Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 12 (2004) 3553–3559
Bioorganic & Medicinal Chemistry

Synthesis and neuropharmacological evaluation of R(−)-*N*-alkyl-11-hydroxynoraporphines and their esters

Csaba Csutoras,[a] Ao Zhang,[a] Kehong Zhang,[b] Nora S. Kula,[b] Ross J. Baldessarini[b] and John L. Neumeyer[a,*]

[a]*Alcohol and Drug Abuse Research Center, McLean Division of Massachusetts General Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478-9106, USA*
[b]*Mailman Research Center, McLean Division of Massachusetts General Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478-9106, USA*

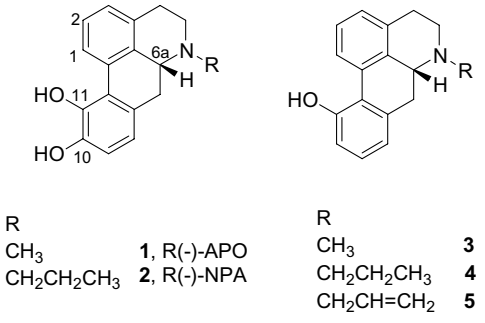
Received 27 February 2004; revised 22 April 2004; accepted 23 April 2004
Available online 18 May 2004

Abstract—We synthesized several *N*-substituted-11-hydroxynoraporphines and their esters of varying chain length, evaluated their binding affinity at dopamine (DA) receptor sites in rat caudate-putamen membranes, and quantified their effects on motor activity in normal adult male rats. The 11-hydroxyaporphines showed similar neuropharmacological properties to the corresponding 10,11-catecholaporphines. At moderate doses, their esters proved to have more prolonged behavioral actions and superior oral bioavailability.

1. Introduction

During previous years, several laboratories including ours have focused on the synthesis of mono-oxygenated aporphines, especially the effects produced by elimination of the 10- or 11-hydroxyl groups in the catecholaporphine, R(−)-apomorphine (APO, **1**) and its *N*-alkyl congener, R(−)-*N*-propylnorapomorphine (NPA, **2**) (Fig. 1). (±)-11-Hydroxyaporphines were first synthesized in 1974 via a Reissert alkylation and Pschorr cyclization route.[1] Our earlier investigations indicated that a hydroxyl group at the 11-position (analogous to the *meta*-hydroxy group of dopamine) plays an important role in receptor binding[2] and that the catechol system is not required for dopaminergic activity.

We first synthesized optically pure R(−)-enantiomers of some 11-hydroxyaporphines, by selective removal of the 10-hydroxyl group on the aporphine ring via a phenyltetrazole ether.[3] Later we prepared R(−)-*N*-*n*-propyl- and R(−)-*N*-allyl-11-hydroxynoraporphine (**4**, **5**) and their S-(+)-antipodes by a total synthesis strategy from 1-benzylisoquinoline and subsequent resolution of the resulting aporphine racemates.[4,5]



R	
CH_3	**1**, R(-)-APO
$CH_2CH_2CH_3$	**2**, R(-)-NPA

R	
CH_3	**3**
$CH_2CH_2CH_3$	**4**
$CH_2CH{=}CH_2$	**5**

Figure 1.

R(−)-APO (**1**) has some efficacy in the treatment of Parkinson's disease, but its poor oral bioavailability limits its clinical utility.[6] As a potential means of avoiding this limitation, we found that several catechol diesters and methylenedioxy prodrugs of **1** and **2** that limited the first-pass metabolic inactivation of catecholaporphines.[7,8] Aporphines containing a single hydroxyl group at C-11 such as **3**, were reported by Schaus et al.[9] to have some affinity for the D_1 dopamine

Keywords: Apomorphine; 11-Hydroxyaporphine; Parkinson's disease; Dopamine receptor; Motor activity; Bioavailability.
* Corresponding author. Tel.: +1-617-855-3388; fax: +1-617-855-2519; e-mail: neumeyer@mclean.harvard.edu

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.04.029

receptor and properties as D_1 antagonists. More recently, Hedberg et al.[10] reported an efficient method for the removal of the phenolic hydroxyl group on the morphine nucleus, which they used to synthesize 11-hydroxyaporphine (**3**). Our current studies focused on the synthesis of several R(−)-11-hydroxyaporphines with varying *N*-substituents, and preliminary investigations of their dopamine receptor affinities in rat brain tissue as well as their oral bioavailability and duration of action indicated as locomotor behavioral activation in normal adult male rats.

2. Results and discussion

2.1. Chemistry

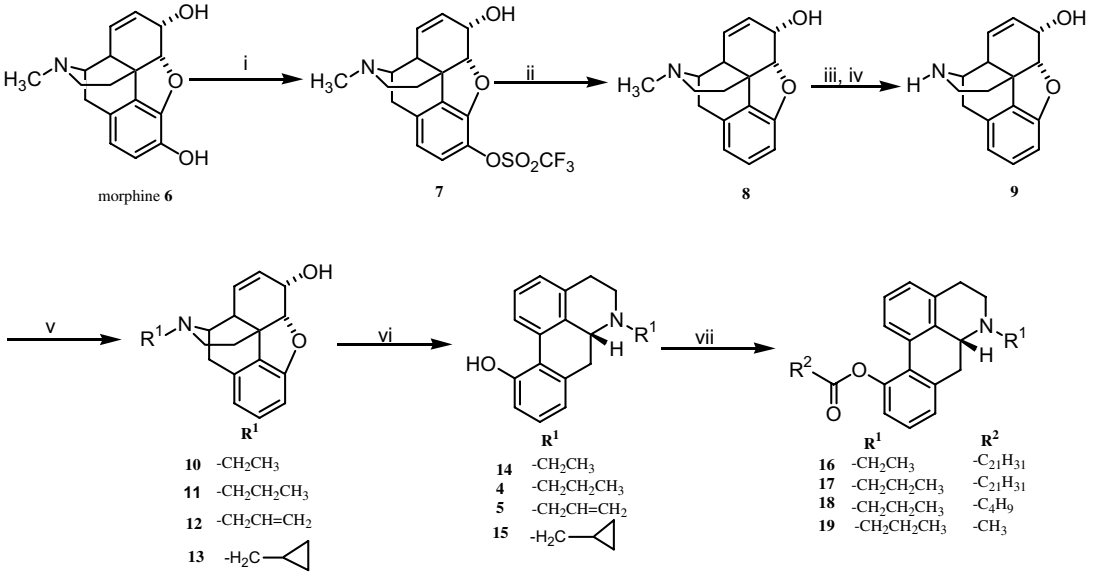
Selective, catalytic removal of the 3-hydroxyl group from morphine (**6**) employing a modification of Hedberg's procedure[10] via 3-*O*-[(trifluoromethyl)sulfonyl]morphine (**7**) resulted in a high yield of 3-deoxymorphine (**8**)[19] (Scheme 1). N-demethylation of **8** was carried out with methyl chloroformate to yield 3-deoxynormorphine (**9**).[19] N-alkylation of **9** with an appropriate alkyl halide led to the *N*-substituted-3-deoxynormorphines **10**–**13**. Acid-catalyzed rearrangement[11] of **10**–**12** with methanesulfonic acid at 90 °C yielded the corresponding R(−)-*N*-alkyl-11-hydroxynoraporphines **4**, **5**, **14**. In the case of *N*-cyclopropylmethyl-3-deoxynormorphine (**13**), the desired aporphine **15** was not obtained, presumably due to the instability of its *N*-substituent at this temperature. However, the *N*-cyclopropylmethyl-11-hydroxynoraporphine (**15**) was obtained by conducting the rearrangement at 60 °C.

Long-chain fatty acid derivatives of clozapine are active after oral administration, with greatly enhanced antidopaminergic potency and prolonged duration of action.[12] Accordingly, we prepared a series of esters of varying chain length, in an effort to improve the bioavailability and duration of action of the 11-hydroxyaporphines. Esters of representative long- (docosahexaenoyl), intermediate- (valeryl), and short-chain (acetyl) acids were prepared by reacting the appropriate acid with *N*-ethyl-(**14**) or *N*-propyl-11-hydroxynoraporphine (**4**) in the presence of dicyclohexyl carbodiimide (DCC). Thus, esters **16**–**19** were obtained in 63–75% yield (Scheme 1).

2.2. Pharmacology

In vitro affinity of R(−)-*N*-alkyl-11-hydroxynoraporphines and their esters for the dopamine D_1 and D_2 receptors was determined using competition assays in rat forebrain tissue (Table 1). The binding affinity of R(−)-*N*-propylnorapomorphine (**2**) for the dopamine D_2 receptor ($K_i = 9.9$ nM) was very similar to that of R(−)-apomorphine (**1**) ($K_i = 13.2$ nM), whereas its D_1 affinity was somewhat lower. Among the four R(−)-*N*-alkyl-11-hydroxynoraporphines **4**, **5**, **14**, and **15**, R(−)-*N*-*n*-propyl-11-hydroxynoraporphine (**4**) had the highest D_2 affinity ($K_i = 28.5$ nM), and lowest D_1 affinity, and so was selected for esterification. Affinity for the dopamine D_2 receptor decreased with increasing size of the ester moiety: it was highest with acetyl (**19**), intermediate with valeryl (**18**), and lowest with the docosohexanoyl ester (**17**), suggesting increasing steric hindrance with increasing chain length of the ester group.

We considered the possibility that the affinity of the esters, especially the acetate **19** may reflect hydrolysis to the parent phenolic aporphine **4** under the conditions of the radioreceptor labeling experiments. For this purpose, we examined the products of the binding experi-



Scheme 1. Synthesis of *N*-alkylated-11-hydroxynoraporphines and their esters. Reagents and conditions: (i) $PhNTf_2$, Et_3N, CH_2Cl_2, overnight; (ii) $Pd(OAc)_2$, Ph_3P, Et_3N, HCOOH, DMF, 60 °C; (iii) $ClCOOCH_3$, $NaHCO_3$; (iv) NH_2NH_2, reflux; (v) R^1X, K_2CO_3, EtOH; (vi) CH_3SO_3H; (vii) R^2COOH, DCC, DMAP, CH_2Cl_2.

Table 1. R(−)-*N*-alkyl-11-hydroxynoraporphines: affinity at rat brain dopamine receptors

Agents	$K_i \pm$ SEM (nM)	
	D_1	D_2
Aporphines (comparison standards)		
(**1**) R(−)-apomorphine	214 ± 18	13.2 ± 2.1
(**2**) R(−)-*N*-*n*-propylnorapomorphine (NPA)	733 ± 74	9.9 ± 1.0
(**3**) R(−)-11-hydroxyaporphine	26.5 ± 1.0	108 ± 10.8
R(−)-N-alkyl-11-hydroxynoraporphines		
(**4**) R(−)-*N*-*n*-propyl-11-hydroxynoraporphine	699 ± 118	28.5 ± 12.8
(**5**) R(−)-*N*-allyl-11-hydroxynoraporphine	397 ± 51	41.1 ± 11.0
(**14**) R(−)-*N*-ethyl-11-hydroxynoraporphine	177 ± 13	88.0 ± 15.5
(**15**) R(−)-*N*-cyclopropylmethyl-11-hydroxynoraporphine	272 ± 18	96.3 ± 15.8
Esters of N-n-propyl-11-hydroxynoraporphine		
(**17**) R(−)-*N*-*n*-propyl-11-docosahexanoyloxynoraporphine	>20,000	>10,000
(**19**) R(−)-*N*-*n*-propyl-11-acetyloxynoraporphine	>10,000	72.3 ± 6.8
(**18**) R(−)-*N*-*n*-propyl-11-valeryloxynoraporphine	>20,000	340 ± 65

ments after 1 h of incubation under the same conditions as used in the radioligand competition assays (see experimental section). We found by thin layer chromatography (TLC, $CHCl_3$/MeOH = 10/1) that acetate **19** was partially hydrolyzed to its phenolic precursor **4**.

In vivo experiments (Table 2) indicated that R(−)-*N*-*n*-propylnorapomorphine (**2**) produced significantly greater behavioral arousal than R(−)-apomorphine (**1**) despite its similar affinity at the D_2 receptor and lower D_1 affinity. However, in contrast to R(−)-apomorphine (**1**), the *N*-*n*-propyl analog (**2**) had unexpected oral behavioral activity at a dose of 20 μmol/kg. Removing the hydroxyl group from the 10-position as in **4** did not significantly change its in vitro receptor-affinity profile. Esterification of **4** significantly improved the oral bioavailability, especially the acetate **19** and valerate **18**. The longer chain valerate ester **18** had somewhat lower

Table 2. Motor activation induced by *N*-alkyl R-(−)-11-hydroxyaporphines and their esters in rats

Agent	Dose (μmol/kg)	Route	*N*	Activity score	Duration (h)
Catecholaporphine standard agents					
(**1**) R(−)-apomorphine	4	i.p.	4	1	1
	4	i.g.	4	Inactive	NA
	20	i.g.	6	Inactive	NA
(**2**) R(−)-*N*-*n*-propylnoraporphine (NPA)	4	i.p.	8	12 ± 5.2	8
	4	i.g.	8	Inactive	NA
	20	i.g.	6	68 ± 20.8	14
N-alkyl R(−)-11-OH-aporphines					
(**4**) R(−)-11-OH-*N*-*n*-propylnoraporphine	4	i.p.	4	24 ± 12.3	8
	4	i.g.	4	Inactive	NA
	20	i.g.	5	76 ± 27.9	18
(**14**) R(−)-11-OH-*N*-ethylnoraporphine	4	i.p.	5	12 ± 5.2	4
	4	i.g.	4	Inactive	NA
	20	i.g.	4	Inactive	NA
Esters of N-propyl-11-hydroxynoraporphine					
(**17**) R(−)-11-*O*-docosahexaenoyl-*N*-*n*-propyl noraporphine	4	s.c.	4	Inactive	NA
	4	i.g.	4	Inactive	NA
	20	s.c.	4	5 ± 2.6	6
	20	i.g.	4	75 ± 33.4	12
(**18**) R(−)-11-*O*-valeryl-*N*-*n*-propyl noraporphine	4	i.p.	4	53 ± 10.0	12
	4	i.g.	4	Inactive	NA
	20	i.g.	4	99 ± 18.0	14
(**19**) R(−)-11-*O*-acetyl-*N*-*n*-propylnoraporphine	4	i.p.	4	12 ± 4.7	8
	4	i.g.	4	Inactive	NA
	20	i.g.	4	168 ± 33.5	16

Activity score (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; i.p.: intraperitoneal; i.g.: intragastric; s.c.: subcutaneous; *N*, number of rats.

activity when given subcutaneously, and moderate oral bioavailability (Table 2).

3. Conclusions

We report an efficient procedure for the preparation of *N*-substituted-R(−)-11-hydroxynoraporphines **4**, **5**, **14**, **15** from morphine (**6**), by a sequence of selective removal of a phenolic hydroxyl group, N-demethylation, and realkylation with an appropriate alkyl halide followed by methanesulfonic acid-catalyzed rearrangement. Esterification of the mono hydroxyl- aporphine **4** with representative acids yielded the corresponding esters **16**–**18**.

Replacing the *N*-methyl group in R(−)-apomorphine (**1**) with the *n*-propyl group slightly enhanced the affinity at the D_2 dopamine receptor, but decreased affinity at the D_1 receptor. Among the present series of 11-hydroxyaporphines, the *N*-*n*-propyl compound **4** gave the highest affinity and selectivity at the D_2 dopamine receptor, and its affinity was lower than that of its catechol precursor **2**. Esterification of **4** resulted in a slightly decreased affinity at dopamine D_2 receptors and substantial loss of D_1 affinity.

In vivo potency and oral activity of the compounds evaluated indicated greater behavioral potency and duration of locomotor behavioral activation of systemically injected (i.p.) *N*-*n*-propyl (**4**) than *N*-ethyl (**14**) 11-hydroxynoraporphine. We esterified the 11-hydroxyl function of **4** with a series of short (acetic, **19**), moderate (valeric, **18**), and long-chain (docosahexaenoic or DHA, **16**) acids and evaluated their in vivo pharmacological activity. We found maximal behavioral potency after systemic injection with the intermediate valeryl ester (**17**) following parenteral injection, but with the acetate ester (**19**) after enteric (intragastric) administration.

4. Experimental

4.1. Chemical synthesis

Melting points were measured with a Thomas Hoover Capillary Melting Point Apparatus, and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on Varian 300 spectrometer, chemical shifts are reported in ppm (δ) from internal TMS and coupling constants (J) were measured in Hz. Thin layer chromatography (TLC) was performed on precoated Merck 5554 Silica gel 40 F_{254} foils, and the spots were visualized with Dragendorff's reagent. Mass spectra were measured with a Hewlett Packard 5972 series GC–MS instrument. APO (**1**) and NPA (**2**) were synthesized by the procedure of Granchelli et al.[11] and Berenyi et al.[13] using the methanesulfonic acid-catalyzed rearrangement of the appropriate morphinanes.

4.2. 3-*O*-[(Trifluoromethyl)sulfonyl]morphine (7)

A slurry of **6**·H_2O (10 g, 32.8 mmol) and Et_3N (7 mL) in anhydrous CH_2Cl_2 (500 mL) under nitrogen was stirred for 1 h at rt. *N*-Phenyltrifluoro-methanesulfonimide (14 g, 39.4 mmol) was added to the reaction mixture. After stirring for 24 h, the reaction mixture was extracted with 10% (w/v) aqueous $KHCO_3$ (3×70 mL). The organic layer was dried on sodium sulfate, filtered, and concentrated in vacuo. A solid product (24.5 g) was obtained, which was dissolved in ether (80 mL), and extracted with 1 M HCl (4×120 mL). The acidic layer was basified with ammonium hydroxide. The mixture was extracted with CH_2Cl_2 (3×100 mL). The organic layer was washed with brine (100 mL), dried with Na_2SO_4, filtered and evaporated, to afford a white solid (13.13 g). The solid residue was washed with a small amount of dry ether to yield 12.4 g (90%) of pure **7**; mp: 122–124 °C (Lit.[10]: 123–124 °C), ^{1}H and ^{13}C NMR spectra were identical with that of the literature data.[10]

4.3. 3-Deoxymorphine (8)

Triphenylphosphine (1.2 g, 4.5 mmol) and palladium acetate (0.48 g, 2.03 mmol) were added to a stirred mixture of **7** (10.0 g, 23.98 mmol), triethylamine (15 mL, 106.9 mmol), and formic acid (1.8 mL, 45.1 mmol) in DMF (32 mL) at 40 °C under nitrogen. The mixture was stirred under nitrogen for 5 h, at 60 °C. After cooling to room temperature (RT), the reaction mixture was added dropwise to a cooled solution of HCl (30 mL) in water (300 mL). The acidic solution was extracted with CH_2Cl_2 (4×100 mL). The aqueous layer was basified with ammonium hydroxide upon cooling, and then extracted with CH_2Cl_2 (3×100 mL). The organic layer was washed with brine (100 mL), dried with sodium sulfate, filtered, and evaporated. The solid residue was filtered from dry ether, washed with ether, to provide 5.7 g (88%) of **8**; mp: 224–227 °C (Lit.[10]: 227–229 °C). ^{1}H and ^{13}C NMR spectra were identical to the reported values.[10]

4.4. 3-Deoxynormorphine (9)

3-Deoxynormorphine (**9**) was prepared according to the reported procedure.[19]

4.5. General procedure for the synthesis of *N*-alkyl-3-deoxynormorphines (10–13)[19]

To a stirred mixture of **9** (0.5 g, 1.96 mmol), and $NaHCO_3$ (0.25 g, 2.98 mmol) in anhydrous ethanol (10 mL) the appropriate alkyl halide (2.5 mmol) was added slowly, under nitrogen. The reaction mixture was allowed to reflux at 80–90 °C for 24 h. Water (40 mL) was then added to the reaction mixture, followed by extraction into ethyl acetate (3×20 mL). The organic layer was washed with brine (20 mL), dried with sodium sulfate, filtered, and evaporated in vacuo. The oily crude product was purified by column chromatography with 9:1 (vols) chloroform:methanol to afford pure oils.

4.6. General procedure for the synthesis of R(−)-*N*-alkyl-11-hydroxynoraporphine hydrochlorides (4, 5, 14, 15)

The appropriate *N*-alkyl-3-deoxynormorphine (**10**–**13**) (1.45 mmol) was dissolved in 99% methanesulfonic acid (4 mL, 62 mmol), under nitrogen at RT. The reaction mixture was stirred for 30 min at 90 °C, and then cooled to RT. Ice-water (20 mL) was added and the mixture was basified with ammonia, extracted with CH_2Cl_2 (3×20 mL), and the organic layer was washed with brine (20 mL), dried over sodium sulfate and evaporated in vacuo to provide an oily crude product. Purification by column chromatography with 19:1 (vols) chloroform:methanol provided a pure oily product, which was converted into the hydrochloride salt with 1 M HCl–ether.

4.7. R(−)-*N*-ethyl-11-hydroxynoraporphine hydrochloride (14)

White solid (53%), mp>250 °C (dec.); ^{1}H NMR (CD_3OD) δ 1.47 (3H, t, CH_3), 2.85 (1H, m, C–H), 3.30 (5H, m, C–H), 3.97 (2H, m, C–H), 4.43 (1H, m, C–H), 6.88 (2H, m, H-8, H-10), 7.12 (1H, t, H-9), 7.18 (1H, d, $J_{2,3} = 9$ Hz, H-3), 7.37 (1H, t, H-2), 8.40 (1H, d, $J_{1,2} = 9$ Hz, H-1); MS *m*/*z* (rel. intensity) 265 (M, 60%). Anal. ($C_{18}H_{19}NO\cdot HCl$) Calcd: C, 71.64; H, 6.63; N, 4.64. Found: C, 71.58; H, 6.65; N, 4.62.

4.8. R(−)-*N*-*n*-propyl-11-hydroxynoraporphine hydrochloride (4)

White solid (52%); mp>250 °C (dec.) (Lit. [4]: 257–258 °C).

4.9. R(−)-*N*-allyl-11-hydroxynoraporphine hydrochloride (5)

White solid (50%), mp: 186–190 °C. ^{1}H NMR (CD_3OD) δ 2.86 (1H, m, C–H), 3.30 (4H, m, C–H), 3.98 (2H, m, C–H), 4.38 (2H, m, C–H), 5.72 (2H, m,=C–H), 6.09 (1H, m, =C–H), 6.89 (2H, d, $J = 8.5$ Hz, H-8, H-10), 7.12 (1H, t, H-9), 7.18 (1H, d, $J = 8.2$ Hz, H-3), 7.36 (1H, t, H-2), 8.41 (1H, d, $J = 8.2$ Hz, H-1); MS *m*/*z* (rel. intensity) 277 (M, 50%). Anal. ($C_{18}H_{17}NO\cdot HCl\cdot H_2O$) Calcd: C, 65.16; H, 6.03; N, 4.22. Found: C, 65.25; H, 6.04; N, 4.23.

4.10. R(−)-*N*-cyclopropylmethyl-11-hydroxynoraporphine hydrochloride (15)

The reaction was conducted at 60 °C and the hydrochloride was obtained as a white solid (36%); mp: 195–200 °C (dec.). ^{1}H NMR (base, $CDCl_3$) δ 0.20 (2H, m, cyclopropyl C–H), 0.56 (2H, m, cyclopropyl C–H), 1.00 (1H, m, cyclopropyl C–H), 2.40 (1H, q, C–H), 2.58 (2H, m, C–H), 2.79 (1H, m, C–H), 3.08 (3H, m, C–H), 3.45 (2H, m, C–H), 6.78 (1H, d, $J = 8.5$ Hz, H-8), 6.84 (1H, d, $J = 8.5$ Hz, H-10), 7.06 (2H, t, H-9, H-3), 7.26 (1H, t, H-2), 7.94 (1H, d, $J = 7.9$ Hz, H-1); ^{13}C NMR (base, $CDCl_3$) δ 2.9, 5.0, 7.4, 29.1, 34.8, 49.1, 59.1, 59.2, 115.5, 120.4, 121.3, 124.3, 126.3, 127.6, 128.0, 131.3, 133.7, 136.1, 138.3, 152.7; MS *m*/*z* (rel. intensity) 291 (M, 70%), 290 (M-1, 100%). Anal. ($C_{20}H_{21}NO\cdot HCl$) Calcd: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.25; H, 6.76; N, 4.25.

4.11. General procedure for the synthesis of R(−)-*N*-alkyl-11-hydroxynoraporphine esters (16–19)[14]

The appropriate R(−)-*N*-alkyl-11-hydroxynoraporphine (**4**, **14**) (0.5 mmol), corresponding acid (0.6 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were dissolved in anhydrous dichloromethane (20 mL) under nitrogen. To the stirred mixture, a solution of *N*,*N*′-dicyclohexyl-carbodiimide (130 mg, 0.6 mmol) in anhydrous dichloromethane (6 mL) was added at RT. After stirring for 4 h, the reaction mixture was filtered and evaporated to dryness. The crude oily product was purified by column chromatography with 5:2 (vols) hexane–ethyl acetate to obtain a pure oily product.

4.12. R(−)-*N*-ethyl-11-docosahexaenoyloxynoraporphine (16)

Starting from **R**(−)-*N*-ethyl-11-hydroxynoraporphine (**14**) and *cis*-4,7,10,13,16,19-docosahexaenoic acid (DHA), the product is a syrupy oil (180 mg, 63%): ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, CH_3), 1.16 (3H, t, CH_3), 2.07 (2H, m, C–H), 2.50 (8H, m, C–H), 2.85 (10H, s, C–H), 3.15 (4H, m, C–H), 3.48 (1H, m, C–H), 5.37 (12H, s, =C–H), 7.00 (1H, d, $J_{9,10} = 8$ Hz, H-10), 7.07 (1H, d, $J_{8,9} = 8$ Hz, H-8), 7.21 (3H, m, H-2, H-3, H-9), 7.74 (1H, d, $J_{1,2} = 8$ Hz, H-1). Anal. ($C_{40}H_{49}NO_2$) Calcd: C, 83.43; H, 8.58; N, 2.43. Found: C, 83.22; H, 8.60; N, 2.43.

4.13. R(−)-*N*-*n*-propyl-11-docosahexaenoyloxynoraporphine (17)

Starting from R(−)-*N*-propyl-11-hydroxynoraporphine (**4**) and *cis*-4,7,10,13,16,19-docosahexaenoic acid (DHA), the product was obtained as a syrupy oil (210 mg, 71%): ^{1}H NMR ($CDCl_3$) δ 0.97 (6H, t, $2\times CH_3$), 1.58 (2H, m, C–H), 2.07 (2H, m, C–H), 2.55 (9H, m, C–H), 2.85 (10H, s, C–H), 3.10 (3H, m, C–H), 3.41 (1H, d, C–H) 5.37 (12H, s, =C–H), 7.00 (1H, d, $J_{9,10} = 8$ Hz, H-10), 7.07 (1H, d, $J_{8,9} = 8$ Hz, H-8), 7.21 (3H, m, H-2, H-3, H-9), 7.72 (1H, d, $J_{1,2} = 8.5$ Hz, H-1). Anal. ($C_{41}H_{51}NO_2$) Calcd: C, 83.49; H, 8.71; N, 2.37. Found: C, 83.25; H, 8.74; N, 2.36.

4.14. R(−)-*N*-*n*-propyl-11-valeryloxynoraporphine hydrochloride (18)

Starting from R(−)-*N*-*n*-propyl-11-hydroxynoraporphine (**4**) and valeric acid, the oily product was

converted to the hydrochloride salt with HCl–ether to provide a white solid product (150 mg, 75%): mp: 232–234 °C (dec.). ^{1}H NMR (base, $CDCl_3$) δ 0.95 (6H, m, $2\times CH_3$), 1.37 (2H, m, C–H), 1.75 (4H, m, C–H), 2.50 (5H, m, C–H), 2.75 (1H, d, C–H), 2.90 (1H, m, C–H), 3.18 (3H, m, C–H), 3.41 (1H, d, $J = 13$ Hz, C–H), 7.00 (1H, d, $J_{9,10} = 8$ Hz, H-10), 7.07 (1H, d, $J_{8,9} = 7$ Hz, H-8), 7.21 (3H, m, H-2, H-3, H-9), 7.74 (1H, d, $J_{1,2} = 7.5$ Hz, H-1); ^{13}C NMR (base, $CDCl_3$) δ 12.0, 13.6, 19.5, 22.2, 26.7, 29.3, 34.3, 35.0, 48.8, 56.5, 59.1, 122.1, 124.7, 125.8, 125.9, 127.3, 127.6, 128.1, 130.6, 133.6, 135.8, 138.6, 147.3, 171.9; MS m/z (rel. intensity) 363 (M, 60%); HPLC: 99% purity. Anal. ($C_{24}H_{29}NO_2$·HCl) Calcd: C, 72.07; H, 7.56; N, 3.50. Found: C, 71.91; H, 7.58; N, 3.51.

4.15. R(−)-*N*-*n*-propyl-11-acetyloxynoraporphine hydrochloride (19)

Starting from R(−)-*N*-propyl-11-hydroxynoraporphine (**4**) and glacial acetic acid, column chromatographic purification was carried out with 19:1 (vols) chloroform:methanol, and an oily product obtained was converted to the hydrochloride salt with HCl–ether to provide a white solid product (120 mg, 67%); mp: 250–252 °C (dec.). ^{1}H NMR (base, $CDCl_3$) δ 0.96 (3H, t, CH_3), 1.65 (2H, m, C–H), 2.27 (3H, s, $COCH_3$), 2.50 (3H, m, C–H), 2.75 (1H, m, C–H), 2.90 (1H, m, C–H), 3.12 (3H, m, C–H), 3.40 (1H, m, C–H), 7.02 (1H, d, $J_{9,10} = 8$ Hz, H-10), 7.07 (1H, d, $J_{8,9} = 8$ Hz, H-8), 7.21 (3H, m, H-2, H-3, H-9), 7.75 (1H, d, $J_{1,2} = 7.5$ Hz, H-1); ^{13}C NMR (base, $CDCl_3$) 12.0, 19.5, 21.3, 29.3, 35.0, 48.8, 56.5, 59.2, 122.0, 124.5, 125.9, 126.0, 127.3, 127.7, 128.2, 130.6, 133.7, 135.9, 138.6, 147.2, 169.2; MS m/z (rel. intensity) 321 (M, 70%); HPLC: 97% purity. Anal. ($C_{21}H_{23}NO_{2*}$HCl) Calcd: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.42; H, 6.80; N, 3.89.

4.16. Pharmacology

In vitro neuropharmacology: Affinity of R(−)-*N*-alkyl-11-hydroxynoraporphines (**4**, **5**, **14**, **15**) and their esters (**17**–**19**) for dopamine D_1 and D_2 receptors was determined 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 following 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 and resuspended in the same buffer. For the D_1 receptor assay, homogenate was incubated with 300 pM [^{3}H]SCH-23390 (NEN; Boston, MA) for 30 min at 30 °C; nonspecific binding was defined with excess (10 μM) *cis*-flupenthixol.[15] For the D_2 receptor assay, homogenate was incubated with 75 pM [^{3}H]nemonapride (NEN; Boston, MA) for 90 min at 30 °C; nonspecific binding was defined with 10 μM haloperidol.[16,17] Experiments were carried out in triplicate. Results from these radioligand competition assays are shown in Table 1.

In vivo pharmacology: In vivo potency and oral bioavailability of synthesized aporphine derivatives were determined by measuring stimulation of motor activity in adult male Sprague–Dawley rats using a microcomputer-controlled photobeam activity monitoring system (San Diego Instruments; San Diego, CA), as was detailed previously.[18] The number of rats in each experimental group ranged from 4 to 8. Oral delivery of test agents was achieved using a permanently surgically preimplanted polyethylene gastric tube to avoid stress associated with conventional oral intubation. For this surgery, rats were anesthetized with 60 mg/kg sodium pentobarbital (injected intraperitoneally, i.p.). PE50 tubing was inserted and sutured to the stomach, and led subcutaneously to a point of access on the back of the neck, where it was sutured in place. Animals were allowed at least two weeks to recover prior to 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 drugs delivered using this method did not reach sites other than 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) produced by i.p. injection of 4 μmol/kg R(−)-apomorphine (**1**), the effects of which lasted for one hour. In addition to the activity sum-score, duration of action is also shown in Table 2.

Acknowledgements

The authors acknowledge the Branfman Family Foundation, as well as the Bruce J. Anderson Foundation and the McLean Private Donors Neuropharmacology Research Fund for financial support of this work. Morphine was generously supplied by Mallinkrodt Inc. We also thank Jane McNeil for the mass spectroscopy determinations and Xuemei Peng for assistance in the preparation of the manuscript.

References and notes

1. Neumeyer, J. L.; Granchelli, F. E.; Fuxe, K.; Ungerstedt, U.; Corrodi, H. *J. Med. Chem.* **1974**, *17*, 1090.
2. Neumeyer, J. L.; Arana, G. W.; Law, S. J.; Lamont, J. S.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1981**, *24*, 1440.
3. Ram, V. J.; Neumeyer, J. L. *J. Org. Chem.* **1982**, *47*, 4372.
4. Gao, Y.; Zong, R.; Campbell, A.; Kula, N. S.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **1988**, *31*, 1392.
5. Neumeyer, J. L.; Gao, Y.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1991**, *34*, 24.
6. Neumeyer, J. L.; Baldessarini, J. L.; Booth, R. G. In *Burgers Medicinal Chemistry*, 6th ed.; Abraham, D. J., Ed.; John Wiley & Sons: New York 2003; Vol. 6, pp 711–742.
7. Baldessarini, R. J.; Walton, K. G.; Borgman, R. J. *Neuropharmacology* **1976**, *15*, 471.

8. Campbell, A.; Baldessarini, R. J.; Ram, V. J.; Neumeyer, J. L. *Neuropharmacology* **1982**, *21*, 953.
9. Schaus, J. M.; Titus, R. D.; Foreman, M. M.; Mason, N. R.; Truex, L. L. *J. Med. Chem.* **1990**, *33*, 600.
10. Hedberg, M. H.; Johansson, A. M.; Nordvall, G.; Yliniemela, A.; Li, H. B.; Martin, A. R.; Hjorth, S.; Unelius, S.; Sundell, S.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 647.
11. Granchelli, F. E.; Filer, C. N.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1980**, *45*(12), 2275.
12. Baldessarini, R. J.; Campbell, A.; Webb, N. L.; Swindell, C. S.; Flood, J. G.; Shashoua, V. E.; Kula, N. S.; Hemamalini, S.; Bradley, M. O. *Neuropharmacology* **2000**, *24*, 55.
13. Berenyi, S.; Hosztafi, S.; Makleit, S.; Molnar, I. *Acta Chim. Hung.* **1983**, *113*, 51.
14. Venema, F.; Nelissen, H. F. M.; Berthault, P.; Birlirakis, N.; Rowan, A. E.; Feiters, M. C.; Nolte, R. J. M. *Eur. J. Chem.* **1998**, *4*, 2237.
15. Faedda, G.; Kula, N.; Baldessarini, R. J. *Biochem. Pharmacol.* **1989**, *38*, 473.
16. Baldessarini, R. J.; Kula, N. S.; Campbell, A.; Bakthavachalam, V.; Yuan, J.; Neumeyer, J. L. *Mol. Pharmacol.* **1992**, *42*, 856.
17. Kula, N. S.; Baldessarini, R. J.; Kebabian, J. W.; Bakthavachalam, V.; Xu, L. *Eur. J. Pharmacol.* **1997**, *331*, 333.
18. Zhang, K.; Tarazi, F. I.; Baldessarini, R. J. *Neuropsychopharmacology.* **2001**, *25*, 624.
19. Csutoras, C.; Zhang, A.; Bidlack, J. M.; Neumeyer, J. L. *Bioorg. Med. Chem.* **2004**, *12*, 2687.