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Synthesis and Biological Activity of 8β-Substituted Hydrocodone Indole and Hydromorphone Indole Derivatives

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Abstract—The 8β-unsubstituted and substituted analogues of hydrocodone indole and hydromorphone indole were synthesized and their binding affinities to opioid receptors were determined. Introduction of an 8β-methyl group into the indolomorphinan nucleus increased affinity at all opioid receptors. 6,7-Dehydro-4,5α-epoxy-8β-methyl-6,7,2′,3′-indolomorphinan (**9**) was found to be a δ antagonist with subnanomolar affinity (0.7 nM) for the δ-opioid receptor, and to have good δ-selectivity (μ/δ = 322). Published by Elsevier Science Ltd.

Three types of opioid receptors (δ, κ, and μ) have been identified and cloned and there is substantial pharmacological evidence for subtypes for each.[1] It is known that each receptor mediates distinct pharmacological events.[2,3] Opioid antagonists that selectively interact with the δ receptor may find utility as drug abuse treatment agents,[4,5] while agonists that interact with μ and/or δ receptors effect the perception of pain. Ligands selective to μ or κ receptors have side effects that may not be shared by δ-selective receptor ligands, although the latter are likely to have other, perhaps less detrimental, types of side effects. The development of potent and selective agonists and antagonists for the δ receptor is currently being vigorously undertaken.

Oxymorphindole (OMI, **1**) is a nonpeptide that has been found to possess partial agonist activity and binds with high affinity and selectivity to δ receptors (Fig. 1).[6] It has been extensively reported that the 14-hydroxy group is an important contributor to the efficacy of **1** at δ receptors.[7,8] However, there are few reports on the effects of substitution in the C-8 position of oxymorphindole-like compounds on opioid receptors.[9]

Previous studies have shown that 8β-methyl dihydrocodeinone and dihydromorphinone retain good antinociceptive activity compared to dihydrocodeinone and dihydromorphinone.[9a,c] Studies also showed that a bulkier substituent in the 8β-position, such as ethyl, *n*-propyl, or *n*-butyl, decreased antinociceptive activity.[9a] In addition, substitution of the *N*-methyl moiety with *N*-substituents known to convert opioid agonists to antagonists in these epoxymorphinans, resulted in partial agonists with mixed agonist and antagonist properties.

In an effort to develop new opioid receptor ligands, especially those that might interact with good affinity and selectivity at δ receptors, we decided to synthesize and evaluate the biological activities of several 8-alkyl substituted hydrocodone indole- and hydromorphone indole-based derivatives, since Portoghese et al. reported that the addition of an indole ring to the epoxymorphinans increased affinity for δ receptors.[10] Based on the reported SAR for dihydromorphinone and dihydrocodeinone,[9a,c] we chose to evaluate the indole derivatives of both 8β-methyl- and 8β-*n*-butyl-hydromorphone and hydrocodone. In addition, several 8β-methylhydromorphone indole derivatives were also prepared with different *N*-substituents (**13**–**15**).[11]

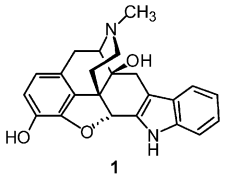

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Figure 1. Structure of oxymorphindole (**1**).

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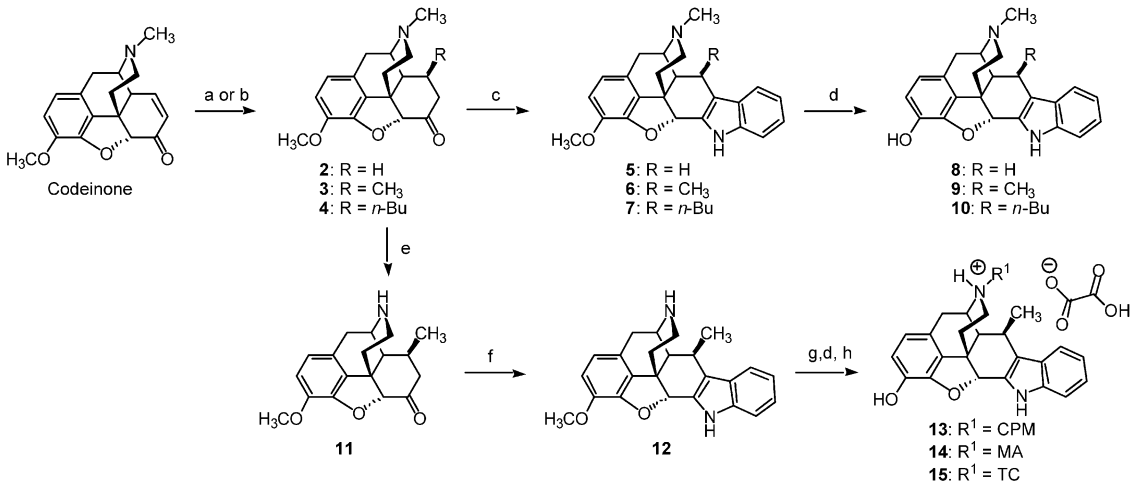


Scheme 1. (a) 10% Pd/C, MeOH–EtOAc, H_2; (b) RLi, CuI, Et_2O; (c) $PhNHNH_2$, HOAc; (d) BBr_3, CH_2Cl_2; (e) (1) CNBr, $CHCl_3$; (2) 2 N HCl; (f) $PhNHNH_2$, HCl, MeOH; (g) RX, K_2CO_3, DMF; (h) oxalic acid, acetone.

The starting material, codeinone, was synthesized from thebaine following a known procedure (Scheme 1).[9] Hydrogenation of codeinone led to 8-unsubstituted dihydrocodeinone **2**. Alternatively, 1,4-addition to the codeinone with alkyllithium and CuI gave the 8-alkyl substituted hydrocodone **3** or **4**, with the substitution predominately in the β position as previously determined.[9] The ketones (**2**–**4**) were converted into the corresponding indoles (**5**–**7**) by heating with phenylhydrazine hydrochloride and HOAc under reflux.[12] The hydrocodone indole derivatives were then converted to hydromorphone indole derivatives **8**–**10** using BBr_3 in CH_2Cl_2 at 0 °C.

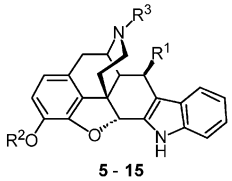
N-Alkylated derivatives **13**–**15** were prepared in several steps from 8β-methyldihydrocodeinone (**3**).[13–16] Compound **3** was *N*-demethylated to **11** with cyanogen bromide followed by acid hydrolysis.[9] Treatment of **11** with phenylhydrazine under Fisher indolization conditions gave indole **12**. Alkylation of indole **12** with the appropriate alkylating agent in DMF, followed by treatment with BBr_3 in CH_2Cl_2, afforded targets **13**–**15**.

The binding affinities of compounds **5**–**10** and **13**–**15** for μ, δ, and κ receptors were determined using previously described methods (Table 1).[17] Compounds **5** (hydrocodone indole) and **8** (hydromorphone indole) were resynthesized and found to be in reasonable agreement with previous reported values.[18] These binding data indicated, as expected, that hydromorphone indole derivatives have higher affinity than the hydrocodone indole derivatives. The results also showed that a β-methyl group in the C-8 position of hydromorphone indole, for example, 6,7-dehydro-4,5α-epoxy-8β-methyl-6,7,2′,3′-indolomorphinan (**9**), increased affinity at all opioid receptors compared to **8**. However, the extension of the 8β-methyl group to an *n*-butyl group (**10**) led to a reduction in affinity at all three opioid receptor sites, compared to **9**, in accord with previous SAR.[9a,c] The introduction of an 8β-methyl group to **5** (i.e., **6**) led to a modest increase in μ/δ selectivity.

After our initial efforts identified compound **9** as a very selective δ ligand with high affinity, we attempted to further enhance the μ/δ selectivity of this ligand by modifying the *N*-substituent. Based on our previous work, the cyclopropylmethyl, 2-methylallyl, and the *trans*-crotonyl groups were selected.[11] The replacement of the methyl group in **9** with either a cyclopropylmethyl group (i.e., **13**) or a 2-methylallyl substituent (i.e., **14**) led to a decrease in μ/δ selectivity compared to **9**. The introduction of the *trans*-crotonyl group (i.e., **15**) decreased δ affinity and gave only a modest enhancement of μ/δ selectivity.

Several of the more interesting analogues were examined in GTPγS functional assays (Table 2).[19] Hydrocodone indole derivatives (i.e., **5**, **6**, and **7**) were inactive as antagonists at μ and κ receptors. Compounds **5** and **6**, however, had a little δ antagonist activity. The hydromorphone indoles were more active than the

Table 1. Opioid receptor affinity of compounds **5**–**15**[a]



Compd	R^1	R^2	R^3	μ[b]	δ[c]	κ[d]	μ/δ
5[e]	H	Me	Me	> 5000	95 (±8)	> 6100	> 53
6	Me	Me	Me	> 4800	27 (±1)	> 6300	> 177
7	*n*-Bu	Me	Me	> 4300	370 (±11)	> 7000	> 12
8[f]	H	H	Me	710 (±66)	2.4 (±0.3)	> 6000	296
9	Me	H	Me	240 (±15)	0.7 (±0.1)	126 (±5)	322
10	*n*-Bu	H	Me	1100 (±74)	22 (±1)	720 (±60)	50
13	Me	H	CPM	66 (±4)	2.3 (±0.2)	36 (±3)	29
14	Me	H	MA	1080 (±122)	9 (±1)	850 (±118)	120
15	Me	H	TC	1020 (±39)	2.3 (±0.2)	120 (±22)	441

CPM, cyclopropylmethyl; MA, 2-methylallyl; TC, *trans*-crotonyl.
[a]The K_i values were determined in the above assays as described in ref 11.
[b]Displacement of [^{3}H]DAMGO.
[c]Displacement of [^{3}H]DADL.
[d]Displacement of [^{3}H]U69593.
[e]Hydrocodone indole[18] re-evaluated.
[f]Hydromorphone indole[18] re-evaluated.

Table 2. Inhibition of opioid agonist stimulated [^{35}S]GTPγS binding ($K_i \pm$SD, nM)[a]

Compd	R^1	R^2	R^3	μ[b]	δ[c]	κ[d]	μ/δ
5[e]	H	Me	Me	Inactive[f]	290 (±19)	Inactive[g]	—
6	Me	Me	Me	Inactive[f]	330 (±29)	Inactive[g]	—
7	*n*-Bu	Me	Me	Inactive[f]	Inactive[h]	Inactive[g]	—
8[i]	H	H	Me	202 (±36)	15 (±2)	731 (±72)	14
9	Me	H	Me	Inactive[f]	49 (±5)	398 (±36)	—
10	*n*-Bu	H	Me	561 (±54)	46 (±4)	272 (±24)	12

[a]The K_i values were determined in the above assays as described in ref 11.
[b]Inhibition of DAMGO.
[c]Inhibition of SNC80.
[d]Inhibition of U69593.
[e]Hydrocodone indole[18] re-evaluated.
[f]$K_i > 600$ nM = inactive.
[g]$K_i > 350$ nM = inactive.
[h]$K_i > 750$ nM = inactive.
[i]Hydromorphone indole[18] re-evaluated.

hydrocodone indoles. Interestingly, compound **8** appears to be a more efficacious δ antagonist than **9** despite the fact that **9** binds with higher affinity at δ receptors (3-fold) and was found to be slightly more μ/δ selective than **8**. Compound **9** was found to have little μ antagonist activity ($K_i > 1100$ nM). If its μ-opioid affinity is mostly due to its μ-agonist activity, this compound may represent a new lead for the development of a μ agonist/δ antagonist dual ligand. Further studies are currently underway to further explore this possibility. Compounds with that mixed activity might prove very valuable as new analgesics or treatment agents.

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References and Notes

1. Reisine, T. *Neuropharmacology* **1995**, *34*, 463.
2. Goldstein, A.; Naidu, A. *Mol. Pharmacol.* **1989**, *36*, 265.
3. Mansour, A.; Fox, C. A.; Akil, H.; Watson, S. J. *Trends Neurosci.* **1995**, *18*, 22.
4. Suzuki, T.; Tsuji, M.; Ikeda, H.; Narita, M.; Tseng, L. F. *Life Sci.* **1997**, *60*, PL283.
5. Calcagnetti, D. J.; Keck, B. J.; Quatrella, L. A.; Schechter, M. D. *Life Sci.* **1995**, *56*, 475.
6. Takemori, A. E.; Portoghese, P. S. *Annu. Rev. Pharmacol. Toxicol.* **1992**, *32*, 239.
7. Kshirsagar, T. A.; Fang, X.; Portoghese, P. S. *J. Med. Chem.* **1998**, *41*, 2657.
8. Schmidhammer, H.; Krassnig, R.; Greiner, E.; Schutz, J.; White, A.; Berzetei-Gurske, I. P. *Helv. Chim. Acta* **1998**, *81*, 1064.
9. (a) Kotick, M. P.; Leland, D. L.; Polazzi, J. O.; Schut, R. N. *J. Med. Chem.* **1980**, *23*, 166. (b) Kotick, M. P.; Polazzi, J. O. *J. Heterocyclic Chem.* **1981**, *18*, 1029. (c) Ghozland, F.; Maroni, P.; Viloria, I.; Cros, J. *Eur. J. Med. Chem., Chim. Ther.* **1983**, *18*, 22.
10. Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281.
11. McLamore, S.; Ullrich, T.; Rothman, R. B.; Xu, H.; Dersch, C.; Coop, A.; Davis, P.; Porreca, F.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2001**, *44*, 1471.
12. General procedure. A mixture of **3**[9] (2.4 g, 7.7 mmol) and phenylhydrazine hydrochloride (2.2 g, 15.3 mmol) in HOAc (40 mL) was heated under reflux for 3 h. After the reaction mixture was cooled, 40 mL of water was added, followed by 10 mL of NH_4OH. The mixture was extracted with CH_2Cl_2 (3×80 mL), and the layers were separated. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give **6**, which is crystallized from MeOH as **6**·H_2O (1.7 g, 4.5 mmol, 58% yield) as a white solid: mp 152 °C, ^{1}H NMR δ 8.23 (s, 1H, NH), 7.64 (d, J=9.0 Hz, 1H, H-7′), 7.32 (d, J=9.0 Hz, 1H, H-4′), 7.15 (t, J=7.2 Hz, 1H, H-6′), 7.02 (t, J=7.2 Hz, 1H, H-5′), 6.61 (s, 2H, H-1 and H-2), 5.64 (s, 1H, H-5), 3.75 (s, 3H, OCH_3), 2.50 (s, 3H, NCH_3), 1.58 (d, J=6.9 Hz, 3H, CH_3), EIMS m/z 386 (M^+), Anal. ($C_{25}H_{26}N_2O_2 \cdot H_2O$) C, H, N.
13. General procedure. Phenylhydrazine hydrochloride (1.4 g, 9.6 mmol) was added to a solution of 8β-methyldihydronorcodeinone hydrochloride (**11**)[9] (3.2 g, 9.6 mmol) in a mixture of absolute MeOH (40 mL) and 6 N HCl (10 mL). The resulting mixture was heated at reflux for 6 h. The precipitate was collected, washed with $CHCl_3$ (3×30 mL), and dried to afford 3.2 g (82%) of 6,7-didehydro-4,5α-epoxy-3-methoxy-8β-methyl-[6,7:2′,3′]-indolomorphinan hydrochloride (**12**) as a white solid, mp >300 °C.
14. General procedure. A suspension of **12** (1.1 g, 2.7 mmol), K_2CO_3 (1.1 g, 8.1 mmol), and bromomethylcyclopropane (0.4 g, 3.2 mmol) in dry DMF (30 mL) was heated at reflux for 2 h. H_2O (200 mL) was added and the mixture was extracted with ethyl acetate (3×50 mL). The combined ethyl acetate portion was washed with H_2O (2×75 mL) and saturated NaCl (50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in dry acetone. An excess of oxalic acid was added and the solvent was removed under reduced pressure. Anhydrous Et_2O was added and the precipitate was collected and dried to afford 1.2 g (86%) of *N*-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3-methoxy-8β-methyl-[6,7:2′,3′]-indolomorphinan oxalate as a white solid, mp 276–279 °C. A solution of the above compound (0.5 g, 1.3 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was treated with BBr_3 (4 mmol, 4 mL of 1.0 M solution in CH_2Cl_2). The mixture was stirred at room temperature for 1 h, 2 N HCl (25 mL) was added and the mixture was heated at reflux for 30 min. The pH was adjusted to pH 9 by the addition of concd NH_4OH and the mixture was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a crude solid that was dissolved in dry acetone. An excess of oxalic acid was added and the precipitate was collected and dried. Recrystallization from absolute EtOH afforded 0.3 g (50%) of **13** as a white solid, mp 236–238 °C.
15. Compounds **6**, **7**, **9**, and **10** were characterized by ^{1}H NMR (300 MHz, DMSO-d_6) and by elemental analysis of their free base or hydrochloride salt. The results were in agreement with the assigned structures: **6**: mp 152 °C, ($C_{25}H_{26}N_2O_2 \cdot H_2O$): δ 8.23 (s, 1H, NH), 7.64 (d, J=9.0 Hz, 1H, H-7′), 7.32 (d, J=9.0 Hz, 1H, H-4′), 7.15 (t, J=7.2 Hz, 1H, H-6′), 7.02 (t, J=7.2 Hz, 1H, H-5′), 6.61 (s, 2H, H-1 and H-2), 5.64 (s, 1H, H-5), 3.75 (s, 3H, OCH_3), 2.50 (s, 3H, NCH_3), 1.58 (d, J=6.9 Hz, 3H, CH_3), EIMS m/z 386 (M^+), **7**: mp >215 °C, ($C_{28}H_{32}N_2O_2 \cdot HCl$): δ 8.23 (s, 1H, NH), 7.57 (d, J=7.8 Hz, 1H, H-7′), 7.30 (d, J=8.1 Hz, 1H, H-4′), 7.15 (t, J=6.0 Hz, 1H, H-6′), 7.01 (t, J=7.2 Hz, 1H, H-5′), 6.60 (s, 2H, H-1 and H-2), 5.64 (s, 1H, H-5), 3.75 (s, 3H, OCH_3), 2.51 (s, 3H, NCH_3), CIMS m/z 429 (MH^+), **9**: mp 202 °C, ($C_{24}H_{24}N_2O_2 \cdot H_2O$): δ 8.11 (s, 1H, NH), 7.65 (d, J=9.0 Hz,

1H, H-7′), 7.32 (d, $J=9.0$ Hz, 1H, H-4′), 7.16 (t, $J=7.8$ Hz, 1H, H-6′), 7.02 (t, $J=7.8$ Hz, 1H, H-5′), 6.56 (m, 2H, H-1 and H-2), 5.65 (s, 1H, H-5), 2.51 (s, 3H, NCH_3), 1.58 (d, $J=6.9$ Hz, 3H, CH_3), EIMS m/z 372 (M^+), **10**: mp 172 °C, ($C_{27}H_{30}N_2O_2 \cdot H_2O$): δ 8.23 (s, 1H, NH), 7.74 (d, $J=8.1$ Hz, 1H, H-7′), 7.24 (m, 1H, H-4′), 7.11 (t, $J=7.2$ Hz, 1H, H-6′), 6.99 (t, $J=7.5$ Hz, 1H, H-5′), 6.56 (m, 2H, H-1 and H-2), 5.62 (s, 1H, H-5), 2.48 (s, 3H, NCH_3), CIMS m/z 415 (MH^+).

16. Compounds **13**–**15** were characterized by ^1H NMR (300 MHz, DMSO-d_6) and by elemental analysis of their oxalate salt. The results were in agreement with the assigned structures: **13**: mp 236–238 °C, ($C_{27}H_{28}N_2O_2 \cdot C_2H_2O_4 \cdot 1.25H_2O$): δ 11.0 (s, 1H, NH), 6.6–7.3 (m, 4H, indole), 6.3 (m, 2H, aromatic), 5.4 (s, 1H, H5), 5.0 (bs, H_2O), 2.2 (s, 2H, NCH_2), 1.2 (m, 3H, CH_3), 0.8 (s, 1H, CH), 0.3 (s, 2H, CH_2), 0.1 (s, 2H, CH_2), **14**: mp 216–220 °C, ($C_{27}H_{28}N_2O_2 \cdot C_2H_2O_4 \cdot 1.0H_2O$): δ 11.0 (s, 1H, NH), 6.6–7.3 (m, 4H, indole), 6.4 (m, 2H, aromatic), 5.5 (s, 1H, H5), 4.8 (d, 2H, $J=20$ Hz, $=CH_2$), 4.2 (bs, H_2O), 2.2 (s, 3H, NCH_2), 1.6 (s, 3H, CH_3), 1.4 (m, 3H, CH_3), **15**: mp 200–204 °C, ($C_{27}H_{28}N_2O_2 \bullet C_2H_2O_4 \bullet 1.0H_2O$): δ 11.3 (s, 1H, NH), 6.9–7.6 (m, 4H, indole), 6.6 (s, 2H, aromatic), 5.9 (m, 1H, CH=), 5.7 (s, 1H, H5), 5.6 (s, 1H, CH=), 4.4 (bs, H_2O), 2.5 (s, 3H, NCH_2), 1.7 (d, 3H, $J=4.8$ Hz, CH_3), 1.5 (m, 3H, CH_3).

17. Kubota, K.; Rothman, R. B.; Dersch, C.; McCullough, K.; Pinto, J.; Rice, K. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 799.

18. Maguire, P. A.; Perez, J. J.; Tsai, N. F.; Rodriguez, L.; Beatty, M. F.; Villar, H. O.; Kamal, J. J.; Upton, C.; Casy, A. F.; Loew, G. H. *Mol. Pharmacol.* **1993**, *44*, 1246.

19. Coop, A.; Rothman, R. B.; Dersch, C. M.; Partilla, J.; Porreca, F.; Davis, P.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **1999**, *42*, 1673.