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Discovery of antibacterial inhibitors with benzamide skeleton targeting the Bacterial Cell Division Protein FtsZ

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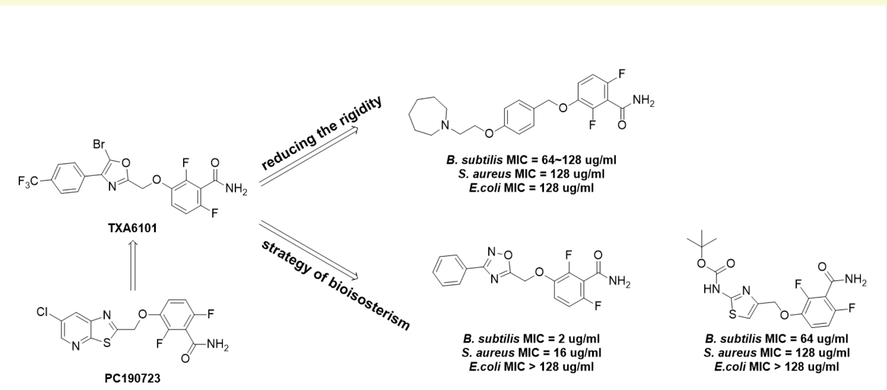
Abstract

The emerging of bacteria with antibiotics resistance has become a new threat to human health in this world. Apart from the rational use of the existing antibiotics, development of antibiotics with new mechanisms to kill the bacteria is becoming more and more important. FtsZ is an essential protein in the cycle of bacterial replication. Without FtsZ, bacteria cannot complete the cell division. Thus, FtsZ has become an attractive target to inhibit the bacteria. PC1907232 is one of the ligands binding to the active site of FtsZ. Here taking PC190723 as lead compound, this research aims to develop a novel class of benzamide-skeleton compounds through inhibiting FtsZ protein to kill bacteria.

Graphical Abstract



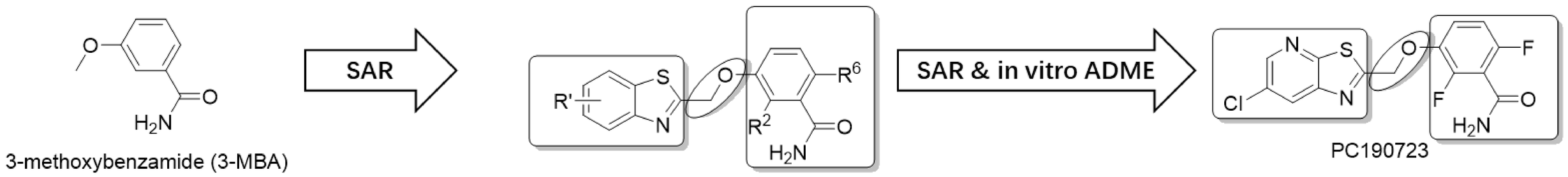
The analyzed structure-activity relationship of PC190723 derivatives

Derivatives with benzamide moiety

1. The amide and 3-ether substituents appeared to be critical for inhibition of cell division.

Derivatives with benzothiazole moiety

1. Improved activity was observed for the 5-chloro and 5-phenyl derivatives.
2. Hydrophobic substitutions at the 5-position resulted in improved on-target activity compared to the unsubstituted benzothiazole.
3. Methyl ester and 1,2,4-oxadiazol-5-yl substitutions resulted in improved on-target activity.
4. When the 6th atom of thiazolopyridine was N leads to 32-fold less active than the benzothiazole.
5. When the 7th atom was N, the antibacterial activity was equivalent or only 2−4-fold less potent than the corresponding benzothiazole.



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