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

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Résumé en anglais	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 worldwide1, 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 tuberculosis3, 4, 5, several of which are currently in clinical trials6, 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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