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Inhibitors of HCV NS5B polymerase: Synthesis and structure–activity relationships of *N*-1-benzyl and *N*-1-[3-methylbutyl]-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine analogs containing substituents on the aromatic ring

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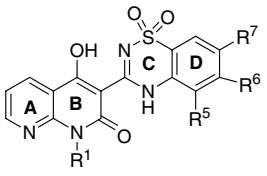
Abstract—A series of non-nucleoside HCV NS5B polymerase inhibitors based on the *N*-1-benzyl or *N*-1-[3-methylbutyl]-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine core substituted in the D-ring aromatic moiety have been prepared and evaluated. Aromatic substituents extending from position 7 of the D-ring exhibited excellent potency against both genotypes 1a and 1b.

Hepatitis C virus (HCV) is a human pathogen affecting approximately 3% of the world's population.[1] Left untreated, HCV infection can lead to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. Viral isolates of hepatitis C are classified into six genotypes with genotypes 1 and 2 being the most prevalent in the United States, Europe, and Japan.[2] The current standard for drug therapy consists of a combination of pegylated α-interferon (IFN-α) and ribavirin the use of which is often limited by safety and tolerability issues. The response rate for patients infected with viral genotypes 1, 4, 5, and 6 virus is approximately 48%, while patients infected with genotypes 2 and 3 exhibit an 88% response rate.[3] Therefore, the need for more effective and tolerable agents for the treatment of HCV, especially for patients with genotype 1 virus, has stimulated an intense research effort. Significant efforts have been directed toward several targets within the HCV genome, including NS3 protease/helicase complex and NS5B RNA-dependent RNA polymerase (RdRp).[4] Recent publications[5–12] have described efforts toward the development of small molecule inhibitors of NS5B RdRp. Nucleoside[5] and non-nucleoside inhibitors binding within the palm region[7–10] of the NS5B RdRp as well as allosteric[6,11,12] inhibitors binding in the palm domain at the junction with the thumb region of the enzyme have been described. We recently described preliminary structure–activity inhibition data of the non-nucleoside *N*-1-alkyl-4-hydroxy-quinolon-3-yl benzothiadiazine class of NS5B RdRp inhibitors.[8] The benzothiadiazine class of molecule is illustrated in Figure 1.



R^1 = Benzyl (**1**) R^1 = 3-Methylbutyl (**2**)

Figure 1. General naphthyridone-based benzothiadiazine structure depicting the A-, B-, C-, D-rings, where the B-ring substituent is designated by R^1 and the D-ring substituent positions 5, 6, and 7 are designated by R^5, R^6, and R^7.

Keywords: HCV NS5B polymerase; *N*-1-Benzyl or *N*-1-3-methylbutyl-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine.
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The benzothiadiazine class of HCV inhibitors can be described as a tetracyclic system containing four distinct regions defined by each of the rings labeled A, B, C, and D. The A- and B-rings are represented by the *N*-1-substituted-1,8-naphthyridonyl ring system, initially described by Darcy et al. in 2003.[13] The C- and D-ring structure describes the benzothiadiazine moiety, where the C-ring contains the cyclic amino sulfonamide moiety and the D-ring is depicted by the aromatic ring moiety.

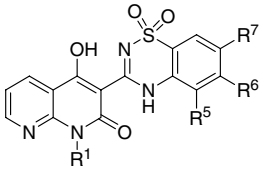
This report describes the synthesis and biological evaluation of analogs based on both the *N*-1-benzyl-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine class, **1**, and the *N*-1-[3-methylbutanyl]-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine class, **2**, possessing substituents on the D-ring in positions 5, 6, and 7. Initial studies were directed toward an investigation of the effect of D-ring substituents on polymerase inhibition of compound **1**. The analogs in this series were designed to test the effect of small D-ring substituents on enzyme inhibition. Compound **1** was substituted with either methoxy or hydroxy groups in positions 5, 6, and 7 on the D-ring and most of the compounds exhibited potent genotype 1b enzyme inhibition but weak genotype 1a inhibition.

The data presented in Table 1 suggest that analogs substituted in position 7 proved to be the least affected by substituents, maintaining essentially the same potency as parent compound **1**. Position 5, compound **3**, and position 6, compound **4**, however, exhibited at least a 20- to 30-fold loss in potency compared to compound **1**. Removal of the methyl group in compounds **3** and **4** produced compounds **6** and **7**. In this case, compound **6** was equipotent to compound **1** against genotype 1b, however, compound **7** showed no improvement in potency from **4**. We concluded from this study that position 6 in the D-ring was possibly very close to the enzyme and could not tolerate groups other than hydrogen at this position. Inspection of the recently published X-ray structure of compound **2**[10] suggested to us that position 6 of the D-ring is indeed close to the protein. Therefore, position 6 on the D-ring did not appear to be amenable for further modification. However, the possibility of improving potency with larger substituents in positions 5 and 7 was still open to investigation.

Table 2 illustrates the effect of either hydrophobic or larger polarizable substituents at position 5 or 7 on the genotype 1 inhibition potency.

Small hydrophobic groups, for example, methyl groups, are tolerated in both positions 5 and 7, compounds **8** and **9**, respectively, with no loss in genotype 1b potency. However, increasing the size of the substituent to bromo produced a 3-fold loss in potency for the position 7 analog (compound **10**), and a 12-fold loss in potency for the position 5 analog **11**. We compared the effect of replacing the benzyl group in the *N*-1 position on the B-ring, compound **1** with a B-ring, *N*-1-3-methylbutyl substituent, compound **2**. The potency for each compound in genotype 1b was similar, however, the genotype 1a potency of compound **2** was superior to compound **1**, exhibiting a 7-fold improvement in enzyme inhibitory potency. We next tested the effect of either hydroxyl or methoxy substituents in positions 5 and 7 on the more potent compound **2**. Table 3 illustrates the effect of these substituents on genotype 1a and 1b inhibitory potency.

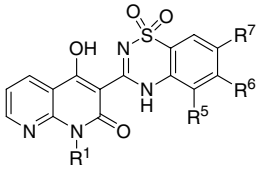
Table 1. Effect of D-ring hydroxy and methoxy substituents on genotype 1 inhibition in the *N*-1-benzyl series of analogs[18]



Compound	R^1	R^5	R^6	R^7	IC_{50} (μM)[a]	
					1b	1a
1	Benzyl	H	H	H	0.083	5.8
3	Benzyl	OMe	H	H	2.12	18
4	Benzyl	H	OMe	H	3.9	ND
5	Benzyl	H	H	OMe	0.076	8.31
6	Benzyl	OH	H	H	0.054	8.37
7	Benzyl	H	OH	H	2.51	ND

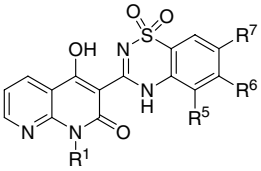
[a] IC_{50} values in all tables are means of at least two independent determinations, standard deviation ± 10%. Detailed protocols can be found in the supplementary material.

Table 2. Effect of large or hydrophobic substituents on genotype 1 potency in the *N*-1-benzyl series of analogs



Compound	R^1	R^5	R^6	R^7	IC_{50} (μM)	
					1b	1a
8	Benzyl	H	H	Me	0.23	25.7
9	Benzyl	Me	H	H	0.096	6.7
10	Benzyl	H	H	Br	0.756	16.75
11	Benzyl	Br	H	H	1.17	6.2

Table 3. Effect of methoxy and hydroxyl D-ring substituents on genotype 1 inhibition in the *N*-1-[3-methylbutyl] series of analogs



Compound	R^1	R^5	R^6	R^7	IC_{50} (μM)	
					1b	1a
2	3-Methylbutyl	H	H	H	0.041	0.81
12	3-Methylbutyl	OMe	H	H	1.17	17.58
13	3-Methylbutyl	H	H	OMe	0.065	1.13
14	3-Methylbutyl	H	H	OH	0.042	0.39

In this series of compounds, there is a more pronounced effect of D-ring substituents on the genotype 1a enzyme inhibitory potency. Although compound **13** is equipotent to compound **5** in genotype 1b, compound **13** is 8-fold more potent in genotype 1a and 15- to 18-fold more potent than the position 5 analog, **12**, in both genotypes 1a and 1b. Removal of the methyl group from compound **13** produced compound **14**, which exhibited submicromolar potency in both genotypes 1a and 1b. Although, the genotype 1b potency for both *N*-1-benzyl and *N*-1-isoamyl series was similar, compound **14** was chosen as the lead compound for further modification because this analog possessed improved genotype 1a potency.

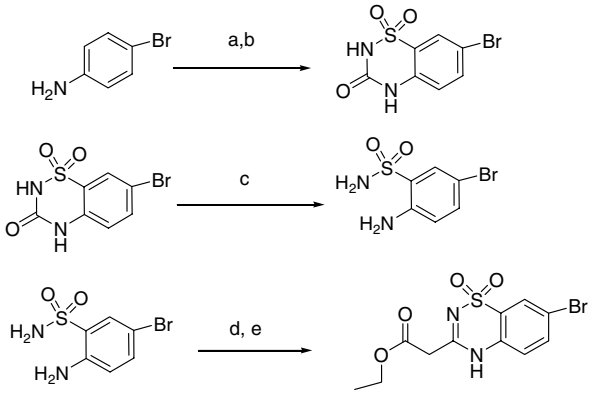
Scheme 1 represents our synthetic approach for the preparation of suitably substituted position 5 and 7 sulfonamide precursors. Provided the necessary aniline was commercially available, the procedure described by Girard et al.[14] successfully produced many position 5 and 7 substituted analogs.

The synthetic route described in Scheme 1 when applied to meta-substituted anilines could provide two possible compounds. An alternative procedure outlined in Scheme 2 was used to prepare the corresponding position 6 D-ring sulfonamide precursors. The method described by Topliss et al.[15] provided position 6 analogs with unequivocal regiochemistry.

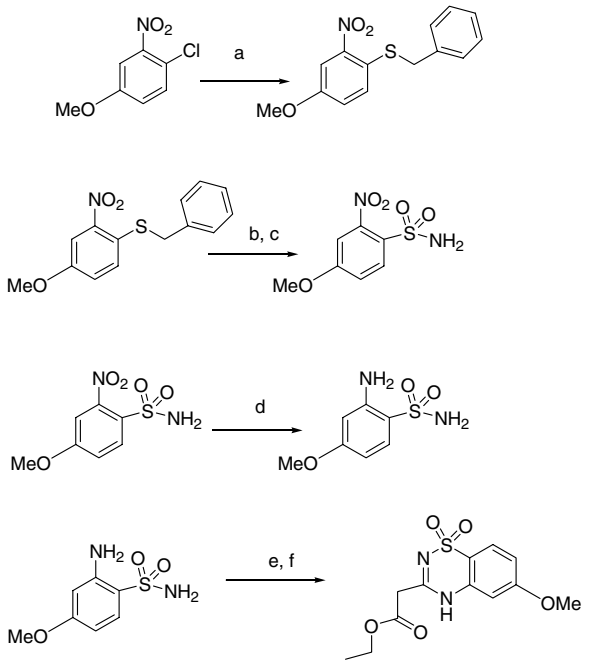
In order to rapidly prepare a diverse set of O-alkylated position 7 D-ring derivatives, the synthetic route outlined in Scheme 3 was chosen.

The assembly of the 7-methoxy analog, **12**, was achieved according to literature procedures.[8,14,15]

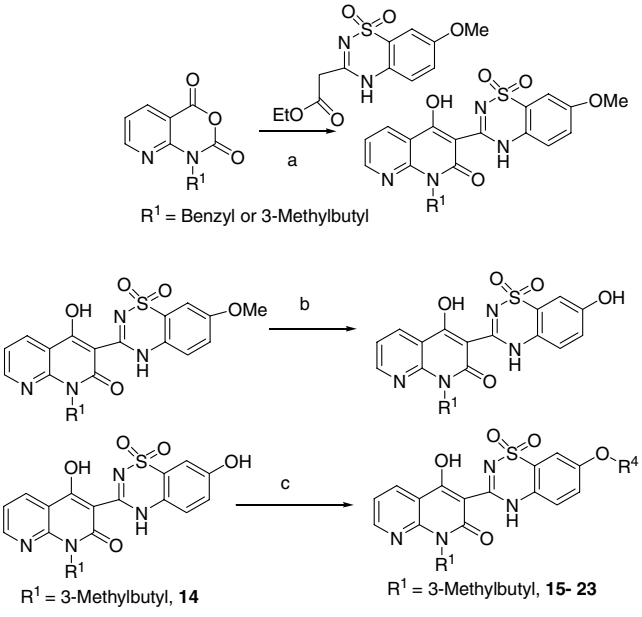
Deprotection of the methyl group with boron tribromide provided compound **14**. Alternatively, removal of the benzyl group from the 7-benzyloxy analog, **16**, was effected by refluxing **16** in THF for 1 h with ammonium formate, palladium hydroxide, and 10% palladium on carbon. All analogs listed in Table 4 were prepared from compound **14** as outlined in Scheme 3.



Scheme 1. Reagents and conditions: (a) chlorosulfonyl isocyanate, nitroethane, −40 °C, then warm to 0 °C, 15 min; (b) $AlCl_3$, 110 °C, 30 min; (c) 50% aqueous H_2SO_4, reflux, 4 h (42%); (d) $EtCO_2CH_2COCl$, Et_3N, CH_2Cl_2, 20 °C, 3.5 h; (e) Na_2CO_3, EtOH, 3.5 h, reflux, 82%.



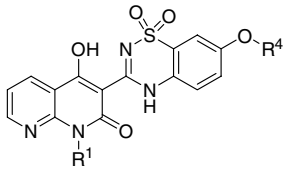
Scheme 2. Reagents and conditions: (a) BnSH, Na_2CO_3, EtOH, H_2O, 5 h, reflux, 96%; (b) Cl_2 (g) HOAc, H_2O, 15 min, 5 °C; (c) NH_4OH (concd), CH_2Cl_2, 30 min, 5 °C, 88%; (d) Fe, NH_4Cl, MeOH/H_2O, 1.5 h, reflux, 71%; (e) $EtCO_2CH_2COCl$, Et_3N, CH_2Cl_2, 20 °C, 3.5 h; (f) Na_2CO_3, EtOH, 3.5 h, reflux, 82%.



Scheme 3. Reagents and conditions: (a) NaH, THF, reflux, 3 h then HOAc, reflux, 1 h; (b) BBr_3/solvent, −78 to 0 °C, 20 h; (c) RX/DMF, Cs_2CO_3, TBAI, rt, 8–15 h.

Analogs possessing hydrophobic groups, compounds **15–17**, exhibit modest to weak genotype 1b and 1a potency. The incorporation of more polar substituents in position 7, compounds **18–23**, exhibited only a slight (approximately 2- to 3-fold) improvement in genotype

Table 4. Comparison of non-polar and polar alkoxy D-ring position 7 substituents of compound **14** on Genotype 1 inhibition potencies



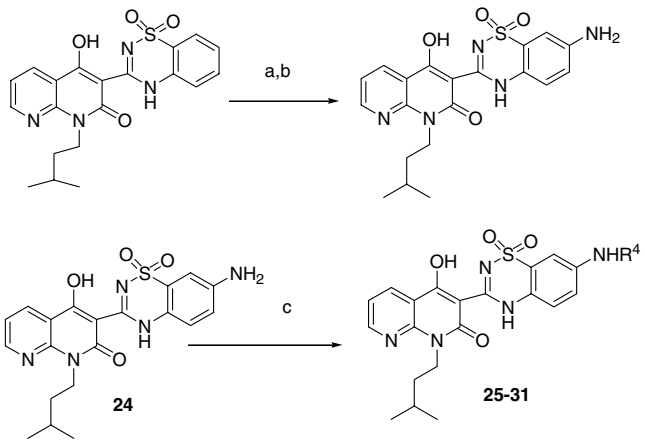
Compound	R^1	R^4	IC_{50} (μM)	
			1b	1a
15	3-Methylbutyl	$CH_2CH_2CH_3$	0.93	1.62
16	3-Methylbutyl	CH_2Ph	1.49	ND
17	3-Methylbutyl	CH_2CO_2tBu	0.85	5
18	3-Methylbutyl	CH_2COOH	0.057	0.367
19	3-Methylbutyl	CH_2CONMe_2	0.07	0.934
20	3-Methylbutyl	$CH_2CONHMe$	0.08	0.18
21	3-Methylbutyl	CH_2CONH_2	0.016	0.046
22	3-Methylbutyl	$CH_2CH_2NH_2$	0.051	0.637
23	3-Methylbutyl	CH_2CN	0.025	0.141

1b inhibitory potency compared to compound **13**, but a marked improvement in the inhibitory potency for genotype 1a. Compound **21** was approximately 10-fold more potent in genotype 1a inhibitory potency over the precursor analog **14**. The substantial improvement in potency for compound **21** suggested to us that extension from position 7 of the D-ring especially with a polar group effected a more favorable interaction of the inhibitor with the enzyme. The recently published structure[10] illustrated that position 7 of the benzothiadiazine D-ring was amenable to substitution with polar groups which extend into an open mainly hydrophilic region.

We investigated the effect on enzyme inhibition potency when the oxygen atom at position 7 was replaced with a nitrogen atom. The goal was to determine whether the hydrogen bond-accepting capability of the oxygen atom at position 7 was contributing to improved inhibitory potency or the replacement with a potential hydrogen bond-donating NH would improve the potency further. We prepared a series of analogs according to the sequence outlined in Scheme 4.

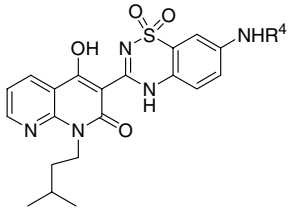
Nitration of compound **2** with ammonium nitrate in cold concentrated sulfuric acid provided nitration exclusively in position 7 of the D-ring in approximately 30 min. Reduction of the nitro group with iron and ammonium chloride in refluxing methanol, tetrahydrofuran, and water cleanly produced D-7 amino compound, **24**, in good yield. Alkylation of the amino group using standard conditions, Cs_2CO_3, RX, DMF, and room temperature, was sluggish requiring long reaction times and low yields, even when heating to 100 °C. Alternatively, alkylation of compound **24** was achieved cleanly by heating the reagents mentioned previously at 100 °C for 1 h in a microwave reactor.

Table 5 presents the genotype 1 inhibition for a series of D-ring position 7 amino compounds. The two most potent oxygen-alkylated analogs, **21** and **23**, were prepared in the amino series and exhibited no improvement in



Scheme 4. Reagents and conditions: (a) NH_4NO_3, concd H_2SO_4, 0 °C, 30 min, 81%; (b) Fe, NH_4Cl, MeOH/THF/H_2O (3:3:1), 65 °C, 1 h, 65%; (c) RX, Cs_2CO_3, DMF, microwave, 100 °C, 1 h or RSO_2Cl, CH_2Cl_2, Et_3N, 20 h, rt.

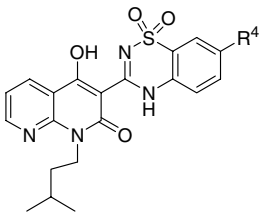
Table 5. Effect of D-ring position 7 amino substituents on genotype 1 inhibition



Compound	R^4	IC_{50} (μM)	
		HCV NS5B genotype 1b	HCV NS5B genotype 1a
24	H	0.023	0.31
25	CH_2CN	0.024	0.12
26	CH_2CONH_2	0.034	0.47
27	$COCF_3$	0.070	0.906
28	SO_2Ph	0.007	0.041
29	SO_2iPr	0.003	0.008
30	$SO_2(CH_2)_3CH_3$	0.005	0.022
31	SO_2Me	0.006	0.002

genotype 1a and 1b inhibitory potency. In fact, compound **26** was approximately 10-fold less potent in genotype 1a than the corresponding oxygen-alkylated analog **21**. The amide analog, **27**, showed no improvement in potency, however, the incorporation of alkyl or phenyl sulfonyl groups, compounds **28–31**, improved potency significantly. Compound **31** exhibited potent genotype 1 inhibition, approximately 3-fold more potent in genotype 1b than compound **21** and 20-fold more potent than compound **21** in genotype 1a. Presently, we can only speculate as to the importance of the NH versus the oxygen with respect to improved enzyme inhibition. Comparing the enzyme inhibition potencies between analogs, **21** and **26,** for example, compound **26** shows a loss of approximately 10-fold in genotype 1a inhibition suggesting that the position 7 amino group has either no interaction with the protein or produces a different position of the acetamide side chain such that the interaction

Table 6. Comparison of position 7 D-ring substituents on genotype 1b inhibition in cell culture



Compound	R^4	HCV NS5B genotype 1b EC_{50} (μM)[a]	HCV NS5B genotype 1b EC_{50} (μM)[a], 40% human serum
21	OCH_2CONH_2	0.078	2.74
24	NH_2	0.48	ND
26	$NHCH_2CONH_2$	0.45	ND
28	$NHSO_2Ph$	1.69	ND
29	$NHSO_2iPr$	0.11	ND
30	$NHSO_2(CH_2)_3CH_3$	1.00	ND
31	$NHSO_2Me$	0.003	1.31

[a] EC_{50} values in all tables are means of at least two independent determinations, standard deviation ± 10%. Detailed protocols can be found in the supplementary material.

of the side chain with the protein is weaker. The significant improvement in enzyme inhibition potency, especially genotype 1a, for the sulfonamide analogs suggests that this substituent apparently improves the inhibitor–protein interaction, again, by extending a polar substituent into a hydrophilic region. However, without the aid of an X-ray structure of a compound **31**–protein complex, we cannot determine whether any significant protein–inhibitor interactions contribute to the observed enzyme inhibitory potency enhancement. Several analogs containing either D-7 alkoxy, compound **14** or D-7 amino, compound **24**, substituents were evaluated in the cell-based HCV replicon system[16,17] against genotype 1b, and the data are listed in Table 6.

Compound **21** exhibited an approximately 5-fold loss in the cell-based system inhibition potency when compared with the corresponding genotype 1b isolated enzyme inhibitory potency. Analogs **24**, **26**, and **29** show a 10- to 40-fold loss in cellular inhibition potency while analogs **28** and **30** exhibited a further loss (200-fold) in cellular inhibitory potency when compared with the isolated enzyme inhibitory potency. Analog **31**, however, showed no loss in cellular inhibitory potency when compared with the corresponding enzyme inhibition potency. Compounds **21** and **31** were tested in the cell-based HCV replicon system containing 40% human serum, in order to determine the effect of plasma protein binding on biological activity. Each compound showed an approximate loss of 30- to 400-fold when compared to the replicon assay performed in 5% fetal calf serum, indicating the compounds to be highly plasma protein bound. Compounds **21** and **31** were subsequently determined to be greater than 99% plasma protein bound.

Finally, we evaluated the pharmacokinetic properties of compound **21** as an orally administered agent in rats. The analog was administered as a solution in vehicle at a dose of 5 mg/kg and exhibited 35% bioavailability. The C_{max} was low (0.18 μM), the plasma AUC was 2.54 (mg h)/ml with modest clearance (0.74 L/h/kg), and the half-life was 2 h. We analyzed the liver tissue drug concentrations for compound **21** and determined the liver to plasma ratio at 8 h to be 54. Suggesting that a significant amount of the compound accumulated in the liver over the course of the experiment.

A series of *N*-1-benzyl and *N*-1-[3-methylbutyl]-4-hydroxy-1,8-naphthyridon-3-yl benzothiadiazine analogs were prepared and evaluated as inhibitors against NS5B RdRp genotype 1 enzyme. The oxyacetamide, compound **21**, exhibited excellent inhibition of both genotype 1 strains and showed excellent genotype 1b inhibition of viral replication in a cell-based assay. Compound **21** exhibited modest pharmacokinetic properties, however, the liver to plasma ratio suggested that the compound was accumulating in the liver, the site of HCV replication. Compounds **21** and **31,** when evaluated in the HCV replicon assay containing 40% human serum, showed an approximate 30- to 400-fold loss in potency when compared to the values obtained in 5% fetal calf serum. Subsequent measurements of compounds **21** and **31** in the presence of serum plasma proteins demonstrated that these compounds were highly protein bound. The corresponding N-alkylated acetamide, **26**, exhibited comparable enzyme inhibition potency, however, the cell-based replicon activity was reduced approximately 6-fold. The sulfonamide series of D-ring position 7 analogs, **28**–**31**, exhibited excellent genotype 1b and 1a enzyme inhibition. However, only compounds **29** and **31** exhibited potent cell-based enzyme inhibition. The improved inhibitory potency of compound **31** in the cell-based system may be explained by the smaller size of the methylsulfonamide group when compared to the oxyacetamide group in compound **21**.

In summary, we have discovered a series of position 7 D-ring substituted *N*-1-3-methylbutyl-4-hydroxy-1,8-naphthyridone benzothiadiazines exhibiting improved enzyme inhibition potency and significantly improved cell culture activity. Further evaluation and structural improvements of this particular substituted class of benzothiadiazines are continuing.

Detailed biological protocols for biochemical IC_{50} determinations and cell culture replicon assay EC_{50} determinations are available in the Supplementary data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.04.022.

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