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Discovery of *N*-(4′-(indol-2-yl)phenyl)sulfonamides as novel inhibitors of HCV replication

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ABSTRACT

A series of novel 2-phenylindole analogs were synthesized and evaluated for activity in subgenomic HCV replicon inhibition assays. Several compounds containing small alkyl sulfonamides on the phenyl ring exhibiting submicromolar EC_{50} values against the genotype 1b replicon were identified. Among these, compound **25d** potently inhibited the 1b replicon (EC_{50} = 0.17 μM) with 147-fold selectivity with respect to cytotoxicity. Compound **25d** was stable in the presence of human liver microsomes and had a good pharmacokinetic profile in rats with an IV half-life of 4.3 h and oral bioavailability (F) of 58%.

Chronic hepatitis C virus (HCV) infection is a significant worldwide health concern. According to the WHO, an estimated 150 million people or ~2% of the world population are currently infected with HCV.[1] Approximately 60–80% of HCV infections develop into chronic hepatitis which can lead to liver fibrosis, cirrhosis and hepatocellular carcinoma. In the United States, 3–4 million people are infected with HCV and HCV infection is the leading cause for liver transplantation.[2] Up to 10,000 deaths per year in the United States alone are attributed to complications that arise from chronic HCV infection. Through 2011, the standard of care (SOC) for the treatment of HCV infection had been combination therapy with pegylated interferon-α and the nucleoside ribavirin. After 48 weeks of treatment with this therapy, HCV patients infected with genotype 1 achieved only 40–50% sustained virologic response (SVR).[3,4] Recently, two HCV protease inhibitors, Incivek™ (telaprevir) and Victrelis™ (boceprevir), showing clinical efficacy[5] have been approved. The new SOC, comprising pegylated interferon, ribavirin, and a protease inhibitor have increased the SVR to >70% in patients infected with HCV genotype 1.[5,6] However, the rebound of viremia after cessation of treatment with these direct acting antivirals and the emergence of resistance prompt the need to develop novel anti-HCV agents that act on new targets and that can be used in combination with the current therapies to enhance efficacy and decrease the emergence of resistant viral variants.[7–9]

Through a high throughput screening campaign utilizing a reporter construct containing the 5′-untranslated region (UTR) of the HCV genome driving the expression of luciferase,[10] we identified several *N*-phenyl indole analogs that inhibited the expression of the reporter at single digit μM EC_{50}s (data not shown). The HTS hits identified in this screen were subsequently optimized for potency utilizing a subgenomic HCV replicon assay system carrying a luciferase reporter gene.[11–13] One of the hits identified, compound **1**, was weakly active against the genotype 1b replicon with an EC_{50} of 50 μM (Fig. 1). Initial exploration of structure–activity relationships (SAR) led to the identification of **2**, where the 4-methoxyphenyl group was moved to the indole 2-position and the indole nitrogen was alkylated with an ethyl group. Further, the structurally undesirable 3-NO_2 group was replaced with a CN group. This led to a more than 10-fold improvement in potency against the replicon with an EC_{50} of 4.1 μM. Compound **3**, the 3-nitro analog of **2**, was significantly less active, with less than 50% inhibition in the replicon assay at a concentration of 51 μM, indicating the importance of the 3-cyano group for activity. We then evaluated the effect of the regiochemistry of the pendant methoxy group attached to the 2-phenyl ring of **2** on activity. Changing the point of attachment for the 4′-methoxy group to either the 2′- or 3′-positions of the phenyl ring was detrimental to activity against HCV replication (data not shown). Based on these observations, we chose compound **2** as the starting point for optimization, focusing on the 4′-substituted-2-phenyl indole core and the results of these studies are reported herein.

Our goal was to systematically explore the effect of substitution around the indole ring, including the N-1 and C-4 to C-6 positions

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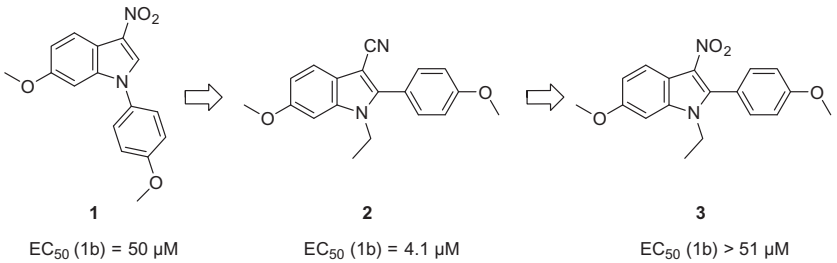
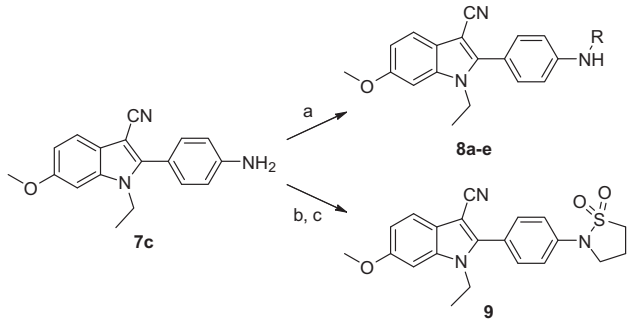


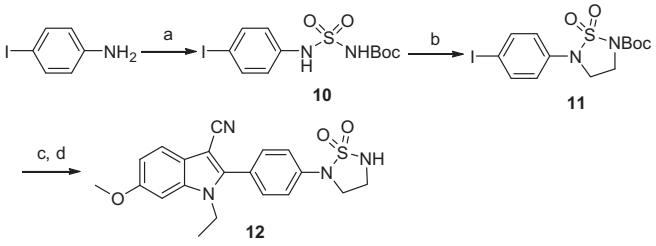
Figure 1. Identification of hit **1** and analogs **2** and **3** identified during preliminary SAR exploration and activity against the HCV genotype 1b replicon.

as well as the 2-phenyl ring, on biological activity. We first surveyed various substituents to replace the 4′-methoxy group on the 2-phenyl ring of **2** to establish a preliminary SAR. The syntheses of compounds **7a**–**f** were accomplished through a Suzuki coupling strategy by allowing the key intermediate **6** to react with 4-substitued phenyl bromides or iodides as depicted in Scheme 1. Compound **6** was prepared by treating commercially available 6-methoxy indole **4** with chlorosulfonyl isocyanate in DMF, leading to efficient cyanation at the 3-position with 85% yield. Treatment of **4** with ethyl iodide and sodium hydride in DMF provided **5** in quantitative yield. This was followed by LDA treatment of a mixture of **5** and triisopropyl borate at −78 °C to room temperature. Acidic aqueous workup furnished **6** in quantitative yield. As depicted in Scheme 2, the 4′-aminophenyl derivative **7c**, was converted to carbamate **8a**, amides **8b** and **8c** and sulfonamides **8d** and **8e** by treatment with the corresponding acylation or sulfonylation reagents. The sultam **9** was prepared by reacting **7c** with 3-chloropropanesulfonyl chloride, followed by base-induced cyclization (potassium carbonate in DMF) of the γ-chloropropanesulfonamide intermediate. The sulfamide **12** was prepared in four steps by treatment of 4-iodoaniline with chlorosulfonyl isocyanate and *t*-butanol in dichloromethane to afford *N*-Boc-4′-iodophenylsulfamide **10**. Compound **10** was then converted to **11** by alkylation followed by cyclization upon treatment with bromochloroethane and potassium carbonate in DMF. Suzuki coupling of **11** with **6**, followed by deprotection afforded sulfamide **12** (Scheme 3).

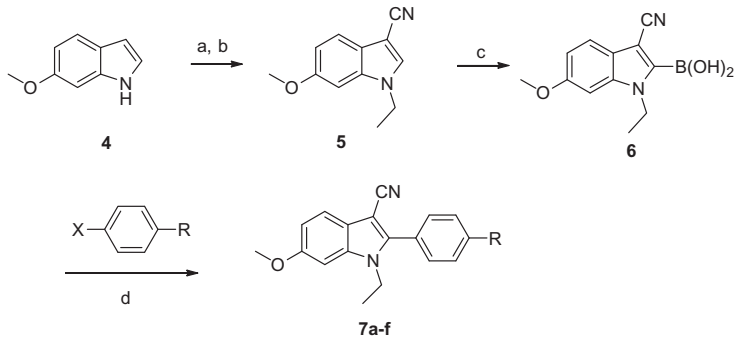
Evaluation of the compounds in the HCV 1b replicon assay revealed that replacing the 4′-methoxy group with either a hydroxy (**7a**) or ethoxy (**7b**) group had no marked effect on activity (Table 1). No improvement in activity was achieved either with the sulfoxide (**7d**), sulfone (**7e**), or carboxamide (**7f**) analogs. We then turned our attention to nitrogen derivatives and demonstrated that several aniline derived compounds gave improved activity. Carbamate **8a** and amide **8b** gained ∼threefold potency in the replicon assay. The 4′-*N*-benzoylamide **8c**, however, was devoid of activity, suggesting that a large aromatic group is not tolerated at this position. The sulfonamide **8d** with an EC_{50} of 0.47 μM in the replicon assay, exhibited a nearly ninefold improvement in potency compared to the initial hit compound **2**. Compounds were also evaluated in parallel for cytotoxicity in replicon-containing Huh7 cells, the same cells as those used in the replicon assay. Good selectivity



Scheme 2. Reagents and conditions: (a) acyl chloride or chloroformate or sulfonyl chloride, pyridine, CH_2Cl_2, 0 °C to rt; (b) $ClSO_2CH_2CH_2CH_2Cl$, pyridine, CH_2Cl_2, 0 °C to rt; (c) K_2CO_3, DMF, rt.

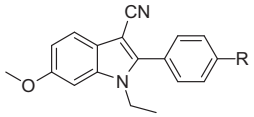


Scheme 3. Reagents and conditions: (a) *t*-BuOH, chlorosulfonyl isocyanate, Et_3N, CH_2Cl_2, 0 °C to rt; (b) $BrCH_2CH_2Cl$, Cs_2CO_3, DMF, 70 °C, 2 h; (c) compound **6**, $PdCl_2$(dppf), K_2CO_3, DMF, H_2O, rt; (d) 20% TFA, CH_2Cl_2, rt, 2 h.



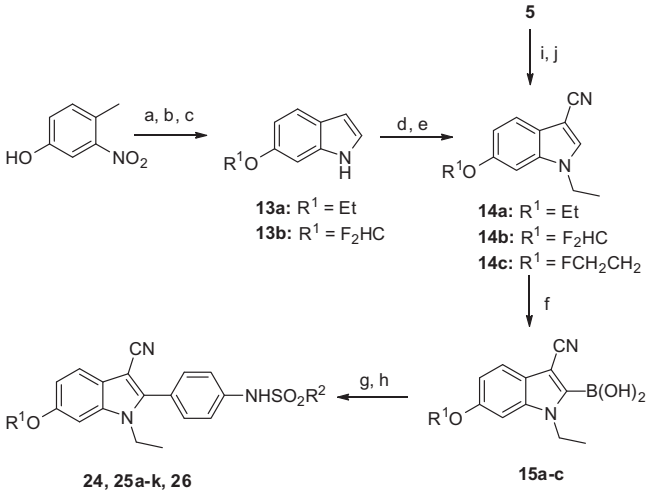
Scheme 1. Reagents and conditions: (a) chlorosulfonyl isocyanate, DMF, 0 °C to rt; (b) EtI, NaH, DMF, rt; (c) (*i*-PrO)$_3$B, THF, LDA, then HCl, −78 °C to rt; (d) $PdCl_2$(dppf), K_2CO_3, DMF, H_2O, rt.

Table 1
Activity of selected 4′-substituted-3-cyano-2-phenylindoles



Compd	R	HCV replicon 1b EC_{50}[a] (μM)	CC_{50}[a] (μM)
2	OMe	4.1	>100
7a	OH	6.1	50
7b	OEt	3.0	>100
7c	NH_2	7.7	100
7d	SOMe	4.0	52
7e	SO_2Me	2.6	42
7f	$CONH_2$	7.8	>100
8a	$NHCO_2Et$	1.3	41
8b	NHCOMe	1.3	89
8c	NHCOPh	>100	>100
8d	$NHSO_2Et$	0.47	62
9		2.0	>50
12		0.90	30

[a] See Ref. 13 for assay conditions.



Scheme 4. Reagents and conditions: (a) HCF_2Cl, NaOH (20%), dioxane, 80 °C, 80%, or K_2CO_3, EtI, MEK, reflux, 99%; (b) DMF–DMA, pyrolidine, DMF, 110 °C; (c) H_2, Pd/C, EtOAc, 60 psi, rt; (d) chlorosulfonyl isocyanate, DMF, 0 °C to rt; (e) EtI, Cs_2CO_3, DMF, rt; (f) $(i\text{-PrO})_3B$, THF, LDA, then HCl, −78 °C to rt; (g) $PdCl_2(dppf)$, K_2CO_3, DMF, H_2O, 4-iodoaniline, rt; (h) R^2SO_2Cl, pyridine, CH_2Cl_2, 0 °C to rt; (i) BBr_3, CH_2Cl_2, −78 °C to rt; (j) FCH_2CH_2Br, NaH, DMF, 0 °C to rt.

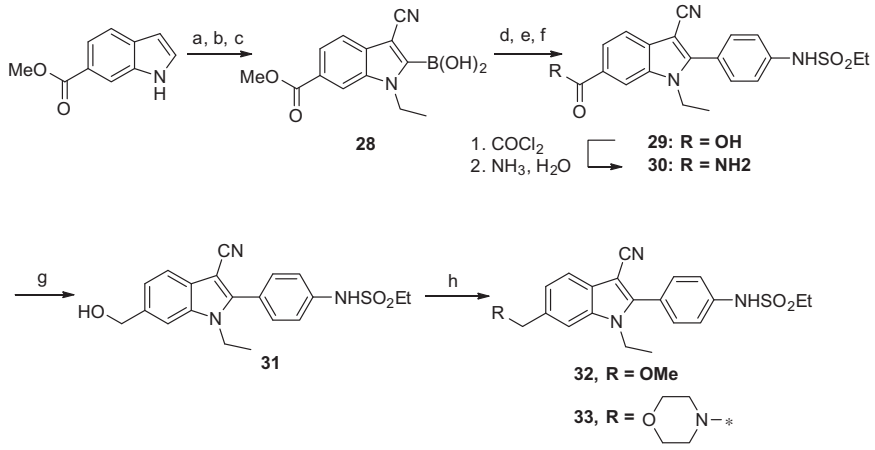
with respect to cytotoxicity was maintained for these compounds, with the sulfonamide **8d** possessing a selectivity index of >130. Cyclization of the sulfonamide functionality led to a small decrease in activity; sultam **9** was ~fourfold less active than was sulfonamide **8d**. Interestingly, compound **12**, a cyclic sulfamide derived by replacing a methylene group in **9** with an NH, led to a twofold gain in replicon activity, demonstrating submicromolar EC_{50} potency.

Based on these encouraging results, we focused our efforts on the sulfonamide series for further optimization. In order to investigate the effect of various functional groups and substitution patterns on the indole benzenoid ring towards activity in the replicon assay, we prepared a number of substituted *N*-(4′-(1-ethylindol-2-yl)phenyl)sulfonamide derivatives with a range of electronic, steric, and hydrophilic properties.

Compounds **16**–**21**, **23**, and **27** were synthesized from the corresponding commercially available indoles following the synthetic sequence outlined in Scheme 1. Compounds **24**, **25a**–**k**, and **26** were prepared as shown in Scheme 4. The 6-ethoxyindole and 6-difluoromethoxyindole compounds were prepared by converting 4-methyl-3-nitrophenol to 4-ethoxy-2-nitrotoluene via ethylation and 4-difluoromethoxy-2-nitrotoluene via difluoromethylation[14] with Freon 22 and NaOH in dioxane, respectively. Batcho–Leimgruber indole synthesis provided the indole intermediates **13a** and **13b**.[15] Cyanation and N-ethylation furnished **14a** and **14b**. The 6-fluoroethoxyindole intermediate **14c** was obtained by BBr_3 demethylation of **5** followed by O-alkylation with 1-bromo-2-fluoroethane in the presence of NaH in DMF. Compounds **14a**–**c** were then converted to boronic acids **15a**–**c**. Suzuki coupling of **15a**–**c** with 4-iodoaniline followed by the treatment with sulfonyl chlorides furnished compounds **24**, **25a**–**k** and **26**. Compound **22** was obtained by BBr_3 demethylation of **8d**. The 6-carboxylic acid derivative **29** was obtained from commercially available methyl indole-6-carboxlate using chemistry described in Scheme 5. Carboxamide **30** was obtained from **29** via the acid chloride followed by treatment with ammonia. Borane reduction of **29** provided the 6-hydroxymethyl analog **31**. Methylation of **31** with methyliodide and NaH furnished the 6-methoxymethyl analog **32**. The 6-morpholinomethyl derivative **33** was obtained by converting **31** to the 6-chloromethyl derivative with thionyl chloride, followed by treatment with morpholine (Scheme 5).

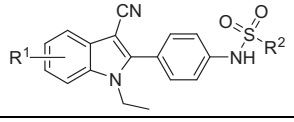
It is readily apparent that substitution with lipophilic groups on the indole benzenoid ring is favored as the unsubstituted compound **16** showed only modest activity (EC_{50} = 9.0 μM) in the replicon assay (Table 2). The 6-methoxy analog **8d** is nearly 20-fold more potent (EC_{50} = 0.47 μM) than **16**. The related 6-methoxy isopropanesulfonamide **8e**, is nearly equipotent (EC_{50} = 0.65 μM). Moving the methoxy group to the 5-position (**17**) led to a more than 10-fold loss in activity. Introducing an additional methoxy group at the 5-position (**18** vs **8d**) also leads to reduced potency against the replicon. In general, compounds containing fluorinated substituents, for example, **23**, **25a**, **26,** and **27**, had good potencies against the replicon (EC_{50} range 0.29–0.59 μM) and good selectivity with respect to cytotoxicity (50- to 140-fold). The 5-fluoro analog **20** (EC_{50} = 0.59 μM) is much more potent than the corresponding 5-chloro analog **19** (EC_{50} = 7.5 μM). Introduction of a polar carboxylic acid group at the indole 6-position (**29**) led to a complete loss of activity (EC_{50} >11 μM) while the 6-carboxamide **30** showed only marginal activity. In general, hydrophilic groups are not well tolerated. Compounds **31**–**33** containing hydroxymethyl, methoxymethyl and morpholinomethyl groups, respectively, have only modest activity against HCV replication (EC_{50} range 3–5 μM).

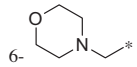
Based on the very encouraging activity of the 6-difluoromethoxy derivative **25a**, we targeted several additional analogs of compound **25a** for further evaluation. We prepared and evaluated the activity of compounds bearing small alkyl groups both on the indole nitrogen and the sulfonamide moiety. Several additional analogs were identified as potent HCV replicon inhibitors with EC_{50}s <0.3 μM (Table 3). Compounds containing small lipophilic substituents on the indole N-1 have similar potency against the replicon, including ethyl, *n*-propyl, isopropyl, cyclobutyl, and cyclopropylmethyl. These compounds contain substituents on the sulfonamide moiety including ethyl, *n*-propyl, isopropyl, and cyclopropyl. Compound **25d** was selected as an advanced lead compound considering its potential for further evaluation based on its favorable overall profile, including potency against HCV replication (EC_{50} = 0.17 μM), excellent selectivity with respect to cyto-



Scheme 5. Reagents and conditions: (a) chlorosulfonyl isocyanate, DMF, 0 °C to rt; (b) EtI, Cs_2CO_3, DMF, rt; (c) (*i*-PrO)$_3$B, THF, LDA, then HCl, −78 °C to rt; (d) $PdCl_2$(dppf), K_2CO_3, DMF, H_2O, 4-iodoaniline, rt; (e) $EtSO_2Cl$, pyridine, CH_2Cl_2, rt; (f) NaOH, MeOH, 60 °C, 1 h; (g) BH_3·THF, rt; (h) NaH, MeI or $SOCl_2$, CH_2Cl_2, then morpholine, rt.

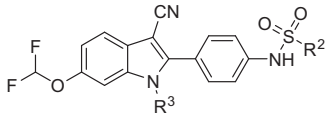
Table 2
Activity of selected *N*-(4′-(3-cyanoindol-2-yl)phenyl)sulfonamides



Compd	R^1	R^2	HCV replicon 1b EC_{50}[a] (μM)	CC_{50}[a] (μM)
16	H	Et	9.0	40
8d	6-OMe	Et	0.47	62
8e	6-OMe	*i*-Pr	0.65	70
17	5-OMe	*i*-Pr	7.4	36
18	5,6-$(OMe)_2$	Et	4.0	>100
19	5-Cl	Et	7.5	40
20	5-F	Et	0.59	39
21	4-Cl	Et	3.5	55
22	6-OH	Et	2.0	55
23	6-CF_3	Et	0.36	18
24	6-OEt	Et	0.53	42
25a	6-$OCHF_2$	Et	0.29	20
26	6-OCH_2CH_2F	Et	0.59	39
27	6-OCF_3	Et	0.17	24
29	6-COOH	Et	>11[b]	>100
30	6-$CONH_2$	Et	9.0	55
31	6-CH_2OH	Et	3.5	60
32	6-CH_2OMe	Et	5.0	>100
33		Et	3.0	35

[a] See Ref. 13 for assay conditions.
[b] Highest concentration tested.

Table 3
Activity of selected *N*-(4′-(3-cyano-6-difluoromethoxyindol-2-yl)phenyl)sulfonamides



Compd	R^2	R^3	HCV replicon 1b EC_{50}[a] (μM)	CC_{50}[a] (μM)
25a	Et	Et	0.29	20
25b	Et	*i*-Pr	0.20	12
25c	Et	*c*-PrCH_2	0.30	13
25d	*c*-Pr	*c*-PrCH_2	0.17	25
25e	*c*-Pr	*c*-Bu	0.19	20
25f	*c*-Pr	*n*-Pr	0.25	>100
25g	*c*-Pr	*i*-Pr	0.075	13
25h	*n*-Pr	Et	0.22	26
25i	*c*-Pr	Et	0.10	23
25j	*i*-Pr	Et	0.12	19
25k	*i*-Pr	*c*-PrCH_2	0.08	22

[a] See Ref. 13 for assay conditions.

toxicity (147-fold), sufficient metabolic stability and sufficiently high exposure in the rat. The anti-HCV replicon activity was further confirmed in a subgenomic monocistronic replicon assay in which the reduction in HCV RNA was quantified (EC_{50} = 0.18 μM),[16] consistent with activity derived from the luciferase readout. Compound **25d** was metabolically stable to human liver microsomes and had a good pharmacokinetic profile in the rat with an IV half-life and clearance of 6.3 h and 4.5 mL/min/kg, respectively, and with an oral bioavailability of 58% (Table 4). Compound **25d** was evaluated for inhibitory activity against HCV protease and polymerase enzymatic inhibition assays and was inactive against these enzymes at concentrations up to 10 μM, the highest concentration tested.

Table 4
Activity and DMPK profile of **25d**

HCV replicon 1b EC_{50}[a] (μM)	HCV replicon 1b RNA EC_{50}[b] (μM)	CC_{50}[a] (μM)	HLM metabolism, Cl_{int}[c] (mL/min/kg)	Rat PK[d]					
				IV			PO		%F
				$T_{1/2}$ (h)	Vss (L/kg)	CL (mL/min/kg)	C_{max} (μg/mL)	AUC_{0-inf} (μM h)	
0.17	0.18	25	<1	6.3	2.2	4.5	0.77	6.8	58

[a] See Ref. 13 for assay conditions.
[b] See Ref. 16 for assay conditions.
[c] See Ref. 17 for assay conditions.
[d] Dosed in a solution of PEG-300, 3 mg/kg PO and 1 mg/kg IV to female Sprague–Dawley rats.

In summary, we have identified a novel series of *N*-(4′-(indol-2-yl)phenyl)sulfonamides with potent and selective activity against the HCV 1b replicon. Through preliminary SAR optimization, several compounds with submicromolar activity against the replicon have been identified. Compounds from this class generally are metabolically stable in microsomes and have good exposure in the rat. Compound **25d** was profiled to assess the potential developability of this scaffold. This class of novel compounds, represented by **25d**, has no activity against the HCV protease or polymerase enzymes. Results of further optimization of this class of compounds and the selection and characterization of resistant replicon variants to identify the viral target and begin to elucidate the mechanism of action will be reported in a subsequent publication.[18]

Acknowledgments

The authors would like to thank Dr. Valerie Clausen, Christine Espiritu and Shirley Yeh for their support during the course of this work.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.04.050. These data include MOL files and InChiKeys of the most important compounds described in this article.

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13. Huh7 cells harboring a genotype 1b HCV bicistronic replicon were plated at 5000 cells/well in 96 well plates remained subconfluent for the duration of the experiment. Compounds were added to the plates with a final concentration of 0.5% DMSO and plates were incubated at 37 °C. Luciferase activity was measured after 2 days. Cytotoxicity was evaluated in parallel by MTS assay in the genotype 1b HCV replicon-containing Huh7 cells (CellTiter 96® Aqueous Non-Radioactive Cell Proliferation Assay, Promega).
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16. Huh7 cells harboring a genotype 1b HCV monocistronic replicon were plated at 5000 cells/well in 96 well plates. Compounds were added to the plates with a final concentration of 0.5% DMSO and plates were incubated at 37 °C. Cells were harvested 3 days post dosing and replicon RNA was quantified by real time RT-PCR with GAPDH RNA as an endogenous control.
17. Compounds were incubated at 1 μM with human liver microsomes (0.5 mg/mL protein concentration) for 0, 10, 20, 30 and 60 min, in the presence of 1 mM EDTA, 3 mM $MgCl_2$, 1.3 mM NADP, 3.3 mM D-glucose-6-phosphate and 1 unit/mL of glucose-6-phosphate dehydrogenase. Incubated samples were centrifuged at 2000 rpm and the supernatants were analyzed by LC/MS.
18. Zhang, X.; Zhang, N.; Chen, G.; Turpoff, A.; Ren, H.; Takasugi, J.; Morrill, C.; Zhu, J.; Li, C.; Lennox, W.; Paget, S.; Liu, Y.; Almstead, N.; Njoroge, F. G.; Gu, Z.; Komatsu, T.; Clausen, V.; Espiritu, C.; Graci, J.; Colacino, J.; Lahser, F.; Risher, N.; Weetall, M.; Nomeir, A.; Karp, G. M. *Bioorg. Med. Chem. Lett.* **2013**. http://dx.doi.org/10.1016/j.bmcl.2013.04.049.