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Identification of 3-sulfonylindazole derivatives as potent and selective 5-HT$_6$ antagonists

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ABSTRACT

As part of our efforts to develop agents for cognitive enhancement, we have been focused on the 5-HT$_6$ receptor in order to identify potent and selective ligands for this purpose. Herein we report the identification of a novel series of 3-sulfonylindazole derivatives with acyclic amino side chains as potent and selective 5-HT$_6$ antagonists. The synthesis and detailed SAR of this class of compounds are reported.

1. Introduction

The 5-HT$_6$ receptor was identified by molecular biology in early 1990s[1–4] and was the most recent addition to a group receptors called the 5-HT receptors. This G-protein-coupled receptor (GPCR) is positively coupled to adenylate cyclase and is localized primarily in the central nervous system.[5] Extensive investigation has shown that the 5-HT$_6$ receptor is expressed in brain regions known to be associated with learning and memory.[6] In addition, studies have shown that blockade of 5-HT$_6$ receptor function increases neurotransmission, specifically cholinergic and glutamatergic,[7,8] and this leads to improvement in cognition in a number of rodent behavioral models.[9,10]

In the last decade, a great number of 5-HT$_6$ ligands of both agonists and antagonists have been reported.[11–13] These compounds have served as excellent tools to investigate the functional roles of the 5-HT$_6$ receptor in great detail and selected 5-HT$_6$ ligands are depicted in Figure 1 (**1–7**) showing the diversity of structural types in this area. Currently a number of compounds from these classes are active in Phase I and II clinical trials for cognitive impairment in AD and schizophrenia.[14,15]

We have previously reported the identification of 1-sulfonylindazole derivatives **9** as potent and selective 5-HT$_6$ antagonists (Fig. 2).[22] Herein we report the identification of a series of 3-sulfonylindazoles **10** by migrating the arylsulfonyl group from the 1-position to the 3-position of the indazole core of **9**. This C/N flip strategy has been successfully used by us for identification of other series of novel 5-HT$_6$ ligands in the past and has allowed for extensive modification of the drug-like properties of this class of molecules.[16]

2. Results and discussion

The general synthesis of 3-sulfonylindazole derivatives **17** with a primary amine side chain is depicted in Scheme 1. Commercially available 4-, 5-, 6-, or 7-NO_2 indazoles **11** were treated with I_2/KOH in DMF to provide 3-iodo-indazoles **12** cleanly in excellent yields. Coupling of **12** with a thiol using a procedure reported by

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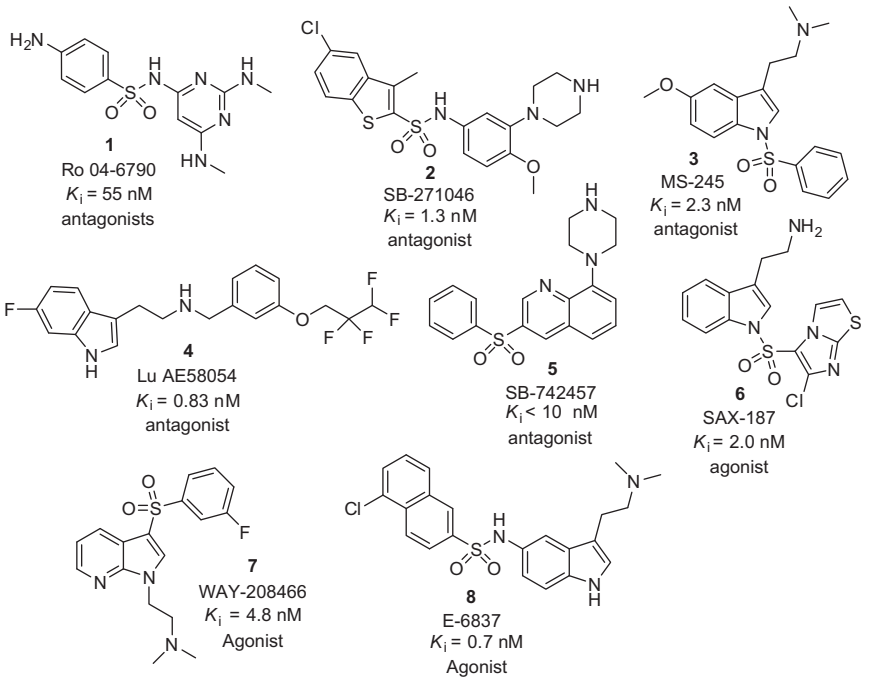


Figure 1. Selected 5-HT_6 ligands.

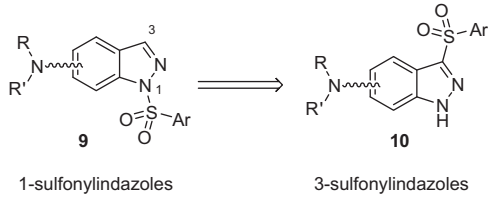
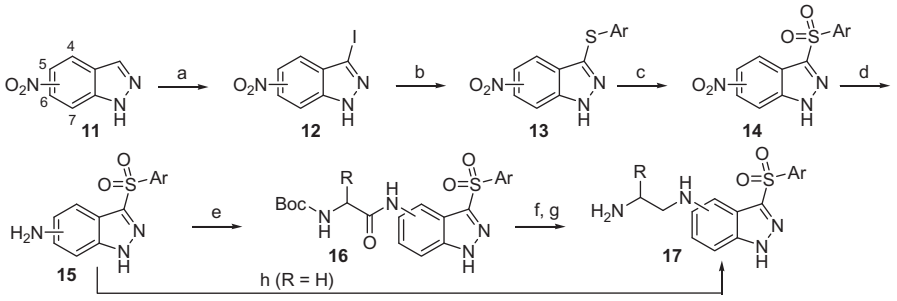


Figure 2. Identification of 3-sulfonylindazoles as 5-HT_6 ligands.

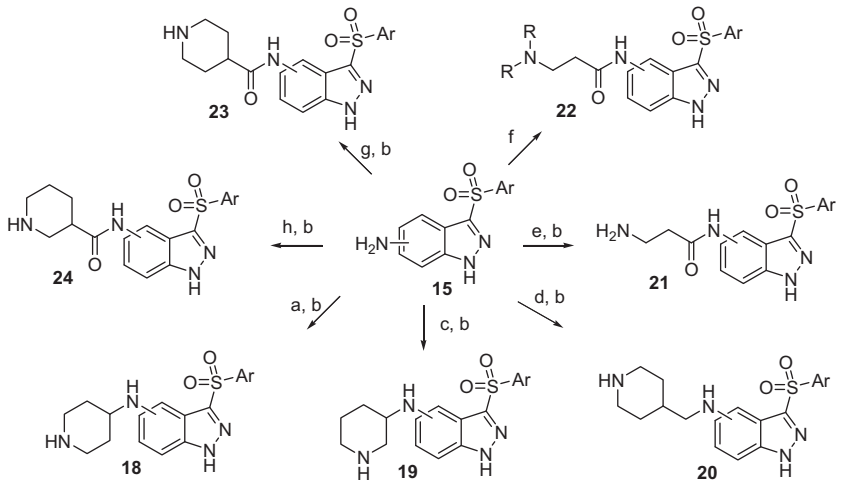
Buchwald[17] gave sulfides **13** which were subsequently oxidized with *m*-CPBA to afford sulfones **14**. Nitro group reduction with Sn/HCl or with catalytic hydrogenation provided common aniline intermediates **15** for rapid synthesis of a wide range of final target compounds with different amino side chains. Among these final compounds, amines **17** were synthesized by coupling of **15** with *N*-Boc amino acids followed by Boc deprotection and BH_3 reduction. Alternatively, **17** (R = H) could be more efficiently synthesized through a single-step chemical transformation between **15** and 2-oxazolidinone. Our initial attempts for the ring opening of 2-oxazolidinone with the free base of **15** only provided mixtures of products. We solved this by first converting **15** into its HCl salt with the expectation that the reaction would be better catalyzed by acid. To our satisfaction the reaction went smoothly with the HCl salt of **15** to provide product **17** in good yield and with minor side-products.

Scheme 2 outlines the synthesis of other target compounds (**18–24**) through common intermediates **15**. These final compounds were synthesized by derivatization on **15** either through reductive amination with an aldehyde bearing a cyclic amino group (**18–20**) or amide bond formation with a β-amino acid (**21–24**).

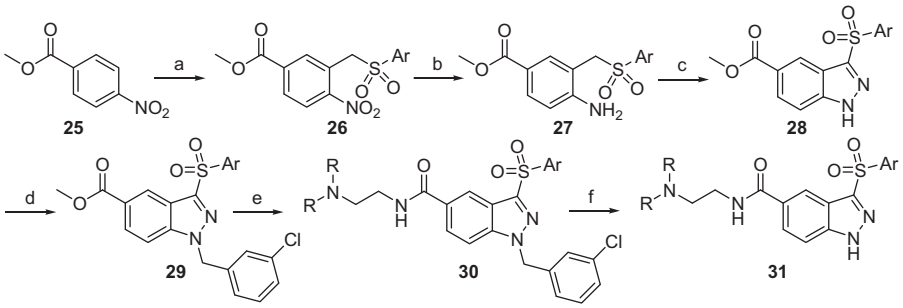
Synthesis of the reverse amide derivatives **31** is depicted in Scheme 3. Vicarious nucleophilic substitution[18] of methyl 4-nitrobenzoate **25**, which was easily synthesized from 4-nitrobenzoic acid, with a chloromethyl arylsulfone provided **26** in good yield with excellent regioselectivity. A variety of chloromethyl arylsulfones, needed to build in the diversity we desired, were conveniently synthesized from commercially available arylsulfonyl chlorides.[19] Nitro group reduction of **26** by catalytic hydrogenation followed by diazotization of **27** and subsequent cyclization under basic conditions provided 3-sulfonylindazole intermediates **28** in excellent yield without necessity of purification. The indazole 1-position of **28** was temporarily protected with 3-Cl-Bn group to provide **29** for direct amidation in order to generate intermediates **30**. The



Scheme 1. Reagents and conditions: (a) I_2, KOH, DMF, 90–98%; (b) ArSH, CuI, K_2CO_3, ethylene glycol, *i*PrOH, 45–85%; (c) *m*-CPBA, CH_2Cl_2, 65–90%; (d) Sn, HCl, 70–80%; (e) *N*-Boc amino acid, EDC, CH_3CN, 48–90%; (f) TFA, CH_2Cl_2, 90–100%; (g) $BH_3{\cdot}Et_2O$, THF, 38–70%; (h) (i) HCl, (ii) 2-oxazolidinone, diethylene glycol monomethyl ether, 20–70%.



Scheme 2. Reagents and conditions: (a) 1-*N*-Boc-4-piperidone, $NaBH(OAc)_3$, 1,2-dichloroethane, 60–80%; (b) TFA, CH_2Cl_2, 90–100%; (c) 1-*N*-Boc-3-piperidone, $NaBH(OAc)_3$, 1,2-dichloroethane, 60–80%; (d) 1-*N*-Boc-4-piperidinecarboxaldehyde, $NaBH(OAc)_3$, 1,2-dichloroethane, 60–80%; (e) *N*-Boc-glycine, EDC, CH_3CN, 60–90%; (f) *N*,*N*-dialkyl glycine, EDC, CH_3CN, 60–90%; (g) 1-*N*-Boc-piperidine-4-carboxylic acid, 60–95%; (h) 1-*N*-Boc-piperidine-3-carboxylic acid, 60–90%.

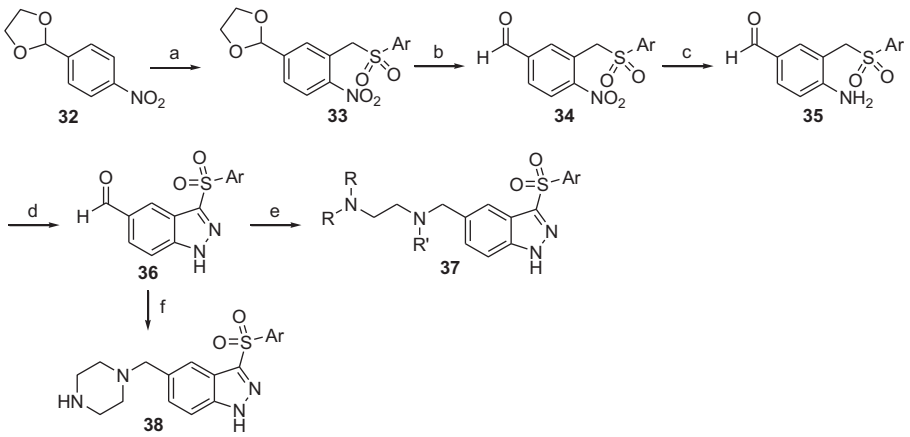


Scheme 3. Reagents and conditions: (a) $ArSO_2CH_2Cl$, KO*t*Bu, THF, 87%; (b) H_2, Pd/C, MeOH, 64%; (c) (i) $NaNO_2$, HCl, (ii) $NaHCO_3$, 90%; (d) 3-Cl-BnBr, Cs_2CO_3, DMF, 92%; (e) 1,2-diamines, LDA, THF, 20–50%; (f) air, KO*t*Bu, *t*-BuOH, DMSO.

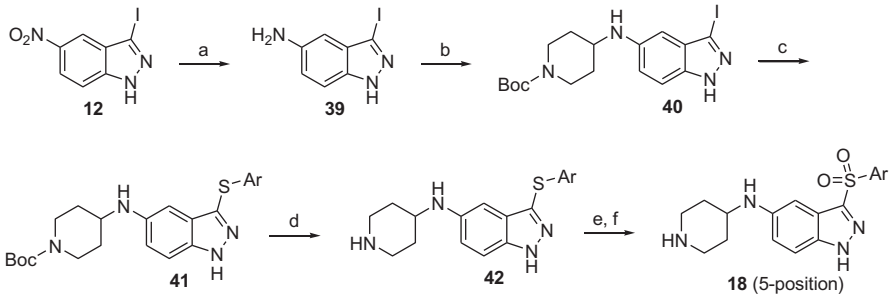
3-Cl-Bn protecting group was then successfully removed through air oxidation of in situ generated carbanions[20] to provide the reverse amide final compounds **31**.

Synthesis of derivatives with a carbon spacer between the basic amine and the indazole core (**37** and **38**) is depicted in Scheme 4. In this synthesis, the formyl group was protected as a 1,3-dioxolane (**32** and **33**) initially in the synthetic sequence in order to achieve a clean and regioselective vicarious nucleophilic substitution.[18] A similar and uneventful synthetic sequence to that depicted in Scheme 3 was then followed to provide versatile intermediates **36** for further derivatization through reductive aminations.

Scheme 5 depicts an alternative synthesis of **18** or other 3-sulfonylindazole target molecules. This alternative synthesis allows rapid exploration of the SAR of the arylsulfonyl moiety and enhances the diversity of the derivatives. Nitro group reduction of 3-iodoindazole **12** with $SnCl_2$ provided aniline **39**. The aniline



Scheme 4. Reagents and conditions: (a) $ArSO_2CH_2Cl$, KO*t*Bu, THF, 80%; (b) HCl, THF, 95%; (c) H_2, Pd/C, MeOH, 95%; (d) (i) $NaNO_2$, HCl, (ii) $NaHCO_3$, 80%; (e) 1,2-diamines, $NaBH(OAc)_3$, 1,2-dichloroethane; (f) (i) 1-Boc-piperazine, $NaBH(OAc)_3$, 1,2-dichloroethane, (ii) TFA, CH_2Cl_2.



Scheme 5. Reagents and conditions: (a) $SnCl_2$, EtOH; (b) 1-*N*-Boc-4-piperidone, $NaBH(OAc)_3$, 1,2-dichloroethane; (c) ArSH, CuI, K_2CO_3, ethylene glycol, *i*PrOH, 70–90%; (d) TFA, CH_2Cl_2, 90%; (e) HCl, MeOH; (f) oxone, $MeOH/H_2O$.

amino group allows installation of the amino side chains such as 4-piperidinylamino side chain as exemplified in Scheme 5 through reductive amination or other straightforward chemical transformations. A variety of thiols were then coupled with **40** to provide the needed sulfides **41**. Our initial attempts to oxidize sulfides **41** to their corresponding sulfones with a number of oxidants such as *m*CPBA and H_2O_2 under a variety of reaction conditions were not fruitful as the reactions gave complex mixtures with over-oxidized products. To reduce the electron-rich nature of the sulfides **41** in order to potentially prevent undesired oxidations, the Boc protecting group was removed and the resulting piperidines **42** were converted to their HCl salts. Oxidation of HCl salts of **42** with oxone went smoothly to provide clean sulfone products **18** (5-position, Scheme 5).

The 3-sulfonylindazole target compounds **17–24, 31, 37, 38** were evaluated for their binding affinity to human 5-HT_6 receptor in a standard competition binding assay.[21] The results are summarized in Tables 1–3.

To allow for the full exploration of the SAR of the amine side chains (Tables 1 and 2), we initially chose derivatives bearing the 1-naphthalenesulfonyl group. The basis of this was founded in our earlier determination that this particular sulfonyl group has been shown to be one of the optimal sulfonyl groups for a number of classes of 5-HT_6 ligands with related cores.[22–24] Compounds with a variety of amino groups at the 4–7 positions of the indazole core were synthesized in order to identify the optimal amine side chain location for 5-HT_6 activity. Data obtained for 4-piperidinylamino indazoles (**18a–d**), 3-piperidinylamino indazoles (**19a–d**), and 4-piperidinylmethylamino indazoles (**20a–d**) (Table 1) provided a consistent and clear SAR trend for the amine side chain position in the indazole. For all three amine side chains in **18–20**, the 5-position provided the most potent compounds (i.e., K_i = 0.7, 1.7, and 3.5 nM for **18b**, **19b**, and **20b**, respectively), as compared to other positions. While the 4-position (K_i = 2.8, 4.2, and 9.5 nM for **18a**, **19a**, and **20a**, respectively) was only slightly less potent than the 5-position, the 6- and 7-positions were significantly less potent with up to 70-fold reduction in affinity (K_i = 53 and 30 nM for **18c** and **18d**, respectively). The preference for certain positions of the amino side chain on the heterocyclic template further underscores our hypothesis that the relative positions of the basic amine and the arylsulfonyl pharmacophores, but not the chemical nature of the template, are important for effective interaction with the 5-HT_6 receptor.[11,13] Although it varies slightly among a number of heterocyclic templates, in general it appears that the optimal angle for basic amine/template/sulfonyl group interaction with the 5-HT_6 receptor is around 120°.[11] Further support that derivatives substituted at the 5-position are optimal in this class is seen from the data for the amide derivatives **21a–c** and **23a–c** depicted in Table 2. In this case, while the 5-position provided compounds **21a** and **23a** with a potency of 1.5 and 1.1 nM, respectively, the corresponding 6- and 7-position analogs afforded compounds with significant loss of potency (i.e., K_i = 24 and 31 nM for **21b** and **23b**, respectively).

Now with the amine position optimization complete, a number of different amino side chains were explored in order to identify

Table 1
SAR of the amino side chains of 3-sulfonylindazoles **17–20** and **37–38**

Compound	Position	R	R′	Ar	K_i[a] (nM)	IC_{50} (nM)	I_{max}[b] (%)
18a	4	—	—	1-Naph	2.8	56	92
19a	4	—	—	1-Naph	4.2	88	98
20a	4	—	—	1-Naph	9.5	21	95
17a	5	H	—	1-Naph	6.7	13	100
17b	5	Me	—	1-Naph	1.4	30	100
17c	5	(*R*)-*i*Pr	—	1-Naph	4.3	103	99
18b	5	—	—	1-Naph	0.7	15	100
19b	5	—	—	1-Naph	1.7	95	99
20b	5	—	—	1-Naph	3.5	174	98
17d	6	H	—	1-Naph	17	87	97
18c	6	—	—	1-Naph	53	—	—
19c	6	—	—	1-Naph	57	—	—
20c	6	—	—	1-Naph	44	—	—
17e	7	H	—	1-Naph	17	93	100
18d	7	—	—	1-Naph	30	—	—
19d	7	—	—	1-Naph	66	—	—
20d	7	—	—	1-Naph	17	87	96
37a	5	H	H	1-Naph	12	156	100
37b	5	CH_3	CH_3	1-Naph	14	91	94
38a	5	—	—	1-Naph	0.24	19	100

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[21] All compounds tested were HCl salts. K_i values were determined in triplicate.
[b] I_{max} is defined as the percentage of maximal antagonism as compared to that obtained with SB-271047.

Table 2
SAR of the amino side chains of 3-sulfonylindazoles **21–24** and **31**

Compound	Position	R	Ar	K_i[a] (nM)	IC_{50} (nM)	I_{max}[b] (%)
21a	5	—	1-Naph	1.5	3.8	100
23a	5	—	1-Naph	1.1	8.2	100
21b	6	—	1-Naph	24	456	96
22a	6	CH_3	1-Naph	44	—	—
22b	6	CH_3CH_2	1-Naph	65	—	—
22c	6	$-CH_2CH_2CH_2CH_2CH_2-$	1-Naph	12	90	100
23b	6	—	1-Naph	31	—	—
21c	7	—	1-Naph	3.4	23	100
22d	7	CH_3	1-Naph	4.8	137	99
22e	7	CH_3CH_2	1-Naph	27	—	—
22f	7	$-CH_2CH_2CH_2CH_2CH_2-$	1-Naph	24	—	—
23c	7	—	1-Naph	28	—	—
24a	7	—	1-Naph	9.8	48	99
31a	5	CH_3	1-Naph	2.9	103	98
31b	5	$-CH_2CH_2CH_2CH_2CH_2-$	1-Naph	107	—	—

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[21] All compounds tested were HCl salts. K_i values were determined in triplicate.
[b] I_{max} is defined as the percentage of maximal antagonism as compared to that obtained with SB-271047.

Table 3
SAR of the sulfonyl groups of 3-sulfonylindazoles **18**

Compound	Position	Ar	K_i (nM)	IC_{50}[a] (nM)	I_{max}[b] (%)
18b	5	1-Naph	0.7	15	100
18e	5	Ph	3.1	125	100
18f	5	3-F-Ph	6.7	94	100
18g	5	3-Cl-Ph	1.0	12	100
18h	5	3-Me-Ph	0.8	19	100
18i	5	4-F-Ph	6.3	118	99
18j	5	4-Cl-Ph	2.3	44	99
18k	5	4-*i*Pr-Ph	1.0	14	99
18l	5	4-CF_3-Ph	1.5	27	86
18m	5	4-MeO-Ph	9.8	126	96
18n	5	2-Naph	0.6	16	97

[a] Displacement of [^{3}H]-LSD binding to cloned human 5-HT_6 receptors stably expressed in HeLa cells.[21] All compounds tested were HCl salts. K_i values were determined in triplicate.
[b] I_{max} is defined as the percentage of maximal antagonism as compared to that obtained with SB-271047.

the optimal substitution at the 5-position. These include acyclic amines **17a–c** and **37**, cyclic amines **18–20** and **38**, amides **21a** and **23a**, and reverse amides **31a–b** (Tables 1 and 2). In general, these compounds displayed high 5-HT_6 affinity, with many examples possessing K_i values below 10 nM. Among these compounds, unsubstituted ethylenediamine **17a** was noted as a milestone derivative with potency of 6.7 nM (Table 1). Substitution with a methyl group at the α-position of the this basic amine sidechain (**17b**) further improved the potency by fivefold. Substitution with a bulkier *i*Pr group (**17c**) failed to improve the potency compared to its methyl analog **17b**. Attempts to explore the scope by insertion of a methylene group between the aniline nitrogen and the indazole template of **17a** generated compound **37a** with twofold reduction in potency. Dimethylation of the terminal nitrogen of **37a** resulted in **37b** with comparable potency (Table 1), although one might predict inferior metabolic stability. After further investigation of the diversity of sidechains and substitution patterns, it became apparent to us that compounds with a cyclic amine at 5-position were more potent than their acyclic analogs. One of the most potent compounds identified in this 3-sulfonylindazole series was the 4-piperidinyl derivative **18b** which displayed a potency of 0.7 nM (Table 1). Furthermore, we soon discovered that insertion of a carbonyl group between the piperidine and aniline nitrogen of **18b**, affording **23a** (Table 2), gives an amide analog with comparable 5-HT_6 affinity. Moving the aniline nitrogen into the cyclic amine ring afforded piperazine derivative **38a** with slightly increased potency (Table 1), and a reduced aniline character, something that caused us some pause. The comparable potency among **18b**, **23a**, and **38a** indicates that the linkage between the basic terminal amine and the indazole template has little effect on 5-HT_6 affinity. Indeed, reverse amide **31a** also displayed great potency (K_i = 2.9 nM, Table 2) and this further underscores the lack of importance of the linkage for receptor affinity. The effect of N-substitution on the terminal amine was also briefly investigated. To that end, we quickly discovered that for the 5-position analogs small groups (i.e., **31a**) are tolerated, but larger groups (i.e., **31b**) significantly reduce potency. Not surprisingly we found that in general this trend holds for the other positional isomers, such as 6- and 7-positions, but it is somewhat less pronounced (all data not shown).

As per our optimization strategy, select compounds from Tables 1 and 2 were further evaluated for their functional activity in a 5-HT_6 receptor cyclase assay.[21] The functional antagonism was determined against natural 5-HT_6 agonist 5-HT and the efficacy was expressed as I_{max} in percentage of maximal antagonism as obtained with SB-271047. All of the 3-sulfonylindazole derivatives evaluated showed full antagonism as determined by blockage of 5-HT induced cyclic AMP (cAMP) formation. The data is summarized in Tables 1 and 2.

Based on the binding and functional data, the 4-piperidinylamino substituted analog **18b** (Table 1) was identified as one of the optimal amine side chain derivatives and was used to further explore the SAR of the sulfonyl group at 3-position of the indazole core. A number of arylsulfonyl groups were explored for this purpose and the data is summarized in Table 3. While the benzenesulfonyl group (**18e**) resulted in a 4–5-fold reduction in potency as compared to its 1-naphthalenesulfonyl analog **18b**, certain substitution on the phenyl ring such as 3-Cl (**18g**), 3-Me (**18h**), or 4-*i*Pr (**18k**) provided compounds with comparable potency to that of **18b** in both binding and cyclase functional assays. Note also that the 2-naphthalenesulfonyl derivative **18n** also displayed similar potency to that of **18b**.

In line with our compound advancement strategy, a number of compounds which displayed excellent potency in both binding and cyclase functional assays were further profiled for their binding selectivity against a panel of receptors including several other 5-HT receptor subtypes, adrenergic α2A and dopamine D_2 receptors and the data is summarized in Table 4. In general, all three compounds highlighted showed >400-fold selectivity over all the receptors with the exception of 5-HT_{2B} in the cases of **18g**, **21a**, and **23a**. This was initially some concern to us as 5-HT_{2B} agonism

Table 4
Selectivity of selected 3-sulonfylindazole derivatives[a]

Compound	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)
18b	0.5	>5000	>5000	>5000	675	>5000	>5000	>5000	>5000
18g	1.0	455	1659	410	155	2427	3970	>5000	>5000
18k	1.0	859	2726	1496	1760	1767	3216	>5000	>5000
18n	0.6	4347	>5000	>5000	675	>5000	>5000	>5000	>5000
21a	1.5	>5000	>5000	>5000	344	573	>5000	>5000	>5000
23a	1.1	3011	>5000	1340	33	>5000	>5000	>5000	>5000

[a] K_i values were determined in triplicate.

activity has been indicated by several studies to possibly be responsible for adverse cardiovascular effects associated with some serotonin ligands.[25] To rule out the adverse potential of these analogs, they were then screened for their potential functional agonist activity in a 5-HT_{2B} FLIPR assay.[25] To our satisfaction, no agonist activity was observed for all compounds at concentrations of 0.1 nM–10 μM in this functional assay. All the six compounds (**18b, 18g, 18k, 18n, 21a,** and **23a**) have excellent water solubility (>100 μg/ml) and microsomal stability ($t_{1/2}$ >30 min both rat and human). None of them was shown to be P-gp substrates. Though in general this class of compounds displayed poor brain penetration (brain/plasma <0.2), the free drug levels at multiple folds of the 5-HT_6 receptor potency was easily achieved in the brain due to the low protein binding (<80%) of the compounds. In deed, compounds **18b** and **23a** demonstrated in vivo efficacy to significantly block scopolamine-induced memory deficit following administration at 10 mg/kg orally in rats in a novel object recognition assay (NOR) (data not shown).[26]

3. Summary

In summary, we have identified a novel series of 3-sulfonylindazole derivatives as potent and selective 5-HT_6 ligands. Synthesis and detailed SAR of this class of compounds has been reported. The compounds were shown to be full antagonists in a cyclic AMP functional assay. Further profiling of this class of compounds, including efficacy in a number of in vivo behavioral assays, will be detailed in subsequent reports.

4. Experimental section

4.1. 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 nM and 254 nM wavelengths. All final compounds reported here have purity ⩾95%.

4.2. 3-Iodo-5-nitro-1*H*-indazole (12b)

Iodine (26.46 g, 104.27 mmol) and potassium hydroxide pellets (11.70 g, 208.5 mmol) were successively added into a DMF (104 ml) solution of 5-nitroindazole (8.50 g, 52.13 mmol) at room temperature and stirred for 4 days. The reaction mixture was then poured into $NaHSO_3$ solution (11.06 g in 200 ml water). The brown color faded away, and the formed yellow precipitate was filtered and washed with water and dried in vacuo to provide the title compound as a yellow solid (14.74 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 9.2 Hz, 1H) 8.22 (dd, J = 9.2 and 2.2 Hz, 1H) 8.30 (d, J = 2.0, 1H). MS (ES^+) *m/e* 290 (MH^+).

4.3. 3-(Naphthalen-1-ylsulfanyl)-5-nitro-1*H*-indazole (13b)

A mixture of 3-iodo-5-nitro-1*H*-indazole (10.00 g, 34.60 mmol), 1-naphtylenethiol (5.54 g, 34.60 mmol), CuI (0.659 g, 3.46 mmol), ethylene glycol (4.30 g, 69.20 mmol) in isopropanol (49.40 ml) was heated at 90 °C under nitrogen overnight, cooled, diluted with 30% MeOH in CH_2Cl_2, and passed through a pad of silica gel. The solution was concentrated in vacuo and purified by chromatography with 1% MeOH in CH_2Cl_2 to provide the title compound (5.5 g, 49%). MS (ES^+) *m/e* 322 (MH^+).

4.4. 3-(Naphthalen-1-sulfonyl)-1*H*-indazol-5-ylamine (15b)

A mixture of 3-(naphthalen-1-ylsulfanyl)-5-nitro-1*H*-indazole (5.50 g, 17.11 mmol) and 3-chloroperoxybenzoic acid (17.91 g, 103.80 mmol) in $CHCl_3$ (115 ml) was stirred at room temperature for 4 h, diluted with EtOAc, washed with Na_2SO_3 solution, water, brine, dried over Na_2SO_4, and concentrated in vacuo to afford the crude intermediate which was carried out directly for the next step reaction without further purification.

The mixture of the crude nitro intermediate, tin mossy (15.79 g, 133.01 mmol) in MeOH and conc. hydrochloric acid was heated at 60 °C, diluted with CH_2Cl_2, and neutralized to basic with NaOH or Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4 and concentrated in vacuo followed by chromatography purification to provide the title compound (2.50 g, 45% overall yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 8.9 and 1.6 Hz, 1H) 7.56–7.78 (m, 5H) 8.04 (d, J = 1.7 Hz, 1H) 8.28 (d, J = 8.2 Hz, 1H) 8.47 (dd, J = 7.4 and 1.1 Hz, 1H) 8.73 (d, J = 8.5 Hz, 1H) 14.4 (s, 1H). MS (ES^+) *m/e* 324 (MH^+).

4.5. *N*1-3-(Napthalene-1-sulfonyl-1*H*-indazol-5-yl)-ethane-1,2-diamine HCl (17a)

A mixture of 3-(naphthalen-1-sulfonyl)-1*H*-indazol-5-ylamine hydrochloride (334 mg, 0.93 mmol), 2-oxazolidone (81 mg, 0.93 mmol), and diethylene glycol monomethyl ether (0.16 ml) was heated at 170 °C overnight, diluted with MeOH, and purified by reverse phase HPLC followed by conversion to HCl salt by treatment with HCl solution to provide the title compound as a white solid (86 mg, 21% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.02 (q, J = 6.1 Hz, 2H) 3.32 (t, J = 6.1 Hz, 2H) 6.82 (d, J = 1.7 Hz, 1H) 6.86–6.99 (m, 1H) 7.42 (d, J = 9.0 Hz, 1H) 7.55–7.70 (m, 2H) 7.70–7.82 (m, 1H) 7.93–8.15 (m, 4H) 8.28 (d, J = 8.0 Hz, 1H) 8.53 (dd, J = 7.4, 1.1 Hz, 1H) 8.78 (d, J = 8.5 Hz, 1H) 13.93 (br s, 1H); MS (ES^+)

m/e 367 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{19}H_{19}N_4O_2S^+$: 367.1222, Found: 367.1223.

4.6. *N*1-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)propane-1,2-diamine HCl (17b)

A mixture of 3-(naphthalen-1-sulfonyl)-1*H*-indazol-5-ylamine (500 mg, 1.55 mmol), *N*-*t*-Boc-alanine (381 mg, 2.01 mmol), 1-[3-(dimethylamino)propyl)]-3-ethylcarbodimide hydrochloride (386 mg, 2.01 mmol) in CH_3CN was stirred at room temperature overnight, concentrated, and purified by chromatography with 3% MeOH in CH_2Cl_2 to provide the title compound (110 mg, 48%), characterized by NMR and mass spectral analyses.

{1-[3-(Naphthalene-1-sulfonyl)-1*H*-indazol-5-ylcarbamoyl]-ethyl}-carbamic acid *tert*-butyl ester (120 mg, 0.37 mmol) was subjected to TFA at room temperature for 2 h and concentrated to dryness. The resulting residue was heated with BH_3 in THF (1 M, 4.5 ml) at reflux overnight. To the mixture was slowly added HCl (6 M, 1 ml). The resulting solution was heated at 80 °C for 20 min, concentrated, and purified by reverse phase HPLC followed by treatment with HCl solution to provide the title compound (35 mg, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.28 (d, J = 6.3 Hz, 3H) 3.12–3.23 (m, 1H) 3.24–3.32 (m, 1H) 3.32–3.41 (m, 1H) 6.82 (d, J = 1.7 Hz, 1H) 6.95 (dd, J = 9.1, 2.1 Hz, 1H) 7.41 (d, J = 9.0 Hz, 1H) 7.53–7.71 (m, 2H) 7.71–7.83 (m, 1H) 7.93–8.18 (m, 4H) 8.28 (d, J = 8.3 Hz, 1H) 8.53 (dd, J = 7.4, 1.1 Hz, 1H) 8.78 (d, J = 8.1 Hz, 1H) 13.91 (br s, 1H); MS (ES^+) *m/e* 381 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{20}H_{21}N_4O_2S^+$: 381.1379, Found: 381.1374.

4.7. (*S*)-3-Methyl-*N*1-[3-(naphthalen-1-sulfonyl)-1*H*-indazol-5-yl]-butane-1,2-diamine HCl (17c)

The title compound was prepared following the procedure for the synthesis of **17b** and employing (*S*)-*t*-Boc-Valine as the starting material. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.04 (d, J = 6.9 Hz, 6H) 1.89–2.16 (m, 1H) 3.02–3.25 (m, 2H) 3.25–3.41 (m, 1H) 6.83 (d, J = 1.7 Hz, 1H) 6.96 (dd, J = 9.1, 2.0 Hz, 1H) 7.43 (d, J = 9.1 Hz, 1H) 7.52–7.70 (m, 2H) 7.70–7.82 (m, 1H) 7.85–8.17 (m, 4H) 8.29 (d, J = 8.2 Hz, 1H) 8.51 (dd, J = 7.3, 1.1 Hz, 1H) 8.66–8.88 (m, 1H) 13.92 (br s, 1H); MS (ES^+) *m/e* 409 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{25}N_4O_2S^+$: 409.1692, Found: 409.1693.

4.8. *N*1-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)ethane-1,2-diamine HCl (17d)

The title compound was prepared following the procedure for the synthesis of **17a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.93–3.01 (m, 2H) 3.29 (t, J = 6.2 Hz, 2H) 6.44 (d, J = 1.5 Hz, 1H) 6.75 (dd, J = 8.9, 1.8 Hz, 1H) 7.52–7.69 (m, 3H) 7.75 (t, J = 8.1 Hz, 1H) 7.86–8.16 (m, 4H) 8.29 (d, J = 8.3 Hz, 1H) 8.50 (dd, J = 7.4, 1.1 Hz, 1H) 8.77 (d, J = 8.3 Hz, 1H) 13.58 (s, 1H); MS (ES^+) *m/e* 367 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{19}H_{19}N_4O_2S^+$: 367.1222, Found: 367.1224.

4.9. *N*1-(3-(Naphthalene-1-ylsulfonyl)-1*H*-indazol-7-yl)ethane-1,2-diamine HCl (17e)

The title compound was prepared following the procedure for the synthesis of **17a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98–3.08 (m, 2H) 3.45 (t, J = 6.1 Hz, 2H) 6.47 (d, J = 6.8 Hz, 1H) 7.01–7.19 (m, 2H) 7.52–7.70 (m, 2H) 7.76 (t, J = 7.8 Hz, 1H) 7.94 (br s, 3H) 8.05 (d, J = 8.0 Hz, 1H) 8.53 (d, J = 7.3 Hz, 1H) 8.76 (d, J = 8.5 Hz, 1H) 14.26 (s, 1H); MS (ES^+) *m/e* 367 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{19}H_{19}N_4O_2S^+$: 367.1222, Found: 367.1221.

4.10. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-4-amine HCl (18a)

The title compound was prepared following the procedure for the synthesis of **18b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61–1.86 (m, 2H) 2.24 (d, J = 10.7 Hz, 2H) 2.96–3.20 (m, 2H) 3.34 (d, J = 12.9 Hz, 2H) 3.69–3.95 (m, 1H) 6.40 (d, J = 7.8 Hz, 1H) 6.72 (br s, 1H) 6.78 (m, J = 8.0 Hz, 1H) 7.24 (t, J = 7.9 Hz, 1H) 7.54–7.75 (m, 2H) 7.86 (t, J = 7.8 Hz, 1H) 8.04–8.16 (m, 1H) 8.36 (d, J = 8.0 Hz, 1H) 8.39–8.48 (m, 1H) 8.61–8.73 (m, 1H) 8.74–8.88 (m, 1H) 8.83–8.89 (m, 1H) 14.02 (s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1539.

4.11. [3-(Naphthalen-1-sulfonyl)-1*H*-indazol-5-yl]-piperidin-4-yl-amine HCl (18b)

A mixture of 3-(naphthalen-1-sulfonyl)-1*H*-indazol-5-ylamine (400 mg, 1.24 mmol), 1-Boc-4-piperidone (493 mg, 2.47 mmol), sodium triacetoxyborohydride (524 mg, 2.47 mmol), and acetic acid (149 mg, 2.47 mmol) in 1,2-dichloroethane was stirred at room temperature overnight, diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, concentrated, and purified by chromatography with 1% MeOH in CH_2Cl_2 to provide the title compound (390 mg, 62% yield). MS (ES^+) *m/e* 506 $(M+H)^+$.

4-[3-(Naphthalen-1-sulfonyl)-1*H*-indazol-5-ylamino]-piperidine-1-carboxylic acid *tert*-butyl ester (390 mg, 0.77 mmol) was subjected to 1:1 TFA/CH_2Cl_2 (v/v) at room temperature for 2 h. The reaction mixture was concentrated to dryness and treated with HCl to provide the title compound (359 mg, 98%), characterized by NMR and mass spectral analyses. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52–1.77 (m, 2H) 2.01 (d, J = 11.2 Hz, 2H) 2.94–3.14 (m, 2H) 3.32 (d, J = 12.9 Hz, 2H) 3.61 (t, J = 9.4 Hz, 1H) 6.90–7.16 (m, 2H) 7.46 (d, J = 8.3 Hz, 1H) 7.55–7.68 (m, 2H) 7.74 (t, J = 7.9 Hz, 1H) 8.01–8.11 (m, 1H) 8.29 (d, J = 8.1 Hz, 1H) 8.54 (dd, J = 7.4, 1.1 Hz, 1H) 8.75 (d, J = 8.3 Hz, 1H) 8.77–8.87 (m, 1H) 8.86–9.03 (m, 1H) 14.02 (br s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1541, Found: 407.1534.

4.12. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-6-amine HCl (18c)

The title compound was prepared following the procedure for the synthesis of **18b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44–1.71 (m, 2H) 2.02 (d, J = 13.7 Hz, 2H) 2.85–3.07 (m, 2H) 3.25 (d, J = 9.5 Hz, 2H) 3.48–3.67 (m, 1H) 6.48 (s, 1H) 6.77 (dd, J = 8.9, 1.6 Hz, 1H) 7.49–7.69 (m, 3H) 7.74 (t, J = 8.1 Hz, 1H) 7.97–8.16 (m, 1H) 8.29 (d, J = 8.3 Hz, 1H) 8.50 (dd, J = 7.3, 1.2 Hz, 1H) 8.64–9.03 (m, 3H) 13.52 (s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1535.

4.13. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-7-amine HCl (18d)

The title compound was prepared following the procedure for the synthesis of **18b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.57–1.80 (m, 2H) 1.98–2.17 (m, 2H) 2.89–3.11 (m, 2H) 3.23–3.45 (m, 2H) 3.58–3.83 (m, 1H) 6.48 (dd, J = 6.2, 2.3 Hz, 1H) 6.95–7.16 (m, 2H) 7.52–7.71 (m, 2H) 7.70–7.81 (m, 1H) 8.05 (d, J = 7.6 Hz, 1H) 8.28 (d, J = 8.3 Hz, 1H) 8.53 (dd, J = 7.4, 1.1 Hz, 1H) 8.61–8.73 (m, 2H) 8.76 (d, J = 8.8 Hz, 1H) 14.51 (br s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1535.

4.14. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-3-yl)-1*H*-indazol-4-amine HCl (19a)

The title compound was prepared following the procedure for the synthesis of **18b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.63–1.79 (m,

1H) 1.78–1.94 (m, 1H) 1.92–2.03 (m, 1H) 2.18 (d, *J* = 9.5 Hz, 1H) 2.69–2.85 (m, 1H) 2.87–3.08 (m, 1H) 3.29 (d, *J* = 12.0 Hz, 1H) 3.49 (d, *J* = 12.7 Hz, 1H) 3.79–4.02 (m, 1H) 6.45 (d, *J* = 7.8 Hz, 1H) 6.70 (d, *J* = 7.1 Hz, 1H) 6.83 (d, *J* = 8.0 Hz, 1H) 7.26 (t, *J* = 8.0 Hz, 1H) 7.56–7.72 (m, 2H) 7.75–7.85 (m, 1H) 8.03–8.16 (m, 1H) 8.35 (d, *J* = 8.3 Hz, 1H) 8.44 (dd, *J* = 7.4, 1.1 Hz, 1H) 8.62–8.74 (m, 1H) 9.04 (br s, 2H) 14.06 (s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1539.

4.15. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-5-yl)-1*H*-indazol-4-amine HCl (19b)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.38–1.58 (m, 1H) 1.72–1.86 (m, 1H) 1.87–2.03 (m, 2H) 2.56–2.72 (m, 1H) 2.78–2.97 (m, 1H) 3.14–3.35 (m, 2H) 3.64–3.80 (m, 1H) 6.84 (s, 1H) 6.92 (dd, *J* = 9.1, 1.6 Hz, 1H) 7.40 (d, *J* = 9.0 Hz, 1H) 7.52–7.72 (m, 2H) 7.79 (t, *J* = 7.8 Hz, 1H) 8.05 (d, *J* = 7.6 Hz, 1H) 8.27 (d, *J* = 8.1 Hz, 1H) 8.61 (d, *J* = 6.8 Hz, 1H) 8.78 (d, *J* = 8.5 Hz, 1H) 9.14 (br s, 2H) 13.93 (br s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1540.

4.16. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-6-yl)-1*H*-indazol-6-amine HCl (19c)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.36–1.59 (m, 1H) 1.59–1.81 (m, 1H) 1.79–2.05 (m, 2H) 2.56–2.72 (m, 1H) 2.72–2.96 (m, 1H) 3.07–3.22 (m, 1H) 3.28 (d, *J* = 12.4 Hz, 1H) 3.50–3.84 (m, 1H) 6.48 (d, *J* = 1.5 Hz, 1H) 6.76 (dd, *J* = 9.0, 1.9 Hz, 1H) 7.50–7.70 (m, 3H) 7.70–7.83 (m, 1H) 7.97–8.16 (m, 1H) 8.29 (d, *J* = 8.3 Hz, 1H) 8.50 (dd, *J* = 7.3, 1.2 Hz, 1H) 8.78 (d, *J* = 8.5 Hz, 1H) 8.96 (br s, 2H) 13.58 (s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1536.

4.17. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-7-yl)-1*H*-indazol-7-amine HCl (19d)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.46–1.64 (m, 1H) 1.63–1.83 (m, 1H) 1.86–1.99 (m, 1H) 1.99–2.11 (m, 1H) 2.61–2.82 (m, 1H) 2.82–3.00 (m, 1H) 3.14–3.26 (m, 1H) 3.28–3.49 (m, 1H) 3.76–3.76 (m, 1H) 5.73 (d, *J* = 6.8 Hz, 1H) 6.53 (d, *J* = 7.1 Hz, 1H) 7.00–7.22 (m, 2H) 7.51–7.69 (m, 2H) 7.76 (t, *J* = 8.1 Hz, 1H) 7.96–8.12 (m, 1H) 8.29 (d, *J* = 8.3 Hz, 1H) 8.33–8.50 (m, 1H) 8.54 (dd, *J* = 7.4, 1.1 Hz, 1H) 8.57–8.71 (m, 1H) 8.75 (d, *J* = 8.3 Hz, 1H) 13.86 (s, 1H); MS (ES^+) *m/e* 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1536.

4.18. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-ylmethyl)-1*H*-indazol-4-amine HCl (20a)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.34–1.59 (m, 2H) 1.93 (d, *J* = 14.4 Hz, 2H) 1.97–2.11 (m, 1H) 2.77–3.01 (m, 2H) 3.19 (d, *J* = 6.8 Hz, 2H) 3.29 (d, *J* = 12.2 Hz, 2H) 6.33 (d, *J* = 7.8 Hz, 1H) 6.62 (br s, 1H) 6.76 (d, *J* = 8.0 Hz, 1H) 7.24 (t, *J* = 8.0 Hz, 1H) 7.54–7.71 (m, 2H) 7.71–7.86 (m, 1H) 8.01–8.21 (m, 1H) 8.35 (d, *J* = 8.3 Hz, 1H) 8.43 (dd, *J* = 7.4, 1.1 Hz, 1H) 8.54–8.79 (m, 2H) 8.94 (d, *J* = 8.3 Hz, 1H) 14.02 (s, 1H); MS (ES^+) *m/e* 421 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{23}H_{25}N_4O_2S^+$: 421.1692, Found: 421.1696.

4.19. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-ylmethyl)-1*H*-indazol-5-amine HCl (20b)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 1.25–1.51 (m, 2H) 1.71–1.86 (m, 1H) 1.92 (d, *J* = 13.5 Hz, 2H) 2.74–2.91 (m, 2H) 2.96 (d, *J* = 6.4 Hz, 2H) 3.16–3.45 (m, 2H) 6.78 (br s, 1H) 6.95 (d, *J* = 9.3 Hz, 1H) 7.38 (d, *J* = 9.2 Hz, 1H) 7.54–7.70 (m, 2H) 7.76 (t, *J* = 7.7 Hz, 1H) 7.96–8.15 (m, 1H) 8.29 (d, *J* = 8.2 Hz, 1H) 8.37–8.63 (m, 2H) 8.64–8.93 (m, 2H) 13.89 (br s, 1H); MS (ES^+) *m/e* 421 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{23}H_{25}N_4O_2S^+$: 421.1692, Found: 421.1696.

4.20. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-ylmethyl)-1*H*-indazol-6-amine HCl (20c)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.18–1.46 (m, 2H) 1.75–1.94 (m, 3H) 2.70–2.86 (m, 2H) 2.93 (d, *J* = 6.1 Hz, 2H) 3.22 (d, *J* = 11.7 Hz, 2H) 6.37 (d, *J* = 1.2 Hz, 1H) 6.74 (dd, *J* = 8.9, 1.8 Hz, 1H) 7.56 (d, *J* = 9.0 Hz, 1H) 7.58–7.68 (m, 2H) 7.74 (t, *J* = 8.1 Hz, 1H) 8.00–8.14 (m, 1H) 8.28 (d, *J* = 8.3 Hz, 1H) 8.42–8.64 (m, 2H) 8.66–8.95 (m, 2H) 13.47 (s, 1H); MS (ES^+) *m/e* 421 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{23}H_{25}N_4O_2S^+$: 421.1692, Found: 421.1694.

4.21. 3-(Naphthalen-1-ylsulfonyl)-*N*-(piperidin-4-ylmethyl)-1*H*-indazol-7-amine HCl (20d)

The title compound was prepared following the procedure for the synthesis of **18b**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.22–1.33 (m, 2H) 1.71–1.87 (m, 3H) 2.74–2.84 (m, 2H) 3.07 (d, *J* = 6.2 Hz, 2H) 3.22 (d, *J* = 12.3 Hz, 2H) 6.42 (d, *J* = 2.6 Hz, 1H) 7.05 (s, 1H) 7.54–7.62 (2, 2H) 7.70–7.75 (m, 2H) 8.01–8.15 (m, 2H) 8.26 (d, *J* = 8.3 Hz, 1H) 8.43–8.51 (m, 2H) 8.72 (dd, *J* = 8.4 and 1.0 Hz, 1H). MS (ES^+) *m/e* 421 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{23}H_{25}N_4O_2S^+$: 421.1692, Found: 421.1690.

4.22. 2-(4-Nitrophenyl)-1,3-dioxolane (32)

p-Nitrobenzaldehyde (1.5 g, 10 mmol) and ethyleneglycol (20 mmol) in benzene (100 ml) was refluxed for 6 h in the presence of *p*-toluenesulfonic acid (0.38 g, 2 mmoles) with the Dean–Stark adapter. After completion, the reaction mixture was cooled down and benzene was removed in vacuo. The crude mixture was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with water and dried over sodium sulfate. Evaporation of the solvent afforded the target material as pale crystalline solid (1.85 g, 95%). MS (ES^+) *m/e* 196 (MH^+).

4.23. 2-[3-(Naphthalene-1-sulfonylmethyl)-4-nitro-phenyl]-[1,3] dioxolane (33)

A mixture of 2-(4-nitro-phenyl)-[1,3]dioxolane (1.85 g, 9.5 mmol) and 1-chloromethane-sulfonyl-naphthalene (2.74 g, 11.4 mmol) was stirred in THF (50 ml) at −78 °C, in a round bottom flask under nitrogen. A solution of 1 M potassium *t*-butoxide was added dropwise (19 ml, 19 mmol) over a half an hour period. Temperature was allowed to rise to −40 °C, and the reaction mixture was stirred at this temperature for 5 h. The reaction mixture was poured into cold 2 N HCl, extracted with EtOAc, dried over Na_2SO_4, and concentrated under vacuum. Compound was purified by normal phase HPLC using as eluent 40% EtOAc/hexane to afford the title compound as an off-white solid (3.03 g, 80%). MS (ES^+) *m/e* 400 (MH^+).

4.24. 3-(Naphthalen-1-sulfonylmethyl)-4-nitro-benzaldehyde (34)

A mixture of 2-[3-(naphthalene-1-sulfonylmethyl)-4-nitro-phenyl]-[1, 3] dioxolane (3.03 g, 7.6 mmol), and 2 N HCl (4 ml,

8 mmol) in THF (30 ml) was stirred at 40 °C for 4 h. The reaction mixture was cooled to room temperature, diluted with water, extracted with EtOAc, dried over Na_2SO_4, and concentrated under vacuum to yield the title compound (2.56 g, 95%). MS (ES^+) *m/e* 356 (MH^+).

4.25. 4-Amino-3-(naphthalen-1-sulfonylmethyl)-benzaldehyde (35)

A mixture of 3-(naphthalen-1-sulfonylmethyl)-4-nitro-benzaldehyde (2.5 g, 7.22 mmol) and 10% Pd/C in THF (10 ml) and methanol (20 ml) was hydrogenated in a Parr hydrogenation bottle (250 ml) at 52 psi overnight. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to afford the title compound as an off-white solid (2.4 g, 95%). MS (ES^+) *m/e* 326 (MH^+).

4.26. 3-(Naphthalen-1-sulfonyl)-1*H*-indazole-5-carbaldehyde (36)

A mixture of 4-amino-3-(naphthalene-1-sulfonylmethyl)-benzaldehyde (2.4 g, 6.85 mmol) in THF (10 ml) and 4 M HCl (20 ml) was stirred in a round bottom flask at 3 °C. A solution of sodium nitrite (0.49 g, 7.19 mmol) in H_2O (2 ml) was added. The reaction mixture was poured into a cold solution of saturated sodium bicarbonate (100 ml) and extracted with EtOAc. The extracts were dried over Na_2SO_4 and concentrated under vacuum to afford the title compound as an off white solid (1.84 g, 80%). MS (ES^+) *m/e* 337 (MH^+).

4.27. *N,N,N′*-Trimethyl-*N′*-{[3-(1-naphthylsulfonyl)-1*H*-indazol-5-yl]methyl}ethane-1,2-diamine HCl (37b)

3-(Naphthalen-1-sulfonyl)-1*H*-indazole-5-carbaldehyde (0.17 g, 0.5 mmol), trimethyl ethylene diamine (0.6 mmol) and sodium triacetoxyborohydride (0.7 mmol) in dichloroethane (5 ml) was stirred at room temperature for 24 h. After completion, the solvent was removed in vacuo, crude material dispersed in water and pH brought to 3.4. Solid material was filtered off and washed with cold water to afford, after drying, the target material as a free base. The latter was converted into the hydrochloride salt by dissolution in methanol, followed by treatment with excess 2 N HCl, and the evacuation of the volatiles in vacuo to afford the title compound hydrochloride salt. Mp >200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.15 (br s, 3H) 2.59–2.80 (m, 8H) 3.14–3.24 (m, 2H) 3.71 (br s, 2H) 7.49 (d, *J* = 8.3 Hz, 1H) 7.55–7.71 (m, 3H) 7.77 (t, *J* = 7.8 Hz, 1H) 7.90 (br s, 1H) 8.02–8.15 (m, 1H) 8.31 (d, *J* = 8.3 Hz, 1H) 8.56 (d, *J* = 7.3 Hz, 1H) 8.78 (d, *J* = 7.3 Hz, 1H) 14.25 (br s, 1H); MS (ES^+) *m/e* 423 (MH^+).

4.28. *N*-{[3-(1-Naphthylsulfonyl)-1*H*-indazol-5yl]methyl}ethane-1.2-diamine HCl (37a)

The title compound was synthesized using the same procedure as described for **37b**. Mp >200 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.11–3.27 (m, 4H) 4.37 (br s, 2H) 7.52–7.86 (m, 5H) 8.07 (s, 1H) 8.19 (br s, 3H) 8.27–8.36 (m, 2H) 8.59 (d, *J* = 6.8 Hz, 1H) 8.78 (d, *J* = 8.3 Hz, 1H) 9.58 (br s, 2H) 14.40 (br s, 1H); MS (ES^+) *m/e* 379 (MH^+).

4.29. 3-(Naphthalen-1-ylsulfonyl)-5-(piperazin-1-ylmethyl)-1*H*-indazole HCl (38a)

The title compound was synthesized using the same procedure as described for **37b**. MS (ES^+) *m/e* 407 (MH^+).

4.30. 3-Amino-*N*-[3-(naphthalen-1-sulfonyl)-1*H*-indazol-5-yl]-propionamide HCl (21a)

A mixture of 3-(naphthalene-1-sulfonyl)-1*H*-indazol-5-ylamine (500 mg, 1.55 mmol), *N*-Boc-β-alanine (381 mg, 2.01 mmol), 1-[3-(dimethylamino)propyl)]-3-ethylcarbodimide hydrochloride (EDC, 386 mg, 2.01 mmol) in CH_3CN was stirred at room temperature overnight and concentrated to dryness. The resulting residue was subjected to TFA cleavage of the Boc protecting group, concentrated, and purified by reverse phase HPLC followed by treatment with HCl solution to provide the title compound as a white solid (180 mg, 24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.77 (t, *J* = 6.3 Hz, 2H) 3.11 (q, *J* = 6.3 Hz, 2H) 7.46–7.71 (m, 4H) 7.77 (t, *J* = 7.6 Hz, 1H) 7.93 (br s, 3H) 8.02–8.13 (m, 1H) 8.30 (d, *J* = 8.3 Hz, 1H) 8.47 (dd, *J* = 7.4, 1.1 Hz, 1H) 8.50 (s, 1H) 8.78 (d, *J* = 8.3 Hz, 1H) 10.46 (s, 1H) 14.24 (s, 1H); MS (ES^+) *m/e* 395 (MH^+).

4.31. 3-Amino-*N*-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)propanamide HCl (21b)

The title compound was synthesized using the same procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.75 (t, *J* = 6.6 Hz, 2H) 3.08 (q, *J* = 5.9 Hz, 2H) 7.33 (dd, *J* = 8.91, 1.3 Hz, 1H) 7.56–7.70 (m, 2H) 7.76 (m, *J* = 7.8, 7.8 Hz, 1H) 7.79 (br s, 3H) 7.89 (d, *J* = 8.8 Hz, 1H) 8.07 (d, *J* = 8.1 Hz, 1H) 8.22 (s, 1H) 8.31 (d, *J* = 8.3 Hz, 1H) 8.55 (d, *J* = 7.3 Hz, 1H) 8.78 (d, *J* = 8.5 Hz, 1H) 10.53 (s, 1H) 14.10 (s, 1H); MS (ES^+) *m/e* 395 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{20}H_{19}N_4O_3S^+$: 395.1172, Found: 395.1172.

4.32. 3-Amino-*N*-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-7-yl)propanamide HCl (21c)

The title compound was synthesized using the same procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.81 (t, *J* = 6.6 Hz, 2H) 3.10 (q, *J* = 6.5 Hz, 2H) 7.29 (t, *J* = 7.8 Hz, 1H) 7.54 (d, *J* = 7.6 Hz, 1H) 7.57–7.70 (m, 2H) 7.70–7.90 (m, 5H) 8.07 (d, *J* = 7.8 Hz, 1H) 8.31 (d, *J* = 8.3 Hz, 1H) 8.58 (dd, *J* = 7.3, 1.0 Hz, 1H) 8.80 (d, *J* = 8.5 Hz, 1H) 10.63 (s, 1H) 14.05 (s, 1H); MS (ES^+) *m/e* 395 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{20}H_{19}N_4O_3S^+$: 395.1172, Found: 395.1172.

4.33. 3-(Dimethylamino)-*N*-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)propanamide HCl (22a)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 (d, *J* = 4.9 Hz, 6H) 2.90 (t, *J* = 7.2 Hz, 2H) 3.35 (q, 2H) 7.34 (dd, *J* = 9.0, 1.7 Hz, 1H) 7.54–7.71 (m, 2H) 7.71–7.81 (m, 1H) 7.85–7.94 (m, 1H) 8.03–8.12 (m, 1H) 8.21 (s, 1H) 8.31 (d, *J* = 8.3 Hz, 1H) 8.55 (dd, *J* = 7.4, 1.1 Hz, 1H) 8.78 (d, *J* = 8.5 Hz, 1H) 9.94 (br s, 1H) 10.64 (s, 1H) 14.11 (s, 1H); MS (ES^+) *m/e* 423 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_3S^+$: 423.1485, Found: 423.1488.

4.34. 3-(Diethylamino)-*N*-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)propanamide HCl (22b)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.21 (t, *J* = 7.3 Hz, 6H) 2.88 (t, *J* = 7.2 Hz, 2H) 3.06–3.19 (m, 4H) 3.35 (q, *J* = 7.2 Hz, 2H) 7.33 (dd, *J* = 8.9, 1.6 Hz, 1H) 7.50–7.71 (m, 2H) 7.76 (t, *J* = 7.8 Hz, 1H) 7.90 (d, *J* = 8.8 Hz, 1H) 7.99–8.14 (m, 1H) 8.22 (d, *J* = 1.0 Hz, 1H) 8.31 (d, *J* = 8.3 Hz, 1H) 8.55 (dd, *J* = 7.4, 1.1 Hz, 1H) 8.78 (d, *J* = 8.5 Hz, 1H) 9.69 (br s, 1H) 10.61 (s, 1H) 14.09 (s, 1H); MS (ES^+) *m/e* 451 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{24}H_{27}N_4O_3S^+$: 451.1798, Found: 451.1802.

4.35. *N*-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)-3-(piperidin-1-yl)propanamide HCl (22c)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27–1.46 (m, 1H) 1.60–1.87 (m, 5H) 2.81–2.97 (m, 4H) 3.33 (q, J = 5.4 Hz, 2H) 3.40 (d, J = 11.5 Hz, 2H) 7.34 (dd, J = 8.8, 1.5 Hz, 1H) 7.57–7.69 (m, 2H) 7.76 (t, J = 7.8 Hz, 1H) 7.89 (d, J = 8.8 Hz, 1H) 8.07 (d, J = 7.6 Hz, 1H) 8.21 (s, 1H) 8.31 (d, J = 8.3 Hz, 1H) 8.55 (d, J = 7.3 Hz, 1H) 8.78 (d, J = 8.5 Hz, 1H) 9.75 (br s, 1H) 10.61 (s, 1H) 14.08 (s, 1H); MS (ES$^+$) *m/e* 463 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{25}H_{27}N_4O_3S^+$: 463.1798, Found: 463.1799.

4.36. 3-(Dimethylamino)-*N*-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-7-yl)propanamide HCl (22d)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.76 (d, J = 4.9 Hz, 6H) 2.99 (t, J = 7.1 Hz, 2H) 3.29–3.44 (m, 2H) 7.28 (t, J = 7.9 Hz, 1H) 7.55–7.86 (m, 5H) 8.07 (d, J = 8.1 Hz, 1H) 8.31 (d, J = 8.3 Hz, 1H) 8.58 (d, J = 7.6 Hz, 1H) 8.79 (d, J = 8.5 Hz, 1H) 9.90 (br s, 1H) 10.83 (s, 1H) 14.39 (s, 1H); MS (ES$^+$) *m/e* 423 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{22}H_{23}N_4O_3S^+$: 423.1485, Found: 423.1485.

4.37. 3-(Diethylamino)-*N*-(3-(naphthalen-1-ylsulfonyl)-1*H*-indazol-7-yl)propanamide HCl (22e)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (t, J = 7.3 Hz, 6H) 2.93 (t, J = 7.0 Hz, 2H) 3.07–3.14 (m, 4H) 3.31–3.36 (m, 2H) 7.25 (t, J = 7.7 Hz, 1H) 7.55–7.76 (m, 5H) 8.03 (d, J = 8.5 Hz, 1H) 8.28 (d, J = 8.2 Hz, 1H) 8.55 (d, J = 7.5 Hz, 1H) 8.76 (d, J = 8.4 Hz, 1H) 9.64 (b, 1H). MS (ES$^+$) *m/e* 451 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{24}H_{27}N_4O_3S^+$: 451.1798, Found: 451.1799.

4.38. *N*-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-7-yl)-3-(piperidin-1-yl)propanamide HCl (22f)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.27–1.47 (m, 1H) 1.58–1.89 (m, 5H) 2.84–2.95 (m, 2H) 2.97 (d, J = 7.1 Hz, 2H) 3.30–3.39 (m, 2H) 3.43 (d, J = 11.5 Hz, 2H) 7.29 (t, J = 7.9 Hz, 1H) 7.55–7.70 (m, 3H) 7.70–7.83 (m, 2H) 8.07 (d, J = 8.1 Hz, 1H) 8.31 (d, J = 8.3 Hz, 1H) 8.58 (d, J = 7.3 Hz, 1H) 8.79 (d, J = 8.5 Hz, 1H) 9.59 (br s, 1H) 10.68 (s, 1H) 14.25 (s, 1H); MS (ES$^+$) *m/e* 463 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{25}H_{27}N_4O_3S^+$: 463.1798, Found: 463.1801.

4.39. *N*-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-5-yl)piperidine-4-carboxamide HCl (23a)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.76–1.93 (m, 2H) 1.93–2.06 (m, 2H) 2.60–2.77 (m, 1H) 2.93 (q, J = 11.8 Hz, 2H) 3.35 (d, J = 12.8 Hz, 2H) 7.52–7.72 (m, 4H) 7.77 (t, J = 7.9 Hz, 1H) 7.97–8.14 (m, 1H) 8.31 (d, J = 8.1 Hz, 1H) 8.37–8.56 (m, 3H) 8.61–8.90 (m, 2H) 10.28 (s, 1H) 14.19 (s, 1H); MS (ES$^+$) *m/e* 435 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{23}H_{23}N_4O_3S^+$: 435.1491, Found: 435.1486.

4.40. *N*-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-6-yl)piperidine-4-carboxamide HCl (23b)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.72–1.88 (m, 2H) 1.95 (d, J = 11.7 Hz, 2H) 2.59–2.74 (m, 1H) 2.81–3.00 (m, 2H) 3.31 (d, J = 12.4 Hz, 2H) 7.34 (dd, J = 9.0, 1.2 Hz, 1H) 7.56–7.69 (m, 2H) 7.76 (t, J = 7.8 Hz, 1H) 7.89 (d, J = 8.8 Hz, 1H) 8.07 (d, J = 7.6 Hz, 1H) 8.22 (s, 1H) 8.30 (d, J = 8.3 Hz, 1H) 8.47–8.61 (m, 2H) 8.76 (d, J = 8.5 Hz, 1H) 8.80–8.91 (m, 1H) 10.42 (s, 1H) 14.07 (s, 1H); MS (ES$^+$) *m/e* 435 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{23}H_{23}N_4O_3S^+$: 435.1491, Found: 435.1486.

4.41. *N*-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-7-yl)piperidine-4-carboxamide HCl (23c)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.71–1.93 (m, 2H) 2.04 (d, J = 12.0 Hz, 2H) 2.75–3.06 (m, 3H) 3.32 (d, J = 12.4 Hz, 2H) 7.27 (t, J = 7.9 Hz, 1H) 7.51–7.88 (m, 5H) 8.07 (d, J = 7.8 Hz, 1H) 8.31 (d, J = 8.3 Hz, 1H) 8.36–8.53 (m, 1H) 8.57 (d, J = 7.6 Hz, 1H) 8.66–8.77 (m, 1H) 8.79 (d, J = 8.5 Hz, 1H) 10.53 (s, 1H) 14.36 (s, 1H); MS (ES$^+$) *m/e* 435 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{23}H_{23}N_4O_3S^+$: 435.1491, Found: 435.1484.

4.42. *N*-(3-(Naphthalen-1-ylsulfonyl)-1*H*-indazol-7-yl)piperidine-3-carboxamide HCl (24a)

The title compound was synthesized following a similar procedure as described for **37b**. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.61–1.76 (m, 2H) 1.76–1.89 (m, 1H) 2.00–2.18 (m, 1H) 2.81–2.96 (m, 1H) 2.95–3.13 (m, 2H) 3.13–3.22 (m, 1H) 3.29–3.44 (m, 1H) 7.28 (t, J = 7.9 Hz, 1H) 7.56–7.70 (m, 3H) 7.72 (d, J = 8.3 Hz, 1H) 7.77 (t, J = 7.9 Hz, 1H) 8.07 (d, J = 8.1 Hz, 1H) 8.31 (d, J = 8.3 Hz, 1H) 8.58 (d, J = 7.3 Hz, 1H) 8.60–8.68 (m, 1H) 8.73–8.87 (m, 2H) 10.62 (s, 1H) 14.19 (s, 1H); MS (ES$^+$) *m/e* 435 (M+H)$^+$; HRMS Calcd for (M+H)$^+$: $C_{23}H_{23}N_4O_3S^+$: 435.1485, Found: 435.1489.

4.43. 4-Nitro-benzoic acid methyl ester (25)

To a solution of 4-nitrobezoic acid (1.0 g, 7.3 mmol) in EtOAc (10 ml) was added trimethyl silyl diazomethane (5 ml, 10.9 mmol) dropwise. The mixture was then diluted with water, extracted with EtOAc, washed with water (2×), brine (1×), dried over Na_2SO_4, and concentrated under vacuum. The product was purified by flash chromatography with 20% EtOAc/hexane to afford the title compound as an off-white solid (0.8 g, 60%). MS (ES$^+$) *m/e* 182 (MH$^+$).

4.44. 3-(Naphthalene 1-sulfonylmethyl)-4-nitro-benzoic acid methyl ester (26)

A mixture of 4-nitro-benzoic acid methyl ester (0.8 g, 4.4 mmol) and 1-chloromethane-sulfonyl-naphthalene (1.3 g, 5.3 mmol) was stirred in THF (50 ml) at −78 °C, in a round bottom flask under nitrogen. A solution of 1 M potassium *t*-butoxide in THF was added dropwise (13 ml, 13 mmol) over a half an hour period. Temperature was allowed to rise to −40 °C, and the reaction mixture was stirred at this temperature for 5 h. The reaction mixture was poured into cold 2 N HCl, extracted with EtOAc, dried over Na_2SO_4, and concentrated under vacuum. The product was purified by normal phase HPLC using as eluent 40% EtOAc/hexane to afford the title compound as an off-white solid (1.5 g, 87%). MS (ES$^+$) *m/e* 386 (MH$^+$).

4.45. 4-Amino-3-(naphthalene-1-sulfonylmethyl)-benzoic acid methyl ester (27)

A mixture of 3-(naphthalene 1-sulfonylmethyl)-4-nitro-benzoic acid methyl ester (1.5 g, 3.9 mmol) and 10% Pd/C in THF (10 ml) and methanol (20 ml) was hydrogenated in a Parr hydrogenation bottle (250 ml) at 52 psi overnight. The mixture was filtered

through Celite, and the filtrate was concentrated under vacuum to afford the title compound as an off-white solid (0.9 g, 64%). MS (ES^+) *m/e* 356 (MH^+).

4.46. 3-(Naphthalen-1-sulfonyl)-1*H*-indazole-5-carboxylic acid methyl ester (28)

A mixture of 4-amino-3-(naphthalen-1-sulfonylmethyl)-benzoic acid methyl ester (0.9 g, 2.5 mmol) in THF (5 ml) and 4 M HCl (10 ml) was stirred in a round bottom flask, under nitrogen, at 3 °C. A solution of sodium nitrite (0.18 g, 2.62 mmol) in H_2O (1 ml) was added dropwise. The reaction mixture was poured into a cold solution of saturated sodium bicarbonate (100 ml) and extracted with EtOAc. The extracts were dried over Na_2SO_4, and concentrated under vacuum to afford the title compound as an off white solid (0.82 g, 90%). MS (ES^+) *m/e* 493 (MH^+).

4.47. 1-(3-Chloro-benzyl)-2-(naphthalen-1-sulfonyl)-1*H*-indazole-5-carboxylic acid methyl ester (29)

A mixture of 3-(naphthalene-1-sulfonyl)-1*H*-indazole-5-carboxylic acid methyl ester (0.82 g, 2.25 mmol), 3-chloro-benzyl bromide (0.34 ml, 2.7 mmol), and cesium carbonate (0.87 g, 2.7 mmol) in DMF (5 ml) was stirred together in a round bottom flask at room temperature for 30 min. Reaction mixture was diluted with H_2O, extracted with EtOAc, washed with water (2×), brine (1×), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by HPLC using as eluent 30% EtOAc/hexane to afford the title compound as an off-white solid (1.01 g, 92%). MS (ES^+) *m/e* 367 (MH^+).

4.48. 1-(3-Chloro-benzyl)-3-(naphthalen-1-sulfonyl)-1*H*-indazole-5-carboxylic acid (2-dimethyl-amino-ethyl)-amide (30a)

To a solution of dimethyl ethylene diamine (0.02 ml, 0.2 mmol) in THF (2 ml), cooled to 0 °C, was added LDA dropwise (0.15 ml, 0.3 mmol). To this mixture was then added a solution of 1-(3-chloro-benzyl)-2-(naphthalene-1-sulfonyl)-1*H*-indazole-5-carboxylic acid methyl ester (0.05 g, 0.1 mmol) in THF (1 ml). The mixture was allowed to warm slowly to room temperature, diluted with water, extracted with EtOAc (1×), CH_2Cl_2 (1×). The organics were washed with brine (1×) and concentrated under vacuo to afford the title compound (0.3 g, 20%). MS (ES^+) *m/e* 547 (MH^+).

4.49. *N*-[2-(Dimethylamino)ethyl]-3-(1-naphthylsulfonyl)-1*H*-indazole-5-carboxamide HCl (31a)

A mixture of 1-(3-chloro-benzyl)-3-(naphthalen-1-sulfonyl)-1*H*-indazole-5-carboxylic acid (2-dimethyl-amino-ethyl)-amide (0.3 g, 0.04 mmol), DMSO (1 ml) and *t*-BuOH (0.2 ml) was stirred at room temperature in a round bottom flask under oxygen atmosphere. A solution of potassium *t*-butoxide (0.05 ml, 0.05 mmol) was added dropwise and the reaction mixture was stirred for 1/2 h and was quenched with saturated ammonium chloride, extracted with EtOAc, dried over Na_2SO_4, and concentrated under vacuum. The crude compound was purified by reverse phase HPLC to afford the title compound. MS (ES^+) *m/e* 423 (MH^+).

4.50. 3-(Naphthalen-1-ylsulfonyl)-*N*-(2-piperidin-1-ylethyl)-1*H*-indazole-5-carboxamide HCl (31b)

The title compound was prepared following the same procedure as described for **31a** using 1-(2-aminoethyl)-piperidine as a starting material. ^1H NMR (500 MHz, DMSO-d_6) δ 1.5–2.24 (m, 10H) 2.66 (t, *J* = 6.6 Hz, 2H) 3.3 t, *J* = 6.1 Hz, 2H 7.4–8.8 (m, 7H) 7.8–8.5 (m, 3H) 12.4 (s, 1H). MS (ES^+) *m/e* 462 (MH^+).

4.51. *tert*-Butyl 4-(3-iodo-1*H*-indazol-5-ylamino)piperidine-1-carboxylate (40)

A mixture of 3-iodo-1*H*-indazol-5-amine (7.0 g, 27.0 mmol), 1-*N*-Boc-4-piperdone (5.34 g, 27.0 mmol), acetic acid (3.1 ml) and sodium triacetoxyborohydride (5.7 g, 27.0 mmol) in 1,2-dichloroethane (90 ml) was stirred at rt for 1 h, neutralized with concentrated sodium carbonate solution, extracted with CH_2Cl_2 and concentrated and purified by chromatography with 1–15% MeOH in CH_2Cl_2 to provide the title compound (8.9 g, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.19–1.34 (m, 2H) 1.36 (s, 9H) 1.86 (dd, *J* = 13.0 and 3.0 Hz, 2H) 2.90–3.00 (m, 2H) 3.35–3.45 (m, 1H) 3.84 (d, *J* = 7.9 Hz, 2H) 5.38 (d, *J* = 8.4 Hz, 1H) 6.26 (d, *J* = 1.5 Hz, 1H) 6.86 (dd, *J* = 9.0 and 2.0 Hz, 1H) 7.24 (d, *J* = 8.8 Hz, 1H). MS (ES^-) *m/e* 442 $(M-H)^-$.

4.52. *tert*-Butyl 4-(3-(phenylthio)-1*H*-indazol-5-ylamino) piperidine-1-carboxylate (41)

Under nitrogen, to a stirred solution of *tert*-butyl 4-(3-iodo-1*H*-indazol-5-ylamino)piperidine-1-carboxylate **40** (0.3 g, 0.68 mmol) in isopropanol (0.85 ml) was added CuI (0.013 mg, 0.07 mmol), K_2CO_3 (0.187 g, 1.36 mmol) and ethylene glycol (0.084 g, 1.36 mmol) followed by addition of benzenethiol (0.075 g, 67.8 mmol). The resulting solution was stirred at 100 °C for 3 h, diluted with 20 ml of 20% MeOH/CH_2Cl_2 and then passed through a pad of silica gel, concentrated to provide the title compound (0.288 g, 100%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.12–1.14 (m, 2H) 1.37 (s, 9H) 1.76 (dd, *J* = 13.0 and 2.9 Hz, 2H) 2.75–2.85 (m, 2H) 3.20–3.30 (m, 1H) 3.79 (d, *J* = 14.2 Hz, 2H) 5.40 (dd, *J* = 8.2 Hz, 1H) 6.32 (s, 1H) 6.84 (dd, *J* = 8.9 and 2.1 Hz, 1H) 7.09–7.11 (m, 3H) 7.13–7.15 (m, 2H) 7.32 (d, *J* = 8.8 Hz, 1H). MS (ES^+) *m/e* 426 (MH^+).

4.53. 3-(Phenylthio)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine (42)

To *tert*-butyl 4-(3-(phenylthio)-1*H*-indazol-5-ylamino)piperidine-1-carboxylate (0.03 g, 0.07 mmol), TFA was added and stirred for 1 h at rt. The reaction was concentrated to provide the title compound (.023 g, 0.07 mmol). MS (ES^+) *m/e* 325 $(M+H)^+$.

4.54. 3-(Phenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18e)

To a mixture of 3-(phenylthio)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine (0.023 g, 0.07 mmol) in MeOH (5 ml) was added 2 N HCl (2 ml) and the mixture was stirred for a few minutes, concentrated and the residue was dissolved in methanol (1.41 ml) and water (1.41 ml) followed by addition of oxone (0.113 g, 0.18 mmol). The reaction was allowed to stir at rt for 30 min, concentrated to dryness and purified by reverse-phase HPLC to provide the title compound (0.025 g, 98%). WAY-319522 HCl ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.59–1.81 (m, 2H) 2.02–2.13 (m, 2H) 3.03 (q, *J* = 9.7 Hz, 2H) 3.32 (d, *J* = 13.0 Hz, 2H) 3.59–3.74 (m, 1H) 7.02–7.35 (m, 2H) 7.46–7.57 (m, 1H) 7.60 (t, *J* = 7.2 Hz, 2H) 7.68 (t, *J* = 7.4 Hz, 1H) 7.98 (d, *J* = 7.2 Hz, 2H) 8.73–8.90 (m, 1H) 8.89–9.03 (m, 1H) 14.11 (br s, 1H); MS (ES^+) *m/e* 357 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{18}H_{21}N_4O_2S^+$: 357.1379, Found: 357.1380.

4.55. 3-(3-Fluorophenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18f)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.59–1.85

(m, 2H) 2.07 (d, J = 11.1 Hz, 2H) 2.92–3.13 (m, 2H) 3.32 (d, J = 12.8 Hz, 2H) 3.70 (t, J = 9.9 Hz, 1H) 7.01–7.40 (m, 2H) 7.45–7.62 (m, 2H) 7.62–7.74 (m, 1H) 7.73–7.89 (m, 2H) 8.70–8.93 (m, 1H) 8.91–9.07 (m, 1H) 14.23 (br s, 1H). MS (ES^+) m/e 375 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{18}H_{20}FN_4O_2S^+$: 375.1285, Found: 375.1291.

4.56. 3-(3-Chlorophenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18g)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.59–1.75 (m, 2H) 2.08 (d, J = 11.7 Hz, 2H) 2.99–3.13 (m, 2H) 3.32 (d, J = 12.7 Hz, 2H) 3.60–3.76 (m, 1H) 6.99–7.22 (m, 2H) 7.51 (d, J = 8.8 Hz, 1H) 7.64 (t, J = 8.1 Hz, 1H) 7.74–7.80 (m, 1H) 7.93 (d, J = 8.1 Hz, 1H) 7.97 (t, J = 1.7 Hz, 1H) 8.69–9.01 (m, 2H) 14.15 (br s, 1H). MS (ES^+) m/e 391 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{18}H_{20}ClN_4O_2S^+$: 391.0989, Found: 391.0989.

4.57. *N*-(Piperidin-4-yl)-3-(*m*-tolylsulfonyl)-1*H*-indazol-5-amine HCl (18h)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.60–1.83 (m, 2H) 2.07 (d, J = 11.4 Hz, 2H) 2.96–3.11 (m, 2H) 3.32 (d, J = 12.8 Hz, 2H) 3.56–3.76 (m, 1H) 6.98–7.42 (m, 2H) 7.43–7.53 (m, 2H) 7.56 (d, J = 8.6 Hz, 1H) 7.71–7.86 (m, 2H) 8.74–8.92 (m, 1H) 8.91–9.10 (m, 1H) 14.13 (br s, 1H). MS (ES^+) m/e 371 (MH^+).

4.58. 3-(4-Fluorophenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18i)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.64–1.82 (m, 2H) 2.08 (d, J = 11.1 Hz, 2H) 2.92–3.10 (m, 2H) 3.32 (d, J = 12.5 Hz, 2H) 3.60–3.74 (m, 1H) 7.13–7.24 (m, 1H) 7.24–7.38 (m, 1H) 7.46 (t, J = 8.8 Hz, 2H) 7.57 (d, J = 8.8 Hz, 1H) 8.05 (dd, J = 8.8, 5.1 Hz, 2H) 8.77–8.94 (m, 1H) 8.93–9.08 (m, 1H) 14.18 (br s, 1H). MS (ES^+) m/e 375 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{18}H_{20}FN_4O_2S^+$: 375.1285, Found: 375.1285.

4.59. 3-(4-Chlorophenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18j)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.66–1.88 (m, 2H) 2.06 (d, J = 11.4 Hz, 2H) 2.90–3.12 (m, 2H) 3.32 (d, J = 12.8 Hz, 2H) 3.60–3.77 (m, 1H) 7.13–7.28 (m, 1H) 7.26–7.46 (m, 1H) 7.59 (d, J = 8.6 Hz, 1H) 7.70 (d, J = 8.6 Hz, 2H) 7.98 (d, J = 8.6 Hz, 2H) 8.74–8.95 (m, 1H) 8.95–9.09 (m, 1H) 14.25 (br s, 1H). MS (ES^+) m/e 391 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{18}H_{20}ClN_4O_2S^+$: 391.0989, Found: 391.0991.

4.60. 3-(4-Isopropylphenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18k)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.18 (d, J = 6.83 Hz, 6H) 1.55–1.78 (m, 2H) 2.07 (d, J = 11.47 Hz, 2H) 2.94 (spt, J = 6.80 Hz, 1H) 2.98–3.14 (m, 2H) 3.32 (d, J = 12.44 Hz, 2H) 3.57–3.74 (m, 1H) 6.98–7.23 (m, 2H) 7.39–7.57 (m, 3H) 7.88 (d, J = 8.30 Hz, 2H) 8.66–8.81 (m, 1H) 8.80–8.95 (m, 1H) 13.99 (br s, 1H). MS (ES^+) m/e 399 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{21}H_{27}N_4O_2S^+$: 399.1848, Found: 399.1851.

4.61. *N*-(Piperidin-4-yl)-3-(4-(trifluoromethyl)phenylsulfonyl)-1*H*-indazol-5-amine HCl (18l)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.50–1.84 (m, 2H) 2.07 (d, J = 13.0 Hz, 2H) 2.94–3.14 (m, 2H) 3.31 (d, J = 12.8 Hz, 2H) 3.54–3.73 (m, 1H) 6.95–7.23 (m, 2H) 7.54 (d, J = 9.0 Hz, 1H) 7.99 (d, J = 8.4 Hz, 2H) 8.18 (d, J = 8.4 Hz, 2H) 8.73–8.91 (m, 1H) 8.90–9.03 (m, 1H) 14.23 (br s, 1H). MS (ES^+) m/e 425 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{19}H_{20}F_3N_4O_2S^+$: 425.1253, Found: 425.1255.

4.62. 3-(4-Methoxyphenylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18m)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.56–1.86 (m, 2H) 2.07 (d, J = 11.8 Hz, 2H) 2.93–3.12 (m, 2H) 3.32 (d, J = 12.3 Hz, 2H) 3.57–3.73 (m, 1H) 3.79 (s, 3H) 7.11 (d, J = 8.9 Hz, 2H) 7.13–7.24 (m, 1H) 7.23–7.39 (m, 1H) 7.55 (d, J = 8.6 Hz, 1H) 7.91 (d, J = 8.9 Hz, 2H) 8.74–8.91 (m, 1H) 8.90–9.04 (m, 1H) 14.06 (br s, 1H). MS (ES^+) m/e 387 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{19}H_{23}N_4O_3S^+$: 387.1485, Found: 387.1487.

4.63. 3-(Naphthalen-2-ylsulfonyl)-*N*-(piperidin-4-yl)-1*H*-indazol-5-amine HCl (18n)

The title compound was synthesized using the same procedure as described for **18e**. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.63–1.89 (m, 2H) 2.06 (d, J = 11.5 Hz, 2H) 2.86–3.14 (m, 2H) 3.31 (d, J = 12.7 Hz, 2H) 3.70 (t, J = 9.9 Hz, 1H) 7.19 (d, J = 3.9 Hz, 1H) 7.31–7.50 (m, 1H) 7.57 (d, J = 8.5 Hz, 1H) 7.62–7.77 (m, 2H) 7.91 (dd, J = 8.7, 1.8 Hz, 1H) 8.02 (d, J = 7.8 Hz, 1H) 8.11 (d, J = 8.8 Hz, 1H) 8.24 (d, J = 7.8 Hz, 1H) 8.75 (s, 1H) 8.79–8.95 (m, 1H) 8.96–9.09 (m, 1H) 14.19 (br s, 1H). MS (ES^+) m/e 407 $(M+H)^+$; HRMS Calcd for $(M+H)^+$: $C_{22}H_{23}N_4O_2S^+$: 407.1535, Found: 407.1538.

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