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In This Issue

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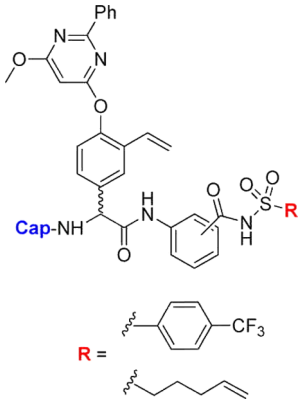
Hepatitis C virus (HCV), a member of Flaviviridae family, is considered a global health threat with infection threatening millions of patients worldwide. The approval of anti-HCV drug, Telaprevir and Boceprevir, provided significant improvement in HCV therapy. However, combination therapy with interferon-alpha and ribavirin still resulted to limited efficacy and side effects. Moveover, because of the fast development of drug resistance, there is a continuous need for new antiviral drugs.

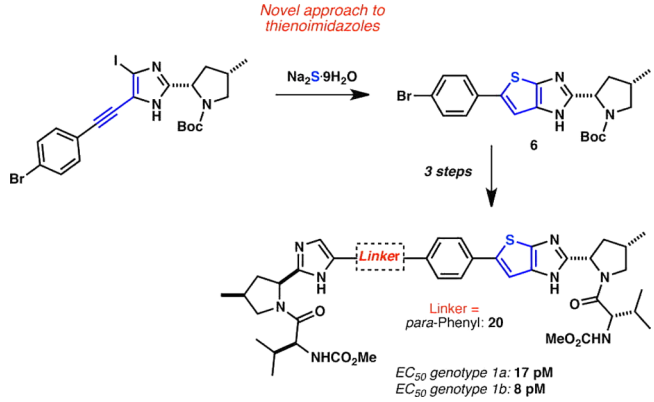
NOVEL PEPTIDOMIMETIC HEPATITIS C VIRUS NS3/4A PROTEASE INHIBITORS SPANNING THE P2−P1′ REGION

In this special issue, the design synthesis of novel preclinical protease inhibitors targeting HCV is presented by Lampa et al. (DOI: 10.1021/ml400217r). The inhibitors are based on unique central scaffold and display promising antiviral activity both on wild-type and drug resistant variants of the protease enzyme. Becuase of their novel overall profile, optimization of these peptidomimetic compounds could lead to the next generation of HCV NS3 protease inhibitors.



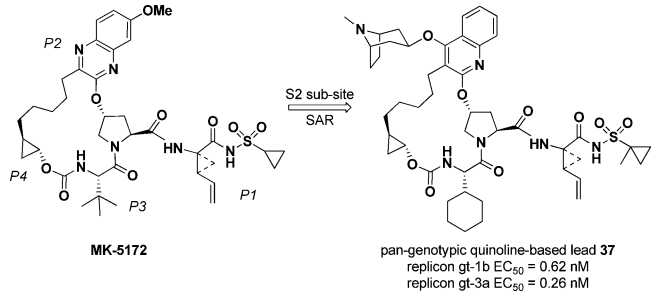
DISCOVERY OF THIENOIMIDAZOLE-BASED HCV NS5A GENOTYPE 1A AND 1B INHIBITORS

Giroux et al. (DOI: 10.1021/ml300461f) describe the synthesis and biological activity of a series of nonsymmetrical linear pyrrolidine amides patterned after a potent inhibitor of HCV NS5A genotype 1a and 1b undergoing clinical trials. The group replaced one of the benzimidazole moieties with an isosteric thienoimidazole moiety and studied the variations in the linker subunits. Excellent in vitro activities were obtained, and one compound was moved as a candidate to study ADME properties.



NOVEL QUINOLINE-BASED P2−P4 MACROCYCLIC DERIVATIVES AS PAN-GENOTYPIC HCV NS3/4A PROTEASE INHIBITORS

Shah et al. (DOI: 10.1021/ml400466p) follows-up on their previous study of HCV NS3/4a protease inhibitor MK-5172, in combination with the NS5a inhibitor MK-8742 that has recently received a breakthrough therapy designation from the US FDA for treatment of chronic HCV infection. On the basis of molecular modeling, the group identified new chemical space, which allowed for additional interactions in the active site of the enzyme. Shah et al. describe the discovery of highly potent inhibitors with pan-genotypic activity and an improved profile over MK-5172.



SYNTHESIS AND ANTI-HCV ACTIVITY OF 4-HYDROXYAMINO α-PYRANONE CARBOXAMIDE ANALOGUES

Konreddy et al. (DOI: 10.1021/ml400432f) present a new molecular scaffold based on 4-hydroxyamino α-pyranone carboxamide as a possible anti-HCV agent for further development. Two compounds showed higher selectivity index over telaprevir in the anti-HCV activity evaluation, indicating that the scaffold can be further optimized as direct acting antivirals.

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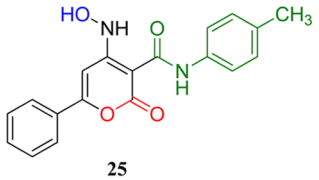

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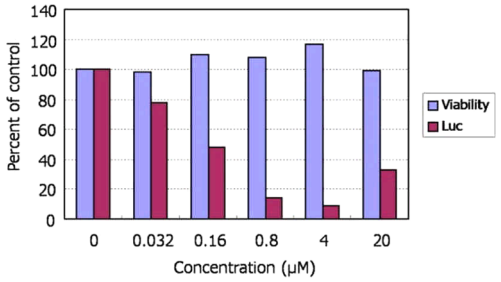
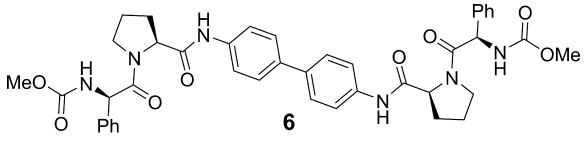
4-hydroxyamino α-pyranone carboxamide



EC_{50} = 0.18 ± 0.09
CC_{50} > 20

POTENT HEPATITIS C VIRUS NS5A INHIBITORS CONTAINING A BENZIDINE CORE

Bae et al. (DOI: 10.1021/ml4003293) reports the discovery of a class of inhibitors that contain a benzidine prolinamide backbone structure. The group takes advantage of the symmetrical structure of the benzidine scaffold in employing a simple synthetic route and exploring expedient modification of the capping groups, which leads a series of highly potent inhibitors. One compound was found to be potent and nontoxic and offer a great potential for further development as anti-HCV agent.

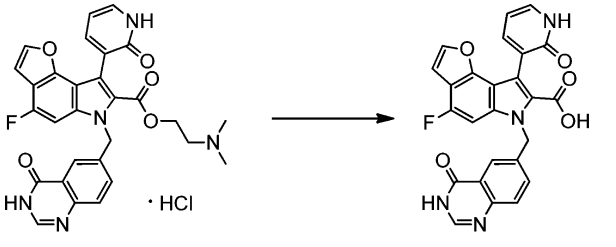


6

Type 2a: EC_{50} = 0.26 nM, G-1b: EC_{50} = 0.028 nM

DISCOVERY OF SCH 900188: A POTENT HEPATITIS C VIRUS NS5B POLYMERASE INHIBITOR PRODRUG AS A DEVELOPMENT CANDIDATE

Intensive efforts have also been focused in discovering novel non-nucleoside HCV NS5B polymerase inhibitors. Starting from indole-based leads, Chen et al. (DOI: 10.1021/ml400192w) conducted SAR investigations of the NS5B inhibitors, leading to the discovery of a novel series of indole N-1 quinazolinone substituted potent HCV polymerase inhibitors. The prodrug of one such inhibitor exhibited excellent potency and PK profile and was selected as a development candidate.



12 (900188, Prodrug) **11 IC_{50} = 5 nM, EC_{50} = 6 nM**

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