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Synthesis and monoamine transporter affinity of 3α-arylmethoxy-3β-arylnortropanes

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ABSTRACT

A series of 3-arylnortrop-2-enes and 3α-arylmethoxy-3β-arylnortropanes were synthesized and evaluated for binding affinity at monoamine transporters. The 3-(3,4-dichlorophenyl)nortrop-2-ene (**6e**) exhibited high affinity for the SERT (K_i = 0.3 nM). The 3α-arylmethoxy-3β-arylnortropanes were generally SERT selective with the 3α-(3.4-dichlorophenylmethoxy)-3βphenylnortrop-2-ene (**7c**) possessing subnanomolar potency (K_i = 0.061 nM). However, 3α-(3,4-dichlorophenylmethoxy)-3β-phenylnortrop-2-ene (**7b**) exhibited high affinity at all three transporters [(DAT K_i = 22 nM), (SERT K_i = 6 nM) and (NET K_i = 101 nM)].

Monoamine transporters have been therapeutic targets for a variety of neurological diseases and disorders. Drug development strategies have focused upon central nervous system (CNS) monoamine transporter selective agents. This approach has been highly successful for the development of medications for the treatment of depression.[1,2] Selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine and paroxetine)[3] as well as selective norepinephrine reuptake inhibitors (SNRIs, e.g., reboxetine)[4,5] have been widely prescribed for patients suffering from this common psychiatric disorder. In addition, dopamine selective uptake inhibitors have been targets for the development of therapeutics for cocaine addiction.[6–8]

Over the past decade, the rationale for the development of new pharmacotherapies has expanded to target compounds that exhibit efficacy at multiple monoamine transporter systems. The dual serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine) have been widely accepted as more efficacious than SSRIs for the treatment of depression with reduced side effects.[9,10] More recently, pharmacological evidence suggests that triple monoamine uptake inhibitors (TUIs), targeting dopamine transporters (DAT) as well as serotonin transporters (SERT) and norepinephrine transporters (NET) may be even more efficacious and exhibit improved safety profiles as antidepressants.[11] The prototypical TUI, DOV 216,303 was found to be both safe and effective in Phase II clinical studies on depression.[12,13] In addition to therapeutics for depression, there is increasing evidence that the reinforcing effects of cocaine may in part be mediated by the SERT.[14–16] In lieu of these findings, dual DAT/SERT uptake inhibitors have become viable pharmacological targets for cocaine addiction (Fig. 1).[17,18]

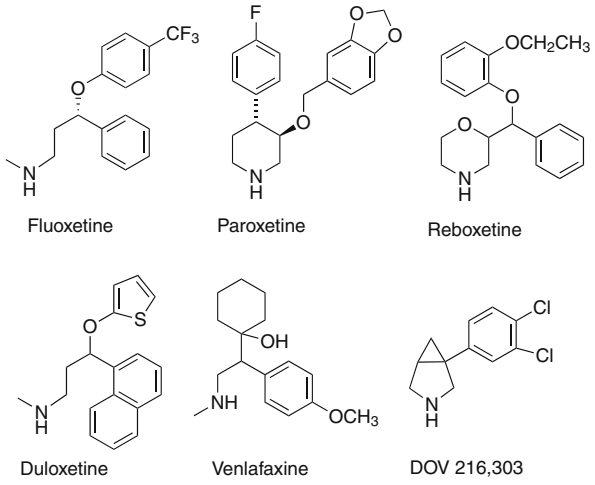

Figure 1. Monoamine transporter reuptake inhibitors.

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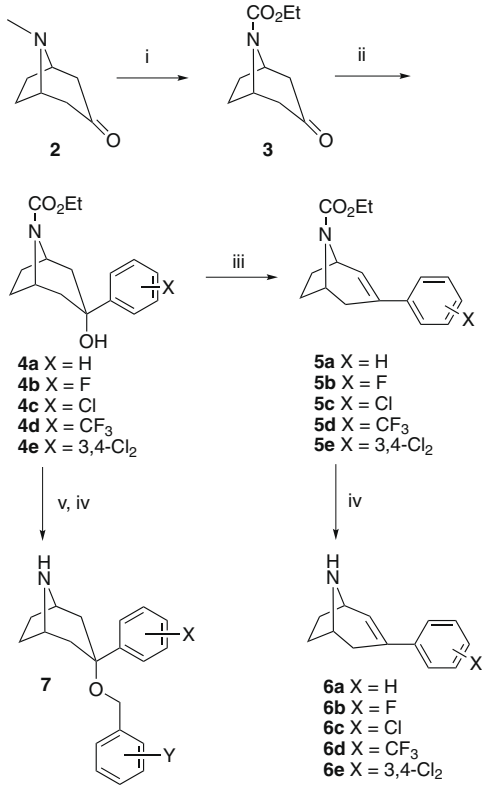
Our efforts to develop novel molecular scaffolds targeting monoamine transporter systems have led to the development of several classes of selective DAT ligands and selective SERT ligands. There have been numerous studies that have shown that 3-aryltropane derivatives exhibit high affinity and selectivity for the DAT.[7,8] More recently, we have reported on a series of piperidine derivatives that exhibit potent and selective affinity for the SERT.[19,20] Given the somewhat similar structural characteristics of these two classes of molecules it was of interest to explore the possibility of merging the two pharmacophores to develop a class of monoamine transporter ligands that would have unique profile of multiple transporter affinity. To this end, the 3α-arylmethoxy-3β-aryltropane pharmacophore (**1**) was envisaged. The pharmacophore **1** was designed not only to incorporate the main skeletal features of the DAT selective tropanes and the SERT selective piperidines, but the arylmethoxy moiety common to many of the prototypical SSRIs and SNRIs also was envisaged to be an important structural feature for molecular recognition at monoamine transporters. Herein we describe the synthesis and monoamine transporter affinities of a series 3α-arylmethoxy-3β-aryl-tropane derivatives (Fig. 2).

As illustrated in Scheme 1, the syntheses of the target compounds were envisaged to proceed from commercially available tropinone (**2**). Conversion of **2** into the carbamate **3** was achieved in a traditional fashion using ethyl chloroformate.[21,22] The preparation of **3** was necessary to reduce the basicity and nucleophilicity of the nitrogen atom. This served to facilitate subsequent chromatography as well as provide a chemical handle for manipulation of potential nitrogen substituents. Introduction of the substituted 3-aryl group was achieved by addition of a preformed aryl lithium reagent to the ketone moiety of **3**. Initially, a mixture of the desired alcohol **4** along with the alkene **5** was obtained in low yields. The formation of the alkene **5** was the result of the dehydration of **4** that occurred during the acidic work-up. To minimize this dehydration side-reaction, the work-up was performed under weakly acidic conditions [10% NH_4Cl (aq)] at cold temperatures (5–10 °C). This afforded the alcohols **4** in good yields (40–65%). Although we were confident that the addition the aryl ring occurred from the less hindered β-face of the tropinone skeleton,[22] the relative stereochemistry was confirmed unequivocally by X-ray crystallography.[23] As illustrated in Figure 3 for **4a**, the 3-phenyl moiety was shown to occupy the 3β-pseudo equatorial position and the hydroxy group was in the 3α-pseudo axial position.

The ease in which the alcohols **4** were dehydrated prompted us to divert our attention toward the synthesis of a series of 3-arylnortrop-2-ene derivatives **6**. It was envisaged that these rigid alkenes might have a similar binding motif at monoamine transporters to that of the DOV 216,303. The alkenes **5** could be



Scheme 1. Reagents and conditions: (i) $ClCO_2Et$, K_2CO_3, toluene, reflux; (ii) X–C_6H_4Br, *n*-BuLi, THF, −78 °C; (iii) TFA, CH_2Cl_2; (iv) KOH, $NH_2NH_2{\cdot}H_2O$, $HOCH_2CH_2OH$, reflux; (v) NaH, DMF, Y–$C_6H_4CH_2Br$, rt.

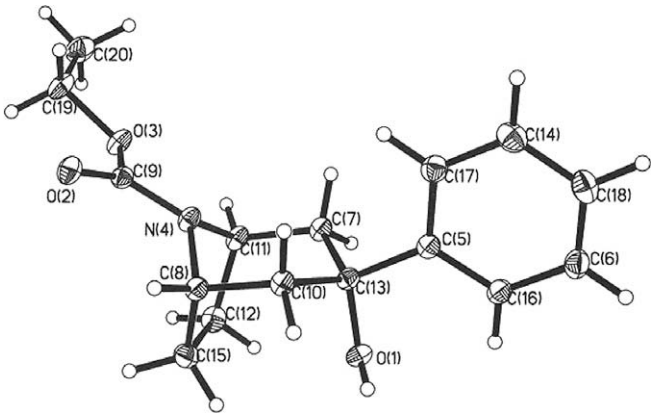


Figure 3. X-ray crystal structure of **4a**.

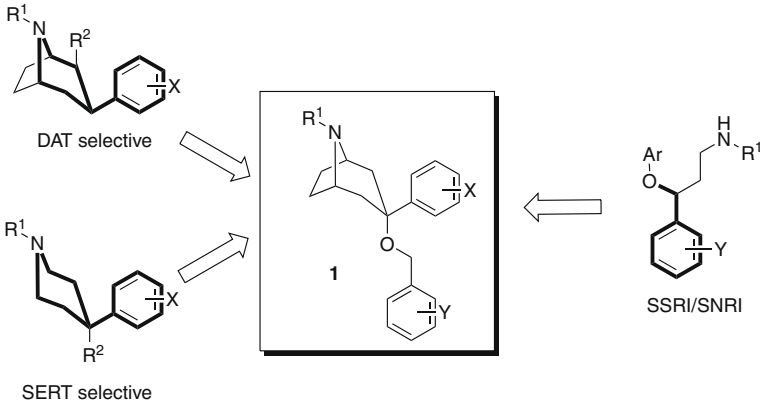
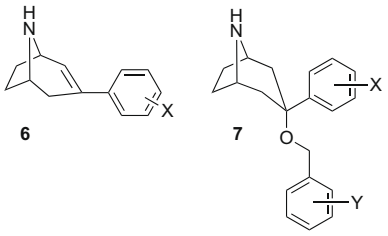


Figure 2. Proposed pharmacophore of novel monoamine uptake inhibitors.

Table 1
Monoamine transporter affinity and selectivity.



Compd[a]	Code	X	Y	DAT (K_i, nM)[b]	SERT (K_i, nM)[b]	NET (K_i, nM)[b]	DAT/SERT	NET/DAT	NET/SERT
6a	HK3-203	H		1222 ± 87	176 ± 26	1289 ± 54	6.9	1.1	7.3
6b	HK3-245	F		1056 ± 201	129 ± 22	1989 ± 268	8.2	1.9	1.5
6c	HK3-241	Cl		231 ± 14	2.8 ± 1.0	120 ± 41	83	0.52	43
6d	HK3-267	CF_3		1494 ± 246	1.8 ±0.3	777 ± 96	830	1.9	432
6e	HK3-263	3,4-Cl_2		16 ± 1.7	0.30 ± 0.10	20 ± 4.6	53	1.3	67
7a	HK2-151	H	H	117 ± 19	247 ± 27	NT	0.47		
7b	HK3-77	H	Cl	22 ± 8	6.1 ± 0.5	101 ± 0	3.6	4.6	17
7c	HK3-45	H	3,4-Cl_2	16 ± 1	0.061 ± 0.024	996 ± 53	258	62	16,300
7e	HK3-87	Cl	H	172 ± 70	65 ± 25	1718 ± 18	2.7	10	26
7f	HK3-35	Cl	Cl	63 ± 7	0.10 ± 0.02	2370 ± 367	630	38	23,700
7g	HK3-135	Cl	3,4-Cl_2	390 ± 28	8.5 ± 1.8	2093 ± 1210	46	5.4	246
7h	HK3-105	CF_3	H	1390 ± 141	534 ± 34	5435 ± 2570	2.6	3.9	10
7i	HK3-119	3,4-Cl_2	H	716 ± 52	62 ± 15	1232 ± 438	11	1.7	20
7j	HK3-49	3,4-Cl_2	3,4-Cl_2	2930 ± 70	4.7 ± 0.3	2552 ± 326	601	0.87	543
	Cocaine			237 ± 33	286 ± 38[c]	3192 ± 877	0.83	12	11

[a] All compounds were tested as the oxalate salts. NT: Not tested.
[b] All values are the mean ± SEM of three experiments preformed in triplicate.
[c] Value taken from Ref. 26.

prepared directly from the crude reaction mixtures containing **4**, by stirring the concentrated residues in dichloromethane containing 1 equiv of trifluoroacetic acid. This furnished the alkenes **5** in good overall yields ranging from 35% to 60%. Since many of the potent monoamine uptake inhibitors (SSRIs, SNRIs and TUIs) possess a NH moiety, it was determined that the tropane nitrogen atom would be converted into a secondary amine as well. Hydrazine mediated removal of the carbamate moiety gave the (±)-3-arylnortrop-2-enes **6** in 85–95% yield.

To complete the synthesis of an initial series of target compounds for biological evaluation, the alcohols **4** were alkylated with a variety of substituted benzyl bromides to afford the corresponding 3α-arylmethoxy derivatives. Subsequent removal of the carbamate protecting group gave the target secondary amines **7**.

Binding affinities for the dopamine, serotonin and norepinephrine transporters were determined by the ability of the drug to displace the radiolabeled ligands [^{3}H]WIN 35,428, [^{3}H]citalopram, and [^{3}H]nisoxetine, respectively, from the monoamine transporters in rat brain tissue using previously reported assays.[19,20,24] The binding affinities of all compounds listed in Table 1 were initially determined for the DAT and SERT. The compounds that exhibited either DAT or SERT binding affinities with K_i values <100 nM were then evaluated at norepinephrine transporters to determine a monoamine transporter selectivity profile. The monoamine transporter binding affinities of the 3-arylnortrop-2-enes **6** were consistent with a previous report that described the SERT selectivity of a series of 3-aryltrop-2-ene derivatives.[25] The nortropenes **6** exhibited selectivity for SERT over both DAT and NET. The 3,4-dichloro congener **6e** (SERT K_i = 0.3 nM) was the most potent of the nortropenes at SERT. However, **6e** was not the most SERT selective nortropene of the series (e.g., **6d**). In fact, **6e** exhibited high affinity at all three monoamine transporters with DAT and NET affinities nearly equipotent (NET/DAT = 1.3).

The 3α-arylmethoxy-3β-arylnortropanes **7** were found to exhibit some similar trends in transporter affinity to those of the nortropenes **6**. As expected the congeners **7** were generally SERT selective and exhibited high affinity for SERT. The most potent SERT ligand of the series was **7c** (SERT K_i = 0.061 nM), which also exhibited the highest affinity for the DAT (DAT K_i = 16 nM) of the series. However, despite the high DAT and SERT affinity of **7c**, the dichloro derivative **7f** was the most SERT selective ligand with DAT/SERT = 630 and NET/SERT = 23,700. It is noteworthy that the mono chloro derivative **7b** exhibited good affinity for all three monoamine transporters. Despite being somewhat SERT selective, **7b** exhibited transporter selectivity that is similar to other reported monoamine TUIs.[11,12]

In comparing the two classes of compounds **6** and **7**, it is interesting to note that the structure–activity relationships of the aryl group of the rigid tropene **6** are more closely aligned with the 3α-arylmethoxy group of **7** than the 3β-aryl group. This is most evident when comparing the effects of the 3,4-dichlorophenyl moiety on SERT affinity of **6e** with that of **7c** and **7i**. When the 3,4-dichlorophenyl moiety occupies the 3α-position (**7c**), the SERT affinity is high but when the 3,4-dichlorophenyl moiety occupies the 3β-position (**7i**), SERT affinity is significantly reduced. This trend is also evident for the mono chloro derivatives **6c**, **7b** and **7e**. For predicted favorable solvated conformers of **6e**, **7c** and **7i** (Fig. 4)[27] the alignment of the 3α-arylmethoxy group of **7c** with the aryl group of **6e** is similar for the ***boat*** conformer, while there is no overlap between these two aryl moieties for the ***chair*** conformer. This suggests that it is the ***boat*** conformer of **7c** that exhibits its high affinity for the SERT.

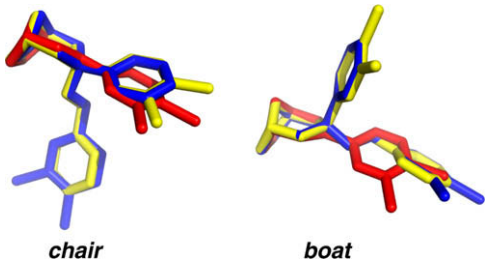


Figure 4. Superimposed predicted favorable solvated conformers of **6e** (red), **7c** (blue) and **7i** (yellow).

The binding affinities of **7** at the DAT were also significantly affected by the substituents on the aryl moieties. Within the series, the unsubstituted 3β-phenyl derivatives **7a**–**7c**, exhibited good to high affinity for DAT. However, substitution of the 3β-aryl moiety afforded compounds with diminished affinity at the DAT. Finally, only the monochloro congener **7b** exhibited good NET binding affinity suggesting that the target pharmacophore **1** may be predisposed toward the development of dual DAT/SERT selective ligands.

In conclusion, we have synthesized a novel class of monoamine transporter ligands. In general, the 3α-arylmethoxy-3β-arylnortropanes **7** exhibited potent affinity and high selectivity for the SERT. However, several derivatives were found to have good affinity for the DAT as well, and the chloro congener **7b** exhibited high affinity at all three transporters. Based upon this preliminary study, the 3α-arylmethoxy-3β-aryl-nortropane scaffold seems to be well suited for the development of new compounds that display a broad spectrum of monoamine transporter selectivity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.10.087.

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27. Structures in Figure 4 were generated using OpenEye Scientific Software's Omega for conformers and OEChem for shape overlays, and the images were generated with PyMol (Delano Scientific LLC).