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Synthesis of Dopamine Transporter Selective 3-{2-(Diarylmethoxyethylidene)}-8-alkylaryl-8-azabicyclo[3.2.1]octanes

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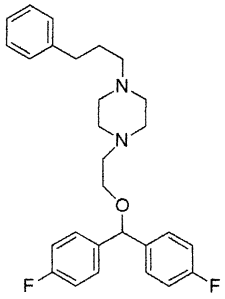
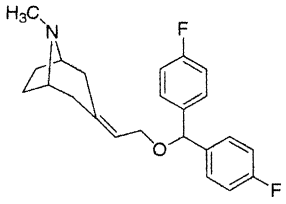
Abstract—A series of 3-{2-(diarylmethoxyethylidene)}-8-alkylaryl-8-azabicyclo[3.2.1]octanes was synthesized and the binding affinities of the compounds were determined at the dopamine and serotonin transporters. The 8-phenylpropyl analogues **8a** ($K_i = 4.1$ nM) and **8b** ($K_i = 3.7$ nM) were the most potent compounds of the series with binding affinities 3 times greater than GBR-12909. In addition, **8a** (SERT/DAT = 327) was over 300-fold more selective for the dopamine transporter than the serotonin transporter.

The disubstituted piperazine GBR 12909 (**1**) is a selective high-affinity dopamine transporter ligand and selective dopamine uptake inhibitor.[1–3] Behavioral studies with GBR 12909 and related derivatives have shown potential for the development of an agonist-based therapeutic agent for cocaine addiction. Although GBR 12909 is self-administered,[4] it has been shown to suppress cocaine self-administration behavior in rhesus monkeys,[5] and exhibit non-stimulant properties in humans.[6–8]



GBR12909 (1)



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Because of the unique pharmacological activity of GBR 12909, it has served as a template for the synthesis of high-affinity selective dopamine transporter ligands.[9–18] From these studies it has been shown that the piperazine ring system is not required for high-affinity selective binding to the DAT. Novel piperidine-based and tropane-based derivatives of **1** have been synthesized and shown to possess moderate to high affinity for the dopamine transporter (DAT) with improved selectivity over the serotonin transporter (SERT).[9]

Recently, a GBR-benztropine hybrid analogue **2**, was reported by Rice and coworkers to be a potent and selective DAT ligand.[15] The pharmacological profile of **2** (DAT affinity, uptake inhibition and transporter selectivity) was reported to be more like the GBR compounds than benztropine. Therefore it was of interest to further investigate the ethylidenyl-8-azabicyclo[3.2.1]-octane ring system as a scaffold for the design of analogues of GBR 12909. Herein, we wish to report the synthesis, dopamine transporter and serotonin transporter affinity of several 3-{2-(diarylmethoxyethylidene)}-8-alkyl-aryl-8-azabicyclo[3.2.1]octanes.

As illustrated in Scheme 1, the synthesis of the target 3-ethylidenyl-8-azabicyclo[3.2.1]octane ring system was achieved conveniently from tropinone (**3**). The demethylation/carbonylation of **3** with ethyl chloroformate furnished the ethyl carbamate **4** in 95% yield. It was

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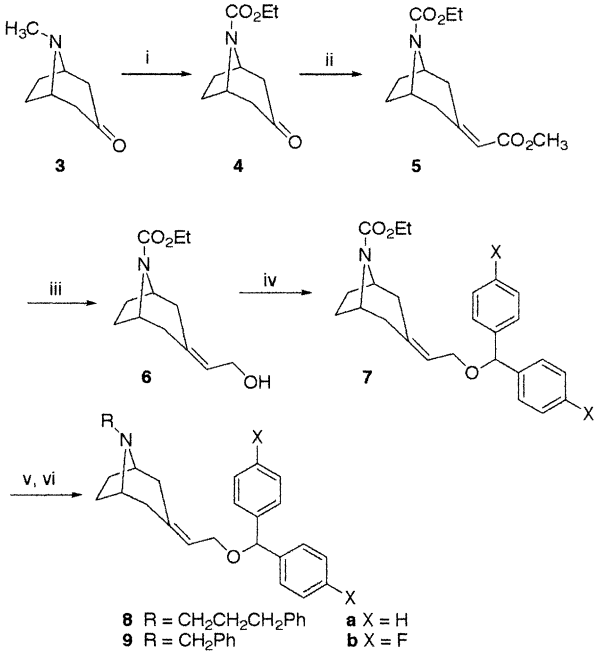
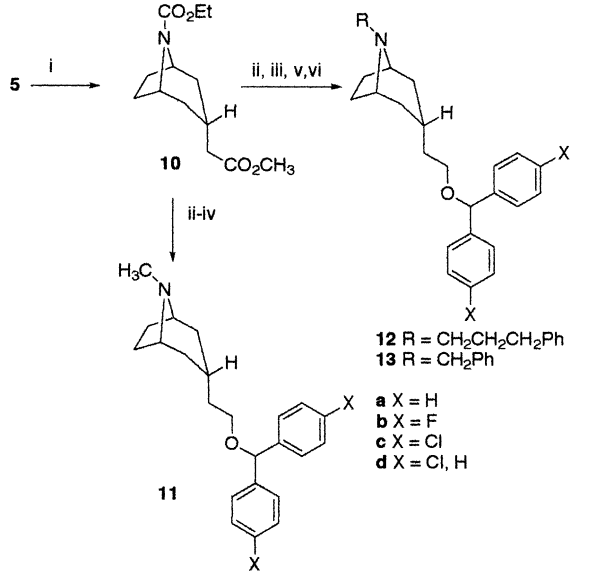


Scheme 1. (i) $ClCO_2Et$, K_2CO_3, toluene, Δ; (ii) $(CH_3O)_2POCH_2CO_2CH_3$, DBU, LiCl, CH_3CN, 25 °C; (iii) $LiAlH_4$, THF, 0 °C; (iv) $ClCH_2CH_2OCH(p\text{-}X\text{-}C_6H_4)_2$, 145 °C; (v) $NH_2NH_2{\cdot}H_2O$, KOH, $HOCH_2CH_2OH$; (vi) RBr, K_2CO_3, DMF.

important to remove the methyl group early in the synthetic sequence since preliminary studies had indicated that demethylation of late intermediates was problematic.[19] Subsequent olefination of **4** with trimethylphosphoroacetate afforded the ethylidene ester **5** in 80% yield. Selective reduction of the ester **5** with lithium aluminum hydride gave the alcohol **6** in 86% yield. The benzhydryl ether moiety was then introduced by heating the corresponding substituted benzhydryl chloride and the alcohol **6** neat at 145 °C. This melt procedure originally reported by Newman for the synthesis of benztropine analogues afforded the corresponding benzhydryl ethers **7** in good yields (60–80%).[20] The carbamate group was removed with hydrazine hydrate and the resulting amine was then alkylated with 3-phenylpropyl bromide and benzyl bromide to afford the desired 3-ethylidenyl-8-azabicyclo[3.2.1]octane analogues **8** and **9**.



Scheme 2. (i) H_2, 10% Pd/C, CH_3OH; (ii) $LiAlH_4$, THF, 0 °C; (iii) $ClCH_2CH_2OCH(p\text{-}X\text{-}C_6H_4)_2$, 145 °C; (iv) $LiAlH_4$, THF, 25 °C; (v) $NH_2NH_2{\cdot}H_2O$, KOH, $HOCH_2CH_2OH$; (vi) RBr, K_2CO_3, DMF.

In addition to the ethylidene analogues **8** and **9**, a series of the 3α-analogues **11**–**13** (Scheme 2) were also prepared. The 3α-analogues were synthesized by hydrogenation of the ester **5** over palladium on carbon to afford the 3α-ester **10** in 90% yield as a single isomer (Scheme 2). Subsequent conversion of **10** into the 3-{2-(diarylmethoxyethyl)} - 8 - methyl - 8 - aza - bicyclo[3.2.1] octanes (**11**) was achieved via a similar synthetic sequence to that established above. However, the final step of the synthesis, introduction of the *N*-methyl group, was achieved by reduction of the carbamate moiety with lithium aluminum hydride to give the *N*-methyl analogue **11**. The 3-{2-(diarylmethoxyethyl)}-8-(3-phenylpropyl)-8-azabicyclo[3.2.1]octanes (**12**) and the 3-{2-(diarylmethoxyethyl)}-8-benzyl-8-aza-bicyclo[3.2.1] octanes (**13**) were prepared from the ester **10** in similar fashion to the ethylidene derivatives (Scheme 2).

The dopamine transporter (DAT) binding affinities and the serotonin transporter (SERT) binding affinities were determined for the GBR-analogues by their ability to displace bound [^{3}H]WIN 35,428 and [^{3}H]citalopram from rat caudate-putamen tissue.[21,22] The K_i values that are reported in Table 1, are inhibition constants derived for the unlabeled ligands. In addition, the K_i value for GBR 12909 (**1**) binding to DAT that was obtained under identical conditions is reported for comparison.[21]

Table 1. DAT and SERT binding affinities

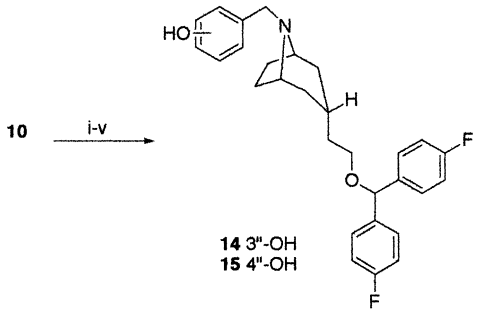
Compd[a]	X	K_i (nM ± SEM)[b]		
		DAT	SERT	SERT/DAT
1		12 ± 1.9[c]		35[d]
8a	H	4.1 ± 0.6	1340 ± 230	327
8b	F	3.7 ± 0.4	562 ± 200	152
9a	H	48 ± 5	5420 ± 74	113
9b	F	7.9 ± 0.5	2220 ± 740	281
11a	H	58 ± 9	14,100 ± 200	243
11b	F	31 ± 3	2470 ± 300	80
11c	Cl	18 ± 4	1160 ± 140	64
11d	Cl, H	48 ± 14	3430 ± 280	71
12a	H	18 ± 2	750 ± 41	42
12b	F	7.4 ± 3	175 ± 23	24
12c	Cl	50 ± 12	177 ± 46	4
12d	Cl, H	30 ± 3	374 ± 12	12
13a	H	99 ± 9	4780 ± 190	48
13b	F	5.7 ± 1.4	1430 ± 230	251
13c	Cl	91 ± 16	822 ± 175	9
13d	Cl, H	82 ± 11	1940 ± 345	24
14	F	20 ± 5	651 ± 7	33
15	F	30 ± 6	809 ± 110	27

[a]All synthesized compounds were tested as the oxalate salt.
[b]All values are the mean ± SEM of three experiments performed in triplicate.
[c]The K_i value is reproduced from ref 21 and was collected under identical conditions.
[d]The SERT/DAT value is reproduced from ref 15.

The ethylidene derivatives **8** and **9** were evaluated as racemic mixtures[15] and demonstrated high affinity for the DAT. The *N*-phenylpropyl analogues **8a** ($K_i = 4.1$ nM) and **8b** ($K_i = 3.7$ nM) were the most potent compounds of this study. Both analogues were 4-fold more potent at DAT than GBR 12909 (**1**).[21] Although direct comparison of the binding affinities of **8a** and **8b** with **2** is not possible since the K_i-values were measured in different assays, it is possible to indirectly compare relative potencies based upon the binding affinities of GBR 12909 in both assays. The *N*-methyl analogue **2** ($K_i = 19$ nM) was reported to be 5-fold less potent than GBR 12909 in the [^{125}I]RTI-55 binding assay.[15] Therefore, the relative potency of the *N*-phenylpropyl ethylidenes **8a** and **8b** can be considered to be significantly greater than the *N*-methyl analogue **2**.

The ethylidene analogues also exhibited high selectivity for binding at the DAT over the SERT, with **8a** (SERT/DAT = 327) nearly 10-fold more selective than GBR 12909 (**1**). To our knowledge, **8a** is one of the most selective DAT ligands reported to date. The binding affinities of the *N*-benzyl ethylidene detivatives **9** were diminished relative to **8**. The largest decrease was observed for the desfluoro analogue **9a**. However, it is noteworthy that despite reduced DAT binding affinity the difluoro analogue **9b** (SERT/DAT = 281) exhibited high selectivity for the dopamine transporter over the serotonin transporter.

The high potency and high DAT selectivity observed for the ethylidene analogues prompted further investigation of the corresponding saturated 3α-derivatives. Although Rice and coworkers had previously reported on several 3α-tropane derivatives (**11a**, **11b**, **12a** and **12b**),[15] it was felt that evaluation of these compounds as well as new analogues along with the ethylidene derivatives in the similar assays would permit a more accurate assessment of the effect of unsaturation at C3 of the 3-ethylidenyl-8-azabicyclo[3.2.1]octane ring system. For the *N*-methyl 3α-analogues **11**, the dichloro derivative **11c** ($K_i = 18$ nM) was determined to be the most potent derivative albeit the least selective of the series (SERT/DAT = 64). The desfluoro and difluoro *N*-methyl 3α-derivatives, **11a** and **11b**, exhibited moderate affinity at DAT. The DAT and SERT binding affinities of **11a** and **11b** were consistent with the previously reported SAR.[15] The binding affinities of the *N*-phenylpropyl derivatives **12** were generally more potent than the corresponding *N*-methyl congeners. The difluoro derivative **12b** ($K_i = 7.4$ nM) exhibited DAT potency equal to that of the ethylidene derivative **8a**. Only the dichloro analogue **12c** ($K_i = 50$ nM) was found to have diminished binding affinity relative to the *N*-methyl derivatives.



Scheme 3. (i) H_2, 10% Pd/C, CH_3OH; (ii) $LiAlH_4$, THF, 0 °C; (iii) $ClCH_2CH_2OCH(p\text{-}F\text{-}C_6H_4)_2$, 145 °C; (iv) $NH_2NH_2{\cdot}H_2O$, KOH, $HOCH_2CH_2OH$; (v) HOC_6H_4CHO, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt.

The *N*-benzyl compounds **13** were generally found to have diminished DAT binding affinity relative to the *N*-phenylpropyl analogues and the ethylidene derivatives. Only the difluoro derivative **13b** ($K_i = 5.7$ nM) possessed high affinity for the DAT. In fact **13b** was the most potent compound of the 3α-analogues and was equipotent with the ethylidene derivatives **8b** and **9b**.

Of the 3α-derivatives only the *N*-methyl analogue **11a** (SERT/DAT = 243) and the *N*-benzyl analogue **13b** (SERT/DAT = 251) exhibited transporter selectivity of a similar magnitude to the ethylidene derivatives. Although **11a** was as selective for the DAT, the binding affinity was 10-fold less than **8a** and this was consistent with previous results reported for this compound.[15] However, **13b** was as potent and selective as the corresponding ethylidene derivative **9b**. Moreover, **13b** was 8-fold more selective than the *N*-phenylpropyl congener **12b**. The observed increase in selectivity of **13b** over **12b** is believed to be due to the *N*-benzyl group. Dutta and coworkers have reported similar SAR for GBR-related piperidine derivatives.[14,23,24] However, surprisingly the DAT selectivity determined for **13b** was not observed for the desfluoro and chloro *N*-benzyl compounds **13a**,**c**,**d**.

The high DAT affinity and selectivity observed for the *N*-benzyl 3α-analogue **13b** led to a brief investigation of potentially less lipophilic analogues and pro-drug precusors.[11] The hydroxylated *N*-benzyl derivatives **14** and **15** were prepared from **10** in straightforward fashion (Scheme 3). The 3″-OH compound **14** and 4″-OH compound **15** exhibited decreased DAT binding affinity and increased SERT binding affinity (Table 1) relative to **13b**. As a result, the hydroxylated analogues **14** and **15** were much less selective for the DAT than **13b**.

Comparison of the racemic ethylidene derivatives **8** and **9** with the achiral 3α-derivatives **11**–**13** revealed that in general sp^2-hybridization of the C3-carbon atom imparted greater binding affinity for the DAT while decreasing affinity for SERT. The *N*-phenylpropyl analogue **8a** was the most selective compound of the study and was nearly 10-fold more selective than the corresponding 3α-analogue **12a**. Consistent with the SAR of the GBR-related compounds, the difluoro derivative **8b** was less selective than the desfluoro compound **8a** but was still 5-fold more selective than the corresponding 3α-derivative **12b**.

Overall, the 3-{2-(diarylmethoxyethylidene)}-8-alkylaryl-8-azabicyclo[3.2.1]octanes exhibited higher affinity and selectivity for the DAT than GBR 12909 and most related-analogues reported to date. It is evident that 3-ethylidenyl-8-azabicyclo-[3.2.1]octane ring system

is an important structural feature of these compounds for selective molecular recognition at the DAT. While the *N*-benzyl group appeared to lead to the DAT selective compound **13b** in the 3α-series the effect was not as significant in the 3-ethylidenyl-8-azabicyclo[3.2.1]octane series. This suggests that the observed SERT/DAT selectivity of **8** and **9** is due to either a conformational effect of the rigid 3-ethylidenyl-8-azabicyclo[3.2.1] octane ring system or a stereochemical effect inherent to unsaturation at C3. Efforts to resolve the 3-ethylidenyl-8-azabicyclo[3.2.1]octane enantiomers are currently under investigation. The results of this study and additional studies to further elucidate the SAR of these compounds will be reported in due course.

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