Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 297–300

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Design, Synthesis and Biological Evaluation of 7-Azatricyclodecanes: Analogues of Cocaine

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Received 29 October 1999; accepted 6 December 1999

Abstract—The synthesis and biological activity of a series of azatricyclodecane analogues of cocaine are described. All compounds studied in this series exhibit nanomolar potency and good selectivity for the serotonin transporter versus the dopamine transporter.

The ability of cocaine to bind at the dopamine transporter (DAT) and to inhibit the reuptake of dopamine (DA) has been implicated in the reinforcing properties of this drug.[1] While cocaine self-administration appears to be best correlated with its activity at the DAT, cocaine is also a potent inhibitor of the serotonin (SERT) and norepinephrine (NET) transporters. In fact, serotonergic systems have been implicated in compulsive cocaine seeking behavior (craving), and 5-HT-based agents have been investigated as possible medications for the treatment of cocaine abuse.[2] To date, a number of potent cocaine analogues have been synthesized in order to better understand the pharmacological properties of this drug.[3] However, the precise binding interaction of these analogues with specific monoamine transporters has been a matter of much discussion.[4,5] Nevertheless, transporter specificity has been exploited in order to identify a number of transporter selective inhibitors as therapeutics for the treatment of several neurological disorders including depression[6–9] and Parkinson's disease.[10]

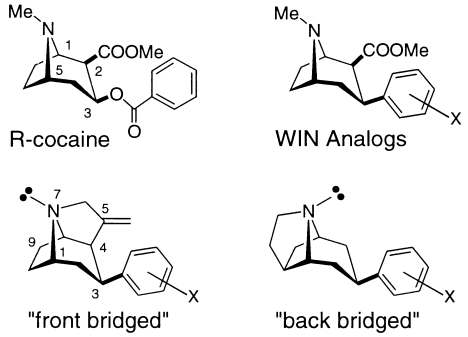

Figure 1.

We have reported recently 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.[11,12] In this work, we demonstrated that the selectivity of these rigid tropane analogues for the monoamine transporters inhibitors was influenced by the orientation of the nitrogen lone pair. Tropane based compounds with the nitrogen lone pair localized over the 2-carbon bridge of the tropane ring (front-bridged) exhibit improved potency and selectivity for the SERT (Fig. 1). We now describe a facile synthesis of the tricyclic intermediates **11** and **12** (Scheme 1) bearing the tether to the 2β-position of the tropane moiety. As is disclosed herein, such compounds can be readily synthesized in enantiomerically pure form starting from (−)-cocaine as the chiral edduct. Data are provided that reveal these analogues to possess good levels of affinity and selectivity for the SERT (Table 1).

Chemistry

Tricyclic compounds **13–17** were synthesized as depicted in Scheme 1. Tropanes **3–6** were prepared using known literature procedures.[14] *N*-demethylation of **3** and **4** was accomplished in two steps by treatment with ACE chloride in dichloroethane[15] in the presence of proton sponge (1.5 mol equiv), followed by methanolysis of the

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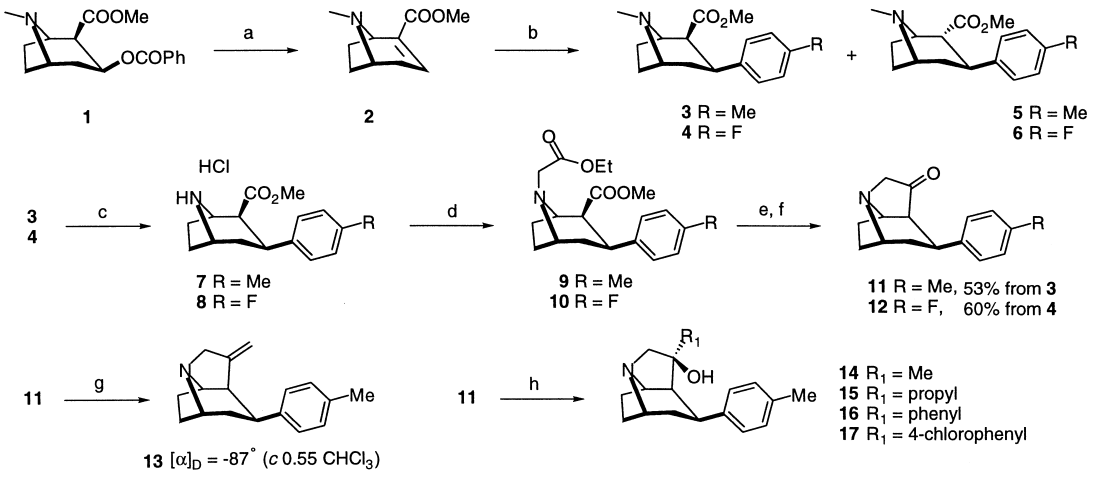
PII: S0960-894X(99)00685-X



Scheme 1. Reagents and conditions: (a) HCl (2 M), reflux; $POCl_3$, reflux; MeOH, −40 °C; (b) 4-RPhMgBr, $(C_2H_5)_2O$, −40 °C; TFA, −78 °C; (c) $CH_3CH(Cl)OCOCl$,1,2-dichloroethane, 1,8-bis-(dimethylamino)naphthalene, reflux; MeOH, reflux; (d) ethyl bromoacetate, K_2CO_3, EtOH; (e) NaH, toluene, 130 °C; (f) aq HCl (10%), reflux; (g) $Ph_3^+MeBr^-$, *n*-BuLi, THF; (h) R_1MgBr, CH_2Cl_2, 0 °C.

resulting carbamate intermediate to afford **7** and **8** in nearly quantitative yields. The resulting tropanes **7** and **8** were then alkylated using ethyl bromoacetate in EtOH to give the corresponding diesters **9** and **10**, respectively (>60% yield). Treatment of the diesters **9** and **10** with NaH in refluxing toluene gave the ester intermediates (structure not shown), which were reacted without further purification with aq HCl (10%) to give ketones **11** and **12**, respectively, in excellent yields.[16] Reaction of the ketone **11** with methylenetriphenylphosphorane gave tropane **13**.[12] Reaction of the ketone **11** with commercially available alkyl or phenyl Grignard reagents in CH_2Cl_2 gave tropanes **14**–**17**. Tropanes **14**–**17** were purified by column chromatography and isolated as the oxalate salts. The relative stereochemistry of the isolated products was assigned by NMR methods.[17] For steric reasons, the R_1 group is believed to have added to the less encumbered convex face of the caged ketone **11**.

Structure–Activity Relationships

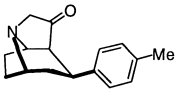
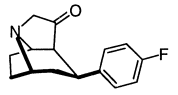
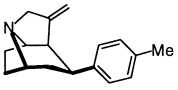
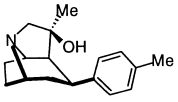
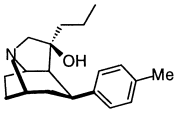
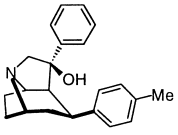
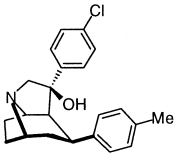
All final compounds were tested by the Cocaine Treatment Discover Program (CTDP) of the National Institute of Drug Abuse (NIDA) for their effects on [^{3}H]DA, [^{3}H]NE, and [^{3}H]5-HT uptake in HEK cells expressing cDNA for the human dopamine, norepinephrine, and serotonin transporters.[18] The transporter activity and selectivity are provided in Table 1. All of the compounds tested in this series generally exhibit a greater potency for inhibition of the SERT compared to their ability to inhibit the DAT. In two cases (**13** and **15**), the activity at the NET is better than that measured at the SERT. While the methylene bearing tricycle **13** is more potent than the ketone **11** from which it was derived, it shows poorer selectivity for the SERT in comparison to the DAT.

With the exception of compound **14**, the alcohols **15**–**17** exhibit reasonably good SERT potency (IC_{50} < 50 nM). Alcohols **15**–**17** are more potent at all three transporters than the ketone **11** from which they were derived. By simply extending the alkyl appendage of **14** by two carbon atoms to give **15**, an improvement in the SERT potency of approximately 4-fold is found, while the DAT activity remains about the same. Introduction of the more hydrophobic phenyl substituents as in analogues **16** and **17** leads to a further enhancement in both the DAT and SERT activity, while the NET activity of **15**–**17** are roughly comparable. It is also noteworthy to point out that the introduction of the chlorine atom in **17** slightly improves potency at the DAT while decreasing activity at the NET and SERT in comparison to the activity found for **16**.

We further call attention to the 5-HT/DA transporter selectivity profiles exhibited by the front-bridged tropane **15** in comparison to the back-bridged tropane **18**.[11,13] The noted 5-HT selectivity of **15** is presumably the result of the stereochemistry of the nitrogen lone pair, with the SERT exhibiting preference for the front bridge. By fixing the direction of the nitrogen lone pair in the opposite direction as in **18**, the tropane shows selectivity for the DAT. The preference of front-bridged tropanes for the SERT is thus not altered by the presence of the sp^3 center bearing a hydroxyl group (Fig. 2).

In conclusion, a facile synthetic pathway for the construction of 7-azatricyclodecanones is reported. The chemistry allows for rapid access to cocaine analogues with a spatially defined nitrogen lone pair. The intermediate 7-azatricyclodecanones are readily functionalized using standard chemical transformations to prepare a novel series of compounds with combined SERT + NET selectivity, and with potencies of <50 nM. The present work thus broadens the scope of structures that can be used to better understand the structural motifs required to achieve potency and selectivity at specific monoamine transporters.

Table 1. IC_{50} values for the inhibition of monoamine uptake at the respective transporters (nM)[a]

Compd no.	Structure	[^{3}H]DA uptake	[^{3}H]NE uptake	[^{3}H]5-HT uptake	5-HT/DA	5-HT/DA
Cocaine	—	301 ± 50	186 ± 225	413 ± 81	1.4	2.2
11		538 ± 47	110 ± 28	68 ± 9.9	0.13	0.62
12		3320 ± 840	620 ± 250	251 ± 38	0.076	0.4
13[b]		67 ± 15	2.2 ± 0.3	33 ± 4.9	0.49	15
14		390 ± 180	296 ± 59	147 ± 38	0.38	0.5
15		373 ± 73	18 ± 2.4	41 ± 9.5	0.11	2.3
16		89 ± 36	11 ± 4.5	7.9 ± 1.0	0.09	0.72
17		44 ± 8.0	23 ± 5.7	13 ± 1.2	0.3	0.57

[a]Numbers represetnt the mean ± SEM from at least three independent experiments, each conducted with at least two determinations.
[b]See ref 13.

Figure 2.

Acknowledgement

We are indebted to the NIH, National Institute on Drug Abuse (DA10458) for support of this work.

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