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Copper Binding of Heterocyclic Compounds Is Vital For Novel Drugs Against Gram-Positive Bacteria

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Background

Multidrug resistant bacteria have the capability to adapt and develop antibiotic resistance to a majority of available drugs. Thus, finding novel drug candidates is vital. Copper Complexes have been experientially determined to exhibit species and target specific activities. Studies have shown that in bacteria infected cells, iron and other nutrients are withheld from the phagosomes, in which the bacteria are taken up, while copper (I) is flooded into the phagosomes to induce toxicity. To determine the preferred structure a standard library of 10,000 compounds was assayed for anti-staphylococcal activity, with hits defined as those compounds with a strict copper-dependent inhibitory activity. Results indicated that the most prominent structure was an extended thiourea core structure. The following image illustrates how copper binds on to the compound.

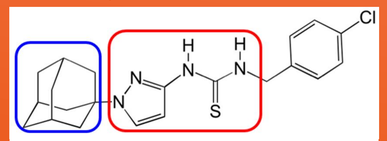


Figure 1: Chemical structure of lead component

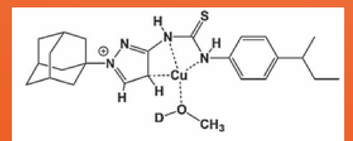


Figure 2: Copper attaching to compound

Synthetic Strategy

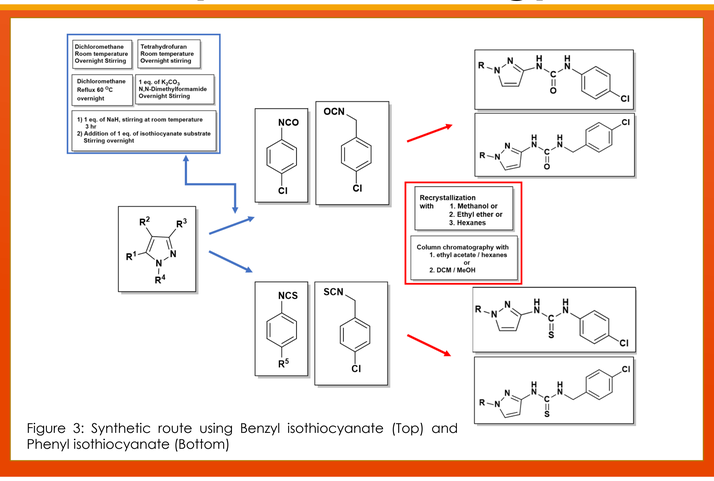
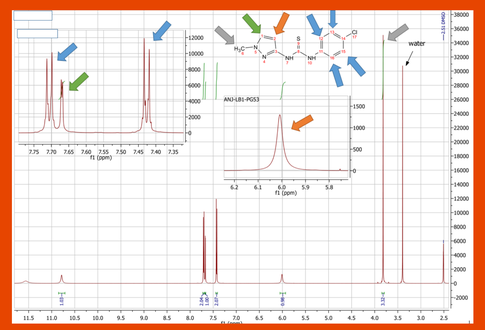


Figure 3: Synthetic route using Benzyl isothiocyanate (Top) and Phenyl isothiocyanate (Bottom)

^{1}H NMR Spectrum



Results of NMR show that compound SB02 was synthesized successfully. A singlet peak is shown with an orange arrow because the proton is easily exchangeable with deuterium. This was verified using 2D COSY NMR.

Synthesized Compounds

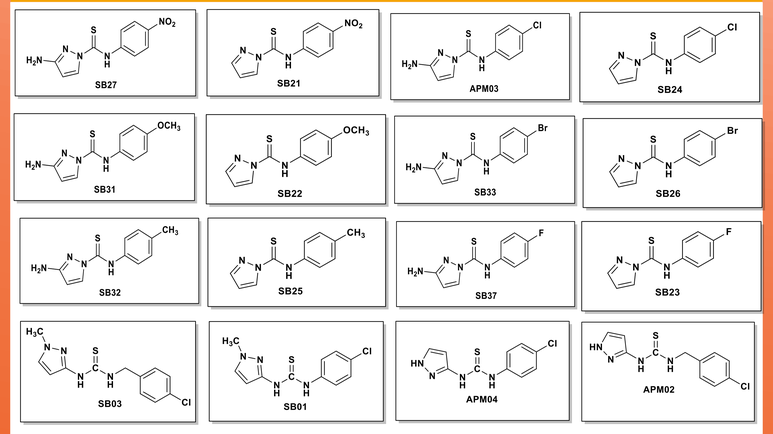


Figure 4: Synthesized Thiourea molecules

Antibiotic Resistance

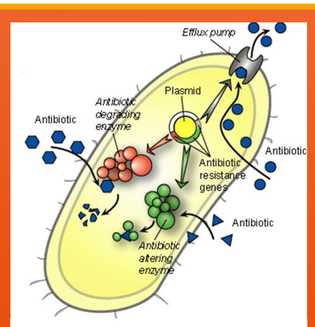


Figure 5: Bacterial mechanism of antibiotic resistance

Bioevaluation

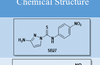
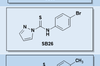
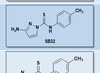
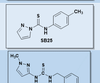
Entry	Code Name	Chemical Structure	MIC against MRSA (μM)
1	SB27		0.3
2	SB21		10
3	APM03		0.07
4	SB24		1.25
5	SB33		1.25
6	SB26		10
7	SB32		2.5
8	SB25		5
9	SB03		5
10	SB01		1.25

Table 1: Results of Minimum Inhibition Concentration (MIC) indicate that the leading compound is APM03 with an MIC value of 0.07. Compounds with low MIC values are shown in green and are much more effective. Those shown in red indicate that the MIC value is significantly high and would not make for viable compounds.

Structure Activity Relationship

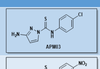
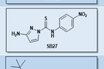
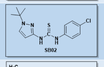
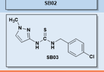
Entry	Code Name	Chemical Structure	MIC Against MRSA (μM)
3	APM03		0.07
1	SB27		0.3
10	SB01		1.25
9	SB03		5

Table 3: Results indicate that the 1-substituted position in pyrazole ring does not have a major effect on the anti-bacterial activity.

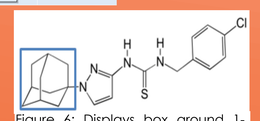


Figure 6: Displays box around 1-substituted position

Future Research

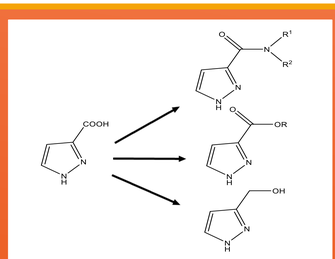


Figure 7: Further structural components will be explored to create an Amide, Ester, and Alcohol

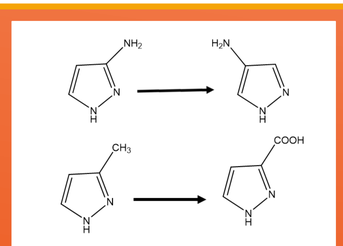


Figure 8: Further structural components will be explored by moving the substituent to different positions (top) and by changing substituents (bottom)

Conclusion

- Designed and synthesized a series of thiourea derivatives with copper boosting anti-MRSA activities.
- 1-substituted position on the pyrazole ring does not have a major effect on the anti-bacterial activity.
- Compound APM03 was discovered as the lead compound with an MIC value of 0.07 μM.

Acknowledgements

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- Department of Chemistry

References

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