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Sulfonyl-containing modulators of serotonin 5-HT_6 receptors and their pharmacophore models

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Data published in recent years on the synthesis of serotonin 5-HT_6 receptor modulators are summarized. Modulators with high affinity for 5-HT_6 receptors exhibiting different degrees of selectivity — from highly selective to semiselective and multimodal — are described. Clinical trial results are reported for the most promising serotonin 5-HT_6 receptor modulators attracting special attention of medicinal chemists.
The bibliography includes 128 references.

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I. Introduction

Serotonin 5-HT_6-receptors (5-HT_6R) were first described in the 1990s: rat receptors were reported in 1993,[1] and mouse and human receptors were reported in 1994[2] and 1996,[3] respectively. The 5-HT_6 receptor couples to the G_s protein to activate adenylate cyclase. The latter converts adenosine triphosphate to cyclic adenosine monophosphate that acts as a secondary mediator.[4] The 5-HT_6 receptors are widely distributed in the central nervous system (CNS), being most abundant in brain areas involved in cognitive processes. Autoradiographic studies on the rat brain have revealed a high level of specific binding of labelled 5-HT_6R ligands in the corpus striatum, nucleus accumbens, islands of Calleja and the olfactory tubercle.[5] These results are on the whole consistent with conclusions of immunological studies.[6]

Numerous studies have demonstrated that blocking of 5-HT_6 receptors leads to considerable enhancement of memory consolidation in various animal models of learning, memory and retrieval.[7–9] In the Morris water maze test, 5-HT_6R antagonist has been found to significantly improve the cognitive functions in aged rats.[7] Recently, a more profound understanding of the role of 5-HT_6 receptors in cognitive processes has been gained and clearer ideas about possible pharmacophore properties of their antagonists have been formulated.[10]

It has been revealed that 5-HT_6 receptors regulate several neurotransmitter signalling pathways, including

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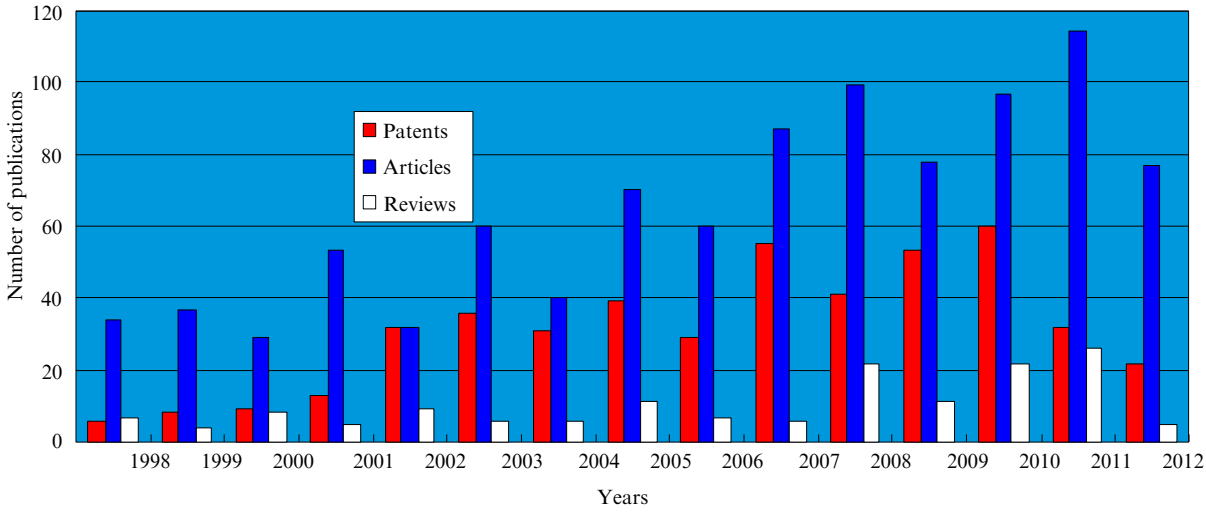


Figure 1. Number of publications on 5-HT$_6$ receptors from 1993 to December 30, 2012. Data were retrieved from the SciFinder database using the keyword '5-HT$_6$R'.

cholinergic, noradrenergic, glutamatergic and dopaminergic systems.[11] Since these systems are of crucial significance in cognitive processes, it is clear that 5-HT$_6$ receptors play an exclusive role in the formation of normal and 'pathological' memory. In addition, the dominant expression of 5-HT$_6$ receptors in the CNS suggests the lack of undesirable peripheral side effects for selective 5-HT$_6$R ligands, which is supported by the results of preclinical and clinical trials.

The 5-HT$_6$ receptors are especially attractive for the development of new drugs for the treatment of various CNS diseases and disorders[12] (cognitive,[13–17] mental[18] and anxiety[19] disorders, depression,[20] Alzheimer's disease,[21,22] dementia,[22] learning and memory impairment[23]). Another attractive property of 5-HT$_6$R antagonists is their ability to suppress appetite, which can lead to the development on their basis of essentially new means for reducing body weight and combating obesity.[24] This effect has been confirmed in many studies,[10,25–29] and its mechanism is based on that 5-HT$_6$R antagonists reduce γ-aminobutyric acid signalling and increase α-melanocyte-stimulating hormone release and thereby suppress food intake.[30]

The unabated interest in 5-HT$_6$ receptors is confirmed by the impressive number of published papers and patents (Fig. 1), as well as by a large number of reviews on this topic.[11–13,18,19,21,22,25,26,31–44]

The vast majority of the known efficient 5-HT$_6$R modulators are compounds with a nucleus composed of aromatic and (or) heteroaromatic rings linked by a sulfonyl or sulfonamide moiety — a hydrogen bond acceptor — and the interest in this ligand chemotype has not disappeared so far.[10,20,26,29,36,45,46]

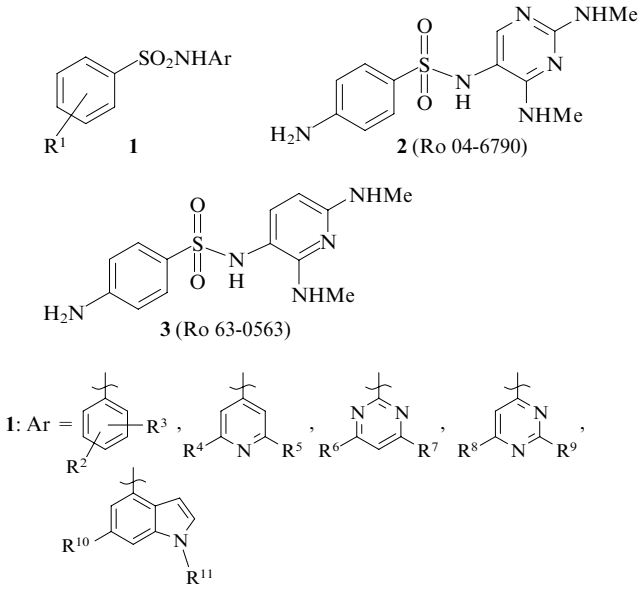
The present review summarizes recent literature data (over a period of 2009–2012) on the synthesis of compounds containing a sulfonyl or sulfonamide moiety and on the relationship between their structure and activity towards 5-HT$_6$ receptors. New chemotypes of 5-HT$_6$R ligands, their molecular docking (MD) and pharmacophore models (PMs) are considered.

II. Serotonin 5-HT$_6$ receptor modulators containing two hydrophobic moieties, sulfonyl group and a highly basic amino group

1. General notions and pharmacophore models

The first ligands **1** active and selective towards 5-HT$_6$ receptors were synthesized more than 15 years ago[47] (1998); among them, *N*-[2,6-di(methylamino)pyrimidin-5-yl]-4-aminobenzenesulfonamide (**2**, Ro 04-6790) and *N*-[2,6-di (methylamino)pyridin-3-yl]-4-aminobenzenesulfonamide (**3**, Ro 63-0563) were characterized.[48,49]

Structures 1–3



R^1, R^3, R^4 = H, Hal, CF_3, Alk, OAlk, NH_2, NHAlk, $NAlk_2$; R^2 = Hal, Alk, OAlk, NH_2, NHAlk, $NAlk_2$, *etc.*; R^5 = H, Hal, OAlk, NHAlk, $NAlk_2$; R^6, R^7 = OAlk, NHAlk; R^8 = Hal, CF_3, Alk, OAlk, NHAlk, $NAlk_2$; R^9 = Alk, OAlk, NH_2, NHAlk, $NAlk_2$, SAlk, pyrrolidino, azetidino; R^{10} = H, Hal; R^{11} = H, Alk

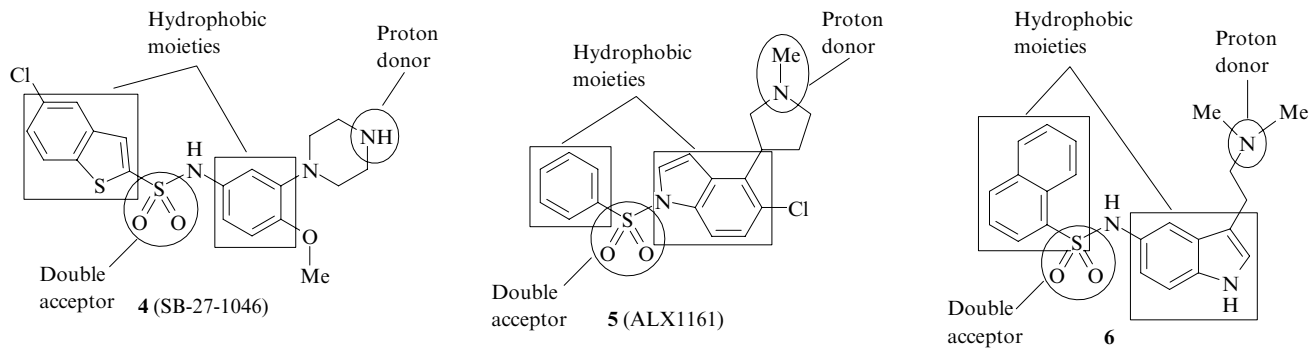


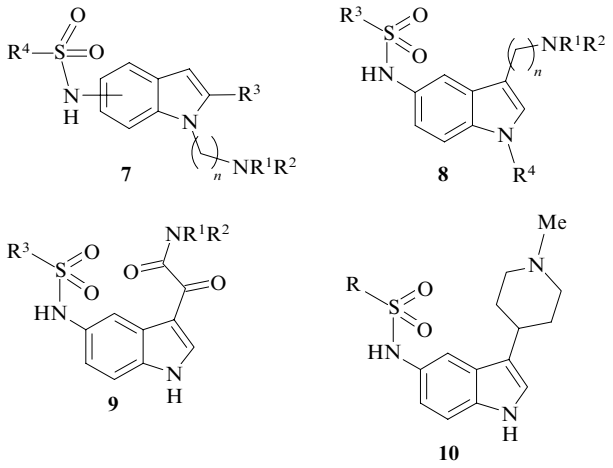
Figure 2. Compounds **4**, **5** and **6** containing a sulfonyl moiety and corresponding to a hypothetical pharmacophore model for 5-HT$_6$R modulators.[51]

Benzenesulfonamides **2** and **3** are rather active ligands for 5-HT$_6$ receptors; for them, negative logarithms of binding inhibition constants (pK_i^b) have been determined using a competitive radioligand binding assay:† 7.35 and 7.83 on mouse 5-HT$_6$ receptors, 7.26 and 7.91 on human 5-HT$_6$ receptors, respectively. Both compounds **2** and **3** are competitive antagonists. The negative logarithms of inhibition constants of the functional cellular response to agonist (pK_i^f) are 6.75 and 7.10 for ligands **2** and **3**, respectively. These ligands exhibits high selectivity: more than 100-fold for 5-HT$_6$ receptors in comparison with 23 receptors (Ro 04-6790) and 69 receptors (Ro 63-0563), including dopamine receptors and other subtypes of serotonin 5-HT receptors. However, pharmacokinetic studies on mice have demonstrated that Ro 04-6790 and Ro 63-0563 insufficiently penetrate the blood–brain barrier and display low brain-to-plasma ratios (B/P < 0.01),[50] which excluded them from further clinical studies.

Based on the previous achievements in the synthesis of potent and selective 5-HT$_6$R modulators, the vast majority of which contained a sulfonyl moiety, in 2005, Holenz *et al.*[51] formulated for the first time approaches to the design of such modulators **4**–**6** and suggested a pharmacophore model (PM) for them. According to this model, 5-HT$_6$R modulators (Fig. 2) should contain two hydrophobic sites (HYD$_1$ and HYD$_2$), which are aromatic or heteroaromatic moieties separated by a double hydrogen bond acceptor (HBA), such as sulfonyl or sulfonamide group, and a proton donor which is a protonated form of a highly basic amino group at physiological pH values (PI is a positively ionized atom).

The efficiency of the hypothetical PM suggested for active modulators was convincingly demonstrated[51] by the example of agonists, partial agonists and antagonists in series of substituted *N*-[1-(dialkylaminoalkyl)-1*H*-indol-4(5,6)-yl]sulfonamides **7**, *N*-[3-(dialkylaminoalkyl)-1*H*-indol-5-yl]sulfonamides **8**, 2-(5-sulfonylamino-1*H*-indol-3-yl)-2-oxoacetylamides **9** and *N*-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl]sulfonamides **10**.

Structures 7–10



7: NR^1R^2 = NMe_2, NEt_2, pyrrolidino, piperidino; R^3 = H, Me; R^4 = Bn, 2-(1-naphthyl)ethyl, *p*-biphenyl, 1-Naph, 2-Naph, 3-methyl-5-chlorobenzo[*b*]thiophen-2-yl, 6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl;
8: NR^1R^2 = NMe_2, NEt_2, NPr^n_2, NBu^n_2, pyrrolidino, piperidino, morpholino; R^3 = Bn, 2-(1-naphthyl)ethyl, *p*-biphenyl, 3,5-$Cl_2C_6H_3$, 1-Naph, 2-Naph, 5-chloro-2-naphthyl, 8-quinolyl, 3-methyl-5-chlorobenzo[*b*]thiophen-2-yl, 6-chloroimidazo[2,1-*b*][1,3]thiazol-5-yl; R^4 = H, Me, *n* = 1–3;
9: NR^1R^2 = NMe_2, NEt_2; R^4 = 1-Naph, 8-quinolyl;
10: R = 1-Naph, *p*-biphenyl, 5-chloro-2-naphthyl, 8-quinolyl, 3-methyl-5-chlorobenzo[*b*]thiophen-2-yl; Naph is naphthyl

Examples of active ligands corresponding to the hypothetical PM (Fig. 2) are agonists **11**–**15** with pK_i^b = 8.27–10.0, partial agonists **16**–**19** with pK_i^b = 8.41–9.3 and antagonists **20**–**22** with pK_i^b = 8.35–9.7. The most potent picomolar‡ 5-HT$_6$R modulators turned out to be agonist **15**, partial agonist **18** and antagonist **22**.

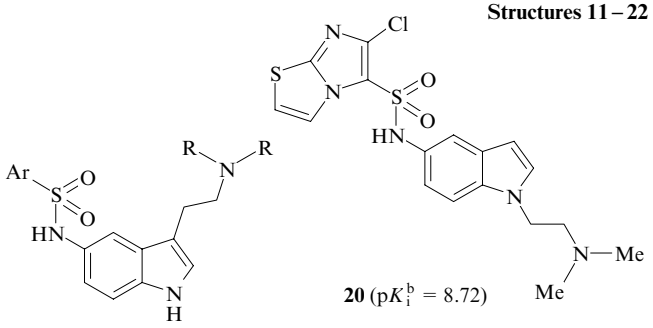
† In general form, K_i is calulated by the equation

$$K_i = \frac{IC_{50}}{(1 + L/K_d)}$$

where IC_{50} is the 5-HT$_6$R antagonist concentration corresponding to the 50% inhibition of the functional cellular response to the 5-HT$_6$R agonist stimulation (IC^f_{50}), or the 5-HT$_6$R antagonist concentration corresponding to the 50% blocking of radioactive ligand binding to 5-HT$_6$ receptor (IC^b_{50}); L is the concentration of an agonist (L^f) or a radioactive ligand (L^b) at which the antagonist concentration is measured; K_d is the dissociation constant of the agonist complex (K^f_d) or the dissociation constant of the radioactive ligand complex (K^b_d) with a 5-HT$_6$R receptor.

‡ Nano- and picomolar modulators (ligands, agonists, *etc.*) are compounds exhibiting activity at nano- and picomolar concentrations, respectively.

Structures 11–22



11–19, **21**, **22**

20 ($pK_i^b = 8.72$)

Compound	Ar	NR_2	pK_i^b
11	biphen-4-yl	NMe_2	9.4
12	biphen-4-yl	NEt_2	9.0
13	1-Naph	NEt_2	8.46
14	2-Naph	NEt_2	8.28
15	3-methyl-5-chlorobenzo[*b*]thiophen-2-yl	NMe_2	10.0
16	1-Naph	NMe_2	9.1
17	2-Naph	NPr^n_2	8.41
18	3-methyl-5-chlorobenzo[*b*]thiophen-2-yl	NPr^n_2	9.3
19	6-chloroimidazo[2,1-*b*][1,3]thiazol-5yl	NMe_2	8.66
21	1-Naph	$N(CH_2)_4$	8.35
22	8-chloro-2-naphthyl	$N(CH_2)_4$	9.7

Later, López-Rodríguez *et al.*[52] have developed a 3D PM for several tens of active 5-HT_6R modulators containing an HBA, which is analogous to the above PM.[51] The 3D

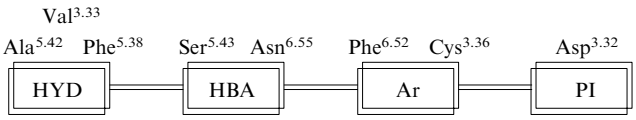


Figure 3. Schematic representation of a 3D PM of basic groups of ligands with $pK_i > 8$ and possible amino acids of the 5-HT_6R active site involved in interaction with the ligands.[52]

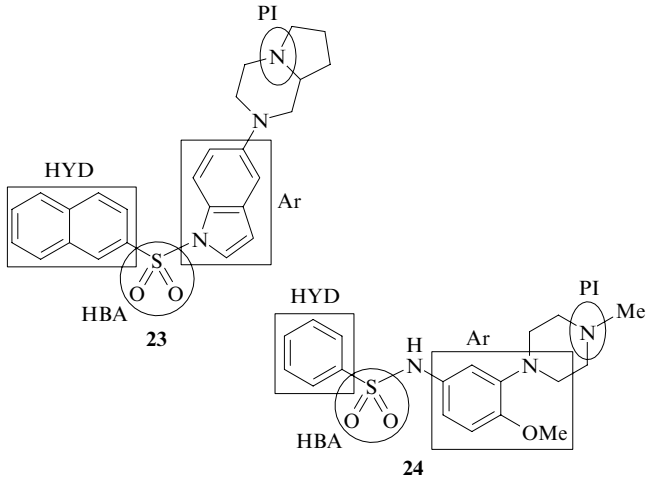


Figure 4. Ligands **23** and **24** corresponding to a 3D PM.[52]

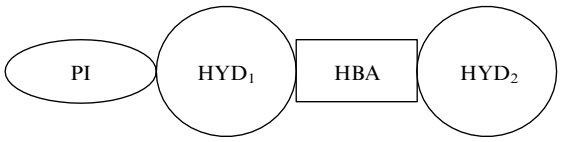


Figure 5. Simplified PM_1 [46] corresponding to the models designed in Refs 51 and 52.

PM comprises a PI, an HBA, an HYD and an aromatic hydrophobic site (Ar). From molecular docking results, the authors determined probable amino acids of the 5-HT_6R active site that interact with the moieties of modulators of this type (Fig. 3), for example, of compounds **23** and **24** (Fig. 4).

For the PM (Fig. 2)[51] and 3D PM (Figs 3 and 4),[52] a simplified PM_1 has been proposed that does not consider interatomic distances and dipole moment directions[46] (Fig. 5).

The above PMs are still widely used in design of active 5-HT_6R modulators. Below is presented information on the synthesis and activity of ligands of this type.

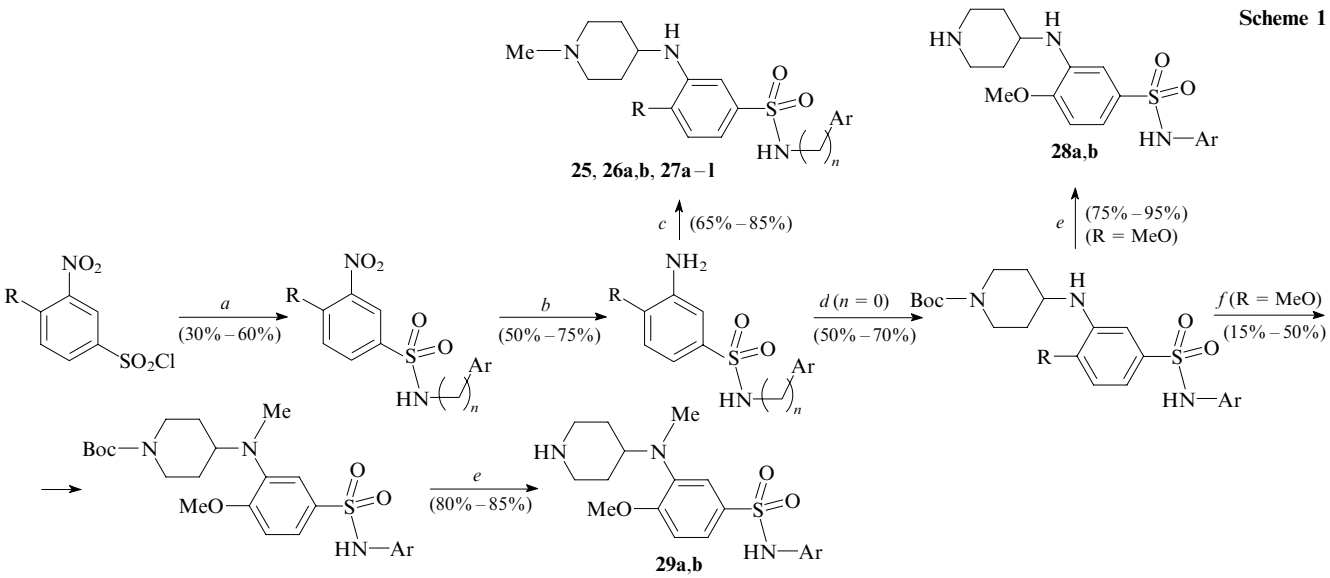
2. Synthesis of substituted *N*-arylbenzenesulfonamides and their activity

In 2010, the synthesis of substituted benzenesulfonamides **25**, **26a**,**b**, **27a–l**, **28a**,**b** and **29a**,**b** from 3-nitrobenzenesulfonamides by well-known reactions has been described.[53, 54] Ligands **25–27** have been synthesized in three steps, ligands **28** were prepared in four steps, and ligands **29** were synthesized in five stages (Scheme 1). The yields of intermediate and end products are, generally, moderate.

Ligands **25–29** can be divided into two groups. The first group contains substituted *N*-benzyl- (**25**) and *N*-phenetylbenzenesulfonamides (**26a**,**b**). As a rule, they are noticeably or significantly less active than the ligands of the other group — substituted *N*-phenylbenzenesulfonamides **27a–l**, **28a**,**b** and **29a**,**b**. It should be noted that ligands **25–29** differ from the ligands corresponding to the PM_1 in that they contain, in addition to HYD_1, HYD_2, HBA and PI, other moieties potentially capable of interacting with 5-HT_6 receptors. Therefore, for the ligands of this type, a more general simplified PM_2 can be suggested: the model includes one or several extra substituents (HS_i and HS_j are hydrophobic substituents) located in the HYD_1 and (or) HYD_2 moieties that can be involved in hydrophobic interactions with the amino acids of the 5-HT_6R active site (Fig. 6). Alkyl, hydroxyl and substituted hydroxyl groups, halogen atom, amino group (including a substituted one) and other substituents, as well as cycloalkyl, hetaryl and aryl moieties *etc.*, can act as HS_i and HS_j.

It is worth noting that the antagonistic activity of ligands **27–29** depends strongly on the nature, number, and position of substituents in both the phenyl ring and the benzenesulfonamide moiety and varies over a wide range. Ligands **27k**,**l** are especially distinguished among the known 5-HT_6R ligands by their presumably record-breaking antagonistic activity ($pK_i^f = 10.7$). The authors[54] do not report definite data on the selectivity of the most active ligands **27k**,**l**, but state that studies of their selectivity on the panel of some serotonin (5-HT_{2A}, 5-HT_{2C} and 5-HT_4), adrenergic (α_{1B}), dopamine (D_2) and histamine (H_1) receptors and transporters (SERT, NET and DAT) point to their more

Scheme 1



(*a*) $Ar(CH_2)_nNH_2$, $N(CH_2CH_2OH)_3$, CH_2Cl_2, 0–5 °C, 2–4 h or KOH–THF, rt, 24–48 h; (*b*) Fe, HCl, EtOH, Δ, 2–4 h; (*c*) 1-methyl-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25–30 °C, 5–10 h; (*d*) 1-Boc-4-piperidone, $NaBH(OAc)_3$, AcOH, Na_2SO_4, 25–30 °C, 5–10 h; (*e*) $Pr^iOH \cdot HCl$, Pr^iOH, heating; (*f*) HCHO, $NaBH_3CN$, MeOH

Compound	Ar	R	*n*	pK_i^f	Compound	Ar	R	*n*	pK_i^f
25	Ph	OMe	1	8.47	**27h**	2-BrC_6H_4	OMe	0	9.53
26a	2-ClC_6H_4	OMe	2	7.59	**27i**	2-BrC_6H_4	Me	0	8.88
26b	2-BrC_6H_4	OMe	2	7.42	**27j**	2-BrC_6H_4	Et	0	9.72
27a	Ph	OMe	0	8.91	**27k**	2-MeO-5-MeC_6H_3	OMe	0	10.70
27b	2-ClC_6H_4	OMe	0	9.23	**27l**	2-MeO-3,5-$Cl_2C_6H_2$	OMe	0	10.70
27c	2,4-$(MeO)_2C_6H_3$	OMe	0	8.0	**28a**	2-BrC_6H_4	OMe	0	9.22
27d	2,4-$Me_2C_6H_3$	H	0	< 5.0	**28b**	2-ClC_6H_4	OMe	0	9.32
27e	2,5-$(MeO)_2C_6H_3$	H	0	7.80	**29a**	2-BrC_6H_4	OMe	0	9.70
27f	4-Br-2-FC_6H_3	H	0	7.91	**29b**	2-ClC_6H_4	OMe	0	9.07
27g	2-Br-4,6-$F_2C_6H_2$	H	0	< 5.0					

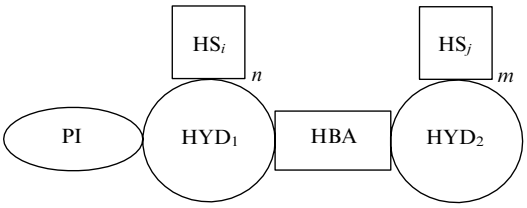


Figure 6. Simplified PM_2 containing *n* HS_i substituents in HYD_1 and *m* HS_j substituents in HYD_2.[55]

than 100-fold selectivity. In addition, the authors present the data supporting good absorption, distribution, metabolism and excretion (ADME) properties and satisfactory pharmacokinetic profile of ligand **27k**, as well as the data on its activity in some animal models demonstrating its influence on cognitive functions.

Korean researchers[56] have studied the activity of polysubstituted ligands, including those corresponding to the PM_2, using the HipHop algorithm provided in Catalyst software. For one of these ligands — compound **30** (Fig. 7), which exhibits activity at the picomolar level and contains three HS_i substituents (two chlorine atoms and a methoxy group) in HYD_1 and two HS_j substituents (a methoxy group and piperazin-1-yl) in HYD_2, they have suggested a six-feature 3D PM. However, no MD evidence in favour of precisely the six-feature rather than eight-feature PM are presented in this work.

Abbott laboratories have patented[57–59] a series of substituted *N*-(difluoromethoxyphenyl)-3-piperazinobenzenesulfonamides **31** and difluoromethoxybenzenesulfonamides

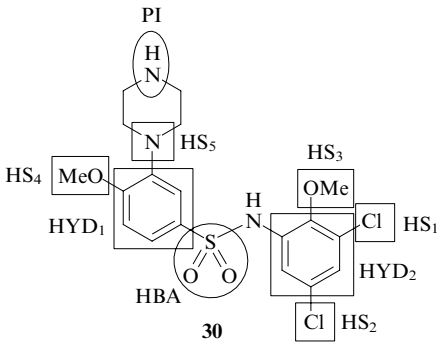
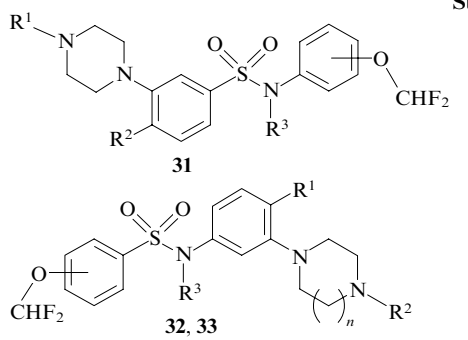


Figure 7. Ligand **30** corresponding to a six-feature PM.[56]

Structures 31–33



31

32, **33**

31: R^1 = H, Me; R^2 = H, Alk, F, AlkO, Alk^FO;
R^3 = H, Alk(C_1-C_4), cyclo-C_3H_5;
32, **33**: R^1 = H, Alk, Hal, AlkO, Alk^F, Alk^FO; R^2 = H, Me;
R^3 = H, Alk, cyclo-C_3H_5; n = 1 (**32**), 2 (**33**);
Alk^F is fluorinated alkyl

32, **33** corresponding to PM_2. These ligands contain at least two HS fragments, and the piperazine moiety simultaneously plays the role of one of the HS fragments and PI, as in ligand **30**. In patents,[58, 59] the nanomolar activity ($pK_i^b > 8$) and some selectivity of ligands **31** and **32** towards 5-HT_6 receptors have been reported.

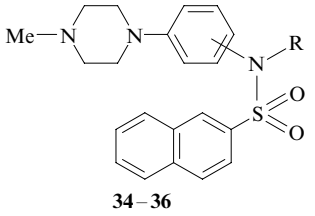
Park *et al.*[60] have reported the synthesis of yet another series of nanomolar arylsulfonamide ligands of 5-HT_6 receptors, namely, substituted *N*-[3-(4-methylpiperazino)-phenyl]-2-naphthylsulfonamides **34**; they correspond to the PM_2, and the piperazine moiety simultaneously functions as the HS and PI.

Ligands **34** are multimodal. In addition to the nanomolar activity to 5-HT_6 receptors, they exhibit nanomolar activity, at least, to serotonin 5-HT_{2C}, 5-HT_{1A} and 5-HT_{2A} and dopamine D_3 receptors (Table 1, IC_{50} is the half maximal inhibitory concentration). It has also been shown[60] that going from ligand **34e** to isomeric analogues **35** and **36** is accompanied by a significant decrease in their activity towards 5-HT_6 receptors (by $\sim$3 orders of magnitude for ligand **36**).

Recently,[55, 61] MD results for 5-HT_6 receptors and *N*-phenylbenzenesulfonamides **37**–**39** have been reported.

It has been demonstrated that, in computational modelling of binding of 5-HT_6 receptors to ligands **37**–**39**, there are interactions of all moieties of these ligands with the active site of 5-HT_6 receptors. This supports the correspondence of ligands **37**–**39** to the PM_2.

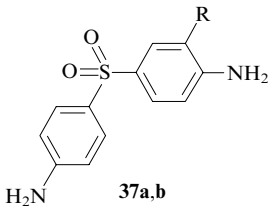
Structures 34–36



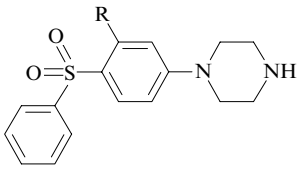
34–**36**

34: *meta*-isomer, R = H, Me, Et, Pr^i, Bu^i, Bn, 3-$PyCH_2$, *etc.*;
35: *para*-isomer, R = Pr^i;
36: *ortho*-isomer, R = Pr^i; Py is pyridyl

Structures 37–39



37a,**b**



38, **39**

Compound	R	K_i^f /nmol litre^{-1}	Compound	R	K_i^f /nmol litre^{-1}
37a	H	183	**38**	H	10.8
37b	NH_2	564	**39**	NMe_2	30.1

It has been found that, in the computational binding model for 5-HT_6 receptors and ligands **37**, one of the amino groups interacts with Asp106(H3); *i.e.*, this amino group acts as a PI [hereinafter, to the right of the symbol and number of the amino acid residue, the moiety (helix H or loop L) in which this residue is located is specified]. This suggests the presence of a similar interaction of nanomolar ligands Ro 04-6790 (**2**) and Ro 63-0563 (**3**) with 5-HT_6 receptors since the latter also contain PI and correspond to the PM_2.

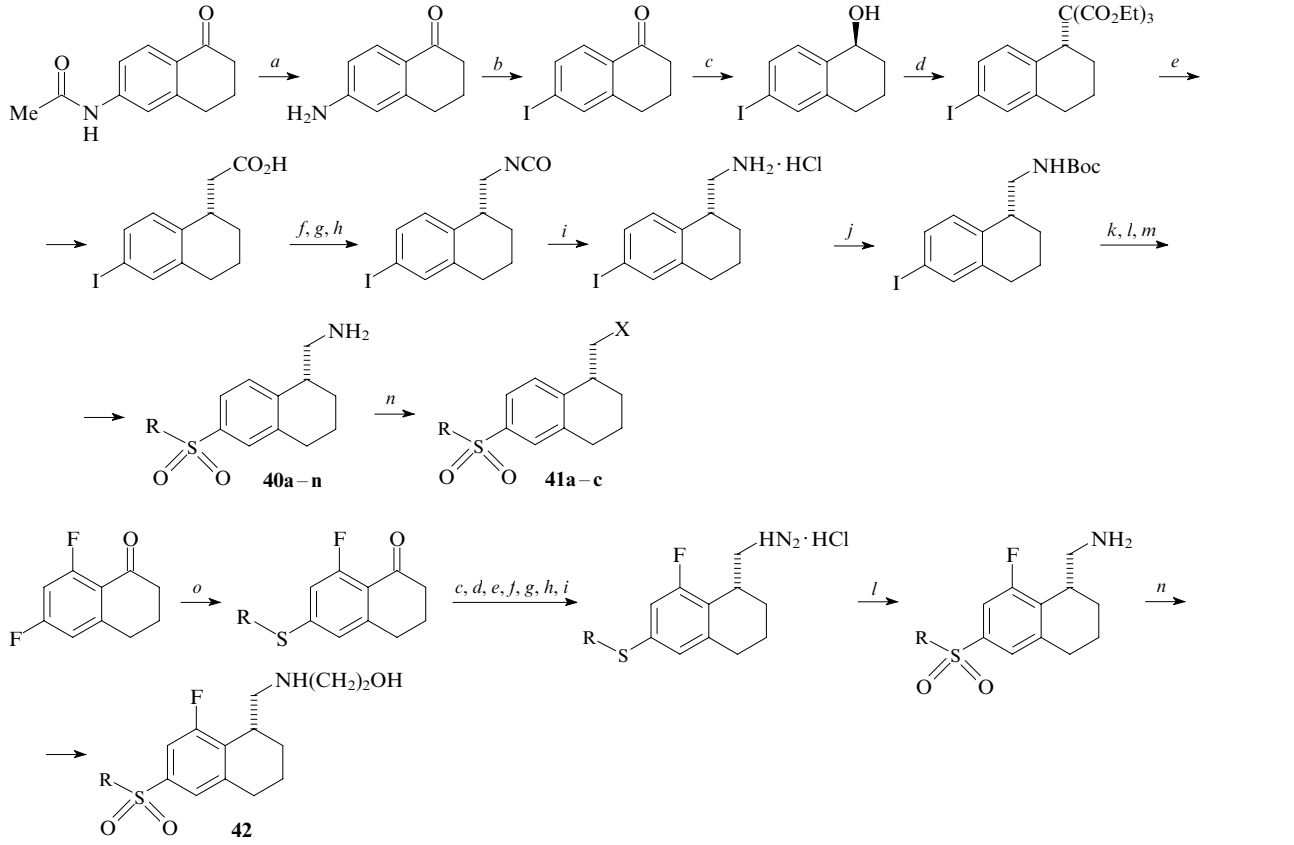
3. Synthesis of 6-arylsulfonyl-1,2,3,4-tetrahydronaphthalenes and their activity

Recently, there has been described a multistep synthesis of [(*R*)-6-arylsulfonyl-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]amines **40a**–**n**, **41a**–**c**, **42**,[62] corresponding to the PM_2, from *N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide or from 6,8-difluoro-3,4-dihydro-2*H*-naphthalen-1-one (Scheme 2).

Table 1. Activity (pIC_{50}^b) of multimodal sulfonamides **34a**–**g** and their isomeric analogues **35**, **36**.[60]

Ligand	R	Receptors							
		5-HT_{1A}	5-HT_{2A}	5-HT_{2C}	5-HT_6	5-HT_7	D_2	D_3	D_4
34a	H	7.24	5.79	5.29	7.89	5.8	< 7.0	5.68	< 7.0
34b	Me	7.02	5.85	7.44	8.15	5.35	< 7.0	5.62	< 7.0
34c	Et	6.31	6.66	7.80	8.52	5.69	< 7.0	5.93	< 7.0
34d	Pr^n	5.43	6.41	8.15	8.40	5.41	< 7.0	5.60	< 7.0
34e	Pr^i	< 6.0	6.93	8.40	8.52	–	< 7.0	6.61	< 7.0
34f	cyclo-$C_3H_5CH_2$	6.17	7.06	8.22	8.22	5.52	< 7.0	5.85	< 7.0
34g	Bn	6.55	7.30	7.49	8.52	5.67	< 7.0	6.02	< 7.0
35	Pr^i	–	–	5.77	7.57	–	–	–	–
36	Pr^i	–	–	5.33	5.66	–	–	–	–

Scheme 2



(*a*) 20% H_2SO_4, 90 °C (yield 100%); (*b*) $NaNO_2$, KI (94%); (*c*) (*S*)-CBS catalyst, $PhNEt_2 \cdot BH_3$, PhMe, 25 °C (95%);
(*d*) $HC(CO_2Et)_3$, PMe_3, DIAD, PhMe, 50 °C (88%); (*e*) NaOH, MeOH – H_2O, then AcOH, Δ (84%); (*f*) oxalyl chloride, Cat. DMF;
(*g*) NaN_3, acetone – H_2O; (*h*) PhMe, 90 °C; (*i*) conc. HCl, 90 °C, then recrystallization from MeOH – EtOAc (67%);
(*j*) Boc_2O, TEA, MeOH (90%); (*k*) RSH, $Pd_2(dba)_3$, xantphos, Pr^i_2NEt, THF (70% – 90%); (*l*) *m*-CPBA, CH_2Cl_2 (90% – 100%);
(*m*) TFA (100%); (*n*) electrophile (70% – 90%); (*o*) RSH, K_2CO_3, DMF, 55°C (70% – 80%);
CBS catalyst is the Corey – Bakshi – Shibata catalyst based on oxazaborolidine, DIAD is diisopropyl azodicarboxylate, xantphos is 4,5-bis(diphenylphosphino)-9,9-dimethylxantene, *m*-CPBA is *m*-chloroperoxybenzoic acid, TEA is triethylamine, dba is dibenzylideneacetone, TFA is trifluoroacetic acid.

Compound	R	pK_i^b	Compound	R	pK_i^b	Compound	R	X	pK_i^b
40a	Ph	9.8	**40h**	cyclo-C_6H_{11}	< 6	**41a**	pyrrol-3-yl	NHMe	9.8
40b	3-HOC_6H_4	9.6	**40i**	pyrrol-3-yl	9.5	**41b**	3-FC_6H_4	$NH(CH_2)_2OH$	9.9
40c	3-$MeOC_6H_4$	9.4	**40j**	1-methylpyrrol-3-yl	8.1	**41c**	3-FC_6H_4	3-hydroxy-azetidino	10.0
40d	3-FC_6H_4	10.1	**40k**	pyrazol-4-yl	8.7				
40e	3-$MeO_2SC_6H_4$	8.4	**40l**	thiazol-5-yl	9.1	**42**	Ph	$NH(CH_2)_2OH$	9.8
40f	3-NCC_6H_4	9.3	**40m**	indol-3-yl	10.3				
40g	Bn	6.8	**40n**	6-fluorobenzimidazol-4-yl	8.3				

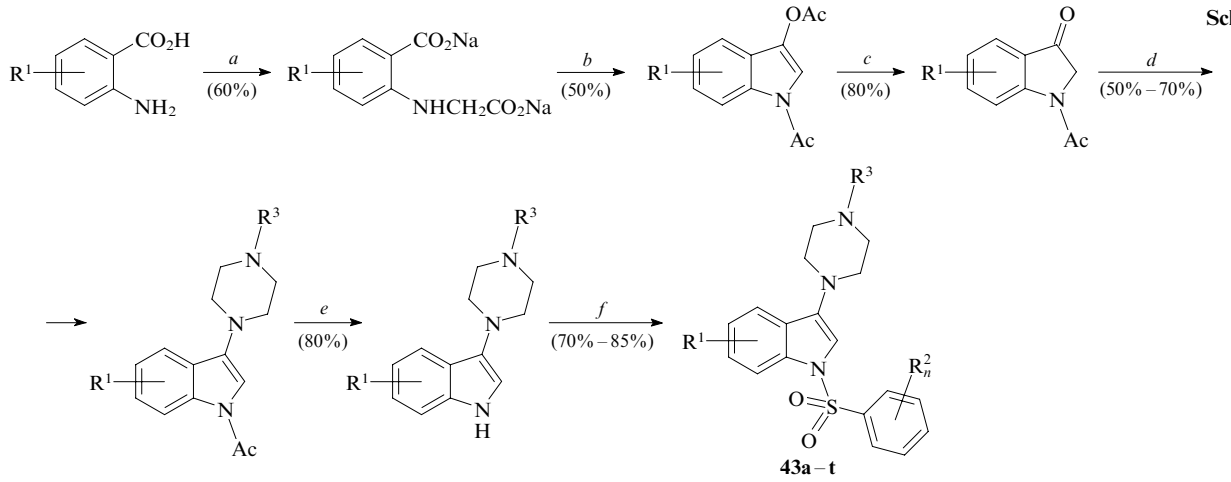
The vast majority of compounds **40**–**42** are picomolar ligands with pK_i^b values from 9.8 to 10.3.[62] The most active ligands contain an aryl or hetaryl substituent as R (phenyl in **40a**, **42**, 3-fluorophenyl in **40d**, **41b**,**c**, 3-pyrrolyl in **41a** and 3-indolyl in **40m**). Ligand **40m** (pK_i^b = 10.3) is the most active in this series. The least active are the ligands containing benzyl (**40g**, pK_i^b = 6.8) and cyclohexyl (**40h**, pK_i^b < 6) moieties as the R substituent.

4. Synthesis of 1-arylsulfonyl-1*H*-indoles and their activity

1-Arylsulfonyl-1*H*-indoles corresponding to PM_2 attract interest of researchers. In particular, Nirogi *et al.*[63] have reported a six-step synthesis of substituted 1-arylsulfonyl-3-piperazino-1*H*-indoles **43a**–**t**; the synthesis includes the classical scheme of preparation of substituted indoles from anthranilic acids and their transformation into target products (Scheme 3).

In this series of ligands, the most active one is 1-(4-isopropylphenylsulfonyl)-3-(4-methylpiperazino)-1*H*-indole (**43a**) with pK_i = 8.47. However, it exhibits low bioavailability in rats (8 ± 0.7%) and moderate (50 – 100-fold) selectivity towards 5-HT_6 receptors (on the panel including other subtypes of 5-HT receptors, as well as dopamine D_2 and histamine H_1 receptors and SERT and NET transporters).

Scheme 3



(*a*) $ClCH_2CO_2H$, H_2O, NaOH, heating; (*b*) Ac_2O, AcONa, H_2O, DMF, heating; (*c*) Na_2SO_3, anhydrous EtOH, heating; (*d*) $(Pr^iO)_4Ti$, *N*-alkylpiperazine, $NaBH(OAc)_3$, EtOH, rt; (*e*) KOH, EtOH, Δ; (*f*) NaH, DMF, $ArSO_2Cl$, rt

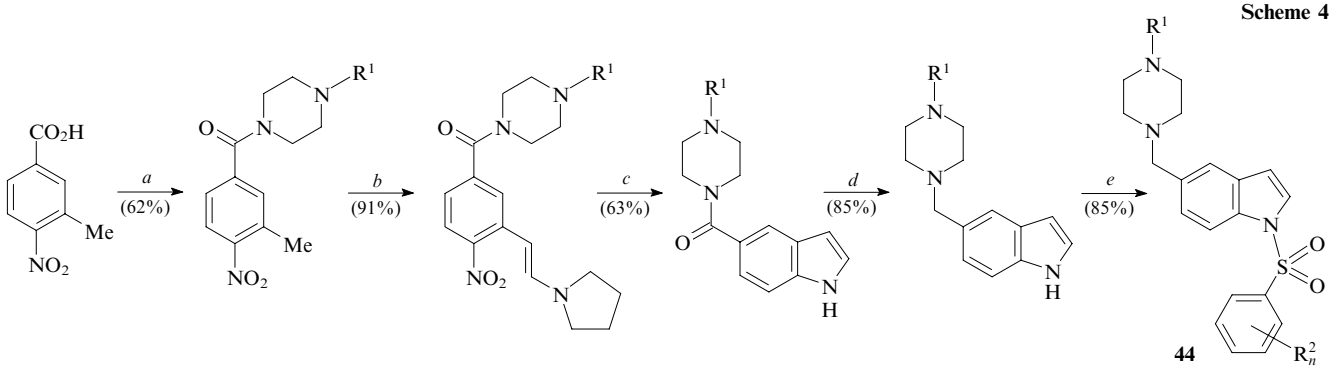
Compound	R^1	R^2_n	R^3	pK_i^b	Compound	R^1	R^2_n	R^3	pK_i^b	Compound	R^1	R^2_n	R^3	pK_i^b
43a	H	4-Pr^i	Me	8.47	**43h**	5-Br	4-F	Me	8.04	**43o**	5-Cl	4-Pr^i	Et	7.52
43b	H	4-F	Me	7.93	**43i**	5-Br	4-F	Et	7.97	**43p**	6-Cl	4-MeO	Et	7.08
43c	H	3-Cl	Me	7.97	**43j**	5-Br	4-Pr^i	Me	7.63	**43q**	6-Cl	4-Pr^i	Me	7.23
43d	H	2-Br	Me	7.82	**43k**	5-Br	2-Pr^i	Et	7.52	**43r**	6-Cl	2,5-$(MeO)_2$	Et	7.20
43e	H	H	Me	7.80	**43l**	5-Br	2-Br	Me	7.99	**43s**	6-Cl	3,4-benzo	Et	7.59
43f	H	4-Pr^i	Et	8.06	**43m**	5-Cl	4-F	Et	7.97	**43t**	6-Cl	2-Br	Me	7.52
43g	5-Br	3-Cl	Me	8.11	**43n**	5-Cl	2-Br	Et	7.69					

Nearly the same activity (pK_i^b from 7.55 to 8.6) is also exhibited by 1-arylsulfonyl-5-piperazinomethyl-1*H*-indoles **44** synthesized from 3-methyl-4-nitrobenzoic acid (Scheme 4).[64] In this series of ligands, the most active ones are 1-phenylsulfonyl-5-piperazinomethyl-1*H*-indole (**44a**, $pK_i^b = 8.60$) and 1-(2-bromophenylsulfonyl)-5-(4-ethylpiperazinomethyl)-1*H*-indole (**44b**, $pK_i^b = 8.59$). The latter is active in an animal model of cognition and shows excellent selectivity against serotonin 5-HT_4 and 5-HT_7 (> 10 000-fold) and muscarinic M_1 receptors (1425-fold). The selectivity of ligand **44b** towards other receptors has not been reported.

1-Arylsulfonyl-3-(pyrrolidin-3-yl)-1*H*-indoles **45** and 1-arylsulfonyl-3-(4-chloro-2,5-dihydro-1*H*-pyrrol-3-yl)-1-*H*-indoles **46** are more active. Ligands **45** have been synthesized by alkylation of 5-substituted indoles with pyrrole-2,5-diones and subsequent sulfonamidation of intermediate products (Scheme 5). Ligands **46** have been synthesized by a similar scheme with the difference that indoles are alkylated with 3,4-dichloropyrrole-2,5-diones (Scheme 5).[65]

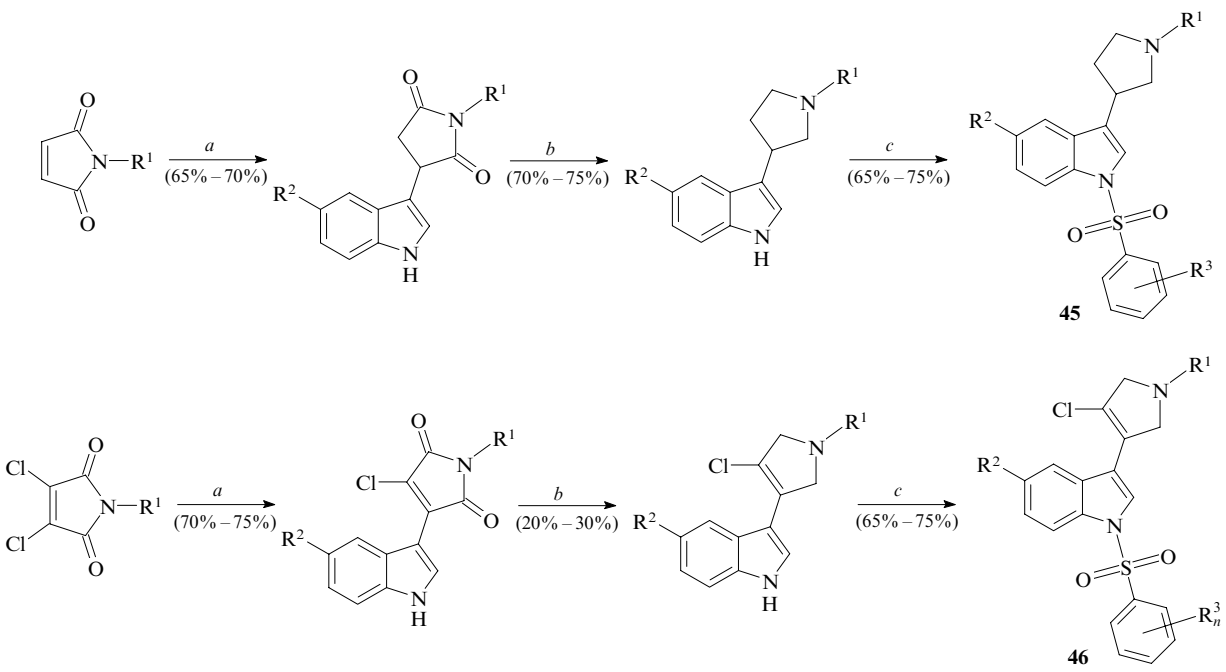
The activity (pK_i^b) of 1-arylsulfonyl-1*H*-indoles **45** and **46** changes depending on the nature of substituents from 7.73 to 10.0, the vast majority of ligands **45** and **46** being picomolar. On the panel comprising 5-HT_{2A}, 5-HT_{2C}, 5-HT_4, 5-HT_7, dopamine D_2, histamine H, adrenergic α_{1B} and muscarinic M_1 receptors and SERT, DAT and NET transporters, 3-(1-methyl-4-chloro-2,5-dihydro-1*H*-

Scheme 4



(*a*) $SOCl_2$, *N*-substituted piperazine, THF, DMF, form 10°C to rt, 4 h; (*b*) DMF-DMA, DMF, pyrrolidine, 100–110 °C, 6 h; (*c*) $N_2H_4 \cdot H_2O$, Raney Ni, THF, MeOH, 70 °C, 5 h; (*d*) $LiAlH_4$, THF, 70 °C, 6 h; (*e*) THF, KH, substituted benzenesulfonyl chlorides, rt, 3 h; **44**: R^1 = H, Me, Et; R^2_n = H, 4-Me, 4-Pr^i, 3-CF_3, 2-Br, 4-F, 4-Cl, 2,4-F_2, 2,3-Cl_2, 2-Cl-5-CF_3; DMF-DMA is dimethylformamide dimethylacetal

Scheme 5

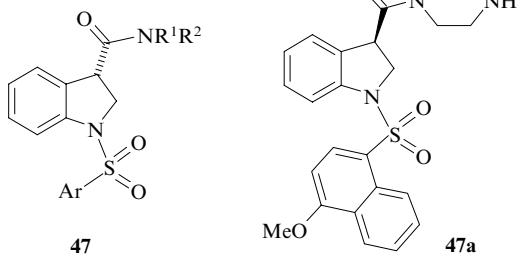


(*a*) Mg, MeI, substituted indole, THF–PhMe, 70 °C, 3–4 h; (*b*) $LiAlH_4$, THF, Δ, 2–3 h; (*c*) substituted arylsulfonyl chloride, NaH, DMF, rt, 3–4 h; **45**, **46**: R^1 = H, Me, Et; R^2 = H, MeO, EtO, Pr^iO, F; R^3_n = H, 4-Pr^i, 4-MeO, 3-Cl, 2-Br, 4-Br, 4-F, 2,4,5-Cl_3

pyrrol-3-yl)-1-phenylsulfonyl-1*H*-indole (**46**: R^2 = R^3 = H, R^1 = Me; pK_i^b = 10.0) is highly selective towards 5-HT_6 receptors (> 5000-fold, the exact values are not reported in this paper). This ligand has low bioavailability (12 ± 4%), but readily penetrates into the rat brain (B/P = 1.79).

1-Arylsulfonyl-1*H*-indoline-3-carboxamides **47** have been synthesized from 1*H*-indole-3-carboxylic acid by known reactions.[66]

Structures 47



47 **47a**

47: Ar = Ph, Naph, Het, *etc*.; R^1 = H, Me; R^2 is substituted aminoalkyl, *N*-methylpiperidin-4-yl, *N*-benzylpiperidin-4-yl, *etc*.; NR^1R^2 is 3-aminoazetidino, piperazino, 4-(3methoxyphenyl)piperazino, 1,4-diazepano, *etc*.

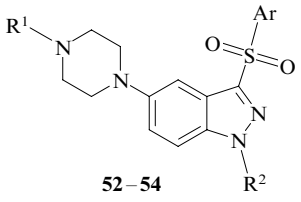
Ligands **47**, with rare exceptions, are nanomolar. The most active among them, (*R*)-1-(4-methoxynaphthalene-1-sulfonyl)-3-(1,4-diazepan-1-yl)carbonyl-2,3-dihydro-1*H*-indole (**47a**) with pK_i^b = 8.9, shows some selectivity towards 5-HT_6 receptors (> 100-fold) on the panel comprising 33 ion channels, enzymes and transporters, including 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors.

5. Synthesis of 3-arylsulfonyl-1*H*-indazoles and their activity

Over the past two years, several studies have been published dealing with the structure–activity relationship for 3-arylsulfonyl-1*H*-indazoles corresponding to PM_2. Haydar *et al*.[67] have described a five-step synthesis, from 4-nitrofluorobenzene, of nanomolar ligands **48**–**51**, which are 5-amino-substituted 3-arylsulfonylindazoles (Scheme 6) with 3-aminoazetidine, (*S*)-3-aminopyrrolidine and other (**49**), (*R*)-3-aminopyrrolidine (**50**, **51**) and 4-aminopiperidine (**48**) moieties in the 5-position of the heterocycle. These moieties simultaneously play the role of PI and HS. Ligands **48**–**51** are 5-HT_6R (pIC_{50}^f = 6.36–7.9, pK_i^b = 7.12–9.29) and 5-HT_{2B}R antagonists (pK_i^b = 5.30–7.68). One of the best ligands **50** (R = Pr^i) shows moderate activity towards 5-HT_6 receptors (pIC_{50}^f = 6.8, pK_i^b = 7.86) and 5-HT_{2B} receptors (pK_i^b = 6.72). It shows good brain penetration in rats (B/P = 0.85) and, in authors' opinion, is of interest for the treatment of psychiatric and neurological disorders with concomitant cognitive dysfunction.

Scientists at Wyeth Research[68] have described the synthesis of a series of piperazine-substituted 3-arylsulfonyl-1*H*-indazoles **52**–**57** corresponding to PM_4 and have

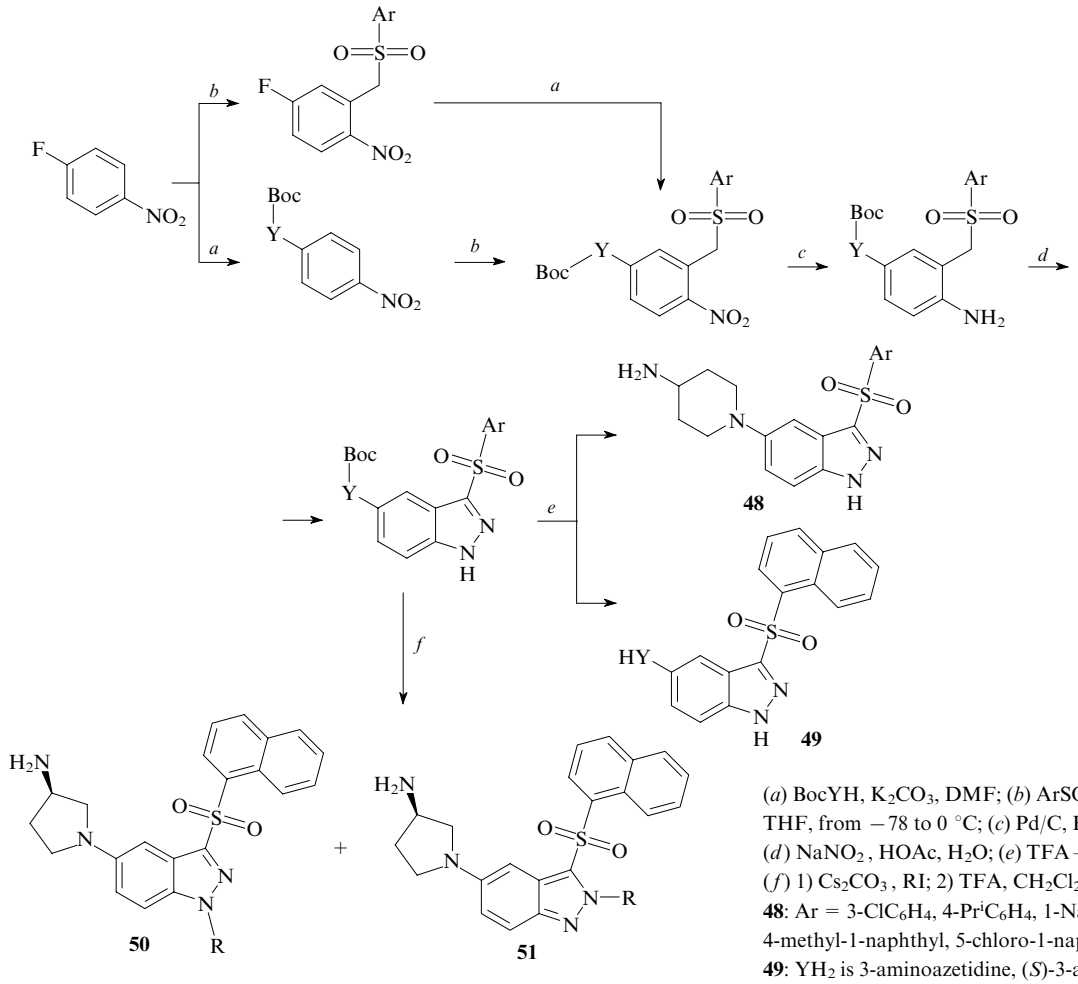
Structures 52–54



52–54

Ar = Ph, XC_6H_4 (X = 2-F, 3-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 3-Me, 4-Me, 3-MeO, 4-MeO), 2,5-$Cl_2C_6H_3$, 2-Th, 1-Naph; R^2 = Me, Et, Pr^n, Pr^i, Bu^i, Bn: R^1 = Me (**52**), H (**53**); R^1 = R^2 = H, Ar = 1-Naph (**54**); Th is thienyl

Scheme 6



(*a*) BocYH, K_2CO_3, DMF; (*b*) $ArSO_2CH_2Cl$, $KOBu^t$, THF, from −78 to 0 °C; (*c*) Pd/C, H_2 (2.7 atm); (*d*) $NaNO_2$, HOAc, H_2O; (*e*) TFA–CH_2Cl_2; (*f*) 1) Cs_2CO_3, RI; 2) TFA, CH_2Cl_2;
48: Ar = 3-ClC_6H_4, 4-$Pr^iC_6H_4$, 1-Naph, 2-Naph, 4-methyl-1-naphthyl, 5-chloro-1-naphthyl;;
49: YH_2 is 3-aminoazetidine, (*S*)-3-aminopyrrolidine, (*R*)-3-aminopyrrolidine, 4-aminopiperidine

studied the structure–activity relationship for them. Ligands **52**–**54** have been synthesized from 4-nitrofluorobenzene and piperazines by a scheme analogous to Scheme 6.

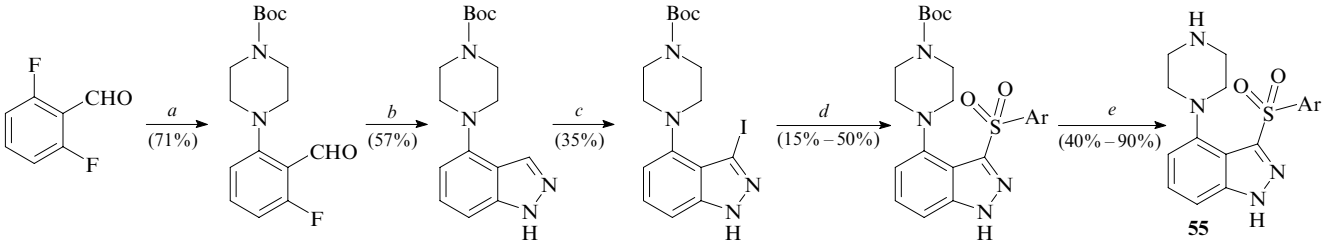
The syntheses of 4-, 6- and 7-piperazino-3-arylsulfonyl-1*H*-indzoles **55**–**57** are presented in Schemes 7–9.[68]

Among 3-arylsulfonyl-1*H*-indazoles **52**–**57**, ligands **52**–**54** are most potent, and of them, most active are 1-naphthylsulfonyl derivatives **52** and **53** (Ar = 1-Naph), which have nanomolar activity (pK_i^b = 8.12–8.96) and high selectivity towards 5-HT_6 receptors. In particular, 3-(1-naphthylsulfonyl)-5-piperazino-1*H*-indazole (**54**, WAY-255315 or SAM-315, pK_i^b = 8.96) exhibits more than 200-fold selectivity towards 5-HT_6 receptors on the panel of more than 80 receptors, ion channels and enzymes.

Researchers of the same company[69] have reported information on other series of 3-arylsulfonyl-1*H*-indazoles **58**–**65** and have studied their structure–activity relationship with respect to 5-HT_6 receptors. Key intermediates, 3-arylsulfonyl-1*H*-indazolylamines **58**, have been synthesized in high yield from nitro-1*H*-indazoles. One of them has been converted into nanomolar ligands **59a**–**e** (Scheme 10).[69]

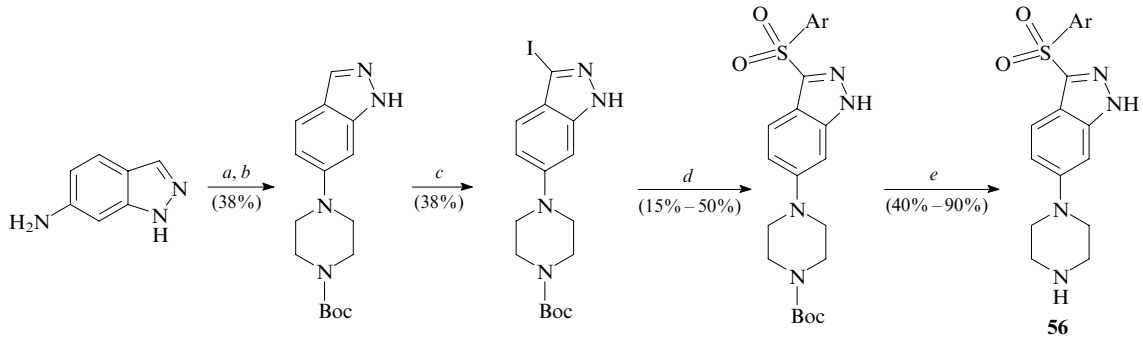
Series of other substituted 3-arylsulfonyl-1*H*-indazolylamines **60**–**63** have also been synthesized from indazolyl-

Scheme 7



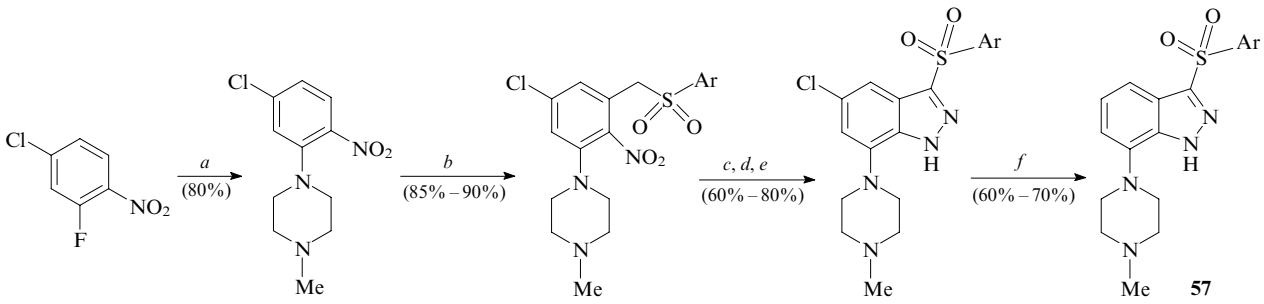
(*a*) *N*-Boc-piperazine, K_2CO_3; (*b*) NH_2NH_2, DMSO; (*c*) I_2, KOH, DMF; (*d*) $ArSO_2Na$, CuI, DMF; (*e*) HCl, MeOH–Et_2O;
55: Ar = XC_6H_5 (X = 3-F, 4-Cl, 4-Me, 4-MeO), 1-Naph

Scheme 8



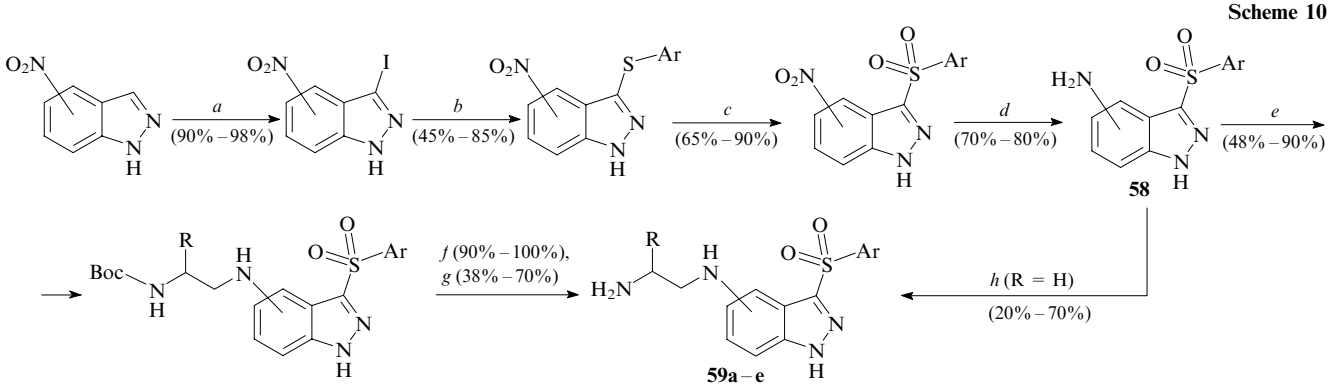
(*a*) $(ClCH_2CH_2)_2NH \cdot HCl$, K_2CO_3, Bu^nOH; (*b*) Boc_2O, KOH, 1,4-dioxane; (*c*) I_2, KOH, DMF; (*d*) $ArSO_2Na$, CuI, DMF; (*e*) HCl, MeOH – Et_2O; **56**: Ar = XC_6H_4 (X = 3-F, 4-Cl, 4-Me, 4-MeO, 4-F_3C), 1-Naph

Scheme 9



(*a*) *N*-methylpiperazine, K_2CO_3, DMF; (*b*) $ArCH_2Cl$, Bu^tOK, THF; (*c*) Sn, HCl or H_2, Pd/C; (*d*) $NaNO_2$, HCl; (*e*) K_2CO_3; (*f*) H_2, PtO_2/C; Ar = 1-Naph

Scheme 10



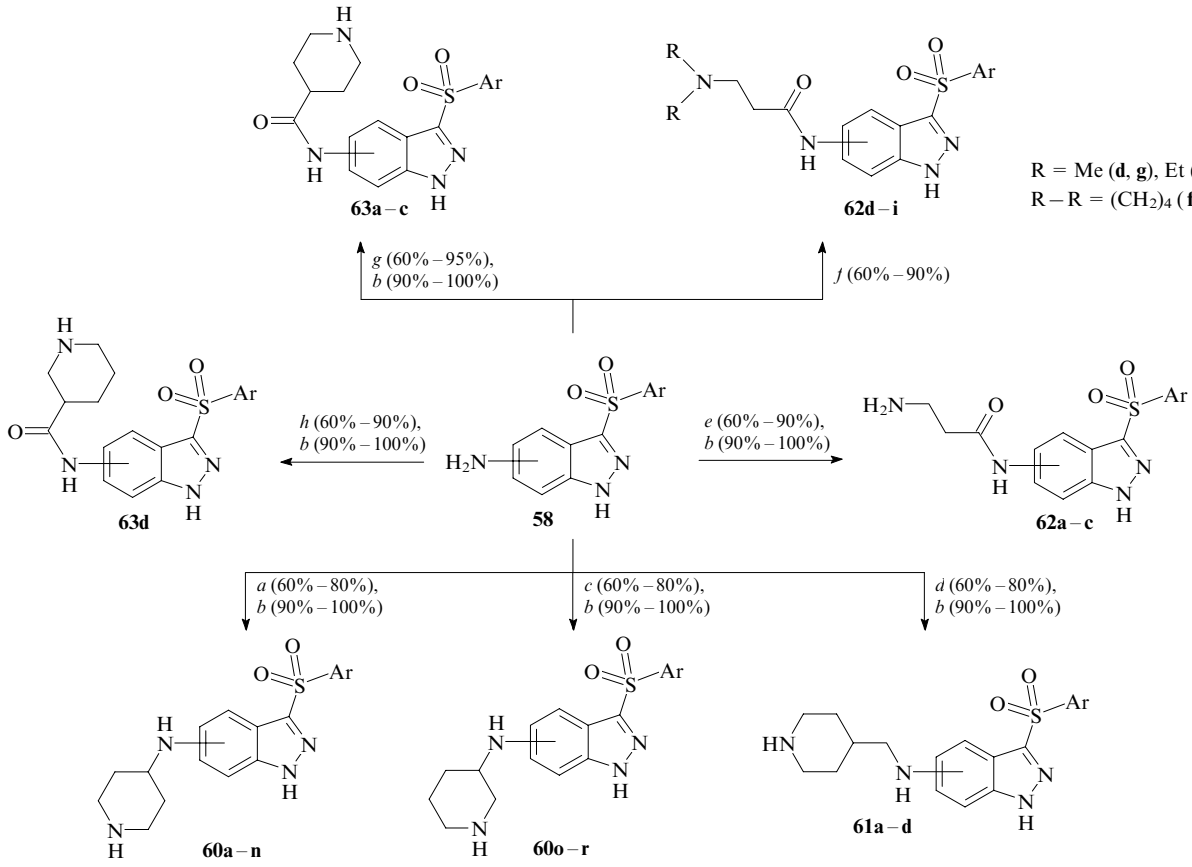
(*a*) I_2, KOH, DMF; (*b*) ArSH, CuI, K_2CO_3, $(CH_2OH)_2$, Pr^iOH; (*c*) *m*-CPBA, CH_2Cl_2; (*d*) Sn, HCl; (*e*) $BocNHCHRCO_2H$, EDC, MeCN; (*f*) TFA, CH_2Cl_2; (*g*) $BF_3 \cdot Et_2O$, THF; (*h*) 1) HCl; 2) 2-oxazolidinone, $HO(CH_2)_2O(CH_2)_2OMe$; EDC — 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide; **58**: Ar = Ph, XC_6H_4 (X = 3-F, 4-F, *etc.*), 1-Naph, 2-Naph; **59**: Ar = 1-Naph

Ligands **59**	Substituent position	R	K_i^b /nmol litre^{-1}	IC_{50}^b /nmol litre^{-1}	Ligands **59**	Substituent position	R	K_i^b /nmol litre^{-1}	IC_{50}^b /nmol litre^{-1}
a	5	H	9.5	21	**d**	6	H	17	87
b	5	Me	1.4	30	**e**	7	H	17	93
c	5	(*R*)-Pr^i	4.3	103					

amines **58** (Scheme 11) and structure–activity relationship for them has been studied.

For (3-arylsulfonyl-1*H*-indazol-5-yl)piperidin-4-yl-amines **60b**,**e**–**m,** the effect of the aryl moiety nature on the activity has been studied.[69] The most potent among them are picomolar ligands **60b**,**o** (K_i^b = 0.7 and 0.6 nmol litre^{-1}, respectively) containing the naphthyl moiety as Ar, as well as ligands **60g**,**h**,**k**, containing, as Ar, 3-methylphenyl (K_i^b = 0.8), 3-chlorophenyl (K_i^b = 1.0) and 4-isopropylphenyl (K_i^b = 1.0) groups, respectively. It should be noted that ligands in which Ar is phenyl (**60e**, K_i^b = 3.1) or 4-substituted phenyl group, for example, 4-fluoro- (**60i**, K_i^b = 6.3), 4-chloro- (**60j**, K_i^b = 2.3), 4-trifluoromethyl- (**60l**, K_i^b = 1.5) and especially 4-methoxy-

Scheme 11



(*a*) 1-*N*-Boc-4-piperidone, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (*b*) TFA, CH_2Cl_2; (*c*) 1-Boc-3-piperidone, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (*d*) 1-*N*-Boc-4-piperidinecarboxaldehyde, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (*e*) *N*-Boc-β-alanine, EDC, MeCN; (*f*) *N*,*N*-dialkylamino acid, EDC, MeCN; (*g*) 1-Boc-4-piperidinecarboxylic acid; (*h*) 1-Boc-3-piperidinecarboxylic acid

Compound	PI position	Ar	K_i^b (see [a])	Compound	PI position	Ar	K_i^b (see [a])	Compound	PI position	Ar	K_i^b (see [a])
60a	4	1-Naph	2.8	**60m**	5	4-$MeOC_6H_4$	9.8	**62c**	7	1-Naph	3.4
60b	5	1-Naph	0.7	**60n**	5	2-Naph	0.6	**62d**	6	1-Naph	44.0
60c	6	1-Naph	53.0	**60o**	4	1-Naph	4.2	**62e**	6	1-Naph	65.0
60d	7	1-Naph	30.0	**60p**	5	1-Naph	1.7	**62f**	6	1-Naph	12.0
60e	5	Ph	3.1	**60q**	6	1-Naph	57.0	**62g**	7	1-Naph	4.8
60f	5	3-FC_6H_4	6.7	**60r**	7	1-Naph	66.0	**62h**	7	1-Naph	27.0
60g	5	3-MeC_6H_4	0.8	**61a**	4	1-Naph	9.5	**62i**	7	1-Naph	24
60h	5	3-ClC_6H_4	1.0	**61b**	5	1-Naph	3.5	**63a**	5	1-Naph	1.1
60i	5	4-FC_6H_4	6.3	**61c**	6	1-Naph	44.0	**63b**	6	1-Naph	31
60j	5	4-ClC_6H_4	2.3	**61d**	7	1-Naph	17.0	**63c**	7	1-Naph	28
60k	5	4-$Pr^iC_6H_4$	1.0	**62a**	5	1-Naph	1.5	**63d**	7	1-Naph	9.8
60l	5	4-$F_3CC_6H_4$	1.5	**62b**	6	1-Naph	24.0				

[a] In nmol $litre^{-1}$.

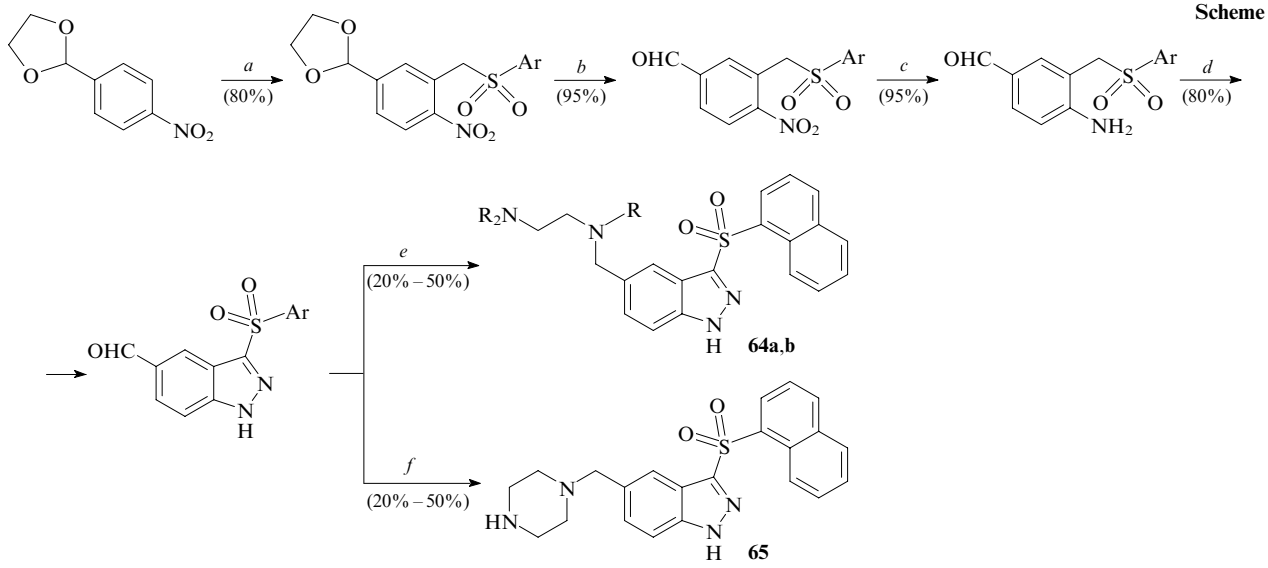
phenyl groups (**60m**, K_i^b = 9.8), are noticeably inferior in activity to the above ligands, including the 4-isopropylphenyl analogue (**60k**, K_i^b = 1.0) (all K_i^b are expressed in nmol $litre^{-1}$).

It has been shown [69] that the PI position in the indazole moiety of these ligands also has a strong effect on their activity. The highest activity is exhibited by 5-substituted ligands. For example, among ligands **60o**–**r**, (3-naphthylsulfonyl-1*H*-indazol-5-yl)piperidin-3-ylamine (**60p**) shows the maximal activity (K_i^b = 1.7 nmol $litre^{-1}$), while ligand **60r** with the PI in the 7-position of the heterocycle shows the minimal activity (K_i^b = 66 nmol $litre^{-1}$).

In addition, *N*,*N*-dimethyl- (**64b**, K_i^b = 12 nmol $litre^{-1}$) and {[3-(1-naphthyl)sulfonyl-1*H*-indazol-5-yl)]methyl}ethylenediamine (**64a**, K_i^b = 17 nmol $litre^{-1}$), as well as 3-(1-naphthylsulfonyl)-5-piperazinomethyl-1*H*-indazole (**65**, K_i^b = 0.24 nmol $litre^{-1}$), which is most active among 3-arylsulfonyl-1*H*-indazoles **58**–**65**, have been synthesized [69] (Scheme 12).

Activity study of 3-arylsulfonyl-1*H*-indazoles **60b**,**h**,**k**,**n**, **62a** and **63a** on the panel including 5-HT_6, 5-HT_{1A},

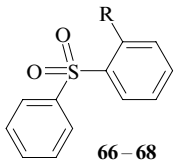
Scheme 12



(*a*) $ArSO_2CH_2Cl$, Bu^tOK, THF; (*b*) HCl, THF; (*c*) H_2, Pd/C, MeOH; (*d*) 1) $NaNO_2$, HCl; 2) $NaHCO_3$; (*e*) ethylenediamine or *N*,*N*,*N*′-trimethylethylenediamine, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (*f*) 1) 1-Boc-piperazine, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; 2) TFA, CH_2Cl_2; R = H (**64a**), Me (**64b**)

5-HT_{1B}, 5-HT_{1D}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_7, α_{2A} and D_2 receptors demonstrates their high selectivity towards 5-HT_6 receptors. It has also been reported [69] that ligands **60b** and **63a**, despite their poor brain penetration in rats (B/P < 0.2), at a concentration of 10 mg kg^{-1} significantly restore their memory impaired by scopolamine (however, no quantitative data are available).

Structures 66–68



66–68

Compound	R	pK_i^f
66	H	5.94
67	OMe	6.06
68	NMe_2	5.69

III. 5-HT_6 receptor modulators without PI moiety

There are numerous known 5-HT_6R modulators, including potent ones, that correspond to PM_3 (Fig. 8) and do not contain the PI moiety.

The simplest ligand of this type is unsubstituted phenylsulfonylbenzene (**66**), which exhibits low antagonistic activity (pK_i^f = 5.94). 2-Methoxyphenylsulfonylbenzene (**67**, pK_i^f = 6.06), containing an electron-donating substituent in the vicinal position to the sulfonyl group, is more active than ligand **66**. At the same time, 2-dimethylaminophenylsulfonylbenzene (**68**, pK_i^f = 5.69), which also contains a stronger electron-donating substituent (but sterically bulkier one), is noticeably inferior in activity not only to ligand **67**, but also to ligand **66**.[55]

Studies of binding models for 5-HT_6 receptors and ligands **66** and **67** by the MD method [55] have shown that the oxygen atoms of the sulfonyl group of these ligands form hydrogen bonds (HB) with amino acids of two transmembrane domains (TM): one of the oxygen atoms forms hydrogen bond with the hydroxyl group of Ser193(H5) and the amino group of Asn288(H6), while the other oxygen atom is bound only to the hydroxyl group of Thr196(H5). The methoxy group of one of the conformers of ligand **67** interacts with amino acids of two (H3 and H6) TMs, while the methoxy group of the other conformer binds to amino acids of three (H6, H7 and L4) TMs. One of the phenyl substituents interacts with amino acids of two (H3 and H6) TMs, and the other phenyl substituent interacts with amino acids of three (H3, H5 and L4) TMs. Molecular docking data for ligand **68** confirm its correspondence to PM_3, since the computational binding modelling reveals the absence of interaction between the D106 amino acid (Asp106) and the dimethylamino group. The computational binding modelling shows interactions of the sulfonyl oxygen atoms through hydrogen bonding to amino acids, hydrophobic interactions of phenyl rings and interactions of amino groups.

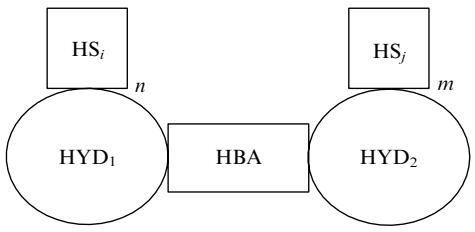
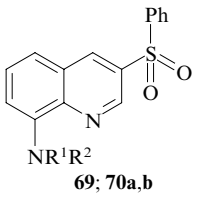


Figure 8. Simplified PM_3 of ligands without the PI moiety.[61]

Structures 69, 70



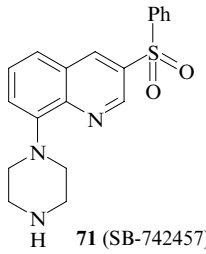
69; **70a**,**b**

Compound	R^1	R^2	pK_i^f
69	H	H	7.16
70a	H	Me	7.09
70b	Me	Me	9.1

Antagonists **69** and **70a**,**b**, obtained from 8-nitro-3-phenylsulfonylquinoline, belong to this ligand type.[70]

In this series of compounds, picomolar 5-HT_6R antagonist 8-dimethylamino-3-phenylsulfonylquinoline (**70b**, $pK_i^f = 9.1$) is most active: its activity is two orders of magnitude higher than the activity of its analogues **69** and **70a**.[70] Noteworthy is that the activity of antagonist **70b**, corresponding to PM_3, is as high as the activity of SB-742457 compound (**71**, $pK_i^f = 9.12$),[70] containing PI and corresponding to PM_2.[23]

Structure 71

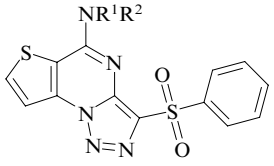


71 (SB-742457)

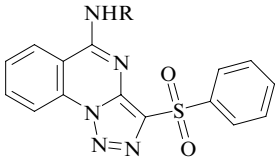
A parallel liquid-phase synthesis (Scheme 13) of combinatorial libraries comprising 466 3-arylsulfonylthieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines **72**[71–73] and 766 3-arylsulfonyl[1,2,3]triazolo[1,5-*a*]quinazolines **73**,[71, 72, 74] corresponding to PM_3 has been reported; their antagonistic activity towards 5-HT_6 receptors has been studied.

Screening of antagonistic activity against 5-HT_6 receptors of these combinatorial libraries revealed nanomolar 5-HT_6R antagonists **72a**–**d** and **73a**–**c** promising for further studies.

Structures 72a–d, 73a–c



72a–d



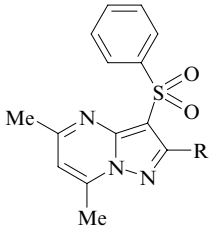
73a–c

Compound **72**	R^1	R^2	pK_i^b	Compound **73**	R	pK_i^b
a	H	2-$ThCH_2$	8.77	**a**	$CyCH_2$	8.54
b	Me	Bn	8.64	**b**	2-$FuCH_2$	8.46
c	H	2-$FuCH_2$	8.55	**c**	2-$thFuCH_2$	7.88
d	H	Cy	8.49			

Cy is cyclohexyl, Fu is furyl, thFu is tetrahydrofuranyl.

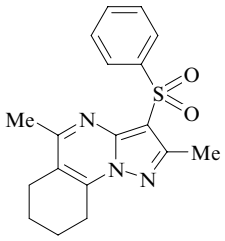
Yet another example of nanomolar 5-HT_6R antagonists corresponding to PM_3 are ligands **74**–**77**. They are substituted 3-phenylsulfonylpyrazolo[1,5-*a*]pyrimidines obtained by the reaction of β-dicarbonyl compounds with 4-phenylsulfonyl-1*H*-pyrazole-3-amines.[75–77]

Structures 74–77

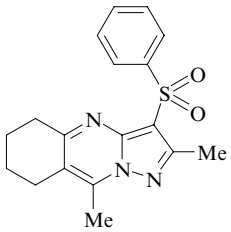


74a,**b**; **75**

Compound	R	pK_i^f
74a	H	6.25
74b	Me	7.76
75	NMe_2	7.84



76



77

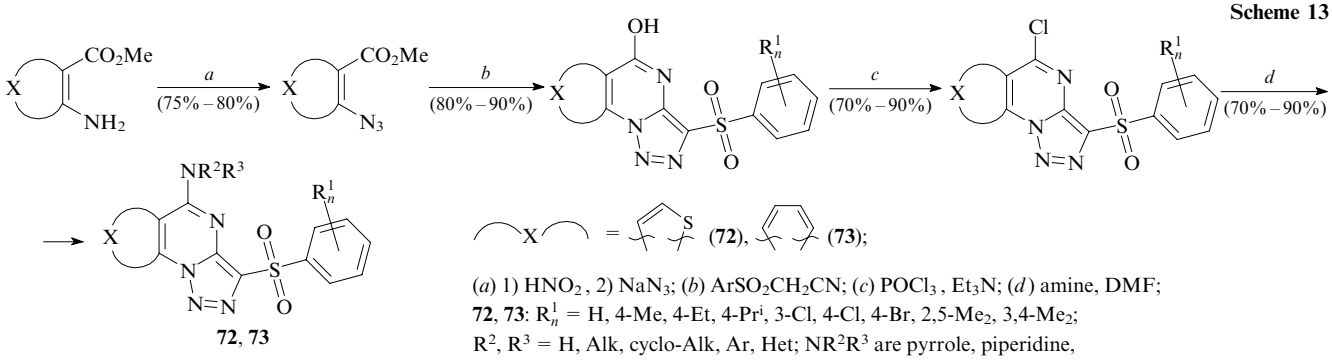
76 + **77** (1 : 1): $K_i^f = 26.8$ nmol litre^{-1}, $K_i^b = 4.42$ nmol litre^{-1}

Recently,[78] the synthesis of nanomolar sulfonimide ligands — *N*′-(arylsulfonyl)pyrazoline-1-carboxamidines **78** and **79** (Scheme 14) — has been reported. According to X-ray crystallography, ligands **78** and **79** with R^5 = H (for example, compounds **78a**,**b**; **79a**) are stabilized by an intramolecular HB involving a sulfonyl oxygen atom and the NHR^6 amidine groups.

According to MD results, the intramolecular HB persists upon the interaction of ligands **78** and **79** with 5-HT_6 receptors, and interactions with D106 (Asp106) amino acid are absent. Apparently, ligand **78** has no PI and corresponds to PM_3. Ligand **79a**, like SB-742457 (**72**), contains PI (the NH group of the piperidine ring), which binds to D106 amino acid and, hence, corresponds to PM_2 (Fig. 6).

Recently, nano- and picomolar ligands, 6-arylsulfonyl-1,2,3,4-tetrahydronaphthalenes, have been synthesized in which the PI moiety is replaced by amide (**80**), carboxamide (**81**) and sulfonamide (**82**) groups. These ligands have been synthesized from [(*R*)-6-arylsulfonyl-1,2,3,4-tetrahydro-

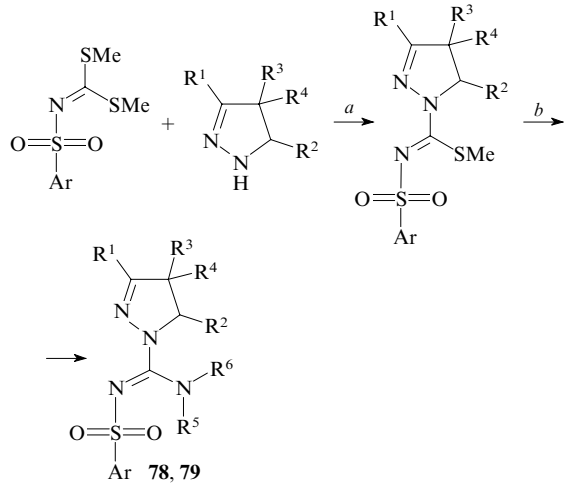
Scheme 13



72, **73**

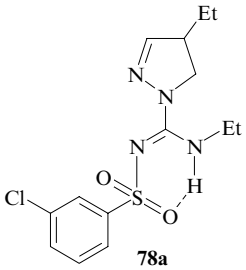
(*a*) 1) HNO_2, 2) NaN_3; (*b*) $ArSO_2CH_2CN$; (*c*) $POCl_3$, Et_3N; (*d*) amine, DMF;
72, **73**: R_n^1 = H, 4-Me, 4-Et, 4-Pr^i, 3-Cl, 4-Cl, 4-Br, 2,5-Me_2, 3,4-Me_2;
R^2, R^3 = H, Alk, cyclo-Alk, Ar, Het; NR^2R^3 are pyrrole, piperidine, morpholine and piperazine moieties, including unsubstituted ones

Scheme 14

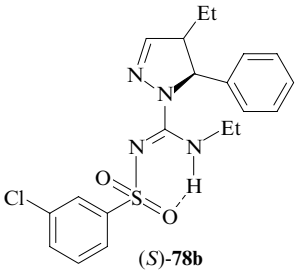


(*a*) PyH, Δ; (*b*) R^4R^5NH, MeOH, rt or NaHMDS, THF, 0–25 °C;
78: R^1 = H, Me; R^2 = H, Ph; R^3, R^4 = H, Me, Et; R^5, $R^6 \neq$ Ar or R^5 = H, R^6 = Ph; Ar = Ph, 2-ClC_6H_4, 3-ClC_6H_4;
79: R^1 = R^2 = H; R^3 = Me, CH_2F, Et; R^4 = H, Me, CH_2F, Et; R^3-R^4 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$, $(CH_2)_2NH(CH_2)_2$; Ar = Ph, 3-ClC_6H_4; PyH is pyridine, NaHMDS is sodium bis(trimethylsilylamide)

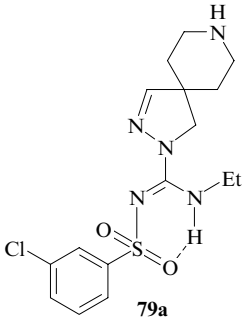
Structures 78a,b; 79a



78a



(*S*)-**78b**



79a

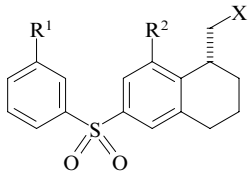
Compound	K_i^b /nmol litre^{-1}
78a	7.9
(*S*)-**78b**	9.3
79a	7.2

naphthalen-1-ylmethyl]amines **40**–**42** (see Scheme 2) corresponding to PM_2.[62]

On the basis of MD of *N*-[(*R*)-6-phenylsulfonyl-8-fluoro-1,2,3,4-tetrahydronaphthalen-1-ylmethyl]acetamide (**80a**), it has been shown that the acetamide moiety forms a hydrogen bond with Ser185(H5) and Thr103(H5). It is worth noting that the potency of ligands **80**–**84** is nearly the same as that of corresponding ligands **40**–**42**,[62, 78] containing the PI moiety and binding to Asp106(H3). No MD data for more complex ligands **80**–**84** are reported and their binding to 5-HT_6 receptors is not discussed.[78]

The authors[78] consider in sufficient detail the relationship between the structure of ligands **80**–**84** and their activity towards 5-HT_6 receptors and note that, as distinct from PI-containing ligands **40**–**42**, ligands **80**–**84** are safer in terms of binding to the potassium channel (hERG) since they do not contain highly basic amino groups. In partic-

Structures 80–84



80–**84**

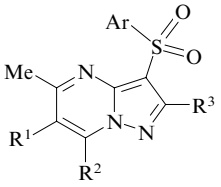
Ligand	R^1	R^2	X	pK_i^b	Ligand	R^1	R^2	X	pK_i^b
80a	H	F	NHAc	9.5	**82g**	F	H	$NHSO_2NMe_2$	8.7
80b	F	H	NHAc	9.9	**82h**	F	H	2-azasulfolan-2-yl	7.5
80c	F	H	N(Me)Ac	8.8	**83a**	F	H	$NHC(O)CH_2OH$	10.0
80d	F	H	NHBoc	8.4	**83b**	F	F	$NHC(O)CH_2OH$	9.6
81a	F	H	$NHC(O)NH_2$	9.7	**83c**	F	H	$NHC(O)CMe_2OH$	8.7
81b	F	F	$NHC(O)NH_2$	9.7	**83d**	F	H	$NHC(O)CH_2OMe$	9.1
81c	F	H	NHC(O)NHMe	9.4	**83e**	F	H	$NHCH_2C(O)NH_2$	10.0
81d	F	H	$NHC(O)NMe_2$	8.6	**83f**	F	H	$NMeCH_2C(O)NH_2$	8.9
81e	F	H	$NMeC(O)NH_2$	7.4	**83g**	F	H	$NHCH_2C(O)NHMe$	9.0
81f	F	H	NHC(O)(2-Pyr)	8.3	**83h**	F	H	$NH(CH_2)_3SO_2OH$	8.9
81g	F	H	NHC(O)(2-thPyr)	9.2	**83i**	F	H	$NHC(O)CH_2NH_2$	9.5
82a	F	H	$NHSO_2Me$	9.7	**83j**	F	H	$NHC(O)CH_2NHMe$	9.8
82b	F	H	$NMeSO_2Me$	9.4	**83k**	F	H	$NHC(O)CH_2NMe_2$	9.4
82c	F	H	$NHSO_2CF_3$	7.5	**84a**	F	H	$NHC(=NH)NH_2$	9.2
82d	F	H	$NHSO_2NH_2$	9.9	**84b**	F	H	NHC(O)(2-Im)	7.8
82e	F	H	$NMeSO_2NH_2$	8.4	**84c**	F	H	piperazin-3-on-1-yl	8.2
82f	F	H	$NHSO_2NHMe$	9.0					

Pyr is pyrrolyl, thPyr is tetrahydropyrrolyl, Im is imidazolyl.

ular, ligands **80**–**84**, as a rule, have hERG $IC_{50} > 50$ μmol litre^{-1}, whereas the same parameter for ligands **40**–**42** is within 0.5–5 μmol litre^{-1}.

It should be noted that acylation of aminoalkyl ligands **85**–**90**[79] has led to 3-arylsulfonylpyrazolo[1,5-*a*]pyrimidines **91**–**96** containing the acetamide moiety, analogous to the above ligands.[80,81]

Structures 85–96



85–**96**

Ligand	Ar	R^1	R^2	R^3	K_i^f	Ref.
85	Ph	CH_2NH_2	Me	SMe	8.34	80
86	Ph	$(CH_2)_2NH_2$	Me	SMe	8.96	80
87	3-FC_6H_4	CH_2NH_2	Me	SMe	8.0	80
88	3-ClC_6H_4	$(CH_2)_2NH_2$	Me	SMe	9.05	80
89	Ph	$(CH_2)_2NH_2$	Me	NHMe	8.86	81
90	Ph	Me	$(CH_2)_2NH_2$	NHMe	8.51	81
91	Ph	CH_2NHAc	Me	SMe	7.47	79
92	Ph	$(CH_2)_2NHAc$	Me	SMe	8.23	79
93	3-FC_6H_4	CH_2NHAc	Me	SMe	7.43	79
94	3-ClC_6H_4	$(CH_2)_2NHAc$	Me	SMe	8.59	79
95	Ph	$(CH_2)_2NHAc$	Me	NHMe	7.96	79
96	Ph	Me	$(CH_2)_2NHAc$	NHMe	6.80	79

Computational models of binding of these ligands to 5-HT_6 receptors, obtained by the MD method, show that all ligand moieties are involved in binding. In particular, the acetamide moiety of ligand **95** forms HB with T306(H7) and Asp106(H3) or with Ser193(H5) and Asn288(L6) amino acids, and a similar moiety of ligand **96** is hydrogen-bonded to Asp106(H3) or Ser193(H5) and Asn288(L6) (Table 2).[79]

It is worth noting that, as distinct from ligands **80**–**84**, which exhibit nearly the same activity as their precursors **40**–**42**,[62,78] ligands **91**–**96** containing the acetamide moiety have a noticeably lower antagonistic activity against 5-HT_6 receptors as compared with their aminoalkyl precursors **85**–**90** corresponding to PM_2. For example, ligands **95** ($pK_i^f = 7.96$) and **96** ($pK_i^f = 6.8$) are inferior in activity to their PI-containing analogues **89** and **90** by a factor of 8 and 51, respectively.[79]

IV. 3-Arylsulfonyl-2-methylsulfanylpyrazolo[1,5-*a*]pyrimidines

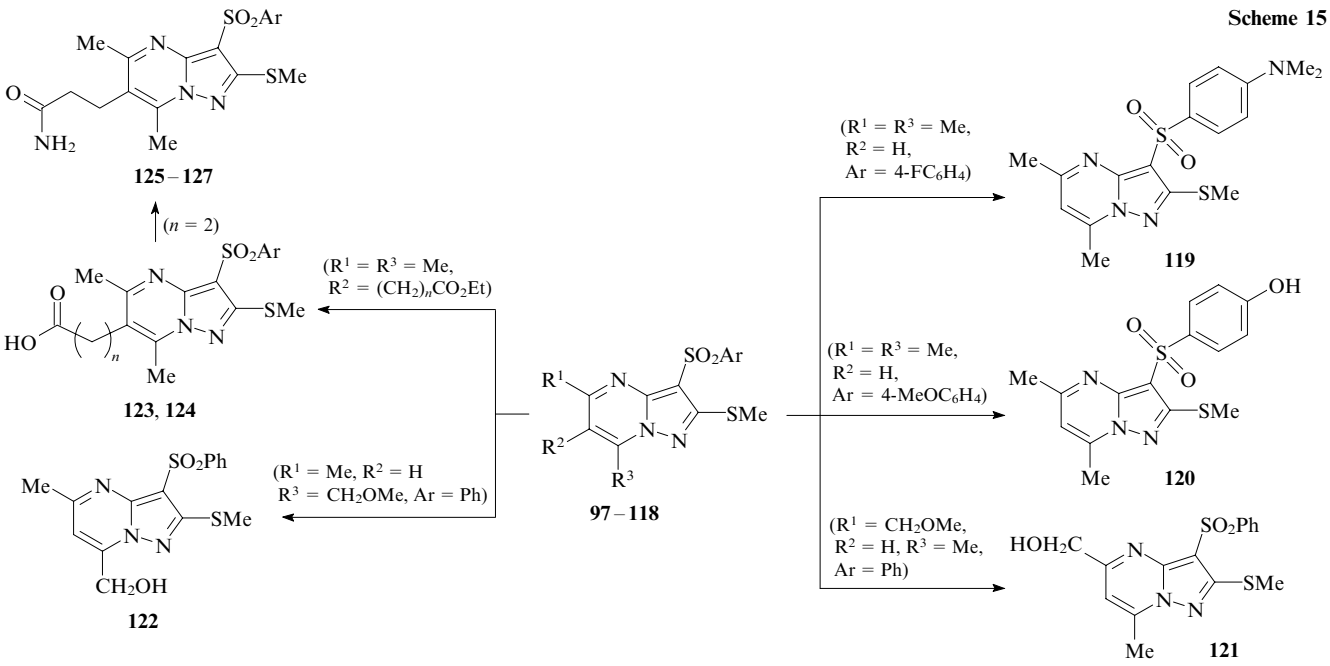
The reaction of appropriate β-diketones with 1*H*-pyrrazole-3-amines affords substituted 3-arylsulfonyl-2-methylsulfanylpyrazolo[1,5-*a*]pyrimidines **97**–**118** (Scheme 15).[82–88] 4-Fluorophenylsulfonylpyrazolo[1,5-*a*]pyrimidine **99** reacted with dimethylamine to give 4-dimethylaminophenylsulfonylpyrazolo[1,5-*a*]pyrimidine **119**; 4-methyloxyphenylsulfonylpyrazolo[1,5-*a*]pyrimidine **103** was demethylated to give 4-hydroxyphenylsulfonylpyrazolo[1,5-*a*]pyrimidine **120**; and methoxymethyl derivatives **106** and **107** were also demethylated into corresponding alcohols **121** and **122**. Esters **116** and **117** were converted into corresponding acids **123** and **124**, and acid **124** was converted into amide **125** (Scheme 15). Analogously, amides **126** and **127** were obtained from corresponding acids. Ligands **97**–**127**, which are mainly nanomolar 5-HT_6R antagonists, do not contain PI and correspond to PM_3.[71,72,75,80,82–88]

It should be noted that the activity of these ligands noticeably depends on the nature of the substituent in the phenyl moiety. In particular, among compounds **97**–**103**, most potent are the ligands containing the phenylsulfonyl

Table 2. Interaction of the moieties of ligands **95** and **96** with the active site of 5-HT_6 receptors.[79]

Moiety	Conformer 1 of ligand **95**	Conformer 2 of ligand **95**	Conformer 1 of ligand **96**	Conformer 2 of ligand **96**
Acetamide	NHC=O···H_2N Asn288(H6), 1.97 Å	NHC=O···HO Thr306(H7), 2.28 Å	NHC=O···HO Ser193(H5), 2.25 Å	CONH···O_2C Asp106(H3), 2.19 Å
Sulfonyl	S=O^1···H_2N Asn288(H6), 2.34 Å S=O^2···HO Thr306(H7), 2.05 Å	CONH···O=C Asp106(H3), 2.39 Å S=O^1···H_2N Asn288(H6), 2.24 Å S=O^2···HO Ser193(H5), 2.31 Å	CONH···O=C Asn288(H6), 2.2 Å S=O^1···H_2N Asn288(H6), 2.21 Å S=O^2···HO Thr306(H7), 2.1 Å	S=O^1···H_2N Asn288(H6), 2.08 Å S=O^2···HO Ser193(H5), 2.23 Å
Phenyl	F302(H7), T306(H7), L182(L4), V07(H3)	A184(L4), F188(H5), H167(L4), L182(L4), V189(H5)	F302(H7), L182(L4), T306(H7), W102(H3)	A184(L4), H167(L4), F188(H5), L162(H4), L182(L4), V189(H5)
Pyrazolo-pyrimidine	F284(H6), F302(H7), L162(H4), L182(L4), V107(H3)	F284(H6), L182(L4), V107(H3)	A192(H5), F284(H6), F302(H7), L162(H4), L182(L4), V107(H3)	F284(H6), F285(H6), F302(H7), T306(H7), L182(L4), V107(H3)
NHMe	C110(H3), D106(H3), V107(H3)	A192(H5), F285(H6), T196(H5), V107(H3)	C110(H3), F284(H6), V107(H3)	A192(H5), F285(H6), T196(H5), V107(H3)
$(CH_2)_2NHAc$	A192(H5), F284(H6), F285(H6), T196(H5), V107(H3), V189(H5)	L182(L4), T396(H7), W102(H3)	V189(H5), V293(L6)	C110(H3), G309(H7), V107(H3), W281(H6), Y310(H7)

Scheme 15

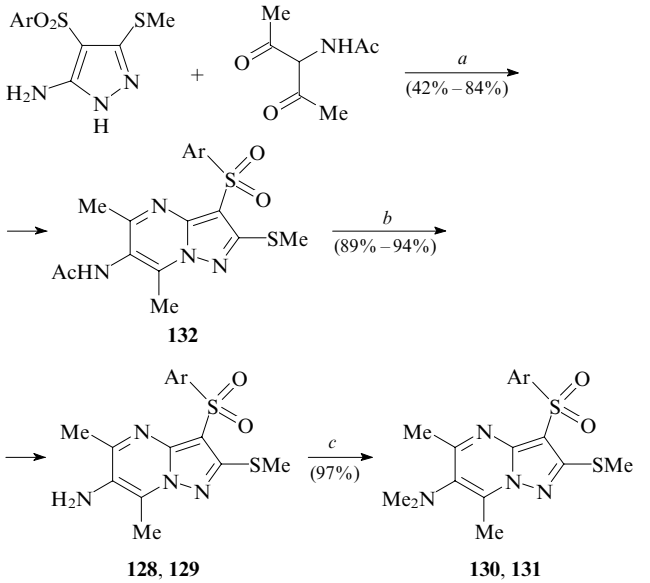


Compound	R^1	R^2	R^3	Ar	pK_i^f	Ref.
97	Me	H	Me	Ph	8.92	85
98	Me	H	Me	3-FC_6H_4	8.97	85
99	Me	H	Me	4-FC_6H_4	8.17	85
100	Me	H	Me	3-ClC_6H_4	9.12	85
101	Me	H	Me	4-ClC_6H_4	8.50	85
102	Me	H	Me	3-Cl-4-FC_6H_3	8.42	85
103	Me	H	Me	4-$MeOC_6H_4$	7.43	85
104	H	H	Me	Ph	6.64	85
105	Me	H	H	Ph	7.78	85
106	CH_2OMe	H	Me	Ph	8.49	85
107	Me	H	CH_2OMe	Ph	6.81	85
108	3-Py	H	Me	Ph	8.35	88
109	H	H	3-Py	Ph	7.73	88
110	Me	H	3-Py	Ph	7.01	88
111	2-Py	H	2-Py	Ph	6.28	88
112	3-Py	H	3-Py	Ph	5.84	88
113	Me	Cl	Me	Ph	8.46	88
114	Me	Br	Me	Ph	7.47	88
115	Me	H	Me	3-ClC_6H_4	8.70	85
116	Me	CH_2CO_2Et	Me	Ph	7.39	80
117	Me	$(CH_2)_2CO_2Et$	Me	Ph	7.04	88
118	Me	3-PyO	Me	3-ClC_6H_4	6.62	88
119	Me	H	Me	4-$Me_2NC_6H_4$	7.43	85
120	Me	H	Me	4-HOC_6H_4	8.4	85
121	Me	H	CH_2OH	Ph	8.67	85
122	CH_2OH	H	H	Ph	9.25	85
123	Me	CH_2CO_2H	Me	Ph	6.31	88
124	Me	$(CH_2)_2CO_2H$	Me	Ph	6.11	88
125	Me	$(CH_2)_2C(O)NH_2$	Me	Ph	8.09	88
126	Me	$(CH_2)_2C(O)NH_2$	Me	3-FC_6H_4	8.34	88
127	Me	$(CH_2)_2C(O)NH_2$	Me	3-ClC_6H_4	8.12	88

(**97**, $pK_i^f = 8.92$), 3-fluorophenylsulfonyl (**98**, $pK_i^f = 8.97$) and 3-chlorophenylsulfonyl moiety (**100**, $pK_i^f = 8.97$), while methoxyphenylsulfonyl- (**103**) and 4-dimethylaminophenylsulfonylpyrazolo[1,5-*a*]pyrimidine (**119**) are the least potent ligands ($pK_i^f = 7.43$). In this series of ligands, transition from 3-halophenyl-substituted ligands **98** and **100** to 4-halophenyl-substituted ligands **99** and **101** is accompanied by a significant decrease in their activity towards 5-HT_6 receptors.

6-Aminomethyl-3-arylsulfonyl-5,7-dimethyl-2-methylsulfanylpyrazolo[1,5-*a*]pyrimidines **128**–**131** have been synthesized by the reaction of 5-amino-4-arylsulfonyl-3-methylsulfanyl-1*H*-pyrazoles and *N*-(acetyl-2-oxopropyl)-acetamide through intermediate acylamines **132**

Scheme 16



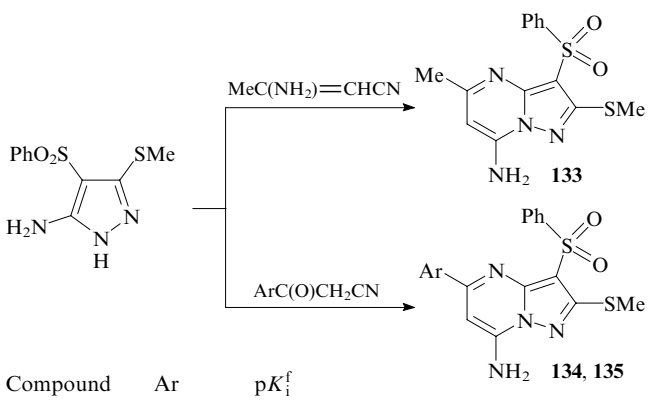
(*a*) AcOH, 80–100 °C, 12 h; (*b*) MeOH, H_2O, KOH, Δ, 72–100 h; (*c*) 1) HCHO, $NaBH_4$, EtOH, 20–25 °C, 12 h; 2) H_2SO_4

Compound	Ar	pK_i^f	Compound	Ar	pK_i^f
128	Ph	9.4	**130**	Ph	9.0
129	3-ClC_6H_4	9.7	**131**	3-ClC_6H_4	9.15

(Scheme 16).[80] The activity of ligands **128**–**131** is noticeably higher than the activity of corresponding ligands **97**–**99**, **101**–**112** and **115,** without a substituent in the 6-position of the heterocycle, or ligands **113**, **114**, **116**–**118** and **123**–**127**, containing substituents other than amino groups in this position.

Ligands **133**–**135**, containing amino group in the 7-position of the heterocycle, have been prepared from 4-phenylsulfonyl-2*H*-pyrazol-3-ylamine and 3-aminobut-2-enenitrile, 3-oxo-3-(2-thienyl)propionitrile or 3-oxo-3-phenylpropionitrile, respectively (Scheme 17).[86]

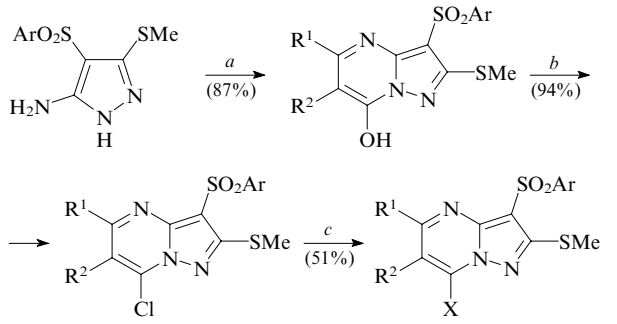
Scheme 17



Compound	Ar	pK_i^f
133		9.15
134	Ph	7.23
135	2-Th	7.19

7-Dimethylamino derivatives **136** and **137** have been synthesized by analogy with the synthesis of (3-arylsulfonyl-2-methylsulfanylpyrazolo[1,5-*a*]pyrimidin-7-yl)-amines **138**, patented earlier by F Hoffmann-La Roche AG. The reaction of β-keto esters with 5-amino-4-arylsulfonyl-3-methylsulfanyl-1*H*-pyrazoles afforded 7-hydroxypyrazolopyrimidines, which were treated with $POCl_3$ to give 7-chloro derivatives. The reaction of the latter with amines at elevated temperature led to the target products (Scheme 18).[85]

Scheme 18



(*a*) β-Keto ester, AcOH, Δ, 1.5 h; (*b*) $POCl_3$, Δ, 45 min; (*c*) amine, DMF, 60 °C, 2 h;
138: Ar = Ph, YC_6H_4 (Y = 4-Me, 3-Me, 2-Me, 4-Pr^i, 4-Bu^t, 4-MeO, 4-Cl, 4-Br, 4-F, 4-I), 2,4-$Cl_2C_6H_3$, 2-Naph, 2-Th, 3-Py; R^1 = H, Me, Pr^n, Pr^i, cyclo-C_3H_5, Bu^t, Cl, CH_2OMe, $(CH_2)_2OMe$, $O(CH_2)_2OH$, NMe_2, CH_2NMe_2, $NH(CH_2)_2NMe_2$, morpholino, morpholinomethyl, 4-methylpiperazino, *N*-methylpiperidino(amino)methyl;
R^2 = H, Me, $(CH_2)_2OH$; R^1-R^2 = $(CH_2)_3$, $(CH_2)_4$, CH_2SCH_2;
X = NH_2, NHMe, $NH(CH_2)_2NMe_2$, NMe_2, OCH_2NMe_2, piperazino, 4-methylpiperazino, 4-benzylpiperazino, 4-(2-hydroxyethyl)piperazino, 2,6-dimethylpiperazino, 4-phenylpiperazino, morpholino, imidazol-1-yl, 2-(morpholino)ethoxy

Compound	R^1	R^2	X	Ar	pK_i^f
136	Me	Me	NMe_2	Ph	9.15
137	Me	Cl	NMe_2	3-ClC_6H_4	8.08

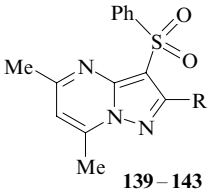
In this series of 7-amino derivatives **133**–**137**, compounds **133** and **136** exhibit the highest (picomolar) activity (pK_i^f = 9.15) towards 5-HT_6 receptors.

It should be noted that the above 5-HT_6R antagonists exhibit not only high activity but also extremely high selectivity.[31] In particular, 5,7-dimethyl-2-methylsulfanyl-3-phenylsulfonylpyrazolo[1,5-*a*]pyrimidine (**97**, AVN-211, K_i^b = 2.0 nmol litre^{-1}) on the panel comprising 67 enzymes, receptors, ion channels and transporters has selectivity towards 5-HT_6 receptors exceeding 5000. An exception is only 5-HT_{2B} receptor for which AVN-211 has IC_{50}^b = 0.196 μmol litre^{-1}. However, functional assay for this ligand has shown that AVN-211 is a complete antagonist of 5-HT_{2B} receptors with IC_{50}^f > 10 μmol litre^{-1}. In addition, it is worth noting that, under functional assay conditions, AVN-211 is also weakly active towards the hERG potassium channel (IC_{50}^b = 18.0 μmol litre^{-1}).

It has been shown[89] that transition from AVN-211 (**97**, K_i^f = 1.2 nmol litre^{-1}), containing the SMe group in the 2-position of the heterocycle, to its analogues **139**–**143**, containing hydrogen atom (**139**), methyl (**140**), 2-hydroxyethoxy (**141**), dimethylamino (**142**) or methylsulfinyl group

(**143**), is accompanied by a significant (**142**, K_i^f = 14.5 nmol litre^{-1}) and even very significant (**143**, K_i^f = 2960 nmol litre^{-1}) decrease in the antagonistic activity against 5-HT$_6$ receptors.

Structures 139–143



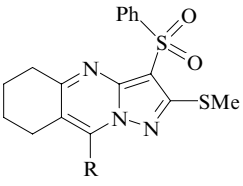
139–143

Compound	R	K_i^f, /nmol litre^{-1}	Compound	R	K_i^f, /nmol litre^{-1}
139	H	561	**142**	NMe_2	14.5
140	Me	88.8	**143**	S(O)Me	2960
141	$O(CH_2)_2OH$	283			

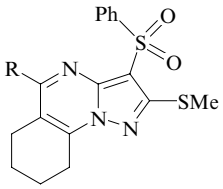
With the use of molecular docking, it has been recently demonstrated that all moieties of the energetically most favourable AVN-211 conformation (**97**) are involved in binding to the amino acids of the 5-HT$_6$R active site (Fig. 9), this conformation being stabilized by n–π-electron interaction of the methylsulfanyl substituent with the phenyl moiety.[87] In authors' opinion, it is precisely the stabilization of this conformation that is mainly responsible for the enhanced activity of most 3-arylsulfonyl-2-methylsulfanylpyrazolo[1,5-*a*]pyrimidines.

3-Phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[5,1-*b*]quinazolines **144** and **145**, 3-phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazolines **146** and **147**, 3-phenylsulfonyl-7,8-dihydro-6*H*-cyclopentano[*e*]pyrazolo[1,5-*a*]pyrimidine (**148**)[75–77] and 5,6,9-trimethyl-2-methylsulfanyl-3-phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]pteridine (**149**), which are picomolar 5-HT$_6$R antagonists,[86] have also been synthesized. Ligands **144–148** have been obtained by the reaction of 5-amino-3-methylsulfanyl-4-phenylsulfonylpyrazole with 2-formyl- and 2-acetylcycloalkanones, and pyrazolo[1,5-*a*]pteridine **149** have been prepared by the reaction of 5-methyl-2-methylsulfanyl-3-phenylsulfonyl-6,7-dichloropyrazolo[1,5-*a*]pteridine with *N*,*N*′-dimethylethylenediamine. Note that this series of ligands also does not contain a PI moiety.

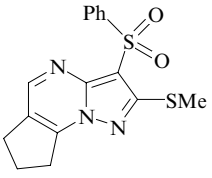
Structures 144–149



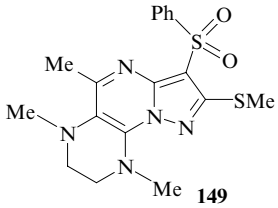
144, 145



146, 147



148



149

Compound	R	pK_i^b	pK_i^f	Compound	R	pK_i^b	pK_i^f
144	H	8.10	7.01	**147**	Me	9.36	7.77
145	Me	9.17	8.11	**148**		9.34	8.23
146	H	9.26	8.12	**149**		—	7.84

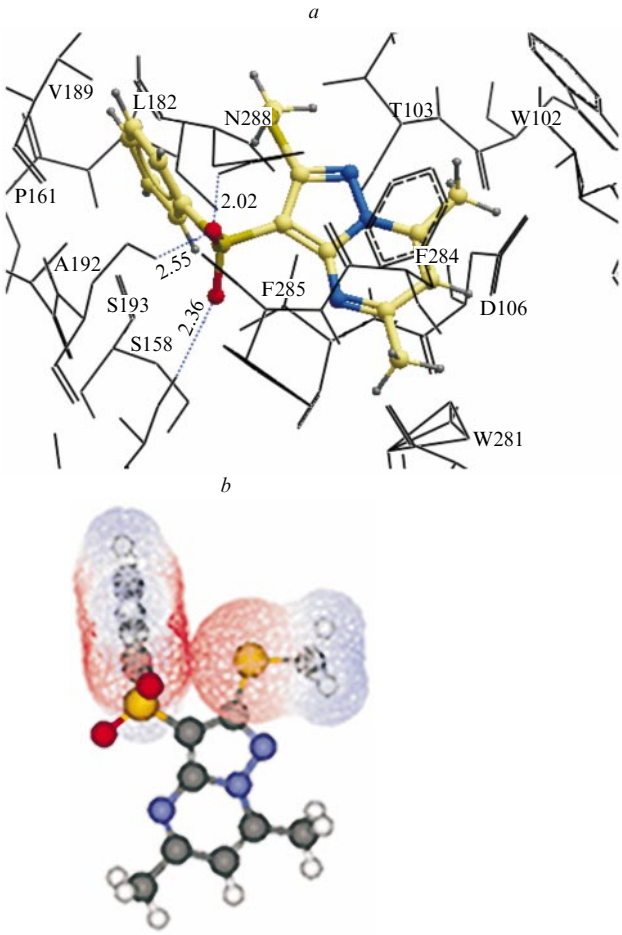


Figure 9. Computational model of binding of the 5-HT$_6$R active site to ligand **97** (*a*) and 3D structure of ligand **97** (*b*).[87] Interaction of the moieties of ligand **97** with the amino acids of the 5-HT$_6$R active site: S=O^1···HO Thr196(H5), 2.36 Å; S=O^2···HO Ser193(H5), 2.55 Å; S=O^2···H$_2$N Asn288(H6), 2.02 Å. Ph: A192(H5), F188(H5), L162(H4), V189(H5). Pyrazolopyrimidine: F284(H6), F285(H6), C110(H3), L182(L4), N306(H7), V107(H3). SMe: L162(L4), L182(L4), T103(H3).

It should be emphasized that, as in the case of 3-arylsulfonyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidines, transition from 2-methylsulfanyl derivatives **145** and **147** to corresponding 2-methyl derivatives **76** and **77** is accompanied by a noticeable decrease in activity towards 5-HT$_6$ receptors. For example, a 1 : 1 mixture of ligands **145** and **147** has K_i^b = 0.479 nmol litre^{-1}, and the activity of the corresponding mixture of ligands **76** and **77** is ~ 10 times lower (K_i^b = 4.42 nmol litre^{-1}).[77]

3-Arylsulfonyl-2-methylsulfanyl-7,8-dihydro-6*H*-cycloalkano[*d*,*e*]pyrazolo[1,5-*a*]pyrimidines **144–148** exhibit high selectivity towards 5-HT$_6$ receptors. In particular, ligands **145** and **146** show more than 1470-fold selectivity on the panel comprising 69 enzymes, GPC receptors, ion

channels and transporters. These ligands do not lead to noticeable 5-HT_{2B}R activation and are 187–749 times less potent for this receptor than for 5-HT_6 receptors. Ligands **145** and **146** at a concentration of 1 μmol litre^{-1} do not noticeably bind to the hERG potassium channel. Under functional assay conditions, ligand **146** exhibits 19000-fold selectivity towards 5-HT_6 receptor (IC_{50}^{hEGR} = 8.4 μmol litre^{-1}), and its analogue **145** with a linear arrangement of the rings shows more than 14700-fold selectivity (at a concentration of 10.0 μmol litre^{-1}, it blocked hERG by ~25%).[77]

V. 3-Arylsulfonyl-2-methylsulfanylpyrazolo-[1,5-*a*]pyrimidines with PI moiety

Ligands corresponding to PM_2 and containing the PI moiety along with the methylsulfanyl substituent are known. An example of such a ligand is Ro 65-7674 (**138a**, R^1 = Me, R^2 = H, X is morpholino, Ar = Ph; pK_i^b = 9.1),[90] which has been synthesized according to Scheme 18. It should be noted that Ro 65-7674 poorly penetrates into the brain (B/P = 0.1 in rats) and actively (IC_{20} = 0.2 μmol litre^{-1}) inhibits the hERG channel.[50]

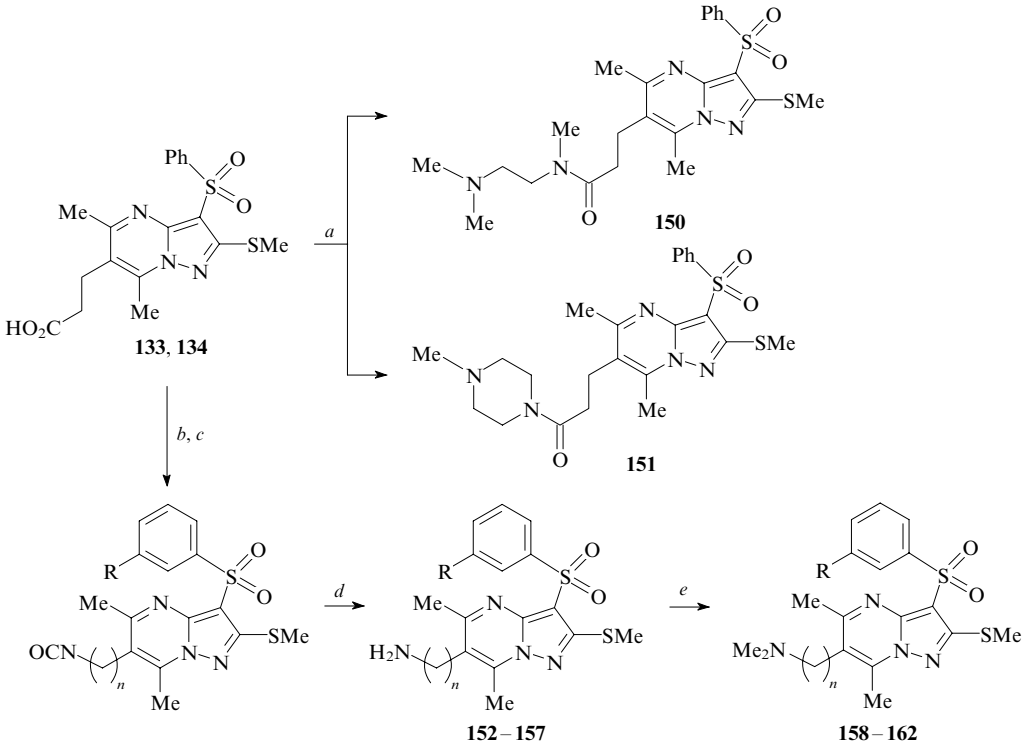
Ligands of this type are also 5,7-dimethyl-2-methylsulfanyl-3-phenylsulfonylpyrazolo[1,5-*a*]pyrimidines **150**–**162**, containing PI in the 6-position of the heterocycle and corresponding to PM_2.[80] The synthesis of this series of nanomolar ligands is shown in Scheme 19.

Amines **163**–**166**, containing the 5-methyl-2-methylsulfanyl-3-phenylsulfonylpyrazolo[1,5-*a*]pyrimidine moiety with the PI group in the 7-position of the heterocycle are also known.[86] These ligands correspond to PM_2. The synthesis of ligands **163** and **164**, which are somewhat less potent than the corresponding 6-substituted analogues **152** and **155**, is shown in Scheme 20. Ligand **165**, which is synthesized by a similar scheme as ligand **138** (see Scheme 18), is converted into ligand **166** by treatment with 3% HBr in AcOH (Scheme 21).

It is worth noting that most of 5-HT_6R antagonists **150**–**166** are noticeably inferior in activity to AVN-211 (**97**, pK_i^f = 8.92). Exceptions are only ligands **155** (pK_i^f = 8.96) and **157** (pK_i^f = 9.05), which are somewhat more potent than AVN-211.[80,86]

5-HT_6R antagonists 2-methysulfanyl-3-phenylsulfonyl-pyrazolo[1,5-*a*]piperidino[4,3-*d*]pyrimidines **167** and **168** and their analogues — pyrazolo[1,5-*a*]piperidino[3,4-*e*]pyrimidines **169** and **170**, synthesized by the reaction of corresponding 1*H*-pyrazol-5-ylamines with 2-carbonyl-substituted 4-oxopiperidines, have also been described.[90–92] Ligand **169** (pK_i^b = 8.11) is the most active antagonist in this series of compounds.

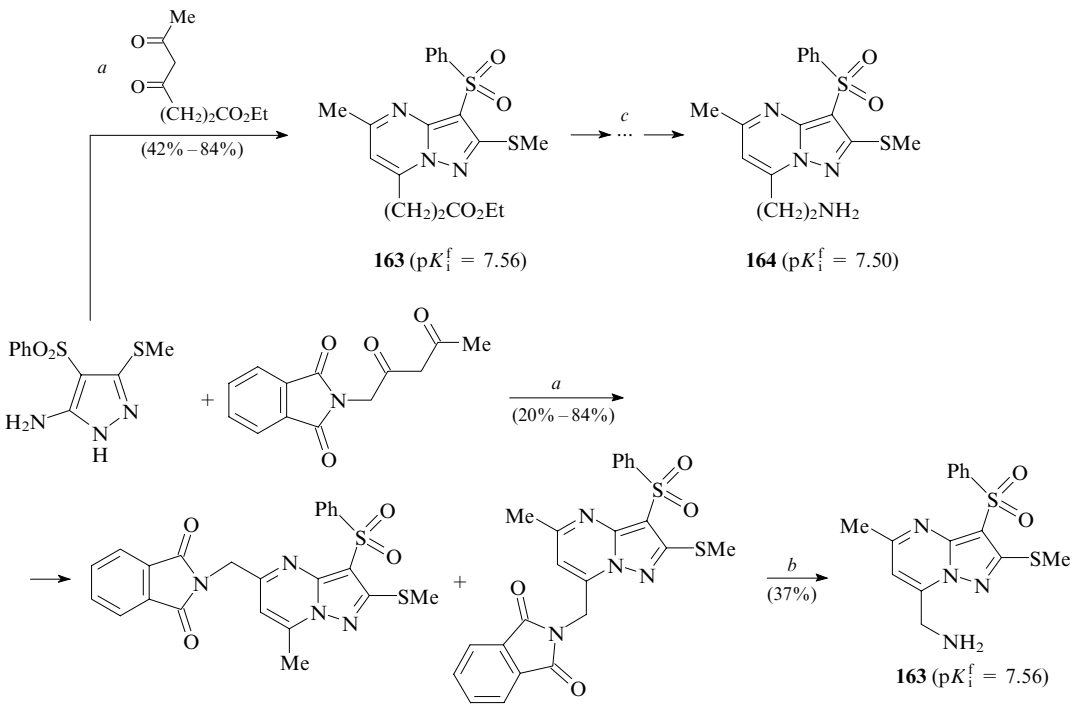
Scheme 19



(*a*) 1) DMF, *N*,*N*′-carbodiimidazole, 2) secondary amine, 75 °C, 12 h; (*b*) 1) Et_3N, $ClCO_2Et$, Me_2CO, 0 °C, 30 min, 2) NaN_3, H_2O, 0 °C, 1 h; (*c*) dioxane, 1 h; (*d*) HCl, H_2O, 20 °C, 2 h; (*e*) CH_2Cl_2, HCHO, $NaBH(OAc)_3$, 20 °C, 12 h

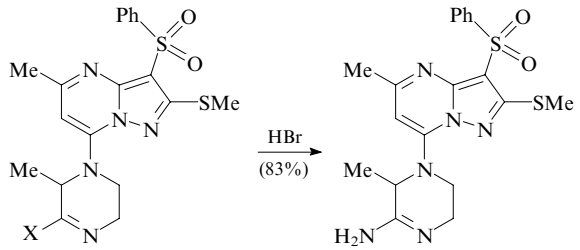
Compound	R	*n*	pK_i^f	Compound	R	*n*	pK_i^f	Compound	R	*n*	pK_i^f
150			8.12	**155**	H	2	8.96	**159**	F	1	8.42
151			5.75	**156**	F	2	8.39	**160**	Cl	1	8.80
152	H	1	8.34	**157**	Cl	2	9.05	**161**	F	2	8.39
153	F	1	8.00	**158**	H	1	8.60	**162**	Cl	2	8.60
154	Cl	1	8.41								

Scheme 20



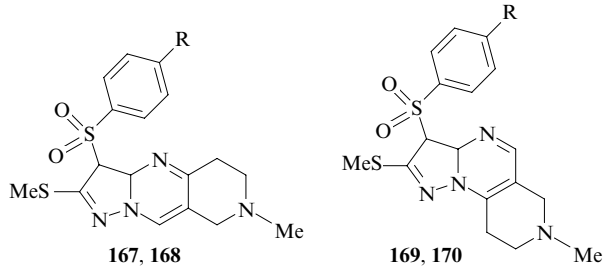
(*a*) AcOH, 80 – 100 °C, 12 h; (*b*) $N_2H_4 \cdot H_2O$, EtOH, Δ, 4 h; (*c*) 1) KOH, EtOH, H_2O, 20 °C, 12 h; 2) Et_3N, $ClCO_2Et$, Me_2CO, 0 °C, 30 min; 3) NaN_3, H_2O, 0 °C, 1 h; 4) DCM, dioxane, 1 h; 5) 20% HCl, 70 – 80 °C, 0.5 h

Scheme 21



X = $NHCMe_2CH_2Bu^t$

Structures 167 – 170



Compound	R	pK_i^b	pK_i^f	Compound	R	pK_i^b	pK_i^f
167	H	6.43	6.31	**169**	H	8.11	7.83
168	F	–	5.94	**170**	F	7.47	–

VI. 5-HT_6 receptor modulators without a PI moiety stabilized by intramolecular hydrogen bond

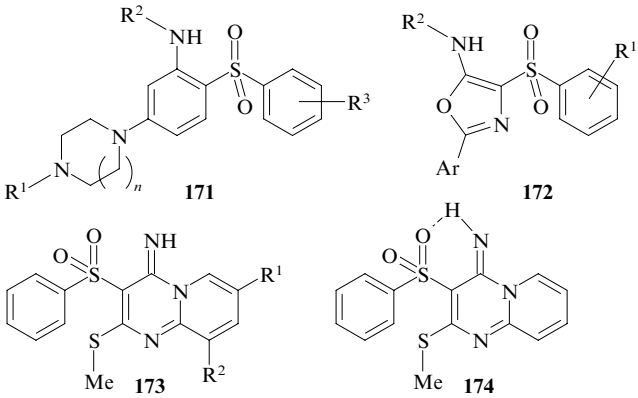
In 1996 – 2003, nanomolar ligands 2-arylsulfonylphenylamines **171**[93] and (2-aryl-4-phenylsulfonyloxazol-5-yl)amines **172**[94 – 96] were patented and the synthesis of (*E*)-2-methylsulfanyl-3-(phenylsulfonyl)pyrido[1,2-*a*]pyrimidin-4-ylideneamines **173** and **174** was reported.[97]

Ligands **171 – 174** are rather active towards 5-HT_6 receptors. They contain an intramolecular hydrogen bond donor (IHBD), which is a primary or secondary amino or imino group vicinal to the HBA, capable of forming an IHB with a sulfonyl oxygen atom. For (*E*)-2-methylsulfanyl-3-(phenylsulfonyl)pyrido[1,2-*a*]pyrimidin-4-ylideneimine (**174**), ligand stabilization by an intramolecular hydrogen bond has been proved by X-ray crystallography,[97] and according to computational modelling, the ligand has one local minimum corresponding to a conformer stabilized by an IHB and n – π-electron interaction of the methylsulfanyl substituent and the phenyl moiety (Fig. 10).§

Note that the effect of such an IHB on the activity of ligands towards 5-HT_6 receptors has not been discussed.[93 – 97] However, a series of recent studies[55, 61, 70, 79, 81, 85, 88, 91, 98 – 103] provides evidence of the high efficiency of ligands of this type.

§ These data were generously supplied by Dr. I M Okun (ChemDiv, Inc., United States).

Structures 171–174



171

172

173

174

171: R^1 = H, Me; R^2 = H, Me, Et; R^3 = H, Me, F; pK_i^b = 7.1–8.85;
172: Ar = Ph, substituted Ph, 2-Fu, 2-Th, 3-Py, 4-Py; R^1 = H, Me, Cl, Br, MeO; R^2 = H, All, $Ar(CH_2)_n$; pIC_{50}^b > 8.4;
173: R^1 = H, F, Me; R^2 = Et, Br; pIC_{50}^b = 6.57–7.15;
174: pIC_{50}^b = 8.40

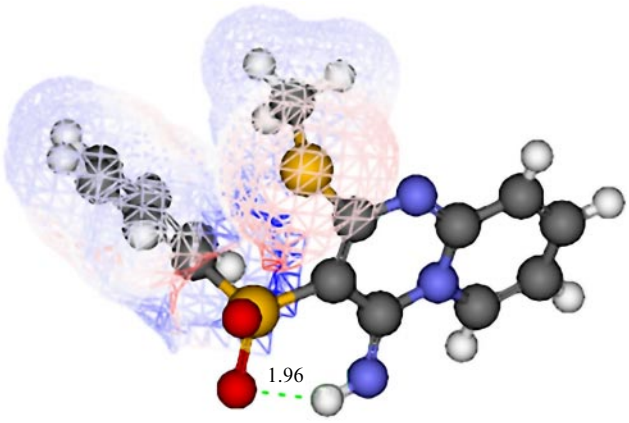
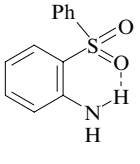


Figure 10. 3D model of a conformer of ligand **174** obtained by computational modelling.

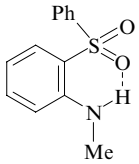
1. 2-Phenylsulfonylphenylamines

Transition from phenylsulfonylbenzene (**66**, pK_i^f = 5.94) to 2-phenylsulfonylanilines **175–178** is accompanied by a noticeable increase in antagonistic activity up to pK_i^f = 7.61 characteristic of *N*-methyl-2-phenylsulfonylaniline (**176**).[55, 104, 105]

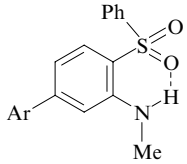
Structures 175–178



175 (pK_i^f = 6.31)



176 (pK_i^f = 7.61)



177 (Ar = Ph, pK_i^f = 6.82);
178 (Ar = 3-Py, pK_i^f = 7.32)

Stabilization of *N*-methyl-2-phenylsulfonylaniline (**176**) by an intramolecular HB has been proved by X-ray crystallography and MD.[55, 61] Molecular docking demonstrates that, in the computational model of binding of 5-HT_6 receptors to ligands **175** and **176**, all moieties of the latter are involved in binding to the amino acids of the 5-HT_6R active site (Table 3). In the computational ligand binding model for these ligands, only some differences in amino acids involved in interactions are observed

2. 5-Alkylamino-4-phenylsulfonyloxazoles

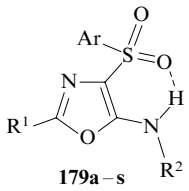
The structure–activity (towards 5-HT_6 receptors) relationship has been studied for a series of 5-alkylamino-4-phenylsulfonyloxazoles **179** stabilized by an IHB.[98, 106]

Among ligands **179a–s**, *N*-methyl (**179j**,**k**), *N*-ethyl (**179b**,**l**) and *N*-allyl derivatives (**179p**) are most active. An increase in the volume of the substituent at the 5-amino group leads to a considerable decrease in antagonistic activity. In particular, going from methyl(2-thienyl-4-phenylsulfonyloxazol-5-yl)amine (**179j**, pK_i^f = 9.36), the most potent picomolar antagonist, to 2-methoxyethyl (**179m**) and cyclopropyl derivatives (**179n**) is accompanied by, respectively, a 100- and 130-fold decrease in activity, and transition to (tetrahydrofuran-2-ylmethyl)amino derivative **179o** results in by a 428-fold decrease in activity.

Table 3. Interaction of the moieties of ligands **175** and **176** with the active site of 5-HT_6 receptors.[55, 61]

Moiety	Conformer 1 of ligand **175**	Conformer 2 of ligand **175**	Conformer 1 of ligand **176**	Conformer 2 of ligand **176**
Sulfonyl	$SO^1\cdots$HO Ser193(H5), 2.1 Å $SO^2\cdots$HO Thr196(H5), 2.2 Å	$SO^1\cdots$HO Ser193(H5), 2.2 Å $SO^2\cdots$HO Thr196(H5), 2.2 Å	$SO^1\cdots$HO Ser193(H5), 2.2 Å $SO^2\cdots$HO Thr196(H5), 2.2 Å	$SO^1\cdots$HO Ser193(H5), 2.2 Å $SO^2\cdots$HO Thr196(H5), 2.2 Å $SO^1\cdots$HN Asn288(H6), 2.4 Å
NH_2 or NHMe	$NH_2\cdots O{=}C$ Asn288(H6), 2.3 Å	$NH_2\cdots O{=}C$ Asn288(H6), 2.4 Å	C110(H3), V107(H3)	C110(H3), V107(H3), N288(H3)
Phenyl-1	V107(H3), L162(H4), A192(H5), V189(H5), A184(L4), L182(L4)	V107(H3), L162(H4), A192(H5), V189(H5), A184(L4), L182(L4)	V107(H3), L162(H4), A192(H5), V189(H5), A184(L4), L182(L4)	V107(H3), L162(H4), A192(H5), V189(H5), A184(L4), L182(L4)
Phenyl-2	V107(H3), F284(H6), F285(H6), N288(H6)	V107(H3), F284(H6), F285(H6), N288(H6)	V107(H3), F284(H6), F285(H6), N288(H6)	V107(H3), C110(H3), F285(H6), N288(H6)

Structures 179



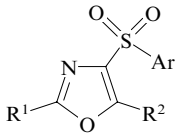
179a–s

Compounds **179**	R^1	R^2	Ar	pK_i^f	Compounds **179**	R^1	R^2	Ar	pK_i^f
a	Me	Me	Ph	8.13	**j**	2-Th	Me	Ph	9.36
b	Ph	Et	Ph	9.04	**k**	2-Th	Me	4-ClC_6H_4	8.66
c	Ph	$MeO(CH_2)_2$	Ph	7.48	**l**	2-Th	Et	4-ClC_6H_4	8.58
d	Ph	Bu^n	Ph	7.34	**m**	2-Th	$MeO(CH_2)_2$	Ph	7.35
e	Ph	Bu^i	Ph	6.55	**n**	2-Th	cyclo-C_3H_5	Ph	7.24
f	Ph	$MeO(CH_2)_3$	Ph	7.12	**o**	2-Th	$thFuCH_2$	Ph	6.72
g	Ph	$Me_2N(CH_2)_3$	Ph	5.71	**p**	2-Fu	All	Ph	8.87
h	Ph	4-$MeC_6H_4CH_2$	Ph	6.78	**r**	2-Fu	$thFuCH_2$	Ph	6.63
i	Ph	$Ph(CH_2)_2$	Ph	7.22	**s**	2-Fu	$thFuCH_2$	4-ClC_6H_4	6.23

It should be noted that, as for the above 2-phenylsulfonylanilines, transition from ligands **179b**,**j**,**k**,**l**, stabilized by an IHB, to 5-piperazino (**180**) or 5-pyrrolidino analogues (**181a–c**), in which an IHB is absent, is accompanied by a substantial decrease in activity. In particular, transition from ligand **179k** ($pK_i^f = 8.66$) to its congener **181c** ($pK_i^f = 5.14$) is accompanied by a 3342-fold decrease in activity. A similar situation is also observed in going from methyl(2-methyl-4-phenylsulfonyloxazol-5-yl)amine (**179a**, $K_i^f = 7.34$ nmol litre^{-1}) stabilized by an IHB to dimethyl(2-methyl-4-phenylsulfonyloxazol-5-yl)amine (**182**, $K_i^f = 3565.5$ nmol litre^{-1}) in which such a stabilization is lacking.[98]

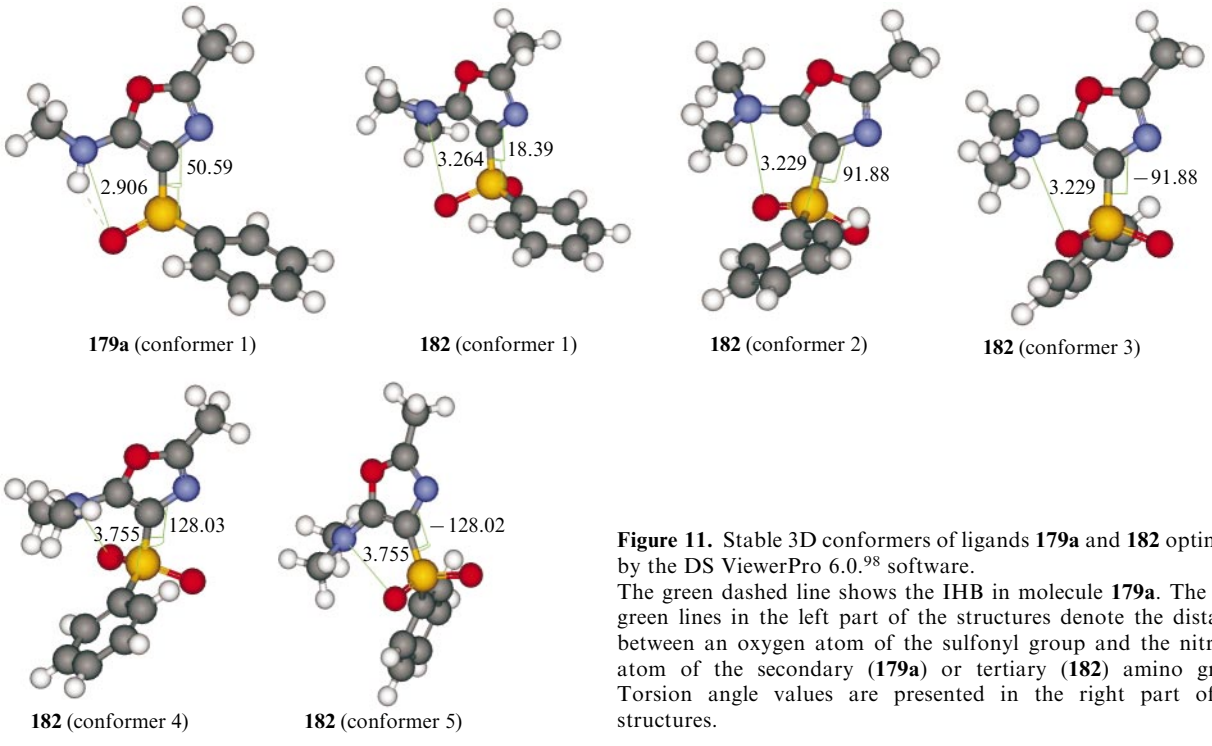
It has been shown that the molecule of amine **179a** stabilized by an intramolecular hydrogen bond has two

Structures 180–182



180, **181a–c**, **182**

Compound	R^1	R^2	Ar	pK_i^f
180	Ph	4-methylpiperazino	Ph	6.37
181a	Ph	pyrrolidino	Ph	5.96
181b	2-Th	pyrrolidino	Ph	6.10
181c	2-Th	pyrrolidino	4-ClC_6H_4	5.14
182	Me	NMe_2	Ph	6.37



179a (conformer 1) **182** (conformer 1) **182** (conformer 2) **182** (conformer 3)

182 (conformer 4) **182** (conformer 5)

Figure 11. Stable 3D conformers of ligands **179a** and **182** optimized by the DS ViewerPro 6.0.[98] software.
The green dashed line shows the IHB in molecule **179a**. The solid green lines in the left part of the structures denote the distances between an oxygen atom of the sulfonyl group and the nitrogen atom of the secondary (**179a**) or tertiary (**182**) amino group. Torsion angle values are presented in the right part of the structures.

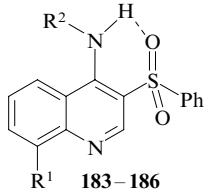
close stable conformations, whereas tertiary amine **182** has five stable conformations (Fig. 11).

In authors' opinion, the effective concentration of molecule **179a** being in the conformation favourable for binding is at least 2.5 times as high as the appropriate concentration of unstabilized molecule **182**. Such thermodynamic dilution of the effective concentration of the molecule in its most favourable conformation can be partially responsible for the higher activity of ligand **179a**. However, only this explanation does not suffice for understanding of more than 400-fold differences in ligand activities. It has also been found that, for each of the five conformations of ligand **182**, the torsion angles determining the position of the phenylsulfonyl moiety with respect to the oxazole ring plane are essentially different from those for ligand **179a**. The distance between an oxygen atom of the SO_2 group and the nitrogen atom of the amino group involved in IHB in ligand **179a** is significantly shorter (2.9 Å) than in any conformation of molecule **182** (3.2–3.8 Å). Ligand **179a** as compared with ligand **182** has a somewhat higher electric dipole moment, a smaller molecular surface accessible for the environment, a lower partition coefficient in the octanol–water system, a somewhat larger average radius of twist and a lower polarizability. On the basis of the data obtained, the authors suggested that it is precisely the topological features of molecules like **179a** and **182** that determine their activity.[98]

3. 3-Arylsulfonylquinolines

Recently, the synthesis and study of the structure–activity relationship have been reported for 3-phenylsulfonylquinolines **183**–**186**, containing a secondary amino group vicinal to the sulfonyl group and stabilized by an IHB.[70, 104, 105, 107] It should be noted that, as in the case of alkyl(4-phenylsulfonyloxazol-5-yl)amines **179**, transition from methyl(3-phenylsulfonylquinolin-4-yl)amine **183** ($pK_i^f = 7.84$) to ligands **184** ($pK_i^f = 6.24$) and **185** ($pK_i^f = 5.76$), containing the bulkier benzyl or phenyl substituent rather than the methyl group, is accompanied by a decrease in activity towards 5-HT_6 receptors by 1.5–2.0 orders of magnitude.

Structures 183–186



183–186

Compound	R^1	R^2	pK_i^f	Compound	R^1	R^2	pK_i^f
183	H	Me	8.9	**185**	H	Ph	5.76
184	H	Bn	6.24	**186**	NMe_2	Me	9.48

Picomolar 5-HT_6R antagonist *N*(4),*N*(8),*N*(8)-trimethyl-3-phenylsulfonylquinoline-4,8-diamine (**186**) ($pK_i^f = 9.48$) is 15.5 times more potent than dimethyl(3-phenylsulfonylquinolin-8-yl)amine (**70b**, $pK_i^f = 9.1$), in which the 4-methylamino group and IHB stabilization are absent, and 2.4 times more potent than methyl(3-phenylsulfonylquinolin-4-yl)amine (**183**, $pK_i^f = 7.84$), which lacks the 8-dimethylamino group.[70]

Table 4. Interaction of the moieties of ligand **186** with the active site of 5-HT_6 receptors.[99]

Fragment	Conformer 1 of ligand **186**	Conformer 2 of ligand **186**
Sulfonyl	$SO^1\cdots$HO Ser193(H5), 2.18 Å $SO^2\cdots$HO Thr196(H5), 2.24 Å	$SO^1\cdots$HO Ser193(H5), 2.25 Å $SO^2\cdots$HO Thr196(H5), 2.36 Å
Phenyl	A184(L4), A192(H5), F188(H5), L162(H4), V107(H3), V189(H5)	A184(L4), A192(H5), H167(L4), F188(H5), L162(H4), V107(H3), V189(H5)
Quinoline	F284(H6), L182(L4), T306(H7), V107(H3)	F284(H6), L182(L4), V107(H3)
Methylamino group	F284(H6), N288(H6)	C110(H3), F285(H6), T196(H5), V107(H3)
Dimethylamino group	D106(H3), T306(H7), W102(H3), Y310(H7)	D106(H3), L182(L4), T103(H3), T306(H7), W102(H3)

Molecular docking of ligand **186** has shown [70, 99] that, in the computational ligand binding model for 5-HT_6 receptors, all the ligand moieties are involved in binding to 5-HT_6R amino acids (Table 4).

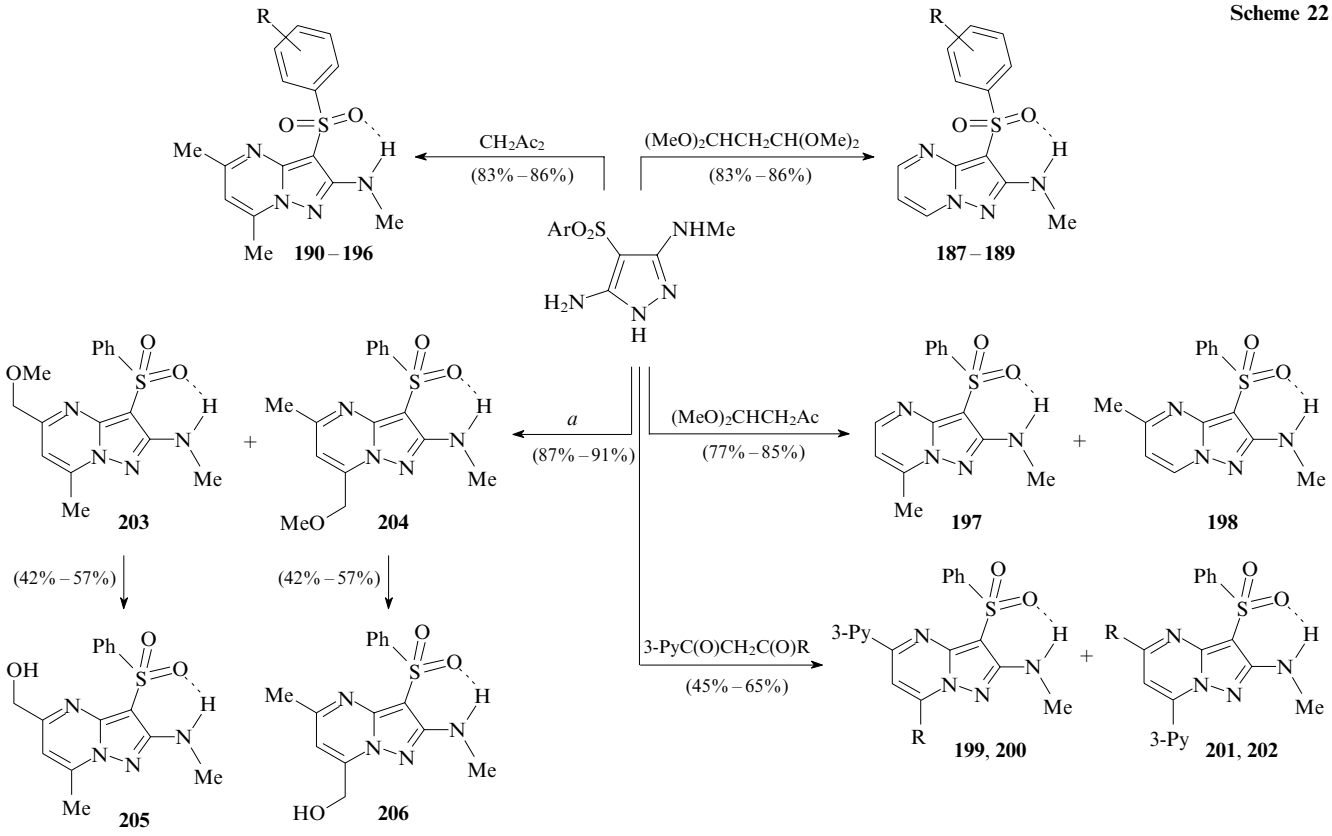
Under competitive radioligand binding conditions, antagonist **186**, on the panel comprising 35 receptors, exhibits moderate selectivity and picomolar activity towards 5-HT_6 receptors. In addition to 5-HT_6 receptors ($K_i^b = 0.11$ nmol litre^{-1}), this ligand is also active towards 5-HT_{2A}R, 5-HT_{2B}R and 5-HT_{2C}R ($K_i^b = 24$, 18 and 270 nmol litre^{-1}, respectively).[70]

4. 3-Arylsulfonyl-2-methylaminopyrazolo[1,5-a]pyrimidines

It has been recently demonstrated that 3-arylsulfonyl-2-methylaminopyrazolo[1,5-*a*]pyrimidines **187**–**196** are promising 5-HT_6R antagonists.[81, 85, 88, 89, 93, 108–120] These compounds are synthesized by the reaction of 5-amino-4-arylsulfonyl-3-methylamino-1*H*-pyrazoles with β-diketones or their analogues in acetic acid at 80–100 °C for 6–12 h. The diversity of ligands in these series has been achieved by using different diketones and their analogues: 1,1,3,3-tetramethoxypropane, pentane-2,4-dione, 4,4-dimethoxybutan-2-one, (3-pyridyl)butane-1,3-dione and sodium salt of 4-hydroxy-1-methoxypent-3-en-2-one (Scheme 22) or ethyl 3-oxobutanoate and 3-oxo-3-(3-pyridyl)propionate, 3-aminobut-2-enecarbonitrile and *N*-(1-acetyl-2-oxopropyl)-acetamide (Scheme 23).[81, 85, 88, 89]

7-Methyl- (**197**) and 5,7-dimethyl-substituted ligands **190**–**193** were found to be one order of magnitude more active than ligands **187**–**189**, **198** with the unsubstituted 7-position (see Scheme 22). For example, ligand **187** with the unsubstituted 5- and 7-positions has $pK_i^f = 8.41$, while its 5,7-dimethyl analogue **190** has $pK_i^f = 9.59$; 5-methyl-substituted ligand **198** has $pK_i^f = 8.84$, while its 7-methyl-substituted analogue **197** has $pK_i^f = 9.62$. The replacement of the methyl substituents in the 5- or 7-position of ligand **190** ($pK_i^f = 9.59$) by 3-pyridyl moieties, potentially capable of acting as PI, does not lead to a noticeable change in activity. 5-(3-Pyridyl)-substituted ligand **200** has $pK_i^f = 9.70$, while 7-(3-pyridyl)-substituted ligand **202** with

Scheme 22



(*a*) $MeOCH_2C(O)CH{=}C(ONa)Me$

Compound	R	pK_i^f	Compound	R	pK_i^f	Compound	R	pK_i^f	Compound	R	pK_i^f
187	H	8.41	**192**	4-F	9.40	**197**		9.62	**202**	Me	7.38
188	3-Cl	8.93	**193**	3-Cl	9.73	**198**		8.84	**203**		9.55
189	4-F	7.93	**194**	3-Cl-4-F	9.22	**199**	3-Py	7.44	**204**		8.12
190	H	9.59	**195**	4-OMe	8.02	**200**	Me	9.70	**205**		8.92
191	3-F	9.30	**196**	4-OH	8.7	**201**	3-Py	7.40	**206**		7.38

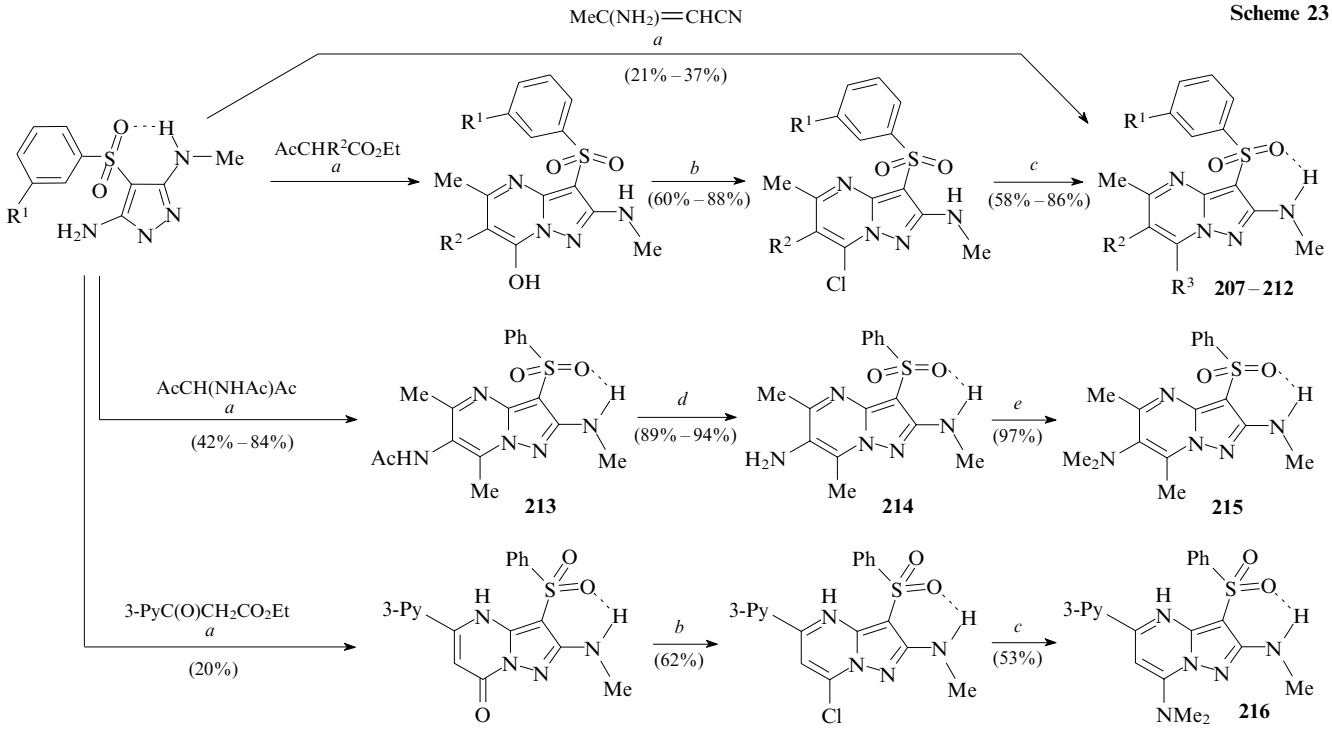
$pK_i^f = 7.38$ is inferior in activity to the latter by more than two orders of magnitude. An analogous correlation is observed upon the substitution of methoxymethyl groups for methyl ones. In particular, the activity of 7-methyl-5-methoxymethyl ligand **203** ($pK_i^f = 9.55$) is close to the activity of 5,7-dimethyl ligand **190** ($pK_i^f = 9.59$), whereas the activity of 5-methyl-7-methoxymethyl ligand **204** ($pK_i^f = 8.12$) is 1.5 orders of magnitude lower than the activity of the latter. Hydroxymethyl derivatives **205** and **206** are one order of magnitude less active than corresponding methoxymethyl ligands **203**, **204**. However, in this case, too 5-hydroxymethyl-7-methylpyrazolopyrimidine **205** ($pK_i^f = 8.92$) is 1.5 orders of magnitude more active than its isomer **206** ($pK_i^f = 7.38$). And finally, it should be noted that, in this series of ligands, 3-chlorophenylsulfonyl derivative **193** ($pK_i^f = 9.73$) exhibits the highest activity towards 5-HT_6 receptors.

In the series of 2,6- and 2,7-diamines **207**–**216**, most of the ligands are active at picomolar concentrations, 7-amino-5-methyl-2-methylamino-3-phenylsulfonyl-6-chloropyrazolo[1,5-*a*]pyrimidine (**209**, $pK_i^f = 9.85$) being the most active among them. A surprising result is that transition from ligand **209**, containing the phenylsulfonyl moiety, to its analogue **210** ($pK_i^f = 7.73$), containing the 3-chlorophenylsulfonyl moiety, is accompanied by a very significant decrease in activity (by more than two orders of magnitude).

It should also be noted that the activity of these ligands stabilized by the IHB involving the 2-NHMe substituent is, as a rule, noticeably higher than the activity of the 2-SMe-substituted analogues (considered above) stabilized by electronic interaction of the 2-SMe group and the phenyl ring (Table 5).

Noteworthy is not only the high antagonistic activity of these ligands against 5-HT_6 receptors but also their extremely high selectivity. In particular, AVN-216 (**190**), on the panel comprising 67 enzymes, receptors, ion channels and transporters, showed the selectivity towards 5-HT_6 receptors exceeding 50 000. The only exception is 5-HT_{2B} receptor for which AVN-216 has $IC_{50}^b = 1.63$ nmol litre^{-1}. However, studying AVN-216 by a functional assay method has shown that this ligand is the complete 5-HT_{2B}R antagonist with $IC_{50}^b = 5.13$ μmol litre^{-1}. Note also that, under functional assay conditions, AVN-216 also exhibited low activity towards the hERG potassium channel (> 30 μmol litre^{-1}).[31,89]

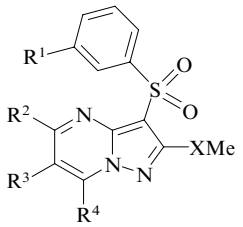
Scheme 23



(*a*) AcOH, 80–100 °C, 12 h; (*b*) $POCl_3$, sulfolane, 70 °C, 3 h; (*c*) amine, dioxane or dioxane–MeOH, or PhMe, Δ, 2–3 h; (*d*) KOH, MeOH, H_2O, Δ, 72–100 h; (*e*) 1) HCHO, $NaBH_4$, EtOH, 20–25 °C, 12 h; 2) H_2SO_4

Compound	R^1	R^2	R^3	pK_i^f	Compound	R^1	R^2	R^3	pK_i^f
207	H	H	NH_2	9.52	**212**	H	H	NMe_2	9.46
208	Cl	H	NH_2	9.66	**213**	H	NHAc	Me	9.33
209	H	Cl	NH_2	9.85	**214**	H	NH_2	Me	9.29
210	Cl	Cl	NH_2	7.73	**215**	H	NMe_2	Me	9.68
211	H	H	NHMe	9.24	**216**	H	H	NMe_2	8.35

Table 5. Antagonistic activity of substituted 2-methylsulfanyl- and 2-methylamino-3-arylsulfonylpyrazolo[1,5-*a*]pyrimidines against 5-HT_6 receptors.[81, 85, 89]



97, **100**, **106**, **107**, **128**, **130**, **133**, **190**, **193**, **203**, **204**, **207**, **214**, **215**

R^1	R^2	R^3	R^4	X = S		X = NH	
				ligand	pK_i^f	ligand	pK_i^f
H	Me	H	Me	**97**	8.92	**190**	9.59
Cl	Me	H	Me	**100**	9.12	**193**	9.73
H	$MeOCH_2$	H	Me	**106**	8.49	**203**	9.55
H	Me	H	$MeOCH_2$	**107**	6.81	**204**	8.12
H	Me	NH_2	Me	**128**	9.4	**214**	9.29
H	Me	NMe_2	Me	**130**	9.0	**215**	9.68
H	Me	H	NH_2	**133**	9.15	**207**	9.52

Table 6. Interactions of the moieties of ligands **190**, **212** and **215** with the active site of 5-HT_6 receptors.[100]

Moiety	Conformer 1 of ligand **190**	Conformer 2 of ligand **190**	Conformer 1 of ligand **212**	Conformer 2 of ligand **212**	Conformer 1 of ligand **215**	Conformer 2 of ligand **215**
Sulfonyl	S═O^1···HO Ser193(H5), 2.23 Å S═O^1···H_2N Asn288(H6), 2.53 Å S═O^2···HO Thr196(H5), 2.30 Å	S═O^1···HO Ser193(H5), 2.23 Å S═O^1···H_2N Asn288(H6), 2.20 Å S═O^2···HO Thr196(H5), 2.20 Å	S═O^1···HO Thr306(H7), 2.12 Å S═O^2···H_2N Asn288(H6), 2.37 Å	S═O^1···HO Thr306(H7), 2.16 Å S═O^2···H_2N Asn288(H6), 2.52 Å	S = O^1···HO Thr306(H7), 2.1 Å S = O^2···H_2N Asn288(H6), 2.41 Å	S = O^2···H_2N Asn288(H6), 2.48 Å
Phenyl	A192(H5), F188(H5), L162(H4), T196(H5), V107(H3)	A192(H5), F188(H5), L162(H4), V107(H3)	L182(L4), W102(H3)	A192(H5), F188(H5), V107(H3), V189(H5)	F302(H7), L182(L4), T103(H3), T306(H7), W102(H3)	F302(H7), L182(L4), T103(H3), T306(H7), V107(H3), W102(H3)
Pyrazolo-pyrimidine	F284(H6), C110(H3), T306(H7), V107(H3)	F284(H6), N288(H6), V107(H3)	A184(L4), A192(H5), F284(H6), F285(H6), L182(L4), V107(H3), V189(H5)	C110(H3), F284(H6), V107(H3)	A184(L4), A192(H5), F285(H6), L182(L4), V107(H3), V189(H5)	G309(H7), F284(H6), F285(H6), T306(H7), V107(H3)
NHMe	L182(L4), T103-Me(H3)	C110(H3),V107(H3)	C110(H3), F284(H6), F285(H6)	A184(H5), A192(H5), V189(H5)	C110(H3), F285(H6)	A192(H5), V107(H3)
NMe_2			A192(H5), T196(H5), V107(H3)	A192(H5), T196(H5), V107(H3)	A184(L4), A192(H5), F188(H5), V189(H5)	G309(H7), C110(H3), W281(H6), Y310(H7)

The high selectivity is also exhibited under competitive radioligand binding conditions by picomolar ligands **207**, **214** and **215** on the panel comprising 33 receptors: the selectivity towards 5-HT_6 receptors is >3300 for ligand **207**, >1900 for ligand **214** and >4800 for ligand **215**.[31, 81, 118]

Molecular docking of this series of ligands has demonstrated that all moieties of the ligands are involved in binding to the 5-HT_6R amino acids. In particular, upon interaction of AVN-216 (**190**) with 5-HT_6 receptors, hydrogen bonds are formed between the oxygen atoms of the SO_2 group and the hydroxyl groups of Ser193(H5) and Thr196(H5), and one of the oxygen atoms form an extra hydrogen bond with Asn288(H6). There are also many hydrophobic interactions of the methylamino group and phenyl and heterocyclic moieties with the amino acids of the 5-HT_6R active site (Table 6).[100]

The computational model of binding of ligands **212** and **215** to 5-HT_6 receptors also reveals the interactions of all ligand moieties with the active site and stabilization of the ligands by an IHB. However, the interactions of the oxygen atoms of the SO_2 group of these ligands differ from the interactions of the SO_2 group of AVN-216 (**190**). In particular, one of the oxygen atoms of the SO_2 group in ligands **212** and **215** forms a hydrogen bond with the hydroxyl group of Thr306(H7) and the other is hydrogen-bonded to the amino group of Asn288(H6).

In the computational model of binding of ligands **200** and **216** to 5-HT_6 receptors, all the ligand moieties are involved in interaction with the amino acids of the 5-HT_6R active site, and the IHB persists (Table 7). However, interactions of the oxygen atoms of the SO_2 group differ from those of the SO_2 group in ligands **212** and **215** and are the same as the interactions of the oxygen atoms of the SO_2 group in AVN-216 (**190**). It is worth noting that, in the computational binding model of ligands **190**, **210, 212**, **215** and **216**, interactions of Asp106(H3) with the ligands through protonation of their amino groups or pyridine ring are absent.

2-Methylamino-3-phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[5,1-*b*]quinazolines **217** and **218**, 2-methylamino-3-phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]quinazolines **219** and **220**, 2-methylamino-8-methyl-3-phenylsulfonyl-7,8-dihydro-6*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidine (**221**) and 2-methylamino-3-phenylsulfonyl-7,8-dihydro-6*H*-cyclopenta[*e*]pyrazolo[1,5-*a*]pyrimidine (**222**) are also known.[101, 121, 122] These ligands have been synthesized by the reaction of corresponding 3-aminopyrazoles with 2-formyl- or 2-acetylcycloalkanones in acetic acid at 80–100 °C for 6–12 h.

Like 2-methylamino-3-arylsulfonylpyrazolo[1,5-*a*]pyrimidines considered above, ligands **217**–**222** are stabilized by an IHB and are more active than their analogues **167**–**170**, **223**, in which the IHB is lacking. For example, transition from ligand **222** (pK_i^f = 9.43) to its 2-dimethylamino-substituted analogue **223** (pK_i^f = 7.54) is accompanied by a 77-fold decrease in antagonistic activity.

On the basis of X-ray crystallography and 3D computational modelling, it has been shown that the structure (bond lengths, torsion angles, dipole moment direction) of IHB-stabilized ligands, for example, ligand **222**, strongly differs from the structure of ligand **223**, which lacks intramolecular hydrogen bonds. It has been suggested that this largely accounts for the significant difference in their activity towards 5-HT_6 receptors.[101]

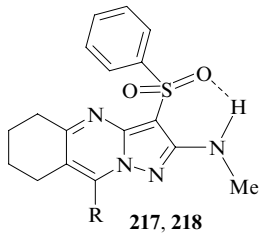
Ligands **217**–**222** are not only picomolar 5-HT_6R antagonists but also have high selectivity of interaction with 5-HT_6 receptors. For example, pyrazolopyrimidine **222** (K_i^b = 88 pmol litre^{-1}), on the panel comprising 55 therapeutic targets, including GPC receptors, ion channels and transporters, showed more than 11 000-fold selectivity towards 5-HT_6 receptors.[102]

Table 7. Interactions of the moieties of ligands **200** and **216** with the active site of 5-HT_6 receptors.[a]

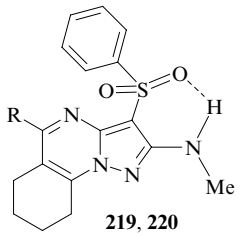
Moiety	Conformer 1 of ligand **200**	Conformer 2 of ligand **200**	Conformer 1 of ligand **216**	Conformer 2 of ligand **216**
Sulfonyl	S=O^1···HO Ser193(H5), 2.1 Å S=O^2···HO Thr196(H5), 2.2 Å	S=O^1···HO Ser193(H5), 2.2 Å S=O^2···HO Thr196(H5), 2.2 Å	S=O^1···HO Ser193(H5), 2.7 Å S=O^2···HO Thr196(H5), 2.8 Å S=O^1···H$_2$N Asn288(H6), 2.3 Å	S=O^1···HO Ser193(H5), 2.7 Å S=O^2···HO Thr196(H5), 2.8 Å S=O^1···H$_2$N Asn288(H6), 2.3 Å
Phenyl	A192(H5), L182(L4), V189(H5)	A192(H5), F284(H6), F302(H7), L182(L4)) V189(H5)	A184(L4), A192(H5), L182(L4), F302(H7), V189(H5)	F302(H7), N288(H6), V189(H5)
Pyrazolo-pyrimidine	Asn288(H6), F284(H6), V107(H3)	C110(H3), F284(H6), T306(H7), V107(H3)	F284(H6), F285(H6), L182(L4), V107(H3)	V107(H3), L182(L4)
Pyridyl	F302(H7), L182(L4)	A184(L4), F188(H5), H167(L4), L162(H4), L182(L4), T103(H3)	C110(H3), F284(H6), F285(H6), G309(H7), W281(H6), Y310(H7)	C110(H3), F284(H6), F285(H6), G309(H7), W281(H6), Y310(H7)
NHMe	C110(H3)	C110(H3), F284(H6), W281(H6)	F188(H5), L162(H4), L182(H4)	C110(H3), F284(H6), T306(H7)
NMe_2			L182(L4), T103(H3), W102(H3)	L182(L4), T103(H3), W102(H3)

[a] Unpublished data generously supplied by Dr. I M Okun (ChemDiv, Inc., United States).

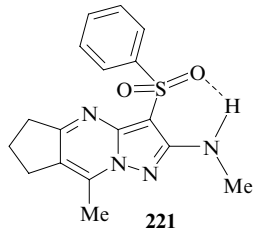
Structures 217–223



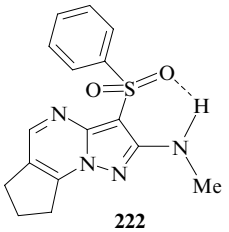
217, **218**



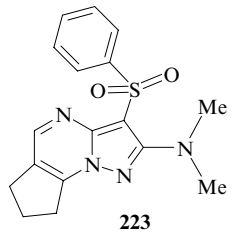
219, **220**



221



222



223

Compound	R	pK_i^b	pK_i^f	Compound	R	pK_i^b	pK_i^f
217	H	9.30	9.27	**220**	Me	9.31	–
218	Me	9.59	–	**221**		9.69	9.38
219	H	9.95	9.59	**222**		10.06	9.43

For the IHB-stabilized ligands without PI considered in this section, the PM_4 has been suggested (Fig. 12); the high activity of the ligands is achieved only when the methylamino group acts as the IHBD.

Attempts to use the hydroxyl group as the IHBD in design of 5-HT_6R modulators have not produce desired results. In particular, it has been demonstrated that 2-phenylsulfonylphenol (**224**, $pK_i^f = 5.44$) is strongly inferior in activity (by one or two orders of magnitude) to 2-phenylsulfonylanilines **175** ($pK_i^f = 6.31$) and **176** ($pK_i^f = 7.61$). Moreover, ligand **224** is less active that unsubstituted phenylsulfonylbenzene (**66**, $pK_i^f = 5.94$) and 2-methoxyphenylsulfonylbenzene (**67**, $pK_i^f = 6.06$).

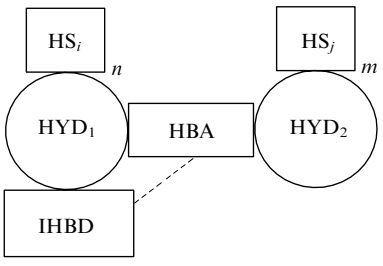
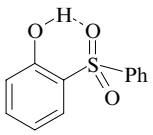


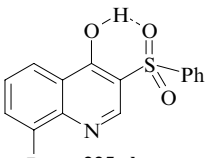
Figure 12. Simplified PM_4 of the ligands stabilized by an IHB and not containing the PI moiety.[105]

A similar situation is also observed for IHB-stabilized 4-hydroxy-3-phenylsulfonylquinoline (**225a**) and 4-hydroxy-3-phenylsulfonyl-8-fluoroquinoline (**225b**), which are much less potent than 4-methylamino-3-phenylsulfonylquinoline (**183**, $K_i^f = 5.1$ nmol litre^{-1}), 4-methylamino-3-phenylsulfonyl-8-fluoroquinoline (**226**) and even 4-methoxy-3-phenylsulfonylquinoline (**227**).[70]

Structures 224–227

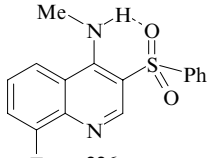


224

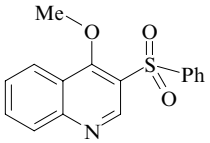


225a,**b**

R = H (**a**), F (**b**)



226



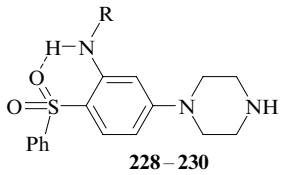
227

Compound	K_i^f/nmol litre^{-1}
225a	1165
225b	1546
226	4.7
227	401.0

VII. 5-HT_6 receptor modulators stabilized by intramolecular hydrogen bond and containing a PI moiety

5-HT_6R modulators stabilized by an IHB and containing a PI moiety have been reported. Examples of such ligands are 2-phenylsulfonyl-5-piperazinoanilines **228**–**230**. The introduction of the piperazine substituent into the molecules of 2-phenylsulfonylanilines **175** ($pK_i^f = 6.31$) and **176** ($pK_i^f = 7.61$) results in a very strong (by more than two orders of magnitude) increase in the antagonistic activity of new ligands **228** ($pK_i^f = 8.78$) and **229** (AVN-561, $pK_i^f = 9.80$).[55, 61]

Structures 228–230



228–**230**

Compound	R	pK_i^f
228	H	8.78
229 (AVN-561)	Me	9.80
230	Ac	8.08

Picomolar AVN-561 antagonist (**229**, $K_i^b = 160$ pmol litre^{-1}) is a multimodal ligand since, at a concentration of 1 mol litre^{-1}, it inhibits serotonin 5-HT_{1B} (by 79%), 5-HT_{2A} (by 92%), 5-HT_{2B} (by 86%), 5-HT_{2C} (by 63%) and 5-HT_6 (by 107%) central imidazoline receptors I_2 (by 73%) and non-selective α_2 (by 68%) and β (by 66%) adrenoreceptors.[55, 123]

According to MD study, in the computational model of binding of 5-HT_6 receptors to ligands **228**–**230** (Table 8), all molecular moieties of the latter are involved in interactions with the amino acids of the receptor active site; the models imply that the ligands are stabilized by an intramolecular hydrogen bond and there is interaction between the most basic nitrogen atom of the piperazine ring and Asp106(H3). Noteworthy is the similarity of interactions of the molecular moieties of ligands **228**–**230** with the amino acids of the 5-HT_6R active site, on the one hand, and a

Table 8. Interactions of the moieties of ligands **228** – **230** with the active site of 5-HT_6 receptors.[61]

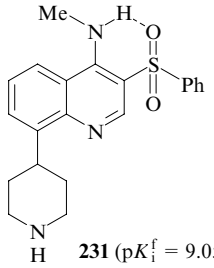
Moiety	Conformer 1 of ligand **228**	Conformer 2 of ligand **228**	Conformer 1 of ligand **229**	Conformer 2 of ligand **229**	Conformer 1 of ligand **230**	Conformer 2 of ligand **230**
Sulfonyl	S═O^1···HO Ser193(H5), 2.11 Å S═O^2···HO Thr196(H5), 2.20 Å	S═O^1···HO Ser193(H5), 2.12 Å S═O^1···H_2NCO Asn288(H6) ,2.47Å S═O^2···HO Thr196(H5), 2.19 Å	S═O^1···HO Ser193(H5), 2.11 Å S═O^2···HO Thr196(H5), 2.20 Å	S═O^1···HO Ser193(H5), 2.12 Å S═O^1···H_2NCO Asn288(H6), 2.50 Å S═O^2···HO Thr196(H5), 2.26 Å	S═O^1···HO Ser193(H5), 2.11 Å S═O^2···HO Thr196(H5), 2.20 Å	S═O^1···HO Ser193(H5), 2.11 Å S═O^2···HO Thr196(H5), 2.25 Å
Piperazine	H_2N^+ ^-O_2C Asp106(H3), 2.17 Å	H_2N^+ ^-O_2C Asp106(H3), 1.84 Å	H_2N^+ ^-O_2C Asp106(H3), 2.14 Å	H_2N^+ ^-O_2C Asp106(H3), 2.07 Å	H_2N^+ ^-O_2C Asp106(H3), 2.15 Å	H_2N^+ ^-O_2C Asp106(H3), 2.02 Å H_2N^+···HO Thr310(H7), 2.41 Å
Phenyl	A184(L4), A192(H5), F188(H5), H167(L4), L162(H4), L182(L4), T103(H3), V107(H3), V189(H5)	A184(L4), A192(H5), F188(H5), H167(L4), V107(H3), L162(H4), S185(L4), V189(H5)	A184(L4), A192(H5), F188(H5), L162(H4), T103(H3), V107(H3), V189(H5)	A184(L4), A192(H5), F188(H5), L162(H4), V189(H5), V107(H3)	A184(L4), A192(H5), F188(H5), H167(L4), L162(H4), V107(H3), V189(H5)	A184(L4), A192(H5), F188(H5), H167(L4), L162(H4), V107(H3), V189(H5)
Aminophenyl	F284(H6), F285(H6), F302(H7), L182(L4), N288(H6), V107(H3)	F284(H6), F285(H6), F302(H7), L182(L4), N288(H6), V107(H3)	₀110(H3), F284(H6), F285(H6), F302(H7), L182(L4), N288(H6), V107(H3)	₀110(H3), F284(H6), F285(H6), L182(L4), N288(H6), V107(H3)	₀110(H3), F284(H6), F285(H6), L182(L4), N288(H6), V107(H3)	F284(H6), F285(H6), L182(L4), N288(H6), V107(H3)
Piperazine	C110(H3), D106(H3), L182(L4), T306(H7), Y310(H7)	C110(H3), D106(H3), L182(L4), T306(H7), Y310(H7)	C110(H3), D106(H3), F284(H6), L182(L4), T306(H7), V79(H2), W102(H3), Y310(H7)	C110(H3), D106(H3), F284(H6), L182(L4), T306(H7), W102(H3), Y310(H7)	C110(H3), F284(H6), L182(L4), T306(H7), W102(H3), Y310(H7)	L182(L4), T306(H7), W102(H3), Y310(H7)
AcNH					F284(H6), F302(H7), L182(L4), N288(H6)	C110(H3), F285(H6), V107(H3)

noticeable difference in the antagonistic activity of these ligands against 5-HT_6R receptors, on the other hand.[61]

On the basis of MD data, dependences of the activity of phenylsulfonylbenzenes **37**–**39**, **66**–**68**, **175**–**178** and **228**–**230** on the number of 5-HT_6R amino acids involved in the computational binding model, as well as on the total surface of interacting amino acids, have been obtained. These dependences demonstrate that the antagonistic activity of such ligands, with higher confidence ($P < 0.0001$) and a Spearman correlation coefficient $r = 0.9$, correlates with the number of amino acids interacting with the ligands.[55]

4-Methylamino-8-(piperazin-4-yl)-3-phenylsulfonylquinoline (**231**), belonging to the same ligand type, has been synthesized and studied. This is a multimodal ligand exhibiting picomolar antagonistic activity against 5-HT_6 receptors.[102]

Structure 231



231 ($pK_i^f = 9.05$)

Under competitive radioligand binding conditions, ligand **231,** on the panel comprising 33 receptors, exhibited picomolar activity towards serotonin 5-HT_6 (IC_{50}^b = 116 pmol litre^{-1}) and 5-HT_{2A} receptors (IC_{50}^b = 318 pmol litre^{-1}) and nanomolar activity towards serotonin 5-HT_{2B}, 5-HT_{2C} and 5-HT_7 receptors; α_{2A}, α_{2B}, α_{2C} and β_1 adrenoreceptors; D_1 and D_{2S} dopamine receptors; H_3 histamine receptors and I_2 central imidazoline receptors (see [70, 102]).

Receptor	IC_{50}^b/nmol litre^{-1}	Receptor	IC_{50}^b/nmol litre^{-1}
5-HT_{2B}	33	β_1	668
5-HT_{2C}	25	D_1	748
5-HT_7	537	D_{2S}	298
α_{2A}	177	H_3	497
α_{2B}	321	I_2	292

In the computational model of binding of ligand **231** (Table 9) to 5-HT_6 receptors obtained by the MD method,[104] all molecular moieties of the ligand interact with the amino acids of the receptor active site, ligand stabilization by an IHB is retained, and there is an interaction between the protonated most basic piperazine nitrogen atom and Asp106(H3).

IHB-stabilized (3-arylsulfonylpyrazolo[1,5-*a*]pyrimidin-2-yl)amines **232**–**245** containing a PI moiety in different positions of the heterocycle have been studied. In particular, 2-dimethylaminoethylamino- (**232**, $pK_i^f = 5.59$) and 2-dimethylaminopropylamino-5,7-dimethyl-3-phenylsulfonylpyrazolo[1,5-*a*]pyrimidines (**233**, $pK_i^f = 6.12$) are 3–4 orders of magnitude less active than their analogue AVN-216 (**190**, $pK_i^f = 9.59$) in which there is a methylamino group in position 2 but PI is absent. In authors' opinion, the observed effect is explained by steric hindrance of bulky substituents, which leads to ligand conformations preventing their efficient binding to the active site of 5-HT_6 receptors.[89]

Table 9. Interactions of the moieties of ligand **231** with the active site of 5-HT_6 receptors.[104]

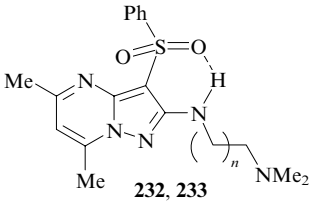
Moiety	Conformer 1 of ligand **231**	Conformer 2 of ligand **231**
Sulfonyl	$SO^1\cdots HO$ Ser193(H5), 2.11 Å $SO^2\cdots HO$ Thr196(H5), 2.18 Å	$SO^1\cdots HO$ Ser193(H5), 2.07 Å $SO^2\cdots HO$ Thr196(H5), 2.27 Å
Piperazine	$H_2N^+ \ ^-O_2C$ Asp106(H3), 2.21 Å	$H_2N^+ \ ^-O_2C$ Asp106(H3), 1.71 Å
NHMe	$MeNH\cdots O$ Thr196(H5), 2.31 Å	
Phenyl	A192(H5), F188(H5), H167(L4), L162(H4), V189(H5)	A192(H5), F188(H5), L162(H4), V107(H3)
Quinoline	C110(H3), F284(H6), F285(H6), L182(L4), N288(H6), V107(H3)	F284(H6), F302(H7), L182(L4), N288(H6), V189(H5)
NHMe	F285(H6)	A184(L4), L182(L4), N288(H6), V189(H5)
Piperazine	D106(H3), L182(L4), T306(H7), W102(H3), Y310(H7)	T103(H3), T306(H7), W102(H3), Y310(H7)

The most potent ligands are 5- (**234**), 6- (**235**–**238**) and 7-aminoalkyl derivatives (**239**–**242**), as well as 7-aminoalkylamino derivatives **243**–**245**, synthesized by a scheme analogous to that for ligands **152**–**164**. However, ligands **234**–**245** are also noticeably inferior in antagonistic activity to AVN-216 (**190**).[81]

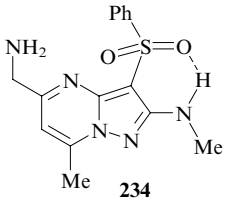
7-Methyl-2-methylamino-3-phenylsulfonyl-6,7,8,9-tetrahydropyrazolo[1,5-*a*]pyrido[3,4-*d*]pyrimidine (**246**), 7-methyl-2-methylamino-3-phenylsulfonyl-5,6,7,8-tetrahydropyrazolo[1,5-*a*]pyrido[3,4-*e*]pyrimidine (**247**, AVN-322) and their analogues, stabilized by IHB (Fig. 13) and containing a highly basic tertiary amino group of the annelated tetrahydropyridine ring as PI, are also known. These ligands have been synthesized by analogy with ligands **187**–**206**.[90, 91, 92] It should be noted that, in this case, too, the activity of ligands **246** (K_i^b = 0.82 nmol litre^{-1}) and **247** (K_i^b = 0.39 nmol litre^{-1}) is somewhat lower than the activity of their analogues **219** (K_i^b = 0.499 nmol litre^{-1}) and **221** (K_i^b = 0.112 nmol litre^{-1}), which do not contain PI.

Computational models of binding of ligands **246** and **247** to 5-HT_6 receptors obtained by the MD method[103] demonstrate that all the moieties of both conformers of AVN-322 (**247**) are involved in interaction with the amino acids of the receptor active site (Table 10); the amino acid environment of the conformers in their computational binding models is different. In particular, under MD conditions, both conformers form hydrogen bonds involving both oxygen atoms of the SO_2 group.

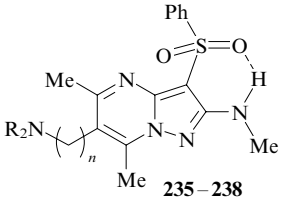
Structures 232–245



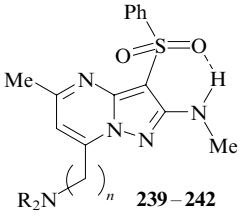
232, 233



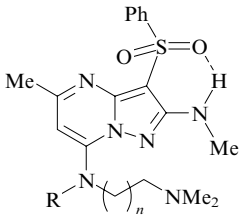
234



235–238



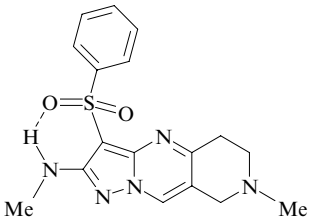
239–242



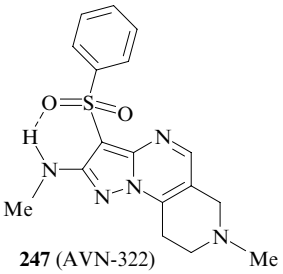
243–245

Compound	R	*n*	pK_i^f	Compound	R	*n*	pK_i^f
232		1	5.59	**239**	H	1	8.73
233		2	6.12	**240**	Me	1	8.74
234			9.01	**241**	H	2	8.51
235	H	1	9.19	**242**	Me	2	7.47
236	Me	1	9.15	**243**	H	1	7.16
237	H	2	8.86	**244**	Me	1	7.65
238	Me	2	8.68	**245**	H	2	6.91

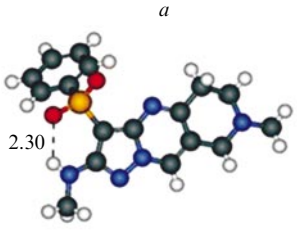
Structures 246, 247



246



247 (AVN-322)



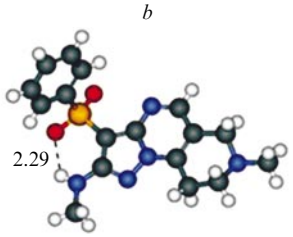


Figure 13. 3D structures of ligands **246** (*a*) and **247** (AVN-322) (*b*) obtained from X-ray crystallography data.[103]

Table 10. Interactions of the moieties of AVN-322 (**247**) with the active site of 5-HT_6 receptors.[103]

Moiety	Conformer 1 of AVN-322 (**247**)	Conformer 2 of AVN-322 (**247**)
Sulfonyl	$SO^1\cdots$HO Ser193(H5), 2.29 Å $SO^2\cdots H_2N$ Asn288(H6), 2.34 Å	$SO^1\cdots$HO Ser193(H5), 2.28 Å $SO^2\cdots H_2N$ Asn288(H6), 2.30 Å
$MeHN^+$	$MeHN^+ \ ^-O_2C$ Asp106(H3)	$MeHN^+$ L182(L4)
Phenyl	A192(H5), F188(H5), L162(H4), V107(H3), N192(H5)	A192(H5), F188(H5), V107(H3)
Methyltetrahydropyridine	C110(H3), T306(H7), Y310(H7)	L182(L4), W102(H3)
Pyrazolopyrimidine	F284(H6), F285(H6), T306(H7), V107(H3), Y310(H7)	V107(H3)
NHMe	L182(L4), T103-Me(H3)	C110(H3), F285(H3)

One of the O atoms forms a hydrogen bond with the hydroxyl group of Ser193(H5) and the other is hydrogen-bonded to the amino group of Asn288(H6). The computational binding models of both conformers show interaction of the MeN group of the tetrahydropyridine ring with Asp106(H3) in one case and with L182(L4) in the other case. The moieties of the conformer binding to Asp106(H3) have a richer amino acid environment and, accordingly, stronger hydrophobic interactions than the other conformer.

The high selectivity of the ligands of this type is noteworthy. In particular, AVN-322 (**247**), which is at the stage of clinical trials, on the panel comprising 69 receptors and other therapeutic targets, showed the selectivity towards 5-HT_6 receptors above 2500. This ligand exhibited weak activity towards 5-HT_{2B}R (IC_{50}^f = 6.16 μmol litre^{-1}) and the hERG potassium channel (IC_{50} = 54.2 μmol litre^{-1}). It is worth noting that its linear analogue **246** is 108 times as active as AVN-322 towards the hERG channel (IC_{50} = 0.5 μmol litre^{-1}).[31]

For the ligands considered in this section, which are stabilized by IHB and contain PI, PM_5 has been suggested (Fig. 14).

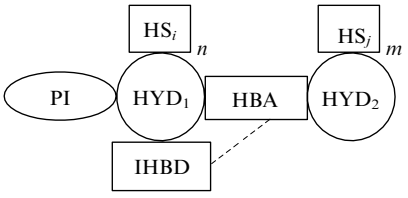


Figure 14. Simplified PM_5 of the ligands stabilized by an IHB and containing the PI moiety.[99]

VIII. Clinical trials of 5-HT$_6$ receptor modulators

Numerous clinical trials (phases I and II) of sulfonyl-containing 5-HT$_6$R antagonists — drug candidates for the treatment of schizophrenia, Alzheimer's disease and obesity — have been carried out,[15, 31, 45] and adverse effects associated with the use of these compounds have never been reported.

Many clinical trials for various reasons proved inconclusive; however, very encouraging results have been achieved in this area in recent years. In particular, phase I clinical trials of selective ligand AVN-322 (**247**) (Avineuro Pharmaceuticals, Inc.) have been successfully completed;[31, 124] this ligand is suggested as a possible drug for the treatment of Alzheimer's disease. In 2011, the same company announced [125] the completion of phase II clinical trials of AVN-211 (**97**),[126, 127] which was administered at a daily dose of 4 mg to 42 patients with schizophrenia taking atypical antipsychotics. These clinical trials have not revealed side effects in patients receiving AVN-211 and demonstrated reduction of psychotic disorders and some improvement of elements of cognitive dysfunction in schizophrenia.[125] In 2013, more extensive phase II clinical trials of AVN-211 were started in 80 patients with schizophrenia receiving stable antipsychotic therapy.

In 2012, H Lundbeck company has completed phase II clinical trials of drug candidate Lu AE58054,[128] which were conducted for 24 weeks in 278 patients suffering from moderate Alzheimer's disease and taking Donepezil. Compound Lu AE58054, which is a selective 5-HT$_6$R antagonist, has shown an improvement of cognitive functions in patients suffering from Alzheimer's disease, as compared with placebo. Further clinical trials of Lu AE58054 for the treatment of this disease are planned.

* * *

Due to the unique diversity of the known 5-HT$_6$ receptor modulators, significant recent progress has been achieved in designing selective, pseudoselective and multimodal picomolar drug candidates. There have been suggested new pharmacophore models for the development of picomolar 5-HT$_6$R modulators with the structure stabilized by an intramolecular hydrogen bond or n–π-electron interactions. Currently, only one ligand simultaneously stabilized by an IHB and n–π-electron interaction is known. Such ligands, as well as the ligands stabilized by several intramolecular hydrogen bonds, seem to be rather promising from the viewpoint of activity and selectivity towards 5-HT$_6$ receptors. And finally, encouraging results of clinical trials have been reported for drug candidates AVN-211 for treatment of patients with schizophrenia receiving stable antipsychotic therapy, and Lu AE58054 for the improvement of cognitive functions in patients suffering from moderate Alzheimer's disease and taking Donepezil. The medical community is looking forward to further progress in using 5-HT$_6$R modulators for the treatment of diseases of the central nervous system.

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