Synthesis and Biological Evaluation of Compounds with Activity against Antibacterial Resistant Bacteria

Elizabeth I. Parkinson and Paul J. Hergenrother

Antibiotic resistance is a global health crisis. This year in the United States, approximately 2 million people will acquire infections resistant to at least one antibiotic and of those an estimated 23,000 people will die. While better antibiotic stewardship is believed to be capable of slowing the spread of this resistance, in order to combat these infections novel antibiotics with activity against resistant strains are needed. Recently, such a compound was discovered. Herein we describe the total synthesis of this molecule as well as further evaluation of its antibacterial activity and mode of action.

Development of a New Reagent for the Rapid Formation of 2-arylbenzimidazoles

Julie A. Pollock, Sung Hoon Kim, and John A. Katzenellenbogen

The 2-aminobenzimidazole core has been an integral component of many compounds having interesting biological activity. This core is found in antagonists against glucagon receptor, G9a histone methyltransferase, IL-1 receptor-associated kinase, inducible T-cell kinase and H3-receptor. Additionally, drugs with this core have shown antimicrobial and antifungal activities including growth inhibition of gram negative bacteria and inhibition of biofilm formation. Furthermore, 2-aminobenzimidazoles have been reported to show antiproliferative and cytotoxic effects against a variety of cancer cells. Because of the diverse biological functions of this class of compounds, a synthetic route that is amendable to multiple substrates, easy to perform and gives high yields is essential to fully realize the immense opportunities for useful bioactivity that is afforded by this core. To that end, we have designed a reagent that reacts rapidly (less than 1 hour) at room temperature with a variety of phenylenediamines to produce the 2-aminobenzimidazole core in high yields. The choice of the CBZ protecting group allows for easy removal and derivatization. Here, we show the scope of the reaction and apply our new reagent to the synthesis of the known carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP).