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Discovery of new small molecule inhibitors of the Hepatitis C virus RNA-dependent RNA polymerase: Pharmacophore modeling, 3D-QSAR studies dnd high-throughput screening

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Hepatitis C Virus (HCV), a blood-borne pathogen belonging to the Flaviviridae family of viruses, is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. The current HCV therapy suffers from inadequate sustained viral response rate, in particular for patients infected with genotype 1 HCV, along with significant side effects, resulting in a continuing medical treatment. Our research has been focused on identifying novel small molecule inhibitors of the HCV NS5B protein, a virally encoded RNA-dependent RNA polymerase (RdRp), the activity of which is critical for the replication of the virus. In this study, a 3D pharmacophore mapping studies were undertaken for different series of synthetic derivatives. A five point pharmacophore with two hydrogen bond acceptors (A), one hydrogen bond donor (D), and two aromatic rings (R) as pharmacophoric features was developed. The pharmacophore was validated using enrichment calculation which yielded a statistically significant 3D-QSAR model with good correlation coefficient (R^2= 0.9715) for training set compounds. The model showed excellent predictive power (Q^2= 0.6063). The model was then employed as 3D search query to screen against public and In-House libraries (Asinex, BITS database) in-order to identify a new scaffold. Top ranked hits were selected, synthesized and were evaluated for their enzyme inhibitory activity against HCV Protease. Inhibitors with IC50 value >50nM were considered as potential inhibitors forHCV Protease. The backbone structural scaffold features and contour maps obtained from the 3D QSAR model could serve as template to design novel small molecule inhibitors for HCV Protease.

Biography

J. T. Patrisha has completed her M.Sc. (Chemistry) from Annamalai University, Tamilnadu. Currently, she is pursuing Ph.D. from Department of Pharmacy, Birla Institute of Technology & Science-Pilani (BITS-Pilani), Hyderabad campus, Jawahar nagar, Hyderabad under the guidance of Prof. P. Yogeeswari since March, 2010. Her research area of interest is antimicrobial drug discovery.

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Polymer controlled delivery of therapeutic nucleic acid for the treatment of cancer

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The lack of selective delivery of therapeutic molecules to tumour cells is a problem in treatment of cancer. As a result of this non-selectivity, cytotoxic agents are delivered to both healthy and diseased cells, resulting in severe side effects for the patient, eventually causing termination of therapy or ineffective therapy resulting in progression or recurrence of the disease. In this context, cationic polymers emerge as a promising option due to their unique properties that enable them to deliver therapeutic genes or molecule to the tumour site to form complexes with negative charged macromolecules such as DNA or RNA. They also form strong interaction with biological membranes and therefore with tumor cells triggering facilitated entrance of those therapeutic molecules into them for effective cytotoxic effect. Cationic polymers have been extensively reported to form nano-size complexes with therapeutic nucleic acids like DNA and small interfering RNA (siRNA). We can deliver these nucleic acids to control disease progression by induction and/or inhibition of genes. Since siRNA's high efficiency for silencing the expression of proteins at the post-transcriptional level, it shows great prospect in therapeutics for diseases. RNA interference (RNAi) is a potential method to cure diseases that mediates sequence-specific inhibition of gene expression through the activation of RNA induced silencing complex (RISC) by interaction with siRNAs. On the other hand, in DNA-based therapeutics DNA are efficiently introduced into tissues and only selected genes are switched off ensuring specificity in controlling the disease status.

Keywords: Cationic Polymers, Therapeutic Nucleic acid, RNAi, Cancer Treatment.

Biography

This presentation will be a group presentation done by Jijnasa Bordoloi, Palakshi Das, Priyanka Tiwari. They are doing M.Sc in Biotechnology from SRM University, Tamilnadu, India.

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