Discovery of Conformationally Constrained Tetracyclic Compounds as Potent Hepatitis C Virus NS5B RNA Polymerase Inhibitors

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Abstract: We report a new series of hepatitis C virus NS5B RNA polymerase inhibitors containing a conformationally constrained tetracyclic scaffold. SAR studies led to the identification of 6,7-dihydro-5*H*-benzo[5,6][1,4]diazepino[7,1-*a*]indoles (**19** and **20**) bearing a basic pendent group with high biochemical and cellular potencies. These compounds displayed a very small shift in cellular potency when the replicon assay was performed in the presence of human serum albumin.

More than 170 million people worldwide are infected with hepatitis C virus (HCV),[1] and a considerable portion of those chronically infected are likely to develop cirrhosis of the liver and hepatocellular carcinoma. However, the current standard treatment for HCV, a combination therapy of pegylated interferon-α with ribavirin, has limited efficacy especially against the genotype 1 virus and is associated with severe adverse events.[2] Therefore, development of an improved anti-HCV agent remains as an unmet medical need.

A viral protein, HCV NS5B RNA polymerase, is the key enzyme involved in the replication of the HCV gene and has been one of the main targets for drug development.[3] Several classes of potent NS5B inhibitors have been reported in the past couple of years.[4−7] Recently, antiviral effects in HCV infected patients were shown by three inhibitors: nucleoside NS5B inhibitors NM283[8] and R-1626,[9] and a non-nucleoside inhibitor HCV-796.[10]

We previously found and reported benzimidazole 5-carboxylic acid derivatives as inhibitors of the NS5B polymerase, which led to the identification of **I** (JTK-109, Figure 1).[7,11] In the study, we investigated the effect of a substituent at a position ortho to the benzimidazole on the central phenyl (C2-ring). We also identified a fluorine atom as the most effective substituent for enzyme inhibition and were able to establish that the biochemical potency was influenced not by electronic effects of the substituent but by the the steric effect of the substituent.[12] We presumed that the fluorine atom at the ortho position to the benzimidazole on the C2-ring might make the dihedral angle between the benzimidazole ring and the C2-ring optimal for binding to NS5B protein. We hypothesized that fixing the dihedral angle between the 6,5-bicyclic core and the C2-ring by bridging them with another ring would increase the potency against NS5B (Figure 1). Herein, we report the discovery of a new class of tetracyclic compounds as potent NS5B inhibitors.[13,14] This initial work led to the identification of **20** with a cellular potency of 84 nM in the presence of human serum albumin. Our assay employed a C-terminally truncated genotype 1b $NS5B_{544}$ enzyme (BK strain) and Huh-5-2 replicon cells as previously reported.[7]

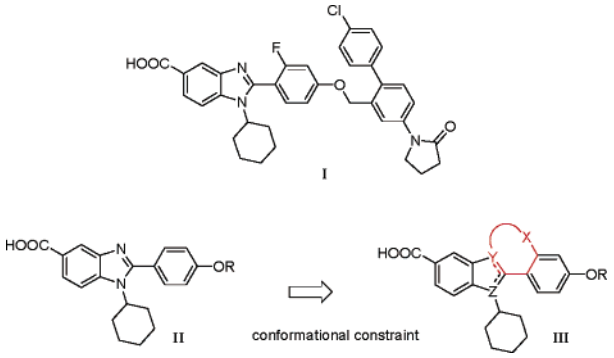
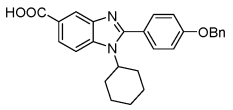
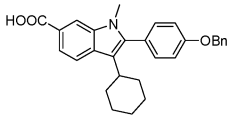
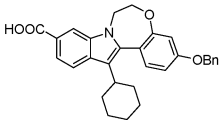
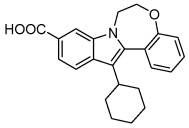


Figure 1.

Table 1. NS5B Enzyme Assay IC_{50} for Compounds **1**−**4** (Formation of Tetracyclic Compounds)

Compound	NS5B IC_{50} (μM)[a]
1 	1.4
2 	0.12
3 	0.017
4 	0.026

[a] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean.

We first designed and synthesized tetracyclic **3** as a conformationally constrained analogue of **1**,[11] in which the 6,5-bicyclic core is linked to the C2-ring through a newly formed seven-membered ring, and the benzimidazole ring was replaced with an indole to allow for the ring fusion. The unfused tricyclic N-substituted indole analogue **2** was also tested for comparison.[15,16] As expected, **3** exhibited a 7-fold increased biochemical potency (IC_{50} = 17 nM) compared to **2** and was 82-fold more potent than the benzimidazole **1** (Table 1). The added conformational constraint translates to approximately a 10-fold gain in potency. Furthermore, **4**, lacking the benzyloxy substituent, showed a comparable potency (IC_{50} = 26 nM), leading one to believe that this additional appendage is unnecessary for the SAR.

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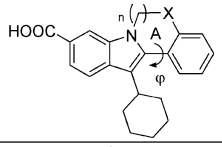
Table 2. Evaluation of the A-Ring Size and X Atom Type



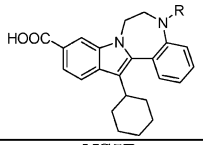
compd	X	n	NS5B IC_{50} (μM)[a]	replicon EC_{50} (μM)[a]	dihedral angle[b] φ (°)
5	CH_2	0	0.21	>10	0
6	CH_2	1	0.14	6.0[c]	29
7	CH_2	2	0.077	3.0	53
8	O	1	0.14	4.2[d]	24
4	O	2	0.026	0.86	43
9	O	3	0.047	1.2	61
10	NH	2	0.021	0.57	46
11	S	2	0.038	1.4	56

[a] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean. [b] The angles were measured in the most stable conformation with a random conformational search.[11] [c] $n = 1$. [d] $n = 2$.

Since bridging the 6,5-bicyclic core and the C2-ring led to a potent tetracyclic scaffold, we studied the effects of the size of the A-ring and of C or O in position X (five- to eight-membered rings, **4**−**9** in Table 2). Regardless of the atom type (X = C, O), the optimal A-ring size was found to be a seven-membered ring. The more planar molecules (five- or six-membered rings) and the more twisted compound (eight-membered ring) were less potent. Oxygen as atom X (**4**, IC_{50} = 26 nM) seems to be better than a CH_2 (**7**, IC_{50} = 77 nM). Next, we fixed the A-ring size to a seven-membered ring and examined other heteroatoms, such as N and S, at X. Compound **10** (X = NH, IC_{50} = 21 nM) was as potent as **4**, whereas sulfur, as atom X (**11**, IC_{50} = 38 nM), does not appear to be as potent as oxygen and NH. These compounds, except **5**, efficiently blocked the replication of HCV RNA in the replicon cells at micromolar to submicromolar concentrations. Compound **10** showed the best EC_{50} value (0.57 μM) in this series. To clarify the relationship between the NS5B inhibitory potency and the dihedral angle, we calculated the most stable conformation of the compounds with a random conformational search.[17] As shown in Table 2, the NS5B inhibitory potency roughly correlates with the measured dihedral angle in the calculated most stable conformation, suggesting that the measured angle reflects the actual angle in the bioactive conformation. The optimal angle seems to be approximately 46° (**4** and **10**). Although we presume the dihedral angle is the most important feature, electronic effects also appear to contribute, as seen by the preference of heteroatoms over a methylene linkage.

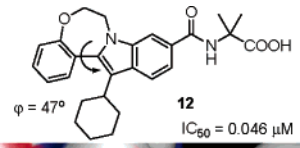
At this point, we were eager to examine the actual angle in the enzyme-bound structure and attempted to obtain a NS5B crystal complexed with this tetracyclic series in various conditions. Although the trials with the compounds in Tables 2 and 3 were unsuccessful, we obtained an enzyme/inhibitor complex of an amide derivative **12** (IC_{50} = 46 nM), which has been newly synthesized for the purpose of a SAR study in the 6-carboxylic acid moiety (the result is not shown in this report), by a soaking method (Figure 2).[18] Compound **12** binds to the allosteric pocket of thumb domain, which was exposed by displacing the tip of the finger loop on the thumb surface, just as the indole compounds that were previously reported.[19] The observed dihedral angle between the indole ring and the C2-phenyl ring in the complex structure is 47°, which is in good agreement with the angle predicted by the above SAR and the conformational calculation.

Table 3. SAR at the N5 Atom of Compound **10**



compd	R	NS5B IC50 (μM)[a]	Replicon EC50 (μM)[a] 10% FCS	10% FCS + 4% HSA[b]
10	H	0.021	0.57	>10 (n =1)
13	Me	0.019	0.59	6.5
14	iPr	0.036	1.5	–
15	Ac	0.12	1.1	–
16	Bn	0.041	0.55	–
17	CH_2CH_2Ph	0.026	0.31	–
18		0.024	0.21	4.3
19		0.018	0.053	0.20
20		0.0090	0.035	0.084

[a] Values are the mean of three independent experiments. Standard deviations are within 30% of the mean. [b] Assays run with 4% human serum albumin. EC_{50} values are the average of two experiments.



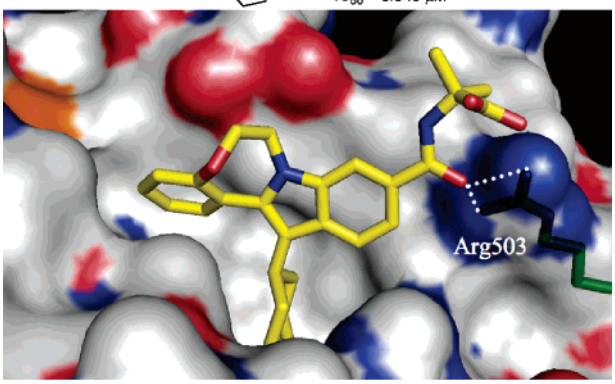
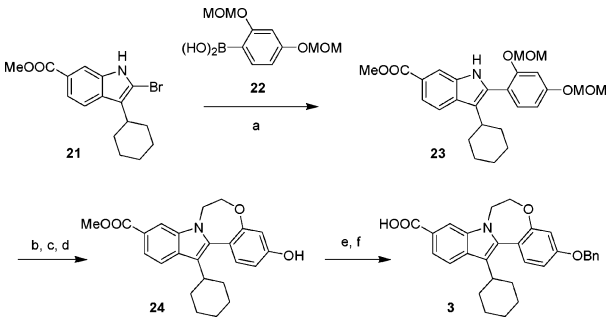


Figure 2. X-ray crystal structure (2.2 Å resolution) of compound **12** bound to the thumb domain of HCV $NS5B_{544}$ polymerase. Nitrogen, oxygen, and sulfur atoms are shown in blue, red, and orange, respectively. Hydrogen bonds between the amide oxygen and Arg503 are shown as white dashed lines.

Following the discovery of low molecular weight tetracyclic compounds with inhibitory potency against NS5B in the 20 nM range, improvement of the cellular potency was attempted through the introduction of various substituents on the N5 atom of the diazepine ring of **10** (Table 3). As a first attempt, a methyl group was introduced (**13**) and this compound showed equivalent biochemical and cellular potencies compared to **10**. Secondary alkyl (^{i}Pr, **14**) and aromatic groups (Bn **16** and phenethyl **17**) were well tolerated, while an acyl group (Ac **15**) led to reduced the potency. Since various substituents on N5 seem to be tolerated, it was hoped that introduction of a polar functionality at this position could also lead to improved cellular activity. A *N*,*N*-dimethylamide analogue (**18**) was synthesized, and it

Scheme 1[a]



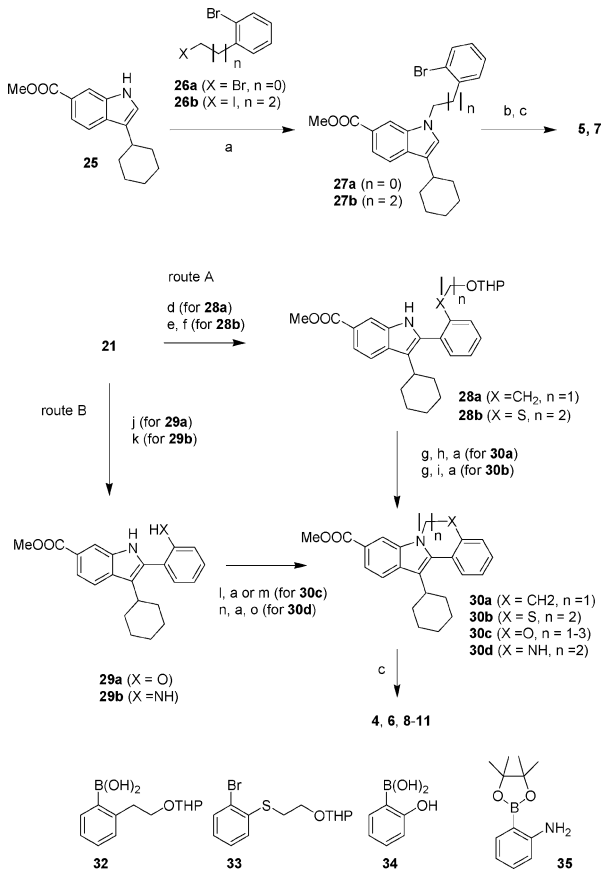
[a] Reagents: (a) $Pd(PPh_3)_4$, Na_2CO_3, LiCl, DME−H_2O; (b) $BrCH_2$-CH_2OTHP, NaH, DMF; (c) 6 N HCl (aq), THF−MeOH; (d) DIPAD, PPh_3, THF; (e) BnBr, K_2CO_3, DMF; (f) 4 N NaOH (aq), THF−MeOH.

exhibited a 3-fold improvement in cellular potency (EC_{50} = 0.21 μM) compared to **10** with no change in biochemical potency. Further improvement in cellular potency was achieved by introduction of a substituent with an amino functionality such as 2-dimethylaminoethyl (**19**), resulting in a 10-fold improvement (EC_{50} = 53 nM). It is believed that the high cellular potency of this compound comes from the lower affinity for serum protein (10% FCS in the assay).[20] This rationale is also substantiated by the fact that **19** did not decrease the cellular potency greatly (EC_{50} = 0.20 μM) in the replicon assay containing additional human serum albumin (HSA), while **10** and **18** show >15-fold shift in potency (Table 3). Additionally, given that HSA is the most abundant protein in human blood plasma and produced in liver, which is the target organ of HCV inhibitors, the reduced affinity to HSA is an attractive feature of **19**. Further improvements include changing the dimethylamino to a piperidine, which led to a more potent compound (**20**) with a 2-fold increase in biochemical potency (IC_{50} = 9 nM) and a 16-fold increase in cellular potency (EC_{50} = 35 nM) compared to **10**. Again, a very small shift in cellular potency (2-fold) was observed in the presence of HSA (EC_{50} = 84 nM). Consequently, a >100-fold improvement in cellular activity in the presence of HSA compared to **10** has been achieved. These compounds showed very weak cytotoxicity (CC_{50} > 20 μM) and good cell permeability using a Caco-2 cell membrane assay.

The tetracyclic compounds tested in this study were prepared as shown Schemes 1−3. Compound **3** was synthesized from 2-bromoindole derivative **21** (Scheme 1).[16] Suzuki coupling[21] with phenylboronic acid **22** provided the 2-phenylindole derivative **23**. N-Alkylation of **23** with NaH/$Br(CH_2)_2OTHP$ followed by unmasking of the OH protections followed by an intramolecular Mitsunobu reaction[22] furnished tetracyclic **24**. Alkylation of the phenol and subsequent hydrolysis of the ester yielded **3**.

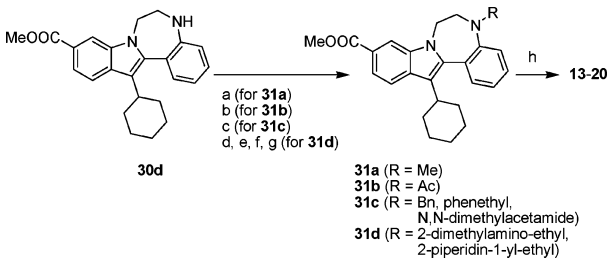
The compounds in Table 2 were synthesized as shown Scheme 2. Compounds **5** and **7** were synthesized from indole **25**[16] in three steps: N-alkylation to afford **27**, intramolecular Heck reaction,[23] and subsequent hydrolysis of the ester. Compounds **4**, **6**, **8**−**11** were synthesized from **21** through route A or route B. Suzuki coupling of **21** or its pinacol borate with **32**−**35** provided **28a**,**b** and **29a**,**b**, respectively. Compounds **28a**,**b** were converted to **30a**,**b** in three steps, respectively: unmasking of the THP ether, conversion of the OH to the bromide or mesylate followed by intramolecular cyclization. Selective O-alkylation of **29a** and subsequent intramolecular alkylation afforded the cyclized **30c**. Acylation of aniline **29b** with chloroacetyl chloride followed by intramolecular alkylation and borane reduction of the resulting lactam furnished **30d**. The esters on **30a**−**d** were hydrolyzed to give **4**, **6**, **8**−**11**.

Scheme 2[a]



[a] Reagents: (a) NaH, DMF; (b) $Pd(PPh_3)_4$, KOAc, DMA; (c) 4 N NaOH (aq), THF−MeOH; (d) **32**, $Pd(PPh_3)_4$, $NaHCO_3$, DME−H_2O; (e) pinacol borane, $Pd(OAc)_2$, PCy_2·biphenyl, Et_3N, 1,4-dioxane; (f) **33**, $Pd(PPh_3)_4$, $NaHCO_3$, DME−H_2O; (g) 6 N HCl (aq), THF−MeOH; (h) CBr_4, PPh_3, $CHCl_3$; (i) MsCl, Et_3N, $CHCl_3$; (j) **34**, $Pd(PPh_3)_4$, $NaHCO_3$, DME−H_2O; (k) **35**, $Pd(PPh_3)_4$, $NaHCO_3$, DME−H_2O; (l) $Cl(CH_2)nBr$, K_2CO_3, acetone; (m) CH_2Br_2, K_2CO_3, DMF; (n) chloroacetyl chloride, AcONa, AcOH, THF; (o) BH_3/THF, THF.

Scheme 3[a]



[a] Reagents: (a) HCHO (aq), $NaBH(OAc)_3$, $CHCl_3$; (b) Ac_2O, pyridine; (c) alkyl halide, K_2CO_3, DMF; (d) bromoacetic acid *tert*-butyl ester, K_2CO_3, DMF; (e) TFA, $CHCl_3$; (f) amine, WSC·HCl, HOBt, DMF; (g) BH_3/THF, THF; (h) 4 N NaOH (aq), THF−MeOH.

Compounds **13**−**20** (Table 3) were synthesized from **30d** (Scheme 3). Reductive aminomethylation of the aniline NH of **30d** and subsequent hydrolysis of the ester **31a** gave **13**. N-Alkylation or N-acylation of **30d** afforded the esters **31b**,**c**. Compound **31d** was derived from **30d** in four steps: N-alkylation with bromoacetic acid *tert*-butyl ester, unmasking of *tert*-butyl ester, coupling with the corresponding amine, and borane reduction of the amide. The ester **31d** was hydrolyzed to afford **19** and **20**.

In summary, we have described the discovery of a new class of tetracyclic compounds as potent HCV NS5B inhibitors. Conformational constraint of benzimidazole and indole inhibitors

through a seven-membered-ring bridge afforded a tetracyclic scaffold with significantly enhanced enzyme inhibition potencies. We also showed that incorporation of a basic group significantly improve the cellular potency with a very small potency shift in the replicon assay containing HSA (**20**, EC_{50} = 84 nM). These findings may offer new prospects for the benzimidazole and indole class of inhibitors in the development of new anti-HCV agents. Further SAR and optimization studies including DMPK profiles of this series will be reported in due course.

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Supporting Information Available: Synthetic procedures and characterization data for **3**−**20**, computational methods, X-ray crystallographic data, and Caco-2 assay data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The random conformational searches were performed with SYBYL 6.9.1 (Tripos Inc., 1669 S. Hanley Road, St. Louis, MO). Details were described in the supporting information.

(18) The cocrystal structure coordinate has been deposited in the Protein Data Bank (PDB code 2DXS). For details, see the Supporting Information. The molecular image was generated with PyMOL (*PyMOL Molecular Graphics System*; DeLano Scientific: San Carlos, CA).

(19) (a) The Boehringer Ingelheim group disclosed an indole derivative's binding pocket: Coulombe, R.; Beaulieu, P. L.; Jolicoeur, E.; Kukolj, G.; Laplante, S.; Poupart, M.-R. Hepatitis C virus NS5B polymerase inhibitor binding pocket. Int. Patent. Appl. WO 2004/099241, 2004. (b) The IRBM group reported in their study of enzyme-bound crystal structure of an indole derivative that the observed dihedral angle is 51°. See ref 5.

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