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Synthesis and binding studies of 2-arylapomorphines

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From codeine, four different 2-aryl substituted apomorphines were synthesised in 6 steps each. Oxidation of codeine with IBX followed by acid catalysed rearrangement gave morphothebaine, which was selectively triflylated at the 2-position and subsequently *O*-acetylated at the 11-position. The resulting triflate was coupled in a Suzuki–Miyaura type reaction with a series of 4-substituted arylboronic esters which, after deprotection, gave the desired 2-aryl apomorphines. The analogues were tested for affinity towards a range of dopaminergic, serotonergic and adrenergic receptors. 2-(4-Hydroxyphenyl)-apomorphine exhibited high affinity for the dopamine D_2 receptor. A putative ligand–receptor interaction was put forward.

Introduction

The alkaloid apomorphine (**1**, Fig. 1), first synthesised in 1869 by Matthiessen and Wright[1] from morphine, displays a number of interesting biological effects toward various disorders such as erectile dysfunction[2–5] and Parkinson's disease.[6–9]

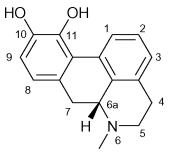
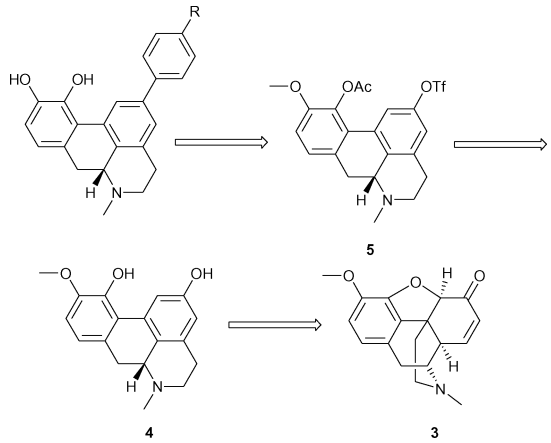


Fig. 1 (*R*)-(−)-Apomorphine, **1**.

The ability of apomorphine for agonistic binding with high efficacy to dopamine receptors has made it an object of intense research. Since apomorphine is not dopamine receptor subtype selective,[3] modifications have been made[10–13] to address the selectivity and binding affinity of apomorphine derivatives by varying the substituents at the 2-position. Many of these modifications equal or increase binding to the dopamine D_2 receptor, suggesting the presence of a receptor-excluded cavity near the 2-position. It has been suggested that this cavity in the dopamine D_2 receptor is delimited by lipophilic residues.[11] To the best of our knowledge, no derivatives of apomorphine with carbon substituents at the 2-position have been prepared so far. We set out to explore the potential hydrophobic interactions near the 2-position of the apomorphine skeleton by introduction of aryl substituents.

Results and discussion

We speculated that if we could prepare the corresponding triflate **5**, this might participate in palladium catalysed cross-coupling reactions to generate the new C–C bond (Scheme 1). The triflate **5** should be available from morphothebaine (**4**), which in turn can be prepared from codeinone (**3**) by an acid-catalysed rearrangement.



Scheme 1 Retrosynthesis of 2-arylapomorphines.

Several papers report the transformation of codeine (**2**) to codeinone (**3**) using potassium permanganate,[14] silver carbonate,[15] chromium trioxide,[16] or manganese dioxide[17,18] as oxidants or Oppenauer conditions.[19] Many of these methods suffer from low yields or toxicity of the oxidising agent.

We found that codeine (**2**) was easily oxidised by IBX[20–22] to give codeinone (**3**) in a yield of 85% (Scheme 2). Subsequent skeletal rearrangement under acidic conditions gave morphothebaine (**4**)[23,24] which was selectively triflylated at the 2-hydroxy group using 2-[*N*,*N*-bis-(trifluorosulfonyl)amino]-5-chloropyridine†. Subsequent acetylation of the 11-OH group provided **5** in 74% overall yield.‡ Triflate **5** was converted into a variety of 2-aryl aporphines (**7a**–**e**, Scheme 3) *via* a

† Triflylation using Tf_2O was attempted, but even at −78 °C extensive decomposition of the compound was observed.

‡ The ester formation proved valuable, allowing separation of the desired product from the sulfonamide formed as a byproduct in the triflylation step.

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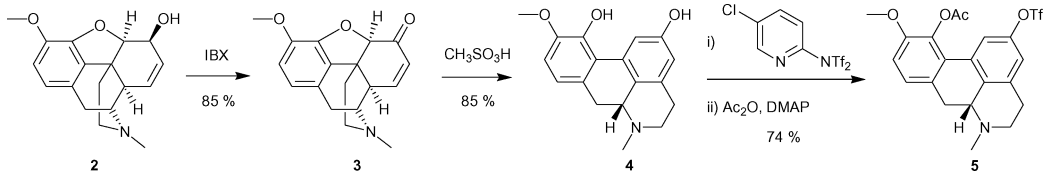
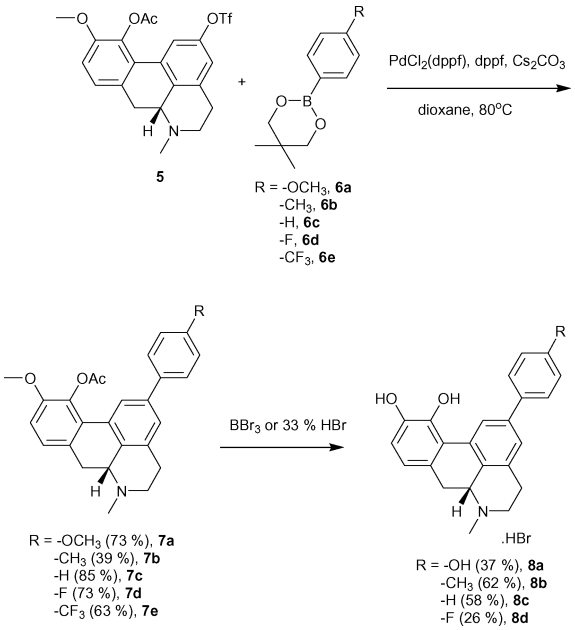


Scheme 2 Synthesis of triflate **5**.



Scheme 3 Synthesis of apomorphines **8a**–**d**.

Suzuki–Miyaura cross-coupling with boronic esters **6a**–**e** (Scheme 3). The yields ranged from 39 to 85%. Boronic esters were found to be superior coupling partners compared with the corresponding aryl potassium trifluoroborates and aryl stannanes, which gave rise to extensive reduction of the triflate to produce the parent 2-H compound. Liberation of the catechol functionality was performed by treatment with boron tribromide. Compounds **8a**–**c** were isolated in 37, 62 and 58%, respectively from aporphines **7a**–**c**. Deprotection of **7d** was not complete when applying the same conditions.§ Liberation of the catechol motif was in this case accomplished by heating in 33% hydrogen bromide in acetic acid for 36 h to give **8d** in 33% yield. Attempts to deprotect **7e** using concentrated aqueous hydrobromic acid, hydrogen bromide in acetic acid or boron tribromide were unsuccessful, since an unidentifiable byproduct was formed as the major product in a 5 : 4 ratio according to ^{1}H-NMR. Attempts to purify this mixture failed.

Binding studies

As can be seen in Table 1, introduction of an aryl group in the 2-position of apomorphine decreases binding slightly to the dopamine D_2 receptor for compounds **8b**–**d** compared to apomorphine (**1**). However, for compound **8a** binding was increased by a factor of 8. Since the corresponding 4-fluorophenyl compound **8d** has a significantly lower affinity (38-fold in binding studies towards [^{3}H]-*N*-methylspiperone and 8-fold in functional assay) for the dopamine D_2 receptor the favorable interaction between **8a** and the receptor can be ascribed to the hydrogen bond donating ability of the 4-hydroxy group. Possibly the receptor has a complementary amino acid residue able to accept this hydrogen bond at a favourable distance to the hydroxy group. Interestingly, not only is 2-(4-hydroxyphenyl)-apomorphine (**8a**) considerably more tightly bound to the dopamine D_2 receptor than apomorphine, it also appears to be more selective than apomorphine. While apomorphine appears to bind selectively to D_4, **8a** binds to D_4 with similar affinity as apomorphine but is much less potent at D_1 and D_5 and much more potent towards D_2. The fact that **8c** has similar affinity for D_2 as apomorphine supports the hypothesis put forward by Ramsby *et al.* that this receptor contains a lipophillic cavity in

§ Cleavage of the ester group occurred readily. The methyl aryl ether bond, however, was found to be difficult to cleave in this case.

Table 1 K_i values in nM[a]

	8a (R=OH)	**8b** (R=CH_3)	**8c** (R=H)	**8d** (R=F)	**1**[3]
h5-**HT**$_{1A}$ [b]	691	4135	1943	N/a	121
h5-**HT**$_{1B}$ [c]	255	1363	1524	683	6000
h5-**HT**$_{1D}$ [c]	56	4243	1509	1145	—
h5-**HT**$_{1E}$ [d]	5024	N/a	N/a	5963	—
h5-**HT**$_{2A}$ [e]	1200	2332	N/a	N/a	1000
r5-**HT**$_{2C}$ [f]	2398	N/a	N/a	N/a	200
h5-**HT**$_6$ [g]	1061	1546	453	684	2000
h5-**HT**$_7$ [g]	217	1755	567	1889	200
h**D**$_1$ [h]	167	1129	755	1217	101
h**D**$_2$ [i]	3.8 (3.2)[m]	347	88	145 (25)[m]	32
r**D**$_2$ [j]	1.0	>100	60	75	—
r**D**$_3$ [i]	3.2	879	16	831	26
h**D**$_4$ [i]	5.2 (n/a)[m]	57	21	18 (n/a)[m]	2.6
h**D**$_5$ [h]	313	4255	2359	4936	10
α_{1A} [k]	444	1676	874	606	—
α_{1B} [k]	392	N/a	N/a	1830	—
α_{2A} [l]	112	828	662	610	—
α_{2B} [l]	82	974	565	461	—
α_{2C} [l]	22	196	38	60	—

[a] Inhibition less than 50% at 10 mM is considered not active (n/a); r = rat, h = human. Data represent mean K_i (N = 4). [b] [^{3}H]-8-OH-DPAT. [c] [^{3}H]-GR125743. [d] [^{3}H]-5-HT. [e] [^{3}H]-Ketanserin. [f] [^{3}H]-Mesulergine. [g] [^{3}H]-LSD. [h] [^{3}H]-SCH23390. [i] [^{3}H]-*N*-Methylspiperone. [j] [^{3}H]-Raclopride. [k] [^{3}H]-Prazosin (1 nM). [l] [^{3}H]-Clonidine (2 nM). [m] EC_{50} value for D_{2long} receptor activation. Biological data of **1** was found in the literature (see ref. 3).

the proximity of the 2-position of apomorphine in its optimal binding mode.[11] Introduction of a methyl group in the 4-position of the 2-aryl moiety, as in compound **8c**, is detrimental to binding to the D_2 receptor compared to 2-phenylapomorphine (**8c**) as binding decreases by a factor of 4. Fig. 2 shows the inhibition curves for **8a**, **8c** and **8d** (with NPA as standard) for binding to rat striatum homogenate. From dose–response studies on receptor function it was found that **8a** and **8d** indeed are dopamine D_2 full agonists having EC_{50} values of 3.2 nM (95% activation compared to quinpirole) and 25 nM (91% activation compared to quinpirole) (Fig. 3), respectively, whereas they do not activate D_4 significantly compared to dopamine. In general, all four synthesised apomorphine analogues display minor affinity for the serotonergic and adrenergic receptors even though some affinity for the α_{2C} was observed for **8a**, **8c** and **8d**.

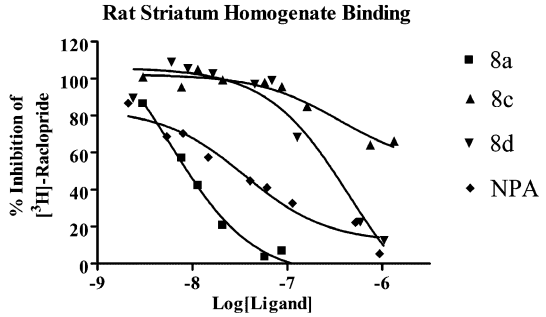


Fig. 2 Inhibition curves for ligands **8a**, **8c** and **8d**.

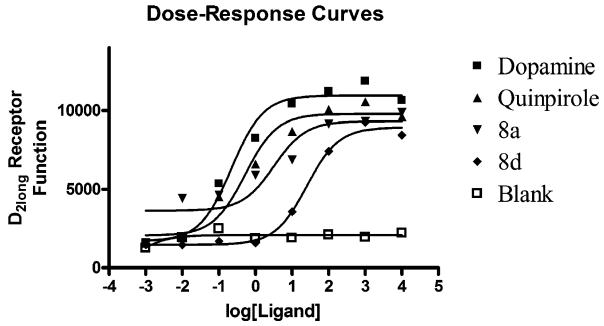


Fig. 3 Dose–response curves of **8a** and **8d** with dopamine and quinpirole as standards.

In summary, we have synthesised four 2-aryl apomorphines in 6 steps from codeine in modest overall yield ranging from 10 to 26%. Binding studies showed that **8a** was much more potent in binding to the dopamine D_2 receptor and more selective than apomorphine. A putative explanation for the high affinity is the ability of the 4-hydroxy group in **8a** to donate a hydrogen bond to a complementary amino acid residue in the receptor. The fact that **8c** has similar affinity to the D_2 receptor as apomorphine supports the hypothesis that this receptor contains a lipophillic cavity in the proximity of the 2-position of apomorphine in its optimal binding mode. **8b** has only some activity at the dopamine D_4 receptor whereas **8d** was highly potent towards the dopamine D_2 receptor in a functional assay.

Experimental section

General

Solvents were distilled under anhydrous conditions. All reagents were used without further purification. Evaporation was performed on a rotary evaporator with the temperature kept below 40 °C. Glassware used for moisture sensitive reactions were flame-dried under reduced pressure and cooled to room temperature under a stream of nitrogen prior to use. Columns were packed with silica gel 60 (230–400 mesh) as the stationary phase. TLC plates (Merck 60, F_{254}) were visualised by dipping in a solution containing ninhydrin (0.6 g), acetic acid (1.5 mL) and water (13.3 mL) in *n*-BuOH (300 mL) and heating until coloured spots appeared. ^{1}H-NMR, gCOSY and gHSQC were performed on a Varian Mercury-plus 300 MHz (IDPFG). ^{13}C-NMR was performed on a Varian Gemini 300 MHz. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a JMS-HX/HX110A tandem mass spectrometer.

Codeinone (3). Codeine (**2**) (1.30 g, 4.34 mmol, 1.0 eq.) was dissolved in DMF (20 mL). Freshly prepared IBX (1.22 g, 4.34 mmol, 1.0 eq.) was added in one portion under vigorous stirring. As the reaction proceeded, the mixture changed appearance from a heterogeneous colourless mixture to a deep red homogeneous solution. The mixture was stirred for 2 h before diluting with DCM (50 mL) and water (50 mL). The two phases were separated and the water phase was extracted with DCM. The combined organic phase was washed three times with a saturated aqueous solution of $NaHCO_3$ before drying (Na_2SO_4), filtration and concentration. The crude product was purified by chromatography ($R_f = 0.40$ in MeOH–$CHCl_3$ 1 : 9) to give codeinone (1.10 g, 85%) as a red-brownish powder. Upon recrystallisation in benzene–cyclohexane (1 : 10),[25] codeinone appeared as slightly red needles which on prolonged standing turned deep red.

Mp: 180–181 °C (lit.[26] 184–185 °C). Spectral data was in agreement with published data.[27]

(*R*)-(−)-2,11-Dihydroxy-10-methoxyaporphine (morphothebaine) (4). Codeinone (**3**) (2.02 g, 6.79 mmol, 1.0 eq.) was dissolved in CH_3SO_3H (15 mL) and the mixture was heated at 95 °C under stirring for 1.5 h. After cooling to room temperature the resultant dark red solution was neutralised by adding it carefully to a slurry of $NaHCO_3$ (50 g) in water (300 mL) under vigorous stirring. The slurry was stirred for another 30 min before extraction ($CHCl_3$), washing of the combined organic phase (brine), drying ($MgSO_3$), filtration and concentration. The resultant solid was purified by flash chromatography ($R_f = 0.18$ in MeOH–$CHCl_3$ 1 : 9) to give morphothebaine (**4**) (1.72 g, 85%) as a greenish powder.

NMR spectral data was in agreement with previously published data.[28]

(*R*)-(−)-11-Acetoxy-10-methoxy-2-(trifluoromethanesulfonyloxy)-*N*-methylaporphine (5). To a slurry of morphothebaine (**4**) (1.48 g, 4.86 mmol, 1.0 eq.) in $CHCl_3$ (30 mL) was added 2-[*N*,*N*-bis-(trifluorosulfonyl)amino]-5-chloropyridine (2.15 g, 5.48 mmol, 1.1 eq.) and NEt_3 (2.1 mL, 14.9 mmol, 3.0 eq.). The mixture was stirred for 3 h before adding acetic anhydride (0.52 mL, 5.48 mmol, 1.1 eq.), another charge of NEt_3 (3.5 mL, 24.9 mmol, 5.0 eq.) and a catalytic amount of DMAP (*ca.* 5 mg). Stirring was then continued for 2 h before washing once with saturated aqueous $NaHCO_3$. The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a syrup which was exposed to column chromatography ($R_f = 0.38$ in MeOH–$CHCl_3$ (1 : 9)) to give triflate **5** (2.99 g, 78% in two steps) as a yellow foam.

δ_H(300 MHz, $CDCl_3$) 7.80 (br s, 1H, H1), 7.15 (d, 1H, H8/H9, J(8,9) = 8.2 Hz), 6.99 (d, 1H, H3, J(3,1) = 2.3 Hz), 6.92 (d, 1H, H8/9), 3.85 (s, 3H, ArOCH_3), 3.44–3.04 (m, 4H), 2.80 (dd, 1H, J = 2.9 Hz, 17.0 Hz), 2.72–2.50 (m, 5H (s, 3H, =NCH_3)), 2.34 (s, 3H, ArOCOCH_3). δ_C(75 MHz, $CDCl_3$) 168.9 (ArO*C*OCH$_3$), 151.2, 148.3, 137.4, 135.0, 133.5, 129.0, 126.7, 126.7, 126.3, 120.5, 119.1 (q, –OSO_2CF_3, J(C,F) = −320 Hz), 118.8, 112.5 (Ar), 62.3 (C6a), 56.7(ArO*C*H$_3$), 52.7 (C5), 44.0 (=N*C*H$_3$), 34.0 (C7), 29.3 (C4), 21.2(ArOCO*C*H$_3$). $[\alpha]_D^{25}$ −63.7 (*c* 1, $CHCl_3$). HRMS (ES): 472.1031, calc for $C_{21}H_{20}F_3NO_6S$ + H: 472.1042.

(*R*)-(−)-11-Acetoxy-2-(4-methoxyphenyl)-10-methoxyaporphine (7a). Triflate **5** (234 mg, 0.50 mmol, 1.0 eq.), boronic ester **6a** (328 mg, 1.49 mmol, 3 eq.), Cs_2CO_3 (485 mg, 1.49 mmol, 3 eq.), dppf (28 mg, 0.050 mmol, 0.10 eq.) and $PdCl_2$(dppf)

(41 mg, 0.050 mmol, 0.10 eq.) were mixed in dry deoxygenated dioxane (2 mL). The mixture was heated to 80 °C under N_2 for 5 h before adding water (20 mL) and EtOAc (20 mL). The phases were separated and the aqeueos phase was extracted (EtOAc). The combined organic phase was washed several times with saturated aqeueos $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resultant syrup was exposed to column chromatography (R_f = 0.11 in EtOAc) to give pure aporphine **7a** (155 mg, 73%) as a yellowish foam. δ_H(300 MHz, $CDCl_3$) 8.05 (br s, 1H, H1), 7.54–7.48 (m, 2H, 2-Ar), 7.27 (s, 1H, H3), 7.13 (d, 1H, H8/H9, J(8,9) = 8.3 Hz), 6.98–6.92 (m, 2H, 2-Ar), 6.86 (d, 1H, H8/H9), 3.84 (s, 6H, 2xArOCH_3), 3.38–3.04 (m, 4H), 2.80 (dd, 1H, J = 2.8 Hz, J = 16.2 Hz), 2.66–2.53 (m, 2H), 2.58 (s, 3H, =NCH_3), 2.23 (s, 3H, –OCOCH_3). δ_C(75 MHz, $CDCl_3$) 168.3 (ArO*C*OCH$_3$), 158.8, 150.6, 138.6, 136.6, 133.1, 132.9, 130.8, 128.8, 127.9, 127.7, 127.5, 126.2, 125.7, 123.6, 114.0, 110.8 (Ar), 61.9 (C6a), 56.1 (ArO*C*H$_3$), 55.2 (ArO*C*H$_3$), 52.7 (C5), 43.5 (=N*C*H$_3$), 34.0 (C7), 28.8 (C4), 21.0 (ArOCO*C*H$_3$). $[\alpha]_D^{25}$ −127.0 (*c* 0.20, $CHCl_3$). HRMS (EI): 429.1925 calc. for $C_{27}H_{27}NO_4$ 429.1940.

(*R*)-(−)-11-Acetoxy-2-(4-tolyl)-10-methoxyaporphine (7b). This compound was prepared in a similar manner to **7a** but using 4-tolylboronic ester **6b** as starting material which gave aporphine **7b** as a brown oil in a yield of 39%. R_f = 0.11 in EtOAc.

δ_H(300 MHz, $CDCl_3$) 8.06 (br s, 1H, H1), 7.48 (d, 2H, 2-Ar, J_{ortho} = 8.1 Hz), 7.29 (d, 1H, H3, J(1,3) = 1.7 Hz), 7.22 (d, 2H, 2-Ar), 7.12 (d, 1H, H8/H9, J(8,9) = 8.2 Hz), 6.85 (d, 1H, H8/H9), 3.38–3.04 (m, 4H), 2.80 (dd, 1H, J = 2.8 Hz, J = 16.2 Hz), 2.65–2.52 (m, 2H), 2.57 (s, 3H, =NCH_3), 2.40 (s, 3H, ArCH_3), 2.23 (s, 3H, ArOCOCH_3). δ_C(75 MHz, $CDCl_3$) 168.5 (ArO*C*OCH$_3$), 150.9, 139.2, 137.9, 137.0, 136.9, 133.3, 133.1, 131.1, 129.5, 129.0, 127.9, 126.7, 126.6, 125.9, 124.1, 111.1 (Ar), 62.0 (C6a), 56.2 (ArO*C*H$_3$), 53.8 (C5), 43.5 (=NCH$_3$), 34.0 (C7), 28.7 (C4), 21.1, 21.0 (Ar*C*H$_3$ and ArOCO*C*H$_3$). $[\alpha]_D^{25}$ −107 (*c* 0.20, $CHCl_3$). HRMS (EI): 413.1959 calc. for $C_{27}H_{27}NO_3$ 413.1991.

(*R*)-(−)-11-Acetoxy-2-phenyl-10-methoxyaporphine (7c). This compound was prepared in a similar manner to **7a** but using phenylboronic ester **6c** as starting material which gave aporphine **7c** as a brown oil in a yield of 85%. R_f = 0.11 in EtOAc.

δ_H(300 MHz, $CDCl_3$) 8.10 (br s, 1H, H1), 7.56 (dd, 2H, 2-Ph, J_{meta} = 1.5 Hz, J_{ortho} = 7.1 Hz), 7.46–7.38 (m, 2H, 2-Ph), 7.37–7.30 (m, 2H, H3 + 2-Ph H), 7.14 (d, 1H, H8/H9, J(8,9) = 8.2 Hz), 6.87 (d, 1H, H8/H9), 3.84 (s, 3H, ArOCH_3), 3.55–3.10 (m, 5H), 2.86 (dd, 1H, J = 17.2 Hz), 2.80–2.72 (m, 2H), 2.68 (s, 3H, =NCH_3), 2.27 (s, 3H, ArOCOCH_3). δ_C(75 MHz, $CDCl_3$) 168.8 (ArO*C*OCH$_3$), 151.2, 141.0, 139.8, 137.2, 133.1, 131.4, 129.1 (2 signals), 128.9, 128.0, 127.6, 127.2, 127.0, 126.2, 124.6, 111.5 (Ar), 62.2 (C6a), 56.4 (ArO*C*H$_3$), 52.9 (C5), 43.4 (=N*C*H$_3$), 33.9 (C7), 28.6 (C4), 21.2 (ArOCO*C*H$_3$). $[\alpha]_{578}^{25}$ −225 (*c* 0.15, $CHCl_3$). HRMS (EI): 399.1839 calc. for $C_{26}H_{25}NO_3$ 399.1834.

(*R*)-(−)-11-Acetoxy-2-(4-fluorophenyl)-10-methoxyaporphine (7d). This compound was prepared in a similar manner to **7a** but using phenylboronic ester **6d** as starting material which gave aporphine **7d** as an off-white solid in a yield of 73%. R_f = 0.13 in EtOAc.

Mp decomp. at 77–79 °C. δ_H(300 MHz, $CDCl_3$) 8.00 (br s, 1H, H1), 7.58–7.48 (m, 2H, 2-Ar), 7.25 (s, 1H, H3), 7.14 (d, 1H, H8/H9, J(8,9) = 7.9 Hz), 7.12–7.05 (m, 2H, 2-Ar), 6.87 (d, 1H, H8/H9), 3.85 (s, 3H, ArOCH_3), 3.32–3.00 (m, 4H), 2.80 (dd, 1H, J = 2.6 Hz, J = 15.8 Hz), 2.63–2.49 (m, 2H), 2.55 (s, 3H, =NCH_3), 2.25 (s, 3H, ArOCOCH_3). δ_C(75 MHz, $CDCl_3$) 168.5 (–O*C*OCH$_3$), 162.4 (d, *C*–F, J(C,F) = 246 Hz), 150.9, 138.2, 137.1, 136.9, 134.2, 133.6, 131.2, 129.3, 128.4, 128.3, 127.9, 126.7, 125.9, 124.0, 115.8, 115.5, 111.2, (Ar), 62.1 (C6a), 56.2 (ArO*C*H$_3$), 52.8 (C5), 43.8 (=N*C*H$_3$), 34.2 (C7), 29.1 (C4), 21.0 (ArOCO*C*H$_3$). $[\alpha]_D^{25}$ −213 (*c* 0.19, $CHCl_3$). HRMS (EI): 417.1711 calc. for $C_{26}H_{24}FNO_3$ 417.1740.

(*R*)-(−)-11-Acetoxy-2-(4-trifluoromethylphenyl)-10-methoxyaporphine (7e). This compound was prepared in a similar manner to **7a** but using 4-trifluoromethylphenylboronic ester **6e** as starting material which gave aporphine **7e** as a yellowish solid in a yield of 63%. R_f = 0.13 in EtOAc.

Mp decomp. 89–91 °C. δ_H(300 MHz, $CDCl_3$) 8.06 (br s, 1H, H1), 7.68 (br s, 4H, 2-Ar), 7.31 (br s, 1H, H3), 7.15 (d, 1H, H8/H9, J(8,9) = 8.2 Hz), 6.89 (d, 1H, H8/H9), 3.85 (s, 3H, ArOCH_3) 3.33–3.02 (m, 4H), 2.82 (dd, 1H, J = 1.9 Hz, J = 15.2 Hz), 2.58 (s, 3H, =NCH_3), 2.65–2.50 (m, 2H), 2.25 (s, 3H, ArOCOCH_3). δ_C(75 MHz, $CDCl_3$) 168.7 (ArO*C*OCH$_3$), 151.1, 144.7, 137.9, 137.1, 135.5, 134.2, 131.7, 129.5, 127.9, 127.3, 127.2, 126.2, 126.0, 125.9, 124.4, 111.5 (Ar), 62.4 (C6a), 56.4 (ArO*C*H$_3$), 53.0 (C5), 44.1 (=N*C*H$_3$), 34.4 (C7), 29.3 (C4), 21.2 (ArOCO*C*H$_3$). $[\alpha]_D^{25}$ −170 (*c* 0.19, $CHCl_3$). HRMS (EI): 467.1702 calc. for $C_{27}H_{24}F_3NO_3$ 467.1708.

(*R*)-(−)-2-(4-Hydroxyphenyl)apomorphine hydromide bromide (8a). Aryl methyl ether **7a** (58 mg, 0.135 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (2 mL). To this solution was carefully added BBr_3 (1.35 mL, 1 M solution in CH_2Cl_2, 1.35 mmol, 10 eq.) under nitrogen. After 1.5 h the mixture was concentrated to dryness. The residue was taken up in MeOH (10 mL) and refluxed under nitrogen for 30 min before concentrating to dryness. After dissolution of the resultant oil in MeOH (10 mL) and addition of activated carbon, the mixture was heated to reflux and quickly filtered through a pad of celite. Concentration of the mother liquid followed by washing of the remaining oil with CH_2Cl_2 and $CHCl_3$ gave pure apomorphine hydrobromide **8a** (22 mg, 37%) as an off-white solid.

Mp > 250 °C. δ_H(300 MHz, DMSO-d_6) 9.90 (br s, 1H, disappears with D_2O), 9.65 (br s, 1H, disappears with D_2O), 9.60 (br s, 1H, disappears with D_2O), 8.85 (br s, 1H, disappears with D_2O), 8.50 (br s, 1H, H1), 7.45 (d, 2H, 2-Ar, J_{ortho} = 8.6 Hz), 7.35 (br s, 1H, H3), 6.35 (d, 2H, 2-Ar), 6.75 (d, 1H, H8/H9, J(8,9) = 7.9 Hz), 6.68 (d, 1H, H8/H9), 4.35 (br s, 1H, H6a), 3.76 (br s, 1H, $H5_a$), 3.20–3.00 (m, 4H, =NCH_3 + $H4_b$), 2.68 (t, 1H, $H7_b$, J(7_b,7_a) = 13.5 Hz). Three signals (from $H4_a$, $H5_b$ and $H7_a$) coincide with the water signal at 3.33 ppm. δ_C(75 MHz, DMSO-d_6) 158.1, 145.9, 144.1, 140.2, 133.5, 131.5, 131.0, 128.6, 127.6, 125.6, 125.3, 125.2, 120.6, 119.6, 116.6, 115.1 (Ar), 62.2 (C6a), 52.2 (C5), 31.6 (C7), 26.7 (C4). Signal corresponding to =N*C*H$_3$ coincides with DMSO. $[\alpha]_D^{25}$ −183 (*c* 0.10, DMSO). HRMS (EI): 358.1454, calc for $C_{23}H_{20}NO_3^+$ (M-1 peak of free amine) 358.1443.

(*R*)-(−)-2-(4-Tolyl)-apomorphine hydromide bromide (8b). Was prepared in a similar way as **8a** except that **7b** (35 mg, 0.0846 mmol) was used as starting material which gave **8b** (23 mg, 62%) as an off-white solid.

Mp > 250 °C. δ_H(300 MHz, DMSO-d_6): 10.05 (br s, 1H, disappears with D_2O), 9.70 (br s, 1H, disappears with D_2O), 8.85 (br s, 1H, disappears with D_2O), 8.52 (br s, 1H, H1), 7.51 (d, 2H, 2-Ar, J_{ortho} = 8.1 Hz), 7.40 (br s, 1H, H3), 7.30 (d, 2H, 2-Ar), 6.85–6.60 (m, 2H, H8 + H9), 4.38 (br s, 1H, H6a), 3.78 (br s, 1H, $H5_a$), 3.20–3.00 (m, 4H, =NCH_3 + $H4_b$), 2.78–2.64 (m, 1H, $H7_b$). Three signals (from $H4_a$ + $H5_b$ + $H7_a$) coincide with the water signal at 3.33 ppm. δ_C(75 MHz, DMSO-d_6) 145.9, 144.2, 140.1, 137.9 (2 signals), 133.7, 131.2, 130.5, 128.3, 127.3, 126.0, 125.7, 125.2, 120.5, 119.6, 115.2 (Ar), 62.2 (C6a), 52.2 (C5), 41.8 (= N*C*H$_3$), 31.5 (C7), 26.6 (C4), 21.6 (Ar*C*H$_3$). $[\alpha]_D^{25}$ −74.8 (c 0.13, DMSO). HRMS (EI): 356.1646, calc for $C_{24}H_{22}NO_2^+$ (M-1 peak of free amine) 356.1651.

(*R*)-(−)-2-Phenylapomorphine hydromide bromide (8c). This compound was prepared in a similar manner to **8a** except that **7c** (29 mg, 0.0726 mmol, 1.0 eq.) was used as starting material which gave **8c** (18 mg, 58%) as a slightly brown coloured oil.

δ_H(300 MHz, CD_3OD) 8.71 (d, 1H, H1, J(1,3) = 1.7 Hz), 7.68–7.58 (m, 2H, 2-Ar), 7.48–7.30 (m, 4H, 2-Ar + H3), 6.75 (d, 1H, H8/H9, J(8,9) = 7.9 Hz), 6.70 (d, 1H, H8/H9), 4.23 (dd, 1H, H6a, $J(6a,7_a)$ = 3.5 Hz, $J(6a,7_b)$ = 13.9 Hz), 3.80 (m, 1H, $H5_a$), 3.50–3.30 (m, 3H, $H4_a$, $H5_b$, $H7_a$), 3.18 (s, 3H, =NCH_3), 3.20–3.10 (m, 1H, $H4_b$), 2.82 (t, 1H, $H7_b$, $J(7_a,7_b)$ = 13.6 Hz). δ_C(75 MHz, CD_3OD) 145.4, 143.8, 141.2, 140.7, 133.6, 130.0, 129.0, 127.7, 127.1, 127.0, 126.4, 125.4, 124.4, 119.8, 119.1, 114.4 (Ar), 63.1 (C6a), 52.7 (C5), 41.2 (=NCH_3), 31.7 (C7), 26.3 (C4). $[\alpha]^{25}_{578}$ −100 (*c* 0.53, MeOH). HRMS (EI) 342.1496, calc for $C_{23}H_{20}NO_2^+$ (M-1 peak of free base) 342.1494.

(*R*)-(−)-2-(4-Fluorophenyl)apomorphine hydrobromide (8d). Aryl methyl ether **7d** (117 mg, 0.280 mmol, 1.0 eq.) was taken up in 33% HBr in AcOH (2.5 mL) and heated to 120 °C under nitrogen for 36 h. The mixture was allowed to cool to room temperature before concentration to dryness. The resultant syrup was then taken up in conc. aqueous HBr (2.5 mL) and heated to 120 °C under nitrogen for 2 h. The mixture was cooled to room temperature before concentrated to dryness. The redish solid was dissolved in MeOH (5 mL) followed by the addition of activated carbon (100 mg) and heated to reflux. The slurry was quickly filtered through a pad of celite and concentrated *in vacuo*. The residue was taken up as a slurry in CH_2Cl_2–EtOAc (1 : 7) and centrifuged. Washing of the solid several times with EtOAc gave apomorphine **7d** (32 mg, 26%) as an off-white solid.

Mp > 250 °C. δ_H(300 MHz, CD_3OD): 8.60 (br s, 1H, H1), 7.60 (dd, 2H, 2-Ar, J = 5.3 Hz, J = 8.7 Hz), 7.30 (br s, 1H, H3), 7.07 (t, 1H, 2-Ar, J = 8.7 Hz), 6.70–6.55 (m, 2H, H8 + H9), 4.20 (br d, 1H, H6a, $J(6a,7_a)$ = 13.1 Hz), 3.70 (br s, 1H, $H5_a$), 3.50–3.15 (m, 3H, $H4_a$, $H5_b$, $H7_a$), 3.15–2.96 (m, 4H, =NCH_3 + $H4_b$), 2.72 (t, 1H, $H7_b$, $J(7_b,7_a)$ = 12.4 Hz). δ_C(75 MHz, CD_3OD): 163.0 (d, 2-Ar, J(C,F) = −245 Hz), 145.3, 144.0, 140.1, 137.0, 133.6, 130.1, 128.8 (d, 2-Ar, J(C,F) = 8.1 Hz), 127.1, 126.2, 125.3, 124.5, 119.7, 119.1, 115.6 (d, 2-Ar, J(C,F) = 21.7 Hz), 114.4 (Ar), 62.8 (C6a), 52.5 (C5), 40.9 (=NCH_3), 31.7 (C7), 25.9 (C4). All aliphatic signals are broad. $[\alpha]^{25}_{578}$ −118.0 (*c* 0.13, MeOH). HRMS (ES): 360.1386, calc. for $C_{23}H_{19}FNO_2^+$ (M-1 peak of free base) 360.1400.

Binding studies

Binding studies and the functional assay,[29] except D_2 (conditions "j"), were performed *via* the NIMH Psychoactive Drug Screening Program (PDSP). Conditions for the individual binding assays are available from the PDSP homepage (http://pdsp.cwru.edu/).

Binding studies (D_2^j) were performed as follows. Membrane preparation for homogenate: Male rats (240–260 g, SPRG) were sacrificed by decapitation. The brains were quickly removed, dissected into the areas of interest, and stored at −80 °C until use. The selected brain areas (striatum and cerebellum) were homogenized in Tris–HCl buffer (5 mmol Trisma Base, 120 mmol NaCl and 5 mmol KCl, pH 7.4) (*ca.* 1 g brain per 10 mL buffer) using a Polytron homogeniser and centrifuged at 33000 G for 10 min. The pellet were homogenized and centrifuged a second time in Tris–HCl buffer. The final pellet were resuspended in Tris–HCl buffer (*ca.* 1 g brain per 10 mL buffer) and distributed in NUNC tubes (4.5 mL per tube). The homogenate was stored at −80 °C until use. Approximately 5 rats are required per NUNC tube of homogenate, equivalent to one binding experiments. In vitro determination of K_i for compounds **8a**, **8c** and **8d** against the dopamine D_2 receptor antagonist [^{3}H]-raclopride in rat brain. Homogenate binding: 50 µL homogenate was incubated in 950 µL Tris–HCl buffer (5 mmol Trisma Base, 120 mmol NaCl and 5 mmol KCl, pH 7.4) containing 0.5 nM [^{3}H]-raclopride and various concentrations of the test compound (0.5 nM–5 µM) for 60 min, at 30 °C, as described by Köhler.[30] Inhibition with various concentrations of NPA (0.5 nM–5 µM) was made as a reference. Non-specific binding (NSB) was determined by the binding of 0.5 nM [^{3}H]-raclopride in cerebellum homogenate. The incubation was terminated, as previously described[31] by filtration using a 24-channel cell harvester (Brandel, Gaithersburg, MD, USA), 5 mL Tris–HCl buffer was used for washing, and the samples filtrated through a Whatman GF/B filter. The filters were soaked with 0.5% poly(ethylenimine) (0.5% PEI) prior to filtration in order to reduce and stabilize non-specific binding to the filters. The filters were then dried overnight and counted in an Ultima Gold counter (Packard Instrument Company, USA). Determinations were made in duplicates with three independent experiments.

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