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5-Piperazinyl-3-sulfonylindazoles as Potent and Selective 5-Hydroxytryptamine-6 Antagonists

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As part of our efforts to develop agents for CNS diseases, we have been focused on the 5-HT_6 receptor in order to identify potent and selective ligands for cognitive enhancement. Herein we report the identification of a novel series of 5-piperazinyl-3-sulfonylindazoles as potent and selective 5-HT_6 antagonists. The synthesis, SAR, and pharmacokinetic and pharmacological activities of some of the compounds including 3-(naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole (WAY-255315 or SAM-315) will be described.

Introduction

The 5-hydroxytryptamine-6 (5-HT_6[a]) receptor, first identified by molecular biology in early 1990s, has been a subject of intense research because of its CNS-selective location and unique pharmacology.[1] Over the past decade, a great number of 5-HT_6 ligands of both agonists and antagonists have been reported.[2−4] These compounds have served as excellent tools to investigate the functional role of the 5-HT_6 receptor in greater detail. Selected ligands are depicted in Figure 1 (**1**,[5,6] **2**,[7,8] **3**,[9,10] **4**,[11] **5**,[12] **6**,[13,14] and **7**[15,16]) showing the diversity of structural types in this area. Currently a number of compounds from these classes are believed to be active in phase I and phase II clinical trials for cognitive impairment in AD and schizophrenia.[12,17]

As part of our continuing efforts in a multitargeted approach to identifying therapeutics for CNS diseases such as schizophrenia and Alzheimer's disease (AD), we have been focused on several monoamine ligand receptors, the 5-HT_6 receptor being one of them, in order to identify potent and selective ligands as potential treatments for cognitive dysfunction.[18−21] Herein we report a series of 3-sulfonylpiperazinylindazoles of general type **8** (Figure 1) as potent and selective 5-HT_6 antagonists. The synthesis, SAR, and pharmacokinetic and pharmacological activities of this potent class of compounds will be described.

Chemistry

The general synthesis of *5-N*-alkyl piperazinyl-3-sulfonylindazoles of type **8** is depicted in Scheme 1. Nucleophilic substitution of 4-fluoronitrobenzenes **9** with *N*-alkylpiperazine provided **10**. Vicarious nucleophilic substitution with readily available chloromethylsulfones introduced the sulfonyl group to the core molecules (**11**). Reduction of the nitro group of **11** with Sn/HCl or catalytic hydrogenation followed by diazotization and cyclication under basic conditions afforded the final indozole compounds **14**. The indazoles **14** were further alkylated at the 1-position to provide additional substituted compounds such as **15**. In the case of the substitution reaction at the 1-position of the indazoles, alkylation at the 2-position occasionally was observed. However, the undesired isomer can be easily separated from the desired product through chromatography. In order to prepare the *N*-unsubstituted piperazine derivatives **16**, **15** was treated initially with ACECl followed by decomposition with MeOH. Although we successfully prepared a number of compounds **16** through this synthesis, in general the reaction required harsh reaction conditions (reflux with ACECl) and long reaction time (2 days) and often provided poor yields or no desired product. To address this issue, an improved synthesis of *N*-unsubstituted periazines **16** was developed and is depicted in Scheme 2. In this synthesis, the piperazine was initially protected with a carboxybenzyl (Cbz) group. The acid labile Cbz protecting group was chosen with the consideration that it can survive the subsequent diazotization conditions and yet be removed easily at the completion of the synthesis. Initially we attempted the vicarious nucleophilic substitution on 4-*N*-Cbz-piperazinyl substituted nitrobenzene (structure not shown). Failure to identify any desired product led us to modify the sequence of the functionalization of the nitrobenzene. In this case vicarious nucleophilic substitution on fluorobenzene **9** was carried out first, followed by addition of the substituted piperazine to **17** to afford the desired indazole precursors **18**. A similar reaction sequence to that depicted in Scheme 1 was then followed to provide the final compounds **16**.

Syntheses of compounds with the piperazine substituted at other positions of the aromatic core (4-, 6-, 7-) are depicted in Schemes 3−5. For the synthesis of 4-piperazyl analogues **26**, commercially available 2,6-difluorobenzaldehyde **21** was

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[a] Abbreviations: ACECl, 1-chloroethyl chloroformate; 5-HT_6, 5-hydroxytryptamine-6; AD, Alzheimer's disease; Cbz, carboxybenzyl; MED, minimum effective dose.

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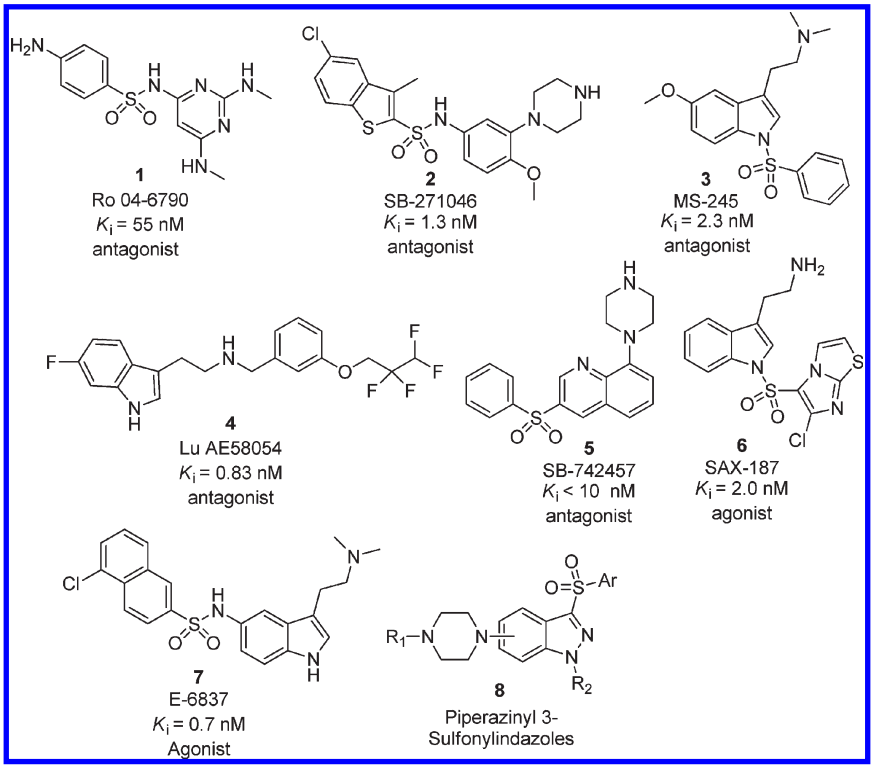
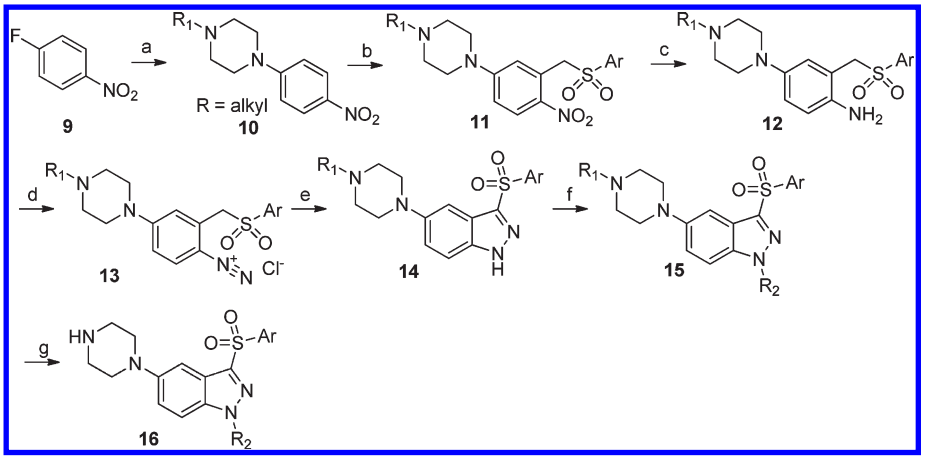


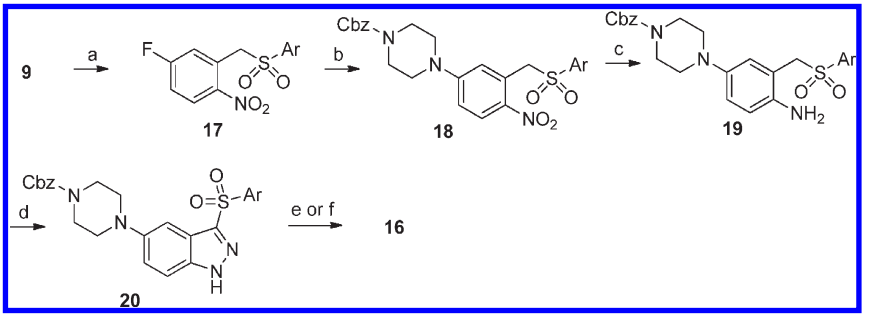
Figure 1. Selected 5-HT6 ligands.

Scheme 1[a]



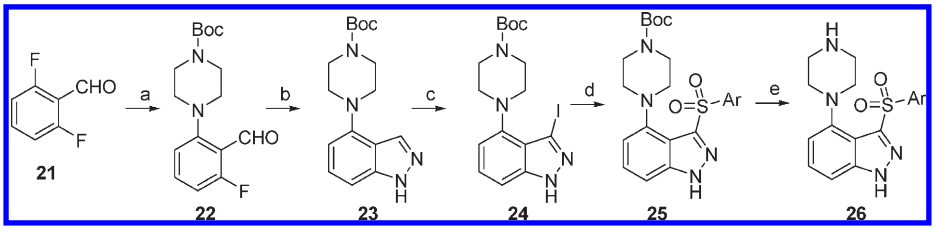
[a] Reagents and conditions: (a) *N*-alkylpiperazine, K_2CO_3, DMF (85−98%); (b) $ArCH_2Cl$, *t*-BuOK, THF (85−90%); (c) Sn, HCl or H_2, Pd/C (95−98%); (d) $NaNO_2$, HCl; (e) K_2CO_3 (80−95%, two steps); (f) R_2X, K_2CO_3 (50−90%); (g) ACECl, MeOH (20−50%).

Scheme 2[a]



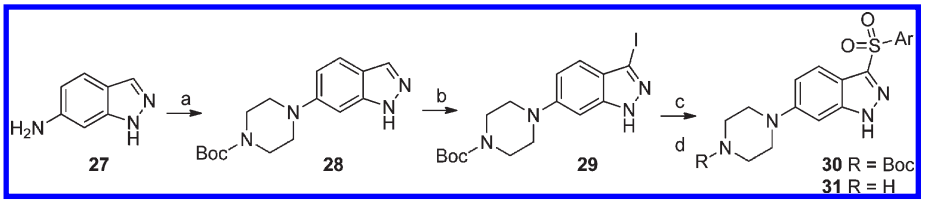
[a] Reagents and conditions: (a) $ArCH_2Cl$, *t*-BuOK, THF (80−90%); (b) *N*-Cbz-piperazine, K_2CO_3, DMF (85−98%); (c) $SnCl_2$/HCl, EtOH; (d) (i) $NaNO_2$, HCl, (ii) K_2CO_3 (60−85%, three steps) (e) HBr in HOAc (70−90%); (f) (i) HBr in HOAr, (ii) Boc_2O, (iii) R_2X, K_2CO_3, (iv) TFA (50−80%, three steps).

Scheme 3[a]



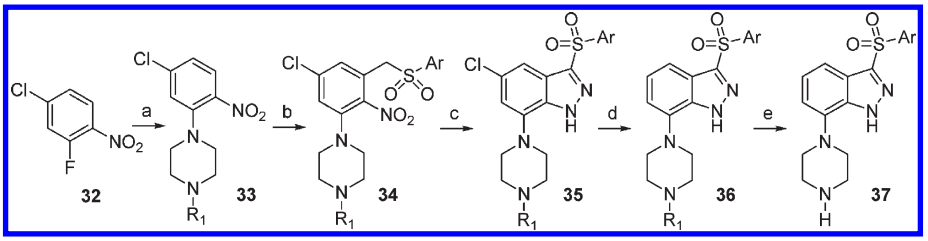
[a] Reagents and conditions: (a) *N*-Boc-piperazine, K_2CO_3 (71%); (b) NH_2NH_2, DMSO (57%); (c) I_2, KOH, DMF (35%); (d) $ArSO_2Na$, CuI, DMF (15−50%); (e) HCl, MeOH/Et_2O (40−90%).

Scheme 4[a]



[a] Reagents and conditions: (a) (i) $(ClCH_2CH_2)NH\cdot HCl$, K_2CO_3, *n*-BuOH; (ii) Boc_2O, KOH, 1,4-dioxane (38%, two steps); (b) I_2, KOH, DMF (38%); (c) $ArSO_2Na$, CuI, DMF (15−50%); (d) HCl, MeOH/Et_2O (40−90%).

Scheme 5[a]



[a] Reagents and conditions: (a) *N*-alkylpiperazine, K_2CO_3, DMF (80%); (a) $ArCH_2Cl$, *t*-BuOK, THF (85−90%); (c) (i) Sn, HCl or H_2, Pd/C, (ii) $NaNO_2$, HCl, (iii) K_2CO_3 (60−80%, three steps); (d) H_2, PtO_2/C (60−70%); (e) ACECl, MeOH (20−30%).

chosen as the starting point. Nucleophilic substitution with 1 equiv of *N*-Boc-piperazine provided the monosubstituted product **22**, which was then treated with NH_2NH_2 to form indazole **23**. Iodonation at the 3-position of indazole **23** under strong basic conditions afforded **24**. Coupling of **24** with a variety of sodium arylsulfinates provided compounds **25**, which readily furnished final compounds **26** by facile removal of the Boc protecting group.

For the preparation of 6-substituted piperazyl analogues **31**, shown in Scheme 4, commercially available 6-aminoindazole **27** was reacted with bis(chloroethyl)amine followed by capture of the product with a Boc protecting group. A reaction sequence similar to that utilized for the 4-substituted analogues (iodination, sulfination, deprotection) was then followed to provide the final compounds **31**.

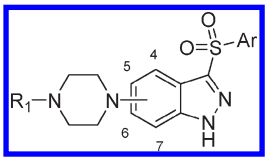
For the synthesis of the 7-substituted piperazinyl derivatives **37** (Scheme 5) we had to overcome issues with regiospecific functionalization of the aromatic core. To that end, a chloro group was used to block one of the possible substitution sites. Addition of the *N*-alkylpiperazine to 4-chloro-2-fluoronitrobenzene afforded 2-substituted derivatives **33**. Now with the 4-position effectively blocked from nucleophilic substitution, the addition of the sulfonyl moiety is uncomplicated and carried out in excellent yields to afford **34**. Cyclization as before affords indazoles **35**, and removal of the chloro group is effected under standard dehalogenating reductive conditions. Removal of the alkyl group of the piperazine **36**, as before, afforded the desired 7-substituted indazoles **37**.

Results and Discussion

With access to all possible regioisomeric piperazinylindazoles **8** at hand, evaluation of their binding affinity to the target receptor, human 5-HT_6 receptor, in a standard competition binding assay was conducted.[22] Potent compounds (K_i < 20 nM) were further investigated for their functional activity in a 5-HT_6 receptor cyclase assay.[22] The results are summarized in Tables 1 and 2.

Initially we carried out extensive SAR of the arylsulfonyl groups with the piperazine substitution at the 5-position (**8af-8at**, Table 1). In general, this chemical series has a relatively flat SAR in this region. A variety of arylsulfonyl group substitution provided very potent compounds including the unsubstituted phenyl derivative **8af** (K_i = 1.9 nM). Nonetheless, there is a clear trend that the 3-substituted phenylsulfonyl groups such as 3-F-$PhSO_2$ (**8ah**, K_i = 1.7 nM), 3-Cl-$PhSO_2$ (**8ak**, K_i = 1.0 nM), 3-MeO-$PhSO_2$ (**8am**, K_i = 1.1 nM), and 3-Me-Ph-SO_2 (**8ao**, K_i = 0.9 nM) are preferred over other their 2- or 4-substituted counterparts. Heterocyclic and disubstituted phenylsulfonyl groups were also tolerated and afforded potent analogues (e.g., **8aq** and **8ar**). One of the more preferred sulfonyl groups identified was 1-naphthalenesulfonyl group (**8at**) with K_i = 1.1 nM. In general, and in alliance with our experience with other active 5-HT_6 series, the majority of compounds (**8af** −**at**) in the molecular binding assay with good potency also showed excellent activity in the cell-based 5-HT_6 receptor cyclase assay. Although in general there is a

Table 1. SAR of Piperazine Positions and $ArSO_2$ Groups[a]



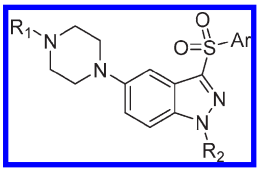
compd	position	R_1	Ar	K_i (nM)	IC_{50} (nM)	I_{max} (%)
8aa	4	H	3-F-Ph	134		
8ab	4	H	4-Cl-Ph	125		
8ac	4	H	4-Me-Ph	134		
8ad	4	H	4-MeO-Ph	88		
8ae	4	H	1-Naph	48		
8af	5	Me	Ph	1.9	8.8	99
8ag	5	Me	2-F-Ph	5.5	54	100
8ah	5	Me	3-F-Ph	1.7	132	99
8ai	5	Me	4-F-Ph	5.2	467	98
8aj	5	Me	2-Cl-Ph	4.0	101	100
8ak	5	Me	3-Cl-Ph	1.0	62	100
8al	5	Me	4-Cl-Ph	8.1	108	100
8am	5	Me	3-MeO-Ph	1.1	57	100
8an	5	Me	4-MeO-Ph	12	544	100
8ao	5	Me	3-Me-Ph	0.9	38	100
8ap	5	Me	4-Me-Ph	4.9	112	100
8aq	5	Me	2-thienyl	7.8	331	96
8ar	5	Me	2,6-diCl-Ph	2.6	40	100
8as	5	Me	1-Naph	1.6	8	100
8at	5	H	1-Naph	1.1	13	100
8au	6	H	3-F-Ph	11		
8av	6	H	4-Cl-Ph	110		
8aw	6	H	4-Me-Ph	27		
8ax	6	H	4-MeO-Ph	124		
8ay	6	H	4-CF_3-Me	207		
8bz	6	H	1-Naph	22		
8ba	7	Me	1-Naph	4.6	17	100

[a] Displacement of [^{3}H]LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[22] All compounds tested were HCl salts. K_i values were determined in triplicate.

correlation between the data of the binding and functional assays, exceptions happened more than sporadically. In these cases, unfortunately, we do not have good explanations. In the past we have seen differential functional efficacy within a series of compounds. However, all the compounds in this chemical series tested in the functional assay demonstrated full antagonism. Worthy of note is that alkylsulfonyl groups were not tolerated in this region and often provided significantly less active compounds (data not shown).

With the 1-naphthalenesulfonyl group (**8at**, K_i = 1.1 nM) identified as the preferred aryl substituent within 5-piperazinyl series derivatives, we then prepared the corresponding compounds with the piperazine at other alternative positions (4-, 6-, and 7-) on the phenyl ring. One can easily see that 5-piperazinyl derivative defines the optimal position for these arylsulfonyl substituted analogues. Compound **8ba** with the piperazine at the 7-position (K_i = 4.6 nM) is nearly 5-fold less potent than the 5-substituted analogue, **8at**, while compounds **8ae** (K_i = 48 nM) and **8az** (K_i = 22 nM), with a piperazine at 4- and 6-positions, respectively, are much less potent than **8at**. This trend of the 5-piperazinyl analogues being preferred was further affirmed by the decreased potency of other compounds with the piperazine at the 4- or 6-position (**8aa**−**ad**, **8au**−**ay**) compared to their 5-position counterparts. In addition, it was observed that unsubstituted piperazine and *N*-Me piperazine derivatives **8at** and **8as** have comparable potency

Table 2. SAR of the *N*1-Substitution[a]



compd	R_1	R_2	Ar	K_i (nM)	IC_{50} (nM)	I_{max} (%)
8bb	H	Me	Ph	3.2	46	100
8bc	H	Et	Ph	2.9	108	100
8bd	Me	Me	1-Naph	1.7	16	100
8be	H	Me	1-Naph	1.6	80	99
8bf	Me	Et	1-Naph	1.7	18	100
8bg	H	Et	1-Naph	1.9	92	100
8bh	Me	*n*-Pr	1-Naph	1.8	18	100
8bi	H	*n*-Pr	1-Naph	2.2	40	99
8bj	Me	*i*-Pr	1-Naph	1.8	17	98
8bk	H	*i*-Pr	1-Naph	2.9	52	100
8bl	Me	*i*-Bu	1-Naph	1.4	8	100
8bm	H	*i*-Bu	1-Naph	4.6	50	100
8bn	Me	Bn	1-Naph	2	7.2	100
8bo	H	Bn	1-Naph	7.5	32	100

[a] Displacement of [^{3}H]LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[22] All compounds tested were HCl salts. K_i values were determined in triplicate.

(K_i = 1.1 and 1.6 nM, IC_{50} = 13 and 8 nM, respectively). However, larger alkyl and benzyl substituted derivatives afforded compounds with significantly reduced potency at the 5-HT_6 receptor (data not shown).

Next we investigated the SAR of the *N*1-substitution, shown in Table 2. In general, substitution at this position resulted in a slight loss of potency with larger alkyl groups in particular. Although the compounds were less potent, we did discover that these *N*1-substituted compounds possess improved pharmacokinetic properties worthy of additional interest (vide infra).

A number of selected compounds that displayed satisfactory potency in both the binding and cyclase functional assays were further profiled for their selectivity against a panel of receptors including several other 5-HT receptor subtypes, adrenergic α2A and dopamine D_2 receptors, and the data are summarized in Table 3. In general, these compounds showed >200-fold selectivity over all the receptors examined with the exception of 5-HT_{2B}. This was initially some concern to us, as 5-HT_{2B} agonism activity has been indicted by several studies to possibly be responsible for adverse cardiovascular effects associated with some serotonin ligands.[23] To rule out the adverse potential of these analogues, they were then screened for their potential functional agonist activity in a 5-HT_{2B} FLIPR assay.[24] To our satisfaction, no agonist activity was observed for all compounds at 0.1 nM to 10 μM in this functional assay.

In pharmacokinetic studies **8as** displayed 5% bioavailability following oral administration in rats at a 10 mg/kg dose. However, the des-methyl derivative **8at** (WAY-255315, later designated SAM-315), an independently synthesized analogue as well as the metabolite of **8as**, was identified as having optimized pharmacokinetic properties. To our satisfaction, **8at** showed improved bioavailability relative to **8as** in both rodents and dogs (F > 20%), although it maintained relatively poor brain exposure properties (brain/plasma of <0.20). Compound **8at** has excellent water solubility (>100 μg/mL) and low brain and plasma protein binding (80−85%) and

Table 3. Selectivity of Selected 5-Piperazinyl-3-sulfonylindazole Derivatives[a]

compd	5-HT$_6$ (nM)	5-HT$_{1a}$ (nM)	5-HT$_{1b}$ (nM)	5-HT$_{1d}$ (nM)	5-HT$_{2b}$ (nM)	5-HT$_{2c}$ (nM)	5-HT$_7$ (nM)	α2a (nM)	D$_2$ (nM)
8af	1.9	> 5000	> 5000	> 5000	978	3067	753	> 5000	355
8as	1.6	> 5000	> 5000	> 5000	601	> 5000	579	> 5000	334
8at	1.1	573	> 5000	> 5000	236	> 5000	1563	> 5000	> 5000
8be	1.6	1780	3624	2761	87	3648	> 5000	> 5000	2243
8bk	2.9	> 5000	> 5000	> 5000	96	1075	> 5000	> 5000	2036
8bm	4.6	> 5000	> 5000	> 5000	281	1880	> 5000	> 5000	1903
8bo	7.5	> 5000	> 5000	> 5000	141	1070	> 5000	> 5000	605

[a] K_i values were determined in triplicate.

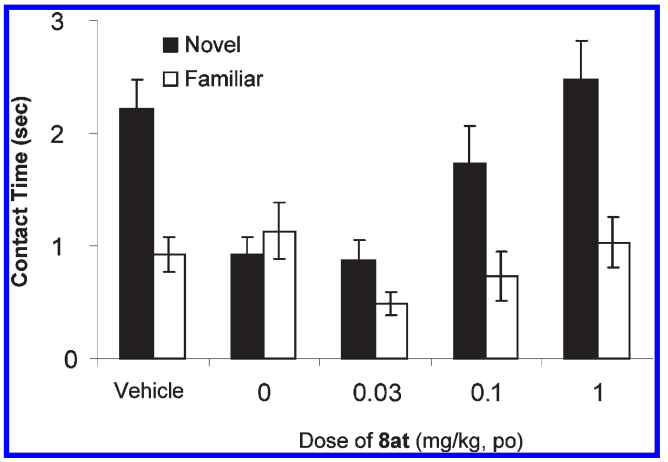


Figure 2. 8at blocks a scopolamine-induced memory deficit in a novel object recognition task in rats.

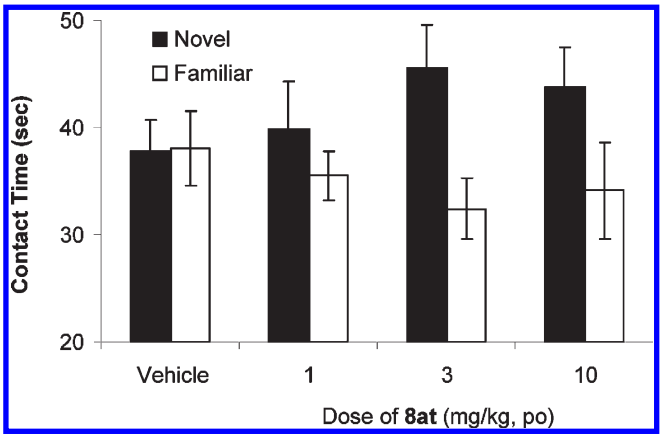


Figure 3. 8at enhances memory after a 48 h delay in a novel object recognition task in rats.

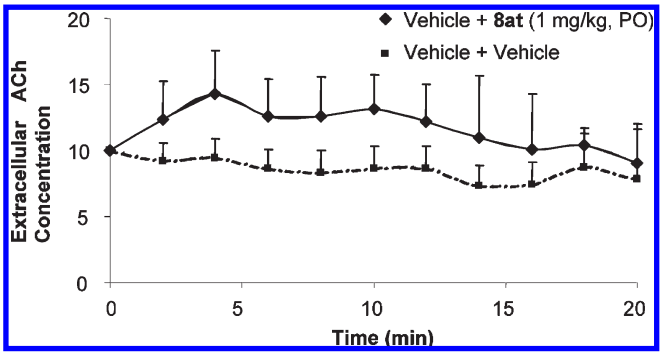


Figure 4. 8at increases in acetylcholine (ACh) release in rat brains.

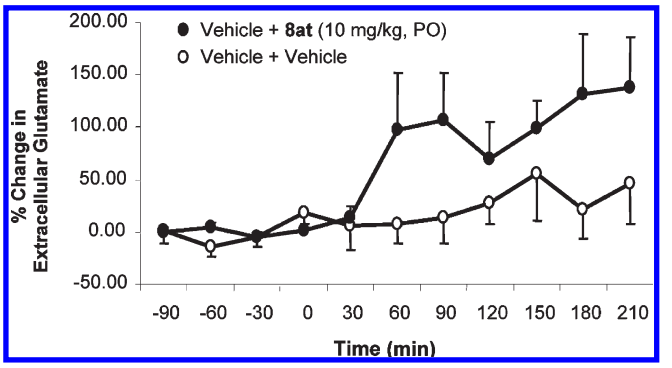


Figure 5. 8at increases glutamate release in rat brains.

displayed over 200-fold selectivity over more than 80 other receptors, enzymes, and ion channels. In the novel object recognition assay (NOR) in rats,[25] **8at** significantly blocked scopolamine-induced memory deficit with an MED of 0.03 mg/kg (Figure 2) and enhanced retention after a 48 h delay with an MED of 3 mg/kg (Figure 3) in a dose-dependent manner. In the in vivo microdialysis studies in rats,[26] **8at** significantly increased acetylcholine and glutamate release in hippocampus of the brain in a time-course study (Figures 4 and 5).

To further improve the physical properties of the 5-piperazinyl-3-sulfonylindazoles series, compounds with *N*1-alkyl substitution were synthesized. As mentioned previously, *N*1-alkyl compounds (e.g., **8bk**, **8bm**, and **8bo**) displayed improved pharmacokinetic properties including both oral bioavailability and brain penetration. For example, compound **8bo** showed > 50% oral bioavailability in rodents and a brain/plasma ratio greater than 0.5 following oral administration. Further profiling of these *N*1-alkylated compounds will be reported in due course.

In summary, we have identified a novel series of 5-piperazinyl-3-sulfonylindazoles as potent, selective, orally available, and brain-penetrant 5-HT$_6$ antagonists. Synthesis and detailed SAR of this class of compounds have been reported. Compound **8at** has been identified as an advanced candidate with greater than 200-fold selectivity verses more than 80 receptors, ion channels, and enzymes and desired physical and pharmacokinetic properties. Compound **8at** displayed good efficacy in a variety of cognitive behavioral assays and increased release of neurotransmitters such as acetylcholine and glutamate in the brain as measured by microdialysis.

Experimental Section

General. All solvents and reagents were obtained commercially and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a Varian instrument in the cited deuterated solvents. Chemical shifts are given in ppm, and coupling constants are in hertz. All final compounds were purified by flash chromatography using 220−400 mesh silica gel or reverse-phase HPLC with CH_3CN/water as the solvents. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 nm thickness)

plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol. Nominal (low resolution) mass spectra were acquired on either a Waters LCT or an Applied Biosystems API 3000 mass spectrometer. High resolution mass spectra (HRMS) were acquired on either a Waters LCT or an Agilent TOF mass spectrometer. All other LC−MS experiments were done on an Agilent 1100 HPLC coupled with an Agilent single quadrupole mass spectrometer. Compound purity was determined by a LC−MS with 230 and 254 nm wavelengths. All final compounds reported here have purity of ≥95%.

1-Me-4-(4-nitrophenyl)piperazine (10, R_1 = Me). A stirred solution of 1-methylpiperazine (3.55 g, 35.4 mmol), 4-fluoronitrobenzene (5.0 g, 35.4 mmol), and K_2CO_3 (4.9 g, 35.4 mmol) in DMF is heated at 70 °C under nitrogen for 18 h, cooled, diluted with water, and extracted with EtOAc. The combined extracts are dried over $MgSO_4$ and concentrated in vacuo to give a solid residue. The solid is triturated with 20:80 ethyl acetate−hexanes and filtered. The filtercake is air-dried to afford the title compound as orange crystals, 7.8 g (89% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.19 (d, 3 H), 2.40 (t, J = 5.1 Hz, 4H), 3.47 (t, J = 5.0, 4H), 7.00 (d, J = 9.9 Hz, 2H), 8.01 (d, J = 9.8 Hz, 2H). MS (ES$^+$) m/e 222 (M + H)$^+$.

1-Methyl-4-{4-nitro-3-[(1-naphthalenesulfonyl)methyl]phenyl}-piperazine (11, R_1 = Me, Ar = 1-Naph). A stirred solution of 1-methyl-4-(4-nitrophenyl)piperazine (4.0 g, 18.1 mmol) and chloromethyl-1-naphthalenesulfonyl (4.35 g, 18.1 mmol) in dry THF under nitrogen at −60 °C is treated with 1.0 M KO-*t*-Bu in THF (40 mL, 40 mmol), warmed to −20 °C over a 1 h period, quenched with acetic acid, and treated sequentially with water, saturated aqueous $NaHCO_3$, and ether. The phases are separated, and the aqueous phase is extracted with ether. The combined ethers are washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue is chromatographed (silica gel, 1:1 and 1:0 ethyl acetate−hexanes as eluent) to give the title compound as a yellow solid, 6.72 g (87% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (d, 3 H), 2.23 (t, J = 5.1 Hz, 4H), 3.10 (t, J = 5.0, 4H), 5.22 (s, 2H), 6.82−8.60 (m, 10H). MS (ES$^+$) m/e 426 (M + H)$^+$.

4-(4-Methylpiperazine-1-yl)-2-[(1-naphthalenesulfonyl)methyl]-aniline (12, R_1 = Me, Ar = 1-Naph). A mixture of 1-benzyl-4-{4-nitro-3-[(1-naphthalenesulfonyl)methyl]phenyl}piperazine (6.77 g, 15.0 mmol) and granular tin (7.48 g, 63.0 mmol) in methanol and concentrated hydrochloric acid is heated at 45 °C for 4 h, stirred at ambient temperature for 18 h, carefully poured into saturated aqueous $NaHCO_3$, treated with ether, and stirred for 0.5 h. The phases are separated, and the aqueous phase is extracted sequentially with ether and CH_2Cl_2. The extracts and organic phase are combined, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue is dissolved in CH_2Cl_2 and filtered through Celite. The filtrate is concentrated in vacuo to afford the title compound as a pale yellow solid, 6.11 g (97% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.10 (d, 3 H), 2.20 (t, J = 5.1 Hz, 4H), 2.37 (t, J = 5.0, 4H), 4.60 (s, 2H), 6.40−6.50 (m, 2H), 7.61−8.62 (m, 8H). MS (ES$^+$) m/e 396 (M + H)$^+$.

3-(2-Fluorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8ag). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.85 (b, 3H), 3.11−3.30 (m, 4H), 3.53 (b, 2H), 3.78 (b, 2H), 7.32 (s, 1H), 7.39−7.48 (m, 2H), 7.50−7.51 (m, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.75−7.85 (m, 1H), 8.1−8.2 (m, 1H). MS (ES$^+$) m/e 375 (M + H)$^+$.

3-(3-Fluorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8ah). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 (d, J = 4.6 Hz, 3H), 3.10−3.25 (m, 4H), 3.54−3.56 (m, 2H), 3.85−3.86 (m, 2H), 7.36 (d, J = 2.2, 1H), 7.36−7.88 (m, 6H). MS (ES$^+$) m/e 375 (M + H)$^+$.

3-(4-Fluorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8ai). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.15−3.4 (m, 8H), 7.27 (d, J = 1.7 Hz, 1H), 7.25−7.50 (m, 4H), 8.00−8.10 (m, 2H). MS (ES$^+$) m/e 375 (M + H)$^+$.

3-(2-Chlorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8aj). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3H), 3.00−3.20 (m, 8H), 7.05−7.21 (m, 2H), 7.50−7.65 (m, 4H), 8.16 (dd, J = 7.7 and 1.4 Hz, 1H). MS (ES$^+$) m/e 391 (M + H)$^+$.

3-(3-Chlorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8ak). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.10−3.20 (m, 8H), 7.20−7.30 (m, 2H), 7.51−7.95 (m, 5H). MS (ES$^+$) m/e 391 (M + H)$^+$.

3-(4-Chlorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8al). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.20−3.40 (m, 8H), 7.15−7.55 (m, 3H), 7.63 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H). MS (ES$^+$) m/e 391 (M + H)$^+$.

3-(3-Methoxyphenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8am). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.85 (s, 3H), 3.15−3.40 (m, 8H), 7.15−7.55 (m, 7H). MS (ES$^+$) m/e 387 (M + H)$^+$.

3-(4-Methoxyphenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8an). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.16−3.38 (m, 8H), 3.76 (s, 3H), 7.06 (d, J = 9.0 Hz, 2H), 7.15−7.45 (m, 3H), 7.87 (d, J = 9.0 Hz, 2H). MS (ES$^+$) m/e 387 (M + H)$^+$.

5-(4-Methylpiperazin-1-yl)-3-(*m*-tolylsulfonyl)-1*H*-indazole (8ao). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 2.33 (s, 3H), 3.10−3.20 (m, 8H), 7.18 (d, J = 2.1 Hz, 1H), 7.28 (dd, J = 9.2 and 2.1 Hz, 1H), 7.40−7.80 (m, 5H). MS (ES$^+$) m/e 371 (M + H)$^+$.

5-(4-Methylpiperazin-1-yl)-3-tosyl-1*H*-indazole (8ap). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 2.30 (s, 3H), 3.09−3.11 (m, 8H), 7.20−7.30 (m, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.50 (d, J = 7.5 Hz, 1H), 7.82 (d, J = 8.3 Hz, 2H). MS (ES$^+$) m/e 371 (M + H)$^+$.

5-(4-Methylpiperazin-1-yl)-3-(thiophen-2-ylsulfonyl)-1*H*-indazole (8aq). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.10−3.20 (m, 8H), 7.15−7.35 (m, 3H), 7.50 (d, J = 9.1 Hz, 1H), 7.80−8.00 (m, 2H). MS (ES$^+$) m/e 363 (M + H)$^+$.

3-(2,6-Dichlorophenylsulfonyl)-5-(4-methylpiperazin-1-yl)-1*H*-indazole (8ar). The title compound was prepared using essentially the same procedure as described for the preparation of **8as**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.19 (s, 3H), 3.10−3.40 (m, 8H), 7.12 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 9.3 and 2.2 Hz, 1H), 7.50−7.65 (m, 4H). MS (ES$^+$) m/e 425 (M + H)$^+$.

5-(4-Methylpiperazin-1-yl)-3-(1-naphthalenesulfonyl)-1*H*-indazole (8as, R_1 = Me, Ar = 1-Naph). A stirred solution of 4-(4-methylpiperazine-1-yl)-2-[(1-naphthalenesulfonyl)methyl]aniline (5.0 g, 12.6 mmol) in 4.0 M aqueous hydrochloric acid is cooled in an ice bath, treated dropwise with $NaNO_2$ (1.31 g, 19.0 mmol) in water, stirred for 40 min, treated with 2.5 M aqueous NaOH to pH ~14, and filtered. The filtercake is dissolved in CH_2Cl_2 and chromatographed (silica gel, ethyl acetate as eluent) to afford the free indazole of the title product as a yellow solid (4.7 g, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.50 (s, 3H), 3.10 (b, 2H), 3.20 (b, 2H), 3.53 (b, 2H), 3.80 (b, 2H), 7.27 (d, J = 1.8 Hz, 1H), 7.37 (dd, J = 9.2 and 2.1 Hz, 1H), 7.60−7.80 (m, 4H), 8.09 (d, J = 7.9 Hz, 1H), 8.32 (d, J = 8.2 Hz, 1H), 8.59 (d, J = 8.6 Hz, 1H), 8.82 (d, J = 8.4 Hz, 1H). MS (ES$^+$) m/e 407 (M + H)$^+$.

3-(Naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole (8at, Ar = 1-Naph). A mixture of benzyl 4-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl)piperazine-1-carboxylate (2.50 g, 4.75 mmol) and 30% HBr in HOAc (13.6 mL) was stirred at room temperature for 2 h. Et_2O (80 mL) was added. The brown precipitate was filtered, washed with Et_2O, treated with NaOH (1 N, 20 mL), and extracted with 20% MeOH in EtOAc. Combined extracts were dried over Na_2SO_4 and concentrated in vacuo to provide the title compound (1.48 g, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.22 (b, 4H), 3.32−3.33 (m, 4H), 7.21−7.32 (m, 2H), 7.52−7.74 (m, 3H), 8.03 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 7.2 Hz, 1H), 8.52 (d, J = 7.3 Hz, 1H), 8.76 (d, J = 7.5 Hz, 1H), 9.15 (b, 1H). MS (ES$^+$) m/e 393 (MH$^+$).

1-Methyl-5-(4-methylpiperazin-1-yl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazole (8bd). The title compound was prepared using essentially the same procedure as described for the preparation of **8bf**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.20 (s, 3H), 3.15−3.41 (m, 8H), 4.02 (s, 3H), 7.10−7.75 (m, 6H), 8.05−8.80 (m, 4H). MS (ES$^+$) m/e 421 (M + H)$^+$.

1-Methyl-3-(naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole Dihydrochloride (8be). The title compound was prepared using essentially the same procedure as described for the preparation of **7.39** (61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.32−3.52 (m, 8 H), 4.03 (s, 3 H), 7.22 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 9.4 and 2.3 Hz, 1H), 7.55−7.73 (m, 2H), 8.02 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.51 (d, J = 7.4 Hz, 1H), 8.75 (d, J = 8.5 Hz, 1H), 9.18 (b, 2H). MS (ES$^+$) m/e 407 (MH$^+$).

1-Ethyl-5-(4-methylpiperazin-1-yl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazole Hydrochloride (8bf, R_1 = Me, Ar = 1-Naph). A mixture of 5-(4-methylpiperazin-1-yl)-3-(1-naphthalenesulfonyl)-1*H*-indazole hydrochloride (70 mg, 0.17 mmol), bromoethane (27 mg, 0.17 mmol), and KOtBu in THF (0.2 mL, 0.2 mmol) in DMF is stirred for 16 h at room temperature and diluted with water and EtOAc. The organic phase is separated, dried over $MgSO_4$, and concentrated in vacuo. The resultant residue is chomatographed (SiO_2, 80:20, then 90:10 EtOAc−hexanes as eluent) to afford the free amine of the title product as a white solid (30 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (t, J = 7.2 Hz, 3H), 2.19 (s, 3H), 3.15−3.40 (m, 8H), 4.45 (q, J = 7.2 Hz, 2H), 7.05−7.80 (m, 6H), 8.00−8.50 (m, 4H). MS (ES$^+$) m/e 435 (M + H)$^+$.

1-Ethyl-3-(naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole Dihydrochloride (8bg). The title compound was prepared using essentially the same procedure as described for the preparation of **8bm** (57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (t, J = 7.2 Hz, 3H), 3.2 (b, 4H), 3.30−3.32 (m, 4H), 4.43 (t, J = 7.2 Hz, 2H), 7.16 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 9.3 and 2.1 Hz, 1H), 7.55−7.73 (m, 4H), 8.02 (d, J = 7.6 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.52 (dd, J = 7.4 and 1.2 Hz, 1H), 8.79 (d, J = 8.6 Hz, 1H), 9.10 (b, 2H). MS (ES$^+$) m/e 421 (MH$^+$).

3-(Naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1-propyl-1*H*-indazole Dihydrochloride (8bi). The title compound was prepared using essentially the same procedure as described for the preparation of **8bm** (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.62 (t, J = 7.6 Hz, 3H), 1.73 (q, J = 7.0 Hz, 2H), 3.21 (b, 4H), 3.26−3.32 (m, 4H), 4.38 (t, J = 6.7 Hz, 2H), 7.14 (d, J = 2.1 Hz, 1H), 7.33 (dd, J = 9.4 and 2.2 Hz, 1H), 7.55−7.73 (m, 4H), 8.02 (d, J = 9.3 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.53 (dd, J = 7.3 and 1.2 Hz, 1H), 8.76 (d, J = 8.6 Hz, 1H), 9.09 (b, 2H). MS (ES$^+$) m/e 435 (MH$^+$).

1-Isopropyl-5-(4-methylpiperazin-1-yl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazole (8bj). The title compound was prepared using essentially the same procedure as described for the preparation of **8bf**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 (d, J = 6.6 Hz, 6H), 2.20 (s, 3H), 3.20−3.41 (m, 8H), 4.96−5.03 (m, 1H), 7.00−7.75 (m, 6H), 8.00−8.90 (m, 4H). MS (ES$^+$) m/e 449 (M + H)$^+$.

1-Isopropyl-3-(naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole dihydrochloride (8bk). The title compound was prepared using essentially the same procedure as described for the preparation of **8bm** (30%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (d, J = 6.6 Hz, 6H), 3.21−3.30 (m, 8H), 4.99−5.03 (m, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 9.3 and 2.2 Hz, 1H), 7.55−7.74 (m, 4H), 8.01 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.52 (dd, J = 7.4 and 1.1 Hz, 1H), 8.86 (d, J = 8.8 Hz, 1H), 8.98 (b, 2H). MS (ES$^+$) m/e 435 (MH$^+$).

1-Isobutyl-5-(4-methylpiperazin-1-yl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazole (8bl). The title compound was prepared using essentially the same procedure as described for the preparation of **8bf**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.68 (d, J = 6.7 Hz, 6H), 2.20 (s, 3H), 2.26−2.29 (m, 1H), 3.20 (b, 3H), 3.30−3.40 (m, 8H), 4.22 (d, J = 7.2 Hz, 2H), 7.00−7.75 (m, 6H), 8.01−8.80 (m, 4H). MS (ES$^+$) m/e 463 (M + H)$^+$.

1-Isobutyl-3-(naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole Dihydrochloride (8bm). *tert*-Butyl 4-(1-isobutyl-3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl)piperazine-1-carboxylate (0.40 g, 0.73 mmol) was treated with TFA (20 mL) at room temperature for 1 h. The reaction mixture was concentrated to dryness. The residue was dissolved in EtOAc and was added to Et_2O. The precipitate was filtered and washed with Et_2O and dried in vacuo to provide the title compound (0.34 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.66 (d, J = 6.6 Hz, 6H), 2.05−2.12 (m, 1H), 3.20 (b, 4H), 3.31−3.34 (m, 4H), 4.23 (d, J = 7.2 Hz, 2H), 7.12 (d, J = 2.0 Hz, 1H), 7.33 (dd, J = 9.4 and 2.2 Hz, 1H), 7.54 (m, 2H), 7.70−7.74 (m, 2H), 8.00−8.02 (m, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.54 (dd, J = 7.4 and 1.0 Hz, 1H), 8.75 (dd, J = 9.6 and 1.6 Hz, 1H), 9.29 (b, 2H). MS (ES$^+$) m/e 449 (MH$^+$).

1-Benzyl-5-(4-methylpiperazin-1-yl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazole (8bn). The title compound was prepared using essentially the same procedure as described for the preparation of **8bf**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (s, 3H), 2.45−2.47 (m, 4H), 3.03−3.06 (m, 4H), 5.66 (s, 2H), 7.00−7.74 (m, 11H), 8.01−8.77 (m, 4H). MS (ES$^+$) m/e 497 (M + H)$^+$.

1-Benzyl-3-(naphthalene-1-sulfonyl)-5-piperazin-1-yl-1*H*-indazole Dihydrochloride (8bo). The title compound was prepared using essentially the same procedure as described for the preparation of **8bm** (0.35 g, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.29 (b, 4H), 3.23−3.36 (m, 4H), 7.10−7.20 (m, 5H), 7.32 (dd, J = 9.4 and 2.3 Hz, 1H), 7.58−7.64 (m, 2H), 7.69−7.74 (m, 2H), 8.00−8.04 (m, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.55 (dd, J = 7.4 and 1.0 Hz, 1H), 8.75−8.78 (m, 1H), 9.23 (b, 2H). MS (ES$^+$) m/e 483 (MH$^+$).

1-(5-Fluoro-2-nitrobenzylsulfonyl)naphthalene (17, Ar = 1-Naph). To a stirred mixture of 4-fluoronitrobenzene (4.80 g, 34.1 mmol) and 1-(chloromethylsulfonyl)naphthalene (Aldrich, 8.20 g, 34.1 mmol) in THF (75 mL) at −78 °C was slowly added KO-*t*-Bu (1 M in THF, 75 mL). The stirred mixture was allowed to warm to room temperature for 2 h, quenched with water, and concentrated. The residue was taken into water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide the title compound (9.50 g, 81%). MS (ES$^+$) m/e 346 (MH$^+$).

Benzyl 4-(3-((Naphthalen-1-ylsulfonyl)methyl)-4-nitrophenyl)-piperazine-1-carboxylate (18, Ar = 1-Naph). A mixture of benzyl piperazine-1-carboxylate (3.19 g, 14.5 mmol), 1-(5-fluoro-2-nitrobenzylsulfonyl)naphthalene (5.00 g, 14.5 mmol), and K_2CO_3 (4.00 g, 29.0 mmol) in DMF (32 mL) was stirred at 100 °C for 3 h, cooled to room temperature, diluted with water, and extracted with EtOAc. The organic layer was washed with water (3×), dried over Na_2SO_4, and concentrated in vacuo to provide the title compound (7.82 g, 94%), characterized by NMR and mass spectral analyses. MS (ES$^+$) m/e 546 (MH$^+$).

Benzyl 4-(4-Amino-3-((naphthalen-1-ylsulfonyl)methyl)phenyl)-piperazine-1-carboxylate (19, Ar = 1-Naph). A mixture of benzyl 4-(3-((naphthalen-1-ylsulfonyl)methyl)-4-nitrophenyl)piperazine-1-carboxylate (7.82 g, 14.3 mmol), $SnCl_2$ (16.2 g, 71.7 mmol), and concentrated HCl (1.8 mL) in EtOH (191 mL) was heated at 80 °C overnight, diluted with CH_2Cl_2, and neutralized with Na_2CO_3 to basic condition. The mixture was passed through a pad of Celite. The solution was concentrated in vacuo to provide the crude title compound (7.72 g), which was carried forward into the next step of the reaction without further purification. MS (ES$^+$) m/e 516 (MH$^+$).

Benzyl 4-(3-(Naphthalen-1-ylsulfonyl)-1H-indazol-5-yl)piperazine-1-carboxylate (20, Ar = 1-Naph). To a solution of crude benzyl 4-(4-amino-3-((naphthalen-1-ylsulfonyl)methyl)phenyl)piperazine-1-carboxylate (7.72 g) in 1 N HCl (249 mL) and MeOH (500 mL) at 0 °C was added $NaNO_2$ solution (2.07 g, 29.9 mmol in 20 mL water) dropwise over a period of 10 min. The mixture was stirred for an additional 30 min, and carefully neutralized with $NaHCO_3$ solution to pH ~10. The brown precipitate was filtered and washed with water and dried in vacuo to provide the title compound (5.8 g, 77% overall, two steps), characterized by NMR and mass spectral analyses. MS (ES^+) *m*/*e* 527 (MH^+).

***tert*-Butyl 4-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl)piperazine-1-carboxylate.** A mixture of 3-(naphthalen-1-ylsulfonyl)-5-(piperazin-1-yl)-1*H*-indazole dihydrochloride salt (2.00 g, 4.00 mmol), Boc_2O (1.02 g, 4.66 mmol), and triethylamine (1.65 g, 16.3 mmol) in DMF (15.5 mL) was heated at 50 °C overnight, diluted with water, and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to provide the title compound (2.00 g, 99%), characterized by NMR and mass spectral analyses. MS (ES^+) *m*/*e* 493 (MH^+).

***tert*-Butyl 4-(1-Isobutyl-3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl)piperazine-1- carboxylate.** To a solution of *tert*-butyl 4-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl)piperazine-1-carboxylate (0.50 g, 1.02 mmol) in DMF (5.1 mL) was added KO-*t*-Bu (1 M THF solution, 1.5 mL) followed by isobutyl iodide (0.139 g, 1.02 mmol). The mixture was stirred overnight, diluted with water, and extracted with EtOAc. The organic layer was washed with water (3×), dried over Na_2SO_4, concentrated in vacuo, and purified by chromatography with EtOAc−hexanes to provide the title compound (0.401 g, 73%), characterized by NMR and mass spectral analyses. MS (ES^+) *m*/*e* 549 (MH^+).

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