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5-Cyclic Amine-3-arylsulfonylindazoles as Novel 5-HT$_6$ Receptor Antagonists

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Novel 5-cyclic amine-3-arylsulfonylindazoles were prepared, and several analogues within this class have been identified as high-affinity 5-HT$_6$ receptor ligands with improved pharmacokinetic and pharmacological properties. One selected example, **18b**, showed good brain penetrability and a generally favorable pharmacokinetic profile with procognitive efficacy in the rat novel object recognition assay. The synthesis and structure−activity relationship of this potent class are discussed.

Introduction

The serotonin-6 receptor (5-HT$_6$) is a G-protein-coupled receptor (GPCR[a]) predominantly expressed in the central nervous system (CNS). In particular, it is widely reported to be located in brain regions associated with learning and memory such as the cerebral cortex, the hippocampus, and the striatum.[1] It has been demonstrated that antagonism of the 5-HT$_6$ receptor modulates the release of a wide variety of neurotransmitters including elevating extracellular levels of both glutamate and acetylcholine in brain regions such as the medial prefrontal cortex (mPFC) and the hippocampal formation (HPC).[2,3] This modulatory activity suggests potential utility for 5-HT$_6$ receptor antagonists in the treatment of cognitive impairments associated with Alzheimer's disease and schizophrenia.

Research efforts in this area have led to the discovery of a number of potent and selective 5-HT$_6$ agonists and antagonists over the past decade. In 1998, scientists at Roche described a series of pyrimidinyl- and pyridinylsulfonamides, Ro 04-6790 (**1**) and Ro 63-0563 (**2**),[4] respectively (Figure 1), which were among the first selective 5-HT$_6$ receptor antagonists reported. Shortly thereafter, Bromidge and co-workers further reported a series of sulfonamides, including SB-271046 (**3**)[5] and SB-357134 (**4**)[6] as potent and selective 5-HT$_6$ receptor antagonists. A series of compounds, such as MS-245 (**5**), built on a tryptamine backbone[7] were reported by Russell and co-workers. One can not help but note the similar structural features of these ligands, with each of these novel antagonists sharing a common sulfonamide moiety. Further progress in this area led to an increase in the diversity of the structure types being identified. In a second generation of 5-HT$_6$ receptor antagonists reported, Cole et al. replaced the indole backbone with an indazole core exemplified by WAY-101 (**6**).[8−10] In a marked departure from the sulfonamide or tryptamine moieties of the compounds listed previously, scientists at Hoffmann-LaRoche and Pharmacia-Upjohn reported analogues (**7**)[11] and (**8**),[12] respectively, bearing an aromatic sulfone, showing the nondiscriminative nature of the serotonin receptor subtype.

There is an impressive preclinical proof-of-concept support for the utility of the 5-HT$_6$ receptor. In a variety of animal studies, antagonism of the 5-HT$_6$ receptor has been demonstrated to increase acetylcholine- and glutamate-mediated neurotransmission in brain regions such as the cortex and hippocampus.[2,3,13−15] The observed increase in these neurotransmitters, in brain regions associated with cognition, are consistent with potential procognitive effects of selective 5-HT$_6$ receptor antagonists. However, despite the high affinity and selectivity of many of these chemotypes, several of these leads suffered from poor penetration across the blood−brain barrier,[6,12] potentially impeding their further development although providing excellent tools for proof-of-concept studies. Clinical proof-of-concept is encouraging, as recent phase II clinical data with SB-742457 (**9**) have demonstrated efficacy in cognition trials. Positive effects have been reported with this selective 5-HT$_6$ receptor antagonist in blocking a scopolamine-induced cognitive deficit in healthy volunteers.[16] Continued clinical research and the optimization of advanced compounds will further explore the potential utility of these ligands for the treatment of Alzheimer's disease, schizophrenia, and other cognitive disorders.

The purpose of our present research was to identify novel, potent 5-HT$_6$ antagonists with enhanced selectivity against neighboring GPCR receptors with good brain-penetrating properties that might be useful as potential therapeutics. Our early research[8−10] identified several potent compounds that demonstrated activity in a variety of rodent cognitive models. These compounds, although excellent tools, suffered from modest brain exposure, limiting their potential utility. To further expand our chemical diversity and identify higher affinity scaffolds, we adapted the principals of a pharmacophore model developed by Holenz et al.[17] to our discovery

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[a] Abbreviations: GPCR, G-protein coupled receptor; CNS, central nervous system; 5-HT, 5-hydroxytryptamine; mPFC, medial prefrontal cortex; HPC, hippocampus; VNS, vicarious nucleophilic substitution; Boc, *tert*-butyl carbonyl; cAMP, cyclic adenosine monophosphate; SAR, structure−activity relationship; NOESY, nuclear Overhauser effect spectroscopy; HMBC, heteronuclear multiple bond correlation; IP, intraperitoneal.

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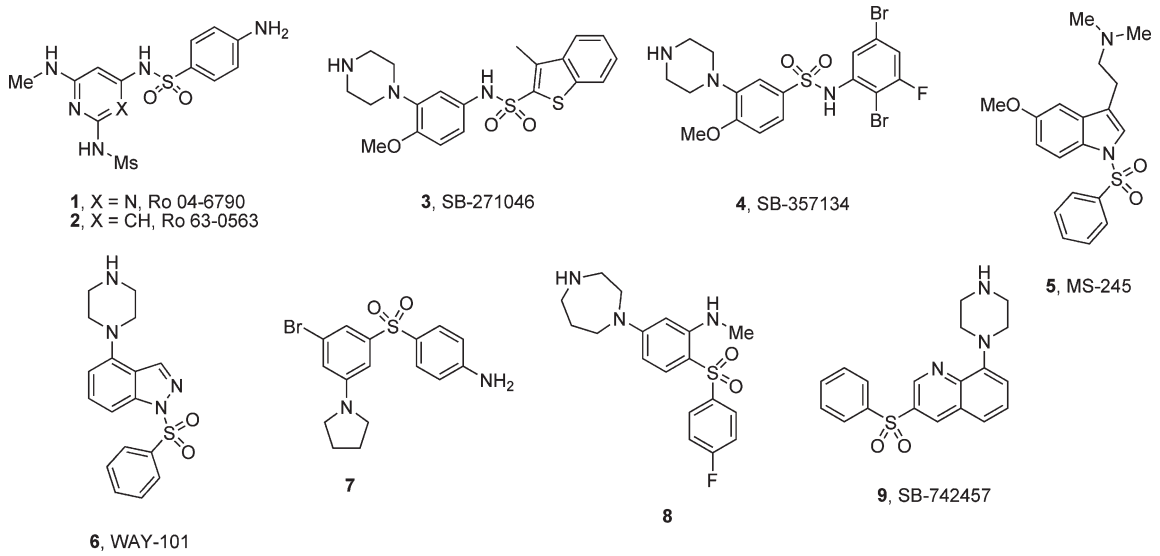


Figure 1. Structures of selected 5-HT$_6$ receptor antagonists.

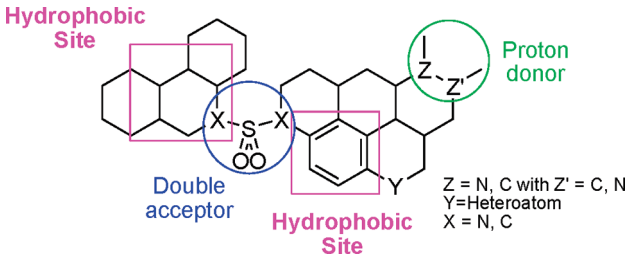


Figure 2. Structural model for 5-HT$_6$ pharmacophore.

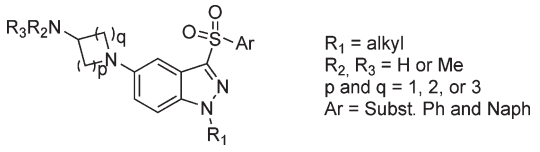


Figure 3. Strategy for SAR of indazole series.

platform. The authors reported a hypothetical framework model based on the structure and biological activity of reference ligands (Figure 2). In his model, he proposed that active compounds possessed two hydrophobic regions flanking a double hydrogen bond acceptor (often sulfonamide or sulfone). Furthermore, the authors noted that one of the hydrophobic sites is terminated by a proton donor (such as amine which can be protonated at physiological pH).

Past reports have demonstrated that the most potent ligands known have structural features in common, such as the presence of a hydrophobic site connected to a sulfone (or sulfonamide) moiety and the presence of a distal amine that can be a hydrogen donor/acceptor.[17] These features have served as a point of departure for further target discovery by medicinal chemists. In particular, our efforts centered around exploring the structure−activity relationship (SAR) of the distal amine (Figure 3).[18]

Results and Discussion

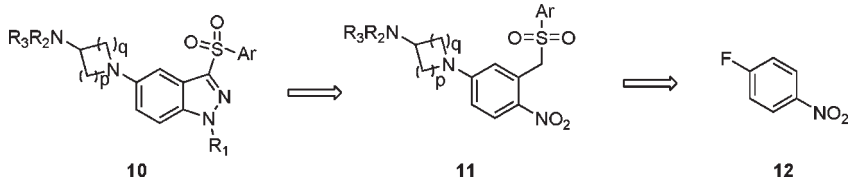
Targeted analogues based on this hypothesis were prepared according to the approach depicted in Scheme 1. Retrospectively, indazole core derivatives (**10**) can be formed from **11** by reduction of the nitro group followed by diazotization and cyclization. The nitro intermediates (**11**) are readily prepared via vicarious nucleophilic substitution (VNS) of commercially available 4-fluoronitrobenzene (**12**) with the appropriately substituted arylchloromethylsulfones, a process we have previously utilized and described in detail.[19]

To expand the diversity, key intermediates **11** can be prepared via two possible routes to allow access to multifunctional analogues. In the first route, commercially available 4-fluoronitrobenzene (**12**) can be reacted with *tert*-butylcarbonyl (Boc)-protected cyclic amine under basic conditions to give 4-aminoalkyl substituted nitrobenzenes (**13**) via S_NAr displacement (Scheme 2). The latter intermediates are then subjected to vicarious nucleophilic substitution (VNS)[20] at the ortho position of the nitro group to yield intermediates (**11**). The arylchloromethylsulfone building blocks can be prepared from the reaction of commercially available arylsulfonyl chlorides with chloromethyl bromide in the presence of tetrabutylammonium bromide, Na_2SO_3, and $NaHCO_3$ in good yields. This route generally gave good yields with the exception of when the amine reactant was a pyrrolidine or an azetidine derivative. In these cases, a much more efficient conversion was achieved with reversal of the order of the S_NAr and VNS steps. Thus, intermediates **14** were prepared from 4-fluoronitrobenzene (**12**) using the VNS conditions described above. Subsequent S_NAr displacement with the corresponding cyclic amines led to the desired chemotype **11**.

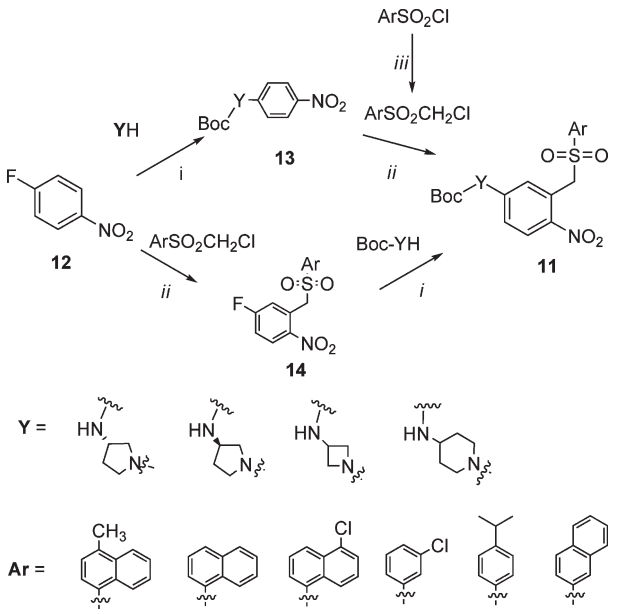
Catalytic hydrogenation of nitroaryls **11** afforded anilines **15** in good to excellent yields. These key intermediates were then diazotized and cyclized in acetic acid to give the target indazole **16** (Scheme 3). In cases where the amine component Y was protected by a Boc group, it was readily hydrolyzed in the presence of TFA or HCl to give the final target **10** (Scheme 3).

With a varied array of analogues prepared, we examined the structure−activity relationship of these indazole core ligands and their potential as 5-HT$_6$ receptor antagonists. All compounds were evaluated for human 5-HT$_6$ receptor binding affinity by competitive inhibition of [^{3}H]LSD binding. Selected compounds were further evaluated for 5-HT$_6$ receptor antagonist activity in a functional cyclic adenosine monophosphate (*c*AMP) assay using HeLa cells stably transfected with the human 5-HT$_6$ receptor. Upon identification of

Scheme 1. Retrosynthesis of Compounds **10**



Scheme 2. Synthesis of Compound **11**[a]



[a] Conditions: (i) K_2CO_3; DMF, (ii) KO*t*-Bu, THF −78 to 0 °C; (iii) $ClCH_2Br$, $NaHCO_3$, Na_2SO_3, TBAB, H_2O, reflux.

compounds demonstrating high affinity and full antagonist function at the 5-HT_6 receptor, selectivity of compounds versus the 5-HT_{2B} receptor was first determined. Further liability was assessed in 5-HT_{2B} functional assay. All compounds reported here were antagonists and showed no agonism at 5-HT_{2B} (data not included). High selectivity for the 5-HT_6 receptor over the 5-HT_{2B} for ligands was of particular interest because of the potential cardiovascular liability associated with this target.[21] Ligands with good binding, functional activity, and selectivity over the 5-HT_{2B} receptor were further advanced to screening against an array of dopaminergic, adrenergic, and other 5-HT receptor subtypes.

Representative compounds describing the structure−activity relationship with regard to changes around the sulfone moiety are detailed in Table 1. Initially, we structured the SAR around examination of compounds with the 4-aminopiperidine substitution as the amine component (Y) to allow for an empirical analysis (Table 1). In general, these derivatives were found to have high 5-HT_6 receptor affinity and to be potent antagonists as determined by the functional assay. From binding data, it can be seen that the 1-naphthylsulfone (**10a**) is 4- to 5-fold more potent than 2-naphthyl analogue **10b** but had less selectivity over the 5-HT_{2B} receptor. Compound (**10c**) with additional substitution at the 4-position of the 1-naphthyl group retained similar potency as the parent compound but possessed higher selectivity against the 5HT_{2B} receptor. In a similar fashion, substitution at the 5-position with chlorine (**10d**) had deleterious effects on potency and functional efficacy with only moderate selectivity against the 5-HT_{2B} receptor. From this limited set of data, it appeared that the selectivity over 5-HT_{2B} is enhanced by the steric effects caused by substitution at the 4-position of the phenyl- or naphthyl sulfones. In summary, for the examination of the sulfone moiety SAR, the substituted 4-methylnaphthyl analogue **10c** was the most potent 5-HT_6 receptor antagonist with greater than 136-fold selectivity over the 5-HT_{2B} receptor.

We next moved on to a more detailed examination of the SAR of the cyclic amine (Y). In this arm of the SAR examination, we maintained the sulfone as the 1-naphthyl substituent. The activity of representative analogues at the 5-HT_6 and 5-HT_{2B} receptors prepared in this effort is detailed in Table 2.

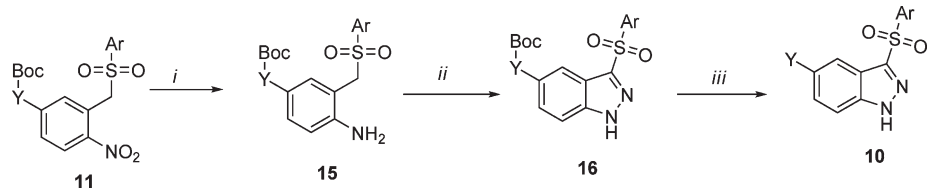
From the data in Table 2, one can infer that the ring size of exocyclic amine, contracting from six-membered ring (**10a**) to four-membered ring (**10i**), had no effect on potency but selectivity was most optimal for the five-membered ring with *R*-stereochemistry (**10h**). Alkylation of the distal amine (**10j**, **k**), led to increased selectivity over parent analogues (**10g**,**h**). It is noteworthy that only in the case of **10j** with the *R*-stereochemistry the alkylation of the distal amine led to improved potency over the parent analogue **10h**. Among all compounds prepared, the (*R*)-dimethylaminopyrrolidine analogue **10j** had the highest binding affinity; however, it did not display the best functional potency in this class of molecules. Its enantiomer (*S*)-dimethylaminopyrrolidine analogue (**10k**) was 50-fold less potent in the binding assay relative to **10j** but surprisingly more potent in the functional assay. The optimized derivative **10h** had excellent binding and most improved functional activity while maintaining selectivity against the 5-HT_{2B} receptor and was selected for additional in vitro and in vivo profiling .

Compound **10h** showed good selectivity against other serotonin receptors (>100-fold). However, this analogue and others from this series were hampered by their potency as inhibitors of CYP3A4 and CYP2C9 (%inhibition of >50% at 3 μM). Upon further examination of the pharmacokinetics of **10h**, it was also found that the drug−brain concentration following a single intraperitoneal dose of 10 mg/kg was below quantifiable levels. To improve this property, alkylation of the nitrogen of the indazole was proposed. The removal of H-bond donors is a well documented tactic to improve CNS penetration.[22,23] To that end, the Boc-protected intermediate **17** was treated with cesium carbonate and an appropriate alkyl halide, followed by deprotection with trifluoroacetic acid to give a mixture of N-1 and N-2 alkylated indazoles (**18a−c and 19a−c**, respectively)(Scheme 4).

The regioisomeric alkylated derivatives were unambiguously assigned by high field NMR studies (nuclear Overhauser effect spectroscopy (NOESY), heteronuclear multiple bond correlation (HMBC)). Details are provided in Supporting Information.

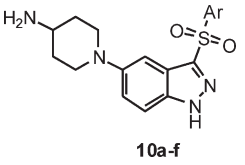
Unfortunately these alkylated compounds **18** and **19** were found to have weaker 5-HT_6 receptor affinity and to be less potent antagonists for 5-HT_6 receptor-dependent cyclase assay (Table 3).

Scheme 3. Synthesis of Indazole **10**[a]



[a] Conditions: (i) Pd/C, H_2 (40 psi); (ii) $NaNO_2$, HOAc, H_2O; (iii) TFA/CH_2Cl_2.

Table 1. SAR of the Arylsulfone Group of **10a−f**[a]



10a-f

Compound	Ar	Binding k_i (nM)		5-HT_6 Functional Cyclase assay	
		5-HT_6 (±SEM)	5-HT_{2B} (±SEM)	IC_{50} (nM) (±SEM)	Imax (±SEM)
10a		4.27(±0.23)	100(±22.6)	28.0(±3.3)	97%(±3.5)
10b		18.22*	1362*	88.9(±9.5)	83%(±2)
10c		3.62*	493*	26.7(±6.2)	100%(±0)
10d		4.52*	78*	70.1(±15.8)	93%(±1)
10e		8.04*	442*	33.7(±5.1)	89%(±0.5)
10f		13.09*	>10,000*	51.7(±15.3)	83%(±1)

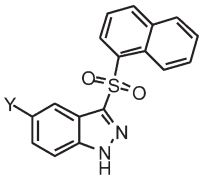
[a] The asterisk (*) indicates $n = 1$.

Despite the weaker potency, these alkylated analogues did display improved pharmacokinetics compared to the unsubstituted indazole analogues. Specifically and by design, **18b** showed improved blood−brain penetration ($B/P = 0.85$; based on AUC ratio) following a single intraperitoneal (ip) dose of 3 mg/kg as compared to the desalkyl congener. Encouraged by this significantly improved CNS exposure, we examined the effects of this ligand in a rat behavioral novel object recognition assay (assay details and literature references are provided in the Supporting Information). Treatment with **18b** (3 mg/kg, ip) 1 h prior to the learning trial produced enhanced recognition memory when evaluated during the testing trial 48 h later (Figure 4). The enhanced recognition memory, during the memory trial, is reflected by the significantly greater amount of time (*, $p < 0.05$) spent exploring the novel object compared to the familiar one in the group treated with 3 mg/kg ip of **18b**, an effect not observed in animals treated with vehicle. These results confirmed the cognitive enhancing capability of selective CNS penetrant 5-HT_6 antagonists. Continued efforts in this area to improve the potency of this and other related compound classes will be the subject of future communications.

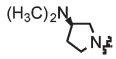
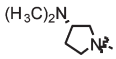
Conclusions

In summary, we have identified a series of novel, potent, selective small molecule antagonists of the 5-HT_6 receptor. One selected example, **18b**, showed good brain exposure when

Table 2. SAR of the Cyclic Amine[a]



10a, g-k

Compound	Cyclic amine (Y)	Binding k_i (nM)		5-HT$_6$ Functional Cyclase assay	
		5-HT$_6$ (±SEM)	5-HT$_{2B}$ (±SEM)	IC$_{50}$ (nM) (±SEM)	Imax (±SEM)
10a		4.27(±0.23)	100(±22.6)	28.0¶	97%¶
10g		3.06(±0.62)	21.0(±4.9)	12.5¶	97%¶
10h		4.46(±0.29)	274(±101)	15.7(±3.7)	97%(±0.5)
10i		3.55(±0.2)	97.9(±8.5)	16.5(±2.5)	94%(±0)
10j		0.51(±0.17)	423(±112)	39.6¶	100%¶
10k		24.4(±1.15)	583(±13.5)	17.5¶	100%¶

[a] The symbol "¶" indicates "not determined".

Scheme 4. *N*-Alkylation of Compounds **17**

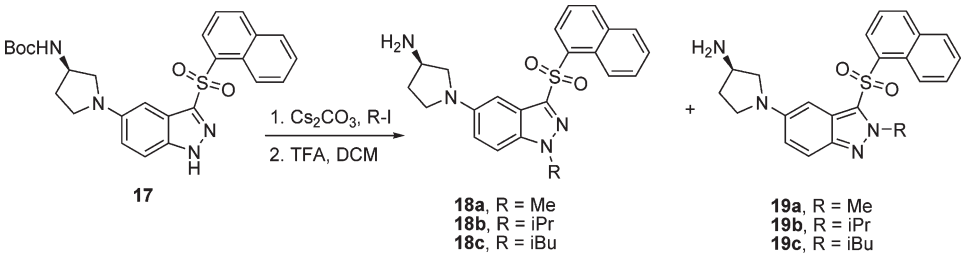


Table 3. SAR of N-1/N-2 Alkylated Indazoles[a]

compd	alkyl group	binding k_i (nM)		5-HT$_6$ functional cyclase assay	
		5-HT$_6$	5-HT$_{2B}$	IC$_{50}$ (nM) (± SEM)	I_{max} (%) (±SEM)
18a	methyl	21.1[b]	185[b]	316[c]	92[c]
18b	isopropyl	13.7[b]	191[b]	157 (±0.032)	83 (±0)
18c	isobutyl	36.9*	> 3300[b]	203 (±0.029)	91 (±0.5)
19a	methyl	54.3[b]	455[b]	444[c]	92[c]
19b	isopropyl	48.7[b]	> 3300[b]	380 (±0.045)	75 (±1)
19c	isobutyl	75.8[b]	260*	433 (±0.043)	77 (±2.5)

[a] The asterisk (*) indicates $n = 1$. [b] $n = 1$. [c] SEM not determined.

the compound was administered ip and a generally favorable pharmacokinetic profile with procognitive efficacy in the rat novel object recognition assay. These data further support the potential utility of 5-HT$_6$ receptor antagonists for the treatment of psychiatric and neurological disorders with associated cognitive dysfunction.

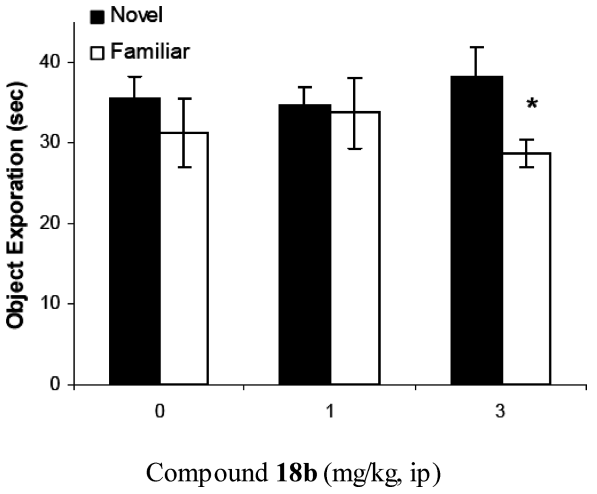


Figure 4. Compound **18b** efficacy in a 48 h novel object recognition: (*) $p < 0.05$.

Experimental Section

General Procedure. All manipulations were conducted under an inert atmosphere of dried nitrogen. All solvents as well as organic acids and bases were reagent grade. All reagents were commercial compounds of the highest purity available and used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F-264 (0.25 mm thickness) plates precoated with a fluorescent indicator (1.00 mm thickness plates were used for preparatory thin-layer chromatography). Visualization was accomplished using ultraviolet light (λ, nm) or Vaughn's stain reagent. Flash column chromatography was carried out with the use of standard 220−400 mesh silica gel or Biotage Flash 40 cartridges/apparatus. Proton magnetic resonance spectra (^{1}H NMR) were determined in cited solvent on a Varian Unity Plus system (300, 400, and 500 MHz) Fourier transform spectrometer, and chemical shifts were expressed in parts per million (δ) relative to tetramethylsilane (TMS-0 ppm) as an internal reference. Multiplicities are designated as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), and multiplet (m). Mass spectra were obtained on either a Finnigan single quadrapole SSQ710C or a Finnigan MAT900 high resolution magnetic sector. HPLC spectra were obtained on Agilent 1100. Sample was disssolved in DMSO with sample concentration of 0.002 g/mL. Flow rate was 1.0 mL/min and injection volume was 0.2 μL. Two detection wavelengths were 215 and 254 nm. Two Coupled Onyx Monolithic C18, 0.2 cm × 5 cm column was used. Water and acetonitrile with formic acid were used as mobile phase. HPLC was used to determine purity of all tested compounds (at least 95%).

1-[3-(1-Naphthylsulfonyl)-1*H*-indazol-5-yl]piperidin-4-amine (10a). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.96−2.15 (m, 2 H) 2.22 (d, J = 11.0 Hz, 2 H) 3.23−3.50 (m, 2 H) 3.73 (d, J = 11.5 Hz, 2 H) 3.88 (s, 3 H) 7.58−7.64 (m, 1 H) 7.65−7.71 (m, 1 H) 7.71−7.81 (m, 3 H) 8.07 (d, J = 7.8 Hz, 2 H) 8.31 (d, J = 8.3 Hz, 1 H) 8.47 (s, 2 H) 8.60 (dd, J = 7.3, 1.0 Hz, 1 H) 8.81 (d, J = 8.5 Hz, 1 H) 14.53 (s, 1 H). MS (ESI) m/z 407.2, $[M + H]^+$.

1-[3-(2-Naphthylsulfonyl)-1*H*-indazol-5-yl]piperidin-4-amine (10b). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88−2.07 (m, 2 H) 2.09−2.25 (m, 2 H) 3.18−3.31 (m, 1 H) 3.32−3.43 (m, J = 7.1, 7.1, 7.1 Hz, 1 H) 3.43−3.90 (m, 7 H) 7.60−7.76 (m, 3 H) 7.97 (dd, J = 8.7, 1.8 Hz, 1 H) 8.03 (d, J = 7.8 Hz, 1 H) 8.13 (d, J = 8.8 Hz, 1 H) 8.27 (d, J = 7.8 Hz, 1 H) 8.36 (s, 2 H) 8.77−8.83 (m, 1 H) 14.40 (s, 1 H). MS (ESI) m/z 407.2, $[M + H]^+$.

1-{3-[(4-Methyl-1-naphthyl)sulfonyl]-1*H*-indazol-5-yl}piperidin-4-amine (10c). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.76−1.94 (m, 2 H) 2.02−2.14 (m, 2 H) 2.69 (s, 3 H) 3.34−3.79 (m, 8 H) 7.48−7.56 (m, 1 H) 7.56−7.66 (m, 4 H) 8.07−8.14 (m, 1 H) 8.25 (s, 2 H) 8.43 (d, J = 7.6 Hz, 1 H) 8.75−8.81 (m, 1 H) 14.21 (s, 1 H). MS (ESI) m/z 421.2, $[M + H]^+$.

1-{3-[(5-Chloro-1-naphthyl)sulfonyl]-1*H*-indazol-5-yl}piperidin-4-amine (10d). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 (d, J = 9.3 Hz, 2 H) 2.16 (d, J = 11.0 Hz, 2 H) 3.19 (s, 1 H) 3.35 (s, 1 H) 3.72 (d, J = 11.0 Hz, 2 H) 7.69 (dd, J = 8.8, 7.6 Hz, 1 H) 7.83 (dd, J = 7.6, 1.0 Hz, 1 H) 7.95 (dd, J = 8.1 Hz, 1 H) 8.28−8.44 (m, 3 H) 8.58 (d, J = 8.5 Hz, 1 H) 8.71 (dd, J = 7.4, 1.1 Hz, 1 H) 8.84 (d, J = 8.8 Hz, 1 H) 14.44 (s, 1 H). MS (ESI) m/z 441.1, $[M + H]^+$.

1-Piperidin-4-amine (10e). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.97−2.13 (m, 2 H) 2.21 (d, J = 9.5 Hz, 2 H) 3.24−3.51 (m, 3 H) 3.77 (d, J = 11.2 Hz, 2 H) 3.91 (s, 5 H) 7.59−7.72 (m, J = 8.3, 8.3 Hz, 2 H) 7.71−7.87 (m, 2 H) 8.45 (s, 2 H) 14.63 (s, 1 H). MS (ESI) m/z 391.1, $[M + H]^+$.

1-{3-[(4-Isopropylphenyl)sulfonyl]-1*H*-indazol-5-yl}piperidin-4-amine (10f). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.90−2.08 (m, 6 H) 2.11−2.23 (m, J=11.0 Hz, 2 H) 2.84−3.03 (m, J=20.7, 13.7, 6.8 Hz, 1 H) 3.18−3.44 (m, J=7.1, 7.1, 7.1 Hz, 3 H) 3.54−3.96 (m, J=11.5 Hz, 8 H) 7.49 (dt, J=8.5, 2.0 Hz, 2 H) 7.64−7.75 (m, 1 H) 7.82−7.99 (m, 1 H) 7.95 (dt, J=8.5, 2.1 Hz, 1 H) 8.32−8.44 (m, 2 H) 14.39 (s, 1 H). MS (ESI) m/z 399.2, $[M + H]^+$.

(3*S*)-1-[3-(1-Naphthylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (10g). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.03−2.15 (m, 1 H) 2.28−2.42 (m, 1 H) 3.27−3.41 (m, 2 H) 3.44−3.60 (m, 3 H) 4.00 (br s, 1 H) 6.78 (d, J = 1.7 Hz, 1 H) 6.98 (dd, J = 9.3, 2.2 Hz, 1 H) 7.53 (d, J = 9.0 Hz, 1 H) 7.58−7.69 (m, 2 H) 7.76 (dd, J = 7.8 Hz, 1 H) 8.03−8.12 (m, J = 7.3, 2.0 Hz, 4 H) 8.30 (d, J = 8.3 Hz, 1 H) 8.53 (dd, J = 7.6, 1.2 Hz, 1 H) 8.80 (dd, J = 8.4, 1.3 Hz, 1 H) 13.95−14.00 (m, 1 H). MS (ESI) m/z 393.1, $[M + H]^+$.

(3*R*)-1-[3-(1-Naphthylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (10h). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.06−2.19 (m, J = 4.9 Hz, 1 H) 2.28−2.42 (m, 1 H) 3.27−3.41 (m, 2 H) 3.49−3.61 (m, 2 H) 3.96 (br s, 1 H) 6.77 (d, J = 2.0 Hz, 1 H) 6.97 (dd, J = 9.0, 2.2 Hz, 1 H) 7.52 (d, J = 9.0 Hz, 1 H) 7.56−7.68 (m, 2 H) 7.76 (dd, J = 7.8 Hz, 1 H) 8.03−8.10 (m, 1 H) 8.25−8.37 (m, 3 H) 8.52 (dd, J = 7.3, 1.2 Hz, 1 H) 8.80 (d, J = 8.8 Hz, 1 H) 14.02 (br s, 1H). MS (ESI) m/z 392.9, $[M + H]^+$.

1-[3-(1-Naphthylsulfonyl)-1*H*-indazol-5-yl]azetidin-3-amine (10i). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.82 (d, J=4.6 Hz, 2 H) 4.11−4.19 (m, 3 H) 6.73 (d, J = 2.0 Hz, 1 H) 6.83 (dd, J=9.0, 2.2 Hz, 1 H) 7.53 (dd, J=9.0, 0.5 Hz, 1 H) 7.59−7.68 (m, 2 H) 7.73−7.78 (m, J = 7.8, 7.8 Hz, 1 H) 8.05−8.09 (m, 1 H) 8.27−8.36 (m, J = 8.3 Hz, 3 H) 8.55 (dd, J = 7.3, 1.2 Hz, 1 H) 8.76−8.81 (m, 1 H) 14.01 (s, 1 H). MS (ESI) m/z 379.1, $[M + H]^+$.

(3*R*)-*N*,*N*-Dimethyl-1-[3-(1-naphthylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (10j). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.75−1.88 (m, 1 H) 2.11−2.19 (m, 1 H) 2.21 (s, 6 H) 2.74−2.86 (m, 1 H) 3.05 (t, J = 8.4 Hz, 1 H) 3.18−3.47 (m, 3 H) 6.67 (d, J = 1.7 Hz, 1 H) 6.92 (dd, J = 9.2, 2.3 Hz, 1 H) 7.46 (d, J = 9.0 Hz, 1 H) 7.56−7.67 (m, 2 H) 7.76 (t, J = 8.1, 7.6 Hz, 1 H) 8.05 (dd, J = 8.2, 1.1 Hz, 1 H) 8.27 (d, J = 8.3 Hz, 1 H) 8.55 (dd, J = 7.4, 1.1 Hz, 1 H) 8.80 (d, J = 8.5 Hz, 1 H) 13.85 (br s, 1 H). MS (ESI) m/z 421.2, $[M + H]^+$.

(3*S*)-*N*,*N*-Dimethyl-1-[3-(1-naphthylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (10k). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.76−1.92 (m, 1 H) 2.13−2.20 (m, 1 H) 2.22 (s, 6 H) 2.76−2.88 (m, 1 H) 3.06 (t, J = 8.7 Hz, 1 H) 3.33−3.46 (m, 3 H) 6.67 (d, J = 1.5 Hz, 1 H) 6.93 (dd, J = 9.3, 2.0 Hz, 1 H) 7.46 (d, J = 9.0 Hz, 1 H) 7.57−7.67 (m, 2 H) 7.76 (t, J = 7.8 Hz, 1 H) 8.06 (d, J = 7.3 Hz, 1 H) 8.28 (d, J = 8.5 Hz, 1 H) 8.55 (d, J = 7.8 Hz, 1 H) 8.79 (d, J = 8.5 Hz, 1 H) 13.85 (br s, 1 H). MS (ESI) m/z 421.2, $[M + H]^+$.

(3*R*)-1-[1-Methyl-3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (18a). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.7 (m, 1H) 2.1 (m, 2H) 2.9 (m, 1H) 3.4 (m, 2H) 3.6 (m, 1H) 6.6 (m, 1H) 6.9 (m, 1H) 7.6 (m, 3H) 7.7 (t, J = 8.0 Hz, 1H) 8.0 (m, 1H) 8.25 (m, 1H) 8.5 (m, 1H) 8.8 (m, 1H). MS (ESI) m/z 407.1, $[M + H]^+$.

(3*R*)-1-[1-(1-Methylethyl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (18b). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.4 (d, J = 6.5 Hz, 6H) 1.7 (m, 1H) 2.0 (m, 2H) 2.8 (m, 1H) 3.2 (m, 1H) 3.4 (m, 1H) 3.6 (m, 1H) 5.0 (m, 1H) 6.6 (m, 1H) 6.8 (m, 1H) 7.6 (m, 3H) 7.7 (t, J = 8.0 Hz, 1H) 8.0 (m, 1H) 8.2 (m, 1H) 8.5 (m, 1H) 8.9 (m, 1H). MS (ESI) m/z 435.2, $[M + H]^+$.

(3*R*)-1-[1-(2-Methylpropyl)-3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl]pyrrolidin-3-amine (18c). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.7 (d, J = 6.75 Hz, 6H) 1.7 (m, 1H) 2.1 (m, 2H) 2.9 (m, 1H) 3.1 (m, 1H) 3.4 (m, 2H) 3.6 (m, 1H) 4.2 (m, 2H) 6.6 (m, 1H) 6.9 (m, 1H) 7.6 (m, 3H) 7.8 (t, J = 8.0 Hz, 1H) 8.0 (m, 1H) 8.3 (m, 1H) 8.5 (m, 1H) 8.9 (m, 1H). MS (ESI) m/z 449.2, $[M + H]^+$.

(3*R*)-1-[2-Methyl-3-(naphthalen-1-ylsulfonyl)-2*H*-indazol-5-yl]pyrrolidin-3-amine (19a). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.75 (m, 1H) 2.1 (m, 2H) 3.0 (m, 1H) 3.5 (m, 2H) 3.6 (m, 1H) 4.1 (s, 3H) 6.6 (m, 1H) 7.0 (m, 1H) 7.6 (m, 3H) 7.8 (t, J = 8.0 Hz, 1H) 8.1 (m, 1H) 8.3 (m, 1H) 8.4 (m, 1H) 8.5 (m, 1H). MS (ESI) m/z 407.1, $[M + H]^+$.

(3*R*)-1-[2-(1-Methylethyl)-3-(naphthalen-1-ylsulfonyl)-2*H*-indazol-5-yl]pyrrolidin-3-amine (19b). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (d, J = 6.5 Hz, 6H) 1.8 (m, 1H) 2.1 (m, 2H) 3.0 (m, 1H) 3.5 (m, 2H) 3.7 (m, 1H) 5.2 (m, 1H) 6.7 (m, 1H) 7.0 (m, 1H) 7.6 (m, 3H) 7.7 (t, J = 8.0 Hz, 1H) 8.1 (m, 1H) 8.3 (m, 1H) 8.5 (m, 2H). MS (ESI) m/z 435.1, $[M + H]^+$.

(3*R*)-1-[2-(2-Methylpropyl)-3-(naphthalen-1-ylsulfonyl)-2*H*-indazol-5-yl]pyrrolidin-3-amine (19c). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.6 (d, J = 6.5 Hz, 6H) 0.8 (m, 1H) 1.8 (m, 1H) 2.2 (m, 2H) 3.0 (m, 1H) 3.5 (m, 2H) 3.6 (m, 1H) 4.2 (m, 2H) 6.6 (m, 1H) 7.0 (m, 1H) 7.6 (m, 3H) 7.8 (t, J = 8.0 Hz, 1H) 8.1 (m, 1H) 8.4 (m, 1H) 8.5 (m, 2H). MS (ESI) m/z 449.2, $[M + H]^+$.

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Supporting Information Available: In vitro and in vivo biological assay protocols; in vitro profile of **10h**; HPLC data of **10a**−**k**, **18a**−**c**, and **19a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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