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Synthesis and neuropharmacological evaluation of 2-aryl- and alkylapomorphines

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Abstract—A novel synthesis has been elaborated for the pharmacologically remarkable 2-arylapomorphines described and characterized in the last few years. This new procedure contains two alternative synthetic routes and has allowed the preparation of several hitherto unknown compounds as well. The pharmacological profile of the previously published and the novel 2-alkyl- and arylapomorphines has been determined with the application of in vitro and in vivo techniques. For 2-phenyl- (**2**) and 2-(4-hydroxyphenyl)apomorphines (**3**) the superior dopamine agonist profile has been confirmed and for the novel compounds some remarkable results have been observed.

1. Introduction

The ability of (*R*)-apomorphine (**1**, Fig. 1) and its 2-substituted derivatives for binding to dopamine receptors has been widely studied in the last decades.[1] As a result of that, drug products are now commercially available containing apomorphine hydrochloride as active substance. The indications aimed are those disorders which are in connection with the abnormal functioning of dopaminergic system, especially Parkinson's disease and erectile dysfunction. It is also known that apomorphine is not dopamine-receptor subtype selective, this feature suggests the need for the preparation of apomorphines modified in 2-position.

Several studies into dopamine-receptor binding emphasize the effect of the presence of a hydrophobic group in the proximity of 2-position of the aporphine skeleton.[2] This effect is in agreement with the model of dopamine D_2 receptors suggested by Ramsby et al. According to this model there is a lipophilic cavity on the surface of the receptor next to the binding site.

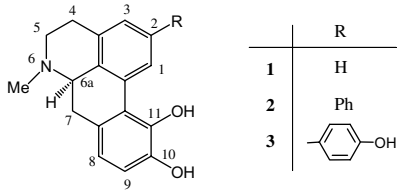

Figure 1. Apomorphine and its 2-aryl derivatives.

On the basis of this principle, Søndergaard et al.[3] synthesized 2-phenylapomorphine (**2**) and 2-(4-hydroxyphenyl)-apomorphine (**3**) among other 2-arylapomorphines. These two derivatives have superior affinity to D_2 receptors in comparison to apomorphine (**1**). Furthermore, the D_3/D_2 selectivity of the above-mentioned derivatives **2** and **3** also exceeded the same ratio for reference compound **1**.

2. Chemistry

Our conception for the formation of new C–C bond at 2-position was based on Suzuki reaction.[4] Several papers report remarkable effectiveness of palladium catalyzed cross-couplings in the formation of aryl–aryl and aryl–alkyl type C–C bonds starting from aryl halides.

Keywords: Apomorphine; Dopamine receptor subtypes; D_3/D_2 selectivity; Suzuki–Miyaura reaction.
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In the field of aporphine chemistry Hedberg et al.[5] used this coupling reaction in the synthesis of 11-phenyl and methyl-aporphine. Søndergaard et al.[3] used Suzuki-type reaction in the preparation of four different 2-arylapomorphines. These syntheses used triflates in the cross-coupling.

In preliminary publications we reported the application of Suzuki reaction for either the preparation of 2-arylapomorphines from 2-bromoapocodeine (**5**)[6a] or the application of a double strategy to obtain 3-alkyl- and arylapomorphines.[6b]

In this paper a successful extension of the double strategy has been presented for the synthesis of 2-alkyl- and arylapomorphines **2, 3, 11–13**.

Both reaction routes were based on 6-bromo-6-demethoxythebaine (**4**). The synthesis of this compound[7] was first reported by our research group in 1984. The preparation and the chemical behavior of halo-substituted morphinandienes were extensively studied in our laboratory.[8,9] We found that 6-chloro-6-demethoxythebaine could also be used to give rise of the target molecules, however, with considerably lower yield in comparison to its bromo congener **4**.

The original conception (synthesis route I) was to accomplish the acid-catalyzed rearrangement of 6-bromo-6-demethoxythebaine (**4**) into 2-bromo-apocodeine (**5**), a potentially suitable partner for Suzuki reaction (Scheme 1). The obtained 2-substituted apocodeines **6–10** were converted into the aimed 2-substituted apomorphines via an *O*-demethylation step using methanesulfonic acid/methionine reactant mixture.

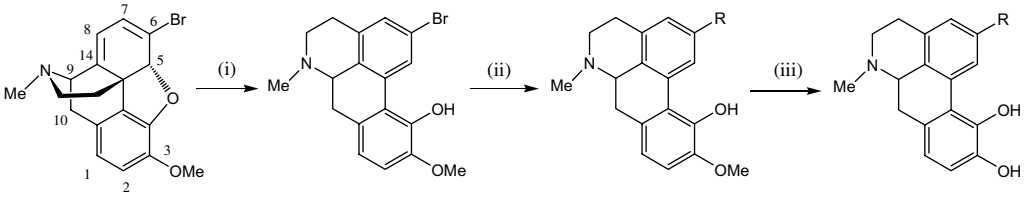
The aryl halide type 2-bromoapocodeine (**5**), as the basic compound of the Suzuki reaction, was prepared by acid-catalyzed rearrangement of 6-bromo-6-demethoxythebaine (**4**). The average yields of the palladium-catalyzed reaction were high and the products were easily obtained from the reaction mixtures. The cross-coupling step on the original 6-bromo-6-demethoxythebaine (**4**) was also attempted (synthesis route II). The same Suzuki cross-coupling conditions were applied as in the case of 2-bromoapocodeine (**5**, Scheme 2).

In Table 1 the yields of every single 2-aryl- and alkyl-apocodeines **6–10** prepared via either 2-bromoapocodeine (**5**) or 6-aryl- and alkyl-morphinandienes **14–18** were compared. It can be concluded that the yields for vinyl halide type morphinandienes were lower than that of the aryl halide, but still practically suitable for the synthesis of the target molecules.

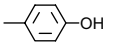
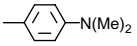
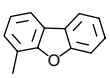
The acid-catalyzed rearrangement of the morphinandienes and the *O*-demethylation of the obtained apocodeines by methionine/methanesulfonic acid reaction mixture[10] are routinely performed in our laboratory and presented in several papers. The apomorphine derivatives were prepared in HCl salt form to assure the water solubility of the compounds in the pharmacological studies.

3. Results and discussion

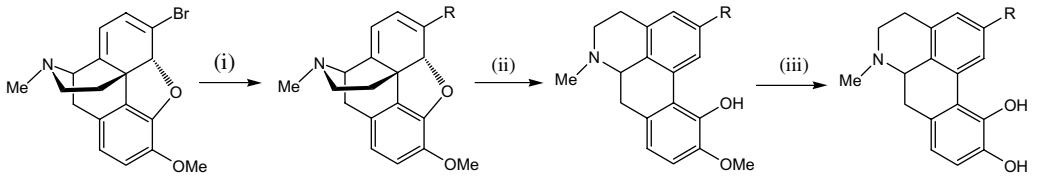
In vitro affinity for the dopamine D_2 and D_3 receptors of the hydrochloride salts of the presented 2-methyl- and arylapomorphines (**2, 3, 11–13**) was determined in order to discover their pharmacological profile. In the case of dopamine D_2 affinity rat-brain striatal membrane homogenate was prepared and displacement of [^{3}H]spiperone (0.5 nM) was determined. Membrane preparation containing recombinant rat D_3 receptors expressed in Sf9 cells was used for the determination of D_3 affinity and the displacement of radioligand [^{3}H]spiperone was studied. The obtained K_i results for the characterization



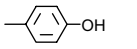
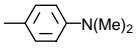
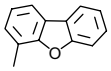
4 **5** **6 - 10** **2, 3, 11 - 13**

R	
Me	**6, 11**
Ph	**7, 2**
	**8, 3**
	**9, 12**
	**10, 13**

Scheme 1. Synthesis route I. Reagents: (i) CH_3SO_2OH, 90 °C, 30 min; (ii) R-$B(OH)_2$, $Ba(OH)_2.8H_2O$, $PdCl_2(PPh_3)_2$, 1,4-dioxane:H_2O = 4:1, 90 °C, 30 min; (iii) CH_3SO_2OH, methionine, 90 °C, 2 h.

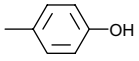
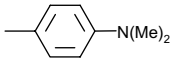
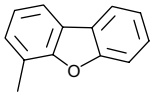


4 14 - 18 6 - 10 2, 3, 11 - 13

R	
Me	**14, 6, 11**
Ph	**15, 7, 2**
	**16, 8, 3**
	**17, 9, 12**
	**18, 10, 13**

Scheme 2. Synthesis route II. Reagents: (i) R-$B(OH)_2$, $Ba(OH)_2.8H_2O$, $PdCl_2(PPh_3)_2$, 1,4-dioxane:H_2O = 4:1, 90 °C, 30 min; (ii) CH_3SO_2OH, 90 °C, 30 min; (iii) CH_3SO_2OH, methionine, 90 °C, 2 h.

Table 1. Comparison of yields of 2-aryl- and alkylapocodeines **6**–**10** (synthesis routes I & II)

Compound	R	Yield* (%) Synthesis route I	Yield* (%) synthesis route II
6	Me	60	66
7	Ph	74	74
8		53	63
9		30	53
10		29	54

* All yields are referred to the starting 6-bromo-6-demethoxythebaine (**4**) and are the averages of 3 runs.

of D_2 and D_3-binding affinities and the D_3/D_2-binding selectivity data are presented in Table 2. The affinity of (*R*)-(−)-2-phenylapomorphine (**2**) and (*R*)-(−)-2-(4-hydroxyphenyl)-apomorphine (**3**) for the D_2 and D_3 receptors was significantly higher than those for (*R*)-(−)-apomorphine (**1**) in accordance with Søndergaard's results. The D_3/D_2 binding selectivities of these compounds are similar to those of the reference compound **1**.

In connection with novel compounds it could be emphasized that the affinity of 2-methyl- and 2-(4-dibenzofuranyl)-congeners to D_3 receptor subtype was found to be similar to that of the apomorphine (**1**). However, in case of the presence of small methyl substituent, the binding potency for D_2 subtype was superior in comparison with that of the reference compound **1**, on the other hand in case of the insertion of large heteroaromatic substituent (i.e. dibenzofuranyl) at 2-position in case of compound **13** the affinity for D_2 receptor was very low which led to a remarkable increase of D_3 selectivity. For (*R*)-(−)-2-(4-*N,N*-dimethyl-aminophenyl)-apomorphine (**12**) moderate binding-affinities were observed for both dopamine-receptor subtypes. The in vivo activity of compounds **2, 3, 11**–**13** was determined by the determination of dopamine turnover index in male mice. Apomorphine derivatives **2, 3, 11**–**13** were subcutaneously given to mice at a dose of 3.29 μmol/kg (equivalent to 1.0 mg/kg apomorphine.HCl administration). After their sacrifice dopamine (DA), dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA) concentrations were determined from the striatum and olfactory

Table 2. D_2 and D_3-binding data for displacing [^{3}H]spiperone

Compound	D_3[a]		D_2[a]		D_2/D_3 selectivity
	IC-50	K_i	IC-50	K_i	
(*R*)-(−)-Apomorphine·HCl (**1**)	69.5	36.4	87	47.7	1.31
(*R*)-(−)-2-Methyl-apomorphine·HCl (**11**)	82.6	40.1	43.0	20.7	0.52
(*R*)-(−)-2-Phenyl-apomorphine·HCl (**2**)	14.7	7.70	23.3	11.7	1.52
(*R*)-(−)-2-(4-Hydroxyphenyl)-apomorphine·HCl (**3**)	3.70	1.78	8.5	4.14	2.33
(*R*)-(−)-2-(4-*N,N*-Dimethylaminophenyl)-apomorphine·2HCl (**12**)	178	78.4	484	242	3.09
(*R*)-(−)-2-(4-Dibenzofuranyl)-apomorphine·HCl (**13**)	49.4	22.3	3259	1627	72.96

Results are means for three experiments each performed in triplicate.
[a] IC-50 and K_i results are reported in nM.

Table 3. Effects of 2-alkyl- and arylapomorphine derivatives on the dopaminergic activity in mouse striatum and olfactory tubercle

Compound	Dopamine turnover index (% of control ± SEM)[a]	
	Mouse striatum	Mouse tuberculum olfactorium
(*R*)-(−)-Apomorphine·HCl (**1**)	48.6 ± 1.9*	57.7 ± 5.2*
(*R*)-(−)-2-Methyl-apomorphine·HCl (**11**)	42.3 ± 1.5*	43.6 ± 1.3*
(*R*)-(−)-2-Phenyl-apomorphine·HCl (**2**)	44.2 ± 1.2*	50.9 ± 4.0*
(*R*)-(−)-2-(4-Hydroxyphenyl)-apomorphine·HCl (**3**)	43.6 ± 2.4*	39.6 ± 0.7*
(*R*)-(−)-2-(4-*N,N*-Dimethylaminophenyl)-apomorphine·2HCl (**12**)	52.3 ± 1.3*	84.5 ± 6.5
(*R*)-(−)-2-(4-dibenzo-furanyl)-apomorphine·HCl (**13**)	92.0 ± 3.1	106.1 ± 7.1

[a] Dopamine turnover index ([DOPAC] + [HVA]/[DA]) was calculated as a measure of dopamine turnover. Control values for this index varied from 0.139 to 0.193 (with SEM ±1.9–4.6%) in five independent experiments.
* Differ from control ($p < 0.05$) ($n = 5$).

tubercle. The calculated dopamine turnover indices are presented in Table 3.

These results show that (*R*)-(−)-2-phenylapomorphine (**2**), (*R*)-(−)-2-(4-hydroxyphenyl)-apomorphine (**3**) and (*R*)-(−)-2-methylapomorphine (**11**) are well absorbed, enter the brain and seem to possess remarkable dopamine agonistic properties over (*R*)-(−)-apomorphine (**1**) indicated by the substantial decrease in dopamine turnover index. The obtained results for (*R*)-(−)-2-(4-*N,N*-dimethylaminophenyl)-apomorphine (**12**) confirmed its dopamine agonistic property only in the nigrostriatal dopaminergic system. The 4-dibenzofuranyl-substituted congener **13** was found to be inactive in both dopaminergic systems.

4. Conclusion

We have established an efficient procedure for preparing 2-alkyl- and arylapomorphines **2, 3, 11**–**13** including two synthesis routes differing in the target system of the Suzuki–Miyaura cross-coupling. It was found that this palladium-catalyzed reaction was very well applicable and produced from high to very high yields in case of both vinyl halide-type morphinandiene **4** and aryl halide-type apocodeine **10**. The overall yields of the syntheses of 2-alkyl- and arylapomorphines **2, 3, 11**–**13** were in the range of 29–36% referred to thebaine. In conclusion of the in vitro and in vivo pharmacological results the superior dopamine-binding activity of 2-phenyl- (**2**) and 2-(4-hydroxyphenyl)-apomorphines (**3**) are in accordance with the literature results[3] and the high affinity of compound **3** to D_3 receptor subtype could result in therapeutic application as well. These results also supported the assumption of the existence of a lipophilic cleft on the surface of the receptor in the proximity of 2-position of aporphine backbone in optimal binding mode. In the case of compound **3** an additional amplifying effect could be the appearance of an H-bond between surface peptides and the phenolic hydroxyl.

The neuropharmacological profile of the newly synthesized 2-substituted apomorphine derivatives **11**–**13** varies on a wide range. In this group of novel compounds **11**–**13** the most remarkable binding properties were observed for 2-methyl derivative **11** as it was proved to be more potent agonist in both in vitro and in vivo studies than apomorphine (**1**). The brain penetration of compound **12** is comparable with the same property of the reference compound **1** on the basis of the dopamine-turnover data. It could be concluded regarding optimal spatial size of substituents in 2-position that the size of the hydrophobe moiety on the range from methyl to phenyl groups is favorable. The modest to weak in vivo agonistic properties of **13** could be explained by either the presence of unfavorably large substituents in 2-position or the poor penetration of these molecules into the brain. The specific property of compound **12** regarding the in vivo activity in nigrostriatal dopaminergic system and inactivity in mesolimbic system is also noticeable. Further experiments will be based on the introduction of spatially more fitting substituent-bearing charges at 2-position.

5. Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography was performed on precoated Merck 5554 Kieselgel 60 F_{254} foils using chloroform/methanol = 4:1 mobile phase. The spots were visualized with Draggendorf's reagent. ^{1}H NMR spectra were recorded on a Bruker WP 200 SY spectrometer, chemical shifts are reported in ppm (δ) from internal TMS and coupling constants (J) are reported in Hz. Mass spectral measurements were performed with an Automass Multi (ThermoQuest) instrument in the EI mode (direct inlet). The source temperature was 140 °C, ionization was 70 eV. Optical rotation was determined with a Perkin-Elmer Model 241 polarimeter. Elemental analyses (C, H, N, S) were obtained on a Carlo Erba 1106 analyzer.

5.1. Acid-catalyzed rearrangement of morphinandienes (General procedure I)

A mixture of the diene (1.48 mmol) and methanesulfonic acid (5 ml) was stirred for 20 min at 0 °C. Then the reaction mixture was added dropwise, with stirring and external ice-cooling, to a solution of potassium hydrogen carbonate (10 g) in water (50 ml). After extraction with chloroform (3 × 15 ml), the combined extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated in vacuum. The residue was submitted to purification by means of column chromatography (Kieselgel 40, chloroform/methanol = 1:1) to yield apocodeines.

5.2. Cross-coupling of bromo-derivatives with aryl- and methylboronic acids (General procedure II)

A mixture of the bromo-derivative (3.00 mmol), the aryl- or methylboronic acid (3.00 mmol), $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$ (0.15 mmol) and $Ba(OH)_2.8H_2O$ (3.00 mmol) was boiled in 1,4-dioxane/H_2O = 4:1 under reflux for 30 min. After evaporation at reduced pressure the residue was dissolved in chloroform (20 ml) and filtered. The filtrate was evaporated and the residue was purified by flash chromatography (silica, chloroform/methanol = 1:1) to yield aryl and alkyl derivatives.

5.2.1. Synthesis route I

5.2.1.1. (*R*)-(−)-2-Bromoapocodeine (5). Compound **5** was prepared from 6-bromo-6-demethoxythebaine (**4**) according to General procedure I. White crystalline solid; mp 217–219 °C. Yield: 464 mg (87%); spectral data were in agreement with previously published results.[7]

5.2.1.2. (*R*)-(−)-2-Methylapocodeine (6). Compound **6** was prepared from 2-bromoapocodeine (**5**) according to General procedure II. White crystalline solid; mp 160–163 °C. Yield: 674 mg (76%); Anal. calcd for $C_{19}H_{21}NO_2$ (%): C, 77.26; H, 7.17; N, 4.74; O, 10.83; found (%): C, 77.32; H, 7.15; N, 4.75; O, 10.78; $[\alpha]_D^{25}$ −123 (c 0.5, chloroform); MS *m/z* (%) 295 (M^+, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.04 (d, 1H, H1, J_{1-3} = 1.9), 6.85 (d, 1H, H3, J_{1-3} = 1.9), 6.72 (2d, 2H, H8, H9, J_{8-9} = 7.9), 6.18 (br s, 1H, OH), 3.87 (s, 3H, O–CH_3), 3.38–2.90 (m, 5H, $H4_a$, $H5_a$, $H5_b$, $H6_a$, $H7_a$), 2.78–2.41 (m, 5H, $H4_b$, $H7_b$, N–CH_3), 2.3 (s, 3H, Ar–CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 148.26 (C10), 146.24 (C11), 138.21–114.25 (10 Ar-C), 61.25 (C6′), 55.96 (O–CH_3), 51.26 (C5), 40.84 (N–CH_3), 35.19 (C7), 33.26 (C4), 32.56 (C–CH_3).

5.2.1.3. (*R*)-(−)-2-Phenylapocodeine (7). Compound **7** was prepared from 2-bromoapocodeine (**5**) according to General procedure II. White crystalline solid; mp 85–88 °C, Yield: 911 mg (85%); spectral data were in agreement with previously published results.[6a]

5.2.1.4. (*R*)-(−)-2-(4-Hydroxyphenyl)-apocodeine (8). Compound **8** was prepared from 2-bromoapocodeine (**5**) according to General procedure II. White crystalline solid; mp 130–131 °C, Yield: 806 mg (72%); spectral data were in agreement with previously published results.[6a]

5.2.1.5. (*R*)-(−)-2-(4-*N*,*N*-dimethylphenyl)-apocodeine (9). Compound **9** was prepared from 2-bromoapocodeine (**5**) according to General procedure II. White crystalline solid; mp 108–111 °C, Yield: 732 mg (61%); Anal. calcd for $C_{26}H_{28}N_2O_2$ (%): C, 77.97; H, 7.05; N, 6.99; O, 7.99; found (%): C, 77.85; H, 7.00; N, 7.09; O, 8.06; $[\alpha]_D^{25}$ −180 (c 0.2, methanol); MS *m/z* (%) 400 (M^+, 69); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.11 (d, 1H, H1, J_{1-3} = 2.3), 7.81–7.19 (m, 5H, H3, 2-Ar), 6.80 (2d, 2H, H8, H9, J_{8-9} = 8.2), 6.38 (br s, 1H, OH), 3.96 (s, 3H, O–CH_3), 3.84 (dd, 1H, $H6_a$, J_{6a-7b} = 2.6, J_{6a-7a} = 4.6), 3.56–3.18 (m, 10H, $H4_a$, $H5_a$, $H5_b$, $H7_a$, N–$(CH_3)_2$), 2.90–2.52 (m, 5H, $H4_b$, $H7_b$, N–CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 151.21 (C4′), 149.04 (C10), 146.78 (C11), 139.65–113.34 (15 Ar-C), 60.83 (C6′), 56.05 (O–CH_3), 53.32 (C5), 41.66 (N–CH_3), 40.72 (N–$(CH_3)_2$), 35.67 (C7), 34.54 (C4).

5.2.1.6. (*R*)-(−)-2-(4-Dibenzofuranyl)-apocodeine (10). Compound **10** was prepared from 2-bromoapocodeine (**5**) according to General procedure II. Brown crystalline solid; mp 98–102 °C. Yield: 831 mg (62%); Anal. calcd for $C_{30}H_{25}NO_3$ (%): C, 80.51; H, 5.63; N, 3.13; O, 10.72; found (%): C, 80.48; H, 5.65; N, 3.18; O, 10.69; $[\alpha]_D^{25}$ −78 (c 0.12, chloroform); MS *m/z* (%) 447 (M^+, 51); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.84 (d, 1H, H1, J_{1-3} = 1.9), 8.19–7.26 (m, 8H, H3, 2-Ar), 6.84 (2d, 2H, H8, H9, J_{8-9} = 8.1), 6.26 (br s, 1H, OH), 3.96 (s, 3H, O–CH_3), 3.60–2.87 (m, 5H, $H4_a$, $H5_a$, $H5_b$, $H6_a$, $H7_a$), 2.85–2.57 (m, 5H, $H4_b$, $H7_b$, N–CH_3); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 158.43 (C6′), 149.31 (C10), 147.78 (C4′), 146.09 (C11), 136.74–111.06 (20 Ar-C), 60.66 (C6′), 56.36 (O–CH_3), 52.45 (C5), 41.25 (N–CH_3), 36.56 (C7), 26.29 (C4).

5.2.2. Synthesis route II

5.2.2.1. 6-Methyl-6-demethoxythebaine (14). Compound **14** was prepared from 6-bromo-6-demethoxythebaine (**4**) according to General procedure II. White crystalline solid; mp 190–192 °C. Yield: 743 mg (84%); $[\alpha]_D^{25}$ −247 (c 0.38, chloroform) spectral data were in agreement with previously published results.[11]

5.2.2.2. 6-Phenyl-6-demethoxythebaine (15). Compound **15** was prepared from 6-bromo-6-demethoxythebaine (**4**) according to General procedure II. Yellow crystalline solid; mp 84–87 °C. Yield: 975 mg (91%); Anal. calcd for $C_{24}H_{23}NO_2$ (%): C, 80.64; H, 6.49; N, 3.92; O, 8.95; found (%): C, 80.72; H, 6.52; N, 3.99; O, 8.77; $[\alpha]_D^{25}$ −286 (c 0.5, chloroform); MS *m/z* (%) 357 (M^+, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.65 (m, 2H, 6-Ar), 7.52–7.10 (m, 3H, 6-Ar), 6.65 (2d, 2H, H1, H2, J_{1-2} = 7.6), 6.32 (d, 1H, H8, J_{7-8} = 7.2), 5.95 (s, 1H, H5), 5.79 (d, 1H, H7, J_{7-8} = 7.2), 3.74 (s, 3H, O–CH_3), 3.45–2.75 (m, 4H, $H9_a$, $H10_a$, $H10_b$, $H16_b$), 2.52 (s, 3H, N–CH_3), 2.30–2.08 (m, 2H, $H15_b$, $H16_a$), 1.21 (dt, 1H, $H15_a$, $J_{15a,15b;16a,16b}$ 12.7, $J_{15a,15b}$ 5.1); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 147.26 (C3), 146.76 (C4), 142.30 (C6), 139.21–120.85 (10 Ar-C, C14), 118.32 (C7), 116.32 (C8), 111.12 (C2), 90.43 (C5), 62.76 (C9), 57.43 (O–CH_3), 51.21 (C16), 46.78 (C13), 40.80 (N–CH_3), 37.13 (C15), 30.87 (C10).

5.2.2.3. 6-(4-Hydroxyphenyl)-6-demethoxythebaine (16). Compound **16** was prepared from 6-bromo-6-demethoxythebaine (**4**) according to General procedure II. Off-white crystalline solid; mp 145–147 °C. Yield: 828 mg (74%); Anal. calcd for $C_{24}H_{23}NO_3$ (%): C, 77.19; H, 6.21; N, 3.75; O, 12.85; found (%): C, 77.35; H, 6.20; N, 3.69; O, 12.76; $[\alpha]_D^{25}$ −516 (c 0.05, chloroform); MS *m/z* (%) 373 (M^+, 85); ^{1}H NMR (200 MHz, DMSO-d_6) δ = 9.50 (br s, 1H, OH), 7.45 (m, 2H, 6-Ar), 6.82–6.51 (m, 4H, H1, H2, 6-Ar), 6.30 (d, 1H, H8, J_{7-8} = 7.9), 5.83 (s, 1H, H5), 5.65 (d, 1H, H7, J_{7-8} = 7.9), 3.54 (s, 3H, O–CH_3), 3.45–2.45 (m, 4H, $H9_a$, $H10_a$, $H10_b$, $H16_b$), 2.35 (s, 3H, N–CH_3), 2.33–2.00 (m, 2H,

$H15_b$, $H16_a$), 1.08 (dt, 1H, $H15_a$, $J_{15a,15b;16a,16b}$ 12.4, $J_{15a,15b}$ 4.9); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 158.89 (C4′), 146.92 (C3), 146.11 (C4), 141.46 (C6), 130.13–118.45 (8 Ar-C, C14), 117.54 (C7), 114.89 (C8), 112.56 (C2), 88.88 (C5), 61.36 (C9), 55.78 (O–CH_3), 50.01 (C16), 45.11 (C13), 40.40 (N–CH_3), 35.23 (C15), 29.81 (C10).

5.2.2.4. 6-(4-*N*,*N*-Dimethylphenyl)-6-demethoxythebaine (17). Compound **17** was prepared from 6-bromo-6-demethoxythebaine (**4**) according to General procedure II. Yellow crystalline solid; mp 89–91 °C. Yield: 756 mg (63%); Anal. calcd for $C_{26}H_{28}N_2O_2$ (%): C, 77.97; H, 7.05; N, 6.99; O, 7.99; found (%): C, 77.65; H, 7.09; N, 7.10; O, 8.16; $[\alpha]_D^{25}$ -480 (c 0.20, methanol); MS *m/z* (%) 400 (M^+, 70); ^1H NMR (200 MHz, $CDCl_3$) δ = 7.61 (m, 2H, 6-Ar), 6.75–6.52 (m, 4H, H1, H2, 6-Ar), 6.30 (d, 1H, H8, J_{7-8} = 7.8), 5.95 (s, 1H, H5), 5.82 (d, 1H, H7, J_{7-8} = 7.7), 3.75 (s, 3H, O–CH_3), 3.45–2.55 (m, 10H, $H9_a$, $H10_a$, $H10_b$, $H16_b$, N–$(CH_3)_2$), 2.50 (s, 3H, N–CH_3), 2.43–2.17 (m, 2H, $H15_b$, $H16_a$), 1.87 (dt, 1H, $H15_a$, $J_{15a,15b;16a,16b}$ 12.6, $J_{15a,15b}$ 5.0); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 149.11 (C4′), 147.34 (C3), 146.65 (C4), 141.09 (C6), 134.73 (C14), 130.13–118.45 (8 Ar-C), 117.39 (C7), 115.25 (C8), 111.67 (C2), 90.12 (C5), 61.23 (C9), 56.19 (O–CH_3), 50.98 (C16), 47.23 (C13), 41.56 (N–CH_3), 40.23 (N–$(CH_3)_2$), 35.76 (C15), 30.30 (C10).

5.2.2.5. 6-(4-Dibenzofuranyl)-6-demethoxythebaine (18). Compound **18** was prepared from 6-bromo-6-demethoxythebaine (**4**) according to General procedure II. Yellow crystalline solid; mp 84–88 °C. Yield: 885 mg (66%); Anal. calcd for $C_{30}H_{25}NO_3$ (%): C, 80.51; H, 5.63; N, 3.13; O, 10.72; found (%): C, 80.52; H, 5.72; N, 3.08; O, 10.68; $[\alpha]_D^{25}$ −346 (c 0.48, chloroform); MS *m/z* (%) 447 (M^+, 100); ^1H NMR (200 MHz, $CDCl_3$) δ = 8.11–7.18 (m, 9H, H1, H2, 6-Ar), 7.04 (d, 1H, H8, J_{7-8} = 7.2), 6.34 (s, 1H, $H5_a$), 5.95 (d, 1H, H7, J_{7-8} = 7.2), 3.73 (s, 3H, O–CH_3), 3.70–2.75 (m, 4H, $H9_a$, $H10_a$, $H10_b$, $H16_{eq}$), 2.62 (s, 3H, N–CH_3), 2.52–2.20 (m, 2H, $H15_b$, $H16_a$), 2.01 (dt, 1H, $H15_a$, $J_{15a,15b;16a,16b}$ 12.3, $J_{15a,15b}$ 4.8); ^{13}C NMR (200 MHz, $CDCl_3$) δ = 158.23 (C6′), 152.32 (C4′), 147.55 (C3), 146.27 (C4), 141.72 (C6), 134.87–121.18 (13 Ar-C, C14), 117.65 (C7), 115.56 (C8), 112.43 (C2), 91.39 (C5), 61.73 (C9), 56.88 (O–CH_3), 50.45 (C16), 47.01 (C13), 41.45 (N–CH_3), 36.83 (C15), 31.34 (C10).

5.2.2.6. (*R*)-(−)-2-Methylapocodeine (6). Compound **6** was prepared from 6-methyl-6-demethoxythebaine (**14**) according to General procedure I. Yield: 630 mg (71%); all the physical and spectral data are in agreement with the details presented at Synthesis route I.

5.2.2.7. (*R*)-(−)-2-Phenylapocodeine (7). Compound **7** was prepared from 6-phenyl-6-demethoxythebaine (**15**) according to General procedure I. White crystalline solid; mp 85–88 °C. Yield: 868 mg (81%); spectral data were in agreement with previously published results.[6a]

5.2.2.8. (*R*)-(−)-2-(4-Hydroxyphenyl)-apocodeine (8). Compound **8** was prepared from 6-(4-hydroxyphenyl)-6-demethoxythebaine (**16**) according to General procedure I. White crystalline solid; mp 130–131 °C. Yield: 627 mg (56%); spectral data were in agreement with previously published results.[6a]

5.2.2.9. (*R*)-(−)-2-(4-*N*,*N*-Dimethylphenyl)-apocodeine (9). Compound **9** was prepared from 6-(4-*N*,*N*-dimethylphenyl)-6-demethoxythebaine (**17**) according to General procedure I. Yield: 576 mg (48%); all the physical and spectral data are in agreement with the details presented at Synthesis route I.

5.2.2.10. (*R*)-(−)-2-(4-Dibenzofuranyl)-apocodeine (10). Compound **10** was prepared from 6-(4-dibenzofuranyl)-6-demethoxythebaine (**18**) according to General procedure I. Yield: 589 mg (44%); all the physical and spectral data are in agreement with the details presented at Synthesis route I.

5.3. *O*-demethylation of 2-substituted apocodeines to yield corresponding 2-substituted apomorphines (General procedure III)

A mixture of 2-substituted apocodeine (4.65 mmol), methionine (1000 mg, 6.70 mmol) and CH_3SO_2OH (4 ml) was boiled at 90 °C for 2 hours. After cooling, the pH of the mixture was set to 10 by concentrated NH_3 solution and extracted with chloroform (3 × 15 ml). The organic layers were collected, washed with saturated NaCl solution, dried over anhydrous $MgSO_4$ and evaporated. The residue was subjected to silica-gel column chromatography. Elution with chloroform:methanol = 1:1 gave apomorphines.

5.3.1. (*R*)-(−)-2-Methylapomorphine hydrochloride (11). Compound **11** was prepared from 2-methylapocodeine (**6**) according to General procedure III. Off-white crystalline solid; mp 208–212 °C (HCl salt). Yield: 868 mg (91%); Anal. calcd for $C_{18}H_{20}ClNO_2$ (%): C, 68.03; H, 6.34; Cl, 11.16; N, 4.41; O, 10.07; found (%): C, 68.11; H, 6.37; N, 4.38; Cl, 11.18; O, 9.96; $[\alpha]_D^{25}$ −28 (c 0.4, methanol); MS *m/z* (%) 318 (M^+, 100); ^1H NMR (200 MHz, DMSO-d_6) δ = 10.75 (br s, 1H, Ar–OH), 9.85 (br s, 1H, Ar–OH), 8.85 (d, 1H, H1, J_{1-3} 2.2), 7.25 (d, 1H, H3, J_{1-3} 2.1), 7.82 (d, 1H, H9, J_{8-9} 8.1), 7.75 (d, 1H, H8, J_{8-9} 8.1), 3.78 (dd, 1H, $H6_a$, J_{6a-7b} 2.7, J_{6a-7a} 4.9), 3.42–2.57 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, N–CH_3), 2.32 (s, 3H, Ar–CH_3); ^{13}C NMR (200 MHz, DMSO-d_6) δ = 145.62 (C10), 144.83 (C11), 139.01–111.85 (10 Ar–C), 60.82 (C6′), 53.02 (C5), 40.13 (N–CH_3), 35.54 (C7), 32.76 (C4), 32.09 (C–CH_3).

5.3.2. (*R*)-(−)-2-Phenylapomorphine hydrochloride (2). Compound **2** was prepared from 2-phenylapocodeine (**7**) according to General procedure III. Yield: 818 mg (92.2%); mp >230 °C (HCl salt); spectral data were in agreement with previously published results.[3]

5.3.3. (*R*)-(−)-2-(4-Hydroxyphenyl)-apomorphine hydrochloride (3). Compound **3** was prepared from 2-(4-hydroxyphenyl)-apocodeine (**8**) according to General procedure III. Yield: 762 mg (87.2%); mp > 230 °C (HCl salt); spectral data were in agreement with previously published results.[3]

5.3.4. (*R*)-(−)-2-(4-*N,N*-Dimethylphenyl)-apomorphine dihydrochloride (12). Compound **12** was prepared from 2-(4-*N,N*-dimethylphenyl)-apocodeine (**9**) according to General procedure III. Brown crystalline solid; mp >230 °C (HCl salt). Yield: 1239 mg (90%); Anal. calcd for $C_{25}H_{28}Cl_2N_2O_2$ (%): C, 65.36; H, 6.14; Cl, 15.34; N, 6.10; O, 6.97; found (%): C, 65.44; H, 6.18; Cl, 15.22; N, 6.10; O, 7.06; $[\alpha]_D^{25}$ −129 (c 0.2, methanol); MS *m*/*z* (%) 459 (M^+, 78); ^{1}H NMR (200 MHz, DMSO-d_6) δ = 10.65 (br s, 2H, 10-OH, 11-OH), 8.62 (d, 1H, H1, J_{1-3} = 2.1), 7.42 (d, 1H, H3, J_{1-3} 2.1), 6.81 (d, 1H, H8, J_{8-9} 7.9), 6.76 (d, 1H, H9, J_{8-9} 7.9), 4.32 (dd, 1H, $H6_a$, J_{6a-7b} 2.4, J_{6a-7a} 4.6), 3.81–2.51 (m, 15H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, N–CH_3, N–$(CH_3)_2$); ^{13}C NMR (200 MHz, DMSO-d_6) δ = 150.06 (C4′), 146.87 (C10), 145.49 (C11), 138.48–112.92 (15 Ar–C), 61.28 (C6′), 53.82 (C5), 42.66 (N–CH_3), 41.05 (N–$(CH_3)_2$), 36.68 (C7), 33.81 (C4).

5.3.5. (*R*)-(−)-2-(4-Dibenzofuranyl)-apomorphine hydrochloride (13). Compound **13** was prepared from 2-(4-dibenzofuranyl)-apocodeine (**10**) according to General procedure III. Brown crystalline solid; mp >230 °C (HCl salt). Yield: 1113 mg (79%); Anal. calcd for $C_{29}H_{24}ClNO_3$ (%): C, 74.12; H, 5.15; Cl 7.54; N, 2.98; O, 10.21; found (%): C, 74.20; H, 5.10; Cl 7.62; N, 3.03; O, 10.05; $[\alpha]_D^{25}$ −182 (c 0.20, methanol); MS *m*/*z* (%) 470 (M^+, 58); ^{1}H NMR (200 MHz, DMSO-d_6) δ = 9.01 (s, 1H, H1, J_{1-3} 2.1), 8.32–7.20 (m, 8H, H3, 2-Ar), 6.84 (2d, 2H, H8, H9, J_{8-9} 8.4), 3.90–2.72 (m, 7H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H6_a$, $H7_a$, $H7_b$), 2.57 (s, 3H, N–CH_3); ^{13}C NMR (200 MHz, DMSO-d_6) δ = 156.11 (C6′), 148.21 (C4′), 147.27 (C10), 146.46 (C11), 137.24–113.00 (20 Ar-C), 61.19 (C6′), 53.45 (C5), 40.92 (N–CH_3), 37.24 (C7), 26.55 (C4).

6. Biological experiments

6.1. In vitro pharmacology

In vitro pharmacology involved determinations of affinity (K_i, nM) of test compounds for dopamine D_2 and D_3 receptors in radioligand competition assays, using membrane preparations from dopamine-rich corpus striatum (caudatoputamen) tissue from rat forebrain and recombinant rat D_3 receptors expressed in Sf9 cells, respectively. The applied radioligand was in both cases [^{3}H]spiperone, while non-specific bindings were determined in the presence of 2 mM (+)-butaclamol. Binding assays were performed in accordance with the literature procedures.[12–16] IC-50 (the concentration of the compound causes 50% inhibition) and K_i (inhibitory constants calculated on the basis of Cheng–Prusoff equation[17]).

6.2. In vivo pharmacology

In vivo pharmacology involved the determination of monoamine and metabolite levels. Male, CD-1 mice (20–22 g) were treated with the test compounds subcutaneously at a dose of 3.29 μmol/kg (equivalent to 1.0 mg/kg apomorphine.HCl administration). Each group consisted of 5 mice. One hour later the animals were decapitated, striatum and tuberculum olfactorium were dissected and the concentration of dopamine and its metabolites (dihydroxyphenylacetic acid and homovanilic acid) were determined by reverse phase-HPLC coupled with electrochemical detection essentially by the method for Saller and Salama.[18] Dopamine turnover index ([DOPAC] + [HVA]/[DA]) was calculated as a measure of dopamine-turnover.

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