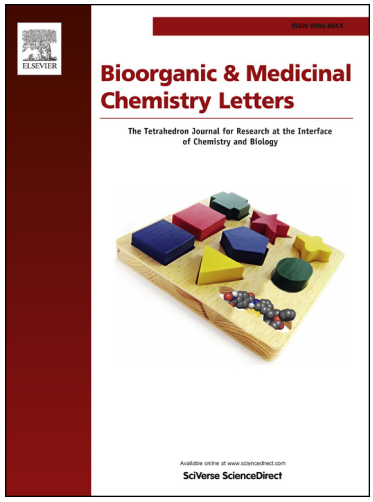

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Synthesis and anti-HCV determinant motif identification in pyranone carboxamide scaffold

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ABSTRACT

Hepatitis C Virus exhibits high genetic diversity. The current treatment for genotype-1 with ~80% sustained virologic responses is a combination of pegylated interferon, ribavirin and boceprevir/telaprevir/simeprevir which is associated with several side effects and need close monitoring. Therefore, novel therapies are invited for safer and more efficient treatment. This study was designed for synthesis of new α-pyranone carboxamide analogs for evaluation of anti-HCV activity to delineate structure-activity relationship (SAR) and to identify anti-HCV determinant motif on this new scaffold. Forty four new α-pyranone carboxamide analogs were synthesized. Six potential anti-HCV candidates **11a** (EC_{50} = 0.35 μM), **11e** (EC_{50} = 0.48 μM), **12f** (EC_{50} = 0.47 μM), **12g** (EC_{50} = 0.39 μM), **12h** (EC_{50} = 0.20 μM) and **12j** (EC_{50} = 0.25 μM) with lower cytotoxicity (CC_{50} > 20 μM) were discovered through cell based HCV replicon system. The activity profile of forty four new α-pyranone carboxamide analogs suggests the role of an aromatic motif in the **B** region to add a synergistic effect to NHOH motif at 4-position and revels an anti-HCV activity determinants motif under this scaffold. The biochemical assay against most promising HCV target protein "NS3 protease and NS5B polymerase" showed no activity and open a scope to explore new mechanism inhibitor.

Hepatitis C Virus (HCV) is a positive stranded RNA virus of *Flaviviridae* family that exhibits high genetic diversity.[1] HCV is classified into six major types of genomes (genotype 1-6) which are further divided into subtypes and has different geographic distributions.[2] The major part of liver epidemiology and related death toll corresponds to chronic HCV infection.[3] The current treatment for genotype-1 with ~80% sustained virologic responses is a combination of pegylated interferon, ribavirin and boceprevir/telaprevir/simeprevir.[4] This therapy is associated with flu-like symptoms, anaemia, loss of appetite, depression etc. and need close monitoring.[5, 6] Therefore, novel therapies are invited for safer and more efficient treatment. In our previous investigation,[7] we had evaluated anti-HCV activities of new analogs based on 4-hydroxyamino-α-pyranone carboxamide (**I**, **Fig. 1**) with various combinations of **A** (phenyl/ substituted phenyl) and **B** (phenyl/substituted phenyl/alkyl/alkanol/alkyl ester/ benzyl). We observed that when **A** and **B** both were phenyl, the compound was highly active with EC_{50} 0.35 μM.[7] However, substitution on **A** shown a tendency to decrease the anti-HCV potential of compounds irrespective of whether **B** is phenyl/substituted phenyl/alkyl/ alkanol/alkyl ester/benzyl.

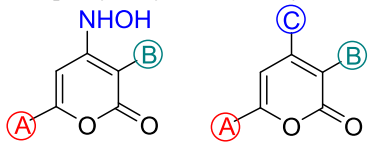

Figure 1 4-hydroxyamino-α-pyranone carboxamide scaffold **I** and the scaffold for present investigation (**II**).

Interestingly, **B** as substituted phenyl/alkyl/alkanol/benzyl and **A** as phenyl, resulted highly active analogs with EC_{50} in the range of 0.15-0.55 μM. Therefore, in the current study several new α-pyranone carboxamide analogs **II** (**Fig. 1**) with; **i**) **A** (phenyl/thiophen-2-yl), **B** (substituted phenyls), **C** (4-NHOH) or **ii**) **A** (phenyl/substituted phenyl), **B** (cycloalkyls), **C** (4-NHOH) were synthesized and evaluated for anti-HCV potential to

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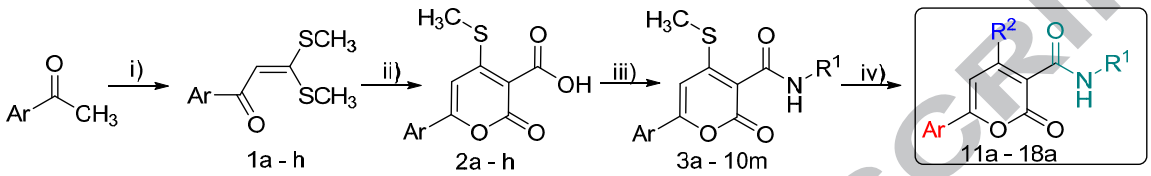
delineate possible structure activity relationship (SAR). We were also interested to investigate the determining role of 4-NHOH moiety on the pyranone carboxamide scaffold towards anti-HCV activity. Thus, replacement studies were carried out with very close motif 4-NH$(CH_2)_2$OH. The role of "NH" and "OH" in the substitution at 4-position was evaluated by replacing the 4-substituent with a -NHOMe (OH absent) or piperidinyl (both OH and NH absent) group.

Ketene dithioacetals are versatile synthons to generate various key intermediates for further exploration towards several new chemical scaffolds.[8] Functionalized ketene dithioacetals (**1a-h, Scheme 1**) were synthesized from the reaction of appropriate aromatic ketones with CS_2 followed by methyl iodide. Our final compounds (**11a-18a**, **Table 1**) contain an amide bond at C-3 position on α-pyranone ring. To achieve this amide linkage, α-pyranone-3-carboxylic acids (**2a-h**) were synthesized from ketene dithioacetals (**1a-h**) by reacting them with diethylmalonate (DEM) in presence of NaH.[7] Appropriate amines were coupled with **2a-h** to get the key amide intermediates **3a-10m**. The SMe group at 4-position of amides was substituted by the reaction of hydroxylamine/2-aminoethanol/piperidine/*O*-methyl hydroxylamine to get the final compounds (**11a-18a**).[9,10] All the synthesized compounds were characterized by physical and spectroscopic analysis.



Scheme 1. Synthesis of 4-substituted α-pyranone carboxamide based analogs (**11a-18a**).
Reagents and conditions: **i**) NaH, CS_2, CH_3I, THF, 0 °C-rt, 4h; **ii**) NaH, diethylmalonate, dioxane, 0-110 °C, 6h; **iii**) R_1NH_2, HATU, DMF, rt, 1-2h; **iv**) appropriate amine, $NaHCO_3$, ethanol, 80 °C, 4h.

The anti-HCV assay of **11a-18a** was carried out in cells harbouring subgenomic HCV RNA replicons (genotype 1b) with a luciferase reporter (LucNeo#2).[11] The anti-HCV activities were determined by their ability to reduce luciferase activity in HCV RNA replicons. The cytotoxicities were evaluated by reduction in number of viable cells using a tetrazolium dye method. The 50% effective concentration (EC_{50}) and 50% cytotoxic concentration (CC_{50}) were determined from the inhibition of luciferase activity and reduction in viable cell number respectively (**Table 1**). The compounds **11a-b, 11e, 12b, 12e-h, 12j** were highly active with EC_{50} ranging between 0.2 to 0.7 μM and in addition showed lower cytotoxicity (CC_{50} > 20 μM). The compounds **11c-d, 11f-n, 12a, 12c, 12i** were moderately active (EC_{50} ranging between 1 to 5 μM). The compounds with EC_{50} > 5 μM were considered inactive. Telaprevir, a US FDA approved NS3 protease inhibitor (EC_{50} = 0.36 μM, CC_{50} > 20 μM) was used as reference. Compounds **11a** (EC_{50} = 0.35 μM, CC_{50} > 20 μM) and **12g** (EC_{50} = 0.39 μM, CC_{50} > 20 μM) were very close to telaprevir in their biological profiles while **12h** (EC_{50} = 0.2 μM, CC_{50} > 20 μM) and **12j** (EC_{50} = 0.25 μM, CC_{50} > 20 μM) showed higher activity. The anti-HCV activity assay of **12j** in subgenomic HCV RNA replicon cells is shown in **Fig. 2.**

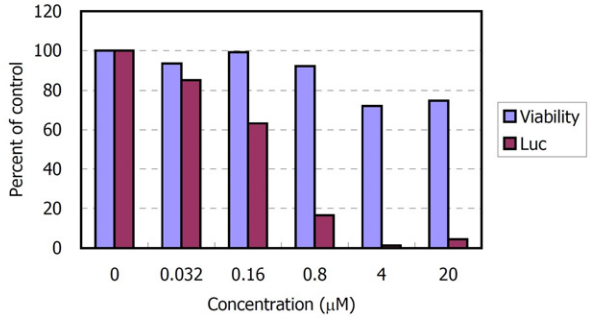


Figure 2. Anti-HCV activity of **12j** (EC_{50} = 0.25 μM, CC_{50} > 20 μM) in subgenomic HCV RNA replicon cells (LucNeo#2). The cell viability and luciferase activity are shown in bars with blue and brown colors respectively.

In the current study, we found that α-pyranone carboxamide analogs (**11a-f**) with **A** as phenyl, **B** as substituted phenyl and **C** as 4-NHOH (A, B & C: **Fig. 1**) were significantly potent which supports our previous results.[7] Cycloalkyl (**B**) with phenyl/substituted phenyl (**A**) and 4-NHOH (**11h-n**) were evaluated to analyze the replacement of an aromatic moiety at **B** with a non-aromatic. We observed drop in activity, however, still noticeable with EC_{50} ranging between 2 to 5 μM. In addition, thiophen-2-yl moiety (**A**) with phenyl/substituted phenyl (**B**), 4-NHOH (**12a-j**) were evaluated and found to be equally good as phenyl analogs with only two exceptions (**12c-d**). The anti-HCV assay of eighteen other analogs (**13a-b, 14a-f, 15a-f** and **16a-d**) with 4-NH$(CH_2)_2$OH and various combination of phenyl/substituted phenyl/thiophen-2-yl were carried out. None of them were found to be active (EC_{50} > 5 μM). These results suggest that an aromatic motif in the **B** region adds a synergistic effect to NHOH at 4-position. This fact is further supported by complete loss of activity in **17a** (EC_{50} > 100 μM) and **18a** (EC_{50} > 100 μM), in which both of them were replaced. It is important to highlight that we have generated several other compounds based on pyranone carboxamide scaffold without NHOH group, which were found inactive in HCV screening (data not shown), however showed antiviral activity against herpes simplex virus.[12, 13] The structure-based descriptors[14] were analyzed and we found that most of the compounds neither violated the Lipinski rule of 5[15] or Jorgensen rule of 3.[16] The synthesized compounds with calculated log $P_{oct/water}$ (clogP, **Table 1**) of 2.7±0.1 and molecular weight (mol. wt.) of 350±10 has potential anti-HCV activity with EC_{50} < 1μM (**Fig. 3**). Whereas compounds of mol. wt. > 360 have higher clogP values (3.0 to 4.5) as well as were inactive.

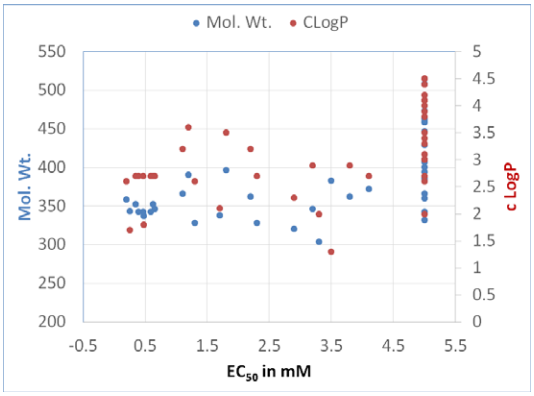


Figure 3. Correlation of anti-HCV activity (EC_{50}) with mol. wt. and calculated clogP of synthesized compounds. The EC_{50} ≥ 5 μM was normalized at 5 to consider as inactive compounds to add clarity in graph.

Table 1 Anti-HCV activities of **11a**- **18a** (**Scheme 1**) and Telaprevir (drug reference).

Comp. no	Ar	R^1	R^2	EC_{50}	CC_{50}	M.wt	clogP[a]
11a	phenyl	2-OMe-phenyl	NHOH	0.35	>20	352.3	2.7
11b	phenyl	3-OMe-phenyl	NHOH	0.63	>20	352.3	2.7
11c	phenyl	2-OEt-phenyl	NHOH	1.1	>20	366.3	3.2
11d	phenyl	3-CF_3-phenyl	NHOH	1.2	19	390.3	3.6
11e	phenyl	2-NH_2-phenyl	NHOH	0.48	>20	337.3	1.8
11f	phenyl	2-OH-phenyl	NHOH	1.7	14.0	338.3	2.1
11g	phenyl	2-OH-5-NO_2-phenyl	NHOH	3.5	>20	383.3	1.3
11h	Phenyl	cyclohexyl	NHOH	2.3	10.5	328.3	2.7
11i	4-F-Ph	cyclopropyl	NHOH	3.3	>20	304.2	2.0
11j	4-F-Ph	cyclohexyl	NHOH	3.2	11.4	346.3	2.9
11k	4-Cl-Ph	cyclopropyl	NHOH	2.9	12.8	320.7	2.3
11l	4-Cl-Ph	cyclohexyl	NHOH	2.2	8.8	362.8	3.2
11m	4-CH_3-Ph	cyclohexyl	NHOH	5.0	10.1	342.3	3.0
11n	4-OCH_3-Ph	cyclohexyl	NHOH	4.1	13.9	372.4	2.7
12a	thiophen-2-yl	Phenyl	NHOH	1.3	>20	328.3	2.6
12b	thiophen-2-yl	4-F-phenyl	NHOH	0.65	>20	346.3	2.7
12c	thiophen-2-yl	4-Cl-phenyl	NHOH	3.8	>20	362.7	2.9
12d	thiophen-2-yl	4-Br-phenyl	NHOH	6.0	>20	407.2	3.0
12e	thiophen-2-yl	2-Me-phenyl	NHOH	0.59	>20	342.3	2.7
12f	thiophen-2-yl	3-Me-phenyl	NHOH	0.47	>20	342.3	2.7
12g	thiophen-2-yl	4-Me-phenyl	NHOH	0.39	>20	342.3	2.7
12h	thiophen-2-yl	4-OMe-phenyl	NHOH	0.20	>20	358.3	2.6
12i	thiophen-2-yl	3-CF_3-phenyl	NHOH	1.8	11	396.3	3.5
12j	thiophen-2-yl	2-NH_2-phenyl	NHOH	0.25	>20	343.3	1.7
13a	Phenyl	2-OEt-phenyl	$NH(CH_2)_2OH$	>20	>20	394.4	3.5
13b	Phenyl	2-OH-phenyl	$NH(CH_2)_2OH$	>20	>20	366.3	2.7
14a	3-Br-Ph	phenyl	$NH(CH_2)_2OH$	>20	>20	429.2	3.9
14b	3-Br-Ph	4-F-phenyl	$NH(CH_2)_2OH$	5.5	>20	447.2	4.2
14c	3-Br-Ph	4-Cl-pheny	$NH(CH_2)_2OH$	7.1	17	463.7	4.4
14d	3-Br-Ph	4-Br-phenyl	$NH(CH_2)_2OH$	13	>20	508.1	4.5
14e	3-Br-Ph	2-OMe-phenyl	$NH(CH_2)_2OH$	6	>20	459.2	3.8
14f	3-Br-Ph	2-OEt-phenyl	$NH(CH_2)_2OH$	>20	>20	473.3	4.1
15a	4-Br-Ph	4-Cl-phenyl	$NH(CH_2)_2OH$	10	>20	463.7	4.4
15b	4-Br-Ph	4-Br-phenyl	$NH(CH_2)_2OH$	14.4	>20	508.1	4.5
15c	4-Br-Ph	2-OMe-phenyl	$NH(CH_2)_2OH$	>20	>20	459.2	4.1
15d	4-Br-Ph	3-OMe-phenyl	$NH(CH_2)_2OH$	>20	>20	459.2	4.1
15e	4-Br-Ph	4-OMe-phenyl	$NH(CH_2)_2OH$	14	>20	459.2	4.0
15f	4-Br-Ph	2-OEt-phenyl	$NH(CH_2)_2OH$	>20	>20	473.3	4.1
16a	thiophen-2-yl	2-Br-ethyl	$NH(CH_2)_2OH$	15	>20	387.2	2.6
16b	thiophen-2-yl	2-OMe-phenyl	$NH(CH_2)_2OH$	>20	>20	386.4	3.1
16c	thiophen-2-yl	3-OMe-phenyl	$NH(CH_2)_2OH$	>20	>20	386.4	3.3
16d	thiophen-2-yl	2-OEt-phenyl	$NH(CH_2)_2OH$	5.1	10	400.4	3.4
17a	4-F-Ph	$NH(CH_2)_2OH$	piperidinyl	>100	>100	360.3	3.0
18a	4-CH_3-Ph	$NH(CH_2)_3OH$	NHOMe	>100	>100	332.3	2.0
Telaprevir (Drug Reference Molecule)				**0.36**	**>20**		

[a]The clogP value calculated using QikProp module of Schrodinger.

The clogP values were estimated using QikProp module of Schrödinger Software Suite and reported in **Table 1**.

All compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 20 mM or higher to exclude the cytotoxicity of DMSO and stored at -20°C until use. Huh-7 cells containing self-replicating subgenomic replicons with a luciferase reporter, LucNeo#2,[17] were grown and cultured in Dulbecco's modified Eagle medium with high glucose (Gibco/BRL) supplemented with 10% heat-inactivated fetal bovine serum (Gibco/BRL), 100 U/ml penicillin G, and 100 µg/ml streptomycin. LucNeo#2, were maintained in culture medium containing 1 mg/ml G418 (Nakarai Tesque). The anti-HCV activity of the test compounds was determined in LucNeo#2 cells by the previously described method with some modifications.[18] Briefly, the cells (5×10^3 cells/well) were cultured in a 96-well plate in the absence of G418 and in the presence of various concentrations of the compounds. After incubation at 37°C for 3 days, the culture medium was removed, and the cells were washed twice with phosphate-buffered saline (PBS). Lysis buffer was added to each well, and the lysate was transferred to the corresponding well of a non-transparent 96-well plate. The luciferase activity was measured by addition of the luciferase reagent in a luciferase assay system kit (Promega) using a luminometer with automatic injectors (Berthold Technologies). The number of viable cells was determined by a dye method using the water soluble tetrazolium Tetracolor One® (Seikagaku Corporation), according to the manufacturer's instructions.

In the present study, 44 new analogs (**Scheme 1**, **Table 1**) based on α-pyranone carboxamide scaffold were synthesized to study the role of aromatic moiety and NHOH group towards anti-HCV activity. Six potential anti-HCV candidates **11a** (EC_{50} = 0.35 µM), **11e** (EC_{50} = 0.48 µM), **12f** (EC_{50} = 0.47 µM), **12g** (EC_{50} = 0.39 µM), **12h** (EC_{50} = 0.20 µM) and **12j** (EC_{50} = 0.25 µM) with lower cytotoxicity (CC_{50} > 20 µM) were discovered. We observed that an aromatic motif in the **B** region adds a synergistic effect to NHOH at 4-position and may be suggested as anti-HCV activity determinants for the pyranone carboxamide scaffold. The compounds with $NH(CH_2)_2OH$ at 4-position had shown several fold less activity. A quantum mechanics pKa calculation by Jaguar module of Schrodinger for OH of NHOH and $NH(CH_2)_2OH$ showed 6.5 and 16.6 respectively.[19] Therefore, quantum calculation characterizes the strong donating nature of OH of NHOH group over the OH of $NH(CH_2)_2OH$ functional group. This analyses hint a plausible metal chelation mechanism involving NHOH responsible for the anti-HCV activity.[20] In

addition, the assay of most active compound in this series on NS3 protease or NS5B polymerase (data not shown) did not show any inhibitory effect on them. Though further biochemical evidence is necessary to delineate the complete mechanism of action, this preliminary result supports identification and discovery of inhibitors following new mechanism. Thus, the current study opens a future scope and may yield newer drugs for combination therapy to strengthen the current treatment along with positive effect on the appearance of drug resistant virus.

Acknowledgments

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9 General method for synthesis of **11a**-**12j**, **13a**-**16d**, **17a** and **18a**

Typical procedure: To a solution of appropriately substituted **3a**-**10f** (0.56 mmoles) in ethanol, hydroxylamine hydrochloride (1.8 mmoles), $NaHCO_3$ (1.45 mmoles) were added and refluxed for 2 h at 80 °C for synthesis of **11a**-**12j**. The reaction was monitored by TLC for completion. The solvent was evaporated under reduced pressure. Ice cold water was added into crude and so formed precipitate was filtered and washed with ice cold water. The dried crude product was purified on silica gel (100-200 mesh) column chromatography with ethyl acetate and n-hexane (20% EtOAc:n-hexane) as eluents to obtain pure solid compound in 75-85% yield.

For synthesis of **13a**-**16d**, 2-aminoethanol was used in place of hydroxylamine and followed the typical procedure as above to yield **13a**-**16d**. A solution of compound **4c** (200 mg, 0.65 mmol) in 5 mL of dioxane, piperidine (0.98 mmol) was added then the reaction mixture was refluxed for 5 h and followed the above procedure to yield **17a**. For synthesis of **18a**, to a solution of compound **6b** (200mg, 0.65 mmol) in 5mL of ethanol, O-methyl hydroxyl amine hydrochloride (54 mg, 0.97 mmol) and potassium carbonate (132 mg, 0.97 mmol) were added. The reaction mixture was refluxed for 5 to 6 h and followed the above typical procedure to yield **18a**.

10 4-(hydroxyamino)-N-(4-methoxyphenyl)-2-oxo-6-(thiophen-2-yl)-2*H*-pyran-3-carboxamide (**12h**):
Yield: 90%; mp: 196 °C; IR: (KBr) (ν, cm^{-1}) 3210 (OH -Stretching), 1689 (C=O Stretching); MS (ESI) (m/z): [M+] 358.90; 1H NMR: (400 MHz, DMSO-d6): δ 3.79 (s. 3H, CH3), 6.90-6.92 (d, *J* = 8 Hz, 2H, ArH), 7.0 (s, 1H, pyranone), 7.2-7.4 (m, 1H, thiophen-2-yl), 7.5 (d, *J* = 8 Hz, 2H,Ar H), 7.93-7.96 (m, 2H, thiophen-2-yl), 10.5 (s, NH amide), 11.0 (s, 1H, NH), 12.4 (s, 1H, OH).

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Graphical Abstract

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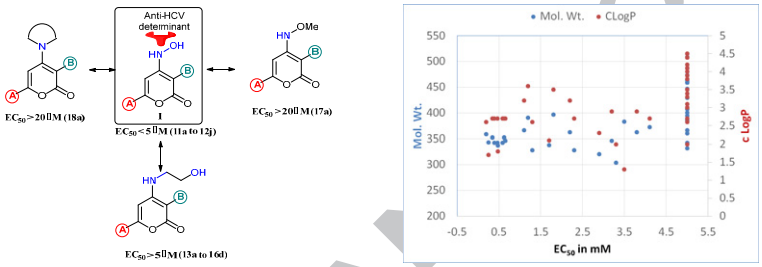
Synthesis and anti-HCV determinant motif Identification in pyranone carboxamide scaffold

Tuniki balaraju, Ananda Kumar Konreddy, Afsana Parveen, Massaki Toyama, Wataru Ito, Srinivas Karampuri, Masanori Baba, Ashoke Sharon, Chandralata Bal



The promising candidates with average mol.wt ~ 350 & cLogP ~ 2.7 identified with ± 0.5 µM of EC_{50} in cell based HCV replicon system. The –NHOH motif identification as activity determinant cliff in pyranone carboxamide scaffold **I**.