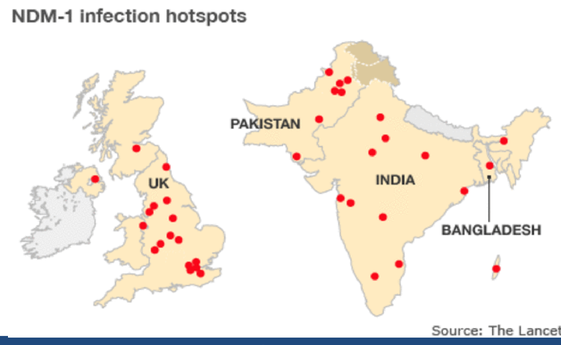
1,2-HOPTOs as a Novel Scaffold for the Development of New Delhi Metallo-β-lactamase-1 inhibitors

Iqra Hajidamji, Rebecca Adamek, Allie Chen, and Seth Cohen

The Department of Chemistry & Biochemistry, University of California San Diego, 9500 Gilman drive, La Jolla, California

Abstract

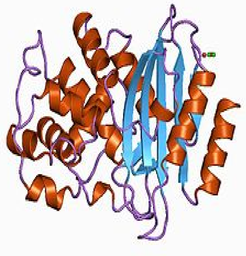
New Delhi Metallo β- lactamase 1 (NDM-1) is an enzyme that makes the bacteria in our body resistant to a broad range of antibiotics. This enzyme contains two zinc ions with various amino- acids in the active site. NDM-1 was first detected in a bacteria in a Swedish patient. It was later detected in India, Pakistan, USA and Japan. In past, researchers have tried to synthesize these enzymes with single stranded DNAs, peptides but no single inhibitor has been able to exhibit promising potential for clinical application. Lastly bacteria that have become resistant are difficult to treat however they are susceptible only to polymyxins and tigecycline.



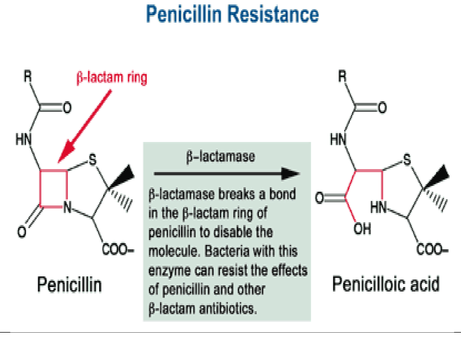
NDM-1 as a Therapeutic Target

NDM-1 has been associated with an enzyme called beta- lactamase. Bacteria often synthesize this enzyme in order to develop a resistance to antibiotics called B-lactam. β-lactam antibiotics are a broad class of antibiotics, consisting of all antibiotic agents that contain a β-lactam ring in their molecular structures. This includes penicillin, cephalosporins, monobactams, and carbapenems. Beta-lactamase provides antibiotic resistance by breaking the antibiotics' structure. These antibiotics all have a common element in their molecular structure: a four-atom ring structure. Through hydrolysis, the lactamase enzyme breaks the β-lactam ring open, deactivating the molecule's antibacterial properties. This is one of the main reasons why it is difficult to inhibit NDM-1 and beta- lactamase. The resistance has caused it difficult for researchers to develop the inhibitors that can fit in the active site. Despite the difficulty, NDM-1 has been chosen as the target in order to weaken the resistance bacteria develops through Beta- Lactamase and decrease the growth of diseases spread the resistance of bacteria towards antibiotics.

Beta Lactamase:

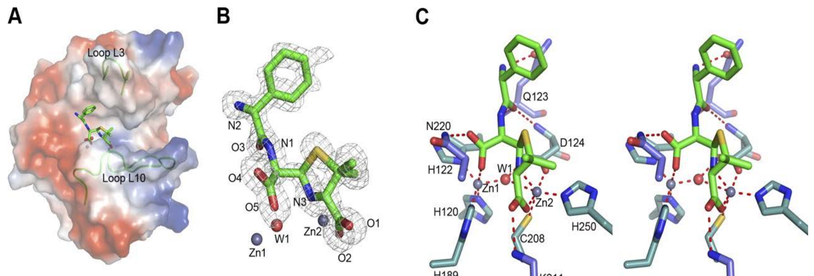


An example of resistance



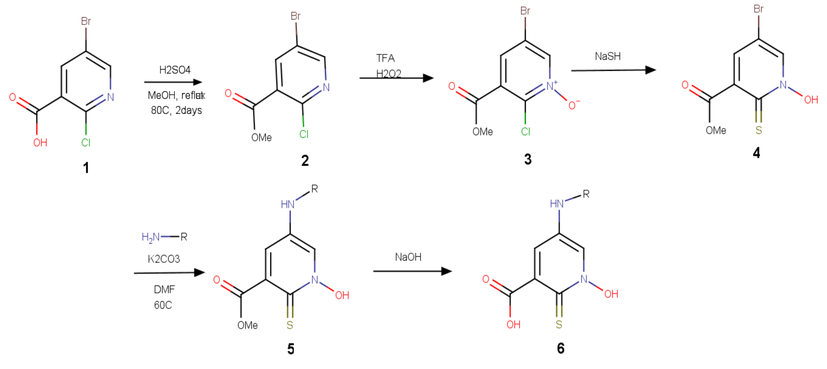
Metal Binding Pharmacores

NDM-1 is a metallo enzyme which makes the bacteria resistant to antibiotics. Due to this, we are making inhibitors that can form metallic bonds in the active site of the enzyme, NDM-1. This metallic bond displays the concept of lock and the key. The active site of the NDM-1 is the lock which requires a key. And the inhibitors are the key to the active site. In the lab we try to create inhibitors that can form metal bonds with the active site and make the bacteria unresisting to the antibiotics.

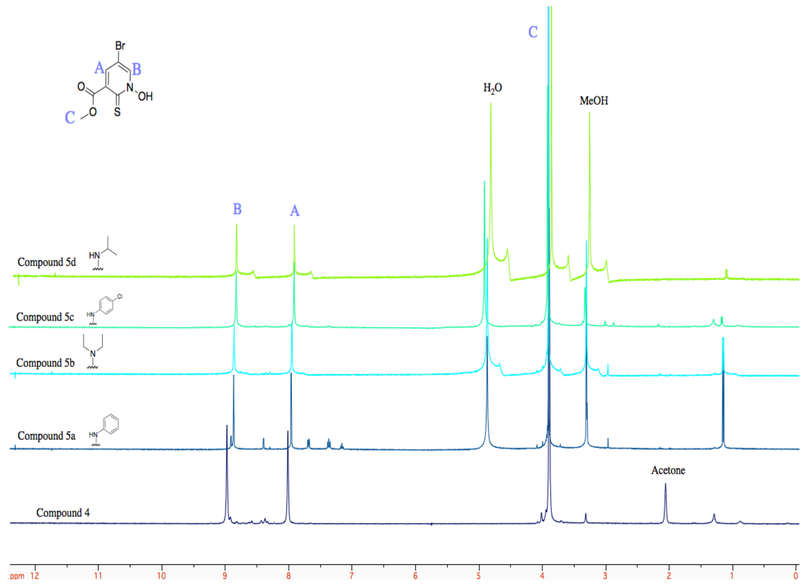


Synthesis

The picture portrays the procedure performed to get inhibitors for the enzyme.



Results (NMR)



Discussion and Conclusions

We succeeded in getting two perfect results. Through this research I have learnt a lot of new things. It was one of the best experiences and I realized that there is so much to explore in the field of science and bio chemistry. I got a chance to dig deep into the background of NDM-1 and the reason of working on it in the lab. After we got our results we conducted NMRs which were then tested on different proteins to see if the our solutions were able to break the resistance created by the bacteria. However some solutions did not turn out the way we thought it should, which was due to various reasons. The first solution contain chloride and the second one had bromine in it. The colors were different for both solution with white and yellow respectively. Research is still going on and is making progress to develop inhibitors for the enzyme.

References

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