SYNTHESIS OF 3,6-DIAZABICYCLO[3.1.1]HEPTANES AS NOVEL LIGANDS FOR THE OPIOIDS RECEPTORS.

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Crude opium has been used since antiquity as an analgesic. In modern medicine, only the purified opium alkaloids are commonly employed. Among these, morphine remains one of the most valuable analgesics for relief of severe pain. However, they can cause severe side effects such as respiratory depression, constipation, vomiting, and, moreover, their chronic use results in tolerance and dependence.

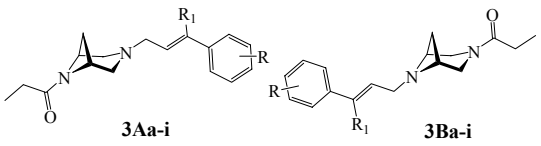
Opioids interact with three major opioid receptor types (μ, δ and κ) and while each of the opioid receptors is associated with analgesia, side effects have been attributed to non specific recognition of subtype receptors. Selective ligands are therefore desirable to reduce adverse side effects. *N*-3(8)-Arylpropenyl-*N*-8(3)-propionyl-3,8-diazabicyclo[3.2.1]octanes **1A,B**, belonging to the bridged diazabicyclic systems, are potent analgesics selectively labelling μ-opioid receptors [1].

Compounds bearing a NO_2 or a Cl groups at the *para* position of the arylpropenyl moiety were reported to elicit reduced physical dependence and tolerance compared to morphine.

Moreover, results on *N*-3(9)-arylpropenyl-*N*-9(3)-propionyl-3,9-diazabicyclo[3.3.1]nonane congeners **2A,B** provided evidence that the endopropano bridge, present in these analogues instead of endoethane of DBO series, had a major impact on the ability of the compounds to interact with opioid receptors [2]; in general N_9-arylpropenyl-substituted DBN derivatives **2B** exhibited markedly higher binding affinities than that of the isomeric ones **2A**. Molecular modeling studies established that the DBN diaza skeleton in its chair-chair favoured conformation oriented the propano bridge towards *N*-3 and this would result in an unacceptable steric bulk around this atom with reduced μ-receptor interaction of the corresponding derivatives.

On the basis of these considerations, it was of interest to evaluate the affinity towards opioid receptors of 3,6-diazabicyclo[3.1.1]heptanes (DBH), which, having an endomethano bridge, represent a further diazabicyclic variant of **1** and **2** characterized by increased rigidity.

Accordingly, representative 3-arylpropenyl-6-propionyl DBH (**3Aa-i**) and their 6-arylpropenyl-3-propionyl isomers (**3Ba-i**) have been synthesized and tested *in vitro* towards opioid receptors.



3A, 3B	a	b	c	d	e	f	g	h	i
R	H	4-NO_2	2-Cl	3-Cl	4-Cl	H	4-Cl	3,4-Cl_2	H
R_1	H	H	H	H	H	CH_3	CH_3	CH_3	Et

[1] Cignarella, G.; Barlocco, D.; Tranquillini, M. E.; Volterra, A.; Brunello, N.; Racagni, G. *Pharmacol. Res. Commun.* **1988**, *20*, 383-394.

[2] Pinna, G. A.; Cignarella, G.; Loriga, G.; Murineddu, G.; Mussinu, J. M.; Ruiu, S.; Fadda, P.; Fratta, W. *Bioorg. Med. Chem.* **2002**, *10*, 1929-1937.