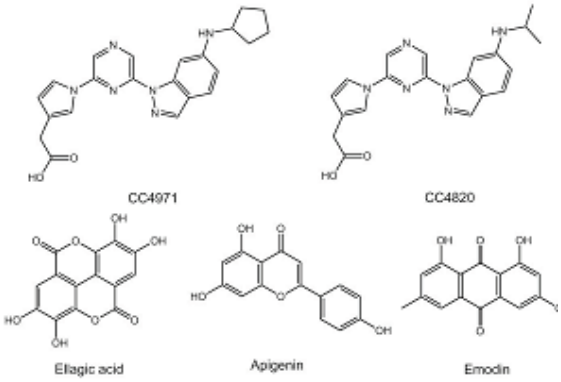
inhibitors. Thermodynamic data, specifically enthalpy (ΔH) and entropy (ΔS), reveal the forces that drive complex formation. Furthermore, binding affinity - K_d in range of millimolar to nanomolar is a powerful information for drug design targeting highly homologous kinases. Supported with computational analysis, these data show the specific contributions of some important residues in ligand-binding, and lead to design a potent inhibitor.



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Keywords: CK2; kinase inhibitor; drug design

FA1-MS07-P11

Structural Characterization of Human Glutathione Transferase A1-1 in Complex with the Anti-cancer Drug Chlorambucil. Lykourgos Chiniadis[a], Kostas Bethanis[a], Nikos Labrou[b], Irene Axarli[b], Katholiki Skopelitou[b], Michael Karpusas[a]. [a]*Physics Lab., Department of Science, Agricultural University of Athens.* [b]*Lab. of Enzyme Technology, Department of Agricultural Biotechnology, Agricultural University of Athens.*
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The glutathione transferases (GSTs) are detoxification enzymes that protect the cell from a wide range of potentially harmful electrophilic compounds [1]. Although this action of GSTs protects the organism from harmful environmental toxins, it results also in neutralization of certain therapeutic drugs such as chlorambucil, an anti-cancer drug used to treat chronic lymphocytic leukemia (CLL) [2]. Design of GST inhibitors that mimic chlorambucil binding may be useful in improving the bioavailability of chlorambucil when they are co-administered with the drug. To enable structure-based design of such inhibitors, human GST A1-1 was crystallized in the presence of glutathione and chlorambucil and its structure was determined at 2.3 Å resolution. Chlorambucil is observed to form a conjugate with glutathione, adopting a conformation different from the one observed in the structure of GST P1-1 and to induce local conformational changes in nearby protein residues. In addition it reacts with the only cysteine residue of the enzyme, in agreement with biochemical evidence.

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Keywords: glutathione transferase; anticancer drugs; crystallographic structure determination

FA1-MS07-P12

Targeting Telomeric RNA Quadruplexes. Gavin Collie[a], Stephen Neidle[a], Gary Parkinson[a]. [a]*CRUK Biomolecular Structure Group, The School of Pharmacy, London, UK.*
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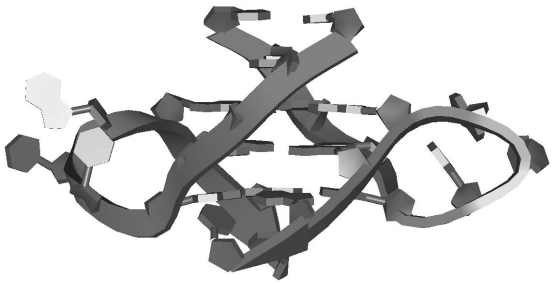
Following the discovery that mammalian telomeres are transcribed into telomeric-repeat containing RNA [1],[2], there has been a move to determine the role these molecules play in telomere regulation. We report here the first crystal structure of a telomeric RNA G-quadruplex, providing atomic-resolution insights into RNA-quadruplex folding. The structure, formed from the sequence r(U_{Br}AGGGUUAGGGU), folds as a bimolecular, parallel stranded G-quadruplex with linking propeller-type external loops, a topology previously observed for the equivalent telomeric DNA sequence [3].
As telomeric DNA G-quadruplexes are well established targets for small molecule anti-cancer therapeutics, it is reasonable to consider telomeric RNA G-quadruplexes as potential targets too. The structure reported here provides the basis for computer aided drug design, and will hopefully allow the differences between RNA and DNA G-quadruplexes to be identified and exploited for improved specificity of quadruplex-interacting ligands. These issues will be addressed and the structural basis for drug design explored.



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Keywords: RNA structure; anticancer drug structural study; drug targets