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Thiophene Derivatives: A New Series of Potent Norepinephrine and Serotonin Reuptake Inhibitors

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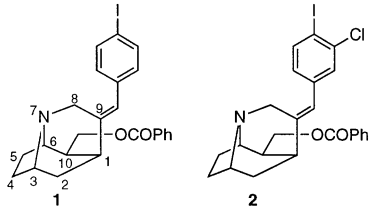
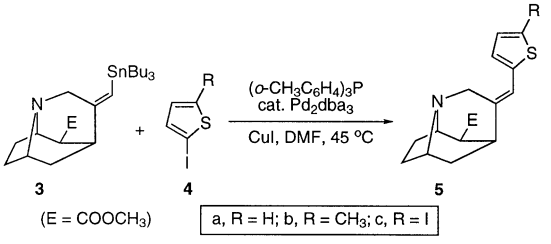
Abstract—A series of (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(thienylmethylene- or substituted thienylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decanes was prepared and evaluated for the ability to block dopamine, serotonin, and norepinephrine reuptake by their respective transporters. Compound **5b** is a NET-selective inhibitor, **5c** is a mixed NET- and SERT-selective inhibitor, while **11** is a SERT-selective inhibitor.

The biological actions of cocaine are believed to be centered around its interaction at the dopamine, serotonin, and norepinephrine transporters (DAT, SERT, and NET).[1–4] However, in contrast to the substantial body of research on dopamine in the nucleus accumbens, comparatively little attention has been given to the role of serotonin and norepinephrine.[5–7] As part of a project in pursuit of possible medications for cocaine abuse, we have paid particular attention on the design of ligands with selectivity for the SERT or the NET.[8–10] In a series of conformationally constrained tricyclic tropane analogues, several novel, highly potent and selective serotonin reuptake inhibitors have been identified,[9,10] which can be used as starting points for further research. For example, (1*S*,3*S*,6*R*,10*S*) - (*Z*) - 9 - (4 - iodophenylmethylene) - 10 - (benzoyloxymethyl)-7-azatricyclo[4.3.1.0^{3,7}]decane (**1**) displayed a K_i of 0.1 nM for 5-HT reuptake inhibition, while the 3-chloro-4-iodophenyl analogue (**2**) exhibited an even higher inhibitory potency ($K_i = 0.06$ nM) at the SERT. It is of further note that (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(2 - thienylmethylene) - 7 - azatricyclo[4.3.1.0^{3,7}]decane - 10 - carboxylic acid methyl ester (**5a**), in contrast to the phenyl analogues, is a NE selective reuptake inhibitor ($K_i = 26$ nM). Since there are rather few studies on NE-selective reuptake inhibitors, and the thienyl group is an interesting pharmacophoric function, we decided to further investigate the SAR of thienyl analogues with ligand **5a** as the lead. Herein, we report the synthesis and biological activity of a series of (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(thienylmethylene- or substituted thienylmethylene)-7-azatricyclo[4.3.1.0^{3,7}]decanes, some of which exhibit good activities at the SERT or at the NET.



The general strategy for the synthesis of these compounds is based on the procedures we developed previously to prepare the lead **5a**.[9] Thus, compounds **5b** and **5c** were prepared by Stille coupling reaction from the tributylstannyl precursor **3** in moderate yields (Scheme 1).[11]



Scheme 1.

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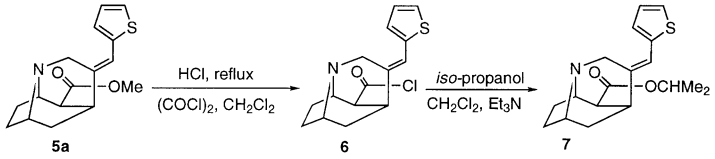
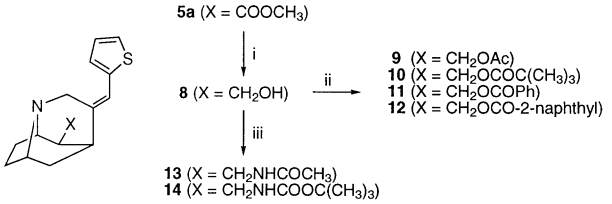


Scheme 2.

To gain insight into the effect of the ester substituent, a variety of chemical modifications were carried out. First, isopropyl ester **7** was prepared from the methyl ester **5a** as shown in Scheme 2.[12] Reverse esters **9**–**12** were obtained by a two-step procedure in which ester **5a** was reduced with $LiAlH_4$ or DIBAL-H to give the alcohol **8**. This intermediate was then treated with the corresponding acid chloride (Scheme 3). The alcohol **8** was also transformed into amides **13**–**14** by use of a Mitsunobu reaction.[13]

Compounds **5a**–**5c** were tested as the free bases, and compounds **7**–**14** were tested as their hydrochloride salts. The effect of candidate compounds in antagonizing biogenic amine high-affinity uptake was determined using a method similar to that previously employed for [^{3}H]DA uptake.[14a] Striatum, midbrain, and parietal/occipital cortex were dissected and used as a source of rat DAT, SERT, and NET, respectively. The Cheng–Prusoff equation for classic, competitive inhibition was used for calculating the K_i from the IC_{50} values of the uptake experiments. The K_m values used were about 67 nM for [^{3}H]DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE. For comparison purposes, the data for compound **5a**, which has been reported previously, and the data for cocaine are also included (Table 1).[9]

A SAR study of (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-(thienylmethylene- or substituted thienylmethylene)-7-azatricyclo [4.3.1.0^{3,7}]decane-10-carboxylic acid methyl esters **5a**–**5c** revealed that introduction of an additional substituent in the thienyl ring resulted in distinct differences. Compared to cocaine, the lead **5a** gave an essentially similar potency at the DAT, but a 4-fold higher potency at the NET and a 13-fold lower potency at the SERT. Introduction of a methyl or iodo substituent into the 5-position of the thienyl ring improved both the SERT and



Scheme 3. Reagents and conditions: (i) $LiAlH_4$ or DIBAL-H, THF, rt; (ii) Ac_2O or acid chloride, Et_3N, THF, 0 °C to rt; (iii) (a) Ph_3P, EtOOCN=NCOOEt, diphenyl azidophosphate, THF, −70 °C to rt; (b) Ph_3P, MeOH, 5 h, then Ac_2O or di-*tert*-butyl dicarbonate, Et_3N, THF, overnight.

NET activities ($K_i = 5$ nM) while a slight decrease of activity at the DAT was observed. Compound **5b** also displayed a potency at the SERT comparable to that of cocaine, while compound **5c** exhibited an improved inhibitory activity at the SERT ($K_i = 29$ nM).

According to our previous SAR studies, subtle modifications of the C10-ester can produce more potent inhibitors. Thus, the second set of ligands was based on the modification of this moiety. The bulky ester **7** had 2-fold lower activity at the NET compared to the lead **5a**. Reduction of the ester **5a** to alcohol **8** decreased the activity at the NET greatly. Reesterification of the alcohol **8** produced different results depending on the acyl group. Acetate **9** remained somewhat NET-selective but with a 10-fold loss in potency compared to **5a**, while the bulky ester **10** displayed selectivity for the SERT with a potency at the SERT similar to that of cocaine. The benzoate **11** is an excellent SERT inhibitor with a K_i value of 1.5 nM and selectivity over the DAT and NET of 1140- and 584-fold, respectively. The naphthoate **12** is also a SERT-selective inhibitor with the same potency as **10**. The amide analogues **13** and **14** are poorly active at all three monoamine transporters.

Table 1. Inhibition of reuptake at monoamine transporters, ($K_i \pm$SEM (nM))[a]

Compd	[^{3}H]DA Uptake	[^{3}H]5-HT Uptake	[^{3}H]-NE Uptake	5-HT/DA	NE/DA	NE/5-HT
Cocaine	259±19.9	155±0.40	108±3.50	0.60	0.42	0.70
5a	268±16.6	2046±42	26.4±1.9	7.63	0.10	0.01
5b	403±20	179±38	4.9±0.2	0.44	0.01	0.03
5c	368±1.6	29.0±1.6	5.0±1.3	0.08	0.01	0.17
7	428±45.7	1150±10	52.3±12.0	2.69	0.12	0.05
8	~3000	~1000	~300	~0.33	~0.1	~0.30
9	610±53.0	1530±150	283±16.0	2.51	0.46	0.18
10	1020±70	168±53.5	1180±130	0.16	1.16	7.02
11	1750±140	1.53±0.19	894±126	0.0009	0.51	584
12	1678±124	169±16	1234±166	0.10	0.74	7.28
13	6140±50	13300±3150	2430±340	2.17	0.39	0.18
14	2300±380	2360±30	1700±60	1.03	0.74	0.72

[a] K_i values are mean ±SEM from two to four independent experiments, each consisting of six drug concentrations (in triplicate) that were selected on the basis of preliminary screening experiments to bracket the approximate IC_{50} value.

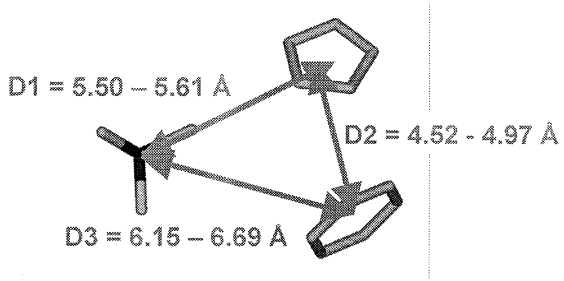


Chart 1.

In our previous study of substituted phenyl analogues, replacement of the methyl ester in position 10 with a reverse benzoate resulted in highly potent SERT-selective inhibitors (such as compounds **1** and **2**). In the thienyl series, the same result is observed. Benzoate **11** is the most potent compound in this series at the SERT. Structurally, the tertiary amine nitrogen, the phenyl group of the benzoate and the thienyl group are the crucial functional groups believed to be responsible for activity at the SERT. A systematic conformational search[15] revealed that there are four local low-energy conformations for structure 11. The distance map calculated from these conformations shows that the distance D1 between the nitrogen atom and the thienyl group is 5.50–5.61 Å, the distance D2 between the thienyl group and the phenyl group is 4.52–4.97 Å, and the distance D3 between the nitrogen atom and the phenyl group is 6.15–6.69 Å. Similar distances were found in the 9-substituted phenyl analogues (especially the benzoates).[9,10] Thus, a new pharmacophore may be constructed (Chart 1).

Although modeling of the DAT and the resulting pharmacophore model have been well studied, related work on the NET and the SERT has been limited.[14,16,17] However, a simple common pharmacophore model for central nervous system ligands has been proposed which consists of a phenyl ring and a nitrogen atom.[18] In our model, the additional phenyl ring in the benzoate moiety, which is positioned at the optimal distance from the 9-aryl ring (thienyl or phenyl) may provide a specific interaction site for binding to the 5-HT transporter.

In summary, a series of thiophene-derived, conformationally constrained tropane analogues was synthesized and evaluated for their uptake inhibition at all three monoamine transporters. Compounds **5a**–**5c** and **7** are NET-selective inhibitors. Among these compounds, **5b** and **5c** are the most potent ligands at the NET with the same K_i value of 5 nM. Compound **5b** is equipotent to cocaine at the DAT and SERT. Furthermore, **5c** also displayed an improved potency at the SERT. Modification of the C10 ester resulted in compound **11**, which is the most SERT-selective ligand in the current series with a K_i value of 1.5 nM. Further SAR work, together with pharmacological and behavioral studies, is being carried out and will be reported in due course.

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11. Selected data for compound **5c**: (1*S*,3*S*,6*R*,10*S*)-(*Z*)-9-[2-(5-iodothienyl)methylene]-7-azatricyclo[4.3.1.$0^{3,7}$]decane-10-carboxylic acid methyl ester: $[\alpha]_D^{25}$ +50.9° (*c* 1.1, $CHCl_3$); ^1H NMR δ 1.47 (m, 3H), 2.01 (m, 1H), 2.18 (m, 2H), 2.40 (t, *J* = 3.0 Hz, 1H), 2.68 (m, 1H), 3.27 (m, 1H), 3.62 (s, 3H), 3.73 (m, 1H), 3.76 and 3.86 (ABq, *J* = 18.3 Hz, both d with *J* = 1.8 and 2.1 Hz, respectively, 2H), 6.30 (t, *J* = 3.0 Hz, 1H), 6.54 (d, *J* = 3.9 Hz, 1H), 7.13 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR δ 32.24, 32.79, 36.57, 36.76, 48.61, 52.15, 52.45, 53.93, 56.57, 114.59, 127.36, 137.09, 140.55, 147.19, 174.31; MS *m*/*z* (%) 415 (M^+, 12), 288 (100), 256 (11), 147 (11), 115 (36), 83 (18), 68 (31). Anal. calcd for $C_{16}H_{18}INO_2S$: C 46.27, H 4.37, N 3.37; found: C 46.64, H 4.21, N 3.25.
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