Brief Articles

14-Amino, 14-Alkylamino, and 14-Acylamino Analogs of Oxymorphindole. Differential Effects on Opioid Receptor Binding and Functional Profiles

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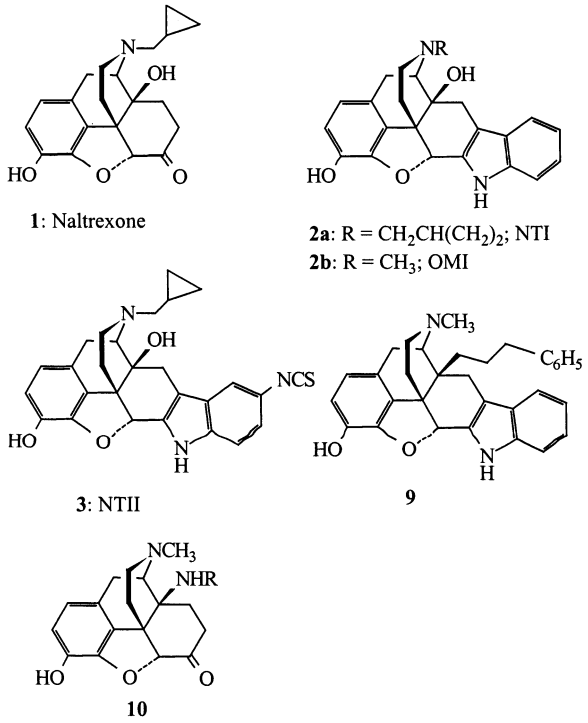
The 14-amino analogue of oxymorphindole (OMI) was synthesized and found to possess δ-opioid binding affinity and selectivity similar to OMI. Substitution of the amino group with alkyl, arylalkyl, and acyl groups had relatively little effect on δ-affinity but δ-selectivity was reduced. In functional assays the 14-phenylacetylamino derivative **6d** was a selective δ-agonist whereas the phenethylamino analogue **5d** was a μ-agonist and low efficacy δ partial agonist that warrants further investigation as an analgesic with low tolerance and dependence.

Introduction

The search for agonists and antagonists selective for each of the three types of opioid receptor, μ, κ, δ, has engaged the interest of medicinal chemists for over 20 years because of their potential usefulness as therapeutic agents and pharmacological tools.[1−3] The message-address concept has been used to design ligands selective for δ and κ receptors by elaborating the structure of the modestly selective μ antagonist naltrexone (**1**). δ-Receptor selectivity was achieved in indolomorphinan structures, notably naltrindole (**2a**), still the most widely used δ-antagonist, and oxymorphindole (**2b**), a selective δ partial agonist, together with the isothiocyanate derivative (**3**), a selective irreversible δ-antagonist.[4−10]

δ-Agonists have antinociceptive effects in animals but show little evidence of dependence, constipation, or respiratory depression, which are unwanted effects of μ analgesics. They have been shown to stimulate respiration[11] and to have antidiarrhoeal effects possibly due to an increase in absorption and decrease in secretion of salts and water.[12] Stimulation of the immune system by δ-agonists has been demonstrated in vitro[13] and in human subjects.[14] δ-Antagonists are able to reduce alcohol intake in rats[15,16] and to reduce the behavioral effects of cocaine and amphetamine.[17−19] They are immunosuppressive[20−23] and antitussive.[24−26] In addition, δ-antagonists are able to suppress the development of tolerance and physical dependence induced by μ-agonists, e.g., morphine.[27,28] This lead to interest in compounds with mixed μ agonist and δ-antagonist actions with potential to be effective analgesics lacking the propensity to produce tolerance and dependence.[29−31]

Our interest in opioid δ-ligands was particularly directed to the analgesic potential of δ-agonists and μ-agonist/δ-antagonists. Thus we targeted analogues of oxymorphindole (**2b**) in which the 14-OH group was replaced by amino (**4**) which was then alkylated (**5**) and acylated (**6**). The 17-*N*-methyl series was chosen to enhance δ-efficacy; introduction of an aryl group into the 14-substituent could also have this effect on δ-efficacy, but it may also enhance μ affinity as it does in the related ketones (**10**).[32]



Synthesis

14-Amino-7,8-dihydrocodeinone (**7**)[33,34] was reacted with phenylhydrazine in the Fischer indole synthesis to give 14-aminocodeindole (**8**) which was acylated with the appropriate acyl chloride in dichloromethane in the

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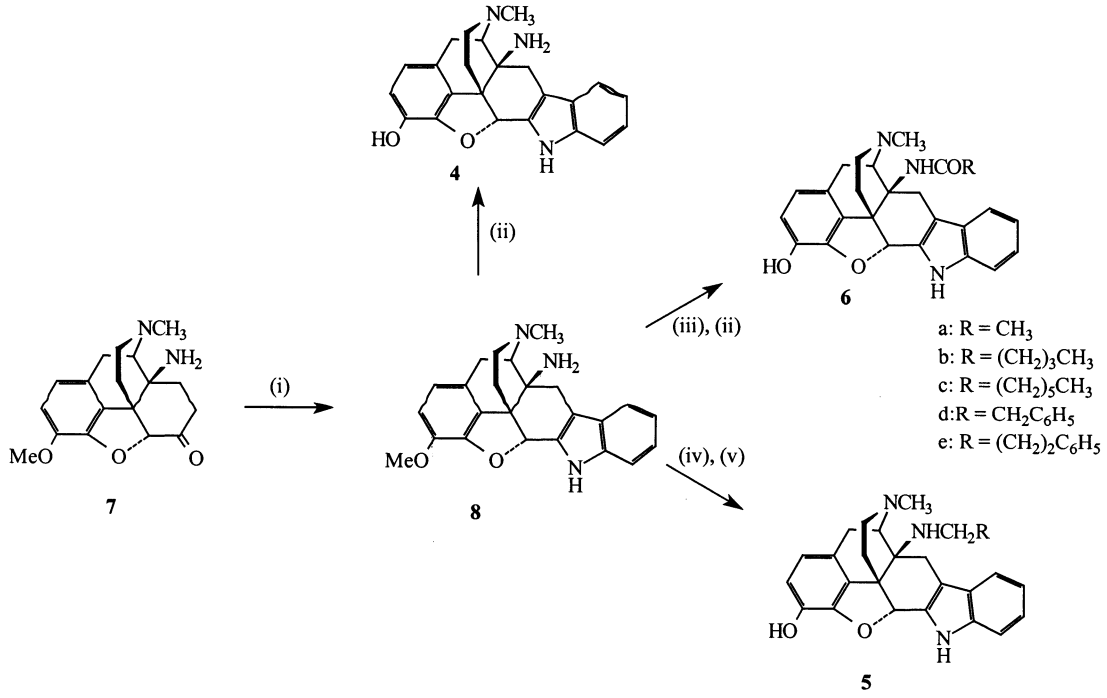
Scheme 1[a]



[a] (i) $C_6H_5NHNH_2$, HOAc/HCl (ii) BBr_3, DCM, −78 °C (iii) RCOCl, DCM, TEA (iv) RCH_2I, CH_3CN, $NaHCO_3$, sealed tube, 120 °C (v) PrSNa, HMPA, 110 °C.

presence of triethylamine to give the acylamino derivatives; these were 3-O-demethylated with BBr_3 to give the 14-acylaminomorphindoles (**6**) (Scheme 1). The 14-alkylaminomorphindoles (**5**) were prepared from **8** by reaction with the alkyl iodides and sodium bicarbonate in acetonitrile in a sealed tube at 120 °C to give the 14-alkylaminocodeindoles which were 3-O-demethylated to **5** with sodium propanethiolate in hexamethylphosphoramide at 110 °C (Scheme 1). BBr_3 gave poor yields in the 3-O-demethylation of the 14-alkylaminocodeindoles.

Results and Discussion

The new ligands were evaluated in receptor binding assays in recombinant human opioid receptors transfected into Chinese hamster ovary (CHO) cells by displacement of [^{3}H]Cl-DPDPE (δ), [^{3}H]-U69593 (κ), and [^{3}H]DAMGO (μ).[37] 14-Aminomorphindole (**4**) showed high affinity for δ with 139-fold selectivity over κ and 365-fold selectivity over μ. When compared to equivalent values for OMI,[36] the 14-amino analogue had half the δ affinity but fairly similar selectivity (Table 1); however, the procedures in the μ and δ binding assays were rather different so that the comparison is only approximate. Alkylation of the amino group (**5a**,**b**) resulted in slightly higher δ-affinity but greater increases in κ and μ affinities, resulting in lower δ-selectivity, particularly over μ (Table 1). The phenethylamino- (**5d**) and phenylpropylamino (**5e**) derivatives had δ-affinity similar to the amino and alkylamino derivatives but even lower δ-selectivity, with **5d** having almost equal δ and μ affinity. Thus alkylation of 14-aminomorphindole had very little effect on δ-affinity but κ and μ affinity markedly increased with the size of substituent, particularly in the arylalkyl derivatives (**5d**,**e**). The acylaminomorphindoles (**6b**,**d**,**e**) had slightly lower δ-affinity than the equivalent alkylamino derivatives. The pentanoylaminomorphindole (**6b**) had very low κ-affinity resulting in 350-fold selectivity for δ over κ. Otherwise selectivities for δ receptors for the 14-acylamino derivatives (**6**) were similar to those in series **5**. The relative lack of sensitivity of δ-affinity in **4** and series **5** and **6** to different sizes and nature of substituents suggests that the NH group may be involved in a hydrogen bonding interaction with the δ-opioid receptor. This was confirmed by comparison of the binding profiles of **5d** and the 14-(3′-phenylpropyl)morphindole **9**[35] in which the NH of **5d** is replaced by CH_2. **9** had highest affinity for μ with 5-fold selectivity for μ over δ and 13-fold selectivity for μ over κ (Table 1). The δ-affinity of **9** was 20-fold lower than for **5d** whereas the μ and κ affinity was only 3−4-fold lower.

Table 1. Binding Affinities of 14-Aminomorphindole (**4**) and Derivatives (**5**, **6**) to Recombinant Human Opioid Receptors

	K_i (nM)				
structure	δ	κ	μ	κ/δ	μ/δ
4	2.88 ± 0.82	399 ± 30.5	1051 ± 241	139	365
5a	0.73 ± 0.18	63.8 ± 10.9	76.3 ± 14.8	87	105
5b	1.39 ± 0.16	36.1 ± 5.6	37.2 ± 3.2	26	27
5d	1.10 ± 0.18	13.8 ± 0.78	1.68 ± 0.02	13	1.5
5e	1.95 ± 0.15	7.79 ± 0.34	10.2 ± 0.98	4	5
6b	2.07 ± 0.51	723 ± 149	51.1 ± 2.0	349	25
6c	10.3 ± 2.7	409 ± 1.4	33.4 ± 0.27	40	3.2
6d	6.55 ± 2.4	148 ± 58	29.3 ± 4.8	23	4.5
6e	4.23 ± 0.62	24.5 ± 6.4	9.61 ± 2.2	5.8	2.3
9[a]	23.6 ± 2.6	63.3 ± 16.4	4.91 ± 0.47	2.7	0.2
NTI (**2a**)	0.2 ± 0.05	10.1 ± 0.65	6.3 ± 2.3	50.5	31.5
OMI (**2b**)[b]	1.28 ± 0.26	396 ± 75	363 ± 137	309	284
DPDPE	1.7 ± 0.1	>10000	504 ± 10	5880	296
NTX (**1**)	10.8 ± 3.0	0.4 ± 0.1	0.2 ± 0	0.037	0.019
DAMGO	300 ± 59	305 ± 46	0.5 ± 0.05	1.0	1.7×10^{-3}
norBNI	5.7 ± 0.9	0.2 ± 0.05	21.0 ± 5.0	0.035	3.68
U69,593	>10000	0.3 ± 0	1145 ± 335	$<3 \times 10^{-5}$	<0.11

[a] Data from ref 35. [b] Data from ref 36.

The morphindoles were evaluated in opioid receptor functional assays involving stimulation of [^{35}S]GTPγS binding in recombinant human opioid receptors trans-

Table 2. Stimulation of [^{35}S]GTPγS Binding in Recombinant Human Opioid Receptors

	δ		κ		μ	
structure	EC_{50} (nM) or (K_e/nM)[a]	% stim	EC_{50} (nM) or (K_e/nM)[b]	% stim	EC_{50} (nM) or (K_e/nM)[c]	% stim
4	8.6 ± 4.6	38	(86.8 ± 21.5)	ANT	—[d]	
5a	0.33 ± 0.12	43	(98.4 ± 11.1)	ANT	184 ± 54	50
5b	4.71 ± 0.26	36	936 ± 8.2	33	272 ± 38	40
5d	0.95 ± 0.05	33	16.4 ± 1.7	74	5.33 ± 2.4	93
5e	0.87 ± 0.21	37	27.2 ± 9.8	65	45.1 ± 13	50
6b	3.3 ± 0.7	74	(56.9 ± 23)	ANT	149 ± 32	31
6c	19.0 ± 8.8	55	(57.3 ± 13.1)	ANT	51.4 ± 3.4	44
6d	1.2 ± 0.1	89	99.6 ± 20	36	95.0 ± 1.1	53
6e	1.4 ± 0.25	72	(9.5 ± 2.4)	ANT	5.2 ± 1.65	27
9[e]	7.53 ± 0.58	65	96.5 ± 0.9	67	21.5 ± 7.7	91
NTI (**2a**)	(0.11 ± 0.005)	ANT	(4.95 ± 0.32)	ANT	(4.26 ± 0.33)	ANT
DPDPE	1.3 ± 0.5	100	>10000		>10000	
NTX (**1**)	(5.44 ± 0.75)	ANT	(1.86 ± 0.16)	ANT	(0.59 ± 0.04)	ANT
DAMGO	>10000		4365 ± 1660	62	13.7 ± 5.28	100
norBNI	(4.42 ± 0.38)	ANT	(0.039 ± 0.004)	ANT	(18.9 ± 1.8)	ANT
U69593	>10000		26.1 ± 10.7	100	>10000	

[a] K_e (nM) vs DPDPE. [b] K_e (nM) vs U69593. [c] K_e (nM) vs DAMGO. [d] Not determined since K_i > 1000 nM. [e] Data from ref 35.

fected into CHO cells. In these assays, efficacy is measured against standard δ (DPDPE), κ (U69593), and μ (DAMGO) agonists.[37,38] Ligands without efficacy, or those with efficacy <20%, are investigated as antagonists with potency recorded as K_e values (Table 2). 14-Aminomorphindole (**4**) and the alkylamino- and arylalkylaminomorphindoles (**5**) showed δ-partial agonist effects of remarkably similar efficacy (33−43%); **4** and the longer chain alkylamino derivative (**5b**) had lower potency than the ethylamino (**5a**) and arylalkylamino (**5d**,**e**) derivatives.

In addition to their δ-partial agonist effects in [^{35}S]-GTPγS assays 14-aminomorphindole (**4**) and the ethylamino analogue (**5a**) were low affinity κ-antagonists and **5b** was a low efficacy and very low potency κ-partial agonist, whereas **5d** and **5e** were moderately potent κ-partial agonists of significant efficacy. The alkyl- and arylalkylaminomorphindoles were μ partial agonists of moderate or low potency with the notable exception of the phenethyl derivative (**5d**) which had high potency in line with its μ binding affinity and was a nearly full agonist. Thus **5d** is a potent μ agonist and an even more potent low efficacy δ-partial agonist. Such low δ-efficacy in vitro would be expected to translate into δ-antagonist activity in vivo[36] giving a profile for **5d** which should produce analgesia with low levels of tolerance and physical dependence.[31,39−41] The other members of the series were δ-partial agonists with substantial selectivity (**5e**) or high selectivity (**5a**,**b**) over κ and μ. The phenylpropyl analogue (**9**) had a similar functional profile to **5d** but with all round lower potency and somewhat higher δ efficacy.

In the GTPγS assay the 14-acylaminomorphindoles (**6b**,**d**,**e**) had higher δ efficacy than the equivalent alkylamino derivatives (**5b**,**d**,**e**) but very similar potencies. The heptanoyl derivative (**6c**) for which there was no alkylamino equivalent was significantly less potent as a δ-agonist. In equivalent GTPγS assays the acylamino derivatives were κ antagonists (**6b**,**c**,**e**) or κ-partial agonists (**6d**), substantially lower in efficacy than the equivalent alkylamino derivatives (**5b**,**d**,**e**). μ-Efficacy of the acylaminomorphindoles (**6**), determined in GTPγS assays, was in the low efficacy partial agonist range; μ potency was modest except for the dihydrocinnamoylamino derivative (**6e**) which had very similar δ- and μ-partial agonist potencies, as did the heptanoylamino derivative (**6c**). δ-Efficacy was substantially higher than μ-efficacy for **6b**,**d** and **6e** and **6b** and **6d** also had selectivity of δ-potency over μ. The most interesting profile among the acylaminomorphindoles (**6**) was that of the phenylacetylamino derivative (**6d**) which was a potent δ-agonist with 80-fold selectivity over κ- and μ-partial agonism. This profile was very different to that of the equivalent alkylamino derivative (**5d**) which was a μ-agonist, low efficacy δ-partial agonist with little δ-selectivity.

Conclusions

It is clear that alkylation or acylation of 14-aminomorphindole has little effect on δ-affinity but markedly increases μ and κ affinity. When the substituent has an aryl group with a two- or three-carbon chain to the amino group (**5d**,**e**), δ-selectivity is all but lost, particularly over μ. Replacement of the amino group of **5d** by methylene (**9**) results in substantial loss of δ-affinity and modest μ selectivity, indicating that the μ preferring phenylpropyl substituent is a dominant binding motif. This also applies to a lesser extent to the phenethylamino group of **5d** and to the dihydrocinnamoylamino group of **6e**. In opioid functional assays the 14-phenylacetylamino derivative (**6d**) was a selective δ-agonist whereas the phenethylamino analogue (**5d**) was a μ agonist and low efficacy δ-partial agonist that warrants further investigation as an analgesic with low tolerance and dependence.

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Supporting Information Available: Procedures for the synthesis of all compounds, including spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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