestinal tract, giddiness, hypersomnia, decreased locomotor activity, and psychotic reactions [110,111].

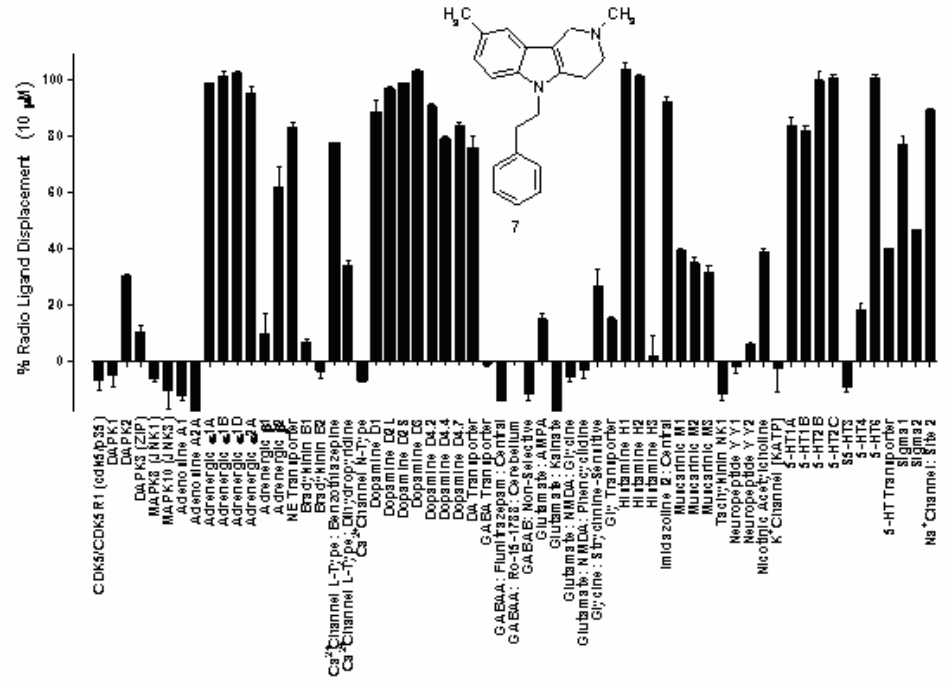


Fig. (5). Assessment of AVN-101 (**29**) binding potency (10 μM) against a panel of 61 diverse targets, including enzymes, ion channels, neuromediator transporters, and GPCRs. All activities, except enzymatic ones, were measured using radioligand displacement experiments.

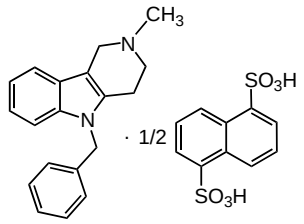


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Fig. (6). Diazolin (Mebhydrolin, Fabahistin).

A 60-target panel reveals that Dimebon, AVN-101 and Diazolin act on adrenergic, imidazoline I_2 (central), dopamine, histamine H_1, and serotonin receptors with sub-nanomolar potency (Table **3**). As shown in the table below, among the listed multimodal ligands (compounds **28**-**30**), the most prominent agent is AVN-101 (**29**), especially against 5-HT_{2A}, 5-HT_{2B}, 5-HT_6, and 5-HT_7 receptors.

Several isosteric analogues of Dimebon have been investigated [112], including 2,6-dimethyl-5-benzyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole **31** and 5-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indoles **32**-**37**. The latter set contain a 6-methyl-pyridine-3-yl moiety in position 5, connected to a pyrido[4,3-b]indole fragment by different linkers (Table **4**).

As shown in (Table **4**), ligands **31**-**33** have a narrow spectrum of pharmacological activity. In particular, compounds **31** and **32** demonstrate a tangible potency against histamine H_1 (Inh. = 87% and 89%), serotonin 5-HT_7 (Inh. = 76% and 78%), adrenergic α_{1A} (Inh. = 51% and 58%), and sigma σ_1 (Inh. = 51% and 35%) receptors. In contrast to ligands **31** and **32**, compound **33** lacks activity towards histamine H_1 (Inh. = 23%), while it does effectively block serotonin 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_6 receptors (Inh. = 83%, 90%, 72%, 70%, respectively), adrenergic α_{1B} and α_{1D} (Inh. = 74% and 56%, respectively) receptors, and the norepinephrine transporter (Inh. = 53%). Multimodal ligands **34**-**37** demonstrate a fairly wide spectrum of pharmacological targets, including adrenergic α_{1A}, α_{1B}, α_{1D}, dopamine D_1, histamine H_1, H_2, imidazoline I_2 (Central), and serotonin 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors. The exceptions are ligand **34**, which shows no activity against histamine H_1 receptor (Inh. = 9%), and compound **37**, which has a relatively weak potency towards the dopamine D_1 receptor (Inh. = 34%). Recently, several novel multimodal 5-substituted saturated γ-carbolines have been synthesized [113-134]. In addition, the series of 8-sulfonyl-substituted tetrahydro-1*H*-pyrido[4,3-b]indoles **38, 39** (Figs. **6**,**7**) has also been described. These compounds show an appropriate antagonistic activity against 5-HT_6R [135-137].

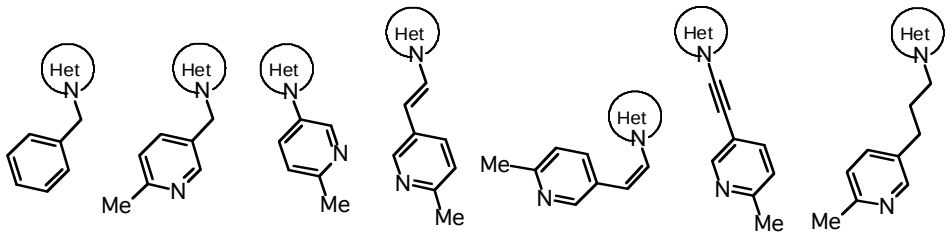
A generalized target-specific profile for 2-methyl-*N*-(3-fluorophenyl)-2,3,4,5-tatrahydro-1*H*-pyrido[4,3-b]indole-8-sulphonamide **38** (1μM) is shown in (Fig. **7**). The data were obtained in an integrated CRBA targeted to 32 different proteins. As shown in the figure, compound **28** reveals a significant activity against α_{2A} and sigma σ_1 receptors (57% and 58% radioligand displacement, respectively), and serotonin receptors (80-102% ligand displacement): K_i^b = 7.05 nM for 5-HT_{2A}; K_i^b = 38.7 nM for 5-HT_{2C}; K_i^b = 2.15 nM for 5-HT_6, and K_i^b = 41.7 nM for 5-HT_7.

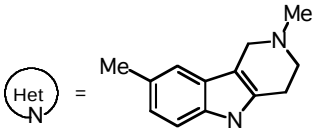
Table 3. The common activity profile of Dimebon (28), AVN-101 (29) and Diazolin (30)* (annotated space)

Biological target	Dimebon		AVN-101		Diazolin	
	IC_{50}^b	K_i^b	IC_{50}^b	K_i^b	IC_{50}^b	K_i^b
	nM					
rt Adrenergic α_{1A}R	136	55	77	19	510	206
rt Adrenergic α_{1B}R	87	48	17	9	1580	872
h Adrenergic α_{1D}R	239	118	62	30	1330	656
h Adrenergic α_{2A}R	286	107	128	48	123	46
rt Imidazoline I_2 R Central	312	208	268	179	169	113
h Dopamine D_{2L}R	1730	575	436	145	-	-
h Dopamine D_{2S}R	1750	629	237	85	3000	1080
h Dopamine D_3R	-	-	256	87	1360	462
h Histamine H_1R	4	10	<10	-	4	2
h 5-HT_{2A}R	212	61	5	1.6	30	9
h 5-HT_{2B}R	300	-	17	11	31	20
h 5-HT_{2C}R	145	76	-	-	14	7
h 5-HT_6R	74	34	6	3	103	48
h 5-HT_7R	14	8	0.27	0.15	110	63

* - CRBA

Table 4. Activity of 5-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indoles 31-37 in a CRBA [112]



31-37: 

Biological target	31	32	33	34	35	36	37
	Inhibition, %						
Adrenergic α_{1A}	51	58	57	95	95	95	76
Adrenergic α_{1B}	27	31	74	99	100	97	92
Adrenergic α_{1D}	8	32	56	93	91	90	71
Adrenergic α_{2A}	26	15	13	93	97	97	55
Dopamine D_1	-	6	8	79	62	74	34
Dopamine D_{2L}	-	19	6	17	30	20	27
Dopamine D_{2S}	-	20	6	24	35	32	28
Dopamine D_3	-	6	17	21	31	25	26
Histamine H_1	87	89	23	9	100	89	99
Histamine H_2	8	10	32	85	55	75	80
Histamine H_3	-	14	–10	5	5	1	6
Imidazoline I_2 Central	-	-	-	66	75	70	45
5-HT_{1A}	-	15	2	21	38	41	–5
5-HT_{2A}	12	13	83	101	93	90	79
5-HT_{2B}	-3	5	90	87	70	62	60
5-HT_{2C}	-1	14	72	102	96	92	74
5-HT_6	44	42	70	74	86	89	94
5-HT_7	76	78	30	88	100	95	82
Tachykinin receptor NK_1		0	4	–8	1	4	–16
Sigma σ_1	51	35	46	1	43	39	31
Ca^{2+} channel L-type (benzothiazepine)	-	3	–2	33	30	–13	–1
Ca^{2+} channel L-type (dihydropyridine)	-	–4	0	2	15	10	–8
Ca^{2+} channel N-type	-	3	5	–3	7	1	–4
K^+ channel [K_{ATP}]	-	5	6	13	1	7	9
Na^+ channel	-	20	15	17	31	38	20
Dopamine transporter	-	–1	8	4	0	7	5
GABA transporter		–13	13	18	–6	13	22
Glycine transporter	-	6	0	8	18	10	15
Noradrenaline transporter	-	15	–3	53	14	15	22
Serotonin transporter	-	6	2	–5	–1	–3	4

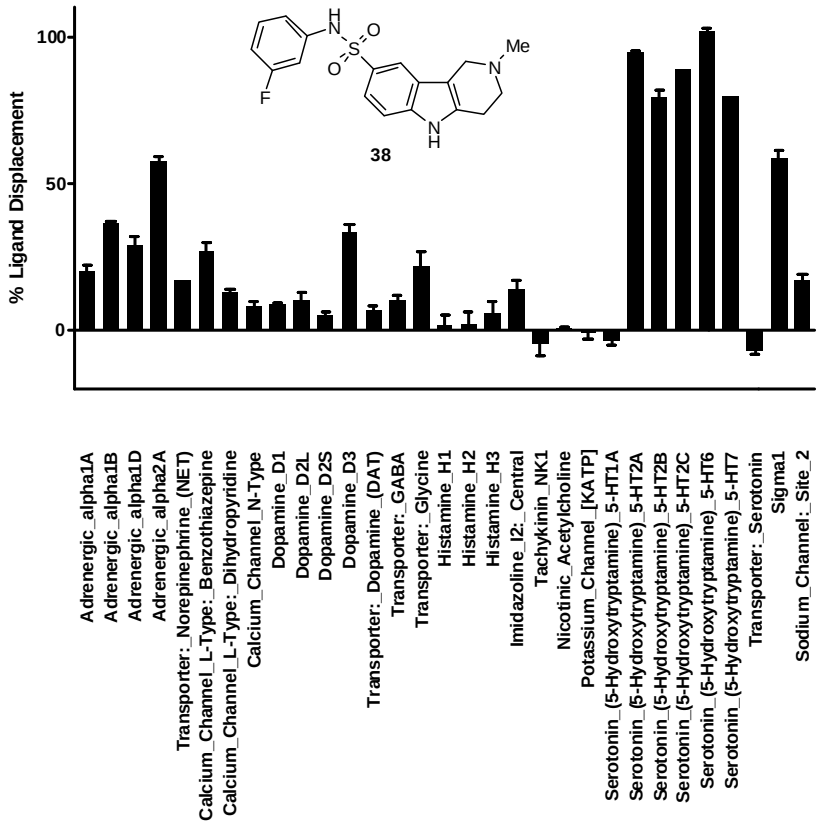


Fig. (7). Target-specific profile for 2-methyl-*N*-(3-fluorophenyl)-2,3,4,5-tatrahydro-1*H*-pyrido[4,3-b]indole-8-sulphonamide (1μM).

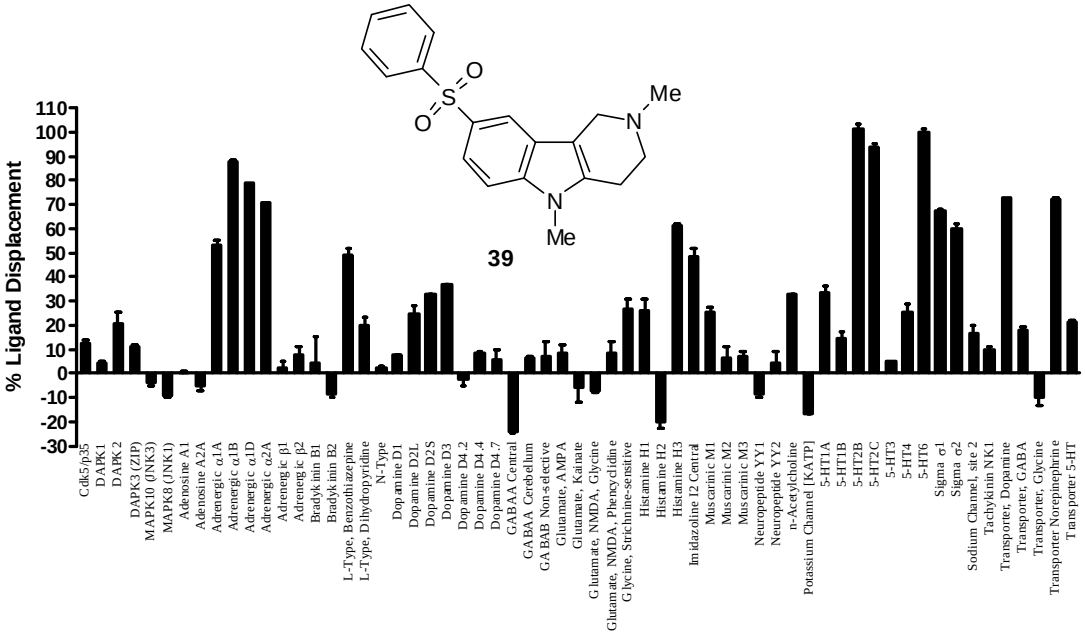
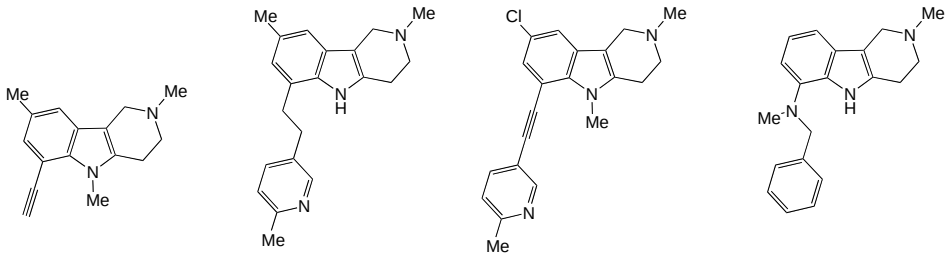


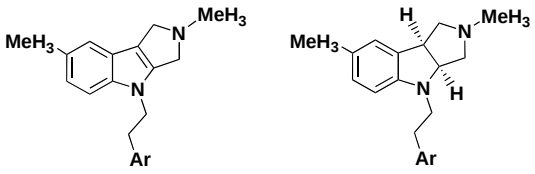
Fig. (8). Activity profile for 2,5-dimethyl-8-(phenylsulphonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indole **39** (10 μM), as determined in a radiolabeled binding assay.

The pharmacological profile of γ-carboline **39** (10 μM) against a panel of key biological targets is depicted in (Fig. **8**). As clearly shown in the figure, the compound shares a broad spectrum of activity, particularly against adrenergic α_{1A}, α_{1B}, α_{1D}, α_{2A}, histamine H_3, sigma σ_1 and σ_2, and serotonin 5-HT_{2B}, 5-HT_{2C}, 5-HT_6 receptors, as well as dopamine (DAT) and norepinephrine (NET) transporters. It should be noted that compound **39** has a weaker activity than ligand **38** against serotonin receptors: K_i^b = 96.1 nM for 5-HT_{2A}, K_i^b > 100 nM for 5-HT_{2C} and K_i^b = 5.7 nM for 5-HT_6.



40 **41** **42** **43**

Fig. (9). 6-Substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **40**-**43.**



44-48 **49, 50**

44: Ar = pyridin-2-yl, IC_{50}^{f}= 12,7 μM. **45:** Ar =6-methylpyridin-3-yl, IC_{50}^{f}= 26,1 μM. **46:** Ar = pyridin-4-yl, IC_{50}^{f}= 16,1 μM. **47:** Ar =6-methylpyridin-3-yl, IC_{50}^{f}>50 μM. **48:** Ar = pyridin-4-yl, IC_{50}^{f}>50μM. **49**: Ar = pyridin-3-yl, IC_{50}^{f}= 1,26 μM. **50**: Ar = pyridin-3-yl-4-Me, IC_{50}^{f}= 0,02 μM.

Fig. (10). Hydrogenated 4-(2-arylethyl)-pyrrolo[3,4-*b*]indoles **44**-**50.**

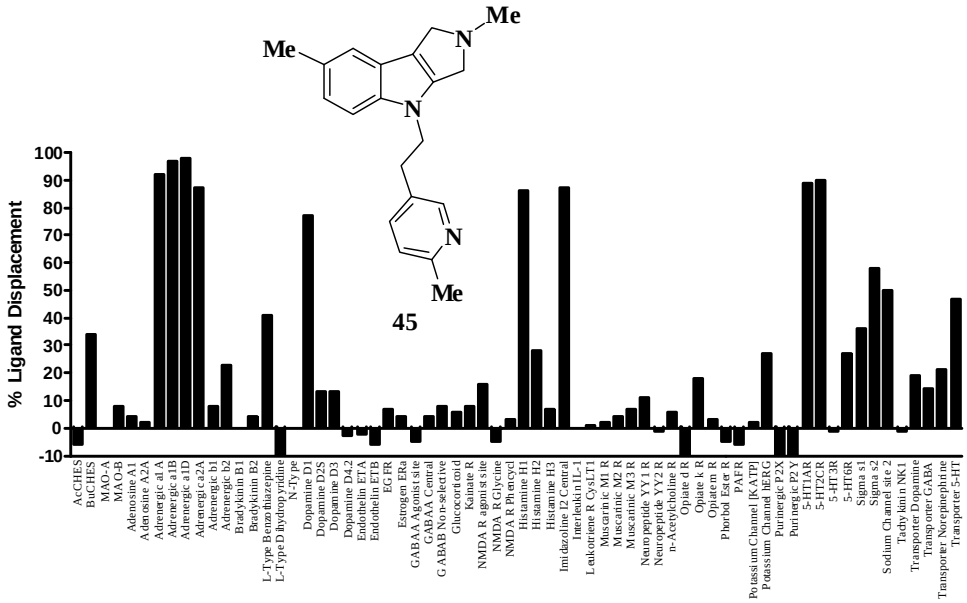
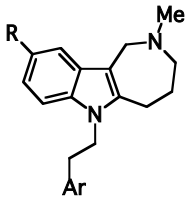


Fig. (11). Pharmacological profile of 2,7-dimethyl-4-[2-(6-methylpyridine-3-yl)ethyl]-3,4-dihydro-1*H*-pyrrolo[3,4-*b*]indole 45 (10 μM) in a CRBA.

It should be noted that multimodal ligands **38** and **39** may be more attractive as CNS-targeted drug candidates, as compared to the 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles described above, because they have no activity against histamine H_1 and H_2 receptors, which are generally associated with deleterious side effects. Moreover, ligand **39** has significant activity against the histamine H_3 receptor, which is deeply implicated in various CNS diseases.

The synthesis and biological evaluation of novel 6-substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles have been described in a patent application [132]. It has been generally shown that these compounds have a relatively poor binding potency in a CRBA against adrenergic, dopaminergic, histaminergic and serotonergic receptors at a concentration of 0.1 μM. For instance, almost all the tested compounds have demonstrated an antagonistic potency towards adrenergic receptors of <38%. Several exceptions include ligand **40** (Fig. **9**), with an inhibitory potency of up to 78% against dopamine receptors; compound **42**, with Inh=58% against histamine H_1 receptors; and ligand **43**, with Inh=80% against serotonin 5-HT_{2A} receptors. One compound **44** exhibits activity against several serotonin receptor subtypes: 5-HT_{2A} (Inh=73%), 5-HT_{2C} (Inh=55%) and 5-HT_6 (Inh=44%).

Table 5. Activity of 1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indoles 51(a-t) against 5-HT$_6$R



51(a-t)

cmpd	R	Ar	IC_{50}[f], μM
51a	Me	Ph	0.9
51b	Me	4-MeO-Ph	2.0
51c	Me	4-F-Ph	2.0
51d	Me	4-CF_3-Ph	15.0
51e	F	Ph	4.1
51f	F	4-Me-Ph	6.4
51g	F	4-MeO-Ph	5.5
51h	F	4-F-Ph	5.9
51i	F	4-CF_3-Ph	10.5
51j	H	2-Py[a]	>20
51k	H	4-Py	>20
51l	Me	2-Py	13.4
51m	Me	3-Py	7.1
51n	Me	6-Me-3-Py	>20
51o	Me	4-Py	14.5
51p	F	2-Py	3.0
51r	F	3-Py	>20
51s	F	6-Me-3-Py	>20
51t	F	4-Py	3.2

[a]Py = pyridyl

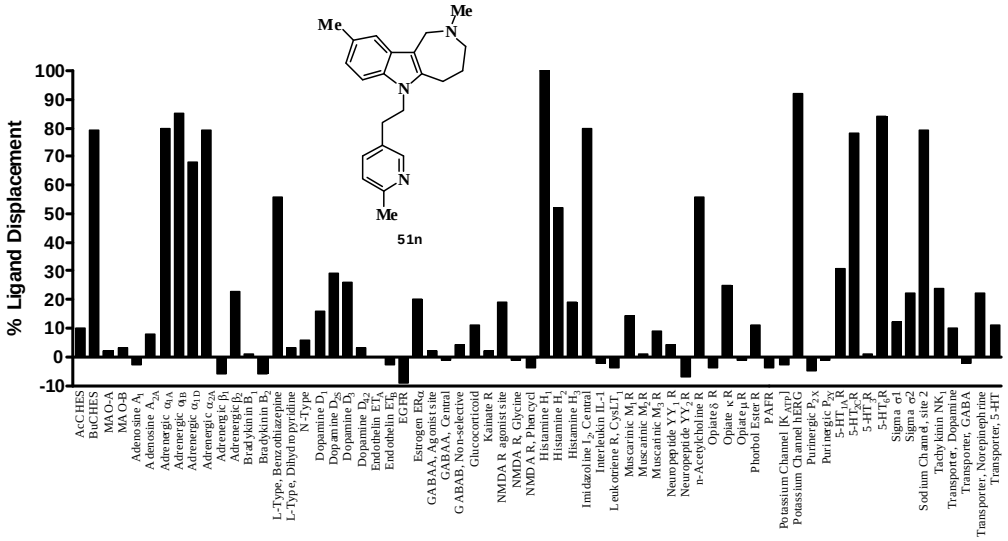


Fig. (12). Pharmacological profile for 2,9-dimethyl-6-(methylpyridin-3-yl)-1,2,3,4,5,6-hexahydroazepine[4,3-b]indole **51n** (10 μM) determined for 66 therapeutic targets in a CRBA [149].

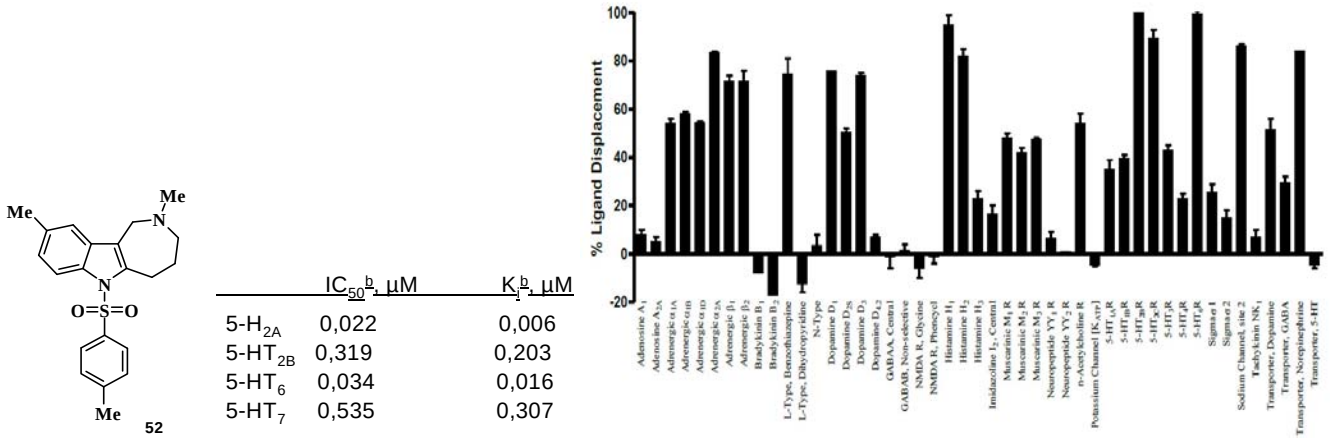
Pharmacological profiles obtained for multimodal hydrogenated pyrrolo[3,4-*b*]indoles **44-50** (Fig. **10**) have been published [138-140]. (Fig. **11**) demonstrates the spectrum of binding potency determined for compound **45** as an example. However, the compounds from this series exhibit weak activity against 5-HT$_6$ receptors (IC_{50} from 12.7 μM up to 26.1 μM) or no activity at all (IC_{50} > 50 μM). In particular, ligand **45** has an IC_{50} value of 26.1 μM [141].

Hydrogenated azepino[4,3-*b*]indoles **51**(a-t) have also been revealed as multimodal 5-HT$_6$R antagonists with micromolar activity [142-149]. Among these compounds, 2,9-dimethyl-6-phenetyl-1,2,3,4,5,6-hexahydroazepino[4,3-*b*]indole **51a** is the most potent ligand (IC_{50}[f] = 0.9 μM, Table **5**) [147].

The pharmacological profiles of these compounds, especially for 2,9-dimethyl-6-(6-methylpyridin-3-yl)-1,2,3,4,5,6-hexahydroazepino[4,3-b]indole **51n** (Fig. **12**), are very similar to those determined for 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indoles, as described above.

The activity profile of 2,9-dimethyl-6-(*N*-tolylsulfonyl)-1,2,3,4,5,6-hexahydroazepine[4,3-b]indole **52** was investigated in a 47 target panel (Fig. **13**) [146]. This compound is a potential multimodal 5-HT$_6$R ligand.

It seems interesting, from the medicinal chemistry point of view, that the *cis*- **53** and *trans*- **54** isomers of 1,2,3,4,5,5a,6,10b-octahydroazepine[4,3-b]indoles (Fig. **15**) show different activity and selectivity in a 66 target panel, including enzymes, receptors and transporters. The highest binding affinity was determined for histamine H$_1$ and 5-HT$_{2C}$ receptors [149]. The pharmacological profiles of these compounds and their analogues were compared to that obtained for 1,2,3,4,5,6-hexahydroazepine[4,3-b]indoles **51** (see Table **5**, Fig. **12**).



	IC_{50}[b], μM	K_i[b], μM
5-H_{2A}	0,022	0,006
5-HT_{2B}	0,319	0,203
5-HT_6	0,034	0,016
5-HT_7	0,535	0,307

Fig. (13). Pharmacological profile of 2,9-dimethyl-6-(*N*-tolylsulfonyl)-1,2,3,4,5,6-hexahydroazepine [4,3-b]indole **52** (10 μM).

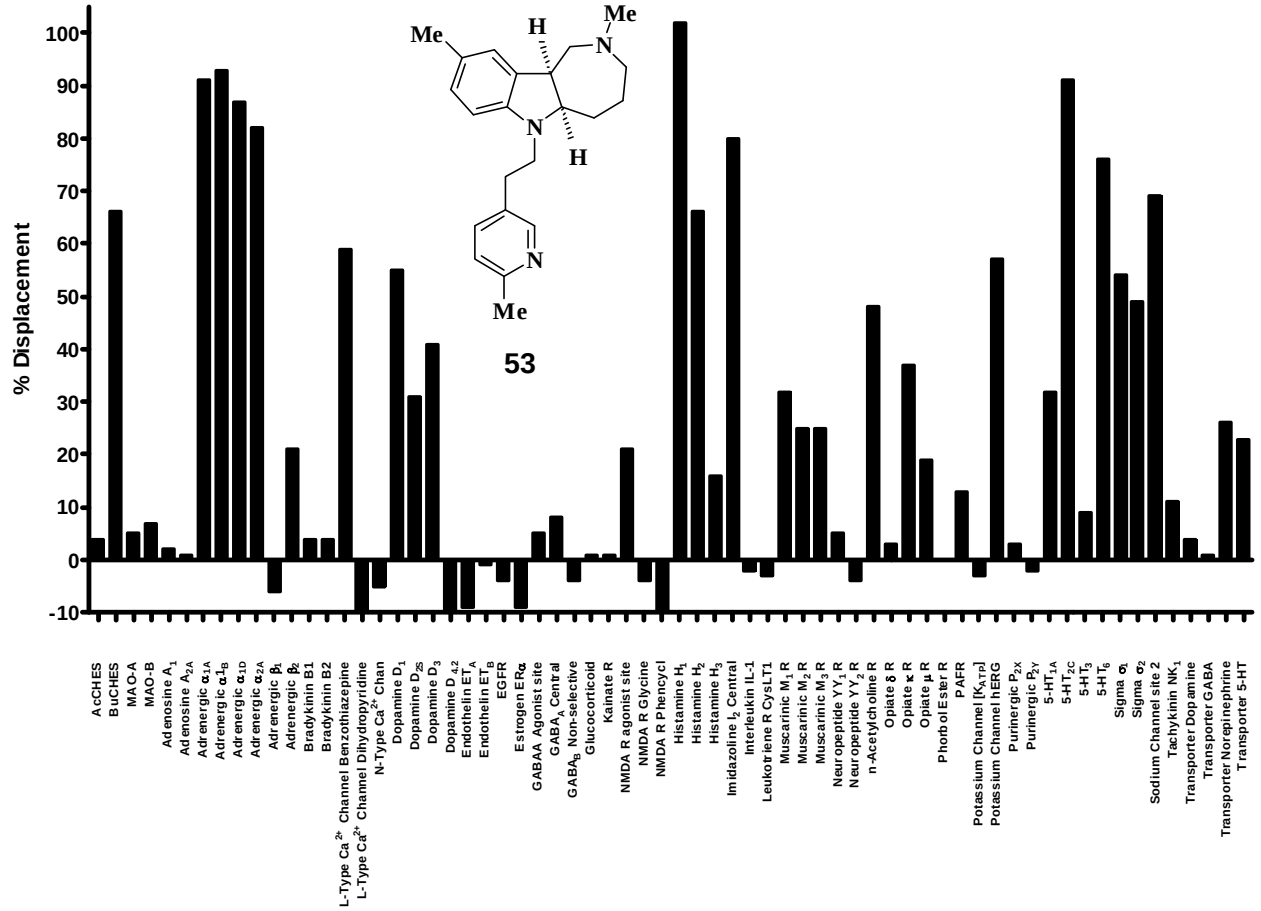


Fig. (14). Binding profile of *cis*-2,9-dimethyl-6-(methylpirydin-3-yl)-1,2,3,4,5,5a,6,10b-octahydroazepine[4,3-b]indole **53** (10 μM); IC_{50}[b] = 790 nM (for 5-HT_6R) [149].

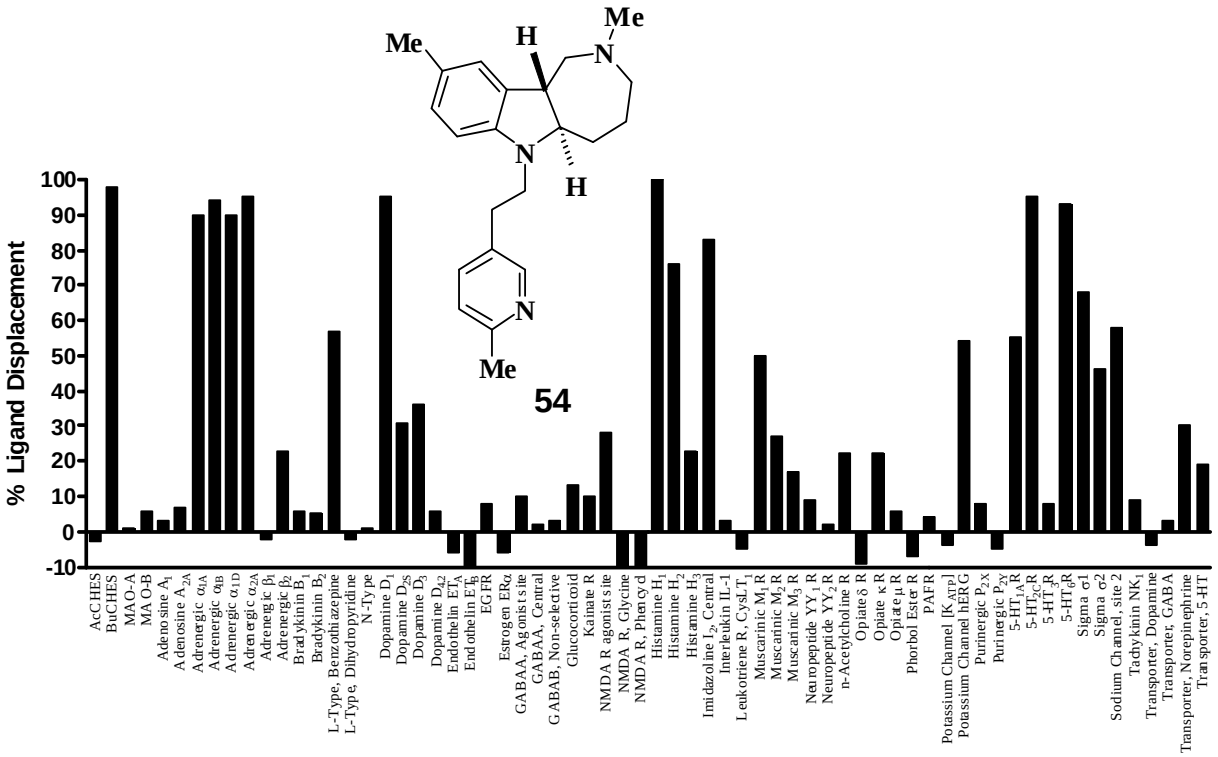


Fig. (15). Binding profile of *trans*-2,9-dimethyl-6-(methylpyridin-3-yl)-1,2,3,4,5,5a,6,10b-octahydroazepine[4,3-b]indole **54** (10 μM); $IC_{50}{}^{b}$ = 260 nM (for 5-HT_6R) [149].

A series of novel substituted 1,2,3,4,5,6-hexahydro-azepino[4,5-b]indoles, including **55**-**65** (Table **6**), has been synthesized and evaluated in a CRBA towards histamine H_1 and H_2, adrenergic α_{1D}, α_{2A}, α_{2B}, dopamine D_{2L}, and serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 receptors [150]. It was clearly demonstrated that 6-phenylethyl-substituted derivatives **55**-**57** and their pyridinyl-containing analogues **58**-**63** show significant activity against the listed targets within the panel, excluding dopamine D_{2L}. Conversely, no activity was demonstrated for the corresponding amides **64** and **66** under the same conditions. It should be noted that, in general, 9-chloro-substituted ligands **55**, **58**, **60** and **62** exhibit slightly more activity in comparison to 9-methyl-substituted derivatives **56**, **59**, **61** and **63**. Tetracyclic pyrrido[2,3-b]indoles **66**-**70** (Fig. **16**) and their structural analogues lack activity in a CRBA against the targets listed above [151-153].

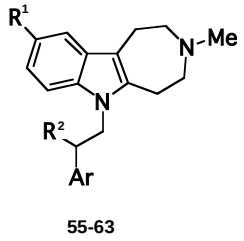
A series of 1,2,3,4,5,10-hexahydro-azepino[3,4-b]indoles, including 1-aza-bicyclo[3.2.1]octane-containing derivatives and compounds **71**-**77** (Table **7**), has been described [150]. Of these compounds, multimodal 4-chlorosteryl derivative **76** (1 μM) was found to be the most active ligand against the same target panel (*see above*) in a CRBA (Inh=80-98%), except dopamine D_{2L}. Similar activity has also been found for fluorine-containing derivatives **75**-**77**; these compounds lack activity against histamine H_2 and dopamine D_{2L} (Inh=25%). Phenylethyl-containing ligands as well as heteroanalogues **142**-**145** exhibit activity (Inh=50%) against only a few targets within the assay panel. With regard to the 5-HT_6 receptor, these compounds possess weak inhibition potency, for example Inh=56% for **71**, or no activity at all, and Inh=2-33% for **72**-**74**.

Several 5,6,7,8,9,10-hexahydro-7,10-epiminocyclohepta [*b*]indoles with the core scaffold **78** and 6,7,8,9,10,11-hexahydro-5*H*-7,11-epiminocycloocta[*b*]indoles **79** (Fig. **17**) have been tested for their activity against 5-HT_6R [154]. Among these compounds, 2-arylsulphonyl-substituted derivatives are the most active ligands against the receptor, including compound **80** with $K_i{}^{b}$ = 0.28 nM, **81** with $K_i{}^{b}$ = 0.26 nM, and **82** with $K_i{}^{b}$ = 0.59 nM.

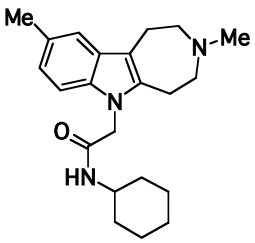
It should be particularly noted that compounds without the sulphonyl moiety have been found to be less than half as active under the same conditions as compared to ligands **80**-**82**. By analogy to the substituted 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles and their derivatives described above, it can be reasonably suggested that ligands **80**-**82,** and close structural analogues, have a multimodal potential; however, pharmacological profiles of these compounds are not presented in the related patent applications.

A series of promising 5,6,7,8-tetrahydro-4*H*-thieno[2',3':4,5]pyrrolo[3,2-c]pyridines **83**, **84** and 4,5,6,7-tetrahydro-4*H*-thieno[2',3':4,5]pyrrolo[3,2-c]pyridines **85**-**87** has been successfully synthesized and thoroughly evaluated against a panel of 19 relevant GPCR-assigned targets [155,156] (Table **8**). Ligands **83**-**87** have revealed significant inhibition potency against histaminergic H_1, H_2 and serotonergic 5-HT_{2A}, 5-HT_{2B}, 5-$HT_{2C,}$ 5-HT_6, 5-HT_7 receptors. In addition, ligands **84**-**87** have been found to be active against adrenergic α_{1A}, α_{1B}, α_{1D}, and α_{2A} receptors, while compounds **84** and **87** possess potency against dopaminergic D_{2L}, D_{2S} and D_3 receptors as well.

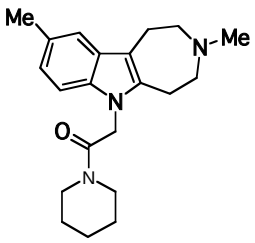
Table 6. Inhibition Potency of 1,2,3,4,5,6-hexahydro-azepino[4,5-b]indoles 126-136 (1 μM) in a CRBA



55-63

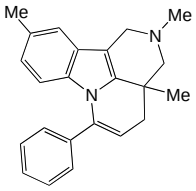


64



65

cmpd	R^1	Ar	R^2	H$_1$	H$_2$	α$_{1D}$	α$_{2A}$	α$_{2B}$	D$_{2L}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_6$
				Inhibition, %								
55	Cl	Ph	H	105	74	83	95	91	62	97	95	104
56	Me	Ph	H	98	79	12	11	98	7	12	101	-4
57	Me	Ph	OH	91	47	96	100	104	43	97	94	93
58	Cl	Py-2	H	97	68	91	95	103	42	97	95	100
59	Me	Py-2	H	99	44	80	88	90	20	96	93	81
60	Cl	6-CF$_3$-Py-3	H	96	58	90	90	107	23	98	79	86
61	Me	6-CF$_3$-Py-3	H	99	37	91	68	88	13	95	77	46
62	Cl	Py-4	H	102	82	89	91	112	27	95	94	92
63	Me	Py-4	H	100	59	76	85	93	2	95	89	93
64	Me	-	-	12	5	1	-14	-7	0	-2	-4	-12
65	Me	-	-	11	-5	4	39	22	-4	60	48	4



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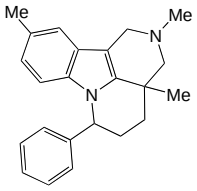

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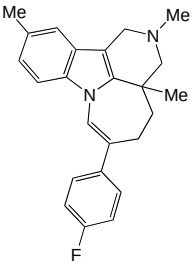

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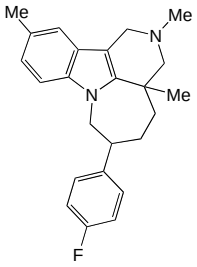

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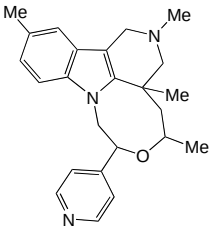
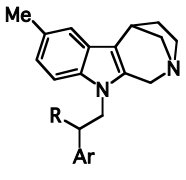


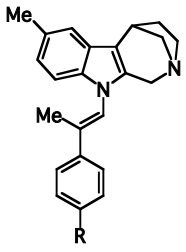
70

Fig. (16). Tetracyclic 2,3,4,5-tetrahydro-1*H*-pyrido[4,3-b]indoles with no activity against histamine H$_1$ and H$_2$, adrenergic α$_{1D}$, α$_{2A}$, α$_{2B}$, dopamine D$_{2L}$, and serotonin 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_6$ receptors.

Table 7. Inhibition profile for multimodal ligands 71-77 (1 μM) in a CRBA



71-74



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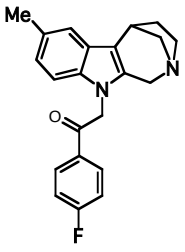
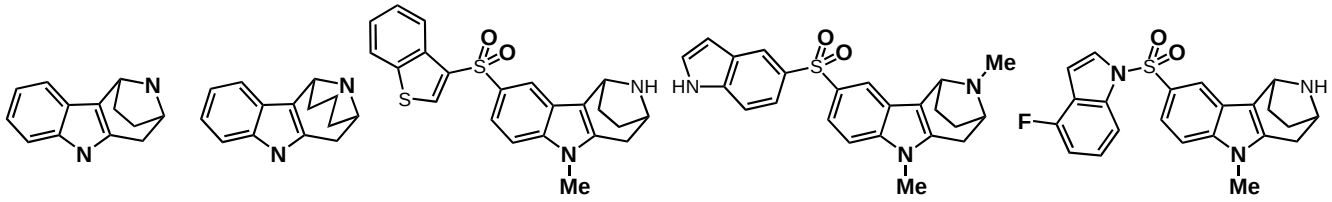


77

cmpd	R	Ar	H$_1$	H$_2$	α$_{1D}$	α$_{2A}$	α$_{2B}$	D$_{2L}$	5-HT$_{2A}$	5-HT$_{2C}$	5-HT$_6$
			Inhibition, %								
71	OH	Ph	67	5	54	54	89	3	49	31	56

Table (7). Contd….

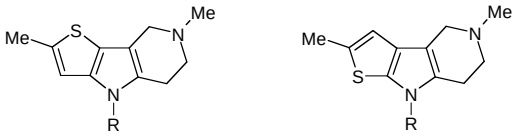
72	H	Py-2	77	-2	26	-15	48	-6	10	17	20
73	H	6-Me-Py-3	59	4	25	-4	16	0	17	5	2
74	H	Py-4	76	18	40	84	76	10	71	85	33
75	F	-	52	15	81	93	95	21	97	96	102
76	Cl	-	85	82	80	96	98	-12	86	92	97
77	-	-	59	25	93	93	93	13	94	97	105



78 **79** **80** **81** **82**

Fig. (17). Epiminocyclohepta[*b*]indoles **78**, epiminocycloocta[*b*]indoles **79** and 2-arylsulphonyl-substituted derivatives **80-82** are potent 5-HT_6 receptor antagonists.

Table 8. Pharmacological profiles of thieno-pyrrolo[3,2-c]pyridines 83-87 (1 μM) in a CRBA.



83, 84 **85-87**

83, 85: R = Ph-CH_2. **84, 86**: R = Ph-CH_2CH_2. **87**: R = Ph-$CH_2CH(OH)$.

Biological Target	**Ligands**					
	83	**84**	**85**	**86**	**87**	
	Inhibition, %					**K_i^b, nM**
Adrenergic α_A	42	77	83	79	97	20.7
Adrenergic α_{1B}	10	57	90	89	99	-
Adrenergic α_{1D}	21	44	64	86	92	-
Adrenergic α_{2A}	34	64	80	91	100	3.87
Dopaminergic D_1	5	5	15	47	70	185.0
Dopaminergic D_{2L}	8	14	76	35	87	-
Dopaminergic D_{2S}	-6	23	73	29	86	42.2
Dopaminergic D_3	16	19	62	23	73	-
Dopaminergic $D_{4.2}$	-3	-5	14	33	71	-
Histaminergic H_1	96	96	97	89	98	0.77
Histaminergic H_2	44	91	56	57	96	-
Histaminergic H_3	-4	18	-15	-3	-17	-
Serotonergic 5-HT_{1A}	3	42	16	18	48	-
Serotonergic 5-HT_{1B}	6	10	18	30	47	-
Serotonergic 5-HT_{2A}	93	100	99	97	101	17.6
Serotonergic 5-HT_{2B}	91	90	79	63	92	-
Serotonergic 5-HT_{2C}	84	97	89	94	99	-
Serotonergic 5-HT_6	55	85	98	99	103	4.3
Serotonergic 5-HT_7	92	95	98	96	99	0.88

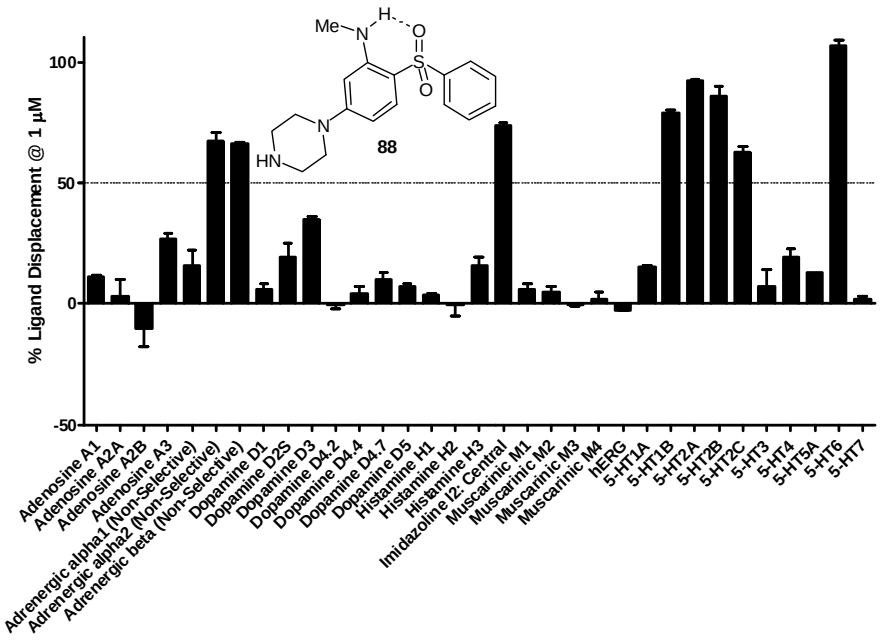


Fig. (18). Binding affinity profile for *N*-methyl-5-(piperazin-1-yl)-2-phenylsulphonyl-aniline **88** (1 µM) determined in a CRBA against 33 different targets.

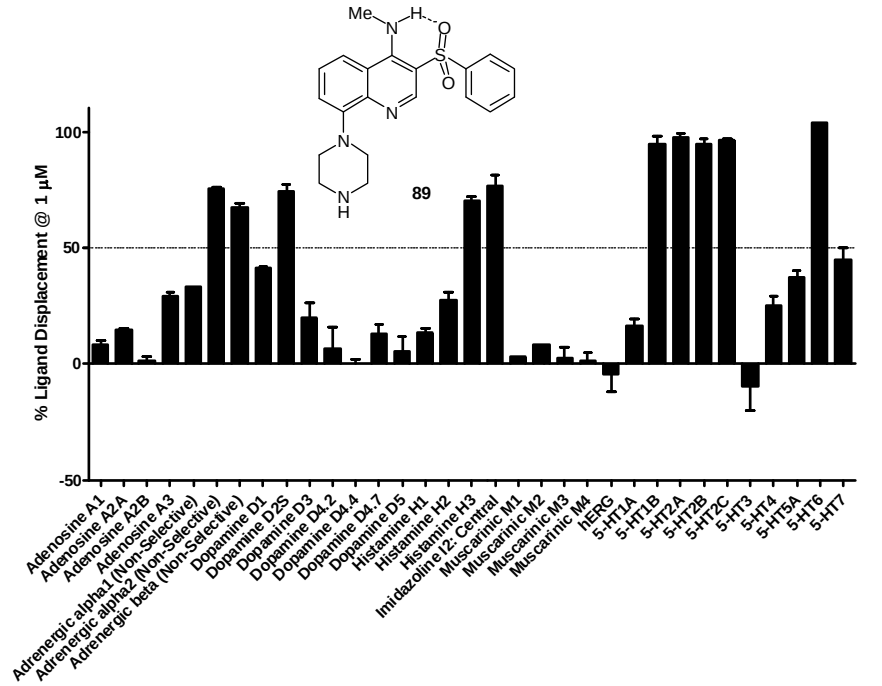


Fig. (19). Pharmacological profile of compound **89** determined in a CRBA against 33 different targets. [160].

Among the described ligands **83-87,** a wide spectrum of pharmacological activity has been determined for 4,5,6,7-2,5-dimethyl-8-phenylethyl-tetrahydro-4*H*-[3',2':4,5]pyrrolo [3,2-c]pyridine **86**. Based on the pharmacokinetic curves of compound **86** towards several receptors from the assay panel, it was found that this ligand has sub-picomolar activity against histaminergic H_1 and serotonergic 5-HT_7 receptors, nanomolar activity against adrenergic α_{2A} and serotonergic 5-HT_6 receptors, sub-nanomolar activity against adrenergic α_{1A}, dopaminergic D_1 and D_{2S}, as well as serotonergic 5-HT_{2A} receptors. The profile is very similar to that obtained for Saphris^R (**1**). Thus, ligand **86** can be reasonably regarded as a potent drug candidate with antipsychotic activity.

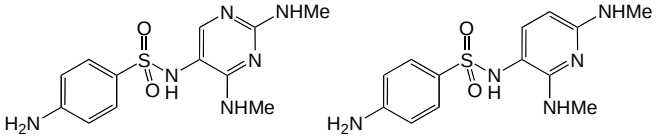
1.3. Other Multimodal Ligands

It has recently been shown that *N*-methyl-5-(piperazin-1-yl)-2-phenylsulphonyl-aniline **88** (Fig. **18**) effectively blocks

the 5-HT_6 receptor with sub-picomolar potency (K_i^f = 0.16 nM) [157,158]. The pharmacological profile of this compound reveals a comprehensive multimodality. In a CRBA with 33 different receptors, ligand **88** (1 μM) possesses an inhibition potency against 5HT_6R of up to 107%, for adrenergic α_2 (non-selective) 66% and adrenergic β (non-selective) 73%, for imidazoline I_2 (central) and serotonin 5-HT_{1B} - 79%, 5-HT_{2A} - 92%, 5-HT_{2B} 86%, and for 5-HT_{2C} receptors 63%.

The bioisosteric replacement of the core aromatic ring in **88** by quinoline has created a novel 5-HT_6R antagonist (3-benzenesulfonyl-8-piperazin-1-yl-quinolin-4-yl)-methyl-amine **89** (Fig. **19**) [159, 160].

Compound **89** exhibits clear multimodality with sub-micromolar activity against serotonin 5-HT_6 (IC_{50}=116 pM) and 5-HT_{2A} (IC_{50}=318 pM) receptors, nanomolar activity towards serotonin 5-HT_{2B} (IC_{50}=33 nM) and 5-HT_{2C} (IC_{50}=25 nM) receptors, and sub-picomolar activity against adrenergic α_{2A} (IC_{50}=177 nM), α_{2B} (IC_{50}=321 nM), α_{2C} (IC_{50}=951 nM), adrenergic β_1 (IC_{50}=668 nM), dopamine D_1 (IC_{50}=748 nM), D_{2S} (IC_{50}=298 nM), histamine H_3 (IC_{50}=497 nM), imidazoline I_2 (central, IC_{50}=292 nM), as well as serotonin 5-HT_7 (IC_{50}=537 nM) receptors. It should specially be noted that ligand **88** is the first compound that has shown activity against dopamine D_2 and serotonin 5-HT_{2A}, 5-HT_{2C}, 5-HT_6 receptors and the histamine H_3 receptor. Importantly, this compound possesses no potency at 1 μM against histamine H_1 and H_2 receptors (Inh%=14 and 28, respectively); therefore, potential adverse effects may be substantially reduced. This compound is currently described as a promising antipsychotic [160].



90 (Ro 04-6790) **91** (Ro 63-0563)

Fig. (20). One of the first classes of 5HT_6R ligands previously described as selective antagonists.

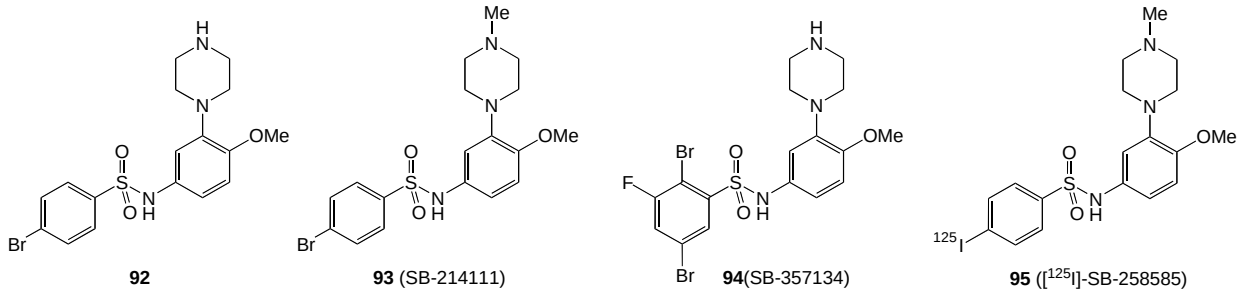
2. PSEUDO-SELECTIVE 5-HT_6R LIGANDS

This group of ligands includes small molecule compounds with activity against 5-HT_6 receptors less than 250-fold higher as compared to other biological targets in the assigned pharmacological profile. While the 250-fold margin between pseudo-selective and selective ligands is somewhat subjective, we suggest this as the most reliable categorization within the scope of the current discussion. Using this assumption, many of the compounds published previously and described as selective 5-HT_6R ligands should therefore be re-classified as pseudo-selective antagonists. This is particularly relevant for the first class of 5HT_6R ligands including 4-amino-*N*-(2,6-bis-methylamino-pyrimidin-4-yl)-benzene sulphonamide **90** (Ro-046790) with pK_i^b = 7.35±0.04 and 4-amino-*N*-(2,6 bis-methylamino-pyridin-4-yl)-benzene sulphonamide **91** (Ro-63-0563) with pK_i^b = 7.83±0.01 (Fig. **20**). These ligands are 100-fold more selective toward 5-HT_6R than toward 23 and 69 different biotargets (for Ro-046790 and Ro-63-0563, respectively), as well as towards other receptors including various dopamine and 5-HT receptor subtypes [161-167].

Among their direct bioisosteric analogues, 4-bromo-*N*-(4-methoxy-3-piperazin-1-yl-phenyl)-benzenesulfonamide **92** exhibits weaker selectivity. However, it shows >50-fold higher selectivity for a number of key receptors, including 5-HT receptor subtypes [164]. At the same time, its analogue SB-214111 **93** was found to have no appreciable affinity for over 50 receptors, enzymes, and ion channels [165-168], whereas SB-357134 **94** has displayed >200-fold higher selectivity towards 5HT_6R versus 72 other receptors and enzymes [168]. It should also be noted that ligand **95** ([^{125}I]-SB-258585) exhibits >100-fold higher selectivity against 5-HT receptor subtypes [169] (Fig. **21**).

The *N*-phenyl-benzenesulfonamide core fragment in compounds **92-95** has been replaced by the bioisosteric morphology *N*-phenyl-benzo[b]thiophene-2-sulfonamide, resulting in compounds **96** (SB-271046) and **97** (SB-258510) (Fig. **22**). This modification has led to an increase in 5-HT_6R activity and selectivity. Thus, SB-258510 **97** is a sub-nanomolar 5-HT_6R ligand with >300-fold selectivity over a range of other receptors [169,170]. It should be noted that a metabolite of SB-271046 (with K_i^b = 1.3 nM and >200-fold increase in selectivity compared to 69 receptors, enzymes, and ion channels) has a weaker potency and selectivity as compared to the parent compound SB-258510 [170]. Moreover, the metabolite has poor blood brain barrier permeability (B/P <0.1) [171].

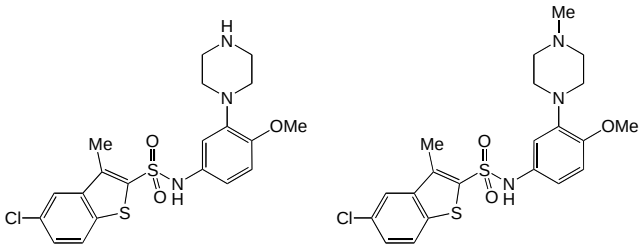
5-Chloro-naphthalene-2-sulfonic acid [3-(2-dimethylamino-ethyl)-1*H*-indol-5-yl]-amide **97a** (E-6837, Fig. **23**) has displayed partial agonistic activity against rat 5-HT_6 receptors (EC_{50}=0.6 nM, E_{max}=67%), and full agonistic effect (EC_{50}=0.3 nM, E_{max}=96%) against human receptors, and >150-fold selectivity over more than 60 other targets [172]. This selectivity is significantly higher as compared to 1-



92 **93** (SB-214111) **94**(SB-357134) **95** ([^{125}I]-SB-258585)

Fig. (21). Compounds **92-95** with the benzenesulfonamide core as 5HT_6R ligands.

phenylsulfonyl-1*H*-indoles **98**, **99** (Fig. **23**). [2-(1-phenylsulfonyl-5-methoxy-1*H*-indol-3-yl)-ethyl]-dimethyl-amine **98** (with K_i^b = 2.9 nM) exhibits >100-fold higher selectivity over serotonin receptors, such as 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1E}$, 5-HT$_3$ and 5-HT$_7$. However, this compound was found to have binding potency against 5-HT$_{2A}$R (K_i = 120 nM) and 5-HT$_{2C}$R (K_i = 23 nM) [165]. 2-[1-(6-Chloro-imidazo[2,1-b]thiazole-5-sulfonyl)-1*H*-indol-3-yl]-ethylamine **99** (WAY-181187, SAX-187) is a well described 5-HT$_6$R agonist and was found to have >50-fold selectivity in a panel of 31 other receptors and ion channels [173].



96 (SB-271046) **97** (SB-258510)

Fig. (22). 5-Chloro-3-methyl-benzo[b]thiophene-2-sulfonamides **96** and **97** with high activity and selectivity against 5HT$_6$R.

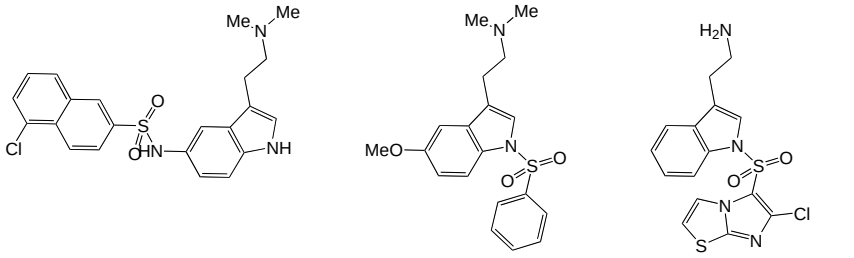
The 5-HT$_6$R agonists 1-phenylsulfonyl-5-chloro-3-((R)-1-methyl-pyrrolidin-2-ylmethyl)-1*H*-indole **100** (with K_i^b = 1.4 nM) and 5-fluoro-3-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-1-(naphthalene-1-sulfonyl)-1*H*-indole **101** (with K_i^b = 1 nM) exhibit >100-fold higher selectivity over 40 other receptors and binding sites in a panel (Fig. **24**) [165]. The sub-picomolar 5-HT$_6$R antagonist 5-chloro-1-(3-chloro-phenylsulfonyl)-3-piperazin-1-yl-1*H*-indole **102 (**with K_i^b = 0.3 nM) demonstrates >100-fold selectivity over 50 other biological targets [174,175].

A series of potent 1-phenylsulfonyl-3-(4-chloro-1-methyl-2,5-dihydro-1*H*-pyrrol-3-yl)-1*H*-indoles, including several highly active 5HT$_6$R ligands such as **103** (Fig. **25**) with K_i^b ~ 0.1 nM, has been synthesized and tested against a panel of biological targets [176]. The authors have reported that these ligands have excellent selectivity (*data not shown*) over a range of closely related receptors like 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_4$, 5-HT$_7$, histamine H$_1$, dopamine D$_2$, adrenergic α_{1b}, muscarinic M$_1$, and acetylcholine receptors and transporters like SERT, DAT and NET. All the tested compounds produced <50% inhibition at a concentration of 0.5 μM.

It should be pointed out that 1-phenylsulfonyl-3-(4-alkylpiperazin-1-yl)-1*H*-indoles **104** are slightly less active and selective than their analogues **103** against 5-HT$_6$R. These ligands (**104**) have been shown to possess activity versus several targets including other 5-HT receptor subtypes, dopamine D$_2$, histamine H$_1$ and transporters like SERT and NET; however, against 5HT$_6$R these compounds exhibit 50–100-fold higher selectivity over all the tested receptors (*data not shown*) [177].

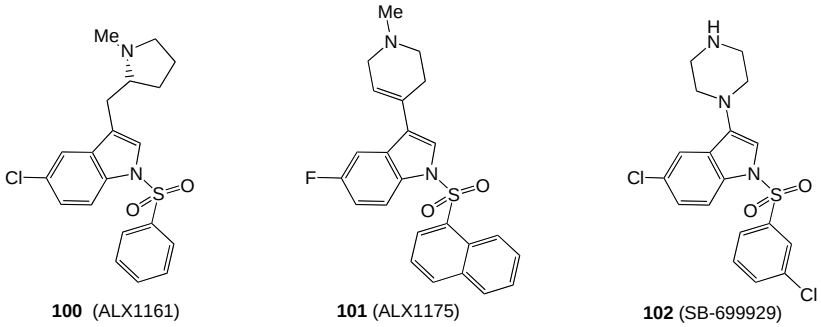
The synthesis and comprehensive biological evaluation of (piperazin-1-yl-phenyl)-arylsulfonamides **105** (Fig. **26**) have been described [178]. These compounds demonstrate high affinities for both 5-HT$_{2C}$ and 5-HT$_6$ receptors. Among them, naphthalene-2-sulfonic acid isopropyl-[3-(4-methyl-piperazin-1-yl)-phenyl]-amide **105** exhibits the highest binding affinity towards both 5-HT$_{2C}$ (IC_{50}^b = 4 nM) and 5-HT$_6$ receptors (IC_{50}^b = 3 nM) with good selectivity over other serotonin receptor family members, including 5-HT$_{1A}$ (IC_{50}^b = 118 nM), 5-HT$_{2A}$, and 5-HT$_7$ and dopamine D$_2$-D$_4$ receptor subtypes. In 5-HT$_6$ and 5-HT$_{2C}$ receptor functional assays, this compound possesses considerable antagonistic potency for both receptors.

Nirogi and colleagues have described a series of 5-HT$_6$R ligands with >100-fold higher selectivity over other biological targets in a panel including several 5-HT receptor subtypes including 5-HT$_4$, 5-HT$_{2A}$ and 5-HT$_{2C}$, adrenergic α_{1b},



97a **98** **99** (WAY-181187, SAX-187)

Fig. (23). 1*H*-Indol-3-yl-ethyl-amines **97a-99.**

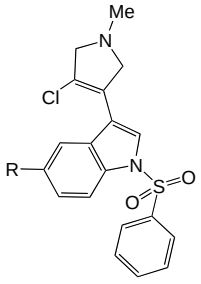


100 (ALX1161) **101** (ALX1175) **102** (SB-699929)

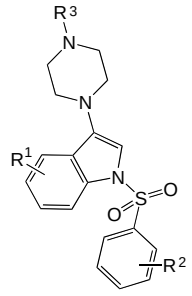
Fig. (24). Substituted 1-arylsulfonyl-1*H*-indoles **100-102**, effective 5-HT$_6$R ligands with >100-fold selectivity over a panel of 40-50 other receptors.

dopamine D_2, histamine H_1, and transporters like SERT, NET and DAT [179]. Among the tested compounds, the highest binding affinity (K_i^b = 20 pM) was observed for ligands **106** and **107** (Fig. **27**).

2-Alkyl-5(7)-(4-methyl-piperazin-1-yl)-1-(naphthalene-2-sulfonyl)-2,3-dihydro-1*H*-quinolin-4-ones **108-110** (Table **9**) have nanomolar potency against 5-HT_6R [180]. Interestingly, their target activity is strongly dependent on stereochemical properties, whereas their selectivity is connected to the position of 4-methyl-piperazin-1-yl moiety. Thus, compound **108** with IC_{50}^b = 8 nM for 5-HT_6R possesses significant potency against 5-HT_{2A} and 5-HT_{2C} receptors (IC_{50}^b = 48 nM and IC_{50}^b = 30 nM, respectively), while ligand **110** with IC_{50}^b = 28 nM demonstrates high activity against 5-HT_{2C} and D_2 receptors (IC_{50}^b = 558 nM and IC_{50}^b = 136 nM, respectively).

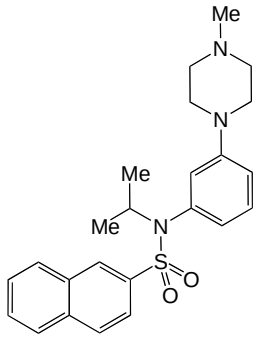


103: R = H, MeO, F



104: R^1= H, 5-Cl, 6-Cl, 5-Br. R^2= i-Pr, F, Cl, Br,MeO, F, 2,5-di-MeO, 2-naphtyl. R^3= Me

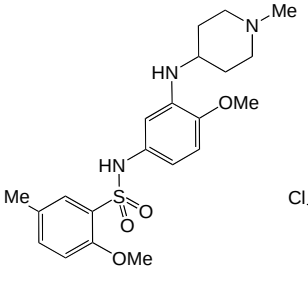
Fig. (25). Substituted 1-phenylsulfonyl-1*H*-indoles **103** and **104**, highly potent pseudo-selective 5HT_6R ligands.



105

IC_{50}^b, nM
5-$HT_6$3
5-HT_{1A}>1000
5-HT_{2A}118
5-HT_{2C}4
D_2>10000
$D_3$248
D_4>1000

Fig. (26). Substituted sulfonamides such as **105** are atypical antipsychotics.



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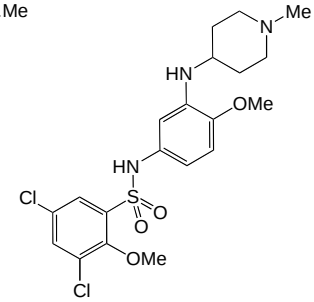
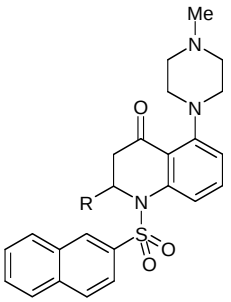


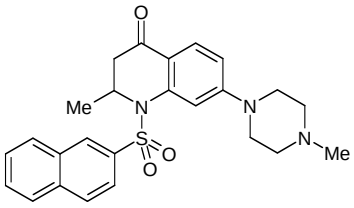
107

Fig. (27). Substituted sulfonamides **106** and **107.**

Table 9. Binding affinity of substituted 2,3-dihydro-1*H*-quinolin-4-ones 108-110 against serotonin (5-HT_{1A}–5-HT_7) and dopamine (D_2–D_4) receptor subtypes

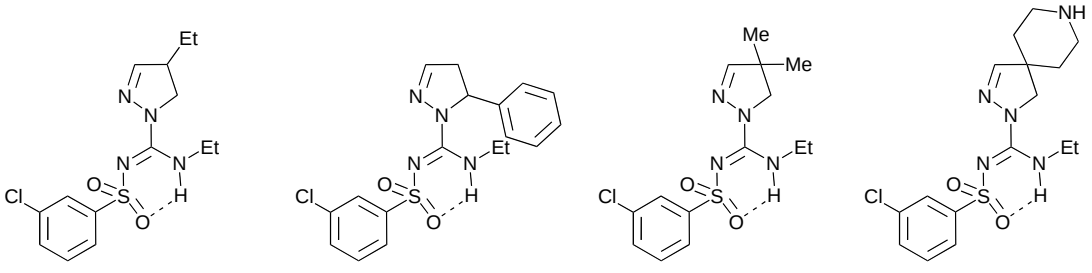


108: R = Me
109: R = Et.



110

cmpd	5-HT_6	5-HT_{1A}	5-HT_{2A}	5-HT_{2c}	5-HT_7	D_2	D_3	D_4
	IC_{50}^b, nM							
108	8	1210	48	30	2007	>10000	482	5522
108-(*R*)	353	-	-	-	-	-	-	-
108-(*S*)	7	-	-	-	-	-	-	-
109	9	999	455	4	>10000	>1000	623	>10000
110	28	1598	1462	558	>10000	136	482	5522
110-(*R*)	43	-	-	-	-	-	-	-
110-(*S*)	17	-	-	-	-	-	-	-



111 K_i^b= 7,9 nM

112 K_i^b= 23,9 nM; (*S*)- K_i^b= 9,3 nM; (*R*)- K_i^b> 1000 nM

113 K_i^b= 24,1 nM

114 K_i^b= 7,2 nM

Fig. (28). *N'*-(Arylsulfonyl)pyrazoline-1-carboxamidines **111-114** as promising 5-HT$_6$R ligands.

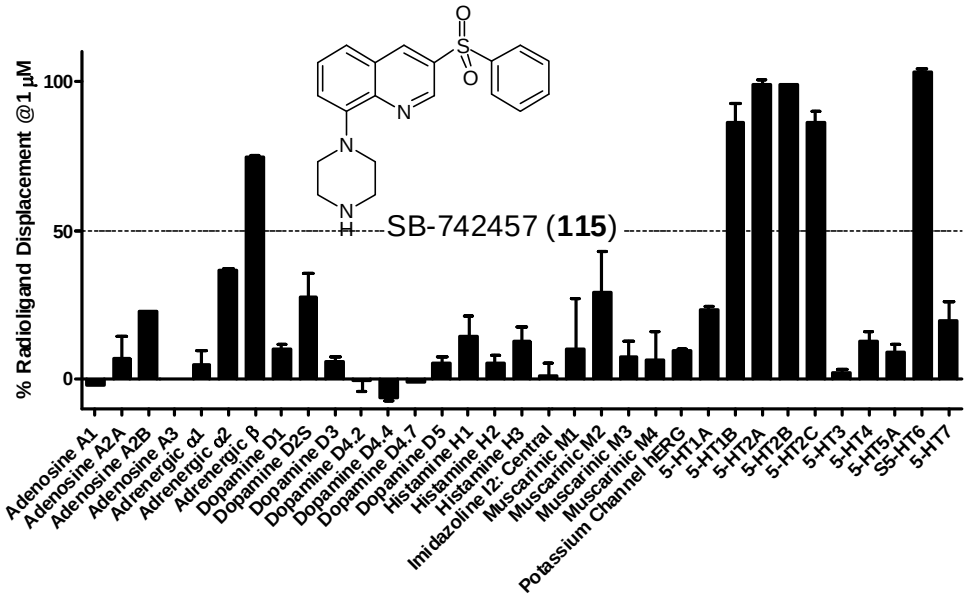
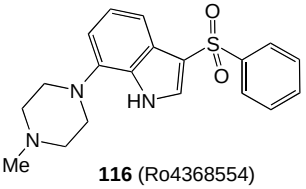


Fig. (29). Spectrum of the binding affinity determined for SB-742457 in a CRBA.

Recently, a novel series of unique *N'*-(arylsulfonyl)pyrazoline-1-carboxamidines (Fig. **28**) has been described as promising 5-HT$_6$R ligands [181]. The conformation of these compounds is internally stabilized by intramolecular H-bonding. In a binding assay targeted to 86 different receptors, ion channels, and transporters, as well as 27 enzymes, several of these compounds (**111-114)** exhibit nanomolar activity against the title receptor. A relatively good 5-HT$_6$R selectivity, approximately 220-fold higher than for other targets in the assay, was determined for compound **114**. The only off-target affinities revealed thus far have been for the peripheral benzodiazepine receptor, pK_i^b of 5.8 (1585 nM) and for 5-HT$_{2B}$ receptor, pK_i^b of 5.1 (7943 nM).

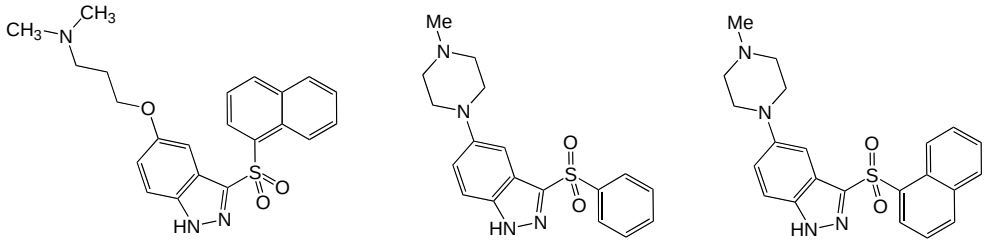
The 5-HT$_6$R antagonist 3-phenylsulfonyl-8-piperazine-1-yl-quinoline **115** (SB-742457, Fig. **29**), with pK_i^f = 9.2 and pK_i^b = 9.6, has been thoroughly evaluated in the clinic over the last several years [182]. This compound shows >100-fold increase in target activity versus 23-85 other receptors, enzymes, and ion channels. The related pharmacological profile of SB-742457 (1 µM, Fig. **29**) has been determined in a CRBA with 33 different receptors, and demonstrates high activity for not only 5-HT$_6$R but also 5-HT$_{1B}$ (87%), 5-HT$_{2A}$ (99%), 5-HT$_{2B}$ (99%), 5-HT$_{2C}$ (86%) receptor subtypes, and adrenoceptor в (74 %).

Moderate 5-HT$_6$R selectivity has been shown for a series of 3-arylsulfonyl-7-(piperazin-1-yl)-1*H*-indoles (Fig. **30**) with sub-picomolar activity [183]. For instance, Ro4368554 **116** with K_i^b = 0.5 nM displays >50-fold target selectivity over more than 50 other receptors, enzymes, and ion channels [183] and >100-fold selectivity over other monoamine receptor subtypes (pK_i = 7.1 for 5-HT$_{2A}$).



116 (Ro4368554)

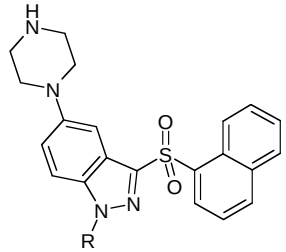
Fig. (30). 3-Phenylsulfonyl-7-(4-methyl-piperazin-1-yl)-1*H*-indole **116** with 5-HT$_6$R activity.



117 (Cerlapiridine, WAY-262531, SAM-531, PF-05212365, PF-5212365) **118** **119**

Fig. (31). 3-Arylsulfonyl-1*H*-indazoles **117-119** with nanomolar activity against 5-HT_6R.

Table 10. Selectivity Profiles of 3-arylsulfonyl-5-piperazinylindazoles 118-124



120-124

120 - R = H, **121** - R = Me, **122** - R = *i*-Pr, **123** - R = *i*-Bu, **124** - R = Bu.

cmpd	5-HT_6	5-HT_{1a}	5-HT_{1b}	5-HT_{1d}	5-HT_{2b}	5-HT_{2c}	5-HT_7	α_{2A}	D_2
	nM								
118	1.9	>5000	>5000	>5000	978	3067	753	>5000	355
119	1.6	>5000	>5000	>5000	601	>5000	579	>5000	334
120	1.1	573	>5000	>5000	236	>5000	1563	>5000	>5000
121	1.6	3780	3624	2762	87	3648	>5000	>5000	2243
122	2.9	>5000	>5000	>5000	96	1075	>5000	>5000	2036
123	4.6	>5000	>5000	>5000	281	1880	>5000	>5000	1903
124	7.5	>5000	>5000	>5000	141	1070	>5000	>5000	605

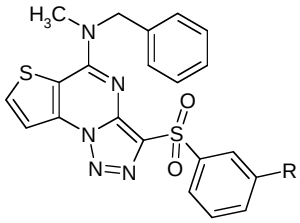
Relatively high selectivity has been determined for 3-arylsulfonyl-1*H*-indazole-containing 5-HT_6R antagonists [117]. WAY-262531 (**117**) with K_i^b = 1.3 nM, 3-benzenesulfonyl-5-(4-methyl-piperazin-1-yl)-1*H*-indazole **118** with K_i^b = 1.9 nM and 5-(4-methyl-piperazin-1-yl)-3-(naphtalene-1-sulfonyl)-1*H*-indazole **119** with K_i^b = 1.6 nM (Figs. **31**, Table **10**) exhibit >200-fold selectivity over more than 80 other receptors, enzymes, and ion channels [184,185].

Selectivity profiles of indazoles **118-124** towards a panel of different receptors including several 5-HT receptor subtypes, adrenergic α_{2A} and dopamine D_2 receptors are shown in (Table **10**) [186]. In general, these compounds exhibit >200-fold selectivity over all other receptors tested with the exception of 5-HT_{2B}. However, in a 5-HT_{2B} FLIPR-based functional assay (FLIPR is Fluorescent Imaging Plate Reader), no activity was observed for these compounds at the concentration in the range of 0.1 nM - 10 μM.

Several 5-HT_6R antagonists, 3-phenylsulfonyl-thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidines and 3-phenylsulfonyl-[1,2,3]triazolo[1,5-a]quinazolines, demonstrate a relatively moderate activity and selectivity *in vitro* [187,188]. For example, in a panel of 5-HT receptors, benzyl-methyl-(3-phenylsulfonyl-thieno[2,3-e][1,2,3]triazolo[1,5-a]pyrimidin-5-yl)-amine **125**, with K_i^f = 2.3 nM and IC_{50}^f = 5.0 nM, exhibits >200-fold selectivity over other subtypes of 5-HT receptors (Table **11**) [189]. Within the same assay, compound **126** with K_i^f = 3.5 nM and IC_{50}^f = 7.5 nM displays >150-fold selectivity, and (tetrahydro-furan-2-ylmethyl)-(3-phenylsulfonyl-[1,2,3]triazolo[1,5-a]quinazolin-5-yl)-amine **127** with K_i^f = 13.2 nM and IC_{50}^f = 28.4 nM displays >50-fold selectivity (Fig. **32**) [190]. In a patch clamp assay, two of the 5-HT_6R antagonists **125** and **126** demonstrate a comparatively weak inhibition of hERG potassium ion channels (20% inhibition at 15.0 μM and 30 μM, respectively, for **125** and **126**) [190].

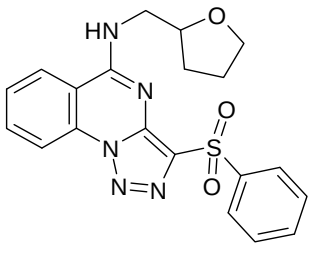
Relatively high selectivity has been demonstrated for the 5-HT_6R antagonist 2-(methylthio)-3-(phenylsulfonyl)-4*H*-pyrido[1,2-*a*]pyrimidin-4-imine **128** with IC_{50}^b = 4 nM (Fig.

Table 11. The percentage of competitive radioligand displacement from the active binding sites of serotonin receptors by compounds 125 and 126 (1 μM) in a CRBA



125 (R=H), **126** (R=Cl)

Subtypes of serotonin receptor	Compound 125	Compound 126
	% Displacement	
5-HT$_{1A}$	2	9
5-HT$_{1B}$	1	3
5-HT$_{2A}$	15	50
5-HT$_{2B}$	12	46
5-HT$_{2C}$	2	15
5-HT$_3$	-7	-3
5-HT$_4$	33	41
5-HT$_6$	103	106
5-HT$_7$	-2	6



127

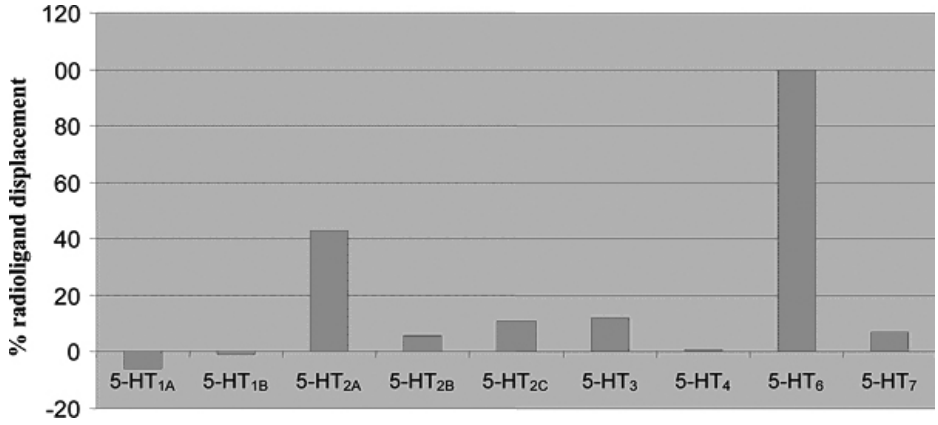


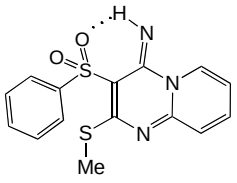
Fig. (32). 5-HTR selectivity profile for ligand **127** (1 μM) determined in a CRBA.

33). This compound has been tested in a commercial screening package and did not exhibit significant (i.e. <20% inhibition at 10 мM concentration) interactions with 70 other receptors including all seven 5-HT receptors assayed (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_{5A}$, 5-HT$_7$) [191].

The sub-picomolar 5-HT$_6$R antagonist Lu AE58054 ([2-(6-fluoro-1*H*-indol-3-yl)-ethyl]-[3-(2,2,3,3-tetrafluoro-propoxy)-benzyl]-amine) **129** (Fig. **34**) with K_i^b = 0.83 nM is currently being evaluated in a Phase II clinical trial [192]. This compound possesses a moderate affinity towards adrenergic α_{1A} and α_{1B} receptors as well as >50-fold higher selectivity against a wide range of other biological targets.

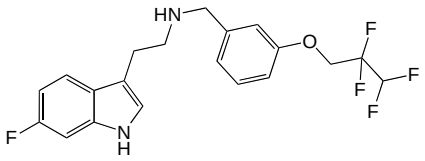
3. SELECTIVE 5-HT$_6$R LIGANDS

Selective 5-HT$_6$R ligands (antagonists, agonists, and partial agonists) are exclusively active against 5-HT$_6$R or interact simultaneously with some targets (*e.g.* receptors, enzymes, ion channels), but show an activity level far less than for the core biological target. High 5-HT$_6$R selectivity allows scientists to determine the underlying mechanism of action more robustly. In addition, undesired side effects can be significantly reduced. Given these considerations, medicinal chemists primarily focus on the development of novel drug candidates with high selectivity and activity sufficient for the achievement of the desired therapeutic result.



128

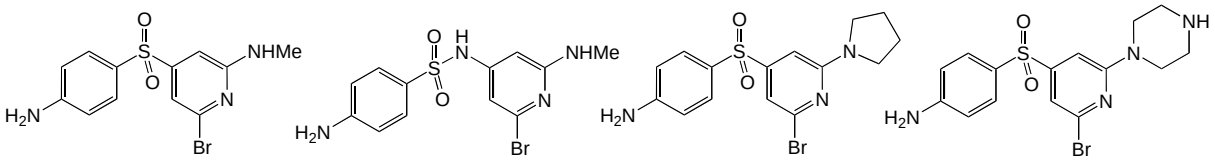
Fig. (33). 2,3-Substituted pyrido[1,2-*a*]pyrimidin-4-imine **128** with high 5-HT_6R activity and selectivity.



129

Fig. (34). Sub-picomolar 5-HT_6R antagonist Lu AE58054 **129.**

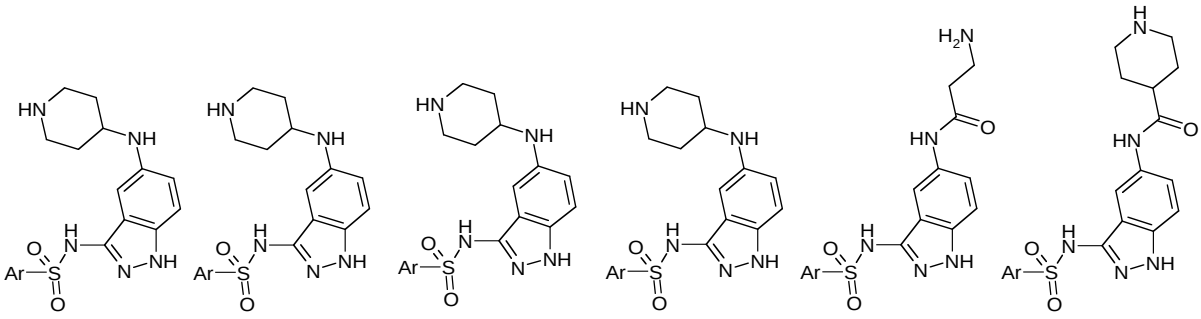
Following further structural optimization of 3-arylsulfonyl-1*H*-indazoles **90** and **91** (Fig. **19**) as well as their close analogues, Riemer and colleagues have shown that phenylsulphonylpyridines **130, 132** and **133** (Fig. **35**) are much more active in a 5-HT_6R binding assay opposite the corresponding sulphonamides [193,194] (*e.g.* compound **131**). Thus, [4-(4-amino-benzenesulfonyl)-6-bromo-pyridin-2-yl]-methyl-amine **130** (pK_i^b = 8.64) was found to be significantly more potent as a 5-HT_6R antagonist compared to 4-amino-*N*-(2-bromo-6-methylamino-pyridin-4-yl)-benzenesulfonamide **131** (pK_i^b = 7.38). It seems absolutely incredible that among the tested compounds, 4-(2-bromo-6-pyrrolidin-1-yl-pyridine-4-sulfonyl)-phenylamine **132** with pK_i^b = 9.00 possesses >100K-fold higher selectivity over more than 50 other biological targets including muscarinic, purinergic, dopaminergic, opiate, GABAergic, histaminergic, adrenergic, nicotinergic, and tachykinin receptors, as well as different types of calcium and potassium ion channels. It should be noted that besides an impressive 5-HT_6R antagonistic potency, its sub-picomolar analogue 4-(2-bromo-6-piperazin-1-yl-pyridine-4-sulfonyl)-phenylamine **133** with pK_i^b = 9.94 exhibits a significant binding affinity (pK_i^b = 7.69) against 5-HT_{2C}R as well [193].



130 **131** **132** **133**

Fig. (35). Substituted 4-phenylsulfonylpyridines **130, 132, 133** and 4-(phenylsulfonylamino)pyridine **131** with activity against 5-HT_6R.

Table 12. Selectivity profile of 3-sulfonylindazoles 134-139

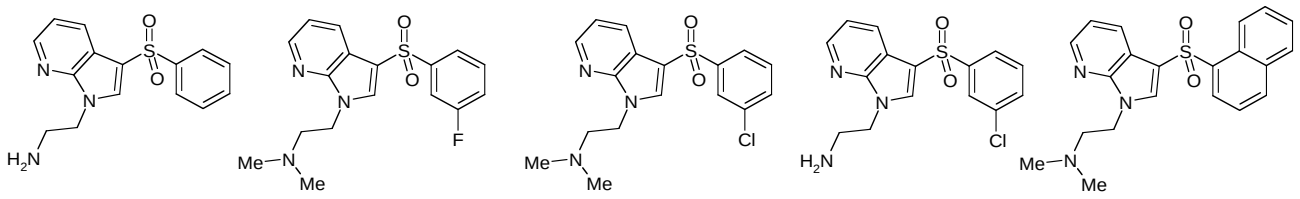


134 **135** **136** **137** **138** **139**

Ar = 1-naphtyl (**134, 138, 139**), 3-chlorophenyl (**135**), 4-*iso*-propylphenyl (**136**), 2-naphtyl (**137**)

Cmpd	5-HT_6	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2B}	5-HT_{2C}	5-HT_7	α_{2A}	D_2
	K_i^b, nM								
134	0.5	>5000	>5000	>5000	675	>5000	>5000	>5000	>5000
135	1.0	455	1659	410	155	2427	3970	>5000	>5000
136	1.0	859	2726	1490	1760	1767	3216	>5000	>5000
137	0.6	4347	>5000	>5000	675	>5000	>5000	>5000	>5000
138	1.5	>5000	>5000	>5000	344	573	>5000	>5000	>5000
139	1.1	3011	>5000	1340	33	>5000	>5000	>5000	>5000

Table 13. Binding affinity profile for 5-HT$_6$R agonists 140-144



140 **141** (WAY-208466) **142** **143** **144**

Receptor	140	141	142	143	144
	IC$_{50}$[b], nM or % inhibition at 1 μM				
5-HT$_6$	5.5	4.8	2.3	2.0	1.0
5-HT$_{1B}$	11%	30%	46%	NT	40%
5-HT$_{1D}$	16%	16%	10%	NT	0%
5-HT$_{1F}$	14%	22%	29%	NT	10%
5-HT$_{2A}$ (ag)	>5000	351	131	11	938
5-HT$_{2C}$ (ag)	>5000	644	477	44	1135
5-HT$_7$	>5000	4764	1217	1362	511
D$_2$	>5000	>5000	>5000	>5000	>5000
D$_3$	>5000	>5000	>5000	>5000	>5000
D$_4$	>5000	>5000	>5000	>5000	>5000

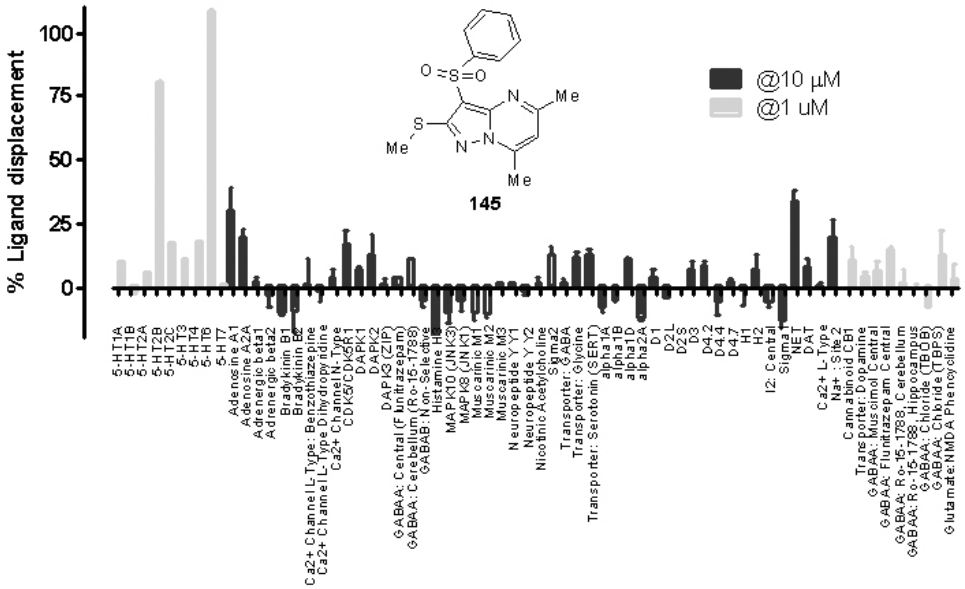


Fig. (36). Target-specific profile determined for AVN-211 **145** (1 μM and 10 μM) in a CRBA.

5-HT$_6$R antagonists, 3-sulfonylindazoles **134-139** (Table **12**), have displayed excellent potency in both binding and adenylate cyclase functional assays [186]. These compounds have further been profiled for their binding selectivity against a panel of targets including several 5-HT receptor subtypes, adrenergic α_{2A} and dopamine D$_2$ receptors; these data are summarized in (Table **12**). It should be especially noted that 5-HT$_6$R ligands **134, 136** and **137** have demonstrated >1K-fold higher selectivity over all the other receptors evaluated in the trial.

Compounds **140-144** from the 3-(arylsulfonyl)-pyrrolo[2,3-b]pyridine series are shown in (Table **13**). These compounds have been found to be full 5-HT$_6$R agonists with target activity in the nanomolar range [195]. The most selective ligand **140** has demonstrated >1K-fold higher selectivity

over other serotonergic and dopaminergic receptors investigated in the trial.

The 3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines are among the most powerful 5-HT_6R antagonists discovered to date, and form the most prominent class of drug candidates [196-212]. For instance, 5,7-dimethyl-2-methylsulfanyl-3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidine (AVN-211) **145** (Fig. **36**) with K_i^b = 2.0 nM and (5,7-dimethyl-3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidin-2-yl)-methyl-amine (AVN-216) **146** (Fig. **37**) with K_i^b = 0.2 nM [213] exhibit 5K-fold [214] and 50K-fold [213] higher selectivity, respectively, over 67 other receptors, enzymes, and ion channels, excepting only 5-HT_{2B}R. Against this subtype, ligands **145** and **146** exhibit an extensive range of micromolar activity: IC_{50}^b = 0.196 μM, IC_{50}^f > 10 μM for compound **145** [214] and IC_{50}^b = 1.63 μM, IC_{50}^f = 5.13 μM for compound **146** [213].

A series of 3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines **147-150** (Fig. **38**) has recently been described as highly potent sub-picomolar 5-HT_6R antagonists [215]. Particularly, it has been clearly shown that the target selectivity of these agents over all the other 32 receptors is >3.3K-fold for compound **147**, 1K-fold for compound **148**, 1.9K-fold for ligand **149**, and 4.8K-fold for antagonist **150**.

As shown in (Fig. **38**), at the concentration of 1 μM, compound **147** (PI in the position 7) exhibits a relatively clean activity profile with 100% inhibition of the 1.5 nM [3H]lysergic acid diethylamide binding to 5-HT_6R. Besides 5-HT_6R, of the 32 receptors tested, only one, 5-HT_{2B}R, weakly interacts with compound **147** (approx. 50% inhibition of the 1.2 nM [3H]lysergic acid diethylamide binding, IC_{50} ~ 1 μM). The relocation of the amino group into position 5 (compound **148**) or 6 (compound **149**) seems to specifically improve 5-HT_6R selectivity by reducing the ability of these compounds to interact with 5-HT_{2B}R. Interestingly, the substitution of the amino moiety in position 6 by the dimethyl amino group (compound **150**) leads to the recovery of a weak activity against 5-HT_3R.

Annelated 3-phenylsulfonyl-pyrazolo[1,5-a]pyrimidines **151-153** (Figs. **39** and **40**) have been found to have a high level of *in vitro* selectivity and antagonistic potency against 5-HT_6R [216]. In particular, against the core target in a panel of 67 receptors and ion channels, the mixture of 1:1 (1 μM) of 5-methyl-5-methylsulfanyl-3-phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[1.5-a]quinazoline **151** and 5-methyl-5-methylsulfanyl-3-phenylsulfonyl-9-methyl-5,6,7,8-tetrahydro-pyrazolo[5.1-b]quinazoline **152** (Fig. **39**) displayed >2K-fold higher selectivity, except for 5-HT_{2B}R [216]. However, against 5-HT_{2B}R, the tested compounds exhibit ~10-fold and ~16-fold less potency compared to 5-HT_6R. Ligands **151** and **152** at 1 μM did not demonstrate a relevant interaction with a target of potential liability, the hERG channel. In a functional patch clamp assay (CHO cells with exogenously expressed hERG channel), the compounds exhibit very low channel blocking activity (Fig. **39**). Angular ligand **151** blocked the hERG channel with an IC_{50} value of 8.4 μM. The direct analogue, compound **152**, reduced channel permeability only by approximately 25% at 10.0 μM. It should be noted that weak sub-nanomolar activity was determined for the benzodiazepine receptor (Inh% = 66±7, Fig. **39**).

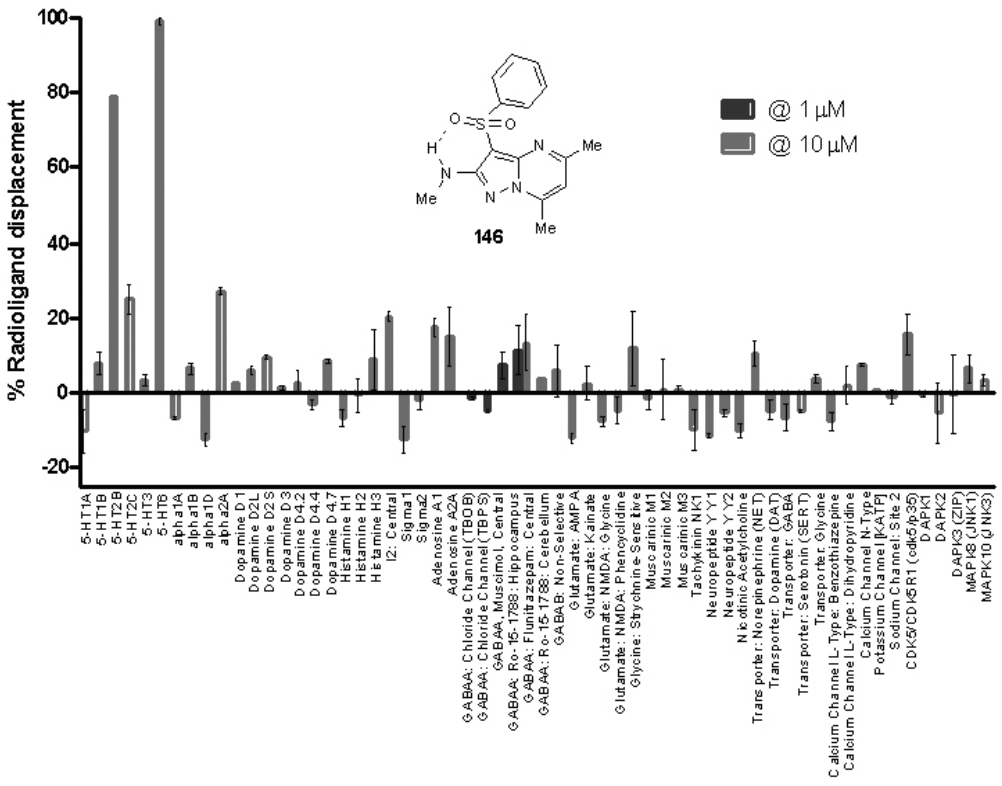


Fig. (37). Target-specific profile determined for AVN-216 **146** (1 μM and 10 μM) in a CRBA.

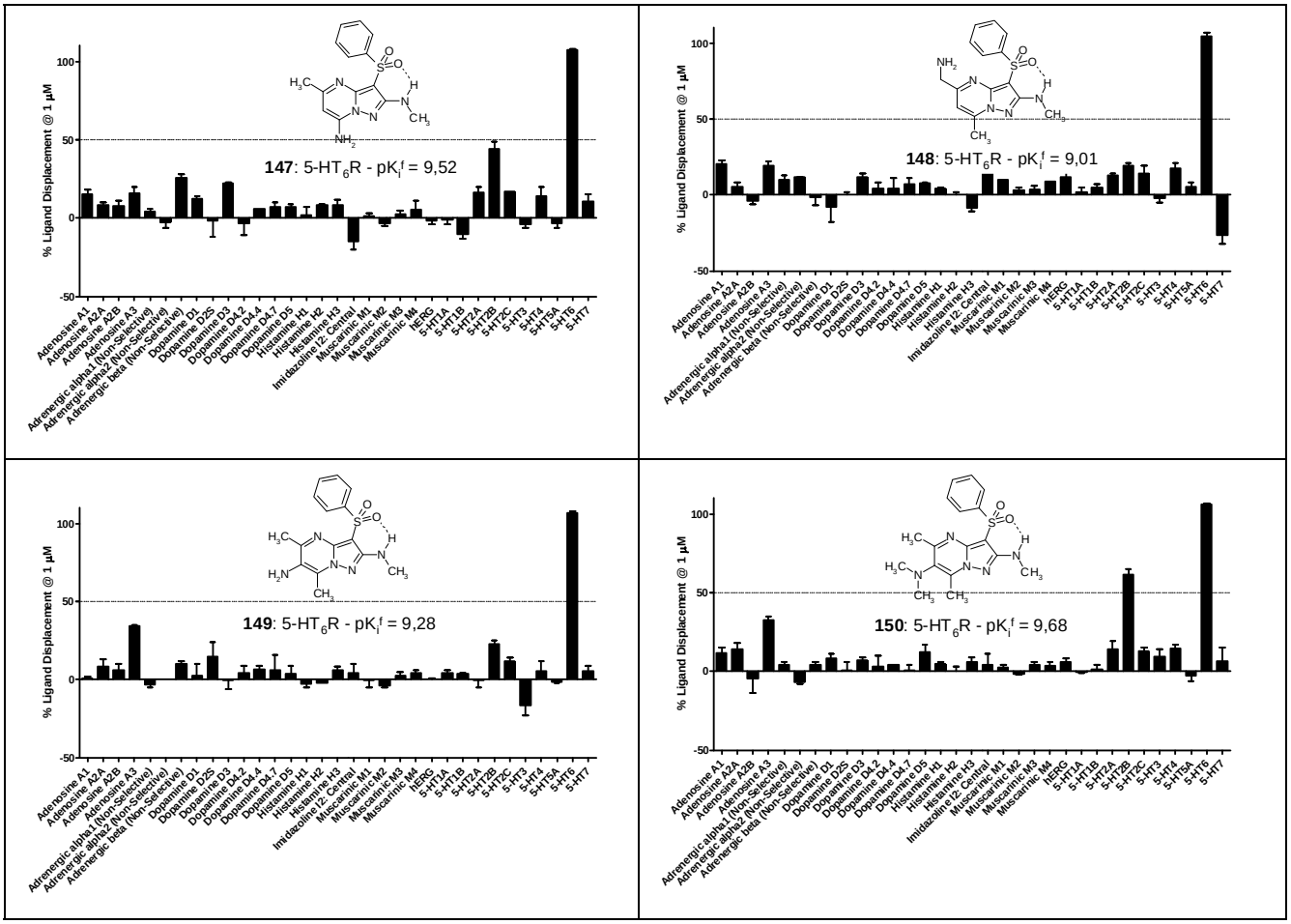


Fig. (38). Specificity profiles of 5-HT$_6$R antagonists **147-150** determined in a panel of 33 different receptors in a CRBA (compounds were tested at 1 µM in duplicate, and average values of radioligand displacement ± SD were plotted).

The highly selective 5-HT$_6$R antagonist (3-phenylsulfonyl-7,8-dihydro-6*H*-cyclopenta[e]pyrazolo[1,5-a]pyrimidin-2-yl)methylamine **153** with K_i^b = 88 pM and K_i^f = 375 pM has also been described as a potent drug candidate. This compound demonstrated >12K-fold higher selectivity towards 5-HT$_6$R over 55 other therapeutic targets within an assay panel including GPCRs, ion channels, and neurotransmitter transporters (Fig. **40**) [217]. It was shown that at concentrations of up to 10 µM, ligand **153** has no 5-HT$_{2B}$R agonistic activity and exhibited rather weak antagonistic potency (IC_{50}^f = 3.5 µM). The obtained data strongly suggest the safety of **153** with regard to potential for causing Viral Hemorrhagic Disease (VHD). In addition, compound **153** demonstrated a selectivity index between the 5-HT$_6$R and 5-HT$_{2B}$R of three orders of magnitude. Ligand **153** has not shown interaction with hERG potassium channel either in binding (Inh% = 2 at 1 µM) or functional (Inh% = 29.5±3.9 at 90 µM) assays. These data clearly indicate the safety of compound **153** and make it a promising candidate as a therapeutic tool in probing the role of the 5-HT$_6$R in different CNS diseases [217].

Two similar 5-HT$_6$R antagonists, methyl-(7-methyl-3-phenylsulfonyl-6,7,8,9-tetrahydro-pyrazolo[1,5-a]pyrido[4,3-e]pyrimidin-2-yl)-amine (AVN-322) **154** (K_i^b = 0.39 nM, K_i^f = 1.8 nM, Fig. **41**) and methyl-(7-methyl-3-phenylsulfonyl-6,7,8,9-tetrahydro-pyrazolo[1,5-a]pyrido [4,3-d]pyrimidin-2-yl)-amine **155** (K_i^b = 0.82 nM, K_i^f = 14.3 nM, Fig. 42) have been successfully synthesized and evaluated *in vitro* [218]. Compound **154** demonstrated >2.5K-fold higher selectivity for 5-HT$_6$R within a panel of 70 relevant therapeutic targets including receptors from the common GPCR family, ion channels, as well as neurotransmitter transporters (Fig. **41**). Ligand **155** displayed over 1.2K-fold selectivity in the same assay panel (Fig. **42**). It should be noted that compound **154** (1 µM) inhibited 5-HT$_{2B}$ receptor activity up to 52% (Fig. **41**). However, in a functional binding assay, this ligand acted as a 5-HT$_{2B}$R antagonist with IC_{50}^f= 6.165 µM. Angular ligand **154** demonstrated blockage of the hERG channel with IC_{50} = 54 µM, and its direct analogue, compound **154**, inhibited hERG with IC_{50} < 1 µM.

4. 5-HT$_6$R LIGANDS IN CLINICAL TRIALS

Since the discovery of 5-HT$_6$R, great effort has been made to advance several drug candidates to the clinic . In 2009, 5-HT$_6$R multimodal ligand Asenapine maleate **27** (Fig. **3**) successfully passed clinical trials as an antipsychotic

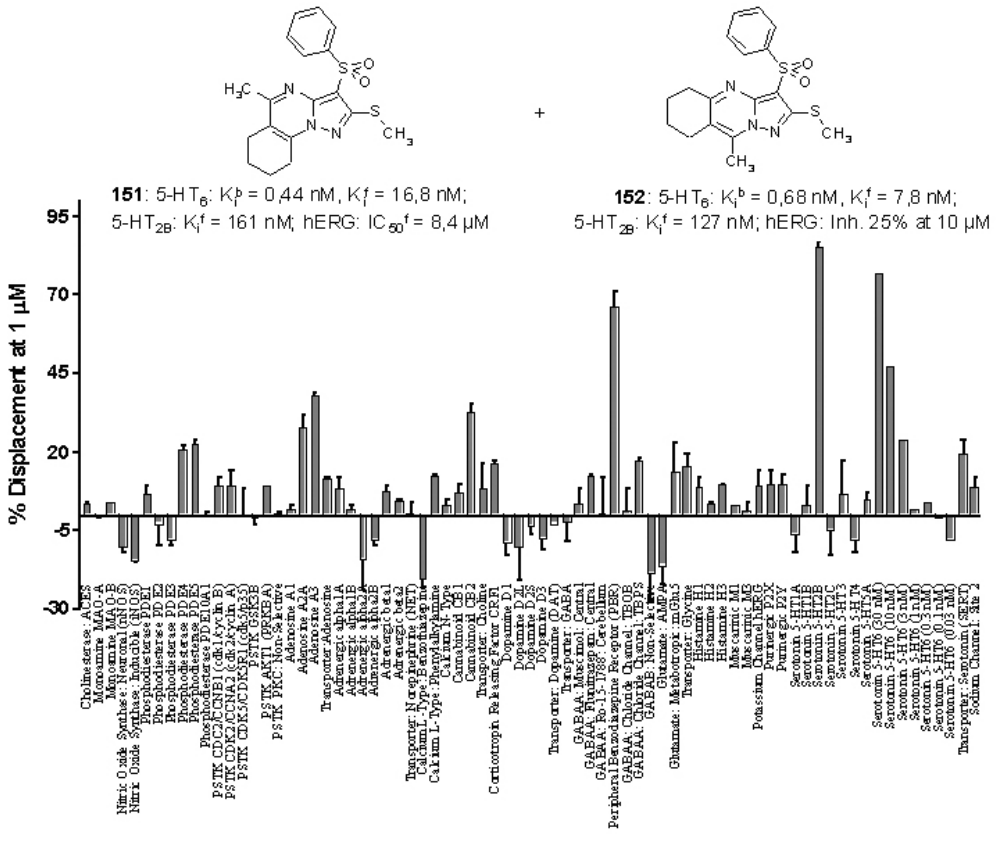


Fig. (39). Target-specific profile determined for the drug mixture of compounds **151** and **152** (1:1, 1 µM).

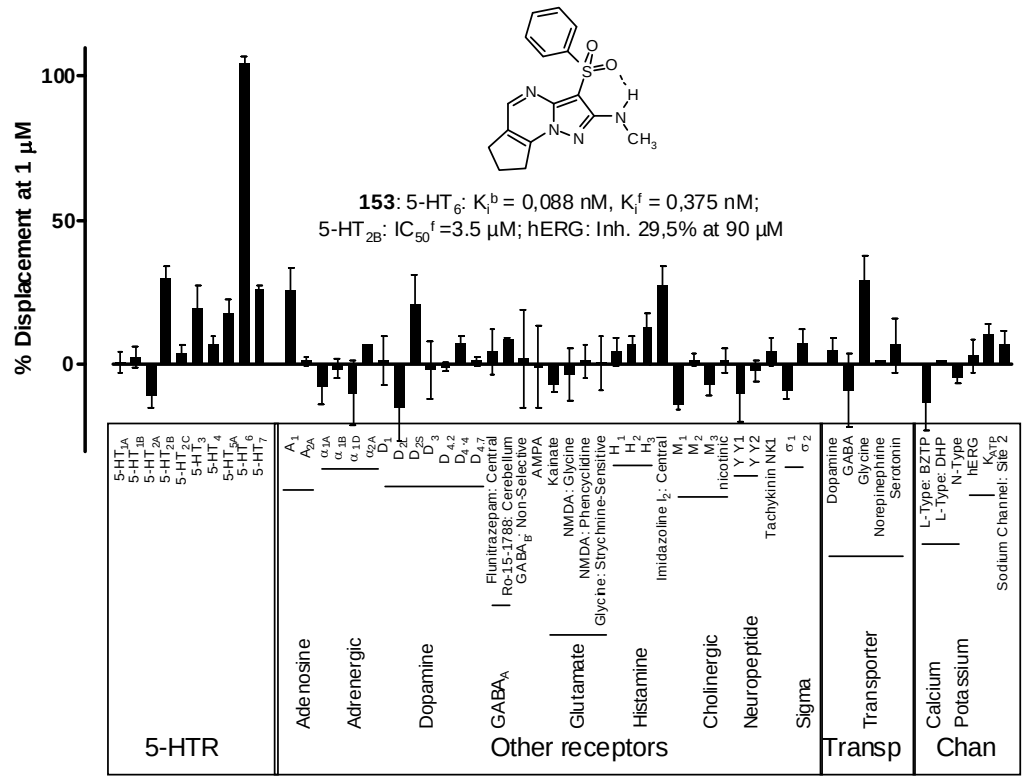


Fig. (40). Target-specific profile of 5-HT$_6$R antagonist **153** (1 µM) determined in a CRBA.

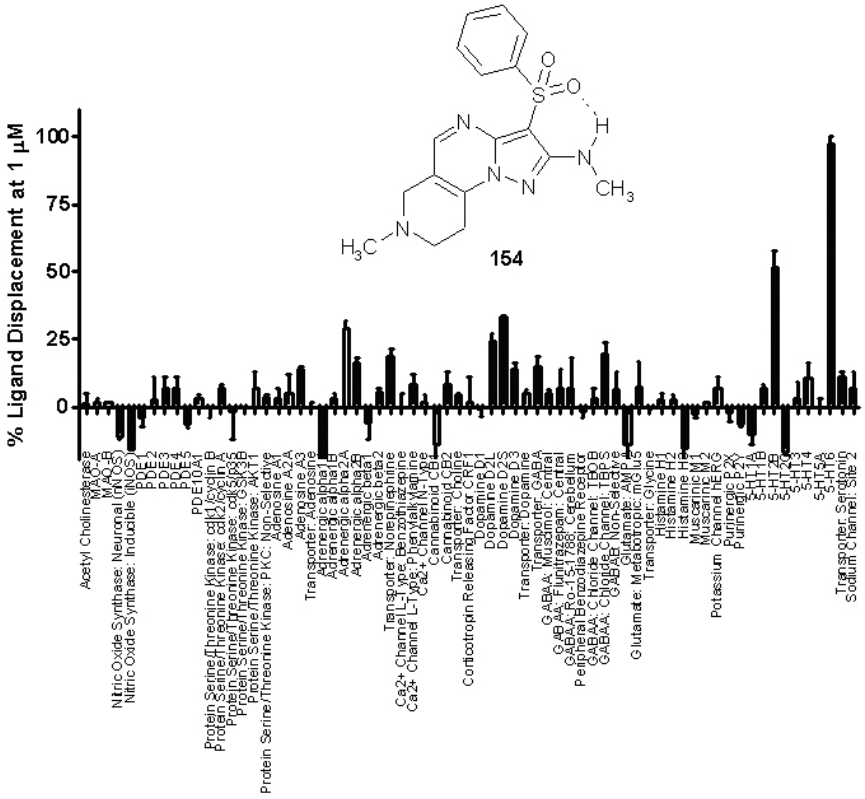


Fig. (41). Specificity profile determined for 5-HT$_6$R antagonist AVN-322 (1 µM).

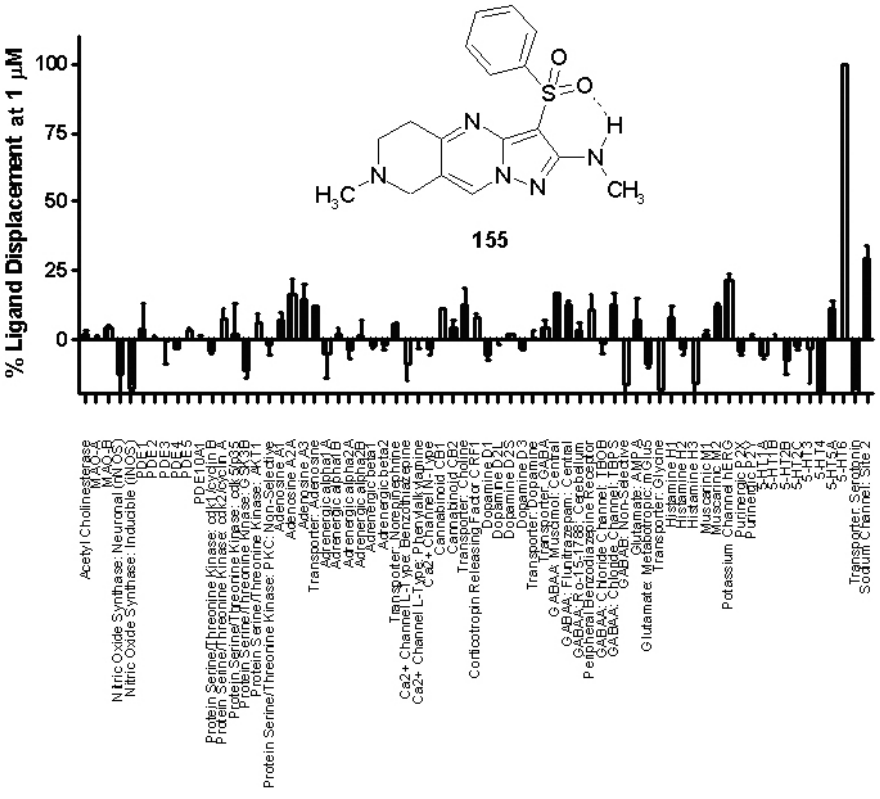


Fig. (42). Specificity profile determined for 5-HT$_6$R antagonist compound **155** (1 µM).

medication, and has been marketed as Saphris® [42]. It is approved for the treatment of schizophrenia in adults and for acute treatment, alone or with a mood stabilizer (lithium or valproate), of manic or mixed episodes associated with bipolar disorder in adults [43].

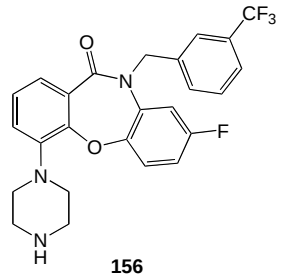
In Phase I studies, the multimodal ligand AVN-101 (Avineuro Pharmaceuticals) **29** (Fig. **4**) was well tolerated in a wide range of doses, and no adverse events were observed. This compound has demonstrated an excellent exposure and half-life time of >14 hours. Phase II clinical trials (Q4 2012) include a study of AVN-101 for the treatment of generalized anxiety disorders [91].

Clinical evaluation of the pseudo-selective 5-HT_6R antagonist Lu-AE-58054 (**129),** developed by Lundbeck (Fig. **34**), continues for the treatment of moderate Alzheimer's type dementia as an add-on treatment to Donepezil. However, in 2010, Lundbeck discontinued pursuing this drug as a treatment of cognitive impairment associated with schizophrenia (CIAS) based on efficacy data which did not sufficiently support further development for this therapeutic indication [219, 220].

5-HT_6R antagonist AVN-211 (**145**), developed by Avineuro Pharmaceuticals is currently being evaluated in clinic (Fig. **36**). This compound provided beneficial results in a Phase IIa clinical trial as an augmentative therapy to improve cognitive performance in patients diagnosed with schizophrenia. In a double blind trial of 50 patients stabilized on atypical antipsychotic therapy, AVN-211 met the protocol's criteria for positive results on primary efficacy outcome measures. AVN-211, when administered orally at a dose of 4 mg, was well tolerated, and no adverse events were observed. Phase II/III clinical trials for improved cognition in schizophrenia were scheduled to begin in the 3rd quarter of 2012 [221].

A Phase Ib clinical trial of the selective 5-HT_6R antagonist AVN-322 (**154**) has also been advanced by Avineuro Pharmaceuticals (Fig. **41**) for the treatment of Alzheimer's disease and cognitive impairment [222, 223].

Biotie Therapies has conducted clinical trials for the selective 5-HT_6R antagonist SYN-120 (structure not yet disclosed). This compound is an orally-administered small molecule drug candidate with high potency and selectivity against the 5-HT_6 receptor. SYN-120 is under development for the treatment of Alzheimer's disease and other cognitive disorders, including schizophrenia. As described in the introduction, 5-HT_6 receptors are located exclusively within the brain. Therefore, agents able to regulate its activity may yield increased concentrations of acetylcholine and glutamate, two known pro-cognitive neurotransmitters. SYN-120 represents a third generation of small molecule 5-HT_6R antagonists. It was designed to overcome some of the cardiovascular side effects that have previously impacted this class of drugs. Moreover, the specific expression of 5-HT_6 receptors in areas of the brain important in cognition is expected to substantially improve the efficacy and safety profile of SYN-120 versus currently available therapies [224]. This agent has successfully completed single and multiple ascending dose Phase I studies and is currently under intensive clinical evaluation to establish the optimal range of therapeutic doses. An alternate compound, SYN-114 (**156**, Fig. **43**) with pK_i^b = 9.55 has also satisfactorily completed Phase I trials [225,226].



156

Fig. (43). SYN-114, a 5-HT_6R antagonist showing clinical promise, developed by Biotie Therapies.

Suven Life Sciences Ltd has recently announced that clinical drug candidate SUVN-502 (structure not yet disclosed) has successfully passed long-term safety studies including 6-month rat toxicology and 9-month dog toxicology studies. Additional developmental toxicology studies including prenatal development toxicology in rats and rabbits, embryo-fetal development toxicology in rats, and male fertility toxicology in rats. The drug candidate has demonstrated a very high margin of safety (MOS). These regulatory toxicology studies are essential for FDA approval to initiate human Phase 2a clinical trials. SUVN-502 has been tested in human Phase 1 trials in Switzerland and has demonstrated sufficient safety at all doses and durations tested, with excellent bioavailability. The next stage of evaluation will be Phase IIa clinical trials in patients with Alzheimer's disease and Schizophrenia [227].

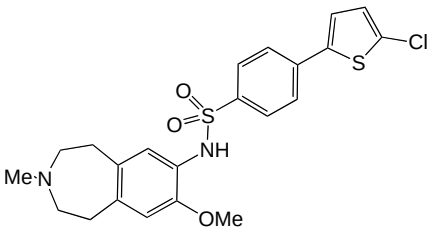
Several clinical studies have been discontinued, typically due to the absence of the desired therapeutic outcome. In particular, Pfizer Inc. and partner Medivation Inc. ended the multimodal ligand Dimebon's **28** (Fig. **3**) development after it failed to meet two primary endpoints [the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog), which measures cognitive ability, and the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL), which measures self care and daily functioning] in a Phase III trial studying its use with the existing treatment Aricept in patients with mild-to-moderate Alzheimer's [104].

A randomized, placebo-controlled study of the pseudo-selective 5-HT_6R antagonist SB-742457 (GlaxoSmithKline) **115** (Fig. **28**) has investigated the effectiveness of SB-742457 and Donepezil in treating Alzheimer's disease. In this exploratory study, treatment with SB-742457 and Donepezil was associated with improvement in global function. However, the effect on cognition was smaller than that observed in previous clinical studies with Donepezil alone [228].

Pfizer has ceased development of the 5-HT_6R antagonist Cerlapiridine (SAM-531, PF-05212365, PF-5212365, WAY-262531) **117** (Fig. **30**). Phase II clinical trials for the oral treatment of Alzheimer's type dementia and schizophrenia were discontinued following a 6-month interim analysis which revealed all dosage levels to be ineffective. No safety concerns were reported [229].

The multimodal 5-HT_6R ligand SB-737050A (GlaxoSmithKline) **157** (Fig. **44**) has been in Phase II clinical trials for the treatment of schizophrenia. SB-737050A exhibits specific antagonism of five key receptors identified as targets for antipsychotic drug design: dopamine D_2 and D_3, and 5-HT_{2A}, 5-HT_{2C} and 5-HT_6. SB-737050A appears to be se-

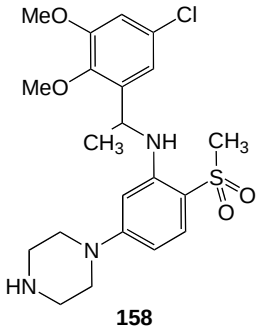
lective versus cytochrome p450 enzymes, and there is no evidence that it has any interaction with muscarinic M_1-M_4, dopamine D_1 or histaminic H_1 receptors [230]. The development status of SB-737050A is currently unknown.



157

Fig. (44). Multimodal 5-HT$_6$R ligand SB-737050A, developed by GlaxoSmithKline.

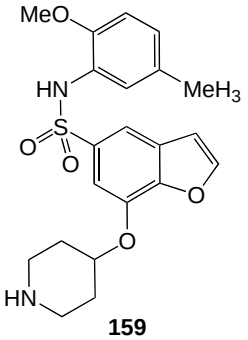
PRX-07034 **158** (Fig. **45**), developed by Epix Pharm, is a potent (K_i^b=4-8 nM) pseudo-selective 5-HT$_6$R antagonist with >100-fold selectivity for 5-HT$_6$ receptors over 68 other GPCRs, ion channels, and transporters, excepting D_3 (K_i^b=71 nM) and 5-HT$_{1B}$ (K_i^b=260 nM) receptors [231,232]. This compound has been in Phase Ib clinical trails for potential use as a therapeutic for obesity and produced positive results [233]. PRX-07034 was selected by the Treatment Units for research on neurocognition and schizophrenia for a future Phase II trial. Unfortunately, the current development status of PRX-07034 remains unclear.



158

Fig. (45). 5-HT$_6$R antagonist PRX-07034 developed Epix Pharm.

The selective 5-HT$_6$R antagonist BVT-74316 **159** (Fig. **46**), developed by Swedish Orphan Biovitrum, has been in Phase I clinical trials for the treatment of obesity. This compound controls food intake by stimulating the sense of satiety in the brain. The current development status of BVT-74316 is confidential.



159

Fig. (46). BVT-74316, a selective 5-HT$_6$R antagonist developed by Swedish Orphan Biovitrum.

Pfizer has completed Phase I clinical trials of 5-HT$_6$R antagonists PF-5212377 (SAM-760, WYE-103760) [234] and SRA-444 [235]. The structures of these ligands have not been published yet, and the development status of these compounds is unknown. The development status of the pseudo-selective 5-HT$_6$R agonist WAY-181187 (Wyeth, now Pfizer) **99** (Fig. **22**), which has been in Phase I clinical trials for the treatment of acute anxiety and generalized anxiety disorder [236], has also not been reported.

Finally, the development of the pseudo-selective 5-HT$_6$R antagonist SB-271046 **96** (Fig. **21**), developed by GSK [7,166,170], was aborted after Phase I clinical trials, probably due to insufficient blood-brain-barrier permeability [237].

CONCLUSION

This systematic review has attempted to properly summarize available data published in the scientific literature, including related patent applications, describing the pharmacological profiles of 5-HT$_6$R ligands. These ligands are reasonably grouped into three different categories based on their specific mode of action: *multimodal*, *pseudo-selective* and *selective ligands*. Through this analysis, it has been established that almost all of the drug candidates currently being evaluated in clinical trials share a multimodal mode of action or pseudo-selective binding. Recently, Asenapine maleate, a multimodal atypical antipsychotic, has been released onto the market under the brand name Saphris^R. In recent years, a variety of selective 5-HT$_6$R ligands have been synthesized and biologically evaluated. The best example is a series of pyrazolo[1,5-a]pyrimidines, in particular the compounds AVN-216 **146** (Fig. **37**), AVN-211 **145** (Fig. **36**) and AVN-322 **154** (Fig. **41**). These ligands exhibit >50K-fold, >5K-fold and >2.5K-fold higher selectivity, respectively, against other therapeutic targets in assay panels including GPCR subtypes, ion channels, and neurotransmitter transporters. It is highly encouraging for the industry that AVN-211 and AVN-322 have successfully reached Phase II/III and Phase II clinical trials, respectively. Indeed, the medical community awaits convincing evidence supporting clinical applications for 5-HT$_6$R ligands, particularly selective antagonists of 5-HT$_6$R.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

I would like to extend my sincere gratitude to Dr. F. Lakner (ChemDiv) for his language and proofreading help during the manuscript preparation.

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Received: June 14, 2012 Revised: November 12, 2012 Accepted: November 29, 2012