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Design and efficient synthesis of novel arylthiourea derivatives as potent hepatitis C virus inhibitors

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ABSTRACT

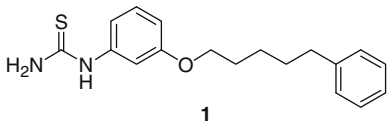
A novel class of arylthiourea HCV inhibitors bearing various functionalities, such as cyclic urea, cyclic thiourea, urea, and thiourea, on the alkyl linker were designed and synthesized. Herein we report the synthesis and structure–activity relationships (SARs) of this novel class of arylthiourea derivatives that showed potent inhibitory activities against HCV in the cell-based subgenomic HCV replicon assay. Among compounds tested, the new carbazole derivative **64**, which has an eight-carbon linkage between the phenyl and carbazole rings and a tolyl group at the N-9 position of carbazole, was found to possess strong anti-HCV activity (EC_{50} = 0.031 μM), lower cytotoxicity (CC_{50} >50 μM), and higher selectivity index (SI >1612) compared to its derivatives.

Hepatitis C virus (HCV) infection is a major health problem with an estimated 170 million infected people worldwide.[1] HCV, a small (+)-RNA virus in the family *Flaviviridae*, was initially described in 1989 and has six genotypes with numerous subtypes.[2] If left untreated, hepatitis C can progress to cirrhosis, hepatocellular carcinoma (HCC), and liver failure, a major cause for liver transplantation.[3] No vaccine is currently available to prevent hepatitis C and existing treatments are not optimal.[4] Interferon, with or without ribavirin, is the current standard care for treating chronic hepatitis C virus infections.[5] However, this therapy in genotype 1 HCV patients has limited efficacy and poor tolerability.[6] Consequently, there is a large unmet medical need for new therapies with better efficacy and fewer side effects.

According to literature review, many emerging antiviral agents are targeted against specific HCV enzymes, such as NS3 serine protease and NS5B RNA-dependent RNA polymerase.[7] The development of the HCV replicon provides a cell-based assay system for the evaluation of antiviral agents targeted to viral and host proteins involved in HCV replication.[8] Moreover, the use of combinations of anti-HCV agents with different mechanisms of action seems to be an important strategy to prevent viral resistance.[7]

Recently, the thiourea compound **1**[9] (Fig. 1) has been reported to exert strong anti-HCV activity in a cell-based subgenomic HCV replicon assay.[10] The initial structure–activity relationships of this class of compounds was explored by maintaining the arylthiourea portion. Tough the mechanism of action of this class of compounds is not yet fully understood,[11] they show significant activity in a cell-based HCV replicon assay. In our continuing efforts to discover novel HCV inhibitors, we carried out further SAR studies on the effect of incorporating a cyclic urea, cyclic thiourea, urea, or thiourea structural unit separated from the arylthiourea portion by a methylene linker (**2**, Fig. 1). In this Letter, we would like to report the synthesis of these new scaffolds and evaluation of their inhibitory activities against HCV. Details of this investigation will be described herein.

Aryl cyclic urea and aryl cyclic thiourea derivatives consisting of five-, six-, and seven-membered ring systems containing *N*-aryl substituents were prepared as shown in Scheme 1. The five- and six-membered cyclic urea **6** (n = 1, 2) were synthesized starting from the coupling reaction of aniline **3** with chloroalkyl isocyanate



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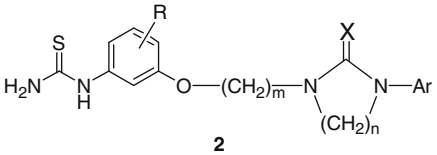

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Figure 1. Arylthiourea compounds **1** and **2**.

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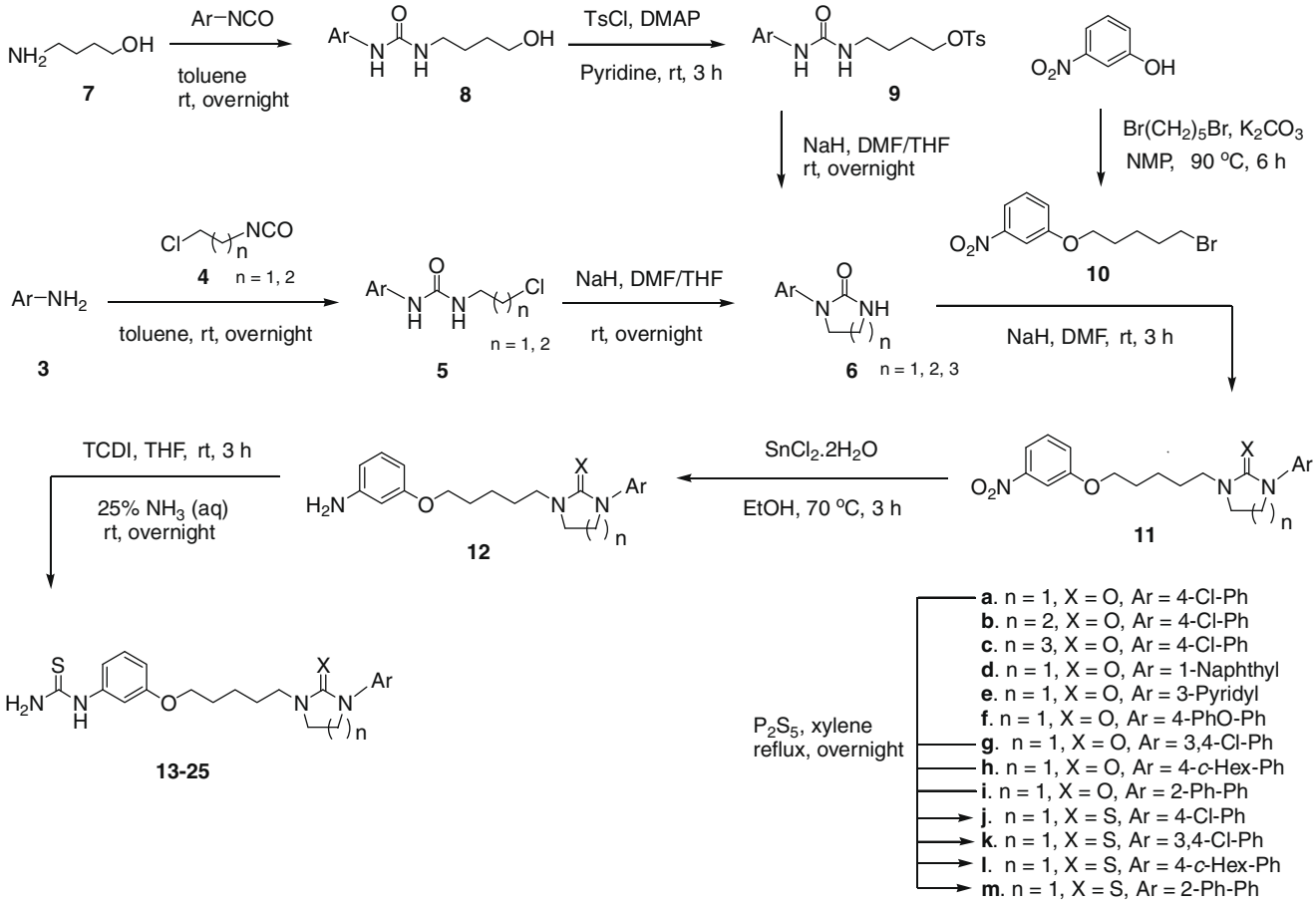
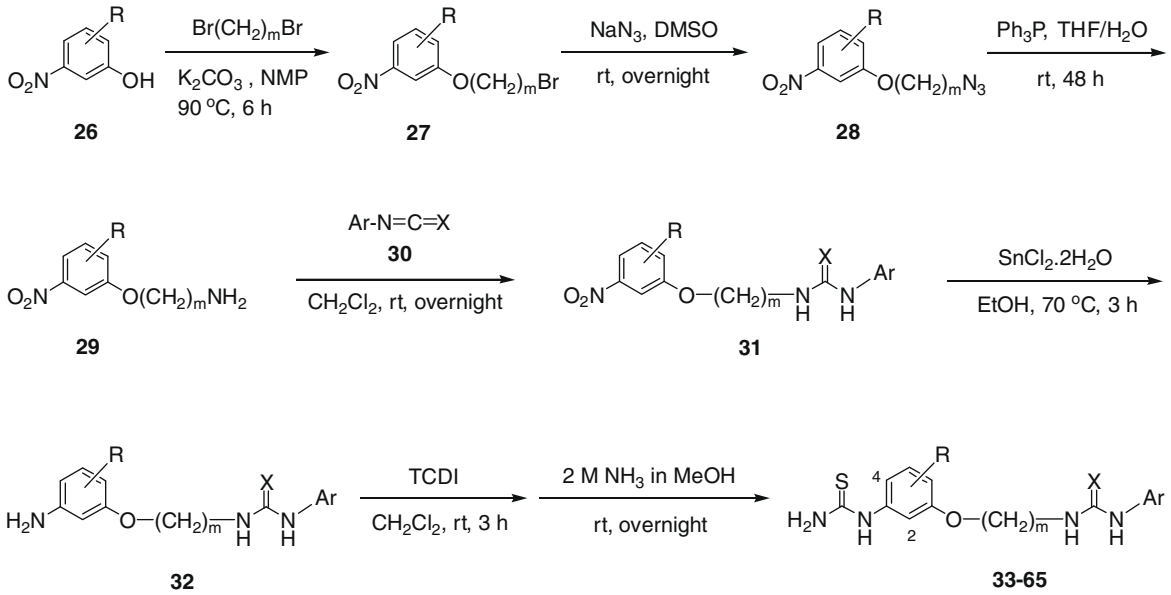
4 to give urea **5**, followed by intramolecular cyclization by treatment with NaH in THF/DMF cosolvent system at room temperature. On the other hand, the seven-membered cyclic urea **6** ($n = 3$) was synthesized starting from the coupling reaction of 4-amino-1-butanol **7** with aryl isocyanate to give urea **8**, which was then reacted with *p*-toluenesulfonyl chloride in the presence of 4-dimethylaminopyridine (DMAP) to give the corresponding tosylate **9**. Subsequent intramolecular cyclization of **9** under basic conditions afforded the seven-membered cyclic urea **6** ($n = 3$). The cyclic urea **6** was reacted with **10**, which was generated from



Scheme 1. Synthesis of compounds **13–25**.



Scheme 2. Synthesis of compounds **33–65**.

3-nitrophenol and 1,5-dibromopentane in NMP, in the presence of NaH in DMF provided compound **11**. Treatment of **11a** and **11g–i** with P_2S_5 in xylene at reflux temperature gave the corresponding five-membered cyclic thioureas **11j–m**, respectively. Unfortunately, treatment of **11b–c** with P_2S_5 in xylene gave poor or completely unsuccessful results in the production of the six- and seven-membered cyclic thioureas. The nitro group of **11** was reduced with tin (II) chloride to afford aniline **12**, which was converted to the desired arylthiourea compounds **13–25** by treatment with 1,1′-(thiocarbonyl)diimidazole (TCDI) in THF and subsequent reaction with 25% ammonia solution.

Arylurea and arylthiourea derivatives **33–65** were synthesized as shown in Scheme 2. Nucleophilic substitution of 3-nitrophenol **26** with dibromo compound yielded **27**, which was converted to the corresponding azide **28** by the treatment with sodium azide in DMSO. Azido reduction of **28** with triphenylphosphine in THF/H_2O provided amine **29**, which was treated with the appropriate isothiocyanate (or isocyanate) **30**[12] in CH_2Cl_2 providing compound **31**. Subsequent nitro reduction of **31** in the presence of tin (II) chloride in ethanol provided aniline **32**. Treatment of **32** with TCDI in CH_2Cl_2 followed by reaction with 2 M ammonia in methanol gave the desired compounds **33–65**.

In our previous Letter,[9] it was demonstrated that the arylthiourea compound **1** with a five-carbon methylene linker was identified as a potent inhibitor of HCV replication (EC_{50} = 0.048 μM). In a logical extension of the investigation of the distal phenyl ring of compound **1**, our attention turned toward cyclic urea, cyclic thiourea, urea, and thiourea compounds (**2**, Fig. 1). All synthesized compounds were tested for anti-HCV activity using an in vitro assay system that is suitable for monitoring anti-HCV activities of compounds. This system is composed of a human hepatocarcinoma cell line (Huh-7) supporting multiplication of a HCV replicon.[10] We first examined the cyclic urea ring moiety and the effect of substituents on the ring nitrogen. In order to understand the relationship between ring size and activity, the five-, six-, and seven-membered cyclic ureas were synthesized. As shown in Table 1, the five-membered cyclic urea **13**, although less potent than compound **1**, exhibited moderate inhibitory activity with an EC_{50} of 0.28 μM. An expansion of the ring size to six-membered cyclic urea (**14**) showed fivefold decreased activity (cf. **13** with **14**). Unexpectedly, further ring expansion to a seven-membered cyclic urea (**15**) showed similar activity (EC_{50} = 0.25 μM) to the corresponding five-membered cyclic urea (**13**). However, significant cytotoxicity was observed with increasing ring size. It seems that a five-membered ring is optimal in terms of antiviral activity and cytotoxicity.

Using compound **13** as a reference, we then replaced the 4-chlorophenyl group on the ring nitrogen with a naphthyl group (**16**), which resulted in a twofold decrease in activity. However, a significant loss of activity was observed when the 4-chlorophenyl group was replaced with a pyridyl (**17**) or 4-phenoxyphenyl (**18**) group. Interestingly, replacing the 4-chlorophenyl group with a 3,4-dichlorophenyl (**19**), 4-cyclohexylphenyl (**20**), or biphenyl (**21**) group also resulted in moderate HCV inhibitors. Bioisosteric replacement of the oxygen atom by sulfur in the five-membered urea ring resulted in no significant change in activity, but the selectivity index for these five-membered cyclic thioureas was rather high (cf. **13** and **19–21** with **22–25**, respectively).

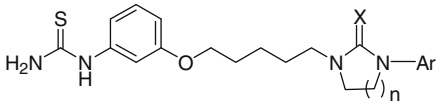
We next investigated the impact of replacing the cyclic urea and cyclic thiourea moieties with an acyclic urea and acyclic thiourea, respectively (Table 2). This led to a twofold drop in activity (cf. **33** with **16** and **34** with **22**). The difference in antiviral activity of the cyclic and acyclic compounds may be attributed to conformational change as well as lipophilicity. Interestingly, replacement of the urea oxygen (**33**) with sulfur (**35**) increases the activity by threefold. Furthermore, addition of a methyl group at the 2- (**36**) or 4- (**37**) position of the left-hand phenyl ring caused a partial or complete loss of activity compared to the parent compound **35**. It appears that the additional methyl group on the aromatic ring of the arylthiourea moiety had a detrimental effect on anti-HCV activity.

To clarify the effect of linker length on activity, compounds **38–41** with linkers of five to eight carbons were prepared and tested in the same assay. The activity of the molecules in this homologous series increased dramatically as the length of the linker was increased from five to eight carbon atoms. Compound **41** with a linker of eight carbons was more active against HCV (EC_{50} = 0.034 μM) than its corresponding shorter compounds, but also more cytotoxic. These findings indicate that the spatial distance of the right-hand thiourea functionality from the oxygen atom is a critical determinant of activity.

The removal of two chlorine atoms on the phenyl ring of **41** resulted in compound **42** with decreased antiviral activity. We then turned our attention to study the substituent effects on the distal phenyl ring of **42**. Introduction of a bromine atom at the *para*-position (**43**) improved the activity over the parent compound **42**. However, the *meta*- and *ortho*-bromo isomers (**44**, **45**) were less active than the *para* isomer (**43**). These initial results suggested that the *para*-position may be a favorable site for further SAR study of the substituent effects on the distal phenyl ring. For this purpose, several functional groups with various steric properties were introduced. Small substituents such as chlorine (**46**) at the *para*-position of the phenyl ring were tolerated. Larger groups such as *t*-butyl (**47**) or cyclohexyl (**48**) showed good activity similar to that of *para*-chlorine (**46**) substituent. This result indicates that the steric effect of the substituents on the phenyl ring have a negligible consequence on activity. However, a heterocycle such as morpholine (**49**) at the *para*-position led to a notable decrease in activity, indicating that this position cannot tolerate the introduction of a relatively hydrophilic moiety (cf. **48** with **49**).

In an effort to further improve the antiviral activity and yet maintain low cytotoxicity, we evaluated the effect of the fused rings (**50–54**) on the thiourea nitrogen. Replacement of the distal phenyl ring of **42** by an indanyl (**50**) or fluorenyl (**52**) group demonstrated a similar or slightly improved activity. Introduction of a nitrogen atom into the bicyclic ring dropped the activity by about twofold (cf. **50** with **51**). Interestingly, the carbazole **53** also maintained good levels of activity despite the fact that there is a nitrogen atom in the tricyclic ring (cf. **52** with **53**). In addition,

Table 1
Anti-HCV activity and cytotoxicity for compounds **13**–**25**

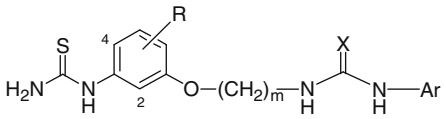


Compound	*n*	X	Ar	1b EC_{50}[a] (μM)	CC_{50}[a] (μM)	SI[b]
1	—	—	—	0.048	22	458
13	1	O	4-Cl-Ph	0.28	39	139
14	2	O	4-Cl-Ph	1.50	15	10
15	3	O	4-Cl-Ph	0.25	13	52
16	1	O	1-Naphthyl	0.57	15	26
17	1	O	3-Pyridyl	>50	>50	>1
18	1	O	4-PhO-Ph	27	>50	>2
19	1	O	3,4-Cl-Ph	0.21	13	62
20	1	O	4-*c*-Hex-Ph	0.29	12	41
21	1	O	2-Ph-Ph	0.396	12	30
22	1	S	4-Cl-Ph	0.26	>50	>192
23	1	S	3,4-Cl-Ph	0.2	>50	>250
24	1	S	4-*c*-Hex-Ph	0.167	>50	>299
25	1	S	2-Ph-Ph	0.234	>50	>214

[a] Mean of triplicate well values. All experiments were performed at least twice. 1b: there are several genotypes in HCV, our assay employed genotype 1b subgenomic replicon.

[b] In vitro selectivity index (CC_{50}/EC_{50}).

Table 2
Anti-HCV activity and cytotoxicity for compounds **33–54**



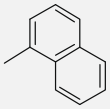
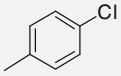
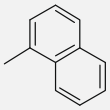
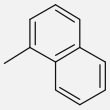
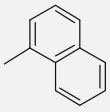
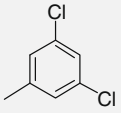
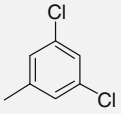
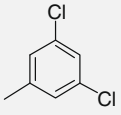
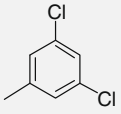
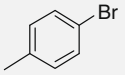
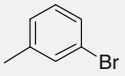
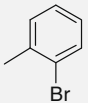
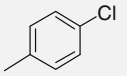
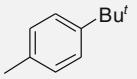
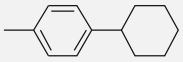
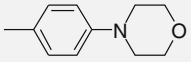
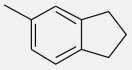
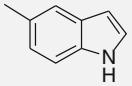
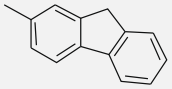
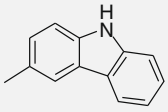
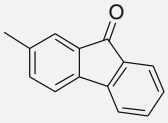
Compound	*m*	X	R	Ar	1b EC_{50}[a] (μM)	CC_{50}[a] (μM)	SI[b]
1	—	—	—	—	0.048	22	458
33	5	O	H		1.39	>50	>36
34	5	S	H		0.51	>50	>98
35	5	S	H		0.45	>50	>111
36	5	S	2-Me		>50	>50	>1
37	5	S	4-Me		1.03	>50	>49
38	5	S	H		0.177	18	102
39	6	S	H		0.122	21	172
40	7	S	H		0.088	20	227
41	8	S	H		0.034	12	353
42	8	S	H		0.109	>50	>459
43	8	S	H		0.047	18	383
44	8	S	H		0.093	20	215
45	8	S	H		0.131	36	275

Table 2 (*continued*)

Compound	*m*	X	R	Ar	1b EC_{50}[a] (μM)	CC_{50}[a] (μM)	SI[b]
46	8	S	H		0.062	18	290
47	8	S	H		0.06	17	283
48	8	S	H		0.071	>50	>704
49	8	S	H		0.316	>50	>158
50	8	S	H		0.08	34	425
51	8	S	H		0.148	18	122
52	8	S	H		0.118	25	212
53	8	S	H		0.089	>50	>562
54	8	S	H		0.053	>50	>943

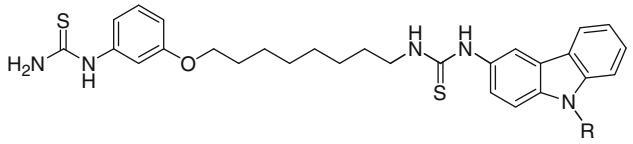
[a] Mean of triplicate well values. All experiments were performed at least twice. 1b: there are several genotypes in HCV, our assay employed genotype 1b subgenomic replicon.

[b] In vitro selectivity index (CC_{50}/EC_{50}).

replacement of the carbazole nitrogen (**53**) by carbonyl (**54**) is well tolerated and results in further improved activity against HCV (EC_{50} = 0.053 μM for **54**). Cabazole analog **53** was selected for further evaluation due to its high activity, low cytotoxicity, and easily functionalized structure.

The effects of the substituents at N-9 of the carbazole moiety were investigated (Table 3). Introduction of a methyl group (**55**) at the N-9 position showed similar activity to **53**. Increasing the length of the alkyl substituent on the carbazole ring from methyl to hexyl (**55**–**60**) resulted in a progressive increase in activity. This may be due to the increase in lipophilicity of the compound. Replacement of the alkyl group on the carbazole ring with a benzyl (**61**) or phenethyl (**62**) group also showed potent activity against HCV (EC_{50} values of 0.036 and 0.033 μM, respectively). Removal of the methylene group of benzyl moiety (**61**) produced compound **63** with decreased activity. Interestingly, addition of one (**64**) or two (**65**) methyl groups on the *N*-phenyl ring of **63** resulted in an increase in activity (**64**, EC_{50} = 0.031 μM and **65**, EC_{50} = 0.044 μM). More importantly, no cytotoxicity was observed for compounds of this type, the CC_{50} values for compounds **53** and **55–65** being above 50 μM. These data indicated that this series of carbazole derivatives exhibited high anti-HCV activity and have an excellent selectivity index. In all cases examined, compound **64** appears to be the most promising candidate for further development as anti-HCV agent.

Table 3
Anti-HCV activity and cytotoxicity for compounds **55**–**65**



Compound	R	1b EC_{50}[a] (μM)	CC_{50}[a] (μM)	SI[b]
1	—	0.048	22	458
53	H	0.089	>50	>562
55	Me	0.080	>50	>625
56	Et	0.054	>50	>926
57	*n*-Pr	0.048	>50	>1042
58	*n*-Bu	0.045	>50	>1111
59	*n*-Pent	0.042	>50	>1190
60	*n*-Hex	0.036	>50	>1389
61	CH_2Ph	0.036	>50	>1389
62	CH_2CH_2Ph	0.033	>50	>1515
63	Ph	0.096	>50	>521
64	4-Me-Ph	0.031	>50	>1612
65	3,5-Me-Ph	0.044	>50	>1136

[a] Mean of triplicate well values. All experiments were performed at least twice. 1b: there are several genotypes in HCV, our assay employed genotype 1b subgenomic replicon.

[b] In vitro selectivity index (CC_{50}/EC_{50}).

In summary, we have developed an efficient synthesis to provide a novel class of arylthiourea HCV inhibitors bearing various functionalities, such as cyclic urea, cyclic thiourea, urea, and thiourea, on the alkyl linker. According to our SAR investigation, variation in the ring size from five-membered to seven-membered cyclic urea resulted in an interesting pattern of activity. The five-membered cyclic urea **13** demonstrated moderate inhibitory activity with an EC_{50} of 0.28 μM. An expansion of the ring size to six-membered cyclic urea **14** reduced the activity. Interestingly, further ring expansion to a seven-membered ring **15** showed six-fold increased activity. This effect might be due to their drastically conformational change and steric requirement between the rings of different size. However, the underlying cause of this biological result is not fully understood and worthy of further study. Incorporation of a methyl group at the left-hand phenyl ring resulted in diminished activity. Increasing the alkyl chain length from five to eight carbon atoms provided a corresponding increase in activity. Among compounds tested, the new carbazole derivative **64**, which has an eight-carbon linkage between the phenyl and carbazole rings and a tolyl group at the N-9 position of carbazole, was found to possess strong anti-HCV activity (EC_{50} = 0.031 μM), lower cytotoxicity (CC_{50} >50 μM), and higher selectivity index (SI >1612) compared to its derivatives. Further mechanistic and pharmacokinetic studies on this class of compounds are currently under active investigation and will be reported in due course.

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