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SYNTHESIS AND OPIOID BINDING PROPERTIES OF 2-CHLOROACRYLAMIDO DERIVATIVES OF 7,8-DIHYDROMORPHINANS

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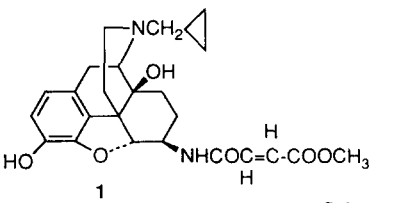
Abstract: 14β-2-chloroacrylamido-7,8-dihydromorphinones **7** and **8** and the corresponding 6β-7,8-dihydromorphinans **19** and **20** were prepared and the binding affinities to μ, δ and κ receptors in bovine striatal membranes were determined. Only **20** produced wash-resistant inhibition of m binding despite the fact that it formed adducts with *N*-acetylcysteine at pH 10 and not at pH 8. Copyright © 1996 Elsevier Science Ltd

β-FNA **1** was the first non-equilibrium ligand to be designed, synthesized and studied pharmacologically.[1] Since that time there have been other types of opioid ligands described. 14β-Cinnamoyl derivatives,[2,3] thiols and disulfides,[4,5] and bromoacetamides[6] have been shown to bind irreversibly to μ opioid receptors, presumably by binding to the thiol group present on the receptor.[7,8] Portoghese[9] and his group and, independently, Archer et al.[10] reported the preparation of **2**. Although both groups agreed that **2** was a non-equilibrium ligand the compound was not well-characterized pharmacologically. Here we report the synthesis and opioid binding properties of a series of chloroacrylamido compounds related to **2**.



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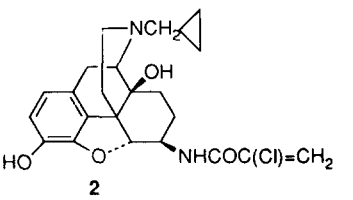
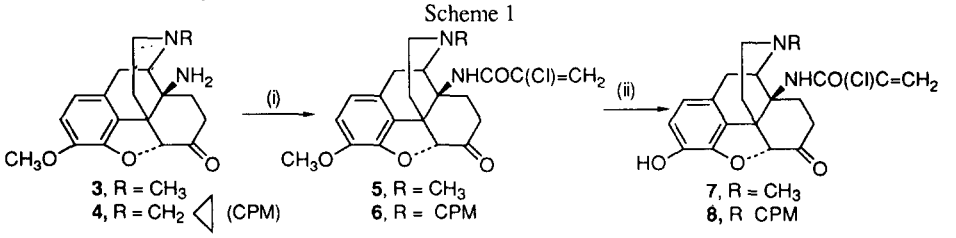


2

Scheme 1



3, R = CH_3
4, R = CH_2 ◁ (CPM)

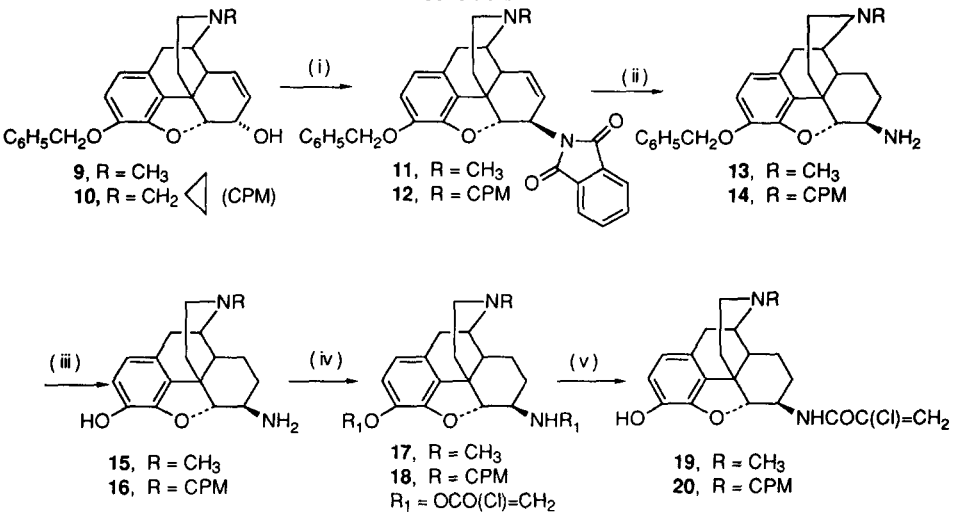
5, R = CH_3
6, R = CPM

7, R = CH_3
8, R CPM

(I) CH_2=C(Cl)COCl, Et_3N, CH_2Cl_2, 0° C, 30 min, 80%, (ii) BBr_3, $CHCl_3$, -5°C, 10 min, 83%

The synthesis of 14β-(2-chloroacrylamido)-7,8-dihydromorphinone **7** and the corresponding *N*-cyclopropylmethyl-7,8-dihydronormorphinone **8** is shown in Scheme 1. The 14β-amino-7,8-dihydrocodeinones **3** and **4** were prepared from thebaine and *N*-CPM-northebaine, respectively, by the procedure described previously.[11] The yields quoted in the footnote in Scheme 1 are for the synthesis of **7**. Coupling of **3** with 2-choroacryloyl chloride gave **5** which on demethylation with BBr_3 furnished the target ligand **7**. The N-CPM derivative **8** was prepared in an analogous manner. The synthesis of the 6β compounds is shown in Scheme 2. 3-O-benzylmorphine **9** [12] was converted to the corresponding *N*-CPM derivative **10** by demethylation

Scheme 2



(i) Phthalimide, Ph_3P, $EtO_2CN{=}NCO_2Et$, benzene, 25° C, 24 hr, 72%;(ii) a) N_2H_4, EtOH, 45 min b) 2M AcOH, 25°C 2 hr, 92%: (iii) Pd/C, H_2, 40 psi, 12 hr, 93%; (iv) $CH_2{=}C(Cl)$-COCl; CH_2Cl_2, Et_3N, 5°C 30 min, 85%; (v) aq Na_2CO_3, MeOH, 5°C, 1 hr, 89%. (The yields cited are for preparation of **19**.)

followed by treatment with cyclopropylcarbonyl chloride and subsequent reduction of the amide with lithium aluminum hydride.[13] The preparation of the 6β-amino compounds **15** and**16** was carried out by a slight modification of the procedure of Simon, Hosztafi and Makleit.[14] Compounds **9** and **10**, were treated with phthalimide, triphenylphosphine , diethyl azodicarboxylate to furnish the 6β-phthalimido compounds **11** and **12**, which were hydrolyzed in dilute hydrazine

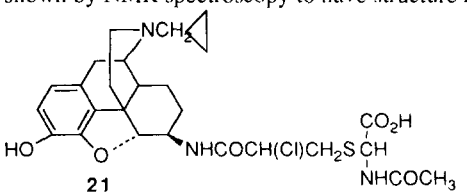
to afford **13** and **14**. The reduction to **15** and **16** was carried out in the presence of palladium on charcoal. Treatment with 2-chloroacryloyl chloride gave the mixed ester-amides **17, 18** which were hydrolyzed with dilute sodium carbonate to the target compounds, **19** and **20**.

The binding to μ, δ and κ receptors in bovine striatal membranes was carried out as descibed previously.[5] The results are summarized in Table 1.

TABLE 1. IC_{50} Values for the Inhibition of μ, δ and k Binding to Bovine Striatal Membranes by the Affinity Ligands.

Compound	IC_{50} (nM) 0.25 nM [^{3}H] DAMGO μ	1nM [^{3}H] U69593 δ	0.2 nM [^{3}H] pCl-DPDPE κ
7	5.8	178	184
8	23.5	177	501
19	0.56	45	26
20	0.21	0.53	1.53

The 6β-substituted compounds, **19** and **20** were more potent affinity ligands than the 14β-substituted compounds **7** and **8.** Only **20** showed wash-resistant inhibition of μ binding. A qualitative test for binding of the affinity ligands to N-acetylcysteine was carried out as follows. The ligands and *N*- acetylcysteine were dissolved in an aqueous buffers at pH 8 and 10 with the aid of a minimum amount of methanol and TLCs were carried out until the reactions appeared to be over. The solvent system (CH_2Cl_2/CH_3OH [19:1]) was such that the ligand migrated with the solvent and the *N*-acetylcysteine and the adducts did not. At pH 10, all the ligands appeared to form adducts with the *N*-acetylcysteine but only **7** and **8** did at pH 8. The phenomenon for which we have no adequate explanation is why only **20** which formed adducts at pH 10 and not at pH 8 did not wash out of the bovine striatal membrane preparations. The adduct from *N*-acetylcysteine and **20** was isolated and shown by NMR spectroscopy to have structure **21.**



21

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