

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
 Bogotá, D.C.,

Abogado
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ASUNTO	Radicación	10-011252
	Trámite	011
	Evento	378
	Actuación	519
	Oficio	
	Folios	91 - 196 4 5

Patente de Invención	☐	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☐	Cap. I	☐ Cap. II ☐

No. Solicitud Internacional PCT/US2008/071881
 Fecha de Presentación Internacional 01/agosto/2008

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 336 a 720	03/febrero/2010
Reivindicaciones:	Folios 721 a 761	03/febrero/2010
Prioridad:	US 60/954,814	01/agosto/2007
	US 61/049,944	02/mayo/2008
	US 12/180,994	28/julio/2008

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

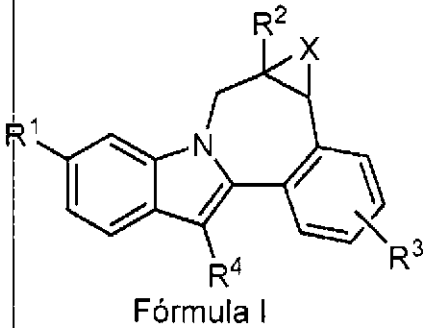
3. Objeto de la invención

Título de la solicitud: "Compuestos de indolobenzazepina sustituida por heteroarilo" modificado FI.788

El problema planteado en esta solicitud consiste en la necesidad de suministrar

compuestos efectivos para el tratamiento del virus de la hepatitis C.

Para resolver este problema técnico la solicitud en estudio proporciona compuestos de la fórmula (I) para el tratamiento del virus de la hepatitis C.



El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07D487/04, A61K31/55, A61P31/20.

4. Excepción a la Patentabilidad (Art 20 D486 literal d)

Las reivindicaciones 17 y 18 están relacionadas con un método de tratamiento, el cual no es patentable de acuerdo con el Art 20 literal d. Aunque las reivindicaciones están encabezadas por un procedimiento, su contenido se refiere a un método de tratamiento.

5. De la Solicitud de Patente

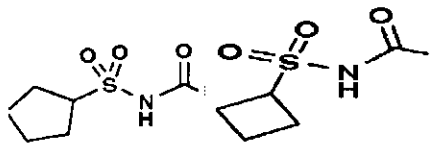
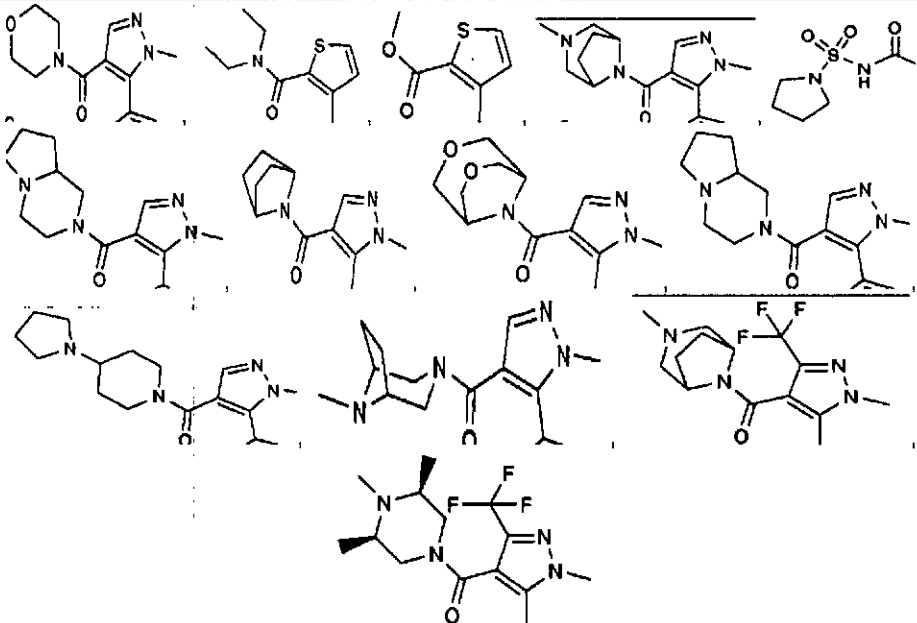
Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 no es clara porque se definen los radicales R16 y R17 pero estos no se encuentran en la fórmula (I), o en algún radical de la fórmula (I). Se le sugiere al señor solicitante hacer la aclaración a la que haya lugar.

La reivindicación 1 no es concisa porque los radicales R1 y R4 son cicloalquilo, el cual es ambiguo y no define de manera inequívoca los sustituyentes de los compuestos reclamados. Por lo tanto se le sugiere al solicitante, en lo posible, restringir el capítulo reivindicatorio de la solicitud a una generalización razonable de las realizaciones preferidas.

En la definición de los radicales más representativos de la fórmula (I), de acuerdo con lo que se encuentra debidamente sustentado en el capítulo descriptivo, se encuentra que siempre varían entre los siguientes sustituyentes y átomos:

Radical	Soporte en la descripción
R ¹	

	
R ²	
R ³	
R ⁴	
X	

Por lo tanto se sugiere al solicitante presentar una generalización razonable y eliminar aquellas definiciones que exceden el sustento descriptivo.

La reivindicación 16 define la composición en términos de la función del agente terapéutico (inhibidores de serina, inhibidores de metaloproteasa, etc.) por lo tanto se considera que tal reivindicación se refiere a todo agente que permita cumplir la función de inhibir una enzima, por consiguiente se sugiere definir bajo la denominación común internacional los compuestos que fueron objeto de comprobación para el caso de la composición de la presente solicitud.

6. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de prioridad (01/agosto/2007) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	WO2007033032	cyclopropyl fused indolobenzazepine HCV NS5B inhibitors	22/marzo/2007
D2	WO2006046039	tetracyclic indole derivatives as antiviral agents	04/mayo/2006

D1. <http://worldwide.espacenet.com/publicationDetails/biblio?CC=WO&NR=2007033032&KC=&FT=E&locale=en> EP

Divulga la fórmula estructural de derivados fusionados de indolobenzapinas como

inhibidores HCV NS5B para ser usados en el tratamiento del virus de la hepatitis C (Pág. 135 y 136).

D2. http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=WO&NR=2006046039A2&KC=A2&FT=D&ND=3&date=20060504&DB=EPODOC&locale=en_EP

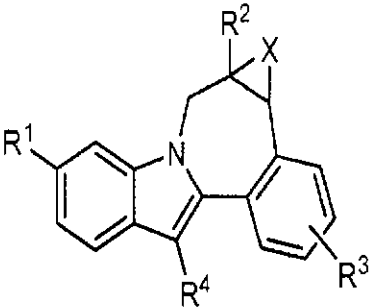
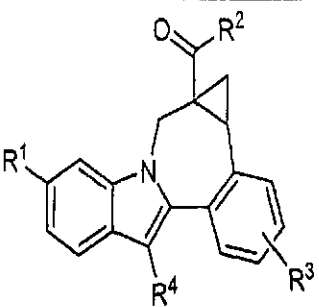
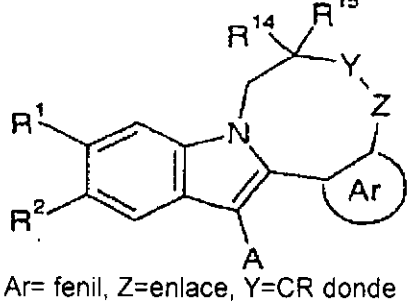
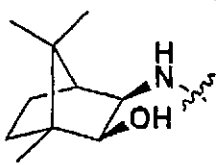
Divulga la fórmula estructural de derivados de anillos tetraciclicos de indol como inhibidores del HCV para ser usados en el tratamiento del virus de la hepatitis C (Pág. 30 y 31).

7. Examen de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 consiste en un compuesto de fórmula (I) donde: (Fl. 721).

Comparación de las **características técnicas esenciales**, con las del Estado de la Técnica:

Características esenciales	D1	D2
<u>Compuesto de fórmula I</u> 	<u>Compuestos de fórmula I</u> 	<u>Compuestos de fórmula I</u>  Ar= fenil, Z=enlace, Y=CR donde R=H
R ¹ = CO ₂ R ₅ o CONR ₆ R ₇	R ¹ = CO ₂ R ₅ o CONR ₆ R ₇	R ¹ =CONHSO ₂ R ₆ R ₇ , CONHR ₆ R ₇
R ² = furanilo, pirrolilo, tienilo, pirazolilo, isotiazolilo, oxazolilo, triazolilo	R ² = hidroxilo, alcoxi, 	R ¹⁴ o R ¹⁵ = heteroarilo, heterociclo
R ³ =H, alquilo, halógeno, alcoxi	R ³ =H, alquilo, halógeno, alcoxi	Sustituyente no definido
R ⁴ = cicloalquilo	R ⁴ = cicloalquilo	A= cicloalquilo
X= metileno, un enlace o no está presente	X= metileno Pág. 135 y 136	no está presente Pág. 30 y 31

Los documentos D1 y D2 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1.

El documento D1 divulga la fórmula estructural de derivados fusionados de indolobenzapinas como inhibidores HCV NS5B para ser usados en el tratamiento del virus de la hepatitis C (Pág. 135 y 136).

El documento D2 divulga la fórmula estructural de derivados de anillos tetraciclicos de indol como inhibidores del HCV para ser usados en el tratamiento del virus de la hepatitis C (Pág. 30 y 31).

La diferencia entre la invención, definida en la reivindicación 1 y la fórmula del documento D1 consiste en que la invención tiene anillos heterociclos sustituidos en el radical R2.

La diferencia entre la invención, definida en la reivindicación 1 y el compuesto del documento D2 consiste en que la invención tiene el radical R3.

No se evidencia que por el hecho de tener anillos heterociclos sustituidos en el radical R2, se tenga un efecto técnico inesperado.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: “cómo modificar los compuestos de fórmula I conocidos en el documento D1 para conseguir compuestos derivados de anillos fusionados de indolobenzapinas como inhibidores HCV NS5B”.

Sin embargo, es conocido en el documento D2 los anillos heterociclos sustituidos en el radical R2. Adicionalmente es conocido en el diseño de fármacos que los estudios de relación estructura-actividad han demostrado que los compuestos tetracíclicos son inhibidores potentes de la enzima implicada en HCV NS5B, por lo tanto, se ha modificado el anillo de 7 miembros del núcleo tetracíclico para evaluar la actividad farmacológica y es conocido que la sustitución heterocíclica del anillo de 7 miembros tiene un efecto marcado en la actividad de inhibición y mayor efectividad en el tratamiento del virus de la hepatitis C.¹

En consecuencia, la persona del oficio normalmente versada en la materia, estaría motivada a emplear los anillos heterociclos sustituidos en el radical R2. Por lo cual se considera obvia.

Conclusión:

La reivindicación 1 no cumple con el requisito de nivel inventivo (Art. 18).

Puesto que las reivindicaciones dependientes 2 a 15 no mencionan características inventivas adicionales y tampoco se pueden considerar inventivas.

8. Conclusión

Los requisitos de patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2007033032	1 a 15	Nivel inventivo
D2	WO2006046039	1 a 15	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

1 Kazutaka Ikegashira. Discovery of Conformationally Constrained Tetracyclic Compounds as Potent Hepatitis C Virus NS5B RNA Polymerase Inhibitors. *J. Med. Chem.* 2006, 49. Pág. 6950-6953. <http://jac.oxfordjournals.org/content/51/supp/1.full.pdf>
Primer Artículo 45- Expediente 10-011252

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.


JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
30 OCT. 2012

Elaborado por: Ruth Angélica Lizarazo Pedraza 
Revisado por: Consuelo Leguizamón Leguizamón 

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

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Received August 25, 2006

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 NM283⁸ 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 **1** (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 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

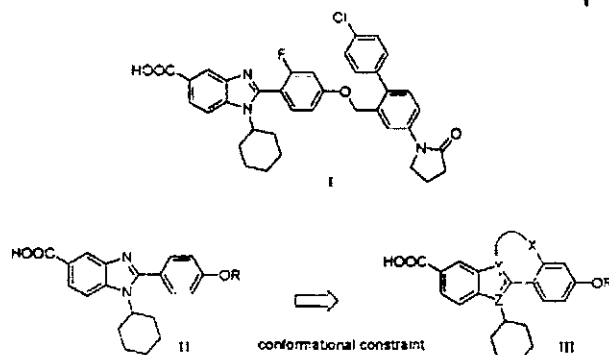
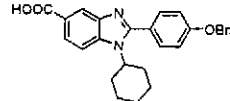
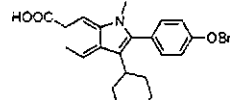
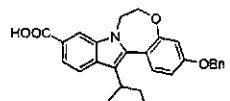
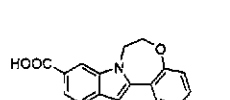


Figure 1.

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

Compound	NS5B IC_{50} (μ M)*
	1.4
	0.12
	0.017
	0.026

* Values are the mean of three independent experiments. Standard deviations are within 30% of the mean.

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 NS5B₅₄₄ enzyme (BK strain) and Huh-5-2 replicon cells as previously reported.⁷

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.

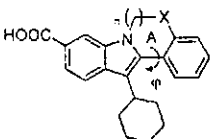
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Table 2. Evaluation of the A-Ring Size and X Atom Type



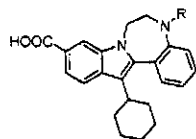
compd	X	n	NS5B IC ₅₀ (μM) ^a	replicon EC ₅₀ (μM) ^a	dihedral angle ^b φ (°)
5	CH ₂	0	0.21	>10	0
6	CH ₂	1	0.14	6.0 ^c	29
7	CH ₂	2	0.077	3.0	53
8	O	1	0.14	4.2 ^d	24
4	O	2	0.026	0.86	43
9	O	3	0.047	1.2	61
10	NH	2	0.021	0.57	46
11	S	2	0.038	1.4	56

^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. ^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, IC₅₀ = 26 nM) seems to be better than a CH₂ (7, IC₅₀ = 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, IC₅₀ = 21 nM) was as potent as 4, whereas sulfur, as atom X (11, IC₅₀ = 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 EC₅₀ 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 (IC₅₀ = 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-

Table 3. SAR at the N5 Atom of Compound 10



compd	R	NS5B IC ₅₀ (μM) ^a	Replicon EC ₅₀ (μM) ^a 10% FCS	10% FCS + 4% HSA ^b
10	H	0.021	0.57	>10 (<i>n</i> = 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 ₂ CH ₂ Ph	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. EC₅₀ values are the average of two experiments.

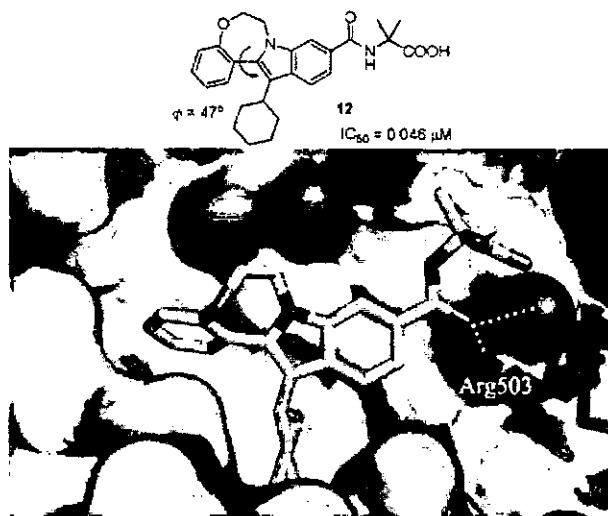
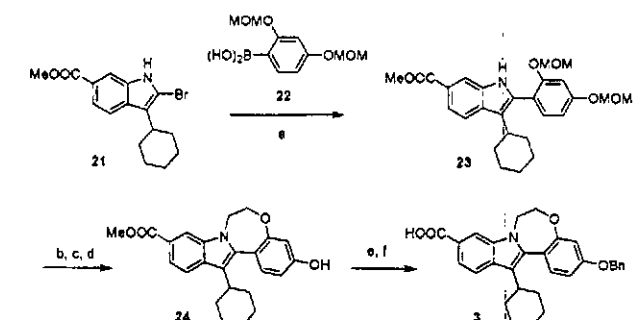


Figure 2. X-ray crystal structure (2.2 Å resolution) of compound 12 bound to the thumb domain of HCV NS5B polymerase. Nitrogen, oxygen, and sulfur atoms are shown in blue, red, and orange, respectively. Hydrogen bonds between the amide oxygen and Arg503 are shown as white dashed lines.

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.

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 (iPr, 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

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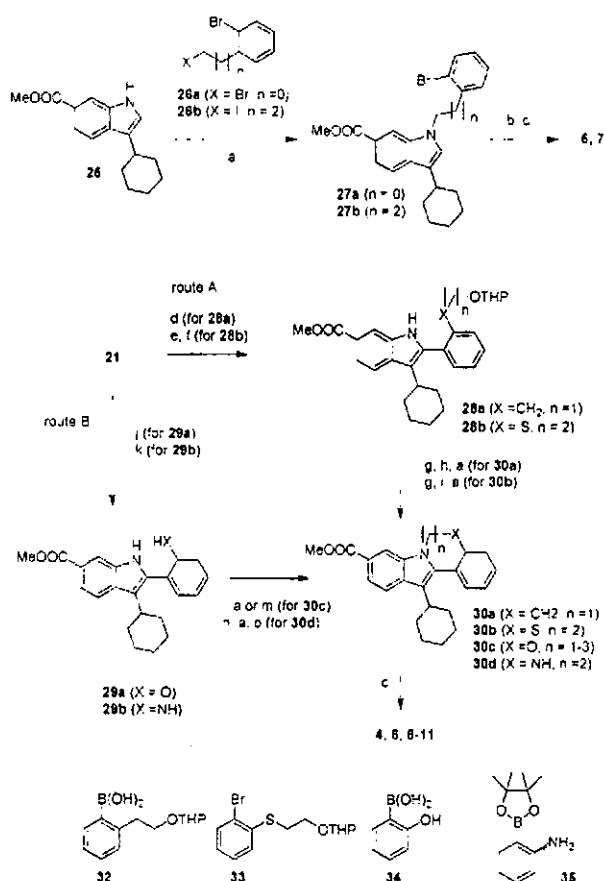
Scheme 1^a

^a Reagents: (a) $\text{Pd}(\text{PPh}_3)_4$, Na_2CO_3 , LiCl , $\text{DME-H}_2\text{O}$; (b) $\text{BrCH}_2\text{-CH}_2\text{-OTHP}$, 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 .

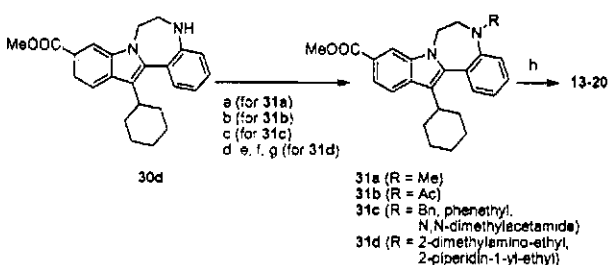
exhibited a 3-fold improvement in cellular potency ($\text{EC}_{50} = 0.21 \mu\text{M}$) compared to 10 with no change in biochemical potency. Further improvement in cellular potency was achieved by introduction of a substituent with an amino functionality such as 2-dimethylaminoethyl (19), resulting in a 10-fold improvement ($\text{EC}_{50} = 53 \text{ nM}$). 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 ($\text{EC}_{50} = 0.20 \mu\text{M}$) 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 dimethyl-amino to a piperidine, which led to a more potent compound (20) with a 2-fold increase in biochemical potency ($\text{IC}_{50} = 9 \text{ nM}$) and a 16-fold increase in cellular potency ($\text{EC}_{50} = 35 \text{ nM}$) compared to 10. Again, a very small shift in cellular potency (2-fold) was observed in the presence of HSA ($\text{EC}_{50} = 84 \text{ nM}$). 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 ($\text{CC}_{50} > 20 \mu\text{M}$) and good cell permeability using a Caco-2 cell membrane assay.

The tetracyclic compounds tested in this study were prepared as shown in Schemes 1–3. Compound 3 was synthesized from 2-bromoindole derivative 21 (Scheme 1).¹⁶ Suzuki coupling²¹ with phenylboronic acid 22 provided the 2-phenylindole derivative 23. N-Alkylation of 23 with $\text{NaH/Br(CH}_2)_2\text{OTHP}$ followed by unmasking of the OH protections followed by an intramolecular Mitsunobu reaction²² 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 25¹⁶ 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) $\text{Pd}(\text{PPh}_3)_4$, KOAc , DMA ; (c) 4 N NaOH (aq), THF-MeOH ; (d) 32, $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , $\text{DME-H}_2\text{O}$; (e) pinacol borane, $\text{Pd}(\text{OAc})_2$, PCy_2 -biphenyl, Et_3N , 1,4-dioxane; (f) 33, $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , $\text{DME-H}_2\text{O}$; (g) 6 N HCl (aq), THF-MeOH ; (h) CBr_4 , PPh_3 , CHCl_3 ; (i) MsCl , Et_3N , CHCl_3 ; (j) 34, $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , $\text{DME-H}_2\text{O}$; (k) 35, $\text{Pd}(\text{PPh}_3)_4$, NaHCO_3 , $\text{DME-H}_2\text{O}$; (l) $\text{Cl(CH}_2)_n\text{Br}$, 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), $\text{NaBH}(\text{OAc})_3$, 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.

Acknowledgment. We thank Mr. Mitsumasa Takahashi and Mr. Eita Nagao for analytical support. We are grateful to Mr. Yasushi Niwa and Ms. Yukiyo Tomonaga for support in running the biological assays and to Mr. Yukihiro Nomura for Caco-2 experiments. We also thank Dr. Ken Murase, Mr. Takuya Orita, Mr. Akihiro Nomura, and Dr. Masafumi Kamada for assistance with the synchrotron data collection, Prof. Soichi Wakatsuki for the data collection at the Photon Factory, KEK, and finally Dr. Jun-ichi Haruta for support.

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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JM0610245