STRUCTURE-ACTIVITY HYPOTHESIS IN THE DESIGN OF NEW AMPA RECEPTOR ANTAGONISTS

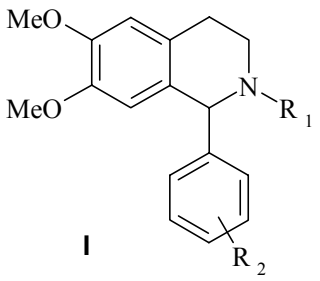
Laura De Luca[a], Maria L. Barreca[a], Rosaria Gitto[a], Roberta Caruso[a], Silvana Quartarone[a], Giovambattista De Sarro[b], and Alba Chimirri[a]

[a]Dipartimento Farmaco-Chimico, Università di Messina, Viale Annunziata, 98168 Messina, Italy
[b]Dipartimento di Medicina Sperimentale e Clinica, Università Magna Græcia,Via T. Campanella, 88100 Catanzaro, Italy

In the past, serendipity played an important role in the discovery of new drugs. Nowadays it has been demonstrated that the search for new drug candidates may be more efficient by establishing biological or structure-activity hypotheses and/or selecting certain scaffolds and substituents. Our research group, long since involved in designing new anticonvulsant agents, has recently developed a predictive pharmacophore hypothesis which led to the discovery 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives as a new class of noncompetitive AMPA receptor antagonists [1-2].

AMPA receptor is one of the three subtypes of glutamate receptor ion channels and its antagonists have been reported as agents useful in the prevention and treatment of a variety of neurological diseases such as epilepsy [3-4].

In this work, the module HypoGen/Catalyst has been used to perform SAR-based hypothesis generation and to derive 3D pharmacophore models with quantitative predictive ability in terms of anticonvulsant activity. Several tetrahydroisoquinolines (**I**) characterized by different efficacy against seizures in DBA/2 mice were thus selected as the training set.



I

The HypoGen-generated hypothesis, consisting of five features (two hydrogen bond acceptors, two hydrophobic features, and one hydrophobic aromatic part), showed high correlation coefficient (r=0.919) and predictive power.

The obtained model was validated using an external test set of anticonvulsant agents. The results of our study have been useful to improve the understanding of the structure-activity relationships and furnished interesting suggestions to design new ligands able to interact with AMPA receptor complex in a noncompetitive fashion.

[1]Barreca ML, Gitto R, Quartarone S, De Luca L, De Sarro G, Chimirri A. "Pharmacophore Modeling as an Efficient Tool in the Discovery of Novel Noncompetitive AMPA Receptor Antagonists". *J Chem Inf Comput Sci*, **43** (2), 651-655 (2003)

[2] Gitto R, Barreca ML, De Luca L, De Sarro G, Ferreri G, Quartarone S, Russo E, Constanti A, Chimirri A. "Discovery of a Novel and Highly Potent Noncompetitive AMPA Receptor Antagonist". *J Med Chem*, **46** (1), 197-200 (2003)

[3] De Sarro G, Gitto R, Russo E, Ferreri Ibbadu G, Barreca ML, De Luca L, Chimirri A. "AMPA Receptor Antagonists as Potential Anticonvulsant Drugs". *Current Topics in Medicinal Chemistry*, **5** (1), 79-84 (2005)

[4]Gitto R, Barreca ML, De Luca L, Chimirri A. "New trends in the development of AMPA receptor antagonists". *Expert Opin Ther Pat*, **14** (18), 1199-1213 (2004)