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Synthesis and dopamine receptor binding of sulfur-containing aporphines

Miklós Tóth,[a] Sándor Berényi,[a] Csaba Csutorás,[b,*] Nora S. Kula,[c] Kehong Zhang,[c] Ross J. Baldessarini[c] and John L. Neumeyer[c]

[a]*University of Debrecen, Department of Organic Chemistry, H-4010 PO Box 20, Debrecen, Hungary*
[b]*Eszterházy Károly College, Department of Chemistry, H-3300 Leányka Str. 4, Eger, Hungary*
[c]*McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478-9106, USA*

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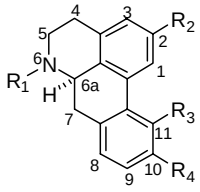
Dedicated to professor Sándor Makleit on the occasion of his 75th birthday.

Abstract—We investigated acid-catalyzed rearrangement of thebaine **14** and its *N*-propyl analog **15** with methanesulfonic acid in the presence of the nucleophiles methanethiol and hydrogen sulfide. *R*(−)-2-methylthioapocodeine **16**, *R*(−)-2-methylthioapomorphine **18**, and their *N*-*n*-propyl analogs **17**, **19** were obtained by rearrangement in the presence of methanethiol. However, with hydrogen sulfide, rearrangement of thebaine **14** and its *N*-*n*-propyl analog **15** produced sulfide-linked bis-aporphines **21**–**24** instead of expected *R*(−)-2-mercaptoapocodeines **12**, **13** and *R*(−)-2-mercaptoapomorphines **10**, **11**. *R*(−)-2-Methylthio-*N*-*n*-propylnorapomorphine **19** had higher affinity (K_i = 3.7 nM) at D_2 receptors in rat forebrain tissue than other novel 2-substituted sulfur-containing aporphines ($K_i \geqslant 50$ nM). Behavioral testing of the novel agents in rat indicated moderate locomotor arousal after systemic injection, and none after intragastric administration, indicating poor oral bioavailability.

1. Introduction

R(−)-Apomorphine **1** (Fig. 1), the product of the acid-catalyzed rearrangement of morphine,[1] is a well-known central dopamine receptor agonist.[2] It was recently US FDA-approved for clinical use in the treatment of Parkinson's disease if administered by injection to circumvent its poor oral bioavailability.[2,3] In the last 20 years, several laboratories have synthesized many novel-substituted aporphines. Several 2-substituted aporphines were found to have high potency at dopamine D_2 receptors, including 2-hydroxy, 2-methoxy, and 2-halogen congeners. *R*(−)-2-Fluoro-*N*-propylnorapomorphine **3** was found to be a particularly potent D_2 agonist, surpassing the potency of the 2-unsubstituted standard comparator, *R*(−)-*N*-*n*-propylnorapomorphine **2**.[4,5] We previously reported development of a route for the synthesis of 2-alkoxy- and 2-alkylthio-



	R_1	R_2	R_3	R_4
1	Me	H	OH	OH
2	Pr	H	OH	OH
3	Pr	F	OH	OH
4	Pr	H	OH	H
5	Pr	H	OAc	H
6	Me	SPr	OH	OH
7	Me	SEt	OH	OH
8	Pr	SPr	OH	OH
9	Pr	SEt	OH	OH
10	Me	SH	OH	OH
11	Pr	SH	OH	OH
12	Me	SH	OH	OMe
13	Pr	SH	OH	OMe
16	Me	SMe	OH	OMe
17	Pr	SMe	OH	OMe
18	Me	SMe	OH	OH
19	Pr	SMe	OH	OH

Figure 1. Structure of aporphine derivatives.

Keywords: Apomorphine; Aporphine derivatives; Dopamine agonists; D_2 receptors.
* Corresponding author. Tel.: +36 36 520471; fax: +36 36 520471; e-mail: csuti@ektf.hu

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substituted aporphines.[6–8] An essential component of these novel syntheses is that the methanesulfonic acid-catalyzed rearrangement of thebaine **14** in the presence of nucleophiles (water, alcohols, and thiols) results in nucleophilic substitution of the 6-methoxy group of thebaine **14**, in addition to promoting its rearrangement to aporphines [6,7] (Scheme 1).

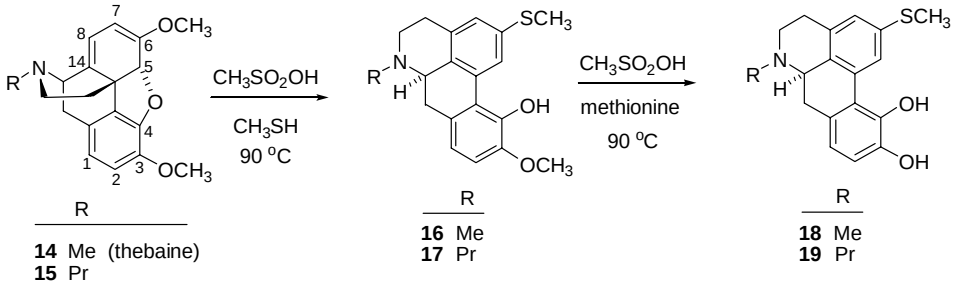
An important aim of the medicinal chemistry of dopamine agonists is to discover orally active agents. Neumeyer et al.[9] and more recently Csutoras et al.[10] found that non-catechol, 11-monohydroxyaporphines (such as compound **4** in Fig. 1) and their esters in 11-position (e.g., **5**) have superior oral bioavailability to catechol-aporphines such as apomorphine **1** and *N*-*n*-propylnorapomorphine **2**. Berényi et al.[7] have previously synthesized *R*(−)-2-propylthio- and *R*(−)-2-ethylthioapomorphines **6**, **7** and their *N*-propyl analogs **8**, **9** (Fig. 1).

Neuropharmacological studies found compounds **6**, **7**, **8**, and **9** to have high affinity at dopamine (D_2) receptors, as well as ability to induce locomotor behavioral arousal even after enteral (orogastric) administration.[11,12] Introduction of a methylthio group on the ergoline skeleton has also resulted in effective dopaminergic compounds.[13] However, experience with aporphines also indicates that steric characteristics of substituents at 2-position influence the pharmacological properties of the resulting compounds.[14] Relatively small and apolar substituents are favored.[13,14] Because of this fact, we aimed in the present study to prepare *R*(−)-2-methylthioapomorphine **18**, *R*(−)-2-mercaptoapomorphine **10**, and their *N*-*n*-propyl analogs **19**, **11**, and to evaluate them neuropharmacologically.

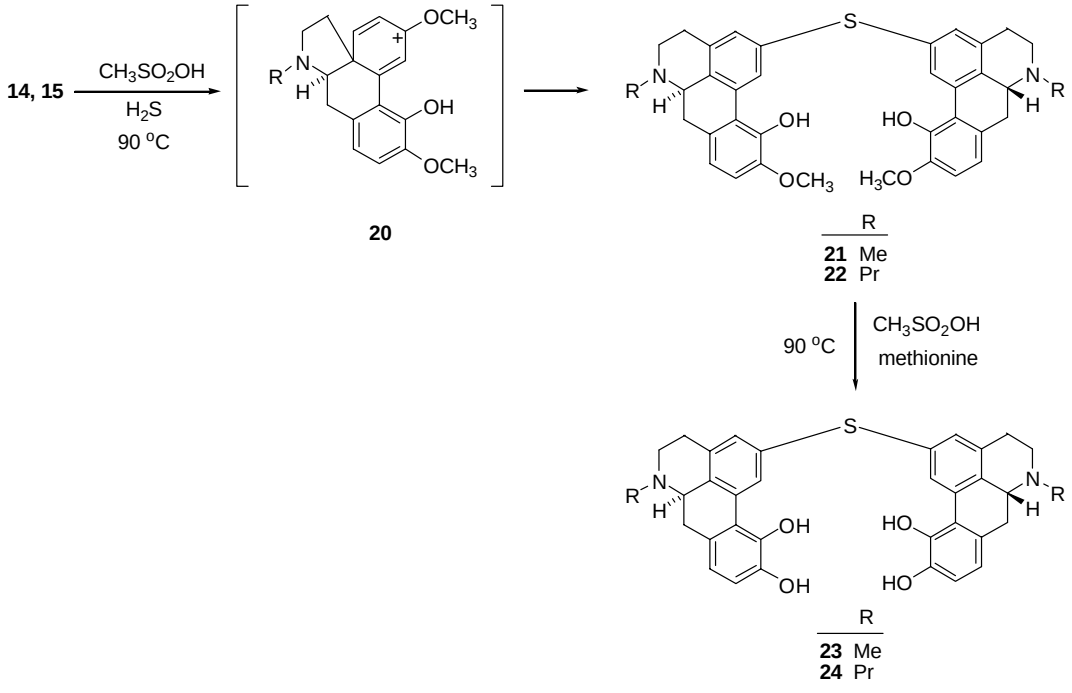
2. Results and discussion

2.1. Chemistry

We found that our previously reported synthetic method[7] was suitable for the synthesis of *R*(−)-2-methylthioapomorphine **18** and its *N*-*n*-propyl analog **19** with a minor modification (Scheme 1). The acid-catalyzed rearrangement of **14** and **15** with methanesulfonic acid was carried out in the presence of a continuous gas-flow of methanethiol. We succeeded in O-demethylating the resulting *R*(−)-2-methylthioapocodeine **16** and



Scheme 1. Synthesis of 2-methylthioapomorphines.



Scheme 2. Preparation of sulfide cross-linked aporphines.

2-methylthio-*N*-*n*-propylnorapocodeine **17** to the corresponding apomorphines **18**, **19** with methanesulfonic acid/methionine system used previously to *O*-demethylate aporphines.[15,16] In the present case, we considered that methanethiol could substitute for methionine as an alkyl acceptor resulting in O-demethylation. However, because of the high cost of methanethiol, methionine was used (Scheme 1). The acid-catalyzed rearrangement of thebaine **14** and its *N*-*n*-propyl congener **15** with methanesulfonic acid in the presence of a continuous gas-flow of hydrogen sulfide failed to give *R*(−)-2-mercaptoapocodeines **12**, **13**, in contrast to the rearrangement in the presence of methanethiol. Rearrangement of **14** and **15** resulted in the formation of bis-aporphines **21**, **22**, whose O-demethylation with methanesulfonic acid/methionine led to **23** and **24** (Scheme 2). Formation of the sulfide cross-linked bis-aporphines **21**, **22** can be explained by a previously proposed, two-step rearrangement.[17] In the first step, hydrogen sulfide is the nucleophilic partner of the methoxonium ion intermediate **20** formed from **14** and **15** in acidic media. We propose further that the formed 2-mercaptoapocodeines **12** and **13** will be the nucleophilic partners of the methoxonium ion intermediate **20** to produce the corresponding bis-aporphines **21**, **22**.

2.2. Pharmacology

In vitro affinity for the dopamine (D_2) receptor of *R*(−)-2-methylthioapocodeines **16**, **17** and *R*(−)-2-methylthioapomorphines **18**, **19**, as well as the novel bis-aporphines **21**–**24** was determined with radioreceptor competition assays using rat forebrain tissue (Table 1). The potency of *R*(−)-2-methylthio-*N*-*n*-propylnorapomorphine **19** for the dopamine (D_2) receptor was higher than those of both *R*(−)-apomorphine **1** and its *N*-*n*-propyl analog **2**. Moreover, the 2-methylthio **19** (D_2 K_i = 3.73 nM), 2-ethylthio **9** (K_i = 7.8 nM), and 2-propylthio **8** (K_i = 9.9 nM) congeners form a potency series that indicates decreasing affinity for the dopamine D_2 with increasing size of 2-alkylthio substituents. The novel bis-aporphines **21**–**24** showed very low affinity for dopamine D_2 receptors (Table 1) and no evidence of in vivo behavioral activity (Table 2), suggesting increasing steric hindrance of their receptor interactions. Since only *R*(−)-2-methylthio-*N*-*n*-propylnorapomorphine **19** had high in vitro D_2 receptor affinity among the eight compounds examined, it was also evaluated for in vivo behavioral activity (Table 2). These experiments indicated that parenterally injected equimolar doses (4.0 μmol/kg, ip) of *R*(−)-2-methylthio-*N*-*n*-propylnorapomorphine **19** produced much greater behavioral arousal (18.3 U) than *R*(−)-apomorphine (**1**; 1.0 U), and somewhat greater than with *R*(−)-*N*-*n*-propylnorapomorphine (**2**; 12.0 U of activation; Table 2).

In contrast to *R*(−)-apomorphine **1**, the *N*-*n*-propyl analog **2** showed activity at an enteral dose of 20, but not 4 μmol/kg, whereas *R*(−)-2-methylthio-*N*-*n*-propylnorapomorphine **19**, inexplicably, proved to be inactive behaviorally following intragastric doses of 4 or 20 μmol/kg (Table 2).[11,12]

Table 1. Affinity (K_i) of aporphines at dopamine (D_2) receptors in rat brain tissue

Agents	K_i ± SEM (nM)
(**9**) *R*(−)-2-Ethylthio-*N*-*n*-propylnorapomorphine	7.80 ± 1.00
(**2**) *R*(−)-*N*-*n*-Propylnorapomorphine	9.90 ± 1.00
(**1**) *R*(−)-Apomorphine	13.2 ± 2.1
(**8**) *R*(−)-2-Propylthio-*N*-*n*-propylnorapomorphine	15.6 ± 2.2
(**19**) *R*(−)-2-Methylthio-*N*-*n*-propylnorapomorphine	3.73 ± 0.44
(**18**) *R*(−)-2-Methylthioapomorphine	54.7 ± 2.3
(**16**) *R*(−)-2-Methylthioapocodeine	75.4 ± 2.3
(**17**) *R*(−)-2-Methylthio-*N*-propylnorapocodeine	1108 ± 147
(**21**) Di-(apocodeine-2-yl)sulfide	>10,000
(**22**) Di-(apomorphine-2-yl)sulfide	>10,000
(**23**) Di-(*N*-propylnorapocodeine-2-yl)sulfide	>10,000
(**24**) Di-(*N*-propylnorapomorphine-2-yl)sulfide	>10,000

3. Conclusions

We report an efficient procedure for preparing the *R*(−)-2-methythioapocodeines **16**, **17** and *R*(−)-2-methylthioapomorphines **18**, **19**. The key step in their synthesis was acid-catalyzed rearrangement of thebaine **14** and its *N*-propyl analog **15** with methanesulfonic acid in the presence of the nucleophile methanethiol. Using hydrogen sulfide as the nucleophilic partner, we obtained bis-aporphines **21**–**24** instead of the expected 2-mercaptoaporphines **10**–**13**. The 2-alkylthio-substituted aporphines **9**, **8**, **19**, and **18** showed variable affinity at the cerebral dopamine (D_2) receptor (Table 1) and variable in vivo behavioral activity (Table 2). The bis-aporphines **21**–**24** showed low affinity for the dopamine

Table 2. Motor activation induced by *R*(−)-aporphines in adult rats

Agent	Dose (μmol/kg)	Route	Activity score	Duration (h)
(**1**) *R*(−)-Apomorphine	4	ip	1.0 (standard)	1
	4	ig	Inactive	—
	20	ig	Inactive	—
(**2**) *R*(−)-*N*-*n*-Propylnorapomorphine	4	ip	12.0 ± 5.2	8
	4	ig	Inactive	—
	20	ig	68.0 ± 20.8	14
(**19**) *R*(−)-2-Methylthio-*N*-*n*-propylnorapomorphine	4	ip	18.3 ± 6.5	6
	4	ig	Inactive	—
	20	ig	Inactive	—

Activity scores are based on total locomotor activity counts from start to return to baseline, normalized to a value of 1.0 for apomorphine, as (mean ± SEM); NA, not applicable; ip, intraperitoneal; ig, by orogastric intubation.

(D_2) receptor, and were inactive behaviorally, suggesting steric interference with receptor interactions. *R*(−)-2-methylthio-*N*-*n*-propylnorapomorphine **19** had the highest D_2 receptor affinity of the eight novel aporphines examined. It was also behaviorally effective when injected systemically (ip), but not after intragastric administration, indicating poor oral bioavailability. Moreover, the D_2 receptor affinity and behavioral potency of compound **19** exceeded those of both *R*(−)-apomorphine **1** and *R*(−)-*N*-*n*-propylnorapomorphine **2** (Table 2). These findings are consistent with previous indications that 2-substitution can enhance affinity of aporphines at dopamine receptors.[14]

4. Experimental

4.1. Chemical syntheses

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silicagel (Merck 60, 70–230 mesh). Thin layer chromatography was performed on precoated Merck 5554 silicagel 60 F_{254} foils, using a 9:1 (vols) dichloromethane/methanol developing system. The spots were visualized with Dragendorff's reagent. Elemental analyses (C, H, N, S) were performed on a Carlo Erba 1106 analyzer. NMR spectra were recorded on a Bruker WP 200 SY spectrometer. Chemical shifts are reported in ppm (δ) from internal $CHCl_3$ (7.26). The coupling constants (*J*) are measured in Hz. Mass spectra were measured with a Finnigan LCQ Classic ion trap mass spectrometer.

4.1.1. General procedure for the synthesis of 2-substituted sulfur-containing apocodeines. Methanethiol or hydrogen sulfide was bubbled through 99% methanesulfonic acid (5 mL) with stirring and external ice cooling. To this stirred mixture, thebaine **14** or *N*-propylnorthebaine **15** (3.2 mmol) was added. After stirring for 30 min at 0 °C, the temperature was raised to 90 °C and held for 30 min with continuous bubbling of methanethiol or hydrogen sulfide gas into the reaction mixture. After cooling to room temperature, water (50 mL) was added, and pH was adjusted to 8–9 with 25% ammonia. The reaction mixture was extracted with chloroform/methanol 3:1 (3× 20 mL), and then the organic layer was washed with brine (25 mL), dried with magnesium sulfate, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (ethyl acetate/methanol, 7:3), to provide pure oils, which were converted to the solid hydrochlorides with HCl–ethanol.

4.1.2. 2-Methylthioapocodeine hydrochloride (16). The rearrangement was carried out according to the general method starting from **14**, in the presence of methanethiol. Yield: (0.46 g, 40%), mp: 222–225 °C (from diethyl ether–ethanol). ^{1}H NMR: δ_H (base, $CDCl_3/CD_3OD$ 2:1): 2.52 (3H, s, SCH_3), 2.58 (3H, s, N-CH_3), 2.55–3.31 (7H, m, C-H), 3.90 (3H, s, OCH_3), 6.55 (1H, s, OH), 6.78 (2H, s, 8-H, 9-H), 7.00 (1H, d, 3-H), 8.26 (1H, d, 1-H). MS *m*/*z* (rel intensity): 327 (M, 75%), 280 (M-47, 80%). Anal. ($C_{19}H_{22}ClNO_2S$) Calcd: C, 62.71; H, 6.09; N, 3.85; S, 8.81. Found: C, 62.59; H, 6.11; N, 3.83; S, 8.79.

4.1.3. 2-Methylthio-*N*-*n*-propylnorapocodeine hydrochloride (17). The rearrangement was carried out according to the general method starting from **15**, in the presence of methanethiol. Yield: (0.7 g, 56%), mp: 220–227 °C (from diethyl ether–ethanol). ^{1}H NMR: δ_H (base, $CDCl_3/CD_3OD$ 2:1): 1.01 (3H, t, CH_3), 1.14 (2H, m, –CH_2–), 2.52 (3H, s, SCH_3), 2.56 (2H, t, N-CH_2–), 2.60–3.47 (7H, m, C-H), 3.92 (3H, s, OCH_3), 4.60 (1H, s, OH), 6.79 (2H, s, 8-H, 9-H), 6.97 (1H, d, 3-H), 8.26 (1H, d, 1-H). MS *m*/*z* (rel intensity): 355 (M, 55%). Anal. ($C_{21}H_{26}ClNO_2S$) Calcd: C, 64.35; H, 6.69; N, 3.57; S, 8.18. Found: C, 64.22; H, 6.72; N, 3.54; S, 8.20.

4.1.4. Di-(apocodeine-2-yl)sulfide dihydrochloride (21). The rearrangement was carried out according to the general method starting from **14**, in the presence of hydrogen sulfide. Yield: (0.62 g, 58%), mp: >250 °C dec (from diethyl ether–ethanol). ^{1}H NMR: δ_H (base, $CDCl_3/CD_3OD$ 2:1) 2.54 (6H, s, N-CH_3), 2.73–2.45 (6H, m, CH_2), 3.30–2.96 (8H, m, CH_2), 3.82 (6H, s, O-CH_3), 6.67 (2H, d, J = 7.5 Hz, H-9, H-9′), 6.72 (2H, d, J = 7.5 Hz, H-8, H-8′), 7.05 (2H, d, J = 1.2 Hz, H-3, H-3′), 8.19 (2H, d, J = 1.2 Hz, H-1, H-1′). ^{13}C NMR: δ_C (base, DMSO) 18.5, 25.4, 30.2, 40.7, 50.8, 56.1, 60.7, 111.5, 118.6, 126.3, 128.2, 128.8, 129.2, 131.7, 133.0, 133.7, 144.0, 147.3. LC–MS (*m*/*z*): 593 (M+1, 100%). Anal. ($C_{36}H_{38}Cl_2N_2O_4S$) Calcd: C, 64.95; H, 5.75; N, 4.21; S, 4.82. Found: C, 64.93; H, 5.78; N, 4.21; S, 4.80.

4.1.5. Di-(*N*-*n*-propylnorapocodeine-2-yl)sulfide dihydrochloride (22). The rearrangement was carried out according to the general method starting from **15**, in the presence of hydrogen sulfide. Yield: (0.56 g, 49%), mp: >250 °C dec (from diethyl ether–ethanol), ^{1}H NMR: δ_H (base, CD_3OD 2:1) 0.95 (6H, t, CH_3), 1.63 (4H, m, –CH_2–), 2.48–3.55 (14H, m, CH), 2.60 (4H, t, NCH_2–), 3.84 (6H, s, O-CH_3), 6.72 (4H, s, H-8, H-8′, H-9, H-9′), 7.08 (2H, d, H-3, H-3′), 8.19 (2H, d, H-1, H-1′). LC–MS (*m*/*z*): 649 (M+1, 100%). Anal. ($C_{40}H_{46}Cl_2N_2O_4S$) Calcd: C, 66.56; H, 6.42; N, 3.88; S, 4.44. Found: C, 66.55; H, 6.44; N, 3.89; S, 4.43.

4.1.6. General procedure for the O-demethylation of sulfur-containing apocodeines. Methionine (1 g; 6.7 mmol) was added to a stirred solution of the appropriate apocodeine derivative (1.7 mmol) in methanesulfonic acid (10 mL). The reaction mixture was kept at 90 °C, for 90 min. Column chromatographic purification was accomplished in chloroform/methanol 8:2 eluent system, to afford oils that were converted to the solid hydrochloride salts with HCl–ethanol.

4.1.7. 2-Methylthioapomorphine hydrochloride (18). Yield: (0.45 g, 75%), mp: >250 °C (from diethyl ether–ethanol), ^{1}H NMR: δ_H (base, CD_3OD) 2.52 (3H, s, SCH_3), 2.58 (3H, s, N-CH_3), 2.55–3.34 (7H, m, C-H), 5.69 (2H, s, OH), 6.58 (2H, s, 8-H, 9-H), 6.92 (1H, d, 3-H), 8.18 (1H, d, 1-H). MS (*m*/*z*): 313 (M, 80%), 266 (M-47, 55%). Anal. ($C_{18}H_{20}ClNO_2S$) Calcd: C, 61.79;

H, 5.76; N, 4.00; S, 9.16. Found: C, 61.77; H, 5.79; N, 4.01; S, 9.16.

4.1.8. 2-Methylthio-*N*-propylnorapomorphine hydrochloride (19). Yield: (0.46 g, 72 %), mp: 210 °C (dec) (from diethyl ether–ethanol). ^{1}H NMR: δ_H (base, $CDCl_3$/CD_3OD 2:1) 1.01 (3H, t, CH_3), 1.14 (2H, m, $-CH_2-$), 2.52 (3H, s, SCH_3), 2.56 (2H, t, N-CH_2-), 2.60–3.47 (7H, m, C-H), 4.60 (2H, s, OH), 6.79 (2H, s, 8-H, 9-H), 6.97 (1H, d, 3-H), 8.26 (1H, d, 1-H). MS (*m*/*z*): 341 (M, 85%). Anal. ($C_{20}H_{24}ClNO_2S$) Calcd: C, 63.56; H, 6.40; N, 3.71; S, 8.48. Found: C, 63.55; H, 6.42; N, 3.72; S, 8.48.

4.1.9. Di-(apomorphine-2-yl)sulfide dihydrochloride (23). Yield: (0.43 g, 42 %), mp: >250 °C (from diethyl ether–ethanol). ^{1}H NMR: δ_H (base, $CDCl_3$/CD_3OD 2:1) 2.54 (6H, s, N-CH_3), 2.45–2.73 (6H, m, CH_2), 2.96–3.30 (8H, m, CH_2), 6.58 (H-9, H-9′, d, 8.0 Hz), 6.65 (H-8, H-8′, d, 8.0 Hz), 7.05 (H-3, H-3′, d, 1.2 Hz), 8.19 (H-1, H-1′, d, 1.2 Hz). ^{13}C NMR: δ_C (DMSO) 18.5, 25.4, 30.2, 40.8, 50.9, 61.0, 114.8, 118.6, 124.6, 128.1, 128.9, 129.2, 131.5, 133.4, 133.7, 143.3, 144.9. LC–MS (*m*/*z*): 565 (M+1, 75%), 522 (M-42, 10%), 491 (M-73, 12%), 283 (M-281, 100%). Anal. ($C_{34}H_{34}Cl_2N_2O_4S$) Calcd: C, 64.05; H, 5.37; N, 4.39; S, 5.03. Found: C, 63.88; H, 5.40; N, 4.37; S, 5.01.

4.1.10. Di-(*N*-*n*-propylnorapomorphine-2-yl)sulfide dihy-c drochloride (24). Yield: (0.42 g, 38%), mp: >250 °C (from diethyl ether–ethanol). ^{1}H NMR: δ_H (base, CD_3OD) 1.18 (6H, t, CH_3), 1.83 (4H, m, $-CH_2-$), 2.65–3.74 (14H, m, CH), 2.76 (4H, t, NCH_2-), 6.83 (2H, d, H-9, H-9′), 6.92 (2H, d, H-8, H-8′), 7.31 (2H, d, H-3, H-3′), 8.44 (2H, d, H-1, H-1′). LC–MS (*m*/*z*): 621 (M+1, 80%). Anal. ($C_{38}H_{42}Cl_2N_2O_4S$) Calcd: C, 65.79; H, 6.10; N, 4.04; S, 4.62. Found: C, 65.88; H, 6.12; N, 4.05; S, 4,59.

4.2. Pharmacology

4.2.1. In vitro pharmacology. In vitro pharmacology involved determinations of affinity (K_i, nM) of test compounds for dopamine D_2 receptors in radioligand competition assays, using membrane preparations from DA-rich corpus striatum (caudatoputamen) tissue from rat forebrain. Adult male Sprague–Dawley rats were sacrificed by decapitation under carbon dioxide narcosis. Brains were quickly removed and dissected on ice. Tissue was homogenized in 50 mM Tris–HCl buffer (pH 7.4) containing 150 mM NaCl, washed twice with fresh buffer, and resuspended in fresh buffer. For assays, the membrane-containing brain preparation was incubated with 75 pM [^{3}H]nemonapride (NEN; Boston, MA, USA) for 90 min at 30 °C; non-specific binding was defined by co-incubation with 10 μM haloperidol in some tubes, with assays carried out in triplicate.[18,19] Findings are summarized in Table 1.

4.2.2. In vivo pharmacology. In vivo pharmacology involved determining the potency and oral bioavailability of test agents by measuring stimulation of motor activity in adult male Sprague–Dawley rats (N = 4–5/group) using a microcomputer-controlled infrared photobeam activity monitoring system (San Diego Instruments, San Diego, CA, USA), as detailed previously.[20] Oral delivery of test agents was achieved using a permanently surgically pre-implanted polyethylene (PE-50) intragastric tube to avoid stress associated with conventional oral intubation. For this surgery, rats were anesthetized with 60 mg/kg sodium pentobarbital (injected intraperitoneally, ip). Tubing was inserted through the mid-lateral wall of the stomach, sutured in place, and led subcutaneously to a point of access on the back of the neck, where it was anchored with an additional suture. Animals were allowed at least two weeks for recovery after surgery before behavior testing. At the end of the experiments, rats were sacrificed with carbon dioxide. The function of the gastric tube was checked postmortem by injecting dye to ensure that drug delivery was limited to the gastric lumen. Potency of aporphine test agents was expressed as the sum of behavioral scores at each time of rating until locomotor responses returned to their pre-injection baseline levels, and relative to that (standard score = 1.0) produced by ip injection of 4 μmol/kg *R*(−)-apomorphine **1**, the effects of which lasted for approximately 1 h. Locomotor activity scores and the duration of behavioral activation effects are shown in Table 2.

Acknowledgments

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