OCTAHYDRO-1,2,3,4,4a,5,11,11a-PYRIDO[3,4-c][1,5]BENZOXAZEPINES: CONFORMATIONALLY RESTRICTED FENTANYL ANALOGS

Linas V. Kudzma*, Suzanne M. Evans, Stanhope P. Turnbull Jr., Sherry A. Severnak and Edward F. Ezell†

Ohmeda Pharmaceutical Products Division Inc., 100 Mountain Avenue, Murray Hill, NJ 07974 USA
†The BOC Group Inc., BOC Group Technical Center, 100 Mountain Avenue, Murray Hill, NJ 07974 USA

Abstract. Synthesis, analgesic activity and preliminary molecular modeling studies of the cis- and trans-fused octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-c][1,5]benzoxazepines 8 and 9, the first rigid fentanyl analogs with a conformationally restricted 4-anilido group that retain antinociceptive properties, are reported.

Fentanyl (1) is the prototype of the highly potent 4-anilidopiperidine class of synthetic opioid analgesics. Although 1 lacks any obvious structural relationship to morphine, it is a significantly more potent analgesic, with specific affinity for the μ opioid receptor.

 Attempts to define the bioactive conformation of 4-anilidopiperidines by synthesizing rigid analogs have generally been unsuccessful. A noteworthy exception is a tropane derivative of fentanyl synthesized by Riley and Bagley which retained high analgesic potency, suggesting that the piperidine ring adopts the chair form in the bioactive conformation of 4-anilidopiperidines. However, all attempts to tie back the propionyl group or the anilido phenyl ring of 4-anilidopiperidines produced inactive compounds. Therefore, little remained known about the conformational requirements of the 4-propionanilido group for biological activity. In this paper, we report on the novel octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-c][1,5]benzoxazepine ring system 2 in which the C-9a to C-11a linkage effectively tethers the ortho position of the anilido phenyl ring to the C-3 position of the piperidine ring. We report the synthesis, analgesic activity and preliminary molecular modeling studies of both cis- and trans-fused octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-c][1,5]benzoxazepines 8 and 9, the first rigid
Scheme 1.

Reagents: (a) 2-Fluoroaniline, NaCNBH₃, MeOH, HCl, 3Å sieves; (b) LiAlH₄, Et₂O, 0 °C; (c) NaH, DMF, 80 °C; (d) CH₃CH₂COCl, EtOAc/aqueous Na₂CO₃; (e) ACE-Cl, 1,2-dichloroethane, reflux; (f) MeOH, reflux; (g) PhCH₂CH₂Br, CH₃CN, Na₂CO₃.
fentanyl analogs with a conformationally restricted 4-anilido group that retain potent antinociceptive properties.

Results and Discussion

The synthesis of benzoxazepines 8 and 9 is outlined in Scheme 1. Reductive amination of carbomethoxypiperidone 3 with 2-fluoroaniline and NaCNBH$_3$ in methanol gave an approximately 2:1 mixture of the 4-anilidopiperidines 4a and 4b, respectively. The diastereomers were separated by flash chromatography on silica, and the esters were reduced with LiAlH$_4$ to give the pair of diastereomeric alcohols 5a and 5b. Compounds 5a and 5b were cyclized via SN$_2$ displacement of fluoride$^6$ to give cis- and trans-fused benzoxazepines 6a and 6b, respectively. The trans configuration of compound 6b was suggested by $^1$H NMR data and unequivocally confirmed by single crystal X-ray analysis.$^7$ Compounds 6a and 6b were successively acylated with propionyl chloride, debenzylated with 1-chloroethylchloroformate and alkylated with phenylethyl bromide to give racemic cis- and trans-fused octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-c][1,5]benzoxazepine derivatives 8 and 9, respectively.

A modification of the rat-tail flick method$^8$ was employed to evaluate the analgesic activity of compounds 8 and 9 (Table 1). The cis-fused compound 8 was found to be a highly potent analgesic, with an ED$_{50}$ of 0.007 mg/kg, equipotent to fentanyl. The trans-fused diastereomer 9, while less potent than 8, was a highly potent analgesic as well, with an ED$_{50}$ of 0.012 mg/kg. Compounds 8 and 9 are the first 4-anilidopiperidine derivatives with conformational restriction of the anilido group to exhibit analgesic activity. In vitro affinities of 8 and 9 for the mu (µ), kappa (κ) and delta (δ) opioid receptors were determined by previously described methods$^9$ and are also summarized in Table 1. Opioid receptor binding followed the same trend observed for fentanyl (1): high affinity at the µ receptor and lower affinities at the κ and δ receptor sites. Compounds 8 and 9 both inhibited binding of [³H]DAGO, a µ-opioid receptor ligand, with IC$_{50}$'s of 5.1 nM and 5.8 nM, respectively.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Compound 8</th>
<th>Compound 9</th>
<th>fentanyl (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat tail-flick ED$_{50}$, mg/kg iv</td>
<td>0.0071 (0.0053-0.0096)$^a$</td>
<td>0.012 (0.0014-0.10)</td>
<td>0.006 (0.0044-0.0082)</td>
</tr>
<tr>
<td>opioid receptor binding: IC$_{50}$, nM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>µ [³H]DAGO</td>
<td>5.1 ±0.54 (6)$^b$</td>
<td>5.8 ±0.49 (3)</td>
<td>3.1</td>
</tr>
<tr>
<td>κ [³H]EKC</td>
<td>6986 ±1791 (6)</td>
<td>2164 ±752 (3)</td>
<td>5893</td>
</tr>
<tr>
<td>δ [³H]DPDPE</td>
<td>387 ±46 (7)</td>
<td>111 ±293 (3)</td>
<td>187</td>
</tr>
</tbody>
</table>

$^a$ 95% confidence limits in parentheses. $^b$ N in parentheses.
Figure 1. Superimposition of compounds 8 (red) and 9 (blue), hydrogens suppressed.

Figure 2. Superimposition of compound 8 (red) and X-ray structure of fentanyl (green), hydrogens suppressed.
We utilized molecular modeling to probe the three-dimensional similarities of compounds 8 and 9 to fentanyl. We speculated that these two conformationally restricted compounds might provide an overall shape similar to the bioactive conformation of fentanyl by controlling the orientation of the anilido moiety. Compounds 8 and 9 were assembled from X-ray crystallographic coordinates for the fused ring systems (obtained from the Cambridge Structural Database) and standard fragments for the appendages, and then optimized using AM1 as implemented in MOPAC 5.0. Fentanyl's geometry was extracted from the Cambridge Structural Database. Figure 1, a superimposition of rigid compounds 8 and 9, shows that these compounds have nearly overlapping anilido rings, yet maintain different 7-membered ring conformations as a result of their respective cis and trans fusions to the piperidine ring (chair conformation). We have previously shown that 2-methoxy substitution of the anilido ring has minimal effect on the biological activity of fentanyl derivatives. Therefore, we speculate that the analogous 10-oxa feature of the benzoxazepine ring contributes little to the pharmacological profile of compounds 8 and 9. Figure 2, a superimposition of compound 8 onto the crystallographic structure of fentanyl, illustrates that compound 8 contains chemical functionality which overlaps well onto fentanyl, a prototype ligand for opioids. Although the aromatic ring appears edge on, a rotation of merely 30° from the crystallographic position would provide a nearly exact superimposition of the anilido rings.

**Conclusion**

The synthesis of the novel octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-c][1,5]benzoxazepine ring system is reported. The cis- and trans-fused pyrido[3,4-c][1,5]benzoxazepines 8 and 9 are the first rigid fentanyl analogs with a conformationally restricted 4-anilido group that retain potent antinociceptive properties. The cis-fused isomer, compound 8, has chemical functionality that overlaps well onto fentanyl and is an equipotent analgesic.

**Acknowledgment**

The authors thank Dr. Cynthia T. Psaras and Cindy Tsai for the receptor binding data: Patricia Kellerhouse and Sarah Harris for carrying out the rat tail-flick experiments: Dr. Jerome R. Bagley for useful discussions.

**References**


7. ORTEP plot of the X-ray structure of trans-fused compound 6b, with 30% probability ellipsoids, is shown below:

[Diagram of the ORTEP plot]

Full X-ray crystal and NMR data, together with full synthetic details for this new ring system will appear in a forthcoming full paper.


(Received in USA 24 January 1995; accepted 25 April 1995)