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# Synthesis and opioid receptor activity of indolopropellanes

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ABSTRACT

A series of skeletal rearranged indolomorphinans **7a–d** were obtained by N-demethylation of 3-methoxy-*N*-methyl-14-hydroxymorphinan-6-one **12** followed by N-realkylation, reduction and Fischer indole cyclization. The structure of the novel skeleton was confirmed by X-ray analysis. These new indoles displayed moderate binding affinity and selectivity at the μ receptor, with compound **7b** showing the highest affinity at this receptor with a $K_i$ value of 40 nM, and 6- and 25-fold selectivity against δ and κ receptors, respectively. Function assays showed that indolopropellanes **7b** and **7c** possessed full agonistic activity at all the opioid receptors indicating a different interaction model existed.



Morphinan opioids with a 6-keto function are important synthetic building blocks for generating new analogues containing a cyclic or acyclic heteroatom group, especially for the indole-derived morphine derivatives.[1–18] Oxymorphindole (**1**, OMI) and its *N*-cyclopropyl analog, naltrindole (**2**, NTI) (Fig. 1) represented the earliest 6,7-indole-derived morphine analogues which were prepared through Fischer indole formation of the corresponding 6-ketones.[2–4,18] These compounds displayed high δ opioid receptor binding and selectivity, and served as a tool drug for characterization of the δ receptor, and as a potential treatment for a number of CNS disorders.[19–23] From the corresponding 6-ketones, Coop and Rice[9,15,16] prepared indolomorphinans **3** and **4** by breaking the 4,5-furan ring of **1** and **2**, an approach to modify the morphine's core structure. Since it has been suggested that the presence of the 4-hydroxyl/methoxy group is detrimental to the interactions between the morphinans compounds and the corresponding target receptors,[9] we recently decided to synthesize and evaluate indolomorphinans[17] lacking the 4-methoxy/hydroxyl group in compounds **3** and **4** using 6-ketone intermediates **5** and **6** as the key intermediates. Interestingly, during our synthesis, we found that the typical N-demethylation of the 3-methoxy analog of *N*-methyl-14-hydroxy-morphin-6-one (**5**) using ClCOOEt/$K_2CO_3$ did not give the expected *N*-H normorphinan. Instead a skeletal rearrangement occurred and a series of novel indolopropellanes **7a–d** were obtained. Herein, we report the chemistry and pharmacological investigation of these new indole analogs.

The synthesis of indolomorphinan **12** was straightforward by following a slightly modified procedure we reported recently (Scheme 1).[17] The alkaloid, thebaine was oxidized with *m*-CPBA followed by hydrogenation yielding (−)-14-hydroxydihydrocodeinone **8**[9,24,25] in 79% overall yield. The reductive opening of the 4,5-furan *O*-bridge in compound **8** provided 4-hydroxyl-3-methoxy-morphinan-6-one **9**[26] in 90% yield using a slightly modified literature procedure[9,17,26] (activated Zn powder, solid $NH_4Cl$ in MeOH under reflux). A similar Sawa's modification of the Ullmann coupling[17,27–32] between compound **9** and PhBr (Cu/$Cs_2CO_3$/Py) proceeded very sluggishly and transferred the 4-hydroxyl to its phenyl ether (**10**[32]) in 50% yield. After protection of the 6-keto group, the resulting ketal intermediate **11** was subjected to Na/$NH_3$ (liquid) reduction at −78 °C followed by acid hydrolysis to yield the key intermediate 6-oxomorphinan **12**[32] in 84% overall yield (two steps).

*N*-CPM (cyclopropylmethyl) analog **6** was proposed to be prepared by N-demethylation of ketone **12** with chloroformates followed by realkylation of the resulting normorphinan **13** with CPM-Br (Scheme 2). Surprisingly, following a similar procedure we reported before,[17] treating ketone **12** with ClCOOEt/$K_2CO_3$ followed by acidic hydrolysis (concd HCl, HOAc) did not give the expected normorphinan **13**. Instead, a rearranged propellane skeleton **14** and its O-demethylated analog **15** were obtained in 74% and 9% yields, respectively. To explore the mechanism of the rearrangement of 14-hydroxymorphinan **12**, a sequential reaction procedure was conducted. First, morphinan **12** was treated with ClCOOEt and $K_2CO_3$.[17] After chromatography, 14-*O*-ethoxycarbonyl-*N*-carbamate **16** was obtained as the major product in 68% yield, along with a small amount of 14-*O*-ethoxycarbonyl-*N*-meth-

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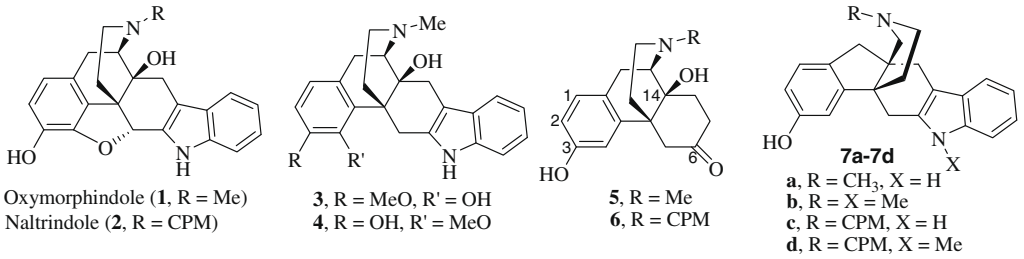
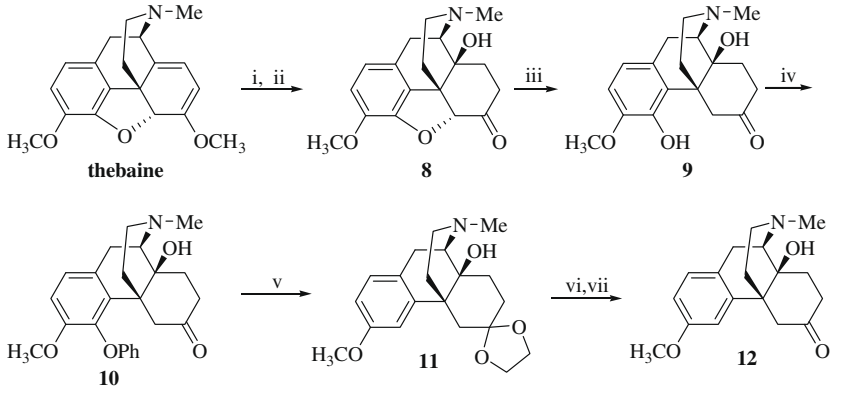
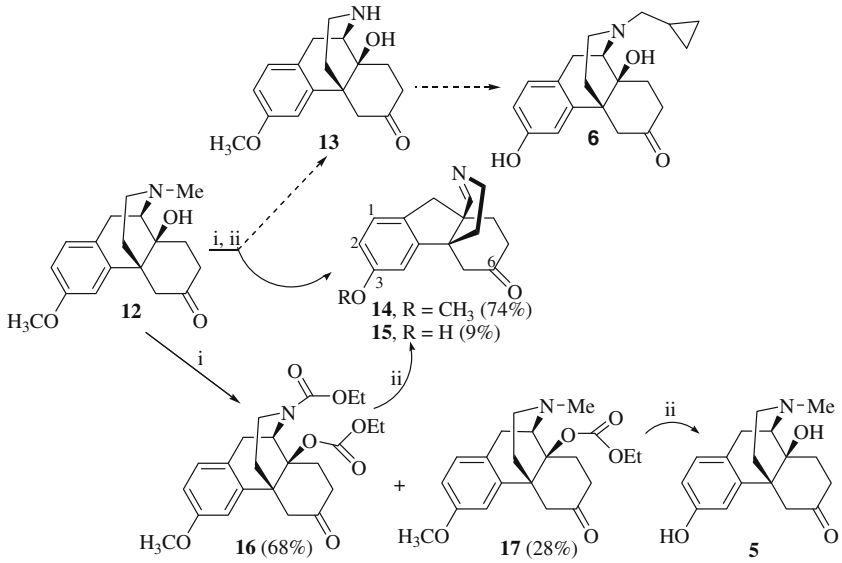



**Figure 1.** Reported indoles **1**–**4** and new indolopropellanes **7a**–**d**.




**Scheme 1.** Reagents and conditions: (i) *m*-CPBA, TFA, 95 °C; (ii) 10% Pd/C, $H_2$, AcOH, 79% for two steps; (iii) Zn (dust), $NH_4Cl$, MeOH, 90%; (iv) PhBr, Cu, $Cs_2CO_3$, Py., 110 °C, 50%; (v) ethylene glycol, $TsOH{\cdot}H_2O$, benzene, reflux; (vi) Na, $NH_3$ (liquid), −78 °C–rt; (vii) HCl (1 M), 84% for three steps.




**Scheme 2.** Reagents and conditions: (i) $K_2CO_3$, ClCOOEt, $ClCH_2CH_2Cl$, reflux, 48 h; (ii) con·HCl/AcOH (2:3), reflux, 24 h.

ylmorphinan **17** (28%). Hydrolysis of carbamate **16** with concd HCl and HOAc under reflux gave the rearranged products **14** and **15**. However, hydrolysis of morphinans **17** under same conditions only yielded **12** and corresponding 3-O-demethylated morphinan **5**, and no skeletal rearranged products were obtained. This result indicated that elimination of 14-OH (OCOOEt) and skeletal rearrangement occurred simultaneously, and the N-carbamation (**16**) is critical to such process. The propellane skeleton of the rearranged products was confirmed by the existence of an imino vinyl proton with chemical shift of 7.7 ppm in the $^1H$ NMR of compounds **14** and **15** and the imino vinyl carbon with chemical shift of 168 ppm in the $^{13}C$ NMR of these compounds. The CD spectra of compound **14** further confirmed the high stereoselectivity of such rearrangement (see Supplementary data). After carefully recrystallization from $CHCl_3$ containing a little MeOH, compound **15** was obtained as a colorless crystalline solid. The X-ray diffraction crystallography of crystal **15** (cd 28350, CCDC code) further secured the absolute configuration of such rearranged product (Fig. 2). Alkylation of imine **14** with $CH_3I$ followed by reduction with $NaBH(OAc)_3$[33] gave *N*-methyl propellane **18**[34] in 92% yield. Reduction

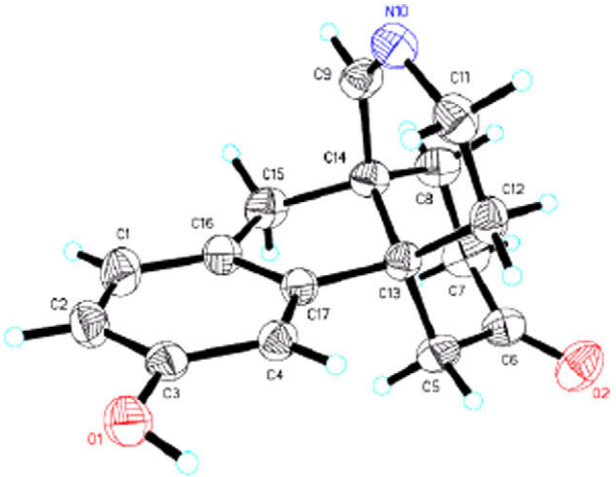
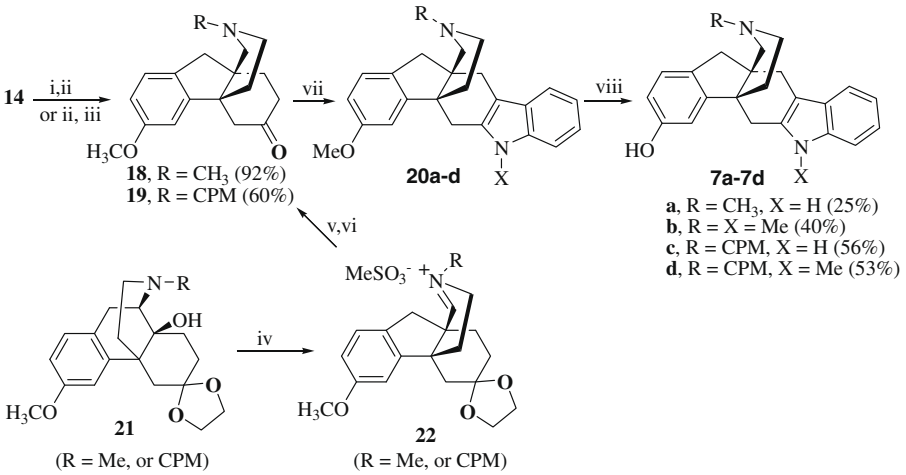



**Figure 2.** ORTEP drawing of compound **15**.

of imine **14** with $NaBH(OAc)_3$ followed by alkylation with CPM-Br provided *N*-cyclopropylmethyl (CPM) propellane **19**[34] in overall 60% yield (Scheme 3). It has to be pointed out that during our study, Nagase et al. recently reported[34] a very similar rearrangement of *N*-alkyl-morphinan-6-ketals **21** (Scheme 3). In their Letter,[34] ketals **21** were treated with NaH and MsCl leading to a skeletal rearranged iminium salts **22** which were stably crystallized. This unusual salt **22** was then used to prepare propellanes **18** and **19** by $NaBH_4$-reduction followed by acid hydrolysis (Scheme 3). Although both rearrangements gave same products, quaternated ammonium salt **22** is the key intermediate in Nagase's report, whereas our protocol involved carbamate **16** as the rearrangement precursor.

With ketones **18** and **19** as the key intermediates, indolopropellanes **7a–d** were prepared in 25–56% isolated yields by treating ketones **18** and **19** with $PhNHNH_2$·HCl or $PhNCH_3NH_2$·HCl in refluxing EtOH followed by O-demethylation with $BBr_3$ (Scheme 3). The low yields are probably due to the high polarity of these compounds which causes difficulty in isolation and purification.

The new synthetic indolopropellanes **7a–d** were evaluated for their binding affinity at all three opioid receptors (μ, δ, and κ) using a previously reported procedure.[17,35,36] The corresponding MeO-precursors **20a–c** were also screened for comparison. Data for indoles **2**,[16,18] **3**,[16] **4**[16] were directly taken from corresponding references for comparison. The results are summarized in Table 1.




**Scheme 3.** Reagents and conditions: (i) MeI, reflux; (ii) $NaHB(OAc)_3$, $CH_2Cl_2$, −40 to −5 °C; (iii) CPM-Br, $NaHCO_3$, DMF, 70 °C, 48 h; (iv) MsCl, NaH, THF; (v) $NaBH_4$, MeOH; (vi) HCl (1 N); (vii) $PhNHNH_2$·HCl or PhNMeNH2·HCl, TsOH, EtOH, reflux; (viii) $BBr_3$ (1 M, $CH_2Cl_2$), −78 °C, then MeOH.

**Table 1**
$K_i$ values inhibition of δ, κ and μ opioid binding to CHO membranes by novel compounds[a]

| Compd | $K_i$ (nM) ± SE | | | Selectivity | | |
|---|---|---|---|---|---|---|
| | [$^3$H]naltrindole (δ) | [$^3$H]DAMGO (μ) | [$^3$H]U-50,488 (κ) | δ/κ | δ/μ | κ/μ |
| β-FNA | – | 1.59 ± 0.08(1.03[b]) | – | – | – | – |
| **2** (NTI) | 1.97 ± 0.35(1.6[c],0.2[d]) | 151 ± 14[c] | 75 ± 7[c] | – | – | – |
| **3**[d] | 21.8 ± 7.0 | 1850 | 3160 | 145 | 85 | 0.6 |
| **4**[d] | 4.50 ± 0.5 | 474 ± 220 | 582 ± 160 | 129 | 105 | 0.8 |
| **20a** | 765 ± 226 | 1820 ± 396 | 5120 ± 860 | 6.7 | 2.4 | 0.4 |
| **20b** | >10 μM | 713 ± 151 | 3810 ± 333 | – | – | 0.2 |
| **20c** | 6650 ± 1880 | 1420 ± 278 | 2550 ± 726 | 0.4 | 0.2 | 0.6 |
| **7a** | 1120 ± 250 | 104 ± 31.0 | 1190 ± 285 | 1.1 | 0.09 | 0.09 |
| **7b** | 268 ± 65 | 40.2 ± 11.8 | 1120 ± 136 | 4.2 | 0.2 | 0.04 |
| **7c** | 2550 ± 1370 | 523 ± 175 | 704 ± 217 | 0.3 | 0.2 | 0.7 |
| **7d** | 1790 ± 510 | 469 ± 96.7 | 1520 ± 108 | 0.8 | 0.3 | 0.3 |

[a] CHO membranes, 0.5 mg of protein/sample, were incubated with 12 different concentrations of the compounds in the presence of receptor-specific radioligands at 25 °C, in a final volume of 1 mL of 50 mM Tris–HCl, pH 7.5. Nonspecific binding was determined using 10 μM naloxone. Data are the mean values SEM from three experiments, performed in triplicate.
[b] Data were from Ref. 4.
[c] Data were from Ref. 18.
[d] Data were from the Ref. 16.

**Table 2**
$E_{max}$/$EC_{50}$ values for the stimulation of [$^{35}$S]GTPγS binding by novel compounds[a]

| Compd | μ (mean ± SE) $EC_{50}$ (nM)/$E_{max}$ (%) | κ (mean ± SE) $EC_{50}$ (nM)/$E_{max}$ (%) | δ (mean ± SE) $EC_{50}$ (nM)/$E_{max}$ (%) |
|---|---|---|---|
| **7b** | 173.9 ± 26.8/95.7 ± 2.9 | 62.1 ± 13.5/76.2 ± 1.2 | 65.0 ± 17.0/77.3 ± 3.2 |
| **7c** | 33.0 ± 10.0/88.6 ± 1.2 | 67.1 ± 3.0/79.9 ± 1.4 | 10 ± 0.4/91.4 ± 1.4 |

[a] CHO membranes, expressing either the κ or μ receptor, were incubated with varying concentrations of the novel compounds in the presence of 0.8 nM [$^{35}$S]GTPγS. Data are the mean values (SE from three experiments, performed in triplicate.

β-FNA and NTI were also tested in our current assays as reference compounds. Our data are somewhat lower than that reported in the literature (Table 1). Consistent with observation on other indole analogs,[16,17,35,36] all 3-MeO indoles **20a–c** showed poor affinity at all the opioid receptors. The *N*-Me analog **20a** shows moderate affinity and selectivity for the δ receptor, whereas the *N*-CPM analog **20b** prefers the μ receptor. All 3-OH indolopropellanes **7a–d** showed improved affinity and selectivity for the μ receptor than their 3-MeO congeners with $K_i$s of 40–500 nM. *N*-Me indolopropellane **7a** showed potency of 104 nM for the μ receptor and 10-fold selectivity against both κ and δ receptors. Masking the indole-NH moiety with Me-group (**7b**) caused a 2.5- and 4-fold improvement in binding at the μ and δ receptors, respectively. *N*-CPM analogs **7c** and **7d** displayed similar affinity (523 and 469 nM) for the μ receptor, while indole **7c** is twofold more potent than the *N*-Me protected indole **7d** at the κ receptor. In this regard, indole **7b** is the most potent propellanes at the μ receptor with a $K_i$ value of 40 nM among the skeletal rearranged morphinans series.

Compounds **7b** and **7c** with highest binding affinity for the μ receptors were selected for stimulation of [$^{35}$S]GTPγS binding studies (Table 2) to determine agonistic properties. Both indolopropellanes **7b, c** showed full agonistic activity at all three receptors. However, in comparison to compound **7c**, the higher binding of **7b** at the μ receptor was not relevant to higher efficacy. The former compound (**7c**) has an $EC_{50}$ value of 33 nM, fivefold more potent than the latter compound (**7b**).

In conclusion, a series of skeletal rearranged indolopropellanes **7a–d** were obtained through a typical N-demethylation approach of 3-methoxy-*N*-methyl-14-hydroxy-morphinan-6-one **12** followed by alkylation, reduction and Fischer indole cyclization. These novel compounds generally displayed moderate binding potency and selectivity at the μ receptor. The most potent compound in this series is compound **7b**, which has $K_i$ value of 40 nM at the μ receptor, and is 6- and 25-fold more potent against δ and κ receptors, respectively. All these compounds displayed good agonistic activity at the μ receptor. The different binding and receptor selectivity profiles of these indolopropellanes suggest that the new propellane skeleton has a different binding mode favorable for the μ opioid receptors, compared to the δ-selective indoles **1**–**4**.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.06.093.

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