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# Synthesis and SAR of novel 1,1-dialkyl-2(1*H*)-naphthalenones as potent HCV polymerase inhibitors

Todd D. Bosse,* Daniel P. Larson, Rolf Wagner, Doug K. Hutchinson, Todd W. Rockway, Warren M. Kati, Yaya Liu, Sherie Masse, Tim Middleton, Hongmei Mo, Debra Montgomery, Wen Jiang, Gennadiy Koev, Dale J. Kempf and Akhter Molla

*Infectious Disease Research, Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL 60064, USA*

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**Abstract**—A series of *gem*-dialkyl naphthalenone derivatives with varied alkyl substitutions were synthesized and evaluated according to their structure–activity relationship. This investigation led to the discovery of potent inhibitors of the hepatitis C virus at low nanomolar concentrations in both enzymatic and cell-based HCV genotype 1a assays.


Hepatitis C virus (HCV) is a small RNA virus that belongs to the family flaviviridae and is the sole member of the genus hepacivirus. Six major genotypes and more than 100 subtypes of HCV have been identified, having marked geographic variation in relative frequencies. The most common genotypes in the United States are genotypes 1a and 1b (approximately 75%), 2a and 2b (approximately 15%), and 3 (approximately 7%).[1]

An estimated 180 million people are chronically infected with HCV worldwide; with 3–4 million newly infected patients each year. In the United States, an estimated 4.1 million people (1.6%) have been infected with HCV, of whom 3.2 million are chronically infected. Chronic HCV infection is a major cause of liver fibrosis and hepatocellular carcinoma.[2] Currently, the standard of care for the treatment of HCV is pegylated interferon-α (IFN-α) in combination with ribavirin.[3] This combination therapy yields a sustained viral response (SVR) for about 50% of patients with genotype 1, 4, 5, and 6 HCV and a response for about 85% of patients infected with genotype 2 and 3 HCV.[2] A sustained viral response occurs when there is no trace of HCV RNA present in the patient's blood immediately after treatment and also six months post-treatment. Besides being only somewhat effective, the current therapies are costly and cause a variety of side effects, including depression, irritability, headaches, anemia, and nausea. HCV infection represents a major unmet medical need, therefore, the discovery of novel, small molecules that successfully treat HCV infection remains an area of intense focus for the pharmaceutical industry.

The virus is made up of a core protein, two enveloped proteins E1 and E2, and non-structural proteins NS2–NS5 that are essential for viral replication, translation, and polyprotein processing.[3] Efforts to develop anti-HCV agents have focused on the inhibition of key viral enzymes. Most pharmaceutical research can be categorized into the following types: E2 binding inhibitors, NS2 protease inhibitors, NS3 protease inhibitors, NS5A inhibitors, helicase inhibitors, IRES inhibitors, and polymerase inhibitors. Our research has focused on the virally encoded RNA-directed RNA polymerase as the primary initial antiviral target. The NS5B portion of the HCV genome encodes for the polymerase, an enzyme that is pivotal in viral replication and is thus a primary target for drug development.[3]

Previous work described the discovery of *N*-1-heteroalkyl-4-hydroxyquinolon-3-yl-benzothiadiazines, analog **1** (Fig. 1), which eventually led to a new series where the B ring was transformed to include a quaternary carbon center, analog **2** (Fig. 1). This new scaffold was the basis

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* Corresponding author. Tel.: +1 847 938 4442; fax: +1 847 938 2756; e-mail: todd.bosse@abbott.com

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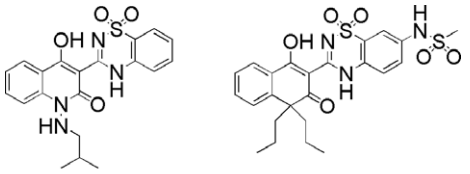


**Figure 1.** Examples of *N*-1-heteroalkyl-4-hydroxyquinolon-3-yl-benzothiadiazine (**1**) and symmetrical *gem*-dialkyl naphthalenone (**2**) HCV polymerase inhibitors.

for a series of symmetrically substituted *gem*-dialkyl naphthalenones.[4,5] The scaffold consisted of four six-membered rings; the A-ring consisted of a phenyl ring that lacks any substitution, the B-ring containing the *gem*-dialkyl substitution site, the C-ring containing the thiadiazine ring, and the D-ring consisting of a phenyl ring with a methane sulfonamide substitution (Fig. 2). In the *N*-1-heteroalkyl-4-hydroxyquinolon-3-yl-benzothiadiazine series, the most potent inhibitors contained small alkyl or carbocyclic substituents and exhibited $IC_{50}$'s between 50–100 and 200–400 nM against genotype 1b and 1a HCV polymerase, respectively.[4] Our lead compound became the dipropyl substituted compound **2** (Fig. 1), which is a selective inhibitor of HCV genotype 1a replication, with an $IC_{50}$ of 99 nM in the HCV polymerase enzyme assay and an $EC_{50}$ of 603 nM in a cell-based assay.[5] In a logical extension of the investigation of dialkyl analogs, our attention turned toward unsymmetrical dialkyl compounds. Specifically, we investigated the SAR of methyl/alkyl substitution at the 1-position of the tetracyclic core.[6] Most of our SAR investigations were limited to analogs with substitutions on the 1-position of the B-ring and 7-position of the D-ring. Since earlier investigations of the SAR at the 7-position of the tetracyclic thiadiazines revealed the optimal substitution to be the methyl sulfonamide, analogs with this substituent were chosen as the basis for our unsymmetrical dialkyl series.[7]

The synthesis of the *gem*-dialkyl naphthalenones is outlined in Scheme 1. The synthesis was initiated by the deprotonation of commercially available benzyl 2-phenylpropanoate **3** (or benzyl 2-butanoate in the synthesis of ethyl/isoamyl derivative **4h**) with lithium hexamethyldisilazane in THF. This step was followed by alkylation using the appropriate vinyl or alkyl halide[8] to yield the racemic benzyl ester.

Hydrogenation of the double bond and hydrogenolysis of the benzyl ester occurred in a one-pot reaction to give the corresponding carboxylic acids (**4a**–**g**). The diethyl esters (**5a**–**g**) were synthesized by first converting the carboxylic acids (**4a**–**g**) to the corresponding acid chlorides, followed by addition of the acid chlorides to the magnesium enolate of diethyl malonate. The esters (**5a**–**g**) were treated with neat methanesulfonic acid to afford the dihydronaphthalene esters, which were then decarboxylated to afford the hydroxynaphthalenone analogs **6a**–**g**. The next step of the synthesis involved treatment of analogs **6a**–**g** with tris-methylsulfanyl-methane sulfuric acid monomethyl ester salt[9] to give the dithioketene acetal compounds (**7a**–**g**). Treatment with (4-amino-3-sulfamoyl-phenyl)-carbamic acid *tert*-butyl ester[10] followed by deprotection with HCl yielded the hydrochloride

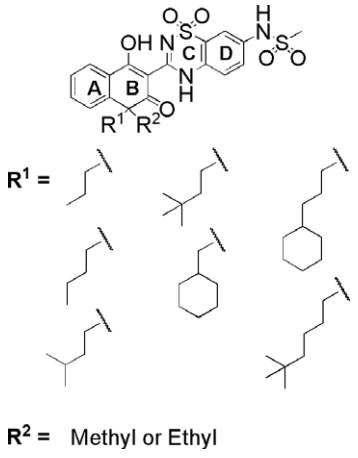
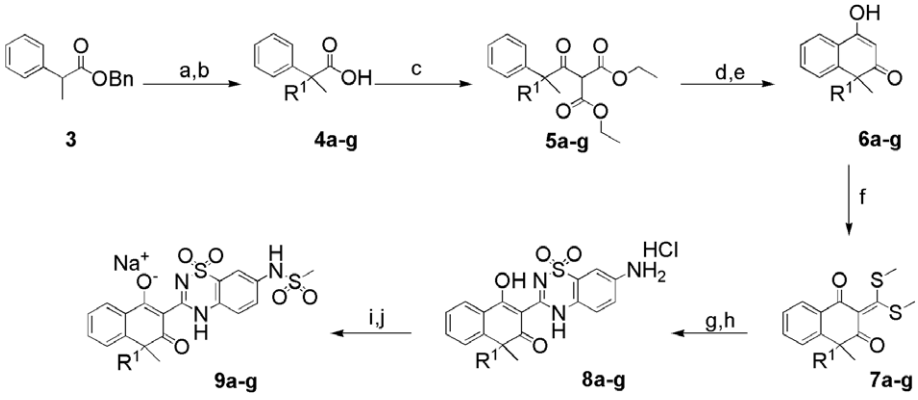



**Figure 2.** Unsymmetrical *gem*-dialkyl naphthalenone HCV polymerase inhibitors.



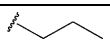
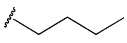
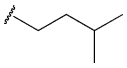
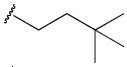
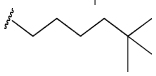
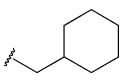
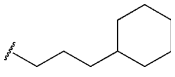
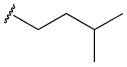

**Scheme 1.** Reagents and conditions: (a) LiHMDS, THF, −78 °C, 30 min, then DMI, $RCH_2Br$, LiI, 72–99%; (b) Pd/C, $H_2$, EtOAc, 93–98%; (c) oxalyl chloride, DMF, hexane, 2 h, then $MgCl_2$, diethyl malonate, $Et_3N$, acetonitrile, 50 °C, 18 h, crude; (d) methanesulfonic acid, 18 h, 51–89%; (e) 1 N aqueous HCl, dioxane, 100 °C, 2 h, 57–75%; (f) $(MeS)_3C^+MeSO_4^-$, pyridine, dioxane, 100 °C, 1 h, 30–99%; (g) (4-amino-3-sulfamoyl-phenyl)-carbamic acid *tert*-butyl ester, toluene, reflux, 6 h, 77–98%; (h) 4 M HCl/dioxane, $CH_2Cl_2$, 1 h, 84–90%; (i) methane sulfonyl chloride, pyridine, acetone, 18 h, 75–96%; (j) aqueous NaOH, 2 h, 95–99%.

salts of the aniline tetracycles (**8a**–**g**). The methane sulfonamides were prepared from **8a**–**g** and then converted to their corresponding sodium salts to afford the target compounds (**9a**–**g**).

The in vitro biological activity of this series of *gem*-dialkyl naphthalenones is shown in Table 1. Our SAR plan involved systematically increasing the steric bulk of substituent R to find the optimal size and shape. The initial set of compounds in our SAR library demonstrated an improvement in potency compared to the lead compound **2**. Even the weakest analog of the initial set, compound **9a**, showed a 5-fold increase in $IC_{50}$ and a 3-fold increase in $EC_{50}$. Compound **9h**, where $R^2$ is ethyl, was synthesized to establish if methyl substitution was best for the series. This compound showed the methyl substitution to be 2-fold more potent in $IC_{50}$ and equipotent in $EC_{50}$ when compared to the corresponding ethyl analog. As the synthesis of our library expanded, we continued to see improvements in activity that corresponded to the increased size of the substituent in the 1-position. Analogs with substitutions of *iso*-amyl (compound **9c**) and *neo*-hexyl (compound **9d**) emerged as the most potent inhibitors. Although the enzymatic assay showed compounds **9c** and **9d** to have nearly equal potency, the cell-based assay showed analog **9d** to have nearly a 5-fold improvement in replicon potency. Compound **9d** showed a 10-fold improvement in $IC_{50}$ and a 75-fold improvement in $EC_{50}$ compared to the lead compound **2**. Substituents slightly larger in size than that in compound **9d**, as shown by the methylcyclohexyl analog **9f**, resulted in roughly equal potency in the enzyme assay but showed a 15-fold decrease in the cell-based assay as compared to compound **9d**.

Since it was our hypothesis, based on modeling data, that larger substituents than the *neo*-hexyl group would result in an overall decrease in potency, our next step in the SAR investigation was to identify an alkyl chain size that was large enough to result in diminished activity. Our theory was confirmed with large alkyl substituted compounds **9e** and **9g**, a 14- and 79-fold decrease, respectively, in $IC_{50}$'s relative to compound **9d**.

**Table 1.** In vitro enzymatic and cell-based inhibitory activities

| Compounds | R1 | R2 | Genotype 1a $IC_{50}$ (nM) | Replicon 1a $EC_{50}$ (nM) |
|---|---|---|---|---|
| **9a** |  | Me | 20 | 184 |
| **9b** |  | Me | 15 | 52 |
| **9c** |  | Me | 7 | 38 |
| **9d** |  | Me | 10 | 8 |
| **9e** |  | Me | 138 | NT |
| **9f** |  | Me | 13 | 121 |
| **9g** |  | Me | 791 | NT |
| **9h** |  | Et | 17 | 49 |

In summary, the structure–activity relationships of novel *gem*-dialkyl naphthalenones as HCV polymerase inhibitors were explored. Attempts to increase potency by modifications on the 1-position carbon of the B-ring have been successful. This series of inhibitors proved to have nanomolar inhibition of both genotype 1a HCV polymerase and the genotype 1a HCV replicon, with the optimized methyl-*neo*-hexyl compound showing a 10- and 75-fold increase in potency, respectively, over the initial lead compound.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.11.088.

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8. All vinyl halides were commercially available except 1-iodo-3,3-dimethyl-butane, 1-bromo-5,5-dimethyl-hex-2-ene, and (3-bromo-propenyl)-cyclohexane. 1-Iodo-3,3-dimethyl-butane was made by conversion of the hydroxyl group of 3,3-dimethyl-butan-1-ol with iodine, triphenylphosphine, and imidazole in dichloroethane. 1-Bromo-5,5-dimethyl-hex-2-ene was made by reacting 3,3-dimethyl-butyraldehyde with vinylmagnesium bromide to give 5,5-dimethyl-hex-1-en-3-ol, which was then reacted with 1,5-hexadiene and thionyl bromide to yield the desired vinyl bromide. (3-bromo-propenyl)-cyclohexane was synthesized using the same procedure described for 1-bromo-5,5-dimethyl-hex-2-ene.
9. The tris-methylsulfanyl-methane sulfuric acid monomethyl ester salt was synthesized by reacting dimethylsulfate with dimethyl trithiocarbonate at 90 °C for 1 h and washing with diethyl ether.
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