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Synthesis of thiazolone-based sulfonamides as inhibitors of HCV NS5B polymerase

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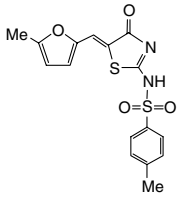
Abstract—Several thiazolone-based sulfonamides were prepared, utilizing various hetero-aryl sulfonyl chlorides and different aldehydes, as inhibitors of NS5B polymerase, to target HCV. The best compound showed 0.6 nM of IC_{50} inhibitory activity.

Hepatitis C virus (HCV) infection constitutes a health problem that affects people globally and is the leading cause of chronic liver disease. At present there is no vaccine against HCV, and no generally effective therapy for all genotypes of HCV is available. Currently, the treatment involves immunotherapy using recombinant interferon-α in combination with ribavirin. The clinical benefit of this treatment is limited, and some undesirable side effects are associated with these therapies.[1] The virus establishes chronic infection in up to 80% infected and persist for decades, with a substantial risk of developing liver cirrhosis and hepatocellular carcinoma.[2] Therefore, effective antiviral therapies that prevent and alleviate complications suffered by millions of individuals chronically infected with HCV are needed.

HCV is an enveloped positive-sense single stranded RNA virus, belonging to the *Flaviviridae* family.[3] It encodes its own RNA dependent RNA polymerase (NS5B) in order to replicate its genome. This viral specific enzyme is essential for viral replication; therefore it is a potential target for structure-based drug design. During the last several years, both nucleoside and non-nucleoside inhibitors of NS5B have been discovered as anti-HCV agents.[4] From our in-house high-throughput screening program, we identified thiazolone sulfonamide (**1**, IC_{50}: 11 μM) as a lead inhibitor of NS5B polymerase of HCV.



HTS Lead **1**, IC_{50}: 11 μM

As part of a structure–activity relationship study we systematically modified (Fig. 1) every part of this scaffold, in order to improve binding and inhibition of NS5B polymerase. In this communication, we are reporting the results of this study (Table 1).

At the outset we modified the left portion of the molecule by introducing various substituted furanyl moieties (Scheme 1). This involved the condensation of two components, *p*-toluenesulfonyl chloride and thiazolone amine **7**, to form the key sulfonamide intermediate **8**. Following a parallel solution-phase synthesis, various heterocyclic aldehydes **9** were condensed with thiazolone **8** at 85 °C in a mixture of *n*-BuOH and piperidine for 8 h, to afford the adducts (**10**–**19**), which usually precipitated, as an orange-brown to tan colored solid in 50–75% yield.

Initially we had some concerns about the olefin linker in these compounds that it may be susceptible to Michael addition and may become a future metabolic liability. We reduced the bridge double bond to

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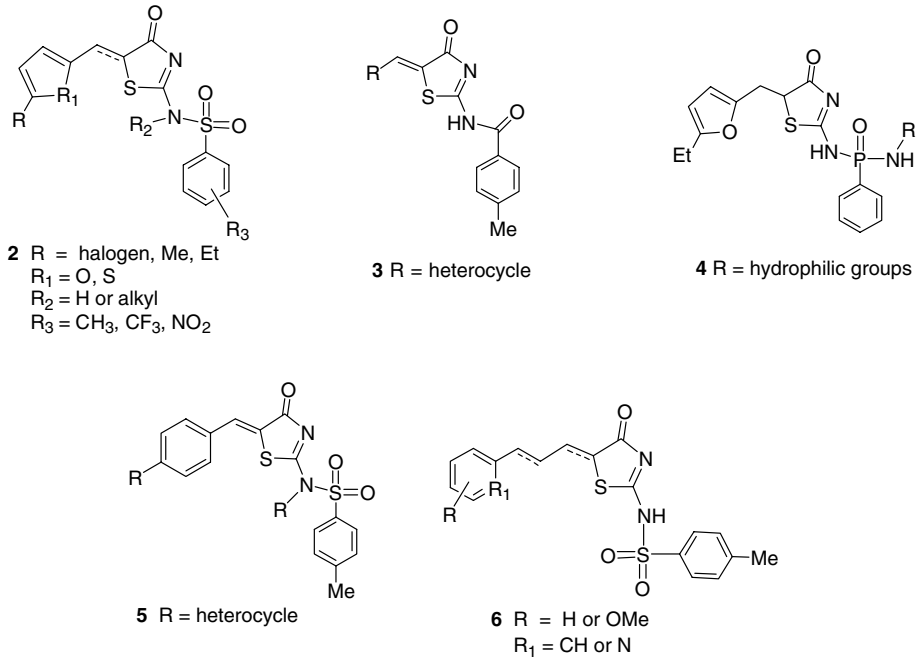


Figure 1. Structures of potentially new NS5B polymerase inhibitors, **2**–**6**.

the more flexible single bond for compounds **10**–**13**. Reduction of sulfonamides **10**–**13** was carried out with $NaCNBH_3$ in THF, to afford compounds **20**–**23**.

Within the library of modified furan analogues (**10**–**19**), we identified only a few compounds that showed interesting activity. The iodo derivative **11** showed 2.8 μM IC_{50} and an EC_{50} of 38 μM, along with a CC_{50} of 200 μM. Replacing the halogen in **11** with an ethyl group (**13**) improved the in vitro activity twofold (IC_{50}: 1.4 μM) along with 25 μM and 80 μM for the EC_{50} and CC_{50}, respectively. The reduced compounds **20**–**23** did not show improved potency.

Other analogues investigated in this series involved the replacement of the furan with thiophene (**16**–**19**), in an effort to explore the effect of removal of the H-bond acceptor 'oxygen' in furan would have on the substrate's binding affinity and its potency against the NS5B polymerase enzyme. Interestingly, this modification led to an overall decrease in activity (**18**: IC_{50} = 8.0 μM; EC_{50} = 40 μM, CC_{50} = 70 μM) and adding an extra substituent (**17**: where R_2 = Me) proved to be toxic, compared to the initial lead compound **1**. The modifications in the above series confirmed that a furan moiety coupled to a thiazolone core by a *sp2* hybridized carbon linker is essential for activity improvement of the lead molecule **1**.

We then focused on the modifications of the sulfonamide link. The substituents at this link could potentially be useful in exploring the lipophilic requirements of the polymerase enzyme, and may have an effect on the dihedral angle of the sulfonamide bond in regard to the steric interaction between these and the *p*-toluyl group. Compound **13** was chosen for further study as it was identified to be the best active compound thus far. The N-alkylation of sulfonamide **13** was carried out readily, by heating with an appropriate alkyl halide, under mild basic conditions, which afforded **24**–**27** in moderate yields (Scheme 2). However, the activities of **24**–**27** in this study were not very interesting, relative to the original lead.

Replacement of the sulfonamide of the lead compound **1** with an amide was also studied. This modification may also bring adjustments in the orientation of the phenyl group with respect to changes in the dihedral angle at this position. Using standard peptide coupling conditions, the amine **7** and 4-methyl-benzoyl chloride were reacted to form amide **28**. Thus the desired derivatives (**29**–**34**) were obtained from the condensation of amide **28** with the appropriate aldehydes (Scheme 3).

Unfortunately the activities of these amides **29**–**34** were lower than those of the sulfonamide derivatives. Presumably, this is due to the absence of an extra oxygen atom in the amide derivatives unlike in the case of sulfonamides, which may be necessary for H-bonding with adjacent polar residues within the polymerase binding site.

A modification involving replacement of the sulfonamide with phosphoramide was also considered. This was achieved by condensing 5-ethyl furfural with **7** to afford compound **35** which was then reacted with the commercially available phenyl phosphonyl dichloride to obtain mono-amination product **36**. The halo derivative **36** was then treated with polar nucleo-

Table 1. Results of replicon assay, showing IC_{50}, EC_{50}, and CC_{50} of NS5B polymerase inhibitors **10**–**55**

Compound	IC_{50} (μM)	EC_{50} (μM)	CC_{50} (μM)
10	11	60	80
11	2.8	38	200
12	2.7	50	120
13	1.4	25	80
14	5.5	55	55
15	3.2	200	200
16	12	80	80
17	10	200	200
18	14	70	40
19	4.2	7	7
20	74	200	>300
21	15	40	200
22	40	64	>300
23	7.3	33	>300
24	>100	33	45
25	>100	55	55
26	>100	70	130
27	>100	90	120
29	33	100	100
30	16	60	150
31	13	200	>300
32	44	120	220
33	>100	220	>300
34	11	70	180
39	3.2	30	33
40	3.2	200	200
41	8.0	40	70
42	18	90	180
43	11	27	200
44	34	200	200
45	32	100	220
46	>100	60	>300
47	4.9	9	25
48	10	70	90
49	1.4	20	200
50	1.4	25	200
51	12	180	>300
52	>100	90	120
53	5.0	55	150
54	0.6	35	>300
55	>100	180	>300

All values are means of three experiments.

philes, such as 3-amino propanoic acid and glycol, to afford the desired phosphoramide derivatives **37** and **38**, in good yields (Scheme 4). Surprisingly, addition of polar side-arms in this region had little effect on potency.

Utilizing various commercially available sulfonyl chlorides, a number of derivatives of **13** that bear modified sulfonyl components were prepared (**39**–**44**) to probe the phenyl ring of the sulfonyl moiety. Initially we prepared an analogue which replaced the methyl group of *p*-toluyl derivative **13** (IC_{50} = 1.4 μM) with a 4-trifluoromethyl group (**39**). However, the activity of **39** was not improved (IC_{50} = 3.2 μM). The *p*-nitro analogue **40** and thiophene replacement **41** were found to be inactive, as well. Some ortho-substituted compounds including the nitro analogue **42**, which was reduced to the corresponding aniline **43**, and its *N*-acetyl derivative **44**, did not show improved activity either (Scheme 5).

The lack of improvement in activity from these modifications over compound **13** was disappointing. In a reevaluation of the left part of lead compound **1**, we synthesized several derivatives (**45**–**52**, Fig. 2) to probe the space in this region with groups larger than a furanyl group which incorporated phenyl groups tethered with a heterocycle.

Thus various substituted benzaldehydes were condensed with sulfonamide **8** to afford the desired analogues **45**–**52** that contained phenyl groups extended with both aromatic and non-aromatic heterocycles at the *para* position.

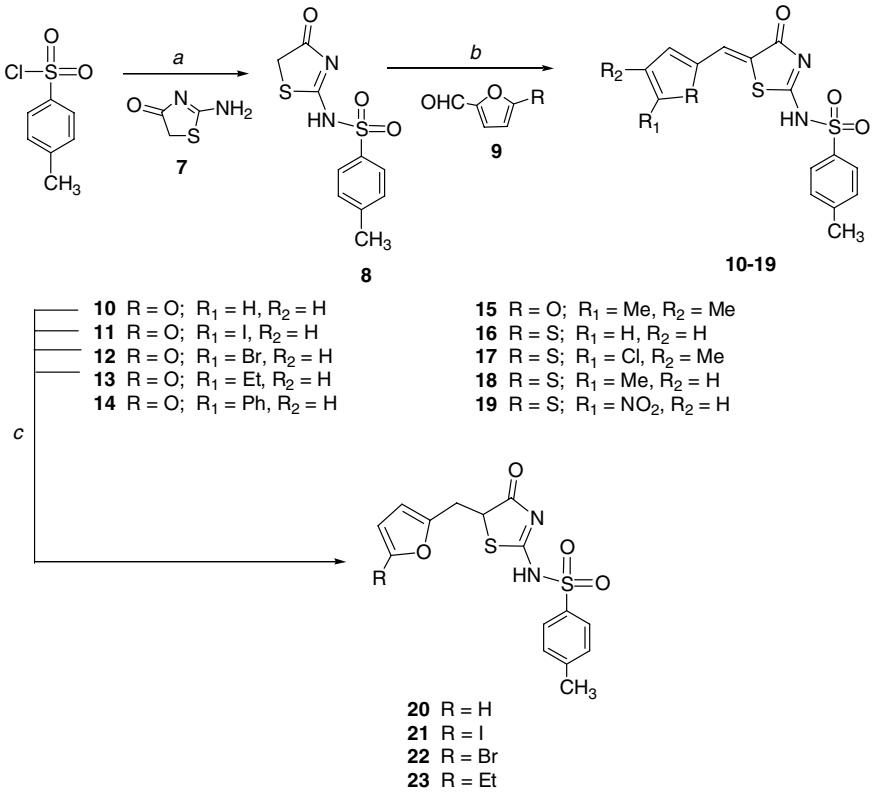
The most active of these was the sulfur containing heterocyclic analogue **49**, which showed an IC_{50} of 1.4 μM while EC_{50} and CC_{50} showed 20 μM and 200 μM, respectively. It is gratifying to note that from the above effort we were able to retain the activity obtained for compound **13** while improving the cellular and toxicity profile. Having been encouraged by this, we focused further in this part of the lead compound.

We envisioned that the inductive electron-withdrawing nature of sulfur in **49** may be responsible for a reduction in its basic character unlike the rest of the derivatives in this series. In seeking to mimic the electronic properties of **49** and to decrease its basicity, we decided to investigate compounds that contained pyridine (bioisostere of thiazole) as a terminal heterocycle with an extended olefin spacer group.

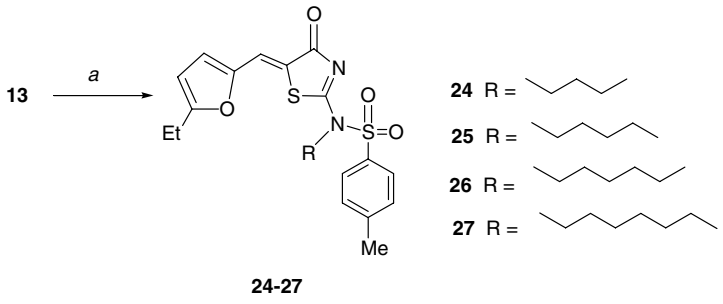
Accordingly an appropriate olefin or aliphatic aldehyde was condensed (same conditions as in Scheme 1) with thiazolone **8** to afford derivatives with a furanyl (**53**), pyridyl (**54**) or an aliphatic-tethered pyridyl group (**55**) as shown in Figure 3.

As expected, the most active compound in this series, was the pyridine analogue, **54**, with an IC_{50} of 0.6 μM (EC_{50} = 35 μM, CC_{50} = >300 μM). The corresponding saturated derivative **55** showed a decrease in potency, which was comparable to our earlier results with the reduction of our initial hit compound, and was not explored further.

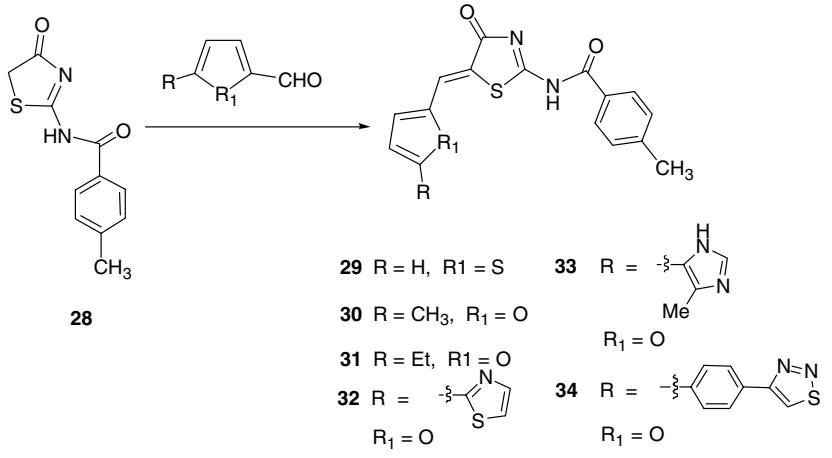
In summary, we were able to make significant improvements in the potency of HTS lead compound **1**. Thus, a nearly fourfold (**11**, IC_{50} = 2.8 μM) improvement was achieved in the first series of compounds prepared. Further improvement in the activity was achieved by replacing the iodo in **11** by an ethyl group (**13**, IC_{50} = 1.4 μm). Exploration in condensation reactions utilizing substituted benzaldehydes led us to a derivative (**49**, IC_{50} = 1.4 μM) which showed a similar in vitro activity to that of **13**, but with a better cellular and toxicity profile. Finally additional 2-fold improvement in potency was achieved when the heterocycle group of **49** was replaced with bioisosteric



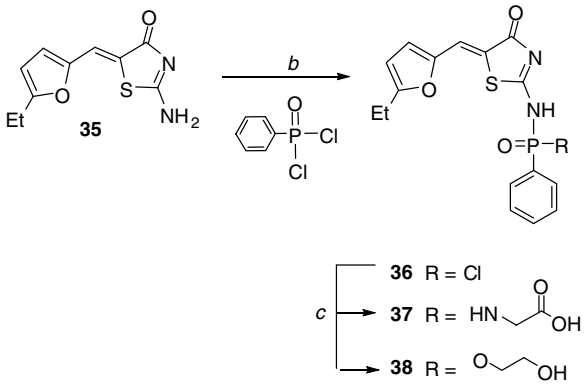
Scheme 1. Reagents and conditions: (a) **7**, THF, Et_3N, 80°, 1 h; (b) **9**, *n*-butanol, piperidine, 85 °C, 8 h; (c) **10**–**13**, $NaCNBH_3$, THF, 40 °C, 1 h.



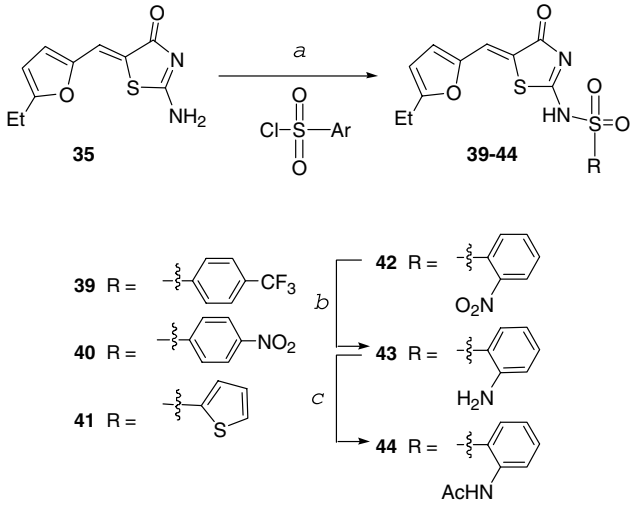
Scheme 2. Reagents and conditions: (a) **13**, THF, Et_3N, RBr, 80 °C, 10 h, 40–70% yields.



Scheme 3. Reagents and conditions: **28**, substituted aldehyde, *n*-BuOH, piperidine, 85 °C, 2 h.



Scheme 4. Reagents and conditions: (b) phenyl phosphorus oxychloride, DBU, THF, −15 °C to rt; (c) 2-aminoacetic acid or ethylene glycol, Et_3N, THF, 0 °C to rt, 8 h.



Scheme 5. Reagents and conditions: (a) aryl sulfonyl chloride, THF, Et_3N, 45 °C, 8 h; (b) $SnCl_2$, EtOH; (c) Ac_2O/MeOH.

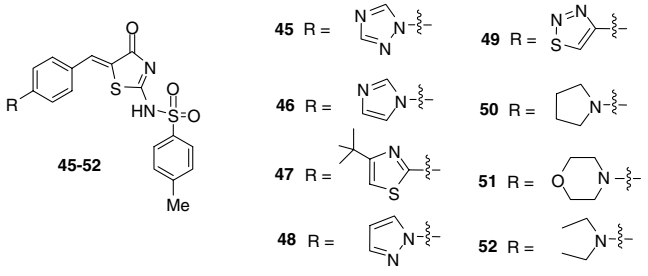


Figure 2. Modified furan replaced analogues, phenyl derivatives with heterocyclic substituents.

pyridine with extended olefin linker to afford the most potent compound **54** (IC_{50} of 0.6 μM) in the present study.

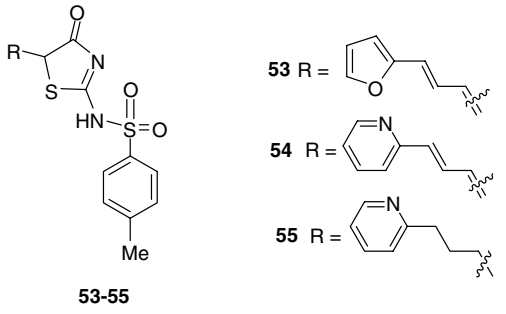


Figure 3. Extended chain analogues, utilizing aldehydes with both rigid (**50** and **51**) and a flexible (**52**) spacer.

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