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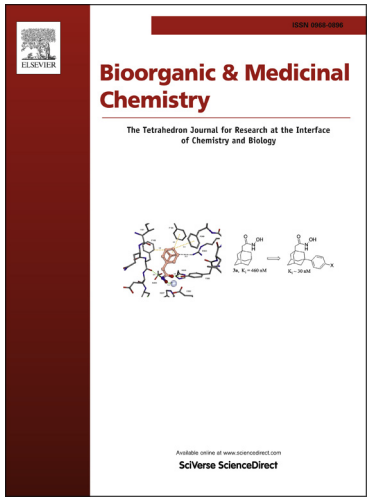

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PII: S0968-0896(13)00500-2
DOI: http://dx.doi.org/10.1016/j.bmc.2013.05.051
Reference: BMC 10877

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 27 March 2013
Revised Date: 24 May 2013
Accepted Date: 24 May 2013

Please cite this article as: Hayat, F., Cho, S., Rhim, H., Ambily Nath, I.V., Pae, A.N., Lee, J.Y., Choo, D.J., Choo, H.P., Design and synthesis of novel series of 5-HT_6 receptor ligands having indole, a central aromatic core and 1-amino-4methyl piperazine as a positive ionizable group, *Bioorganic & Medicinal Chemistry* (2013), doi: http://dx.doi.org/10.1016/j.bmc.2013.05.051

Design and synthesis of novel series of 5-HT$_6$ receptor ligands having indole, a central aromatic core and 1-amino-4methyl piperazine as a positive ionizable group

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Abstract:

The exclusive distribution of 5-HT$_6$ receptor in the brain regions and high affinity for antipsychotic and antidepressant drugs makes 5-HT$_6$ receptor a promising target in treatment of CNS diseases. Based on a pharmacophore model reported in the literature, we designed and synthesized a novel series of 5-HT$_6$ receptor ligands having indole as a central aromatic core and 1-amino-4-methyl piperazine as positive ionizable group. Out of 32 compounds we have successfully identified 10 new compounds as 5-HT$_6$ receptor antagonists. The structure-activity relationship (SAR) studies have been carried out by mapping the compounds with the 3D QSAR model.

Keywords:

5-HT$_6$ receptor antagonist, 1-amino-4-methylpiperazine, Sulfonyl indole, 3D QSAR, pharmacophore mapping

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1. Introduction

5-Hydroxytryptamine (5-HT, serotonin) is a major neurotransmitter in both the central and peripheral nervous system, which modulates a variety of important biological processes by interaction with a family of receptors called 5-HT receptors. These receptors are divided into seven subclasses (5-HT_{1-7}), 5-HT_6 being the most recently discovered and cloned member of this class. The 5-HT_6 receptor is almost exclusively expressed in the central nervous system, especially in the areas associated with learning and memory. A thorough literature search reveals that several antipsychotic and antidepressant drugs have significant affinity for 5-HT_6 receptors.[1] The specific localization of 5-HT_6 receptors in CNS and high affinity of antipsychotic and antidepressant drugs have promoted interest in this receptor as a promising target in treatment of CNS disorders.[2-8] In recent years several studies and reviews show that serotonergic neurotransmission is implicated in modulation of learning and memory.[9] In particular, 5-HT_6 receptor antagonists are in beneficial on cognition in several animal models.[10] In addition, 5-HT_6 antagonists have been shown to reduce appetite and produce weight loss, and are being investigated for the treatment of obesity.[11] Therefore, agents such as latrepirdine, Lu AE58054, and SB-742,457 are being developed as novel treatments for Alzheimer's disease, while PRX-07034, BVT-5,182, and BVT-74,316 are being investigated for the treatment of obesity.

In the last decade, a large number of 5-HT_6 ligands have been synthesized, and many are comprised of an indole core with a basic amine and an arylsulfonyl moiety as shown in Fig.1. Piperazine nucleus also plays a very important role to enhance the activity of 5-HT_6 receptor ligands. A series of piperazinylbenzenesulfonamides, including SB-271046 and SB-357134 were developed by Smith Kline-Beecham.[12, 13] Cole and co-workers showed 4-piperazinyl- 1-sulfonylindoles as potential 5-HT_6 receptor antagonist.[14] The 3- as well as 2-sulfonylindole derivatives with a basic amine such as piperazine or piperidine at positions 4 through 7 on an indole nucleus have been claimed as potent 5-HT_6 antagonists.[15-17]

As part of our continuous efforts to develop agents for CNS diseases, we have focused on the 5-HT_6 receptor to identify potent ligands for cognitive enhancement. Prompted by the above described 5-HT_6 ligands having indole and piperazine nucleus, here we report a novel series of 5-HT_6 receptor antagonist having a central indole core with 1-amino-4 methyl piperazine nucleus as positive ionizable group. This is certainly the first report of the use of 1-amino-4 methyl piperazine as a positive ionizable group at the C-3 position of the indol ring for

synthesis of 5-HT_6 receptor antagonists.

2. Results

2.1. Chemistry

The synthesis of a novel series of 5-HT_6 receptor antagonists (**5**-**36**) was performed as outlined in scheme 1. Initially, the coupling of 2-methylindole-3-carboxaldehyde (1 mmol) and 2-phenylindole-3-carboxaldehyde (1 mmol) with 1-amino-4-methyl piperazine (1.5 mmol) was chosen as a model reaction to establish the optimized reaction conditions. All reactions were performed in the presence of various solvents using 2-3 drops of acetic acid as a catalyst at different temperature ranges under anhydrous conditions. The desired products were isolated in good yield (60-70%) when the reactions were carried out using anhydrous ethanol at reflux temperature for 12-14 hrs. The reactions completed within 12-14 hrs. A further improvement of yield was observed when anhydrous DMF was used in place of ethanol and the products were isolated in very good yield (85-90%). These reactions were performed in anhydrous DMF at refluxed temperature for 20 to 22 hrs. In conclusion, for the synthesis of (2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine and N-(4-methyl piperazin-1-yl)(2-phenyl-1H-indol-3-yl)methanimine, the best reaction conditions are (a) anhydrous DMF (b) high temperature up to 150-155 ^{o}C and (c) 20-22 hrs refluxing. With final products synthesis, three test reactions were performed in three different solvents (DCM, THF and DMF) in different temperature ranges by using Et_3N (1.5 to 3.0 mmol) and NaH (1.2-1.5 mmol) as base. After 24 hours of stirring at room temperature, TLC did not progress in the first test reaction using DCM as solvent and Et_3N as a base In two other test reactions with DMF and THF as solvents and NaH as base, TLC showed little progress in the reactions but yield of the desired products was very poor. We also did not get the desire products in good yield after heating the reactions up to reflux temperature. The desired products were isolated in good yield when the reactions were carried out in presence of anhydrous THF as solvent and KH as base at room temperature. The reactions were complete within 13-15 hrs. Each compound synthesized was characterized by ^{1}H NMR, ^{13}C NMR and high resolution MS.

2.2. Biological evaluation

All synthesized compounds were evaluated in vitro against the human recombinant serotonin

receptors. They were evaluated for their functional profile by determining the adenylate cyclase activity. HEK293 cell line stably expressed 5-HT_6 receptor (HEK293/6R) was used for 5-HT_6 receptor activities. For the selectivity, HEK 293 cells transiently transfected with 5-HT_4 or 5-HT_7 receptor were used for 5-HT_4 or 5-HT_7 receptor activities, respectively. The known 5-HT_6 antagonist, SB258585 was used as reference having IC_{50} = 19.9 ±5.5 nM in our experiment. The results were estimated as the percentage inhibition compared with the untreated controls.

Three out of thirteen compounds prepared in 3-methyl indole series (**5**-**17**) showed higher than 70% inhibition activity at 10 uM. Compounds **5, 6,** and **12** showed IC_{50} values in the range 2.0 to 4.7 μM as shown in Table 1. Compound **12** with 2-naphthyl group showed inhibitory activity with an IC_{50} value of 4.74 μM. Compounds **5** and **6** with 5-chloro-2-methoxy-4-methylphenyl and 4-fluorophenyl showed inhibitory activity with IC_{50} values of 2.04 and 2.4 μM, respectively. Compounds **8** and **11** with 4-nitrophenyl and 4-methylphenyl were marginally active with 52% and 49% inhibition, respectively, at 10 μM. In the case of biphenyl, 4-chlorobiphenyl as Ar, compounds **10** and **11** showed no activity. Compounds **16** and **15**, with substituted azobenzene and 2-(1-naphthyl)ethyl as Ar respectively, showed no activity, either.

In 3-phenyl indole series (**18**-**36**), seven compounds **(18, 19, 20, 29, 32, 33, and 35)** showed IC_{50} values in the range 1.4 to 7.4 μM as shown in Table 2. Compound **18** with phenyl showed good inhibitory activity with an IC_{50} value of 1.4 μM. Various substitutions, such as methyl, isopropyl, n-buthyl, methoxy, chloro, and iodo on phenyl group decreased the activity. Only compounds **19** and **20** with 5-chloro-2-methoxy-4-methylphenyl and 4-fluorophenyl showed slightly decreased inhibitory activity with IC_{50} values of 2.9 and 7.4 μM, respectively.

Compound **29** with 1-naphthyl showed moderate activity with IC_{50} values of 6.6 μM, while **20** with 2-naphthyl showed lower activity. The compound **32** with 1-(5-(dimethylamino)naphthyl showed the highest activity with IC_{50} values of 1.4 μM in this series of compound prepared. However compound **31** with 1-(5-(dibuthylamino)naphthyl showed much decreased activity. Compounds **33** and **35** containing heterocycles such as 1-methylimidazole and 2,3-dihydro-1,4-benzodioxane, showed good activity with IC_{50} values of 3.6 and 3.8 μM, respectively. Compounds **34** and **36**, with substituted chromone and dihydrobenzofuran as Ar respectively, showed no activity.

Ten compounds that showed good 5-HT_6 inhibitory activity were selected to test selectivity

toward other serotonergic receptors in same Gs family, 5-HT_4 and 5-HT_7 receptor. Compounds **5** and **29** showed excellent selectivity as shown in Table 3. Compound 29 showed only 9.4% and 5.0% inhibition at 10 μM for the 5-HT_4 and 5-HT_7 receptors, respectively. Compound **5** showed 17.9% and 18.4% inhibition at 10 μM for the 5-HT_4 and 5-HT_7 receptors, respectively. SB258585 (a known 5-HT_6 antagonist) and SB269970 (a known 5-HT_7 antagonist) were employed as positive control.

2.3 Pharmacophore mapping

The present design and synthesis approach was guided by a previously reported pharmacophore model[18]. Hence, the statistical validation of our compounds has been carried out by the regeneration and subsequent mapping of the model with active and inactive compounds. The mapping study derived satisfactory correlation between fitvalue and activity of compounds. The active compounds, with the proper fitting of all features showed higher fitvalues whereas the inactive compounds missed some key features which resulted in lower fitvalues.

Using HypoGen, we generated total ten hypotheses, all with same features as in the reported model ie., AR, PI, HBA and HYD. The top ranked hypothesis Hypo1 outperformed other hypotheses in the cost analysis procedure. The Fixed, Null and Total costs of Hypo1 were 177.04, 257.86 and 198.16 bits respectively. The highest cost difference (59.7), lowest error cost (167.97), lowest root mean square divergence (0.95) and best correlation coefficient (0.91) demonstrates good predictability of Hypo1 (Fig. 2).

The mapping of most active compounds **32**, **18**, **6** and inactive compounds **10** and **34** with Hypo1 is visualized (Fig.3). Compounds **32**, **18** and **6** showed reasonable fitting with fitvalues of 7.08, 7.51 and 7.65 respectively. The inactive compounds **10** and **34** displayed poor mapping with the features as it is evident from the low fitvalues of 4.21 and 1.00. The pharmacophoric features are observed to match with the key structural moieties of the compounds feasibly well.

3. Discussion

Indole and piperazine nucleus are one of the most explored chemical classes of 5-HT_6

receptor ligands. The structural requirements for the 5-HT_6 receptor ligands that are postulated by several research groups are comprised of four key requirements, a central aromatic/heterocyclic ring (AR) flanked by a positive ionizable group (PI, such as a basic nitrogen) and a strong, multiple hydrogen bond acceptor (HBA, such as sulfonyl group) attached to a hydrophobic group (HYD, such as phenyl ring).[18] A large number of 5-HT_6 ligands with an indole core have been synthesized.[19-22] It is suggested that the basic amine and arylsulfonyl moieties are the necessary receptor pharmacophores and the indole core serves merely as a template to hold these pharmacophores in the necessary orientation that effectively interacts with the 5-HT_6 receptor active site residues.[23] As arylsulfonyl moieties, substituted benzene and naphthalene are most often reported. The nature and position of the substituents in the aryl fragment strongly influenced activity, since a substitute group likely served to constrain the arylsulfonyl moiety in an appropriate conformation that affected the binding affinity.

As a basic amine (PI), piperazine, methyl piperazine, piperidine, aminoethyl or N,N-dimethylaminoethyl, have been reported in 5-HT_6 antagonists. The 5-HT_6 receptors are transmembrane-embedded G-protein coupled receptors containing an aspartate moiety in TM helix 3 that, presumably, serves as a ligand–amine binding site.[24] Recently, we reported novel 5-HT_6 antagonists which contain N,N-dimethylformimidamide as a basic amine moiety.[25] As part of our continuous efforts to develop 5-HT_6 antagonists, here we introduced N-(4-methylpiperazin-1-yl)methanimine as a basic amine moiety. None N-(4-methylpiperazin-1-yl)methanimine on indole ring derivative was reported as 5-HT_6 receptor antagonists yet. Among the whole series of 32 compounds, 10 compounds were found to be a potent 5- HT_6 receptor antagonist. In this series, it has been expected that 2-methyl and 2-phenyl indole rings, a –SO_2 group, and benzene or napthalene served as AR, HBA, or HYD, respectively. In terms of structure activity relationship of arylsulfonyl moiety among the 2-methyl indole series (**5**-**17**), compound **5**, **6** and **12,** substituted 3-chloro-6-methoxy-4-methylphenyl, 2-naphtyl, and 4-fluorophenyl ring at the position number N-1 of the indole ring attached with the –SO_2- system showed good activity with 5-HT_6 receptor. Both electron donating (-CH_3) or withdrawing (-NO_2) substituent showed similar biological activity (**8** and **11**). Large substituents such as biphenyl showed the decreased activity (**10**). Compounds **6**, substituted with fluoro group at para position of phenyl ring, showed good biological activity among the series, probably due to the small size. For selectivity, compounds **5,** substituted 3-chloro-6-methoxy-4-methylphenyl, showed excellent selectivity for 5-HT_6 over 5-HT_4 and 5-HT_7

receptors. Compound 6 showed good activity but showed poor selectivity over 5-HT_4.

In case of 2-phenyl indole series (**18**-**36**), 5-(dimethylamino) naphthalene, 1-methylimidazole, 4-chlorophenyl, phenyl, 4-fluorophenyl, 5-chloro-2-methoxy-4 methyl phenyl and1-naphtyl ring at the position N-1 of the indole ring attached with the $–SO_2$- system also showed good activity with 5-HT_6 receptor (IC_{50} = 1.4 - 7.4 μM). Some compounds substituted with phenyl ring at position number 2 of indole ring were noticeably less potent than their congeners with methyl group at C-2 position of indole ring. (**5>19**, **12> 30**). On the other hand, a significant change in biological activity (**32> 13**) was observed in compounds **32** and **13**, both the compounds are substituted with dimethyl amino group at 5- position on naphthyl ring but only compound **32** showed good biological activity. So in case of compound **32**, the presence of another amino binding site may fit with phenyl group at C-2 position of indole ring. For selectivity, compounds **29,** substituted 1-naphthyl, showed excellent selectivity over 5-HT_4 and 5-HT_7 receptors.

Pharmacophore mapping studies with Hypo1 have demonstrated that active compounds with IC50 values under 5.0 μM are found to map all features with fitvalues of ≥ 7.0 whereas the inactive compounds with ~22% inhibition showed lower values of ≤ 5.0. In the most active compounds **32**, **18** and **6** the indole, sulfonyl and piperazine moieties mapped with aromatic, acceptor and positive ionizable features. The naphthyl, phenyl and fluorophenyl groups in **32**, **18** and **6** possessed hydrophobic feature. The least active compound **11** failed to map with Hypo1. In compounds **10** and **34**, the pharmacophoric features does not fit well with the structure and even showed variations in the mapping pattern of ring aromatic feature. The indole ring which was supposed to merge with aromatic feature fitted with hydrophobic feature in **10** whereas it occupied the aromatic feature in **34**. The sulfonyl and piperazine groups showed poor fitting with acceptor and positive ionizable features.

The present mapping analysis validated the potential of our synthetic compounds as good 5-HT_6 antagonists and this in turn strongly supported the inference that ring aromatic, positive ionizable, hydrogen bond acceptor and hydrophobic features are the essential requirement for the activity of 5-HT_6 antagonists. Further research in this direction could lead to the design and development of novel diverse scaffolds as potential 5-HT_6 antagonists.

4. Conclusion

Novel 2-methyl/phenyl-1-(substituted arylsulfonyl)-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimines were designed and synthesized as 5-HT_6 ligands using N-(4-methylpiperazin-1-yl)methanimine as basic amine moiety. Compounds **5** and **32** significantly inhibited the 5-HT-induced cAMP level (IC_{50} = 2.4 μM and 1.4 μM, respectively), indicating that these compounds are potent 5-HT_6 receptor antagonists. Compounds **5** and **29** showed good selectivity for 5-HT_6 over 5-HT_4 and 5-HT_7 receptors. The mapping of aromatic, positive ionizable, hydrogen bond acceptor and hydrophobic features of the 3D QSAR model with key structural moieties showed good agreement with the activity profile of the compounds.

5. Experimental

5.1. Materials and methods

All melting points of the synthesized compounds were taken in Pyrex capillaries using electrothermal digital melting point apparatus (Buchi) and were not corrected. ^{1}H NMR spectra were recorded on a 400 MHz Varian FT-NMR using tetramethylsilane as an internal standard. Chemical shifts are expressed in ppm (δ), and peaks are listed as singlet (s), doublet (d), triplet (t), quintet (q), multiplet (m), with coupling constants (J) expressed in Hertz. Mass spectra data were obtained on a Agilent 6220 Accerate -Mass TOF LC/MS. Most of the reagents were purchased from Aldrich Chemical Company and Merck Company. TLC was run on the silica gel coated plastic sheets (Silica Gel 60, 230–400 mesh, Merck, Germany) and visualized in UV light (254 or 365 nm).

5.2. General procedure for the preparation of (2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine and -N-(4-methylpiperazin-1-yl)(2-phenyl-1H-indol-3-yl)methanimine (3 and 4)

A mixture of substituted indole 3-carboxaldehydes (1 mmol), the respective 1-amino-4-methyl piperazine (1.5 mmol) in 5 mL dry DMF was heated to reflux under N_2 until no starting material could be detected by TLC. The resulting mixture was allowed to cool at room temperature and poured into water and extracted with EtOAc. The combined organic

layers were washed with aqueous HCl (1 N), saturated aqueous $NaHCO_3$ and brine solution and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by column chromatography using hexane: ethyl acetate (7:3) as eluent.

5.2. 1. (2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (3)

Brown solid (78%), mp 153–156 ^{o}C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.25 (m, 1H), 7.98 (s, 1H), 7.89 (s, 1H), 7.28-7.23 (m, 1H), 7.17-7.11 (m, 2H), 3.20 (t, J = 5.0 Hz, 4H), 2.65 (t, J = 5.0 Hz, 4H), 2.53 (s,3H), 2.37 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 135.67 (Ar-C=N), 135.47, 135.46, 126.38, 122.16, 121.57, 120.76, 110.23 (aromatic), 77.23, 54.86, 52.26 (N-C-C-N), 46.15 (N-C), 12.36 (C-C), HR-EI Calcd for $C_{15}H_{21}N_4$ $(M+H)^+$: 257.1761 found: 257.1766.

5.2. 2. N-(4-methylpiperazin-1-yl)(2-phenyl-1H-indol-3-yl)methanimine (4)

Brown solid (85 %), mp 183–184 ^{o}C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.47 (m, 1H), 8.38 (s, 1H), 7.58-7.55 (m, 2H), 7.50-7.46 (m, 2H),7.43-7.35 (M, 2H), 7.26-7.18 (m, 3H), 3.19 (t, J = 5.0 Hz, 4H), 2.65 (t, J = 5.0 Hz, 4H), 2.34 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 138.65, 136.44(Ar-C=N), 135.36, 133.52, 129.18, 128.96, 128.55, 126.54, 123.46, 123.30, 121.33, 110.90, 110.75 (aromatic), 77.23, 54.78, 51.97 (N-C-C-N), 46.15 (1C, N-C).

5.3. General procedure for the preparation of (2-methyl-1-(Ar-sulfonyl)-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (5-17) and N-(4-methylpiperazin-1-yl)(2-phenyl-1-(Ar-sulfonyl)-1H-indol-3-yl)methanimine (18-36)

(2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (**3**) or N-(4-methylpiperazin-1-yl)(2-phenyl-1H-indol-3-yl)methanimine (**4**) (0.5 mmol) dissolved in 5 mL THF, was added slowly to 25 mL flask containing a suspension of potassium hydride (1.17 mmol) in 15 mL THF under nitrogen atmosphere, while maintaining the mass temperature below 10 ^{o}C. The reaction mixture was then stirred for a period of 1 h at 25 ^{o}C. Ar-sulfonylchloride (1 mmol) was added slowly to the above well-stirred solution maintaining the mass temperature below 10 ^{o}C. The reaction mixture was further stirred over night. After completion of the reaction, the reaction mixture was poured on to ice-water and extracted with ethyl acetate (3 x 20 mL). The combined ethyl acetate extracts were then washed with water (20 mL), brine (20 mL) and dried over anhydrous sodium sulphate. The volatiles were removed under the reduced pressure and the resulting thick syrupy mass was

purified over silica gel column using hexane: ethyl acetate (8:2) as eluent.

5.3.1. (1-(5-chloro-2-methoxy-4-methylphenylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (5)

Brown solid (11%), mp 179–181 ^{o}C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.30-8.28 (m, 1H), 8.05 (s, 1H), 7.93-7.90 (m, 1H), 7.78 (s, 1H), 7.25-7.20 (m, 2H), 6.66 (s, 1H), 3.42 (s, 3H), 3.24 (t, J = 5.0 Hz, 4H), 2.66 (t, J = 4.4 Hz, 4H), 2.62 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 155.85, 144.81(Ar-C=N), 137.29, 137.01, 131.39, 130.60, 127.24, 125.97, 125.75, 124.27, 123.58, 122.08, 115.84, 114.98, 114.38 (aromatic), 56.10, 54.67, 51.26 (N-C-C-N), 46.09 (N-C), 29.11 (O-C), 21.10, 13.28 (C-C). HR- MS Calcd for $C_{23}H_{28}N_4O_3SCl$ $(M+H)^+$: 475.1565 found: 475.1576.

5.3.2. (1-(4-fluorophenylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (6)

Dark brown oil (23%): ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.29 (d, J = 6.4Hz, 1H), 8.16 (d, J = 5.6 Hz, 1H), 7.78-7.75 (m, 2H), 7.72 (s, 1H), 7.31-7.28 (m, 2H), 7.07 (t, J = 8.6 Hz, 2H), 3.22 (t, J = 5.0 Hz, 4H), 2.67 (s, 3H), 2.63 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.03, 164.47, 162.73 (Ar-F), 136.66 (Ar-C=N), 135.45, 130.29, 129.39, 128.02, 124.94, 124.38, 122.42, 117.71, 116.93, 116.72, 114.29 (aromatic), 54.63, 51.11 (N-C-C-N), 46.11 (N-C), 13.26 (C-C). HR-MS Calcd for $C_{21}H_{24}N_4O_2SF$ $(M+H)^+$: 415.1599 found: 415.1605.

5.3.3. (1-(4-iodophenylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (7)

Light brown solid (52%), mp 123–125 ^{o}C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.29-8.26 (m, 1H), 8.14 (d, J = 5.2 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.70 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.29-7.27 (m, 3H), 3.23 (t, J = 4.8 Hz, 4H), 2.65 (s, 3H), 2.63 (s, 4H), 2.36 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 162.74 (Ar-I), 138.73, 138.68, 136.63(Ar-C=N), 135.39, 130.23, 128.04, 127.69, 124.97, 124.45, 122.46, 117.83, 114.30, 101.71 (aromatic), 54.61, 51.07 (N-C-C-N), 46.09 (N-C), 13.26 (C-C). HR-MS Calcd for $C_{21}H_{24}N_4O_2SI$ $(M+H)^+$: 523.0659 found:523.0658.

5.3.4. (1-(4-nitrophenylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-

yl)methanimine (8)

Dark brown solid (28%), mp 174–176 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.28 (d, J = 4.8Hz, 1H), 8.22 (d, J = 8.8 Hz, 2H), 8.14 (d, J =5.6 Hz, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.68 (s, 1H), 7.35-7.26 (m, 2H), 3.24 (t, J = 5.0 Hz, 4H), 2.68 (s, 3H), 2.65 (t, J = 4.8 Hz, 4H), 2.38 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 150.70 (Ar-NO_2), 144.22 (Ar-C=N), 136.54, 135.01, 129.65, 128.26, 127.81, 125.34, 124.93, 124.72, 124.47, 122.75, 118.69, 114.31 (aromatic), 54.55, 50.92 (N-C-C-N), 46.05 (N-C), 13.40 (C-C). HR-MS Calcd for $C_{21}H_{24}N_5O_4S$ $(M+H)^+$: 442.1544 found: 442.1550

5.3.5. (1-(p-tolylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (9)

Red oil (34%): ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.27 (d, J = 5.6 Hz, 1H), 8.19 (d, J = 6.4 Hz, 1H), 7.73 (s, 1H), 7.63 (d, J = 8.4 Hz, 2H), 7.31-7.23 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 3.22 (t, J = 5.0 Hz, 4H), 2.67 (s, 3H), 2.63 (t, J = 5.0 Hz, 4H), 2.36 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 162.38 (Ar-SO_2), 144.77 (Ar-C=N), 136.31, 135.78, 135.39, 130.29, 129.73, 127.52, 124.32, 123.72, 121.95, 116.86, 113.88 (aromatic), 54.22, 50.74 (N-C-C-N), 45.66 (N-C), 21.29, 12.77 (C-C). HR-MS Calcd for $C_{22}H_{27}N_4O_2S$ $(M+H)^+$: 411.1849 found: 411.1857.

5.3.6. (2-methyl-1-(biphenylsulfonyl)-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (10)

Brown solid (56%), mp 163–165 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.29 (d, J = 6.0Hz, 1H), 8.23 (d, J = 6.4 Hz, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.75 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.50-7.47 (m, 2H), 7.45-7.36 (m, 3H), 7.34-7.25 (m, 2H), 3.24 (t, J = 4.8 Hz, 4H), 2.71 (s, 3H), 2.66 (t, J = 4.8 Hz, 4H), 2.38 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 162.73 (Ar-Ar), 146.88 (Ar-C=N), 139.01, 137.64, 136.75, 135.72, 130.63, 129.20, 128.84, 128.04, 127.94, 127.43, 127.02, 124.83, 124.23, 122.31, 117.36, 114.36 (aromatic), 54.61, 51.12 (N-C-C-N), 46.07 (N-C), 13.27 (C-C). HR-MS Calcd for $C_{27}H_{29}N_4O_2S$ $(M+H)^+$: 473.2006 found: 473.2008.

5.3.7. (1-(4-chlorobiphenylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (11)

Brown solid (38%), mp 211–213 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.29 (d, J = 5.6

Hz, 1H), 8.22 (d, J = 6.8 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.74 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.43-7.38 (m, 4H), 7.34-7.27 (m, 2H), 3.23 (t, J = 4.8 Hz, 4H), 2.71 (s, 3H), 2.63 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 145.56 (Ar-Cl), 137.99, 137.46, 136.76 (Ar-C=N), 135.66, 135.18, 130.48, 129.45, 128.69, 128.01, 127.90, 127.14, 124.89, 124.32, 122.36, 117.52, 114.41 (aromatic), 54.64, 51.13 (N-C-C-N), 46.12 (N-C), 13.32 (C-C). HR- MS Calcd for $C_{27}H_{28}N_4O_2SCl$ $(M+H)^+$: 507.1616 found: 507.1620.

5.3.8. (2-methyl-1-(naphthalensulfonyl)-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (12)

Brown solid (10%), mp 189–190 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.42 (s, 1H), 8.29-8.26 (m, 2H), 7.91 (d, J = 7.6 Hz,1H), 7.80 (t, J = 8.0 Hz, 2H), 7.71 (s,1H), 7.63-7.55 (m, 2H), 7.33-7.23 (m, 3H), 3.20 (t, J = 5.0 Hz, 4H), 2.71 (s, 3H), 2.61 (t, J = 5.0 Hz, 4H), 2.35 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 136.87 (Ar-C=N), 136.17, 135.76, 135.39, 132.04, 130.71, 129.63, 129.53, 128.20, 128.10, 127.98, 127.90, 124.86, 124.21, 122.34, 121.28, 117.29, 114.37 (aromatic), 54.61, 51.11 (N-C-C-N), 46.09 (N-C), 13.30 (C-C). HR-MS Calcd for $C_{25}H_{27}N_4O_2S$ $(M+H)^+$: 447.1849 found: 447.1856.

5.3.9. 5-((3-(4-methylpiperazin-1-ylimino)methyl)-2-methyl-1H-indol-1-yl)sulfonyl)-N,N-dimethylnaphthalen-1-amine (13)

Yellow solid (42%), mp 162–164 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.49 (d, J = 6.0 Hz, 1H), 8.38-8.36 (m, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.79-8.15 (s, 1H), 7.77 (m, 1H), 7.46 (t, J = 8.0 Hz, 1H), 7.40-7.26 (m, 4H), 7.14 (d, J = 7.6 Hz, 1H), 3.25 (s, 4H), 2.84 (s, 6H), 2.65 (s, 4H), 2.56 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 149.85, 137.39, 136. 50, 136.13(Ar-C=N), 132.45, 130.86, 129.75, 128.71, 127.09, 126.90, 124.83, 124.05, 123.24, 122.40, 119.91, 119.13, 116.31, 114.43 (aromatic), 54.67, 54.43, 51.18 (N-C-C-N), 46.11 (N-C), 29.28, 20.61 (N-C), 13.05 (C-C). HR-MS Calcd for $C_{27}H_{32}N_5O_2S$ $(M+H)^+$: 490.2271 found: 490.2273.

5.3.10. 5-((3-(4-methylpiperazin-1-ylimino)methyl)-2-methyl-1H-indol-1-yl)sulfonyl)-N,N-dibutylnaphthalen-1-amine (14)

Light green solid (14%), mp 171–174 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.59-8.56 (m,1H), 8.39-8.37 (m,1H),8.29(d, J = 8.8 Hz, 1H), 8.18-8.16 (m, 1H), 7.79 (s,1H), 7.49 (t, J = 8.2 Hz, 1H), 7.33-7.27 (m, 4H),7.26-7.23 (m, 1H), 3.26 (t, J = 4.6 Hz, 4H), 3.07-3.04 (m, 6H), 2.65 (s, 4H), 2.58 (s, 3H) , 2.37 (s, 3H), 1.45-1.37 (m, 6H), 1.28-1.18 (m, 6H).^{13}C NMR

(chloroform-d_6,100 MHz): δ 152.09, 137.40, 136.40, 136.28 (Ar-C=N), 131.29, 130.85, 130.16, 129.78, 129.00, 127.06, 124.85, 124.06, 123.24, 122.44, 118.70, 116.37, 115.88, 114.44 (aromatic), 54.69, 51.20 (N-C-C-N), 45.55 (N-C), 13.03 (C-C). HR-MS Calcd for $C_{33}H_{44}N_5O_2S$ $(M+H)^+$: 574.321 found: 574.3213.

5.3.11. (1-(2-(naphthalen-1-yl)ethylsulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (15)

Brown solid (31%), mp 195–197 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.28 (d, J = 5.6 Hz, 1H), 8.20 (d, J = 6.4 Hz, 1H), 7.74 (s, 1H),7.32-7.27 (m, 2H), 7.26-7.23 (m, 1H), 7.18 (d, J = 8.4 Hz,3H), 3.23 (s, 4H), 2.71 (s, 3H), 2.68 (s, 3H) , 2.64 (s, 4H), 2.57 (t, J = 7.8 Hz, 4H), 2.37 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 149.87, 136. 77, 136.51 (Ar-C=N), 135.84, 130.82, 129.43, 127.85, 126.57, 124.73, 124.10, 122.23, 117.08, 114.35 (aromatic), 54.65, 51.18 (N-C-C-N), 46.11 (N-C), 22.41, 13.98 (S-C-C), 13.22 (C-C). HR- MS Calcd for $C_{27}H_{31}N_4O_2S$ $(M+H)^+$: 475.2162 found: 475.2156.

5.3.12. 5-((3-((E)-(4-methylpiperazin-1-ylimino)methyl)-2-methyl-1H-indol-1-yl)sulfonyl)-N,N-dimethyl (1, 2-diphenyldiazene)-1-amine (16)

Red solid (17%), mp 153–155 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.30-8.24 (m, 1H), 7.85-7.76 (m, 3H), 7.73 (s, 1H), 7.33-7.24 (m, 7H), 6.72 (d, J = 9.2 Hz, 1H), 3.22 (t, J = 5.0 Hz, 4H), 3.10 (s, 6H), 2.69 (s, 3H) 2.62 (t, J = 5.0 Hz, 4H), 2.35 (s, 3H).^{13}C NMR (chloroform-d_6,100 MHz): δ 156.46, 153.43, 143.79 (Ar-C=N), 138.27, 136.82, 135.71, 130.64, 128.00, 127.59, 126.07, 124.86, 124.26, 122.87, 121.39, 117.48, 114.41, 111.62 (aromatic), 54.68, 51.19 (N-C-C-N), 46.16, 40.47 (N-C), 13.28 (C-C). HR-MS Calcd for $C_{29}H_{34}N_7O_2S$ $(M+H)^+$: 544.2489 found: 544.2494.

5.3.13. (1-(4-chlorobenzo[c][1,2,5]oxadiazol-7-sulfonyl)-2-methyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (17)

Brown solid (43%), mp 188–191 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.24-8.22 (m, 1H), 7.99 (s, 1H), 7.92 (s, 1H), 7.27-7.24 (m, 2H), 7.16-7.13 (m, 2H), 3.21 (t, J = 4.8 Hz, 4H), 2.68 (t, J = 5.0 Hz, 4H), 2.52 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 135.65 (Ar-C=N), 135.57, 135.52, 126.38, 122.20, 121.58, 120.79, 110.22, 109.88 (aromatic), 54.81, 52.23 (N-C-C-N), 46.11 (N-C), 12.38 (C-C). HR-MS Calcd for $C_{21}H_{22}N_6O_3SCl$ $(M+H)^+$: 473.1157 found:473.1166.

5.3.14. N-(4-methylpiperazin-1-yl)(2-phenyl-1-(phenylsulfonyl)-1H-indol-3-yl)methanimine (18)

Brown solid (33%), mp 188–190 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.37-8.33 (m. 2H), 7.48-7.35 (m, 10H), 7.33-7.26 (m, 3H), 3.13 (t, J = 5.0 Hz, 4H), 2.63 (t, J = 5.0 Hz, 4H), 2.38 (s, 3H).^{13}C NMR (chloroform-d_6,100 MHz): δ 139.72 (Ar-C=N), 138.14, 137.75, 133.87, 132.08, 131.92, 130.60, 129.30, 128.95, 128.11, 127.77, 126.98, 125.80, 124.92, 123.34, 120.12, 115.90 (aromatic), 54.36, 50.59 (N-C-C-N), 45.81 (N-C). HR-MS Calcd for $C_{26}H_{27}N_4O_2S$ $(M+H)^+$: 459.1849, found: 459.1846.

5.3.15. (1-(5-chloro-2-methoxy-4-methylphenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (19)

Light brown solid (17%), mp 139–141 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.44 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.43-7.26 (m, 7H), 7.08-7.06 (m, 2H), 6.60 (s, 1H), 3.26 (s, 3H), 3.06 (t, J = 5.0 Hz, 4H), 2.53 (t, J = 5.0 Hz, 4H), 2.32 (s, 3H), 2.30 (s, 3H).^{13}C NMR (chloroform-d_6,100 MHz): δ 155.97, 144.44 (Ar-C=N), 139.53, 139.09, 132.13, 132.05, 131.21, 129.64, 129.18, 128.93, 127.51, 126.70, 126.16, 125.32, 125.25, 123.89, 123.07, 118.72, 115.87, 114.34 (aromatic), 56.18, 54.59, 51.02 (N-C-C-N), 46.07 (N-C), 21.06 (methoxy). HR-MS Calcd for $C_{28}H_{30}N_4O_3SCl$ $(M+H)^+$: 537.1722, found: 537.1713.

5.3.16. (1-(4-fluorophenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (20)

Brown solid (53%), mp 177–179 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.47 (d, J = 8.8 Hz, 1H), 8.39 (d, J = 6.4 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 8.20 (s, 1H), 8.03 (s, 1H), 7.58-7.56 (m, 1H), 7.51-7.47 (m, 2H), 7.47-7.36 (m, 3H), 7.34-7.19 (m, 2H), 6.93 (t, J = 7.6 Hz, 1H), 5.29 (s, 1H), 3.09 (t, J = 5.0 Hz, 4H), 2.54 (t, J = 5.0 Hz, 4H), 2.31 (s,3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.04, 164.49 (C-F aromatic), 139.81 (Ar-C=N), 138.72, 137.73, 136.42, 135.71, 131.86, 131.24, 130.61, 129.90, 129.53, 128.95, 128.58, 128.32, 127.83, 125.90, 125.09, 123.52, 123.27, 121.33, 120.58, 110.77 (aromatic), 54.64, 50.52, 51.80, 50.85 (N-C-C-N), 46.06 (N-C). HR-MS Calcd for $C_{26}H_{26}N_4O_2SF$ $(M+H)^+$: 477.1755 found: 477.1763.

5.3.17. (1-(4-chlorophenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (21)

Brown solid (38%), mp 169–171 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.39 (d, J = 6.0 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H),7.48-7.30 (m, 10H), 7.22 (d, J = 8.8 Hz, 2H), 3.08 (t, J = 5.0 Hz, 4H), 2.53 (t, J = 5.0 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 140.54, 139.21, 137.70, 136.36 (Ar-C=N), 131.86, 131.05, 130.60, 129.37,129.25, 128.41, 127.85, 125.93, 125.16, 123.58, 120.74, 115.95 (aromatic), 54.56, 50.89 (N-C-C-N), 46.11 (N-C). HR-MS Calcd for $C_{26}H_{26}N_4O_2SCl$ $(M+H)^+$: 493.1460 found: 495.1458.

5.3.18. (1-(4-iodophenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (22)

White solid (42%), mp 178–181 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.38 (d, J = 6.4 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.47-7.33 (m, 7H), 7.31 (s, 1H), 7.07 (d, J = 8.8 Hz, 2H), 3.07 (t, J = 5.0 Hz, 4H), 2.52 (t, J = 5.0 Hz, 4H), 2.30 (s, 3H).^{13}C NMR (chloroform-d_6,100 MHz): δ 139.19, 138.19, 137.67, 137.55 (Ar-C=N), 131.86, 131.04, 130.60, 129.36, 128.39, 128.22, 127.85, 125.93, 125.16, 123.58, 120.75, 115.94, 101.82 (aromatic), 54.56, 50.89 (N-C-C-N), 46.12 (N-C). HR-MS Calcd for $C_{26}H_{26}N_4O_2SI$ $(M+H)^+$: 585.0816 found:585.0813.

5.3.19. (1-(p-tolylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (23)

Lihgt brown solid (78%), mp 159–162 °C:^{1}H NMR (chloroform-d_6,400 MHz) δ 8.37 (d, J = 6.8 Hz, 1H), 8.33 (d, J = 7.2 Hz, 1H),7.72 (dd, J = 5.6 Hz, 3.2 Hz, 1H), 7.52 (dd, J = 14.8 Hz, 3.6 Hz, 1H), 7.46-7.44 (m, 2H), 7.40-7.37 (m, 2H), 7.34-7.27 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 3.08 (t, J = 5.0 Hz, 4H), 2.54 (t, J = 5.0 Hz, 4H), 2.31 (s, 3H), 2.29 (s, 3H).^{13}C NMR (chloroform-d_6,100 MHz): δ 167.84 (1C, C=N-N), 144.90 (Ar-C=N), 139.64, 137.77, 135.20, 132.44, 131.91, 131.65, 131.14, 130.84, 129.53, 129.20, 129.04, 128.24, 127.71, 127.04, 125.68, 124.83, 123.31, 120.21, 115.98 (aromatic), 61.82, 54.59, 50.96 (N-C-C-N), 46.10 (N-C), 14.30 (C-C). HR-MS Calcd for $C_{27}H_{29}N_4O_2S$ $(M+H)^+$: 473.2006 found: 473.2010.

5.3.20. (1-(4-methoxyphenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine(24)

Dark brown solid (38%), mp 162–164 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.37 (d, J = 7.2 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 7.47-7.44 (m, 4H), 7.40-7.38 (m, 2H), 7.34-7.31 (m, 4H), 6.70 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.08 (t, J = 5.0 Hz, 4H), 2.54 (t, J = 5.0 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.80, 139.69 (Ar-C=N), 138.81, 131.90, 131.76, 130.87, 129.79,129.26, 129.18, 128.93, 128.23, 127.71, 125.65, 124.78, 123.29, 120.12, 115.99, 114.08 (aromatic), 55.76, 54.56, 50.94 (N-C-C-N), 46.07 (N-C). HR-MS Calcd for $C_{27}H_{29}N_4O_3S$ $(M+H)^+$: 489.1955 found: 489.1960.

5.3.21. (1-(4-(trifluoromethoxy)phenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine(25)

Brown solid (44%), mp 175–178 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.39 (s, 1H), 8.31(d, J = 8.0 Hz, 1H), 7.47-7.40 (m, 6H), 7.37-7.34 (m, 3H), 7.27 (d, J = 11.6 Hz, 1H), 7.06 (d, J = 6.8 Hz, 2H), 3.09 (t, J = 5.0 Hz, 4H), 2.54 (t, J = 5.0 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 153.11, 143.30(Ar-C=N), 140.73, 137.53, 136.18, 135.50, 131.86, 129.88,129.79, 129.28, 128.07, 128.01, 127.62, 126.24, 125.25, 123.26, 121.53, 120.80, 120.63, 119.37, 115.81 (aromatic), 53.10, 48.38 (N-C-C-N), 44.03 (N-C). HR-EI Calcd for $C_{27}H_{26}N_4O_3SF_3$ $(M+H^+$: 543.1672, found: 543.1670

5.3.22. (1-(4-butylphenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (26)

Brown solid (63%), mp 119–121 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.38 (d, J = 6.4 Hz, 1H), 8.34 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.47-7.28 (m, 9H), 7.04 (d, J = 6.8 Hz, 2H), 3.08 (t, J = 5.0 Hz, 4H), 2.56-2.52 (m, 7H), 2.32 (s, 3H), 1.66-1.62 (m, 2H), 1.52-1.46 (m, 2H), 1.41-1.36 (m, 2H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 149.90, 142,21 (Ar-C=N), 140.42, 137.67, 135.46, 134.01, 131.92, 130.43, 129.38, 128.96, 128.50, 127.77, 127.03, 126.00, 125.80, 124.80, 123.12, 119.38, 115.86 (aromatic), 53.71, 49.60 (N-C-C-N), 44.95 (N-C), 35.67, 33.07, 22.40, 13.98 (C-C). HR-MS Calcd for $C_{30}H_{35}N_4O_2S$ $(M+H)^+$: 515.2475 found: 515.2481.

5.3.23. (1-(4-isopropylphenylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (27)

Brown solid (56%), mp 155–157 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.38 (d, J = 7.6 Hz, 1H), 8.34 (d, J = 8.4Hz, 1H), 7.47-7.35 (m, 8H), 7.31 (t, J = 7.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 3.07 (t, J = 5.0 Hz, 4H), 2.84 (m, 1H), 2.54 (t, J = 5.0 Hz, 4H), 2.31 (s,3H), 2.04 (s,

6H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 155.52, 139.81, 137.68 (Ar-C=N), 135.64, 132.35, 131.94, 130.67, 129.24, 127.99, 127.70, 127.22, 127.08, 125.71, 124.77, 123.20, 119.82, 115.86 (aromatic), 34.51 (N–C), 54.34, 50.62 (N-C-C-N), 45.78 (N-C), 34.31 (C-C). HR-MS Calcd for $C_{29}H_{33}N_4O_2S$ $(M+H)^+$: 501.2319 found: 501.2311.

5.3.24. (1-(benzylsulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (28)

Light brown solid (12%), mp 171–13 ^{o}C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.52 -8.50 (m, 1H), 8.04-8.01 (m, 1H), 7.40-7.36 (m, 3H), 7.32-7.27 (m, 3H), 7.21 (s, 1H), 7.16 (t, J = 7.6 Hz, 2H), 6.94 (d, J = 7.2 Hz, 2H), 6.74 (d, J = 7.2 Hz, 2H), 4.29 (s, 2H), 3.08 (t, *J* = 5.0 Hz, 4H), 2.55 (t, J = 5.0 Hz, 4H, 2.32 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 141.00, 137.26 (Ar-C=N), 132.48, 131.26, 130.99, 130.30 129.36, 129.09, 128.90, 127.51, 126.80, 125.79, 124.72, 123.77, 118.39, 114.59 (aromatic), 59.25, 54.26, 50.54 (N-C-C-N), 45.68 (N-C). HR-MS Calcd for $C_{27}H_{29}N_4O_2S$ $(M+H)^+$: 477.1755 found: 477.1763.

5.3.25. N-(4-methylpiperazin-1-yl)(1-(naphthalensulfonyl)-2-phenyl-1H-indol-3-yl)methanimine (29)

Dark brown solid (18%), mp 148–152 ^{o}C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.43 (t, J = 7.6 Hz, 2H), 8.12 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 11.6 Hz, 1H), 7.52-7.29 (m, 5H), 7.21 (t, J = 7.6 Hz, 2H), 7.17-7.10 (m, 2H), 6.99 (d, J = 6.8 Hz, 2H), 3.10 (t, J = 5.0 Hz, 4H), 2.49 (t, *J* = 5.0 Hz, 4H), 2.28 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 139.12, 137.97, 135.01 (Ar-C=N), 134.59, 133.88, 132.06, 131.67, 131.31, 131.15, 130.17, 129.74,129.03, 128.93, 128.80, 128.20, 127.67, 127.14, 126.94, 125.71, 124.36, 123.89, 123.51, 118.82, 115.63 (aromatic), 54.54, 50.93 (N-C-C-N), 46.04 (N-C). HR-MS Calcd for $C_{30}H_{29}N_4O_2S$ $(M+H)^+$: 509.2006 found: 509.2014.

5.3.26. N-(4-methylpiperazin-1-yl)(1-(naphthalene-2-sulfonyl)-2-phenyl-1H-indol-3-yl)methanimine (30)

Brown oil (46 %): ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.42 (d, *J* = 6.8 Hz, 1H), 8.36 (d, *J* = 7.2 Hz, 1H),7.91 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.60-7.40 (m, 7H), 7.37-7.32 (m, 4H), 3.03 (t, J = 5.0 Hz, 4H), 2.50 (t, J = 5.0 Hz, 4H), 2.28 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 139.48, 137.85, 135.34 (Ar-C=N),

135.09, 132.09, 131.74, 131.46, 130.67, 129.57, 129.41, 128.94, 128.04, 127.75, 127.71, 125.79, 124.87, 123.39, 123.30, 121.62, 121.33, 120.20, 120.63, 115.94, 110.74 (aromatic), 54.54, 50.89 (N-C-C-N), 46.07 (N-C). HR-MS Calcd for $C_{30}H_{29}N_4O_2S$ $(M+H)^+$: 509.2006 found:509.2001.

5.3.27. 5-((3-((4-methylpiperazin-1-ylimino)methyl)-2-phenyl-1H-indol-1-yl)sulfonyl)-N,N-dibutylnaphthalen-1-amine (31)

Brown solid (39%), mp 113–115 ^oC: ^1H NMR (chloroform-d_6,400 MHz) δ 8.49 -8.42 (m, 3H), 7.79 (d, J = 8.4 Hz, 1H),7.54-7.52 (m, 1H), 7.46 (t, J = 7.2 Hz, 1H),7.39-7.36 (m, 2H), 7.33-7.29 (m, 1H), 7.22 (d, J = 8.4 Hz, 1H),7.18-7.13 (m, 3H), 7.05 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 6.8 Hz, 2H), 3.05-3.00 (m, 7H), 2.49 (t, *J* = 5.0 Hz, 4H), 2.28 (s, 3H), 1.40-1.35 (m, 5H), 1.27-1.21 (m, 5H), 0.82 (t, J = 7.2 Hz, 5H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.85, 149.64, 139.15, 138.00 (Ar-C=N), 134.61, 132.45, 131.98, 131.40, 131.14, 130.18, 129.77, 129.60, 129.05, 128.94, 128.65, 127.59, 126.75, 125.64, 124.21, 123.38, 122.95, 119.68, 118.72, 118.50, 115.60 (aromatic), 61.82, 54.64, 54.58, 50.97 (N-C-C-N), 46.07 (N-C), 29.36, 20.65, 14.31, 14.14 (C-C). HR-MS Calcd for $C_{38}H_{46}N_5O_2S$ $(M+H)^+$: 636.3367 found: 636.3362.

5.3.28. 5-((3-(4-methylpiperazin-1-ylimino)methyl)-2-phenyl-1H-indol-1-yl)sulfonyl)-N,N-dimethylnaphthalen-1-amine (32)

Brown oil (11%): ^1H NMR (chloroform-d_6,400 MHz) δ 8.45-8.36 (m, 2H), 7.76-7.70 (m, 3H), 7.58-7.30 (m, 7H), 7.23-7.15 (m, 2H), 7.10-7.02 (m, 1H), 6.97 (d, J = 7.2 Hz, 1H), 3.03 (t, *J* = 5.0 Hz, 4H), 2.81 (s, 6H), 2.54 (t, *J* = 5.0 Hz, 4H), 2.31 (s, 3H).^{13}C NMR (chloroform-d_6,100 MHz): δ 167.79, 151.76, 139.21(Ar-C=N), 138.95, 137.94, 136.39, 134.69, 132.37, 131.96, 131.08, 130.09, 129.67, 129.06, 128.44, 128.23, 127.57, 125.59, 124.19, 123.37, 123.32, 123.09, 122.82, 121.17, 118.09, 115.54, 110.88 (aromatic), 61.76, 54.40, 54.36, 51.60, 50.73 (N-C-C-N), 45.81, 45,72, 45.45 (N-C). HR-MS Calcd for $C_{32}H_{34}N_5O_2S$ $(M+H)^+$: 552.2428, found: 552.2431.

5.3.29. (1-(1-methyl-1H-imidazol-4-sulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (33)

Brown solid (10%), mp 183–185 ^oC: ^1H NMR (chloroform-d_6,400 MHz) δ 8.46 (d, *J* = 5.6 Hz, 1H), 8.23 (d, J = 7.6 Hz, 1H),7.72 (dd, J = 5.6 Hz, 3.6 Hz, 1H), 7.53 (dd, J = 9.6 Hz, 3.4

Hz, 1H), 7.43-7.26 (m, 6H), 6.96 (s, 1H), 6.77 (s, 1H), 3.43 (s, 3H), 3.09 (t, *J* = 5.0 Hz, 4H), 2.54 (t, *J* = 5.0 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.84, 141.17 (Ar-C=N), 139.8, 137.78, 132.43, 131.82,131.13, 129.77, 129.27, 129.03, 127.82, 125.87, 125.45, 124.83, 123.49, 120.01, 115.37 (aromatic), 61.81, 54.53, 50.93 (N-C-C-N), 46.07 (N-C), 14.29 (N-C). HR-MS Calcd for $C_{24}H_{27}N_6O_2S$ $(M+H)^+$: 463.1911 found: 463.1919.

5.3.30. (1-(3,4-dihydro-2,2,5,7,8-pentamethyl-2H-chromen-6-sulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (34)

Brown solid (17%), mp 177–180 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.47 (d, J = 6.4 Hz, 1H), 8.32 (d, J = 7.6 Hz, 1H), 7.73-7.71 (m, 1H), 7.54-7.52 (m, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.09 (t, J = 6.8 Hz, 2H), 6.91 (d, J = 6.8 Hz, 2H), 3.03 (t, J = 4.8 Hz, 4H), 2.52 (t, *J* = 4.8 Hz, 4H), 2.36 (t, J = 6.8 Hz, 2H), 2.29 (s, 3H), 2.04 (s, 6H), 1.96 (s, 3H), 1.93 (s, 3H), 1.89 (s, 3H), 1.75 (t, J = 6.8 Hz, 2H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.84, 160.69 (Ar-O), 140.89 (Ar-C=N), 138.83, 138.39, 135.36, 132.45, 132.40, 131.46, 131.14, 129.59, 129.41, 128.20, 127.35, 125.54, 125.31, 124.92, 123.48, 123.16, 117.92, 117.50, 115.52 (aromatic), 87.27 (O-C), 61.82, 54.59, 51.06 (N-C-C-N), 46.05 (N-C), 42.91, 28.81 (O-C), 18.63, 16.70, 14.30, 12.31 (C-C). HR-MS Calcd for $C_{34}H_{41}N_4O_3S$ $(M+H)^+$: 585.2894 found: 585.2897.

5.3.31. (1-(2,3-dihydrobenzo[b][1,4]dioxin-6-sulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (35)

Brown solid (38%), mp 196–198 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.37 (d, *J* = 6.4 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H),7.47-7.38 (m, 6H), 7.33 (t, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 7.6 Hz, 1H), 4.22-4.20 (m, 2H), 4.17-4.09 (m, 2H), 3.09(t, J = 5.0 Hz, 4H), 2.54(t, J = 5.0 Hz, 4H), 2.31 (s, 3H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 148.47, 143.33 (Ar-C=N), 139.66, 137.69, 131.90, 131.77, 130.86, 130.37, 129.19, 128.20, 127.71, 125.71, 124.81, 123.23, 121.04, 120.12, 117.48, 116.74, 115.93 (aromatic), 64.63 (O-C), 54.60, 51.01 (N-C-C-N), 46.12 (N-C). HR-MS Calcd for $C_{28}H_{29}N_4O_4S$ $(M+H)^+$: 517.1904 found:517.1898.

5.3.32. (1-(2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran-5-sulfonyl)-2-phenyl-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (36)

Brown solid (22%), mp 143–146 °C: ^{1}H NMR (chloroform-d_6,400 MHz) δ 8.47 (d, *J* = 8.0 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H),7.73 -7.70 (m, 2H), 7.55-7.51 (m, 3H), 7.40 (t, J = 7.8 Hz, 1H),7.32 (t, J = 7.4 Hz, 1H), 7.14 (t, J = 7.6 Hz, 3H), 6.99-6.95 (m, 1H), 3.04 (t, *J* = 5.0 Hz, 4H), 2.52 (t, *J* = 5.0 Hz, 4H), 2.30 (s, 3H), 1.92 (d, J = 4.8 Hz, 6H), 1.87 (s, 3H), 1.39 (s, 6H). ^{13}C NMR (chloroform-d_6,100 MHz): δ 167.85, 155.67 (Ar-C=N), 139.03, 138.36, 137.77, 137.60, 132.79, 129.72, 129.39, 129.04, 128.12, 127.17, 125.44, 125.29, 124.58 123.42, 123.12, 118.15, 117.18, 117.18, 115.41 (aromatic), 74.36 (O-C), 61.81, 54.49, 50.92 (N-C-C-N), 45.91 (N-C), 32.78, 26.88, 21.27, 17.41, 16.42, 14.29, 11.97 (C-C). HR-MS Calcd for $C_{33}H_{39}N_4O_3S$ $(M+H)^+$: 571.2737 found: 571.2732.

5.4 Biological evaluation

5.4.1. *cAMP accumulation assay for 5-HT$_6$, 5-HT$_4$ and 5-HT$_7$ receptors*

To analyze cAMP levels, cAMP dynamic 2 HTRF kits (Cisbio, France) which provide homogeneous high-throughput assay were used. Cells incubated at 37℃ in 5% CO_2 and 95% air atmosphere were suspended in PBS containing 2 mM IBMX (3-isobutyl-1-methylxanthine) and stimulated by 5-HT for 30 min and with or without pretreatment with compounds for 10 min. After 30 min, cAMP labeled with the dye d2 and anti-cAMP antibodies labeled with cryptate were added into the cell plates. The plates were incubated at room temperature for 1 hour. The fluorescence intensity of accumulated cAMP level was measured at 314 nm excitation, and 668 and 620 nm emission using Flexstation3 microplate reader (Molecular Devices, Downingtown, PA). The results were estimated as the percentage inhibition compared with the untreated controls.

5.5 3D QSAR pharmacophore generation and mapping

HypoGen algorithm (catHypo/Discovery Studio (DS) 3.5/Accelrys (San Diego, USA), running on an Intel(R) Core ™ computer with Linux Red Hat Enterprise WS release 4 OS) was employed for the generation of predictive models. The 45 antagonists that were used for the previous study by Lopez-Rodriguez et al. (2005) constituted the training set. The two-dimensional (2D) structures of the compounds were drawn in ChemDraw Ultra 11.0. Applying Poling algorithm, maximum 255 conformers were generated using the 'Best' option with an energy cutoff of 20 kcal/mol. Other parameters were also set as follows: min points

(6), min subset points (6), inter-feature distance (2.97 Å), weight variation (0.3), tolerance variation (1.0) and activity uncertainty (3). The following chemical features were selected: hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), hydrophobic (HYD), positive ionizable (PI) and ring aromatic (AR). The mapping studies were performed with 'Ligand Pharmacophore Mapping' module of DS using the 'Best/Flexible' option.

Acknowledgment

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2010-0004-883), and Korea Institute of Science and Technology.

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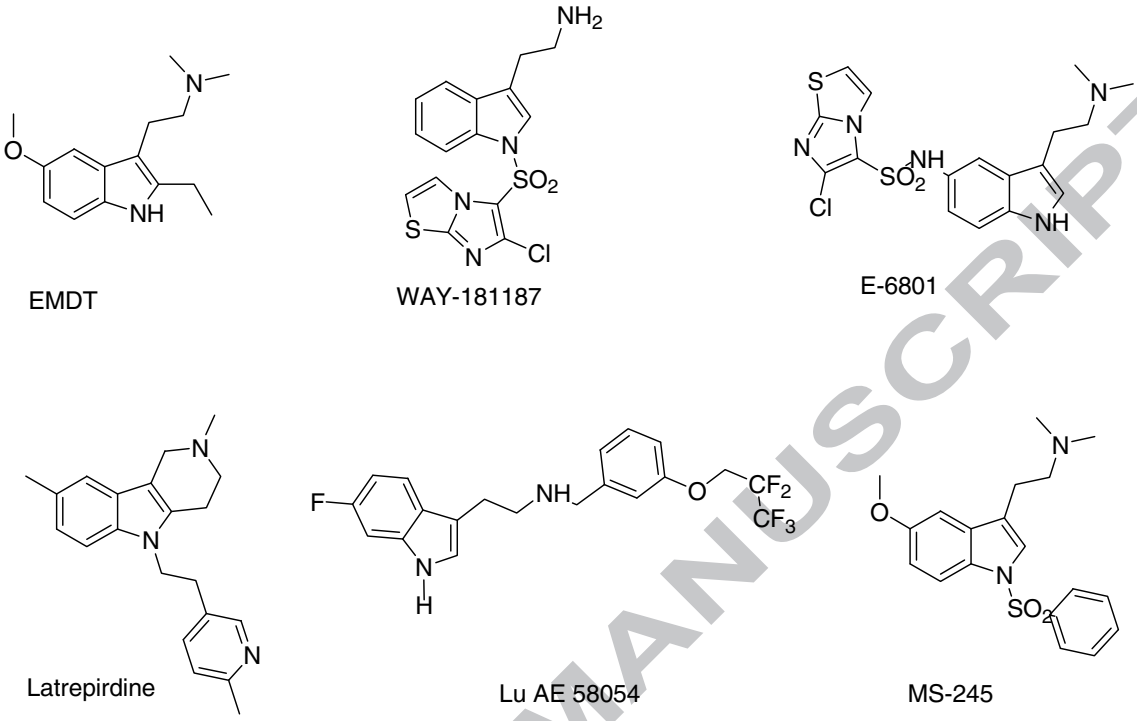


Fig 1. 5-HT_6 agonists and antagonists with indole core

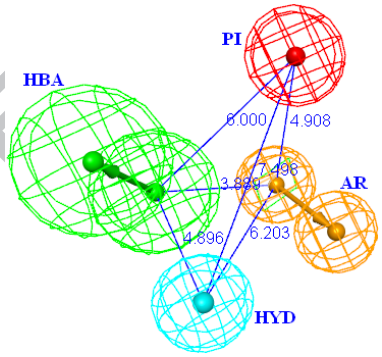
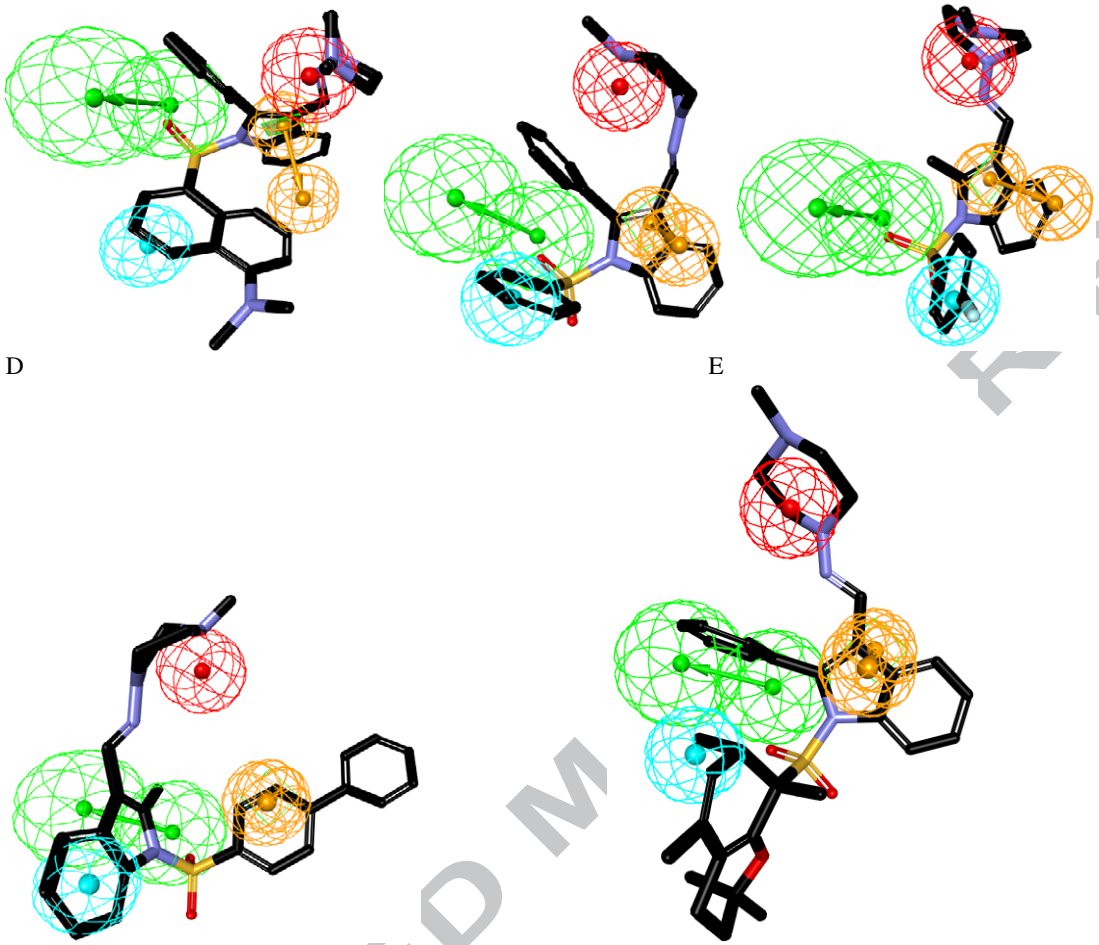


Fig 2. Best hypothesis Hypo1. The features are color-coded as follows: hydrogen bond acceptor (HBA, green), positive ionizable (PI, red), ring aromatic (AR, orange) and hydrophobic (HYD, blue).

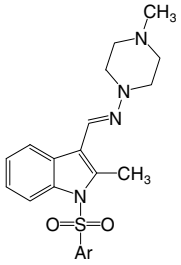
A B C



D E

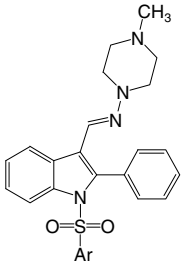
Fig 3. Mapping of compounds **32** (A), **18** (B), **6** (C), **10** (D) and (E) **34.**

Table 1. Percent Inhibition and IC_{50} values of the 2-methylindole derivatives against 5-HT_6 receptor.



Compound	Ar	% Inhibition	IC_{50} (μM)
5	5-chloro-2-methoxy-4-methylphenyl	88.6 ± 6.5	2.40 ± 0.40
6	4-Fluorophenyl	71.7 ± 9.1	4.74 ± 2.81
7	4-Iodophenyl	13.5 ± 12.6	
8	4- Nitrophenyl	52.4 ± 7.1	
9	4-Methylphenyl	49.1 ± 3.7	
10	Biphenyl	15.1 ± 5.7	
11	4-Chlorobiphenyl	0.1 ± 4.7	
12	2-Naphtyl	78.9 ±8.6	2.04 ± 1.31
13	5-(Dimethylamino)napthyl	9.5 ± 0.1	
14	5-(Dibutylamino)napthyl	44.6 ± 8.0	
15	2-(1-Naphthyl)-ethane	12.2 ± 4.9	
16	4- (Dimethylamino) azobenzene	16.1 ± 7.1	
17	4-Chloro-2,1,3-benzoxadiazole	27.2 ± 2.7	

Table 2. Percent Inhibition and IC_{50} values of the 2-phenylindole derivatives against 5-HT_6 receptor.



Compound	Ar	% Inhibition	IC_{50} (μM)
18	Phenyl	83.5 ± 5.4	1.8 ± 0.5
19	5-Chloro-2-methoxy-4-methyl phenyl	55.3 ± 4.2	7.4 ± 1.2
20	4-Fluorophenyl	74.2 ± 4.2	2.9 ± 0.2
21	4-Chlorophenyl	30.5 ± 8.7	
22	4-Iodophenyl	24.3 ± 6.9	
23	4-Methylphenyl	33.2 ± 8.7	
24	4-Methoxyphenyl	31.2 ± 11.1	
25	4-Trifluoro methoxy phenyl	38.7 ± 7.9	
26	n-Butylphenyl	14.3 ± 15.9	
27	4-Isopropyl phenyl	35.4 ± 4.5	
28	1-Benzylphenyl	36.5 ± 16.6	
29	1-Napthyl	54.0 ± 5.3	6.6 ± 2.5
30	2-Naphthyl	39.6 ± 1.2	
31	5-(Dibutylamino)napthyl	21.8 ± 8.1	
32	5-(Dimethylamino)napthyl	85.3 ± 8.3	1.4 ± 0.5
33	1-Methylimidazole	67.4 ± 6.4	3.6 ± 1.3
34	2,2,5,7,8-Pentamethyl chromane	20.6 ± 7.5	
35	2,3 –Dihydro-1,4-benzodioxan	67.3 ± 3.4	3.8 ± 1.4
36	2,2,4,6,7-Pentamethyl dihyro benzofuran	22.4 ± 10.6	

Table 3. Percent inhibition of selected compounds against 5-HT receptors.

Compound	% Inhibition(10μM) (n=3)		
	5-HT_4 receptor	5-HT_6 receptor	5-HT_7 receptor
5	17.9 ± 7.2	88.6 ± 6.5	18.4 ± 5.0
6	83.0 ± 5.4	71.7 ± 9.1	12.3 ± 6.9
12	92.2 ± 6.5	78.9 ± 8.6	17.1 ± 8.1
18	79.9 ± 10.0	83.5 ± 5.4	34.6 ± 3.2
19	13.0 ± 11.9	55.3 ± 4.2	72.8 ± 3.9
20	37.3 ± 10.1	74.2 ± 4.2	28.5 ± 7.6
29	9.4 ±1 0.8	54.0 ± 5.3	5.0 ± 5.4
32	65.0 ± 5.3	85.3 ± 8.3	42.2 ± 5.2
33	31.1 ± 12.0	67.4 ± 6.4	46.4 ± 5.6
35	28.9 ± 9.0	67.3 ± 3.4	45.2 ± 3.9
SB258585	5.8 ± 3.8	97.7 ± 1.7	5.0 ± 13.6
SB269970	-		104 ± 8.5

SB258585 : 5-HT6 antagonist

SB269970 : 5-HT7 antagonist

Graphical Abstract

Design and synthesis of novel series of 5-HT$_6$ receptor ligands having indole, a central aromatic core and 1-amino-4methyl piperazine as a positive ionizable group

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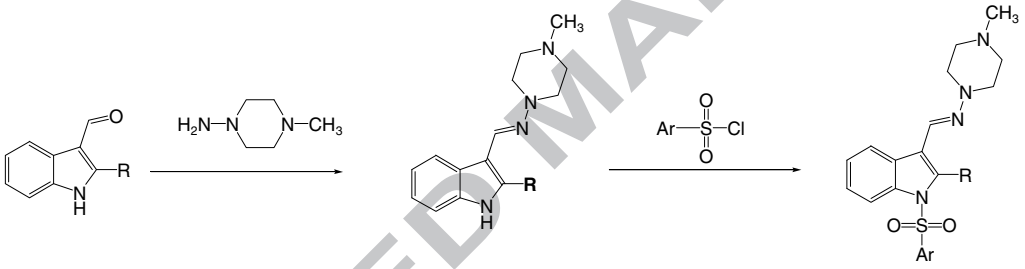

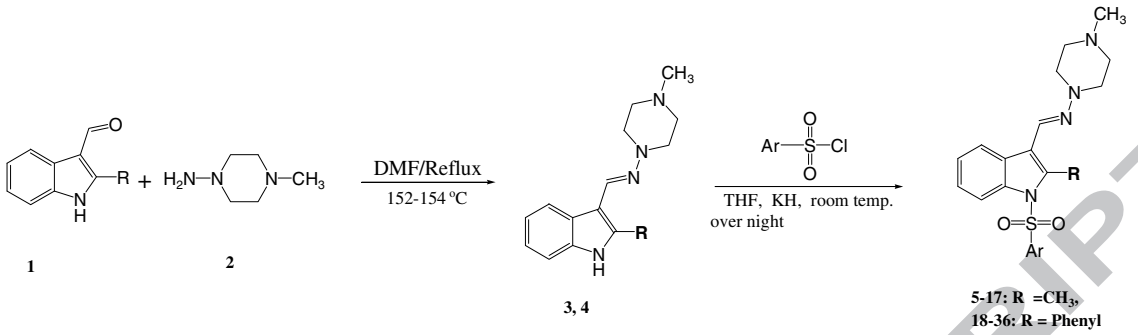

Scheme 1: General Method for the Synthesis of (2-methyl-1-(Ar-sulfonyl)-1H-indol-3-yl)-N-(4-methylpiperazin-1-yl)methanimine (5-17) and N-(4-methylpiperazin-1-yl)(2-phenyl-1-(Ar-sulfonyl)-1H-indol-3-yl)methanimine (18-36)