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ABSTRACT: We describe the study leading to the discovery of compound **11**, a pan-genotypic HCV NS5A inhibitor with excellent potency, metabolic stability, and pharmacokinetics. Compound **11** incorporating a 4-silapiperidine group was discovered by further optimizing our previous lead with a triethylsilyl moiety. It displayed great potency against GT1a, -1b, -2a, -3a, -4a, -5a and -6a with an EC_{50} range of 0.33~17 pM and improved potency against resistance-associate variant GT1a_ M28T. Pharmacokinetics (PK) study indicated that compound **11** has reasonable PK exposures with a high liver distribution in preclinical animal species (mouse, rat and dog). The results of a 14-day repeat-dose toxicity study identified safety of compound **11**.

INTRODUCTION

The World Health Organization (WHO) estimates that about 71 million people worldwide are infected with hepatitis C virus (HCV).[1] HCV infection often leads to severe liver diseases including cirrhosis, hepatocellular carcinoma and other complications.[2] Traditional therapy for HCV infection relies upon a combination of pegylated interferon-α and ribavirin, a poorly tolerated regimen with relative low sustained virologic response (SVR) rates (40-65%).[3] In recent years, a significant improvement in treating HCV has been made due to the development of direct-acting antiviral agents (DAAs) with higher rates of SVR and less side effects, such as the NS3/4A protease inhibitors simeprevir,[4] paritaprevir,[5] grazoprevir [6] and glecaprevir,[7] the NS5B polymerase inhibitors sofosbuvir [8] and dasabuvir,[9] the NS5A inhibitors daclatasvir,[10] ombitasvir,[11] ledipasvir,[12] elbasvir, [13] velpatasvir [8] and pibrentasvir [14] (Figure 1). Administration of a combination of all oral DAAs has become the current treatment paradigm for HCV with improved efficacy, shorter treatment duration and less adverse effects. Several DAA-based regimens have been approved for the treatment of pan-genotypic HCV infection with SVR rates over 95% only requiring 12 or 8 weeks of therapy, such as sofosbuvir/velpatasvir,[8,15] grazoprevir/elbasvir [16] and glecaprevir/pibrentasvir.[17]

Hepatitis C virus nonstructural protein 5A (NS5A) has been treated as an attractive viral target for HCV therapy. NS5A has no known enzymatic activity, but plays an essential role in HCV RNA replication and virus assembly.[18] The mechanism of HCV NS5A inhibitors remains unclear. In the absence of enzymatic activity for NS5A, the identification of inhibitors has been driven by cell-based replicon activities. The NS5A inhibitors have become the most commonly used DAAs combined with an NS5B polymerase inhibitor and/or an NS3/4A protease inhibitor for treating patients who have HCV. First generation NS5A inhibitors demonstrated high SVR rates in patient with HCV genotype 1 subtype a (GT1a) while exhibited weak activity against several other genotypes. In addition, most of NS5A inhibitors approved for market showed a low resistance barrier to GT1a.[19] Therefore, many research groups have been working toward the discovery of more potent HCV NS5A inhibitors against a wider variety of genotypes as well as NS5A resistance mutations particularly in the prevalent GT1a.

Incorporation of a silicon atom into drug molecules provides an innovative avenue and a source of chemical diversity in drug discovery.[20] Silicon has a larger covalent radius than carbon, and also a larger carbon-silicon bond length compared to the corresponding carbon-carbon bond. Silicon-containing analogs are more lipophilic than their carbon counterparts. These unique physicochemical properties of silicon render it ideal for medicinal applications that no other element can effectively achieve.[21] Our previous research efforts have identified a pan-genotype HCV NS5A inhibitor **1** through a "silicon-carbon switch" strategy [22] (Figure 2). Despite its potency against HCV genotypes 1a, 1b, 2a, 3a, 4a, and 5a in single picomolar range, **1** showed relatively low activity against 6a with sub-nM activity. In a continued effort to develop pan-genotype HCV NS5A inhibitors, we explored the impact of structural modifications to **1** (Figure 2), with the goal of improving the potency against GT6a and maintaining the good potency against the other genotypes. Herein, we disclose a novel series of silicon-containing NS5A inhibitors and identification of compound **11** with pan-genotypic potency and ideal PK profiles.

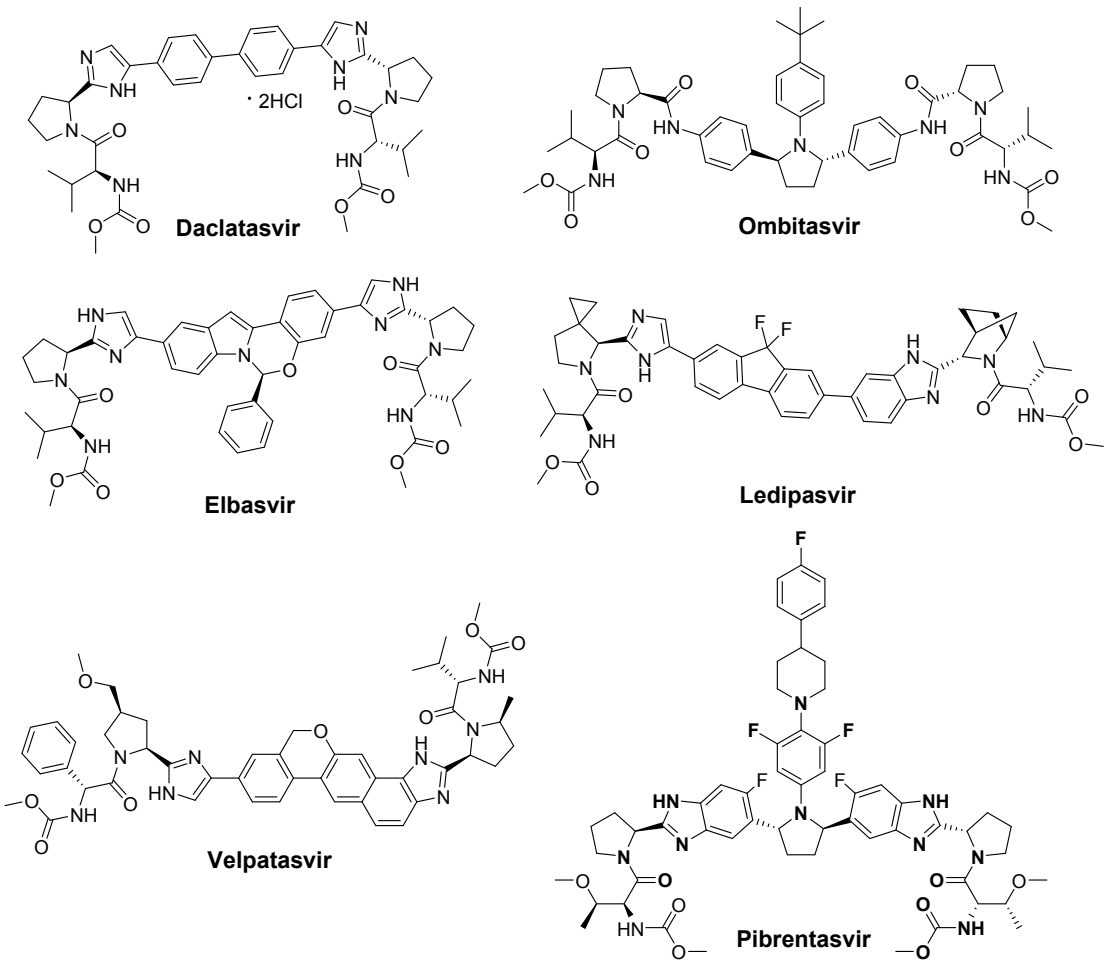


Figure 1. Chemical structure of HCV NS5A inhibitors approved by FDA.

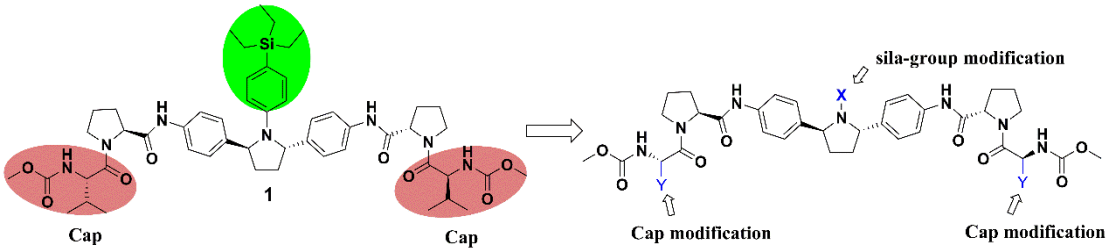


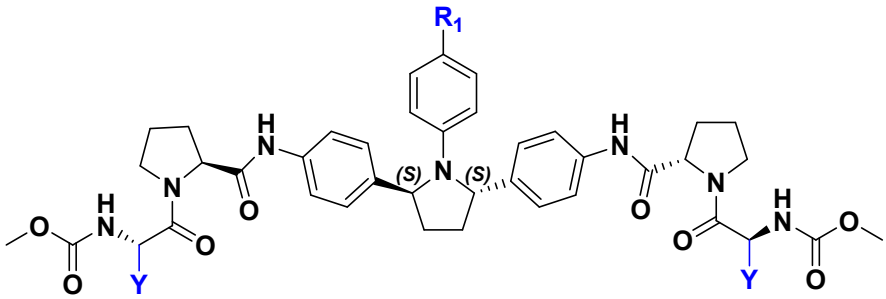
Figure 2. Chemical structure of compound **1** and structural modifications strategy for novel NS5A inhibitor design.

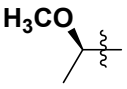
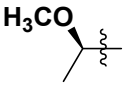
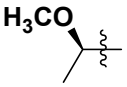
RESULTS AND DISCUSSION

In our previous work, compound **1** was discovered as a silicon-containing pan-genotype HCV NS5A inhibitor with considerably less potency against GT6a than GT1~5 [22]. We sought to explore the impact of silicon-containing groups as "X groups", and the "cap" groups as "Y groups", with a goal of improving the potency against GT6a (Figure 2). Replacing the Moc-

Val-"end-capping" group of compound **1** with the Moc-Thr(OMe)-capping group led to compound **3** and modifying the 4-position of the central *N*-phenyl ring with silyl groups yielded compound **2** and **4** (Table 1). These compounds were tested in GT1a, GT1b, GT3a and GT6a sub-genomic replicon assays. *In vitro* biological data for those compounds are demonstrated in Table 1. As indicated in the Table 1, all the compounds provided picomolar activity against the genotypes GT1a, -1b, -3a, and new compounds **2**, **3** & **4** delivered an obvious improvement in performance against GT6a (80~274 pM vs. 817 pM). However, those compounds still exhibited

Table 1. In Vitro Activity of Compounds 1-6 against HCV GT1a, GT1b, GT3a and GT6a in the Replicon Assay



Compound	R_1	Y	Replicon EC_{50} (pM) [a]			
			GT1a	GT1b	GT3a	GT6a
1[b]	$SiEt_3$		11.0	2.80	5.80	817
2	$SiMe_3$		12.0	1.60	7.00	247
3	$SiEt_3$		2.30	1.00	2.00	121
4	$SiMe_2t$-Bu		7.90	1.40	3.00	80.0

[a] Mean of triplicate well values. EC_{50} stands for 50% effective concentration. [b] In vitro biological data for compound **1** are slightly different from previous report and the differences might result from experimental error.

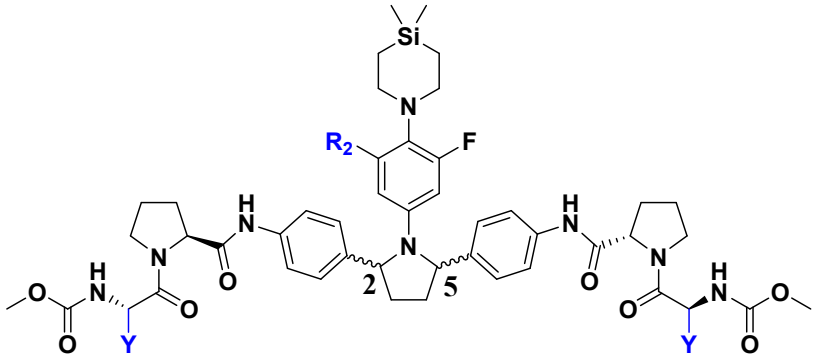
relatively weaker potencies against GT6a than other genotypes. Compared with compound **1**, Moc-Thr(OMe)-cap analogue **3** showed potency improvement across the genotypes tablulated. Particularly, the compound **3** was approximately 7-fold more potent than compound **1** against GT6a, suggesting that the incorporation of *O*-methylthreonine might be beneficial for GT6a

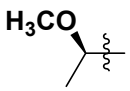
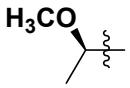
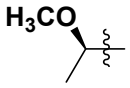
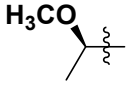
inhibition. Of the three new compounds, compound **4** which has a $SiMe_2$t-Bu group at the 4-position of the central *N*-phenyl ring showed the best activity against GT6a. It was approximately 10-fold more potent than compound **1** against GT6a. While the $SiMe_3$-substituted analogue **2** showed the least potency improvement in GT6a compared with **3** and **4**. There appears to be a general trend that bulky substituents at the 4-position of the central *N*-phenyl ring correlate with an improved ability to suppress GT6a.

Improvement in potencies against GT6a was attainable by modifying "X group" and "Y group", while retaining potent activities against GT1a, GT1b and GT3a. Our primary results gave us confidence that greater potencies with comparable activities across the various HCV genotypes could be achieved by exploring modifications of "X group" and/or "Y group". We next followed the trend mentioned above to introduce more bulky sila-groups to the 4-position of the central *N*-phenyl ring with the aim to obtain potent pan-genotype inhibitors. Analogues with a 4-silapiperidine group at the 4-position of the central *N*-phenyl ring were synthesized and evaluated in our research. In order to avoid the possible undesired PK properties, a fluorine atom was introduced to 3-position of the central *N*-phenyl ring. As demonstrated in Table 2, the compounds were tested as either the pure 2*S*, 5*S* or 2*R*, 5*R* diastereomers. The valine capped compounds **5-8** showed high potent activities against GT1a and GT1b, with replicon potencies in the 0.4-0.9 pM range of EC_{50}. A comparison of the 2*S*, 5*S* *trans*-pyrrolidine compound **5** with the 2*R*, 5*R* isomer **6** revealed that the stereochemistry at carbons 2 and 5 was unrelated with their potencies against GT1a and GT1b. Difference was also not observed between the 2*S*, 5*S* *trans*-pyrrolidine compound **7** and its 2*R*, 5*R* counterpart **8** in GT1a and GT1b inhibition. The trend was not in line with what we and others reported that a stereochemical dependence for potencies of compounds against GT1a.[22,23] However, the antiviral activities of the valine capped compounds **5-8** against GT3a and GT6a revealed a stereochemical dependence. The 2*S*, 5*S* isomer **5** was approximately 5.8- and 4.6-fold more potent than the 2*R*, 5*R* isomer **6** against GT3a and GT6a, respectively. Likewise, the 2*S*, 5*S* isomer **7** was more active against GT3a (3.4-fold) and GT6a (5.3-fold) than the 2*R*, 5*R* isomer **8**. Comparison of compound **5** and **7** revealed that introduction of additional fluorine atom to the 5-position of the central *N*-phenyl ring of the valine capped compounds barely affected the potencies against GT1a, GT1b and GT3a, but led to 2-fold improved potency against GT6a.

Testing the *O*-methylthreonine capped compounds also demonstrated a stereochemical dependence for their replicon potencies. The 2*S*, 5*S* isomer **9** was 1.9- to 5.5-fold more potent against genotypes tested than the corresponding 2*R*, 5*R* isomer **10**. Activity comparison of compound **11** with **12** revealed a similar trend of increased potency for the 2*S*, 5*S* isomer against genotypes tested vs the corresponding 2*R*, 5*R* isomer, with the exception of that the potencies of the two isomers agaist GT1b remained unchanged. Compound **12** (2*R*, 5*R* isomer) was

Table 2. In Vitro Activity of Compounds 5-12 Against HCV GT1a, GT1b, GT3a and GT6a in the Replicon Assay



Compounds	Configuration	Y	R_2	Replicon EC_{50} (pM) [a]			
				GT1a	GT1b	GT3a	GT6a
5	2*S*,5*S*		H	0.800	0.400	8.80	182
6	2*R*,5*R*		H	0.800	0.500	51.0	831
7	2*S*,5*S*		F	0.900	0.400	11.0	88.0
8	2*R*,5*R*		F	0.900	0.400	37.0	463
9	2*S*,5*S*		H	12.0	2.90	6.00	242
10	2*R*,5*R*		H	65.0	16.0	14.0	454
11	2*S*,5*S*		F	**1.20**	**1.70**	**3.00**	**17.0**
12	2*R*,5*R*		F	12.0	1.70	4.80	114

[a] Mean of triplicate well values. All experiments were performed at least twice. EC_{50} stands for 50% effective concentration.

significantly less active against GT1a (10-fold) and GT6a (6.7-fold) than the compound **11 (**2*S*, 5*S* isomer), with similar activity against GT3a. The compound **11** exhibited significantly improved activity against GT6a (14.2-fold) *vs* the compound **9**, indicating that introduction of additional fluorine atom to the 5-position of the central *N*-phenyl ring contributed to the improvement of potency against GT6a.

As a result of its desirable potency shown in Table 2, compound **11** was selected for further *in vitro* virologic evaluation. As shown in Table 3, **11** demonstrated picomolar potency across GT1~GT6, with replicon potencies in the 0.33-3.0 pM range for GT1-GT5 and 17 pM for GT6a . To determine the *in vitro* resistance profile of compound **11,** replicon resistance selection was conducted with **11** in HCV replicons containing NS5A from GT1a or GT1b. As indicated in Table 4, the greatest resistance emerged with the Q30E, Y93H, Y93C, and Y93N variants in genotype 1a. GT1a_Q30E, GT1a_Y93H, GT1a_Y93C , and GT1a_Y93N conferred 175.3- to >833-fold resistance to **11**. Examination of the data reveals that **11** demonstrated a similar potency against resistant variants in GT1a when compared to the known NS5A inhibitor ombitasbir, although there are some differences in fold-resistance and variants selected. One particular exception is found for GT1a_ M28T, which was susceptible to **11** (1.9-fold) but showed high fold resistance for Ombitasbir.[23] Variants of genotype 1b, where tested, showed lower fold resisitance to **11** when compared to variants of genotype 1a, especially for Y93H (>833 *vs* 12.2) and L31V (>23 *vs* 2.3). GT1b_L31W and GT1b_ L31V conferred 11.4- and 2.3-fold resistance, respectively. GT1b_ P32L remained fully susceptible to inhibition by **11.**

Table 3. Antiviral Activity of 11 in HCV Replicon Cell Lines Containing NS5A from GT1-6

Replicon EC_{50} (pM) [a]						
GT1a	GT1b	GT2a	GT3a	GT4a	GT5a	GT6a
1.2	1.7	0.38	3.0	0.33	1.6	17

[a] Mean of triplicate well values. All experiments were performed at least twice. EC_{50} stands for 50% effective concentration.

Table 4. Activity of 11 against HCV Genotype 1a and 1b NS5A Resistance-associated Variants in *vitro*

HCV genotype	variant	EC50 (pM) [a]	Fold-resistance [b]
1a	M28T	2.37	1.90

	L31M	12.2	9.90
	L31V	27.0	23.0
	Q30K	37.5	30.5
	Q30E	216	175
	Y93H	>1000	>833
	Y93C	>250	>203
	Y93N	>250	>203
1b	Y93H	20.4	12.2
	L31W	19.1	11.4
	L31V	3.81	2.30
	P32L	1.64	1.00

[a] As determined in transient-transfection assays.

[b] Fold-resistance is relative to the value of the respective wild-type replicon.

Given its in *vitro* pan-genotypic potency, we turned our attention to pharmacokinetic (PK) profiles of compound **11**. In *vitro* metabolic stability in mouse, rat and human microsomes (MLM, RLM and HLM, respectively) for compound **11** and ombitasvir was shown in Table 5. The rat and human microsomal stability of compound **11** was similar to ombitasvir.

Table 5. In Vitro Metabolic Stability Data

compound	MLM (% remaining [a])	RLM (% remaining [a])	HLM (% remaining [a])
11	60.4	76.3	80.9
Ombitasvir	63.5	73.5	82.5

[a] Percentage of parent compound remaining after 60 min of incubation.

Pharmacokinetic characterization of compound **11** in mouse was summarized in Table 6. Its $T_{1/2}$ (half-life) and AUC (area under curve) were similar to ombitasvir. A low oral bioavailability (7.2%) of compound **11** was observed, with similarity to the reported oral bioavailability of pibrentasvir (7.9%),[24] an approved pan-genotype HCV NS5A inhibitor. Dog PK profile of compound **11** was also investigated. As shown in Figure 3 and Table 7, compound **11** demonstrated a longer $T_{1/2}$ in dog than in mouse (21.2 *vs* 12.2). The AUC was also acceptable considering its picomolar level potency against GT1~6 and the similar AUCs with ombitasvir.

Table 6. Pharmacokinetics of Compound 11 in Mouse [a]

	iv					po					
compound	dose (mg/kg)	$T_{1/2}$ (h)	V_c (L/kg)	AUC_{last} (ng·h/mL)	CLp (L/h/kg)	dose (mg/kg)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	F (%)

11	2	12.2	1.56	17863	0.1	10	8.0	7.3	454	6446	7.2%
ombitasvir[c]	-	-[b]	-	-	-	10	7.7	3.0	583	6480	-

[a]Formulation: po 2:2:96 (v/v) Alcohol : Tween 80 : Glucose injection, iv: diluted po formulation for 2.5 times with 10% glucose injection. [b] Not tested. [c] The data was disclosed in our previous report.[22]

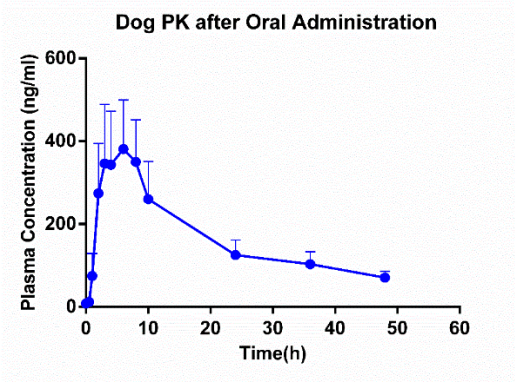


Figure 3. PK study of compound **11** in dog (PO 5 mpk).

Table 7. Dog PK Profile of Compound 11 after Oral Administration[a]

dose (mpk)	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	$AUC_{0\text{-}48h}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	MRT (h)
5	21.2	5.3	395	8020	10104	17.5

[a]Formulation: Phosal 53 MCT / PEG-400 / Poloxamer 124 / Cremophor RH40 (40/20/20/20, by weight).

In order to learn more metabolic properties, the liver distribution of both **11** and pibrentasvir were evaluated in mouse and rats. The concentrations of **11** and pibrentasvir in plasma and liver after oral administration are summarized in Table 8. At each time point, the concentration of **11** in mouse and rat plasma was lower than that of pibrentasvir, but the situation in the liver was just the opposite. The maximum concentration of **11** and pibrentasvir occurred at 3 h in plasma and liver. The liver concentration of **11** was much higher than its plasma concentration at the same time point, suggesting **11** was a NS5A inhibitor with high liver distribution. The mean plasma concentration ratios (LPRs) of **11** at 3 h in mouse and rat were 24.6 and 5.2, respectively, suggesting that **11** can distribute into liver easily. By contrast, LPRs of pibrentasvir were much lower in mouse and rat, with LPRs of 0.39 and 1.1 at 3 h in mouse and rat, respectively, indicating that pibrentasvir did not possess liver targeting effect.

Table 8. Liver Distribution of 11 and Pibrentasvir in Mouse and Rat (mean ± SD, n = 3)[a]

species	Time (h)	**11**			Pibrentasvir		
		Plasma	Liver	LPR[b]	Plasma	Liver	LPR[b]

		(ng/ml)	(ng/g)		(ng/ml)	(ng/g)	
mouse	0.5	160 ± 57.5	436 ± 126	8.8	414 ± 97.9	94 ± 42	0.43
	3	308 ± 57.6	1585 ± 131	24.6	1541 ± 171	193 ± 67	0.39
	24	58.6 ± 6.8	625 ± 147	17.9	718 ± 114	69.6 ±13	0.11
rat	0.5	40.9 ± 16.2	359 ± 107	2.7	103 ± 17.0	155 ± 23.2	1.5
	3	45.2 ± 7.2	1111 ± 202	5.2	96.4 ± 40.2	102 ± 50.6	1.1
	8	16.4 ± 6.4	293 ± 39.1	10.7	30.1 ± 5.85	18.9 ± 4.71	0.63

[a] Dosing at 10 mg/kg. [b] Mean liver concentration / Mean plasma concentration ratio (LPR).

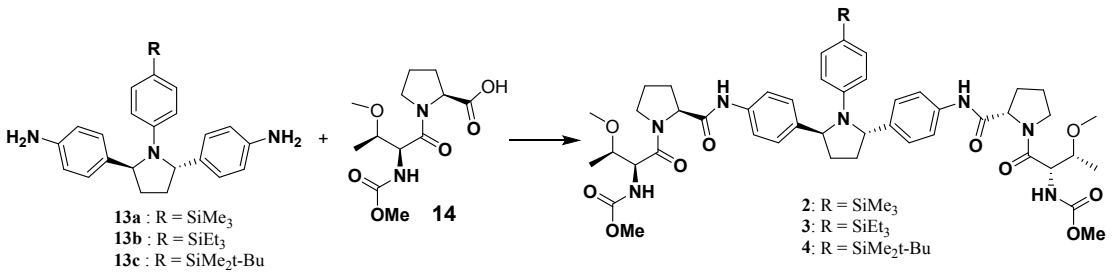
The in *vitro* cell toxicity of compound **11** was assessed by using Huh7 cells. CC_{50} value of compound **11** was determined to be > 50 μM, indicating no cell toxicity was observed in the assay.

To evaluate the safety of compound **11**, a 14-day repeated oral dose toxicity study was conducted and the results were available in supporting information. Mice were administered **11** once daily by gavage at a high dose of 300 mg/kg. All animals were observed daily and detailed clinical signs untill they were killed after the 14th adminstration. As demonstrated in Table 9, there was no statistically significant difference in body weight between the control and **11**. In addition, no abnormality was observed on the organs. Also, hematology data showed no statistically significant difference between the control and **11** (Table 10). Blood chemistry data indicated a statistically significant increase of cholesterol in **11** ($P < 0.01$) (Table 11), with no abnormality in other liver-related indicators. In summary, animal studies identified no toxicity with **11**.

CHEMISTRY

As shown in Scheme 1, compounds **2**-**4** (Table 1) were synthesized starting from silicon-containing di-aniline compounds **13a**, **13b** and **13c**, which were prepared according to previous methods and purified as single 2*S*, 5*S* isomers.[22] The amide side chains were attached to the central pyrrodine core by peptide-coupling compounds **13a**, **13b** and **13c** with *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline **14**.

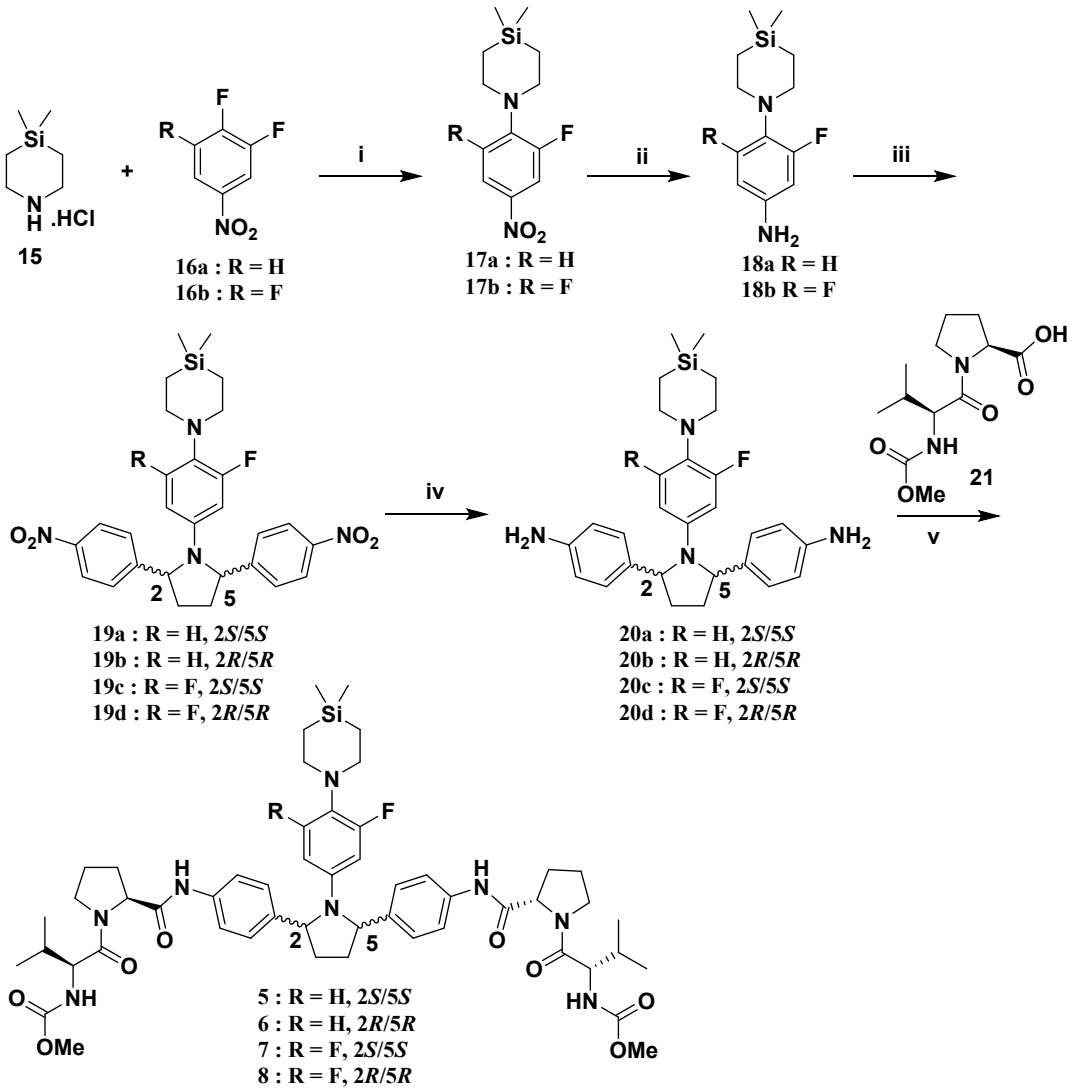
Scheme 1[a]. Preparation of Compound 2-4



[a] Reagents and conditions: EDCI, HOBt, NMM, DMF, 60 °C, 2 h, 29-47% yield.

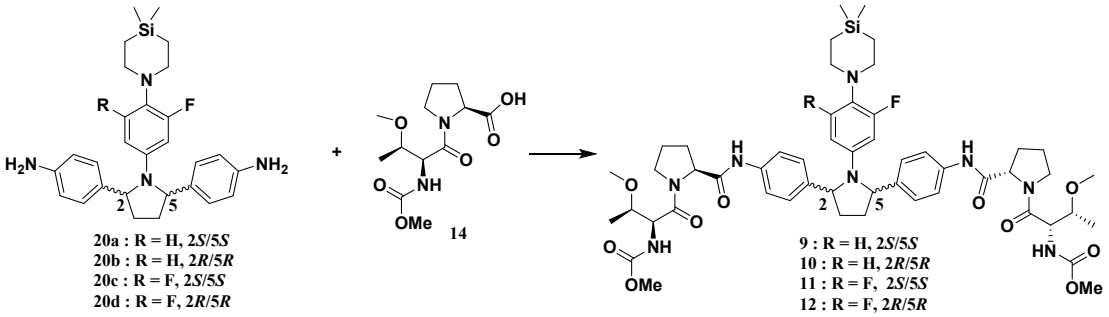
Compounds **5-8** (Table 2) were obtained using the preparation illustrated in Scheme 2. 4,4-Dimethyl-1,4-azasilinane hydrochloride **15**, 3,4-difluoronitrobenzene **16a** and 3,4,5-trifluoronitrobenzene **16b** were purchased, while (1*R*,4*R*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate and (1*S*,4*S*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate were prepared based on known procedures.[22] **16a** and **16b** was treated with **15** under alkaline condition to give nitro compounds **17a** and **17b**, respectively, which were in turn reduced by hydrogen under Pd/C to the corresponding aniline compounds **18a** and **18b**. The aniline compounds were reacted with *S*, *S*-dimesylate or *R*, *R*-dimesylate to give *R*, *R*-pyrrolidine derivatives (**19b**, **19d**) or *S*, *S*-pyrrolidine derivatives (**19a**, **19c**), respectively. Reduction of the nitro groups by catalytic hydrogenation gave di-aniline compounds (**20a**, **20b**, **20c** and **20d**). Hydrogenation with platinum (IV) oxide was the best condition to minimize stereochemical isomerization. A (methoxycarbonyl)-*L*-valyl-*L*-proline moiety was finally introduced to give **5~8**. As demonstrated in Scheme 3, compound **9~12** were also synthesized in a similar method by switching the valine and *O*-methylthreonine "caps" in the preparation.

Scheme 2[a]. Preparation of Compound 5-8



[a] Reagents and conditions: (i) triethylamine, DMF, r.t, 12 h; (ii) H_2, 10% Pd/C, THF, r.t, 12 h; (iii) (1*R*,4*R*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (**19r**) or (1*S*,4*S*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (**19s**), DMF, 60 °C, 24 h; (iv) H_2, platinum dioxide, THF, r.t, 3 h; (v) EDCI, HOBt, *N*-methylmorpholine, DMF, 55 °C, 2 h.

Scheme 3[a]. Preparation of Compound 9-12



[a] Reagents and conditions: EDCI, HOBt, *N*-methylmorpholine, DMF, 60 °C, 2 h.

CONCLUSIONS

In summary, we have disclosed several novel silicon-containing *N*-phenylpyrrolidines as HCV NS5A inhibitors. By incorporating a 4-silapiperidine group with a *O*-methylthreonine "cap" we identified compound **11** as a HCV NS5A inhibitor with significantly improved potency against the GT 6a (EC_{50} = 17 pM). This lead also showed an excellent in *vitro* profile in many other genotypes with an EC_{50} range of 0.33-3.0 pM against GT 1a, 1b, 2a, 3a, 4a and 5a. An improved potency against variant GT1a_ M28T was also observed for compound **11** when compared to ombitasvir. Compound **11** showed a good stability profile in in mouse, rat and human microsomes, and furter in *vivo* studies revealed that **11** also demonstrated an acceptable rat and dog PK profile in combination with high liver distribution in both mouse and rat. Results of the cytotoxicity test and the 14-day repeat-dose toxicity study identified the good safety profile of compound **11.** All the encouraging results suggested that compound **11** is a promising silicon-containing pan-genotype HCV NS5A inhibitor.

EXPERIMENTAL SECTION

Replicon Assays. Detailed replicon biological assays were conducted according to our previous report.[22] The methods to measure the effects of individul amino acid variants on the activity of an inhibitor in HCV replicon cell culture assays were described previously. Briefly, the resistance-associated variants in NS5A were each introduced into GT 1a-H77, GT 1b-Con1, or chimeric replicons. In transient assays, the replicon containing the variant was transfected via electroporation into a Huh-7 derived cell line. The inhibitory effect of compounds on HCV replication was determined by measuring decrease in luciferase signal. The percent inhibition of HCV replicon replication was calculated for each compound concentration and the EC_{50} value was calculated using nonlinear regression curve fitting to the 4-parameter logistic equation in the GraphPad Prism software.

Pharmacokinetic Profiles. In *vitro* PK assessment was performed using pooled mouse, rat and human liver microsomes obtained from BD Gentest. A typical standard reaction mixture 300 mL consisted of the pooled liver microsomes 0.5 mg/mL, 1 mM NADPH, 5 mM $MgCl_2$, 100

mM potassium phosphate buffer (pH 7.4) and 1 μM of test compounds. After a 5 min pre-incubation at 37 °C, the reactions were initiated by addition of NADPH and incubation proceeded for 60 min at 37 °C in a shaking metal bath. The reaction was stopped by transferring 60 mL aliquots to the tubes on ice and adding 120 mL amounts of ice-cold acetonitrile containing internal standards. Concentration of the test compounds was measured by UPLC-MS/MS.

In *vivo* PK assessment: Compound **11** was dosed in overnight fasted mice, rats or dogs via iv and po administration. Unless otherwise noted, compound **11** was formulated in 2:2:96 (v/v) Alcohol : Tween 80 : Glucose injection for single 10 mg/kg po dosing in mouse. And po formulation was diluted by Glucose injection for 2.5 times as iv formulation for single 2 mg/kg iv dosing in mouse. Compound **11** was formulated in Phosal 53 MCT / PEG-400 / Poloxamer 124 / Cremophor RH40 (40/20/20/20, by weight) for single 5 mg/kg po dosing in dog. The concentration of compounds in the plasma and liver was measured by the ultra-performance liquid chromatography-mass spectrometry analysis (UPLC-MS/MS).

Toxicity study. Cytotoxicity test was performed as previous method.[22] Repeated-dose toxicity study was carried out for 14 days. After acclimation, animals were randomly allocated to two groups, each containing five males and five females, and orally administered compound **11** at the dose of 300mg/kg or the vehicle alone once daily by gavage. Mice were killed after the 14th administration. Animals in all groups were observed daily and detailed clinical signs evident. Their body weights and food intake were monitored on day 1 of administration and thereafter twice per week. Body weights were used for calculation of the volume of the test chemical to be administered. Hematology, blood biochemistry and serum hormone measurements and histopathology was performed according to previous methods.

Chemistry. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra (500 MHz) were collected on a Bruker-500 FT NMR spectrometer with tetramethylsilane (TMS) as internal standard. Mass spectra (HRMS) were recorded on an AB SCIEX 3200 Q TRAP Mass Spectrometer. High resolution mass spectra (HRMS) were recorded on an AB SCIEX Triplet TOF 4600 Mass Spectrometer. All

final compounds were purified to > 96% purity as determined by HPLC analyse. Reverse phase HPLC purity determinations were performed on an Agilent 1260 HPLC system. Compound **14**, **15, 16a, 16b** and **21** were purchased from commercial resources. Compounds **13a**, **13b** and **13c**, (1*S*,4*S*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate, (1*R*,4*R*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate and compound **1** were prepared according to the reported methods.[22] Ombitasvir and pibrentasvir were synthesized according to the reported methods with 99% purity.[23,24]

Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(trimethylsilyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-1,2-diyl))dicarbamate (2). A mixture of **13a** (0.54 g, 1.35 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (1.16 g, 4.04 mmol), EDCI (0.77 g, 4.0 mmol), HOBt (0.55 g, 4.04 mmol) and *N*-methylmorpholine (0.41 g, 4.04mmol) in *DMF* (10 mL) was stirred at 60 °C for 2 h. The mixture was diluted with ethyl acetate (50 mL) and washed with water, brine and dried over sodium sulfate. The drying agent was filtered off, and the solvent was concentrated in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate to give compound **2** (0.36 g, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 2 H), 7.44-7.42 (m, 4 H), 7.13-7.11 (m, 4 H), 6.99-6.96 (m, 2 H), 6.33-6.31 (m, 2 H), 5.73-5.71 (m, 2 H), 5.14-5.13 (m, 2 H), 4.83-4.81 (m, 2 H), 4.69-4.67 (m, 2 H), 3.79-3.77 (m, 2 H), 3.75-3.72 (m, 4 H), 3.75-3.72 (s, 6 H), 3.34 (s, 6 H), 2.50-2.45 (m, 4 H), 2.06-2.01 (m, 8 H), 1.20 (d, *J* =6 Hz, 6 H), 0.16 (s, 6 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.0, 156.8, 144.7, 139.5, 136.6, 128.6, 126.6, 120.0, 114.0, 62.7, 60.8, 60.4, 57.4, 55.5, 52.4, 48.0, 32.3, 27.6, 24.9, 14.7, 1.92, 1.32; MS (ESI) m/z 964.5 $(M+Na)^+$; HPLC: 98.2% purity; HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{49}H_{67}N_7O_{10}Si$: 942.4797, found 942.4854.

Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(triethylsilyl)phenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-1,2-diyl))dicarbamate (3). A mixture of **13b** (0.60g, 1.35 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (1.23 g, 4.05 mmol), EDCI (0.63 g, 4.05 mmol), HOBt (0.54 g, 4.05 mmol) and *N*-methylmorpholine (0.68 g, 6.75 mmol) in DMF (10 mL) was stirred at 60 °C for 4 h. The mixture was poured into water (50 mL), extracted with

dichlormethane (50 mL× 3), and the combined organic layers were dried with Mg_2SO_4. The drying agent was filtered off, and the solvent was concentrated in vacuo. The residue was purified on C18 column (DAC 100*250mm,YMC Triart Prep C18-S), eluting with a mixture of 82% acetonitril and 18% water to give compound **3** (0.43g, 32.4%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.93(s, 2H), 7.51 (d, *J* = 8.5 Hz, 4 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 7.15 (d, *J* = 8.5 Hz, 4 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 6.28(d, *J* = 8.5 Hz, 2 H), 5.19 (d, *J* = 6.5 Hz, 2 H), 4.43 (dd, *J* = 5.0 Hz, 8.0 Hz, 2 H), 4.27 (d, *J* = 7.5 Hz, 2 H), 3.68 (m, 2 H), 3.54 (m, 2 H), 3.49 (s, 6 H), 3.47 (m, 2 H), 3.26 (s, 6 H), 2.46 (m, 2 H), 2.07 (m, 2 H), 1.99 (d, *J* = 6.5 Hz, 2 H),1.90 (m, 2 H), 1.88 (t, *J* = 5.0 Hz, 2 H), 1.63 (d, *J* = 5.5 Hz, 2 H), 1.15 (d, *J* = 6.0 Hz, 6 H), 0.83 (t, *J* = 8.0 Hz, 9 H), 0.60 (q, *J* =8.0 Hz, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.6, 157.1, 145.7, 138.1, 134.8, 126.7, 119.6, 113.8, 76.8, 62.3, 60.6, 57.4, 56.6, 51.9, 47.8, 32.4, 29.9, 25.1, 15.9, 7.9, 3.5, 1.6; MS (ESI) m/z: 1006.5 $[M + Na]^+$; HPLC: 99.9% purity; HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{52}H_{73}N_7O_{10}Si$: 984.5266, found 984.5347.

Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(tert-butyldimethylsilyl)phenyl) pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-1,2-diyl))dicarbamate (4). A mixture of **13c** (0.50g, 1.1 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (0.98 g, 3.3 mmol), EDCI (0.65 g, 3.3 mmol), HOBt (0.46 g, 3.3 mmol) and *N*-methylmorpholine (0.34 g, 3.3mmol) in *DMF* (10 mL) was stirred at 60 °C for 2 h. The mixture was diluted with ethyl acetate (50 mL) and washed with water, brine and dried over sodium sulfate. The drying agent was filtered off, and the solvent was concentrated in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate and C18 column (DAC 100*250mm,YMC Triart Prep C18-S), eluting with a mixture of 82% acetonitril and 18% water to give compound **4** (0.32 g, 29%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (s, 2 H), 7.43 (d, *J* = 8.0 Hz, 4 H), 7.12 – 7.09 (m, 6 H), 6.29 (d, *J* = 8.0 Hz, 2 H), 5.72(d, *J* = 7.5 Hz, 2H), 5.12 (d, *J* = 5.0 Hz, 2 H), 4.81 (s, 2 H), 4.67 (s, 2 H), 3.78-3.68 (m, 10 H), 3.40-3.33 (m, 6 H), 2.49-2.44 (m, 4 H), 2.09-2.03 (m, 8 H), 1.74 (d, *J* = 4.5 Hz, 2 H), 1.20 (d, *J* = 4.0 Hz, 6 H), 0.78 (s, 9 H), 0.13 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 169.0, 156.8, 145.2, 139.7, 136.6, 135.0, 126.5, 121.9, 120.0, 113.3, 62.6, 60.8, 57.4, 55.5, 52.4, 48.0, 32.2, 27.5, 26.6, 24.9, 17.1, 14.7, 14.2, -6.1; MS (ESI) m/z 1006.5 $(M+Na)^+$; HPLC: 98.4% purity; HRMS (ESI) m/z calcd for $[M+H]^+$

$C_{52}H_{73}N_7O_{10}Si$: 984.5266, found 984.5347.

1-(2-fluoro-4-nitrophenyl)-4,4-dimethyl-1,4-azasilinane (17a). To a suspension of 4,4-dimethyl-1,4-azasilinane hydrochloride (**15**, 19.3g, 105.8mmol) in *DMF* (200mL) was added triethylamine (48.2 g, 349.1 mmol) dropwise at room temperature and stirred for 10 min. Then，3,4-difluoronitrobenzene (16.8 g, 105.8 mmol) was added dropwise at 0 °C, and the mixture was stirred at room temperature overnight. The reaction solution was poured into water (1L) and stirred for 10 min. The solid was collected by filtration and washed with water to give compound **17a** as a yellow solid (28.1g, 99.0%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91-7.95 (m, 2 H), 7.10 (d, J = 9.5 Hz, 1 H), 3.71 (t, J = 6.3 Hz, 4 H), 0.86 (t, J = 6.3 Hz, 4 H), 0.10 (s, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.5, 144.3, 137.2, 122.1, 117.0, 113.3, 49.1, 13.7, -2.4; MS (ESI) m/z 269.1 $[M + H]^+$.

4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluoroaniline (18a). To a solution of 1-(2-fluoro-4-nitrophenyl)-4,4-dimethyl-1,4-azasilinane (**17a,** 28.0 g, 104.3 mmol) in THF (200 mL) was added 10% palladium on carbon (5.0 g). The reaction container was flushed with N_2, and the mixture was stirred under 1 atm H_2 overnight. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a crude product that was purified by stirring in petroleum ether. The title compound was obtained as a white solid (22.1 g, 88.9%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.75-6.79 (m, 1H), 6.25-6.31 (m, 2H), 4.90 (s, 2H), 3.04-3.06 (m, 4H), 0.79-0.81(m, 4H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.8, 145.5, 131.8, 122.5, 109.9, 102.3, 52.2, 15.1, -2.4; MS (ESI) m/z 239.1 $[M + H]^+$.

1-(4-((2S,5S)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)-4,4-dimethyl-1,4-azasilinane (19a). The mixture of (1*R*,4*R*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (1.5 g, 3.1 mmol) and 4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluoroaniline (**18a**, 7.32 g, 31 mmol) in *DMF* (15 mL) was stirred at 60 °C for 24 h. The reaction solution was poured into 2 N aq HCl (100 mL) and stirred for 10min. The solid was collected by filtration and dissolved in dichloromethane (50 mL). The mixture was washed with water and dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 10% ethyl acetate in petrol to give **19a** as a yellow solid (1.2 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 4 H), 7.36 (d, J = 8.0 Hz, 4 H), 6.71 (s, 1 H), 6.00 (m, 2 H), 5.29 (s, 2 H), 3.11 (s, 2 H), 2.63

(s, 2 H), 1.96 (s, 2 H), 1.58 (m, 2 H), 0.85 (m, 4 H), 0.07 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7, 126.8, 124.4, 63.4, 32.1, 27.1, 11.1, -3.0; MS (ESI) m/z: 535.1 $[M + H]^+$.

4,4'-((2*S*,5*S*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)pyrrolidine-2,5-diyl)dianiline (20a). To a solution of **19a** (1.67 g, 3.13 mmol) in THF (20 mL) was added platinum dioxide (0.7 g, 3.13 mmol). The reaction container was flushed with N_2, and the mixture was stirred under 1 atm H_2 for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-20% ethyl acetate in petrol to give **20a** as a white solid (1.2 g, 81%). ^{1}H NMR (500 MHz , $CDCl_3$): δ 6.95 (d, *J* = 8.0 Hz, 4 H), 6.64 (d, *J* = 8.5 Hz, 4 H), 6.06 (m, 3 H), 4.98 (d, *J* = 7.0 Hz, 2 H), 3.12 (s, 2 H), 2.50 (s, 2 H), 1.75 (d, *J* = 5.0 Hz, 2 H), 1.26 (m, 2 H), 0.88 (m, 4 H), 0.12 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.7, 147.6, 137.3, 131.4, 126.9, 120.7, 115.5, 114.4, 108.1, 107.9, 62.6, 52.1, 50.9, 32.9, 15.1, 14.5, -2.4, -2.5; MS (ESI) m/z 475.1 $[M + H]^+$.

Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene)) bis(azanediyl))bis(carbonyl)) bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-1,2-diyl))dicarbamate (9). The mixture of **20a** (0.53 g, 1.12 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (0.97 g, 3.35 mmol), EDCI (0.64 g, 3.35 mmol), HOBt (0.45 g, 3.35 mmol) and *N*-methylmorpholine (0.68 g, 6.75 mmol) in *DMF* (10 mL) was stirred at 55 °C for 12 h. The mixture was poured into water (50 mL). The solid was collected by filtration and dissolved in dichloromethane (50 mL). The mixture was washed with brine and dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0–66% ethyl acetate in petrol to give **9** as a white solid (0.5 g, 44%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 9.93 (s, 2 H), 7.50 (d, *J* = 8.5 Hz, 4 H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 4 H), 6.71 (m, 1 H), 5.96 (m, 2 H), 5.13 (d, *J* = 6.0 Hz, 4H), 4.44 (m, 2 H), 4.28 (m, 2 H), 3.82 (m, 2 H), 3.65 (m, 2 H), 3.54 (s, 6 H), 3.48 (m, 2 H), 3.26 (s, 6 H), 2.98 (m, 4 H), 2.45 (m, 2 H), 2.16 (m, 2 H), 2.09 (m, 2 H), 1.89 (m, 4 H), 1.62 (d, *J* = 5.5 Hz, 2 H), 1.14 (d, *J* = 6.0 Hz, 6 H), 0.73 (t, *J* = 5.5 Hz, 2 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 169.2, 157.1, 139.1, 138.1, 126.7, 119.7, 76.8, 62.6, 60.7, 57.4, 56.6, 52.0, 47.8, 32.6, 29.2, 25.1, 22.6, 16.0, 15.0, 14.4, -2.5; MS (ESI) m/z

1015.7[M + H]$^+$; HPLC: 96.0% purity; HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{52}H_{71}FN_8O_{10}Si$: 1015.5124, found1015.5170.

1-(2,6-difluoro-4-nitrophenyl)-4,4-dimethyl-1,4-azasilinane (17b). To a suspension of 4,4-dimethyl-1,4-azasilinane hydrochloride (20.6g, 124.4 mmo) in *DMF* (200mL) was added triethylamine (51.6g, 3373.0mmol) dropwise at room temperature and stirred for 10 min. Then 3,4,5-trifluoronitrobenzene (20.0 g, 113.0 mmol) was added dropwise at 0 °C and the mixture was stirred at room temperature overnight. The reaction solution was poured into water (1L) and stirred for 10min. The solid was collected by filtration and washed with water to give compound **17b** as a yellow solid (31.2 g, 96.4%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (dd, J = 10.0 Hz, 1.0 Hz, 2 H), 3.49-3.51(m, 4H), 0.85-0.88(m, 4 H), 0.12 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.8, 153.9, 136.6, 109.4, 50.8, 15.1, -2.6; MS (ESI) m/z 287.1 [M + H]$^+$.

4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluoroaniline (18b). To a solution of 1-(2,6-difluoro-4-nitrophenyl)-4,4-dimethyl-1,4-azasilinane (31.0 g, 108.3 mmol) in THF (200 mL) was added 10% palladium on carbon (5.0 g). The reaction container was flushed with N_2, and the mixture was stirred under 1 atm H_2 overnight. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a crude product that was purified by stirring in petroleum ether. The title compound was obtained as a white solid (23.4 g, 84.3%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.10-6.12 (m, 2 H), 5.34 (s, 2 H), 3.10-3.13 (m, 4 H), 0.77-0.79 (m, 4 H), 0.08 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d) δ 161.2, 159.3, 118.9, 97.3, 52.4, 15.7, -2.4; MS (ESI) m/z 257.1 [M + H]$^+$.

1-(4-((2*R*,5*R*)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)-2-fluorophenyl)-4,4-dimethyl-1,4-azasilinane (19b). The mixture of (1*S*,4*S*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (2.5 g, 5.1 mmol) and 4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluoroaniline (9.8 g, 40.9 mmol) in *DMF* (20 mL) was stirred at 60 °C for 24 h. The reaction solution was poured into 2 N aq HCl (100 mL) and stirred for 10min. The solid was collected by filtration and dissolved in dichloromethane (50 mL). The mixture was washed with water and dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 10% ethyl acetate in petrol to give **19b** as a brown solid (1.5 g, 53.6%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 8.21(d, J = 5.5 Hz, 4 H), 7.37 (d, J = 6.5 Hz, 4 H), 6.74 (s, 1 H), 5.99 (m, 2 H), 5.28 (s, 2 H), 3.11 (s, 2

H), 2.59 (s, 2 H), 1.89 (s, 2 H), 1.58 (s, 2 H), 0.85 (s, 4 H), 0.07 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.4, 127.0, 124.1, 121.8, 109.1, 62.9, 51.9, 32.2, 14.8, -3.1; MS (ESI) m/z: 535.1 $[M + H]^+$.

4,4'-((2*R*,5*R*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)pyrrolidine-2,5-diyl)dianiline (20b). To a solution of **19b** (1.5 g, 2.72 mmol) in THF (20 mL) was added platinum dioxide (0.3 g, 1.36 mmol). The reaction container was flushed with N_2, and the mixture was stirred under 1 atm H_2 for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a crude product that was purified by by column chromatography on silica gel using a solvent gradient of 0-20% ethyl acetate in petrol to give **20b** as a white solid (0.6 g, 46.5%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95(d, *J* = 8.0 Hz, 4 H), 6.64(d, *J* = 8.0 Hz, 4 H), 6.05 (m, 3 H), 4.98 (s, 2 H), 3.11 (s, 4 H), 2.49 (s, 2 H), 1.74 (s, 2 H), 0.85 (m, 4 H), 0.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 127.0, 115.3, 102.2, 62.9, 32.6, 29.7, -3.0; MS (ESI) m/z: 475.1 $[M + H]^+$.

Dimethyl ((2S,2'S,3R,3'R)-((2S,2'S)-(((((2R,5R)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene)) bis(azanediyl))bis(carbonyl))bis (pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-1,2-diyl))dicarbamate (10). The mixture of **20b** (0.55 g, 1.2 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (1.0 g, 3.5 mmol), EDCI (0.67 g, 3.5 mmol), HOBt (0.5 g, 3.5 mmol) and *N*-methylmorpholine (0.71 g, 7 mmol) in *DMF* (10 mL) was stirred at 55 °C for 12 h. The mixture was poured into water (50 mL). The solid was collected by filtration and dissolved in dichloromethane (50 mL). The mixture was washed with brine and dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0–66% ethyl acetate in petrol to give **10** as a white solid (0.55 g, 46.6%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (s, 2 H), 7.51 (d, *J* = 8.5 Hz, 4 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 4 H), 6.70 (m, 1 H), 5.96 (m, 2 H), 5.13 (d, *J* = 6.0 Hz, 2 H), 4.44 (dd, *J* = 5.0 Hz, 8.0 Hz, 2 H), 4.28 (t, *J* = 7.5 Hz, 2 H), 3.69 (m, 2 H), 3.54 (m, 2 H), 3.49 (s, 6 H), 3.47 (d, *J* = 6.5 Hz, 2 H), 3.25 (s, 6 H), 2.98 (m, 4 H), 2.44 (m, 2 H), 2.15 (m, 2 H), 2.00 (d, *J* = 6.0 Hz, 2 H), 1.89 (m, 4 H), 1.62 (d, *J* = 5.5 Hz, 2 H), 1.13 (d, *J* = 6.5 Hz, 6 H), 0.74 (t, *J* = 6.0 Hz, 4 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.6, 169.2, 157.2, 155.3, 141.7, 139.1, 138.1, 131.1, 126.7, 122.1,

119.6, 109.5, 101.9, 76.8, 62.5, 60.7, 57.5, 56.6, 52.0, 47.8, 32.6, 29.9, 25.1, 16.0, 15.0, 1.6, -2.5; MS (ESI) m/z: 1037.50 $[M + Na]^+$; HPLC: 97.9% purity; HRMS (ESI)m/z calcd for $[M+H]^+$ $C_{52}H_{71}FN_8O_{10}Si$: 1015.5124, found 1015.5170.

1-(4-((2*S*,5*S*)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-dimethyl-1,4-azasilinane (19c). The mixture of (1*R*,4*R*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (1.5 g, 3.0 mmol) and 4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluoroaniline (7.88 g, 30.71 mmol) in *DMF* (10 mL) was stirred at 60 °C for 24 h. The reaction solution was poured into 2 N aq HCl (200 mL) and stirred for 10min. The solid was collected by filtration and dissolved in dichloromethane (50 mL). The mixture was washed with water and dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 10% ethyl acetate in petrol to give **19c** as a yellow solid (1.2 g, 70.6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 4 H), 7.37 (d, *J* = 8.5 Hz, 4 H), 5.78 (d, *J* = 11.5 Hz, 2 H), 5.25 (d, *J* = 6.5 Hz, 2 H), 3.29 (s, 4 H), 2.60 (s, 2 H), 2.06 (s, 2 H), 0.97 (s, 4 H), 0.10 (s, 6 H); ^{13}C NMR(125MHz, $CDCl_3$): δ 149.7, 147.4, 126.8, 124.3, 97.9, 97.7, 63.0, 53.1, 32.1, 14.6, -3.2; MS (ESI) m/z: 553.2 $[M+H]^+$.

4,4'-((2*S*,5*S*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)dianiline (20c). To a solution of **19c** (2.1 g, 3.8 mmol) in THF (20 mL) was added platinum dioxide (0.43 g, 1.9 mmol). The reaction container was flushed with N_2, and the mixture was stirred under 1 atm H_2 for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a crude product that was purified by by column chromatography on silica gel using a solvent gradient of 0-20% ethyl acetate in petrol to give **20c** as a white solid (0.72 g, 40%). ^{1}H NMR (500 MHz , $CDCl_3$) δ 6.94 (d, *J* = 8.0 Hz, 4 H), 6.65 (d, *J* = 8.5 Hz, 4H), 5.82 (d, *J* = 12.0 Hz, 2 H), 4.95 (d, *J* = 5.5 Hz,2 H), 3.17 (s, 4 H), 2.49 (s, 2 H), 1.73(d, *J* = 5.5 Hz, 2 H), 0.82 (s,4 H), 0.07 (s, 6 H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 160.8, 158.9, 145.0, 142.6, 133.2, 126.9, 115.4, 97.3, 63.0, 52.3, 32.6, 15.5, 14.1, -3.0; MS (ESI) m/z : 493.1 $[M + H]^+$.

Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-

oxobutane-1,2-diyl))dicarbamate (11). The mixture of **20c** (0.50 g, 1.02 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (0.9 g, 3.05 mmol), EDCI (0.58 g, 3.05 mmol), HOBt (0.42 g, 3.05 mmol) and *N*-methylmorpholine (0.62 g, 6.1 mmol) in *DMF* (10 mL) was stirred at 55 °C for 12 h. The mixture was poured into water (50 mL). The solid was collected by filtration and dissolved in dichloromethane (50 mL). The mixture was washed with brine and dried over sodium sulfate, filtered, and concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0–66% ethyl acetate in petrol to give **11** as a white solid (0.6 g, 57.1%). ^{1}H NMR (500 MHz , DMSO-d_6) δ 9.95 (s, 2 H), 7.52 (d, J = 8.5 Hz, 4 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.14 (d, J = 8.5 Hz, 4 H), 5.81 (d, J = 12.5 Hz, 2 H), 5.15 (d, J = 6.0 Hz, 2 H), 4.44 (dd, J = 4.5 Hz, 8.0 Hz, 2 H), 4.28 (d, J = 8.0 Hz, 2 H), 3.83 (m, 2 H), 3.68 (d, J = 7.0 Hz, 2 H), 3.54 (s, 6 H), 3.49 (t, J = 6.5 Hz, 2 H), 3.23 (s, 6 H), 3.04 (t, J = 5.5 Hz, 4 H), 2.45 (m, 2 H), 2.16 (m, 2 H), 2.00 (d, J = 6.0 Hz, 2 H), 1.90 (m, 4 H), 1.62 (d, J = 5.5 Hz, 2 H), 1.15 (d, J = 6.0 Hz, 6 H), 0.71(t, J = 6.0 Hz, 4 H), 0.04(s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.6, 169.2, 160.7, 158.8, 157.1, 142.8, 138.5, 126.7, 119.7, 118.7, 97.7, 76.8, 62.6, 60.7, 57.4, 56.6, 52.3, 47.8, 32.5, 29.9, 25.1, 16.0; MS (ESI) m/z: 1055.3 $[M + Na]^+$; HPLC: 98.2% purity; HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{52}H_{70}F_2N_8O_{10}Si$: 1033.5030, found 1033.5068.

1-(4-((2*R*,5*R*)-2,5-bis(4-nitrophenyl)pyrrolidin-1-yl)-2,6-difluorophenyl)-4,4-dimethyl-1,4-azasilinane (19d). The mixture of (1*S*,4*S*)-1,4-bis(4-nitrophenyl)butane-1,4-diyl dimethanesulfonate (2.0 g, 4.09 mmol) and 4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluoroaniline (8.4 g, 32.75 mmol) in *DMF* (20 mL) was stirred at 60 °C for 24 h. The reaction solution was poured into 2 N aq HCl (50 mL) and stirred for 10min. The mixture was partitioned between water and ethyl acetate (20 mL × 2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using a solvent gradient of 10% ethyl acetate in petrol to give **19d** as a yellow solid (2.0 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31-8.24 (m, 4 H), 7.60-7.58 (m, 2 H), 7.38-7.36 (m, 4 H), 5.76 (d, J = 11 Hz, 2 H), 3.30-3.20 (m, 4 H), 2.70-2.60 (m, 3 H), 2.03-2.02 (m, 1 H), 0.92-0.90 (m, 4 H), 0.09 (s, 6 H); MS (ESI) m/z 553.2 $[M+H]^+$.

4,4'-((2*R*,5*R*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)dianiline (20d). To a solution of **19d** (2.0 g, 3.62 mmol) in THF (20 mL) was added

platinum dioxide (0.82 g, 3.62 mmol). The reaction container was flushed with N_2, and the mixture was stirred under 1 atm H_2 for 3 h. The mixture was filtered through Celite, and the filtrate was concentrated under vacuum to give a crude product that was purified by column chromatography on silica gel using a solvent gradient of 0-20% ethyl acetate in petrol to give **20c** as a white solid (0.95 g, 53%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8 Hz, 4 H), 6.66 (d, *J* = 8 Hz, 4 H), 5.82 (d, *J* = 11.5 Hz, 2 H), 4.95 (d, *J* = 6 Hz, 2 H), 3.17-3.15 (m, 4 H), 2.51-2.47 (m, 2 H), 1.74-1.72 (m, 2 H), 0.83-0.81 (m, 4 H), 0.08 (s, 6 H); MS(ESI) m/z 493.2 $[M+H]^+$.

Dimethyl ((2*S*,2'*S*,3*R*,3'*R*)-((2*S*,2'*S*)-(((((2*R*,5*R*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl)) bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-1,2-diyl))dicarbamate (12). The mixture of **20d** (0.40 g, 0.81 mmol), *N*-(methoxycarbonyl)-*O*-methyl-*L*-threonyl-*L*-proline (0.70 g, 2.44 mmol), EDCI (0.47 g, 2.44 mmol), HOBt (0.33g, 3.44 mmol) and *N*-methylmorpholine (0.41 g, 4.05mmol) in *DMF* (10 mL) was stirred at 60 °C for 1 h. The mixture was poured into water (30 mL). The mixture was partitioned between water and ethyl acetate (20 mL × 2). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel using a solvent gradient of 66% ethyl acetate in petrol to give **12** as a white solid (0.32g, 38%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.94 (s, 2 H), 7.51 (d, *J* = 8.5 Hz, 4 H), 7.29 (d, *J* = 7.5 Hz, 2 H), 7.13 (d, *J* = 8.5 Hz, 4 H), 6.70 (m, 1 H), 5.96 (m, 2 H), 5.13 (d, *J* = 6.0 Hz, 2 H), 4.44 (dd, *J* = 5.0 Hz, 8.0 Hz, 2 H), 4.28 (t, *J* = 7.5 Hz, 2 H), .3.69 (m, 2 H), 3.54 (m, 2 H), 3.49 (s, 6 H), 3.47 (d, *J* = 6.5 Hz, 2 H), 3.25 (s, 6 H), 2.98 (m, 4 H), 2.44 (m, 2 H), 2.15 (m, 2 H), 2.00 (d, *J* = 6.0 Hz, 2 H), 1.89 (m, 4 H), 1.62 (d, *J* = 5.5 Hz, 2 H), 1.13 (d, *J* = 6.5 Hz, 6 H), 0.73 (t, *J* = 6.0 Hz, 4 H), 0.04 (s, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.6, 169.2, 157.2, 155.3, 141.7, 139.1, 138.1, 131.1, 126.7, 122.1, 119.6, 109.5, 101.9, 76.8, 62.5, 60.6, 57.5, 56.6, 52.0, 47.8, 32.6, 29.9, 25.1, 16.0, 15.0, 1.6, -2.5; MS (ESI) m/z: 1055.50 $[M + Na]^+$; HPLC: 96.73% purity; HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{52}H_{70}F_2N_8O_{10}Si$: 1033.5030, found 1033.5134.

Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis

(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (5). Prepared from **20a** and (methoxycarbonyl)-*L*-valyl-*L*-proline (**21**) in the same method as **9**. ^{1}H NMR (500 MHz , DMSO-d_6) δ 9.97 (s, 2 H), 7.50 (d, J = 8.5 Hz, 4 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 8.5 Hz, 4 H), 6.71-6.72 (m, 1 H), 5.95-6.05 (m, 2 H), 5.12 (d, J = 6.5 Hz, 2 H), 4.44 -4.43 (m, 2 H), 4.04-4.10 (m, 2 H), 3.82-3.75 (m, 2 H), 3.65-3.65 (m, 2 H), 3.53 (s, 6 H), 3.41-3.31 (m, 2 H), 2.97-2.98 (m, 4 H), 2.44-2.48 (m, 2 H), 2.16-2.14 (m, 2 H), 2.09-1.87 (m, 8 H), 1.62 (d, J = 5.5 Hz, 2 H), 0.95-0.86 (m, 12 H), 0.73 (t, J = 6.3 Hz, 2 H), 0.04 (s, 6 H); HPLC: 99.8% purity; HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{52}H_{71}FN_8O_8Si$: 983.5148; found 983.5158.

Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-(((((2*R*,5*R*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3-fluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis (pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (6). Prepared from **20b** and (methoxycarbonyl)-*L*-valyl-*L*-proline (**21**) in the same method as **10**. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.98 (s, 2 H), 7.51 (d, J = 8.0 Hz, 4 H), 7.27 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 8.0 Hz, 4 H), 5.89-6.09 (m, 3 H), 5.15-5.21 (m, 2 H), 4.44 (dd, J = 5.0 Hz, 8.0 Hz, 2 H), 4.04 (t, J = 8.5 Hz, 2 H), 3.75-3.85 (m, 2 H), 3.63-3.69 (m, 2 H), 3.63-3.58 (m, 3 H), 3.53 (s, 6 H), 3.10-2.95 (m, 1 H), 2.51-2.44 (m, 2 H), 2.15-1.86 (m, 10 H), 1.65-1.55 (m, 2 H), 0.94-0.86 (m, 16 H), 0.06 (s, 6 H); **HPLC: 99.7% purity;** HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{52}H_{71}FN_8O_8Si$: 983.5148; found 983.5143.

Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-(((((2*S*,5*S*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis (pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (7). Prepared from **20c** and (methoxycarbonyl)-*L*-valyl-*L*-proline (**21**) in the same method as **11**. ^{1}H NMR (500 MHz , DMSO-d_6) δ 9.98 (s, 2 H), 7.52 (d, J = 8.5 Hz, 4 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 8.5 Hz, 4 H), 5.95-6.05 (m, 2 H), 5.15 (d, J = 6.5 Hz, 2 H), 4.45 -4.43 (m, 2 H), 4.11-4.07 (m, 2 H), 3.82-3.75 (m, 2 H), 3.65-3.63 (m, 2 H), 3.53 (s, 6 H), 3.41-3.31 (m, 2 H), 2.97-2.98 (m, 4 H), 2.44-2.48 (m, 2 H), 2.16-2.14 (m, 2 H), 2.09-1.87 (m, 8 H), 1.62 (d, J = 5.5 Hz, 2 H), 0.95-0.86 (m, 12 H), 0.73 (t, J = 6.3 Hz, 2 H), 0.04 (s, 6 H); HPLC: 99.6% purity; HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{52}H_{70}F_2N_8O_8Si$:1001.5054; found 1001.5092.

Dimethyl ((2*S*,2'*S*)-((2*S*,2'*S*)-(((((2*R*,5*R*)-1-(4-(4,4-dimethyl-1,4-azasilinan-1-yl)-3,5-difluorophenyl)pyrrolidine-2,5-diyl)bis(4,1-phenylene))bis(azanediyl))bis(carbonyl))bis

(pyrrolidine-2,1-diyl))bis(3-methyl-1-oxobutane-1,2-diyl))dicarbamate (8). Prepared from **20d** and (methoxycarbonyl)-*L*-valyl-*L*-proline (**21**) in the same method as **12**. ^{1}H NMR (500 MHz , DMSO-d_6) δ 9.99 (s, 2 H), 7.53 (d, J = 8.5 Hz, 4 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.13 (d, J = 8.5 Hz, 4 H), 5.80 (d, J = 7.0 Hz, 2 H), 5.15 (d, J = 6.5 Hz, 2 H), 4.45-4.43 (m, 2 H), 4.04 (t, J = 8.5 Hz, 2 H), 3.82-3.75 (m, 2 H), 3.65-3.63 (m, 2 H), 3.53 (s, 6 H), 3.12-3.02 (m, 6 H), 2.97-2.98 (m, 4 H), 2.20-1.87 (m, 14 H), 1.62 (d, J = 5.5 Hz, 2 H), 0.94-0.84 (m, 12 H), 0.73 (t, J = 6.3 Hz, 2 H), 0.04 (s, 6 H); HPLC: 99.4% purity; HRMS (ESI) m/z: calcd for $[M+H]^+$ $C_{52}H_{70}F_2N_8O_8Si$:1001.5054; found 1001.5083.

ASSOCIATED CONTENT

The Supporting Information is avilable free of charge on the ACS Publications website at DOI: XXXXXX

Molecular Formula Strings, HPLC spectrum of targeted compounds, ^{1}H and ^{13}C NMR spectra for compound **11**, Body and organ weights, Hematology data for mouse orally treated with **11** for 14 days, blood chemistry data for mouse orally treated with **11** for 14 days.

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ABBREVIATIONS USED

GT, genotype; PK, pharmacokinetics; AUC, area under the curve; CLp, systemic clearance; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; HOBt, 1-hydroxybenzotriazole; NMM, *N*-methylmorpholine; DMF, *N*,*N*-dimethylformamide; THF, tetrahydrofuran.

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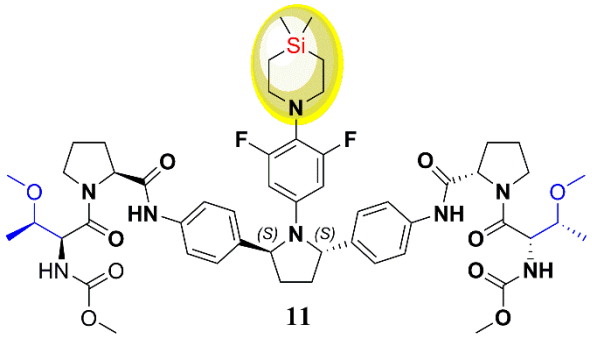
TABLE OF CONTENTS GRAPHIC



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- Silicon-containing NS5A inhibitor
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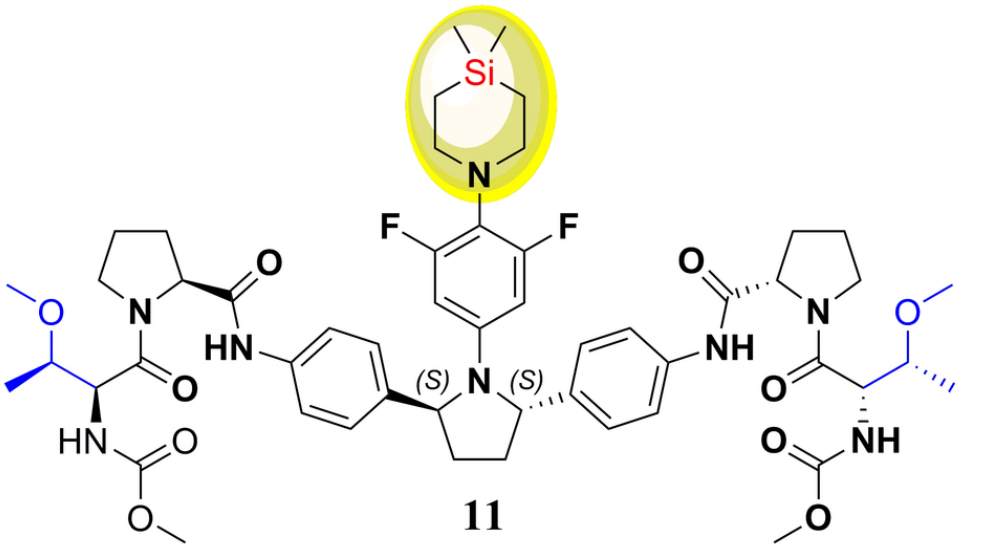
- Improved activity against GT6a HCV
- High liver distribution



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