Mymoona Akhter, J Drug Metab Toxicol 2016, 7:3 (Suppl)
http://dx.doi.org/10.4172/2157-7609.C1.005

Computational design and validation of some novel, non-pteridine analogs as selective *Mycobacterium tuberculosis* dihydrofolate reductase inhibitors

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Dihydrofolate reductase (DHFR) is one of the validated drug targets in *Mycobacterium tuberculosis* infection. DHFR inhibitors have been used to treat various life threatening diseases such as cancer, malaria and several bacterial infections. However, all clinically effective DHFR inhibitors are non-selective and inhibit both human and pathogenic DHFR more or less to a similar extent. The crystal structures of DHFRs are validated and have been used for new drug design. Mycobacterium and human *(h)*-DHFRs show 26% structure similarity but their active sites are not identical and this information forms the basis of our study. Since most of the reported inhibitors of *Mtb* DHFR are pteridine based and are non-selective in nature therefore this study is aimed at to design and develop selective non-pteridine *Mtb* DHFR inhibitors. In the ternary complex of MTX with *Mtb* DHFR, in addition to MTX a glycerol "A" molecule is found in a depression nearby which shows interaction with the side-chains of Trp22, Asp27 and Gln28 which form a pocket in *Mtb* DHFR while glycerol is absent in h-DHFR. The h-DHFRs glycerol is absent and the site is packed with three hydrophobic residue side chains, Leu22, Pro26 and Phe31, which correspond to Leu20, Arg23 and Gln28 in *Mtb* DHFR. A compounds with side chain which could mimic the binding mode of glycerol to protein, may bind to *Mtb* DHFR selectively. Such a derivative should be sterically and chemically hindered from forming a complex with h-DHFR. This assumption forms the basis of present study and these understandings have been used for designing of selective inhibitors of *Mtb* DHFR. Number of novel non-pteridine based molecules has been identified through virtual screening of three databases. The synthesis of best hit has been carried out and tested for anti-tubercular activity. The results are promising and require further work in this direction.

Biography

Mymoona Akhter holds Ph.D. Pharmaceutical Sciences, M. Pharma in Pharmaceutical Chemistry from Jamia Hamdard (Hamdard University) New Delhi. Akhter is working as an Associate Professor of Medicinal Chemistry in Faculty of Pharmacy and is Deputy Co-ordinator of the Bioinformatics Facility Jamia Hamdard. Akhter has been bestowed with several honors like the SERB- fast track research project award for young scientists by Department of Science and Technology, Govt. of India (2012), the Career award for young Teachers by All India Council of Technical Education (2010), SERC Visiting Fellowship by DST (2005). She is supervising scientific research of the post-graduation and the doctoral level. She has guided/under guidance about 20 theses of M. Pharm. and M.Tech Bioinformatics and 5 theses of Ph. D. She has presented his research work in 43 conferences held in India and abroad. She has a list of more than 50 manuscripts in journals of repute and has co-authored a book on Practical Pharmaceutical Analytical Chemistry. She is Editor-in-Chief of International journal of Pharmaceutical Chemistry and Analysis.

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