RATIONAL APPROACHES TO THE DESIGN OF SELECTIVE SIGMA 1 LIGANDS

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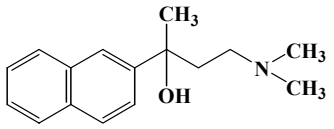
In the present work the naphthylaminoalcohol (*R*/*S*)-**1** previously shown to exert moderate affinity for sigma1 receptors (Ki = 25 nM), was chosen as lead compound to develop novel sigma1 ligands using *Molecular Modeling* techniques.



(R/S)-1

Basing on pharmacophore sigma1 selective models of literature, proposed by Glennon [1] and Gund [1], we designed a virtual library of 171 arylamino analogues with diverse functionalities on the aromatic moiety and on the alkilamine side chain of (*R*/*S*)-**1**. Gund's additional electronegative site (O or S) did not map the O atom of (*R*/*S*)-**1**, thus suggesting to focus on alkanes and alkenes series of the designed library. Each compound of the library was subdued to conformational search with Monte Carlo method. We evaluated the match degree with both pharmacophore models and filtered the library. Interestingly, a shorter distance from amine center to the secondary hydrophobic site of (*R*/*S*)-**1** as well as of all *N*,*N*-dimethylamino derivatives suggested to enhance steric hindrance at the amino group. Further screening using Lipinski's rule-of-five, yielded 30 potential ligands. Subsequent selection by hand on the basis of chemistry compatibility and structural diversity gave rise to a 15-member small library. In this phase, we used a 3D pharmacophore model [3] for sigma1, developed with HypoGen module in Catalyst. Testing this five-point pharmacophore (4 hydrophobic and one positive ionizable features) against conformers of the 15 selected compounds, sustained the hypothesis to direct our synthetic work towards alkenes and alkanes series of compounds with a bulk substituent at the amino group.
Preliminary binding data, prompted us to synthesize new promising ligands bearing either β-naphthyl or 4-diphenyl aromatic moieties [4].

[1] Glennon, R., A.; Ablordeppey, S. Y.; Ismaiel, A, M.; El-Ashmawy, M. B.; Fischer, J. B.; Burke Howie, K.; *J. Med. Chem*. **1994**, *37*, 1214.
[2] Gund, T., M.; Floyd, J.; Jung, D.; *J. Mol. Graphics and Modelling* **2004**, *22*, 221.
[3] unpublished data.
[4] Collina, S.; Loddo, G.; Prezzavento, O.; Ronsisvalle, G.; Azzolina, O.. Synthesis and SAR of novel sigma 1 selective ligands. JMMC June 20-23, 2005; Vienna, Austria.