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Synthesis of 8-thiabicyclo[3.2.1]oct-2-enes and their binding affinity for the dopamine and serotonin transporters

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Abstract—The reinforcing and stimulant properties of cocaine have been primarily associated with its propensity to bind to monoamine transport systems, in particular the dopamine transporter. Inhibition of the dopamine transporter then leads to an increase of synaptic dopamine with substantial pharmacological consequences. The search for medications for cocaine abuse has had a particular focus on tropane analogs of cocaine, and the interchange of nitrogen for oxygen in this class has led to potent and selective inhibitors of monoamine transport. Herein we report that 8-thiatrop-2-enes are highly potent and quite selective inhibitors of the dopamine transporter. The 3,4-dichlorophenyl-8-thiabicyclo[3.2.1]oct-2-ene (**4f**) is particularly potent (IC_{50} = 4.5 nM) and selective (800-fold) with respect to inhibition of the serotonin transporter.

1. Introduction

Cocaine use persists as a problem of national significance. The search for suitable medications to address this problem has not yet yielded a clinically proven candidate. The reinforcing and stimulant properties of cocaine have been primarily associated with its ability to inhibit the dopamine transporter (DAT) on presynaptic neurons in the striatum and nucleus accumbens.[1–3] The reinforcing and addictive properties of cocaine are thought to be related to its pharmacokinetic profile of extremely rapid onset and short duration of activity. Therefore, in the search for a safe replacement therapeutic agent, many researchers have focused their efforts on design of compounds that bind with selectivity to the DAT and manifest slow onset of action and long duration of action.[4] Although the DAT has been considered a prime target of cocaine, and therefore of potential medications designed to inhibit the activity of cocaine, the serotonin transporter (SERT) may also play a substantial role in the pharmacological activity of cocaine.[5,6]

The class of bicyclo[3.2.1]octanes has been a focus of much attention in the design of prospective medications for cocaine abuse.[7–15] Until 1996–1997 when we presented evidence[16,17] that the 8-aza functionality within the bicyclo[3.2.1]octane series is not a prerequisite for DAT and SERT binding activity, it was assumed that the presence of an amine nitrogen was essential for binding to monoamine uptake systems.[18–21] We later demonstrated that the topological properties of tropane-like ligands that bind to monoamine uptake systems was possibly more important than the presence or absence of specific functionality and we replaced an amine nitrogen with an ether oxygen or a methylene carbon, and showed that binding potency was maintained.[17,16,8,22] Of relevance to medications development, compounds without an amine nitrogen retain a spectrum of biochemical and pharmacological properties characteristic of aza-based compounds.[23]

In this report we again explore the functional role of the 8-heteroatom in the unsaturated bicyclo[3.2.1]oct-2-ene skeletal nucleus. We were particularly interested in the effect of a sulfur exchange since sulfur is larger than both nitrogen and oxygen, and therefore might cause the ring to 'splay' and affect an overall topological difference. We now report the synthesis and biological evaluation of an exciting family of 2-carbomethoxy-8-thiabicyclo-[3.2.1]oct-2-enes that reveal potent inhibitors of the DAT while manifesting substantial selectivity versus the SERT.

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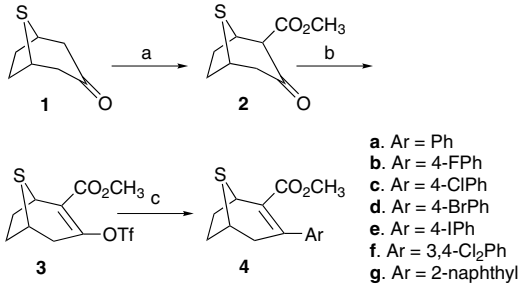
2. Chemistry

The general approach that we have adopted (Scheme 1) for the synthesis of bicyclo[3.2.1]oct-2-enes has pivoted around an enoltriflate, that is, then subjected to palladium catalyzed Suzuki coupling with a suitably substituted arylboronic acid.[16,24] Thus, the 3-ketobicyclo[3.2.1]octane **1** was prepared as described by Parr et al.[25] Introduction of the 2-carbomethoxy group was then achieved under standard conditions[16,26,27] with methylcyanoformate and lithium diisopropylamide to provide the keto ester **2** in 66% yield. This keto ester exists in an equilibrium of three tautomeric forms, namely the 3α-carbomethoxyketoester, the 3β-carbomethoxyketoester and the enol ester itself. This tautomerism is of no stereochemical significance since all optical centers are lost in the ensuing conversion to the enoltriflate **3**. Introduction of the triflate was effected with *N*-phenyltriflimide and sodium bistrimethylsilylamide in 75% yield. ^{1}H NMR of the triflate **3** is diagnostic. The H_1 proton at δ 4.39 appears as a double doublet ($J = 0.9$, 3.6 Hz) while the $H_4\beta$ proton at δ 2.99 appears as a double double doublet [$J = 2.1$ ($H_4\beta$–$H_6\beta$), 4.3 ($H_4\beta$–H_5), 18.6 Hz ($H_4\beta$–$H_4\alpha$)].



Scheme 1. Reagents and conditions: (a) LDA, $NCCOOCH_3$, THF, 78 °C, 1 h, 66%; (b) (i) $NaN(TMS)_2$, THF, −78 °C, 1 h, (ii) $PhN(Tf)_2$, 23 °C, 75%; (c) $ArB(OH)_2$, $Pd(PPh_3)_3$, LiCl, Na_2CO_3, reflux, 3 h, 74–96%.

Intermediate **3** was then utilized to obtain the 2,3-unsaturated compounds **4**. Thus Suzuki coupling of the appropriately substituted boronic acids with **3**, under palladium tetrakistriphenylphosphine catalysis, provided the targets **4a**–**g** in yields of 92–96%. Compounds **4d** (4-bromo; 85%) and **4e** (4-iodo; 74%) provided lower yields as a consequence of biaryl and triaryl byproducts that resulted from further coupling.

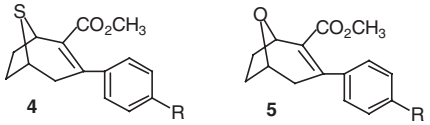
3. Biology

The affinities (IC_{50}) of the 8-thiatropenes for the dopamine (hDAT) and serotonin (hSERT) transporters were determined in competition studies using [^{3}H]-3β-(4-fluorophenyl)tropane-2β-carboxylic acid methyl ester ([^{3}H]WIN 35,428 or [^{3}H]CFT) to label the dopamine transporter and [^{3}H] citalopram to label the serotonin transporter.[28] Competition studies were conducted with a fixed concentration of radioligand and a range of concentrations of the test drug. All drugs inhibited [^{3}H]WIN 35,428 and [^{3}H] citalopram binding in a concentration-dependent manner. Binding constants are presented in Table 1.

4. Discussion

The 2,3-unsaturated bicyclo[3.2.1]oct-2-ene system is of considerable interest with respect to the design of DAT selective inhibitors that might provide leads toward the design of medications for cocaine abuse. This is so because data obtained for the 8-aza, 8-oxa, and 8-carba analogs have shown that these 'flattened' bicyclooctenes are generally more selective than their fully saturated counterparts.[29] Furthermore, these 2,3-enes

Table 1. Inhibition of [^{3}H]WIN 35,428 binding to the human dopamine transporter (hDAT) and [3H]citalopram binding to the human serotonin transporter (hSERT)[a]



R	Compd	Compd #	IC_{50} (nM)		SERT/DAT[b]	Compd[d]	Compd #	IC_{50} (nM)		SERT/DAT[b]
			DAT[c]	SERT[c]				DAT	SERT	
H	**4a**	O-2682	910	>10 μM	>11	**5a**	O-1141	>10 μM	>10 μM	—
F	**4b**	O-2643	220	28 μM	130	**5b**	O-1132	2730	>50 μM	>18
Cl	**4c**	O-2683	13	>10 μM	>770	**5c**	O-1134	238	>60 μM	>250
Br	**4d**	O-2752	9.1	>25 μM	>2500	**5d**	O-1155	62	>30 μM	>480
I	**4e**	O-2838	6.7	8.7 μM	1300	**5e**	O-1165	68	4.8 μM	71
3,4-Cl_2	**4f**	O-2642	4.5	3.6 μM	800	**5f**	O-1014	12	1.9 μM	159
2-Naphthyl[e]	**4g**	O-2795	8.0	1.3 μM	173	**5g**	O-1140	20	0.70 μM	36

[a] Compounds are racemic. Each value is the mean of two or more independent experiments each conducted in triplicate.
[b] Preference for DAT inhibition over SERT inhibition.
[c] DAT = dopamine transporter [^{3}H]WIN 35,428; SERT = serotonin transporter [3H]citalopram.
[d] Data taken from Ref. 29.
[e] 2-Carbomethoxy-3-(2-naphthyl)-8-thiabicyclo[3.2.1]-2-octene.

can be obtained readily and in high yield. Therefore the extension of this field to include 8-thia compounds was considered important, especially since it was anticipated that these compounds that now possess a larger 8-heteroatom, incapable of both hydrogen bonding or ionic bonding, and lending additional chirality upon S oxidation, may reveal attractive SAR, and may throw additional light on the interaction of tropane-like ligands with both the DAT and SERT. Indeed, this has proven to be the case.

8-Thiatropanes are potent inhibitors of the DAT (Table 1). Even the unsubstituted phenyl analog **4a** provided sub-micromolar affinity at the DAT. Noting that the potency (IC_{50}) of cocaine for inhibiting [^{3}H]WIN 34,428 binding sites at the DAT is about 100 nM, it is apparent that the thia analogs are well within a therapeutic range for competition with cocaine and modulation of DAT function. The compounds selected for evaluation in this study parallel those that have been previously examined in our laboratories (8-oxa compounds **5** are presented in Table 1 for purposes of comparison). In this 8-S series, as well as in the aza series,[17] affinity for the DAT increases significantly as a function of the size of a halogen positioned on the aromatic ring. Thus, the 4-F compound, with an affinity of 220 nM, is similar to cocaine. Introduction of a 4-chlorine (**4c**) or 4-bromine (**4d**) increased potencies by 17- and 24-fold, respectively (IC_{50}: 13, 9.1 nM), and the 4-iodo manifests an IC_{50} = 6.7 nM. As with all other 8-heterotropanes (aza, oxa, carba),[8] the 3,4-dichlorophenyl substituent provides a compound (**4f**) with the highest potency in this series, with an IC_{50} = 4.5 nM. For comparison, the 8-aza counterpart of this compound, O-1109 (1*R*-enantiomer), has an IC_{50} = 1.2 nM.[29] These values are similar, considering that **4f** is racemic and potency is anticipated[16] to reside primarily with the 1*R*-enantiomer. In comparison with the 8-oxa compounds (Table 1), the 8-thia compounds manifest an identical rank order of potency, but in contrast they are more potent than their 8-oxa counterparts. As an example, the 3,4-dichlorophenyl-8-thia compound **4f** is about 3-fold more potent than **5f**, while the 8-thia 4-Cl, 4-Br, and 4-I compounds are an order of magnitude, or more, potent than their 8-oxa counterparts.

In parallel with their 8-oxa analogs, the 8-thia analogs have micromolar affinities for the SERT, with higher affinities manifested by the dichlorophenyl analogs (**4f** and **5f**) of both series. Lipophilicity confounded exact quantification of SERT affinities, as the vehicle concentration needed to dissolve the compounds was high. However compound **4d**, as an example, manifests a DAT versus SERT selectivity greater than 2500-fold and consequently is one of the most selective DAT inhibitors (compared with the SERT) that we have generated.

5. Conclusion

Biological evaluation of a series of 8-thiabicyclo[3.2.1]oct-2-enes reveals the feasibility of designing potent inhibitors of [^{3}H]WIN 35,428 binding to the dopamine transporter, with low activity at [^{3}H]citalopram binding sites on the SERT. Their unique structures and high DAT:SERT selectivity provide new approaches for the design of potential medications for cocaine abuse. It remains to be seen whether the pharmacokinetic profile of these compounds will correspond to the long held view of advantageous properties for a cocaine medication—slow onset and long duration of activity. Exploration of the biological effects of reducing the 2,3-double bond is ongoing in our laboratories.

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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.2004.09.080. Synthetic procedures, spectral data, and biological assays are provided.

References and notes

1. Kennedy, L. T.; Hanbauer, I. *J. Neurochem.* **1983**, *34*, 1137.
2. Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. *Science* **1987**, *237*, 1219.
3. Kuhar, M. J.; Ritz, M. C.; Boja, J. W. *Trends Neurosci.* **1991**, *14*, 299.
4. Rothman, R. B.; Mele, A.; Reid, A. A.; Akunne, H. C.; Greig, N.; Thurkauf, A.; deCosta, B. R.; Rice, K. C.; Pert, A. *Pharmacol. Biochem. Behav.* **1991**, *40*, 387.
5. Spealman, R. D. *Psychopharmacology* **1993**, *112*, 93.
6. Rocha, B. A.; Fumagalli, F.; Gainetdinov, R. R.; Jones, S. R.; Ator, R.; Giros, B.; Miller, G. W.; Caron, M. G. *Nat. Neurosci.* **1998**, *1*(2), 132.
7. Carroll, F. I.; Lewin, A. H.; Kuhar, M. J. *Med. Chem. Res.* **1998**, *8*, 59.
8. Meltzer, P. C.; Blundell, P.; Madras, B. K. *Med. Chem. Res.* **1998**, *8*, 12.
9. Tamagnan, G.; Baldwin, R. M.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1783.
10. Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. *J. Med. Chem.* **1994**, *37*, 3875.
11. Lomenzo, S. A.; Izenwasser, S.; Katz, J. L.; Terry, P. D.; Zhu, N.; Klein, C. L.; Trudell, M. L. *J. Med. Chem.* **1997**, *40*, 4406.
12. Newman, A. H.; Kulkarni, S. S. *Med. Res. Rev.* **2002**, *22*, 429.
13. Newman, A. H. *Med. Chem. Res.* **1998**, *8*, 1.
14. Kozikowski, A. P.; Saiah, M. K. E.; Bergmann, J. S.; Johnson, K. M. *J. Med. Chem.* **1994**, *37*, 3440.
15. Singh, S. *Chem. Rev.* **2000**, *100*, 925.
16. Meltzer, P. C.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Chen, Z.; George, C.; Madras, B. K. *J. Med. Chem.* **1997**, *40*, 2661.
17. Madras, B. K.; Pristupa, Z. B.; Niznik, H. B.; Liang, A. Y.; Blundell, P.; Gonzalez, M. D.; Meltzer, P. C. *Synapse* **1996**, *24*, 340.

18. Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 2719.
19. Carroll, F. I.; Abraham, P.; Lewin, A.; Parham, K. A.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 2497.
20. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.
21. Froimowitz, M.; Wu, K.-M.; Moussa, A.; Haidar, R. M.; Jurayj, J.; George, C.; Gardner, E. L. *J. Med. Chem.* **2000**, *43*, 4981.
22. Meltzer, P. C.; Blundell, P.; Chen, Z.; Yong, Y.; Madras, B. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 857.
23. Madras, B. K.; Fahey, M. A.; Miller, G. M.; De La Garza, R.; Goulet, M.; Spealman, R. D.; Meltzer, P. C.; George, S. R.; O'Dowd, B. F.; Bonab, A. A.; Livni, E.; Fischman, A. J. *Eur. J. Pharmacol.* **2003**, *479*, 41.
24. Meltzer, P. C.; Blundell, P.; Yong, Y. F.; Chen, Z.; George, C.; Gonzalez, M. D.; Madras, B. K. *J. Med. Chem.* **2000**, *43*, 2982.
25. Parr, A. J.; Walton, N. J.; Bensalem, S.; McCabe, P. H.; Routledge, W. *Phytochemistry* **1991**, *30*, 2607.
26. Majewski, M.; DeCaire, M.; Nowak, P.; Wang, F. *Synlett* **2000**, 1321.
27. Majewski, M.; DeCaire, M.; Nowak, P.; Wang, F. *Can. J. Chem.* **2001**, *79*, 1792.
28. Goulet, M.; Miller, G. M.; Bendor, J.; Liu, S.; Meltzer, P. C.; Madras, B. K. *Synapse* **2001**, *42*, 129.
29. Meltzer, P. C.; Blundell, P.; Huang, H.; Liu, S.; Yong, Y. F.; Madras, B. K. *Bioorg. Med. Chem.* **2000**, *8*, 581.