World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:14, No:12, 2020

The Structural Alteration of DNA Native Structure of Staphylococcus aureus Bacteria by Designed Quinoxaline Small Molecules Result in Their Antibacterial Properties

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Abstract : Antibiotic resistance by bacteria has proved to be a severe threat to mankind in recent times, and this fortifies an urgency to design and develop potent antibacterial small molecules/compounds with nonconventional mechanisms than the conventional ones. DNA carries the genetic signature of any organism, and bacteria maintain their genomic DNA inside the cell in a well-regulated compact form with the help of various nucleoid associated proteins like HU, HNS, etc. These proteins control various fundamental processes like gene expression, replication, etc., inside the cell. Alteration of the native DNA structure of bacteria can lead to severe consequences in cellular processes inside the bacterial cell that ultimately result in the death of the organism. The change in the global DNA structure by small molecules initiates a plethora of cellular responses that have not been very well investigated. Echinomycin and Triostin-A are biologically active Quinoxaline small molecules that typically consist of a quinoxaline chromophore attached with an octadepsipeptide ring. They bind to double-stranded DNA in a sequence-specific way and have high activity against a wide variety of bacteria, mainly against Gram-positive ones. To date, few synthetic quinoxaline scaffolds were synthesized, displaying antibacterial potential against a broad scale of pathogenic bacteria. QNOs (Quinoxaline N-oxides) are known to target DNA and instigate reactive oxygen species (ROS) production in bacteria, thereby exhibiting antibacterial properties. The divergent role of Quinoxaline small molecules in medicinal research qualifies them for the evaluation of their antimicrobial properties as a potential candidate. The previous study from our lab has given new insights on a 6-nitroquinoxaline derivative 1d as an intercalator of DNA, which induces conformational changes in DNA upon binding.7 The binding event observed was dependent on the presence of a crucial benzyl substituent on the quinoxaline moiety. This was associated with a large induced CD (ICD) appearing in a sigmoidal pattern upon the interaction of 1d with dsDNA. The induction of DNA superstructures by 1d at high Drug:DNA ratios was observed that ultimately led to DNA condensation. Eviction of invitro-assembled nucleosome upon treatment with a high dose of 1d was also observed. In this work, monoquinoxaline derivatives of 1d were synthesized by various modifications of the 1d scaffold. The set of synthesized 6-nitroquinoxaline derivatives along with 1d were all subjected to antibacterial evaluation across five different bacteria species. Among the compound set, 3a displayed potent antibacterial activity against Staphylococcus aureus bacteria. 3a was further subjected to various biophysical studies to check whether the DNA structural alteration potential was still intact. The biological response of S. aureus cells upon treatment with 3a was studied using various cell biology processes, which led to the conclusion that 3d can initiate DNA damage in the S. aureus cells. Finally, the potential of 3a in disrupting preformed S.aureus and S.epidermidis biofilms was also studied.

Keywords : DNA structural change, antibacterial, intercalator, DNA superstructures, biofilms
Conference Title : ICSRD 2020 : International Conference on Scientific Research and Development
Conference Location : Chicago, United States
Conference Dates : December 12-13, 2020