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N-PHENYLALKYL-SUBSTITUTED TROPANE ANALOGS OF BOAT CONFORMATION WITH HIGH SELECTIVITY FOR THE DOPAMINE VERSUS SEROTONIN TRANSPORTER

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Abstract: A series of *N*-phenylalkyl-substituted tropane analogs of boat conformation was synthesized, and these tropanes were evaluated for their ability to inhibit high affinity uptake of dopamine (DA) and serotonin (5-HT) into striatal nerve endings (synaptosomes). Some of these compounds exhibit high affinity for the DA transporter with a 5-HT/DA transporter selectivity ratio of >50.

Cocaine abuse is one of the major concerns of our society as it is coupled with substantial crime-related costs both in the US and abroad.[1,2] While cocaine self-administration appears to be best correlated with its activity at the dopamine transporter (DAT), cocaine is also a potent inhibitor of the serotonin and norepinephrine transporters (5-HTT and NET, respectively).[3] Current research using DAT knockout mice suggests an important serotonergic component to the reinforcing effects of cocaine.[4] Accordingly, issues of transporter specificity will remain pivotal to a complete understanding of cocaine's reinforcing effects. Therefore, a better understanding of the structural elements relevant to creating small molecules displaying tunable levels of transporter selectivity may prove valuable to the development of possible medications.

Drug development targeting the DAT has involved the study of molecules possessing rather diverse chemical structures.[5-7] Comprehensive structure–activity relationship (SAR) studies based on the 3-aryltropanes (**II**) (the WIN series, with cocaine's benzoate group replaced by an aryl ring), has led to the definition of the structural features relevant to achieving varying degrees of selectivity for one of the three biogenic amine transporters.[8-11] To date, however, many of the tropanes reported in the literature simply act as more potent versions of cocaine when tested in animals.[12] Certain disubstituted piperazine derivatives which have come to be known as the GBR series also display high affinity and selectivity for the DAT.[13,14] In particular, GBR 12909 (**III**) is approximately 6-fold more potent as a DAT inhibitor than a 5-HTT inhibitor.[14] Despite the reported in vitro DAT potency and selectivity, GBR 12909 is surprisingly less potent than cocaine as a locomotor stimulant in vivo.[15] Yet, recent studies revealed that GBR 12909 is able to selectively decrease cocaine-seeking behavior in monkeys.[16,17] In man this compound was found to produce sedation, rather than having a stimulant action as might be expected based upon its DAT activity.[18]

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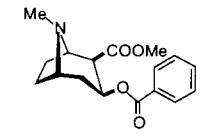
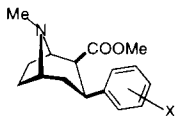
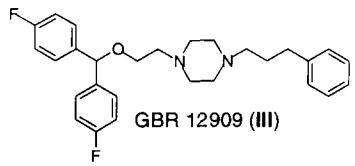


Cocaine (I)



WIN Analogs (II)

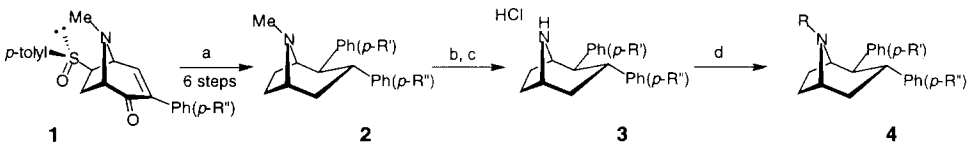


GBR 12909 (III)

In view of the interesting biological activity displayed by the GBR series, we felt that it would be of value to explore the effect of introducing various arylalkyl groups on the nitrogen atom of the tropanes. In particular, as we have recently reported on a new strategy for the rapid construction of tropane derivatives that adopt the boat conformation, and which show high affinity for the dopamine transporter, the aforesaid modifications were made in this series. For example, we had shown previously that the 2β-phenyl-3α-tolyl substituted tropane existing in a twist boat conformation exhibited a K_i of 4.2 nM at the DAT and 287 nM at the 5-HTT.[19] The calculated selectivity ratio of 69-fold is one of the best recorded for a boat tropane, in which the transporter activities were assessed using K_i values and identical buffer systems.[20] In exploring the effect of replacing the *N*-methyl group of these "boat" tropanes by arylalkyl groups, we maintained aryl substitution at both the 2- and 3-positions. Interestingly, and as is discussed below, tropane **4h** shows a selectivity ratio of 113-fold for the DAT versus the 5-HTT while maintaining a K_i of approximately 1 nM in both functional and binding studies of the DAT.

The preparation of the tropanes **4a-h** was accomplished using the general strategy outlined in Scheme 1. Specifically, tropane **2** was prepared stereoselectively as described previously.[19] *N*-Demethylation using α-chloroethyl chloroformate allowed introduction of the required arylalkyl or aryloxyalkyl group. This final alkylation step was carried out in DMF as solvent in the presence of 2 equivalents of K_2CO_3. The reaction yields varied from 60-80% depending on the alkyl bromide used.[21]

Scheme 1.



1 2 3 4

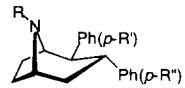
Reagents and conditions: (a) See ref 19; (b) α-chloroethyl chloroformate, proton sponge, 1,2-dichloroethane, reflux, 2 h; (c) MeOH, reflux; (d) RBr, K_2CO_3, DMF, rt.

The tropanes reported in this series were tested for their ability to displace [^{3}H]mazindol binding. Mazindol has been shown to label the cocaine binding sites on the dopamine transporter of rat striatal membranes.[22] This ligand binds with high affinity (K_d = 8.63 ± 0.53 nM) to a single, sodium-dependent site in striatal membranes, representing the dopamine carrier. Additionally, these compounds were tested for their ability to inhibit high-affinity uptake of DA and 5-HT into striatal nerve endings (synaptosomes).[20] The binding and uptake data are provided in Table 1 along with comparison data for cocaine and two related *N*-methyltropanes.

With the exception of **4e,** all of the twist-boat tropanes prepared in this series are more potent than cocaine in both the DAT binding and uptake assays. In general, the mazindol binding affinities parallel the DAT uptake potencies. In this series, benzyltropane **4a** is the least active compound, while tropane **4h** is the most potent compound in both the binding and DAT uptake studies. Extending the linking chain (connecting the nitrogen

atom of the tropane with the phenyl group) in **4a** by one methylene group gave **4b** and resulted in 25- and 6-fold increase in binding and DA uptake, respectively. Tropanes **4b** and **4c** have essentially similar binding and DAT uptake activities. However, tropane **4b** shows improved DAT selectivity. Further extension of the linking chain in **4c** by another methylene group gave **4f** which exhibited a reduced potency at the DAT. Interestingly, tropane **4d** has a potency comparable to that of **4c**, in spite of the presence of an oxygen atom in place of a methylene group in the linking chain. The diphenylpropyl analog **4e** is much less potent than its monophenyl counterpart **4c**, indicating a steric limitation in the transporter's ability to accommodate bulky functional groups on the linking chain in this series. Of considerable interest in respect to DAT versus 5-HTT selectivity is the observation that selectivity is dependent on the number of methylene groups in the linking chain. Among the bis-(*p*-fluorophenyl) bearing tropanes, compound **4b** with the ethylene spacer shows a >50-fold selectivity for the DAT. Previously, we had found that the *N*-methyl compound **4g** which bears a phenyl group at position 2, and a tolyl group at position 3 showed the highest selectivity ratio reported for such boat tropanes.[19] In consideration of the improved selectivity exhibited by the phenylethyl analog **4b** in comparison to its *N*-methyl counterpart **2**, it became of interest to investigate the activity of the boat tropane **4h** which combines the structural features of **4b** and **4g**. Tropane **4h** exhibits not only high binding affinity at the DAT (<1 nM), but also exhibits a 113-fold selectivity for the DAT versus the 5-HTT. As these selectivity data are based upon K_i values which were acquired under identical incubation time, temperature and buffer conditions for both the DAT and 5-HTT uptake studies, the selectivity and potency are rather impressive for a compound whose tropane ring exists in a boat conformation.[23]

Table 1. K_i values for the tropane analogs in mazindol binding, dopamine, and serotonin uptake experiments.



Compd #	R	R'	R"	[^{3}H]mazindol binding K_i (nM)	[^{3}H]DA uptake K_i (nM)	[^{3}H]5-HT uptake K_i (nM)	uptake selectivity 5-HT/DA
Cocaine				230 ± 16	420 ± 150	160 ± 0.40	0.38
2	Me	F	F	31 ± 8.6	14 ± 1.2	460 ± 49	33
3	H	F	F	49 ± 2.6	17 ± 0.40	41 ± 11	2.4
4a	$PhCH_2$	F	F	260 ± 39	170 ± 7.4	490 ± 36	2.9
4b	$Ph(CH_2)_2$	F	F	10 ± 0.10	26 ± 0.74	>1,300	>50
4c	$Ph(CH_2)_3$	F	F	16 ± 0.84	43 ± 0.1	608 ± 127	14
4d	*p*-F-$PhO(CH_2)_2$	F	F	22 ± 1.8	27 ± 3.2	928 ± 27	34
4e	$Ph_2CH(CH_2)_2$	F	F	>7,000	>10,000	>20,000	-
4f	$Ph(CH_2)_4$	F	F	86.4 ± 19	210 ± 0.10	110 ± 11	0.52
4g	Me	H	Me	6.0 ± 0.30	4.6 ± 1.1	120 ± 17	26
4h	$Ph(CH_2)_2$	H	Me	0.95 ± 0.2	1.6 ± 0.2	180 ± 11	113

In summary, the present work demonstrates that certain boat tropanes bearing *N*-arylalkyl groups (molecules that can be broadly viewed as hybrids of GBR and cocaine) are able to retain high affinity for the DAT, while showing a good selectivity ratio for DAT versus 5-HTT. Further studies of the behavioral effects of

4h and related compounds in drug discrimination paradigms using cocaine trained animals are clearly warranted and will be reported in due course.

Acknowledgment: We are indebted to the National Institutes of Health, National Institute on Drug Abuse (DA10458) for their support of these studies.

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23. It is interesting to note that some *N*-arylalkyl "chair" tropanes have been reported, and that in this case the highest affinity ligand, methyl *N*-(3-phenylpropyl)-3β-(4-fluorophenyl)tropane-2β-carboxylate possessed a propylene linker. Meltzer, P. C.; Blundell, P.; Madras, B. K. *Med. Chem. Res.* **1998**, *8*, 12-34.