Pergamon

Bioorganic & Medicinal Chemistry 10 (2002) 3319–3329

BIOORGANIC & MEDICINAL CHEMISTRY

Probes for Narcotic Receptor Mediated Phenomena. Part 28: New Opioid Antagonists from Enantiomeric Analogues of 5-(3-Hydroxyphenyl)-*N*-phenylethylmorphan

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Received 25 January 2002; accepted 16 April 2002

Abstract—Enantiomeric analogues of 5-(3-hydroxyphenyl)morphan ligands were synthesized and evaluated because of our unexpected finding that opioid antagonists can be obtained in the 5-phenylmorphan series of opioids without sterically hindering the rotation of the phenolic ring. We determined the opioid receptor binding affinity of these new analogues, as well as the efficacy of the more interesting ligands. One of the new compounds [(1*R*,5*S*)-(−)-3-[2-(3′-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, **15**] was found to have half of the efficacy of naloxone, a potent opioid antagonist, in the [^{35}S]GTPγS assay, and two others (1*R*,5*S*)-(−)-3-[2-(4′-phenylbutyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, **17**, and (1*R*,5*S*,1′*S*)-(+)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, **26**, acted as moderately potent opioid antagonists. X-ray crystallographic structure data were obtained on three compounds. Two of them had three chiral centers; **25** [(1*R*,5*S*,1′*R*)-(−)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol] was determined to have the 1*R*,5*S*,1′*R* configuration, and **26** the 1*R*,5*S*,1′*S* configuration. Since (1*S*,5*R*)-(+)-2-bromo-5-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**32**) was a position isomer of (1*S*,5*R*)-(+)-4-bromo-3-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**30**), and both showed the same ^{1}H NMR spectrum, the structure of **32** was unequivocally determined by X-ray structure analysis.

Introduction

May and his collaborators began to explore the effect of simplification of the structure of the 5-ring morphine-like compounds (4,5-epoxymorphinans) in the 1950's.[1–4] They hypothesized that molecular simplification might reduce undesired pharmacological effects (tolerance, physical dependence, abuse liability, respiratory depression, and constipation, were well known at that time), while retaining the analgesic activity of the parent epoxymorphinan. Among the various types of compounds that they synthesized were the *m*-substituted phenylcyclohexanes, bicyclic compounds that became known as the 5-phenylmorphans.[5] The parent compound in this series, [(±)-5-*m*-hydroxyphenyl-*N*-methylmorphan ((±)-3-(2-methyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, **1**] was found to be as potent as morphine, levorphanol, and metazocine as an antinociceptive.[5] Only agonists were found in this series until May et al. separated the enantiomers of **1**. The (1*R*,5*S*)-(−)-enantiomer (**2**) was about 4 times more potent than morphine in the mouse hot plate assay,[6] and the (1*S*,5*R*)-(+)-enantiomer (**3**) was an agonist-antagonist. It was found to have weak (nalorphine-like) antagonist activity and it was morphine-like in its antinociceptive potency.[6,7] Ong et al. noted[6] that potent antagonists could not be prepared from analogous potent phenylmorphan agonists. Modification of the *N*-substituent in the phenyl-axial 6,7-benzomorphan, 4,5-epoxymorphinan, and morphinan series (e.g., by replacing the *N*-methyl with an *N*-cyclopropylmethyl, *N*-propyl, or *N*-allyl moiety) was known to convert potent opioid agonists to potent opioid antagonists. This did not occur in the 5-phenylmorphan series. Ong et al. theorized[6] that it might be necessary for the phenylmorphans to have an additional fused ring that

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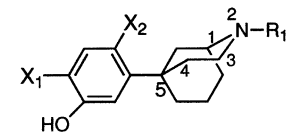
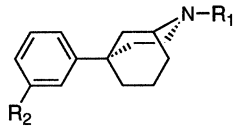
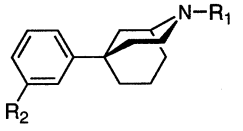
PII: S0968-0896(02)00219-5



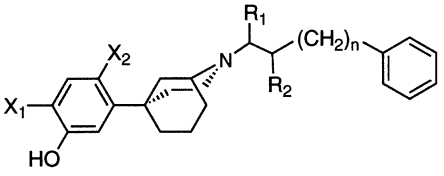
1 (±): $R_1 = CH_3$, $X_1 = X_2 = H$
14 (±): $R_1 = CH_2CH_2C_6H_5$, $X_1 = X_2 = H$
33 (±): $R_1 = CH_2CH_2C_6H_5$, $X_1 = X_2 = Br$



2 (1*R*,5*S*): $R_1 = CH_3$, $R_2 = OH$
4 (1*R*,5*S*): $R_1 = CH_3$, $R_2 = OAc$
6 (1*R*,5*S*): $R_1 = Troc$, $R_2 = OAc$
8 (1*R*,5*S*): $R_1 = H$, $R_2 = OAc$
10 (1*R*,5*S*): $R_1 = H$, $R_2 = OH$

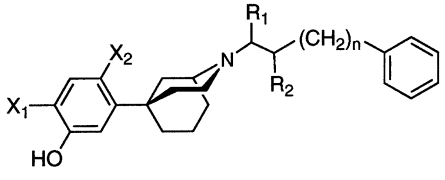


3 (1*S*,5*R*): $R_1 = CH_3$, $R_2 = OH$
5 (1*S*,5*R*): $R_1 = CH_3$, $R_2 = OAc$
7 (1*S*,5*R*): $R_1 = Troc$, $R_2 = OAc$
9 (1*S*,5*R*): $R_1 = H$, $R_2 = OAc$
11 (1*S*,5*R*): $R_1 = H$, $R_2 = OH$



1*R*, 5*S* series

12: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 0$
15: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 1$
17: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 2$
19: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 3$
21: $R_1 = H$, $R_2 = OH$ (*S*), $X_1 = H$, $X_2 = H$, $n = 0$
22: $R_1 = H$, $R_2 = OH$ (*R*), $X_1 = H$, $X_2 = H$, $n = 0$
25: $R_1 = CH_3$ (*R*), $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 0$
26: $R_1 = CH_3$ (*S*), $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 0$
29: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = Br$, $n = 0$
31: $R_1 = H$, $R_2 = H$, $X_1 = Br$, $X_2 = H$, $n = 0$
34: $R_1 = H$, $R_2 = CH_3$ (*R*), $X_1 = H$, $X_2 = H$, $n = 0$
35: $R_1 = H$, $R_2 = CH_3$ (*S*), $X_1 = H$, $X_2 = H$, $n = 0$



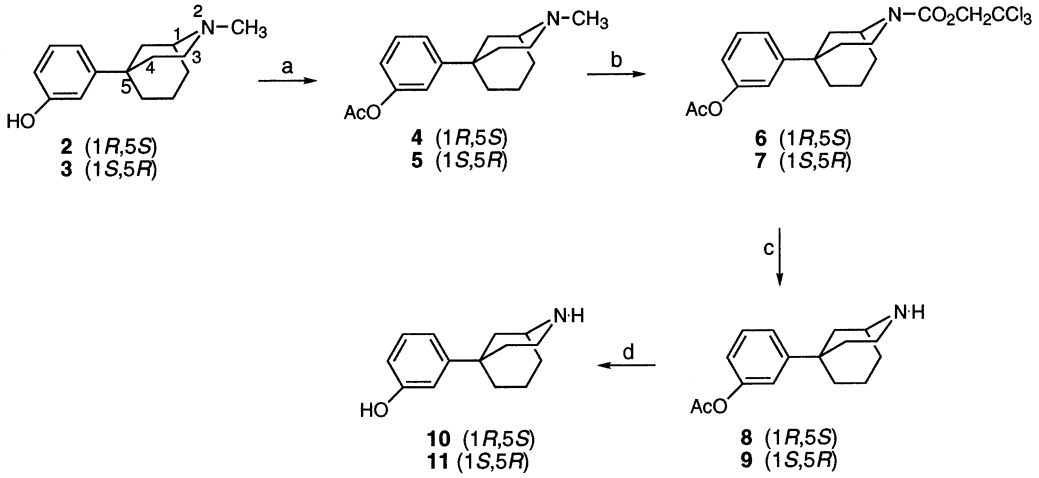
1*S*, 5*R* series

13: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 0$
16: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 1$
18: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 2$
20: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 3$
23: $R_1 = H$, $R_2 = OH$ (*R*), $X_1 = H$, $X_2 = H$, $n = 0$
24: $R_1 = H$, $R_2 = OH$ (*S*), $X_1 = H$, $X_2 = H$, $n = 0$
27: $R_1 = CH_3$ (*S*), $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 0$
28: $R_1 = CH_3$ (*R*), $R_2 = H$, $X_1 = H$, $X_2 = H$, $n = 0$
30: $R_1 = H$, $R_2 = H$, $X_1 = H$, $X_2 = Br$, $n = 0$
32: $R_1 = H$, $R_2 = H$, $X_1 = Br$, $X_2 = H$, $n = 0$

Chart 1.

would fix the position of the phenolic ring, in order to obtain opioid antagonist activity. That idea could conceivably be extended to say that the agonist and antagonist behavior of opioids might be dependent on the position of the phenyl ring in three-dimensional space.

A 'pure' high affinity potent phenylmorphan opioid antagonist was not discovered until quite recently. Thomas et al. found[8] that they could obtain potent 5-phenylmorphan-based antagonists using a method initiated by Zimmerman et al.[9,10] with the structurally reminiscent phenylpiperidines. Prior to Zimmerman's work, none of the phenylpiperidine series of opioid agonists had been converted to opioid antagonists.



2 (1*R*,5*S*)
3 (1*S*,5*R*)

4 (1*R*,5*S*)
5 (1*S*,5*R*)

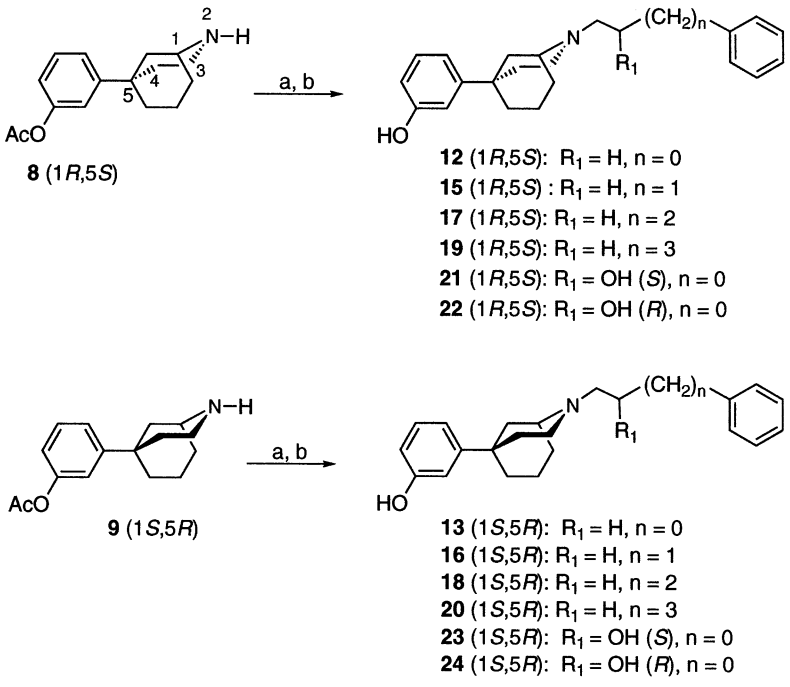
6 (1*R*,5*S*)
7 (1*S*,5*R*)

10 (1*R*,5*S*)
11 (1*S*,5*R*)

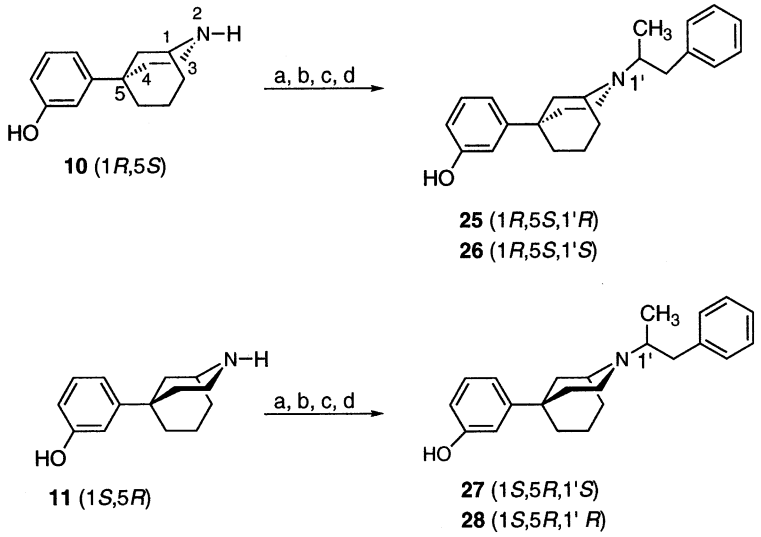
8 (1*R*,5*S*)
9 (1*S*,5*R*)

Scheme 1. Reagents and conditions: (a) Ac_2O, 90 °C, 1 h; (b) 2,2,2-trichloroethoxycarbonyl chloride, $NaHCO_3$, toluene, reflux, 15 h; (c) Zn, AcOH/H_2O, rt, 3 h; (d) NaOH, MeOH, 0 °C.

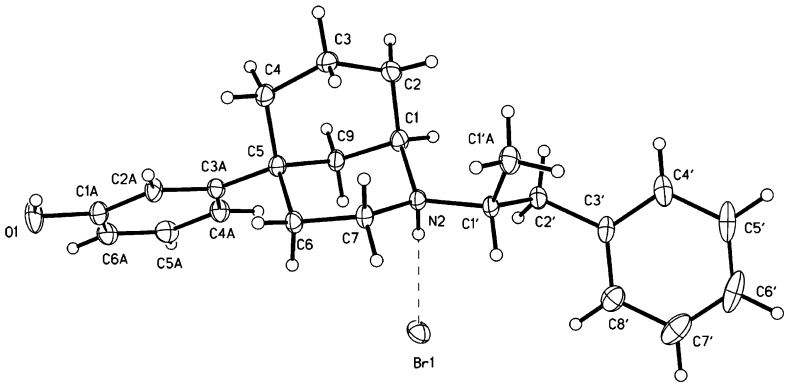
Zimmerman et al. obtained antagonists in the 4-phenylpiperidine series through steric hindrance of the rotation of the aromatic ring, using alkyl groups on the piperidine ring that were vicinal to the phenyl ring. Using that analogy, Thomas et al.[8] added an alkyl moiety to a phenylmorphan which could sterically hinder the rotation of the phenylmorphan's phenolic ring, and found that the resulting racemic 9β-methyl-5-(3-hydroxyphenyl)-*N*-phenylethylmorphan was a pure, potent, modestly selective μ-opioid antagonist (as determined by [^{35}S]GTPγS assays).[8] Steric hindrance was implicated because racemic 5-(3-hydroxyphenyl)-*N*-phenylethylmorphan (**14**), the comparable compound with a freely rotating phenolic ring (without a 9β-methyl group), was known to be a weak agonist.[11] Thus, the data of Thomas et al.,[8] like those of Ong et al., implicated the spatial position of the phenyl ring in the in vivo behavior of the 5-phenylmorphans. Modification of that spatial positioning, then, should modify the in vivo behavior of the compound. Indeed,Awaya et al.[12] have noted that (+)-9α-methyl-5-(3-hydroxyphenyl)-*N*-phenylethylmorphan had weak antagonist actions (about half as potent as nalorphine), and its (−)-enantiomer had a weak agonist effect (about one-tenth as potent as morphine in the hot plate assay). It is likely that the spatial position of the phenyl ring is somewhat different in a 9α-methyl and a 9β-methyl substituted phenylmorphan. Unfortunately, since the *N*-phenylethyl



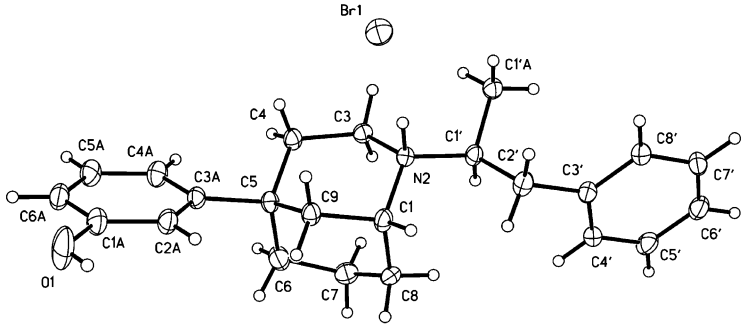
Scheme 2. Reagents and conditions: (a) appropriate alkyl halide, DMF, $NaHCO_3$, 80 °C, 2 h; (b) NaOH, MeOH.



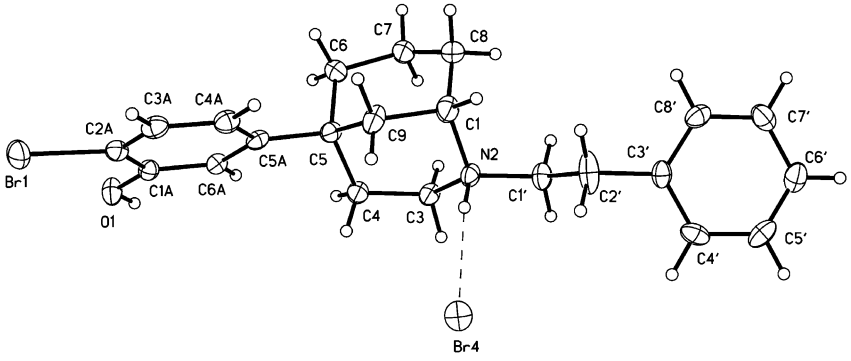
Scheme 3. Reagents and conditions: (a) 1-phenylpropane-2-one, TsOH, benzene, reflux, 15 h; (b) $NaBH_3CN$, MeOH, AcOH; (c) HBr; (d) recryst., MeOH.



Compound 25



Compound 26

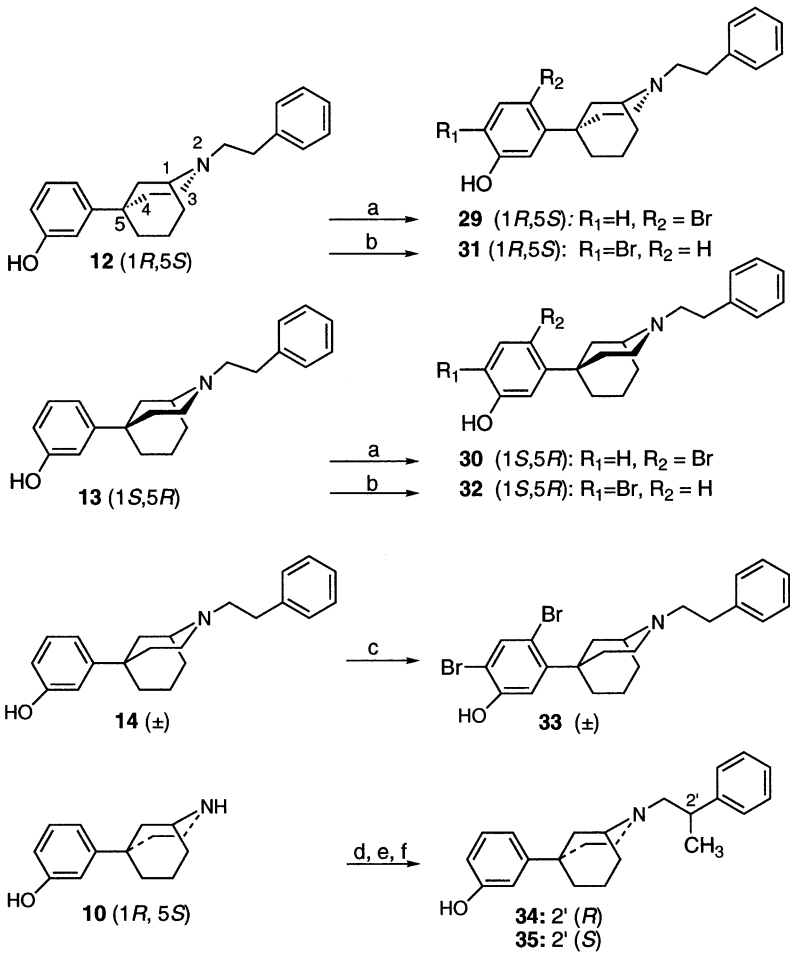


Compound 32

Figure 1. X-ray crystallographic structures of (1*R*,5*S*,1′*R*)-(−)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**25**), (1*R*,5*S*,1′*S*)-(+)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**26**), and (1*S*,5*R*)-(+)-2-bromo-5-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**32**). The figure is drawn using the experimentally determined coordinates with thermal parameters at 20% probability levels.

analogue of the 9α-methyl compound was not prepared, and since Thomas et al.[8] noted that their racemic *N*-methyl analogue in the 9β-methyl series was a low affinity agonist [very reminiscent of the weak in vivo effect of the (+)-racemic *N*-methyl analogue in the 9α-methyl series], it is difficult to conclude that the spatial position of the phenyl ring in the 9β-methyl *N*-phenylethyl series is best for antagonist activity.

Since it seemed clear that a relatively fixed spatial position of the phenyl ring in the 5-phenymorphans was essential for antagonist activity, we were surprised to find that the angular relationship between the aromatic and piperidine rings in the 5-phenylmorphans was, in fact, not essential. We recently reported the preparation and in vitro activity of the enantiomers of 5-(3-hydroxyphenyl)-*N*-phenylethylmorphan,[13] in which the phenolic ring can freely rotate. We hypothesized that one of the enantiomers of the racemate described, by May et al.,[11] as a weak agonist might have appreciable antagonist activity; the racemate was not examined for antagonist activity. We found that the 1*R*,5*S*-(−)-enantiomer (**12**)



Scheme 4. Reagents and conditions: (a) Br_2, CS_2, 0 °C; (b) HBr, DMSO, rt, 24 h; (c) Br_2, CS_2; (d) (*R*)-(−)- or (*S*)-(+)-2-phenylpropionic acid, DPPA, Et_3N, DMF (e) BH_3·THF, THF, reflux; (f) HCl, MeOH.

was indeed a pure, albeit lower affinity, opioid antagonist similar to the comparable racemic 9β-methyl-5-(3-hydroxyphenyl)-*N*-phenylethylmorphan of Thomas et al.,[8] using the same [^{35}S]GTPγS assay criteria. In order to expand upon that unanticipated finding, we have now synthesized and determined the opioid binding affinities of a series of enantiomeric analogues of 5-(3-hydroxyphenyl)-*N*-phenylethylmorphan (Chart 1), and we have examined the efficacy of the more interesting analogues to see whether even more potent antagonists can be found among these sterically unhindered phenylmorphan enantiomers.

Chemistry

Optically pure **2** and **3** were prepared according to the literature.[6,14,15] Acetic anhydride acetylation of **2** or **3** at 90 °C gave the enantiomers of **4** or **5**, respectively (Scheme 1). Without an acetyl protective group, it was difficult to obtain the desired compounds. Demethylation of **4** or **5** was accomplished using 2,2,2-trichloroethyl chloroformate, to give the intermediate **6** or **7**, respectively. Carbamates **6** or **7** were converted to the secondary amine **8** or **9** using zinc-acetic acid. Reaction of **8** or **9** with the corresponding alkyl bromide using sodium bicarbonate in dimethylformamide, followed by deacetylation in aqueous sodium hydroxide, gave enantiomers **12**, **13** and **15** through **24** (Scheme 2). The yield was improved if **8** or **9** was initially deacetylated to **10** or **11**, and then *N*-alkylated with the bromide to give the desired compounds. *N*-Alkylation with 1-phenylpropane-2-one was accomplished using, *p*-toluenesulfonic acid in toluene, followed by reduction with sodium cyanoborohydride to give **25**–**28** (Scheme 3). The molecular structures of **25** and **26**, with three chiral centers, were unequivocally determined by X-ray crystallography. Thus, **25** was found to be the 1*R*,5*S*,1′*R* analogue (Fig. 1), and **26** (Fig. 1) was the 1*R*,5*S*,1′*S* analogue. Bromination of **12** or **13** with a slight excess of bromine in CS_2 gave **29** or **30**, respectively (Scheme 4). These were reacted with HBr in dimethylsulfoxide[16] to give **31** and **32** (Scheme 4). Since both of the position-isomers **32** and **30** showed the same ^{1}H NMR spectrum, the structure of **32** was determined by X-ray structural analysis (Fig. 1). Compound **32** was found to be (1*S*,5*R*)-(+)-2-bromo-5-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol. Bromination of (±)-3-[2-(2′-phenylethyl)-2-azabicyclo [3.3.1]non-5-yl]-phenol (**14**) gave **33** (Scheme 4). Coupling of **10** with the enantiomers of 2-phenylpropionic acid using diphenylphosphoryl azide followed by treatment with BH_3-THF complex, gave **34** and **35** (Scheme 4).

Table 1. Opioid receptor binding affinity of synthesized phenylmorphans[18,19]

Compd	K_i (nM ± SD)		
	μ (DAMGO)[a]	δ (SNC80)[b]	κ (U69,593)[c]
12	14.4 ± 0.7[d]	180 ± 20[d]	180 ± 10[d]
13	27 ± 1.7[d]	240 ± 10[d]	90 ± 7[d]
15	42 ± 2	700 ± 50	390 ± 30
16	100 ± 4	1000 ± 40	380 ± 10
17	30 ± 2	700 ± 50	360 ± 30
18	230 ± 10	1200 ± 130	1300 ± 90
19	220 ± 10	600 ± 70	1300 ± 80
20	540 ± 10	2000 ± 300	2000 ± 140
21	30 ± 2	550 ± 40	1100 ± 60
22	80 ± 5	900 ± 130	760 ± 60
23	150 ± 10	660 ± 60	70 ± 10
24	200 ± 10	1000 ± 70	380 ± 30
25	29 ± 2.8	290 ± 40	240 ± 10
26	31 ± 2.3	170 ± 20	50 ± 4
27	350 ± 30	1400 ± 140	90 ± 8
28	340 ± 40	1100 ± 130	190 ± 30
29	1100 ± 60	1800 ± 200	7700 ± 630
30	1700 ± 70	7000 ± 700	11000 ± 800
31	900 ± 60	1600 ± 120	7000 ± 700
32	1400 ± 70	> 4300	11500 ± 700
33	> 6000	4400 ± 600	> 6400
34	840 ± 60	2100 ± 100	560 ± 30
35	920 ± 50	2400 ± 100	1400 ± 70

[a]DAMGO (D-Ala[2], MePhe[4]Gly-ol[5])enkephalin), agonist selective for μ-opioid receptor.
[b]SNC80 ([(+)-4-[(αR)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxylbenzyl]-*N*,*N*′-diethyl benzamide), agonist selective for δ-opioid receptor.
[c]U69,593 (*trans*-3,4-dichloro-*N*-methyl[2-(1-pyrrolidinyl)cyclohexyl] benzene acetamide), agonist selective for κ opioid receptor.
[d]Data from ref 13.

Table 2. Inhibition of [^{35}S]GTPγS binding in guinea pig caudate stimulated by DAMGO (μ, SNC80 (δ), and U69,593 (κ selective opioid agonists[20]

Compd	K_i (nM ± SD)		
	μ (DAMGO)[a]	δ (SNC80)[b]	κ (U69,593)[c]
12	7.5 ± 0.8[d]	223 ± 15[d]	28 ± 1.2[d]
13	5.5 ± 0.2[d]	10 ± 0.6[d]	16 ± 0.8[d]
15	3.2 ± 0.2	28 ± 3	17 ± 2
17	6.5 ± 0.4	30 ± 3	72 ± 5
21	120 ± 10	> 1000	420 ± 30
25	50 ± 5	490 ± 50	100 ± 9
26	9.3 ± 1	50 ± 5	22 ± 3
Naloxone	1.4 ± 0.1[e]	25 ± 2.0[e]	11 ± 1.2[e]

[a]DAMGO (D-Ala[2],MePhe[4]Gly-ol[5])enkephalin), agonist selective for μ-opioid receptor.
[b]SNC80 ([(+)-4-[(αR)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxylbenzyl]-*N*,*N*′-diethylbenzamide), agonist selective for δ-opioid receptor.
[c]U69,593 (*trans*-3,4-dichloro-*N*-methyl[2-(1-pyrrolidinyl)cyclohexyl] benzeneacetamide), agonist selective for κ opioid receptor.
[d]Data from ref 13.
[e]Data from ref 21.

Results and Discussion

Two longer-chain compounds [the *N*-phenylpropyl (**15**) and *N*-phenylbutyl (**17**) analogues) in the 1*R*,5*S* series had moderate affinity (Table 1) for the μ-opioid receptor (K_i = 42 and 30 nM, respectively). However, the compound with the longest chain, the *N*-phenylpentyl analogue in the 1*R*,5*S* or the 1*S*,5*R* series (**19** and **20**, Chart 1), had poor affinity for any opioid receptor (K_i > 200 nM). The 1′*R* and 1′*S* methyl compounds in the 1*R*,5*S* series (**25** and **26**), and the 2′*S* hydroxyl compound in the 1*R*,5*S* series (**21**), were also found to interact with moderate affinity with the μ-opioid receptor (K_i = 29- 31 nM), comparable to the affinity of the known[1] 1*S*,5*R*-(+)-5-*m*-hydroxyphenyl-*N*-methylmorphan (**3**, K_i = 35 nM). None of the compounds had even moderate (K_i < 100 nM) affinity for δ and κ receptors, with the exception of **26** [(1*R*,5*S*,1′*S*)-(+)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, K_i = 50 nM at κ], **23** [(1*S*,5*R*,2′*R*)-(−)-3-[2-(2′-hydroxy-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, K_i = 70 nM at κ], and **27** [(1*S*,5*R*,1′*S*)-(+)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol, K_i = 90 nM at κ]. Four compounds, **15**, **17**, **21**, and **25** (Chart 1), had some selectivity for the μ-receptor (δ/μ = 17, 23, 18, and 10, respectively), comparable to, or better than, the formerly reported[13] 1*R*,5*S*-(−)-2-phenethyl-5-(3-hydroxyphenyl)morphan (**12**) (δ/μ = 13), and a relatively high affinity compound, the 1′*S* methyl compound in the 1*R*,5*S* series (**26**), had essentially the same affinity for both μ and κ (κ/μ = 1.5) opioid receptors. The 2′*S* hydroxyl compound in the 1*R*,5*S* series, compound **21**, has greater κ/μ selectivity (κ/μ = 37) than the formerly reported **2** (κ/μ = 13), and the 2′*R* compound **22** showed less μ- (K_i = 80 nM) and δ- (K_i = 900 nM) receptor affinity and had less κ/μ selectivity (κ/μ < 10) than **21**. All of the 1*R*,5*S* compounds were found to have higher μ opioid receptor affinity than their enantiomeric 1*S*,5*R* relatives. The introduction of bromine into the phenolic ring of the racemic *N*-phenylethyl-5-phenylmorphan, *ortho* and *para* to the phenolic hydroxyl (**33**), was found to greatly reduce affinity for any of the opioid receptors. Conceivably, the bromine's electron withdrawing effect on the aromatic ring perturbed the necessary hydrogen-bonding interaction of the phenolic hydroxyl group with specific amino acids in the opioid receptors.

Replacement of an *N*-methyl substituent with an *N*-allyl or *N*-cyclopropylmethyl is known to convert opioid agonists, such as morphine and the 6,7-benzomorphan, metazocine, to their respective antagonists, nalorphine and cyclazocine. These *N*-substituents have different effects in the *m*-hydroxyphenylmorphan series.[6] Similarly, when an *N*-substituent like *N*-phenylethyl replaces an *N*-methyl moiety in the morphinans and 6,7-benzomorphans, compounds are obtained with potent agonist activity. This also does not appear to be true for 5-phenylmorphans. Some of our examined *N*-phenylethyl compounds and their analogues in the 5-phenylmorphan series were found to have opioid antagonist activity. We have reported that (1*R*,5*S*)-(−)-5-(3-hydroxyphenyl)-*N*-phenylethylmorphan (**12**) and its enantiomer **13**, are pure opioid antagonists.[13] We now find that several additional analogues, (1*R*,5*S*)-(−)-3-[2-(3′-phenylpropyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**15**), (1*R*,5*S*)-(−)-3-[2-(4′-phenylbutyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**17**), (1*R*,5*S*,2′*S*)-(+)-3-[2-(2′-hydroxy-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**21**), (1*R*,5*S*,

1′*R*)-(−)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**25**), and (1*R*,5*S*,1′*S*)-(+)-3-[2-(1′-methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**26**) are pure antagonists (as determined by the [^{35}S]GTPγS assay). Compound **15** was found to be the most potent antagonist. It was about half as potent as the potent opioid antagonist naloxone, at the μ receptor, **17** was about 0.2–0.25 times as potent as naloxone at μ, and **26** was ca. 0.15 times as potent as naloxone at μ. Compounds **21** and **25** are less potent antagonists. The μ-opioid affinity of these compounds was not in accord with their efficacy in the [^{35}S]GTPγS assay. As seen in Table 2, the 1*R*,5*S*-*N*-phenylpropyl compound **15** had the highest efficacy. However, as seen in Table 1, **15** had the lowest affinity of all of the compounds listed in Table 2. Efficacy and μ-opioid affinity were more in accord in the 1*S*,5*R*-*N*-phenylethyl compound **13** and the 1*R*,5*S*-*N*-phenylbutyl compound **17**. The *N*-phenylethyl compound **12** had the highest μ-opioid affinity, but the affinity of its enantiomer **13** was similar to the affinity of the 1*R*,5*S*-*N*-phenylbutyl compound **17**, the 1*R*,5*S*-*N*-phenyl-2′*S*-hydroxyethyl compound **21**, and the 1*R*,5*S*-*N*-phenyl-2′*R*-methyl compound **25**. The marked structural differences in these compounds make structure–activity analyses difficult. It is apparent that compounds in the 1*R*,5*S*-series were better able to interact with μ-opioid receptors than their structural relatives were in the 1*S*,5*R*-series (Table 1). However, one 1*S*,5*R* compound, the-*N*-phenylethyl compound **13**, had good affinity ($K_i = 27$ nM) for the μ-opioid receptor, as good or better than many of the compounds in the 1*R*,5*S* series. Thus, the distinguishing features that increase efficacy or binding affinity at the μ-opioid receptor are not apparent.

The phenolic ring in the analogues which we prepared was not sterically fixed, unlike the phenolic ring in the 6,7-benzomorphans, and morphinans, nor was it sterically hindered, as it was in the 9β-methyl-5-phenylmorphans prepared by Thomas et al. Yet several of our *N*-phenylethyl analogues were found to be opioid antagonists with moderate affinity and selectivity for the μ-opioid receptor. It is clearly not necessary to hinder the rotation of the phenolic ring to obtain reasonably potent opioid antagonists, confirming our initial observation.[13] However, it is likely that rotational hindrance of the phenolic ring may improve receptor affinity, and antagonist potency in the [^{35}S]GTPγS assay. The question of what the interaction is between these ligands and their receptor that might promote differentiation between opioid agonist and antagonist activity is still unanswerable. The structure–activity relationships that are apparent in our series of compounds indicate that the spatial position of the phenyl ring does not fully determine an opioid's agonist or antagonist actions. The major effect, a change from agonist to antagonist, which can be obtained by a relatively simple change in substitution on the amine function in an opioid continues to be intriguing, and unexplained. Perhaps these data, combined with data from future structural modification, will provide the necessary information to gain insight into the conversion of opioid agonists to antagonists.

Experimental

Melting points were determined on a MEL-TEMP II capillary melting-point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra of the bases were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal standard on a Varian Gemini-300 spectrometer. Mass spectra (MS) were recorded on a VG 7070E spectrometer or a Finnigan 4600 spectrometer in the chemical ionization mode (MS, CI-NH_3). Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 0.25 mm plates. Flash column chromatography was performed with Fluka silica gel 60 (mesh 220–240). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, USA and the results were within 0.4% of the theoretical values unless otherwise indicated.

General procedure for compounds 12, 13 and 15–24

(1*R*,5*S*)-(−)-3-[2-(2′-Phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (12). A mixture of (1*R*,5*S*)-(−)-3-[2-methyl-2-azabicyclo [3.3.1]non-5-yl]-phenol (**2**) (1.5 g, 6.5 mmol) and acetic anhydride (20 mL) was heated at 90 °C for 1 h. The mixture was evaporated. The residue was diluted with chloroform (50 mL). The solution was made basic with sodium carbonate (pH 9) and extracted with chloroform. The combined organic solution was dried over sodium sulfate, and evaporated. The residue was taken up in toluene (30 mL), sodium bicarbonate (168 mg, 2.0 mmol) and 2,2,2-trichloroethyl chloroformate (1.78 mL, 12.9 mmol) were added, and the mixture was refluxed for 15 h, and the solvent removed. Chloroform (50 mL) was added to the residual material. The solution was extracted with aqueous sodium carbonate (pH 9), and the aqueous layer was extracted with chloroform. The combined organic solution was dried over sodium sulfate, and the solvent removed. Zinc (2.1 g) was added to a solution of the residue in aqueous acetic acid [glacial acetic acid (6 mL) + H_2O (2 mL)] at room temperature. After 3 h, concd ammonium hydroxide solution (20 mL) was slowly added, and the aqueous layer was extracted with chloroform. The organic material was collected, dried over sodium sulfate and evaporated. Sodium bicarbonate (1.09 g, 13 mmol) and 1-bromo-2-phenylethane (0.93 mL, 6.8 mmol) were added to a DMF (50 mL) solution of the residue and heated at 80 °C for 2 h. The reaction mixture was extracted with ethyl acetate, dried, and solvent removed. The residue was dissolved in 10% NaOH/methanol solution at 0 °C. A saturated aqueous ammonium chloride solution was added to the reaction mixture after 10 min; it was extracted with ethyl acetate, dried, and solvent removed. The residue was purified by silica gel chromatography to yield 750 mg (36%) mp 140–140.5 °C; $[\alpha]_D^{20}$ −13.3° (*c* 0.6, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (1H, m), 1.66 (2H, m), 1.83–2.15 (5H, m), 2.17 (2H, bd, $J = 11.7$), 2.50–3.50 (1H, bs), 2.84 (4H, m), 3.00–3.08 (2H, m), 3.27 (1H, m), 6.65 (1H, dd, $J = 2.1$, 7.8), 6.81 (1H, d, $J = 1.8$), 6.89 (1H, d, $J = 7.8$), 7.15–7.32 (6H, m). CIMS (NH_3) *m*/*z* 322 $[M+1]^+$. Anal. ($C_{22}H_{27}NO$) C, H, N.

(1*S*,5*R*)-(+)-3-[2-(2′-Phenylethyl)-2-azabicyclo[3.3.1]-non-5-yl]-phenol (13). Free base, mp 140.0 °C; $[\alpha]_D^{20}$ +13.9° (*c* 0.5, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (1H, m), 1.66 (2H, m), 1.83–2.15 (5H, m), 2.17 (2H, bd, *J* = 11.7), 2.50–3.50 (1H, bs), 2.84 (4H, m), 3.00–3.08 (2H, m), 3.27 (1H, m), 6.65 (1H, dd, *J* = 2.1, 7.8), 6.81 (1H, d, *J* = 1.8), 6.89 (1H, d, *J* = 7.8), 7.15–7.32 (6H, m). CIMS (NH_3) *m*/*z* 322 $[M+1]^+$. Anal. ($C_{22}H_{27}NO$) C, H, N.

(1*R*,5*S*)-(−)-3-[2-(3′-Phenylpropyl)-2-azabicyclo[3.3.1]-non-5-yl]-phenol (15). Free base, mp 45–46 °C; $[\alpha]_D^{20}$ −7.8° (*c* 0.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (1H, m), 1.26 (2H, m), 1.62 (2H, m), 1.83–2.16 (7H, m), 2.65 (4H, m), 2.93 (2H, m), 3.18 (1H, s), 3.50–4.50 (1H, bs), 6.63 (1H, dd, *J* = 2.1, 8.1), 6.78 (1H, d, *J* = 1.8), 6.84 (1H, d, *J* = 7.8), 7.1571–7.30 (6H, m). HRMS (FAB) *m*/*z* 336.2321 $(M+H)^+$, $C_{23}H_{30}NO$ requires 336.2327. Anal. ($C_{23}H_{29}NO\cdot 1/5H_2O$) C, H, N.

(1*S*,5*R*) - (+) - 3 - [2 - (3′ - Phenylpropyl) - 2 - azabicyclo[3.3.1]non-5-yl]-phenol (16). Free base, mp 45–46 °C; $[\alpha]_D^{20}$ +8.0° (*c* 0.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (1H, m), 1.26 (2H, m), 1.50–3.50 (1H, bs), 1.61 (2H, m), 1.83–2.16 (7H, m), 2.65 (4H, m), 2.93 (2H, m), 3.17 (1H, s), 6.63 (1H, dd, *J* = 1.8, 7.8), 6.80 (1H, d, *J* = 1.8), 6.87 (1H, d, *J* = 7.8), 7.12–7.30 (6H, m). HRMS (FAB) *m*/*z* 336.2323 $(M+H)^+$. $C_{23}H_{30}NO$ requires 336.2327. Anal. ($C_{23}H_{29}NO\cdot 1/5H_2O$), C, H, N.

(1*R*,5*S*)-(−)-3-[2-(4′-Phenylbutyl)-2-azabicyclo[3.3.1]-non-5-yl]-phenol (17). Free base, mp 123.5–124.5 °C; $[\alpha]_D^{20}$ −6.7° (*c* 0.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (1H, m), 1.29 (2H, m), 1.50–3.00 (1H, bs), 1.64 (4H, m), 1.83–2.14 (7H, m), 2.63 (4H, m), 2.93 (2H, m), 3.15 (1H, s), 6.63 (1H, dd, *J* = 1.8, 7.8), 6.80 (1H, s), 6.88 (1H, d, *J* = 9.0), 7.13–7.30 (6H, m). HRMS (FAB) *m*/*z* 350.2477 $(M+H)^+$. $C_{24}H_{32}NO$ requires 350.2484. Anal. ($C_{24}H_{31}NO$) C, H, N.

(1*S*,5*R*)-(+)-3-[2-(4′-Phenylbutyl)-2-azabicyclo[3.3.1]-non-5-yl]-phenol (18). Free base, mp 123.5–124.5 °C; $[\alpha]_D^{20}$ +6.0° (*c* 0.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (1H, m), 1.29 (2H, m), 1.50–3.00 (1H, bs), 1.63 (4H, m), 1.83–2.14 (7H, m), 2.63 (4H, m), 2.93 (2H, m), 3.15 (1H, t, *J* = 3.0), 6.63 (1H, dd, *J* = 1.8, 7.8), 6.80 (1H, s), 6.88 (1H, d, *J* = 7.8), 7.13–7.30 (6H, m). HRMS (FAB) *m*/*z* 350.2476 $(M+H)^+$. $C_{24}H_{32}NO$ requires 350.2484. Anal. ($C_{24}H_{31}NO\cdot 1/5H_2O$) C, H, N.

(1*R*,5*S*)-(−)-3-[2-(5′-Phenylpentyl)-2-azabicyclo[3.3.1]-non-5-yl]-phenol (19). Free base (as a thick oil), $[\alpha]_D^{20}$ −5.2° (*c* 0.2, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (1H, m), 1.35 (2H, m), 1.62 (6H, m), 1.87 (3H, m), 1.99 (2H, d, *J* = 13.5), 2.13 (2H, d, *J* = 12.6), 2.58 (4H, m), 2.93 (2H, m), 3.19 (1H, s), 3.90–5.20 (1H, bs), 6.60 (1H, dd, *J* = 2.1, 7.8), 6.75 (1H, s), 6.82 (1H, d, *J* = 7.8), 7.13–7.30 (6H, m). HRMS (FAB) *m*/*z* 364.2633 $(M+H)^+$, $C_{25}H_{34}NO$ requires 364.2640. Anal. ($C_{25}H_{33}NO\cdot 1/3H_2O$) C, H, N.

(1*S*,5*R*) - (+) - 3 - [2 - (5′ - Phenylpentyl) - 2 - azabicyclo[3.3.1]non-5-yl]-phenol (20). Free base (as a thick oil), $[\alpha]_D^{20}$ +4.4° (*c* 0.1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (1H, m), 1.00–3.00 (1H, bs), 1.35 (2H, m), 1.62 (6H, m), 1.87 (3H, m),1.99 (2H, d, *J* = 11.7), 2.13 (2H, d, *J* = 12.6), 2.58 (4H, m), 2.94 (2H, m), 3.17 (1H, s), 6.60 (1H, dd, *J* = 1.8, 7.8), 6.78 (1H, s), 6.87 (1H, d, *J* = 7.8), 7.13–7.30 (6H, m). HRMS (FAB) *m*/*z* 364.635 $(M+H)^+$, $C_{25}H_{34}NO$ requires 364.2640. Anal. ($C_{25}H_{33}NO\cdot 1/5H_2O$) C, H, N.

(1*R*,5*S*,2′*S*)-(+)-3-[2-(2′-Hydroxy-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (21). Free base, mp 58–59 °C; $[\alpha]_D^{20}$ +21.9° (*c* 0.09, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (1H, m), 1.50–2.50 (1H, bs), 1.67 (2H, m), 1.88–2.19 (8H, m), 2.53 (1H, t, *J* = 10.8), 2.84 (1H, dd, *J* = 3.0, 12.9), 3.11 (3H, m), 4.71 (1H, dd, *J* = 3.0, 10.8), 6.67 (1H, dd, *J* = 3.0, 7.8), 6.84 (1H, t, *J* = 1.8), 6.93 (1H, d, *J* = 7.8), 7.20 (1H, t, *J* = 7.8), 7.29–7.42 (5H, m). HRMS (FAB) *m*/*z* 338.2112 $(M+H)^+$, $C_{22}H_{28}NO_2$ requires 338.2120. Anal. ($C_{22}H_{27}NO_2\cdot 3/4H_2O$) C, H, N.

(1*R*,5*S*,2′*R*)-(−)-3-[2-(2′-Hydroxy-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (22). Free base, mp 154–155 °C; $[\alpha]_D^{20}$ −31.9° (*c* 0.06, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47–1.76 (3H, m), 1.88–2.14 (8H, m), 2.44 (1H, t, *J* = 10.5), 2.78 (1H, m), 3.03 (1H, dd, *J* = 3.9, 12.6), 3.24–3.33 (2H, m), 4.72 (1H, dd, *J* = 3.0, 10.8), 6.67 (1H, dd, *J* = 3.0, 7.8), 6.82 (1H, t, *J* = 1.8), 6.91 (1H, d, *J* = 7.8), 7.20 (1H, t, *J* = 7.8), 7.25–7.41 (6H, m). CIMS (NH_3) *m*/*z* 338 $[M+1]^+$. Anal. ($C_{22}H_{27}NO_2\cdot 1/2H_2O$) C, H, N.

(1*S*,5*R*,2′*R*)-(−)-3-[2-(2′-Hydroxy-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (23). Free base, mp 58–59 °C; $[\alpha]_D^{20}$ −23.0° (*c* 0.06, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (1H, m), 1.50–2.50 (1H, bs), 1.67 (2H, m), 1.88–2.19 (8H, m), 2.54 (1H, t, *J* = 10.8), 2.85 (1H, dd, *J* = 3.9, 12.6), 3.11 (3H, m), 4.72 (1H, dd, *J* = 3.0, 10.8), 6.67 (1H, dd, *J* = 3.0, 7.8), 6.84 (1H, t, *J* = 1.8), 6.93 (1H, d, *J* = 7.8), 7.20 (1H, t, *J* = 7.8), 7.29–7.42 (5H, m). HRMS (FAB) *m*/*z* 338.2119 $(M+H)^+$, $C_{22}H_{28}NO_2$ requires 338.2120. Anal. ($C_{22}H_{27}NO_2\cdot 3/4H_2O$) C, H, N.

(1*S*,5*R*,2′*S*)-(+)-3-[2-(2′-Hydroxy-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (24). Free base, mp 154–155 °C; $[\alpha]_D^{20}$ +31.6° (*c* 0.07, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43–1.75 (3H, m), 1.88–2.16 (8H, m), 2.44 (1H, t, *J* = 10.8), 2.77 (1H, m), 3.03 (1H, dd, *J* = 3.9, 13.8), 3.23–3.33 (2H, m), 4.72 (1H, dd, *J* = 3.0, 10.8), 6.66 (1H, dd, *J* = 2.1, 7.8), 6.82 (1H, t, *J* = 2.1), 6.90 (1H, d, *J* = 7.8), 7.19 (1H, t, *J* = 7.8), 7.25–7.41 (5H, m). HRMS (FAB) *m*/*z* 338.2114 $(M+H)^+$, $C_{22}H_{28}NO_2$ requires 338.2120. Anal. ($C_{22}H_{27}NO_2\cdot 1/10H_2O$) C, H, N.

(1*R*,5*S*,1′*R*)-(−)-3-[2-(1′-Methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (25). A mixture of

(1*R*,5*S*)-(−)-3-[2-methyl-2-azabicyclo[3.3.1]non-5-yl]-phenol (**2**) (0.5 g, 2.2 mmol) and acetic anhydride (5 mL) was heated at 90 °C for 1 h. Solvent was removed, and chloroform (20 mL) was added. The solution was washed with aqueous sodium carbonate (pH 9). The aqueous layer was extracted with chloroform, and the combined organic solutions were dried over sodium sulfate and solvent removed. The residue was dissolved in toluene (20 mL), sodium bicarbonate (56 mg, 0.7 mmol) and 2,2,2-trichloroethyl chloroformate (0.6 mL, 4.4 mmol) were added, and the mixture was refluxed for 15 h. After removal of solvent, the residue was dissolved in chloroform (30 mL). The solution was washed with aqueous sodium carbonate (pH 9). The aqueous layer was extracted with chloroform. The combined organic solutions were dried over sodium sulfate, and solvent removed. The residue was purified by silica gel chromatography. To a solution of the purified compound in aqueous acetic acid was added 0.7 g of zinc at room temperature. After 3 h, a sodium bicarbonate solution was slowly added, and the aqueous layer was extracted with chloroform. The combined organic material was dried over sodium sulfate and solvent removed. The residue was dissolved in 20 mL of EtOH and 2 mL of ammonium hydroxide solution was added. The reaction mixture was stirred overnight at room temperature, and solvent removed. The residue was dissolved in benzene (30 mL), 1-phenyl-propan-2-one (350 mg, 1.2 equiv) and TsOH (0.01 g) were added, and water removed from the mixture by refluxing overnight with a Dean–Stark trap. Solvent was removed from the reaction mixture. The residue was dissolved in MeOH and $NaBH_3CN$ (136 mg, 1.0 mol equiv) and two drops of acetic acid were added. The reaction mixture was stirred for 3 h at room temperature and solvent was removed. The residue was dissolved in chloroform and washed with aqueous sodium bicarbonate, dried, and solvent removed. The residue was purified by silica gel chromatography to afford a diastereomeric mixture (238 mg, 33%). The free base was dissolved in 10 mL of EtOH and 1 mL of 48% HBr was added. Solvent was removed from the mixture. The residue was dissolved in 2 mL of EtOH and after standing overnight at 0 °C, gave 50 mg of the crystalline HBr salt of **25** (5.6%) mp 287–288 °C; $[\alpha]_D^{20}$ −14.8° (*c* 0.07, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.3), 1.12–1.28 (2H, m), 1.36–1.52 (2H, m), 1.62 (2H, d, *J* = 12.3), 1.80–2.24 (5H, m), 2.49 (1H, dd, *J* = 8.1, 12.9), 2.82–2.93 (2H, m), 2.95–3.10 (2H, m), 3.23 (1H, m), 6.64 (1H, dd, *J* = 2.1, 8.1), 6.79 (1H, t, *J* = 2.1), 6.88 (1H, d, *J* = 7.8), 7.14–7.32 (6H, m). CIMS (NH_3) *m*/*z* 334 $[M-1]^+$. Anal. ($C_{23}H_{29}NO\cdot HBr$) C, H, N; X-ray structure analysis unequivocally determined the molecular structure.

(1*R*,5*S*,1′*S*)-(+)-3-[2-(1′-Methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (26). The residual solution of **25** was evaporated and to the residue was added 1 mL of MeOH and the solution was allowed to stand overnight at 0 °C. Crystalline HBr salt **26** was obtained (20 mg, 2.2%) mp 237–238 °C; $[\alpha]_D^{20}$ +12.0° (*c* 0.08, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, d, *J* = 6.3), 1.30–1.43 (2H, m), 1.46–1.74 (3H, m), 1.85–2.00 (3H, m), 2.00–2.20 (3H, m), 2.45 (1H, dd, *J* = 9.3, 12.9), 2.88–3.10 (4H, m), 3.29 (1H, m), 6.65 (1H, dd, *J* = 1.8, 7.8), 6.80 (1H, t, *J* = 2.1), 6.89 (1H, d, *J* = 7.5), 7.14–7.32 (6H, m). CIMS (NH_3) *m*/*z* 334 $[M-1]^+$. Anal. ($C_{23}H_{29}NO\cdot HBr$) C, H, N; X-ray structure analysis unequivocally determined the structure.

(1*S*,5*R*,1′*S*)-(+)-3-[2-(1′-Methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (27). This material was prepared using the procedure described for **25**: mp 287–288 °C HBr salt; $[\alpha]_D^{20}$ +15.1° (*c* 0.05, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.3), 1.12–1.28 (2H, m), 1.36–1.52 (2H, m), 1.63 (2H, d, *J* = 11.7), 1.80–2.24 (5H, m), 2.49 (1H, dd, *J* = 8.4, 12.9), 2.82–2.93 (2H, m), 2.95–3.10 (2H, m), 3.24 (1H, m), 6.64 (1H, dd, *J* = 2.4, 8.1), 6.78 (1H, t, *J* = 2.4), 6.87 (1H, d, *J* = 8.1), 7.14–7.32 (6H, m). CIMS (NH_3) *m*/*z* 3346 $[M+1]^+$. Anal. ($C_{23}H_{29}NO\cdot HBr$) C, H, N.

(1*S*,5*R*,1′*R*)-(−)-3-[2-(1′-Methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (28). This material was prepared using the procedure described for **26**: mp 236–237 °C HBr salt; $[\alpha]_D^{20}$ −11.2° (*c* 0.09, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, d, *J* = 6.3), 1.30–1.43 (2H, m), 1.46–1.74 (3H, m), 1.85–2.00 (3H, m), 2.00–2.20 (3H, m), 2.45 (1H, dd, *J* = 8.7, 12.6), 2.88–3.10 (4H, m), 3.28 (1H, m), 6.65 (1H, dd, *J* = 2.4, 8.1), 6.81 (1H, t, *J* = 1.8), 6.90 (1H, d, *J* = 7.5), 7.14–7.32 (6H, m). CIMS (NH_3) *m*/*z* 336 $[M+1]^+$. Anal. ($C_{23}H_{29}NO\cdot HBr$) C, H, N.

(1*R*,5*S*)-(−)-4-Bromo-3-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (29). A mixture of (1*R*,5*S*)-(−)-3-[2-(2-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**12**) (50 mg, 0.16 mmol) in 10 mL of CS_2 was cooled to 0 °C and Br_2 (8.09 μL, 1.01 equiv) in CS_2 was added. The solution was evaporated and the residue was dissolved in chloroform and washed with aqueous sodium bicarbonate. The combined organic solutions were dried over sodium sulfate and evaporated. The residue was purified by silica gel chromatography to afford 53 mg of **29** (85%) as the free base. The free base was dissolved in chloroform, 48% HBr aq added, and solvent removed. The residue was recrystallized in MeOH to afford 22 mg (29%) mp 282–283 °C (dec) HBr salt; $[\alpha]_D^{20}$ −12.7° (*c* 0.07, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, m), 1.50–1.76 (2H, m), 1.82–2.22 (8H, m), 2.83 (4H, m), 3.03 (2H, m), 3.24 (1H, m), 6.81 (1H, dd, *J* = 1.8, 8.7), 7.02 (1H, d, *J* = 2.1), 7.18–7.34 (5H, m), 7.38 (1H, d, *J* = 8.7). CIMS (NH_3) *m*/*z* 400 $[M+1]^+$. Anal. ($C_{22}H_{26}BrNO\cdot HBr$) C, H, N.

(1*S*,5*R*)-(+)-4-Bromo-3-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (30). This material was prepared using the procedure described for **29**.: mp 282–283 °C (dec.) HBr salt; $[\alpha]_D^{20}$ +13.4° (*c* 0.06, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, m), 1.50–1.76 (2H, m), 1.82–2.22 (8H, m), 2.83 (4H, m), 3.03 (2H, m), 3.25 (1H, m), 6.81 (1H, dd, *J* = 1.8, 8.7), 7.02 (1H, d, *J* = 2.1),

7.18–7.34 (5H, m), 7.38 (1H, d, $J=8.7$). CIMS (NH_3) m/z 400 $[M+1]^+$. Anal. ($C_{22}H_{26}BrNO\cdot HBr$) C, H, N.

(1*R*,5*S*)-(−)-2-Bromo-5-[2-(2′-phenylethyl)-2-azabicyclo [3.3.1]non-5-yl]-phenol (31). To a solution of (1*R*,5*S*)-(−) -3-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (**12**) (100 mg, 0.31 mmol) in 10 mL of DMSO was added 0.21 mL (6.0 equiv) of 48% HBr aq at room temperature The reaction mixture was stirred for 24 h, neutralized with sodium bicarbonate solution, and extracted with ethyl acetate. The organic solution was dried over sodium sulfate and evaporated. The residue was purified by silica gel chromatography. The free base was dissolved in chloroform, 48% HBr aq added, and solvent removed to give 120.5 mg, of the HBr salt of **31** (80%) The residue was recrystallized in methanol to afford 58 mg (47%) mp 280–281 °C (dec.) HBr salt; $[\alpha]_D^{20}$ −13.8° (*c* 0.07, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, m), 1.50–1.76 (2H, m), 1.82–2.08 (5H, m), 2.15 (1H, m), 2.50–4.00 (1H, bs), 2.85 (4H, m), 3.03 (2H, m), 3.24 (1H, m), 6.76 (1H, dd, $J=3.0$, 7.8), 7.00 (1H, d, $J=2.1$), 7.18–7.34 (5H, m), 7.37 (1H, d, $J=8.7$). CIMS (NH_3) m/z 400 $[M+1]^+$. Anal. ($C_{22}H_{26}BrNO\cdot HBr$) C, H, N.

(1*S*,5*R*)-(+)-2-Bromo-5-[2-(2′-phenylethyl)-2-azabicyclo [3.3.1]non-5-yl]-phenol (32). This material was prepared using the procedure described for **31**: mp 280–281 °C (dec.) HBr salt; $[\alpha]_D^{20}$ +12.5° (*c* 0.05, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (1H, m), 1.50–1.76 (2H, m), 1.82–2.08 (5H, m), 2.15 (1H, d, $J=12.6$), 2.85 (4H, m), 3.03 (2H, dd, $J=3.0$, 5.7), 3.30 (1H, m), 4.00–5.50 (1H, bs), 6.74 (1H, dd, $J=3.0$, 8.7), 6.97 (1H, d, $J=1.8$), 7.18–7.34 (5H, m), 7.37 (1H, d, $J=8.7$). CIMS (NH_3) m/z 400 $[M+1]^+$ Anal. ($C_{22}H_{26}BrNO\cdot$ HBr) C, H, N; X-ray structure analysis unequivocally determined the molecular structure.

(±)-2,4-Dibromo-5-[2-(2′-phenylethyl)-2-azabicyclo[3.3.1] non-5-yl]-phenol (33). A mixture of (±)-3-[2-(2-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (300 mg, 1.3 mmol) in 30 mL of CS_2 was cooled to 0 °C and Br_2 (0.2 mL, 3.0 equiv) was added. The solution was evaporated and the residue was extracted with chloroform and aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, solvent removed, and the residue was purified by silica gel chromatography. The free base was dissolved in chloroform, 48% aq HBr added, and solvents removed. The residue was recrystallized in MeOH to afford 120 mg (17%) of **33**·HBr: mp 239–240 °C (dec). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (1H, m), 1.10–2.10 (8H, m), 2.25 (1H, d, $J=12.0$), 2.80–3.10 (6H, m), 3.49 (1H, s), 2.40–3.80 (1H, bs), 6.86 (1H, s), 7.00 (1H, d, $J=2.1$), 7.22–7.36 (5H, m), 7.61 (1H, s). CIMS (NH_3) m/z 480 $[M+1]^+$. Anal. ($C_{22}H_{25}Br_2NO\cdot HBr$) C, H, N.

(1*R*,5*S*,2′*R*)-(+)-3-[2-(2′-Methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (34). A mixture of (1*R*,5*S*)-(−)-3-[2-methyl-2-azabicyclo[3.3.1]non-5-yl]-phenol (2) (0.5 g, 2.2 mmol) and acetic anhydride (5 mL) was heated at 90 °C for 1 h. Solvent was removed, and chloroform (20 mL) was added. The solution was washed with aqueous sodium carbonate (pH 9). The aqueous layer was extracted with chloroform, and the combined organic solutions were dried over sodium sulfate and solvent removed. The residue was dissolved in toluene (20 mL), sodium bicarbonate (56 mg, 0.7 mmol) and 2,2,2-trichloroethyl chloroformate (0.6 mL, 4.4 mmol) were added, and the mixture was refluxed for 15 h. After removal of solvent, the residue was dissolved in chloroform (30 mL). The solution was washed with aqueous sodium carbonate (pH 9). The aqueous layer was extracted with chloroform. The combined organic solutions were dried over sodium sulfate, and solvent removed. The residue was purified by silica gel chromatography. To a solution of the purified compound in aqueous acetic acid was added 0.7 g of zinc at room temperature. After 3 h, a sodium bicarbonate solution was slowly added, and the aqueous layer was extracted with chloroform. The combined organic material was dried over sodium sulfate and solvent removed. The residue was dissolved in 20 mL of EtOH and 2 mL of ammonium hydroxide solution was added. The reaction mixture was stirred overnight at room temperature, and solvent removed. The residue was added (*R*)-(−)-2-phenylpropionic acid (0.32 mL), DMF (10 mL), Et_3N (0.36 mL), DPPA (0.56 mL) and then stirred for 10 h at room temperature. The reaction mixture was added water (100 mL) and extracted AcOEt (20 mL X3). The organic layer was dried over Na_2SO_4 and then evaporated. The residue was purified by silica gel chromatography. The purified amide in THF (20 mL) was added BH_3–THF complex (1 M/THF, 4.3 mL) and refluxed for 3 days. The reaction mixture was evaporated under reduced pressure. The residue was added MeOH/HCl aq (1/1, 20 mL) and then stirred 2 h at room temperature The reaction mixture was evaporated and then residue was extracted $NaHCO_3$ aq/AcOEt and dried, evaporated. The residue was purified by silica gel chromatography. The free base was dissolved in 10 mL of EtOH and 1 mL of 48% HBr was added. Solvent was removed from the mixture. The residue was dissolved in 1 mL of MeOH and after standing overnight at 0 °C, gave 162 mg of the crystalline HBr salt of **34** (18%) mp 123–124 °C; $[\alpha]_D^{20}$ +16.2° (*c* 0.2, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, d, $J=6.9$), 1.62 (2H, m), 1.77–2.09 (7H, m), 2.53–2.63 (1H, m), 2.79–3.07 (7H, m), 6.64 (1H, dd, $J=2.4$, 8.1), 6.79 (1H, t, $J=1.8$), 6.87 (1H, d, $J=8.1$), 7.13–7.32 (6H, m). CIMS (NH_3) m/z 336 $[M+1]^+$. Anal. ($C_{23}H_{29}NO\cdot 1/2H_2O\cdot HBr$) C, H, N.

(1*R*,5*S*,2′*S*)-(−)-3-[2-(2′-Methyl-2′-phenylethyl)-2-azabicyclo[3.3.1]non-5-yl]-phenol (35). This material was prepared using the procedure described for **34**: mp 127–128 °C HBr salt; $[\alpha]_D^{20}$ −36.3° (*c* 0.2, MeOH, HBr salt). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, d, $J=6.9$), 1.60 (2H, m), 1.77–2.09 (7H, m), 2.58–2.66 (1H, m), 2.72–3.08 (7H, m), 6.63 (1H, dd, $J=2.1$, 8.1), 6.79 (1H, t-like), 6.88 (1H, d, $J=7.8$), 7.13–7.32 (6H, m). CIMS (NH_3) m/z 336 $[M+1]^+$. Anal. ($C_{23}H_{29}BrNO\cdot HBr$) C, H, N.

Single crystal X-ray analyses

X-ray data for compounds **25**, **26**, and **32** were collected on a computer controlled Bruker P4 diffractometer using CuK_α radiation and a graphite monochromator in the incident beam. Data were corrected for Lorentz, polarization and absorption effects. The structures were solved by direct methods with the aid of program SHELXTL[17] and refined by full-matrix least-squares on F^2 values using program SHELXLS.[17] The parameters refined included the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms bonded to carbon atoms were included using a riding model in which the coordinate shifts of the carbon atoms were applied to their attached hydrogens with C–H = 0.96 Å. H angles were idealized and U_{iso} (H) values were set at fixed ratios of U_{iso} values of their bonded atoms. Coordinates were refined for hydrogens involved in hydrogen bonds. **32** ($C_{22}H_{27}NOBr_2$) crystallized in the monoclinic space group $P2_1$ with a = 13.581(1), b = 10.046(1), c 15.384(2) Å and $\beta = 90.44(1)^\circ$ and two molecules per asymmetric unit. Final R-factors were 0.027 for 2942 observed data and 0.028 for all 3014 unique data. **25** ($C_{23}H_{30}NOBr$) crystallized in the triclinic space group P1 with a = 7.481(1), b = 8.669(1), c = 8.871(1) Å, $\alpha = 112.61(1)$, $\beta = 93.95(1)$ and $\gamma = 98.83(1)^\circ$. Final *R*-factors were 0.026 for 1753 observed data and 0.027 for all 1759 unique data. Compound **26** ($C_{23}H_{30}NOBr$) crystallized in the orthorhombic space group $P2_12_12_1$ with a = 9.716(1), b = 9.897(1), and c = 21.814(2) Å. Final R-factors were 0.034 for 2012 observed data and 0.035 for all 2074 unique data. Coordinates for all three compounds have been deposited with the Cambridge Crystallographic Data Centre (Cambridge University Chemical Laboratory, Cambridge CB2 1EW, UK).

Biological assays. Details provided in refs 18–20.

Acknowledgements

We would like to thank the Office of Naval Research and NIDA for financial support. We also thank Noel Whittaker (NIDDK, NIH) for mass spectral data, and Robert Horel (NIDA, NIH) for his expert technical assistance.

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