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Azetidines and spiro azetidines as novel P2 units in hepatitis C virus NS3 protease inhibitors

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ABSTRACT

Herein, we report the synthesis and structure–activity relationship studies of new analogs of boceprevir **1** and telaprevir **2**. Introduction of azetidine and spiroazetidines as a P2 substituent that replaced the pyrrolidine moiety of **1** and **2** led to the discovery of a potent hepatitis C protease inhibitor **37c** (EC_{50} = 0.8 μM).

Hepatitis C virus (HCV) is a major health hazard affecting an estimated 170–200 million individuals worldwide and it is a leading cause of chronic liver disease in the United States.[1] First generation treatment involving α-interferon (IFN) in combination with ribavirin (RBV) was only partially effective with approximately 50% of genotype 1 HCV patients demonstrating sustained viral response. Immense drug discovery efforts towards improved HCV therapy in recent years has led to the 2011 FDA approval of two HCV NS3 protease inhibitors (PI): boceprevir **1** (Victrelis) and telaprevir **2** (Incivek).[2,3] However, despite the existence of treatments involving pegylated IFN and RBV, with these two PIs,[4] (Fig. 1) the limited efficacy and side effects emphasize the need for additional improved therapeutic agents. Following the discovery of telaprevir and boceprevir, numerous modifications have been investigated at various positions of these peptidomimetics in order to improve their overall therapeutic profile.[5] Herein, we detail our studies in the P2 area, specifically the introduction of various new azetidine moieties, which resulted in inhibitors with good potency.

In order to prepare telaprevir and boceprevir analogs **37a–i**, **41a–f** and **42a–b**, we synthesized key 2-azaspiro[3.5]nonane intermediate **12** (Scheme 1), 1′,3′-dihydrospiro[azetidine-3,2′-indene] intermediates **22** and **24** (Scheme 2) along with various P1 precursors **29a–f** (Scheme 3). Thus, 2-azaspiro[3.5]nonane intermediate **12**[6] was prepared from cyclohexyl cyanide **3** by reaction with 2-(benzyloxy)acetaldehyde in presence of LDA to give the hydroxyl derivative **4** as a mixture of enantiomers (Scheme 1). The cyano group was then reduced with $LiAlH_4$ and the resulting amine **5**

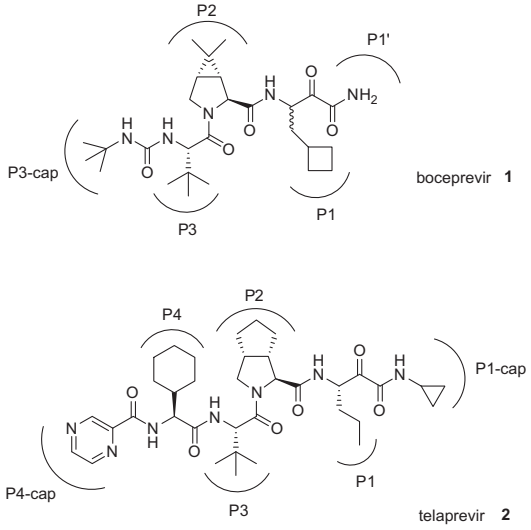

Figure 1. Structures of FDA approved HCV protease inhibitors boceprevir **1** and telaprevir **2**.

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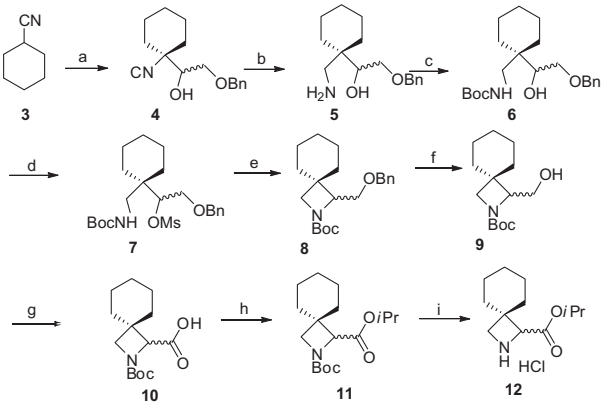
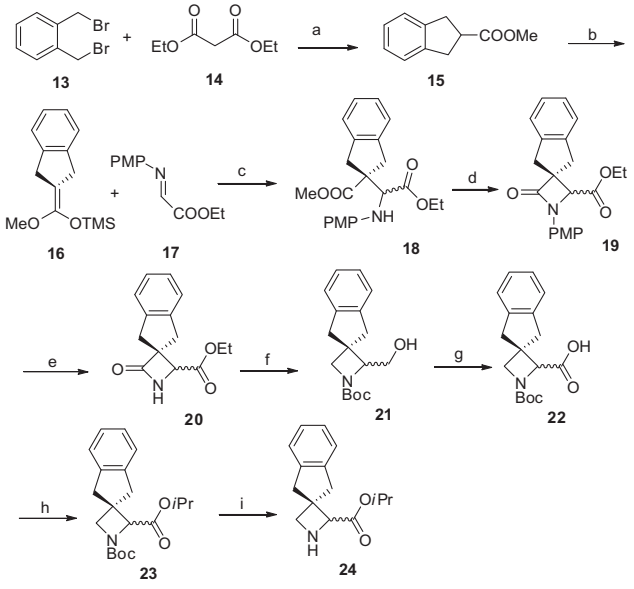


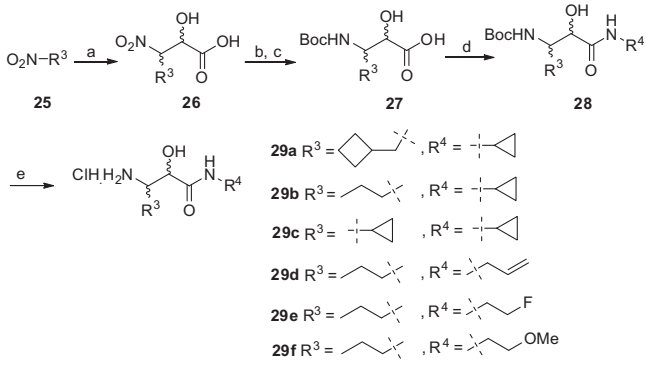
Scheme 1. Reagents and Conditions: (a) 2-(benzyloxy)acetaldehyde, LDA, THF, −78 °C to rt, 7 h, 65%; (b) $AlCl_3$, $LiAlH_4$, Et_2O, −78 °C to rt, 14 h, 60%; (c) Boc_2O, CH_2Cl_2, rt, 24 h, 92%; (d) $MeSO_2Cl$, Et_3N, −10 °C to rt, CH_2Cl_2, 36 h, 67%; (e) NaH, DMF, 45 °C, 1 h, 56%; (f) ammonium formate, 10% Pd/C, MeOH, 60 °C, 2 h, 76%; (g) $NaIO_4$, $RuCl_3$, CCl_4, rt, 2 h, 74%; (h) *i*PrOH, EDC, DMAP, 0–55 °C, 15 h, 63%; (i) 3 N HCl in dioxane, 6 h, rt, 90%.



Scheme 2. Reagents and conditions: (a) (i) Na, KOH, EtOH, Et_2O, H_2O, reflux, 5 h, 73%; (ii) 200 °C, 20 min to rt, MeOH, H_2SO_4, reflux, 1 h, 26% over two steps; (b) LDA, TMSCl, THF, −78 °C, 30 min, 56%; (c) TMSOTf, CH_2Cl_2, 0 °C to rt, 12 h, 79%; (d) MeMgBr, CH_2Cl_2, 0 °C to rt, 18 h, 70%; (e) CAN, CH_3CN, H_2O, 0 °C, 45 min, 56%; (f) (i) LAH, THF, 0 °C to rt, 20 h; (ii) Boc_2O, CH_2Cl_2, rt, 10 h, 46% over two steps; (g) $NaIO_4$, $RuCl_3$, H_2O, CH_3CN, CCl_4, rt, 2 h, 65%; (h) *i*PrOH, EDC, DMAP, CH_2Cl_2, 50 °C, 18 h, 39%; (i) 3 N HCl in dioxane, 6 h, rt, 56%.

was Boc protected. Subsequently, formation of mesylate **7** and cyclisation using NaH gave the 2-azaspiro[3.5]nonane derivative **8** in 56% yield. Palladium catalyzed hydrogenation in presence of ammonium formate to remove the benzyl group followed by oxidation of the formed alcohol with $NaIO_4$ and $RuCl_3$ lead to acid **10**. Finally, esterification with *i*PrOH in presence of EDC and acidic deprotection of the amine gave the desired 2-azaspiro[3.5]nonane ester **12**.

1′,3′-Dihydrospiro[azetidine-3,2′-indene] intermediates **22** and **24** were prepared by a sequence that started with condensation of 1,2-bis(bromomethyl)benzene **13** with diethyl malonate **14** (Scheme 2). The resulting crude diethyl malonate derivative was reacted with sulfuric acid in the presence of methanol at 200 °C which resulted in a hydrolysis, decarboxylation and esterification sequence to produce methyl ester **15**. Treatment of **15** with LDA produced the enolate which was trapped with TMSCl to give silyl



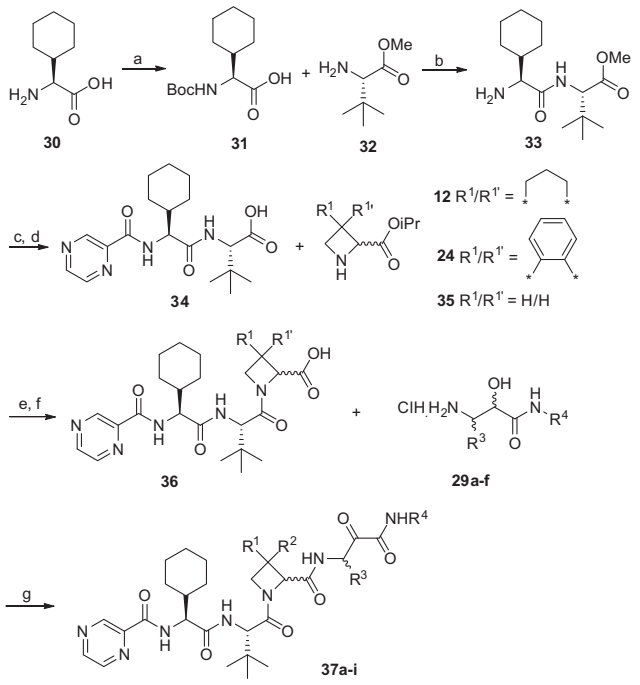
Scheme 3. Reagents and conditions: (a) glyoxalic acid, Et_3N, MeOH, rt; (b) H_2, Pd/C, AcOH, rt; (c) Boc_2O, NaOH, dioxane/H_2O, 80–90% over three steps; (d) appropriate amine, HOBt, EDCI, DIPEA, DMF, 0 °C to rt, 10 h, 60–80%; (e) 4 N HCl in dioxane, rt, 5–6 h, 90–95%.

enol ether **16**. Reaction with *N*-*p*-methoxyphenyl (PMP)-α-imino ethyl glyoxylate, **17**,[7] in the presence of TMSOTf gave compound **18** as a mixture of enantiomers. Cyclisation to form **19** was achieved by treatment with MeMgBr in 70% yield. Removal of the PMP group with CAN, reduction of both the ester and the amide groups with LAH and subsequent reprotection using Boc_2O afforded the hydroxyl derivative **21**. Oxidation to the acid was performed using $NaIO_4$ and $RuCl_3$ in 63% yield. Treatment of the acid **22** with *i*PrOH in presence of EDC and DMAP gave the Boc'ed ester **23**. Finally, Boc removal with HCl in dioxane gave the desired spiro azetidine ester **24**.

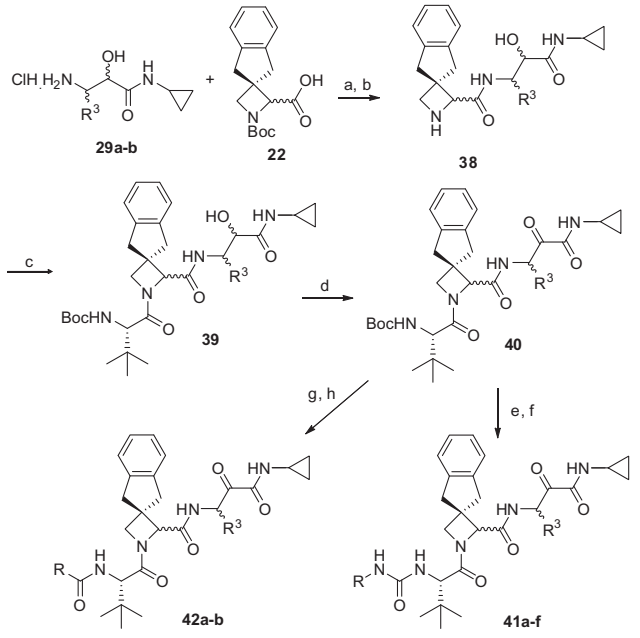
The P1 portion (Fig. 1) of the targeted molecules were prepared from various commercially available nitro alkyl derivatives by reaction with glyoxalic acid in presence of triethylamine to give intermediate **26** (Scheme 3). Nitro groups were then reduced by catalytic hydrogenation and the resulting amines were protected by reaction with Boc_2O in presence of NaOH.[8] Coupling of **27** with various amines in presence of EDCI and HOBt was followed by treatment with 4 N HCl in dioxane to afford the desired intermediates **29a**–**f** in good overall yields.

With these intermediates in hand, synthesis of inhibitors **37a**–**i**, analogs of telaprevir, with either an azetidine, a 2-azaspiro[3.5]nonane or a 1′,3′-dihydrospiro[azetidine-3,2′-indene] at P2 was achieved according to Scheme 4. Commercially available cyclohexyl glycine **30** was Boc protected then coupled with *tert*-butyl glycine ester **32** via a standard EDCI/HOBt protocol. Following deprotection under acidic conditions, the pyrazine P4 cap was introduced and the methyl ester saponified using LiOH to give intermediate **34**. Commercially available azetidine ester **35**, 2-azaspiro[3.5]nonane, **12** or 1′,3′-dihydrospiro[azetidine-3,2′-indene], **24** were then coupled (EDCI/HOBt) with **34** to generate, after saponification of the isopropyl ester with LiOH, compound **36**. Finally, coupling of intermediates **36** with **29a**–**f**, followed by oxidation under Dess–Martin conditions, allowed introduction of the various relevant P1 and P1 caps, and lead to targeted molecules **37a**–**i**.

Synthesis of inhibitors **41a**–**f** and **42a**–**b**, analogs of boceprevir, with a 1′,3′-dihydrospiro[azetidine-3,2′-indene] at P2 was achieved according to the general Scheme 5. 1′,3′-Dihydrospiro[azetidine-3,2′-indene], **22** was coupled to amino acid derivatives **29a**–**b** (EDCI/HOBt) to give, after Boc removal under acidic conditions, compounds **38**. Introduction of the P3 moiety was realized by coupling **18** with commercially available NHBoc–*t*Bu-glycine (EDCI/HOBt). Desired compounds **41a**–**f** and **42a**–**b** were obtained after oxidation, using Dess–Martin reagent, followed by Boc removal and reaction with either substituted an isocyanate or alkyl carboxylic acid, allowing the introduction a large variety of P3 caps.



Scheme 4. Reagents and conditions: (a) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 18 h, 90-95%; (b) (i) HOBt, EDCI, DIPEA, DMF, rt, 12 h, 55–65%; (ii) 4N HCl in dioxane, rt, 3 h, 60–70%; (c) 2-pyrazine carboxylic acid, HOBt, EDCI, DMF, rt, 18 h, 76–80%; (d) LiOH, THF/MeOH/H_2O, rt, 6 h, 90–95%; (e) HOBt, EDCI, DMF, rt, 18 h, 63–70%; (f) LiOH, THF/MeOH/H_2O, rt, 6 h, 77–90%; (g) (i) HOBt, EDCI, DMF, rt, 18 h, 70–75%; (ii) Dess–Martin reagent, CH_2Cl_2, rt, 18 h, 75–85%.



Scheme 5. Reagents and conditions: (a) HOBt, EDCI, DMF, 0 °C to rt, 12–16 h, 59–75%; (b) 4 N HCl in dioxane, rt, 5–6 h, 90–95%; (c) BocNH–*t*Bu-glycine, HOBt, EDCI, DMF, 0 °C to rt, 12–16 h, 73–80%; (d) Dess–Martin reagent, CH_2Cl_2, rt, 6 h, 70–85%; (e) 4 N HCl in dioxane, rt, 6 h, 90–95%; (f) R–N=C=O, NMM, CH_2Cl_2, 0 °C to rt, 12 h, 56–70%; (g) 4 N HCl in dioxane, rt, 5–6 h, 85–90%; (h) R–COOH, HOBt, EDCI, DIPEA, DMF, 0 °C to rt, 65–76%.

Synthesized compounds **37a–i**, **41a–f** and **42a–b** were evaluated for inhibition of HCV RNA replication in Huh7 cells using a subgenomic HCV replicon system (Table 1).[9] Cytotoxicity in Huh7 cells was determined simultaneously with anti-HCV activity by extraction and amplification of both HCV RNA and ribosomal RNA.[10] First of all, replacement of the telaprevir P2 moiety with a simple azetidine moiety proved to be counterproductive as **37d** provided inactive along with the related inactive compounds **37e–g**. More interestingly, introduction of a 2-azaspiro[3.5]nonane moiety at P2 as in compounds **37h** and **37i** displayed EC_{50}values of 2.3 and 5.4 μM, respectively, with no apparent cytotoxicity in Huh7 cells up to 10 μM. Replacement of the pyrole moiety of telaprevir with a 1′,3′-dihydrospiro[azetidine-3,2′-indene] P2 lead to a complete loss of potency (compound **37b**). However, slight tuning at P1 by replacing the propyl chain with a cyclobutyl or a cyclopropyl chain gave compounds **37a** and **37c** that displayed potency similar to telaprevir with EC_{50} values of 0.8 and 0.7 μM, respectively, compared to 0.4 μM for telaprevir. Unfortunately, compound **37a** was found to be toxic toward Huh7 cells at a similar level to the observed anti-HCV activity and thus the anti-HCV readout was most likely due to toxicity. Introduction of the same 1′,3′-dihydrospiro[azetidine-3,28-indene] P2 moiety into the boceprevir scaffold lead first to inactive compounds **41a–d** and **42a–b** but introduction of a cyclohexyl amine as the P4-cap lead to low micromolar derivatives **41e** and **41f** displaying EC_{50} values of 8.9 and 5.8 μM, respectively. However, these two compounds also proved to be toxic to Huh7 cells and thus their anti-HCV activity is most likely due to their toxic effects.

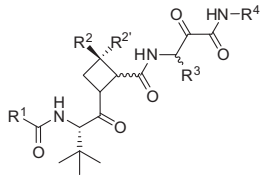
Compound **37h** was one of the first prepared that displayed single digit micromolar activity and we chose to profile it further to determine if the series might differentiate itself from the clinical PIs such as telaprevir, boceprevir and MK-7009[11]. First using a panel of genotype 1b mutant NS3 protease enzymes conferring resistance to other PIs, we found the profile to be similar to boceprevir but less potent versus R155K, V36M and A156S relative to boceprevir. In consideration of fold increase, the resistance profile based on the mutants tested was better than telaprevir (on which the **37h** structure is based) and MK-7009 (Table 2), which encouraged us to profile **37h** further.

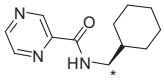
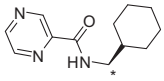
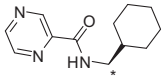
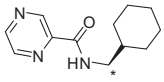
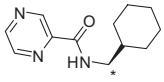
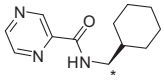
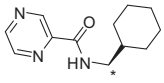
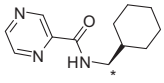
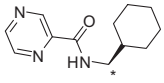
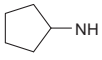
We next looked at compound **37h** side-by-side with telaprevir, boceprevir and MK-7009 versus several human proteases to determine if it may have toxicities associated with inhibition of these proteases. Elastase (Neutrophil), Plasmin, Thrombin, and Cathepsin S were chosen as potentially contributing to the clinical observation of rashes with telaprevir. Elastase (or leukocyte elastase) also known as ELA2 (elastase 2) is a serine protease in the same family as chymotrypsin and has broad substrate specificity. Secreted by neutrophils during inflammation, one of its primary roles is to destroy bacteria in host tissue.[12] Plasmin is a serine protease derived from the conversion of plasminogen in blood by plasminogen activators.[13] Plasmin degrades many plasma proteins, most notably, fibrin clots. Plasmin is also involved in several pathological and physiological processes such as inflammation, neoplasia, metastasis, wound healing, angiogenesis, embryogenesis and ovulation.[14] Thrombin is a protein in the blood that has many effects in the coagulation cascade. It is a serine protease that converts soluble fibrinogen into insoluble strands of fibrin, as well as catalyzing many other coagulation-related reactions.[15] Cathepsin S is a lysosomal cysteine protease that participates in the degradation of antigenic proteins and therefore is key to immune response.[16]

Inspection of the human protease data presented in Table 3 reveals a profile for **37h** that is quite similar to telaprevir. Interestingly MK-7009 did not inhibit any of the four human proteases up to 100 μM, while boceprevir had a similar profile except for its submicromolar inhibition of thrombin (see fig. 2).

Based on these results, our most promising compounds **37c** and **37h** along with a selection of the remaining compounds, were further profiled by assessing their cytotoxicity in primary human PBM (peripheral blood mononuclear) cells, CEM cells (a human-T-cell-derived cell line) and Vero cells (African green monkey kidney

Table 1
Chemical structure, anti-HCV activity and cytotoxicity of compounds **37a–i**, **41a–f** and **42a–b**



Compound	R^1	$R^2/R^{2'}$	R^3	R^4	Anti-HCV[a] (μM)		Cytotoxicity, CC_{50} (μM) in			
					EC_{50}	EC_{90}	PBM	CEM	Vero	Huh7
1	N/A	N/A	N/A	N/A	0.01	0.03	>100	>100	>100	>10
2	N/A	N/A	N/A	N/A	0.4	0.9	ND	ND	ND	>10
37a					0.7	1.0	29	43	>100	1.4
37b					>10	>10	>100	72	>100	>10
37c					0.8	1.5	12	14	>100	>10
37d		H/H			>10	>10	>100	>100	>100	>10
37e		H/H			>10	>10	27	30	>100	>10
37f		H/H			>10	>10	80	52	>100	>10
37g		H/H			>10	>10	>100	38	>100	>10
37h					2.3	6.4	32	16	27	>10
37i					5.4	9.7	32	5.4	21	>10
41a					13	31	>100	ND	>100	27
41b					>10	>10	>100	ND	95	>10
41c					>10	>10	15	ND	46	>10
41d					>10	>10	22	ND	43	>10
41e					8.9	30	30	ND	44	8.2
41f					5.8	9.8	15	15	26	5.5
42a					>10	>10	44	35	46	>10

(*continued on next page*)

Table 1 (*continued*)

Compound	R^1	$R^2/R^{2'}$	R^3	R^4	Anti-HCV[a] (μM)		Cytotoxicity, CC_{50} (μM) in			
					EC_{50}	EC_{90}	PBM	CEM	Vero	Huh7
42b					>10	>10	31	22	43	10

[a] HCV Replicon in Huh7 cells. All concentrations were run in triplicate and reported as mean values.

Table 2
HCV NS3/4A Protease Assay, The EC_{50}/EC_{90} (μM) values are shown for genotype **1b** wild type and mutants

HCV	Boceprevir		Telaprevir		37 h		MK-7009	
Protease	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}
Wild type	0.52	≈1	0.06	0.78	0.78	9.81	0.0062	0.013
A156T	61 (120)	>100 (>100)	46 (780)	>100 (>130)	>100 (>130)	>100 (>10)	0.91 (150)	>1 (>77)
R155K	1.4 (2.7)	4.8 (≈4.8)	0.8 (13)	8.3 (11)	5.5 (7.1)	64 (6.6)	>1 (>160)	>1 (>77)
D168V	0.22 (0.4)	0.9 (≈0.9)	0.08 (1.3)	0.74 (0.9)	0.4 (0.5)	3.3 (0.3)	>1 (>160)	>1 (>77)
V36M	0.35 (0.7)	5.6 (≈5.6)	0.51 (8.5)	5.1 (6.5)	6.9 (8.8)	75 (7.6)	0.045 (7.2)	0.10 (7.8)
A156S	3.7 (7.1)	⩾100 (⩾100)	2.2 (37)	52 (66)	43 (55)	>100 (>10)	<0.001 (<0.16)	0.017 (1.3)
V170A	0.77 (1.5)	7.7 (≈7.7)	0.2 (3.3)	1.5 (1.9)	>1 (>1.2)	8.7 (0.9)	0.0046 (0.7)	0.010 (0.8)
D168A	0.52 (1)	4.7 (≈4.7)	0.58 (1)	0.69 (0.9)	0.72 (0.9)	8.2 (0.8)	2.4 (390)	11 (840)

Fold Increase (FI) data are in parenthesis.

Table 3
Effect of HCV Protease Inhibitors on selected human proteases (μM)[a]

Compound	Elastase		Plasmin		Thrombin		Cathepsin S	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
37h	7.8 ± 0.3	85 ± 2.4	>100	>100	<1	<1.7 ± 0.4	>100	>100
MK-7009	>100	>100	>100	>100	>100	>100	78 ± 14	>100
Telaprevir	8.0 ± 1.6	>100	8.7 ± 2.5	110 ± 32	<1	<1	>100	>100
Boceprevir	⩾100	>100	>100	>100	<1	<1.4 ± 0.9	> 100	>100

[a] Results are average IC_{50} and IC_{90} values ± standard error from 2 independent assays.

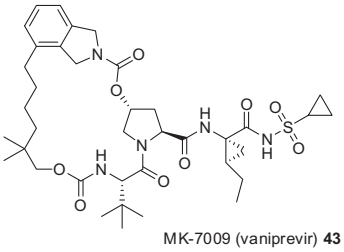


Figure 2. Structure of HCV protease inhibitor vaniprevir (MK-7009).

epithelial cells).[17] Unfortunately, **37h** showed toxicity in the micromolar range in all three lines while **37c** was similar except that it showed no toxicity versus Vero cells up to 100 μM. This cytotoxicity combined with the human protease inhibition drove use to move away from this series of HCV PI.

Through this work, we have demonstrated that substituted azetidines, such as 2-azaspiro[3.5]nonane and 1′,3′-dihydrospiro[azetidine-3,2′-indene], were suitable P2 moieties to build potent HCV NS3 protease inhibitors. Among the 17 analogs prepared, compound **37c**, bearing a 18,3′-dihydrospiro[azetidine-3,2′-indene] at P2, displayed an EC_{50} of 0.8 μM against HCV with no toxicity in Huh7 and Vero cells at concentration up to 10 and 100 μM respectively. Unfortunately, overall cytotoxicity in cell based systems discouraged further development of this new series of HCV NS3 protease inhibitors.

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