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THE LMC DELTA OPIOID RECOGNITION PHARMACOPHORE: COMPARISON OF SNC80 AND OXYMORPHINDOLE

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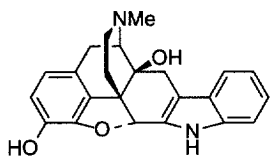
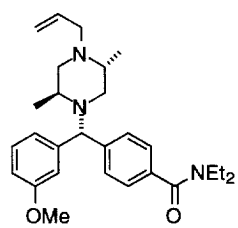
Abstract: A recognition pharmacophore for the delta opioid receptor was developed *de novo*. Through the use of the pharmacophore and a novel four-point recognition model, major differences were observed between oxymorphindole and SNC80. This work suggests that these two classes of delta selective opioids do not bind to the delta opioid receptor in the same orientation. © 1999 Published by Elsevier Science Ltd.

The delta opioid receptor has been shown to be involved in many biological processes, such as modulation of the effects of mu opioid agonists and immunoregulatory effects, and therefore compounds that act at the delta receptor have broad clinical potential.[1] Metabolically stable selective ligands are required to further investigate the delta opioid system and, although many selective peptides are known,[2] a nonpeptide small molecule would offer obvious advantages in terms of stability and CNS penetration. Two major advances in the area of delta selective agonists were the discovery of the indolomorphinans, typified by oxymorphindole (**1**),[3] and the diarylmethylpiperazines, typified by SNC80 (**2**)[4] (Figure 1). Both series of compounds bind selectively to the

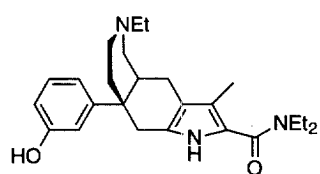
Figure 1. Delta selective agonists



1 Oxymorphindole



2 SNC80



3

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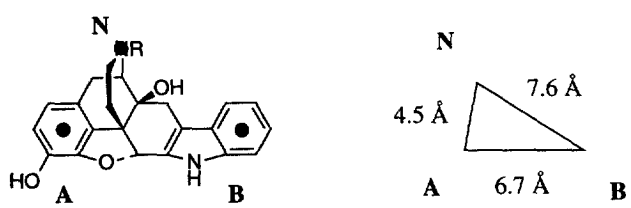
delta opioid receptor, however they possess very different structures. Studies aimed at determining which parts of the two structures correspond when bound to the delta opioid receptor led to the working hypothesis that the phenolic ring, basic nitrogen, and indolic moiety of **1** correspond to the methoxyl substituted aromatic ring, terminal basic nitrogen, and benzamide group of **2**, respectively.[1] This led Dondio *et al.* to design hybrid **3**, an analog of **1** in which the indolic phenyl ring has been replaced by the corresponding amide group of **2**. The good delta selectivity of **3** was suggested as evidence for the above described overlap model.[5]

Although the work of Dondio *et al.* supports the overlap described above, we considered that if the two agonist ligands interacted with the receptor in the same way they should possess similar SAR. However, we noted that they actually possess very different SAR. A 3-phenolic group is essential for the high binding affinity and selectivity of the indolomorphinans,[3] whereas for the diarylmethylpiperazines, an aromatic methoxyl group appears to be the substituent of choice for selectivity, as SNC80 displays greater delta selectivity than phenolic (+)-BW373U86.[4] In addition, it is known that the SAR of the N-substituent differs between the two series. Replacement of the *N*-methyl group of oxymorphindole, a partial delta agonist, with an *N*-allyl group results in a delta antagonist,[3] whereas the *N*-allyl substituted SNC80 is a delta agonist of high efficacy.[6] These SAR studies are not consistent with the proposed overlap between the diarylmethylpiperazines and the indolomorphinans, and suggest that they bind to the delta receptor in different orientations. To further investigate this possibility, we decided to develop a delta opioid recognition pharmacophore *de novo*, and use the pharmacophore to examine the differences and similarities between SNC80 and oxymorphindole.

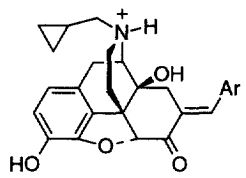
A pharmacophore is a simple model describing distances between important atoms or groups of atoms in a ligand that are required for it to interact with a receptor. A dataset of compounds is chosen, similar groups identified that are required for interaction with the receptor, the ligands computer-modeled to determine an energetically accessible conformer, and the distances between the groups measured to give the pharmacophore. Potential ligands can then be screened against the pharmacophore to determine if they possess the required groups correctly spaced for recognition at the receptor. Such an approach has previously been undertaken by Loew's group,[7,8] who chose three groups to generate a 2-D pharmacophore: a basic nitrogen (N), the centroid of an aromatic ring (A), and the centroid of a lipophilic group (B) for the delta receptor pharmacophore (Figure 2). Loew's ligands were modeled using Molecular Simulation's Quanta/CHARMm.[9] The average distances between the recognition points were determined, and the resulting pharmacophore is shown in Figure 2. Both the indolomorphinans and diarylmethylpiperazines were said to satisfy the pharmacophore, further supporting the working hypothesis about the overlap between these two series of ligands.

Figure 2. Pharmacophore of Loew's Group



Our approach involved a different dataset and different modeling software (Tripos' Sybyl)[9] to determine a pharmacophore for comparison with that of Loew, and to investigate whether SNC80 and oxymorphindole satisfied a pharmacophore prepared without their inclusion in the dataset. Our dataset comprised ligands (**4**, **5**) prepared by Palmer *et al.*[10] (Figure 3), with a range of delta affinities and selectivities.

Figure 3. Dataset for the LMC recognition pharmacophore



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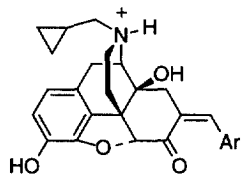

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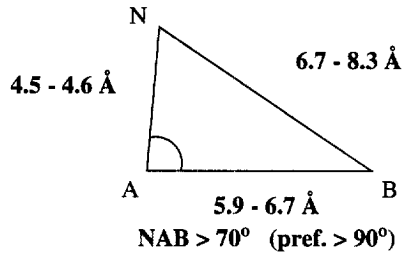
	Distance (Å)			Angle (°)	δ K_i (nM)	μ/δ
	AN	AB	NB	NAB		
5 Ar = 1-Naphthyl	4.6	5.9	8.1	100	0.7	15
5 Ar = 9-Anthracyl	4.6	6.5	8.3	96	2.4	14
5 Ar = Phenyl	4.6	6.3	8.0	93	3.7	8.6
4 Ar = 1-Naphthyl	4.6	6.1	6.7	76	4.6	7.5
4 Ar = Phenyl	4.6	6.7	6.7	70	6.2	4.0
5 Ar = 2-Naphthyl	4.5	8.2	9.0	84	16	3.0
4 Ar = 9-Anthracyl	4.6	6.5	7.0	75	17	6.4
4 Ar = 2-Naphthyl	4.6	7.3	7.2	71	39	0.6
5 Ar = 4-Biphenyl	4.5	9.2	10.1	87	47	4.2
4 Ar = 4-Biphenyl	4.6	8.4	8.0	69	75	0.6

In a similar fashion to Loew, three groups were chosen: a protonated nitrogen (N), the centroid of an aromatic ring (A), and the centroid of the entire electron rich system (B).[11] The five high affinity ligands (defined as less than 10 nM) were modelled, and the resulting pharmacophore is shown in Figure 4. Unlike Loew who gave an average, we decided to determine a range of distances, and as can be seen the distances given by Loew lay within our ranges. Thus, the LMC pharmacophore is in general agreement with that of Loew. As our pharmacophore was created from a set of ligands with high delta affinity but differing degrees of delta selectivity, it is, by its very nature, only a recognition pharmacophore, however an angle NAB of >90° appears important for selectivity.

Although no indolomorphinans were used as part of the dataset to generate the pharmacophore, it can be seen that oxymorphindole basically satisfies the LMC pharmacophore, although an AB distance of 5.7 Å is slightly outside the range of the pharmacophore (Figure 4). SNC80 gave two very different low energy conformations, which were observed to be rotamers about the N-benzylic carbon bond. The 24.4 kcal conformer was shown to be almost identical to the published X-ray structure of SNC80,[4] whereas the 23.7 kcal rotamer was shown to be very different.[12] However, neither conformer satisfied the pharmacophore due to an unusually large AN distance – over 1 Å greater than the range in the pharmacophore (6.2 Å and 5.7 Å vs 4.6 Å).

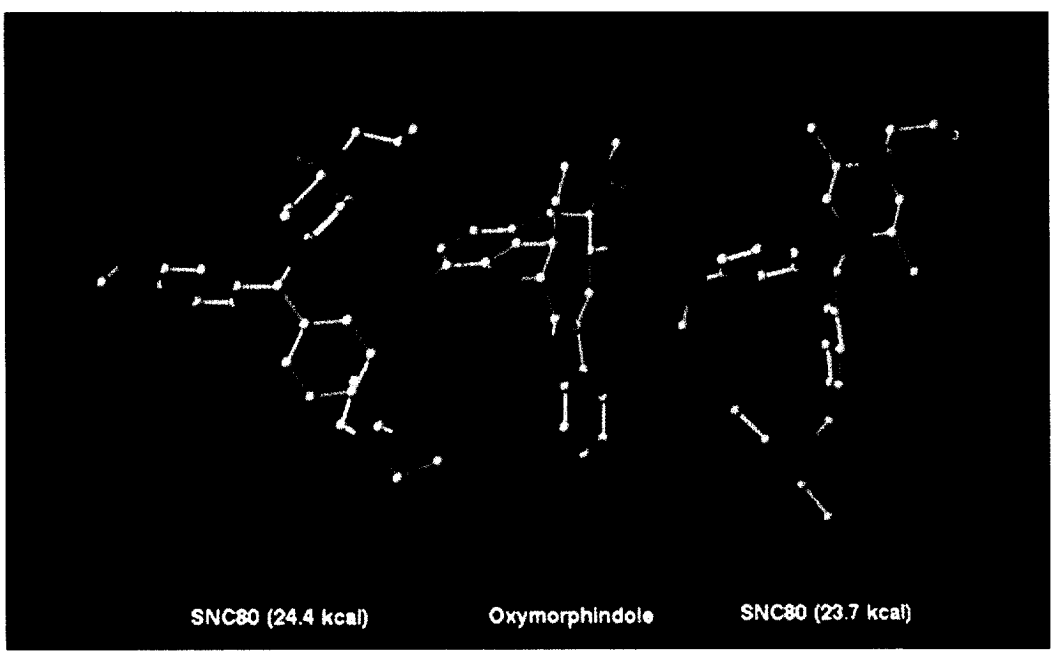
In addition, the angles NAB of 84° and 78° are not consistent with our pharmacophore for a compound of such high delta selectivity as SNC80. It thus appears that the LMC delta opioid recognition pharmacophore is not a satisfactory model for SNC80.

Figure 4. The LMC delta opioid recognition pharmacophore



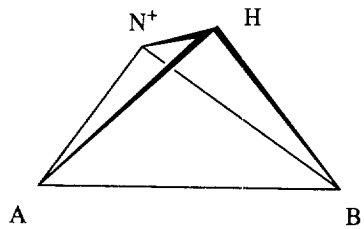
	Distance (Å)			Angle (°)
	AN	AB	NB	NAB
Loew's pharmacophore	4.5	6.7	7.6	83
Oxymorphindole-H^+	4.6	5.7	6.9	84
SNC80-H^+, (23.7 kcal)	6.2	6.3	6.3	84
SNC80-H^+, (24.4 kcal)	5.7	6.4	7.7	78

Figure 5. Comparison of the N-protonated forms of oxymorphindole and SNC80 (all other protons omitted for clarity)



Further to the findings above that SNC80 does not fit the current model, it was noted that in the biologically important protonated forms, the protons on the terminal nitrogens of both low energy conformers of SNC80 occupy different regions of 3-D space than the proton on the nitrogen of oxymorphindole (Figure 5). This difference was shown quantitatively by the development of a four-point model; a model comprising the pharmacophore and the additional point of the proton on the nitrogen (Figure 6). As can be seen, the BH distances differ by more than 1 Å (8.1 Å and 8.9 Å vs 6.8 Å), and the angles ANH, BNH, NHA, and NHB all differ by more than 30°. Thus, the major differences which exist between oxymorphindole and SNC80 are more clearly seen when examined by the four-point model.

Figure 6. The LMC four-point recognition model.



	Angle (°)					Distance (Å)	
	ANH	BNH	AHB	NHA	NHB	AH	BH
Oxymorphindole-H^+	127	77	55	43	94	5.3	6.8
SNC80-H^+ (23.7 kcal)	87	118	45	83	56	6.2	8.9
SNC80-H^+ (24.4 kcal)	62	111	52	108	62	5.3	8.1

The LMC delta opioid recognition pharmacophore was developed *de novo*, and shown to be in general agreement with that of Loew. However, SNC80 does not satisfy our pharmacophore, nor using our software (Tripos' Sybyl) does it satisfy very well the pharmacophore of Loew.[7] In addition to these differences, the LMC four-point model showed major differences between oxymorphindole and both low energy conformers of SNC80. Indeed, the protons on the nitrogens point in very different directions.[13] As these protonated nitrogens probably interact with the same amino acid in the receptor,[14–16] it appears extremely unlikely that these ligands can interact with the receptor in the same orientation. Indeed, when combined with the SAR results above, it appears that the overlap described (phenolic = methoxyl, indolic = benzamido) cannot be valid. Although delta opioid receptor efficacy was not taken into account during this work, the idea of different binding modes for SNC80 and oxymorphindole may explain the difference in efficacy between the *N*-allyl substituted derivatives. Further studies to determine what, if any, overlap there is between the two series of ligands may allow us to conceptualize hybrid molecules with enhanced delta opioid selectivity.

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11. Modeling procedure. Software: Tripos' Sybyl version 6.4 on a Silicon Graphics O2 computer (IRIX OS version 6.3). The protonated molecules were sketched, their chirality checked for accord with the known stereochemistry, and each was then energy minimized using, either individually or sequentially, the conjugate-gradient or Powell optimization programs with gradient termination set at 0.01 kcal/(mol*A) with the Tripos force field and Gasteiger–Huckel charges. Other force-field values were set at the Sybyl default, and a sufficient number of iterations were run to assure optimization for that conformation. To lessen the possibility of obtaining a conformer within a local minimum energy well, and to examine other theoretically possible, higher energy, conformations, simulated annealing was utilized, a Sybyl dynamics procedure. The Sybyl default values were used: initial temperature = 700 K, time to equilibrate at initial temperature = 1000 fs, target temperature for annealing = 200 K, time to spend for annealing = 1000 fs, annealing function = exponential. The resulting conformers were sorted by potential energy and energy minimized. Conformers within 5 kcal/mol were individually examined, overlapped, and those with disparate conformations were used to determine the pharmacophore. The three points chosen for this pharmacophore were the protonated tertiary nitrogen atom, the center of the aromatic ring situated βγ to that nitrogen, and the centroid of the moiety attached to the C7 atom (determined using the Sybyl software).
12. For example: Distance between methoxyl oxygen atom and nitrogen atom of the amide. X-ray - 10.7 Å; 23.7 Kcal conformer - 7.2 Å; 24.4 Kcal conformer - 10.4 Å.
13. It could be envisioned that inversion of the protonated nitrogen of SNC80 may place the protons of SNC80 and oxymorphindole in similar orientations, however this leads to a minimized conformer of higher energy (28.8 Kcal) due to the allyl group occupying an axial position. In addition this conformer is also very different to oxymorphindole in the four point model.
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