therefore, the mass spectrum recorded in scan number 232 was similar mainly to that of II. Since the mass spectra of reference samples of I and II contained no ion with mass number 300, which was the base peak in the mass spectrum of III, the peak in the *m/e* 300 mass chromatogram still indicates that the urine contained III, although in apparently low concentration compared to I, II, and IV. The total recoveries of III and V by the extraction procedure were, however, not determined and may have been lower than the recoveries of I, II, and IV.

The mass spectrum recorded in scan number 300 was similar to the mass spectrum of V, confirming that the urine also contained this metabolite.

It may be concluded from the data given in Table II that all plasma extracts analyzed by combined GLC–mass spectrometry contained I, II, and IV. Some additional peaks of relatively high intensities, originating from the background, appeared in the mass spectra of plasma extracts from Subject 4.

In vitro studies indicated that IV must be considered pharmacologically active with regard to cardiac effects, while chlorpromazine sulfoxide possesses much less activity (3). The chlorpromazine (11–13) and promazine (14) metabolites analogous to II have proved pharmacologically active in different biological systems, and it seems reasonable that II should also possess significant pharmacological activity. Therefore, it would be desirable to have a sufficiently sensitive and specific method for quantitation of I and both of its nonpolar metabolites, II and IV, in plasma.

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Potential Long Acting Opiate Antagonists: Preparation, Pharmacological Activity, and Opiate–Receptor Binding of *N*-Substituted 2′-Hydroxy-5-methyl-9α-propyl-6,7-benzomorphans

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Abstract □ A homologous series of *N*-substituted 2′-hydroxy-5-methyl-9α-propyl-6,7-benzomorphans (hydrogen to octyl inclusive, allyl, and cyclopropylmethyl) was prepared. In contradistinction to the normetazocine, normorphine, and (−)-3-hydroxymorphinan series, the *N*-pentyl and *N*-hexyl derivatives do not have the analgesic potency of the parent *N*-methyl compound; instead, they are narcotic antagonists with a long duration of action. All of the *N*-substituted 9α-propylbenzomorphans, except for methyl, heptyl, and octyl, have antagonist activity. The receptor binding constants of the *N*-alkyl compounds are uniformly two- to threefold lower than those of the *N*-substituted normetazocines.

Keyphrases □ Opiate antagonists, potential—various *N*-substituted benzomorphans synthesized, pharmacological activity and opiate–receptor binding evaluated □ Benzomorphans, *N*-substituted—synthesized, pharmacological activity and opiate–receptor binding evaluated □ Structure–activity relationships—various *N*-substituted benzomorphans synthesized, pharmacological activity and opiate–receptor binding evaluated □ Binding, opiate–receptor—various *N*-substituted benzomorphans evaluated

Narcotic analgesics based on fused ring systems, such as the 6,7-benzomorphans and the more complex morphinans and morphines, have commonly been converted to antagonists by modification of the *N*-substituent (1, 2) [classically by replacing the *N*-methyl with allyl (3), cyclopropylmethyl (1), or propyl (1)]. Many antagonists prepared in this manner are highly potent and some are used clinically (2). Most antagonists studied have only a short duration of action, for reasons that are not exactly clear. Long duration of action is a useful property in treating opiate overdosage and in some addiction treatment programs.

Table I—Data for *N*-Substituted 2′-Hydroxy-5-methyl-9α-propyl-6,7-norbenzomorphans

N-Substituent	Salt Form	Melting Point	Yield, %	Method	Recrystallization Solvent	Empirical Formula	Analysis, %	
							Calc.	Found
H	—	—	—[a]	—	—	—	—	—
H	Hemioxalate monohydrate	287–288° dec.	90	—	Ethanol–water	$C_{34}H_{48}N_2O_6 \cdot H_2O$	C 68.20 H 8.42 N 4.68	68.22 8.70 4.74
Ethyl	—	238.5–240°	—[b]	A	2-Methoxyethanol	$C_{18}H_{27}NO$	C 79.07 H 9.95 N 5.12	79.13 10.16 5.09
Ethyl	Oxalate	217–219° dec.	88		Ethanol	$C_{20}H_{29}NO_5$	C 66.09 H 8.04 N 3.85	66.21 7.84 3.75
Propyl	—	182–184°	92	A	2-Propanol	$C_{19}H_{29}NO$	C 79.39 H 10.17 N 4.87	79.51 10.43 4.77
Propyl	Oxalate monohydrate	108–110°	—[c]		Water	$C_{21}H_{31}NO_5 \cdot H_2O$	C 63.77 H 8.41 N 3.54	63.95 8.34 3.50
Butyl	—	144.5–146°	—[b]	A	Acetonitrile–ethanol	$C_{20}H_{31}NO$	C 79.67 H 10.37 N 4.65	79.87 10.48 4.57
Butyl	Oxalate	138–141° dec.	97		Acetone–methanol	$C_{22}H_{33}NO_5$	C 67.49 H 8.50 N 3.58	67.45 8.57 3.70
Pentyl	—	138.5–140.5°	—[b]	A	Acetonitrile–ethanol	$C_{21}H_{33}NO$	C 79.94 H 10.54 N 4.44	79.86 10.24 4.35
Pentyl	Oxalate	147–150° dec.	91		Acetone–methanol	$C_{23}H_{35}NO_5$	C 68.12 H 8.70 N 3.45	68.12 8.40 3.43
Hexyl	—	131–132°	—[b]	A	Isopropyl ether	$C_{22}H_{35}NO$	C 80.19 H 10.71 N 4.25	80.14 10.74 4.13
Hexyl	Oxalate	120–122° dec.	92		Ethanol	$C_{24}H_{37}NO_5$	C 68.70 H 8.89 N 3.34	68.45 8.94 3.20
Heptyl	—	97.5–98.5°	—[b]	A	Heptane	$C_{23}H_{37}NO$	C 80.14 H 10.86 N 4.08	80.20 10.88 3.88
Heptyl	Oxalate	140.5–142.5° dec.	95		Acetone–methanol	$C_{25}H_{39}NO_5$	C 69.25 H 9.07 N 3.23	68.85 9.23 3.12
Octyl	—	—[d]	—[b]	A	—	$C_{24}H_{39}NO$	—	—
Octyl	Oxalate	182.5–184° dec.	92		Acetone–methanol	$C_{26}H_{41}NO_5$	C 69.76 H 9.23 N 3.13	69.80 9.39 3.04
Allyl	—	208.5–210.5°	—[b]	A	2-Methoxyethanol	$C_{19}H_{27}NO$	C 79.95 H 9.54 N 4.91	80.08 9.82 4.81
Allyl	Oxalate	221.5–223.5° dec.	88		Acetone–methanol	$C_{21}H_{29}NO_5$	C 67.18 H 7.79 N 3.73	67.37 7.84 3.57
Cyclopropylmethyl	—	198.5–200.5°	—[b]	B	Ethanol	$C_{20}H_{27}NO$	C 80.22 H 9.76 N 4.68	79.96 9.95 4.46
Cyclopropylmethyl	Oxalate	163–165° dec.	88		Ethanol	$C_{22}H_{31}NO_5$	C 67.84 H 8.02 N 3.60	67.45 8.04 3.68

[a] See Ref. 18. [b] Isolated as oxalate. [c] As purified free base. [d] Syrup, not analyzed.

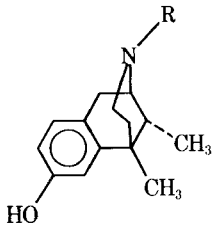
BACKGROUND

This paper explores the effects of replacing a methyl group with a propyl group at the 9α-position of a benzomorphan. This simple substitution has led to a series of compounds with dramatic changes in biological activity. Of particular interest is the fact that some of these compounds are relatively pure antagonists with a long duration of action. Also interesting is the fact that the *N*-pentyl derivative, which in the normetazocine, normorphine, and 3-hydroxymorphinan series is approximately equipotent with the methyl derivative as an agonist, is devoid of analgesic activity in 2′-hydroxy-5-methyl-9α-propyl-6,7-norbenzomorphan.

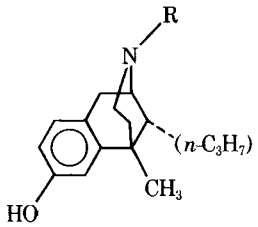
In the metazocine series (I), replacement of the *N*-methyl (I*b*) by saturated alkyl moieties (4, 5) from ethyl to butyl (I*c*–I*e*) caused a diminution or loss of analgesic activity and a concurrent gain in narcotic antagonist activity (6), which was maximal with the *N*-propyl (I*d*) derivative (7). The *N*-ethyl compound (I*c*) (8, 9) was a weak agonist and a longer lasting but less potent antagonist than nalorphine with a steeper dose–response curve (9). The *N*-butyl derivative (I*e*) (7) had 0.2 times the antagonist potency and the same duration of action as nalorphine, and it had little analgesic activity, as measured by the Eddy hot-plate (10, 11) and Nilsen (12) assays.

When a five- or six-carbon side chain was introduced to form the *N*-pentyl (I*f*) or *N*-hexyl (I*g*) compounds, the potent analgesia associated with the parent *N*-methyl compound, metazocine (I*b*), was restored. A slight lessening of agonist potency was noted in I*g* (13). Although I*f* and, presumably, I*g* did not have the high physical dependence capacity associated with morphine, the *N*-pentyl did show a low physical dependence capacity, similar to metazocine, in single-dose suppression tests and in nonwithdrawn monkeys (14). These physical dependence capacity data are presently being reinvestigated.

A similar fluctuation of analgesic potency was noted in the comparable homologous normorphine (15) and (−)-3-hydroxymorphinan (16) series. Maximal analgesic potency was noted with the *N*-methyl and *N*-pentyl compounds in these series; the analgesic potency of the *N*-hexyl compound decreased a little. A considerable loss of analgesic potency was



Ia: R = H
Ib: R = CH_3
Ic: R = C_2H_5
Id: R = C_3H_7
Ie: R = C_4H_9
If: R = C_5H_{11}
Ig: R = C_6H_{13}



IIa: R = H
IIb: R = CH_3
IIc: R = C_2H_5
IId: R = C_3H_7
IIe: R = C_4H_9
IIf: R = C_5H_{11}
IIg: R = C_6H_{13}
IIh: R = C_7H_{15}
IIi: R = C_8H_{17}
IIj: R = $CH_2CH{=}CH_2$
IIk: R = CH_2—▽

noted with the *N*-ethyl and *N*-butyl derivatives. Thus, a binodal curve for analgesic activity could be used to describe the variation in potency in each of the three homologous series of compounds.

From the morphine data, a hypothesis was generated (17) which could be reformulated to say that compounds with narcotic antagonist activity have a saturated, aliphatic, three-carbon side chain on the nitrogen atom or the structural components of an allyl group. Potent analgesics with the physical dependence capacity of the opiate type are usually obtainable from methyl, pentyl, or hexyl substituents.

Since only these three groups of structurally rigid analgesics had been examined in this way, and the hypothesis certainly appeared to be valid for them, it was of interest to see whether it could be verified using a fourth homologous series prepared from a different benzomorphan, 2′-hydroxy-5-methyl-9α-propyl-6,7-norbenzomorphan (IIa). Thus, the methyl to octyl, allyl, and cyclopropylmethyl derivatives (IIb–IIj) of this benzomorphan were prepared by known methods (1, 13, 18).

EXPERIMENTAL[1]

Method A: 2-Alkyl-2′-hydroxy-5-methyl-9α-propyl-6,7-benzomorphans—A mixture of IIa (737 mg, 3.0 mmoles) (18), the appropriate alkyl iodide (allyl bromide for IIj) (3.1 mmoles), anhydrous potassium carbonate (1.0 g, 7.25 mmoles), and dry dimethylformamide (10 ml) was heated at 100–110° for 2.5 hr with stirring. After cooling, the inorganic material was filtered and washed with chloroform, and the filtrate and washings were evaporated *in vacuo*. The residue was dissolved in chloroform, washed with water, and dried (sodium sulfate).

Evaporation of the solvent left a residue, which was dissolved in acetone (15 ml) and treated with oxalic acid (288 mg, 3.2 mmoles) in acetone (5 ml). The crystalline acid oxalate salt that separated was collected, washed with acetone, and dried. Treatment of a methanol–water solution of the oxalate with 12 *M* ammonium hydroxide and extraction of the resulting oil into chloroform, drying (sodium sulfate), and evaporation of the solvent gave the purified base, which was recrystallized from the appropriate solvent for analysis (Table I).

Method B: 2-Cyclopropylmethyl-2′-hydroxy-5-methyl-9α-propyl-6,7-benzomorphan (IIk) Oxalate—A solution of cyclopropylcarbonyl chloride (1.0 g, 9.6 mmoles) in chloroform (5 ml) was added dropwise to a slurry of IIa (18) (737 mg, 3.0 mmoles) in dry pyridine (15 ml) maintained at 5–10°. When the addition was completed, stirring was continued at 5–10° until the solid dissolved and then at 25° for an additional 1 hr. The solution was evaporated to a semisolid, chloroform (70 ml) was added, and the solution was washed successively with water (50 ml), 1 *N* hydrochloric acid (50 ml), and brine (30 ml).

The chloroform solution was dried (sodium sulfate) and evaporated to give a syrupy, crude *O,N*-dicyclopropylcarbonyl derivative (1.265 g). This material was added to a slurry of lithium aluminum hydride (900 mg, 23.8 mmoles) in dry tetrahydrofuran (100 ml), and the mixture was refluxed overnight (stirring). After cooling, 12 *M* ammonium hydroxide (8 ml) was slowly added. The mixture was stirred for 1.0 hr, the tetrahydrofuran was decanted from the semisolid inorganic material and evaporated, the residue was dissolved in chloroform (100 ml), washed with water (50 ml), and dried (sodium sulfate), and the solvent was removed *in vacuo*. The residual base was dissolved in acetone (15 ml) and treated with oxalic acid (300 mg, 3.33 mmoles) in acetone (5 ml). The resulting crystalline salt was filtered, washed with acetone, and dried to give 991 mg of IIk. Recrystallization from 95% ethanol gave pure material (Table I).

[1] Melting points were determined in open capillary tubes using a Thomas-Hoover apparatus and are corrected. Microanalyses were performed by the Laboratory of Chemistry's Section of Microanalytical Services and Instrumentation. IR (Perkin-Elmer 257) and NMR (Varian A-60) spectra were consistent with the assigned structures. Mass spectra of the free bases were obtained using a Hitachi Perkin-Elmer RMU6E spectrometer (70 ev); each spectrum was consistent with the assigned structure and showed the expected molecular ion.

Table II—Pharmacological Activities of the *N*-Substituted 2′-Hydroxy-5-methyl-9α-propyl-6,7-norbenzomorphans

N-Substituent	ED_{50}[a]	ED_{50}[b]	EC_{50}[c]	PDC[d]
H (IIa)	—[e,f]	—[e,g]	50	None
Methyl[h] (IIb)	1.61 (1.03–2.52)	1.8 (1.3–2.6)	10	Low
Ethyl (IIc)	17.5 (9.7–31.6)	—[e,g]	60	None
Propyl (IId)	—[e,i]	—[j]	8	None
Butyl (IIe)	—[e,k]	—[e,g]	20	None
Pentyl (IIf)	—[e,l]	—[j]	30	None
Hexyl (IIg)	4.8 (3.4–6.7)	8.6 (5.5–13.4)	30	None
Heptyl (IIh)	50.8 (24.4–90.9)	—	90	None
Octyl (IIi)	—[m]	—	200	None
Allyl (IIj)	—[n]	—	1.3	None
Cyclopropylmethyl (IIk)	—[n]	7.2 (4.0–13.0)	5	None
Morphine hydrochloride	1.2 (0.9–1.3)	0.8 (0.6–1.2)	3	High
Nalorphine hydrochloride	36.4 (27.2–48.7)	4.8 (2.1–11.0)	1.5	None

[a] Eddy hot-plate assay (95% *SE* limits, as obtained by probit analysis, in milligrams per kilogram), subcutaneous injection in mice using oxalate salts. See Refs. 10 and 11. [b] Nilsen assay (95% *SE* limits, as obtained by probit analysis, in milligrams per kilogram), subcutaneous injection in mice using oxalate salts. See Ref. 12. [c] Binding constant, n*M*. See Ref. 20. [d] Physical dependence capacity, single-dose suppression or nonwithdrawn monkeys. See Ref. 6. [e] Insufficient data for probit analysis due to poor dose–response relationship or toxicity. [f] Six out of 10 mice were affected at 50 mg/kg. [g] Three out of 10 mice were affected at 20 mg/kg. [h] K. C. Rice, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, 18, 854 (1975). [i] Toxic at 20 mg/kg (convulsions). [j] Inactive at 20 mg/kg. [k] Five out of 10 mice were affected at 20 mg/kg; toxic at 50 mg/kg (convulsions). [l] Toxic at 10 mg/kg (convulsions). [m] Inactive at 100 mg/kg. [n] Inactive at 50 mg/kg.

RESULTS AND DISCUSSION

The homologous series prepared from 2′-hydroxy-5-methyl-9α-propyl-6,7-norbenzomorphan did not follow the described biological patterns established by the normetazocines, morphines, and (−)-3-hydroxymorphinans. Analgesic potency dropped considerably in the *N*-ethyl (IIc) and *N*-butyl (IIe) compounds, as compared with the *N*-methyl (IIb), and did not return with the introduction of *N*-pentyl (IIf) into the molecule (Table II). The *N*-ethyl to *N*-hexyl (IIc–IIg) derivatives all appeared to have narcotic antagonist activity (Table III). Both agonist and antagonist activities disappeared in the *N*-heptyl (IIh) and *N*-octyl (IIi) compounds.

The unsubstituted benzomorphan, a secondary amine (IIa), had no antagonist activity (Table III). Benzomorphans unsubstituted on the nitrogen atom generally do not display antagonist behavior in monkeys. Normetazocine (Ia), normorphine, norketobemidone, and norbemidone have been shown to have a weak antagonist component in their pharmacological profile by their actions on the narcotic receptor in the guinea pig ileum (19). A strong agonist component in the pharmacological activity of IIa has been shown by an adenylate cyclase assay[2].

As the number of carbon atoms on the nitrogen increased, the duration of action of the compound as an antagonist also increased (Table III). The *N*-ethyl compound had a moderate duration of antagonist action (Table III). The *N*-propyl compound had a very long duration. Compound IIe was less potent than nalorphine but longer lasting. Compound IIf had a rapid onset and long duration of action as an antagonist. Compound

Table III—Summary of Data Obtained from Monkey Studies

N-Substituent	Test[a] / Dose Range[b]	Duration of Antagonist Action[c]	Comments
H (II*a*)	SDS / 5.0–10.0	—	Did not substitute for morphine and exacerbated withdrawal reaction only slightly
	NW / 10.0–20.0	—	Did not precipitate withdrawal; only a slight increase in respiration
Methyl (II*b*)	SDS / 1.5–6.0	—	Nondose-related reduction in withdrawal signs; did not substitute for morphine
Ethyl (II*c*)	SDS / 2.0–8.0	—	Nondose-related reduction in withdrawal signs; did not exacerbate withdrawal reaction
	NW / 4.0–32.0	1.5	Precipitated withdrawal; quick onset (0–30 min) and moderate duration of action
Propyl (II*d*)	SDS / 0.5–2.0	>3*c*	Did not substitute for morphine and appeared to exacerbate withdrawal; long duration of action
Butyl (II*e*)	SDS / 5.0	—	Increase in severity of abstinence signs
	NW / 1.25–5.0	10	Precipitation of moderate to severe abstinence; very long duration of action
Pentyl (II*f*)	SDS / 3.0–12.0	—	Did not substitute for morphine; severe withdrawal in one-third animals at highest dose
	NW / 4.0–32.0	2.5	Precipitated withdrawal; rapid onset (0–30 min) and long duration of action
Hexyl (II*g*)	SDS / 3.0–12.0	>3*c*	Did not substitute for morphine in the dose range tested and appeared to exacerbate withdrawal reaction; very long duration of action
Heptyl (II*h*)	SDS / 10.0	—	Neither suppresses nor precipitates abstinence syndrome
Octyl (II*i*)	SDS / 10.0	—	No alteration of signs of morphine abstinence
Allyl (II*j*)	SDS / 0.5–1.0	—	Increase in severity of abstinence signs
	NW / 0.125–2.0	10	Possible precipitation of abstinence signs at low doses; precipitation of severe, very long lasting abstinence at high doses
Cyclopropylmethyl (II*k*)	SDS / 0.5	—	Prompt intensification of signs of morphine abstinence
	NW / 0.03–1.25	0.5–1.5	Precipitation of mild abstinence signs at the low doses; severe abstinence signs at highest dose
Naloxone or nalorphine	NW / 0.5	0.5–1.5	Precipitated intense withdrawal reactions; rapid onset (0–30 min) and short to moderate duration of action

[a] SDS is single-dose suppression; NW is nonwithdrawn (see Ref. 6). [b] Milligrams per kilogram, subcutaneous injection, oxalate salts. [c] In hours. The duration of action ascertained by NW studies can be directly compared with nalorphine and naloxone data; SDS test data do not have reference standards (see Ref. 6) and can only be compared with other SDS results.

II*g* was a little different in that it had a slow onset and a very long duration of antagonist action. The *N*-allyl (II*j*) and *N*-cyclopropylmethyl (II*k*) compounds were potent, long acting antagonists.

The binding constants of these homologous compounds to rat brain homogenates known to contain receptors to the narcotic analgesics and their antagonists, as determined by standard techniques (13, 20), are presented in Table II. There appears to be a qualitative agreement between these binding constants and overall *in vivo* activity (analgesic or agonist-antagonist). There can be, of course, no quantitative fit to these data since antagonist activity has not been quantified, and only a few of the compounds show analgesic activity *in vivo* by either the hot-plate or Nilsen assay. However, it is thought that they all have an agonist component. This possible agonist activity will be examined in the future using the guinea pig ileum (21) and adenylate cyclase (22) assays.

There is less variation in the binding constants of the homologous normetazocine series (13) than with II*b*–II*j*. The *N*-unsubstituted normetazocine had a binding constant (EC_{50}) of 50; the *N*-ethyl had an EC_{50} of 20. The *N*-methyl, *N*-propyl, *N*-butyl, *N*-pentyl, and *N*-hexyl normetazocines all had EC_{50} values between 5 and 10. Thus, introduction of the 9α-propyl substituent increases the selectivity with which the opiate receptor recognizes different *N*-alkyl substituents. In all cases, however, binding of the 9α-propyl *N*-alkyl-substituted compounds was two- to threefold weaker than the corresponding 9α-methyl derivatives.

The 9α-alkyl group has been shown to be conformationally oriented toward the aromatic ring (away from the nitrogen atom) (23). The upfield position of those protons in the NMR spectra, as compared with the protons on a 9β-alkyl group, is due to the shielding influence of the aromatic ring (23). The introduction of a larger group in that area, such as a 9α-propyl group, may interfere with the fit of the flat phenolic region to a receptor, a fit that was previously postulated to be of importance to the interaction of the structurally rigid analgesics to the receptor (24).

This sterically generated interference could conceivably alter a conformational fit and, thus, cause a different pharmacological response.

Within the benzomorphans, it is unusual to find a statistically good fit between binding constants and *in vivo* analgesic activity[2]. The only series in which such correlations have been achieved are the structurally less rigid homologous ketobemidones (25), the benzazocines (13), and prodines (26). Evidently, the homologous ketobemidones had predominantly analgesic activity; only a few had an antagonist component in their pharmacological activity, and those were relatively weak antagonists. Thus, pharmacological activity could be closely approximated by analgesic potency with homologous ketobemidones, and analgesic activity was shown to be directly related to their binding constants (26). Unfortunately, homologous benzomorphans do not have pharmacological activity that is predominantly related to an accurately measurable analgesic potency. As has been seen, many *N*-substituted 9α-propylbenzomorphans are long acting antagonists, a pharmacological activity difficult to quantify in monkeys. Even if this activity could be quantified, as it might be using the guinea pig ileum assay procedure, pharmacokinetic factors, such as transport to the active site and metabolism, could complicate a correlation between *in vivo* pharmacological activity and *in vitro* binding constants.

A simple modification of the 9α-position in the benzomorphan molecule converted potent agonists (the *N*-pentyl- and *N*-hexylnormetazocines) to long acting antagonists (the *N*-pentyl- and *N*-hexyl-9α-propylbenzomorphans). The 9α-alkyl moiety has never before been implicated in the change of the pharmacological profile of a benzomorphan. This change, from potent agonist to narcotic antagonist, was thought to be caused only by the *N*-substituent. Further variation of the 9α-alkyl substituent to produce benzomorphans with bulkier and more hydrophobic groups in this position may be worthy of investigation to obtain even longer acting antagonists and to provide more clues to the nature of receptor interactions leading to antagonist activity.

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