Novel compounds against mycobacterium tuberculosis biology essay

Science, Biology

Niteesh kanungo (12msb0117), Prof. Dr. Siva Kumar A. Email - niteeshkanungo@gmail. comAbstract- DNA Gyrase find out to be very important in validating the development of various antibacterial compounds. Fluoroquinolones are already existing inhibitors of DNA gyrase. In treatment of tuberculosis. Fluoroquinolones accounted to be a class of compounds with pharmacokinetic and antimicrobial properties against many pathogenic bacteria’s. Fluoroquinolones said to have less effect on mycobacterium but research with new fluroquilonoes suggested and demonstrated to be having a good activity against M. Tuberculosis. Fluoroquinolones are already used as second line drugs. In the present studies we came across 10 synthetic compounds that do have fundamental properties like DNA gyrase inhibition activity. We have named the compound from S21 to S30. In this study we are docking the Noval Ligands into the active site of DNA gyrase. We want it to investigate inhibitory activities through in-silico analysis.

INTRODUCTIONThe infection caused by Mycobacterium tuberculosis result in highest number of deaths world Wide. Fluoroquinolones are used as a secondary line of drugs against mycobacterial diseases. With the emergence of Extensive drug resistant tuberculosis (XDRTB) and Multi drug resistant tuberculosis (MDRTB) the need to develop better resolution and anti-bacterial drugs are in need . New Drug with efficient design against mycobacterium tuberculosis can help in development of anti "TB drugs [1]. Mycobacterium tuberculosis found to have very unusual possession with only one type II Isomerase, DNA Gyrase[2]. The DNA Gyrase of Mycobacterium tuberculosis with such unusual activities still shows a enhanced activity in DNA cleavage, and deacatination activities. The

molecular structure of DNA Gyrase consist if two Sub Units, Gyrase A (Gyr A) and Gyrase B (GyrB) which together they form a heterodimer structure A2B2. The main fuction of GyrA subunit is to break and then re unite the bacterial DNA. While the function of Gyr B is ATP-ase activity. If the ATP is absent then the DNA catalyses the relaxation of supercoiled DNA.[4, 5] The Bacterial DNA gyrase, is found to be the main target of the antibacterial chemotherapy. Fluoroquinolones are a tpe of synthetic drug found to show inhibition activity against the DNA Gyrase and topoisomerase IV and causes cell death. They found to be very effective as anti- microbial agent. Fluoroquinolones interact with DNA Gyrase and Topoisomerase IV, they specifically binds with the complex formed in between the DNA and the Enzyme, resulting in the stabilization of the covalent enzyme Tyrosyl DNA ester, which is a an intermediate that has been found in the intermediate reaction, Which results in accumulation of Double Stranded DNA fragments leading to cell death. The new sets of Fluoroquinolones designed possess a good potential in treatment, they show very effective in vitro activity against mycobacteria. They possess a good potential to reduce the Tuberculosis treatment regime from 6 months to 4 months or even less. The important factor about the Fluoroquinolones is that there activity strictly relates to that of the inhibitory activities to DNA Gyrase. The development of resistance by Fluoroquinolones still uncommon by the strains of Mycobacterium Tuberculosis, the factor is because of rhe putative Fluoroquinolones binding between the Mycobacterium gyr-A encoded A sub Unit of DNA Gyrase. Thus Mycobacterium tuberculosis is one of the validated targets for anti-tubercular drug discovery. On all research based studies progressed till date

for the point of human testing on tuberculosis the quinolone holds potential in reducing the time of treatment, coming up with new activities against Multi Drug resistant Tuberculosis (MDR-TB) and in the improvement of the therapy given against Tuberculosis HIV Co- Infection. The Fluoroquinolones are also found to be good medication in respiratory diseases like the Respiratory tract infection, UTIs, found helpful in curing other skin disorders and from sexually transmitted diseases.

CHEMICAL STRUCTURE OF THE FLUOROQUINOLONES-

Nalidixic acid is the main synthetic derivative of all clinically important fluoroquinolones. Nalidixic acid is the first member of quinolone class which is 1, 8 napthyridine. It has a quinolone nucleus or a modified dual ring system. The current floroquinolone agents are the result of two separate modifications of 1, 8 napthyridine. 1 is involved in an additional 8-methoxyside chain, which led to the development ofmoxifloxacin and gatifloxacin. Enoxacinwas developed by structural alterations to thenaphthyridine core, and trovafloxacin was produced by a 7azabicyclo modification to this core molecule. And the other one is involved a carbon-for-nitrogen substitution at position 8 of the 6-fluoro, 7-piperazinyl quinolone, in addition to other side-chain modifications, which led to the development of ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, and clinafloxacin.

MECHANISM OF ACTION

the mechanism of quinolone basically involve inhibition of DNA gyrase in gram negative bacteria which inhibits replication and transcription of

bacterial DNA . this inhibition leads to rapid cell death. The primary target in gram positive bacteria i. e topoisomerase lV is also inhibited by quinolones . the newer floroquinolones has decrease susceptibility due to mutation in gyrA , parC, and parE genes

ADVERSE EFFECTS

GI effect such as nausea vomiting and diarrhea skin disturbances and CNS effects, including headaches and dizziness are the most common effects of fluroquinolones. Sleep disturbances, hallucinations, depression, and seizures are less common adverse effects. Patients receiving coadministered cyclosporine and ciprofloxacin are reported with Nephrotoxicity. Maculopapular or Urticarial are dermatologic effects . Pain at the injection site has been reported with IV formulation . .“ 3, 34 Overgrowth of Clostridium diflicile has been identified as the cause of 10% to 25% of cases of antibiotic-associated diarrhea and almost all cases of antibiotic-associated PMC.“ 5 Diarrhea and pseudomembranous colitis (PMC) have long been associated with the use of antibiotics. A well known cause of antibiotic induced diarrhea is clindamycin but all other antibiotics may be responsible . about 878 cases of antibiotic induced PMC has been studied. Derivatives of penicillin are also associated with hemorrhagic colitis . included cefixime, amoxicillin-clavulanic acid, amoxicillin, ofloxacin, and trimethoprim-sulfamethoxazole; are the most frequently used antibiotic and cefaclor, cefuroxime axetil, and tetracyclines are less frequently used. PMC are also found to be associated with Macrolides and fluoroqinolones . Fluoroquinolones have been found to induce tendon lesions in juvenile rats.

hypertrophy, stratification, and an increased number of capillary endothelial cells in juvenile rats, were shown by electron microscopy , as well as an increased number of fibroblasts and macrophages. deposition of collagen in the matrix of the synovial membrane and tendon sheath is also associated with fluoroquinolones. A recent study in dogs was also done where the biochemical changes occurring in tendons after exposure to fluoroquinolones were observed . The dogs were treated for 5 days with oral ciprofloxacin (30 or 200 mg/kg). It was also demonstrated that magnesium deficiency also leads to quinolone-like defects in joint cartilage thus , an additional group was also fed a magnesiumdeficient . Tendons were analyzed using antibodies directed against matrix proteins andintegrins. Animals treated with cip-rofloxacin and fed the magnesium-deficient diet had statistically significant reductions in all proteins (ie, collagen, fibronectin, elastin, and p, integrin) compared with the control group. Thus it can be said that the magnesium antagonistic effects of these agents support the hypothesis of quinolone-induced toxic effects on connective-tissue structures. Their is a a variation in the extent of toxicity of each floroquinolone. In a study it was found that that a single oral dose of 900 mg/kg pefloxacin resulted in more severe lesions in juvenile rats than a comparable dose of levofloxacin. On the other hand a single dose(600mg/kg) of sparfloxacin was sufficient to induce joint cartilage lesions in juvenile rats and 1800mg/kg is sufficient to cause cartilage lesions in the femoral partof the knee joint. Toxicity of these antibiotics were tested and it was found that fleroxacin and pefloxacin had the greatest Achilles tendon toxicity in rats, followed by lomefloxacin, levofloxacin, and ofloxacin. I7 Sparfloxacin andenoxacin were minimally

toxic, and no Achilles tendon toxicity was seen in rats given norfloxacin or ciprofloxacin. other studies showed grepafloxacin had a low potential for joint toxicity in rat. Cutaneous disease and tendon disorders are among the most adverse effects although Fluoroquinolone-induced tendinopathy has also been reported in humans in France, and tendon disorders are the fifth most common such reaction in the United Kingdom. Elder patients are more prone to tendor disorders and are 2 to 3 times more common in men symptoms can be seen within 2 to 42 days and up to two thirds of cases resolve within 1 to 2 months after discontinuation of the drug. Prolonged periods of disability , a need for hospitalization, surgical repair has been reported increase the risk or secondary tendonrupture. By Fluoroquinolone-induced tendinopathy. long-term steroid treatment that can increase the risk of tendon inflammation. Studies shows that tendons are the most common site for fluoroquinolone-induced tendinopathy under high stress, including the Achilles tendon . therefore it is suggested that if any sign of inflammation appears , treatment with fluoroquinolones should be discontinued. arthralgia with or without effusion has been documented, it occurs at a relatively low rate (11. 5%) and resolves completely once drug therapy is discontinued, with no evidence of serious or long-termsequelae. However none of these antibiotics can be used for childrens. They can be used under clinical circumstances eg, cystic fibrosis patients with multidrug resistant gram-negative infection). these drugs were also examined on fracture healing quinolones have demonstrated chondrotoxicity in developing articular cartilage in juvenile mammals. In a process similar to that in developing articular cartilage, fracture re- followed by differentiation into cancellous

bone. A study was done to check the strength of experimental fracture calluses after treatment with ciprofloxacin, trovafloxacin, and no in adult wistar rats treatment. The mechanical strength of fractures was statistically significantly lower among the rats treated with either antibiotic agent, with no statistically significant difference between the two agents. These musculoskeletal effects have led to contraindication of the routine use of fluoroquinolones in children, whose skeletal growth is incomplete, as well as in pregnant and lactating women Although there are a few class effects, there are also significant differences between the safety and tolerability profiles of specific fluoroquinolone agents, in the case of temafloxacin and trovafloxacin 26 It is not possible to predict the extent to which serious side effects and toxicities will occur in a population without involving many thousands of patients. Till date the most extensively studied are ofloxacin, ciprofloxatin, sparfloxacin, grepafloxacin, and levofloxacin. DNA TOPOISOMERASEDNA GYRASESTRUCTURE AND MECHANISM OF ACTIONBACTERIAL DNA AS DRUG TARGETDNA GYRASE FROM MYCOBACTERUIM TUBERCULOSISTHE ROLE OF FLUOROQUINOLONES IN TUBERCULOSISFINAL COMPOUND BASE STRUCTUREBase Compounds

Compound code

Compound Structure

Melting Points

Colour

Yield

S 21

79cBuff69. 79%

S 22

81cBuff66. 55%

S 23

88cGreenish yellow79. 6%

S 24

84cBuff74. 91%

S 25

90cDark green63. 07%

S 26

82cYellowish Green69. 12%

S 27

88cGreenish yellow66. 56%

S 28

92cGreenish yellow75. 98%

S 29

96cDark green60. 06%

S 30

98cBrown71. 42%Materials and MethodsTable1. Comparison of FluoroQuinolone Compounds in Antibacterial Activities and and Activities Against M. tuberculosis DNA GyraseMolecular Modelling. Molecular modelling studies of the interaction of the Ligands at the active sites of the Protein molecule can help in providing valuable information and assisting in the design of the future drug inhibitor. The Literature available online for the testing of the drug against Mtb DNA gyrase, for the studies. Heavily customised docking studies using Software's like Accelrys Draw and taking reference with other software's like Discovery tools and online servers like Patch Dock and Me Dock. As it is not clear, as both the chains kept for the docking solution are entirely similar, we have choose only the GyrA for the possibilities of finding different binding site. In this protocol, the recently revealed crystal structure of Mtb DNA Gyrase GyrA N-terminal domain (3ILW) was employed. The next step is to find out the Active Site and pockets. The Docking Studies are implemented and assigned using AutoDock's two different versions available, The first Docking tool is from the MGL tools package number 1. 5. 6 and the the other version is 1. 5. 6rc, release candidate version for next release. The Docking results that we got from the 10 different compounds showed a relative..... ResultsDISCUSSION AND

CONCLUSIONSThe Fluoroquinolones helps in providing variety of medication with respect to various Infections. With the given number of possible Quinolones in nature the difficult choice is the selection and is a very important task. The research studies conducted in different hospitals showed the adverse effect, of nearly 25% of them getting infection from Drug or after math of the Drugs. Drug designing is a very important note in the objective. The selection profile into the administration and design, a lot of important factors should be kept in mind. Taking the base knowledge from literature provided from different Infections around the world, and the number of drugs that has been administered as well as the long term effect, All these points should be given importance before successfully testing or before post marketing trials and records. ABBREVIATIONSDNA = Deoxyribonucleic acidRNA = Ribonucleic acidATP = Adenosine triphosphateMDR-TB = multiple drug resistant tuberculosisXDR-TB = Extremely/extensively drug resistanttuberculosisQR-MDR-TB = Quinolone resistance- multiple drug resistanttuberculosisTB-HIV = Tuberculosis/Human immunodeficiencyvirusADPNP = 5’-adenylyl ????,-imidodiphosphateGyrA-NTD = N-terminal domain of DNA gyrase subunit AGyrA-CTD = C- terminal domain of DNA gyrase subunit AQRDR = Quinolone resistance determining regionARV = Anti-retroviralSAR = Structure/Activity relationshipSDS = Sodium dodecyl sulphate