Synthesis of Hydrazones as Antibiotics

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Green Chemistry

General Mechanisms for Antibiotics

Combinatorial Chemistry

Active Antibiotic Hydrazone

Para-Substituted Benzaldehydes

Interpretation of Results

Comparison of Zones of Inhibition

Future Directions

Acknowledgments

Para-Substituted Benzaldehydes

Table 1: Deconvolution of Hydrazone Libraries

Our academic activities have been performed. We have been researching the principles of green chemistry into the laboratory curriculum, we can reduce the amount of generated waste. This academic year, we conducted an experiment that adhered to these principles. The combinatorial synthesis and testing of antibiotics were carried out, minimizing excess waste, designing safer products, and increasing synthetic efficiency.

Panel 5. Hydrazones are a family of compounds that display a wide spectrum of biological activities including antibiotic activity. We want to understand how the chemical structure influences the antibiotic ability of this compounds. A small library of hydrazones from various mixtures of aromatic benzaldehydes substituted with electron-donating and electron-withdrawing substituents at the para-position have been synthesized via combinatorial chemistry and screened for antibiotic activity against E. coli in order to contribute to an extensive structure-activity relationship.

Table 1: Deconvolution of Hydrazone Libraries

Panel 4. Verification of the green-chemistry experiment in our lab has found that 5-nitro-2-furaldehyde (A2) and amipronamide (B3) reacted in the presence of acid to give the corresponding guanofuracin (3). This hydrazide demonstrated the greatest antibacterial activity from all sixteen possible combinations present in the biological assay.

The process of determining the common hydrazide first involves identifying the aldehyde and hydrazine mixtures with the largest zone of inhibition. Subsequently, those identified mixtures are then deconvoluted using a combinatorial table. This guanofuracin product was isolated by characterizing the common hydrazide that was visible in the cell cultures of E. coli after incubation for 24 hours. The noticeable rings of inhibition in quadrants M2 and M7 on both sets of plates indicated that the common hydrazide found in both mixtures had the most significant antibacterial activity.

The formation of analogues by the introduction of new substituents into the structure of a lead may result in an analogue with significantly different chemical and hence different pharmacodynamic properties. For example, the introduction of a new substituent may cause changes in lipophilicity, shape, and may introduce a new metabolic pathway for the analogue.

Panel 6. Using an agar cup diffusion method, the antibacterial activity of the eleven hydrazide mixtures in 1% DMSO were tested against E. coli. The rings of inhibition as indicated by the yellow and green areas in the images above indicate that the common hydrazide present in those two mixtures was A2B3 (guanofuracin). It can be inferred from these multiple assays that this hydrazide combination exhibits the greatest antibacterial activity. In these assays, mixture M1-M7 represented the aromatic aldehydes (AA1-AA6, and A7); and mixtures M8-M16 represented the hydrazides used (B1-B4).

Panel 7. A small library of hydrazones from various mixtures of aromatic aldehydes and hydrazines have been synthesized via combinatorial chemistry and screened for antibacterial activity against E. coli. This graph shows the average degree of inhibition and potency of each aldehyde from its respective mixture. Our results indicate that the most active hydrazide is guanofuracin, which is composed of 5-nitro-2-furaldehyde (A2) and amipronamide (B3). Our data shows that a 5-hydroxyl substituent in combination with the heterocyclic furan aldehyde will be more biologically active than its benzene aldehyde counterparts with various electron-donating or electron-withdrawing groups at the para-position (AA1-AA6).

Panel 8. Future research will involve the screening of benzaldehyde derivatives with different electron-donating or electron-withdrawing groups. In addition, we plan on synthesizing the most active hydrazine, guanofuracin, via solution-phase synthesis, purifying it via chromatography and screening for antibiotic activity. We can then compare this product to the mixture of guanofuracin in the combinatorial library.

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