Synthesis and Structural Requirements of N-Substituted Norapomorphines for Affinity and Activity at Dopamine D-1, D-2, and Agonist Receptor Sites in Rat Brain

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A series of N-substituted analogues of (*R*)-(−)-norapomorphine were synthesized to study the optimal structural requirements of the *N*-alkyl side chain to interact with D-1 and D-2 dopaminergic receptors as well as dopamine (DA) agonist binding sites. Evaluations included testing the affinity of these compounds for DA receptor sites in rat striatal tissue and assessing stereotypy as a behavioral index of dopaminergic activity. The electronic, steric, and lipophilic properties of the *N*-alkyl side chain were found to be related to affinity, D-2 selectivity, and dopaminergic activity. All 11 compounds evaluated had relatively low affinity at D-1 sites. Optimum D-2 and agonist-site affinity as well as agonist activity were exhibited by *N*-cyclopropylmethyl (**7**) ≥ *N*-allyl (**8**) ≥ *N*-propyl (**4**) or *N*-ethyl (**3**) substituted compounds. Branching of the *N*-alkyl side chain as in *N*-isopropyl (**5**) and *N*-isobutyl (**6**) markedly reduced the D-2 affinity and activity, presumably due to steric effects. The *N*-trifluoroethyl (**10**) and *N*-pentafluoropropyl (**11**) derivatives had low affinity for all their dopamine receptor sites and no agonistic activity; evidently, the highly electronegative F atoms decrease basicity of the N atom and therefore decrease the ability of the N atom to be cationic at physiological pH, a proposed requirement for high-affinity binding to DA receptors.

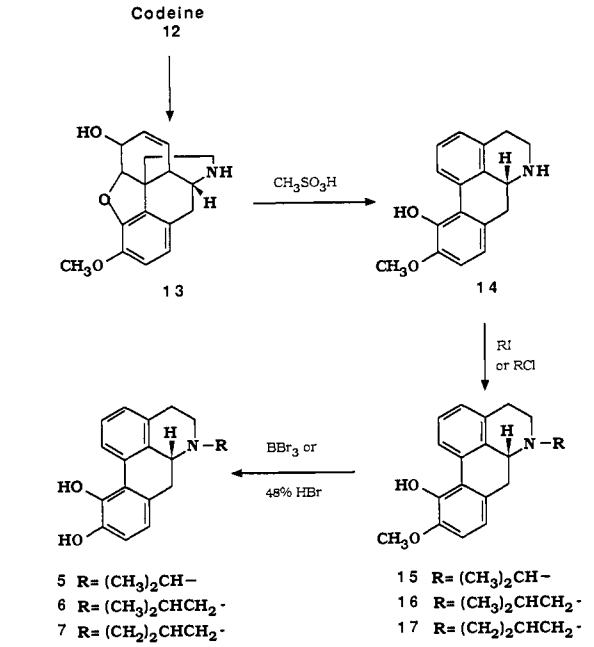
There is increasing evidence of functional interactions between D-1 and D-2 dopamine (DA) receptors in the mammalian central nervous system.[1] For example, in normal animals stimulation of both D-1 and D-2 receptors appears to be necessary for full expression of characteristic behavioral effects of (*R*)-(−)-apomorphine and its congeners, whereas selective D-1 or D-2 agonists given alone do not show these activities.[2] Furthermore, increased locomotor activity and stereotypy induced by apomorphine can be blocked by antagonists selective for either D-1 or D-2 receptors.[3] Recently, the combination of selective D-1 and D-2 antagonists has been used to prevent and treat drug-induced extrapyramidal disorders.[4]

Aporphines demonstrate activity at both D-1 and D-2 receptors. However, the lack of selectivity of these compounds has limited interest in them as pharmacological tools. Recent development of agents capable of interacting selectively at D-1 and D-2 receptors, particularly in the aporphine series, has renewed interest in the structure–activity relationships (SAR) in this group of compounds.[5]

Our studies have focused on delineating portions of the aporphine molecular structure that may contribute to D-1 and D-2 dopaminergic selectivity and potency by evaluating the interactions of such "rigid" analogues of DA and DA receptors.[6] We found previously that substitution of the *N*-alkyl side chain of apomorphine has a profound effect on the dopamine receptor affinity and pharmacological activity of aporphines.[7]

We investigated a series of N-substituted aporphine analogues in order to establish the influence of the N-substituent, with the hope of establishing its relationship to D-1 and D-2 receptors, and as a basis for evaluating the contributions of electronic, steric, and lipophilic effects of such substituents. The synthesis of several N-substituted, aromatic-ring-hydroxylated aporphine derivatives has been documented.[8-15] Most N-substituted derivatives of (*R*)-(−)-apomorphine have been tested pimarily for their central emetic activity. None except the prototype apomorphine (APO) and its N-*n*-propyl analogue *N*-*n*-propylnorapomorphine (NPA) has been well-characterized pharmacologically. In particular, the affinity for D-1, D-2, and DA agonist receptor sites and DA agonistic activity

Scheme I



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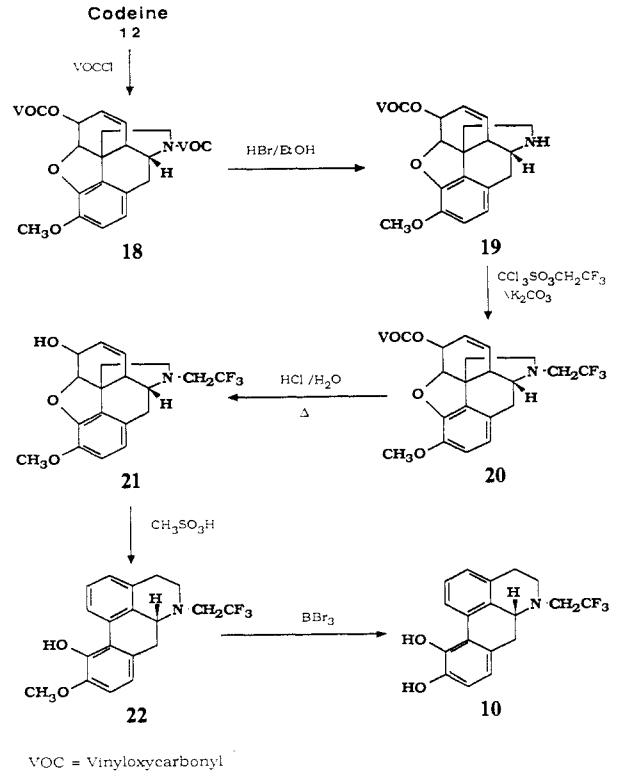
have not been evaluated simultaneously for a series of N-substituted apomorphines. In the present study, we describe the synthesis of novel N-substituted apomorphine derivatives and their comparison with selected known N-substituted analogues with respect to D-1, D-2, and DA-agonist site affinity, D-1/D-2 selectivity, and behavioral dopaminergic activity.

Chemistry

Codeine was N-demethylated to give the intermediate norcodeine (**13**) according to the procedure of Rice.[16] N-Alkylation of norcodeine by appropriate alkyl halides affords good yields of *N*-alkylnorcodeines. However, a cyclopropyl ring can be opened, and there is a possibility of polymerization of isopropyl or isobutyl side chains, under strongly acidic conditions during rearrangement.[9] Accordingly, we utilized an alternative procedure for N-alkylation of norapocodeine so as to avoid *N*-alkyl side chain involvement during the rearrangement step (Scheme I). The rearrangement of norcodeine to norapocodeine (**14**) was carried out by a procedure described by Granchelli et al.[17] The precursors of *N*-isopropyl, *N*-isobutyl, and *N*-(cyclopropylmethyl)norapomorphines were obtained by alkylating norapocodeine (**14**) directly with the appropriate alkyl halides and $NaHCO_3$. All methyl ethers were cleaved with either 48% HBr or BBr_3. Compounds **8** and **9** (*N*-allyl- and *N*-(2-hydroxyethyl)norapomorphine) were synthesized by established procedures reported elsewhere.[14,15]

N-(2,2,2-Trifluoroethyl)norapomorphine and its pentafluoropropyl analogue could not be synthesized by the above procedure as we encountered a lack of reactivity of trifluoroethyl iodide with norcodeine under normal reaction conditions. Therefore, we chose trichlorosulfonyl as a better leaving group, which would allow alkylation with trifluoroethyl on the secondary amine moiety. In analogous studies,[18,19] the synthesis of trifluoroethyl amine derivatives was successful when polyhalosulfonyl was used as the leaving group. However, treatment of norcodeine with trifluoroethyl trichloromethanesulfonate afforded three major products with a poor yield of the expected product because O-alkylation was a competing side reaction. Olofson and Schnur reported[20] the synthesis of nalorphine via the N-demethylation of morphine with vinyl chloroformate, to form the *N*- and *O*-[(vinyloxy)carbonyl] (VOC) intermediate, which was then selectively deprotected by acid hydrolysis without simultaneous loss of the *O*-[(vinyloxy)carbonyl] group. Thus a potentially superior synthesis of *N*-(2,2,2-trifluoroethyl)norapomorphine was developed in which the hydroxyl group remains protected during N-trifluoroethylation (Scheme II). Codeine was converted to *O*-[(vinyloxy)carbonyl]norcodeine (**19**) by N-demethylation using vinyl chloroformate, followed by selective hydrolysis. Trifluoroethylation of **19** with $CCl_3SO_3CH_2CF_3$ and K_2CO_3 in acetone at 70 °C afforded trifluoroethyl amine **20**, which was not purified. Instead, hydrolysis with 1.7 N HCl effected complete removal of the protecting group to give *N*-(2,2,2-trifluoroethyl)norcodeine (**21**). Rearrangement to *N*-(2,2,2-trifluoroethyl)-norapocodeine (**22**) with methanesulfonic acid was carried out as described previously.[17] Subsequent O-demethylation with boron tribromide in methylene chloride at −70 °C yielded N-(2,2,2-trifluoroethyl)norapomorphine hydrobromide (**10**). *N*-(2,2,3,3,3-pentafluoropropyl)norapomorphine (**11**) also was prepared by a similar procedure directly from norcodeine (**13**) (Scheme III). In this case, the hydroxy group of norcodeine was unprotected. The direct fluoroalkylation of compound **13** with $CCl_3SO_3CH_2CF_2CF_3$ and potassium carbonate in acetonitrile gave a 43% yield of compound **23**. Rearrangement of **23** with methanesulfonic acid gave **24** which was then converted to compound **11** following the procedure for conversion of compound **22** to compound **10**.

Scheme II



VOC = Vinyloxycarbonyl

Scheme III

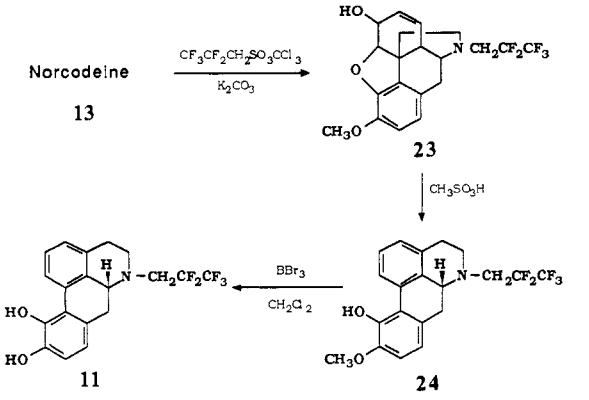


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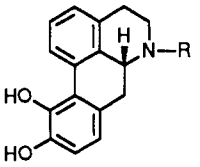
Table I. Effect of *N*-Alkyl Substitution of (*R*)-Apomorphines



agent	N-R	K_i[a] nM D-1	K_i[a] nM D-2	K_i[a] nM agonist	D-2:D-1 selectivity	stereotypy score[b]
1, norapomorphine hydrochloride	H	390	1190	9.8	0.33	26
2, apomorphine-hydrochloride	CH_3	240	11.1	3.7	21.6	100
3, *N*-ethylnorapomorphine hydrochloride	CH_2CH_3	124	0.22	0.23	564	97
4, *N*-*n*-propylnorapomorphine hydrochloride	$CH_2CH_2CH_3$	340	0.8	1.5	425	99
5, *N*-isopropylnorapomorphine hydrobromide[c]	$CH(CH_3)_2$	>10000	895	199	>11.2	0[c]
6, *N*-isobutylnorapomorphine hydrobromide[c]	$CH_2CH(CH_3)_2$	>10000	490	365	>20.4	3[c]
7, *N*-(cyclopropylmethyl)norapomorphine hydrochloride[c]	$CH_2CH(CH_2)_2$	730	0.43	13.5	1698	106
8, *N*-allylnorapomorphine hydrobromide	$CH_2CH{=}CH_2$	615	0.24	4.2	2563	86
9, *N*-(2-hydroxyethyl)norapomorphine hydrochloride	CH_2CH_2OH	>10000	1460	12.9	>6.9	0
10, *N*-(trifluoroethyl)norapomorphine hydrochloride	CH_2CF_3	>50000	>100000	>100000		2
11, *N*-(pentafluoropropyl)norapomorphine hydrochloride	$CH_2CF_2CF_3$	>50000	>100000	>100000		

[a] Dopamine receptor affinity in vitro (rat striatal membranes) was tested with tritiated SCH-23390 (0.3 nM; K_d = 0.3 nM) for D-1, spiperone (0.15 nM; K_d = 0.03 nM) for D-2, and ADTN (0.5 nM; K_d = 1.5 nM) for agonist sites. [b] Stereotyped behavior was tested in rats (N = 6) given 3 mg/kg ip of each of the test compounds, and each compound's scores were compared as the percent of that obtained with apomorphine as a standard (set at 100%). Data are means of computer-fit inhibition curves (SEM averaged ±11% of the mean K_i), and of behavior scores (SEM averaged ±17% of the mean stereotypy score). [c] Compounds 5 and 6 (at 3 mg/kg ip) also failed to block apomorphine-induced stereotypy or to induce catalepsy in the rat, in doses up to 10 mg/kg ip.

Pharmacology

The binding affinity of N-substituted norapomorphine derivatives at DA receptor sites was evaluated with a membrane preparation of corpus striatum from rat brain and three tritium-radiolabeled ligands (these included a dopaminergic agonist, [^{3}H]ADTN[(±)-6,7-dihydroxy-2-aminotetralin], a D-1 antagonist, [^{3}H]SCH-23390, and a D-2 antagonist, [^{3}H]spiperone) by using methods reported in detail elsewhere.[21-24] The mixed D-1, D-2 dopaminergic agonist ligand was incubated at 0.5 nM (60 min at 25 °C), the D-1 antagonist was done at 0.3 nM (30 min at 30 °C), and the D-2 antagonist was done at 0.15 nM (15 min at 37 °C). Specific binding was determined by utilizing the following quenching agents: (*R*)-(−)-apomorphine, 10 μM; *cis*-(*Z*)-flupenthixol (a gift of Dr. John Hyttel), 300 nM; and (+)-butaclamol, 1 μM for the agonist, D-1, and D-2 assays, respectively. Half-maximally inhibitory concentrations (IC_{50} ± SEM) of each test agent were determined using a microcomputer-assisted nonlinear least squares analysis, typically with five or six concentrations of each test agent in each radioreceptor assay.[25,26]

Behavioral experiments in young adult, male, Sprague–Dawley, albino rats involved assessment of the ability of the N-substituted apomorphines (injected intraperitoneally, ip) to induce stereotyped sniffing, licking, and gnawing behaviors typical of dopaminergic agonists such as (*R*)-(−)-apomorphine (2) or (*R*)-(−)-*N*-*n*-propylnorapomorphine (4) for 1 h, as described in detail elsewhere.[27]

Results and Discussion

The present study evaluated the effects of N-substitution on the affinity, selectivity, and agonistic activity of a series of apomorphines at DA receptors in rat brain. The dopaminergic activity of N-substituted (*R*)-(−)-norapomorphines has been attributed to their structural similarity with DA.[28,29] Preliminary assessments of a limited number of N-substituted apomorphine analogues suggested that significant changes in DA receptor affinity and activity would be produced by small changes in the *N*-alkyl structure.[8-15] For example, substitution of a *N*-*n*-propyl group for the *N*-methyl in apomorphine yields a more potent compound.[13] These preliminary observations stimulated the pursuit of a more extensive SAR study of such aporphines and suggested an hypothesized optimal size of the *N*-alkyl substituent on the aporphine skeleton.[6] The results of relevant pharmacological studies that test this hypothesis are tabulated below in Table I.

All 11 compounds evaluated had relatively low affinity at D-1 sites, so the discussion of our results (Table I) pertains to their D-2 and agonist site affinity, selectivity, and in vivo activity. Norapomorphine (1), lacking an *N*-alkyl substituent altogether, had a moderately high affinity for the site defined by [^{3}H]ADTN, which may interact with high-affinity sites of both the D-1 and D-2 types,[21,30] a lower affinity for the D-1 receptor, a very low D-2 affinity, and also a low DA agonistic activity in vivo. This pattern may be explained by its relatively high polarity and consequently repulsive interaction with a putative lipophilic cleft which adjoins a putative hydrogen/ionic/reinforced bonding group on the receptor.[31] Apomorphine (2) with an *N*-methyl group showed higher affinity and 22-fold selectivity for the D-2 over D-1 receptor sites and relatively high agonist-site affinity as well as relatively high agonistic activity, as expected. Lengthening

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the alkyl group to ethyl (3) enhanced D-2 over D-1 selectivity, increased D-2 and agonist-site affinities, and retained high agonistic activity. Further lengthening to propyl (4; NPA) resulted in similar affinity and selectivity for D-2 receptor as well as high agonist affinity and strong agonistic activity. Increasing lipophilicity may contribute to these results, but other structural aspects of the increase from zero to two or three carbon chain length of the *N*-alkyl substituent may be involved. Presumably, on the D-2 receptor a lipophilic cavity can best accommodate an *N*-*n*-propyl group of the aporphines.[6,7,30] When the alkyl side chain is branched as in *N*-isopropyl- (5) or *N*-isobutylnoraporphine (6), there was a marked decrease in D-1, D-2, and ADTN affinities and agonistic activity. However, cyclopropylmethyl substitution, curiously, resulted in high D-2 affinity, selectivity, and high agonistic activity; this compound (7) was found to have even higher affinity and D-2 selectivity than NPA (4). This result can be explained by envisioning a lipophilic cleft as just long enough to accommodate a 3-membered side chain and just wide enough to permit an interaction with a conformationally restricted branched side chain as in *N*-cyclopropylmethyl substitution, but not wide enough to permit interaction with a conformationally flexible branched side chain as in *N*-isopropyl (5) or *N*-isobutyl (6) substitutions. The behaviorally virtually inactive branched-chain substituted compounds 5 and 6 also lacked activity as antagonists of apomorphine and did not induce catalepsy as may occur with DA antagonists (Table I).

The *N*-allyl-substituted compound 8 also had high D-2 affinity, selectivity, and behavioral activity. Its particularly high affinity for agonist binding sites (ADTN) could result from additional π-bond interactions of the allylic double bond with certain groups at sites in the vicinity of an hypothesized lipophilic cleft of the D-2 receptor.[30] Compound 9, containing an *N*-2-hydroxyethyl substituent, had relatively low affinity for all DA receptor sites tested and lacked agonistic activity. The polar 2-hydroxyl group would probably be repulsed from a lipophilic cleft, if such a site exists in the D-1 as well as the D-2 receptors, to account for its low affinity at both sites. The polar hydroxy group apparently also reduces the efficacy of the compound, but may contribute to the moderately high affinity for DA agonist sites.

The last two *N*-multihaloalkyl-substituted compounds studied (10 and 11) had very low affinity for all DA receptor sites and no agonistic activity. Substitution of the hydrogens by fluorine atoms probably enhances the lipophilicity of the compounds, but at the same time the highly electronegative F atoms decrease the electron charge density on the N by spreading the charge across the entire side chain. The compound then becomes less basic and there is decreased tendency to become cationic at physiological pH, a proposed requirement for high-affinity binding to DA receptors.[31]

An interesting observation from the present study is that the D-1 affinity for various alkylated norapomorphine (compounds 1–4, 7, 8) remained relatively low but within a narrow range (124–730 nM), while the D-2 affinity varied widely, especially toward much lower values of K_i (0.2–1200 nM) (Table I). These observations may indicate that the D-1 binding site lacks a lipophilic cleft present in the D-2 site or that participation of a lipophilic cleft is not necessary for efficient binding at the D-1 site. In contrast, at the D-2 site, a lipophilic cleft appears to be more actively involved in high-affinity binding of various ligands, including the aminotetralins and other common dopaminergic agents exhibiting D-2 selectivity.[30,32]

Thus, in conclusion, this SAR study of 11 alkylated (*R*)-(−)-norapomorphines suggests some valuable insights into the molecular structure of binding sites at dopaminergic receptors, especially of the D-2 type. The results also suggest optimal structural requirements for the *N*-alkyl substituent of aporphines for interaction with DA receptors to produce characteristic DA-like effects in vivo. We conclude that a lipophilic three-carbon side chain confers high affinity for D-2 as well as agonist binding sites, which may include a high-affinity D-2 site;[30] a double bond in the side chain (as in 8) had little effect on affinity for D-1 and D-2 sites but slightly enhanced affinity for the agonist binding site. Conformational restriction (as in 7) of a branched three-carbon side chain (cyclopropylmethyl) resulted in higher affinity, greater selectivity for D-2 receptors, and maximum agonistic activity. We propose also that interaction between the cationic N of aporphines at physiological pH and a presumptive negatively charged group on the receptor is essential for high-affinity binding and that the D-2 receptor, in particular, may have a nearby lipophilic cleft just long and wide enough to accommodate a three-carbon chain. This chain evidently can be a conformationally restricted branched chain, but not a branched chain of any length. Recently, the molecular size of the D-1 and D-2 receptors have been reported to be 74 and 94 kD, respectively.[33-36] The higher molecular size of the D-2 receptor may reflect the presence of additional hydrophobic sites, which may include the putative lipophilic cleft at a *N*-alkylnorapomorphines binding site. These findings may aid in the design and development of more potent and selective DA agonists and antagonists.

Experimental Section

All chemicals were used as received from the manufacturer. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian T-60 or XL-300 spectrometer using TMS as the internal reference. Mass spectra of novel compounds were determined by high-resolution mass spectrometry using a Finnigan 4021 mass spectrometer. The IR spectra were measured in KBr with a Perkin-Elmer Model 700 spectrometer. Optical rotations were obtained on a Perkin-Elmer polarimeter Model 241. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA. Analyses reported by symbols of elements indicate results within ±0.4% of the calculated values.

(*R*)-(−)-*N*-Isopropylnorapocodeine Hydrochloride (15·HCl). A mixture of norapocodeine (14, 0.5 g, 1.6 mmol), isopropyl iodide (0.4 g, 2.3 mmol), and $NaHCO_3$ (0.37 g, 4.4 mmol) in CH_3CN (15 mL) was refluxed for 24 h under nitrogen. The mixture was cooled and filtered, the filtrate was evaporated to dryness, and the crude product was purified on a silica gel column using ether as eluent. The free base thus isolated was converted to the hydrochloride with ethereal HCl to yield 0.16 g of product (28%): mp 185–186 °C; ^{1}H NMR (acetone-d_6, TMS) δ = 1.3 (d, 3 H, CH_3), 1.64 (d, 3 H, CH_3), 2.93–3.83 (m, 6 H), 3.82 (s, 3 H, OCH_3), 4.08–4.57 (m, 2 H), 6.82 (m, H, 8-, 9-H), 7.05 (d, J = 8 Hz, 1 H, 3-H), 7.24 (t, J = 8 Hz, 1 H, 2-H), 8.29 (d, J = 8 Hz, 1 H, 1-H); mass spectra m/z 309 (M^+); $[\alpha]^{24.5}_D$ = −68.1° (c 0.455, MeOH). Anal. ($C_{20}H_{23}NO_2$·HCl·H_2O) C, H, N.

(*R*)-(−)-*N*-Isobutylnorapocodeine Hydrochloride (16·HCl). A suspension of 14 (0.7 g, 2.3 mmol) in CH_3CN (15 mL) was refluxed with isobutyl iodide (0.45 g, 2.4 mmol) and $NaHCO_3$ (0.4 g, 4.8 mmol) for 48 h. The mixture was cooled and filtered, the

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filtrate was evaporated to dryness, and the crude material was separated on a silica gel column using ether/hexane (1:1) as eluent. Treatment of the free base with ethereal HCl yielded 0.5 g of the hydrochloride (60%): mp 135–140 °C dec; ^{1}H NMR (acetone-d_6, TMS) δ = 0.99 (d, 3 H, CH_3), 1.12 (d, 3 H, CH_3), 2.8–3.6 (m, 8 H), 3.78 (s, 3 H, OCH_3), 4.15–4.55 (m, 2 H), 6.7 (m, 2 H, 8-, 9-H), 6.88 (d, J = 8 Hz, 1 H, 3-H), 7.10 (t, J = 8 Hz, 1 H, 2-H), 8.19 (d, J = 8 Hz, 1 H, 1-H). Mass spectra m/z 323 (M^+), 322 (M − 1), 280 [M − $CH(CH_3)_2$]; $[\alpha]^{24.5}_D$ −52.2° (c 0.0536, MeOH). Anal. ($C_{21}H_{25}NO_2$·HCl·H_2O) C, H, N.

(*R*)-(−)-*N*-(Cyclopropylmethyl)norapocodeine Hydrochloride (17·HCl). A mixture of 14 (0.5 g, 1.6 mmol), cyclopropylmethyl chloride (0.2 g, 2.2 mmol), and $NaHCO_3$ (0.3 g, 3.5 mmol) was allowed to reflux for 24 h with catalytic amount of KI in CH_3CN. The mixture was cooled and filtered, the filtrate was evaporated to dryness, and the crude product was purified on a silica column using ether as a solvent. The free base was converted into the hydrochloride with ethereal HCl: yield 0.3 g (51%); mp 236–237 °C; mass spectra m/z 321 (M^+). Anal. ($C_{21}H_{23}NO_2$·HCl·0.25H_2O) C, H, N.

(*R*)-(−)-*N*-Isopropylnorapomorphine Hydrobromide (5·HBr). Apocodeine derivative 15·HCl (0.3 g, 0.82 mmol) in 12 mL of HBr (48%) was heated at 130–135 °C for 4 h under N_2 and then cooled. The resulting solution was evaporated to dryness under reduced pressure. The residue was dissolved in dry MeOH and filtered, and the filtrate was added dropwise to an excess of anhydrous ether under stirring. The white precipitate thus obtained was filtered and dried to yield 0.3 g (92%): mp 200–206 °C; IR (KBr) ν = 3200 (OH), 2930 (CH_2), 1580 (C=C) cm^{-1}; ^{1}H NMR (acetone-d_6 + DMSO-d_6) δ = 1.24 (d, 3 H, CH_3), 1.55 (d, 3 H, CH_3), 2.85–3.8 (m, 6 H), 4.25 (m, 2 H), 6.73 (m, 2 H, 8-, 9-H), 7.05 (d, J = 8 Hz, 1 H, 3-H), 7.3 (t, J = 8 Hz, 1 H, 2-H), 8.35 (d, J = 8 Hz, 1 H, 1-H); $[\alpha]^{24.5}_D$ −57.3 (c 0.733, MeOH). Anal. ($C_{19}H_{21}NO_2$·HBr·0.5H_2O) C, H, N.

(*R*)-(−)-*N*-Isobutylnorapomorphine Hydrobromide (6·HBr). Apocodeine derivative 16 HCl (0.35 g, 0.92 mmol) in 8 mL of HBr (48%) was heated at 130–135 °C for 4 h under N_2 and then cooled. The excess of HBr was removed under reduced pressure and the residue was dried completely by azeotropic distillation. A solution of dried material in EtOH was added dropwise to ether, affording a white precipitate: yield 0.38 g (100%); mp 180–185 °C; ^{1}H NMR (acetone-d_6) δ = 1.09 (d, 3 H, CH_3), 1.18 (d, 3 H, CH_3), 2.86–3.92 (m, 8 H), 4.05–4.4 (m, 2 H), 6.45 (m, 2 H, 8-, 9-H), 7.05 (d, J = 8 Hz, 1 H, 3-H), 7.23 (t, J = 8 Hz, 1 H, 2-H), 8.35 (d, J = 8 Hz, 1 H, 1-H); $[\alpha]^{24.5}_D$ −43.7° (c 0.641, MeOH). Anal. ($C_{20}H_{23}NO_2$·HBr·H_2O) C, H, N.

(*R*)-(−)-*N*-(Cyclopropylmethyl)norapomorphine Hydrochloride (7·HCl). A solution of 17·HCl (0.255 g, 0.7 mmol) in CH_2Cl_2 (10 mL) was treated with BBr_3 (1 mL, 1 M solution in CH_2Cl_2) by stirring overnight at room temperature under N_2 and then quenching with a small quantity of MeOH. After evaporation of the solvent, the residue obtained was treated with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over anhydrous Na_2SO_4 and treated with HCl/ether to form the hydrochloride: yield 0.15 g (63%); mp 185–190 °C dec (lit.[9] mp 260-263 °C); ^{1}H NMR (DMSO-d_6) δ = 2.85–3.97 (m, 12 H), 4.23-4.42 (m, 2 H), 6.8 (m, 2 H, 8-, 9-H), 7.05 (d, J = 8 Hz, 1 H, 3-H, 7.26 (t, J = 8 Hz, 1 H, 2-H), 8.32 (d, J = 8 Hz, 1 H, 1-H); mass spectra m/z 307 (m^+), 306 (M − 1); $[\alpha]^{23}_D$ −56.3° (c 0.444, MeOH). Anal. ($C_{20}H_{21}NO_2$·HCl·H_2O) C, H, N.

***ON*-Bis[(vinyloxy)carbonyl]norcodeine (18).** A mixture of codeine (15 g, 0.05 mol), vinyl chloroformate (17.6 g, 0.165 mol), and Proton Sponge (17.2 g, 0.08 mol) in dichloroethane was heated at under 65 °C overnight. The mixture was filtered and washed with CH_2Cl_2, and the combined filtrate and washings were concentrated to dryness and extracted with ether. The extract was filterd to remove insoluble material. Evaporation of the dried etherextract gave 18 as an oil, which was purified by flash chromatography ($CHCl_3$/MeOH, 20:1) to afford 18 g of 18 (84%) as an oil that produced only a single spot on TLC (CH_2Cl_2/MeOH, 9:1).

***O*-[Vinyloxy)carbonyl]norcodeine Hydrobromide (19·HBr).** Selective removal of *N*-VOC on 18 (18 g) was achieved with 2 equiv of anhydrous HBr in EtOH/ether (200 mL). The reaction mixture was stirred overnight at room temperature, and then filtered to afford 17.2 g (93%) of product: mp 254–255 °C; ^{1}H NMR (CD_3OD, TMS) δ = 7.1 (q, 1 H), 6.78 (d, 1 H, ArH), 6.65 (d, 1 H, ArH), 5.75 (d, 1 H, CH=), 5.59 (d, 1 H, CH=), 5.21 (m, 2 H), 5.0 (q, 1 H), 4.72 (q, 1 H), 4.3 (s, 1 H, NH), 3.5 (s, 3 H, OCH_3), 3.44 (m, 1 H), 3.25 (d, 1 H), 3.0 (m, 3 H), 2.7 (m, 1 H), 2.24 (m, 1 H), 1.93 (d, 1 H); mass spectra m/z 355 (M^+). Anal. ($C_{20}H_{21}NO_5$·HBr) C, H, N.

2,2,2-Trifluoroethyl Trichloromethanesulfonate. A mixture of 5 g (0.05 mol) of (2,2,2-trifluoroethyl)ethanol and 11.3 g (0.052 mol) of trichloromethanesulfonyl chloride in 15 mL of water was stirred at 50 °C as 2.2 g (0.055 mol) of NaOH in 9 mL water was added. After 2 h at this temperature, the mixture was allowed to cool to room temperature. Ether was used to extract the sulfonate ester; this extract was washed twice with concentrated aqueous NH_3 and then with H_2O. After filtration and evaporation of the solvent, the remaining oil was distilled. The constant fraction was collected at 47 °C (4 mmHg) in almost quantitative yield (lit.[18] 102–103 °C/38 mmHg).

***O*-[(Vinyloxy)carbonyl]-*N*-(2,2,2-trifluoroethyl)norcodeine (20).** Alkylation of 19 (14.4 g, 0.033 mol) with 2,2,2-trifluoroethyl trichloromethanesulfonate (11 g, 0.0391 mol) and K_2CO_3 (6.6 g, 0.04 mol) in acetone was carried out at 70 °C for 6 h. Completion of the reaction was verified with TLC (CH_2Cl_2/MeOH, 9:1). The solvent was removed under reduced pressure to leave an oil, which was extracted with ether. The ether was removed to give an oil, which was used without further purification in next step.

***N*-(2,2,2-Trifluoroethyl)norcodeine Hydrochloride (21·HCl).** In a N_2 atmosphere, 200 mL of 1.7 N HCl solution was added to 20 from the previous step. The reaction mixture was stirred and heated at 100 °C for 3 h and then allowed to cool; the pH was adjusted to 8 with concentrated aqueous NH_3. The mixture was extracted with $CHCl_3$, which was washed with H_2O and dried over anhydrous $MgSO_4$. The filtered, dried $CHCl_3$ extract was concentrated to afford an oil, which was purified by flash column ($CHCl_3$/MeOH, 20:1) and then converted to the HCl salt with HCl/ether to yield 3.9 g of 21 (29.3%, two steps): mp 149–152 °C; ^{1}H NMR (CD_3OD, TMS) δ = 6.8 (d, 1 H, ArH), 6.68 (d, 1 H, ArH), 5.8 (d, 1 H, Ch=), 5.4 (d, 1 H, CH=), 4.95 (d, 1 H), 4.5 (t, 1 H), 4.42 (m, 1 H, $CHCF_3$), 4.3 (m, 1 H, $CHCF_3$), 3.85 (s, 3 H, OCH_3), 3.55 (q, 1 H), 3.35–3.3 (m, 3 H), 3.2 (m, 1 H), 3.04 (q, 1 H), 2.5 (m, 1 H), 3.13 (q, 1 H); mass spectra m/z 367 (M^+). Anal. ($C_{19}H_{20}NO_3F_3$·HCl·H_2O) C, H, N.

***N*-(2,2,2-Trifluoroethyl)norapocodeine Hydrochloride (22·HCl).** Compound 21 (3.7 g) was dissolved into 15 mL of CH_3SO_3H. The mixture was heated at 90–95 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with H_2O and adjusted to pH 8 with concentrated aqueous NH_3. The mixture was extracted with $CHCl_3$, and the combined extracts were washed and dried over anhydrous $MgSO_4$, filtered, and then evaporated to dryness. The residue was purified by a flash column eluting with $CHCl_3$ and MeOH (20:1, vol). The desired fraction was collected and then converted to the HCl salt with HCl/ether to yield 840 mg of 22 (24%): mp 140–143 °C; mass spectra m/z 349 (M^+); ^{1}H NMR (CD_3OD, TMS) δ = 8.45 (d, 1 H, 1-H), 7.4 (t, 1 H, 2-H), 7.21 (d, 1 H, 3-H), 6.9 (q, 2 H, 9-H), 4.75 (m, 1 H, $CHCF_3$), 4.65 (q, 1 H), 4.4 (m, 1 H, $CHCF_3$), 4.05 (q, 1 H), 3.9 (s, 3 H, OCH_3), 3.85 (m, 1 H), 3.55–3.45 (m, 2 H), 3.28 (q, 1 H), 2.9 (t, 1 H). Anal. ($C_{19}H_{18}NO_2F_3$·HCl·H_2O) C, H, N.

***N*-(2,2,2-Trifluoroethyl)norapomorphine Hydrobromide (10).** Base 22 (91 mg, 0.236 mmol) was dissolved in CH_2Cl_2 (10 mL) under N_2 and the solution was cooled to −70 °C in acetone/dry ice bath. BBr_3 in hexane (1 M, 7 mL) was added to the stirred solution and the mixture was left at room temperature for 1 h. Dry N_2 then was bubbled into the reaction to remove excess BBr_3, the solution was cooled to −70 °C, and MeOH was added carefully. The solvent was removed under reduced pressure, and the resulting oil was dissolved in MeOH and refluxed for 30 min. The solution was then evaporated to dryness. Crystallization of the product with ether and MeOH gave 101 mg of 10 (94%): mp 165–166 °C; mass spectra m/z 355 (M^+); ^{1}H NMR (CD_3OD, TMS) δ = 8.45 (d, 1 H, 1-H), 7.39 (t, 1 H, 2-H), 7.2 (d, 1 H, 3-H), 6.73 (q, 2 H, 8-, 9-H), 4.73 (m, 1 H, $CHCF_3$), 4.5 (q, 1 H), 4.38 (m, 1 H, $CHCF_3$), 4.02 (q, 1 H), 3.7 (m, 1 H), 3.45–3.35 (m, 2 H), 3.12 (q, 1 H), 2.85 (t, 1 H). Anal. ($C_{18}H_{16}NO_2F_3$·HBr) C, H, N.

***N*-(2,2,3,3,3-Pentafluoro-*n*-propyl)norcodeine Methanesulfonate (23·CH_3SO_3H).** Norcodeine 13 (1.8 g, 6.3 mmol) was

dissolved in 50 mL of CH_3CN containing 5.6 g (16.9 mmol) of 2,2,3,3,3-pentafluoropropyl trichloromethanesulfonate and 1.5 g (10.9 mmol) of anhydrous K_2CO_3. The mixture was stirred at 80 °C overnight. After solvent removal, the residue was treated with 30 mL of H_2O and extracted with ether. This extract was washed with H_2O and dried with $MgSO_4$. After filtration, the methanesulfonic acid in ether was dropped into the filtrate. The methanesulfonate salt of **23** was collected by filtration to afford 1.4 g of white solid: 43%; mp 204–205 °C; mass spectra m/z 417 (M^+); ^1H NMR ($CDCl_3$, TMS) δ = 6.82 (d, 1 H, ArH), 6.7 (d, 1 H, ArH), 5.8 (d, 1 H, CH=), 5.4 (d, 1 H, CH=), 5.0 (d, 1 H), 4.6–4.3 (m, 3 H), 3.9 (s, 3 H, OCH_3), 3.6 (q, 1 H), 3.45 (m, 1 H), 3.35 (m, 2 H), 3.2 (m, 1 H), 3.15 (m, 1 H), 2.75 (s, 3 H, CH_3SO), 2.5 (m, 1 H), 2.15 (q, 1 H). Anal. ($C_{20}H_{20}NO_3 \cdot CH_3SO_3H \cdot 0.5H_2O$) C, H, N.

***N*-(2,2,3,3,3-Pentafluoro-*n*-propyl)norapocodeine (24).** The methanesulfonate of **23** (1 g, 1.95 mmol) was converted to **24** with 5 mL of methanesulfonic acid by following the procedure for the arrangement of **21** to **22**. The crude free base was purified by flash column ($CHCl_3$/MeOH, 20:1) to afford 300 mg (39%) of clear oil of **24**, which showed a single spot on TLC ($CHCl_3$/MeOH, 9:1 vol): ^1H NMR ($CDCl_3$, TMS) δ = 8.2 (d, 1 H, 1-H), 7.1 (t, 1 H, 2-H), 6.9 (d, 1 H, 3-H), 6.7 (d, 1 H, 8-H), 6.6 (d, 1 H, 9-H), 3.8 (s, 3 H, OCH_3), 3.4 (q, 1 H, $CHCF_2$), 3.23 (m, 1 H), 3.1–2.9 (m, 3 H), 2.75 (q, 1 H), 2.62 (m, 2 H), 2.33 (t, 1 H).

***N*-(2,2,3,3,3-Pentafluoro-*n*-propyl)norapomorphine Hydrobromide (11·HBr).** The free base of **24** (0.2 g, 0.5 mmol) was converted to **11** by using the procedure for **10** to yield 140 mg of **11** (60%); mp 238–239 °C. The HCl salt of **11** also was obtained by treatment of the free base of **11** in ether with HCl/ether solution: mp 149–153 °C; mass spectra m/z 385 (M^+); ^1H NMR (CD_3OD, TMS) δ = 8.3 (d, 1 H, 1-H), 7.25 (t, 1 H, 2-H), 7.05 (d, 1 H, 3-H), 6.62 (m, 2 H, 8-, 9-H), 4.3 (q, 1 H, $CHCF_2$), 4.15 (d, 1 H), 3.96 (q, 1 H, $CHCF_2$), 3.7 (q, 1 H), 3.5–3.1 (m, 3 H), 2.92 (d, 1 H), 2.65 (t, 1 H). Anal. ($C_{19}H_{16}NO_2F_5 \cdot HCl$) C, H, N.

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Registry No. **1**, 478-76-2; **1**·HCl, 20382-69-8; **2**, 58-00-4; **2**·HCl, 314-19-2; **3**, 18426-16-9; **3**·HBr, 123240-93-7; **4**, 18426-20-5; **4**·HCl, 20382-71-2; **5**, 123241-06-5; **5**·HBr, 115017-81-7; **6**, 123241-07-6; **6**·HBr, 115017-82-8; **7**, 18426-18-1; **7**·HCl, 63907-00-6; **8**, 18426-17-0; **8**·HBr, 123240-94-8; **9**, 79640-90-7; **9**·HCl, 75846-02-5; **10**, 123241-08-7; **10**·HCl, 123240-95-9; **10**·HBr, 123241-10-1; **11**, 123241-09-8; **11**·HCl, 123240-96-0; **11**·HBr, 123241-11-2; **12**, 76-57-3; **13**, 467-15-2; **14**, 478-77-3; **15**, 115017-67-9; **15**·HCl, 115017-68-0; **16**, 115017-69-1; **16**·HCl, 115017-70-4; **17**, 115017-65-7; **17**·HCl, 115017-66-8; **18**, 57933-97-8; **19**·HBr, 123240-97-1; **20**, 123240-98-2; **21**, 123241-12-3; **21**·HCl, 123240-99-3; **22**, 123241-04-3; **22**·HCl, 123241-00-9; **23**, 123241-01-0; **23**·CH_3SO_3H, 123241-02-1; **24**, 123241-03-2; CF_3CH_2OH, 75-89-8; CCl_3SO_2Cl, 2547-61-7; $CF_3CH_2OSO_2CCl_3$, 23199-56-6; $CF_3CH_2CH_2OSO_2CCl_3$, 123241-05-4.

Synthesis, Structure, and Antiparasitic Activity of Sulfamoyl Derivatives of Ribavirin

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The triazole nucleoside derivatives 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-carboxamide (**2**), 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)[1,2,4]triazole-3-thiocarboxamide (**3**), and 1-(5′-*O*-sulfamoyl-β-D-ribofuranosyl)-[1,2,4]triazole-3-carbonitrile (**4**) were synthesized. Suitably protected triazole nucleosides were converted to their corresponding 5′-sulfamoyl derivatives, which on subsequent deprotection gave the desired compounds in good yields. The structures of compounds **2**–**4** were confirmed by X-ray crystallographic analysis. All three compounds showed significant antiparasitic activity in vitro, while **2** showed significant activity in vivo against *Leishmania donovani* and *Trypanosoma brucei*.

Certain nucleosides have been known to exhibit antiparasitic properties.[1-5] We have previously synthesized several nucleosides that have shown activity against a variety of parasites.[6-9] Robins et al. reported the chemical synthesis of the first sulfamoyl nucleoside, 5′-*O*-sulfamoyladenosine.[10,11] 5′-Sulfamoyladenosine, while active in vitro against a wide variety of parasites, is also extremely toxic. Ribavirin, 1-β-D-ribofuranosyl[1,2,4]-triazole-3-carboxamide, first synthesized by Robins et al.,[12] is a relatively nontoxic broad-spectrum antiviral agent.[13,14] It has also been shown[15] to be a substrate for adenosine kinase in certain human cell lines in vitro. Thus, as part of our ongoing program of the synthesis of nucleosides as potential antiparasitic agents, the 5′-*O*-sulfamoyl nucleoside derivatives of ribavirin **2**–**4** were synthesized, their

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