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Bioorganic & Medicinal Chemistry Letters 17 (2007) 5647–5651
Bioorganic & Medicinal Chemistry Letters

Conformationally restricted homotryptamines. Part 4: Heterocyclic and naphthyl analogs of a potent selective serotonin reuptake inhibitor

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Received 25 April 2007; revised 19 July 2007; accepted 20 July 2007
Available online 22 August 2007

Abstract—A series of hybrid molecules containing the cyclopropylmethylamino side chain found in homotryptamine (1*S*,2*S*)-**2c** and an isosteric heteroaryl or naphthyl core were prepared and their binding affinities for the human serotonin transporter determined. The most potent isosteres were CN-substituted naphthalenes. These results demonstrate that isosteric aromatic cores which lack an H-bond donor site may be substituted for the indole nucleus without substantial loss in hSERT binding.

The serotonergic system is a well-characterized target in the treatment of depression. Inhibition of the human serotonin transporter (hSERT), which is responsible for the regulation of synaptic serotonin levels, forms the full or partial basis for the mechanism of action of many antidepressants known as selective serotonin reuptake inhibitors (SSRIs).[1] Figure 1 illustrates some examples of marketed SSRIs. Though structurally diverse, they share a common characteristic of having a terminal alkylamino group separated from an aromatic nucleus by a 3–4 atom spacer.

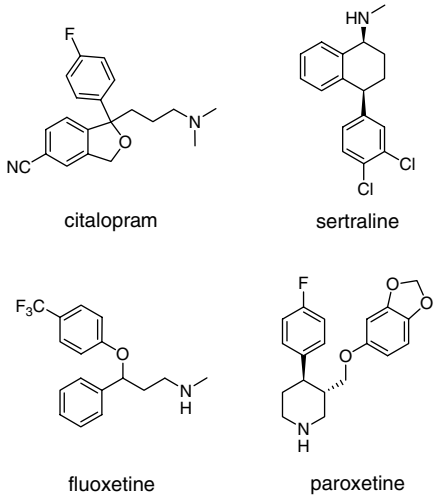

Figure 1. Examples of marketed SSRIs.

Additionally, a number of indole,[2–6] thiophene,[7] and naphthalene[8] systems sharing a similar terminal amino function have been reported to inhibit hSERT. We have recently reported a new class of homotryptamine analogs which are potent inhibitors of hSERT.[2] In the simplest manifestation, an indole **1** is linked at the 3-position to a *N*,*N*-dimethyl-*N*-propylamine (Fig. 2). Substitution of the indole with electron-withdrawing groups as in **1b** and **1c** resulted in higher hSERT binding affinities. We further refined this system by conformationally restricting the aminopropyl side chain with a cyclopropyl group as shown in **2**. This led to the hSERT inhibitor *trans-rac*-**2c**. Upon resolution, a highly potent hSERT inhibitor, (1*S*,2*S*)-**2c**, was obtained.[3,9] (1*S*,2*S*)-**2c** was more potent than **1c**, suggesting that

Keywords: Homotryptamines; SSRI.
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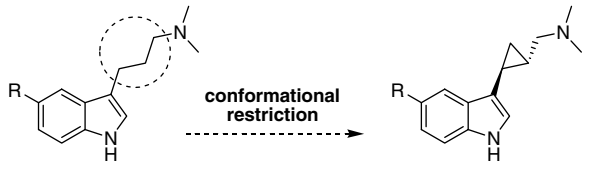
doi:10.1016/j.bmcl.2007.07.083



	hSERT IC_{50}, nM		hSERT IC_{50}, nM
1a, R=H	58±6	*rac*-**2a**, R=H	99±36
1b, R=F	4.0±0.3	*rac*-**2b**, R=F	4.1±2.1
1c, R=CN	2.0±0.4	*rac*-**2c**, R=CN	1.1±1.0
		(1S,2S)-**2c**, R=CN	0.48±0.16

Figure 2. Homotryptamine analogs.[2,3]

cyclopropyl conformational restriction of the aminopropyl chain afforded a favorable binding interaction with hSERT in (1*S*,2*S*)-**2c**.

The broad activity of these divergent systems suggested that hSERT might recognize a wide range of aromatic groups in place of the indole of **2**. With this in mind, we constructed hybrid molecules which combined the side chain found in **2** with an isosteric aryl or heteroaryl ring (Fig. 3). Our novel core structures may be grouped into four broad classes: (i) azaindoles **3**–**5**, (ii) benzothiophene **6**, (iii) quinoline/isoquinoline **7**–**8**, and (iv) naphthalenes **9**–**10**. Herein we describe the synthesis and hSERT binding affinities of these molecules.[10]

We initially synthesized a *trans* racemic series[11] of azaindole analogs in which the additional ring nitrogen was placed at either the 2-position (indazoles, **3**), 7-position (7-azaindoles, **4**), or the 9-position (imidazo[1,2-a]pyridines, **5**) of the indole nucleus.

Synthesis of indazole **3** was carried out as shown in Scheme 1. The initial ketone **12** was synthesized via Pd-catalyzed Cu(I) carboxylate-mediated coupling of boronic acid **10** with thiol ester **11**.[12] The key step in the construction was the closure of **13** under basic conditions at 100 °C to the tosyl-protected indazole **14**. Similar cyclizations have been reported for unprotected hydrazones,[13,14] but high temperatures were required and hydrazone dimers were often formed. In our reaction tosyl protection blocked the formation of dimers and allowed for milder cyclization conditions. The sequence was completed by reduction of the side chain to the corresponding alcohol with LAH, followed by reoxidation to the aldehyde under Swern conditions. Reductive amination incorporated the dimethylamino group, and mild base treatment removed the tosyl protecting group to give **3**.

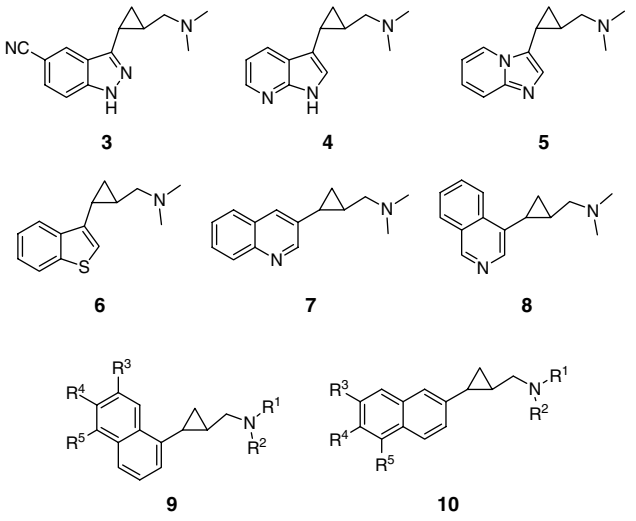
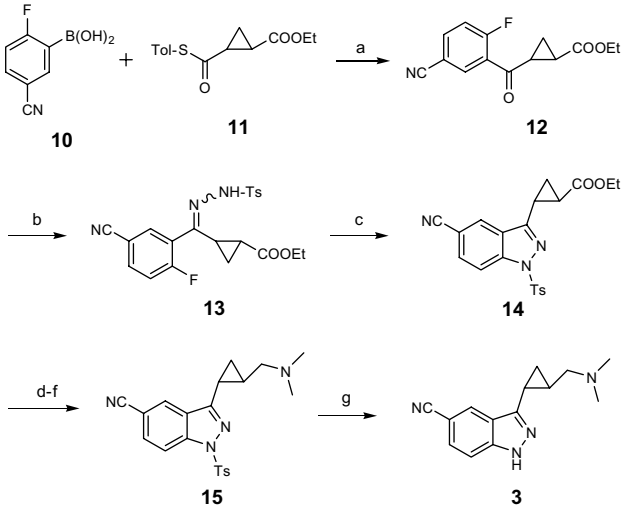
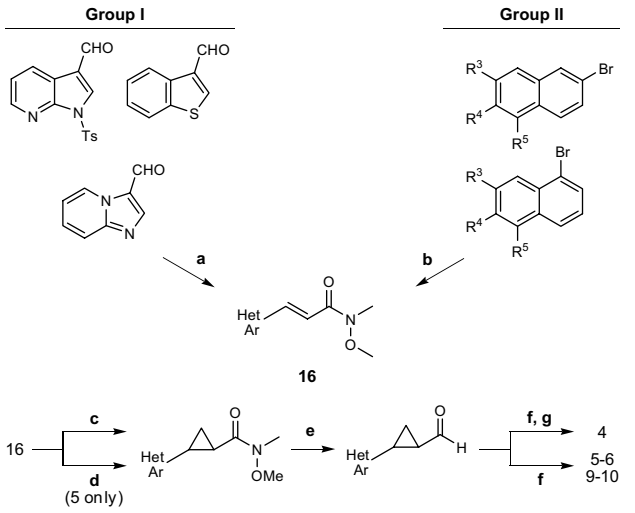


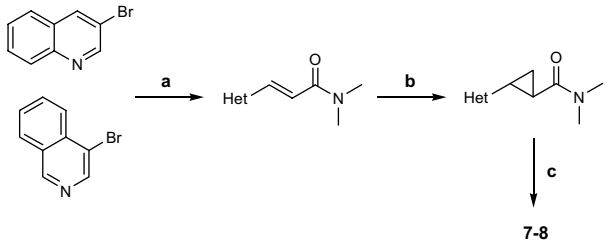
Figure 3. Hybrid SSRIs.



Scheme 1. Synthesis of indazole **3**. Reagents and conditions: (a) Copper(I) thiophene-2-carboxylate, $Pd_2dba_3 \cdot CHCl_3$, trifurylphosphine, rt, 4 h, 78%; (b) Ts-$NHNH_2$, 68%; (c) K_2CO_3/DMF, 100 °C, 15 min, 45%; (d) LAH, 88%; (e) oxalyl chloride, DMSO, Et_3N, 100%; (f) $(CH_3)_2NH$, $NaBH(OAc)_3$; (g) NaOH/H_2O/MeOH, 68% (two steps).



Scheme 2. General synthetic scheme for **4**–**6**, **9**–**10**. Reagents and conditions: (a) diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate, NaH, 77–93%; (b) *N*-methoxy-*N*-methyl acrylamide, $Pd(OAc)_2$, NaOAc, (*o*-tolyl)$_3$P, DMF, reflux, 36–52%; (c) CH_2N_2, $Pd(OAc)_2$, 84–100%; (d) Me_3SOI, NaH, 60%; (e) LAH, THF, −40 to 0 °C, 61–100%; (f) R^1R^2NH, $NaBH(OAc)_3$, EtOH, 15–75%; (g) aq NaOH, quant.



Scheme 3. General synthetic scheme for **7**–**8**. Reagents and conditions: (a) *N*,*N*-dimethylacrylamide, $Pd(OAc)_2$, NaOAc, (*o*-tolyl)$_3$P, DMF, reflux, 58–69%; (b) Me_3SOI, NaH, 59–63%, or CH_2N_2, $Pd(OAc)_2$, 64%; (c) AlH_3, 89%.

Table 1. hSERT binding affinities of **3**–**8**

Compound	hSERT IC_{50}[a] (nM)
2a	99 ± 36
3	71 ± 34
4	410
5	>1000
6	25 ± 11
(+)-6	55 ± 36
(−)-6	150 ± 60
7	130 ± 70
8	>1000

[a] Where indicated with ±SEM, $n = 3$ for the reported IC_{50} values. Otherwise, $n = 2$. IC_{50} values were determined from a four-parameter competition curve equation fit on a five point concentration curve and are reported as the average value of all determinations.

Synthesis of compounds **4**–**6** followed a common pathway as outlined in Scheme 2. Heterocyclic aldehydes (Group I)[3,15] were subjected to Horner–Wadsworth–Emmons conditions with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate to give the *trans*-olefins **16**. Cyclopropanation was accomplished with diazomethane (7-azaindole **4** and benzothiophene **6**) or via sulfur ylide (imidazo[1,2-*a*]pyridine **5**). After reduction to the aldehyde followed by reductive amination, and in the case of **4**, basic deprotection, **4**–**6** were obtained.

Compounds **9**–**10** were synthesized according to Scheme 2 starting from the corresponding bromides (Group II). The aryl bromides were initially alkenylated via Heck coupling. Synthesis was completed following a pathway identical to **4**–**6**.

Compounds **7**–**8** were synthesized according to Scheme 3. The quinoline and isoquinoline bromides were alkenylated with *N*,*N*-dimethylacrylamide. Cyclopropanation was accomplished by treatment with the sulfur ylide or diazomethane. Final reduction of the amides to **7**–**8** was most efficient with AlH_3.

The hSERT binding affinities of **3**–**8** were determined as previously described[2] and expressed here as hSERT IC_{50} values (Table 1). The azaindoles **3**–**5** offered no potency advantages versus the indoles. Indazole **3** was at best equipotent with the analogous unsubstituted indole **2a**, while 7-azaindole **4** and imidazopyridine **5** were significantly less active. Benzothiophene **6** was slightly improved relative to the indole **2a** and indazole **3**. When **6** was resolved by preparative chiral HPLC, the relative binding affinity of the (+)-enantiomer for hSERT was approximately 3-fold higher than the (−)-enantiomer.

Table 2. hSERT binding affinities of naphthalenes **9a–k** and **10a–g**

Compound	R^1	R^2	R^3	R^4	R^5	SERT IC_{50}[a] (nM)
rac-**2a**	—	—	—	—	—	99 ± 36
rac-**2c**	—	—	—	—	—	1.1 ± 1.0
(1*S*,2*S*) − **2c**	—	—	—	—	—	0.48 ± 0.16
9a	H	Me	H	H	H	89 ± 42
9b	Me	Me	H	H	H	15 ± 14
(+)-9b	Me	Me	H	H	H	18 ± 8
(−)-9b	Me	Me	H	H	H	170 ± 50
9c	Me	Et	H	H	H	58 ± 25
9d	Et	Et	H	H	H	120 ± 20
9e	H	Me	H	CN	H	17 ± 4
9f	H	Et	H	CN	H	37 ± 11
9g	Me	Me	H	CN	H	4.1 ± 2.0
9h	Et	Et	H	CN	H	67 ± 60
9i	–$(CH_2)_4$–		H	CN	H	51 ± 16
9j	Me	Bn	H	CN	H	16 ± 6
9k	Me	Me	H	H	CN	48 ± 11
10a	H	Me	H	H	H	52 ± 13
10b	Me	Me	H	H	H	8.6 ± 7.8
(+)-10b	Me	Me	H	H	H	8.6 ± 2.4
(−)-10b	Me	Me	H	H	H	140 ± 10
10c	Me	Et	H	H	H	310
10d	Et	Et	H	H	H	550
10e	Me	Me	CN	H	H	0.88 ± 0.43
10f	Me	Me	H	CN	H	13 ± 6
10g	Me	Me	CN	CN	H	5.9 ± 2.0

[a] Where indicated with ± SEM, $n \geqslant 3$ for the reported IC_{50} values. Otherwise, $n = 2$. IC_{50} values were determined from a four-parameter competition curve equation fit on a five point concentration curve and are reported as the average value of all determinations.

Table 3. Inhibition of dopamine and norepinephrine transporters.

Compound	SERT IC_{50}[a] (nM)	DAT % inhibition[b]	DAT IC_{50}[c] (μM)	NET % inhibition[b]	NET IC_{50}[c] (μM)
3	71 ± 34	0	44 ± 21	−4.9	>100
(+)-6	55 ± 36	24	ND[d]	13	ND
(+)-9b	18 ± 8	12	33 ± 6	2.3	68 ± 18
9g	4.1 ± 2.0	16	8.7 ± 1.9	20	19 ± 5
9k	48 ± 11	9.5	12 ± 4	25	39 ± 5
(+)-10b	8.6 ± 2.4	31	2.4 ± 0.4	18	8.7 ± 0.7
10e	0.88 ± 0.43	83	0.26 ± 0.04	68	0.71 ± 0.13
10f	13 ± 6	41	1.1 ± 0.4	69	0.56 ± 0.05
10g	5.9 ± 2.0	80	ND	82	ND

[a] From Tables 1 and 2.
[b] Test concentration 1 μM.
[c] $n = 3$ for the reported IC_{50} values.
[d] ND, not done.

Both **7** and **8** were less active than the indoles, but quinoline **7** has a higher binding affinity for hSERT than isoquinoline **8**.

Unlike the previous heteroaryl analogs **3**–**8**, several members of the naphthalene series **9**–**10** were more potent than the corresponding indole **2** (Table 2). For example, **9b** and **10b** were approximately 10-fold more potent against hSERT than **2a**. In most cases, unsubstituted members of series **9** were roughly equipotent to similar unsubstituted members of series **10**. The optimum amine substitution pattern was still observed to be dimethyl (**9b** and **10b**). Both **9b** and **10b** were resolved by preparative chiral HPLC, yielding in each case the (+)-enantiomer as the more active of the pair (10- to 16-fold). In the indole series **2**, we found that substitution with electron-withdrawing groups increased hSERT binding affinity.[3] Substitution of **9** with $R^4 = CN$ was optimal, resulting in a 2- to 5-fold increase in hSERT binding. Compound **9g** was the most potent of series **9**, with hSERT IC_{50} equal to 4.1 nM. Substitution of **10** with CN groups was also effective. An optimal hSERT IC_{50} of 0.88 nM was achieved with the racemate **10e** ($R^3 = CN$) corresponding to a 10-fold increase in binding affinity over the unsubstituted (+)-**10b**.

To confirm selectivity for the serotonin transporter, several of the compounds reported in this study were evaluated for binding affinity at dopamine (DAT) and norepinephrine (NET) transporters. Table 3 shows results for a selected group, chosen on the basis of hSERT potency within their respective classes. Most of these compounds were only weak inhibitors of DAT or NET, with the most potent being the CN-substituted members of naphthalene series **10**. For example, DAT and NET IC_{50} values for **10e** were 260 and 710 nM, respectively. Selectivity for the serotonin transporter varied widely without apparent correlation to hSERT IC_{50}. Selectivity ratios varied 80- to 2000-fold for DAT and 40- to 5000-fold for NET.

In this work we synthesized hybrid molecules which contain the *N*,*N*-dialkyl-*N*-cyclopropylmethylamino side chain found in **2** and an isosteric naphthyl or heteroaryl core. The optimal members of the azaindole **3**–**5**, benzothiophene **6**, quinoline **7**, and isoquinoline **8** series were *N*,*N*-dimethyl substituted. Though exhibiting moderate binding potency at hSERT (25–130 nM), they are at best equipotent with prototype unsubstituted indole **2a**. By contrast, many members of the naphthalene series **9**–**10** exhibited hSERT binding at <10 nM. The optimal member of this series was the CN-substituted *rac*-**10e**, which also possesses the *N*,*N*-dimethyl substitution pattern. The hSERT binding IC_{50} of this compound, 0.88 nM, was essentially equimolar to that of *rac*-**2c** and approached that of the more active enantiomer (1*S*,2*S*)-**2c**. We have previously speculated that the indole NH may provide an important H-bonding interaction with hSERT.[3] However, these results challenge that conclusion and demonstrate that isosteric aromatic cores such as naphthalenes which lack the H-bond donor site may be substituted for the indole nucleus without substantial loss in hSERT binding.

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10. Compounds **3**–**8** are presented here with *N*,*N*-dimethyl substitution (R^1, $R^2 = CH_3$). In fact, many other N-substituents were surveyed across this series. In each case though, the *N*,*N*-dimethyl analogs were the most potent. For the sake of brevity, we only include these in this report (Table 1). Because some members of series **9**–**10** possesssed significantly higher hSERT potency, the entire range of substituents is presented in Table 2.
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