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AD#: AD-P008 306
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Structural requirements for substitution on the Phe³ side chain aromatic ring in a δ opioid receptor selective, cyclic tetrapeptide dermohpin 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 δ 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 a 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
Table I  Opioid receptor binding profiles of cyclic(2-4) tetrapeptides; Phe\(^3\) residue aromatic substitution

<table>
<thead>
<tr>
<th>Peptide analog</th>
<th>Cmpd no.</th>
<th>Binding IC(50) (nM)</th>
<th>IC(50(\mu)/IC3(\delta))</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAMGO</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPDPE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyr-d-Cys-Phe-d-PenOH</td>
<td>JOM-13</td>
<td>182</td>
<td>2.90</td>
</tr>
<tr>
<td>Tyr-d-Cys-pFPhe-d-PenOH</td>
<td>1</td>
<td>274</td>
<td>1.65</td>
</tr>
<tr>
<td>Tyr-d-Cys-pClPhe-d-PenOH</td>
<td>2</td>
<td>556</td>
<td>1.56</td>
</tr>
<tr>
<td>Tyr-d-Cys-pMePhe-d-PenOH</td>
<td>3</td>
<td>2980</td>
<td>8.64</td>
</tr>
<tr>
<td>Tyr-d-Cys-4-tBuPhe-d-PenOH</td>
<td>4</td>
<td>&gt;1000</td>
<td>&gt;170</td>
</tr>
<tr>
<td>Tyr-d-Cys-Tyr-d-PenOH</td>
<td>5</td>
<td>6550</td>
<td>41.0</td>
</tr>
<tr>
<td>Tyr-d-Cys-mTyr-d-PenOH</td>
<td>6</td>
<td>1210</td>
<td>14.9</td>
</tr>
<tr>
<td>Tyr-d-Cys-pNO(_2)Phe-d-PenOH</td>
<td>7</td>
<td>233</td>
<td>2.66</td>
</tr>
</tbody>
</table>

DAMGO = \([3H]\)\(^{[D-Ala^2, NMePhe^4, Gly^5]}\)enkephalin

DPDPE = \([3H]\)\(^{[D-Pen^2, \alpha-Pen^5]}\)enkephalin

electronic features of the aromatic ring resulting from \(\text{meta}\) rather than \(\text{para}\) substitution. In fact, a \(\text{meta}\) hydroxyl group has a positive \(\sigma\) value.

Introduction of a \(\text{para}\) nitro substituent on the Phe aromatic moiety in both linear [1] and cyclic [2] \(\mu\)-selective dermorphin-related tetrapeptides induces a sharp decline in \(\mu\) binding affinity. However, the \(p\)-NO\(_2\)Phe\(^3\) (7) substitution does not affect \(\mu\) or \(\delta\) 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 \(n\)-nitro group has a high positive \(\sigma\) 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 \(\sigma\) value enhance activity, while those with a negative \(\sigma\) value, those lacking lipophilic character, or those possessing larger van der Waals radii decrease binding.

References