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Discovery of SCH 900188: A Potent Hepatitis C Virus NS5B Polymerase Inhibitor Prodrug As a Development Candidate

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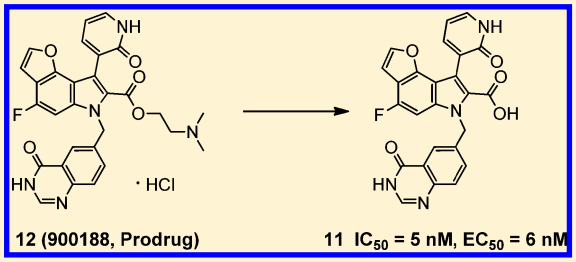
Supporting Information

ABSTRACT: Starting from indole-based hepatitis C virus (HCV) NS5B polymerase inhibitor lead compound **1**, structure modifications were performed at multiple indole substituents to improve potency and pharmacokinetic (PK) properties. Bicyclic quinazolinone was found to be the best substituent at indole nitrogen, while 4,5-furanylindole was identified as the best core. Compound **11** demonstrated excellent potency. Its C2 *N*,*N*-dimethylaminoethyl ester prodrug **12** (SCH 900188) demonstrated significant improvement in PK and was selected as the development candidate.



KEYWORDS: *HCV, hepatitis C virus, NS5B polymerase, polymerase inhibitor, prodrug*

It is estimated that over 170 million people have been infected by hepatitis C virus (HCV).[1] In most patients, the disease progresses to a chronic state that persists for decades, but eventually leads to cirrhosis, liver failure, or liver cancer.[2] With no anti-HCV vaccines available, the current standard of care (SOC) involves the combination of a protease inhibitor with pegylated-interferon and ribavirin.[3] The sustained virologic response (SVR) rate of the triple combination therapy is about 70% for patients with the most-difficult to treat genotype-1 HCV.[3] However, there are still large unmet medical needs for safer and more effective HCV treatments due to the side effects associated with α-interferon and ribavirin.

HCV was identified more than two decades ago as a positive-sense single-stranded RNA virus.[4] The viral genome encodes a polyprotein, which can be divided into structural and nonstructural (NS) precursor regions. The nonstructural proteins NS2, NS3, NS4A, NS4B, NS5A, and NS5B are essential for the replication of HCV virus; thus, intensive research has been focused on finding drugs directly targeting these proteins.[5,6] Recent approval of the two first-in-class HCV NS3 protease inhibitors, boceprevir[7] and telaprevir,[8] has generated great interest and created a race in the search for new treatments of HCV infection aiming at all-oral therapies with less side effects, higher SVR rate, broader genotype coverage, and shorter treatment period.[5]

The NS5B gene encodes an RNA-dependent RNA polymerase (RdRp), which is critical to the replication of the viral RNA genome.[9,10] X-ray crystal structure of the catalytic domain of N5SB reveals that the NS5B polymerase[11] has a well-conserved active site and multiple allosteric inhibitor binding sites.[12,13] Two distinctive classes of HCV NS5B polymerase inhibitors have been developed: nucleoside active site inhibitors (NIs) and non-nucleoside allosteric inhibitors (NNIs).[12,13] NIs have similar potency against all genotypes and a high genetic barrier to resistance due to the highly conserved NS5B active site.[13] Several NIs are at the advanced stage of clinical trials.[14] NNIs, however, achieve NS5B inhibition by binding to one of the allosteric sites. A number of NNI candidates have been progressed to phase II clinical trials.[12,13] Rapid development of resistant mutants has been observed with NNIs because they bind to the sites that are away from the active site of NS5B enzyme, but mutations at the NNI binding site may not necessarily lead to complete impairment of the enzyme function.[13]

Our early research in HCV NS5B polymerase inhibitor program led to inhibitor **1** (Scheme 1).[15] It has good potency in both genotype 1b NS5B RdRp enzyme assay[16] (IC_{50} = 3 nM) and cell-based replicon assay[17] (EC_{50} = 40 nM). X-ray structure of a similar compound in complex with NS5B enzyme indicated that it bound to an allosteric palm site apoprotein cavity adjacent to the active site.[15] The C3 pyridone carbonyl and N−H formed a pair of key hydrogen bonds with the backbone. The N1, C2, and C5 substituents had hydrophobic interactions with the protein surface. Further optimization was needed to improve cellular potency and PK properties. Structural modifications of compound **1** could either involve the change of indole core to deliver better scaffold or replace

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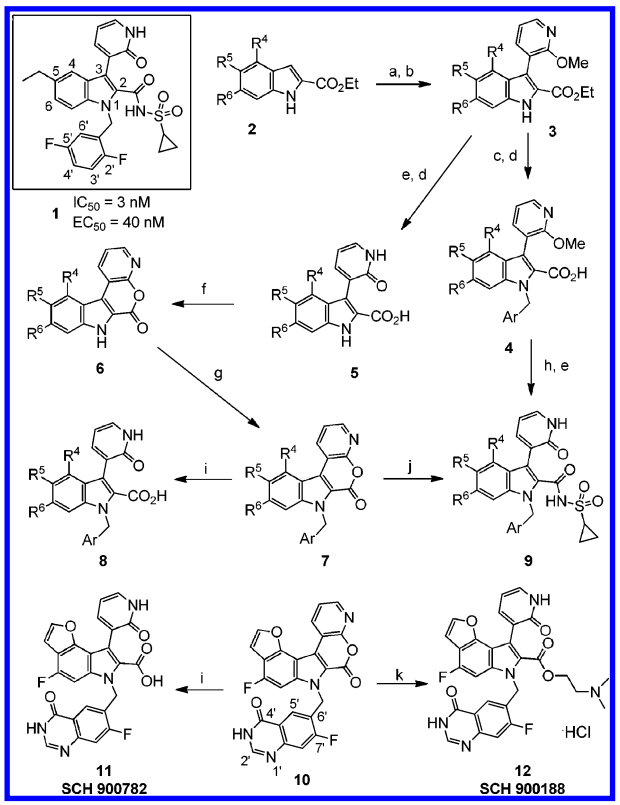
Scheme 1[a]



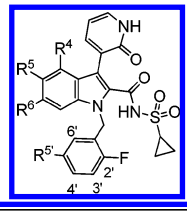
[a]Reaction conditions: (a) NIS, acetone; (b) 2-methoxy-3-pyridineboronic acid, $PdCl_2(dppf)_2$, K_2CO_3, 1,2-dimethoxyethane; (c) $ArCH_2Br$ (or $ArCH_2Cl$), Cs_2CO_3, DMF; (d) LiOH, THF/H_2O; (e) 4 M HCl, dioxane; (f) EDC, Et_3N, DMF; (g) $ArCH_2Br$ (or $ArCH_2Cl$), Cs_2CO_3, DMF; or $ArCH_2OH$, DIAD, PPh_3, THF; (h) CDI, RSO_2NH_2, DBU, THF; (i) LiOH, THF/H_2O; (j) RSO_2NH_2, DBU, DMF; (k) $(Me)_2NCH_2CH_2OH$, *n*-BuLi, THF, then HCl.

the substituents at various positions of the indole ring to enhance existing or create additional interactions. Herein, we report our progress toward this endeavor and the discovery of an orally bioavailable clinical candidate.

Syntheses of the inhibitors are outlined in Schemes 1.[15] Ethyl indole-2-carboxylate **2** was iodinated at C3 and subsequently converted to **3** through a Suzuki coupling.[18] After alkylation at N1, the C2 ethyl ester was hydrolyzed to give a carboxylic acid **4**, which was elaborated to an acylsulfonamide. Then the 2-methoxypyridine at C3 was demethylated to the pyridone final product **9**. Alternatively, compound **3** could be converted to a pyridone, which was followed by hydrolysis of the ester to give a carboxylic acid **5**. Intramolecular cyclization of the pyridone to the carboxylic acid afforded the tetracyclic lactone **6**. Alkylation at the indole nitrogen and opening of the lactone with a sulfonamide gave rise to the acylsulfonamide product **9**. Compound **7** could also be hydrolyzed to the carboxylic acid inhibitor **8**. The quinazolinone series of inhibitors were synthesized in similar reaction sequences. The final lactone intermediate **10** was either hydrolyzed to the carboxylic acid derivative **11** or converted to the *N*,*N*-dimethylaminoethyl ester (**12**).

Several attempted modifications of the indole core to different bicyclic heterocycles such as 7-azaindole failed to improve potency.[19] Efforts were then focused on the modification of various indole substituents. First, the structure−activity relationship (SAR) of the indole nitrogen substituent was investigated. To identify a group that was capable of establishing additional interactions with protein backbone residues, moieties with different C5′ functionalities were examined (Table 1, **13**−**17**). The C5′ cyano analogue **13**

Table 1. Optimization of R^4, R^5, R^6, and $R^{5'}$ Substituents



Compound	R^5, R^4	R^6	$R^{5'}$	IC_{50} (nM)	EC_{50} (nM)
1	Et, H	H	F	3	40
13	Et, H	H	CN	7	80
14	Et, H	H	CONH2	12	30
15	Et, H	H	SO_2Me	8	80
16	Et, H	H	SO_2NH_2	5	80
17	Et, H	H	OH	5	100
18	Me, H	H	CONH2	4	140
19	CF3, H	H	CONH2	6	170
20	Et, H	F	CONH2	5	60
21	Me, H	F	CONH2	4	50
22	CF3, H	F	CONH2	8	150
23		F	CONH2	5	10

offered no potency improvement in both enzyme (IC_{50} = 7 nM) and cellular assays (EC_{50} = 80 nM) compared to **1**. When C5′ was substituted with a primary amide (**14**), EC_{50} improved slightly to 30 nM. Changing amide to a methyl sulfone or a primary sulfonamide as in **15** and **16** did not result in similar enhancement in biological activity since both IC_{50} and EC_{50} were higher than those of compound **1**. The C5′-hydroxy analogue **17** was also not as potent as **1**. Keeping the C5′ primary amide substituent, the SAR of C4, C5, and C6 substitution at indole core was investigated (Table 1, **18**−**23**). Since our early research indicated that C4 could not tolerate any sizable substituent,[15] most modifications were made at C5 and C6 positions. When C5 ethyl group was changed to a smaller methyl or trifluoromethyl group, the resulting inhibitors **18** and **19** gained some activity in enzyme assay, but lost cellular potency compared to **14**. The addition of a C6-fluoro substituent (**20**−**22**) maintained good IC_{50} (4−8 nM) but gave no improvement in EC_{50} (50−150 nM). Besides investigation on individual C4, C5, and C6 substituents, the SAR of C4,C5-cyclized analogues was also studied in parallel. Among various tricyclic indoles studied, the 4,5-furan-6-F indole was found to be the best core.[20] When this tricyclic indole was incorporated into the current series, the resulting inhibitor **23** demonstrated

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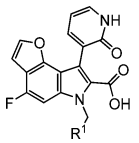
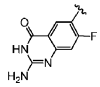
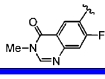
superior potency in replicon assay (EC_{50} = 10 nM), which represented a 3-fold improvement over compound **14**.

Although compound **23** had very good potency, its PK was poor with an area-under-the curve (AUC) of only 0.21 μM·h when dosed orally in rats at 10 mg/kg. The acylsulfonamide and primary amide were potential liabilities. Indeed, when the C2 acylsulfonamide was replaced with a carboxylic acid, the resulting compound **24** (Table 2) demonstrated a significant

Table 2. Optimization of Indole N1 Aromatic Moiety



Compound	R^1	IC_{50} (nM)	EC_{50} (nM)	Rat PK AUC[a] (μM·h)
24		4	15	1.7
25		5	700	--
26		20	70	8.8
27		2000	2000	--
28		7	10	4.0
11		5	6	4.3
29		4	20	0.85
30		4	6	8.3
31		7	7	0.02
32		6	300	--
33		3	250	0.17

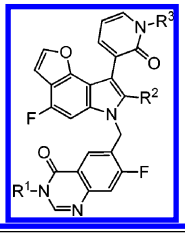
[a]Oral dosing of 10 mg/kg for 0–6 h data.

AUC improvement to 1.7 μM·h in rat PK although it was slightly less potent (EC_{50} = 15 nM) than **23**. Thus, further SAR studies were conducted with C2 carboxylic acids. Various mono- or bicyclic N1 benzyl substituents were designed to replace primary amide moiety (Table 2). The C5′-carboxylic acid derivative **25** was equally active in enzyme assay but lost much of the potency in replicon assay. The C5′-acetyl analogue **26** was 5-fold less potent than **24** in both enzyme and cellular assays, although its rat PK AUC was good (8.8 μM·h). Surprisingly, the C4′,C5′-bicyclic benzoxazolidinedione analogue **27** lost all activities in both assays, while the C4′,C5′-bicyclic benzimidazolidinedione derivative **28** had an impressive EC_{50} of 10 nM along with a good AUC of 4.0 μM·h.

Continued investigation of bicyclic heterocycles led to the discovery of quinazolinone moiety (**11**). Compound **11** (SCH 900782) had excellent potencies in both enzyme (IC_{50} = 5 nM) and replicon assays (EC_{50} = 6 nM). It also had good AUC of 4.3 μM·h in rat PK. Several related bicyclic ring systems were also examined (**29**–**33**) in attempts to further improve potency and PK. Methylation at C2′ (**29**) resulted in higher EC_{50} and a lower AUC. The quinazolinedione derivative **30** had excellent IC_{50}, EC_{50}, and rat PK AUC. Unfortunately, it was not very stable and could be hydrolyzed under basic conditions. The C2′-amino quinazolinone compound **31** also demonstrated impressive IC_{50} and EC_{50}, but it had a negligible AUC. Methylation at N1′ of **30** or N3′ of **11** did not affect IC_{50} (**32** and **33**), but their EC_{50}s were surprisingly much worse than other quinazoline analogues.

Although compound **11** had a very good overall profile, to achieve adequate exposure necessary for the ultimate goal of once-daily (QD) dosing, further improvement in PK properties was necessary. Prodrug is an attractive approach to enhance the exposure level of very polar and less soluble molecules.[21] The pyridone or quinazolinone nitrogens and the C2 carboxylic acid were potential sites for prodrug development. The methylene pivalate prodrug **34** (Table 3) maintained most of the potency, while analogue **35** lost significant activity, probably due to the loss of a hydrogen bond at pyridone. No rat PK AUC was observed for both compounds suggesting inefficient conversion to the active compound **11**. The ethyl ester prodrug (**36**) did

Table 3. Prodrugs of Compound 11[a]



Compound	R^2	R^1 and R^3	IC_{50} (nM)	EC_{50} (nM)	Rat PK AUC[b] (μM·h)
11		R^1, R^3 = H	5	8	4.3
34		R^1 = CH_2Piv R^3 = H	13	10	0.0
35		R^1 = H R^3 = CH_2Piv	51	67	0.0
36		R^1, R^3 = H	9	22	0.22
37		R^1 = CH_2Piv R^3 = H	400	69	0.0
12		R^1, R^3 = H	150	5	22[a]
38		R^1, R^3 = H	110	11	2.3
39		R^1, R^3 = H	75	14	0.79

[a]Oral dosing of 10 mg/kg for 0–24 h data. AUC was for active parent compound **11**. CH_2Piv = $-CH_2OCO$-*t*-Bu. [b]Oral dosing of 10 mg/kg for 0–6 h data.

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Table 4. Profile of Compounds 11 and 12

compound	11			12		
animal species	rat	dog	monkey	rat	dog	monkey
AUC (PO) (μM·h)	10[a]	0.4[b]	8[b]	22[a]	2.4[b]	144[b]
C_{max} (μM)	1.4	0.1	0.8	2.1	0.8	4.1
$t_{1/2}$ (IV) (h)	9.4[b]	3.2[c]	8.9[c]	11[b]	4[c]	22[c]
bioavailability (%) (F)	0.7	4	5	2	29	63
clearance (mL/min/kg)	0.2	11	0.6	2.4		0.8
Mini Ames test	negative			negative		
in vitro micronucleus	negative			negative		

[a]At 10 mg/kg. [b]At 3 mg/kg. [c]At 1 mg/kg. All AUCs were 0−24 h data.

not provide much AUC either. So was the methylene pivalate and ester dual prodrug **37**. Inefficient conversion to active compound **11** and poor solubility of prodrugs **34**−**37** presumably contributed to their poor PK performance. One way to improve solubility was to incorporate a tertiary amine into the C2 ester so that a salt could be made. Indeed, the hydrochloride salt of *N*,*N*-dimethylamino-ethyl ester (**12**, SCH 900188) was highly soluble (0.9 mM at pH 3.0). Its excellent potency in replicon assay (EC_{50} = 5 nM) implied efficient conversion of the prodrug **12** to its parent **11**. Most importantly, when the prodrug **12** was dosed orally in rats at 10 mg/kg, it delivered excellent AUC (22 μM·h) of parent compound **11**. Two other prodrugs with different chain lengths (**38** and **39**) were found to produce much lower AUCs of parent **11** in rat PK. The concentration of the active parent **11** in the liver was also measured for compounds with reasonable PK. When prodrug **12** was dosed in rats, at 6 h after dosing, the liver/plasma concentration ratio is 0.5 for parent **11**. The liver/plasma ratio was 0.4 when compound **38** was dosed. Clearly, compound **12** was the best among the prodrugs studied.

In enzyme assays, compound **11** was equally potent against genotype 1a and 1b NS5B enzymes (IC_{50} = 7 and 5 nM, respectively). Significant loss in potency was observed with genotype 2a, 3a, and 4a enzymes (IC_{50} > 5 μM). Compounds **11** and **12** were cross-resistant to several major mutations (e.g., C316Y, M414T, and G554D) against known palm site inhibitors but were fully active on resistant mutants in the active site and other allosteric sites. The frequency of emergence of resistance was significantly reduced when used in combination with a protease inhibitor. The PK profile and in vitro assay results of compounds **11** and **12** are summarized in Table 4. The oral bioavailability of carboxylic acid **11** in rats, dogs, and monkeys were 0.7%, 4%, and 5%, respectively. When prodrug **12** was dosed, the oral bioavailability of active metabolite **11** increased substantially to 2%, 29%, and 63%, respectively. The low bioavailability in rats was a result of extremely high AUC from IV dosing. Following IV administration of **12**, low clearance of 2.4 and 0.8 mL/min/kg and long half-life of 11 and 22 hours were observed in rats and monkeys, respectively. Compounds **11** and **12** were highly selective for the NS5B polymerase and showed no cell toxicity at up to 10 μM in a variety of cell lines. Both **11** and **12** were negative in the Ames mutagenicity and in vitro micronucleus assays. On the basis of the excellent overall profile, compound **12** was recommended as a preclinical candidate for further development.

The X-ray crystal structure of **11** in complex with HCV NS5B protein has been solved (Figure 1).[22] The compound is bound at the base of the active site cavity at the palm allosteric site, with the furanylindole core packed against the side chains

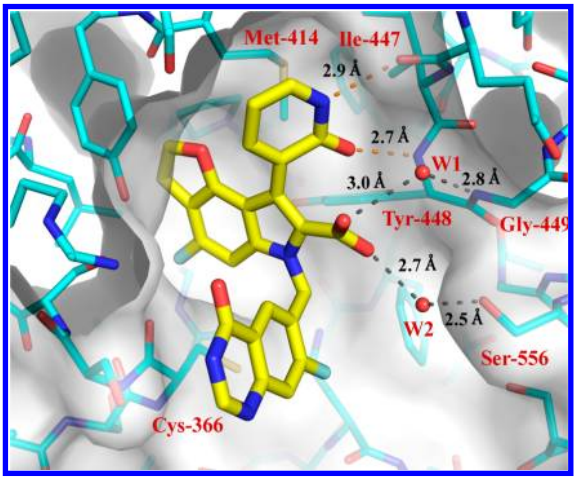

Figure 1. X-ray structure of compound **11** bound to the palm site of HCV NS5B polymerase.

of Met-414 and Tyr-448. The C3 pyridone group forms hydrogen bonds both with the backbone carbonyl oxygen of Gln-446 and with the backbone amide nitrogen of Tyr-448. The pyridone ring rests atop the side chain of Met-414. The C2 carboxylate moiety interacts with the backbone amide nitrogen of Gly-449 via a bridging water molecule. The N1 substituent packs atop the side chain of Cys-366 for hydrophobic interactions. It projects into a hydrophilic zone where it may form some hydrogen bonds through adjacent water molecules.

In summary, SAR studies of the indole substituents were performed to optimize potency and PK properties. The initial good potency of the primary amide group at the indole nitrogen substituent led to the eventual discovery of the novel quinazolinone series of highly potent inhibitors. Optimization of C4, C5, and C6 substituents led to the identification of 4,5-furanylindole as the best core. The C2 carboxylic acids demonstrated better PK than corresponding acylsulfonamides. After all, compound **11** was identified as the lead with very good potency and rat oral PK AUC. Its *N*,*N*-dimethylaminoethyl ester prodrug **12** achieved significant improvement in PK properties and was selected as a preclinical development candidate.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ABBREVIATIONS

HCV, hepatitis C virus; PK, pharmacokinetics; SAR, structure−activity relationship; NS, nonstructural; AUC, area-under-the-curve; SOC, standard of care; SVR, sustained virologic response; RdRp, RNA-dependent RNA polymerase; NIs, nucleoside inhibitors; NNIs, non-nucleoside inhibitors

REFERENCES

(1) Cohen, J. The scientific challenge of hepatitis C. *Science* **1999**, *285*, 26−30.

(2) Shepard, C. W.; Finelli, L.; Alter, M. J. Global epidemiology of hepatitis C virus infection. *Lancet Infect. Dis.* **2005**, *5*, 558−567.

(3) Sheridan, C. New Merck and Vertex drugs raise standard of care in hepatitis C. *Nat. Biotechnol.* **2011**, *29*, 553−554.

(4) Choo, Q. L.; Kuo, G.; Weiner, A. J.; Weiner, A. J.; Overby, L. R.; Bradley, D. W.; Houghton, M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* **1989**, *244*, 359−362.

(5) Chen, K. X.; Njoroge, F. G. A review of HCV protease inhibitors. *Curr. Opin. Invest. Drugs* **2009**, *10*, 821−837.

(6) Watkins, W. J.; Ray, A. S.; Chong, L. S. HCV NS5B polymerase inhibitors. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 441−465.

(7) Njoroge, F. G.; Chen, K. X.; Shih, N.-Y.; Piwinski, J. J. Challenges in modern drug discovery: A case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. *Acc. Chem. Res.* **2008**, *41*, 50−59.

(8) Perni, R. B.; Almquist, S. J.; Byrn, R. A.; Chandorkar, G.; Chaturvedi, P. R.; Courtney, L. F.; Decker, C. J.; Dinehart, K.; Gates, C. A.; Harbeson, S. L.; Heiser, A.; Kalkeri, G.; Kolaczkowski, E.; Lin, K.; Luong, Y.-P.; Rao, B. G.; Taylor, W. P.; Thomson, J. A.; Tung, R. D.; Wei, Y.; Kwong, A. D.; Lin, C. Preclinical profile of VX-950, a potent, selective, and orally, bioavailable inhibitor of hepatitis C virus NS3-4A serine protease. *Antimicrob. Agents Chemother.* **2006**, *50*, 899−909.

(9) Behrens, S. E.; Tomei, L.; De Francesco, R. Identification and properties of the RNA-dependent RNA polymerase of hepatitis C virus. *EMBO J.* **1996**, *15*, 12−22.

(10) Quinkert, D.; Bartenschlager, R.; Lohmann, V. Quantitative analysis of the hepatitis C virus replication complex. *J. Virol.* **2005**, *79*, 13594−13605.

(11) Lesburg, C. A.; Cable, M. B.; Ferrari, E.; Hong, Z.; Mannarino, A. F.; Weber, P. C. Crystal structure of the RNA-dependent RNA polymerase from hepatitis C virus reveals a fully encircled active site. *Nat. Struct. Biol.* **1999**, *6*, 937−943.

(12) Liu, Y.; He, Y.; Molla, A. Hepatitis C Virus Polymerase as a Target for Antiviral Drug Intervention: Non-Nucleoside Inhibitors. In *Antiviral Research: Strategies in Antiviral Drug Discovery*; LaFemina, R. L., Ed.; ASM Press: Washington, DC., 2009; pp 137−151.

(13) Watkins, W. J.; Ray, A. S.; Chong, L. S. HCV NS5B polymerase inhibitors. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 441−465.

(14) Kneteman, N. M.; Howe, A. Y.; Gao, T.; Lewis, J.; Pevear, D.; Lund, G.; Douglas, D.; Mercer, D. F.; Tyrrell, D. L.; Immermann, F.; Chaudhary, I.; Speth, J.; Villano, S. A.; O'Connell, J.; Collett, M. HCV796: A selective nonstructural protein 5B polymerase inhibitor with potent anti-hepatitis C virus activity in vitro, in mice with chimeric human livers, and in humans infected with hepatitis C virus. *Hepatology* **2009**, *49*, 745−52.

(15) Chen, K. X.; Vibulbhan, B.; Yang, W.; Sannigrahi, M.; Velazquez, F.; Chan, T. Y.; Venkatraman, S.; Anilkumar, G. N.; Zeng, Q.; Bennet, F.; Jiang, Y.; Lesburg, C. A.; Duca, J.; Pinto, P.; Gavalas, S.; Huang, Y.; Wu, W.; Selyutin, O.; Agrawal, S.; Feld, B.; Huang, H. C.; Li, C.; Cheng, K. C.; Shih, N. Y.; Kozlowski, J. A.; Rosenblum, S. B.; Njoroge, F. G. Structure−activity-relationship (SAR) development and discovery of potent indole-based inhibitors of the hepatitis C virus (HCV) NS5B polymerase. *J. Med. Chem.* **2012**, *55*, 754−765.

(16) Ferrari, E.; He, Z.; Palermo, R. E.; Huang, H. C. Hepatitis C virus NS5B polymerase exhibits distinct nucleotide requirements for initiation and elongation. *J. Biol. Chem.* **2008**, *283*, 33893−33901.

(17) Lohmann, V.; Körner, F.; Koch, J.-O.; Herian, U.; Theilmann, L.; Bartenschlager, R. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* **1999**, *285*, 110−113.

(18) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-catalyzed cross-coupling reaction of alkoxydiboron with haloarenes: A direct procedure for arylboronic esters. *J. Org. Chem.* **1995**, *60*, 7508−7510.

(19) Unpublished results at Merck Research Laboratories.

(20) The SAR and development of 4,5-cyclzed indole series of inhibitors and their synthesis are being reported in a separate publication.

(21) Rautio, J.; Kumpulainen, H.; Heimbach, T.; Oliyai, R.; Oh, D.; Järvinen, T.; Savolainen, J. Prodrugs: design and clinical applications. *Nature Rev. Drug Discovery* **2008**, *7*, 225−270.

(22) X-ray crystal structure data of HCV NS5B in complex with 11 has been deposited in the Protein Data Bank with access code 2YOJ.