SAR EVALUATION OF CHIRAL *NAPHTYLORFINES* WITH ANTINOCICEPTIVE ACTIVITY

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Although many works concerning analgesia and opioid ligands have been recently published, the molecular basis of opioid action has not yet been completely elucidated [1]. The advance in molecular biology, synthetic methodology and molecular mechanics has made possible a deeper comprehension of the interaction mechanisms of opioid ligands with the different receptor subtypes. With the purpose to obtain analgesic compounds with reduced side effects, subtype selective ligands were designed and prepared. Nevertheless, this approach did not give the expected results and potent opioid analgesics without side effects are still unknown.
As an alternative approach, several attempts were made to identify non selective ligands of mu, kappa and delta receptors, characterized by different profiles of agonism and antagonism. Based on this approach, a non specific pharmacophore model for mu, kappa and delta receptors was proposed [2].
In the last years we dedicated a part of our efforts in the SAR of novel antinociceptive agents. The identified chiral lead compound, which belongs to a series of compounds named *naphtylorfines* shows a non subtype-specific binding with opioid receptors and an interesting *in vivo* analgesic activity (Hot Plate Test, in mice) [1]. Different derivatives of the lead compound were prepared in order to investigate the SAR of these *naphtylorfines*.
We considered the influence of both the structural features of the aliphatic and aromatic moieties, and of the stereochemistry of the tested compounds on their pharmacological properties.

In the present work, the synthesis, the analytical characterization and the configurational assignment of the new compounds is described. Biological results (affinity pattern of the compounds *versus* mu, kappa and delta receptors and *in vivo* evaluation of their antinociceptive activity) are discussed.

[1] Filizola, M.; Villar, H.O.; Loew, G.H. Molecular determinants of non-specific recognition of delta, mu and kappa opioid receptors. *Bioorg. Med. Chem.* **2001**, 9,69.
[2] Azzolina, O.; Collina, S.; Brusotti, G.; Rossi, D.; Linati, L.; Barbieri, A.; Lanza E.; Mennuni L.; Makovec F.; Alcaro S.; Ghislandi, V. XVI Convegno Nazionale Divisione Chimica Farmaceutica, SCI; Sorrento, settembre **2002**.