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Synthesis and Biological Evaluation of 1-Azabicyclo-[3.2.1]octanes: New Dopamine Transporter Inhibitors

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Abstract—The synthesis and biological activity of a series of 6-substituted 1-azabicyclo[3.2.1]octanes are described. 1-Azabicyclo[3.2.1]octanes represent a new class of compounds that exhibit monoamine transporter inhibitory activity highly dependent on the overall topology and the absolute stereochemistry of the molecule. © 2000 Elsevier Science Ltd. All rights reserved.

To date, a large number of compounds that bind at the cocaine binding site of the dopamine (DA) transporter (DAT) have been synthesized in order to better understand the pharmacological properties of this drug.[1] The ability of cocaine to bind to the DAT and to inhibit the reuptake of dopamine has been implicated in it's reinforcing properties.[2,3] However, the precise binding interaction of these analogues with specific monoamine transporters has been a matter of much debate.[4a,b]

We have recently reported on the synthesis of a series of rigid tricyclic tropane analogues in which the conformation of the nitrogen lone pair is fixed by means of a tether to either the 3- or 2-carbon bridge of the tropane moiety.[5a–c] We demonstrated that the selectivity of these rigid tropane analogues as monoamine transporter inhibitors was influenced by the orientation of the nitrogen lone pair. Tropane based compounds (Fig. 1) with the nitrogen lone pair localized over the 2-carbon bridge of the tropane ring (front-bridged) exhibit improved potency and selectivity for the serotonin (5-HT) transporter (SERT). We now present additional structure–activity relationships (SAR) in this series, which serve to further define the binding site topology for these molecules at the respective monoamine transporters. Herein, we describe a facile synthesis of rigid bicyclo[3.2.1]octan-6-one intermediates **4** and **5** (Scheme 1) that are readily converted to *O*-alkyl oximes **6–11**. As is disclosed herein, such rigid compounds can be readily synthesized in enantiomericaly pure form. The SAR developed from this study reveals a better understanding of the pharmacophore of the cocaine binding site at the DAT and therefore can be used towards the design of novel DAT inhibitors as drugs.

Chemistry

Bicyclooctanes **6–11** were synthesized as depicted in Scheme 1. Briefly, *N*-demethylation of (−)-*cis* piperidine **1**[6,7] was accomplished in two steps by treatment with 1-chloroethyl chloroformate[8] in dichloroethane in the presence of proton sponge (1.5 equiv), followed by methanolysis of the resulting carbamate intermediate to afford (−)-**2** in quantitative yield.

The resulting piperidine (−)-**2** was then *N*-alkylated using ethyl bromoacetate in EtOH to give the corresponding diester (−)-**3**. Treatment of the diester (−)-**3** with KOEt in refluxing ethanol gave the β-ketoester intermediate (structure not shown) which was reacted immediately without further purification with aqueous HCl (10%) to give ketones (−)-**4** and (+)-**5**, which were separated using chromatography on silica gel. Similarly, ketones (+)-**4** and (−)-**5** were prepared from (+)-**3**. The absolute stereochemistries of (+)-**4** and (+)-**5** as (*1R*)-(−)-10-camphorsulfonate salts were established by crystallographic methods (Figs 2 and 3).[9a,b]

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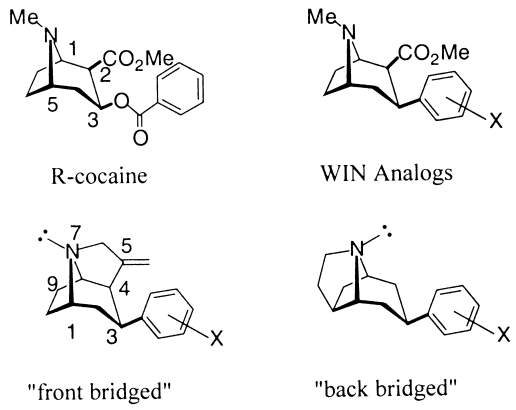


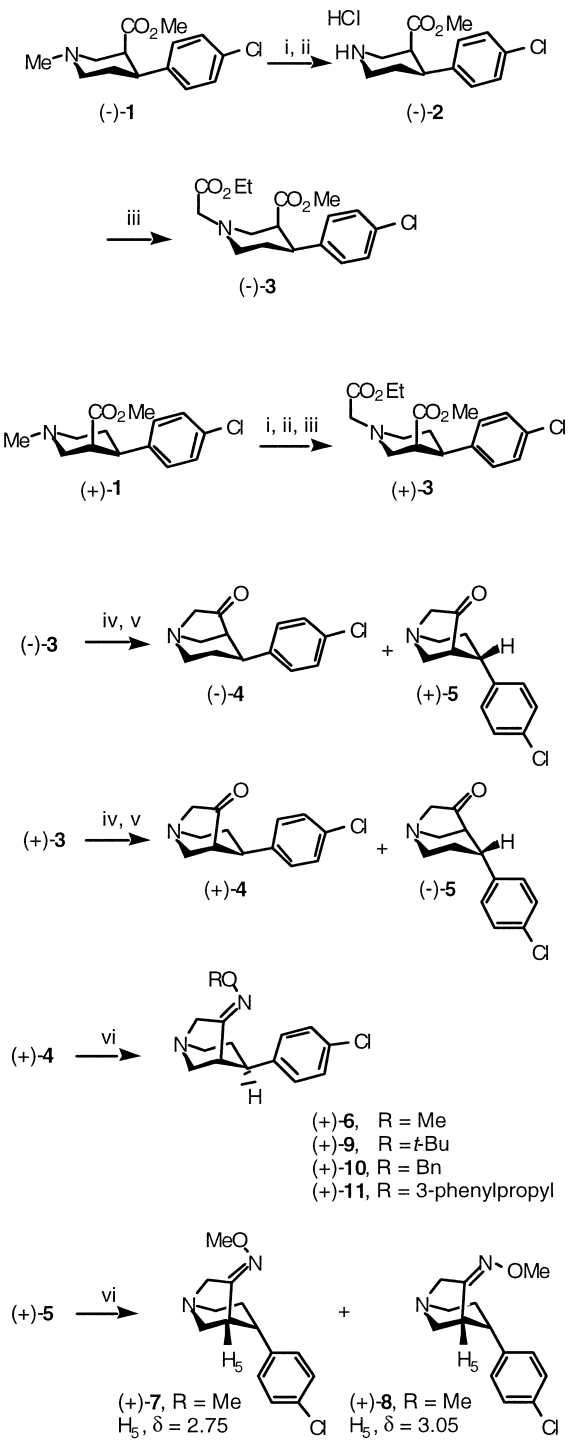
Figure 1.

Reaction of the ketones **4** and **5** with appropriate *O*-substituted hydroxylamine[10] in refluxing toluene gave the *E*- and *Z*-oximes, which are readily separated using chromatography on silica gel.[11] The *Z*-isomer was formed exclusively upon condensation of **4** with hydroxylamines. The stereochemistry of (+)-**6** was established by crystallographic methods (Fig. 4).[9] Piperidines **13**–**15** were prepared as shown in Scheme 2. Treatment of piperidine (−)-**1**[6,7] with NaOMe gave the *trans* piperidine (+)-**12** quantitatively. Hydrolysis of piperidine (+)-**12** using HCl (10% in H_2O) gave the acid intermediate (structure not shown). Reaction of the acid intermediate with $(COCl)_2$ in CH_2Cl_2 gave the acid chloride which was then reacted without purification with the appropriate alcohol in the presence of DMAP and Et_3N in CH_2Cl_2 to give piperidines **13**–**15**.[11]

Structure–Activity Relationships

All compounds were tested for their ability to inhibit high affinity uptake of DA, 5-HT and norepinephrine (NE) into nerve endings (synaptosomes).[12] The uptake data based on the K_i values of these compounds are listed in Table 1. All data are mean values ± SEM of two to five separate experiments, each conducted with six drug concentrations in triplicate. Additionally, all final compounds 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.[13] This ligand binds with high affinity to a single, sodium-dependent site in striatal membranes, representing the dopamine carrier.

In general, the mazindol binding affinities parallel the DAT uptake potencies. With exception of (+)-**8** and (+)-**11**, all *O*-alkyl oximes exhibit lower potency at the DAT when compared to cocaine. In this series oximes (+)-**8** and (−)-**8** exhibit dual potency at the DAT and the norepinephrine transporter (NET) while oxime (−)-**6** exhibits dual potency at the SERT and the NET. Interestingly, oxime (−)-**8** is 2-fold less potent at the SERT than oxime (+)-**8**. Replacement of the methyl group in (+)-**6** with a *t*-butyl group gave (+)-**9** and resulted in a 4- to 5-fold increase in potency at all three transporters. Replacement of the methyl oxime in (+)-**6** with phenylalkyl oximes gave (+)-**10** and (+)-**11**. Oxime **11** exhibits excellent potency at the DAT compared to (+)-**6**. Similar to this effect, we had recently demonstrated that certain boat tropanes bearing *N*-arylalkyl groups (molecules that can be broadly viewed as hybrids of GBR[1a] and cocaine), are able to retain high affinity for the DAT, while showing a good selectivity ratio for the DAT versus the SERT.[14]



Scheme 1. Reagents and conditions: (i) 1-Chloroethyl chloroformate, 1,2-dichloroethane, 1,8-bis-(dimethylamino)naphthalene; (ii) MeOH, reflux; (iii) $EtOCOCH_2Br$, K_2CO_3, EtOH; (iv) KH, ethanol, reflux; (v) HCl (10%), reflux; (vi) *O*-Alkyl hydroxylamine, toluene, reflux.

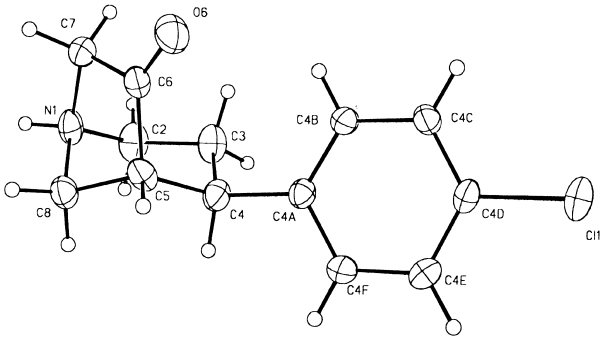


Figure 2. ORTEP drawing of bicyclooctane (+)-**4**. The figure, showing the correct absolute configuration, is drawn using the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.[9]

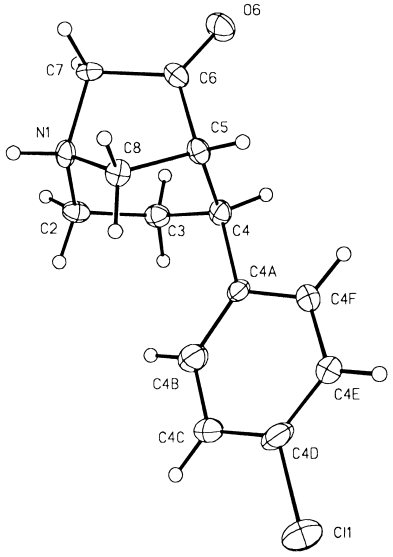


Figure 3. ORTEP drawing of bicyclooctane (+)-**5**. The figure, showing the correct absolute configuration, is drawn using the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.[9]

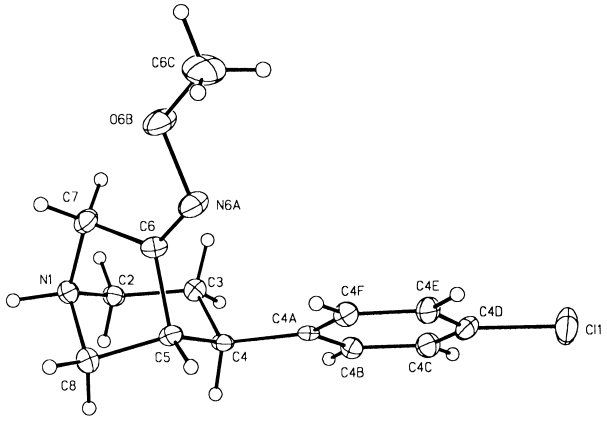
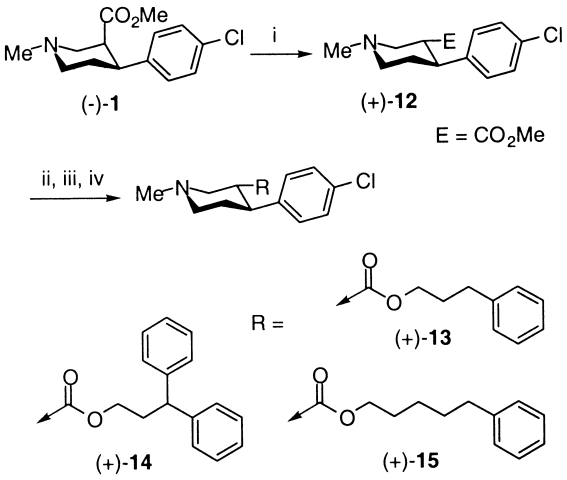


Figure 4. ORTEP drawing of bicyclooctane (+)-**6**. The figure, showing the correct absolute configuration, is drawn using the experimentally determined coordinates with anisotropic thermal parameters at the 20% probability level.[9]



Scheme 2. Reagents and conditions: (i) NaOMe, MeOH, reflux; (ii) HCl (10%), reflux; (iii) $(COCl)_2$, CH_2Cl_2; (iv) ROH, DMAP, Et_3N, CH_2Cl_2.

Compounds **13**–**15** were prepared in order to test the effect of *O*-phenylalkyl substitution in the piperidine series. Over the last few years, we have reported on the chemistry and pharmacology of piperidine-based analogues of cocaine as potent DAT inhibitors that lack the conventional tropane skeleton. Piperidine based compounds such as (+)-**12** possess significant DAT potency and selectivity, while causing little locomotor stimulant activity in animals.[6,7] In fact, one of these piperidine-based ligands (+)-**12** has recently been shown at the National Institute on Drug Abuse (NIDA) to antagonize cocaine-induced locomotor effects in rodents.

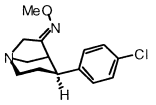
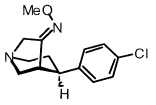
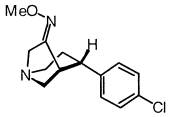
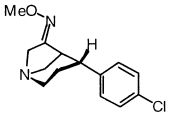
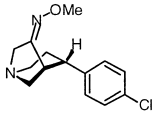
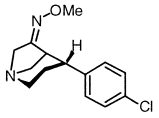
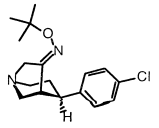
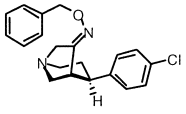
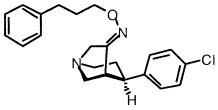
Interestingly, piperidines **13** and **14** are less active at the DAT than the corresponding methyl ester **12**. However, piperidine **15** is more potent at the DAT than the methyl ester **12**. Piperidine **15** exhibits DA and NE reuptake activities that are comparable to those of (+)-**11**, while it is 6-fold less potent at the SERT. These similarities in the biological profiles of the bicyclic oximes in comparison to the piperidines encouraged us to further examine the quantitative SAR (QSAR) in this series of compounds.

Molecular Modeling QSAR

Individual bicyclic oximes **6**–**11** were constructed using the program QUANTA[15a] and the structures minimized until convergence using the adopted-basis Newton Raphson algorithm. Since compounds **10** and **11** have flexible *O*-phenylalkyl groups, the global minima were found using a systematic conformational search with the grid scan method from the conformational analysis module of the QUANTA program.[15a] For each compound two to four torsional angles were modified during the search, thus generating up to 2600 conformations. Each conformation was minimized using the adopted-basis Newton Raphson algorithm with a 2000 iteration limit. A constant dielectric (equal to 1) was used in all calculations. The lowest energy minimized conformation was chosen as the most stable conformation for every compound.

The low energy structures obtained after conformational analysis were used to generate SAR models using the QSAR+ module from the Cerius2 program.[15b] In all

Table 1. K_i values for the 1-azabicyclo[3.2.1]octane analogues in mazindol binding and dopamine, norepinephrine and serotonin uptake experiments (nM)

Compound	Structure	[^{3}H]Mazindol binding[a]	[^{3}H]DA uptake[a]	[^{3}H]NE uptake[a]	[^{3}H]5-HT uptake[a]	5-HT/DA
cocaine	—	230 ± 16	301 ± 50	186 ± 23	413 ± 81	1.4
(−)-**6**		>5000	3640 ± 250	305 ± 1.0	503 ± 21	0.15
(+)-**6**		>36,000	>45,000	>4000	1790 ± 30	0.076
(+)-**7**		1430 ± 10	2520 ± 470	871 ± 97	2640 ± 450	1.0
(−)-**7**		2790 ± 120	2660 ± 330	652 ± 180	2530 ± 10	0.95
(+)-**8**		796 ± 121	292 ± 18	240 ± 18	856 ± 109	2.9
(−)-**8**		434 ± 34	304 ± 12	232 ± 19	>2000	6.6
(+)-**9**		641 ± 44	725 ± 103	287 ± 25	137 ± 25	0.19
(+)-**10**		1000 ± 40	1860 ± 270	1550 ± 270	117 ± 9.5	0.06
(+)-**11**		53 ± 6.0	41 ± 4.0	483 ± 11	292 ± 33	7.1
(+)-**13**	—[b]	1490 ± 190	1420 ± 90	72 ± 29	2160 ± 10	1.5
(+)-**14**	—[b]	420 ± 31	1160 ± 40	3140 ± 510	2590 ± 40	2.2
(+)-**15**	—[b]	52 ± 6	53 ± 2.6	382 ± 15	1790 ± 10	34
(+)-**12**	—[b]	248 ± 18	228 ± 30	90 ± 5.2	5880 ± 440	26

[a]Numbers represent the mean ± SEM from two to five independent experiments, each conducted with at least three determinations.
[b]Structure shown in Scheme 2.

models $-\log K_i$ (M) of DA, NE, or 5-HT uptake inhibition was correlated with the following parameters: (1) distance between O6B and C4A (D, Fig. 4); (2) the distance between Cl1 and C6C for compounds **6**–**8** (D2), (for compounds **9**–**11** D2 was measured using the distance between the Cl1 and the average distance to the hydrophobic *t*-butyl group or phenyl groups); (3) the angle between O6B-C4-C4A (ψ); (4) the dihedral angle between O6B-N6A-C4-C4A (φ); and finally (5) the molecular volume (V_m) of each compound. The first three parameters characterize the relative position of the substituent at O6B compared to the phenyl group at C4. The differences in volume (ΔV_m) between compounds **9**–**11** and **6** was introduced to take in account the size of the substituent at O6B. In the QSAR equations ΔV_m was used instead of V_m because compounds **6**–**8** have the same volumes, and ΔV_m is directly related to the size of the substituent at the oxygen atom. The values used for generating the models are listed in Table 2.

The genetic function approximation method[15c] was used to generate several QSAR models. Herein we list five such equations with r^2 values greater than 0.8.

Inhibition of DA Uptake

$$-\log K_i = 2.83651 + 0.020935\Delta V_m + 6.4 \times 10^{-5}\Delta V_m^2 - 0.006636\varphi + 0.026145\psi,\ r^2 = 0.78 \quad (1)$$

$$-\log K_i = 3.3879 + 0.02499\Delta V_m - 0.006672\varphi + 0.035676\varphi - 0.1857\,D2, r^2 = 0.81 \quad (1a)$$

Inhibition of NE Uptake

$$-\log K_i = 3.71107 + 0.02131\Delta V_m - 0.004941\varphi - 0.02369\psi + 0.59815\,D2,\ r^2 = 0.95 \quad (2)$$

Inhibition of 5-HT Uptake

$$-\log K_i = 5.6438 + 0.03201\Delta V_m - 0.000218\,\Delta V_m^2 - 0.00364\varphi + 0.0661\ D2,\ r^2 = 0.87 \quad (3)$$

As predicted, all equations derived in this study show that the relative position and the size of the substitutions are very important in determining activity at the three monoamine transporters studied in this series. The QSAR equation developed for the NET shows a linear dependence of $-\log K_i$ on the size of the *O*-alkyl substitution, while the DAT and the SERT exhibit a parabolic dependence. In case of the DAT, the distance between O6B and C4B does not improve the quality of the QSAR model suggesting that this parameter is not important for inhibition of the DAT. However, the distance between Cl1 and the substitution at O6B significantly improves the quality of the QSAR equation. Hence, the relative spatial orientation of the two hydrophobic substituents is important for DAT inhibition.

In conclusion, a series of rigid 6-substituted azabicyclooctanes were prepared in their enantiomerically pure form using a Dieckmann cyclization method. In this series, oxime (+)-**11** exhibits potent activity at the DAT and moderate activity at the SERT and the NET. The present work demonstrates that "front bridged" bicyclic piperidines can be tailored to exhibit good potency at the DAT while showing moderate potency at the NET and the SERT. The present series of compounds that embody some elements of structural rigidity provide further insight into the design of ligands showing certain levels of transporter selectivity that may be useful in the development of medications for the treatment of a variety of neurological disorders.

Table 2. Values used for building QSAR equations. Angles and dihedrals are in degrees, distances are in Å, and V_m is in Å^3

Compd	φ	ψ	D	D2	ΔV_m
(−)-**6**	−114.6	87.6	4.74	7.26	0.00
(+)-**6**	114.6	87.6	4.74	7.26	0.00
(−)-**7**	176.3	156.3	5.80	10.88	0.00
(+)-**7**	177.5	160.0	4.36	10.9	0.00
(−)-**8**	−35.45	125.6	5.84	9.57	0.00
(+)-**8**	35.37	125.6	4.36	9.57	0.00
(+)-**9**	109.2	89.6	4.77	7461	49.9
(+)-**10**	109.8	90.0	4.49	8.93	71.5
(+)-**11**	108.8	84.1	4.82	4.79	105.7

Acknowledgements

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References and Notes

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9. For (+)-**4**: monoclinic crystal (0.08×0.48×0.58 mm) in space group $P2_1$, $a = 6.946(2)$, $b = 10.766(2)$, and $c = 15.631(1)$ Å, $\beta = 96.42(2)^\circ$, $V = 1162(1)$ Å^3, $Z = 2$. $Dx = 1.34$ g cm^{-3}, $\mu = 2.58$ mm^{-1}, $F(000) = 496$, $T = 293$ K. Final agreement factors were $R(F) = 0.046$ and $wR(F^2) = 0.125$ for 1762 observed data. For (+)-**5**: monoclinic crystal (0.06×0.14×0.20 mm) in space group $P2_1$, $a = 11.809(1)$, $b = 11.942(1)$, and $c = 16.926(1)$ Å, $\beta = 104.22(2)^\circ$, $V = 2314(1)$ Å^3, $Z = 4$. $Dx = 1.34$ g cm^{-3}, $\mu = 2.59$ mm^{-1}, $F(000) = 992$, $T = 293$ K. Final agreement factors were $R(F) = 0.056$ and $wR(F^2) = 0.120$ for 2384 observed data. For (+)-**6**: monoclinic crystal (0.04×0.16×0.84 mm) in space group $P2_1$, $a = 12.999(6)$, $b = 7.150(3)$, and $c = 19.413(6)$ Å, $\beta = 108.93(2)^\circ$, $V = 1712(1)$ Å^3, $Z = 4$. $Dx = 1.38$ g cm^{-3}, $\mu = 2.23$ mm^{-1}, $F(000) = 744$, $T = 293$ K. Final agreement factors were $R(F) = 0.057$ and $wR(F^2) = 0.140$ for 2058 observed data. All atomic coordinates have been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EW, UK or by e-mail from software@ccdc.cam.ac.uk.

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