Development of anti-HBV agents through divergent and programmable synthesis of skeletally diverse alkaloidal scaffolds bearing Michael acceptors

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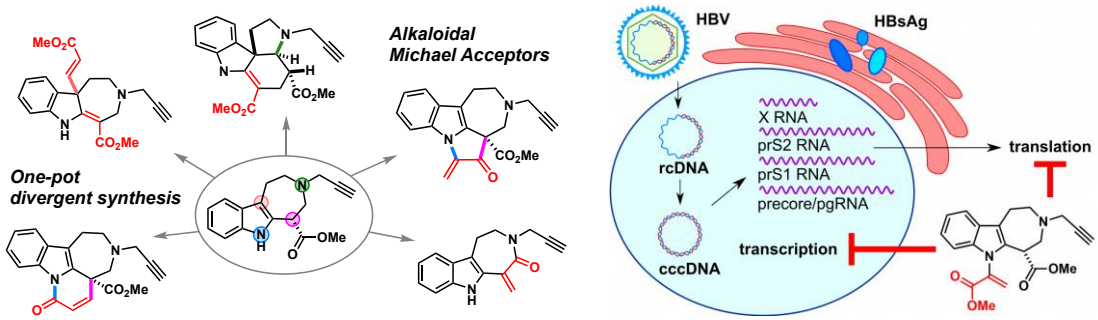
Small molecules with a Michael acceptor exhibit potent biological activities by forming a covalent bond with their target proteins. In this study, a series of nitrogen-containing scaffolds bearing Michael acceptors was designed and synthesized based on the structural motifs relevant to the covalent drugs and natural products exhibiting antiviral activity.

We devised site-selective reactions of the common tricyclic intermediate with methyl propiolate at the four potentially nucleophilic sites involving indole N1, C3, ester alpha position, and aliphatic nitrogen, and achieved divergent synthesis of five alkaloidal Michael acceptors in a programmable manner within two steps.[1,2] This approach allowed rapid and collective synthesis of the alkaloidal Michael acceptors with distinct reactivities and steric hindrances against nucleophilic groups of cellular biomolecules.

Three Michael acceptors were found to exert potent *in vitro* inhibitory activities against hepatitis B virus (HBV) proliferation with low toxicity, and substantially reduced the levels of relaxed circular DNA (rcDNA) and covalently closed circular DNA (cccDNA). The optimal lead candidates are likely to suppress either RNA transcription from cccDNA or protein translation from HBV RNA, which would be a distinct mechanism of action from existing nucleic acid based anti-HBV drugs.[3,4]



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