Discovery of (*R*)-6-Cyclopentyl-6-(2-(2,6-diethylpyridin-4-yl)ethyl)-3-((5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)methyl)-4-hydroxy-5,6-dihydropyran-2-one (PF-00868554) as a Potent and Orally Available Hepatitis C Virus Polymerase Inhibitor

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Abstract: The HCV RNA-dependent RNA polymerase has emerged as one of the key targets for novel anti-HCV therapy development. Herein, we report the optimization of the dihydropyrone series inhibitors to improve compound aqueous solubility and reduce CYP2D6 inhibition, which led to the discovery of compound **24** (PF-00868554). Compound **24** is a potent and selective HCV polymerase inhibitor with a favorable pharmacokinetic profile and has recently entered a phase II clinical evaluation in patients with genotype 1 HCV.

Hepatitis C virus (HCV[a]) infects over 3% of the world population and is one of the leading causes of chronic liver diseases.[1] Currently there is no vaccine available for HCV, and the standard treatment suffers from both poor response rate (ca. 50%) in patients with genotype 1 and severe side effects. Therefore, a safer and more effective HCV therapy remains a significant unmet medical need.[2]

The HCV genome encodes a poly protein of approximately 3000 amino acids, which is further processed by host peptidases and viral proteases to provide a series of structural and nonstructural proteins. Among all viral enzymes, the HCV RNA-dependent RNA polymerase has been the subject of intense research in the past decade because of its essential role in viral replication and distinct nature from human enzymes. A number of HCV polymerase inhibitors, including both nucleosides,[3] compounds **1** (NM-283[4]), **2** (R-1626[5]), **3** (R-7128[6]), and non-nucleosides, compound **4** (HCV-796[7]), VCH-759 (structure not discloased),[8] GS-9190 (structure not disclosed),[9] and **5** (GSK-625433[10]), have entered human clinical trials and yielded encouraging results in viral load reduction and patient response rate (Figure 1). The development of compounds **1**, **2**, **4**, and **5**, however, has been terminated due to significant side effects. Recently, several additional non-nucleoside inhibitors[11−13] and one nucleoside inhibitor[14] were advanced into phase I trials, followed closely by a number of other agents in preclinical evaluation. The ongoing challenge for all clinical developments of these polymerase inhibitors will be in achieving the appropriate balance between improved efficacy and an acceptable safety profile.

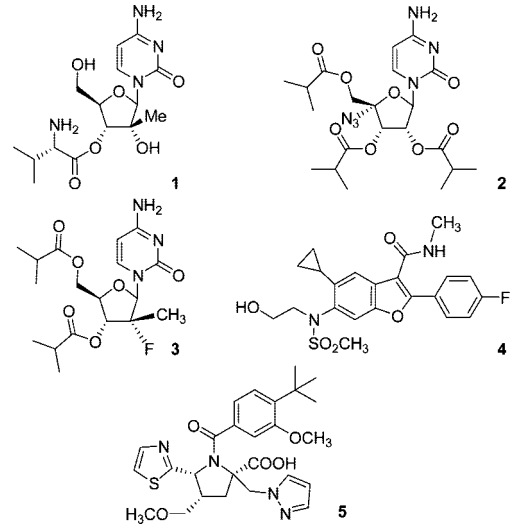
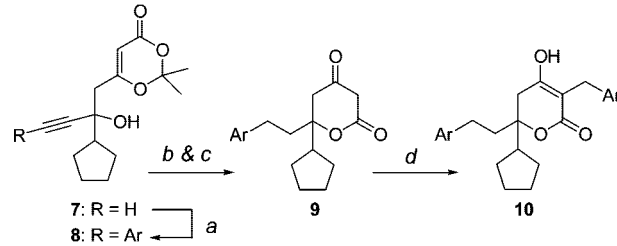


Figure 1. HCV NS5B polymerase inhibitors in clinical trials.

Scheme 1. Synthesis of Carbon-Linked Dihydropyrone[a]



[a] Reagents and conditions: (a) ArBr, $Pd(PPh_3)_2Cl_2$, CuI, *i*-Pr_2NH, DMF, 90 °C; (b) $Pd(OH)_2$, H_2, MeOH, 25 °C; (c) K_2CO_3, MeOH, 45 °C; (d) Ar′CHO, MeOH, $BH_3 \cdot SMe_2$, 25 °C.

We have identified and optimized a series of dihydropyrones as HCV polymerase inhibitors that bind to an allosteric site in the thumb domain of the protein.[15] In our previous communications,[16,17] we reported the structure−activity relationship (SAR), which led to the identification of compound **6**, a potent and selective HCV polymerase inhibitor with favorable pharmacokinetic profiles. During the subsequent scale up effort, however, a new crystalline form emerged with significantly lower solubility (ca. 80-fold less). In vivo animal pharmacokinetic studies later confirmed that this new form of compound **6** displayed significant reduction in exposure levels and bioavailability after oral dosing, which made further development of this compound unlikely.

In addition to its low aqueous solubility, compound **6** was a potent inhibitor of the cytochrome P450 isozyme 2D6 (CYP2D6) with an IC_{50} of 0.3 μM. Although representing only approximately 2−4% of the total human liver cytochrome P450 content, CYP2D6 plays a prominent role in the oxidation of xenobiotics.[18] Because most HCV patients are on combination therapy with other medications and a portion of human population already has a deficiency in this key metabolism enzyme due to genetic polymophism, it is highly desirable for any new anti-HCV therapy to avoid potential complications of

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[a] Abbreviations: HCV, hepatitis C virus; CYP2D6, cytochrome P450 isozyme 2D6.

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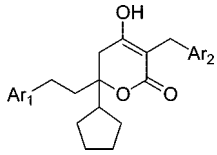
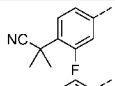
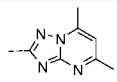
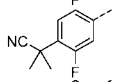
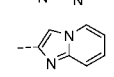
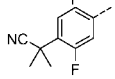
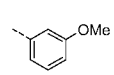
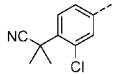
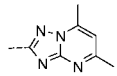
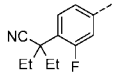
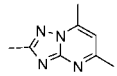
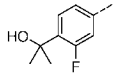
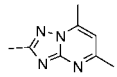
Table 1. CYP2D6 Inhibitory Profiles of C-Linked Dihydropyrones



Compd	Ar_1	Ar_2	CYP 2D6 IC_{50} (uM)	IC_{50}[a] (uM)	EC_{50}[b] (uM)	CC_{50}[b] (uM)
6			0.30	0.003	0.015	>32
11			0.70	0.18	0.15	>32
12			0.77	0.088	2.9	>32
13			3.9	0.002	0.074	>32
14			>6	0.005	0.016	>32
15			>6	0.14	0.059	>32

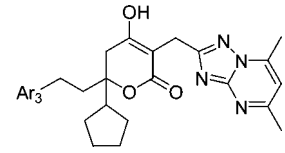
[a] HCV NS5B Δ21 genotype 1b BK strain.[16] [b] Antiviral activity (EC_{50}) and cytotoxicity (CC_{50}) were generated in the genotype 1b-con1 reporter replicon assay.[20]

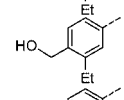
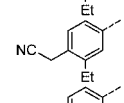
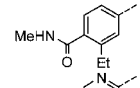
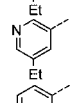
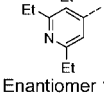
drug−drug interactions in clinical development. In this paper, we report our efforts specifically addressing these two issues associated with compound **6**.

The dihydropyrone was readily synthesized from the acetylene intermediate **7** as reported previously (Scheme 1).[17] A palladium catalyzed Sonogashira reaction between aromatic bromides and alkyne **7** provided compound **8** in good yields. Hydrogenation of the carbon−carbon triple bond in the presence of $Pd(OH)_2$, followed by a cyclization reaction with K_2CO_3 in MeOH at 45 °C, yielded the desired dihyropyrone core **9**. Introduction of the right-hand aromatic group was accomplished through a borane−dimethyl sulfide mediated coupling reaction with aromatic aldehyde in MeOH.

Given the importance of CYP2D6 in drug metabolism, several pharmacophore models have been developed and recently a crystal structure of human CYP2D6 has also been reported. The triazolopyrimidine system in compound **6** is only mildly basic (ACD pK_a ∼ 1.5) and not sufficient to make a salt bridge interaction with acidic residues in the CYP proteins. Indeed, compound **11**, which removed two nitrogen atoms from compound **6**, was still a potent CYP2D6 inhibitor with an IC_{50} of 0.70 μM. A more structurally distinct analogue **12**, containing a simple 3-methoxyphenyl moiety, also demonstrated potent CYP2D6 inhibition (IC_{50} = 0.77 μM) with much reduced activity in the cell-based replicon assay[19,20] (EC_{50} = 2.9 μM) against HCV (genotype 1b). On the contrary, structural modifications in the Ar_1 region had a much more dramatic impact on their CYP2D6 inhibitory properties. Substitution of a fluorine atom at the 3-position with a chlorine (compound **13**, Table 1) resulted in a 13-fold reduction in CYP2D6 inhibition (IC_{50} = 3.9 μM). Alternatively changing from a *gem*-dimethyl-cyano group at the 4-position to the corresponding *gem*-diethyl-cyano dramatically reduced its potency against CYP2D6 (compound **14**, CYP2D6 IC_{50} > 6 μM). Finally, replacement of the cyano group of compound **6** with a hydroxyl group completely eliminated detectable inhibition of CYP2D6 (compound **15**, Table 1).

Table 2. Further Optimization of C-Linked Dihydropyrones



Compd	Ar_3	IC_{50}[a] (uM)	EC_{50}[a] (uM)	CC_{50}[a] (uM)	Hu Hepatocyte[b] % remaining
16		0.010	0.59	>32	NA
17		0.003	0.028	>32	37.1
18		0.008	0.025	>32	54.2
19		0.006	0.19	>32	85.1
20		0.007	0.33	>32	33.9
21		0.008	0.043	>32	77.8
22		0.010	0.10	>32	93.9
23		0.016	0.067	>32	84.7
24	Enantiomer 1 of 23	0.007	0.041	320	88.5
25	Enantiomer 2 of 23	0.012	0.31	320	83.8

[a] Genotype 1b. [b] Percentage remaining after 4 h incubation with human hepatocytes.

With all the observations, it became evident that the cyano group of compound **6** was likely involved in the interaction with the CYP2D6 enzyme, possibly through hydrogen bond interactions. Removal of such interactions or introduction of steric hindrance around the cyano group could alleviate the undesirable drug−drug interaction potential. Modifications in this region of the molecule were also well tolerated with regard to compound potency against the HCV polymerase enzyme, which provided good opportunity for further optimization of HCV potency and selectivity over CYP2D6.

From previous SAR and X-ray cocrystal structural information,[16,17] the left portion of the dihydropyrone inhibitors (Ar_1 in Table 1) provides key hydrophobic interactions as well as a direct hydrogen bond interaction between the nitrogen atom from the cyano group (compound **6**) and the Leu-497 backbone NH in the HCV polymerase protein. In particular, the fluorine at the 3-position and one of the methyl groups off the 4-position in compound **6** occupied two small hydrophobic pockets formed by adjacent amino acid residues, including Leu-419, Met-423, Val-485, Ala-486, Leu-489, and Leu-497. Further examination of X-ray cocrystal structure suggested that an ethyl substitution from the 3-position of the phenyl ring could occupy these two hydrophobic pockets simultaneously. Indeed, compound **16** (Table 2, IC_{50} = 0.01 μM) provided good enzymatic potency and moderate cell-based replicon activity (EC_{50} = 0.59 μM). Further analogues with this key structural feature were synthe-

sized, and their potency against HCV polymerase and metabolic stability in human hepatocyte are summarized in Table 2.

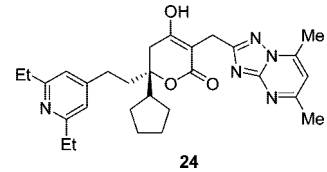
Substitutions at the 4-phenyl position of Ar_3 were well tolerated. Compound **17**, which has a 4-hydroxymethyl group, achieved a 20-fold potency improvement in the replicon assay with low metabolic stability (37.1% remaining after 4 h incubation with human hepatocyte). A cyano replacement of the hydroxyl group in compound **17** resulted in compound **18**, which showed a comparable EC_{50} of 0.025 μM with moderate metabolic stability (54.2% remaining). Introduction of an amide functionality provided the 4-methylbenzamide analogue **19**, which demonstrated significantly improved stability (85.1% remaining). However, its replicon potency improved only 3-fold (EC_{50}= 0.19 μM) as compared to the simple 3-ethylphenyl analogue **16**. Various regioisomers of Et-pyridine as Ar_3 group were also prepared. Substitution of a phenyl ring with a pyridine not only lowered the overall molecular lipophilicity but also provided a basic center for aqueous solubility optimization. While all three isomers showed similar enzymatic potencies with IC_{50} below 0.010 μM, their EC_{50} and metabolic stabilities varied significantly. The 4-Et-pyridine analogue **20** was slightly more potent than the corresponding phenyl analogue **16** in the cellular assay (EC_{50} of 0.33 μM as compared to 0.59 μM) and its metabolic stability was fairly poor, with only 33.9% remaining after hepatocyte incubation. Migration of the ring nitrogen to 3-Et-pyridine (Compound **21**, Table 2) achieved an 8-fold improvement in cell potency (EC_{50} = 0.043 μM) and also increased the compound metabolic stability (77.8% remaining). The 2-Et-pyridine analogue **22** demonstrated the best metabolic stability (93.9% remaining) with a slight decrease in replicon activity (EC_{50} = 0.10 μM) compared to the 3-Et-pyridine analogue **21**. Introduction of another ethyl group (compound **23**, Table 2) further improved EC_{50} to 0.067 μM while maintaining good metabolic stability (84.7% remaining).

Compound **23** was further separated into its enantiomers **24** and **25** by chiral HPLC. The two enantiomers exhibited similar metabolic stability, however, enantiomer **24** was about 8-fold more potent in the cell-based replicon assay than enantiomer **25**.

Examination of the X-ray cocrystal structure of compound **24** bound to HCV polymerase[21] confirmed key protein−ligand interactions (Figure 2). As reported previously in cocrystal structures, binding of dihydropyrone is anchored by the key hydrophobic interactions between the cyclopentyl group and the surrounding hydrophobic pocket (Leu-419, Met-423, Tyr-477, and Trp-528) and the hydrogen bonding network between the dihydropyrone carbonyl and the donor−donor motif of the protein (NH from Ser-476 and Tyr-477) through one direct hydrogen bond and one water-mediated hydrogen bond. The triazolopyrimidine, connected to the dihydropyrone core through a methylene linker, formed a $\pi-\pi$ stacking interaction with His-475. Consistent with our previous hypothesis, hydrophobic interaction between one of the ethyl groups from the pyridine of compound **24** and the polymerase enzyme provided comparable enzymatic potency in spite of the loss of the direct hydrogen bond between the Leu-497 residue and the cyano group of compound **6**.

Compound **24** (PF-00868554) was a potent HCV polymerase inhibitor in both biochemical and cell-based replicon assays and showed no cytotoxicity up to 320 μM concentration. It did not inhibit any of the major CYP isoforms (IC_{50} >30 μM for 1A2, 2C8, 2D6, 3A4, 2C9, and 2C19) and has an aqueous solubility of 2.55 mg/mL (pH 6.2, free base, crystalline material). The in vitro hepatic clearance in monkey microsomes (27 mL/min/kg) as well as in rat microsomes (<20 mL/min/kg) closely correlated with the in vivo clearances (21 ± 4.8 and 21 ± 5 mL/min/kg for rats and monkeys, respectively) (Table 3). The in vivo pharmacokinetic parameters of compound **24** in Sprague−Dawley rats, beagle dogs, and cynomolgus monkeys are summarized in Table 3. In both rats and monkeys, **24** showed moderate plasma clearance and volume of distribution. In dogs, however, **24** exhibited both a low plasma clearance (0.93 ± 0.1 mL/min/kg) and a low volume of distribution (0.25 L/kg). The preclinical results suggested that **24** would be amenable for a twice-daily (BID) dosing regimen.

Table 3. Pharmacokinetic Profiles of Enantiomer **24**



24

species	rat	dog	monkey
po dose (mg/kg)[a]	2	2	NA[f]
iv dose (mg/kg)[b]	2	1	2
CL (ml/min/kg)[c]	21 ± 4.8	0.93 ± 0.1	21 ± 5
V_{dss} (L/kg)[d]	1 ± 0.4	0.25	0.8 ± 0.05
$T_{1/2}$ (h) terminal	2.5 ± 1	4.4 ± 1.1	2.1 ± 0.4
T_{max} (h)	0.94 ± 0.9	1	NA[f]
F (%)[e]	75	49	NA[f]

[a] IV formulation: 50% PEG 200/10% ethanol/40% water. [b] PO formulation: 50%PEG200/10% ethanol/40% water. [c] Total plasma clearance. [d] Volume of distribution. [e] Bioavailability. [f] Data not available.

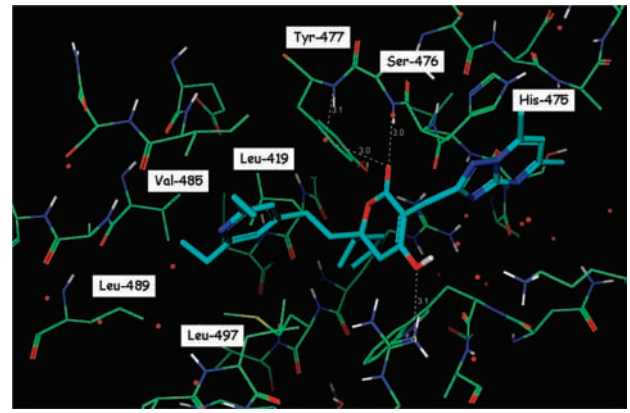


Figure 2. Key protein−ligand interactions from X-ray cocrystal structure of compound **24** in complex with the HCV polymerase 1b-BK NS5B Δ21 construct.

In summary, we have described the discovery of compound **24** as a potent and selective inhibitor of the HCV polymerase. Removal of a cyano group from the previous lead molecule (compound **6**) eliminated the undesirable CYP2D6 inhibition, and introduction of a pyridine aromatic system achieved a good balance between antiviral potency and favorable pharmacokinetic profiles. Compound **24** has recently entered human clinical trials in patients infected with genotype 1 hepatitis C virus. The complete characterization of biological activities of this compound is detailed in a separate paper,[22] and its clinical outcome will be published in future communications.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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