Hepatitis C virus (HCV) is the most frequent cause of chronic viral hepatitis, with about 3% of the world's population infected.1 In the majority of acutely infected individuals, HCV evades the immune response and establishes a chronic infection associated with liver cirrhosis and in some cases hepatocellular carcinoma.2 There is currently no broadly effective therapy, making the development of HCV-specific antiviral agents an urgent need.3,4 HCV is a small, enveloped, single stranded positive RNA virus in the Flaviviridae family.The nonstructural protein NS5A is an active component of HCV replicase5,6, possibly involved in regulation of viral replication and resistance to the antiviral effect of interferon.7,8 NS5A is a large phosphoprotein (56-58 kDa) organized into three domains, including an amphipathic a-helix at its amino terminus that promotes membrane association and a zinc binding domain.Whilst HCV replicative enzymes, such as NS3 protease and NS5B polymerase, have been extensively explored, efforts to target NS5A have largely been hampered by an incomplete understanding of the role of this multifunctional protein in replication--and a resultant lack of a screening protocol for enzyme inhibition.A few years ago, the development of subgenomic replicons that replicate in a human hepatoma cell line provided a system to test or screen compounds that inhibit genome replication11,12, and thus make it possible to identify structural classes that disrupt the function of any of the viral proteins involved in replication--including those with no known enzymic activity (such as NS5A).In this report, we describe a class of piperazinyl-N-(aryl)benzamides (identified from screening the in-house compound collection) as potent inhibitors of HCV replication in such a surrogate cell-based assay (Fig.The compounds described herein were assessed for their ability to inhibit replication of subgenomic HCV RNA, measured in HUH-7 cells using a modification of the procedure of Bartenschlager.The RNA replication machine of .(HCV is a multi-subunit membrane-associated complex.1