

Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis

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New therapeutic strategies are needed to combat the tuberculosis pandemic and the spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) forms of the disease, which remain a serious public health challenge worldwide^{1, 2}. The most urgent clinical need is to discover potent agents capable of reducing the duration of MDR and XDR tuberculosis therapy with a success rate comparable to that of current therapies for drug-susceptible tuberculosis. The last decade has seen the discovery of new agent classes for the management of tuberculosis^{3, 4, 5}, several of which are currently in clinical trials^{6, 7, 8}. However, given the high attrition rate of drug candidates during clinical development and the emergence of drug resistance, the discovery of additional clinical candidates is clearly needed. Here, we report on a promising class of imidazopyridine amide (IPA) compounds that block Mycobacterium tuberculosis growth by targeting the respiratory cytochrome bc₁ complex. The optimized IPA compound Q203 inhibited the growth of MDR and XDR M. tuberculosis clinical isolates in culture broth medium in the low nanomolar range and was efficacious in a mouse model of tuberculosis at a dose less than 1 mg per kg body weight, which highlights the potency of this compound. In addition, Q203 displays pharmacokinetic and safety profiles compatible with once-daily dosing. Together, our data indicate that Q203 is a promising new clinical candidate for the treatment of tuberculosis.

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