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Discovery of novel conformationally constrained tropane-based biaryl and arylacetylene ligands as potent and selective norepinephrine transporter inhibitors and potential antidepressants

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Abstract—To further explore the structure–activity relationships of conformationally constrained tropanes, a number of new biaryl and arylacetylene analogs were designed and synthesized. Some of these compounds such as **3a**–**b**, **3d**, **3f**–**h**, **5b**, and **7g** were found to be highly potent and selective or mixed norepinephrine transporter (NET) inhibitors with K_i values of 0.8–9.4 nM. Moreover, all of these compounds display weak to extremely weak muscarinic receptor binding affinity, indicating that as potential antidepressants, they may overcome certain side effects that are of concern with other antidepressants, which are thought to be mediated by their anticholinergic properties.

World-wide public health surveys point to an increased global health burden for serious psychiatric disorders, particularly depression, which has been referred to as the 'common cold' of mental illness. By 2020 it is expected that depression may be the second most serious medical condition with respect to global disease burden.[1] For more than four decades, norepinephrine (NE) has been postulated to play an important, possibly primary, role in the pathophysiology and subsequent treatment of major depressive disorder.[2] To date, a number of potent and selective or mixed norepinephrine transporter (NET) inhibitors have been marketed as antidepressants (Fig. 1). From 1960 to 1990, the tricyclic antidepressants (TCAs) such as desipramine (Norpramin®), nortriptyline (Aventyl®, Pamelor®), protriptyline (Vivactil®), and amoxapine (Asendin®) were the first-choice medications for major depressive disorder.[3] TCAs are relatively selective NET and/or SERT inhibitors, but they also possess a moderate affinity for α_1-adrenoceptors and muscarinic cholinergic receptors. Muscarinic blockade and inhibition of norepinephrine reuptake contribute to cardiac stimulation and tachycardia, and these actions cause a number of troublesome side effects. Cardiac arrhythmias that occur upon overdose are difficult to treat and can be life-threatening. Other peripheral antimuscarinic side effects, including dry mouth, urinary retention, and constipation, are also prominent. These first-generation antidepressants including the tetracyclic NET inhibitor maprotiline are no longer widely used in the US due to the emergence of newer, more effective drugs. However, TCA use remains fairly common in other countries. A new generation of antidepressants resulted from the discovery of selective serotonin reuptake inhibitors (SSRIs), which have come to dominate the treatment of depression over the last two decades. Although SSRIs such as fluoxetine (Prozac®) and paroxetine (Paxil®) are very effective antidepressant drugs with substantially fewer side effects than the older TCAs, they are not universally effective and can also have bothersome side effects of their own, such as anxiety, sleep disturbances, weight gain,

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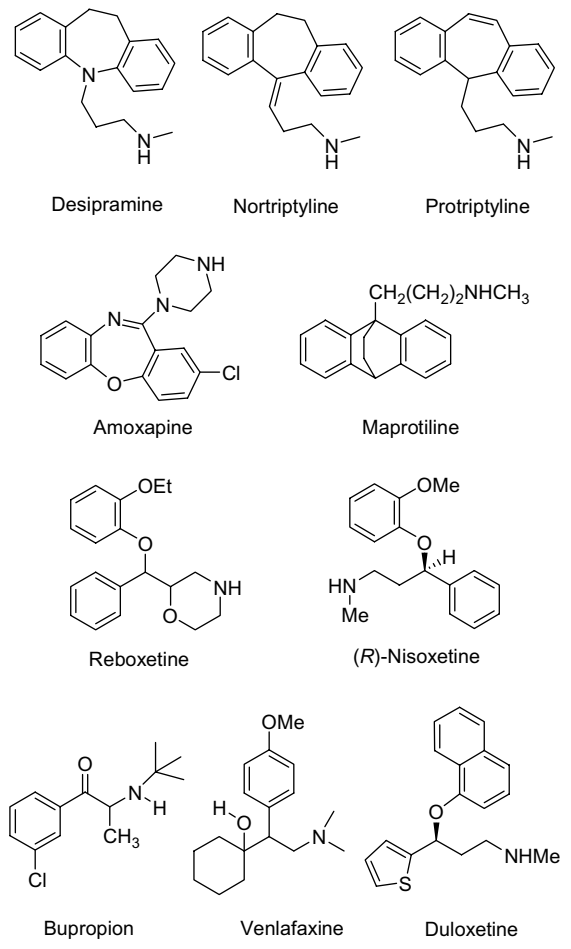


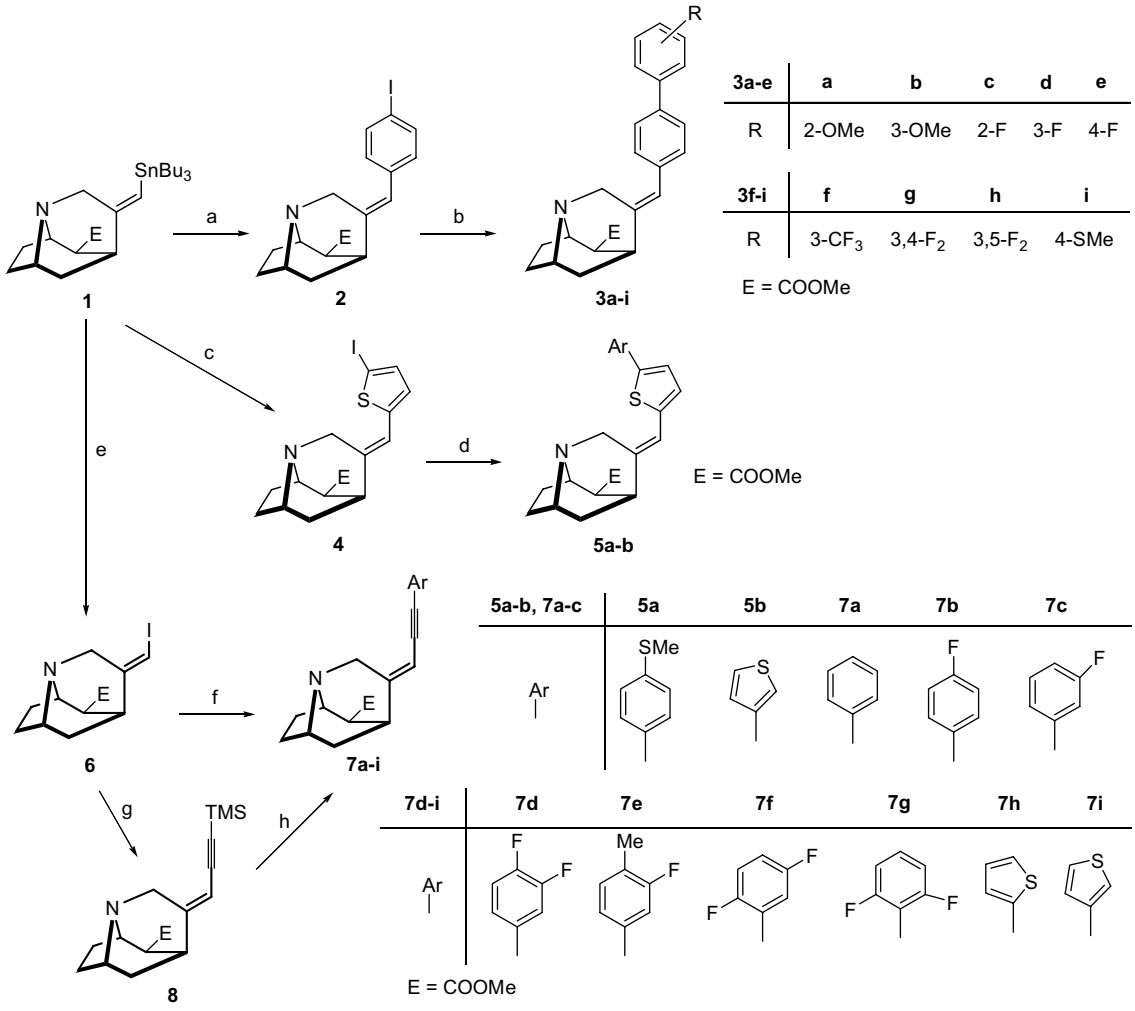
Figure 1. Selective or mixed NET inhibitors used as antidepressants.

sexual dysfunction, and gastrointestinal disturbances.[4] The success and challenges of the SSRIs rekindled interest in the development of selective NET inhibitors as potential antidepressants. Pharmacologically and chemically unrelated to TCAs or SSRIs, reboxetine (Edronax®) is the first truly selective NET inhibitor that is currently being marketed as an antidepressant in over 50 countries including Europe. The selectivity of reboxetine for the NET and its benign side effect profile cause the drug to be well tolerated.[5,6] Some dual transporter inhibitors also display a unique clinical profile. Bupropion (Wellbutrin®) for example, a dual NET/DAT ligand, has demonstrated efficacy comparable to that of other antidepressants and without the side effects of SSRIs.[7] As a dual NET/SERT inhibitor, venlafaxine (Effexor®) represents a new class of antidepressants and has a higher rate of efficacy and a lower dropout rate when compared to TCAs and SSRIs.[8] Another dual NET/SERT inhibitor, duloxetine (Cymbalta®), FDA-approved in 2004, is a well-tolerated antidepressant and even more effective than venlafaxine.[9]

Recently, the FDA issued warnings to the public about an increased risk of suicidal thoughts and behavior ('suicidality') in children and adolescents being treated with antidepressant medications.[10] Such side effect issues have prompted a new search for safer, faster-acting and better tolerated antidepressants. Previously, we reported two classes of molecules, namely conformationally constrained tropanes and piperidine-based nocaine/modafinil hybrid ligands, as potent NET inhibitors.[11–14] To further explore the structure–activity relationships of conformationally constrained tropanes, a number of new biaryl and arylacetylene analogs were designed, synthesized and their monoamine transporter activity tested. To gain insights into their potential applications for the treatment of depression, we have also investigated the binding affinity of these compounds at the muscarinic receptor in continuation of our previous work, and the results will be discussed herein.

In the course of our extensive synthetic studies in the field of conformationally constrained tricyclic tropane compounds, we have developed a satisfactory synthesis for the key intermediate, (*Z*)-vinylstannane **1**.[11] Scheme 1 outlines our synthetic approach to the newly designed biaryl and arylacetylene analogs. The key intermediates **2** and **4** were prepared in moderate yields by the Stille coupling of the vinylstannane **1** with 1,4-diiodobenzene or 2,5-diiodothiophene, utilizing previously reported procedures.[11,12] The subsequent Suzuki coupling of the iodides **2** and **4** with substituted phenylboronic acids or heteroarylboronic acids in the presence of $Pd(OAc)_2$ as the catalyst provided the desired biaryl analogs **3a**–**i** and **5a**–**b** in moderate to high yields. Our synthesis of the arylacetylene ligands makes use of the Sonogashira coupling reaction. Thus, the vinyl iodide **6**, which was obtained by iodination of **1**, upon coupling with arylacetylenes generated the analogs **7a**–**b** and **7i**. Due to the limited availability of arylacetylenes, the remaining compounds **7c**–**h** were synthesized in a stepwise manner by two consecutive Sonogashira coupling reactions via key intermediate **8**, utilizing readily available aryl iodides or bromides for the introduction of the aryl or heteroaryl moiety. In this reaction, the coupling with iodides for **7c**–**e** and **7h** gave much better yields than that with bromides for **7f**–**g**. The structures and purity of all synthesized compounds were confirmed by ^{1}H and ^{13}C NMR, EI-MS, and by HPLC or elemental analysis.[15]

All compounds were tested as the free base for their ability to inhibit high-affinity reuptake of DA, 5-HT, and NE into nerve endings (synaptosomes) prepared from brain regions enriched in transporters for these biogenic amine neurotransmitters.[16] 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.[17] Rat striatum, midbrain, and parietal/occipital cortex were dissected and used as a source of DAT, SERT, and NET, respectively. The Cheng–Prusoff equation for classic, competitive inhibition was used for calculating K_i from IC_{50} values in uptake experiments. The K_m values used were 67 nM for [^{3}H]DA, 53 nM for [^{3}H]5-HT, and 54 nM for [^{3}H]NE. [^{3}H]Quinuclidinyl benzilate (QNB) is a muscarinic antagonist that has a high affinity for all muscarinic receptor subtypes. It was used to label muscarinic receptors in rat cortex, and displacement of [^{3}H]QNB from these sites by NET-selective compounds was used to



Scheme 1. Synthesis of new conformationally constrained tropanes as NET inhibitors. Reagents and conditions: (a) 1,4-diiodobenzene, Ph_3As, $Pd_2(dba)_3$, CuI, DMF, 50 °C, 57%; (b) arylboronic acids, $Pd(OAc)_2$, K_2CO_3, H_2O/THF, 70–80 °C, 41–78%; (c) 2,5-diiodothiophene, Ph_3As, $Pd_2(dba)_3$, CuI, DMF, 50 °C, 55%; (d) aryl- or heteroarylboronic acids, $Pd(OAc)_2$, K_2CO_3, H_2O/THF, 70–80 °C, 40%; (e) I_2, CH_2Cl_2, rt, 88%; (f) arylacetylenes (for **7a**–**b** and **7i**), $PdCl_2(PPh_3)_2$, CuI, Et_3N, DME, 80 °C, 62–80%; (g) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DME, 80 °C, 17 h, 70%; (h) aryl iodides (for **7c**–**e** and **7h**) or aryl bromides (for **7f**–**g**), $PdCl_2(PPh_3)_2$, CuI, Et_3N, TBAF, DME, 80 °C, 17–80%.

screen for muscarinic receptor affinity as previously published.[18,19] The DA, 5-HT, and NE uptake data and selectivity profiles (based on the K_i values) as well as the muscarinic receptor affinity data of all compounds are listed in Table 1. For comparison purposes, the inhibition data of reuptake at monoamine transporters for the known compound **5a**[12] from our previous paper are also included. All data are mean values ± SEM from two to four independent experiments, each consisting of six concentrations of test compound in triplicate. The concentrations chosen for testing were based on a preliminary screening designed to approximate the IC_{50}.

The data shown in Table 1 demonstrate that some of the newly designed biaryl and arylacetylene analogs such as **3a**–**b**, **3d**, **3f**–**h**, **5b**, and **7g** exhibit a very high potency at the NET. On the other hand, all compounds, including those that are remarkably potent NET inhibitors, display weak to extremely weak (K_i >10,000 nM) binding affinity at the muscarinic receptor.

In the series of conformationally constrained tropane ligands, modifications of the substituents on the outer phenyl ring led to a significant improvement of potency and selectivity at the NET. Ligands **3a** with 2-methoxy, **3b** with 3-methoxy, **3d** with 3-fluoro, **3f** with 3-trifluoromethyl, **3g** with 3,4-difluoro, and **3h** with 3,5-difluoro substituents display a remarkable potency from nanomolar to subnanomolar at the NET, and all of these potent NET ligands exhibit very low binding affinity at the muscarinic receptor with K_i values higher than 2830 nM. Particularly, both ligands **3a** and **3g**, like (*R*)-nisoxetine,[20] display not only an excellent potency with K_i values of 6.5 and 0.8 nM at the NET, but also more than 100-fold selectivity versus both the SERT and the DAT. Ligand **3h** is a potent and dual NET/SERT inhibitor with K_i values around 1 nM having a selectivity profile like duloxetine[21,22] and venlafaxine,[23,24] and it displays a very weak muscarinic receptor binding affinity with a K_i value of 2830 nM. The bithienyl tropane ligand **5b** is a potent NET inhibitor with a K_i value of

Table 1. Binding affinity at the muscarinic receptor and inhibition of reuptake at monoamine transporters ($K_i \pm$ SEM (nM))[a]

Compound	[^{3}H]QNB binding K_i (nM)	[^{3}H]DA uptake K_i (nM)	[^{3}H]5-HT uptake K_i (nM)	[^{3}H]NE uptake K_i (nM)	Uptake ratio (based on K_i)		
					5-HT/DA	NE/DA	NE/5-HT
Desipramine[b]	—	>10,000	163[c]	7.36	—	—	—
3a	>10,000	787 ± 234	1340 ± 7	6.5 ± 2.1	1.70	0.008	0.004
3b	4060 ± 1240	114 ± 40	346 ± 66	9.4 ± 1.1	3.04	0.08	0.03
3c	>10,000	3400 ± 545	466 ± 44	393 ± 102	0.14	0.12	0.84
3d	>10,000	646 ± 29	138 ± 23	5.0 ± 2.3	0.21	0.01	0.04
3e	1060 ± 279	161 ± 9	1390 ± 56	53 ± 2	8.62	0.33	0.04
3f	7060 ± 2377	556 ± 19	1170 ± 425	8.8 ± 0.5	2.10	0.02	0.007
3g	3400 ± 809	106 ± 6	295 ± 36	0.8 ± 0.2	2.78	0.007	0.002
3h	2830 ± 779	228 ± 28	1.2 ± 0.7	1.3 ± 0.3	0.005	0.005	1.09
3i	>10,000	1050 ± 81	1080 ± 96	62 ± 3	1.02	0.06	0.06
5a[d]	>10,000	1650 ± 47	3320 ± 525	273 ± 37	2.01	0.16	0.08
5b	2140 ± 446	114 ± 4	32 ± 2	5.9 ± 0.9	0.28	0.05	0.18
7a	11,900 ± 421	>10,000	207 ± 20	>10,000	N/d	N/d	N/d
7b	15,100 ± 2580	>10,000	17 ± 3	104 ± 9	N/d	N/d	6.20
7c	13,500 ± 791	>10,000	317 ± 3	2110 ± 41	N/d	N/d	6.66
7d	7090 ± 2010	3150 ± 1150	69 ± 4	110 ± 21	0.02	0.03	1.59
7e	>10,000	7070 ± 1794	914 ± 9	52 ± 1	0.13	0.007	0.06
7f	>10,000	>10,000	215 ± 60	1720 ± 262	N/d	N/d	7.99
7g	>10,000	>10,000	32 ± 6	5.3 ± 0.7	N/d	N/d	0.17
7h	13,900 ± 799	>10,000	142 ± 32	1570 ± 503	N/d	N/d	11.8
7i	2740 ± 366	>10,000	86 ± 17	22 ± 3	N/d	N/d	0.25

[a] K_i values are means ± 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.
[b] Data taken from Ref. 20.
[c] Data for cloned human receptors.
[d] Inhibition data of reuptake at monoamine transporters were taken from Ref. 12.

5.9 nM, and exhibits a fairly low binding affinity at the muscarinic receptor with a K_i value of 2140 nM. Among all compounds tested, ligand **3e** has the highest [^{3}H]QNB binding affinity with a K_i value of 1060 nM, but it merely shows a moderate potency at the NET with a K_i value of 53 nM. The arylacetylene analogs **7a–i** were designed based on the structures of our biaryl ligands by the replacement of inner phenyl ring with a triple bond as an aromatic ring bioisostere. Generally, they display a reduced potency particularly at the DAT and NET. Interestingly, compound **7b** exhibits a fairly good potency at the SERT with a K_i value of 17 nM. Compound **7g** is a potent NET inhibitor with a K_i value of 5.3 nM and a selectivity profile resembling that of desipramine,[20] however, it has substantially no binding affinity at the muscarinic receptor (K_i >10,000 nM).

In conclusion, a number of new biaryl and arylacetylene analogs were designed, synthesized and some of them such as **3a–b**, **3d**, **3f–h**, **5b**, and **7g** were found to be highly potent and selective or mixed NET inhibitors. Moreover, the binding affinities of these tropane ligands at the muscarinic receptor have also been investigated. The data demonstrate that there is no direct correlation between the muscarinic receptor affinity and the transporter activities of these ligands. It was found that this class of selective or mixed NET inhibitors display weak to extremely weak muscarinic receptor binding affinity, indicating that as potential antidepressants they may overcome certain side effects of existing antidepressant drugs that are thought to be mediated by their anticholinergic properties. Behavioral assessment of some of these ligands is currently underway.

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