

SYNTHESIS AND SAR OF NOVEL SIGMA1 SELECTIVE LIGANDS

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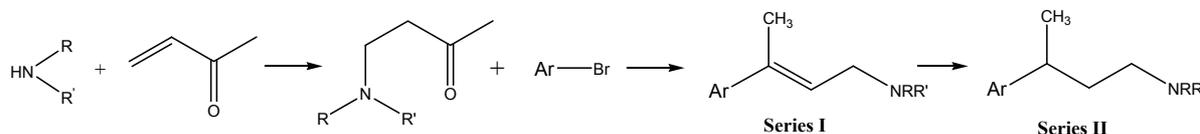
A research on a series of naphthylalkylamines, previously synthesized to account for its possible involvement in opioid analgesia [1], indicated several dimethylaminoalkylnaphthalenes as novel potential ligands for sigma receptors.

Binding assays revealed that some compounds possess also affinity for sigma₁ receptors in nanomolar range.

These encouraging results led to the development of a small library [2] of new arylalkylamino analogues, characterized by suitable modifications of the aromatic moiety and of the alkylamine sidechain.

The proofing library for this approach was constructed as outlined in Scheme 1.

The β-aminoketones intermediates were prepared using Michael reaction, in which the methylvinylketone was allowed to react with the appropriate amines. Thus, the olefinic compounds (Series I) were obtained by nucleophilic addition of the aromatic anions to the β-aminoketones and quenching of the reaction with chloridric acid. Series II compounds were obtained by microwave assisted reduction of the corresponding alkenes.



Scheme 1

A careful evaluation of the sigma₁ binding data ranging from 0.78 to 229 nM provided interesting SAR observations.

[1] Azzolina, O.; Collina, S.; Brusotti, G.; Rossi, D.; Callegari, A.; Linati, L.; Barbieri, A.; Ghislandi, V. Chemical and biological profile of racemic and optically active dialkylaminoalkylnaphthalenes with analgesic activity. *Tetrahedron: Asymmetry* **2002**, *13*, 1073-1081

[2] Azzolina, O.; Collina, S.; Urbano, M.; Alcaro, S.; Lagner, C.; Langer, T. Rational approaches to the design of selective sigma₁ ligands. *JMMC* June 20-23, 2005; Vienna, Austria.