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Synthesis and Dopamine Transporter Binding Affinities of 3α-Benzyl-8-(diarylmethoxyethyl)-8-azabicyclo[3.2.1]octanes

Amy L. Bradley,[a] Sari Izenwasser,[b] Dean Wade,[b] Cheryl Klein-Stevens,[c] Naijue Zhu[c] and Mark L. Trudell[a,*]

[a]*Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA*
[b]*Department of Psychiatry, University of Miami School of Medicine, Miami, FL 33136, USA*
[c]*Department of Chemistry, Xavier University of Louisiana, New Orleans, LA 70125, USA*

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Abstract—A series of 3α-benzyl-8-(diarylmethoxyethyl)-8-azabicyclo[3.2.1]octanes was synthesized and the binding affinities of the compounds were determined at the dopamine transporter. The unsubstituted analogue **7b** ($K_i = 98$ nM) was the most potent compound of the series with binding affinity three-times greater than cocaine and only 5-fold less than GBR-12909. The structure–activity data for **7a**–**f** suggests that these compounds may be binding at the dopamine transporter in a similar fashion to GBR 12909.

The search for new therapeutic agents for the treatment of cocaine (**1**) addiction has led to the study of a number of structurally unique compounds with varied pharmacological profiles.[1,2] Although a cocaine antagonist has yet to be identified, it has been hypothesized that compounds that exhibit high affinity for the dopamine transporter (DAT) yet have weak agonist activity may be useful in an agonist-based pharmacotherapy.[2,3] The disubstituted piperazine, GBR 12909 (**2**) is a selective high-affinity dopamine transporter ligand.[4–6] Studies have shown that GBR 12909 (**2**) dissociates very slowly from the dopamine transporter and attenuates the increase in the level of extracellular dopamine induced by cocaine (**1**).[3,7] Although GBR 12909 (**2**) is self-administered,[8] it has been shown to block cocaine self-administration behavior in rhesus monkeys,[9] and exhibits non-stimulant properties in humans.[7,10,11]

The unique pharmacological activity of **2** has prompted numerous studies of the structure–activity relationships (SAR) of disubstituted piperazines and related disubstituted piperidines in search of high affinity DAT selective ligands (Fig. 1).[12–22] From these studies it has been shown that the piperazine ring system is not required for high affinity selective binding to the DAT. It has been demonstrated that the piperidine derivative **3** possessed high affinity for DAT while the benzyl analogue **4** exhibited high affinity and increased selectivity over serotonin transporters.[12,13] However, the piperidine isomer **5** was found to exhibit significantly decreased binding affinity.[12] More recently it has been shown that the benztropine-like analogues **6** were found to exhibit selective high affinity binding with reduced muscarinic receptor affinity.[21]

The high binding affinity observed for the tropane analogues **6** is consistent with the structural similarities between **2** and **3**. However, it was of interest to further investigate the SAR of this class of compounds to determine whether an isomeric tropane-like analogue would exhibit a SAR similar to that of the GBR-like piperidine analogues (**4** and **5**).

Alternatively, it was envisaged that a tropane-like analogues of compounds **3** and **4** could exhibit binding affinity more closely aligned with that of the 3α-phenyl tropanes, a potent class of DAT uptake inhibitors.[23] Herein, we wish to report the synthesis and dopamine transporter affinity of a series of novel 3α-benzyl-8-(diaryl-methoxyethyl)-8-azabicyclo-[3.2.1]octanes (**7a**–**f**).

As illustrated in Scheme 1, the synthesis of the tropane-like analogues **7** was achieved in straightforward fashion from 3-tropinone (**8**). Demethylation of **8** afforded the

*Corresponding author. Tel.: +1-504-280-7337; fax: +1-504-280-6860; e-mail: mtrudell@uno.edu

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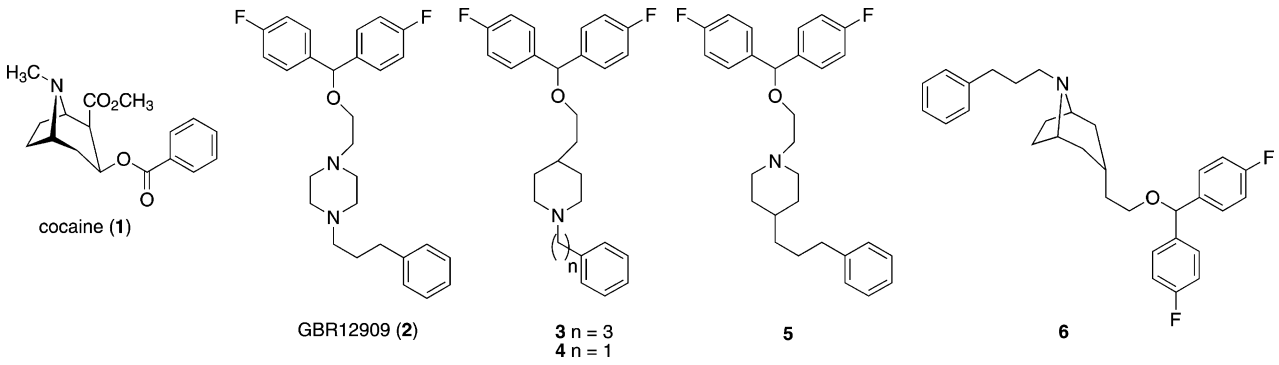
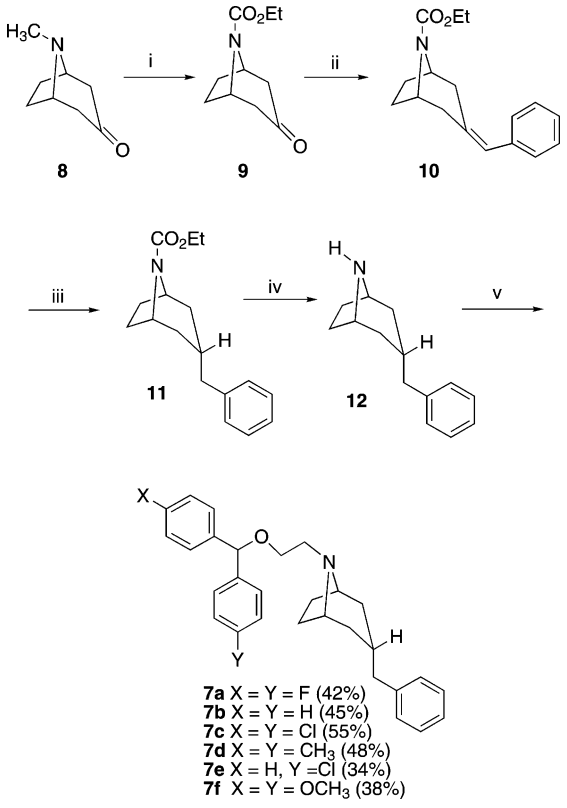


Figure 1. Cocaine and GBR 12909-related analogues.



Scheme 1. (i) $ClCO_2Et$, K_2CO_3, toluene, reflux. (ii) KH, $C_6H_5CH_2PO(OCH_3)_2$, DMF, 25 °C. (iii) H_2, 10% Pd/C, HCl, *i*-PrOH. (iv) TMSI, $CHCl_3$. (v) $BrCH_2CH_2OCH(p\text{-X-}C_6H_4)(p\text{-Y-}C_6H_4)$ (**13a–f**) K_2CO_3, DMF, 50 °C.

ethyl carbonate **9** which was followed by Horner–Wadsworth–Emmons olefination to provide the benzylidene **10** in 55% overall yield. Hydrogenation of **10** over 10% palladium on carbon furnished the 3α-benzyltropane **11** stereoselectively in 60% yield. Removal of the ethyl carbamate was achieved with trimethylsilyl iodide in chloroform to afford the amine **12**. Concomitant addition of 2-di(*p*-fluorophenyl)-methoxyethyl bromide (**13a**) furnished the tropane-like analogue **7a** in 42% overall yield.

In addition to the difluorophenyl analogue **7a**, a series of substituted benzhydrol derivatives (**7b–f**) was prepared in good yield (Scheme 1). The required 2-di(aryl)methoxyethyl bromides **13a–e** were prepared in similar fashion to procedures previously reported in the literature.[4,12] However, the di(*p*-methoxyphenyl)-methoxyethyl bromide **13f** was prepared using Williamson conditions (Scheme 2) due to the apparent lability of the dimethoxybenzhydrol moiety under acidic conditions.[24] The relative stereochemistry of the 3α-benzyl-8-diarylmethoxyethyl-8-azabicyclo[3.2.1]octanes was unequivocally established by X-ray crystallographic analysis of the oxalate salt of **7a**.[25]

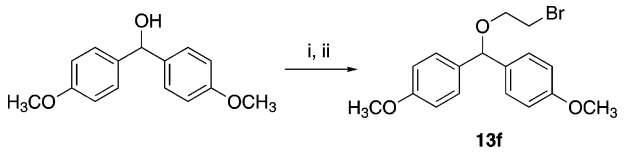
The dopamine transporter (DAT) binding affinity was determined for the 3α-benzyltropanes **7** by their ability to displace bound [^{3}H]WIN 35,428 from rat caudate-putamen tissue.[26] The K_i values that are reported in Table 1, are inhibition constants derived for the unlabeled ligands. In addition, the K_i values for cocaine (**1**) and GBR 12909 (**2**) that were obtained under similar conditions are reported for comparison.[26]

The binding affinities at the dopamine transporter of the 3α-benzyl-8-diaryl-methoxyethyl-8-azabicyclo-[3.2.1] octanes **7a–f** were generally found to be more potent than cocaine (**1**) but were 10-fold less potent than GBR-12909 (**2**). The most potent analogue of the series was the unsubsituted compound **7b** ($K_i = 98$ nM). This was somewhat surprising since it has been shown in numerous studies of GBR-related compounds that the difluoro-analogues usually exhibit comparable binding affinities (within ± SEM) for a series of derivatives.[4,12,13,21] The least potent derivative was the dichloro compound **7c** ($K_i = 346$ nM). It was noteworthy that the mono-chloro

Table 1. In vitro binding affinity of **7a–f** at the dopamine transporter

Compd[a]	X	Y	K_i (nM)[b]
1			187 ± 19[c]
2			12 ± 31[c]
7a	F	F	144 ± 25
7b	H	H	98 ± 5
7c	Cl	Cl	346 ± 50
7d	CH_3	CH_3	217 ± 20
7e	H	Cl	198 ± 20
7f	CH_3O	CH_3O	135 ± 15

[a]All new compounds were tested as the oxalate salt.
[b]All values are the mean ± SEM of three experiments performed in triplicate.
[c]The K_i values are reproduced from ref 26 and were collected under identical conditions.



Scheme 2. (i) $SOCl_2$, reflux. (ii) $BrCH_2CH_2OH$, K_2CO_3, benzene.

analogue **7e** ($K_i = 198$ nM) exhibited intermediate binding affinity relative to **7b** and **7c**.

A significant feature of the SAR of compounds **7a**–**f** is the relative order of binding affinities. For the disubstituted compounds, the order from most potent to least was $H > F > OCH_3 > CH_3 > Cl$. This trend is similar to that observed for the GBR piperazine derivatives.[4] This suggests that 3α-benzyl-8-(diaryl-methoxyethyl)-8-azabicyclo[3.2.1]-octanes **7a**–**f** bind to the DAT in a similar fashion to GBR 12909 (**2**). Moreover, the equipotent affinity of the dimethoxy analogue **7f** ($K_i = 135$ nM) is in contrast to the effect of the dimethoxy substitution reported in the benztropine system ($K_i = 2000$ nM).[27]

However, the most striking aspect of this SAR is the similar potency of **7b** relative to the tropane isomer **14** ($K_i = 99 \pm 9$ nM)[28] recently prepared in our laboratories (Fig. 2). This is quite different than the 23-fold decrease in binding affinity reported for the piperidine derivative **5** ($K_i = 595$ nM) relative to its isomer **3** ($K_i = 25$ nM).[12] The high binding affinity of **7b** suggests that the tropane ring system may be a critical feature for molecular recognition of these compounds at DAT. The rigid tropane system may hold the diaryl moiety and the phenyl ring in a conformation suited for high affinity binding. The proper spatial orientation of the diaryl moiety and the phenyl ring may overcome the positional effect of the nitrogen atom observed in the piperidine analogues.[12] Similar structural effects have been reported for the phenyltropanes. The 3-phenyl-oxatropane and the 3-phenyl-carbatropane analogues exhibited potent binding affinity despite the absence of a bridging nitrogen atom.[29,30] Overall, these results further support suggestions that steric effects and molecular topology play a greater role in molecular binding at the DAT than electronic effects and functionality.[30–34]

In summary, the 3α-benzyl-8-(diarylmethoxyethyl)-8-azabicyclo[3.2.1]octanes **7a**–**f** appear to bind in similar fashion to GBR 12909 and related analogues at the dopamine transporter but different than derivatives of benztropine . The high-binding affinity observed for **7b** suggests that the relative positions of the diaryl moiety and the phenyl ring (molecular topology) may be more important for high affinity binding than the position of the nitrogen atom. Studies to further elucidate the SAR of these and related compounds are currently under investigation and will be reported in due course.

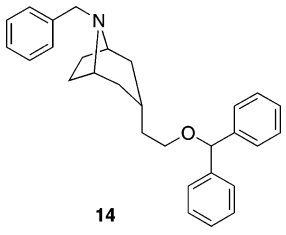


Figure 2. 3α-(2-Benzhydryloxyethyl)-8-benzyl-8-azabicyclo-[3.2.1]octane (**14**).

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