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Synthesis and monoamine transporter affinity of front bridged tricyclic 3β-(4′-halo or 4′-methyl)phenyltropanes bearing methylene or carbomethoxymethylene on the bridge to the 2β-position

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Abstract—A series of front bridged tricyclic 3β-(4′-halo or 4′-methyl)phenyltropanes bearing methylene or carbomethoxymethylene on the bridge to the 2β-position was synthesized, and their binding affinities were determined in cells transfected to express human norepinephrine transporter (NET), serotonin transporter (SERT), and dopamine transporter (DAT) via competition binding assays. All compounds studied in this series exhibit a moderate to high potency at all three transporters with SERT or DAT selectivity. 3β-(4′-iodo)phenyltropane bearing methylene on the bridge to the 2β-position (**24**) presents a particularly attractive pharmacological profile, with very high SERT affinity (K_i = 0.09 nM) and selectivity versus NET (65-fold) and DAT (94-fold).

Cocaine (**1**, Fig. 1) elicits its behavioral and pharmacological effects by binding with moderate and roughly equal affinity to all three of the monoamine transporters (dopamine [DAT], serotonin [SERT], and norepinephrine [NET]).[1,2] In recent years, cocaine analogues have been extensively explored to develop compounds with defined selectivities at particular monoamine transport sites.[3–7] Such selectivity is useful in developing biochemical probes for behavioral studies and for transporter imaging.

Kozikowski et al. reported a structure–activity relationship study exploring the factors influencing the binding selectivity for 3β-tropane based ligands at specific monoamine transporters.[8] In this study Kozikowski and coworkers determined that rigidified tricyclic analogues bearing linkages from the nitrogen to the 2β-position and 7-position of the tropane moiety yielded analogues that showed low nanomolar uptake inhibition for the NET and higher selectivity for NET over DAT and SERT. A front bridged tricyclic analogue (**2**, Fig. 1) bearing a methylene and bearing a 3β-4′-methylphenyl substituent on the tropane moiety was found to show low nanomolar inhibition of monoamine uptake for the NET (IC_{50} = 2.2 nM vs (−)-[^{3}H]NE) and to be 30 and 15 times more selective for the NET than the DAT and SERT, respectively.[9] These findings prompted us to synthesize new front bridged tricyclic 3β-phenyltropane derivatives bearing methylene on the bridge to the 2β-position which may offer promise as potential NET imaging agents. Target molecules were designed and prepared to allow radiolabeling with ^{11}C, ^{76}Br, or ^{124}I for PET or ^{123}I for SPECT. Reported herein are the synthesis and in vitro monoamine transporter binding evaluation of several front bridged tricyclic tropanes bearing methylene or carbomethoxymethylene substituents on the bridge to the 2β-position and bearing 3β-(4′-halo-, 4′-methyl)phenyl substituents.

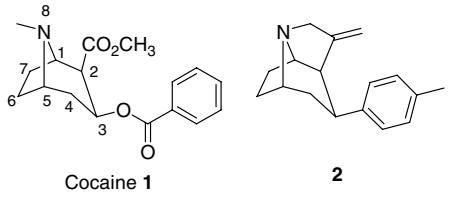

Figure 1.

Keywords: PET; NET; SERT; Tropane; Carbon-11.
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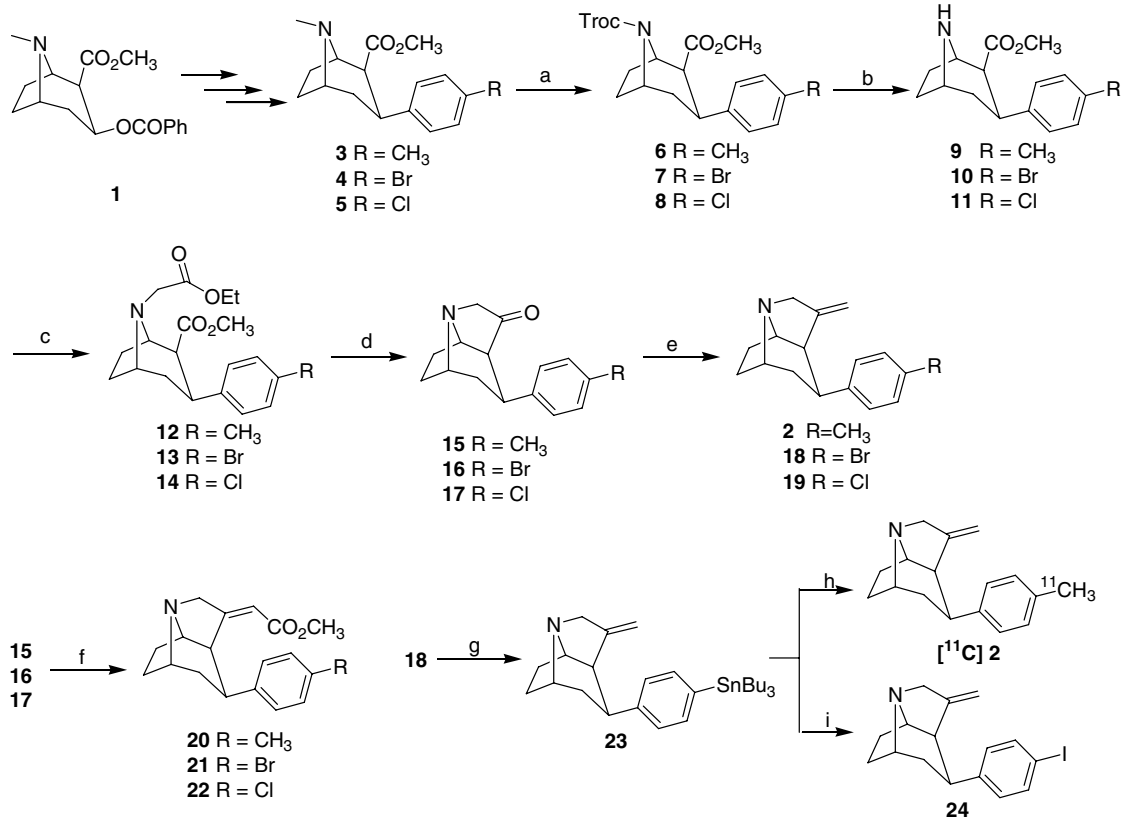

Scheme 1. Reagents and conditions: (a) Troc-Cl, toluene, reflux; (b) Zn dust, AcOH, H_2O, rt; (c) ethyl bromoacetate, EtOH, K_2CO_3, rt; (d) NaH, toluene, 130 °C; AcOH, 5 N HCl, reflux; (e) PPh_3CH_2Br, *n*-BuLi, THF, 37 °C; (f) methyl diethylphosphonoacetate, NaH, THF, 60 °C; (g) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene, 130 °C; (h) [^{11}C]CH_3I, $Pd_2(dba)_3$, (*o*-Tol)$_3$P, CuCl, K_2CO_3, DMF, 60 °C; (i) I_2, CH_2Cl_2, rt.

The synthesis of front bridged tricyclic tropanes was performed (as shown in Scheme 1) based on the procedure reported by Kozikowski with some modification.[9] Tropanes **3**–**5** were synthesized in three steps starting from cocaine (**1**) in good yield according to known literature procedures.[10] The conversion of **3**–**5** to its corresponding carbamate using trichloroethylchloroformate followed by Zn-acetic acid reduction gave the nortropane **9**–**11**, respectively. Alkylation of **9**–**11** using ethyl bromoacetate gave diesters **12**–**14**, which then underwent Dieckmann condensation (effected with NaH) followed by decarboxylative hydrolysis with HOAc and HCl at reflux to lead to the formation of tricyclic ketones **15**–**17**. Wittig reaction of **15**–**17** with methyltriphenylphosphonium bromide gave tropanes **2**, **18**, and **19**, bearing methylene substituent on the bridge to the 2β-position. Reaction of **15**–**17** with methyl diethylphosphonoacetate produced (*E*)-vinyl methyl esters **20**–**22** whose relative stereochemistry was assigned by NMR methods. Tributylstannyl tropane **23**, prepared by palladium-catalyzed coupling of **18** with bis(tributyl)tin, was used as the precursor for radiosynthesis of [^{11}C]**2**. Iodotropane **24** was prepared by halodestannylation of **23** with I_2.

The affinities of tropanes **2**, **18**–**22**, and **24** for the human NET, SERT, and DAT were determined through in vitro competition assays in transfected HEK-293 cells according to a previously reported procedure.[11]

The data shown in Table 1 indicate that all methylene bearing tricyclic tropanes **2**, **18**, **19**, and **24** display

Table 1. Transporter binding properties of front bridged tricyclic tropanes[a]

Compound	K_i for hNET	K_i for hSERT	K_i for hDAT
2	17.28 ± 2.36	7.77 ± 3.21	40.99 ± 4.05
18	2.94 ± 0.14	0.28 ± 0.01	41.92 ± 3.44
19	4.84 ± 0.14	0.82 ± 0.06	12.25 ± 3.17
24	5.87 ± 1.30	0.09 ± 0.02	8.48 ± 1.72
20	25.50 ± 2.83	98.31 ± 3.24	13.25 ± 1.68
21	12.53 ± 1.47	5.63 ± 1.42	2.94 ± 0.46
22	13.03 ± 2.65	18.75 ± 1.88	4.54 ± 0.83

[a] All K_i values are reported with nanomolar (nM) units. The data are expressed as means ± standard deviation of at least three separate experiments performed in triplicate. The following radiotracers were used: [^{3}H]nisoxetine for hNET, [^{3}H]citalopram for hSERT, and [^{125}I]RTI-55 for hDAT.

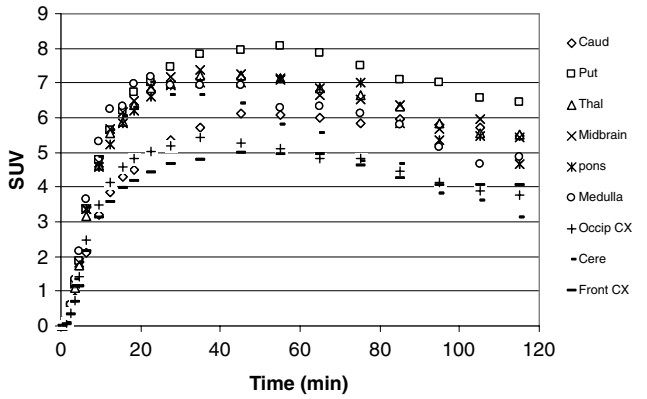

Figure 2. MicroPET time–activity curves for brain regions for a rhesus monkey after intravenous injection of 10.37 mCi [^{11}C]**2**. Images were acquired for a total time of 120 min.

greater affinity for the SERT than for NET or DAT, with 3β-4′-iodophenyl compound **24** having the highest affinity (K_i = 0.09 nM) for SERT and selectivity versus the NET (65-fold) or DAT (94-fold). To our disappointment, 3β-4′-methylphenyl compound **2** exhibited moderate affinity for both the NET (K_i = 17.28 nM) and SERT (K_i = 7.77 nM), and relatively low affinity for the DAT (K_i = 41 nM) which differs from the literature reports based on uptake inhibition studies.[9] To confirm the affinity of **2**, microPET imaging studies were performed with [^{11}C]**2**[12] to assess the regional distribution in anesthetized rhesus monkeys according to a previously reported procedure.[11] Time–activity curves obtained after administration of [^{11}C]**2** demonstrated a mix of SERT and NET selectivity profile with a high uptake in putamen, midbrain, pons, thalamus, medulla, caudate, and cerebellum (Fig. 2). The highest ratios relative to occipital cortex, a brain region with low SERT and NET density, occurring at 105 min were 1.83, 1.53, 1.52, 1.48, 1.47, and 1.36 for the putamen, midbrain, pons, thalamus, caudate, and medulla, respectively, while 1.39 for cerebellum which occurred at 25 min. The uptake of [^{11}C]**2** reflects the known distribution of the SERT and NET in monkey brain, and is in agreement with its in vitro binding affinities we found. Introduction of methyl ester group on methylene as in analogues **20**–**22** led to a significant reduction of binding affinity at the SERT by 13- to 23-fold and a increase of DAT activity by 3-, 14-, and 3-fold, respectively, while the potency at the NET slightly decreased by 1.2- to 4-fold. Selectivity profiles of these compounds switch to selectivity for the DAT versus SERT and NET.

In summary, we have synthesized and determined the monoamine transporter binding affinity of several new methylene or carbomethoxymethylene bearing front bridged tricyclic tropane derivatives. The binding results showed that all of these derivatives exhibited a moderate to high potency at all three transporters with SERT or DAT selectivity, instead of NET selectivity. Compound **24** presented a particularly attractive pharmacological profile, with very high SERT affinity (K_i = 0.09 nM) and selectivity versus NET (65-fold) and DAT (94-fold).

Acknowledgment

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References and notes

1. Hytell, J. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **1982**, *6*, 277.
2. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.
3. For papers published before 2003, see Zhou, J.; Zhang, A.; Kläss, T.; Johnson, K. M.; Wang, C. Z.; Ye, Y. P.; Kozikowski, A. P. *J. Med. Chem.* **2003**, *46*, 1997, and references cited there.
4. Carroll, F. I. *J. Med. Chem* **2003**, *46*, 1175.
5. Carroll, F. I.; Pawlush, N.; Kuhar, M. J.; Pollard, G. T.; Howard, J. L. *J. Med. Chem.* **2004**, *47*, 296.
6. Carroll, F. I.; Tyagi, S.; Blough, B. E.; Kuhar, M. J.; Navarro, H. A. *J. Med. Chem.* **2005**, *48*, 3852.
7. Tamagnan, G.; Alagille, D.; Fu, X.; Kula, N. S.; Baldessarini, R. J.; Innis, R. B.; Baldwin, R. M. *Biorg. Med. Chem. Lett.* **2006**, *16*, 217.
8. Smith, M. P.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 9072.
9. Tamiz, A. P.; Smith, M. P.; Kozikowski, A. P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 297.
10. Holmquist, C. R.; Keverline-Frantz, K. I.; Abraham, P.; Boja, J. W.; Kuhar, M. J. K.; Carroll, F. I. *J. Med. Chem.* **1996**, *39*, 4139.
11. Plisson, C.; McConathy, J.; Martarello, L.; Malveaux, E. J.; Camp, V. M.; Williams, L.; Votaw, J. R.; Goodman, M. M. *J. Med. Chem.* **2004**, *47*, 1122.
12. [^{11}C]**2** was prepared by palladium-catalyzed cross coupling of tin precursor **23** with [^{11}C]CH_3I according to a procedure developed by Björkman et al.; see Björkman, M.; Doi, H.; Resul, B.; Suzuki, M.; Noyori, R.; Watanable, Y.; Långstrom, B. *J. Labelled Cpd. Radiopharm* **2000**, *43*, 1327.