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

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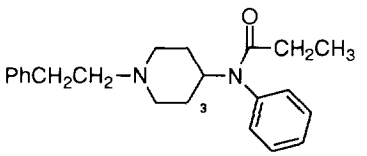
Abstract. Synthesis, analgesic activity and preliminary molecular modeling studies of the cis- and trans-fused octahydro-1,2,3,4,4a,5,11,11a-pyrido[3,4-*c*][1,5]benzoxazepines **8** and **9**, the first rigid fentanyl analogs with a conformationally restricted 4-anilido group that retain antinociceptive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



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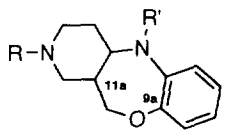

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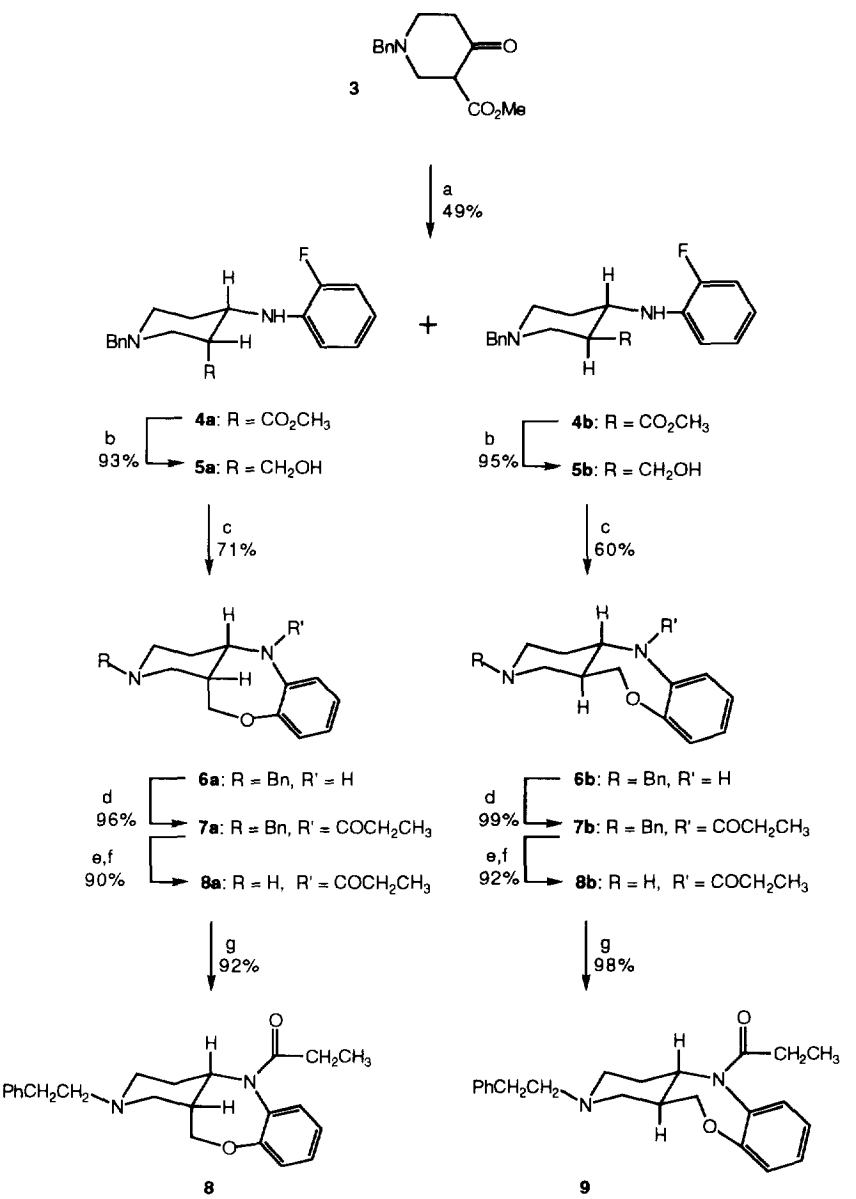
Attempts to define the bioactive conformation of 4-anilidopiperidines by synthesizing rigid analogs have generally been unsuccessful.[2] A noteworthy exception is a tropane derivative of fentanyl synthesized by Riley and Bagley[3] which retained high analgesic potency, suggesting that the piperidine ring adopts the chair form in the bioactive conformation of 4-anilidopiperidines. However, all attempts to tie back the propionyl group[4] or the anilido phenyl ring[5] 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, $NaCNBH_3$, MeOH, HCl, 3Å sieves; (b) $LiAlH_4$, Et_2O, 0 °C; (c) NaH, DMF, 80 °C; (d) CH_3CH_2COCl, EtOAc/aqueous Na_2CO_3; (e) ACE-Cl, 1,2-dichloroethane, reflux; (f) MeOH, reflux; (g) $PhCH_2CH_2Br$, CH_3CN, Na_2CO_3.

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_{Ar} displacement of fluoride[6] 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 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 [^{3}H]DAGO, a μ-opioid receptor ligand, with IC_{50}'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.

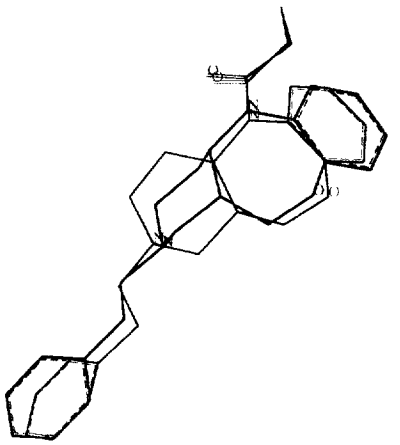


Figure 1. Superimposition of compounds **8** (red) and **9** (blue), hydrogens suppressed.

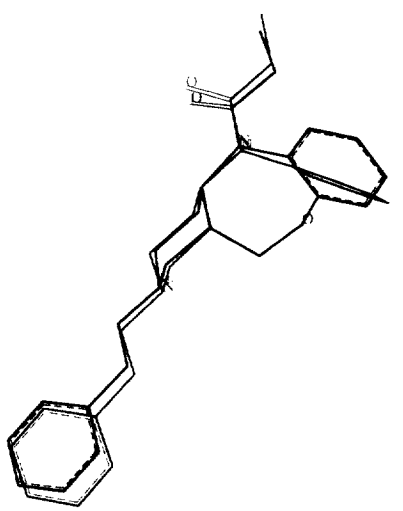


Figure 2. Superimposition of compound **8** (red) and X-ray structure of fentanyl (green), hydrogens suppressed.

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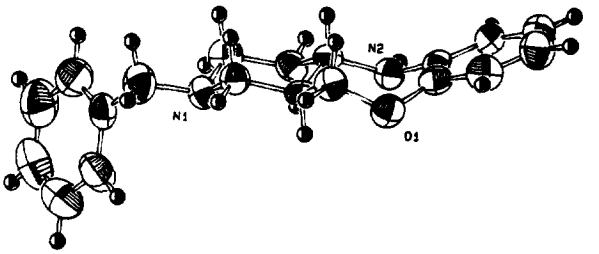
7. ORTEP plot of the X-ray structure of trans-fused compound **6b**, with 30% probability ellipsoids, is shown below:



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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