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4-(2-Aminoethoxy)-*N*-(phenylsulfonyl)indoles as novel 5-HT$_6$ receptor ligands

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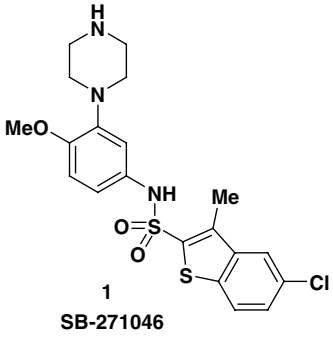
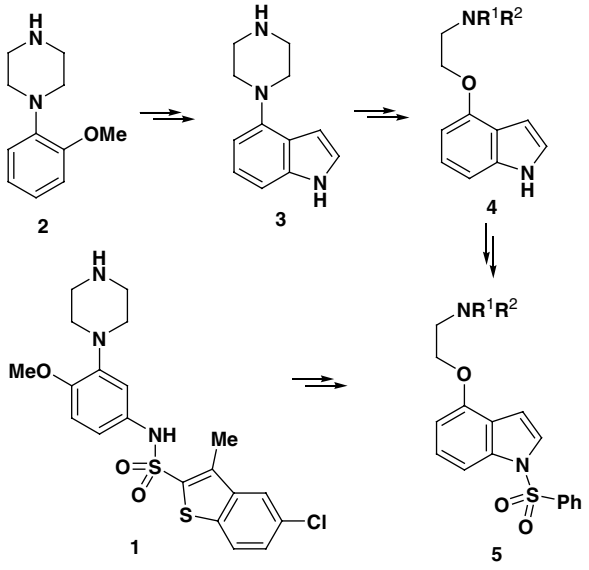
Abstract—The preparation of a novel class of 4-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles which exhibit high affinity towards the 5-HT$_6$ receptor is reported here. Among these compounds, 4-(2-methylaminoethoxy)-*N*-(phenylsulfonyl)indole **5g** showed superior affinity (K_i = 1 nM) towards the 5-HT$_6$ receptor as well as excellent selectivity (>2000-fold) against the closely related subtype 5-HT$_7$ receptor.

The potential role of 5-HT$_6$ receptor ligands in the treatment of various central nervous system disorders such as learning and memory impairments has stimulated a surge of interest in this area.[1] In 1998, Bromidge and co-workers reported SB-271046 (**1**), a potent and selective 5-HT$_6$ antagonist which later entered into clinical trials.[2–4] SB-271046 is a benzothiophene-sulfonamide, which incorporates an *o*-methoxy-piperazinyl-benzene moiety **2**.



1
SB-271046

During the course of our previous studies in the design and synthesis of novel 5-HT$_{1A}$ inhibitors, we found 4-piperazinylindole **3** was a good replacement for the *o*-methoxy-piperazinyl-benzene moiety **2**.[5,6] Additional work showed that the 4-(2-aminoethoxy)indole piece **4** (Scheme 1) was equally valuable as an aromatic headpiece for ligand design in this area.[5,6] Hence we envisioned that 4-(2-aminoethoxy)indole *N*-phenylsulfonamides **5** would be an interesting class of target molecules for 5-HT$_6$ receptor. By this analogy, the



2 **3** **4** **1** **5**

Scheme 1. Design of 4-(2-aminoethoxy)-*N*-phenylsulfonylindoles as 5-HT$_6$ ligands.

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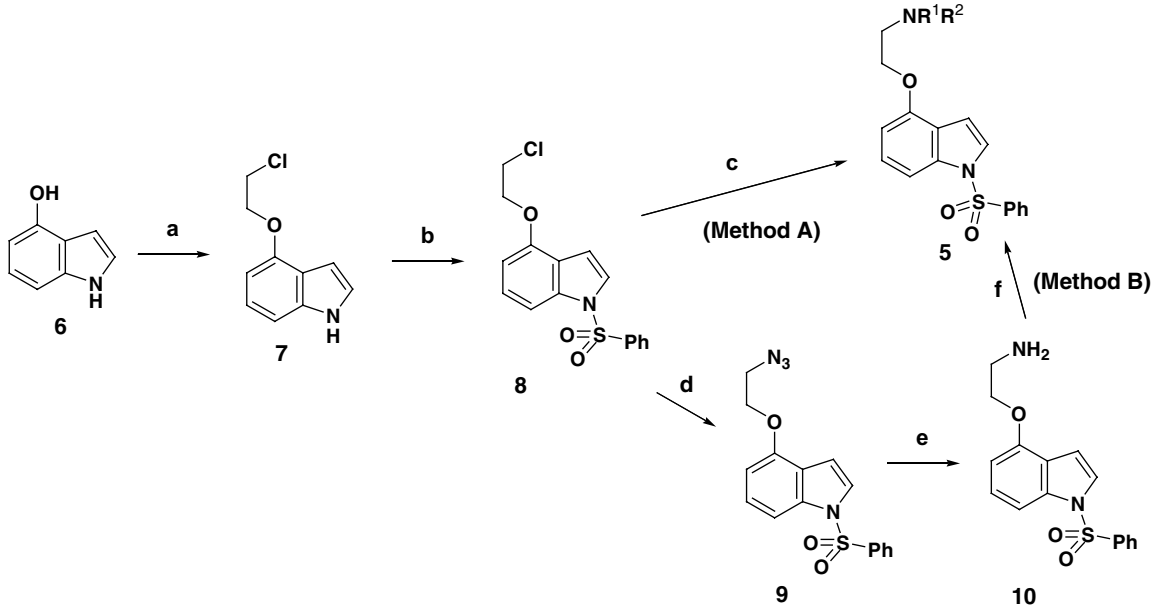
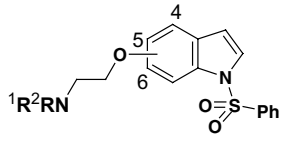


Scheme 2. Synthesis of 4-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles. Reagents and conditions: (a) $HOCH_2CH_2Cl/PPh_3$/DEAD/THF, 82%; (b) NaH/THF/$PhSO_2Cl$, 86%; (c) R^1R^2NH, heat, 57–92%; (d) NaN_3/DMF, 96%; (e) PPh_3/H_2O, 80%; (f) aldehyde or ketone, $NaBH(OAc)_3$, 31–98%.

4-(2-aminoethoxy)indole moiety can be viewed as a replacement for the *o*-methoxy-piperazinyl-benzene unit of SB-271046 (**1**) (Scheme 1). Herein, we describe the synthesis of this novel class of compounds **5** and their affinity towards the 5-HT_6 receptor.[7]

The synthesis of 4-(2-aminoethoxy)indole *N*-phenylsulfonamides **5** was carried out as shown in Scheme 2, and summarized in Table 1. Thus, treatment of commercially available 4-hydroxyindole **6** with 2-chloroethanol in the presence of triphenylphosphine and DEAD in THF at ambient temperature for 2 h afforded 4-(2-chloroethoxy)indole **7** in 82% yield.[8] Reaction of **7** with sodium hydride and subsequent treatment with phenylsulfonyl chloride gave *N*-phenylsulfonylindole **8** in excellent yield.[9] Treatment of the chloride **8** with an excess of the appropriate amines in DMF at 80 °C overnight (Method A) gave 57–92% yields of the target compounds **5a–j** after chromatography and HCl salt formation. Alternatively, compounds **5k–n** could be prepared via reductive alkylation of the primary amine **10** with aldehydes or ketones in the presence of $NaBH(OAc)_3$ (Method B).[10] The requisite primary amine **10** was readily obtained in two steps from the corresponding chloride

Table 1. Synthesis of 4-, 5- and 6-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles **5**, **10**, **13** and **16**



Compound	R^1	R^2	Point attached	Method	Overall yield (%)	Mp[a] (°C)
5a	–$CH_2CH_2OCH_2CH_2$–		4-	A	59	140–142
5b	–$CH_2(CH_2)_2CH_2$–		4-	A	65	90–92
5c	–$CH_2(CH_2)_3CH_2$–		4-	A	62	131–133
5d	–$CH_2(CH_2)_4CH_2$–		4-	A	58	195–197
5e	–$CH_2CH_2N(Me)CH_2CH_2$–		4-	A	60	238–240
5f	–$CH_2CH_2N(Me)CH_2CH_2CH_2$–		4-	A	36	200–202
5g	H	Me	4-	A	60	202–204
5h	H	Et	4-	A	63	188–190
5i	H	*i*-Pr	4-	A	61	196–198
5j	H	$PhCH_2$	4-	A	64	214–216
5k	H	$O(CH_2CH_2)_2CH$–	4-	B	49	229–230
5l	H	3-$MeOC_6H_3CH_2$–	4-	B	17	189–190
5m	3-$MeOC_6H_3CH_2$–	3-$MeOC_6H_3CH_2$–	4-	B	19	194–196
5n	Me	Me	4-	B	34	140–142
10	H	H	4-	—	54	198–200
13	H	H	5-	—	11	171–173
16	H	H	6-	—	33	183–185

[a] Melting points were taken on mono HCl salts except compounds **5e**,**f**, which were prepared as di HCl salts.

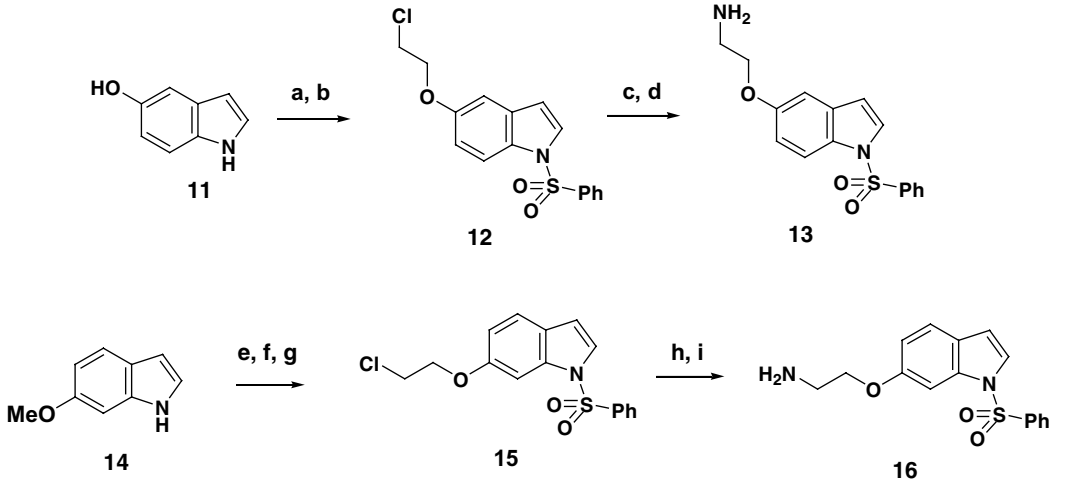
8 via the intermediate azide **9**. While the reductive alkylation of **10** with a ketone led to mono-alkylated product (Table 1, **5k**), reactions of **10** with an aldehyde afforded mixtures of mono- and dialkylated products with the latter predominating (Table 1, **5l–n**).

The synthesized compounds **5a–n** were evaluated in radioligand binding assays to measure their 5-HT_6 and 5-HT_7 affinities and the results are summarized in Table 2. For cyclic disubstituted aminoethoxy compounds **5a–f**, it appears that the 5-HT_6 affinity decreases as the ring size increases. For example, piperidinylethoxy indole **5c** has a K_i value of 7 nM whereas its homopiperidinyl analogue **5d** shows 3-fold reduced affinity. This trend is more apparent for the *N*-methyl piperazinyl **5e** and *N*-methylhomopiperazinyl compounds **5f**, where introduction of an additional methylene unit resulted in more than 6-fold decrease in activity. Similar observation was also made for the acyclic substituted aminoethoxy indoles. Disubstituted compounds showed diminished activities compared with its corresponding monosubstituted analogues (compare Table 2, **5m** vs **5l** and **5n** vs **5g**). For monosubstituted **5**, again the smaller the size of the substituent group, the higher the 5-HT_6 affinity. For example, *N*-isopropylaminoethoxy indole **5i** has a K_i = 19 nM whereas its *N*-ethyl and methyl analogue **5h** and **5g** displaces K_i value of 6 and 1 nM, respectively. Based on these observations, examination of intermediate **10**, which has the smallest R^1 and R^2 (both are hydrogen substituents), in the 5-HT_6 assay showed it to have high superior affinity (K_i = 2 nM). Consequently, compound **13** and **16**, which are the regioisomers of **10**, were also synthesized from commercially available 5-hydroxyindole and 6-methoxyindole, respectively, as shown in Scheme 3. Both analogues **13** and **16** showed, however, reduced affinities for the 5-HT_6 receptor compared to **10**, underscoring the importance of the 4-substitution pattern for these derivatives. Further

Table 2. Biological activities of 4-, 5- and 6-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles **5a–n**, **10**, **13** and **16**

Compound	5-HT_6 K_i (nM)	5-HT_7 K_i (nM)	K_i ratio 5-HT_7/5-HT_6	cAMP 5-HT_6	
				IC_{50} (nM)	I_{max} (%)
5a	28 ± 3.1	7800 ± 560	279	ND	ND
5b	8 ± 0.5	6100 ± 372	763	400 ± 73	100 ± 0
5c	7 ± 0	1800 ± 5	257	198 ± 27	90 ± 10
5d	22 ± 1	2000 ± 152	91	ND	ND
5e	18 ± 0.5	5500 ± 83	306	ND	ND
5f	120 ± 1	2700 ± 25	23	ND	ND
5g	1 ± 0.1	2200 ± 154	2200	308 ± 63	100 ± 0
5h	6 ± 0.1	3700 ± 21	617	334 ± 32	100 ± 0
5i	19 ± 0.5	7700 ± 374	405	ND	ND
5j	50 ± 0.5	1700 ± 14	34	ND	ND
5k	6 ± 0	1000 ± 755	1000	223 ± 19	91 ± 1
5l	12 ± 0.5	1300 ± 276	108	ND	ND
5m	156 ± 4	ND	ND	ND	ND
5n	4 ± 1	3000 ± 269	753	345 ± 103	83 ± 1
10	2 ± 0.4	2700 ± 720	1350	222 ± 64	92 ± 2
13	10 ± 1	2600 ± 223	260	ND	ND
16	23 ± 0.5	1600 ± 140	70	ND	ND

ND = not determined.



Scheme 3. Synthesis of 5- and 6-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles. Reagents and conditions: (a) $HOCH_2CH_2Cl/PPh_3$/DEAD/THF, 24%; (b) NaH/THF/$PhSO_2Cl$, 68%; (c) NaN_3/DMF, 99%; (d) PPh_3/H_2O, 67%; (e) NaH/THF/$PhSO_2Cl$, 86%; (f) BBr_3/CH_2Cl_2, 54%; (g) $HOCH_2CH_2Cl$/PPh_3/DEAD/THF, 89%; (h) NaN_3/DMF, 91%; (i) PPh_3/H_2O, 87%.

optimization led to the secondary amine **5g** which was more potent than the parent amine **10**.

The synthesized compounds **5a**–**n**, **10**, **13** and **16** were also evaluated in radioligand binding assay to measure 5-HT_7 affinity except compound **5m** and the values were used for the determination of binding selectivity of 5-HT_6 over 5-HT_7 receptor. As shown in Table 2, the selectivity, calculated as K_i ratio of 5-HT_7/5-HT_6, ranging from 20- to >2000-fold was seen for these compounds, with **5g** being the most selective (>2000-fold). For those compounds which demonstrated 5-HT_6 affinity less than 10 nM, additional cellular profiling (cAMP accumulation) was conducted to determine intrinsic activity at the 5-HT_6 receptor. The results indicated that compounds, **5b**, **5g** and **5h**, were able to fully block the effect of 5-HT with I_{max} of 100%. These derivatives showed moderate antagonist potencies (IC_{50} range: 308–344 nM), and future work will be focused on optimization of their intrinsic activities.

In summary, a novel class of 4-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles were designed and synthesized. Radioligand binding assays indicate they are potent 5-HT_6 receptor ligands. Among these compounds, 4-(2-methylaminoethoxy)-*N*-(phenylsulfonyl)indole **5g** showed high affinity towards the 5-HT_6 receptor with a K_i = 1 nM and excellent selectivity (>2000-fold) over the 5-HT_7 receptor. Furthermore, it was shown that **5g** was a full antagonist at the 5-HT_6 receptor with moderate intrinsic potency.

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