

## SYNTHESIS OF NOVEL ANALOGUES OF THE DELTA OPIOID LIGAND SNC-80 USING $\text{AlCl}_3$ -PROMOTED AMINOLYSIS

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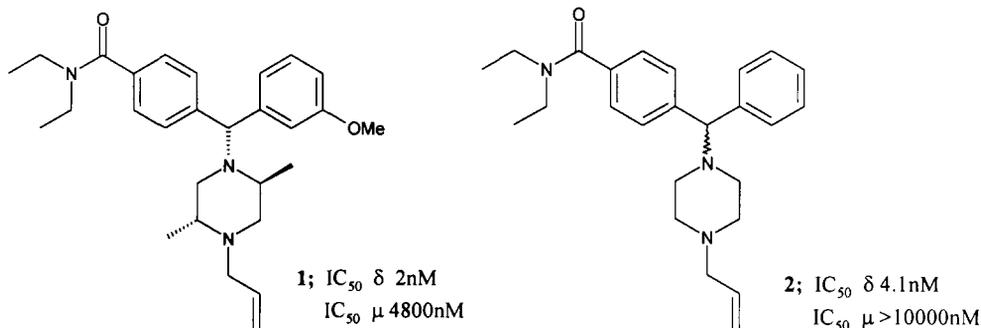
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**Abstract:**

Two focused libraries of delta opioid ligands were synthesised using  $\text{AlCl}_3$  facilitated aminolysis. Several compounds were identified with DOR binding affinities higher or similar to SNC-80. A novel acyclic derivative of SNC-80 produced antinociception in the acetic acid abdominal constriction test, which is at least partially mediated via the  $\delta$ -opioid receptor. © 1999 Elsevier Science Ltd. All rights reserved.

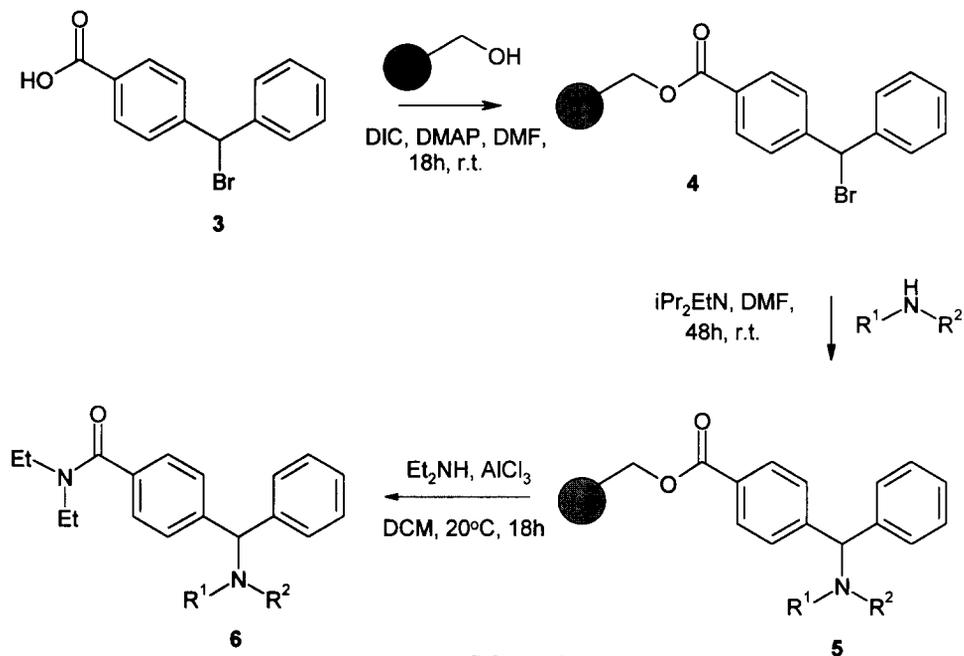
Aluminium chloride-assisted aminolysis<sup>1</sup> allows the synthesis of amides from resin-bound esters under mild reaction conditions in good yield and purity. We have now applied this methodology to the synthesis of libraries of delta opioid ligands. Delta opioid receptor (DOR) agonists have been demonstrated to produce antinociception in a range of animal models,<sup>2,3</sup> implying that the DOR is an attractive target for the design of novel analgesics. SNC-80 **1** was recently reported to show good affinity and selectivity at the DOR.<sup>4</sup> In our initial SAR study around SNC-80, we found that neither the methoxy group nor the two methyl groups on the piperazine were essential for high affinity at the DOR or selectivity over the mu opioid receptor (MOR):



It was decided to synthesise a lead optimisation library containing twenty diverse analogues of compound **2**, in which the piperazine moiety was replaced by various substituted piperazines and ethylenediamines. Since the diethyl amide group of **2** is important for high affinity, it was decided to keep this functionality constant. Carboxylic acid **3**<sup>5</sup>, was coupled to Wang resin using diisopropylcarbodiimide (DIC) and 4-(N-dimethylamino)pyridine (DMAP) (Scheme 1). The Wang resin-bound bromo ester **4** was then reacted with various substituted piperazines and diamines<sup>6</sup>. Aminolysis of Wang resin-bound esters normally requires prolonged heating, which often results in product decomposition and, consequently, poor yield and purity. We found that in the presence of  $\text{AlCl}_3$ , the aminolysis of **5** occurred at room temperature to give amides **6**. Crude material from the cleavage was purified in parallel by solid phase extraction (SPE) to afford the products in an average 46% yield.

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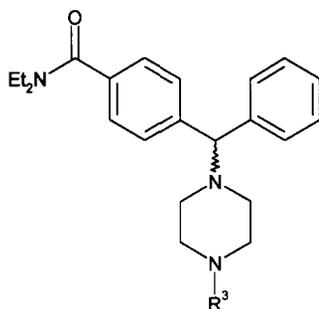
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**Table 1:** Yields and  $\delta$  opioid binding affinities<sup>7</sup> for some library 1 compounds

Compound	R <sup>1</sup> -N-R <sup>2</sup>	% Yield	IC <sub>50</sub> $\delta$ (nM)
6{1} (2)		57	8
6{2}		55	13
6{3}		41	29
6{4}		86	42
6{5}		25	70
6{6}		34	120
6{7}		15	845

## Discussion

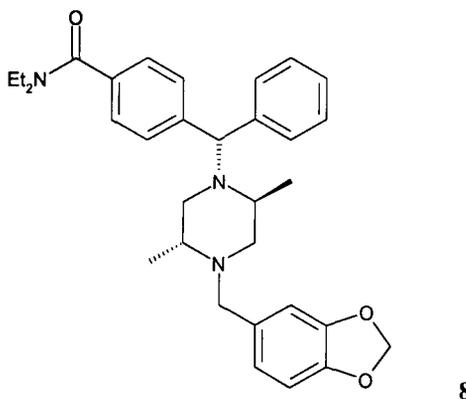
Representative members of library 1 are shown in Table 1. None of the compounds in Library 1 were as active as compound **2**. The highest binding affinities were found for cyclic diamines, eg. piperazine **6{1}** and homopiperazine **6{2}**. The most active open chain diamine analogue was **6{5}**. Since substantial modification of the piperazine moiety failed to produce a compound with DOR binding affinity higher than for **2**, we decided to concentrate upon the region around the lower piperazine nitrogen. Therefore, a 46 compound library was prepared by the same synthetic route using various N-substituted piperazines, (Scheme 1). Representative analogues from the library are listed in Table 2. Having affinity 4 to 5 times greater than compound **2**, **7{2}** and **7{3}** were identified as the most active compounds from library 2 in the DOR binding assay. **7{2}** in particular also showed greater selectivity over the  $\mu$  opioid receptor than compound **2**. Several other compounds from Library 2 showed affinities similar to **2**, indicating a wide tolerance in the SAR around the lower piperazine nitrogen in terms of both polarity and steric bulk.



**Table 2:**  $\delta$  and  $\mu$  opioid binding affinities<sup>7</sup> for selected library 2 compounds

Compound	R <sup>3</sup> -N	IC <sub>50</sub> $\delta$ (nM)	IC <sub>50</sub> $\mu$ (nM)
<b>7{1}</b> ( <b>2</b> )		8	>50000
<b>7{2}</b>		1.4	>10000
<b>7{3}</b>		1.8	6236
<b>7{4}</b>		5.5	>10000
<b>7{5}</b>		5.8	-
<b>7{6}</b>		10	>10000
<b>7{7}</b>		11.4	>10000

Since the structural simplification of SNC-80 to the lead compound **2** resulted in a slight reduction in the binding affinity, it was reasonable to assume that the analogue of **1** with the allyl group replaced by a piperonyl group might show affinity higher than **7{2}**. Therefore, the chiral compound **8** was synthesised, following the reported route used for the synthesis of SNC-80.<sup>8</sup> In the DOR binding assay **8** showed 4 fold higher affinity than **1**(Table 3), whereas selectivity over the MOR was similar for **8** (1300 fold) and SNC-80 **1** (2400 fold).



SNC-80 **1** was found to be antinociceptive when administered subcutaneously (s.c.) in the acetic acid-induced abdominal constriction model in mice with an ED<sub>50</sub> of 30.4 μmol/kg (Table 3).<sup>9,10</sup> This activity was completely abolished by naltrindole, a selective antagonist at the DOR. Compound **2** was less active in this test, presumably due at least in part to its lower affinity at the DOR. The compound also exhibited lower potency in the mouse vas deferens (MVD) and hamster vas deferens (HVD) functional assays.<sup>11,12</sup> Despite the high affinity of compounds **7{2}** and **8**, both were inactive in the *in vivo* model at concentrations up to 200 μmol/kg. Although **7{2}** clearly behaves as an agonist and has higher potency in the MVD than **2**, the lower *in vivo* activity may suggest rapid metabolism or a problem with CNS penetration arising from the 3,4-(methylenedioxy)-benzyl group. This conclusion is supported by the fact that compound **8**, despite being much more active than **2** in the MVD and HVD, also lacks any *in vivo* activity in the acetic acid model and also contains the 3,4-(methylenedioxy)-benzyl group. In contrast, compound **6{5}**, which has much lower affinity at the DOR and low efficacy and potency in the MVD, was surprisingly active *in vivo*. However, whilst naltrindole pretreatment only partially inhibited the antinociception, naloxone produced marked inhibition, confirming that the response is opioid-mediated, although apparently not mediated entirely via δ opioid receptors. Cloccinamox, a μ-selective antagonist also produced partial inhibition, whereas the κ-selective antagonist, nor-BNI, was completely ineffective. These data, together with the low affinity of **6{5}** at both μ and κ receptors (>10000nM and 500nM respectively) suggest that a metabolite acting via μ opioid receptors may be contributing to its antinociceptive activity.

**Table 3.** Biological data for  $\delta$ -opioid ligands

	IC <sub>50</sub> $\delta$ nM	IC <sub>50</sub> $\mu$ nM	IC <sub>50</sub> $\kappa$ nM	MVD pIC <sub>50</sub>	HVD pIC <sub>50</sub>	Acetic acid test ED <sub>50</sub> ( $\mu$ mol/kg)
<b>1</b>	2	4800	4100	8.1 (100%) <sup>a</sup>	7.3 (90%)	30.4
<b>2</b>	4.1	>10000	1990	6.2 (87%)	< 5.0 (4%)	145
<b>7{2}</b>	1.4	>10000	3900	7.0 (98%)	5.6 (52%)	>200
<b>8</b>	0.54	702	nd	7.4 (100%)	5.9 (68%)	>200
<b>6{5}</b>	70	>10000	483	< 5.0 (7%)	< 5.0 (13%)	48.4

<sup>a</sup>Maximum efficacy at 10<sup>-10</sup> to 10<sup>-5</sup>M

### Summary

Two optimisation libraries around **2** were synthesised using aluminium chloride facilitated aminolysis. Several compounds were identified with DOR binding affinities higher or similar to compound **2**. The most active compound from these libraries, **7{2}**, had slightly higher affinity than SNC-80 **1**. Furthermore, using the SAR obtained, we went on to synthesise a compound, **8**, with four fold higher affinity than SNC-80. Whereas these higher affinity compounds did not produce antinociception after s.c. administration in the acetic acid constriction test, the acyclic SNC-80 derivative **6{5}** did produce antinociception, which is at least partially mediated via the  $\delta$ -opioid receptor.

### Acknowledgement

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- 5) Compound **3** was prepared in 2 steps from 4-benzoyl-benzoic acid: ketone reduction with NaBH<sub>4</sub> in EtOH, followed by bromination with PBr<sub>3</sub> in dichloromethane.
- 6) The following experimental conditions were typical for the array: To a solution of the substituted piperazine or diamine (0.53 mmol) in DMF (3 mL), was added diisopropylethylamine (0.106 mmol) and the resin-bound bromo-ester **4** (0.104 mmol). The mixture was agitated for 18 hours at 20°C, then the resin was collected by filtration, washed (2 x 4mL DMF; 2 x 4mL DCM, 2 x 4mL CH<sub>3</sub>OH) and dried *in vacuo* at 50°C. A suspension of AlCl<sub>3</sub> (0.028 g, 0.212 mmol) was stirred at room temperature and diethylamine (0.062 g, 0.848mmol) was added, forming a colourless solution. This solution was added to the resin-

bound ester **5** and the mixture was agitated for 18 hours at 20°C. Aqueous 2M potassium carbonate solution (0.20 mL) was added to the reaction mixture, then the resin was separated by filtration and washed with DCM (2 x 4 mL). The filtrate and washings were evaporated to dryness under reduced pressure, and the amide was purified by solid phase extraction using an ISOLUTE-XL™ column packed with 500mg of silica. [Eluent: CH<sub>2</sub>Cl<sub>2</sub> : CH<sub>3</sub>OH : aq.NH<sub>4</sub>OH; 90 : 10 : 0.5]. Fractions containing products were evaporated to dryness.

- 7) The binding affinities of the compounds described for the delta opioid receptor were determined by inhibition of binding of [<sup>3</sup>H]-naltrindole (0.15nM) to membranes from CHO cells expressing the human DOR. Mu opioid binding affinity was determined by the ability of test compounds to displace binding of [<sup>3</sup>H]-DAMGO (1.5nM) to rat brain membranes. Kappa opioid binding affinity was determined by the ability of test compounds to displace binding of [<sup>3</sup>H]-U69593 (1.5nM) to guinea pig brain membranes.
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- 10) Activity in the acetic acid-induced abdominal constriction model was assessed by administering compounds s.c. 20 minutes prior to the intraperitoneal injection of acetic acid (0.6%). The number of abdominal constrictions was counted for the 15 minute period immediately following the injection of acetic acid and the number of constrictions compared for compound-treated and control groups. Log-dose response (% antinociception) curves were drawn and IC<sub>50</sub> values calculated.
- 11) Henderson, G.; Hughes, J.; Kosterlitz, H.W. *Br. J. Pharmacol.*, **1972**, *46*, 746.
- 12) Vasa deferentia from mice (40-60g) or Syrian hamsters (100-150g) were placed between two parallel platinum electrodes in 10ml tissue baths, filled with a modified, Mg<sup>2+</sup>-free, Krebs-Henseleit buffer (CaCl<sub>2</sub> concentration: 2.5mM for mice, 1.25mM for hamsters) at 37°C, bubbled with 95% oxygen and 5% carbon dioxide. Developed force was measured with an isometric Grass FT03 force-displacement transducer. An initial force of 3-4 mN was applied on each preparation. After a 30min stabilisation period, constant current electrical field stimulation was started using a Digitimer MultiStim D330. Stimulation parameters: 400mA (mouse) or 100mA (hamster), trains of four pulses of 2ms duration at a frequency of 10Hz. Interval between trains: 10s. After 45 min of field stimulation, a cumulative concentration-response curve was constructed. Concentration range: 10<sup>-10</sup> - 10<sup>-5</sup>; 0.5 log unit increments at 3 min. intervals. pIC<sub>50</sub> values are calculated from results obtained in four animals and are expressed as mean values.