Screening of novel synthetic agents against *Clostridioides difficile*

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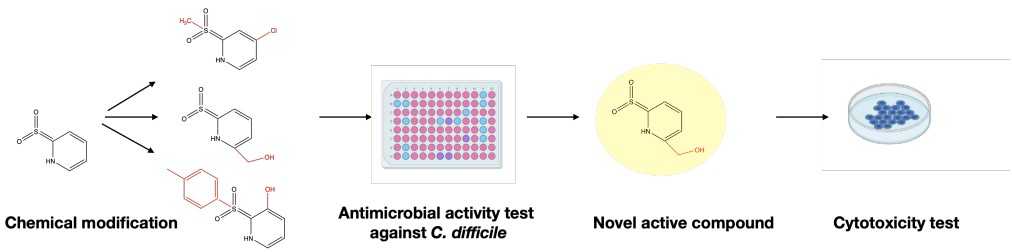
Abstract: Antibiotic resistance (AR) is the biggest concern in public health that causes tremendous economic loss and fatalities. *Clostridioides difficile* is the most common cause of hospital-acquired diarrhea, with symptoms ranging from mild diarrhea to life-threatening colitis. On top of that, the pathogen is being known to resist multiple antibiotics. Due to the high background of AR, reduced susceptibility to prescribed antibiotics have been continuously reported in this pathogen. Chemical synthesis allows us to access to the first antimicrobial agents before the discovery of penicillin, and the process also enables the development of drug with the desired characteristics and higher efficiency. This study integrated the science of chemistry together with biology to seek novel antimicrobial agents against *C. difficile*. A series of compounds were chemically synthesized from five different core structures; (i) 3-methyl-5-pyrazolones, (ii) 2-sulfonylquinolines, (iii) 2-sulfonylpyridines, (iv) sulfoximines, (v) pentacyclic triterpene as they were reported to link with biological activities. A total of 77 compounds of 5 different groups were tested for antimicrobial activity against *C. difficile* strain R20291 using broth microdilution method. None of the chemical synthetic compounds in group i to iv exhibited inhibition concentration of lower than 10 μM against *C. difficile* R20291, while 2 semisynthetic compounds, AM1 and AM2 from the group v could inhibit *C. difficile* R20291 with MIC of 5-10 μM. Interestingly, all pentacyclic triterpene derivatives exhibited lower cytotoxicity to HaCaT cells compared to the parental compound.

Graphical abstract:



Keywords: antibiotic resistance; *Clostridioides difficile;* medical chemistry

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