

as an attractive target for inhibitor drug design to increase the efficacy of treatment [2].

Drug resistance remains a limiting factor in cancer chemotherapy and thus understanding the mechanisms of this effect represents an essential step in improving cancer treatment. There are many reports correlating over-expression of GST and reduced sensitivity to chemotherapy in lung, liver, breast, ovarian, and other forms of cancer[1]. GSTs are hypothesized to catalyse conjugation of GSH to anticancer drugs forming inactive conjugates, therefore, decreasing efficacy in treatment. The precise mechanisms responsible for the development of resistance to these commonly used anti-cancer agents is currently unknown. Gaining insight, through structural studies by X-ray crystallography, of this enzyme complexed to these compounds, will aid in the design of effective, and specific, inhibitors.

One of the major aims of this work is to determine the 3D structures of these complexes and subsequently pursue structure-based drug design of human GST pi class enzyme (hGSTP1-1) with the hope of discovering potent specific inhibitors. I have collected over 25 data sets of GST complexed to a range of compounds, several of which have been solved and the structures completed. The structure of the hGSTP1-1 in complex with these compounds will identify critical residues which will aid drug design of novel, therapeutic, GST inhibitors.

[1] Sheehan D., et al., *Biochem. J.*, 2001, **360**, 1. [2] Farmer G., *Nature Rev. Drug. Discov.*, 2004, **3**, 547.

**Keywords:** anticancer drugs, inhibitor design, protein crystallography drug design

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#### X-ray Crystallography of the Antiepileptic Drug Zonisamide with CA II

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Zonisamide, ZNS, is a widely used antiepileptic drug [1] whose mechanism of action is still not fully clarified. Recently a patent[2] claimed that ZNS is also effective for reducing weight in obese subjects and for treating eating disorders.

In a previous study we showed by means of solution and X-ray studies, that another sulfonamidic antiepileptic drug, Topiramate, is a strong inhibitor of physiologically relevant human carbonic anhydrase (hCA) [3]. Thus we decided to investigate the interaction of ZNS with the CA isozymes involved in lipogenesis and other metabolic processes, through the crystallographic analysis. Here we report the X-ray crystal structure of the complex ZNS-hCA II at a resolution of 1.70 Å, showing that the ZNS participates in the classical inhibitory interactions with the Zn(II) ion and with specific residues in the active site of the hCA II.

Thus the activity of this drug in different metabolic pathways must be reconsidered also according to its possibility of interaction with different CAs.

[1] Leppik I. E. , *Seizure*, 2004, **13**(1), S5-9. [2] Elan Pharmaceuticals WO03092682, 2003. [3] Casini A., Antel J., Abbate F., Scozzafava A., David S., Waldeck H., Schafer S., Supuran C. T., *Bioorg. Med. Chem. Lett.*, 2003, **13**, 841-5.

**Keywords:** drug design, sulfonamides, carbonic anhydrase

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#### Structures of 5-methylthioribose Kinase: Catalytic Mechanism and Drug Design

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The essential amino acid methionine plays critical roles in a variety of cellular functions but is energetically costly to synthesize. As a consequence, pathways to salvage methionine have evolved in almost all organisms. 5-methylthioribose (MTR) kinase is a key enzyme in this pathway in microorganisms and certain plants, and the absence of a mammalian homolog suggests that the enzyme is a good target for the design of novel antibiotics against MTR kinase containing pathogens and selective herbicides. Recombinant *B. subtilis* MTR kinase has been expressed, purified and crystallized with the detergent CHAPS, and structures of the apo enzyme, ADP, ATP and ATP-MTR complexes have been determined. The first structure was determined by MAD technique using holmium in complex with ADP as the phasing derivative. The structure of MTR kinase has a eukaryotic protein kinase fold, and is similar to 3',5'-aminoglycoside phosphotransferase and choline kinase. Structures of MTR kinase with and without its substrate reveal local conformational flexibility and illuminate a detailed catalytic mechanism of the enzyme. These structures also provide a blueprint for future structure or mechanism based drug design.

**Keywords:** protein crystallography drug design, methylthioribose kinase enzymatic mechanism, methionine recycling pathways

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#### Dobexilate as a Lead Compound in Angiogenesis Inhibition Search

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Fibroblast growth factors (FGFs) are powerful angiogenic polypeptides, whose mitogenic activity requires the presence of heparin-like compounds. Inhibition of angiogenesis-promoting factors such as fibroblast growth factor is considered to be a potential procedure for inhibiting solid tumor growth. Although several peptide-based inhibitors are currently under study, the development of antiangiogenic compounds of small molecular size is a pharmacological goal of considerable interest. We have study the effect of dobexilate *in vitro* and *in vivo* in order to find a minimum compound capable of inhibiting angiogenesis and tumor growth. Cell cultures as well as animal model experiments have shown clearly an angiogenesis suppressing effect event at low concentration as 50 µM. To provide structural information of this process we have solve the three-dimensional structure of a dobexilate-FGF complex. The structure gave us a clear image of the antiangiogenesis mechanism of the dobexilate molecule which consists in the steric hindrance of interaction between the FGF molecule and the low affinity membrane receptor of this molecule in the plasma membrane, hampering in this way the beginning of the signalling cascade. Further studies of different groups in the minimal dobexilate structure could give us a more powerful and less toxic antiangiogenic compound using the disruption of the interaction of FGFs with heparin and heparan sulphates as its principal mechanism.

**Keywords:** FGFs, antiangiogenesis, dobexilate

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#### HIV Protease Inhibition Seen by X-ray Diffraction and Molecular Dynamics

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Binding of inhibitor into the complex with HIV protease is accompanied by a large movement of protease flaps. X-ray crystallography shows the stable inhibited protease complexes [1], or unliganded proteases with "semi-opened" flaps and larger atomic displacement parameters. This work inspects conformational mobility