scaffold. The establishment in this work of SAR within this compound class could form the basis for further optimization cycles, allowing access to more-potent NPY5 receptor antagonists that maintain a balanced pharmacokinetic and pharmacodynamic profile.

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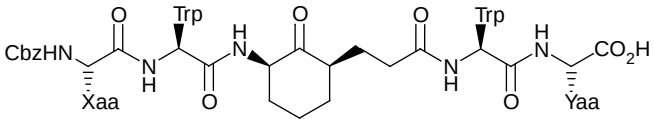
PII: S1359-6446(05)03708-6

Inhibitors of the serine protease plasmin

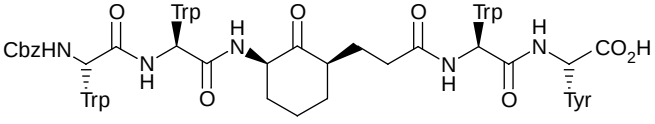
Proteases are involved in the regulation of a multitude of physiological processes, including diverse events such as growth, cellular migration and remodelling of the extracellular matrix (ECM) [1]. Plasmin is a serine protease that is crucial for ECM remodelling because of its role in degrading ECM components such as fibrin, fibronectin, laminin and proteoglycans. In addition to this direct role, plasmin also plays a more indirect role by initiating a protease cascade via the activation of the matrix metalloproteases (MMPs) MMP-1, -3, and -9. In turn, these MMPs regulate matrix deposition and remodelling.

Recently, several studies have shown that ECM remodelling is one of key processes associated with angiogenesis, tumour growth and invasion [2,3]. Thus, potent and selective inhibitors of plasmin could represent potent chemotherapeutic agents through the inhibition of angiogenesis, blocking the rapid growth of primary tumours, as well as the spread of secondary metastases. Recent work [4] has disclosed the generation of a library of putative inhibitors with the general structure **(i)**. This library of 400 compounds, synthesized in mixtures of 20, was prepared on solid support (Wang resin). Compounds were screened against plasmin, a serine protease, identifying several active mixtures. Following a deconvolution procedure, several active compounds, now as singletons, were discovered. One of the most potent inhibitors of plasmin was **(ii)**, which possessed an IC_{50} of 2.7 μM.

The specificity of **(ii)** was determined against three other trypsin-like serine proteases (kallikrein, thrombin and trypsin). Against these enzymes, no inhibition was observed at a concentration of 400 μM, indicating that **(ii)** possessed >150-fold selectivity for plasmin over kallikrein, thrombin and trypsin. Given that compounds in the series typified by **(i)** have high molecular weights and are peptide-like



(i)



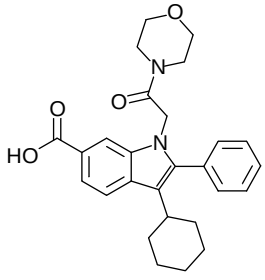
(ii)

compounds, it is unlikely they will have good oral bioavailability. However, because they are designed to control remodelling and degradation of the ECM, the inhibitors do not need to penetrate through the cell membrane. One way to improve their pharmacokinetic characteristics would be to replace the amide bonds by appropriate nonhydrolyzable analogues, decreasing their susceptibility to hydrolysis by proteases. Further work in this area is warranted to achieve these aims.

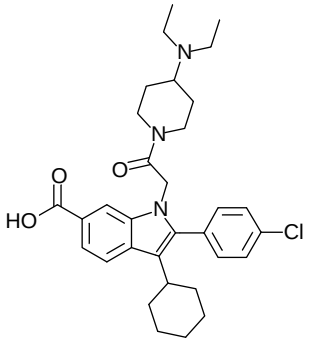
Inhibitors of subgenomic hepatitis C virus RNA replication

The hepatitis C virus (HCV) has been identified as the pathogen responsible for most cases of non-A and non-B hepatitis [5]. HCV infection represents a significant global health problem and it is now thought that there could be as many as 170 million carriers of the virus around the world. HCV can lead to life-threatening liver disorders, such as cirrhosis, and is now recognized as the largest single factor necessitating liver transplantation [6]. New therapies aimed at tackling HCV are urgently required but efforts to discover and develop them have been impeded by the problems arising with HCV replication in cell culture or in small-animal models. The recent introduction of the HCV replicon assay [7], a surrogate cell-based system in which replication of subgenomic viral RNA is studied, has facilitated drug discovery efforts that target HCV proteins. Using this assay, a potent inhibitor of the HCV nonstructural (NS)3 protease was shown to be capable of eliciting a strong reduction in viral titre in a clinical setting. In addition to NS3, the nonstructural region of the HCV genome encodes additional enzymes that are believed to play important roles in the viral life cycle, and are thus viable targets for drug discovery. The NS5B protein is one such target and it has been characterized as the RNA polymerase, which catalyzes the synthesis of a complementary (–)-stranded HCV RNA intermediate and the (+)-stranded viral genome itself. NS5B has emerged as an attractive target for drug discovery efforts aimed towards antivirals for HCV, and it has been described as the most druggable HCV protein [8].

Several series of NS5B inhibitors that show activity in the replicon assay have been reported and it is hoped that they could represent potential new HCV therapeutics. Although, to date, no non-nucleoside inhibitors capable of binding at the active site of NS5B, as well as possessing cell-based activity, have been reported. However, allosteric inhibition by small-molecule inhibitors of NS5B has emerged as one potential route for the inhibition of subgenomic



(iii) NS5B IC_{50} = 26 nM



(iv) NS5B EC_{50} = 127 nM

HCV RNA replication, and several structurally diverse inhibitor classes have now been identified. Recent work has been disclosed [9] that has sought to optimize a series of compounds that show inhibition against the NS5B enzyme, as well as promising activity in a replicon assay [typified by **(iii)**] with respect to improved cell-based potency and a more suitable overall profile for clinical development as anti-HCV agents.

To these ends, a library of 500 compounds was designed and these compounds were assessed for activity against the purified ΔC55 NS5B enzyme in the presence of heterogenic template RNA. Inhibition of replication of subgenomic HCV RNA was measured in HUH-7 cells. From this study several actives were obtained, of which **(iv)** was one of the most potent in the NS5B cell-based assay, displaying an EC_{50} of 127 nM. This compound also displayed encouraging pharmacokinetics in rat and dog. Further work in this area is warranted because the current research efforts highlight the potential of this structural series in the development of novel anti-HCV agents.

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PII: S1359-6446(05)03709-8