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HCV NS5A replication complex inhibitors. Part 3[1]: discovery of potent analogs with distinct core topologies

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ABSTRACT

In a recent disclosure,[1] we described the discovery of dimeric, prolinamide-based NS5A replication complex inhibitors exhibiting excellent potency towards an HCV genotype 1b replicon. That disclosure dealt with the SAR exploration of the peripheral region of our lead chemotype, and herein is described the SAR uncovered from a complementary effort that focused on the central core region. From this effort, the contribution of the core region to the overall topology of the pharmacophore, primarily vector orientation and planarity, was determined, with a set of analogs exhibiting <10 nM EC_{50} in a genotype 1b replicon assay.

Hepatitis C virus (HCV) infection is a worldwide health problem that affects an estimated 170 million individuals and more than 4 million Americans.[2] In about 80% of the patients, the disease progresses to a chronic state that in many cases is asymptomatic, but without treatment places the patients at risk of developing more serious liver disease. Liver failure resulting from chronic HCV infection is now considered to be the leading cause of liver transplantations in the US.[2] HCV is an exceptionally heterogeneous virus and has been classified into six major genotypes and with a total of over 100 subtypes.[3] This, coupled with the high replication rate of the virus and its error-prone replicase enzyme, provide possible explanations for the lack of protective immunity from HCV infection.[4] For many years, the standard of care has been a combination of pegylated interferon-α (IFN-α) and ribavarin. This treatment is not only poorly tolerated but also less effective toward genotype 1, the most prevalent strain in Europe, the USA and Asia, with cure rates of only 40–50%.[5]

The recent addition of protease inhibitors to this regimen greatly improved the response rates (67–75% among genotype 1 treatment-naïve patients) although the tolerability of these therapies is less than desirable.[6] Combinations of direct acting antiviral agents (DAAs) have shown the potential for eliminating interferon from current therapies and, therefore, distinct classes of inhibitors with orthogonal resistance profiles are currently being explored in an effort to identify the optimal compounds for use in combination therapy.[7]

NS5A appears to play an important function in regulating HCV replication and, although its precise role is largely unknown, it has been implicated in HCV resistance to IFN-α therapy.[8] The NS5A protein exists in multiple phosphorylation states, designated p56 (basally phosphorylated) and p58 (hyperphosphorylated), and though some NS5A adaptive mutations affect the phosphorylation state of NS5A in HCV replicons, a definitive understanding of the role of NS5A phosphorylation in replication has not been established.[9] NS5A is comprised of three domains and the crystal structure of the well-conserved amino-terminal domain I has been determined by two independent groups.[10] Both structures are that of a dimer, but their mode of dimerization is different, a phenomenon of unknown consequence. However, biochemical studies have provided further evidence for the formation of dimers, thereby corroborating the crystallographic data.[11]

Clinical proof-of-concept of NS5A as a viable target was obtained with the potent HCV inhibitor daclatasvir (**1**).[12] Herein we describe the initial investigation of the core region of the stilbene lead (**2**),[13] showing that subtle changes to planarity, vectorial

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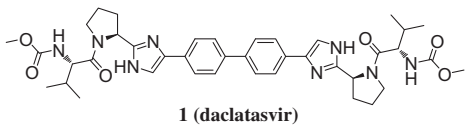
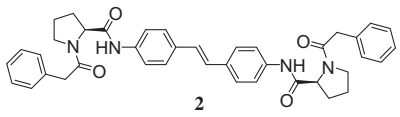
orientation and polarity in this part of the molecule contribute in an important way to the ability of these molecules to inhibit HCV replication.



1 (daclatasvir)



2

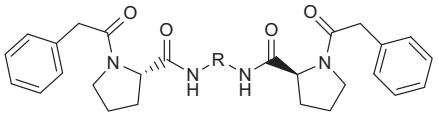
During sample handling, it was observed that **2** was susceptible to *cis*/*trans* isomerization when stored in DMSO under ambient light. Although the exact *cis*/*trans* composition under the assay conditions was not monitored, an independent synthesis and profiling of the *cis* isomer **3** revealed a 140-fold reduction in potency, suggesting a strong preference for the *trans* isomer (Table 1).[14] In an effort to avoid isomerization issues, we prepared a series of olefin isosteres of fixed geometries that sought to approximate both the vectorial orientation and molecular length of **2** and **3** (see examples **4**–**12** in Table 1). From this series, the *trans*-cyclopropyl derivative **4**, although weaker than the stilbene analog **2**, was 140-fold more potent than its *cis*-cyclopropyl counterpart (**5**), consistent with the relative potency observed between the *cis* and *trans*-stilbenes **2** and **3**. Replacement of the *trans* olefin with an amide linkage yielded compound **6**, with an EC_{50} of 11 nM, N-methylation (**7**) of which resulted in a significant potency loss (568-fold). These results agree with structural studies by Shudo et al. that show that unsubstituted benzanilides prefer to exist in a *transoid* conformation, whereas *N*-methyl benzanilides exist in a predominantly *cisoid* conformation, stabilized by favorable π–π interactions between the phenyl rings.[15,16]

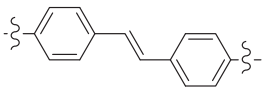
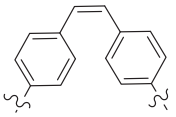
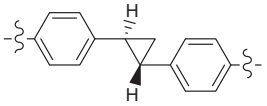
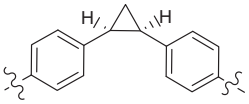
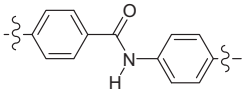
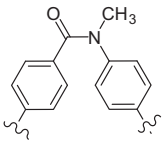
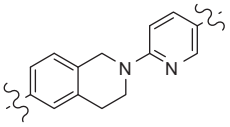
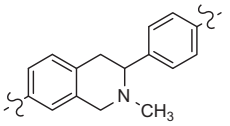
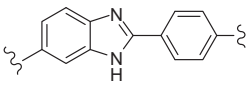
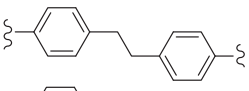
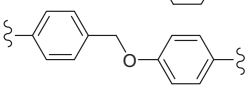
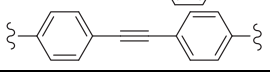
To further probe the association of the *trans* geometry with enhanced potency, conformationally restricted analogs **8** and **9** that could mimic the *trans* disposition of stilbene **2** were prepared, and indeed, both demonstrated good inhibitory potency in the genotype 1b replicon. Moreover, the introduction of polarity into the linker region offered a means to improve the pharmaceutics properties of the lead series if, for example, solubility were to become an issue.[1,17]

The more flexible bibenzyl analog **11** exhibited a 67-fold potency loss in comparison to **2** while the ether-linked analog **12** suffered further potency erosion when compared to its all-carbon counterpart **11**. The potency disparity between **11** and **12** was surprising in light of the tolerance for polarity observed with **6**. Analysis of X-ray data previously reported in the literature of relevant core structural fragments suggests that the biaryl rings in **2**, **11** and **12** may favor different conformational topologies.[18] The erosion in potency may be explained by a preference of the aromatic rings to be coplanar as in **2** or in parallel planes, as in **11** (Fig. 1). However, ether **12** has a preferred conformation where the aromatic rings are in orthogonal planes, likely resulting in a different topology of the peripheral pharmacophoric elements, particularly the amide NH, as compared to **2** and **11**. It is noteworthy that alkyne **13**, where overall planarity is restored, exhibits an EC_{50} of 6.24 nM.

The reduced inhibitory activity associated with the *cis*-disposed aryl core moieties, as in **5** and **7**, suggested that this configuration was less preferred. In addition, the reduced planarity across this region of the linker may also be a contributing factor. Therefore, we sought to explore this more fully by examining 1,2-disubstituted, five-membered heterocyclic linkers (see Table 2, examples **14**–**16**). These analogs were found to possess better potency than **5** and **7** and analyses of X-ray data of relevant core structural fragments of these analogs reported in the literature further corroborates the preference for planarity in this region. Indeed, these data reveal a difference in preferred topology in analogs containing a *cis*-cyclopropyl linker (**5**) or an *N*-methyl amide linker (**7**) in

Table 1
Activity of phenylacetamide analogs



R	Compound	1b EC_{50}[a,b] (nM)
	**2**	0.09
	**3**	12.4
	**4**[c]	5.66
	**5**	796
	**6**	11.0
	**7**	6250
	**8**	1.74
	**9**[c]	13.9
	**10**	1050
	**11**	6.01
	**12**	97.8
	**13**	6.24

[a] Genotype-1b CC_{50} and BVDV EC_{50} >10^4 nM in all cases.
[b] Values are means of at least two experiments.
[c] Mixture of *trans*-diastereomers.

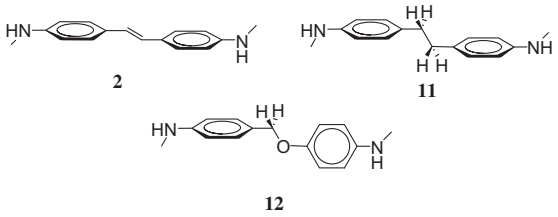
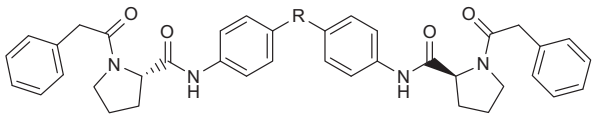
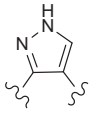


Figure 1. Relative disposition of the phenyl rings in analogs **2**, **11** and **12**.

Table 2
Activity of 1,2-heterocyclic analogs



R	Compound	1b EC_{50}[a,b] (nM)
	**14**	20.9
	**15**	8.18
	**16**	4.57

[a] Genotype-1b CC_{50} and BVDV EC_{50} >10^4 nM in all cases.
[b] Values are means of at least two experiments.

which both phenyl rings are facing each other presenting ring planes that are orthogonal to that of the linker.[15,19] On the other hand, when the linker is a *Z* alkene (e.g., **3**) or a 1,2-disubstituted five membered ring (e.g., **14**), one phenyl ring is coplanar with the linker while the other ring adopts an orthogonal plane (Fig. 2).[20] These topographical differences will affect the presentation of the pharmacophoric elements to NS5A and may provide an explanation for the observed variations in potency.

While the topological disposition observed in **2** is preferred, the optimal distance between the peripheral moieties was not known. Our attention was therefore directed towards examining this aspect, and the outcome of this investigation is shown in Table 3. Ta-

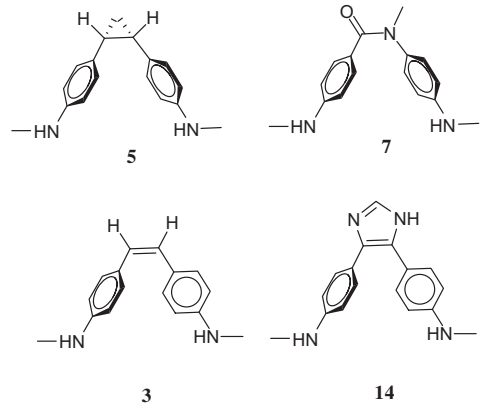
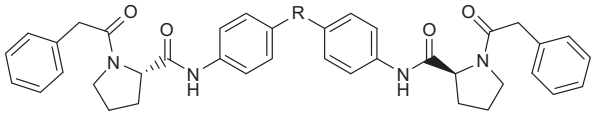


Figure 2. Proposed relative disposition of the phenyl rings in analogs **3**, **5**, **7** and **14**.

Table 3
Activity of shortened analogs



R	Compound	1b EC_{50}[a,b] (nM)
	**17**	1700
	**18**	1990
	**19**	3950
	**20**	638

[a] Genotype-1b CC_{50} and BVDV EC_{50} >10^4 nM in all cases.
[b] Values are means of at least two experiments.

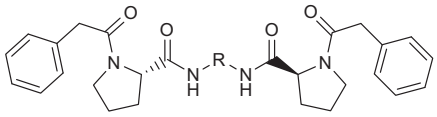
ken in aggregate, these results suggest that replacing the alkene moiety with a simple methylene, as in **17**, is significantly detrimental to potency. Similar results were observed with polar variants **18** and **19**, as well as with the lipophilic dimethyl homologue **20**, and were consistent with a preferred linear topology of the pharmacophore.[21]

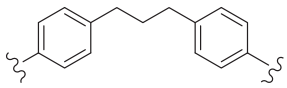
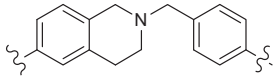
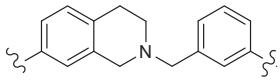
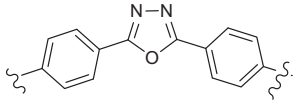
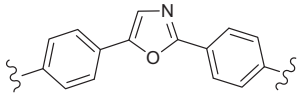
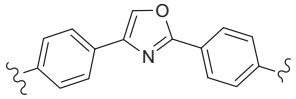
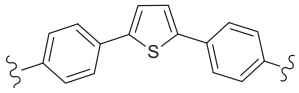
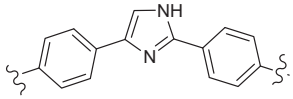
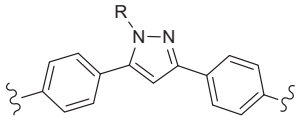
Results from an examination of longer central linkers are illustrated in Table 4. Extending the two carbon atom linker of **11** (EC_{50} = 6 nM) by one carbon was detrimental to inhibitory potency (**21**, EC_{50} = 36 nM), although the level of potency of **21** suggests that some flexibility in length is tolerated. While introducing conformational constraints and overt basicity, as in **22** and **23**, was detrimental to potency, a subset of compounds with more rigid and planar linkers exhibited enhanced potency. Two analogs, **25** and **26**, had EC_{50}s <10 nM while exhibiting some tolerance for polarity. Certain facets of the SAR that emerged, for example, the potency disparity between analogs **24** and **25**, and the poor potency observed with the benzimidazole **10** are not well understood. However, the 180-fold potency spread between pyrazoles **29** and **30** may be due to steric effects associated with the *N*-methyl group distorting the adjacent phenyl group out of planarity, thereby affecting the relative disposition of the peripheral pharmacophoric elements. [20,22]

In general, it appears that the impact on potency stemming from changes to the central core of the pharmacophore is related to a combination of molecular length, planarity, and polarity. In addition, it is noteworthy that there was not a considerable difference in potency when the phenyl rings were attached in a 1-2 or in a 1-3 fashion to the heterocycle. For example, 3,4-substituted pyrazole **16** and 3,5-substituted pyrazole **29** had similar potency in spite of the significantly different vectorial orientation of the two molecules. While the more potent inhibitors indicate a preference for planarity in the central linker region, molecules with a remarkably diverse set of topologies exhibit nearly comparable levels of inhibitory activity, as indicated by analogs **4**, **16** and **25**. The structural basis for these observations remains enigmatic and may only be illuminated by more detailed mechanistic studies or the co-crystallization of an inhibitor-NS5A complex in order to be fully appreciated.

Notably, almost all of these analogs of **2** exhibited weak potency toward a genotype 1a replicon (EC_{50} = 1–10 μM), with the exception of compound **25** which showed modest levels of inhibition, with an EC_{50} of 345 nM. All compounds were also tested for target specificity by evaluation in a bovine viral diarrhea virus (BVDV)

Table 4
Activity of elongated analogs



R	Compound	1b EC_{50}[a,b] (nM)
	**21**	36.1
	**22**	159
	**23**	3890
	**24**	149
	**25**	2.38
	**26**	1.32
	**27**	14.7
	**28**	67.2
	**29** R = H **30** R = Me	0.71 181

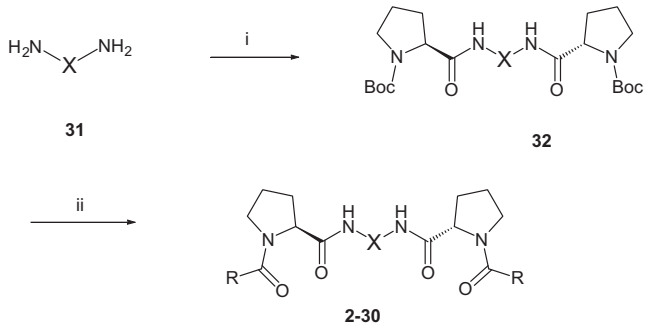
[a] Genotype-1b CC_{50} and BVDV EC_{50} >10^4 nM in all cases.
[b] Values are means of at least two experiments.

replicon as well as for cellular toxicity in genotype 1b replicons and, in all cases, EC_{50} or CC_{50} values remained over 10 μM.

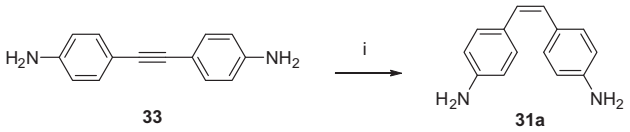
Compounds **2**–**30** were synthesized in a straightforward manner by coupling the respective bis-anilines **31** with Boc-L-proline. After deprotection of the Boc group in acidic conditions, the products were coupled with phenylacetic acid under standard conditions and purified by reverse phase preparatory HPLC (Scheme 1). The bis-aniline precursors of **2**, **3**, **11**, **12**, **13**, **18**, **19** and **20** were obtained from commercial sources while **31a** was derived from 4,4′-(ethyne-1,2-diyl)dianiline (Scheme 2).

Cyclopropyl derivatives *trans*-**31b** and *cis*-**31b** (Scheme 3) were obtained from the *trans* and *cis* stilbene, respectively, by bromination and palladium-mediated amination (for *trans*-**34**, the resulting racemic mixture was used for the synthesis of final compound **4**). Bis-aniline **31c** was obtained via direct reduction of bis(4-nitrophenyl)methane by standard methods (Scheme 4), while 4-amino-*N*-(4-aminophenyl)-*N*-methylbenzamide **31d** was readily obtained by standard methods as shown in Scheme 5.

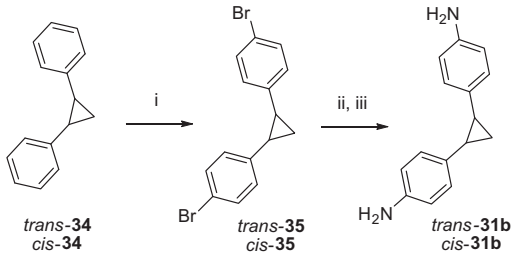
Precursor **31e** was prepared as follows: Heck coupling of aryl bromide **38** and styrene derivative **39** afforded carbamate **40** (Scheme 6). After deprotection of the primary amine, intermediate **41** was cyclized by heating under microwave irradiation to afford the desired tetrahydro-isoquinoline **42**. Methylation followed by



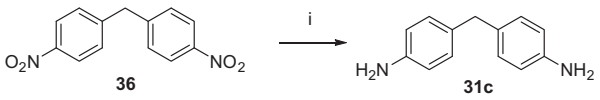
Scheme 1. Reagents and conditions: (i) Boc-L-proline, EEDQ, CH_2Cl_2; (ii) (a) 4 N HCl, dioxane; (b) RCOOH, EDCI, DIEA, THF.



Scheme 2. Reagents and conditions: (i) Lindlar catalyst, H_2 (1 atm), EtOAc.



Scheme 3. Reagents and conditions: (i) NBS, DME, H_2O; (ii) LiHMDS, Pd_2dba_3, 2-dicyclohexylphosphophinobiphenyl; (iii) 1 N HCl.



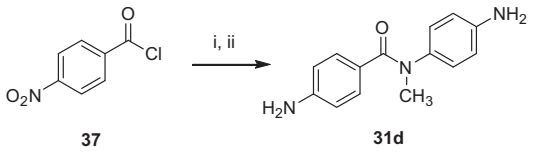
Scheme 4. Reagents and conditions: (i) $SnCl_2{\cdot}2H_2O$, EtOH, 70 °C; (ii) H_2 (1 atm), Pd/C, MeOH.

hydrogenation afforded racemic **31e**. Intermediates **33f**, **33g** and **33h** were obtained by direct coupling of tetrahydro-isoquinolines **44a**–**b** with their corresponding bromides, followed by reduction of the nitro groups.

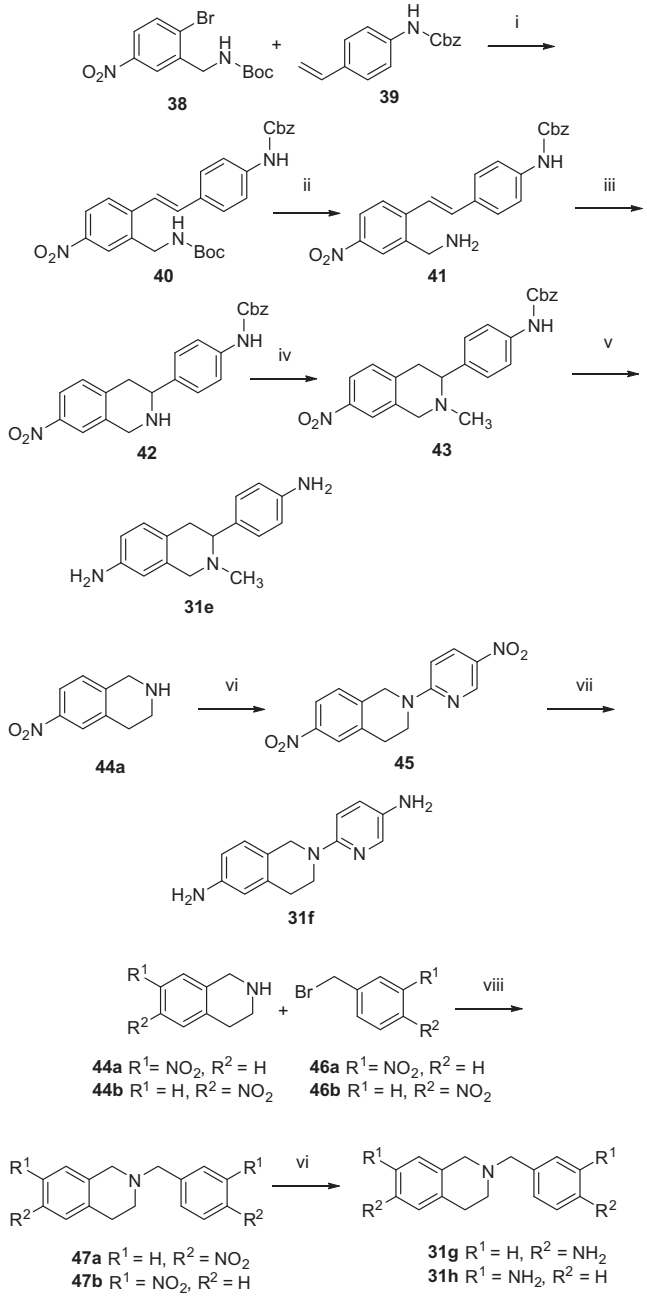
Condensation of **48** and **49** followed by reduction, readily afforded benzimidazole **31i** (Scheme 7).

The heterocyclic-linked templates **31j**–**q** were synthesized following well-known procedures in the literature, as exemplified in Scheme 8.[23]

In summary, a series of new cores have been identified as suitable replacements for the alkene moiety present in the original stilbene-based lead series of HCV NS5A inhibitors represented by **2**. Several linkers that explored aspects of varied geometry, length and polarity were prepared, with many exhibiting excellent potency against a genotype 1b HCV replicon. Moreover, these compounds exhibit minimal activity in a BVDV replicon inhibition assay, indicating good virus specificity, and possess an excellent therapeutic index. These results demonstrate the flexibility of the binding site on NS5A as well as a preference for an overall planar topography while accommodating a diverse set of linker elements. In the particular case of example **25**, modest potency towards a

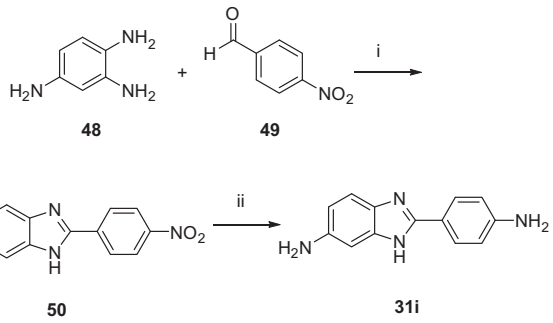


Scheme 5. Reagents and conditions: (i) *N*-methyl-4-nitroaniline, THF; (ii) H_2 (1 atm), Pd/C, MeOH.

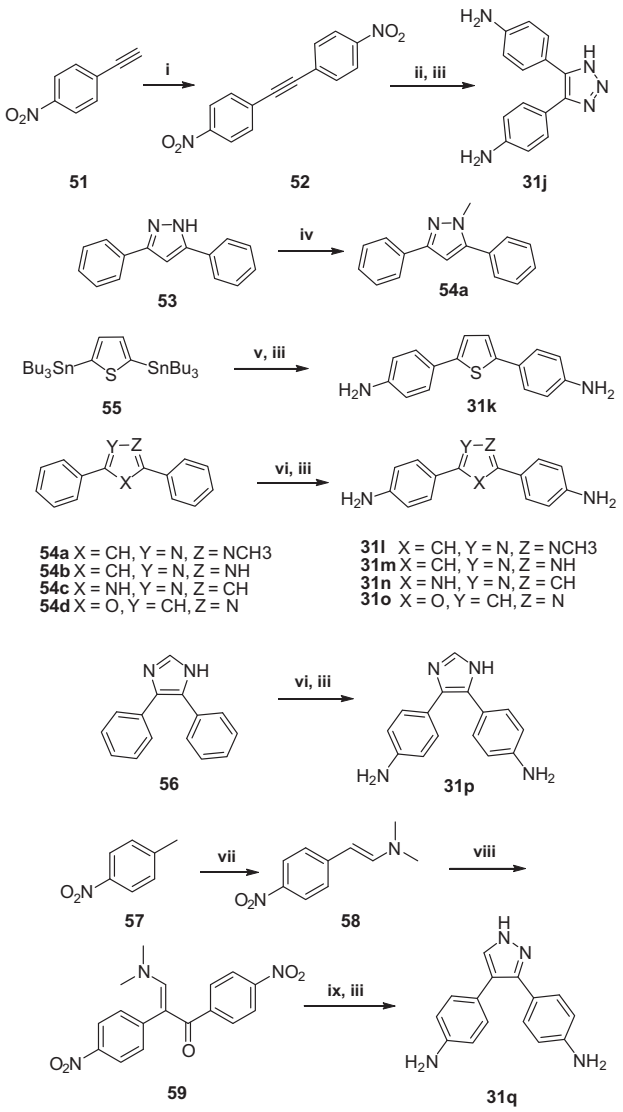


Scheme 6. Reagents and conditions: (i) $Pd(OAc)_2$, $Ph_2P(t\text{-}Bu)_2$, NaOAc, DMF, 100 °C; (ii) 10% TFA/CH_2Cl_2; (iii) microwave, 160 °C, 4 h, EtOH; (iv) formaldehyde, formic acid, $ClCH_2CH_2Cl$, 70 °C; (v) H_2 (1 atm), 10% Pd/C, EtOAc; (vi) 2-chloro-5-nitropyridine, Et_3N, EtOH; (vii) Raney nickel, $NH_2NH_2{\cdot}H_2O$, THF/H_2O; (viii) Et_3N, CH_2Cl_2.

genotype 1a replicon was observed. The subsequent SAR investigation effort that enhanced the inhibitory potency towards genotype 1a, a prelude to the discovery of dacalatasvir (**1**), will be the subject of future communications.



Scheme 7. Reagents and conditions: (i) *N*-methylmorpholine, MeOH; (ii) H_2 (1 atm), 10% Pd/C, EtOAc.



Scheme 8. Reagents and conditions: (i) 4-iodo-nitrobenzene, CuI, $Pd(PPh_3)Cl_2$, K_2CO_3, Bu_3N, H_2O; (ii) NaN_3, DMF, 200 °C, microwave; (iii) H_2, $Pd(OH)_2$, MeOH; (iv) NaH, MeI, DMF; (v) $Pd(PPh_3)_2Cl_2$, 1-bromo-4-nitrobenzene, reflux; (vi) fuming nitric acid, 0 °C; (vii) Bredereck reagent, 100 °C; (viii) *p*-nitrobenzoylchloride, DIEA, THF; (ix) $NH_2NH_2{\cdot}H_2O$, CH_2Cl_2.

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21. When the linker was completely removed and the two aryl groups were directly attached, the genotype 1b EC_{50} of the resulting analog was 205 nM suggesting that planarity as well as length might play a role in defining the pharmacophore.
22. Conformational differences between **29** and **30** were investigated using a mixed torsional/low mode sampling protocol within Macromodel [Schrodinger, Maestro v9.2, OPLS2005 FF, water solvent]. An overlay [rmsd minimized heterocyclic ring] of both structures showed the phenyl ring adjacent to the methyl substituent in **30** being taken out of co-planarity with a dihedral angle of 47.0° as compared with 18.5° in the case of **29**.
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