

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

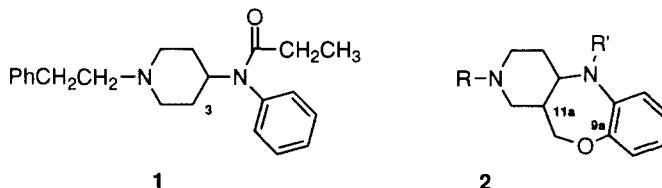
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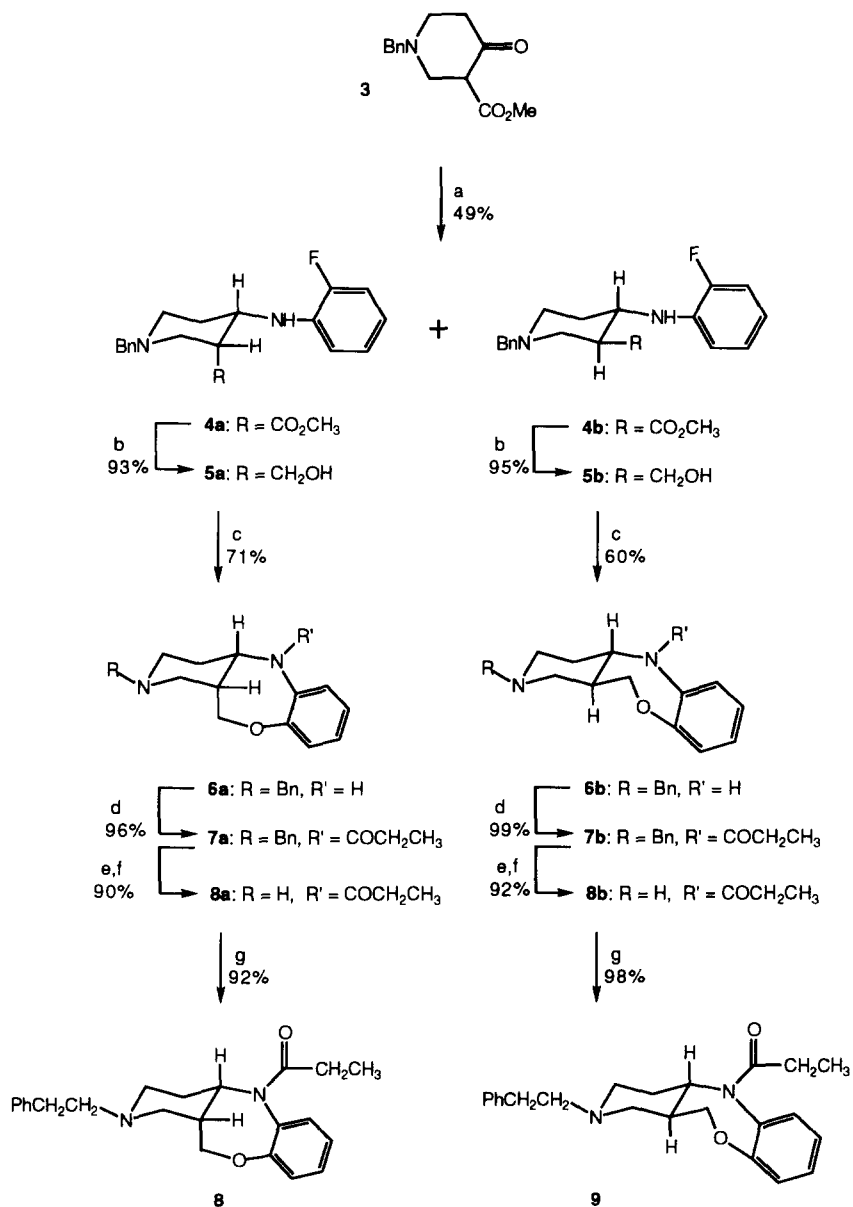
Abstract. Synthesis, analgesic activity and preliminary molecular modeling studies of the *cis*- and *trans*-fused octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-c][1,5]benzoxazepines **8** and **9**, the first rigid fentanyl analogs with a conformationally restricted 4-anilido group that retain antinociceptive 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 analgesic¹, 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.² A noteworthy exception is a tropane derivative of fentanyl synthesized by Riley and Bagley³ 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 group⁴ or the anilido phenyl ring⁵ 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 NaCNBH₃ 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 LiAlH₄ to give the pair of diastereomeric alcohols **5a** and **5b**. Compounds **5a** and **5b** were cyclized via S_NA_r displacement of fluoride⁶ to give cis- and trans-fused benzoxazepines **6a** and **6b**, respectively. The trans configuration of compound **6b** was suggested by ¹H 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 method⁸ 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 ED₅₀ 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 ED₅₀ 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 methods⁹ 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 IC₅₀'s of 5.1 nM and 5.8 nM, respectively.

Table 1

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

^a 95% confidence limits in parentheses. ^b N in parentheses.

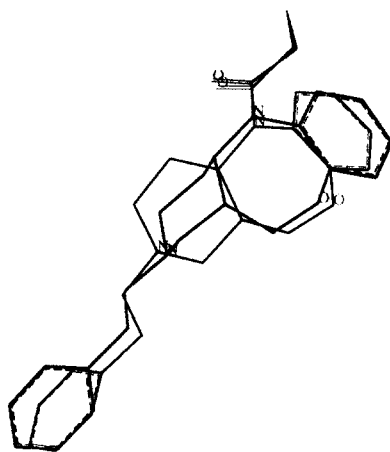


Figure 1. Superimposition of compounds **8** (red) and **9** (blue), hydrogens suppressed.

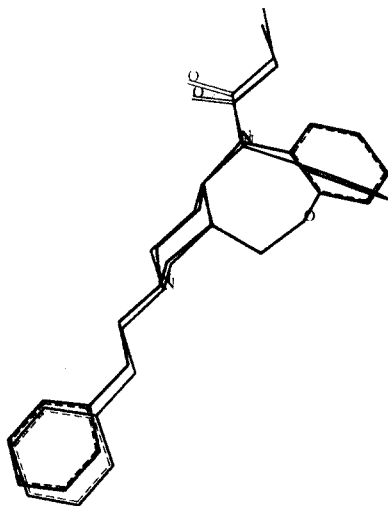


Figure 2. Superimposition of compound **8** (red) and X-ray structure of fentanyl (green), hydrogens suppressed.

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)¹⁰ and standard fragments for the appendages, and then optimized using AM1 as implemented in MOPAC 5.0.^{11,12} 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.² 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.

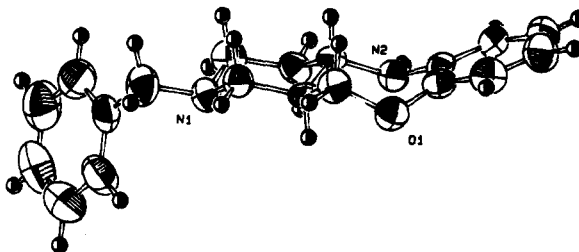
Acknowledgment

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



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

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