MS05.01.05 INHIBITORS OF GLYCOGEN PHOSPHORYLASE: IN SEARCH OF AN ANTIDIABETIC DRUG. K.A. Watson, M. Gregoriou and L.N. Johnson. Universtiy of Oxford, Laboratory of Molecular Biophysics, South Parks Road, Oxford, OX1 3QU U.K.

The aim of this work has been to design specific regulators of glycogen phosphorylase (GP) that shift the balance from glycogen degradation to glycogen synthesis. Such compounds have potential therapeutic interest in the treatment of non-insulin dependent (Type II) diabetes mellitus (NIDDM). Several compounds have been designed based on the three-dimensional rabbit muscle GP structure (Watson et al., *Biochemistry* 1994, 33, 5745-5758). Analysis of the crystallographically refined complexes has offered some understanding of the factors influencing sugar-protein interactions. To date, the best inhibitor, a glucopyranose analogue of hydantocidin, shows a 1000 fold improvement over the parent glucose moiety (Bichard et al.,Tetrahed. Lett. 1995, 36, 2145-2148). It has been shown, with an earlier analogue (showing two orders of magnitude improvement over glucose) that the compound is an effective regulator of liver glycogen metabolism and is considerably more effective than glucose (Board & Johnson, *Biochem. J.* 1995, 311, 845-852). The results indicate a positive hypoglyceaemic effect and suggest a potential use for these analogues in the treatment of Type II diabetes.

Both structure-based and quantitative structure-activity relationship (QSAR) drug design strategies have been used (Watson et al., *Acta Crystallogr.* 1995, D51, 458-472). The additional information from the QSAR approach provides a quantitative method for the design and prediction of new potential drug molecules. We have used the program combination GRID (Wade & Goodford, *J. Med. Chem.* 1993, 36, 140) and GOLPE (Baroni et al., *Quant. Struct.-Act. Relat.* 1993, 12, 9-20). The latest version of GOLPE (V3.0) has been adapted to use structural information of both the ligand and the protein molecules (traditional methods focus only on the ligand). To date, there is no QSAR methodology that simultaneously uses the inhibitor-macromolecular complex structures and biological data to predict the activity of new drug molecules. Our GP dataset, together with the latest program GOLPE, have provided a unique opportunity to explore such an approach.

MS05.01.06 RELIBase - AN OBJECT-ORIENTED COMPREHENSIVE RECEPTOR-LIGAND DATABASE. M. Hendlich, F. Rippmann, G. Barnickel, Preclinical Research, Merck KGaA, 6427 L Darmstadt, Germany, K. Hemm, K. Aberer, GMD-IPSI, 64293 Darmstadt, Germany

New biomolecular and computational methods have led to an explosion in the available data about receptor/ligand complexes. Unfortunately, existing data is spread over different databases or is not available in electronic format at all. Therefore, we have developed a comprehensive database system for receptor/ligand complexes which combines crystallographic information from the Brookhaven Protein Databank (PDB) with biomolecular information like sequence alignments and information about mutations from various other data sources. RELIBase allows complex queries (including substructure searches, similarity searches and searches for specific interactions) regarding both small molecule and protein aspects.

As a technical platform an object-oriented database management system is used, which offers a structured data model, flexible retrieval mechanisms, persistent storage and sharing of data in a multi-user environment. A rather complex database schema was designed as the foundation for linking heterogenic entities.

The receptor/ligand complexes in the PDB constitute the core data of the RELIBase. The relevant information is identified and extracted using an automatic parser. In order to allow a detailed chemical analysis of receptor/ligand interactions information about bond orders and hybridisation which is not stored in the PDB was defined for each ligand.

Based on this database a detailed analysis of receptor ligand interactions has been undertaken.

MS05.01.07 A MODEL FOR THE DOPAMINE D_4 PHARMACOPHORE. C. G. Chidester, R. E. TenBrink, J. A. Leiby, M. W. Smith, A. G. Romero, M. D. Ennis, N. B. Ghazal, S. K. Schlachter, C. L. Bergh, T. J. Poel, R. M. Huff, Pharmacia & Upjohn, Kalamazoo, MI 49001, USA

A model for the dopamine D_4 pharmacophore that rationalizes differences in affinities and selectivity for D_4 over other CNS receptors will be described. The dopamine D_4 receptor is an attractive target for antipsychotic drug development because clozapine, an "atypical" neuroleptic, binds to it with high affinity. Clozapine is an atypical dopamine antagonist because it lacks the extrapyramidal side effects and eventual tardive dyskinesias associated with dopamine antagonists that act at the D_2 receptor Although it does have many other side effects, it is not selective for the D_4 receptor and the side effects could be due to interactions with other CNS receptors. A selective D_4 antagonist could provide an effective treatment for schizophrenia with fewer side effects. U-101387, a highly selective, high affinity antagonist at the D_4 receptor is the result of a determined synthetic chemistry effort which was based on an isochroman lead and used cloned receptors to test affinities of analogs. U-101387 is now in Phase I clinical trials.

Models for the D_2 and $5HT_{1A}$ pharmacophores reported previously were developed using less flexible structures, including tricyclic angular and linear benzindoles, imidazoquinolinones, benzoquinolines, ergolines, and amino-tetralins. In this study we considered affinities for the D_4 receptor of structures used to develop the previous models and in addition we studied ligands in two new series, analogs of either U-101387 or U-99363. These are highly selective ligands, but many of their analogs do have affinity for the D_2 and $5HT_{1A}$ receptors. Crystal structures of several ligands, including U-101387 and analogs of U-99363E were determined and molecular mechanics calculations were used to verify that proposed conformations of structures were reasonable. The D_4 pharmacophore model is similar to the D_2 and 5-HT_{1A} models previously developed, but has features that help to rationalize the observed differences in selectivity.