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An Enantioselective Synthesis and Biobehavioral Evaluation of 7-Fluoro-3-(*p*-fluorophenyl)-2-propyltropanes

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Abstract—Optically pure 7-fluorotropanes **3a–c**, were synthesized as structural probes of the dopamine transporter. The synthesis of these compounds was accomplished through the asymmetric 1,3-dipolar cycloaddition reaction of the oxidopyridinium betaine **4** with the chiral dipolarophile (*R*)-*p*-tolyl vinyl sulfoxide. In the preliminary analysis, tropane **3a** was found to reduce the rewarding effects of cocaine in the brain stimulation reward paradigm.

Cocaine abuse is a major health and social problem worldwide, and thus strategies are needed to solve this addiction problem.[1] The predominant theoretical explanation for cocaine's behavioral effects is the so-called 'dopamine hypothesis'.[2] According to this hypothesis, the reinforcing properties of cocaine are the direct result of inhibition of dopamine (DA) reuptake. Since the dopamine transporter (DAT) is the primary mechanism for the removal of DA from the synaptic cleft after its release,[3] inhibition of DA reuptake results in a buildup of DA, leading to significant potentiation of dopaminergic transmission. In addition to the DAT, cocaine also binds with high affinity to the serotonin (SERT) and the norepinephrine transporters (NET).[4] Recent findings suggest that both the SERT and the NET may also play prominent roles in cocaine addiction.[5] As such, we believe it to be of continued value to explore the effects of novel ligands that show varying levels of transporter selectivity in behavioral models, with the aim to better define the transporter profile(s) and ligand structures that may lead to useful medications.[6]

Previously, we have studied the synthesis and transporter activity of 3-aryltropanes with a substituent on the 2-carbon bridge, (i.e., the 6- and 7-substituted tropanes,[7]) and we have shown that such substitution generally leads to a loss in binding affinity compared to the 6- and 7-unsubstituted compounds. However, of some biological interest with respect to this 2-carbon bridge substituted series was our earlier finding that the methoxylated pseudococaine **2**, although showing poor binding affinity, was able to antagonize cocaine's ability to inhibit dopamine reuptake in a functional assay.[7a] Based upon this finding, together with preliminary work that revealed the ability of certain racemic, fluorinated tropane analogues to maintain good transporter activity, we now chose to investigate the chemistry and biology of the optically pure analogues **3a–c** (Fig. 1).

Chemistry

A variety of methods have now been detailed in the literature for the preparation of 6- and 7-substituted tropane analogues.[7] The synthetic strategies employed include a double Mannich reaction,[7a] a [3+2] cycloaddition reaction,[7c,7e–g] and the intramolecular cyclization of substituted aminocycloheptane derivatives.[7d]

The compounds required for the present study were conveniently prepared by use of our previously disclosed oxidopyridinium ion-based dipolar cycloaddition strategy. As detailed in the accompanying Scheme 1, the 1,3-dipolar cycloaddition[8] of betaine **4**[9] with (*R*)-*p*-tolyl vinyl sulfoxide was investigated.

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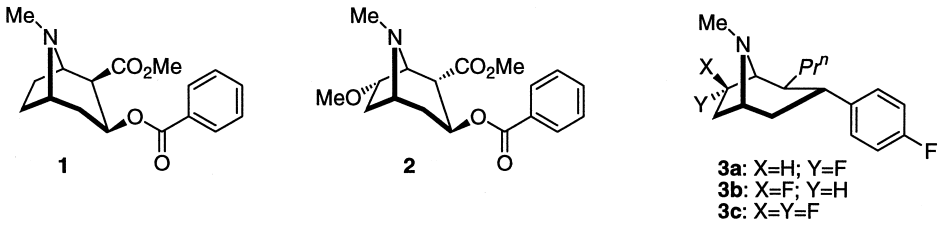
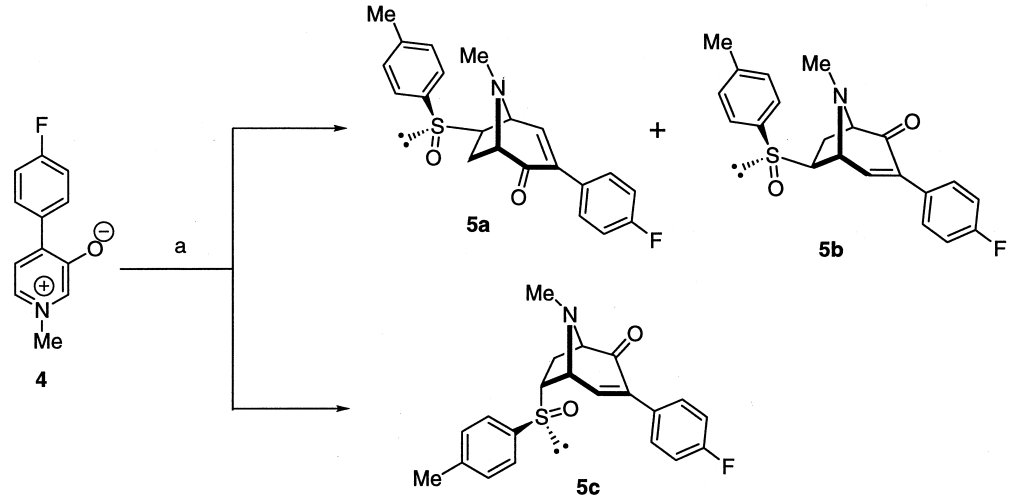


Figure 1.



Scheme 1. Reagents and conditions: (a) (*R*)-*p*-tolyl vinyl sulfoxide, dioxane, reflux, 24 h.

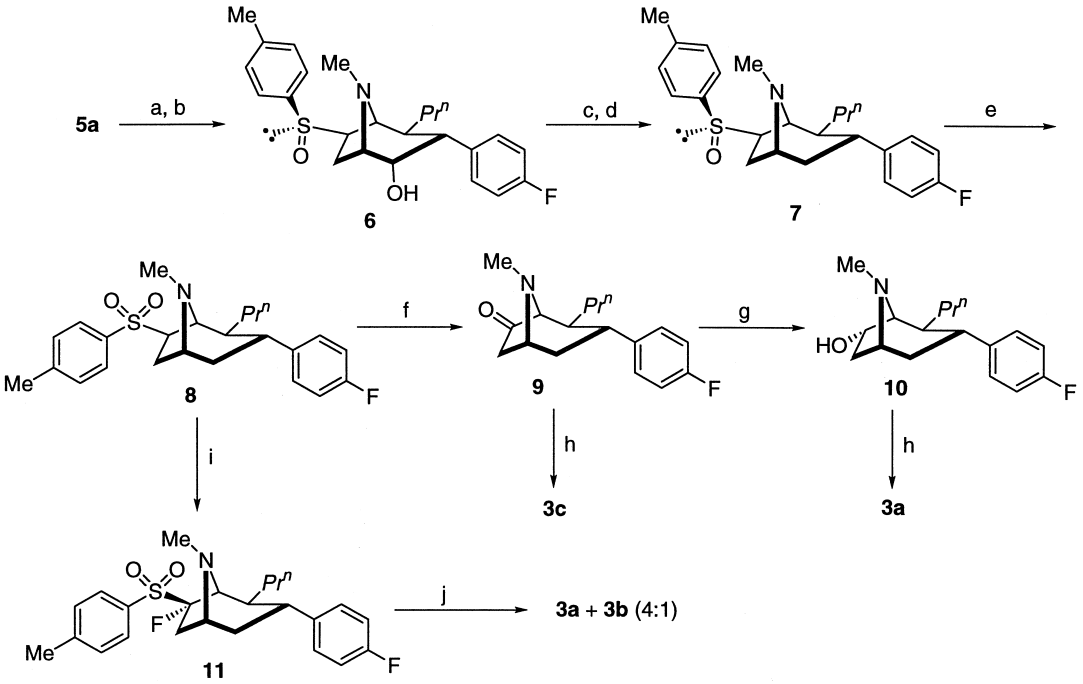
The required cycloaddition reaction was performed in dioxane at reflux for 24 h to give, with complete regioselectivity, a mixture of *exo* and *endo* cycloadducts in a 70:30 ratio. Silica gel flash column chromatography of the crude mixture led to the separation of the *exo* tropenones **5a** and **5b** (4:1 mixture of the diastereomers) from the *endo* tropenone **5c**. The major *exo* diastereomer **5a** was obtained in 45% yield by crystallization of the above mixture from EtOAc and had $[\alpha]_D^{25}$ −77° (*c* 1.25, $CHCl_3$) and mp 186 °C. The absolute configuration of **5a** was determined by comparing its NMR and optical rotation data with those of similar compounds previously reported.[8]

Copper catalyzed 1,4-addition of *n*-PrMgBr to tropenone **5a** in the presence of TMSCl and HMPA followed by reduction of the ketone thus obtained with $LiBH_4$ afforded the alcohol **6** exclusively (Scheme 2). Barton type deoxygenation[10] then gave the tropane **7** in 50% yield. Oxidation of the sulfoxide with MoOPH was not satisfactory (low yield), and to overcome this problem the sulfoxide **7** was oxidized to sulfone **8** using oxone as oxidizing agent.[11] The yields were not satisfactory with other oxidizing agents (*m*-CPBA, *t*-BuOOH, H_2O_2, etc.), whereas oxone gave an 87% yield. Compound **8** was further oxidized with MoOPH[12] to afford the ketone **9**, which was reduced in turn to alcohol **10** with DIBAL-H. The alcohol **10** was converted by treatment with DAST[13] exclusively to the α-fluoride **3a** as shown by comparison of its ^1H NMR spectrum with that of a known reference compound.[7b] While an S_N2 displacement should have given the β-fluoro compound, the observed outcome can be explained by the neighboring group participation of the ring nitrogen.

To prepare the β-fluoro compound **3b**, we used a two-step protocol which involved fluorination of the sulfone **8** followed by reductive desulfonylation. The fluorination was achieved by treating the sulfone with *n*-BuLi/*N*-fluorobenzenesulfonimide to afford the fluorosulfone **11** in 70% yield.[14] The structure was confirmed by comparing the NMR data with those of a similar compound reported earlier.[7b] The reductive desulfonylation[15] of **11** readily afforded the tropanes **3a** and **3b** in a 4:1 ratio. Treatment of the ketone **9** with DAST[13] gave the 7,7-difluorotropane **3c** in 50% yield.[16]

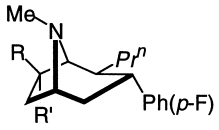
Pharmacological and Behavioral Studies

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.[17] This ligand binds with high affinity ($K_d = 8.63 \pm 0.53$ nM) to a single, sodium-dependent site on the dopamine carrier in striatal membranes. Additionally, these compounds were tested for their ability to inhibit high-affinity uptake of [^{3}H]DA, [^{3}H]NE, and [^{3}H]5-HT into striatal, parietal and occipital cortex, and midbrain nerve endings (synaptosomes), respectively.[18] The binding and uptake data are provided in Table 1 along with comparison data for cocaine.



Scheme 2. Reagents and conditions: (a) *n*-PrMgBr, CuBr·Me_2S, TMSCl, HMPA, THF, −78 °C; (b) $LiBH_4$, THF, rt; (c) *n*-BuLi, THF, then PhOC(S)Cl, −78 °C; (d) *n*-Bu_3SnH, AIBN, toluene, 60 °C; (e) oxone, MeOH/H_2O (2:1), rt; (f) *n*-BuLi, MoOPH, THF, −78 °C; (g) DIBAL-H, CH_2Cl_2, 0 °C; (h) DAST, CH_2Cl_2, rt; (i) *n*-BuLi, *N*-fluorobenzenesulfonimide, THF, −78 °C to rt; (j) 6% Na(Hg), Na_2HPO_4, MeOH, rt.

Table 1. K_i values (nM) for the tropane analogues in mazindol binding and dopamine, serotonin and norepinephrine reuptake experiments



Compound	R	R′	[^{3}H]mazindol binding	[^{3}H]DA uptake	[^{3}H]5-HT uptake	[^{3}H]NE uptake
Cocaine			280 ± 16	420 ± 150	160 ± 1	108 ± 4
3a	H	F	30 ± 1	49 ± 7	561 ± 32	52 ± 1
3b	F	H	1150 ± 50	304 ± 1	1250 ± 40	126 ± 13
3c	F	F	860 ± 60	1450 ± 50	7910 ± 70	3790 ± 100

Pharmacological experiments revealed **3a** to be the most DAT-potent of the three fluorinated analogues presented here, inhibiting mazindol binding with a K_i of 30.0 nM and dopamine reuptake with a K_i of 49.0 nM, as compared to 280 and 420 nM for (−)-cocaine. Analogues **3b** and **3c** were less active, showing affinities of 1150 and 860 nM in mazindol binding and K_is of 304 and 1450 nM in the dopamine reuptake studies, respectively. The parent compound lacking substitution on the 2-carbon bridge showed an affinity of 21.1 nM in the mazindol binding studies and a K_i of 12.1 nM in the DA reuptake studies.[19] As is also apparent from Table 1, **3a**–**3c** show poor SERT activity, while the NET potency of **3a** is comparable to its DAT potency.

The more active analogue **3a** was evaluated in the brain stimulation reward paradigm, a behavioral assay that allows the measurement of the intrinsic hedonic properties of compounds separately from the concomitant changes in the rate of responding. Male rats were implanted with unipolar electrodes into the lateral hypothalamus and trained to bar press for electrical stimulation of that structure, as described previously.[20,21] The data, obtained under the baseline and drug conditions, were compared and two variables were analyzed: (1) The maximum response rate, which reflects the motor/performance capacity. (2) The frequency of stimulation necessary to sustain half-maximal rate of responding, a measure reflecting reward threshold. Cocaine (as little as 10 mg/kg) is well known to enhance reward, by lowering the reward threshold necessary to maintain baseline responding and to increase motor/performance capacity (especially at medium to high doses, 15–30 mg/kg). Preliminary results have shown that unlike cocaine, **3a** is hedonically neutral when administered alone, with a slight increase in reward at 20 mg/kg (intraperitoneally, IP), the highest dose tested to date. However, when 5 mg/kg or 10 mg/kg IP of this derivative were combined with 10 mg/kg cocaine (IP), an approximate 60% reduction in cocaine-induced reward enhancement was noted. No changes in motor/performance capacity were observed, either when the derivative was administered alone or in combination

with cocaine. These findings suggest that **3a** may constitute a promising new lead compound that could be effective in reducing cocaine's reinforcing properties. Although the lack of affinity of **3a** for SERT may render it incapable of producing complete cocaine-like reinforcing effects, the mechanism for its antagonistic activity is uncertain.

In conclusion, synthetic pathways for the construction of cocaine analogues bearing one or two fluorine atoms at position 7 of the tropane ring together with their activity at the DAT are disclosed. While all three compounds are less potent than their unsubstituted counterpart, compound **3a** still retains considerable DAT activity. However, of considerable interest is the finding that this analogue is capable of a causing a reduction in cocaine-induced reward enhancement.

Acknowledgements

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16. Compound **3c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J=6.9 Hz, 3H), 1.10–1.42 (m, 5H), 1.90–2.08 (m, 2H), 2.40 (m, 1H), 2.52 (s, 3H), 2.60–2.85 (m, 2H), 2.93 (d, J=14.1 Hz, 1H), 3.36 (t, J=8.4 Hz, 1H), 6.96 (t, J=8.5 Hz, 2H), 7.13 (dd, J=5.5, 8.3 Hz, 2H); MS m/z (%) 297 (M^+, 40), 268 (50), 254 (100), 132 (65).
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