Short Communication

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Journal of Medical Microbiology and Immunology Research

2022
Vol 5. No. 2

Development Strategy for Universal Anti-resistant Antibacterial agents

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Abstract

Statement of the Problem: Dangerously high levels of antibiotic resistance is rising in all parts of the world. It is threatening our ability to treat infectious disease which are common as new emerging resistance mechanism has arrived and spread globally. As antibiotics becomes less effective, the growing list of infectious disease-such as pneumonia, tuberculosis, gonorrhea, hospital acquired MRSA along with foodborne disease are becoming harder and impossible to treat as these agent became ineffective. "The connections between antimicrobial resistance, environmental health and the climate crisis are becoming increasingly stark"- says co-chair of the Global Leader Group of Who on Antimicrobial Resistance. Methodology and Theoretical Orientation: The antibiotic resistant can be overcome by targeting two enzymes together or dual targeting. If resistance occurs in one generation, it will modify one enzyme but still the other unmodified enzyme will be the place for the drug to produce its activity. The concept for dual inhibitor was reported earlier for novel antibiotics development and several attempts have been done for their findings. For this concept, the enzymes which are involved in the early stage of peptidoglycan synthesis for the bacterial cell wall has been selected as they were tailor made for dual targets. These are known as Mur-family or Murenzymes (Mur A-F) which are present inside the cytoplasm- having similar substrate, similar mechanism of action, similar structure and very importantly they act consecutively. Among them MurD and MurE enzymes are our target of choice as MurE plays the gatekeeper role for adding the amino acid L-Lysine/ D- Diaminopimalic Acid to (species specific) and MurD adds D-glutamic acid to growing strand of peptidoglycan (rigidity to the cell wall). Inhibiting these two enzyme will produce novel bactericidal agents. But all the reported inhibitors were unable to show co-relation between IC50 and MIC values which clearly indicates that these inhibitor are having difficulty in penetration. Findings: we have designed, synthesized 3 different series of scaffold containing 2-amino benzothiazole (2-ABT) one end, the other end containing 2- amino benzothiazole, aromatic primary amine and 1-hydroxy benzotraizole linked with 2-chloro acetyl chloride. All of them has been screened against panel of gram positive and gram negative bacteria (included MRSA ATCC-43300) where the MIC's range was 0.5-50µg/ml along with time kill study against MRSA. The time profile of these 3 series showed different profile i.e 1st and 2nd series took almost 8-12 hours to kill the MRSA and the 3rd series took 2 hours to kill MRSA. So, this results are definitely throwing some lights on the permeability problem of the antibiotics. Conclusion & Significance: The insight mechanism of this agent will also help to identify the area of scaffold which are essential for activity and penetration. From this result, the obtained hits can be further modified to get a lead of Nanomolar range through various in-silico models.

Received: March 15, 2022 **Accepted:** March 20, 2022 **Published:** March 30, 2022

Biography

Niladri Saha joined as an assistant professor at Sister Nivedita University after his thesis submission. He has completed his graduation at 2013 from Institute of pharmacy, Jalpaiguri. Then he moved to Ooty for obtaining masters of pharmacy (2014-16) specializing in pharmaceutical Chemistry. His master's project entitled "Design, Synthesis And 3D QSAR Studies of Novel Anti-bacterial agent Targeting Alanine Racemase Enzyme". After completion he joined on same year as Junior Research associate in Analytical R&D at Steril-Gene Life Sciences for analysis of finished product. During this tenure he analyzed various hormonal, antibiotic product. In 2018 he joined for PhD, again under supervision of Dr. Afzal Azam (Professor and Head) from same Institute at Ooty. His work mainly focused on development of Novel agent against Gram-positive bacteria. His thesis entitled "In-silico design, Synthesis and evaluation of MurD and MurE ligase inhibitors as antibacterial agent''.

