



Canadian Light Source
Centre canadien
de rayonnement
synchrotron

One of only 25 similar facilities worldwide, the Canadian Light Source synchrotron is a national research facility that offers innovative and unique-in-Canada ways to conduct commercial research.

A synchrotron is a multi-faceted facility where intense beams of light are generated to help scientists probe the nature and structure of molecules and materials.

With innovative commercial research access, clear IP regulations and scientists dedicated to promoting industry involvement, the CLS is a valuable tool for commercial research.

Pharmaceutical Research



Protein crystallography is one of the fastest growing fields in synchrotron research, and for good reason: the technique helps solve protein structures more accurately, faster and using smaller crystals. The results from protein crystallography research are leading us closer to finding cures for major diseases such as coronary disease, cancer, diabetes, and viral infections.

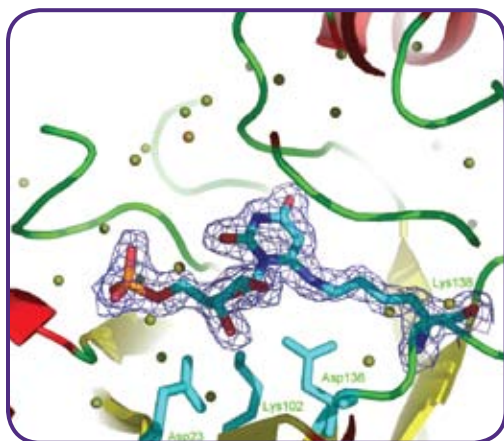
Protein crystallography uses X-rays to study macromolecules in crystalline form. Synchrotron-generated X-rays are diffracted from a crystal and hundreds of diffraction images are collected on a CCD detector. From an analysis of the diffraction pattern, we can determine the atomic details of the macromolecule or complex of molecules that caused the diffraction. Once the atomic details of a macromolecule are known, scientists can begin to understand how it interacts with other molecules. The analysis helps clarify the detailed mechanism by which these macromolecules carry out their functions in living cells and organisms.



Applications to the Pharmaceuticals Sector:

- ***Analysis of protein-ligand complexes at the atomic scale.***
 - ***Fragment-based approaches to drug discovery.***
 - ***Determining structures of target macromolecules.***
- ***Providing information on the suitability of specific proteins as drug targets, through structural genomics.***
- ***Developing new pharmaceuticals and vaccines.***
- ***High-throughput macromolecular crystallography as a key technology in lead optimization strategies.***
- ***Studying the functionality of proteins, hormones, metabolic enzymes, bacteria, viruses and genes.***
- ***Developing 'designer' molecules for pharmaceutical drugs.***

Case Study



Close-up view of the catalytic site of *P. falciparum* ODCase with the inhibitor molecule forming a covalent bond to the side chain of one of the amino acids (Lys138). Other amino acids that contribute to the acceleration of the reaction are shown as sticks. The small spheres represent water molecules that are tightly bound to the protein. The blue mesh represents the electron density deduced from the synchrotron measurements.

Combating malaria using a novel drug-target interaction

Malaria, caused by *Plasmodia* parasites, has re-emerged as a major problem, imposing its fatal effects on human health. One of the leading causes of this resurgence is multidrug resistance, resulting in the need for new drug targets. In *Plasmodia*, orotidine 5'-monophosphate decarboxylase (ODCase) is an essential enzyme for the *de novo* synthesis of uridine 5'-monophosphate. Impairing ODCase in these pathogens is a promising strategy to develop novel classes of therapeutics. The recent discovery that 6-iodo uridine is a potent inhibitor of *P. falciparum* ODCase and an efficient killer of plasmodial parasites has opened the door for novel drug development using this drug-enzyme interaction as a basis. Using derivatives of 6-iodo uridine, three novel antimalarial compounds have been characterized. 6-N-methylamino and 6-N,N-dimethylamino uridine derivatives exhibit moderate antimalarial activities, while 6-azidouridine 5'-monophosphate binds covalently to *P. falciparum* ODCase thus interfering with its mechanism of action. The development of novel inhibitors becomes the more critical the more the prevalence of multidrug resistance increases.

* A. M. Bello, E. Poduch, Y. Liu, L. Wei, I. Crandall, X. Wang, C. Dyanand, K.C. Kain, E. Pai, L.P. Kotra. Structure-Activity Relationships of C6-Uridine Derivatives Targeting Plasmodia Orotidine Monophosphate Decarboxylase. *J. Med. Chem.* 51 (2008) 439-448.

Synchrotron advantages over conventional research techniques:

- Fast MAD/SAD experiments resulting in high-speed access to crystal structures of target molecules
- Sample minimization and high-throughput screening
- Better diffraction pattern quality and higher resolution leading to precise models of lead compounds
- Identification of metals and ions in crystals of proteins
- Crystals as small as 20µm can be analyzed
- Fast analysis of solid polymorphs of drug compounds

