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Synthesis and monoamine transporter affinity of 2β-carbomethoxy-3β-(4′-*p*-substituted phenyl)-piperidine analogs of cocaine

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Abstract—A series of novel piperidine based analogs of cocaine was synthesized and evaluated in vitro against the three monoamine transporters to develop new potential selective SERT radiotracers. Modification of the phenyl substitution with five-membered heterocyclic groups resulted in a wide affinity and selectivity scale. Radiolabeling and mouse in vivo study was performed on the piperidine analog of ZIENT, which crossed the blood–brain barrier but failed to selectively accumulate in the regions of the brain rich in SERT.

Reinforcing and stimulant properties of cocaine (compound **1**; Fig. 1) are associated with its ability to bind to monoamine neurotransmitter transporters for dopamine (DAT), norepinephrine (NET), and to a lesser extent, serotonin (SERT). SERT inhibitors (selective serotonin reuptake inhibitors or SSRIs) are widely used to treat major depression, anxiety disorders, and obsessive-compulsive disorder (OCD).[1] Some tropanes (**2**)[1–4] and piperidines (**3**, the non-controlled substance sister series)[5,6] have SERT-blocking activity. To further evaluate structural characteristics leading to selective interactions with specific monoamine transporters, we have evaluated effects of substitutions of tropanes. We previously evaluated 3′ iodophenyltropane and aromatic analogs.[7] We now report the synthesis and in vitro neuropharmacological evaluation of corresponding 4′-analogs in the piperidine series. Based on the results obtained with ZIENT we also report herein the preliminary in vivo assessment of the piperidine analog radiolabeled with ^{123}I.[8]

Compound **4** (±*cis*, Scheme 1), prepared by Grignard addition on arecoline with 4-trimethylsilyl-phenyl magnesium bromide (49%), upon treatment with a solution of iodine monochloride at 60 °C, afforded **5** by iodination of the aromatic ring (53%). Stille coupling between **5** and tributyl-furan-2-yl-stannane with *trans*-dichlorobis(triphenylphosphine)palladium as catalyst in DMF at room temperature gave furan **6** (68%). The corresponding heterocycles **7** (36%), **8** (51%), and **9** (76%) were prepared by Rieke coupling between **5** and the appropriate five-member-ring zinc halide, in THF at room temperature. Epimerization of **9** with refluxing NaOMe in MeOH afforded (±*trans*) **10** (51%) (Fig. 2).

Vinyl derivative **11** (Scheme 2) was prepared by Grignard addition on arecoline with 4-vinylbenzene magnesium bromide and copper bromide-dimethylsulfide complex (17%). Oxidation of the vinyl group with $OsO_4/NaIO_4$ in THF/H_2O (1:1) gave aldehyde **12** (15%), which upon treatment with $PPh_3CH_2I_2$ in basic conditions afforded the corresponding *Z*-2-iodovinyl analog **13** (68%).[8]

[^{123}I]**13** (Scheme 3) was prepared by iododestannylation of the trimethylstannyl precursor **14** with sodium [^{123}I]iodide and peracetic acid as oxidizing agent at room temperature. Purification by reverse-phase HPLC using $MeOH/H_2O/Et_3N$ (75/25/0.1) with concomitant UV and radioactivity detection allowed identity confirmation of [^{123}I]**13** by comparison to its corresponding unlabeled analog. Product [^{123}I]**13** was obtained with a

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Keywords: SERT; Monoamine transporter; SPECT; Cocaine; Imaging.

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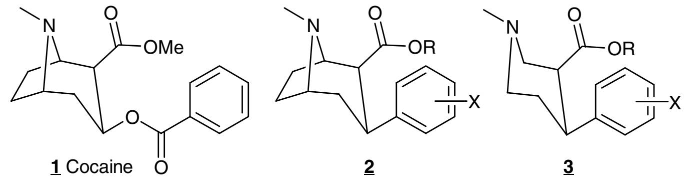
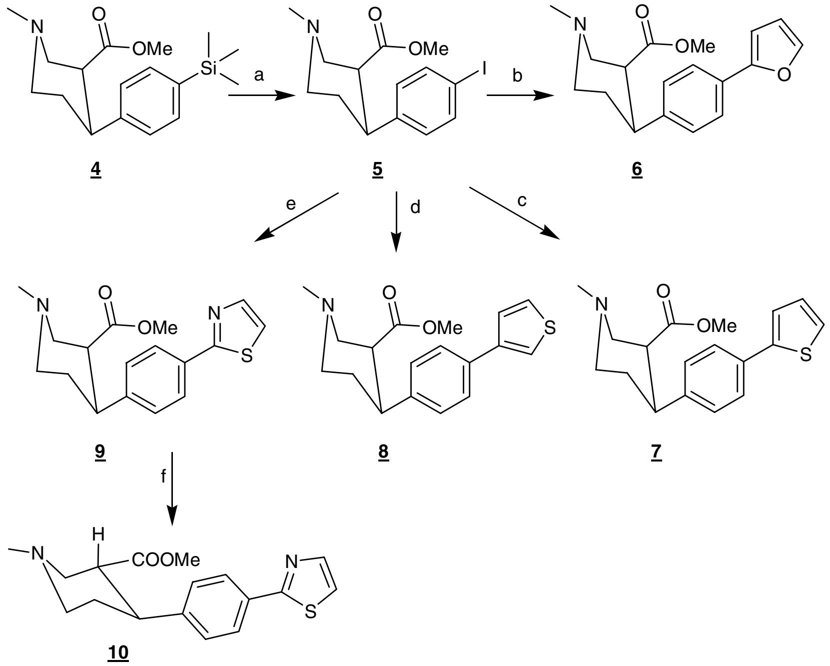


1 Cocaine 2 3

Figure 1.



Scheme 1. Reagents and conditions: (a) ICl, AcOH, 60 °C; (b) tributyl-furan-2-yl-stannane, $PdCl_2(PPh_3)_2$, DMF, rt; (c) 2-thienylzinc bromide, $PdCl_2(PPh_3)_2$, THF, rt; (d) 3-thienylzinc iodide, $PdCl_2(PPh_3)_2$, THF, rt; (e) 2-thiazolylzinc bromide, $PdCl_2(PPh_3)_2$, THF, rt; (f) NaOMe, MeOH, Δ.

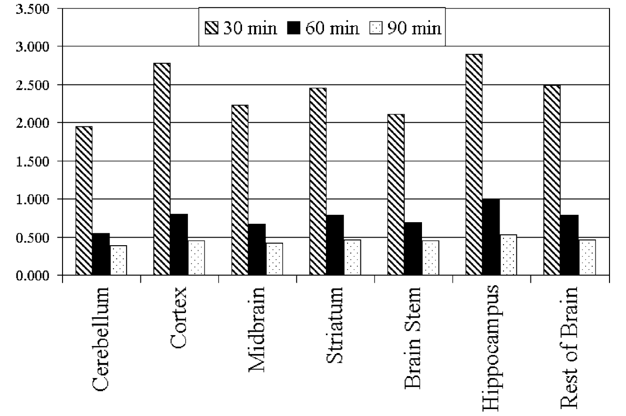


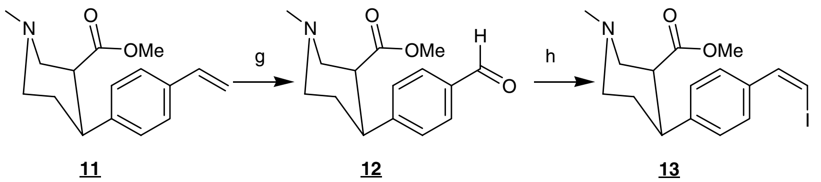
Figure 2. Concentration (% ID/g) of $[^{123}I]$**13** for regions of the brain in mouse at 30, 60, and 90 min post-injection.

no-carrier-added radiochemical yield of 84% and radiochemical purity ⩾95%.

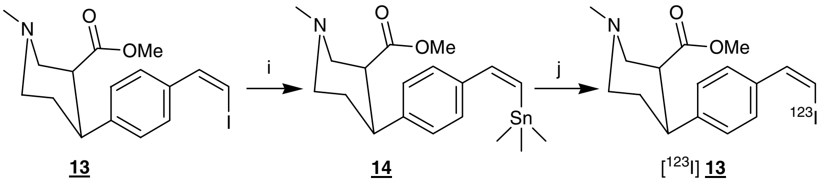
The residue from rotary evaporation was treated with 200 μL (400 μg) aqueous L-ascorbic acid, dissolved in 400 μL ethanol, and diluted with 8 mL 0.9% NaCl.[9]

The potency (K_i, nM) of the substituted piperidine compounds synthesized was evaluated by competition against radiolabeled ligands selective for SERT, DAT, and NET in rat forebrain tissue (Table 1).[10]

Compound **5** was 363-fold less potent for SERT than was β-CIT, its tropane analog, and 203 times less potent for DAT, as well as 1.8 times less selective for SERT-over-DAT (Tables 1 and 2). Hence, in agreement with literature,[11] loss of the two-carbon bridge



Scheme 2. Reagents and conditions: (g) OsO_4, $NaIO_4$, THF/H_2O (1:1), rt; (h) $PPh_3CH_2I_2$, $NaN(SiMe_3)_2$, THF, −78 °C to rt.



Scheme 3. Reagents and conditions: (i) hexamethylditin, Pd(PPh$_3$)$_4$, THF, Δ; (j) 1—H$_3$PO$_4$, CH$_3$CO$_3$H, [^{123}I]NaI; 2—HCl 2 M in ether.

Table 1. Affinity of 4′-substituted phenyl piperidines for dopamine, serotonin, and norepinephrine transporters (K_i ± SEM, nM)

Compound	SERT	DAT	NET
5	167 ± 48	195 ± 63	ca. 10,000
β-CIT	0.46 ± 0.06	0.96 ± 0.15	2.80 ± 0.40
6	18.5 ± 11.5	205 ± 57	>50,000
7	90.8 ± 3.8	⩾5000	>50,000
8	3.18 ± 0.26	598 ± 67	>10,000
9	>10,000	ca. 10,000	>50,000
10	>5,000	>10,000	>20,000
12	1732 ± 120	>10,000	>30,000
13	7.90 ± 0.43	123 ± 42	>30,000

DAT was assayed with 300 pM [^{3}H]β-CIT (Tocris-Cookson), blank: 10 µM GBR-12909 (RBI-Sigma) with homogenates of rat caudate; SERT with 700 pM [^{3}H]cyanoimipramine (DuPont-NEN), blank: 10 µM (±)-fluoxetine (donated by Eli Lilly) with rat cerebral cortex homogenate; and NET with 350 pM [^{3}H]nisoxetine: (DuPont-NEN), blank: 10 µM desipramine-HCl (RBI-Sigma) with rat cerebral cortex.

Table 2. Transporter selectivity ([K_i ratio]$^{-1}$)

Compound	SERT/DAT	SERT/NET
5	11.2	59.9
β-CIT	2.1	6.1
6	11.1	>2700
7	⩾55	>551
8	188	>3140
9	1	5
10	2	4
12	5.8	17.3
13	15.6	⩾3800

(conjugated to the racemic nature of **5**) appears to be of some consequence for SERT potency and also for selectivity over DAT. Interestingly, substitution at position 4′ with larger, five-atom, aromatic groups resulted in striking affinity and selectivity differences among structurally closely related compounds. These piperidine substitutions appear to have a greater influence on transporter affinity than has been found with tropanes.[7,1]

Female Sprague–Dawley mice (30–40 g) were administered 3.7 MBq (100 µCi) of [^{123}I]**13** in 0.50 µL by intravenous tail injection. Groups of three mice were decapitated at intervals of 30, 60, and 90 min post-injection. The brain was removed immediately and dissected into different regions: cerebellum, cortex, midbrain, striatum, brain stem, hippocampus, and rest of brain. Tissue samples were placed into tared polypropylene test tubes, weighed, and counted on the gamma counter.

These results confirm that heteroaromatic substitution of the phenyl ring leads to retention to the in vitro affinity for DAT and 5-HTT. Radiolabeling of **14** with iodine-123 gave **13** in high yield; however, unlike results obtained in the tropane series with ZIENT, biodistribution of [^{123}I]**13** in mice did not show a selective uptake matching the distribution of SERT.

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