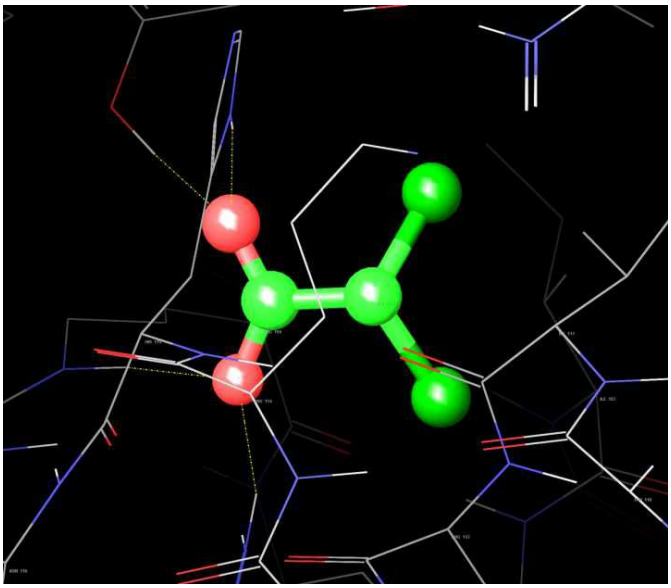
In Silico Design of PDHK Inhibitors

R. Kakkar*

Computational Chemistry Group, Department of Chemistry, University of Delhi, Delhi-110 007, India

*Author for correspondence e-mail: rkakkar@chemistry.du.ac.in

PDC is one of the largest multi-enzyme complexes found in living cells. It catalyzes a key regulatory step in oxidative glycolysis, the irreversible decarboxylation of pyruvate, leading to the conversion of pyruvate to acetyl-CoA. In mammals, the activity of PDC is regulated by the PDHK enzyme, which catalyzes the phosphorylation of PDC, causing its inactivation.[1] As activation of PDC is important for medical conditions such as heart ischemia and insulin resistant diabetes, PDHKs have been targets for development of specific PDHK inhibitors. One such inhibitor is dichloroacetate (DCA). The binding site of DCA in PDHK2 (one of the four PDHK variants) has been examined in detail.[2] It is found to bind more strongly than pyruvate but, because of its toxicity, is not suitable as a drug. In order to find a more suitable ligand, a virtual library of small drug-like molecules was created, and various calculated structural, electronic and topological parameters for the ligands were correlated with various scoring parameters. Similar calculations were performed for molecules similar to pyruvate and DCA. Of a total of about 2000 molecules screened this way, a few were short-listed, based on their strong binding affinity to PDHK2 and the absence of any serious ADME issues. They were tested for inhibitor activity and found to be more potent than DCA. Several synthetic alternatives have also been developed, and these include the potent binding 3,3,3-trifluoro-2-hydroxy-2-methylpropanoyl-containing inhibitors, such as Nov3r, AZ12 and AZD7545. Docking studies on AZ12 analogues have also been performed. Structure-activity relationships have revealed the importance of hydrogen bond acceptor groups and lipophilicity in enhancing inhibition. Another synthetic inhibitor is Pfz3, which owes its activity to its structural similarity to CoA, and its analogues have also been docked into the PDHK2 site.[3] Most of the modifications in the original ligand have yielded more potent analogues.



References

1. M. S. Patel and L. G. Korotchkina, Experimental & Molecular Medicine, 2001, 33, 191-197.
2. R. Kakkar, International Research Journal of Pharmacy, 2011, 1, 51-59.
3. P. Gahlot and R. Kakkar, International Research Journal of Pharmacy, 2011, 1, 1-8.