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Development of Isoquinolinone Derivatives as Potential HCV NS5B Polymerase Inhibitors

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NS5B RNA dependent RNA polymerase plays a crucial role in HCV replication and it has no counterpart in mammalian cells. Therefore, it is popularly regarded as a potential drug target for the treatment of HCV infections. The design, synthesis and SAR of quinazolinone derivatives as NS5B inhibitors will be discussed. Structural optimization of this series revealed that compound **J017171** possess highest potency (IC_{50} = 9.5 μM) to inhibit NS5B activity based on the inorganic pyrophosphate generation and also demonstrated good potency (IC_{50} = 5.9 μM) in another assay method based on NTP incorporation by NS5B enzyme. **J017171** demonstrated moderate cytotoxicity (IC_{50} = 15.7 μM) to HCV genotype 1b replicon containing Ava5 cells. NMR and UV studies have shown that **J017171** forms stable chelates with the Mg^{2+} ions in vitro. Molecular docking confirms that **J017171** forms chelating interactions with two Mg^{2+} ions in the active site of enzyme.