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Short communication

Synthesis and dopamine transporter binding of 2β-isopropyl ester analogs of cocaine

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Abstract

A series of 2β-isopropyl ester analogs of cocaine (**7**–**11**) was synthesised and evaluated in an in vitro dopamine transporter (DAT) binding assays. Ecgonine HCl (**5**) was obtained from (−)-cocaine (**1**) by hydrolysis using 1 N HCl. Acid catalysed esterification of **5** using 2-propanol and HCl gas afforded 2β-isopropyl ecgonine (**6**). Compounds **7**–**9** were obtained via esterification of the 3β-hydroxyl group of **6** using the appropriate acid chloride. Compound **10** was obtained via selective hydrolysis and re-esterification of **7** using 2-propanol and HCl gas. Compound **11** was obtained by reduction of **9** using H_2/Pd–C. Compounds **7**, **10** and **11** showed high binding affinity to the DAT (as indicated from the inhibition of the binding of [^{3}H]WIN 35,428 (**3**)) with IC_{50} values (mean ± S.E.M.) 208.5 ± 9.5, 47.43 ± 1.79 and 11.25 ± 3.37 nM, respectively). Compound **7** is comparatively as active as cocaine, **10** is ca. fivefold more active than cocaine and **11** is ca. 20-fold more active than cocaine and even twice more active than the radioligand **3**. Compound **11**, like its methyl ester analog (2′ aminococaine), exhibited the highest affinity to the DAT. These results, along with previous results, emphasise the importance of a hydrogen-bond donor group at the 2′-position of cocaine and its isopropyl ester analogs to enhance binding affinity to the DAT. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Cocaine analogs; Isopropyl cocaine analogs; Dopamine transporter binding assays

1. Introduction

Cocaine (**1**), a naturally occurring local anesthetic first isolated from Coca leaves (Erythroxylum coca) has been recognised to be a potent central nervous stimulant and binds to specific sites in the mammalian brain [1–3]. The behavioural effects of cocaine are characterised by reinforcement of responding and drug seeking [4], drug discrimination ability [5] and locomotor activity stimulation [6,7]. While cocaine inhibits the neuronal uptake of dopamine (DA) [8], serotonin (5-HT) [9] and norepinephrine (NE) [10], the rewarding properties of cocaine clearly require activation of the dopaminergic system.

The current view, termed, 'the dopamine hypothesis' is that behaviours associated with cocaine addiction result, to a large extent, not from a direct message elicited by the binding of (−)-cocaine but rather from the accumulation of DA in the synapse and its action at one or more of the D_1–D_5 dopamine receptors [11–14]. In experiments involving knockout mice genetically lacking the DA transporter, cocaine had no stimulant effect [15]. This finding directly confirms the crucial role of dopamine transporter (DAT) in cocaine action [15].

It has been reported that modification of substituents at the 2β-position has led to improved binding affinities and transporter selectivities in the phenyltropanes [16–19]. The compounds of this investigation have been prepared on the basis of the observation that replacement of the methyl ester in the 2β-position by an

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isopropyl moiety resulted in enhancement of binding selectivity for DAT compared to NE and 5-HT bindings [18,20]. Compounds **7**, **10** and **11** were prepared in view of high binding affinities exhibited by 2′-acetoxy-, 2′-hydroxy- and 2′-amino-cocaines (IC_{50} (mean $\pm$ S.E.M.) were 69 ± 1, 25 ± 4 and 18 ± 2 nM, respectively) [20], which were in the range of the 3-phenyltropane WIN-35,428 (**3**) (IC50; mean $\pm$ S.E.M., 24 ± 4 nM), which is unusual for the benzoyl ester class of tropanes [20–23].

Systematic evaluation of substitution at 4′-position has resulted in the identification of high affinity ligand selection for 5-HT transporter [24]. In contrast, few publications have described the effects of substitution at the 2′-position [21–23,25–27]. For these reasons, we began a limited characterisation of the chemical nature at 2′-substituents of 2β-isopropyl ester analogs of cocaine on binding affinities to the DAT. In contrast to most substituted cocaines, certain substituents at the 2′-position increase significantly the binding potency of 2β-isopropyl ester analogs of cocaine for DAT.

The structures of cocaine, WIN-35,428 and the prepared compounds are shown in Fig. 1.

2. Results and discussion

2.1. Chemistry

The intermediate compound 2β-isopropyl ecgonine (**6**) was synthesised, according to Fig. 2, via hydrolysis of cocaine with aqueous 1 N HCl, followed by acid catalysed esterification using 2-propanol and HCl gas. Compounds **7** and **8** were prepared by esterification of 3β-hydroxyl group of **6** using the appropriate acid chloride in presence of benzene and Et_3N, Fig. 2. Compound **9** was prepared using the same method after preparing the acid chloride from the corresponding acid using $SOCl_2$, Fig. 3. Compound **11** was prepared, according to Fig. 3, by reduction of **9** using H_2/Pd–C, while **10** was obtained from **7** by selective hydrolysis using 2-propanol saturated with HCl gas (Fig. 4).

Preparation of salicyloyl chloride using $SOCl_2$ or oxalyl chloride activated DMF [28] was not feasible due to the intramolecular hydrogen bonding found in salicylic acid and the possibility of the formation of β-lactone and/or acid anhydride. So, **10** was prepared by adapting a procedure that was reported by our group to prepare 2′-acetoxy- and 2′-hydroxy-cocaines [21,22,29]. This procedure depends on selective hydrolysis and re-esterification of the 2′-acetoxy group of **7**. The 2′-acetoxy group and 2β-isopropyl ester of **7** were hydrolysed, while re-esterification of the 2-carboxylic group took place in a condition of acid catalysed esterification (2-propanol, HCl gas and reflux overnight). The 3β-benzoyl ester was not affected. Compound **11** was prepared by the reduction of **9** using H_2/Pd–C, because of the same reasons that have been mentioned in the preparation of **10**.

2.2. Dopamine transporter binding assays

The IC_{50} values of 2β-isopropyl ester analogs of cocaine **7**–**11**, for inhibiting 4 nM of the radioligand [^{3}H]WIN 35,428 (**3**) to the DAT, are listed in Table 1. The prepared compounds comprised 2′-substituents of different nature such as: (1) a bulky group, **8**; (2) electron-donating groups, **7** and **8**; (3) an electron-withdrawing group, **9** and; (4) hydrogen-bond donor groups, **10** and **11**.

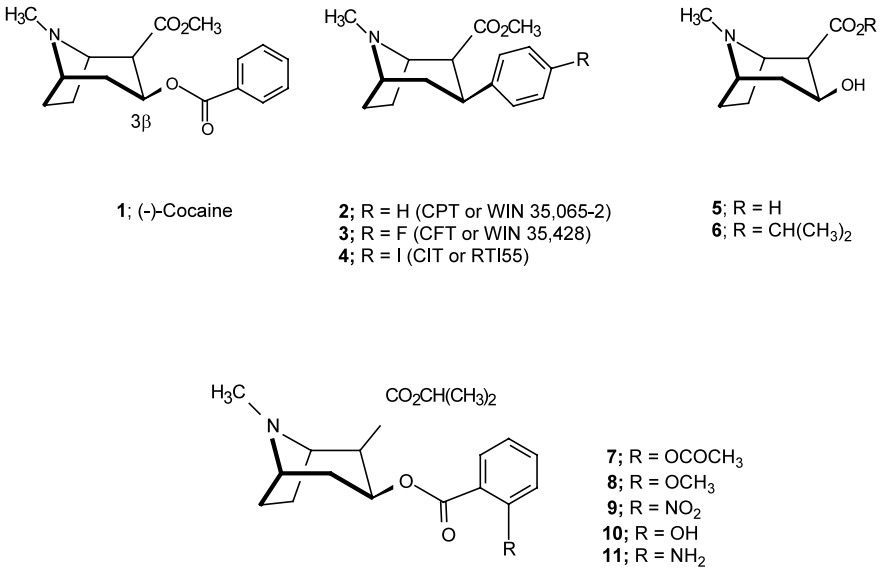

Fig. 1. Structures of the investigated compounds.

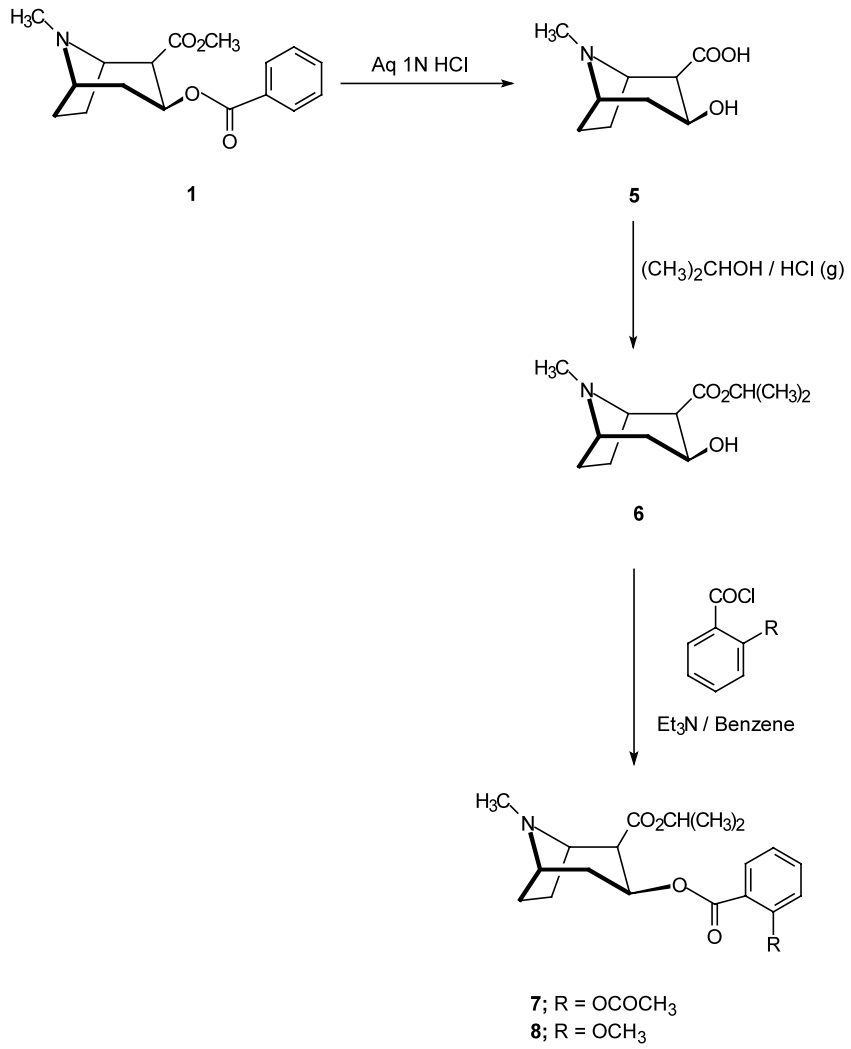

Fig. 2. Preparation of **5**–**8**.

It is apparent from Table 1 that compounds **8** and **9** have low binding affinities, while **7**, **10** and **11** showed high binding affinities with IC_{50} values less than that of cocaine. The IC_{50} values (mean $\pm$ S.E.M.) for **7**, **10** and **11** were 208.5 ± 9.5, 47.43 ± 1.79 and 11.25 ± 3.37 nM, respectively. So, compound **7** has IC_{50} close to that of cocaine (249 ± 37 nM), **10** is ca. fivefold more active than cocaine and **11** is ca. 20-fold more active than cocaine and even twice more active than the radioligand [^{3}H]WIN 35,428 (**3**). These results are in accordance with our previously published ones that showed high binding affinities exhibited by 2′-acetoxy-, 2′-hydroxy- and 2′-amino-cocaines (IC_{50}; mean $\pm$ S.E.M.; 70 ± 1, 25 ± 4 and 18 ± 2 nM, respectively) [21–23]. These results emphasise that 2β-isopropyl ester and 2′-substituents are optimal and a hydrogen-bond donor group is crucial in enhancing binding affinity to the DAT.

It was postulated that the hydroxyl group, and similarly the amino group, may engage in an intermolecular hydrogen-bond with the serine residue at the acceptor site of DAT [21].

3. Experimental

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab LTD, Indianapolis, IN, USA and were $\pm 0.4\%$ of the calculated values. NMR spectra were recorded on a Varian XL-300 spectrometer. All organic reagents were obtained from Aldrich Co. and were used without further purification. Silica gel (200–400 mesh, 60 Å) used for column chromatography was obtained from Aldrich and silica gel chromatographic sheets with a fluorescent indicator used for thin layer chromatography (TLC) were obtained from Eastman Kodak Co., Rochester, NY. [^{3}H]WIN-35,428 was obtained from Dupont-New England Nuclear, Boston, MA.

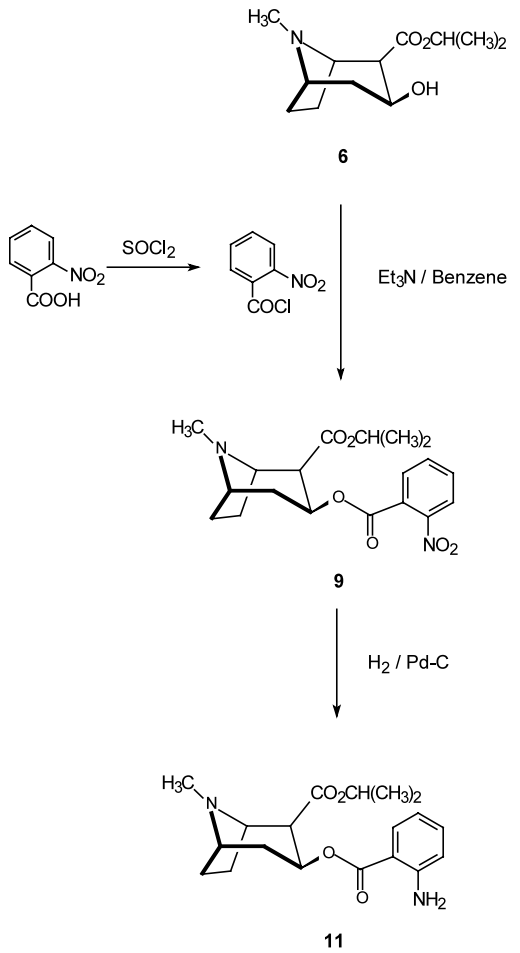

Fig. 3. Preparation of **9** and **11**.

Homogenisation of the striata was performed using a Polytron Homogenizer, Kinematic Kriens-Luzern, Switzerland. Centrifugation of the membrane homogenate was carried out using a Dupont Sorvel RC-5 superspeed refrigerated centrifuge (rotor SS-34). Filtration of the bound-membrane was carried out using a Brandel Cell Harvester. Counting of the activity of the receptor-bound ligand was performed using a Beckman LS 1701, liquid scintillation counter.

3.1. 3β-Hydroxy-1R-(exo,exo)-8-methyl-8-azabicyclo-[3.2.1]octane-2-carboxylic acid isopropyl ester (6)

To ecgonine HCl (**5**) (5.0 g, 22.5 mmol) was added 200 mL of 2-propanol, the mixture was saturated with dry HCl gas and refluxed overnight to obtain a solution. After cooling, the mixture was saturated again with HCl gas while maintained cool in ice. The reaction mixture was stirred at room temperature (r.t.) for 24 h. 2-Propanol was evaporated under vacuum. The remaining solution was neutralised with 20% NH_4OH and extracted with $CHCl_3$ (3×40 mL). The combined organic extracts were dried over $MgSO_4$ (anhyd), concentrated under vacuum, passed through a silica gel plug and eluted with EtOAc–petroleum ether (50:50) to obtain an oil (4.19 g, 82% yield). ^{1}H-NMR ($CDCl_3$, δ): 5.19–5.11 (m, 1H, **CH**$(CH_3)_2$); 3.82 (s, br, 2H, C-3, OH); 3.59–3.58 (m, 1H, C-1); 3.17–3.16 (m, 1H, C-5); 2.72 (m, 1H, C-2); 2.2 (s, 3**H**, N–CH_3); 2.11–1.81 (m, 4H, C-4, C-7); 1.56–1.52 (m, 2H, C-6); 1.30–1.28 (d, 6H, CH(**CH**$_3)_2$).

Table 1
DAT binding affinities of compounds **7**–**11**

Compound	IC_{50} (nm) [a]
Cocaine (**1**)	249 ± 37
WIN 35,428 (**2**)	24 ± 4
7	208.5 ± 9.5
8	$35{,}985 \pm 206$
9	1881.5 ± 506
10	47.42 ± 1.79
11	11.25 ± 3.37

[a] IC_{50} values are mean $\pm$ S.E.M. of two experiments performed in triplicates.

3.2. 3β-[(2′-Acetoxybenzoyl)oxy]-1R-(exo,exo)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid isopropyl ester (7)

Ecgonine isopropyl ester free-base (**6**) (0.30 g, 1.32 mmol) was dissolved in 15 mL dry C_6H_6, to this was added 1 mL (10 mmol) Et_3N. To the stirred solution was added acetylsalicyloyl chloride (0.39 g, 1.98 mmol) under dry N_2. The reaction mixture was stirred at 40 °C overnight. The reaction was stopped and the benzene layer was washed with 10 mL water and 5% aq. Na_2CO_3 solution (3×5 mL) and dried over $MgSO_4$ (anhyd), and the solvent was removed under vacuum to give an oil. The oil was purified over silica gel column

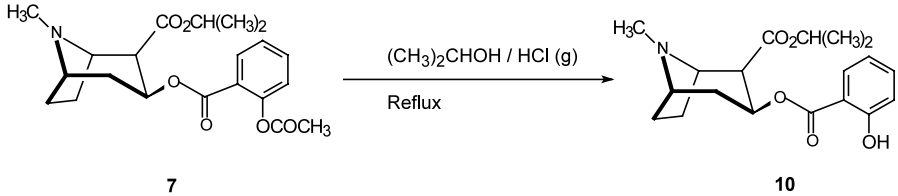

Fig. 4. Preparation of **10**.

(EtOAc–petroleum ether, 50:50) to afford 0.35 g (69% yield) of the clear oil. The oil was converted to the tartrate salt, which was recrystallised from EtOH–Et_2O. M.p. 87–90 °C. Anal. $C_{25}H_{33}NO_{12}$: ^{1}H-NMR (D_2O, δ): 7.87–7.83 (d, 1H, C(6′)H); 7.58–7.52 (m, 1H, C(4′)H); 7.29–7.24 (m, 1H, C(5′)H); 7.08–7.05 (d, 1H, C(3′)H); 5.40–5.30 (m, 1H, C(3)H); 4.80–4.70 (m, 1H, **CH**$(CH_3)_2$); 4.03–4.02 (m, 1H, C(1)H); 3.89 (m, 1H, C(5)H); 3.41–3.38 (m, 1H, C(2)H); 2.68 (s, 3H, NCH_3); 2.27–2.23 (m, 4H, C(4,7)H); 2.19 (s, 3H, CH_3COO); 2.02–1.98 (m, 2H, C(6)H); 0.95–0.93 (d, 3H, CH**CH**$_3$); 0.62–0.60 (d, 3H, CH**CH**$_3$).

3.3. 3β-[(2′-Methoxybenzoyl)oxy]-1R-(exo,exo)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid isopropyl ester (**8**)

Ecgonine isopropyl ester free-base (**6**) (0.30 g, 1.32 mmol) was dissolved in 15 mL dry C_6H_6, to this was added 1 mL (10 mmol) Et_3N. To the stirred solution was added anisoyl chloride (0.34 g, 1.98 mmol) under dry N_2. The reaction mixture was stirred at 40 °C overnight. The reaction was stopped and the C_6H_6 layer was washed with 10 mL water and 5% aq. Na_2CO_3 solution (3 × 5 mL) and dried over $MgSO_4$ (anhyd) and the solvent was removed under vacuum to give an oil. The oil was purified over silica gel column (EtOAc–petroleum ether, 50:50) to afford 0.34 g (72% yield) of the clear oil. The oil was converted to the tartrate salt and recrystallised from isopropyl alcohol. M.p. 184–186 °C. Anal. $C_{24}H_{33}NO_{11}$: ^{1}H-NMR (D_2O, δ): 7.67–7.64 (d, 1H, C(6′)H); 7.46–7.43 (m, 1H, C(4′)H); 7.02–6.99 (d, 1H, C(3′)H); 6.90–6.85 (m, 1H, C(5′)H); 5.38–5.18 (m, 1H, C(3)H); 4.74–4.61 (m, 1H, **CH**$(CH_3)_2$); 4.02–4.00 (m, 1H, C(1)H); 3.88 (m, 1H, C(5)H); 3.72 (s, 3H, $ArOCH_3$); 3.44–3.41 (m, 1H, C(2)H); 2.68 (s, 3H, NCH_3); 2.24–2.20 (m, 4H, C(4, 7)H; 2.03–2.00 (m, 2H, C(6)H); 0.92–0.90 (d, 3H, CH**CH**$_3$); 0.56–0.54 (d, 3H, CH**CH**$_3$).

3.4. 3β-[(2′-Nitrobenzoyl)oxy]-1R-(exo,exo)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid isopropyl ester (**9**)

2-Nitrobenzoic acid (0.33 g, 1.98 mmol) and 10 mL thionyl chloride were refluxed for 3 h. The solution was cooled and evaporated under vacuum to remove excess thionyl chloride. The residue obtained was taken in 5 mL dry C_6H_6 and added to ecgonine isopropyl ester free-base (**6**) (0.30 g, 1.32 mmol) and 1 mL (10 mmol) Et_3N in 15 mL of dry C_6H_6. The mixture was stirred at r.t. for 6 h. The reaction was stopped and the organic layer was washed with 10 mL water and 5% aq. Na_2CO_3 solution (3 × 5 mL) and dried over $MgSO_4$ (anhyd) and the solvent was removed under vacuum to give an oil. The oil was purified over silica gel column and eluted with EtOAc to afford 0.45 g (90.66% yield) of the clear oil. The oil was converted to the tartrate salt and recrystallised from isopropyl alcohol. M.p. 159–161 °C. Anal. $C_{23}H_{30}N_2O_{12}\cdot H_2O$: ^{1}H-NMR ($D_2O$, δ): 7.88–7.85 (d, 1H, C(3′)H); 7.70–7.62 (m, 3H, C(4′,5′,6′)H); 5.48–5.44 (m, 1H, C(3)H); 4.80–4.76 (m, 1H, **CH**$(CH_3)_2$); 4.05–4.03 (m, 1H, C(1)H); 3.90 (m, 1H, C(5)H); 3.32–3.29 (m, 1H, C(2)H); 2.68 (s, 3H, NCH_3); 2.30–2.28 (m, 4H, C(4,7)H; 2.05–2.00 (m, 2H, C(6)H); 0.98–0.96 (d, 3H, CH**CH**$_3$); 0.59–0.57 (d, 3H, CH**CH**$_3$).

3.5. 3β-[(2′-Hydroxybenzoyl)oxy]-1R-(exo,exo)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid isopropyl ester (**10**)

2′-Acetoxyisopropyl cocaine free-base (**7**) (0.1 g; 0.26 mmol) was dissolved in 10 mL isopropyl alcohol and dry HCl gas was passed. The resulting solution was refluxed with stirring for 48 h. It was then cooled and the solvent was evaporated under vacuum to obtain a white solid, which was recrystallised from MeOH–Et_2O to afford 0.84 g (85% yield) of the desired compound. M.p. 165–167 °C. Anal. $C_{19}H_{25}NO_5$: ^{1}H-NMR (D_2O, δ): 7.66–7.63 (d, 1H, C(6′)H); 7.42–7.35 (t, 1H, C(4′)H); 6.86–6.76 (m, 2H, C(3′,5′)H); 5.44–5.36 (m, 1H, C(3)H); 4.81–4.76 (m, 1H, **CH**$(CH_3)_2$); 4.05–4.03 (m, 1H, C(1)H); 3.92 (m, 1H, C(5)H); 3.49–3.47 (m, 1H, C(2)H); 2.71 (s, 3H, NCH_3); 2.31–2.25 (m, 4H, C(4, 7)H; 2.05–2.02 (m, 2H, C(6)H); 0.93–0.91 (d, 3H, CH**CH**$_3$); 0.64–0.62 (d, 3H, CH**CH**$_3$).

3.6. 3β-[(2′-Aminobenzoyl)oxy]-1R-(exo,exo)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid isopropyl ester (**11**)

To a 100 mL vacuumed sealed round-bottomed flask were added, 0.3 g (0.79 mmol) of **9**, 30 mg of Pd on activated carbon (Pd content 10%) and 40 mL cyclohexane. A hydrogen balloon was attached to the flask while it was under vacuum to allow hydrogen to be sucked into the flask. The mixture was allowed to stir for 24 h. The crude product was filtered over celite and the solvent evaporated to obtain 0.26 g (95% yield) of a pure oil. The oil was converted to the tartrate salt and recrystallised from MeOH–Et_2O. M.p. 172–174 °C. Anal. $C_{23}H_{32}N_2O_{10}$: ^{1}H-NMR (D_2O, δ): 7.62–7.59 (d, 1H, C(6′)H); 7.24–7.18 (t, 1H, C(4′)H); 6.71–6.68 (d, 1H, C(3′)H); 6.59–6.54 (t, 1H, C(5′)H); 5.32–5.26 (m, 1H, C(3)H); 4.78–4.74 (m, 1H, **CH**$(CH_3)_2$); 4.01 (m, 1H, C(1)H); 3.90 (m, 1H, C(5)H); 3.42–3.39 (m, 1H, C(2)H); 2.69 (s, 3H, NCH_3); 2.32–2.22 (m, 4H, C(4,7)H; 2.03–2.00 (m, 2H, C(6)H); 0.94–0.92 (d, 3H, CH**CH**$_3$); 0.66–0.64 (d, 3H, $CHCH_3$).

3.7. Dopamine transporter binding assays

The binding was performed in rat striatal tissue using the method of Reith [30].

1. *Materials:* [^{3}H]WIN-35,428 was obtained from Dupont-New England Nuclear, Boston, MA.
2. *Preparation of test substances:* stock solutions of the test substances were prepared freshly by dissolving them in the incubation buffer (phosphate buffer pH 7.4).
3. *Phosphate buffer:* obtained by mixing 35 mM NaH_2PO_4 and 17.5 mM Na_2HPO_4 to obtain pH 7.4.
4. *Membrane preparation:* Whole brains from male Sprague–Dawley rats weighing from 350 to 400 g (Sasco Inc., Wilmington, MA) were rapidly harvested after decapitation with a guillotine. The striata were isolated and homogenised using Polytron Homogenizer (setting six for 15 s) in ice-cold 0.32 M sucrose solution (1.5 mL/100 mg of tissue). The Homogenizer and blade were then rinsed with twice the volume of 0.32 M sucrose solution and added to the homogenate. The combined mixture was centrifuged at 3300 rpm for 10 min at 4 °C. The resulting supernatant was subsequently centrifuged at 13,800 rpm for 20 min at 4 °C to obtain a pellet (P_2), which was homogenised in ice-cold 35 mM phosphate buffer.

   Each assay tube contained 130 μL buffer or buffer plus 10 μL of unlabeled test compound (1×10^{-10}–100×10^{-6} M), [^{3}H]WIN-35,428 in the same buffer (20 μL, 4 nM) and 50 μL of membranes (4 mg mL^{-1}) to a total volume of 200 μL. (−)-Cocaine (100 μM) was used for non-specific binding. Assays performed in triplicates were incubated for 2 h in an ice bath and terminated by rapid filtration through Whatman GF/B glass fiber filters presoaked for 30 min in 0.05% polylysine solution. Membranes were rapidly washed three times with ice-cold buffer. Filters containing membrane-bound radioligand were added to vials containing 10 mL of scintillation fluid (Ecolume, Costa Mesa, CA), stored overnight and counted for 5 min on a Beckman LS 1701, liquid scintillation counter.
5. *Calculation of IC_{50}:* IC_{50} values were determined from competition curves of 12 points using the curve-fitting program EBDA (Biosoft software, Ferguson, MO). Mean values and standard errors were calculated from two to three assays for each test compound.

Acknowledgements

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References

[1] B.K. Madras, J. Bergman, M.A. Fahey, D.R. Canfield, R.D. Spealman, J. Pharmacol. Exp. Ther. 251 (1988) 131–141.
[2] D.O. Calligaro, M.E. Eldefrawi, Membr. Biochem. 7 (1988) 87–106.
[3] C.E. Johanson, M.W. Fischman, Pharmacol. Rev. 41 (1989) 3–52.
[4] M.J. Kuhar, M.C. Ritz, J.W. Boja, Trends Neurosci. 14 (1991) 299–302.
[5] J.M. Witkin, Neurosci. Biobehav. Rev. 18 (1994) 121–142.
[6] B.K. Tolliver, J.M. Canery, Pharmacol. Biochem. Behav. 50 (1995) 163–169.
[7] J.L. Neisewander, L.E. O'Dell, J.C. Redmond, Brain Res. 671 (1995) 201–212.
[8] M.C. Ritz, R.J. Lamb, S.R. Goldberg, M.J. Kuhar, Science 237 (1988) 1219–1223.
[9] S. Ramamoorthy, A.L. Bauman, K.R. Moore, H. Han, T. Yang-Feng, A.S. Chang, V. Ganapathy, R.D. Blakey, Proc. Natl. Acad. Sci. USA 90 (1993) 2542–2546.
[10] T. Pacholczyk, R.D. Blakely, S.G. Amara, Nature 350 (1991) 350–354.
[11] A. Ricci, E. Bronzetti, F. Mannino, F. Mignini, C. Morosetti, S.K. Tayebati, F. Amenta, Naunyn Schmiedebergs Arch. Pharmacol. 363 (2001) 376–382.
[12] N. Maurice, T. Tkatch, M. Meisler, L.K. Sprunger, D.J. Surmeier, J. Neurosci. 21 (2001) 2268–2277.
[13] J.K. Seamans, D. Durstewitz, B.R. Christie, C.F. Stevens, T.J. Sejnowski, Proc. Natl. Acad. Sci. USA 98 (2001) 301–306.
[14] N.A. Gorelova, C.R. Yang, J. Neurophysiol. 84 (2000) 75–87.
[15] B. Giros, M. Jaber, S.R. Jones, R.M. Wightman, M.G. Caron, Nature 379 (1996) 606–612.
[16] A.H. Lewin, Y. Cao, P. Abraham, J.W. Boja, M.J. Kuhar, I.F. Carroll, J. Med. Chem. 35 (1992) 135–140.
[17] I.F. Carroll, J.L. Gray, P. Abraham, M.A. Kuzemko, A.H. Lewin, J.W. Boja, M.J. Kuhar, J. Med. Chem. 36 (1993) 2886–2890.
[18] F.Y. Carroll, P. Kotain, A. Dehghani, G.L. Gray, M.A. Kuzemko, K.A. Parham, P. Abraham, A.H. Lewin, J.W. Boja, M.J. Kuhar, J. Med. Chem. 38 (1995) 379–388.
[19] A.P. Kozikowski, M.K. Eddine Saiah, K.M. Johanson, J.S. Bergman, J. Med. Chem. 38 (1995) 3086–3093.
[20] K.S. Avor, S. Singh, T.W. Seale, B. Pouw, G.P. Basmadjian, J. Med. Chem. 41 (1998) 2380–2389.
[21] S. Singh, G.P. Basmadjian, K.S. Avor, B. Pouw, T.W. Seale, J. Med. Chem. 40 (1997) 2474–2481.
[22] T.F. El-Moselhy, K.S. Avor, G.P. Basmadjian, Med. Chem. Res. 10 (2000) 50–57.
[23] T.F. El-Moselhy, K.S. Avor, G.P. Basmadjian, Arch. Pharm. Pharm. Med. Chem. 334 (2001) 275–278.
[24] B.E. Blough, P. Abraham, A.H. Lewin, M.J. Kuhar, J.W. Boja, I.F. Carroll, J. Med. Chem. 39 (1996) 4027–4035.
[25] T.W. Seale, K.S. Avor, S. Singh, N. Hall, H. Cahan, G.P. Basmadjian, NeuroReport 8 (1997) 3571–3575.
[26] D.W. Yu, S.J., Gatley, A.P. Wolf, R.R. MacGregor, S.L. Dewey, J.S. Fowler, D.J. Schlyer, J. Med. Chem. 35 (1992) 2178–2183.
[27] R.H. Kline Jr., J. Wright, K.M. Fox, M.E. Eldefrawi, J. Med. Chem. 33 (1990) 2024–2027.
[28] Ed. Ward, K. Rhee, Tetrahedron Lett. 32 (1991) 7165–7166.
[29] S. Singh, G.P. Basmadjian, K.S. Avor, B. Pouw, T.W. Seale, Synth. Commun. 27 (1997) 4003–4012.
[30] M.E. Reith, L.L. Coffey, J. Neurochem. 61 (1993) 167–177.