CHAPTER 6

BIOMEDICINE

Doctoral Theses

029. JAIN (Akash Kumar)
Nonintercalating DNA Binding Ligands : Synthesis and their interaction with double and triple helical DNA.
Supervisor : Dr. Vibha Tandon
Th 14343

Abstract

A bisbenzimidazole-maleimide-DNA conjugate has been prepared in good yield and this conjugate stabilizes the DNA triple helix. Some new bisbenzimidazokes and terbenzimidazoles have been synthesized which binds with AT rich DNA sequences more strongly than parent compound Hoechst 33258. Terbenzimidazoles stabilize Hoogsteen duplex and DNA triple helix.

Contents

1. Introduction. 2. Synthesis of a novel bisbenzimidazole-maleimide-DNA conjugate and its effect on the stabilization of DNA triple helix. 3. Synthesis of new bisbenzimidazoles and terbenzimidazoles and their interaction with DNA. 4. Interaction of new bisbenzimidazoles and terbenzimidazoles with DNA triple heliz and hoogsteen paired parallel stranded duplex DNA. 5. Summary and Conclusions. Bibliography.

030. KAPOOR (Gauri)
Development of Molecular Diagnostics and Study of Chromatin Remodeling in Acute Lymphoblastic Leukemia.
Supervisor : Prof. Vani Brahmachari
Th 14176

Abstract

Attempts to change a generic treatment strategy for ALL to patient specific course depending on the molecular specification of ALL as well as pharmocogenetic profiling of individuals. The in silico analysis and the limited experimental

analyses strongly suggest that there perhaps is a significant role for chromain organization in differentiation in general and leukemogenesis in particular. The association of DNA with chromatin proteins can be one of the mechanisms by which pathobiology of complex diseases can be better understood. Polycomb and trithorax group are global regulatory protein in Drosophilla. These proteins form a part of chromatin remodeling complexes. The interaction of these proteins with DNA is mediated by sequences referred to as Polycomb Responsive Elements (PRE), which are also the cis-acting elements where trithorax proteins interact Trithorax Responsive Elements (TRE). One of the interesting aspects that have emerged during the present project is that apart from perturbing the regulation of target genes, genetic translocation can result in altered regulation of the chimeric domains due to changes in chromatin architecture of the chimeric genes relative to the wild type specially the sequences coding for the domains from the 3' partners of the translocation. Thus once again proposing a pivotal role for chromatin architecture of gene sequences in cellular functions.

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031. SHAKUN SINGH

Impact of Vegetarian Diet, Aerobic Exercise and Rajyoga Meditation on Hyperinsulinemia, Dyslipidemia and Homocysteinemia in Coronary Artery Disease.

Supervisors : Dr. R C Sawhvey and Dr. W Selvamurthy

Th 14175

Abstract

Evaluates the efficacy of lifestyle intervention like vegetarian diet, aerobic exercise and Rajyoga Meditation on hyperinsulinemia, homocysteinemia and dyslipidemia in coronary disease. The study was performed on 120 angiographically documented coronary artery disease patients in four different batches of thirty patients each. The patients were studied in three different groups, randomized control (n=30), randomized LSI (n=30) for two years and a non-randomized LSI (n=60) group for three years. The intervention groups were treated with lifestyle intervention program consisting of low-fat, high-fiber vegetarian diet, aerobic exercise and stress management through

Rajyoga Meditation whereas control group was kept on conventional medication. These patients were followed at 0, 6, 12, 18, 24 and 36 months. The patients were selected on well-laid down inclusion and exclusion criteria.

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032. TAWAR (Urmila)

Molecular Recognition Studies Between Minor Groove Binding Ligands and Nucleic Acids.

Supervisors : Prof. Yogendra Singh and Dr. Vibha Tandon

Th 14326

Abstract

Desbribes design and synthesis new bisbenzimidazole and terbenzimidazole analogue of Hoechst 33258 and their characterization using IR, ^{1}H NMR, Mass spectrosocopy and purity checking using HPLC. The new ligands were designed on the basis of QSAR and molecular modeling studies earlier reported to increase the lipophilicity and to improve sequence length recognition and sequence specificity. Two ligands were designed, one was bisbenizimidazole 5-(4-methylpiperazin-1-yl)-2'-[2'-(3,4-dimethoxyphenyl)-5'-benzimidazolyl) benzimidazole (DMA) and the other was a terbenzimidazole 5-(4-methypiperazin-l-yl)-2-[2'{2"-(4-hydroxy-3-methoxyphenyl)-5"benzimidazolyl}-5'-benzimidazolyl] benzimidazole (TBZ) both the ligands bearing bisubstitution on the phenyl ring whereas the parent molecule had a single substitution. DMA had two methoxy groups ortho to each other on the phenyl ring whereas TBZ had a hydroxy group at the para position and a methoxy group ortho to it. Both the substituents are electron donating and hence they increase the lipophilicity as well the DNA duplex stability. Presence of electron donating groups on the phenyl ring increases the electron density at the nitrogens of imidazole ring, which are involved in the binding with the DNA. Increasing the number of benzimidazole ring helps in recognizing longer stretches of DNA. Synthesized DMA by condensation of two parts i.e., 2-Amino-4-[5'-(4"-Methylpiperazin-l"-yl)benzimidazol-2'-yl] aniline and 3,4-dimethoxy benzaldehye in nitrobenzene at $140^{0}C$ for 24 h and it was obtained in 80% yield whereas TBZ was synthesized by con-

densation of 4-[5'-(4"-Methylpiperazin-l"-yl)benzimidazol-2'-yl] aniline and 5-Formyl-[(3-methozy-4-hydroxyphenyl-5'-yl)benzimidazole] in nitrobenezene at 140^{0}C for 18 h and was obtained in 70% yield 5-Formyl-[(3-methozy-4-hydroxyphenyl-5'-yl)benzimidazole] was being synthesized by condensation of 3,4-Diamino benzonitrile using nitrobenzene as a solvent under the same conditions as for the final compound. The resulted compound 5-Cyano-2 [(3-methozy-4-hydroxyphenyl-5'-yl)benzimidazole] 5'-yl was then formylated using Raney nickel and formic acid in water. Both the ligands were purified at every step by column chromatography using silica gel as the stationary phase and petroleum ether/ethyl acetate as the eluent system and checked by TLC. Both final compounds were first purified by column chromatography using ethylacetate/ methanol as the eluent system. Further purification was done by HPLC using acetonitrile/methanol as eluent. At every step the intermediates have been characterized using melting point and TLC, which was compared to the reported ones and structural spectroscopy by IR, ^{1}H NMR and Mass spectroscopy. The overall yield for DMA and TBZ has been found to be 30% and 25% respectively, which is considerably good in comparison to earlier reports. The bisubstituted ligands affords two-fold protection due to their ability to alter DNA structure as well as because of scavenging free redicals directly afford a two-fold protection by altering DNA structure as well as through free radical quenching directly in bulk solution in comparison to the parent ligand, which acts only through quenching of nucleotide-derived radicals. And thus both the ligands are better radioprotectors than the parent molecule Hoechst 33342.

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