MS7-P1 **Discovery of Novel Inhibitors of Bacterial -Lactamases using ARP/wARP-based Drug Design.**
Ciaran Carolan[a], Victor Lamzin[a], Vitaly Grigorenko[b], Alexey Egorov[b]. [a] *European Molecular Biology Laboratory Hamburg, Germany,* [b] *Department of Chemical Enzymology, MV Lomonosov Moscow State University, Russia.*
E-mail: ciaran.carolan@embl-hamburg.de

The identification of the endogenous ligands that bind macromolecules and the structural modelling of their interactions with a protein or nucleic acid are fundamental to the understanding of macromolecular function, as well as being a crucial element of efforts to develop drugs to interfere with that function. The ARP/wARP software suite that we have developed for the building of macromolecular structures in crystallographic electron density maps includes an advanced ligand-building module that enables the automatic identification and modelling of bound small molecules. [1] The method relies on features that match the shape and size of a series of candidate ligands - each in a variety of conformations - to the density, and can be calculated exceedingly rapidly.

Drug molecules often interact with biological macromolecules in a manner analogous to endogenous ligands, occupying the same pockets and exploiting similar interaction possibilities. Based on this realisation, we have advanced our software to be applicable to structure-based drug discovery. The software, utilising both established and novel structural features, identifies drug candidates that can, in some feasible conformation, bind similarly to the target macromolecule. As well as topologies, molecular charge information is considered in order to retain advantageous contacts while also providing for possible new interactions with the host. A database of 8 million candidate drug compounds is screened in just a few hours on a single desktop computer. This software will soon be available for free academic use via the ViCi web server.

The method has been applied to identify new inhibitors of the bacterial beta-lactamase enzymes that are responsible for a significant amount of the problematic antibiotic resistance that is developing into an immense clinical issue. Four known inhibitors, binding both at the active and allosteric sites of the enzyme, were used as input, and a total of 550 compounds suggested by the software were screened *in vitro*. Better inhibitors were identified based on each of the four template molecules, with one demonstrating an order of magnitude better inhibition than any similar agent reported previously. These compounds are now being analysed *in vivo*. Furthermore, inhibition of function was seen in different enzyme isoforms, while inhibitors of one enzyme were used as templates for the discovery of compounds active against other resistance enzymes. This suggests that the software might permit the rapid development of new drugs for the resistance isoforms that so often proliferate rapidly within the population upon the introduction of new antibiotic drugs, aiding researchers' efforts to outpace the rapid development of drug-resistant bacterial species.

Crystal structures of the enzyme-bound ligands are also being sought in order to confirm the proposed binding modes and also for use in subsequent lead development research. The results of these efforts will also be reported.

[1] Langer, G. G., Evrard, G. X., Carolan, C. G. & Lamzin, V. S. (2012). *J. Mol. Biol.* **419 (3-4)**, 211-222.

Keywords: antibiotic resistance, drug design, ARP/wARP

MS7-P2 **Structure determination of 9-[(E)-2-(substituted-phenyl)ethenyl]-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione.**
Joo Hwan Cha,[ab] Jae Kyun Lee,[c] Yong Seo Cho,[c] [a]*Korea Institute of Science & Technology, South Korea,* [b] *Advanced Analysis Center, Korea Institute of Science & Technology, Hwarangro 14-gil, Seongbuk-gu, Seoul, South Korea,* [c] *Center for Neuro-Medicine, Korea Institute of Science & Technology, Hwarangro 14-gil, Seongbuk-gu, Seoul, South Korea*
E-mail: jhcha@kist.re.kr

Xanthenes constitute an important class of organic compounds that have attracted strong interest due to their useful biological and pharmacological properties, such as antibacterial, antiviral and antiinflammatory activities. Herewith we present the crystal structure of (E)-9-(4-chlorostyryl)-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione (**A**)[1] and 9-[(E)-2-(2-methoxyphenyl) ethenyl]-3,4,5,6,7,9-hexahydro-2H-xanthene-1,8-dione (**B**)[2]. In the compound (**A**), $C_{21}H_{19}ClO_3$, the two cyclohexenone rings adopt half-chair conformations, whereas the pyran ring adopts a boat conformation. The 4-chlorophenyl ring is almost perpendicular to the plane through the four C atoms of the pyran ring [dihedral angle = 87.97 (6)°]. In the crystal, weak C—H···O hydrogen bonds link the molecules into a chain parallel to the *a*-axis. In the compound (**B**), $C_{22}H_{22}O_4$, the two cyclohexenone rings adopt half-chair conformations, whereas the six membered pyran ring adopts a flattened boat conformation, with the O and methine C atoms deviating from the plane of the other four atoms by 0.142 (2) and 0.287 (2)A° , respectively. In the crystal, weak C—H···O hydrogen bonds link molecules into chains running parallel to the *a* axis.

[1] Lee, J. K., Pae, A. N., Cho, Y. S. & Cha, J, H. (2012). *Acta Cryst.* E**68**, o501.
[2] Cha, J, H., Pae, A. N., Lee, J. K. & Cho, Y. S. (2012). *Acta Cryst.* E**68**, o454.

Keywords: X-ray crystallography of organic compounds; xanthene; absolute structure determination