CHAPTER 6

BIOMEDICINE

Doctoral Theses

034. AHLUWALIA (Jasmine Kaur)
Epigenetic Mechanisms of Incomplete Penetrance and Variable Expressivity : Possible MicroRNA Connectivity.
Supervisors : Prof. Vani Brahmachari and Dr. Sridhar Sivasubbu
Th 18012

Abstract

This work has create a dataset of genes showing incomplete penetrance and/or variable expressivity (IP-VE) in humans and screen these genes to find target or source of miRNA, Experimental validation of microRNA-mediated regulation of IP-VE and gene and Elucidation of differential allelic expression mediated by microRNA. It also adds to the repertoire of regulatory circuits in which miRNA exert their influence in biology but provides a possible explanation to the occurrence of variability in penetrance or expression amongst individuals of the same genotype.

Contents

035. DHAWAN (Gagan)
Novel Methods for the Synthesis of Oligonucleotides and Their Modified Analogs.
Supervisors : Prof. Vani Brahmachari and Dr. K. C. Gupta
Th 18212

Abstract

This study is undertaken to develop improved methods for the

synthesis and rapid, facile and cost effective modification of oligonucleotides. Novel deprotection conditions have been developed to cut-short the post-synthesis work-up time required to obtain fully deprotected oligomers from universal polymer support. Likewise, for modification of oligonucleotides at the 3'-end to attach a variety of ligands for various applications, engineered polymer supports, using gold nanoparticles, have been designed and synthesized.

Contents

1. Review of literature. 2. Materials and methods. 3. Polymine-assisted cleavage of oligonucleotides from cis-diol bearing universal support. 4. Manganese-imidazole complex assisted cleavage of oligonucleotides from cis-diol group bearing universal support. 5. Gold nanoparticle conjugated polymer supports for efficient synthesis of modified oligonucleotides. 6. Results and discussion. References, Summary and appendix.

036. GUPTA (Ruby)
Pharmacophore Design, Virtual Screening and Development of Novel Cox-2 Selective Inhibitors.
Supervisors : Prof. B C Das and Dr. Madhu Chopra
Th 18284

Abstract

This work have designed COX-2 selective inhibitors starting with the development of pharmachophore model. Set of 66 compounds known to be potent COX-2 inhibitors are shorlisted. After the development of pharmacophore, it is validated against the test set of 22 compounds. To evaluate the statistical relevance of the model, the Fischer's randomization test is applied. The 19 hits obtained by following a sequential procedure for virtually screening the two databases, carried out the docking studies and used CHARMm based CDocker module, DS2.5, Accelrys Inc.

Contents

1. Introduction. 2. Review of literature. 3. Molecular modeling study on chemically diverse series of cyclooxygenase-2 selective inhibitors : Generation of predictive pharmacophore model using catalyst. 4. Virtual screening of NCI and MiniMaybridge databases. 5. Docking studies of the training set compounds and resultant leads obtained from the virtual screening of NCI and

MiniMaybridge databases. 6. In vitro screening of the resultant lead compounds obtained from in silico screening of NCI databases.

037. KAUSHIK (Nagendra Kumar)
Synthesis of 1,2,3,4,-Tetrahydropyrazino (1,2-α) Indoles and Their Biological Evaluation.
Supervisors : Dr. Akhilesh Kumar Verma and Prof. Sarman Singh
Th 18213

Abstract

This work carried out the synthesis of pyrazino [1,2-a] indoles (a) by conventional method in one pot at room temprature using cheap and easily available chemical which are easy to handle; (b) by green chemistry approach using Ionic liquid and Microwave assisted clay catalyses organic synthesis. Evaluate toxic and antiproliferative affect of pyrazino [1,2-a] indoles in cancerous as well as in normal cell lines and *In silico* tubulin binding studies and pharmacophore generation with pharmacokinetics profile of pyrazino [1,2-a] indoles alongwith antimicrobial activity of pyrazino [1,2-a] indoles against standard and clinically isolted resistant microbial strains.

Contents

038. MALIK (Sakshi)
Synthesis of 1,4-Dihydropyridine, 3,4-Dihydropyrimidin-2-One and Pyrido[3,2-b][1,4]Oxazine Derivatives.
Supervisors : Prof. B C Das and Dr. Rakesh Kumar
Th 18007

Abstract

Hetrocyclic chemistry is the basic to life and society. This research is designed to rationalize organic reactivity of heterocycles in term of their chemical structures. This enables to develop novel improved synthetic methods for the synthesis of a wide variety of classes of organic compounds. Derivatives of 1,4-dihydropyridine are well known for their pharmaceutical

values. Hantzsch 1,4-dihydropyridines (1,4-DHPs) are biologically active compounds. They are vasodilator, antihypertensive, branchodilator, antiatherodclerotic, hepatoprotective, antitumor, antihypertensive, branchodilator, Antiatherodclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents.

Contents

1. Introduction. 2. Synthesis of 4-[5-chloro-3-methyl-1-phenyl-1-1H-pyrazol-4-yl]-1,4-dihydropyridines. 3. Synthesis of novel 5-substituted-6-methyl-4-[5-chloro-3-methyl-1-pheny1-1H-pyrazol-4-yl]-3,4-dihydropyrimidin-2(1H)-ones. 4. Synthesis of 3,4,4a,5,8,8a-hexahydro-2H-pyrido[3,2-b][1,4]oxazines derivatives. 5. Antibacterial activity of 1.4-dihydropyridine and 3,4-Dihydropyrimidine-2-one derivatives.6. Summary.

039. MANISH

DNA Minor Groove Binder Targeted Agents : Synthesis and Its Biological Evaluation.

Supervisor : Dr. Vibha Tandon

Th 18009

Abstract

It has described the synthesis of four 'head-to-tail' bis-benzimidazoles having the substitution of both electron donating (OCH_3) and electron withdrawing groups (F, Cl) at phenyl ring. The molecules have been named as DFA, DCA, DMA and TMA depending on substitution on phenyl ring. The fluorescence, circular dichroism and temperature dependent UV-absorption spectroscopy have been employed to characterize ligand-DNA binding interaction. All spectroscopic studies revealed the strong A/T selective DNA binding affinities of the DFA, DCA, DMA, and TMA as compared to Hoechst 33342. The antibiotic potential of synthesized benzimidazoles MIC has been calculated by microbroth dilution for *Escherichia coli, Shigella flexneri, Salmonella typhimurium, Pseudomonas areuginosa, Klebsiella plenticola.*

Contents

1. Introduction to DNA and its interaction with small molecules. 2. Synthesis of novel non-symmetrical bisbenzimidazole derivatives. 3. Biophysical characterization of drug-DNA complex in order to elucidate the binding affinity and efficiency of newly synthesized bisbenzimidazoles with d(A/T)n and d(G/C)n rich

oligonucleotides. 4. Biological evaluation of synthesized bisbenzimidazole. 7. References.

040. MONIKA

Comparative Analysis of mce1 Operon Architecture in Mycobacteria : Intergenic Promoter Characterization and its Role in differential Expression in M. Tuberculosis.

Supervisors : Prof. Vani Brahmachari and Prof. Mridula Bose

Th 18233

Abstract

It is focused on understanding the significance of redundancy in mce operons in M. tuberculosis aprt from the analysis of genetic polymorphism in these operons. The mce1 operon has the unusual co-transcription with fadD5, a catalytic enzyme. Apart from this, mce1 operon codes for functional activities as catalytic, transmembrane, cell entry, antigenic and putative transporters as the part of a single polycistronic mRNA. Also undertaken the analysis of genomic organization of mce1 operon and differential expression of fadD5 and yrbE1A homologues in pathogenic and non pathogenic Mycobacteria.

Contents

1. Introduction. 2. Identification and Characterization of the Non-coding intergenic region between RV0166 and RV0167 in MCE1 operon, as a promoter in mycobacterium tuberculosis. 3. Detection and analysis of the effect of point mutation on the intergenic promoter of MCE1 operon in an MDR clinical isolate of M. Tuberculosis, VPC1591. 4. Identification of the regulatory factor(s) interacting with IGPR in M. tuberculosis. 5. Analysis of genomic organization of MCE1 operon and differential expression of FADD5 and YRBE1A homologues in pathogenic and non pathogenic mycobacteria.

041. NAVRINDER KAUR

Modulation of Radiation Response in U87, Human Glioma Cells by DMA (Bisbenzimidazole) : A Molecular Insight.

Supervisor : Dr. Vibha Tandon

Th 18232

Abstract

In this work two new less cytotoxic disubstituted benzimidazoles are synthesized DMA (5-{4-methylpiperazin-1-yl}-2-[2'-(3,4-

dimethoxyphenyl)-5'-benzimidazolyl]benzimidazole) and TBZ (5-{4-methylpiperazin-1-yl}-2-{2'{2"-(4-hydroxy-3-methoxyphenyl)-5"-benzimidazolyl}-5'-benzimidazolyl] benzimidazole) and their radiomodifying effects are investigated on a human glioma cell line exposed to low linear energy transfer radiation by determining cell survival and cell proliferation compared with effects of the parent compound, Hoechst 33342.

Contents

1. Review of literature. 2. Regulation of gene expression in response to DNA minor groove binding ligand DMA and ionizing radiation in U87, human glioma cells. 3. Regulation of protein expression in response to DNA minor groove binding ligand DMA and ionizing radiation in U87 human glioma cells. 4. Regulation of NF_KB inducing kinase signaling pathway in response to DNA minor groove binding ligand DMA and ionizing radiation in U87, human glioma cells.

042. NIRPENDRA SINGH
Identification and Functional Characterization of Cellular Protein Interacting with HIV Integrase and HIV Integrase Inhibition by DNAzyme.
Supervisor : Dr. Vibha Tandon
Th 18010

Abstract

This describes the identification and functional characterization of HIV Integrase interacting T cell protein. Which interacts with HIV Integrase, HIV Integrase are cloned and purified from the bacterial system and purified HIV IN is cross-linked with cellular protein. The complex of HIV IN and cellular protein is purified using Ni-NTA pull down and inentification are done by the trypsin digestion and MALDI. After identification interacting protein is cloned and purified. It also describes the designing of DNAzyme against the mRNA sequence of HIV Integrase using the mfold software and evaluation of target side cleavage activity of DNAzyme on the in vitro transcribed mRNA.

Contents

1. Review of literature. 2. Identification and characterization of HIV-1 integrase interacting host cell protein. 3. In-vitro inhibition of HIV Integrase using 10-23 DNAzyme. Appendix.

043. RAKESH KUMAR

Role of Transcription Factors AP-1 and NF-kB in Breast Carcinogenesis.

Supervisors : Prof. B C Das and Prof. M M Chaturvedi

Th 18008

Abstract

The present study is to investigate the role of two most important transcription factors AP-1 and NF-kB during breast carcinogenesis and correlate their expression and functional activities with the tumor staging, grades and histological type. Further, it investigate if the expresson and DNA binding activity of AP-1 and NF-kB could be modulated with the treatment of curcumin. It also analyses the trans-activation and expression pattern of AP-1 and NF-kB in the breast cancer cell lines, MCF-7 with treatment of herbal antioxidant Curcumin.

Contents

044. WASON (Shuchita)

Bio-Chemical Characterization of Signal Peptidase II Enzyme of Mycobacterium Tuberculosis (H37Rv); Expression, Cloning & Purification of the Enzyme and Substrates.

Supervisor : Prof. Daman Saluja

Th 18011

Abstract

It deals with cloning and purification of signal peptidase II enyzme (IspA) of Mycobacterium tuberculosis and its secondary structure predictions by CD spectra analysis. Cloning and Purification of putative lipoprotein substrates of signal peptidase II enzyme and Genome organization and transcriptional analysis of signal peptidase II and its putative substrates in different growth phases and under stress conditions in M. smegmatis.

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