Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 16 (2008) 4563–4568
Bioorganic & Medicinal Chemistry

Synthesis and neuropharmacological characterization of 2-O-substituted apomorphines

Attila Sipos,[a,*] Csaba Csutorás,[b] Sándor Berényi,[a] Ain Uustare[c] and Ago Rinken[c]

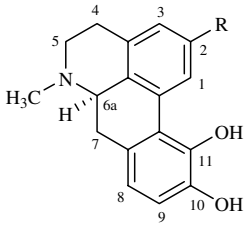
[a]*Department of Organic Chemistry, University of Debrecen, PO Box 20, H-4010 Debrecen, Hungary*
[b]*Department of Chemistry, Eszterházy Károly College, H-3300 Leányka Str. 4, Eger, Hungary*
[c]*Department of Organic and Bioorganic Chemistry, University of Tartu, Jakobi 2, 51014 Tartu, Estonia*

Received 10 December 2007; revised 6 February 2008; accepted 12 February 2008
Available online 15 February 2008

Abstract—We have synthesized novel 2-*O*-substituted apomorphines with both different lengths of lipophilic alkyl chains and alkyl chains carrying free hydroxyl groups. Two bis-apomorphines formed as side products of the reactions with diols were isolated and characterized as well. The neuropharmacological profile of all these new compounds were investigated with respect to their binding affinities and activities to dopamine D_2 and D_1 receptors. The obtained data pointed to the fact that, in the examination of dopaminergic activities of 2-substituted apomorphines, the lipophilicity of the substituent is more important than its spatial parameters.

1. Introduction

Apomorphine (**1**) and its derivatives have been found to be high-affinity and specific ligands of dopaminergic receptors, which has made them as promising precursor for the search of new effective drugs of the receptor connected diseases like Parkinson's disease, schizophrenia, attention-deficit hyperactivity disorder and erectile dysfunctions.[1] Apomorphine itself (**1**, Fig. 1) has already been approved and commercialized for the treatment of several of these disorders.[2] Structure–activity relationships of 2-substituted apomorphines indicate their perspective in the increase of selectivity and affinity for D_2 dopamine receptors.[3] There are available data of some 2-substituted compounds, which have remarkable affinities to D_2 receptors and good D_2/D_1 receptor selectivity (Fig. 1).[4] These data point to the existence of a lipophilic cleft on the surface of the D_2 receptors that can interact with 2-substituents of aporphine backbone.[5] This cleft may be the reason of relatively lower binding affinity of molecules having increasing hydrophilic character in the proximity of 2-position (NH_2, SMe), but it is also obvious that there are other important factors such as steric limitation and strong H-bonding effect to the peptide surface of the receptor. The remarkable binding tendencies of compounds **2** and **3** to D_2 receptors might be a consequence of a strong H-bond acceptor property of the aryl fluoride and phenolic OH moieties. Søndergaard and co-workers prepared a series of 2-aryl substituted apomorphines and found that the presence of aryl substituents (compounds **8** and **9**) in 2-position caused remarkable effect on the lipophilic cleft-lipophilic



1 - 9

	R	Ki, nM
1	H	11.1*, 32.0#
2	F	0.43*
3	OH	0.38*
4	OCH_3	1.12*
5	Br	17.7*
6	SCH_3	54.7*
7	NH_2	19.9*
8	Ph	88#
9	4-OH-Ph	3.8#

Figure 1. 2-Substituted apomorphines and their D_2 binding potencies. Data from Ref. 1 and papers cited therein. Potencies determined in radioligand competition assays using rat striatal membranes (*) or human cloned receptors in CHO cell membranes (#).

Keywords: Apomorphine; 2-Alkoxyapomorphines; Alkyl-type hydroxyl; Bis-apomorphines; Dopamine receptor binding activity; D_2/D_1 receptor selectivity.
* Corresponding author. Tel.: +36 52512900; fax: +36 52512836; e-mail: asipos@puma.unideb.hu

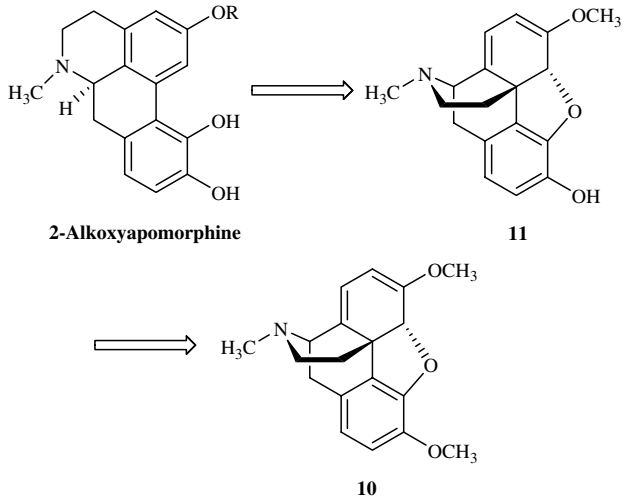
0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.02.038

substituent interactions of D_2 receptors.[6] These results show the need of the reconsideration of the previous findings regarding the favourable size of the substituent at the 2-position of the aporphine backbone. This states that the actual size of the lipophilic cleft is presumed to be not much larger than the spatial size of a hydroxyl group, which is smaller than the size of a 4-hydroxy-phenyl moiety.

We have already shown that several pharmacologically interesting 2-alkoxyapomorphines can be synthesized from thebaine (**10**) in only two steps (Scheme 1).[7]

This synthesis route was based on the conversion of thebaine (**10**) into oripavine (**11**) with a procedure published by Coop et al. (Scheme 1).[8] This L-Selectride-mediated selective *O*-demethylation was slightly modified with respect to the work-up of the crude reaction mixture. Coop and his co-workers isolated oripavine (**11**) in oxalate salt form. We omitted the salt-forming step and obtained oripavine (**11**) as free base with somewhat higher yield in comparison to Coop's data.

We have already proposed a one-pot procedure to obtain 2-alkoxyapocodeines (2-OMe-, 2-OEt-, 2-OPr, 2-OBu-) using acid-catalyzed rearrangement of natural thebaine (**10**) in the presence of alcohols.[9] The yields of these reactions remained in the range of 48–95%. However, the direct and selective 10-*O*-dealkylation of the 2-alkoxyapocodeines either failed due to the very complex crude reaction product or resulted in extremely low yields.



2-Alkoxyapomorphine **11** **10**

Scheme 1. Retrosynthesis of 2-alkoxyapomorphines.

The availability of the selectively *O*-demethylated starting compound **11** opened the way for the synthesis of 2-*O*-alkyl-apomorphines **12**–**15** since the cleavage of $O–CH_3$ bond was performed before the transformation of the backbone (Scheme 2).

2. Results and discussion

Pharmacological data obtained to date have indicated the important role of the 2-substitutions of apomorphines for their activities on D_2 receptors. Among the substituents, 2-*O*-alkyl series, which include electron acceptor for H-bonding, but also alkyl chain for the lipophilic cleft seemed to be the promising direction for the development of new drugs. This kind of substituents tend to increase the water-solubility of apomorphines and have therefore also impact in the increase of oral bioavailability and longer duration of action. Herewith, we have synthesized several new 2-*O*-alkyl-apomorphines and determined their biological activities to find new directions in searches for new effective and specific ligands for dopamine receptors.

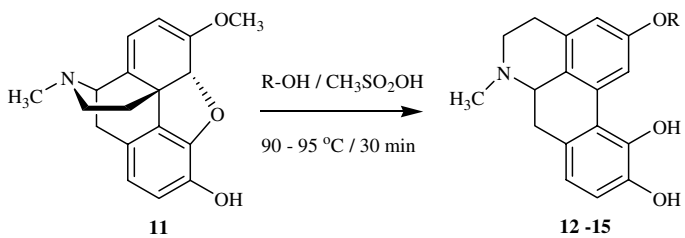
2.1. Synthesis

The acid-catalyzed rearrangement of oripavine (**11**) in the presence of hydroxyl compounds was extended to diols in order to prepare apomorphines having free hydroxyl function in the proximity of 2-position (Scheme 3).

It was observed that, in contrast with the application of monohydroxyl compounds/methanesulfonic acid reactant mixtures, in these reactions we obtained a mixture of two products. After successful isolation and structural characterization of the products, it was revealed that bis-apomorphine-type products **18** and **19** were also produced.

The mechanism of the formation of these bis-apomorphines **18** and **19** is in accordance with the previously proven[4c,9] occurrence of metoxonium ion intermediate of the two-step acid-catalyzed rearrangement of morphinan skeleton in the presence of *O*- or *S*-nucleophiles (Scheme 4).

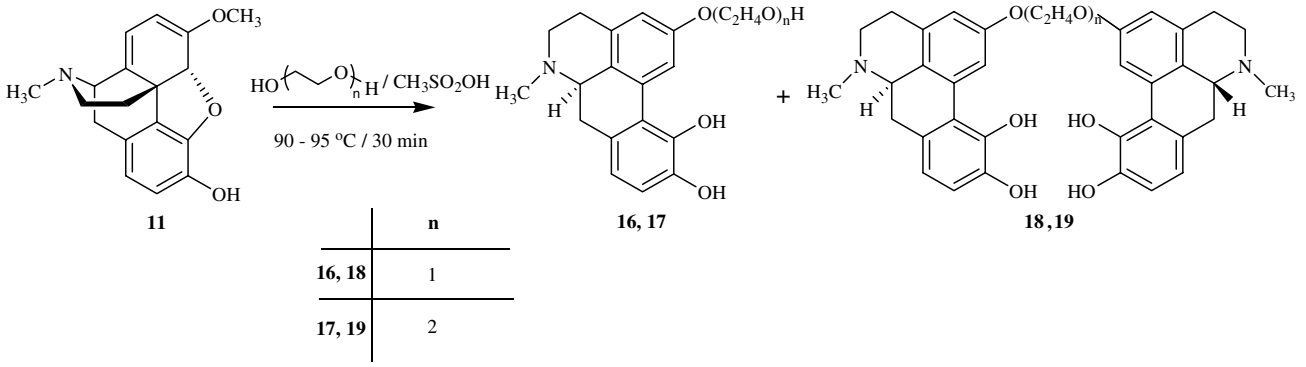
These bis-apomorphines **18** and **19** differ in the length of the spacer between the two aporphine backbone in com-



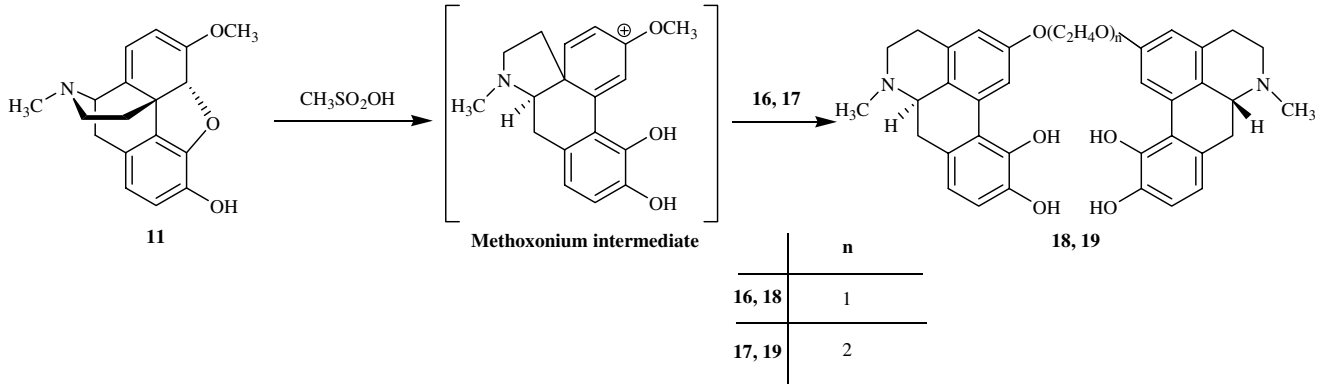
11 **12 -15**

	R
12	methyl
13	ethyl
14	propyl
15	butyl

Scheme 2. Synthesis of 2-alkoxyapomorphines.



Scheme 3. Acid-catalyzed rearrangement of oripavine in the presence of diols.



Scheme 4. Mechanism of the formation of bis-apomorphines.

Table 1. Affinities of synthesized substances in binding to D_2 and D_1 dopamine receptors and in activation of D_2 receptors

Compound	D_2			D_1	D_2/D_1
	vs. [^{3}H]raclopride	Activation of [^{35}S] GTPγS binding		vs. [^{3}H]SCH23390	Specificity fold
	K_i (nM)	EC_{50} (nM)	Efficacy (%)	K_i (nM)	
1*	32	—	—	101	3
12	74 ± 4	114 ± 12	66 ± 4	2600 ± 900	35
13	44 ± 3	55 ± 2	70 ± 1	2900 ± 800	65
14	75 ± 5	76 ± 3	71 ± 2	3500 ± 800	47
15	60 ± 4	58 ± 13	57 ± 6	2100 ± 600	35
16	347 ± 27	315 ± 36	19 ± 1	5300 ± 1800	15
17	587 ± 27	939 ± 98	58 ± 4	7600 ± 2600	13
18	345 ± 4	308 ± 64	18 ± 8	5200 ± 1800	15
19	17,158 ± 3200	>10,000	—	>10,000	—

K_i values characterize the ability of agonists to inhibit [^{3}H]raclopride and [^{3}H]SCH23390 binding to D_2 and D_1 receptors, respectively, and EC_{50} the ability of compounds to activate [^{35}S]GTPγS binding. Efficacy is the level of [^{35}S]GTPγS binding activation in comparison with the effect of quinpirole.

* Data from Ref. 6.

parison with the only semisynthetic 2,2′-bis-apomorphine described by our research group.[4c] All the obtained apomorphines **12**–**19** were isolated in a stable HCl salt form. The solubility of these salts was found to be adequate for neuropharmacological studies.

2.2. Pharmacology

The binding properties of the synthesized compounds to dopamine D_1 and D_2 receptors in membrane preparations of cells expressing corresponding receptors were studied by their abilities to displace the specific binding of [^{3}H]SCH23390 and [^{3}H]raclopride, respectively. In addition, the receptor-dependent activation of [^{35}S]GTPγS binding to G-proteins in CHO cell membranes was used as an assay for determination of the ligands' functional properties for D_2 receptors.[10] All the studied compounds displayed some binding affinity for D_2 receptors, and their affinities remained mainly in the submicromolar range (Table 1). Only bis-apomorphine with longer spacer between backbones (**22**) had problems with solubility in water, and its estimated

affinity for both receptors remained in submillimolar range. In addition to higher affinity all other ligands also had agonistic properties for D_2 receptors, but none of them were full agonists and their efficacies remained below 75% in comparison with the effect caused by quinpirole. All these compounds also had a clear preference to D_2 receptors having affinities more than 10 times higher than for D_1 receptors.

All 2-alkoxyapomorphines **12**–**15** had very similar properties and no tendencies could be found connected with the length of alkoxy group. This means that there are no sterical hindrances, but also lipophilic partners for the chain in 2-*O*-position during the binding of these compounds to D_2 or D_1 receptors.

Changes in pharmacological properties appeared with introduction of a hydrophilic group to the chain (compound **16**). It caused a 5-fold decrease in the ligand binding affinity to D_2 receptors and some loss in its agonistic properties, whereas changes in binding to D_1 receptors were moderate. Introduction of an additional ethoxy group into the chain (compound **17**) led to an additional loss of binding affinity of the compound to both receptors. This indicates that 2-alkoxy chain of the compounds is well localized in the hydrophilic area of the receptors and change its hydrophobicity by the introduction of oxygen atoms weakening interactions. The determinants of ligand binding in this region appear to be the hydrophilic/hydrophobic properties of the substituent in position 2 and not the steric properties as the formatted of bis-apomorphine **18** had similar properties as its parent compounds.

The superposition of the 3D structures of compounds **9**, **13** and **16** (Fig. 2), generated by the superimposition of pharmacologically determining catechol D rings of the energy-minimized structures, revealed that there is a significant impact of the quality of 2-substituent on the form of the aporphine backbone, that is, the relative position of the decisive catechol ring to the *N*-alkyl moiety.[11] This effect predominates via the modification of the electronic structure of the ring A, which directly interacts with ring D as they form a structurally built-in biphenyl moiety. Further study of this interaction is in progress and will be communicated in due course.

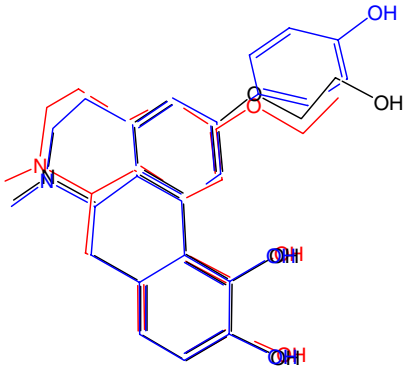


Figure 2. Superposition of energy-minimized 3D structures of compounds **9** (blue), **13** (red) and **16** (black) using AM1 semiempirical method.

As mentioned above, none of these compounds were full agonists for D_2 receptors, while apomorphine and propylnorapomorphine in this system are.[12] Introduction of 2-alkoxy group seems to be not the best choice for the receptor activation, but also not the worst, as at least some agonistic properties of compounds retained. Despite extensive data about the ligand binding of apomorphine derivatives to receptors, there is limited information about their agonistic properties and therefore it is difficult to make final conclusions about the structural requirements of full agonists.

3. Conclusion

We have presented a novel route for the synthesis of 2-methoxyapomorphine (**12**) and its 2-*O*-alkyl-congeners. The method was based on the acid-catalyzed rearrangement of oripavine (**11**). This procedure was extended to the application of diols yielding either 2-*O*-alkyl-apomorphines **16** and **17** with free hydroxyl group or mono- and di(ethylene oxide) bridged bis-aporphinoids **18** and **19**. Most of obtained compounds were high-affinity D_2 dopamine receptors ligands with partial agonistic properties and clear selectivities over D_1 receptors. The obtained results further emphasized the importance of the lipophilic character of the 2-substituent of aporphine backbone over its spatial size.

4. Experimental

4.1. General

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 = 8:2 mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H NMR spectra were recorded at 360 MHz, while ^{13}C NMR spectra at 90.5 MHz, using a Bruker AM 360 spectrometer; chemical shifts were reported in ppm (δ) from internal TMS and coupling constants (J) were measured in Hz. High-resolution mass spectral measurements were performed with a Bruker micrO-TOF-Q instrument in the EI mode. Optical rotation was determined with a Perkin-Elmer Model 241 polarimeter.

4.2. Chemistry

4.2.1. Acid-catalyzed rearrangement of oripavine (11) in the presence of diols. A mixture of **11** (1 g, 3.37 mmol), methanesulfonic acid (5 mL) and diol (1 mL) was stirred for 20 min at 0 °C and for 30 min at 90–95 °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 under reduced pressure. The isolation of the mono- and bis-aporphinoid-type products was performed by means of column chromatography (Kieselgel 40, chloroform/methanol = 8:2). Pure apomorphine bases were immediately converted into the hydrochloride salt form with 1 M HCl in ether.

4.2.1.1. [*R*-(−)-Apomorphine-2-yl]-(2′-hydroxy-ethyl) ether hydrochloride (16). Off-white, plate shape crystals; mp 211–213 °C; yield: 833 mg (68%); R_F (chloroform/methanol = 8:2) 0.62; $[\alpha]_D^{25}$ −211 (*c* 0.1, methanol); HRMS (EI) *m/z* (%) found: 328.1561 (M^+−Cl, 100), calculated: 328.1543 (M^+−Cl); ^{1}H NMR (360 MHz, DMSO-d_6, base) δ = 8.87 (2 s, 2H, 10-OH, 11-OH), 6.72 (s, 1H, H1), 6.50 (m, 3H, H3, H8, H9), 4.35 (dt, 1H, $H6_a$, J_{6a-7a} 5.2, J_{6a-7b} 1.4), 4.25–3.77 (m, 4H, –O–C*H*$_2$–C*H*$_2$–O–), 3.36 (s, 1H, –CH$_2$–O*H*), 3.19–2.41 (m, 6H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.37 (s, 3H, NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ = 156.02 (C2), 146.10 (C10), 145.41 (C11), 138.21, 133.95, 132.27, 129.44, 126.49, 122.66, 116.30, 115.57, 110.51 (Ar, 9C), 73.12 (–O–*C*H$_2$–CH$_2$–OH), 61.11 (–O–CH$_2$–*C*H$_2$–OH), 60.33 (C6), 56.41 (OCH_3), 52.49 (C5), 40.41 (=NCH_3), 35.72 (C7), 28.82 (C4).

4.2.1.2. 2-{[*R*-(−)-Apomorphine-2′-oxy]ethoxy}-ethanol hydrochloride (17). Pale grey, plate shape crystals; mp 201–204 °C; yield: 810 mg (59%); R_F (chloroform/methanol = 8:2) 0.74; $[\alpha]_D^{25}$ −198 (*c* 0.1, methanol); HRMS (EI) *m/z* (%) found: 372.1828 (M^+−Cl, 100), calculated: 372.1805 (M^+−Cl); ^{1}H NMR (360 MHz, DMSO-d_6, base) δ = 8.46 (2 s, 2H, 10-OH, 11-OH), 6.66 (s, 1H, H1), 6.47 (m, 2H, H3, H8), 6.37 (d, 1H, H9, J_{8-9} 8.2), 4.41 (dt, 1H, $H6_a$, J_{6a-7a} 5.4, J_{6a-7b} 1.1), 4.37–3.52 (m, 8H, –O–C*H*$_2$–C*H*$_2$–O–C*H*$_2$–C*H*$_2$–O–), 3.41 (s, 1H, –CH$_2$–O*H*), 3.17–2.60 (m, 6H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.31 (s, 3H, NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ = 155.76 (C2), 145.35 (C10), 144.67 (C11), 138.66, 133.18, 129.43, 128.98, 122.60, 121.11, 117.89, 113.45, 108.71 (Ar, 9C), 73.44, 71.98, 69.04 (Al, 3C), 61.87 (C6), 61.41 (–O–CH$_2$–*C*H$_2$–OH), 56.11 (OCH_3), 53.04 (C5), 40.36 (=NCH_3), 35.66 (C7), 28.56 (C4).

4.2.1.3. 1,2-Bis-[*R*-(−)-apomorphine-2′-oxy]ethane dihydrochloride (18). Pale green, cubic crystals; mp 233–236 °C; yield: 470 mg (21%); R_F (chloroform/methanol = 8:2) 0.34; $[\alpha]_D^{25}$ −298 (*c* 0.1, methanol); HRMS (EI) *m/z* (%) found, for free base: 593.2662 (M^++1, 100), calculated: 593.2646 (M^++1); ^{1}H NMR (360 MHz, CD_3OD, base) δ = 6.84–6.37 (m, 8H, H1, H3, H8, H9, H1′, H3′, H8′, H9′), 4.34–4.12 (m, 6H, $H6_a$, $H6'_a$, –O–C*H*$_2$–C*H*$_2$–O–), 3.32–2.40 (m, 12H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, $H4'_a$, $H4'_b$, $H5'_a$, $H5'_b$, $H7'_a$, $H7'_b$), 2.37 (s, 6H, 2 NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ = 154.45 (C2, C2′), 145.86 (C10, C10′), 145.09 (C11, C11′), 137.66, 133.49, 129.67, 128.29, 126.71, 122.81, 116.67, 113.28, 109.67 (Ar, 18C), 61.23 (C6, C6′), 61.03 (–O–*C*H$_2$–*C*H$_2$–O–), 55.67 (2 OCH_3), 51.63 (C5, C5′), 40.08 (2 =NCH_3), 35.45 (C7, C7′), 27.99 (C4, C4′).

4.2.1.4. Bis-{[*R*-(−)-apomorphine-2-oxy]ethyl} ether dihydrochloride (19). Green, cubic crystals; mp 227–229 °C; yield: 692 mg (29%); R_F (chloroform/methanol = 8:2) 0.29; $[\alpha]_D^{25}$ −336 (*c* 0.1, methanol); HRMS (EI) *m/z* (%) found, for free base: 637.2942 (M^++1, 100), calculated: 637.2908 (M^++1); ^{1}H NMR (360 MHz, CD_3OD, base) δ = 6.76–6.41 (m, 8H, H1, H3, H8, H9, H1′, H3′, H8′, H9′), 4.29–4.04 (m, 6H, $H6_a$, $H6'_a$, –O–C*H*$_2$–C*H*$_2$–O–), 3.17–2.42 (m, 12H, $H4_a$,$H4_b$, $H5_a$,$H5_b$, $H7_a$, $H7_b$, $H4'_a$, $H4'_b$, $H5'_a$, $H5'_b$, $H7'_a$, $H7'_b$), 2.30 (s, 6H, 2 NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ = 155.75 (C2, C2′), 145.11 (C10, C10′), 144.79 (C11, C11′), 138.94, 133.69, 129.41, 128.77, 126.65, 122.01, 116.45, 113.56, 108.32 (Ar, 18C), 71.44 (–O–CH$_2$–*C*H$_2$–O–*C*H$_2$–CH$_2$–O–), 68.19 (–O–*C*H$_2$–CH$_2$–O–CH$_2$–*C*H$_2$–O–), 60.56 (C6, C6′), 55.67 (2 OCH_3), 53.10 (C5, C5′), 41.65 (2 =NCH_3), 36.25 (C7, C7′), 28.67 (C4, C4′).

4.3. Pharmacology

Chinese hamster ovary cells (CHO-K1 cells; CCL61, American Type Culture Collection, Rockville, MD, USA) stably transfecting rat dopamine $D_{2(short)}$ receptor and Ltk$^-$-fibroblast cells expressing D_1 dopamine receptors were obtained from Prof. K. Fuxe laboratory at the division of Cellular and Molecular Neurochemistry, Department of Neuroscience, Karolinska Institutet (Sweden), and grown as described earlier.[13] For radioligand binding experiments, the cells were collected, washed, and homogenized by sonication in incubation buffer (IB, 50 mM Tris–HCl, 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.4) and centrifuged at 28,000*g* for 20 min at 4 °C. The membrane pellets were washed by re-homogenization in IB and centrifugation. The final pellets were re-suspended in IB (2 mg protein/mL) and stored at −80 °C until use.

Binding affinities of compounds to D_2 dopamine receptors were measured by incubation of 1.1 nM [^{3}H]raclopride (74 Ci/mmol, Perkin-Elmer Life Sciences) with appropriate concentrations of ligand with membrane suspension of CHO cells (75 μg protein/point) for 90 min at 25 °C. The reaction was stopped by filtration through GF/B filters using Brandel cell harvester with three washings of 3 mL of ice-cold washing buffer (20 mM K-phosphate buffer, 100 mM NaCl, pH 7.4).[14]

Receptor activation properties of compounds to D_2 receptors were measured by binding of 0.2 nM [^{35}S]GTPγS in the presence of 10 μM GDP with appropriate concentrations of ligand with membrane suspension of CHO cells (40 μg protein/point) for 90 min at 25 °C.[12]

Binding affinities of compounds to D_1 dopamine receptors were measured by incubation of 2 nM [*N*-methyl-^{3}H]R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride ([^{3}H]SCH23390, 71 Ci/mmol, Amersham Biosciences) with appropriate concentrations of ligand with membrane suspension of Ltk$^-$-fibroblast cells in IB for 90 min at 25 °C.[15]

All data were analyzed by means of non-linear least squares regression analysis using the commercial program GraphPad PRISM™ 5.0 (GraphPad Software Inc.). Data are presented as means ± SEM of at least two independent determinations.

Acknowledgments

The authors are grateful for the financial support to the Hungarian National Science Foundation (Grant OTKA Reg. Nos. T049436 and NI61336), Estonian Science Foundation (Grant 6492) and Estonian Ministry of Education and Science (Project 0182734s06). A.S. is indebted to the Eötvös Scholarship of the Hungarian State.

References and notes

1. Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171; Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. *Chem. Rev.* **2007**, *107*, 274.
2. Apomorphine in the treatment of Erectile Dysfunction, see for example (a) Heaton, J. P. W. *Int. J. Impot. Res.* **2001**, *13*, S35; (b) Padma-Nathan, H.; Auerbach, S.; Lewis, R. *J. Urol.* **2001**, *165*, 224; (c) Martinez, R.; Puigvert, A.; Pomerol, J. M.; Rodriguez-Villalba, R. *J. Urol.* **2003**, *170*, 2352; (d) Perimenis, P.; Gyftopoulos, K.; Giannitsas, K.; Markou, S. A.; Tsota, I.; Chrysanthopoulou, A.; Athanasopoulos, A.; Barbalias, G. *Int. J. Impot. Res.* **2004**, *16*, 2; Apomorphine in the treatment of Parkinson's disease, see for example (e) Schwab, R. S.; Amador, L. V.; Lettvin, J. Y. *Trans. Am. Neurol. Assoc.* **1951**, *76*, 251; (f) Muguet, D.; Cotzias, G. C.; Papavasiliou, P. S.; Tolosa, E. S.; Mendez, J. S.; Bell-Midura, M. *N. Engl. J. Med.* **1976**, *294*, 567; (g) Broussolle, E.; Chazot, G. *Biomed. Pharmacother.* **1995**, *49*, 197; (h) Sit, S. Y. *Curr. Pharm. Des.* **2000**, *6*, 1211; (i) Poewe, W.; Wenning, G. K. *Mov. Disord.* **2000**, *15*, 789.
3. Structure–activity relationship for dopamine receptors, see for example Ramsby, S.; Neumeyer, J. L.; Grigoriadis, D.; Seeman, P. *J. Med. Chem.* **1989**, *32*, 1198; Csutorás, Cs.; Zhang, A.; Zhang, K.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem.* **2004**, *12*, 3553; . *Org. Lett.* **2005**, *15*, 3239.
4. (a) Gao, Y.; Baldessarini, R. J.; Kula, N. S.; Neumeyer, J. L. *J. Med. Chem.* **1990**, *33*, 1800; (b) Ramsby, S.; Neumeyer, J. L.; Grigoriadis, D.; Seeman, P. *J. Med. Chem.* **1989**, *32*, 1198; (c) Tóth, M.; Berényi, S.; Csutorás, Cs.; Kula, N. S.; Zhang, K.; Baldessarini, R. J.; Neumeyer, J. L. *Bioorg. Med. Chem.* **2006**, *14*, 1918.
5. (a) Ram, V. J.; Neumeyer, J. L. *J. Heterocycl. Chem.* **1991**, *28*, 1721; (b) Neumeyer, J. L.; Arana, G. W.; Law, S. J.; Lamont, J. S.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1981**, *24*, 1440; (c) Neumeyer, J. L.; Gao, Y.; Kula, N. S.; Baldessarini, R. J. *J. Med.Chem.* **1990**, *33*, 3122.
6. Søndergaard, K.; Kristensen, J. L.; Palner, M.; Gillings, N.; Knudsen, G. M.; Roth, B. L.; Begtrup, M. *Org. Biomol. Chem.* **2005**, *3*, 4077.
7. Berényi, S.; Csutorás, Cs.; Sipos, A.; Gyulai, Zs. *Lett. Org. Chem.* **2007**, *4*, 32.
8. Coop, A.; Janetka, W. J.; Lewis, J. W.; Rice, K. C. *J. Org. Chem.* **1998**, *63*, 4392; L-Selectride (1 M of lithium-tri-*sec*-butylborohydride in THF) was purchased from Aldrich and used undiluted.
9. Berényi, S.; Czirják, M.; Makleit, S. *J. Chem. Soc. Perkin Trans. I* **1993**, 2137.
10. Rinken, A.; Finnman, U. B.; Fuxe, K. *Biochem. Pharmacol.* **1999**, *57*, 155.
11. PC SPARTAN Pro, Version 2.0, Wavefunction Inc., Irvine, CA, 2001.
12. Terasmaa, A.; Finnman, U. B.; Owman, C.; Ferré, S.; Fuxe, K.; Rinken, A. *Neurosci. Lett.* **2000**, *280*, 135.
13. (a) Rinken, A.; Ferré, S.; Terasmaa, A.; Owman, C.; Fuxe, K. *Neuroreport* **1999**, *10*, 493; (b) Ferre, S.; Torvinen, M.; Antoniou, K.; Irenius, E.; Civelli, O.; Arenas, E.; Fredholm, B. B.; Fuxe, K. *J. Biol. Chem.* **1998**, *273*, 4718; (c) Uustare, A.; Vonk, A.; Terasmaa, A.; Fuxe, K.; Rinken, A. *Life Sci.* **2005**, *76*, 1513.
14. Harro, J.; Terasmaa, A.; Eller, M.; Rinken, A. *Brain Res.* **2003**, *976*, 209.
15. Uustare, A.; Reinart, R.; Rinken, A. *Neurosci. Lett.* **2006**, *406*, 169.