s8a.m8.p1 **Design of Inhibitors of the Hepatitis C Virus Serine Protease: Modelling and Experimental Results.** U. Koch, C. Gardelli, F. Narjes, V.G. Matassa, C. Steinkühler, *IRBM - P. Angeletti S.p.A., Via Pontina KM 30.60,* 00040 *Pomezia ,Italy*.
Keywords: drug design.

Inhibition of the proteolytic activity of the NS3 protease is a possible strategy for the development of anti-HCV pharmaceuticals. Unlike other serine proteases NS3 lacks well-defined binding pockets in its substrate binding region which renders the development of small molecule inhibitors of this enzyme a challenging task. To design potent inhibitors we tried to gain a more detailed insight into how the NS3-protease recognizes active site ligands. For this purpose the crystal structure of the enzyme was used as the basis for modelling inhibitor complexes which helped to understand the structure activity relationship. Results from these studies were employed to design site directed mutagenesis experiments which gave valuable informations about interactions between individial aminoacids and the ligand. The substrate binding region is characterized by a strong positive potential which is matched by the potential of its more potent ligands. The relevance of this remarkable electrostatic properties of the NS3-protease for catalysis, substrate recognition and inhibition will be discussed.

The results of the analysis were applied to design highly potent mechanism based inhibitors. Crystal structure analysis and NMR-spectroscopy confirmed the models employed. One class of inhibitors described is capable of forming a transient covalent bond with the hydroxyl group of the catalytic serine. The results obtained for different classes of «serine trap» inhibitors are interpreted in terms of the structural properties of the active site of the enzyme. Reactivity of the thiol group of the P1 cystein has been a major obstacle in this series. Chemically inert replacements of the P1-cystein have been designed and incorporated in various series of inhibitors. This provided a platform to design small and potent inhibitors whose peptidic character was increasingly reduced by peptidomimetic replacements.

s8a.m8.p2 **Comprehensive Comparison of the Ergot Alkaloids Family with 5-HT_{1A} Receptor Pharmacophore Models.** J. Cejka[a], B. Kratochvíl[a] and A. Jegorov[b]. [a]*Prague Institute of Chemical Technology, Department of Solid State Chemistry, Technická 5, 166 28 Prague 6, Czech Republic* [b]*Galena Co., Research Unit, Branišovská 31, 370 05 Ceské Budejovice, Czech Republic.*
Keywords: drug dessign, Ergot alkaloids.

Ergot alkaloids are known with their high affinity to 5-HT receptors. The structure of ergot alkaloid molecule, regarding its nonselectivity among various receptor subgroups, represents a universal key to various serotonine receptor binding sites. Hence, it should be a useful tool for verifying some of known pharmacophore models. Most of those models are based on several, closely relative, compounds, trying to define the most efficient conformation of the molecule. On the other hand, some proposed models run out of range, when applying the rules to structurally different groups of compounds.

Several models of 5-HT_{1A} receptor pharmacophore have been published recently[1,2,3]. However, these models are based on series of compounds, that are more or less different from the ergot alkaloid family. Their geometry was calculated by molecular mechanic methods.

Available X-ray structures of ergot alkaloids (CSD and some unpublished results) were compared with geometrical restrains of the 5-HT_{1A} pharmacophore models. Such a comparison was verifying suitability of X-ray structure analysis results in this kind of application. The graphical presentation of distance values, that seem to be responsible for action and probably quality of action on 5-HT_{1A} receptors, divides ergot alkaloids into small groups. The distribution almost clearly depends on modifications of the lysergic acid skeleton.

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