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Selective δ-Opioid Receptor Ligands: Potential PET Ligands Based on Naltrindole

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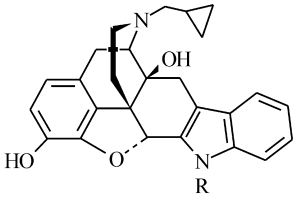
Abstract—Two series of δ-selective ligands related to the prototypic δ-antagonist naltrindole have been prepared and evaluated in opioid binding assays with the aim of developing new PET ligands for the δ-opioid receptor. One compound (**5d**) had significantly higher selectivity than naltrindole, but with substantially reduced binding affinity. For those compounds retaining similar affinity to naltrindole, those having ethyl and fluoroethyl substituents afforded the highest levels of selectivity. However, none of the compounds combined the high level of affinity and selectivity ideally suited to the development of an imaging agent.

Introduction

Selective, non-peptide, competitive antagonists for the δ-opioid receptor have been reported as having possible therapeutic benefits in a number of clinical applications. Naltrindole (NTI: **1**), the standard δ-antagonist has been found to be an immunosuppressant and thus of potential utility in the transplant of organs.[1] It has also been reported to suppress the development of morphine tolerance and physical dependence[2] and to block some of the behavioural effects of cocaine.[3] For these reasons there is continued interest in the development of alternatives to naltrindole, preferably having still higher selectivity for the δ-receptor.



1: R = H, naltrindole
2: R = Me

Important to the further study of δ-opioid receptor function is the development of imaging agents selective for that receptor. Methods such as positron emission tomography (PET) offer a unique means of studying biochemical and pharmacological processes within living beings. The most commonly utilised radioisotopes for PET imaging are C^{11} and F^{18}. Both radioisotopes can often be introduced into a suitable ligand without significant impact on the binding affinity or selectivity. To be successful a radioligand needs not just excellent affinity and selectivity for its target site, but must be able to cross the blood–brain barrier, exhibit a high level of specific binding and should not be metabolised to a large number of labelled metabolites.

Naltrindole remains the standard δ-opioid antagonist and possesses a structure that offers a number of opportunities for the design of new PET ligands. The most detailed SAR studies to date relating to naltrindole have focused on substitutions on the benzenoid ring of the indole moiety. An extensive series of aryl substituted naltrindole analogues have been synthesised,[4,5] with perhaps the major findings being that δ-selectivity is retained by substitution at the C-7′ carbon while introduction of an appropriate basic, or cationic group at C-5′ leads to κ-selectivity.[6]

Schmidhammer and co-workers have studied the effect of substitution at the 14-hydroxy group, synthesising a number of *O*-alkyl derivatives. From this work, it was apparent that a 14-ethoxy group retained δ-selectivity, and was superior to other ether groups such as methoxy

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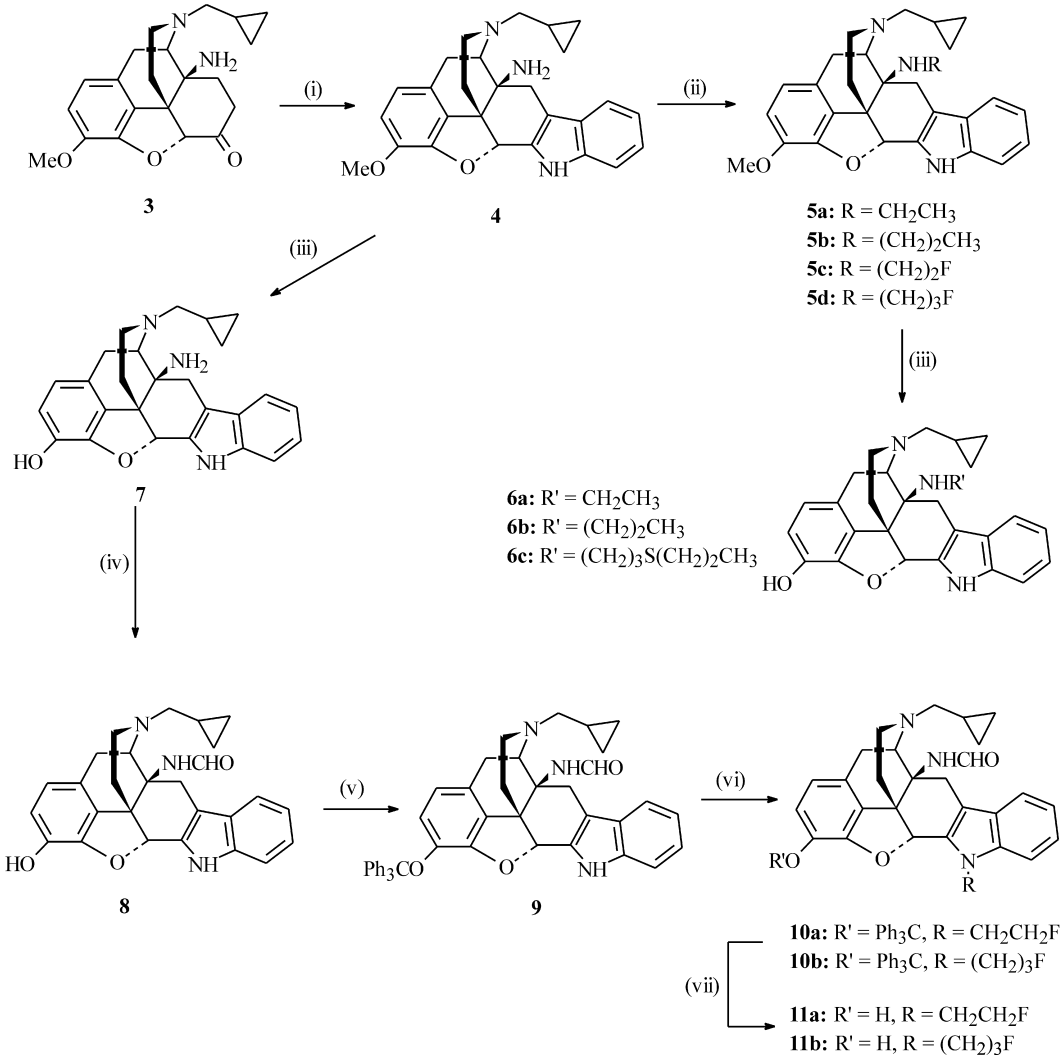
or propyloxy.[7] An alkyl group side chain was of particular interest to us as it allows, with appropriate modification of the chemistry, to introduce a radiolabel into the molecule. However Schmidhammer showed that the 14-hydroxyl group could only easily be alkylated with dimethyl- or diethyl-sulfate, or by an allylic or benzylic alkylating group.[7,8] This limited chemistry clearly reduced the range of options for introduction of a radiolabel. We were therefore interested in determining if alkyl groups such as ethyl and propyl could also be utilised in the more readily alkylated 14-amino series. Additionally, it seemed that the indolic nitrogen would also provide a means of attaching an appropriate side chain† as this modification does not appear to adversely affect selectivity.[9] An example of this latter approach is the δ PET ligand [^{11}C]MeNTI (**2**) studied by the group at Johns Hopkins.[10–14]

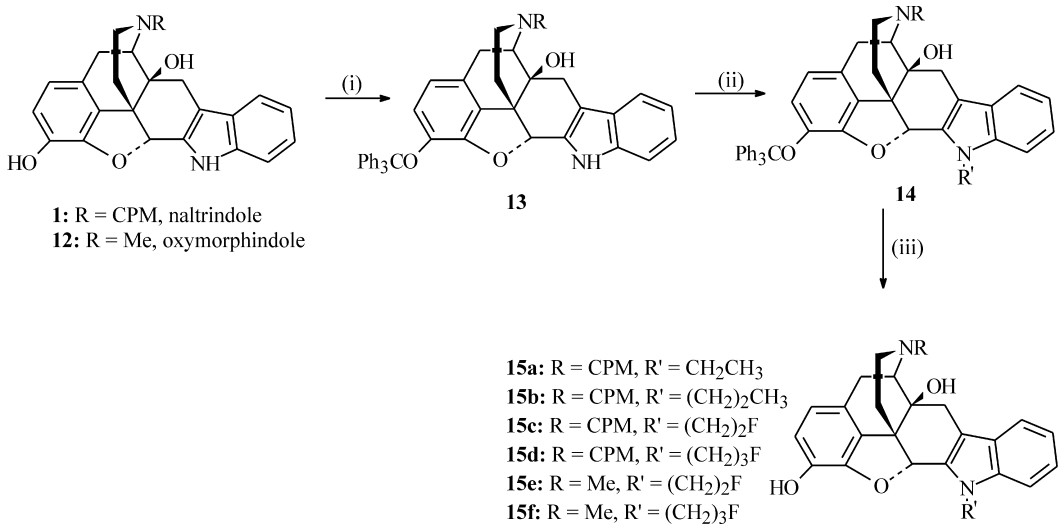
Synthesis

The 14-amino morphindoles (**6**) were prepared from 14-amino dihydrocodeinone (**3**) which is synthesised from *N*-cyclopropylmethylnorthebaine by a previously reported method (Scheme 1).[15] Fischer indole synthesis utilising phenylhydrazine in a 1:1 mixture of HCl and glacial AcOH gave **4** in reproducible yield (55%). In the absence of HCl acetylation of the 14-amino group occurred. Presumably the presence of HCl results in the hydrolysis of any acetylated product to leave only the primary amine (**4**). Alkylation could be achieved in high yield (80–96%) utilising the appropriate alkylhalide at 130 °C in a sealed tube. The alkyl halides used were: $Br(CH_2)_2F$/NaI, $Br(CH_2)_3F$/NaI, CH_3CH_2I, $CH_3(CH_2)_2I$. BBr_3 mediated 3-*O*-demethylation[16] suffered from difficult isolation and poor yields of the desired products



Scheme 1. (i) $PhNHNH_2$·HCl, AcOH/HCl 1:1, heat, 1.5 h, 51%; (ii) RX, MeCN, $NaHCO_3$, 130 °C, sealed tube, 80–96%; (iii) PrSNa, HMPA, 110 °C; (iv) HCO_2H, $CH_3CO_2COCH_3$, 91%; (v) Ph_3CCl, TEA, DMAP, DCM; (vi) NaH, DMF, $Br(CH_2)_nF$; (vii) 33% aq HCO_2H, DCM.

†A preliminary account of this work was made to the European Opioid Conference, Guildford, UK, April 1997.



Scheme 2. (i) Ph_3CCl, TEA, DMAP, DCM; (ii) NaH, DMF, R′-X (X = Br or I); (iii) 50% aq AcOH, DCM.

and for this reason thiolate[17] mediated demethylation was utilised. This cleanly gave the desired products when no fluorine was present in the side chain, but for the fluoroethyl (**5c**) and fluoropropyl (**5d**) analogues it resulted in partial or complete substitution of fluoride by propane thiolate. It was not possible to isolate the products of demethylation for **5c** or **5d** in sufficient quantity for pharmacological testing.

14-Aminocodeindole (**4**) was also utilised in the preparation of 14-formylamido analogues **11a** and **11b** (Scheme 1). Initially demethylation with propane thiolate gave the morphindole (**7**) in good yield (79%) followed by formylation using formic acetic anhydride.[18] Protection of the phenol as the triphenylmethyl ether (**9**) was followed by indolic-N alkylation with NaH and the appropriate alkyl halide ($Br(CH_2)_nF$). Deprotection to leave the phenols was achieved in 33% aq formic acid/dichloromethane.

Indolic *N*-ethyl-, propyl-, fluoroethyl- and fluoropropylnaltrindole analogues (**15a**–**d**) were prepared by alkylation of 3-*O*-triphenylmethylnaltrindole (**13**) using $Br(CH_2)_nF$ or $I(CH_2)CH_3$ followed by deprotection with aqueous acetic acid (Scheme 2). **13** was prepared by tritylation of naltrindole using trityl chloride/triethylamine/DMAP. Analogous derivatives (**15e** and **15f**) of the δ-partial agonist oxymorphindole, where NMe replaces NCPM, were prepared by an identical route.

Results and Discussion

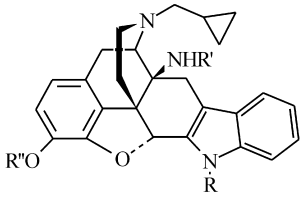
The new ligands were assayed for their ability to displace selective tritiated ligands from guinea pig brain membranes.[19] The radioligands used were [^{3}H]DAMGO (μ), [^{3}H]DPDPE (δ) and [^{3}H]U69593 (κ). Of the 14-aminomorphindole analogues (**6a**–**c**), only **6a** with an ethylamino side chain bound with δ-affinity approaching that of naltrindole (0.77 vs 0.15 nM; Table 1). However, κ and μ affinity was also reduced for **6a** giving a broadly similar selectivity profile to naltrindole. Extension of the side chain by a single methylene unit resulted in a 3-fold further reduction in δ-affinity with no effect at κ or μ, thereby reducing selectivity. The thioether (**6c**) was assayed to determine the effect of further extending the side chain. Whilst δ-affinity remained constant, affinities at κ and μ increased significantly, resulting in very limited δ-selectivity. As would be expected from SAR studies in other series of opioid ligands, the 3-*O*-methyl ethers (**4** and **5a**–**d**; Table 1) were of lower affinity at each receptor compared to their 3-hydroxyl analogues. The 14-amino compound (**4**) was of very low affinity at each receptor, but alkylation provided a dramatic increase in affinity, particularly at δ and μ receptors. Interestingly, in the 3-methoxyl series the propylamino analogues (**5b** and **5d**) were of higher selectivity than their ethylamino counterparts (**5a** and **5c**), reversing the selectivity observed with the 3-hydroxy series and previously reported for naltrindole and its ethers.[7] **5d** proved to be the most selective ligand in this study, but was of too low affinity for consideration as a PET ligand.

Formylation of the 14-amino group led to a compound (**8**) with similar δ-affinity and selectivity as the 14-alkylamino analogues discussed above, indicating that the amino group need not be basic. Subsequent fluoroethylation and fluoropropylation at the indolic nitrogen also had little or no effect on affinity or selectivity of these 14-formylamino analogues.

In the analogues directly related to naltrindole (i.e., having a 14-hydroxyl group) the effects of alkylation at the indolic-N were again relatively minor (Table 2). Ethylation to **15a** gave a compound with a similar binding profile to naltrindole. δ-Selectivity was slightly reduced due to lower δ-affinity, while addition of an extra methylene unit, to **15b**, again caused a further drop in δ-affinity and selectivity. The fluoroalkyl analogues (**15c** and **15d**) behaved similarly with the ethyl analogue having a slightly more favourable profile than the propyl.

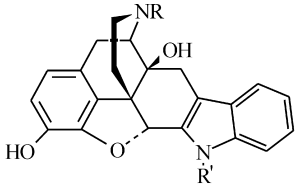
Thus, none of the newly synthesised compounds, or MeNTI (**2**), had an improved binding profile compared

Table 1. Opioid receptor binding affinities of 14-amino analogues of naltrindole



Compound	R	R′	R″	K_i (nM) δ	μ	κ	μ/δ	κ/δ
4	H	H	Me	381±296	14700±4510	7325±3810	39	19
5a	H	CH_2CH_3	Me	27.4±8.8	671.2±446.7	2679±1935	25	74
5b	H	$(CH_2)_2CH_3$	Me	19.0±7.6	5191±776	1784±1339	94	273
5c	H	CH_2CH_2F	Me	10.1±2.3	213.7±69.6	515±62	21	51
5d	H	$(CH_2)_3F$	Me	12.9±2.8	5127±2353	3105±36	397	240
6a	H	CH_2CH_3	H	0.77±0.08	90.3±11.8	57.3±15.3	117	74
6b	H	$(CH_2)_2CH_3$	H	2.41±0.76	124.9±3.9	54.8±22.6	52	23
6c	H	$(CH_2)_3S(CH_2)_2CH_3$	H	1.78±0.48	8.11±3.20	14.5±6.0	5	8
8	H	CHO	H	0.89±0.32	36.2±3.7	26.7±3.4	41	30
11a	$(CH_2)_2F$	CHO	H	0.55±0.15	32.0±2.0	18.0±1.3	58	32
11b	$(CH_2)_3F$	CHO	H	0.82±0.15	20.9±3.5	18.3±2.0	26	9
1: NTI	—	—	—	0.15±0.01	27.5±7.7	14.3±1.1	183	95

Table 2. Opioid receptor binding affinities of naltrindole analogues substituted on the indolic-N



Compound	R	R′	K_i (nM) δ	μ	κ	μ/δ	κ/δ
15a	CPM	CH_2CH_3	0.26±0.05	22.0±8.4	14.0±2.3	85	54
15b	CPM	$(CH_2)_2CH_3$	0.44±0.04	16.4±1.1	11.9±0.3	38	27
15c	CPM	$(CH_2)_2F$	0.24±0.11	16.7±1.3	8.30±1.40	70	35
15d	CPM	$(CH_2)_3F$	0.40±0.10	18.7±0.8	9.84±0.39	47	25
15e	Me	$(CH_2)_2F$	6.44±4.34	30.0±13.5	116.7±11.2	5	18
15f	Me	$(CH_2)_3F$	2.66±1.05	70.7±12.9	200.4±51.1	27	75
1: NTI	CPM	H	0.15±0.01	27.5±7.7	14.3±1.1	183	95
2	CPM	Me	0.49±0.23	39.2±1.9	8.33±0.86	81	17

to NTI. Only **5d** displayed higher selectivity and this was at the expense of substantial loss in affinity. Of those compounds with comparable affinity to NTI, those possessing an ethyl or fluoroethyl group at the 14-position or at the indolic nitrogen displayed greatest selectivity, consistently higher than their propyl analogues. Although the differences were relatively small, the observation that this holds true at both the 14-position (as also reported by Schmidhammer)[7] and at the indolic-nitrogen is intriguing.

Subsequent to our preliminary communication, Mathews et al.[20] disclosed their work with [F-18]fluoroethylnaltrindole (=**15c**). High binding affinity (0.09 nM) and high selectivity (>100-fold over μ and κ) in rat brain homogenates was reported. Although we did not find quite the same level of affinity or selectivity for **15c** in our study, together with **6a**, **15c** had the most promising binding profile. However, these results would suggest that, in fact, neither the newly synthesised compounds nor the current PET ligands has the level of selectivity ideally suited for imaging studies.

Acknowledgements

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