A CHEMOMETRIC APPROACH TO PREDICT A_1 AGONIST EFFECT OF ADENOSINE ANALOGUES

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Many selective agents have been developed until now for the A_1 receptor subtypes and some of these seem promising as potential therapeutic agents in the treatment of Parkinson's disease, cognitive deficits, schizophrenia and epilepsy [1], however there are currently no A_1 adenosine agonists in clinical development. In this context, as a prosecution of our researches in understanding the structural basis of ligand-A_1 receptor interactions [2], we have focused our interest in identifying the molecular properties responsible for affinity toward A_1 AR by means of quantitative structure-activity relationships (QSAR). As is well known, in these methods correlations are derived between experimentally determined binding affinities and a number of different descriptors, which should encode for the thermodynamics of binding of a set of ligands. The base assumption in fact is that a correlation exists between the enthalpy of binding of a congeneric series of molecules (with similar size and flexibility) and their molecular properties. A set of selective A_1 agonists was thus considered. For the prediction, the structural information encoded by a large number of molecular descriptors for topological, electronic, geometric and polar surface properties was taken into account together with atomic charges on those specific positions of the adenosine skeleton highlighted as important by previous structure-activity relationships studies. In addition, calculated receptor-ligand binding energies for the selected compounds were included among variables. The versatile chemometric package PARVUS [3] was subsequently applied to handle such information, discarding all non-informative descriptors and extracting meaningful QSAR models. The results obtained with many both linear and non-linear approaches converge in the selection of few parameters, which result highly informative for the prediction of the biological response. This “a priori” evaluation strategy could be a useful tool in the screening of large libraries of compounds and in the rational design of new selective adenosine agonists.

[1] Fredholm B. B., Ijzerman A. P., Jacobson K. A., Klotz K.-N., Linden J. *Pharmacol. Rev*., 53, 527-552, 2001.

[2] Giordanetto F., Fossa P., Menozzi G., Schenone S., Bondavalli F., Ranise A., Mosti L. *J. Comput. Aided Mol.-Des*., 17, 39-51, 2003.

[3] Forina M., Lanteri S., Armanino C., Cerrato Oliveros C., Casolino C., V-PARVUS Release 1.0, Dip. Chimica e Tecnologie Farmaceutiche, University of Genova, Italy. Available (free, with manual and examples) at **http://parvus.unige.it**