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Bioorganic & Medicinal Chemistry Letters 17 (2007) 2289–2292
Bioorganic & Medicinal Chemistry Letters

Inhibitors of HCV NS5B polymerase: Synthesis and structure–activity relationships of unsymmetrical 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene benzothiadiazine derivatives

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Received 12 December 2006; revised 15 January 2007; accepted 18 January 2007
Available online 27 January 2007

Abstract—Substituted 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene benzothiadiazine derivatives were investigated as inhibitors of genotype 1 HCV polymerase. Structure–activity relationship patterns for this class of compounds are discussed. It was found that the saturated alkane dialkyl units provided the most active analogs.

Hepatitis C virus (HCV) is a (+)-strand RNA virus of the *Flaviviridae* family that was first identified in 1989.[1] HCV is a common pathogen that can lead to cirrhosis, hepatocellular carcinoma (HCC) and liver failure. It is estimated that 170 million people were infected worldwide in the year 2000, and that the virus is responsible for at least 10,000 deaths annually in the United States alone.[2] HCV has six major genotype classes, with genotypes 1 and 2 being the most prevalent in the United States, Europe, and Japan.[3] Currently combination drug treatment of genotype 2 or 3 is more successful than treatment of genotype 1 infection.[4,5] Moreover, existing therapies are hampered by drug-related toxicities. Therefore there is a particular need for new therapies directed toward genotype 1 HCV infection.[6]

Our research group has been pursuing inhibition of the HCV NS5B RNA-dependent RNA polymerase (RdRp) enzyme by hydroxyquinolon-3-yl-benzothiadiazines.[7] Other groups have reported nucleoside as well as other non-nucleoside inhibitors of this viral enzyme.[8] We have also recently transformed the B ring in the hydroxyquinolon-3-yl-benzothiadiazine series into a dialkyl naphthalene unit.[9] We refer to this related series as the 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalenes. Upon generation of a small set of 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs, the SAR data initially suggested that the most potent analogs contain an unsymmetrical dialkyl unit in the B ring as shown in Table 1.[10]

These data imply that the two alkyl groups are binding into different pockets or environments within the HCV polymerase enzyme. The data also imply that one of the two enantiomers of a racemic mixture should be more active than the other. Thus we embarked upon a strategy to assemble a set of unsymmetrical 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs in order to optimize both the biochemical (recombinant HCV polymerase) and antiviral (HCV subgenomic replicon)[11] potencies of this series. We felt that we would be able to construct a number of these desired analogs by employing a late stage olefin metathesis reaction upon the allyl group of thiadiazine **4**, represented in Figure 1. This paper highlights the efforts directed toward that strategy.

The chemistry utilized to prepare the 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs is shown

Keywords: HCV; NS5B; Polymerase; 1-Hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene benzothiadiazine.
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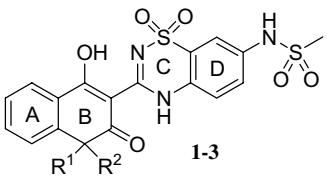
doi:10.1016/j.bmcl.2007.01.072

Table 1. Biochemical and cell culture replicon potency of analogs **1**–**3**



1-3

Compound	R^1	R^2	Polymerase 1a, IC_{50}[a] (nM)	Replicon 1a, EC_{50}[a,b] (nM)
1	Me	Me	933	—
2	Isoamyl	Isoamyl	68	423
3	Me	*n*-Propyl	20	184

[a] IC_{50} and EC_{50} values in all tables are means of at least two independent determinations, standard deviation ± 10%. Detailed protocols can be found in Supplementary material.
[b] Assay run with 5% fetal calf serum.

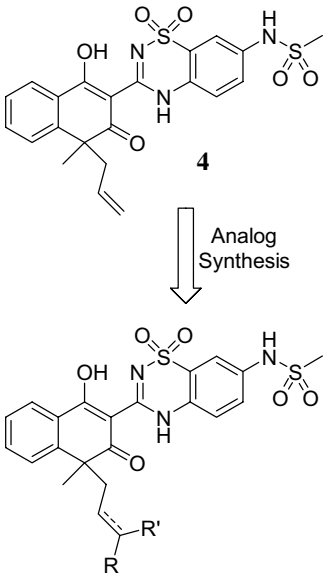
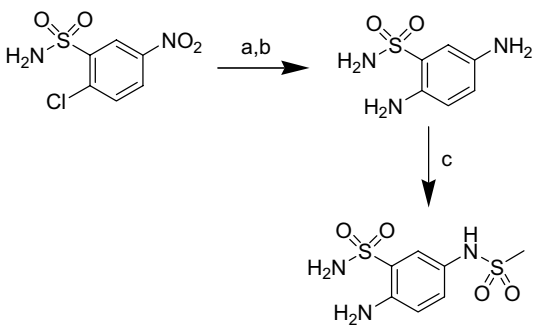


Figure 1. Synthetic strategy for producing C-4 dialkyl analogs.

in Scheme 1–3. First, the bis-sulfonamide aniline, **5**, was prepared as shown in Scheme 1. 2-Chloro-5-nitrobenzene-sulfonamide was converted into 2-amino-5-nitrobenzenesulfonamide.[12] Reduction of the nitro moiety followed by a chemo-selective mesylation gave the desired benzothiadiazine precursor **5**.



Scheme 1. Reagents and conditions: (a) $(NH_4)_2CO_3$, $CuSO_4$, NH_4OH, 120 °C, 4 h, sealed tube, 90%; (b) $Na_2S_2O_4$, 1 N NaOH, 70%; (c) $MeSO_2Cl$, CH_2Cl_2, pyridine, 18 h, 68%.

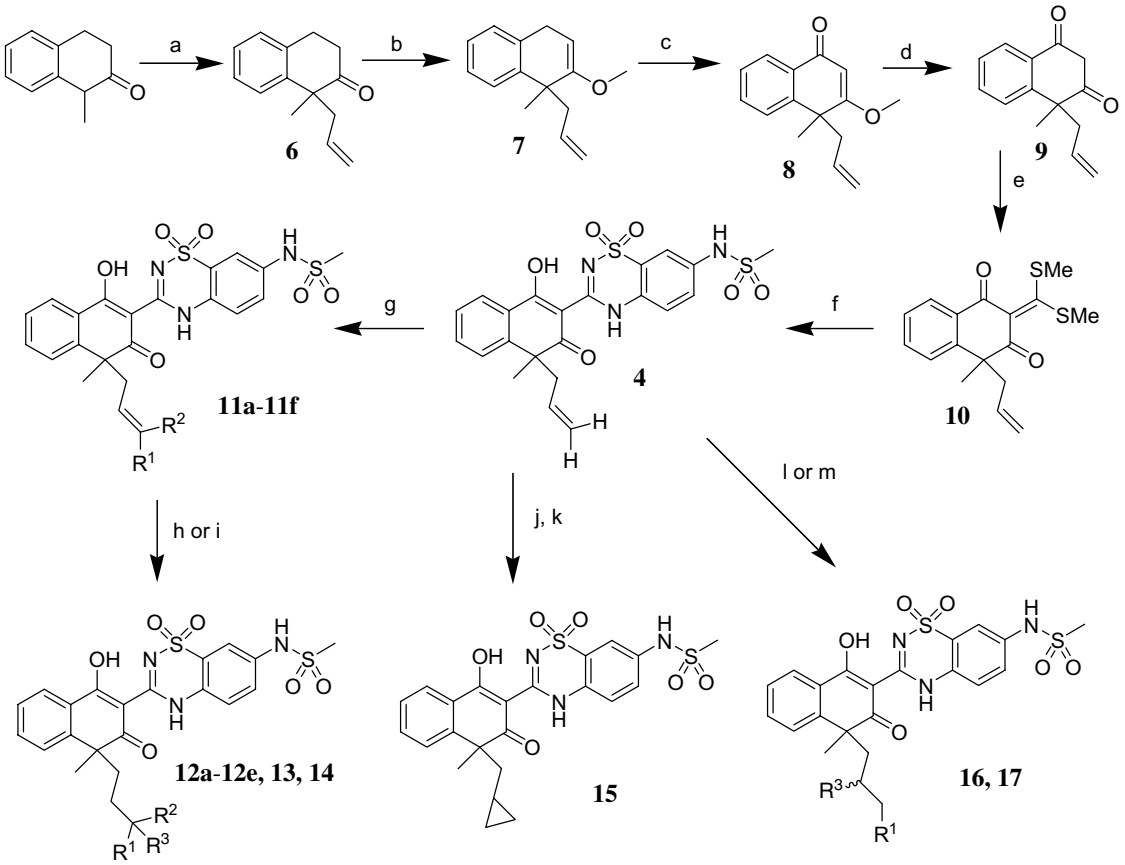
Scheme 2 depicts the synthetic transformations employed to prepare many of the unsymmetrical 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs. Commercially available 1-methyl-2-tetralone was allylated with palladium catalysis employing a racemic mixture of the cyclohexyl 2-DPPBA ligand developed by Trost in order to accelerate the reaction.[13] This reaction provided dialkylated tetalone **6**, from which the corresponding enol ether (**7**) was made followed by oxidation and hydrolysis to the unsymmetrical dialkyl diketone (**9**). Formation of the dithioketene acetal (**10**) allowed a mild, neutral coupling to amino-sulfonamide **5**, which provided the methyl, allyl-benzothiadiazine **4**. Reaction of this material (**4**) with a variety of alkenes employing the Hoveyda–Grubbs 2nd generation catalyst produced a number of differentially substituted alkene analogs (**11a**–**11f**). These alkene analogs could then be transformed easily into the corresponding alkane analogs (**12a**–**12e**) by simple hydrogenation.

Analogs **13** and **14** were both produced upon hydrochloric acid treatment of alkene **11a**. The methyl cyclopropyl analog **15** was generated by reacting **4** with diazomethane and palladium acetate. This reaction generates the requisite cyclopropyl group along with the 1-methyl ether in ring B. This methyl ether was then hydrolyzed back to the enol functionality upon heating with base. Additionally, two hydroxylated analogs (**16**, **17**) were also produced from the methyl allyl compound **4** via hydroboration and osmylation, respectively (Scheme 2).

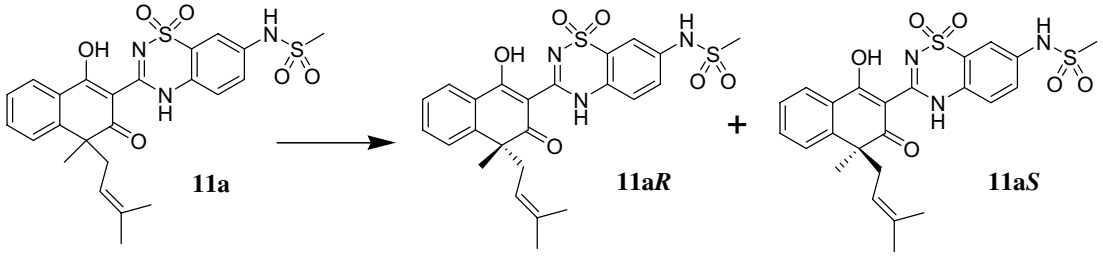
The racemic unsymmetrical 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analog **11a** could be separated into the corresponding enantiomeric isomers (**11a*R*** and **11a*S***) by use of chiral chromatography (Scheme 3). The absolute configuration of each isomer was tentatively assigned as shown.

Table 2 details the biochemical potencies of the unsymmetrical 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs against genotypes 1b and 1a. In addition the activities against the HCV genotype 1a subgenomic replicon in tissue culture are included. All of the analogs are more potent against genotype 1a versus genotype 1b in the biochemical assay. Two of the analogs, **11f** and **17**, which contain more polar ester and diol functionalities respectively, are less potent than other analogs that contain hydrophobic functionalities. This suggests that the binding pocket in this region is hydrophobic in nature.[7a] Analogs **11b** and **12b** each containing a phenyl group, are exceptions to this trend, suggesting that they are too sterically encumbered to fit well within this hydrophobic pocket.

In every case the saturated alkane analogs are several fold more active than the corresponding alkene analogs (**11a**–**11e** vs **12a**–**12e**) in both biochemical and replicon assays. When the isoamyl group in compound **12a** was



Scheme 2. Reagents and conditions: (a) allyl acetate, 0.25 mol % Pd_2dba_3, Cs_2CO_3, 0.5 mol % racemic Trost ligand [1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl)], THF, 24 h, 90%; (b) $(MeO)_3CH$, 5% toluene sulfonic acid, methanol, 60 °C, 2 h, 75%; (c) pyridinium dichromate, *tert*-butylhydroperoxide, Celite, benzene, 1 h, 25%; (d) 1 N aq NaOH, MeOH, reflux, 16 h, 80%; (e) $(MeS)_3C^+$ $MeSO_4^-$, pyridine, dioxane, 100 °C, 1.5 h, 96%; (f) dioxane, sulfonamide **5**, 85 °C, 18 h, 46%; (g) 20 equiv substituted alkene, 4 mol % Hoveyda–Grubbs 2nd generation catalyst, CH_2Cl_2, sealed tube, 70 °C, 18–120 h, **11a**–**11f**, (27–72%); (h) 10% Pd/C, MeOH, THF, hydrogen balloon, 18–24 h, **12a**–**12e**, (50–100%); (i) when R^1, R^2 = Me, dioxane, 6 N aq HCl, 65 °C, 3 h, **13** (14%) and **14** (9%); (j) $Pd(OAc)_2$, CH_2N_2, THF, 3 h; (k) 1 N aq NaOH, dioxane, reflux, **15**, (23%, two steps (j and k)); (l) borane–THF complex, THF, 16 h, **16**, (58%); (m) OsO_4, NMO, acetone, water, 18 h, **17**, (19%).



Scheme 3. Racemic **11a** was chromatographed on a Chiralcel OD (4.6 × 250 cm) column using a mobile phase of Hex/EtOH/MeOH/TFA (70:15:15:0.1) to yield **11a*R*** (43%, 92% ee) and **11a*S*** (42%, >99% ee).

lengthened to the larger ethyl cyclobutyl (**12c**), ethyl cyclopentyl (**12d**), and ethyl cyclohexyl (**12e**), both the biochemical and cell culture activities decreased in that same order. When a slightly smaller methyl cyclopropyl compound (**15**) was tested, it demonstrated activity comparable to the ethyl cyclobutyl (**12c**) compound. Thus, the most potent compound produced in this set was the methyl isoamyl analog (**12a**) with an EC_{50} value of 17 nM in the replicon assay. As expected, when the two enantiomers **11a*R*** and **11a*S*** of a racemic analog (**11a**) were tested separately, one of them was substantially more active than the other in the biochemical assay (approx. 35-fold).

In summary, a number of unsymmetrical 1-hydroxy-4,4-dialkyl-3-oxo-3,4-dihydronaphthalene analogs were synthesized by employing a late stage olefin metathesis reaction. These analogs were assessed for inhibitory potency against genotype 1 HCV polymerase. Overall we observed that the saturated dialkyl analogs displayed the most potent biochemical and cell culture replicon activities.

Table 2. Biochemical and cell culture replicon potency of analogs **4** and **11–17**

Compound	R^1	R^2	R^3	Polymerase 1b, IC_{50} (nM)	Polymerase 1a, IC_{50} (nM)	Replicon 1a, EC_{50} (nM)
4	H	H	—	225	18	690
11a	Me	Me	—	147	38	237
11b	Ph	H	—	1850	460	—
11c	Cyclobutyl		—	425	87	1120
11d	Cyclopentyl		—	550	93	1490
11e	Cyclohexyl		—	910	195	—
11f	COOEt	H	—	5870	1080	>10,000
12a[a]	Me	Me	H	7	4	17
12b	Ph	H	H	280	115	—
12c	Cyclobutyl		H	36	16	190
12d	Cyclopentyl		H	70	32	320
12e	Cyclohexyl		H	194	57	2710
13	Me	Me	OH	193	43	8000
14	Me	Me	Cl	70	39	2170
15	Methyl cyclopropyl			40	21	160
16	OH	—	H	—	—	860
17	OH	—	OH	—	450	—
11a*R*	Me	Me	—	32	19	134
11a*S*	Me	Me	—	—	702	—

[a] See Ref. 14.

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

Acknowledgment

We thank Chong Chen from the GPRD Process Chemistry Group for helping with the chiral chromatography.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.01.072.

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