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Structural requirements for substitution on the Phe³ side chain aromatic ring in a δ opioid receptor selective, cyclic tetrapeptide dermorphin analog

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Introduction

In an effort to develop structure-activity relations for our conformationally restricted, δ -selective opioid tetrapeptide, Tyr-D-Cys-Phe-D-PenOH, electronic, lipophilic, and steric effects at the Phe³ position were assessed by substitution on the side chain aromatic ring. Effects on binding were determined.

Results and Discussion

Substitution of electronegative fluorine at the *para* position of the Phe phenyl ring (1) enhances δ binding affinity in the tetrapeptide, while μ binding is slightly diminished. The improved δ activity of this analog is most likely due to local electronic or lipophilic rather than conformational influences, leading to a favorable δ binding interaction. The *p*-Cl-Phe³ tetrapeptide analog (2) was synthesized to assess further this effect, and the fluoro- and more lipophilic chloro-substituted analogs, 1 and 2, are equiactive at the δ receptor; a slightly greater reduction is observed for 2 in μ binding affinity (three-fold relative to JOM-13). Analog 2 displays a higher affinity and index of selectivity for the δ receptor than do JOM-13 and DPDPE.

The *p*-methyl substituent in 3, like *p*-F and *p*-Cl, is small and lipophilic but is electron-releasing rather than electron-withdrawing; this tetrapeptide modification proves detrimental to both δ and μ receptor binding. The *p*-*t*-BuPhe³ analog (4) is the most lipophilic and bulkiest in the series. The μ binding affinity of 4 is severely compromised relative to the lead compound; negative results are also observed at the δ receptor. These unfavorable consequences can be attributed to steric effects.

In the Tyr³ (5) and *m*-Tyr³ (6) analogs, the hydroxyl substituent is more strongly electron-releasing than the alkyl groups above. In contrast to the lipophilic properties of the halogens and the alkyl groups, the hydroxyl moiety is hydrophilic. Again, 5 displays a reduction in opioid binding relative to the parent compound, about 14-fold at the δ receptor. This may reflect both the reduction in lipophilicity as well as a negative σ effect. It is interesting to note that the *m*-Tyr³ amino acid (6) is better-tolerated than Tyr³ (only five and 6.5-fold reductions in affinity are observed at the δ and μ receptors, respectively), likely due to differing

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Table 1 Opioid receptor binding profiles of cyclic(2-4) tetrapeptides; Phe³ residue aromatic substitution

Peptide analog	Cmpd no.	Binding IC ₅₀ (nM)		IC ₅₀ (μ)/IC ₅₀ (δ)
		DAMGO	DPDPE	
DPDPE		1 000	6.40	203
Tyr-D-Cys-Phe-D-PenOH	JOM-13	182	2.90	63.0
Tyr-D-Cys- <i>p</i> FPhe-D-PenOH	1	274	1.65	166
Tyr-D-Cys- <i>p</i> ClPhe-D-PenOH	2	556	1.56	356
Tyr-D-Cys- <i>p</i> MePhe-D-PenOH	3	2 980	8.64	345
Tyr-D-Cys-4- <i>t</i> BuPhe-D-PenOH	4	>10 000	58.7	>170
Tyr-D-Cys-Tyr-D-PenOH	5	6 550	41.0	160
Tyr-D-Cys- <i>m</i> Tyr-D-PenOH	6	1 210	14.9	81.2
Tyr-D-Cys- <i>p</i> NO ₂ Phe-D-PenOH	7	233	2.66	87.6

DAMGO = [³H][D-Ala², NMePhe⁴, Gly⁵-ol]enkephalinDPDPE = [³H][D-Pen², D-Pen⁵]enkephalin

electronic features of the aromatic ring resulting from *meta* rather than *para* substitution. In fact, a *meta* hydroxyl group has a positive σ value.

Introduction of a *para* nitro substituent on the Phe aromatic moiety in both linear [1] and cyclic [2] μ -selective dermorphin-related tetrapeptides induces a sharp decline in μ binding affinity. However, the *p*-NO₂Phe³ (7) substitution does not affect μ or δ activity. While these results may appear inconsistent, the observation that affinity is not compromised fits the general trend observed for this group of analogs. Specifically, the nitro group has a high positive σ value (a favorable contribution) since it is electron-withdrawing, and a *p*-nitro moiety enhances lipophilicity. However, the large molecular volume of the nitro substituent may lead to an adverse steric effect at the receptor; these properties may neutralize one another.

These effects are generally consistent with reports of analogous modification in the linear pentapeptide enkephalins [1,3-7] and DPDPE [6,8-10] where data are available. Data for this group of modifications imply that while steric, lipophilic, and electronic effects all play a role in influencing binding interactions at this residue, the most important determinant for opioid activity appears to be the electron-withdrawing property of the substituent. In general, those substituents possessing a positive σ value enhance activity, while those with a negative σ value, those lacking lipophilic character, or those possessing larger van der Waals radii decrease binding.

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