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Selective δ opioid receptor agonists for inflammatory and neuropathic pain

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Abstract

In the last decade a number of selective and potent non-peptidic agents became available to explore the usefulness of the δ-opioid receptor in modulation of pain of different origins. As a continuing effort in this field, potent and selective δ-opioid agonists based on the pyrrolomorphinan framework have been designed, synthesised and characterised biologically in our laboratories. In animal models, a selected compound of interest, SB 235863, has proved the concept that selective δ-opioid agonists may have great potential as pain relief agents in inflammatory and neuropathic pain conditions. Importantly, such a compound was free of the unwanted side effects usually associated with narcotic analgesics such as morphine. © 2001 Elsevier Science S.A. All rights reserved.

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1. Introduction

The three opioid receptors, named μ, δ and κ have been localised in discrete areas of the central and peripheral nervous system that are known to be involved with both ascending and descending pain pathways [1]. μ-Opioid receptor agonists (e.g. morphine) are used in the treatment of various pain syndromes. However, their use is limited by severe side effects (e.g. respiratory depression, constipation, dependence liability, addiction, nausea and sedation) [2] or by a limited efficacy in certain neuropathic pain syndromes (see Ref. [3], p. 8). In spite of the identification of many selective and brain penetrant κ-opioid agonists, none of them showed a suitable therapeutic window to be developed clinically as potent analgesics in view of their undesirable side-effect profile which included strong dysphoric and psychotomimetic effects [4]. On the other hand, evidence exists suggesting that activation of the δ-opioid receptors induced antinociception associated with a lesser propensity to cause dependence, constipation or respiratory depression in comparison with μ-agonists [5]. Thus δ-opioid agonists may have relevant clinical potential as safe and effective pain relief agents.

2. Rational design

In the last few years small molecules, selected for the δ-opioid receptor, belonging to different chemical classes have become available for use in pharmacological studies. The design of oxymorphindole (OMI, **1**), the first non-peptide, selective δ-opioid partial agonist was essentially based on the message-address concept [6]. Fragmentation of OMI led to SB 213698 (**2**) (or (−)-TAN67) belonging to a novel class of octahydroisoquinolines [7]. Molecular modelling studies performed on these compounds and the piperazine derivative SNC80 (**3**), allowed extension of the above concept also to non-aromatic δ-opioid addresses [8], i.e. SB 219825 (**4**) (Chart 1). As part of our continuing effort in this field, the naturally occurring morphinan nucleus was considered as a suitable substitute for the octahydroisoquinoline moiety and allowed the synthesis of a novel class of highly potent and selective δ-opioid receptor agonists, the pyrrolomorphinans (**I**) (Table 1).

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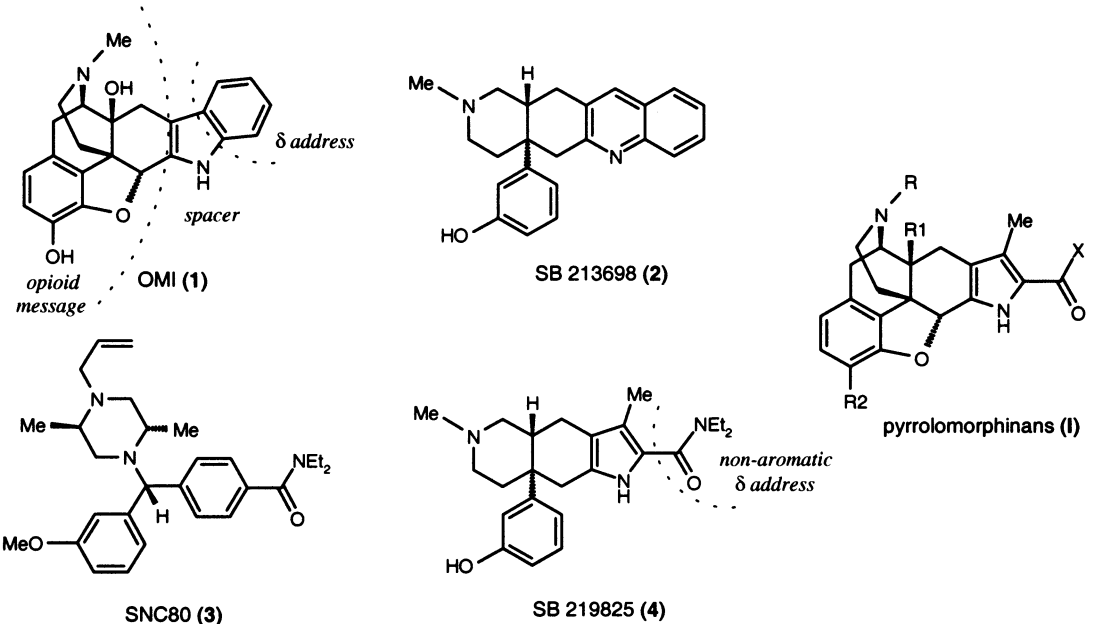
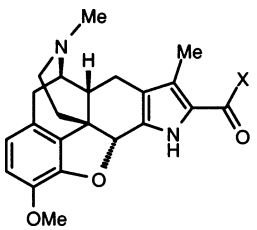


Chart 1.

3. Results and discussion

Structure–activity relationship (SAR) studies aimed at the identification of the best substitution pattern of the morphinan nucleus (Table 1) revealed that compound **5**, formally derived from oxymorphone, showed a subnanomolar affinity for the mouse δ-opioid receptor with good selectivity versus the κ-opioid receptor. However, its μ/δ selectivity ratio was not very high (15-fold).

Table 1
SAR on the morphinan moiety

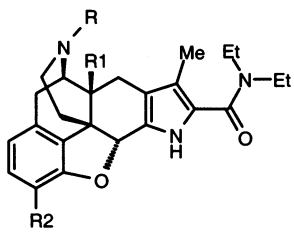


Compound	R	R_1	R_2	Binding [a]		
				NG108-15	K_i ratio	
				K_i δ (nM) [b]	μ/δ	κ/δ
5	Me	OH	OH	0.60 ± 0.01	15	525
6	Me	OH	OMe	2.15 ± 0.43	88	1300
7	Me	H	OMe	1.42 ± 0.11	200	2400
8	H	H	OMe	2.12 ± 0.43	96	>2000

[a] Binding method see Ref. [8].
[b] Data represent the mean ± SEM of independent experiments ($n = 3$).

Compound **6** bearing a MeO group (R_2) showed slightly less binding affinity for the δ-receptor with respect to the parent compound **5,** however its selectivity versus the μ-opioid receptor increased significantly (88-fold). Furthermore, removal of the OH group ($R_1 = H$, compound **7**) was beneficial for both affinity and selectivity for the δ-opioid receptor (K_i δ = 1.4 nM; K_i μ/K_i δ = 200, K_i κ/K_i δ = 2400), while removal of the

Table 2
SAR on the non-aromatic address



Comp.	X	Binding [a]		
		NG108-15	K_i ratio	
		K_i δ (nM) [b]	μ/δ	κ/δ
9	N*i*Pr_2	2.20 ± 0.12	131	820
10	NH*i*Pr	4.80 ± 0.70	82	53
11	N(*i*Pr)Bn	1.11 ± 0.30	333	2000
12	OEt	2.30 ± 0.63	145	300
13	O*i*Bu	6.16 ± 1.83	110	160
14	*i*Pr	1.30 ± 0.13	183	486
15	*i*Bu	2.85 ± 0.86	124	210

[a] Binding method see Ref. [8].
[b] Data represent the mean ± SEM of independent experiments ($n = 3$).

Me group at the basic nitrogen (R = H, compound **8**), although tolerated, decreased slightly the μ/δ selectivity.

Thus the substitution pattern of the morphinan moiety of compound **7** was fixed for further SAR analysis of the non-aromatic address (Table 2).

Overall, amides (**9**–**11**), esters (**12**, **13**) and ketones (**14**, **15**) were found to be suitable non-aromatic addresses displaying good affinity for the δ-opioid receptor and high selectivity versus the mouse μ- and κ-opioid receptors. In general, large substituents (i.e. X = N(*i*-Pr)CH_2Ph, compound **11**) were well tolerated and gave potent and selective δ-opioid ligands.

In addition, all the above compounds behaved as full δ-opioid agonists in inhibiting the adenylate cyclase activity stimulated by forskolin (1 μM) in the NG108-15 cell lines with potency in the nanomolar range.

Compound **13** (SB 235863, K_i δ = 6.2 nM; K_i μ/K_i δ = 110, K_i κ/K_i δ = 160) was chosen for proof-of-concept studies in view of its high brain penetration (brain/plasma concentration ratio of 2) and favourable overall pharmacokinetic profile in the rat. In a rat model of inflammatory pain evoked by intraplantar injection of carrageenan (rat carrageenan plantar test) [9], this compound showed similar antihyperalgesic activity to that of morphine [10]. This activity was reversed selectively by the selective δ-opioid antagonist naltrindole (NTI). Interestingly, following repeated administration of high doses of SB 235863, no tolerance to the antihyperalgesic effect was noted. By contrast, equieffective doses of morphine induced a significant tolerance [10].

In a rat model of established neuropathic pain (Seltzer test), a significant and long lasting thermal hyperalgesia is observed in the operated side following partial ligation of the sciatic nerve. Sustained antihyperalgesic activity was obtained after repeated oral dosing of SB 235863 over a period of 10 days [11].

In addition, SB 235863 was devoid of any narcotic potential associated with morphine usage including constipation, sedation, respiratory depression, abuse/rewarding and physical dependence [10].

4. Conclusions

Insertion of different non-aromatic addresses (amides, ester and ketones) on the pyrrolomorphinan skeleton allowed the discovery of potent and selective δ-opioid agonists. Compounds bearing an ester moiety were found to be very liphophylic and compound **13** (SB 235863) satisfied the criteria of binding selectivity and agonist activity along with favourable pharmacokinetic profile and good brain penetration for proof-of-concept studies in the rat.

In vivo studies demonstrated that the δ-opioid agonist SB 235863 was able to relieve inflammatory and neuropathic pain with none of the unwanted narcotic side-effects associated with opiate usage revealing the great potential of δ-opioid agonists as pain killers in hyperalgesic conditions of different origin.

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