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N-Substituted-2-alkyl- and 2-arylnorapomorphines: Novel, highly active D_2 agonists

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Dedicated to Professor György Kalaus on the occasion of his 70th birthday

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ABSTRACT

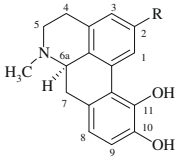
Two synthesis routes have been elaborated for the preparation of novel N-substituted-2-alkyl- and 2-arylnorapomorphines. The first one utilizes the traditional methodology of N-substitution of morphinans before acid-catalyzed rearrangements into aporphinoids, while our new approach involves the N-substitution directly on the aporphine backbone. The aimed compounds were obtained in similar overall yields in different synthesis routes and were investigated with respect to their binding affinities and activities to dopamine D_2 and D_1 receptors. These studies revealed remarkable affinity and selectivity of some compounds for D_2 over D_1 receptor subtypes. Partial or full agonist properties were confirmed for all tested compounds.

1. Introduction

Different brain dopaminergic systems have been in the focus of extensive research over many decades now. The need for high affinity and subtype selective (partial) agonists is connected with treatment and/or prevention of schizophrenia, Parkinson's disease, Tourette's syndrome, depression, addiction etc.[1a] It should be noted that in spite of their similar anatomical distribution in brain striatal and limbic areas, functions of D_1 and D_2 receptors are quite different—at biochemical and as well as at behavioral level.[1b] However, high affinity ligands for one of these receptors have often also similar affinity for the other subtypes, which may cause undesirable side effects in patients. Apomorphine (**1**) (Fig. 1), first synthesized in 1869 from morphine by Matthiessen and Wright, is one of few approved dopamine receptor drugs, which is in use in treatments of Parkinson's disease and erectile dysfunction.[2]

The application of this drug substance has been limited by the above mentioned lack of selectivity among dopamine receptor subtypes, and therefore an intensive search for derivatives with higher subtype selectivity without significant loss of their affinity has been generated. One approach is to change the stereochemistry of the compound. Modification of the only chiral center of the molecule (C6a) results some agonist/antagonist counterparts among enantiomers, but does not generate subtype selectivity.[3a] The introduction of appropriate moieties to the ring A of aporphine backbone gives rise to the change of the selectivity of compounds.[3b] The modification of the substituent at amine-type N6 has high size-sensitivity, ethyl- and propyl-substituted compounds have subnanomolar affinities for D_2 receptors, however compounds with isopropyl and larger substituents have thousand time lower affinities.[4a] This has made propylnorapomorphine (NPA) a powerful tool for studies of dopaminergic receptors,[4b] and an important matrix for the development of new more subtype-selective dopaminergic ligands.

In the present paper we report on the combination of two of the above mentioned approaches and, by varying substituents at positions N6 and 2, the synthesis of new compounds with nanomolar affinity for D_2 receptors and clear selectivity over D_1 receptors



Compound	R
1	H
2	Me
3	Ph
4	4-OH-Ph

Figure 1. Structure of apomorphine (**1**), core structure for design of new compounds and its 2-substituted derivatives.

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based on previous findings regarding significant D_2/D_1 selectivity of 2-arylapomorphines **3**, **4**.[5]

The N-substituted noraporphines are traditionally prepared via the acid-catalyzed rearrangement of the corresponding normorphinans.[1a,6] Syntheses of these N-substituted derivatives involve the conversion of *N*-methyl-substituted opioids to the cyanamides,[7] carbamates[8] or 1,2-dicarbethoxyhydrazinylmethyl-congeners,[9] which are subsequently cleaved to give the *N*-noropioids. Simple N-alkylation provides the desired substitution.[6]

However, in morphinans having double bond between C8 and C14 the formation of cyanamides and carbamates was accompanied by the cleavage of C9–N17 bond;[10] due to this reason diethyl azodicarboxylate (DEAD) was applied.[11]

The direct N-demethylation and consequent N-alkylation of aporphines have not described, however some successful attempts were published regarding the synthesis of noraporphines.[12,13]

2. Results and discussion

2.1. Chemistry

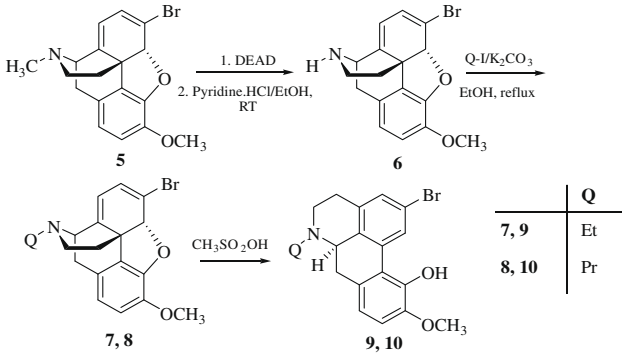
Herewith we report the preparation of 2- and N6-substituted noraporphines as compounds which have perspective as specific activators of D_2 receptors. The synthesis of *N*-ethyl and *N*-propyl-nor derivatives of 2-substituted apomorphines **2–4** was a reasonable step forward in the course of development of novel, highly potent dopamine agonists following from the above-described observations. The conventional synthesis route to N-substituted aporphines involves the consecutive N-deprotection and N-alkylation on morphinan backbone and the acid-catalyzed rearrangement into *N*-alkyl-noraporphine (Scheme 1, Route I). A modified route employs direct rearrangement of 6-Br-6-demethoxythebaine (**5**) into the apocodeine and performs the transformation of *N*-methyl derivatives into *N*-ethyl or *N*-propyl-noraporphines (Scheme 1, Route II). From this point Route II is the same as Route I. Suzuki–Miyaura cross-coupling steps included in the joint part of routes were based on our previous experience in the formation of 2- and 3-substituted aporphines.[14]

The starting product of both synthesis routes is 6-Br-6-demethoxythebaine (**5**) produced from natural thebaine according to the procedure elaborated by our research group in 1984.[15] The N-demethylations and N-alkylations of **5** were carried out in the traditional way applying diethyl azodicarboxylate (DEAD, Scheme 2).[16] The acid-catalyzed rearrangement of *N*-alkyl-nor derivatives **7**, **8** provided *N*-ethyl- and *N*-propyl-2-bromonorapocodeines (**9**, **10**) in excellent yields.

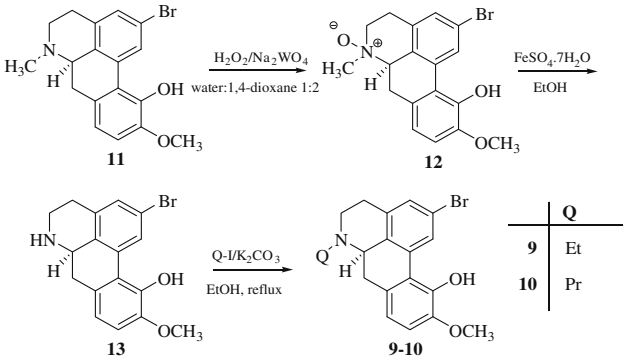
As an alternative synthesis of compounds **9** and **10** the starting diene **5** was rearranged into 2-bromoapocodeine **11** and the N-substitution was achieved on aporphine backbone. The oxidation–cleavage–alkylation sequence proposed by McCamley et al.[17] was successfully adopted to aporphine backbone to obtain *N*-ethyl and *N*-propyl congeners as it was previously communicated in details.[18] The transformation of 2-bromoapocodeine (**11**) into its N-oxide congener **12** (Scheme 3) was achieved with the application of Na_2WO_4-catalyzed, H_2O_2-mediated oxidation in water:1,4-dioxane mixture (1:2).

The HCl salt of N-oxide **12** was then N-deprotected according to Scammells' procedure applying $FeSO_4{\cdot}7H_2O$ in methanol at 0 °C. Noraporphine **13** was alkylated with the same procedure as in Route I to reach *N*-ethyl- and *N*-propyl-2-bromonorapocodeines (**9**, **10**). The traditional procedure (Route I) resulted the compounds **9** and **10** in 34% and 38% yields, respectively; while Route II yielded the same products in 43% and 39%, respectively.

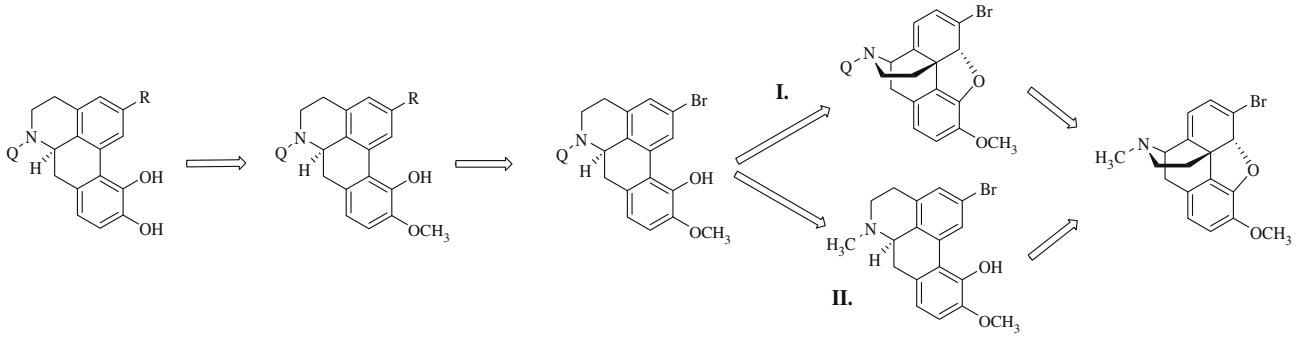
Further steps of joint Routes I and II include the Suzuki–Miyaura cross-coupling of aryl halide-type compounds **9** and **10** resulting 2-alkyl- and 2-arylnorapocodeines **14–19** and the O-demethylation of the apocodeines to form pharmacologically



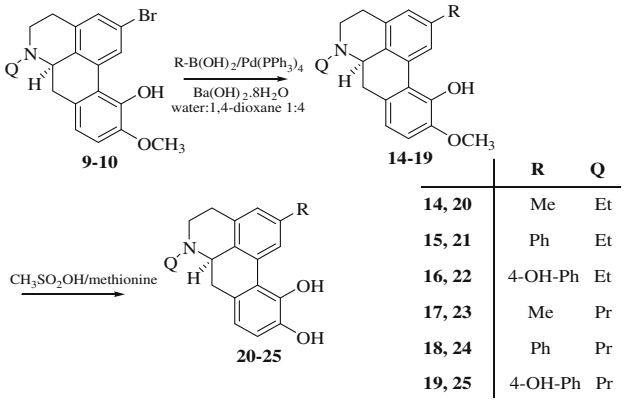
Scheme 2. Synthesis of *N*-Et- and *N*-Pr-2-Br-norapocodeines (**9**, **10**) via Route I.



Scheme 3. Synthesis of *N*-Et- and *N*-Pr-2-Br-norapocodeines (**9**, **10**) via Route II.



Scheme 1. Retrosyntheses of N-substituted 2-methyl- and 2-arylnorapomorphines.



	R	Q
14, 20	Me	Et
15, 21	Ph	Et
16, 22	4-OH-Ph	Et
17, 23	Me	Pr
18, 24	Ph	Pr
19, 25	4-OH-Ph	Pr

Scheme 4. Closing steps of Routes I and II.

more interesting apomorphine **20–25** as stable HCl salts (Scheme 4). These steps are in agreement with parts of our previously presented methodologies yielding 2-alkyl- and 2-arylapomorphines **2–4**, no major difference was observed in the reactivity of aporphines with regard to the change of the substituent at N6.[5b,14]

2.2. Pharmacology

The pharmacological properties of synthesized apomorphines **20–25** were studied in model systems expressing D_2 and D_1 dopamine receptors. The affinities of substances for corresponding receptors were estimated by their ability to displace the specific binding of [^{3}H]raclopride and [^{3}H]SCH23390, respectively. The specificity of ligands was calculated as a ratio of their affinities in radioligand binding assays for corresponding receptors. The agonistic properties of compounds were tested by their ability to activate [^{35}S]GTPγS binding to G proteins in CHO cell membranes, which has been developed as functional assay for D_2 receptors.[19] All tested apomorphine derivatives had higher affinities towards D_2 receptors, the K_i values being in nanomolar/submicromolar range, while their K_i values for D_1 receptors remaining in submicromolar/micromolar range (Table 1).

Highest potency and best subtype selectivity was achieved with 2-(4-hydroxyphenyl) derivatives (**22**, **25**). Both of them had more than fivefold higher affinity for D_2 receptors than apomorphine (**1**), and in [^{35}S]GTPγS activation assay they behaved as full agonists in comparison to dopamine (Table 1). These two compounds had also significantly higher subtype selectivity over D_1 receptors. The 83- and 47-fold difference in binding affinity is considered pharmacologically significant. It is important to mention, that in the case of 2-(4-hydroxyphenyl) derivatives of apomorphine **22**, **25** the influence of the size of substituent in N6 position had quite marginal role. Here we have found very similar properties for *N*-ethyl- (**22**) and *N*-propyl- (**25**) derivatives and *N*-methyl-derivative.[5a,b] The hydrophilic hydroxyl group coupled with 2-phenyl moiety seems to play crucial role in the binding and generation of response. Omitting of this group (compounds **21**, **24**) led to some decrease of affinity and also to loss of subtype selectivity. Higher D_2/D_1 subtype selectivity ratio (>30) was also achieved with 2-O-substituted apomorphines, but their affinities were at least 10 times lower and they behaved as partial agonists compared to dopamine.[3b]

3. Conclusion

In this paper, we have presented two approaches for synthesis of N-substituted-2-alkyl- and 2-arylnorapomorphines. Besides the method, utilizing conventional steps towards the N-substitution of morphinan backbone, a novel synthesis strategy was elaborated achieving N-substitution at aporphine skeleton. Most of the obtained compounds had high affinity for D_2 dopamine receptors and partial or full agonist properties. Highest affinity, subtype selectivity and full agonistic properties was achieved with 2-(4-hydroxyphenyl)- compounds (**22**, **25**). Obtained results indicate important role of size, localization and lipophilic/hydrophilic moieties of 2-substituents of *N*-alkyl norapomorphines.

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 80% CH_2Cl_2/20% CH_3OH mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H NMR spectra were recorded at 400 MHz, while ^{13}C NMR spectra at 100 MHz, using a Bruker Avance DPX400 spectrometer; chemical shifts were reported in ppm (δ) from internal TMS and coupling constants (J) were measured in hertz. Mass spectra (EI and HRMS, 70 eV, m/z) were obtained on a Jeol DX 303/DA 5000 instrument. Optical rotation

Table 1
Binding affinities of synthesized compounds for dopamine D_2 and D_1 receptors and their potencies and efficacies in activation of D_2 receptors

Compound	D_2			D_1	D_2/D_1
	Versus [^{3}H]raclopride	Activation of [^{35}S]GTPγS binding		Versus [^{3}H]SCH23390	Specificity (fold)
	K_i (nM)	EC_{50} (nM)	Efficacy (%)	K_i (nM)	
Dopamine	197 ± 67	1425 ± 813	100	124 ± 23	0.6
1	11.5 ± 0.7	53 ± 2.9	58 ± 1	72 ± 5.6	6.3
2	20.7*	43*	–	–	–
3	11.7*	23*	–	88*	7.5*
4	4.14*	8.5*	–	755*	182*
20	115 ± 47	480 ± 28	112 ± 3	1340 ± 516	12
21	14.0 ± 2.8	51 ± 5.2	72 ± 15	31 ± 1.4	2.2
22	1.5 ± 0.1	8.7 ± 0.6	112 ± 6	124 ± 2.8	83
23	9.2 ± 0.9	40 ± 8.5	65 ± 4	278 ± 5.6	30
24	192 ± 46	577 ± 93	100 ± 5	669 ± 172	3.5
25	2.0 ± 0.1	12.0 ± 2.9	99 ± 16	94 ± 15	47

K_i characterizes the ability of a compound to inhibit [3H]raclopride and [^{3}H]SCH23390 binding to D_2 and D_1 receptors, respectively. EC_{50} is the ability of compounds to activate [^{35}S]GTPγS binding. Efficacy represents the level of [^{35}S]GTPγS binding activation in comparison with the effect of dopamine. Specificity is the ratio of affinity constants of compounds towards D_1 and D_2 receptors.
* Data from Ref. 5.

was determined with a Perkin Elmer Model 241 polarimeter. Elemental analyses (C, H, N, S) were obtained on a Carlo Erba EA1108 analyzer.

4.2. Route I

4.2.1. N-Alkylation of 6-Br-6-demethoxynorthebaine (6)

Compound **6** (135 mg, 0.39 mmol) and K_2CO_3 (84 mg, 0.61 mmol) in anhydrous EtOH (10 mL) were stirred under N_2 at 80–90 °C. After 20 min, alkyl iodide (0.61 mmol) was dropped and the reaction mixture was stirred for 24 h at 90 °C. After cooled to rt, water (20 mL) was added, and the solution was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried with sodium sulfate, filtered and evaporated in vacuo to yield pure oily product.

4.2.1.1. *N*-Ethyl-6-bromo-6-demethoxynorthebaine (7). Slightly yellow oil; yield: 120 mg (81%); $[\alpha]_D^{25}$ − 194 (*c* 0.1, chloroform); R_f (80% CH_2Cl_2/20% CH_3OH) 0.52; MS (EI): *m*/*z* (%) 373 (M^+, 100), 357 (46), 303 (67); HRMS (EI) *m*/*z* (%) calculated for $C_{19}H_{20}BrNO_2^+$: 373.0756 (M^+), found: 374.0741 (M^+, 100); δ_H (400 MHz $CDCl_3$) 6.52–6.44 (2H, 2d, C_1–H, C_2–H, J_{1-2} 7.9), 6.37 (1H, C_7–H, J_{7-8} 6.4), 5.54 (1H, d, C_8–H, J_{7-8} 6.5), 4.78 (1H, s, C_5–H_a), 3.77–3.71 (4H, m, C_9–H, C_3–OCH_3), 2.94–2.09 (7H, m, C_{10}–H_a, C_{10}–H_b, C_{15}–H_b, C_{16}–H_a, C_{16}–H_b, –NCH_2), 2.01 (1H, td, C_{15}–H_a, $J_{15a,15b;16a,16b}$ 10.8, $J_{15a,15b}$ 4.3), 1.07 (1H, t, N–CH_2–CH_3, *J* 4.7); δ_C (100 MHz $CDCl_3$) 146.72 (C_3), 145.31 (C_4), 136.32 (C_{14}), 134.23–111.38 (6C, aromatic, C_6, C_7,C_8), 87.56 (C_9), 61.84 (C_9), 56.34 (C_6–OCH_3), 48.14 (C_{16}), 47.24 (N–CH_2–), 44.61 (C_{13}), 34.39 (C_{15}), 30.69 (C_{10}), 17.24 (N–CH_2–CH_3).

4.2.1.2. *N*-Propyl-6-bromo-6-demethoxynorthebaine (8). Colourless oil; yield: 131 mg (87%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.44; optical rotation and ^1H NMR results were in agreement with data in Ref. 14a. MS (EI): *m*/*z* (%) 387 (M^+, 100), 372 (43), 334 (76); HRMS (EI) *m*/*z* (%) calculated for $C_{20}H_{22}BrNO_2^+$: 387.0907 (M^+), found: 387.0914 (M^+, 100); δ_C (100 MHz $CDCl_3$) 146.52 (C_3), 145.88 (C_4), 135.78 (C_{14}), 133.71–114.32 (6C, aromatic, C_6, C_7,C_8), 87.43 (C_9), 60.91 (C_9), 56.47 (C_6–OCH_3), 47.69 (C_{16}), 47.40 (N–CH_2–), 44.16 (C_{13}), 34.71 (C_{15}), 30.60 (C_{10}), 22.76 (N–CH_2–CH_2–CH_3), 13.33 (N–CH_2–CH_2–CH_3).

4.2.2. Acid-catalyzed rearrangement of compounds 7, 8

A mixture of the diene (3.37 mmol) and methanesulfonic acid (5 mL) was stirred for 20 min at 0 °C and further 20 min at 90 °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 over $MgSO_4$, and concentrated under reduced pressure. Crude products were purified with re-crystallization.

4.2.2.1. *N*-Ethyl-2-bromonorapocodeine (9). Off-white solid; mp: 167–169 °C; yield: 996 mg (79%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.60; $[\alpha]_D^{25}$ − 116 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 373 (M^+, 87), 358 (100), 310 (70); HRMS (EI) *m*/*z* (%) calculated for $C_{19}H_{20}BrNO_2^+$: 373.0750 (M^+), found: 373.0732 (M^+, 87); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.75 (1H, s, C_1–H), 7.64 (1H, s, C_3–H), 6.63–6.57 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.3), 6.12 (1H, br s, OH), 4.21 (1H, dt, H6$_a$, J_{6a-7a} 5.1, J_{6a-7b} 1.4), 3.77 (3H, s, O–CH_3), 3.17–2.44 (6H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$), 2.39 (2H, dd, N–CH_2–CH_3, *J* 4.9), 1.01 (3H, t, N–CH_2–CH_3, *J* 4.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.10 (C_{10}), 144.41 (C_{11}), 135.21–114.57 (Ar, 10C), 59.33 (C_6), 56.44 (OCH_3), 50.41 (C_5), 47.13 (N–CH_2–CH_3), 35.70 (C_7), 27.81 (C_4), 17.13 (N–CH_2–CH_3).

4.2.2.2. *N*-Propyl-2-bromonorapocodeine (10). Off-white solid; yield: 1069 mg (83%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.67; MS (EI): *m*/*z* (%) 387 (M^+, 91), 372 (100), 341 (56); HRMS (EI) *m*/*z* (%) calculated for $C_{20}H_{22}BrNO_2^+$: 387.0907 (M^+), found: 387.0915 (M^+, 91); melting point, optical rotation and ^1H NMR results were in agreement with data in Ref. 11a. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.78 (C_{10}), 144.12 (C_{11}), 136.03–112.87 (Ar, 10C), 59.78 (C_6), 56.11 (OCH_3), 52.45 (N–CH_2–CH_2–CH_3), 49.65 (C_5), 35.37 (C_7), 27.34 (C_4), 24.56 (N–CH_2–CH_2–CH_3), 15.65 (N–CH_2–CH_2–CH_3).

4.2.3. Suzuki–Miyaura cross-coupling of compounds 9, 10

A mixture of the bromo-derivative (3.00 mmol), the aryl- or methylboronic acid (3.00 mmol), $Pd(PPh_3)_4$ (0.15 mmol) and $Ba(OH)_2{\cdot}8H_2O$ (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 oily crude product was purified by flash chromatography (silica, 80% CH_2Cl_2/20% CH_3OH) to yield aryl and alkyl derivatives.

4.2.3.1. *N*-Ethyl-2-methylnorapocodeine (14). Pale yellow solid; mp: 151–153 °C; yield: 769 mg (83%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.69; $[\alpha]_D^{25}$ − 129 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 309 (M^+, 100), 294 (60), 267 (53); HRMS (EI) *m*/*z* (%) calculated for $C_{20}H_{23}NO_2^+$: 309.1802 (M^+), found: 309.1832 (M^+, 100). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.48; H, 7.68; N, 4.29; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.12 (1H, s, C_1–H), 6.99 (1H, s, C_3–H), 6.68–6.61 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.05 (1H, br s, OH), 4.29 (1H, dt, H6$_a$, J_{6a-7a} 4.8, J_{6a-7b} 1.7), 3.82 (3H, s, O–CH_3), 3.20–2.49 (6H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$), 2.41–2.37 (4H, m, N–CH_2–CH_3, C_2–CH_3), 0.98 (3H, t, N–CH_2–CH_3, *J* 4.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.36 (C_{10}), 144.79 (C_{11}), 134.46–113.59 (Ar, 10C), 59.31 (C_6), 56.12 (OCH_3), 50.76 (C_5), 46.94 (N–CH_2–CH_3), 35.30 (C_7), 27.69 (C_4), 15.95 (N–CH_2-CH_3).

4.2.3.2. *N*-Ethyl-2-phenylnorapocodeine (15). Yellow solid; mp: 143–145 °C; yield: 879 mg (79%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.71; $[\alpha]_D^{25}$ − 137 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 371 (M^+, 100), 356 (87), 321 (59); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}NO_2^+$: 371.1958 (M^+), found: 371.1939 (M^+, 100). Anal. Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.58; H, 6.81; N, 3.59; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44–7.04 (7H, m, C_2–*Ar*, C_1–H, C_3–H), 6.65–6.58 (2H, 2d, C_8–H, C_9–H, J_{8-9} 7.8), 6.10 (1H, br s, OH), 4.20 (1H, dt, H6$_a$, J_{6a-7a} 4.6, J_{6a-7b} 1.5), 3.80 (3H, s, O–CH_3), 3.24–2.42 (8H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$, N–CH_2–CH_3), 0.98 (3H, t, N–CH_2–CH_3, *J* 4.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.68 (C_{10}), 144.53 (C_{11}), 136.27–113.21 (Ar, 16C), 58.11 (C_6), 56.48 (OCH_3), 50.17 (C_5), 47.09 (N–CH_2–CH_3), 35.32 (C_7), 28.43 (C_4), 14.45 (N–CH_2-CH_3).

4.2.3.3. *N*-Ethyl-2-(4-hydroxyphenyl)-norapocodeine (16). Off-white solid; mp: 167–169 °C; yield: 836 mg (72%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.52; $[\alpha]_D^{25}$ − 127 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 387 (M^+, 81), 372 (65), 356 (100), 320 (35); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{25}NO_3^+$: 387.1907 (M^+), found: 387.1900 (M^+, 81). Anal. Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.44; H, 6.65; N, 3.49; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.47 (1H, s, C_1–H), (7.41–7.11 (5H, m, C_2–*Ar*, C_3–H), 6.63–6.57 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.22 (2H, 2 br s, C_{11}–OH, $C_{4'}$–OH), 4.09 (1H, dt, H6$_a$, J_{6a-7a} 4.9, J_{6a-7b} 1.8), 3.86 (3H, s, O–CH_3), 3.17–2.38 (8H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$, N–CH_2–CH_3), 1.00 (3H, t, N–CH_2–CH_3, *J* 4.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.01 ($C_{4'}$–OH), 146.79 (C_{10}), 144.47 (C_{11}), 136.71–114.48 (Ar, 15C), 57.92 (C_6), 56.24 (OCH_3), 50.04 (C_5), 47.66 (N–CH_2–CH_3), 35.32 (C_7), 28.11 (C_4), 15.12 (N–CH_2–CH_3).

4.2.3.4. *N*-Propyl-2-methylnorapocodeine (17). Pale yellow solid; mp: 147–149 °C; yield: 755 mg (77%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.69; $[\alpha]_D^{25}$ − 117 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 323 (M^+, 100), 308 (76), 277 (86); HRMS (EI) *m*/*z* (%) calculated for $C_{21}H_{25}NO_2^+$: 323.1958 (M^+), found: 323.1969 (M^+, 100). Anal. Calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.69; H, 7.87; N, 4.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.17 (1H, s, C_1–H), 6.91 (1H, s, C_3–H), 6.71–6.68 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.1), 6.12 (1H, br s, OH), 4.07 (1H, dt, $H6_a$, J_{6a-7a} 4.5, J_{6a-7b} 1.3), 3.84 (3H, s, O–CH_3), 3.26–2.46 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.42–2.34 (4H, m, N–C*H*$_2$–CH_2–CH_3, C_2–CH_3), 1.38 (2H, dt, N–CH_2–C*H*$_2$–CH_3, *J* 4.7, *J* 1.4), 0.88 (3H, t, N–CH_2–CH_2–C*H*$_3$, *J* 4.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.44 (C_{10}), 144.67 (C_{11}), 135.83–115.45 (Ar, 10C), 58.70 (C_6), 56.45 (OCH_3), 51.84 (N–*C*H$_2$–CH_2–CH_3), 49.32 (C_5), 35.75 (C_7), 28.34 (C_4), 22.32 (N–CH_2–*C*H$_2$–CH_3), 13.87 (N–CH_2–CH_2-*C*H$_3$).

4.2.3.5. *N*-Propyl-2-phenylnorapocodeine (18). Yellow solid; mp: 139–141 °C; yield: 970 mg (84%); R_f (80% CH_2Cl_2/20% CH_3OH) 0.77; $[\alpha]_D^{25}$ − 136 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 385 (M^+, 100), 370 (89), 349 (56); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}NO_2^+$: 385.2115 (M^+), found: 385.2126 (M^+, 100). Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.82; H, 7.24; N, 3.48; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.14 (7H, m, C_2-*Ar*, C_1–H, C_3–H), 6.63–6.57 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.02 (1H, br s, OH), 4.09 (1H, dt, $H6_a$, J_{6a-7a} 4.4, J_{6a-7b} 1.4), 3.81 (3H, s, O–CH_3), 3.26–2.46 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.30 (2H, t, N–C*H*$_2$–CH_2–CH_3, *J* 4.4), 1.41 (2H, dt, N–CH_2–C*H*$_2$–CH_3, *J* 4.7, *J* 1.4), 0.91 (3H, t, N–CH_2–CH_2–C*H*$_3$, *J* 4.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.79 (C_{10}), 144.17 (C_{11}), 136.43–114.95 (Ar, 16C), 59.02 (C_6), 56.47 (OCH_3), 50.67 (N–*C*H$_2$–CH_2–CH_3), 49.26 (C_5), 35.76 (C_7), 28.93 (C_4), 21.76 (N–CH_2–*C*H$_2$–CH_3), 12.93 (N–CH_2–CH_2-*C*H$_3$).

4.2.3.6. *N*-Propyl-2-(4-hydroxyphenyl)-norapocodeine (19). White solid; mp: 169–171 °C; yield: 818 mg (68 %); R_f (80% CH_2Cl_2/20% CH_3OH) 0.47; $[\alpha]_D^{25}$ − 146 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 401 (M^+, 80), 386 (100), 349 (67); HRMS (EI) *m*/*z* (%) calculated for $C_{26}H_{27}NO_3^+$: 401.2064 (M^+), found: 401.2047 (M^+, 80). Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.49; H, 6.84; N, 3.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 (1H, s, C_1–H), (7.37–7.11 (3H, m, C_2-*Ar*, C_3–H), 6.88–6.80 (2H, m, C_2-*Ar*), 6.64–6.59 (2H, 2d, C_8–H, C_9–H, J_{8-9} 7.8), 6.18 (2H, 2 br s, C_{11}–OH, $C_{4'}$–OH), 4.07 (1H, dt, $H6_a$, J_{6a-7a} 4.5, J_{6a-7b} 1.7), 3.87 (3H, s, O–CH_3), 3.29–2.41 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.36 (2H, t, N–C*H*$_2$–CH_2–CH_3, *J* 4.7), 1.46 (2H. dt, N–CH_2–C*H*$_2$–CH_3, *J* 4.6, *J* 1.9), 0.98 (3H, t, N–CH_2–CH_2–C*H*$_3$, *J* 4.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.56 ($C_{4'}$–OH), 146.36 (C_{10}), 144.22 (C_{11}), 137.84–113.12 (Ar, 16C), 58.73 (C_6), 56.32 (OCH_3), 53.01 (N–*C*H$_2$–CH_2–CH_3), 49.56 (C_5), 35.70 (C_7), 28.99 (C_4), 22.34 (N–CH_2–*C*H$_2$–CH_3), 12.18 (N–CH_2–CH_2–CH_3).

4.2.4. O-Demethylation of norapocodeines 14–19

A mixture of the apocodeine (4.65 mmol), methionine (1000 mg, 6.70 mmol) and CH_3SO_2OH (4 mL) was boiled at 90 °C for 2 h. 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 brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was subjected to silica gel column chromatography. Elution with chloroform:methanol = 1:1 gave apomorphines which was immediately transformed into stable HCl salt by ethanol saturated with HCl gas.

4.2.4.1. *N*-Ethyl-2-methylnorapomorphine hydrochloride (20·HCl). Greenish gray, cubic crystals; mp: 256–258 °C; yield: 1249 mg (81%); R_f free base (80% CH_2Cl_2/20% CH_3OH) 0.29; $[\alpha]_D^{25}$ − 187 (*c* 0.1, DMSO); MS (EI): *m*/*z* (%) 296 (M^+−Cl, 100), 234 (61), 201 (59); HRMS (EI) *m*/*z* (%) calculated for $C_{19}H_{22}NO_2^+$: 296.1645 (M^+−Cl), found: 296.1662 (M^+−Cl, 100). Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.59; H, 6.69; N, 4.11; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.07 (1H, s, C_1–H), 6.94 (1H, s, C_3–H), 6.65–6.59 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.1), 6.01 (2H, 2 br s, OH), 4.11 (1H, dt, $H6_a$, J_{6a-7a} 4.5, J_{6a-7b} 1.4), 3.15–2.43 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.37–2.32 (4H, m, N–C*H*$_2$–CH_3, C_2–CH_3), 0.96 (3H, t, N–CH_2–C*H*$_3$, *J* 4.4); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 145.11 (C_{10}), 144.89 (C_{11}), 136.43–115.18 (Ar, 10C), 59.12 (C_6), 50.23 (C_5), 46.39 (N–*C*H$_2$–CH_3), 35.66 (C_7), 27.61 (C_4), 14.58 (N–CH_2-*C*H$_3$).

4.2.4.2. *N*-Ethyl-2-phenylnorapomorphine hydrochloride (21·HCl). Grey, needle shape crystals; mp: >260 °C; yield: 1446 mg (79%); R_f free base (80% CH_2Cl_2/20% CH_3OH) 0.33; $[\alpha]_D^{25}$ − 193 (*c* 0.1, DMSO); MS (EI): *m*/*z* (%) 358 (M^+−Cl, 100), 320 (81), 298 (34); HRMS (EI) *m*/*z* (%) calculated for $C_{24}H_{24}NO_2^+$: 368.1802 (M^+−Cl), found: 368.1789 (M^+−Cl, 100). Anal. Calcd for $C_{24}H_{24}ClNO_2$: C, 73.18; H, 6.14; N, 3.56. Found: C, 73.04; H, 6.27; N, 3.42; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.37–7.01 (7H, m, C_2-*Ar*, C_1–H, C_3–H), 6.61–6.56 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.1), 6.10 (2H, 2 br s, OH), 4.08 (1H, dt, $H6_a$, J_{6a-7a} 4.7, J_{6a-7b} 1.8), 3.29–2.41 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.36 (2H, dd, N–C*H*$_2$–CH_3, *J* 4.8), 1.03 (3H, t, N–CH_2–C*H*$_3$, *J* 4.8); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 145.41 (C_{10}), 144.59 (C_{11}), 137.18–114.76 (Ar, 16C), 58.65 (C_6), 50.40 (C_5), 47.10 (N–*C*H$_2$–CH_3), 35.39 (C_7), 28.18 (C_4), 14.89 (N–CH_2–*C*H$_3$).

4.2.4.3. *N*-Ethyl-2-(4-hydroxyphenyl)-norapomorphine hydrochloride (22·HCl). Green, cubic crystals; mp: 203–205 °C; yield: 1410 mg (74%); R_f free base (80% CH_2Cl_2/20% CH_3OH) 0.23; $[\alpha]_D^{25}$ − 169 (*c* 0.1, DMSO); MS (EI): *m*/*z* (%) 374 (M^+−Cl, 100), 331 (62), 307 (34), 276 (23); HRMS (EI) *m*/*z* (%) calculated for $C_{24}H_{24}NO_3^+$: 374.1751 (M^+−Cl), found: 374.1766 (M^+−Cl, 100). Anal. Calcd for $C_{24}H_{24}ClNO_3$: C, 70.32; H, 5.90; N, 3.42. Found: C, 70.02; H, 5.98; N, 3.19; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.44 (1H, s, C_1–H), 7.38–7.09 (5H, m, C_2-*Ar*, C_3–H), 6.68–6.61 (2H, 2d, C_8–H, C_9–H, J_{8-9} 7.9), 6.14 (3H, 3 br s, C_{10}–OH, C_{11}–OH, $C_{4'}$–OH), 4.04 (1H, dt, $H6_a$, J_{6a-7a} 4.4, J_{6a-7b} 1.6), 3.23–2.41 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.34 (2H, dd, N–C*H*$_2$–CH_3, *J* 4.8), 0.98 (3H, t, N–CH_2–C*H*$_3$, *J* 4.8); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 157.71 ($C_{4'}$–OH), 145.72 (C_{10}), 144.55 (C_{11}), 136.12–114.62 (Ar, 15C), 57.30 (C_6), 49.69 (C_5), 47.34 (N–*C*H$_2$–CH_3), 35.39 (C_7), 28.39 (C_4), 14.83 (N–CH_2-*C*H$_3$).

4.2.4.4. *N*-Propyl-2-methylnorapomorphine hydrochloride (23·HCl). Reddish brown, plate shape crystals; mp: >260 °C; yield: 1306 mg (81%); R_f free base (80% CH_2Cl_2/20% CH_3OH) 0.37; $[\alpha]_D^{25}$ − 167 (*c* 0.1, DMSO); MS (EI): *m*/*z* (%) 310 (M^+−Cl, 100), 288 (71), 277 (90); HRMS (EI) *m*/*z* (%) calculated for $C_{20}H_{24}NO_2^+$: 310.1802 (M^+−Cl), found: 310.1810 (M^+−Cl, 100). Anal. Calcd for $C_{20}H_{24}ClNO_2$: C, 69.49; H, 6.99; N, 4.05. Found: C, 69.18; H, 7.09; N, 3.90; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.14 (1H, s, C_1–H), 6.96 (1H, s, C_3–H), 6.59–6.54 (2H, 2d, C_8–H, C_9–H, J_{8-9} 7.9), 6.10 (2H, 2 br s, C_{10}–OH, C_{11}–OH), 4.05 (1H, dt, $H6_a$, J_{6a-7a} 4.6, J_{6a-7b} 1.4), 3.36–2.43 (6H, m, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$), 2.38–2.30 (4H, m, N–C*H*$_2$–CH_2–CH_3, C_2–CH_3), 1.32 (2H. dt, N–CH_2–C*H*$_2$–CH_3, *J* 4.4, *J* 1.5), 0.91 (3H, t, N–CH_2–CH_2–C*H*$_3$, *J* 4.5); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 146.05 (C_{10}), 144.67 (C_{11}), 136.12–114.39 (Ar, 10C), 58.37 (C_6), 50.93 (N–*C*H$_2$–CH_2–CH_3), 49.39 (C_5), 35.37 (C_7), 28.72 (C_4), 23.17 (N–CH_2–*C*H$_2$–CH_3), 14.09 (N–CH_2–CH_2–*C*H$_3$).

4.2.4.5. *N*-Propyl-2-phenylnorapomorphine hydrochloride (24·HCl). Green, plate shape crystals; mp: >260 °C; yield: 1611 mg (85%); R_f free base (80% CH_2Cl_2/20% CH_3OH) 0.39; $[\alpha]_D^{25}$ − 149 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 372 (M^+−Cl, 100), 351 (45), 324

(59); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{26}NO_2^+$: 372.1958 (M^+–Cl), found: 372.1969 (M^+–Cl, 100). Anal. Calcd for $C_{25}H_{26}ClNO_2$: C, 73.71; H, 6.42; N, 3.43. Found: C, 73.49; H, 6.59; N, 3.18; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.34–7.05 (7H, m, C_2–*Ar*, C_1–H, C_3–H), 6.57–6.52 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.2), 5.98 (2H, 2 br s, C_{10}–OH, C_{11}–OH), 4.12 (1H, dt, H6$_a$, J_{6a-7a} 4.5, J_{6a-7b} 1.6), 3.33–2.42 (6H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$), 2.34 (2H, t, N–*CH*$_2$–CH$_2$–CH$_3$, *J* 4.5), 1.45 (2H. dt, N–CH$_2$–*CH*$_2$–CH$_3$, *J* 4.6, *J* 1.7), 0.95 (3H, t, N–CH$_2$–CH$_2$–*CH*$_3$, *J* 4.6); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 145.02 (C_{10}), 144.46 (C_{11}), 135.67–114.32 (Ar, 16C), 59.60 (C_6), 51.18 (N–*CH*$_2$–CH$_2$–CH$_3$), 49.46 (C_5), 35.67 (C_7), 28.23 (C_4), 22.05 (N–CH$_2$–*CH*$_2$–CH$_3$), 13.37 (N–CH$_2$–CH$_2$-*CH*$_3$).

4.2.4.6. *N*-Propyl-2-(4-hydroxyphenyl)-norapomorphine hydrochloride (25·HCl). Grey, cubic crystals; mp: 195–198 °C; yield: 1438 mg (73%); R_f free base (80% CH_2Cl_2/20% CH_3OH) 0.21; $[\alpha]_D^{25}$ − 173 (*c* 0.1, methanol); MS (EI): *m*/*z* (%) 388 (M^+–Cl, 67), 351 (100), 320 (39); HRMS (EI) *m*/*z* (%) calculated for $C_{25}H_{26}NO_3^+$: 388.1907 (M^+–Cl), found: 388.1920 (M^+–Cl, 67). Anal. Calcd for $C_{25}H_{26}ClNO_3$: C, 70.83; H, 6.18; N, 3.30. Found: C, 80.48; H, 6.41; N, 3.19; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.48 (1H, s, C_1–H), 7.33–7.10 (3H, m, C_2–*Ar*, C_3–H), 6.91–6.82 (2H, m, C_2–*Ar*), 6.59–6.52 (2H, 2d, C_8–H, C_9–H, J_{8-9} 8.0), 6.05 (3H, 3 br s, C_{10}–OH, C_{11}–OH, $C_{4'}$–OH), 4.12 (1H, dt, H6$_a$, J_{6a-7a} 4.1, J_{6a-7b} 1.8), 3.37–2.40 (6H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$), 2.29 (2H, t, N–*CH*$_2$–CH$_2$–CH$_3$, *J* 4.4), 1.51 (2H, dt, N–CH$_2$–*CH*$_2$–CH$_3$, *J* 4.5, *J* 1.7), 1.02 (3H, t, N–CH$_2$–CH$_2$–*CH*$_3$, *J* 4.6); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 157.23 ($C_{4'}$–OH), 145.12 (C_{10}), 144.69 (C_{11}), 136.60–114.79 (Ar, 16C), 58.41 (C_6), 53.55 (N–*CH*$_2$–CH$_2$–CH$_3$), 49.29 (C_5), 35.72 (C_7), 29.19 (C_4), 22.30 (N–CH$_2$–*CH*$_2$–CH$_3$), 12.79 (N–CH$_2$–CH$_2$–*CH*$_3$).

4.3. Route II

4.3.1. N-Demethylation of 2-bromoapocodeine (11)

Compound **11** (1.0 g, 2.92 mmol) and Na_2WO_4 (300 mg, 1.02 mmol) was dissolved in water:1,4-dioxane 1:2 (10 mL) and cooled to 0 °C for the dropwise addition of H_2O_2 (30% w/v, 12 mmol). The reaction mixture was stirred at room temperature for 3.5 h. The excess H_2O_2 was quenched by addition of small portions of MnO_2 at 0 °C and the presence of the peroxide determined by KI-starch paper. The reaction mixture, containing some over-oxidized product as dark precipitation, was then vacuum filtered through a short pad of Celite. Solvent was removed in vacuo to give crude product as a pale brown solid. It was immediately turned into hydrochloride salt by dissolving in a few drops of chloroform and dropping some ethanol saturated with HCl gas. After filtration, the mixture of minor apocodeine.HCl and major apocodeine N-oxide·HCl was dissolved in MeOH (10 mL) followed by the addition of $FeSO_4{\cdot}7H_2O$ (2 equiv) at 0 °C. The reaction mixture was then left to stir at room temperature for 1 h. Conversion was followed by TLC (80% CH_2Cl_2/20% CH_3OH). The reaction solvent was removed in vacuo and the residue redissolved in a 0.1 M EDTA solution adjusted to pH 10 by addition of ammonia (70 mL). The aqueous phase was then extracted with $CHCl_3$ (3 × 30 mL). The combined organic phase was dried over $MgSO_4$, filtered and the solvent removed in vacuo to give dark brown mixture of the apocodeine **11** and the norapocodeine **12**. 2-Bromonorapocodeine (**12**) was isolated by means of silica column chromatography as an off-white solid (554 mg, 55 %).

Mp: 146–148 °C; $[\alpha]_D^{25}$ − 98 (*c* 0.1, chloroform); R_f (80% CH_2Cl_2/20% CH_3OH) 0.43; MS (EI): *m*/*z* (%) 345 (M^+, 100), 330 (35), 309 (89); HRMS (EI) *m*/*z* (%) calculated for $C_{17}H_{16}BrNO_2^+$: 345.0437 (M^+), found: 345.0447 (M^+, 100); δ_H (400 MHz $CDCl_3$) 7.40 (1H, s, C_1–H), 7.18 (1H, s, C_3–H), 6.54–6.48 (2H, 2d, C_8–H, C_9–H, J_{8-9} 7.9), 6.05 (1H, br s, C_{11}–OH), 4.06 (1H, dt, H6$_a$, J_{6a-7a} 4.7, J_{6a-7b} 1.8), 3.81 (3H, s, O–CH_3), 3.25–2.24 (7H, m, H4$_a$, H4$_b$, H5$_a$, H5$_b$, H7$_a$, H7$_b$, NH); δ_C (100 MHz $CDCl_3$) 146.78 (C_{10}), 144.89 (C_{11}), 135.93–114.22 (Ar, 10C), 56.47 (OCH_3), 53.61 (C_6), 43.27 (C_5), 36.10 (C_7), 29.01 (C_4).

4.3.2. N-Alkylation of 2-bromonorapocodeine (12)

4.3.2.1. *N*-Ethyl-2-bromonorapocodeine (9). The *N*-ethylation of compound **12** (710 mg, 2 mmol) was carried out according to the method described in Section 4.2.1 to obtain 612 mg of **9** (82%).

4.3.2.2. *N*-Propyl-2-bromonorapocodeine (10). The N-propylation of compound **12** (710 mg, 2 mmol) was carried out according to the method described in Section 4.2.1 to obtain 581 mg of **10** (75%).

4.4. Pharmacology

Chinese hamster ovary cells (CHO-K1 cells; CCL61, American Type Culture Collection, Rockville, MD, USA) stably expressing rat dopamine $D_{2(short)}$ receptor and Ltk$^-$-fibroblast cells expressing D_1 dopamine receptors were obtained from Professor K. Fuxe's laboratory at the division of Cellular and Molecular Neurochemistry, Department of Neuroscience, Karolinska Institute (Sweden), and grown as described earlier.[20] For experiments with D_2 receptors the CHO 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 30,000*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 (2.5 Petri dishes with 95% confluency per mL) and stored at −80 °C until use. For experiments with D_1 receptors the Ltk$^-$-fibroblast cells were collected, washed and homogenized by sonication in Tris–HCl buffer (TB, 50 mM Tris–HCl, pH 7.4) and centrifuged at 30,000*g* for 40 min at 4 °C. The membrane pellets were washed twice by re-homogenization in TB and centrifugation. The final pellets were re-suspended in TB (2 Petri dishes with 95% confluency per 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) and appropriate concentrations of compounds with membrane suspension of CHO cells for 90 min at 25 °C.[21] The reaction was stopped by filtration through GF/B filters using Brandel cell harvester and the filters were washed with 3 mL of ice-cold washing buffer (20 mM K-phosphate buffer, 100 mM NaCl, pH 7.4). Filters were incubated in scintillation cocktail OptiPhase HiSafe (Wallac PerkinElmer Life Sciences, Cambridge, UK) overnight and the radioactivity content of filters was measured by RackBeta 1219 liquid scintillation counter.

D_2 receptor activation properties of compounds were measured by incubating 0.2 nM [^{35}S]GTPγS with 10 μM GDP, appropriate concentrations of compound and membrane suspension of CHO cells for 90 min at 25 °C.[19] The reactions were stopped and bound radioactivity was determined as described above.

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-1*H*-3-benzazepine hydrochloride ([^{3}H]SCH23390, 71 Ci/mmol, GE Life Sciences) with appropriate concentrations of compounds in membrane suspension of Ltk$^-$-fibroblast cells in IB without sodium- and potassium chloride for 60 min at 25 °C.[22] The reactions were stopped and bound radioactivity was determined as described above.

All pharmacological 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 from at least two independent experiments carried out in duplicates.

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