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Synthesis and Monoamine Transporter Affinity of 3β-(4-(2-Pyrrolyl)phenyl)-8-azabicyclo[3.2.1]octanes and 3β-(5-Indolyl)-8-azabicyclo[3.2.1]octanes

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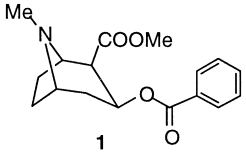
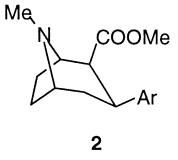
Abstract—3β-(5-Indolyl)-8-azabicyclo[3.2.1]octanes display potent binding affinity for both the dopamine and serotonin transporters, while certain 3β-(4-(2-pyrrolyl)phenyl)-8-azabicyclo[3.2.1]octanes selectively bind to the serotonin transporter.

Introduction

Although the biological actions of cocaine (**1**) are thought to occur primarily through inhibition of dopamine (DA) uptake, cocaine also has moderately high binding affinity to serotonin (5-HT) and norepinephrine (NE) transporters.[1] It has been postulated that a long acting agonist with appropriate binding selectivity for the monoamine transporters may have therapeutic potential for the treatment of cocaine addiction.[2–4] Consequently, there has been considerable interest in the synthesis and biological evaluation of related analogues with defined selectivities at each of these three transport sites.[5–7] A class of compounds that have been actively studied are the 3β-aryl-8-azabicyclo[3.2.1]octane-2β-carboxylates (**2**), which are prepared from cocaine. The early analogues that were prepared were selective for binding to the dopamine transporter or relatively unselective.[6]

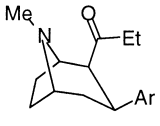


1



2

We have developed a new synthetic approach to tropanes[8,9] that allows elaborate 3β-aryl functionality to be directly introduced onto the tropane.[10–12] This approach has allowed us to prepare various 2β-acyl-3β-aryl-8-azabicyclo[3.2.1]octanes (**3**) and to explore their structure–activity relationships with particular emphasis on their binding affinities to both the DA and 5-HT transport sites. The *p*-tolyl derivative **3a** represents the prototypical member of the class of tropanes that can be derived from this chemistry and has undergone extensive biological evaluation.[11,13–18] During the course of these studies it was discovered that introduction of a 2-naphthyl derivative at the 3β position as in **3b** resulted in one of the most potent tropane analogues.[11,13–15] Furthermore, introduction of bulky aryl substituents as seen with the 4-isopropyl phenyl derivative **3c** resulted in analogues that were quite selective for the 5-HT transporter.[11,13] Another approach that leads to tropanes with increased 5-HT selectivity has been the use of *N*-demethylated derivatives.[19] Since then, more selective compounds to the 5-HT transporter have been prepared by incorporating 4-ispropenyl,[12,20] 4-(4″-substituted biphenyl)[21] and 3,4-disubstitution[22] onto the 3β-aryl ring, as well as by using conformationally restricted tropanes.[23,24] In this paper, the synthesis and binding affinity is described of 3β-(4-(2-pyrrolyl)phenyl) and 3β-(5-indolyl) tropanes, some of which display excellent selectivity for the 5-HT transporter.



	Ar
3a	4-MeC_6H_4
3b	2-naphthyl
3c	4-^{i}Pr-C_6H_4

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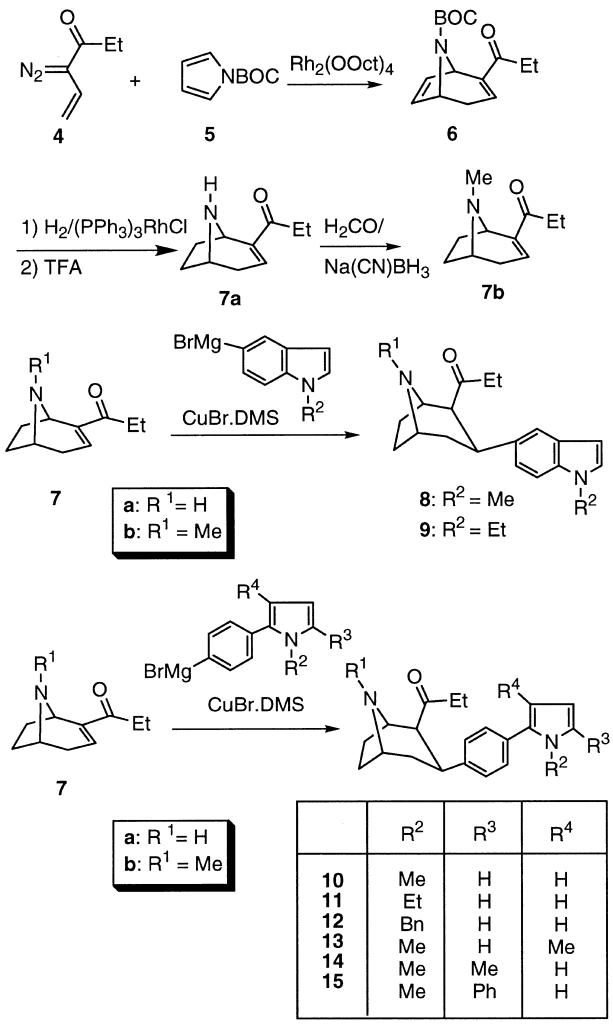
Chemistry

The general strategy for the synthesis of tropane derivatives is summarized in Scheme 1.[8,9] The flexible approach to the tropane skeleton that we have developed is based on the rhodium(II) octanoate catalyzed decomposition of the vinyldiazomethane **4** in the presence of *N*-BOC pyrrole (**5**).[8] Selective hydrogenation and deprotection of **6** resulted in the N-H derivative **7a**, which was readily methylated to produce **7b**. The synthesis of the aryl derivatives was achieved by a copper catalyzed 1,4-addition of the appropriate Grignard reagent to either **7a** or **7b**.[11,25] A major advantage of this approach is that elaborate aryl Grignard reagents can be used for the 1,4-addition to the α,β-unsaturated ketone in **7a** and **7b**, as this was not the case for the synthesis of the ester derivatives **2** derived from cocaine.

Pharmacology

Binding of the tropane analogues **8**–**15** to DA transporters in rat striatum, and to 5-HT transporters in rat frontal cortex, was determined as previously described.[12,26] The results are summarized in Table 1. The indolyl derivatives



	R^2	R^3	R^4
10	Me	H	H
11	Et	H	H
12	Bn	H	H
13	Me	H	Me
14	Me	Me	H
15	Me	Ph	H

Scheme 1. Synthesis of tropane analogues.

Table 1. IC_{50} and K_i values of tropane analogues in displacing [^{125}I]RTI-55 binding in rat striatal membranes and [^{3}H]paroxetine binding in rat frontal cortex membranes

Compd	Dopamine IC_{50} (nm)	5-HT K_i (nm)	5HT/DA potency ratio
8a	2.73 ± 1.16	1.74 ± 0.63	1.57
8b	0.75 ± 0.10	2.84 ± 0.25	0.26
9a	2.37 ± 0.58	3.04 ± 1.36	0.78
9b	1.20 ± 0.51	5.54 ± 1.79	0.22
10a	614 ± 98	1.05 ± 0.18	585
10b	703 ± 222	25.6 ± 4.08	27.4
11a	>1000	15.7 ± 2.50	>63.7
11b	>1000	337 ± 82.6	>2.97
12a	32.2 ± 5.65	6.36 ± 1.01	5.06
12b	58.0 ± 4.46	59.2 ± 3.87	0.98
13a	1472 ± 107	48.8 ± 8.80	30.2
13b	>1000	>1000	—
14a	825 ± 53.6	49.1 ± 10.9	16.8
15a	>1000	112 ± 18.2	>8.93

(**8a**, **8b**, **9a** and **9b**) displayed high binding affinities to both the DA and 5-HT transporters (0.7–5.5 nM). Thus, they have similar structure–activity characteristics to the 2-naphthyl analogues, which tend to be very potent but unselective.[11]

In contrast, some of the 4-(2-pyrrolyl)phenyl derivatives displayed considerable selectivity for the 5-HT transporter. Most notable is the *N*-demethylated derivative **10a** with binding affinities of 1.05 nM at the 5-HT transporter and 614 nM at the DA transporter. Compound **10a** also has very low binding affinity to the norepinephrine transporter (K_i >10,000 nM),[27] making it highly selective for the 5-HT transporter. As previously observed with other tropanes, *N*-demethylation generally results in increased 5-HT binding affinity but has virtually no effect on the DA transporter binding affinity. Increasing the size of the *N*-substituent on the pyrrole from methyl to ethyl causes a decrease in binding affinity to both transporters although the overall 5-HT selectivity is retained. A similar effect occurs from incorporating an alkyl functionality at C-3 or C-5 of the pyrrole. Introduction of an aryl ring on the pyrrole, either as an *N*-benzyl group or a C-5 phenyl group results in diminished binding affinity and selectivity.

These results demonstrate that steric factors are important in differentiating binding to the DA and 5-HT transporters, and suggest that the 5-HT transporter has a larger hydrophobic binding pocket than the DA transporter. These results are in agreement with the binding trends that were observed for 3β-(4-alkenyl)-phenyl substituted tropanes.[12,20] Electronic factors, however, may also have a role in transporter differentiation, as was seen in the 3β-(biphenyl) substituted tropanes.[21]

Acknowledgements

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25. General experimental conditions for 1,4-addition: The arylmagnesium bromide was generated as follows: A portion (10%) of the bromide (1.0 equiv) in THF was added to magnesium turnings (1.1 equiv). Two drops of dibromoethane were added and the reaction was initiated by heating. Once the reaction was started, the remaining bromide was added dropwise. The mixture was refluxed for 3 h after the addition and then cooled to room temperature. The arylmagnesium bromide (4.5 equiv for **7a** or 3.5 equiv for **7b**) in THF was added to thoroughly dried copper bromide–dimethyl sulfide complex (0.74 equiv for **7a** and 0.70 equiv for **7b**). The mixture was stirred at room temperature for 20 min and then cooled to 0 °C. A solution of **7a** or **7b** (1.0 equiv) in dry THF was added dropwise. The ice bath was left in place and stirring was continued overnight. The solution was cooled to −78 °C and a solution of 1M HCl in dry ether (13.5 equiv for **7a** or 10.5 equiv for **7b**) was added in such a way that the temperature was kept below −70 °C at all times. The reaction mixture was warmed to room temperature and then extracted with 10% HCl solution (3×). The aqueous layer was made basic with concentrated NH_4OH, extracted with CH_2Cl_2 (3×), dried (Na_2SO_4), and then concentrated under reduced pressure. Purification by chromatography on silica gel with ether/Et_3N (7:1) as solvent gave the pure amine. Tropanes **8**–**15** were formed in yields of 16–65%.
26. K_i and IC_{50} values in binding assays were calculated from displacement curves using 7–10 concentrations of unlabeled analogues. All data are mean values ± S.E.M. of at least three separate experiments, each of which was conducted in triplicate. Potencies of all analogues in displacing [^{125}I]RTI-55 binding are expressed as IC_{50} values because the biphasic nature of radiolabeled tropane binding to striatal membranes makes determination of accurate K_i values difficult. However, potencies of analogues in displacing [^{3}H]paroxetine binding are expressed as K_i values, as calculated by the method of Cheng and Prusoff using a K_d value of 0.15 nM for [^{3}H]paroxetine binding. For a detailed description, see refs 11 and 12.
27. Binding of analogues at norepinephrine transport sites was determined by displacement of [^{3}H]nisoxetine binding in membranes from rat forebrain, using 0.7 nM [^{3}H]nisoxetine. Nonspecific binding was determined in the presence of 1 μM desipramine. For a detailed description, see ref 12.