Inhibition of New Delhi Metallo-β-lactamase 1 from *Klebsiella pneumoniae* by Hydroxamate Compounds

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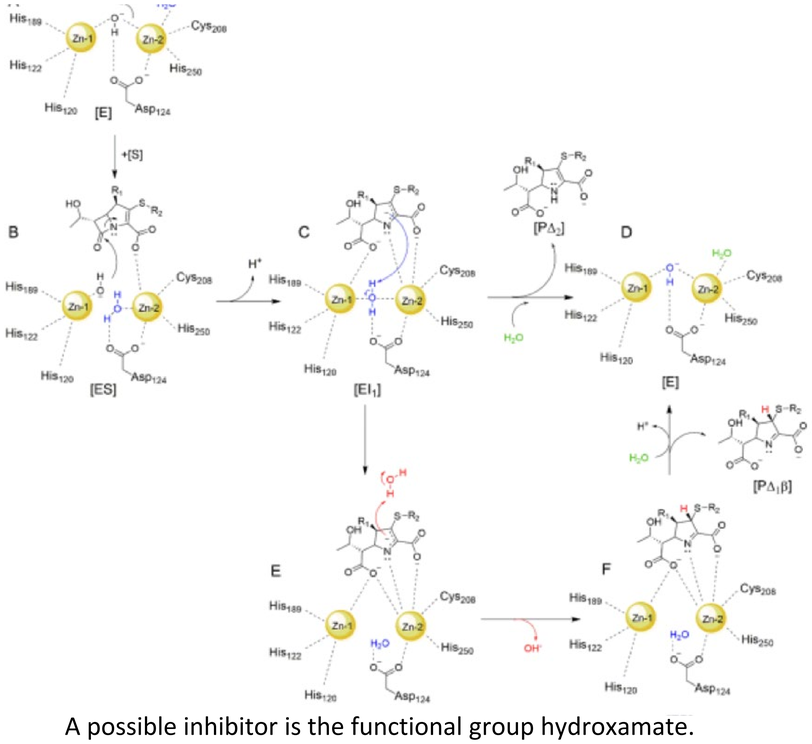
Abstract

Antibiotic resistance is a growing problem not only for scientists but for consumers worldwide. A very pertinent antibiotic resistance we are faced with is caused by metallo-β-lactamases. These enzymes catalyze the hydrolysis of β-lactam antibiotics and have no clinically accepted inhibitor for their resistance. Consequently, it is critical that an inhibitor is discovered so this kind of antibiotic resistance can be treated. This research is concentrated on determining if the hydroxamate functional group is a viable inhibitor for NDM-1.

Introduction

Klebsiella pneumoniae is commonly found within the human body; however, once displaced can cause infections. A strain of this bacteria originating from New Delhi, has been shown to be problematic toward β-lactam antibiotics (Yong et. al, 2009). This type of antibiotic resistance is developing in other bacteria as well as spreading across the world (Yong et. al, 2009). There are currently many efforts in place to discover an inhibitor; however, there has been no success. This research is focused on finding an inhibitor for New Delhi Metallo-β-lactamase 1 (NDM-1) using hydroxamate compounds. Figure 1 depicts the mechanism in which NDM-1 acts (Linciano et. al, 2018).



A possible inhibitor is the functional group hydroxamate. Interest is shown for this structure because it is a known metal binding group.

Methods

Twenty-four potential compounds were prepared as well as the macromolecule (NDM-1) using AutoDock 4. A conf.txt file was made for AutoDock Vina. In this txt file, the ligand and macromolecule were set, exhaustiveness set to 8, and the number of configurations set to 9. Using the commands within Terminal, AutoDock Vina was ran with the conf.txt file. Figure 2 shows all twenty-four structures tested.

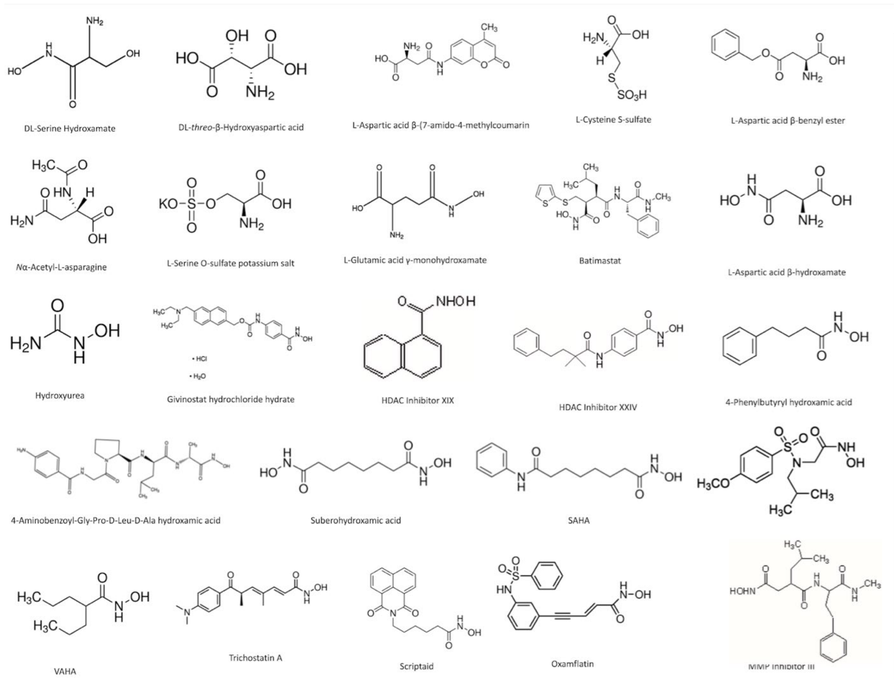


Figure 2 depicts the twenty-four commercially available compounds with hydroxamate functional groups from Sigma Aldrich

Results

After running AutoDock Vina, we selected the top three compounds with the best binding affinity to the active site. Figures 3-5 represent the binding affinities for those three compounds. Table 1 represents the binding affinities for all of the commercially available compounds.

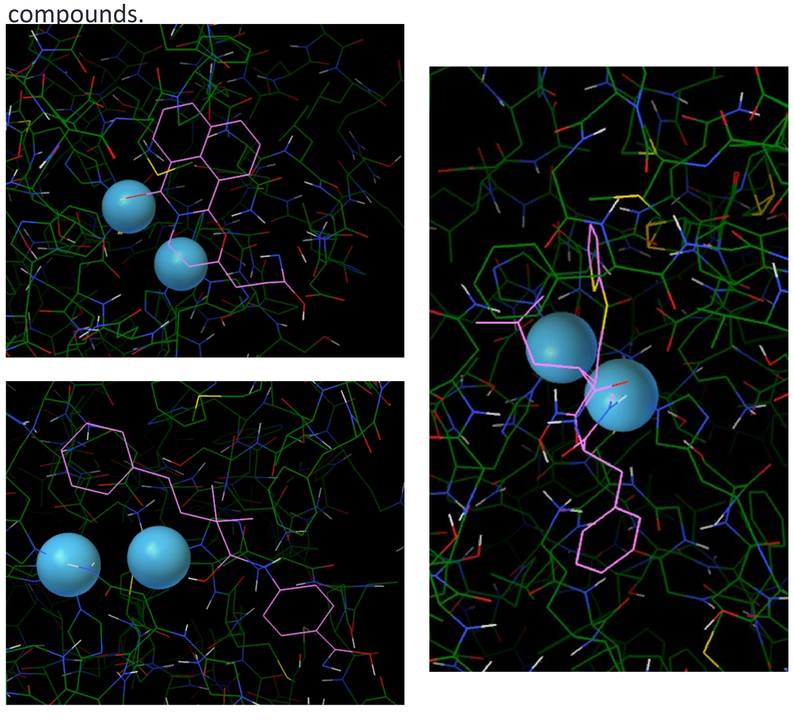


Figure 3 (top left), Figure 4 (bottom left), and Figure 5 (right) depict the possible binding interaction between the catalytic zincs in the NDM-1 active site with the compounds known as Scriptaid (-6.9 kCal/mol), HDAC XXIV (-7.7 kCal/mol), and Batimastat (-6.4 kCal/mol) respectively.

Table 1. Binding affinities for the commercially available compounds to the NDM-1 active site

Compounds	Binding Affinity (kCal/mol)
4-Aminobenzoyl-Gly-Pro-D-Leu-D-Ala hydroxamic acid	-8.6*
4-Phenylbutyryl hydroxamic acid	-6.9*
Batmistat	-6.4
DL-Serine hydroxamate	-4.7*
DL-threo-β-hydroxyaspartic acid	-4.8*
Givinostat Hydrochloride Hydrate	-2.5*
HDAC Inhibitor XIX	-7.6*
HDAC Inhibitor XXIV	-7.7
Hydroxyurea	-3.4
L-Aspartic acid β-(7-amido-4-methylcoumarin)	-6.3
L-Aspartic acid β-benzyl ester	-6.6*
L-Aspartic acid β-hydroxamate	-4.6
L-Cysteine S-sulfate	-4.7
L-Glutamic acid γ-monohydroxamate	-5.0*
L-Serine O-sulfate potassium salt	-5.0*
MMP Inhibitor III	-7.8*
Nα-Acetyl-L-asparagine	-5.1
NNGH	-4.8
Oxamflatin	-8.3*
SAHA	-6.4*
Scriptaid	-6.9
Suberohydroxamic acid	-5.2
Trichostatin A	-7.6*
VAHA	-6.5*

Asterisks (*) denote compounds that did not interact with the zinc atoms.

Discussion

An area of concern with using a metal binding group is the possibility it will target other, useful metal ions within the body. However, according to previous research, hydroxamate has been shown to have high specificity towards its targeted metalloenzyme depending on the backbone of the hydroxamate (Day, J.A., & Cohen, 2013).

The three compounds with the highest binding affinities will be used to check the inhibition of NDM-1 in the lab. If they are found to be useful inhibitors, then they will need to undergo additional testing to check for toxicity of the compounds. Once toxicity is eliminated, clinical testing can then occur.

Literature Cited

Day, J. A., & Cohen, S. M. (2013). Investigating the Selectivity of Metalloenzyme Inhibitors. *Journal of Medicinal Chemistry*, *56*(20), 7997–8007. doi: 10.1021/jm401053m

Linciano, P., Cendron, L., Gianquinto, E., Spyrakis, F., & Tondi, D. (2018). Ten Years with New Delhi Metallo-β-lactamase-1 (NDM-1): From Structural Insights to Inhibitor Design. *ACS Infectious Diseases*, *5*(1), 9–34. doi: 10.1021/acsinfecdis.8b00247

Yong, D.; Toleman, M.A.; Giske, C.G.; Cho, H.S.; Sundman, K.; Lee, K.; Walsh, T.R.Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in Klebsiella pneumoniae sequence type 14 from India. *Antimicrob. Agents Chemother.* 2009, 53, 5046-5054.

Acknowledgements

We would like to thank the NSU College of Health and Sciences for providing the equipment and materials required for these experiments.