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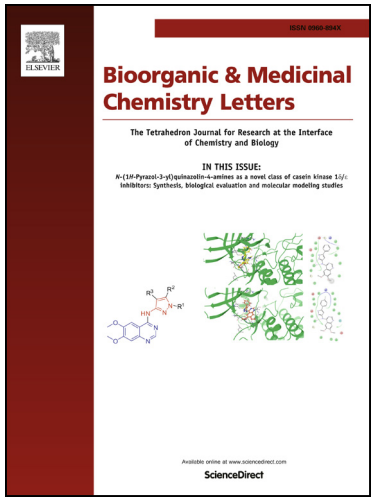

Isosorbide-based peptidomimetics as inhibitors of Hepatitis C virus serine protease

Aline C. Portela, Thalita G. Barros, Camilo H. da S. Lima, Luiza R.S. Dias, Pedro H.R. de A. Azevedo, Anna Sophia C.L. Dantas, Ronaldo Mohana-Borges, Gustavo T. Ventura, Sergio Pinheiro, Estela M.F. Muri

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Graphical Abstract

Isosorbide-based peptidomimetics as inhibitors of Hepatitis C virus serine protease

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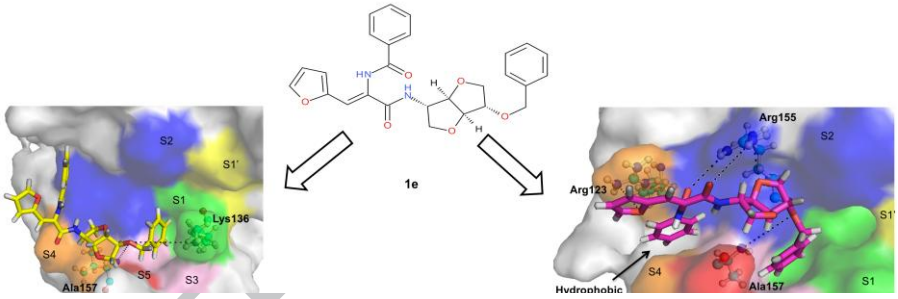

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ABSTRACT

Hepatitis C infection is a cause of chronic liver diseases such as cirrhosis and carcinoma. The current therapy for hepatitis C has limited efficacy and low tolerance. The HCV encodes a serine protease which is critical for viral replication, and few protease inhibitors are currently on the market. In this paper, we describe the synthesis and screening of novel isosorbide-based peptidomimetic inhibitors, in which the compounds **1d**, **1e**, and **1i** showed significant inhibition of the protease activity *in vitro* at 100 μM. The compound **1e** also showed dose-response (IC_{50} = 36 ± 3 μM) and inhibited the protease mutants D168A and V170A at 100 μM, indicating it as a promising inhibitor of the HCV NS3/4A protease. Our molecular modeling studies suggest that the activity of **1e** is associated with a change in the interactions of S2 and S4 subsites, since that the increased flexibility favors a decrease in activity against D168A, whereas the appearance of a hydrophobic cavity in the S4 subsite increase the inhibition against V170A strain.

Hepatitis C virus (HCV) infection is a global health problem with over 170 million people infected worldwide. Chronic HCV infection is associated with liver cirrhosis and hepatocellular carcinoma, being HCV the primary cause of liver transplantation around the world. [1]

The previous standard therapy for the six viral genotypes was based on pegylated interferon alpha and the nucleoside analog ribavirin. However, it resulted in only 40-80% of sustained viral response (SVR) of patients depending on the genotypes and other factors. [2]

The HCV NS3/4A serine protease is a target enzyme in the viral replication, and the protease inhibitors (PI) were the first directly acting antiviral introduced in the therapy. In 2011, boceprevir and telaprevir, two linear PI were approved for use in HCV genotype 1 infection and used in combination with pegylated interferon alpha and ribavirin. [3,4] They present an α-ketoamide moiety that covalently and reversibly binds the SER139 involved in the catalytic triad of the HCV protease. [5] In 2014 simeprevir, the first macrocyclic PI was approved for the treatment of G1 and G4 patients. [6,7] Currently several linear and macrocyclic PIs, as faldaprevir, asunaprevir, vaniprevir and others, are in phase II and III trials. [8–10] In addition to viral protease inhibitors other drugs are available as first-line treatments for Hepatitis C such as sofosbuvir (Solvadi®) and ledipasvir-sofosbuvir (Harvoni®).

Despite the scientific community's efforts, there is no yet an entirely effective therapy for hepatitis C showing the need for investigating new antivirals.

Our group has studied peptidomimetic compounds as inhibitors of serine protease presenting a fused bicyclic structure from isomannide. [11–15] In previous work we synthesized series of HCV protease inhibitors by introducing structural diversity at the C-6 position of isomannide (Figure 1). [11,16] In this work we designed two novel series of compounds derived from isosorbide

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to investigate the influence of different stereochemistry patterns on the biological activity. The first set **1a-j** presenting the side chain from oxazolone opening differs from the lead series by changing C-3 or C-6 stereochemistry. The second series **2a-g** derived from the amino acids coupling represents a stereochemistry change at C-3 *endo* to *exo* (Figure 1).

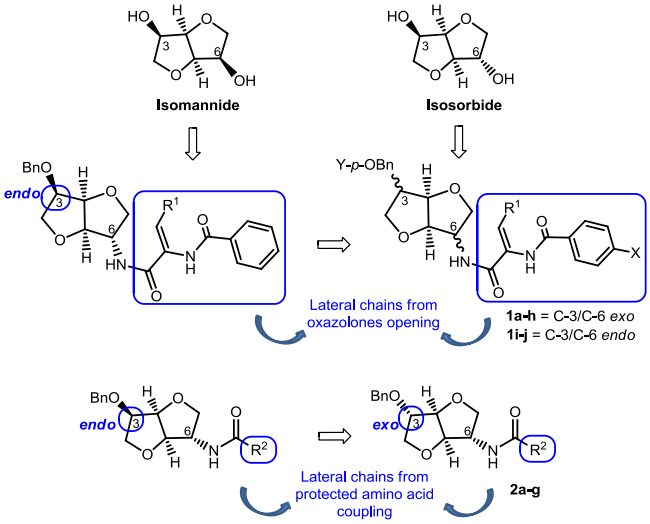
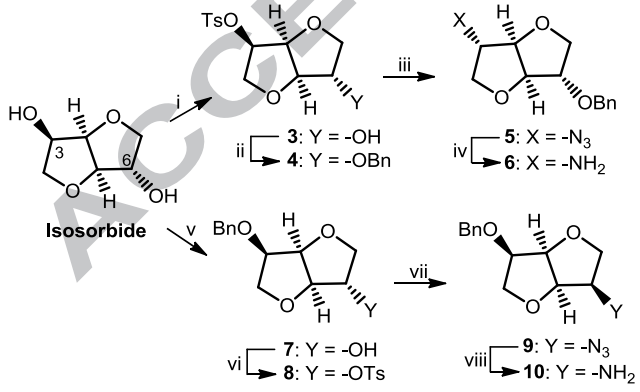


Figure 1. The design of peptidemimetics **1a-j** and **2a-g** from isosorbide.

Readily available isosorbide has been used as starting material for the preparation of two amine intermediates showing distinct configurations (**6**: C-3/C-6 *exo*; **10**: C-3/C-6 *endo*) exploring the different reactivities of the hydroxyl groups present at isosorbide. The amine **6** was synthesized in a four steps sequence already described following a tosylation and benzylation reactions of the start material, obtaining the C-6 *O*-benzyl-*exo*/C-3 *O*-tosyl-*endo* compound **4**. [17–19] The next steps consisted in a nucleophilic substitution followed by hydrogenation of the azido function. [19,20] For the synthesis of the unpublished amine **10** better yields were obtained with a benzylation reaction of the C-3 *endo* hydroxyl group before tosylation (Scheme 1). [21,22] Interesting our catalytic hydrogenation conditions to reduce the azides **5** and **9** were not able to remove the benzyl protecting in any cases. [22,23]

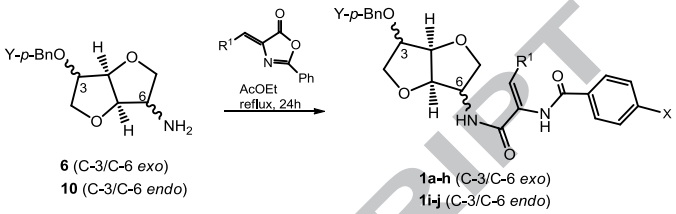


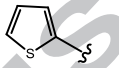
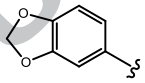
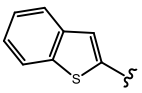
Scheme 1. Py, TsCl, 0ºC, 40h, r.t., 40%. ii: 50% KOH, TBAB, CH_2Cl_2, BnCl, 3d, r.t., 95%. iii: $[Bmim]^+[BF_4]^-$, NaN_3, 20h, 120ºC, 68%. iv: H_2, 10% Pd/C, EtOH, 2.75 bar, 4h, 98%. v: BnCl, LiH, LiCl, DMF, 18h, 90ºC, 55%. vi: Et_3N, TsCl, 24h, r.t., 70%. vii: NaN_3, DMF, 24h, 125ºC, 70%. viii: H_2, 10% Pd/C, EtOH, 2.75 bar, 5h, 98%.

The final products **1a-j** were obtained by the ring opening of the oxazolones previously synthesized by Erlenmeyer conditions using the amines **6** and **10** (Table 1). [11,24,25]

The final products **2a-g** were obtained from the coupling reactions of amine **6** with different *N*-protected amino acids using the standard protocol DCC/DMAP for peptide bond formation (Table 2). [16]

Table 1. Structures and yields of peptidomimetics **1a-j**.

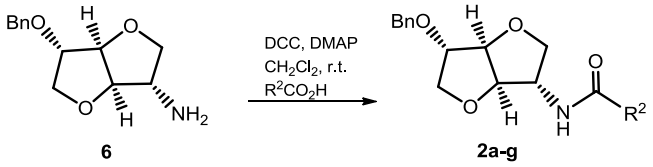


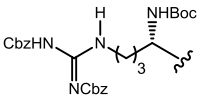
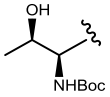
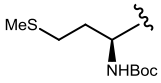
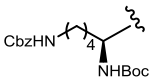
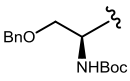
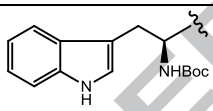
Cpd.	amine	R^1	X	Y	Yield (%)
1a	**6**		-H	-H	50
1b	**6**		-H	-H	50
1c	**6**		-H	-H	79
1d	**6**		-H	-H	54
1e	**6**		-H	-H	80
1f	**6**		-H	-H	78
1g	**6**		-Cl	-H	65
1h	**6**		-H	-OCH_3	65
1i	**10**		-H	-H	60
1j	**10**		-H	-H	65

Initially, it was carried out tests of solubility with all synthesized compounds where the compounds **1h**, **1i**, **2a**, **2b**, **2c**, and **2g** were insoluble in the aqueous buffer used in the enzymatic assays. The inhibitory profile of the compounds which were soluble in the test conditions was examined concerning the residual activity of the enzyme HCV NS3/4Apro using 100 µM of inhibitor concentration. These initial tests showed only the compounds **1d**, **1e** and **1i** significantly inhibited the protease

activity (Figure 2) with the percentage of inhibition of 30.3%, 81.8%, and 45%, respectively. Among these three compounds, **1d** and **1i** have not shown dose-response (data not shown), which was observed for the compound **1e**, that presented an IC_{50} = 36 ± 3 µM (Figure 3).

Table 2. Structures and yields of peptidomimetics **2a-g**.



Cpd.	R^2	Yield (%)
2a		70
2b		50
2c		50
2d		60
2e		65
2f		64
2g		74

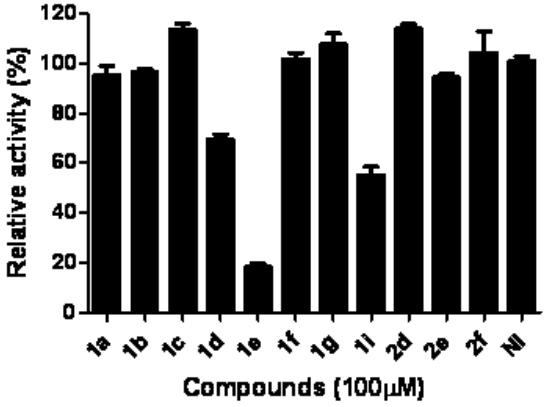


Figure 2. Inhibitory profile of the compounds against the HCV NS3/4A protease at 100 µM. The relative protease activity was obtained using the positive controls as references (reactions without inhibitor - NI). Error bars represent the standard error obtained from three independent experiments.

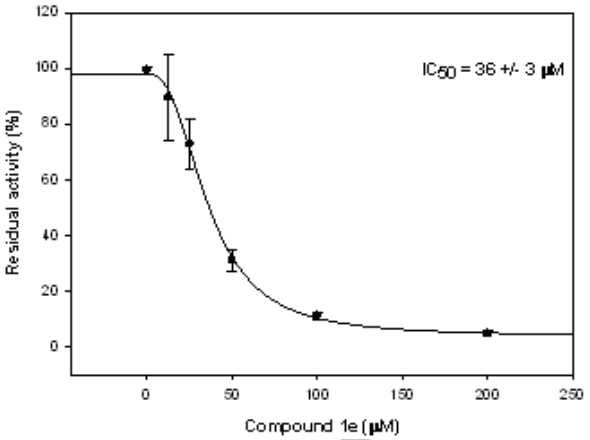


Figure 3. The representative graphic of Inhibitory potency (IC_{50}) for **1e** against wild-type NS3/4Apro. Increasing concentrations of the compound **1e** (from 12.5 to 200 µM) were used to analyze the inhibition of the protease activity of NS3/4A. Closed circles represent the mean of the residual protease activity obtained in three independent experiments and bars indicate the standard error.

Thus, **1e** was considered the most promising compound and was tested at 100 µM concentration against the D168A and V170A NS3/4Apro mutants. These mutants were described as resistant variants of the HCV NS3/4Apro to a broad spectrum of HCV inhibitors both *in vitro* and in HCV patients. [15,26,27]

According to figure 4, we observed that compound **1e** is less efficient against D168A in comparison with the WT (36.7% and 18.2% residual activity at 100 µM, respectively), whereas it has a stronger effect against V170A at the same conditions (6.7% residual activity). This result indicates that **1e** is a promising inhibitor of the HCV NS3/4A protease activity, mainly to V170A strain.

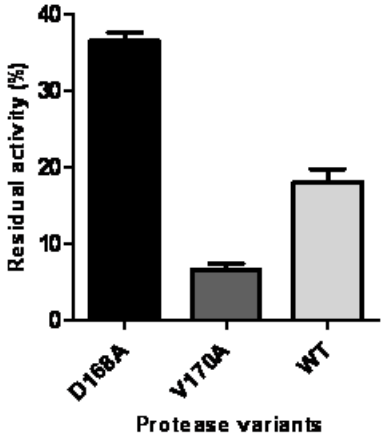


Figure 4. Inhibitory profile of 1e against the wild type (WT) HCV NS3/4A protease and the mutants D168A and V170A at 100 µM.

To understand the activity of **1e** and to identify its probable bioactive conformation, we had performed a molecular modeling study. Firstly, it was applied the molecular docking, from the autodock 4.2 program, to obtain the initial structure for molecular dynamics. From the three-dimensional structure complexed with telaprevir (PDB: 3SV6, resolution 1.4 Å) [28], we identified the significant subsites for the inhibition of NS3/4A and performed the validation of the molecular docking protocol through

molecular redocking, obtaining a pose structure with RMSD below to 2 Å (Figure 5).

Two mutations (D168A and V170A) in the pose obtained from docking protocol were made separately followed by three independent molecular dynamic simulations. In relation to WT NS3/4A, it was observed a significant variation in the first 80 ns of simulation, decreasing mobility at the binding site, with an initial pose variation of approximately 2.5 Å (Supplementary Data - SD1).

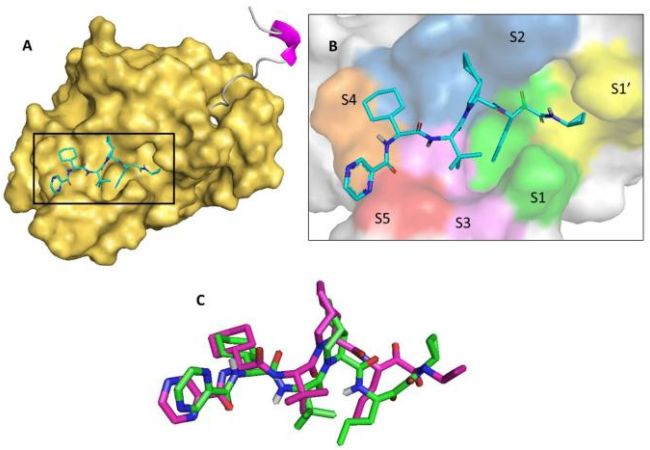


Figure 5. (**A**) 3D structural representation of NS3/4A complexed with telaprevir. (**B**) Binding site divided at S1' (Yellow; Gln41, Thr42, Phe43 and Gly137), S1 (Green; Leu135, Lys136, Ser139 and Phe154), S2 (Blue; Hys57, Arg155, Ala156 and Asp168), S3 (Pink; Ile132 and Ala157), S4 (Orange; Arg123 and Val158) and S5 (Red; Ser159) subsites. (**C**) Superposing at telaprevir structure extracted from 3SV6 (carbon = pink) and the redocking results (carbon = green).

For the D168A, it was observed that **1e** gradually exits the binding site during the 100 ns of simulation, whereas to the V170A, in the first nanosecond of MD simulation, the ligand moves about 3 Å within the binding site remaining stable during the 130 ns (SD1). Regarding the NS3 portion to WT, D168A, and V170A, it was noted stability in the mobility with RMSD values below 2 Å to carbon-alpha all over the MD simulation (SD1).

In order to understand the influence of D168A and V170A on the affinity of **1e**, the H-bonding interaction between Asp123-Asp/Ala168 and Arg155-Asp/Ala168 were monitored (SD2).

The main change caused by the D168A mutation consisted of the loss of H-bonding interaction of Asp168 with Arg123 and Arg155 [27,28], resulting in the increase the flexibility between S2 and S4 subsites (SD2B). In the case of V170A, an improvement to Asp168 and Arg155 interactions was observed, as compared to the wild-type enzyme (SD2A and SD2C). Interestingly, this behavior opens a hydrophobic cavity at S4 subsite, exhibiting the Ala166 and Val167 residues (SD2C).

The modification at binding site changes the H-bonding interactions between **1e** and WT, D168A, and V170A enzymes. To WT NS3/4A, it was observed that the initial interactions occur with Lys136 and Ala157, in the S1 and S3 subsites, mainly in the last 50 ns of MD simulation (Figure 6A and SD3). The H-bonding interaction of **1e** and D168A occurs with residues Gly137 and Ala157, in the S1' and S3 subsites, respectively, in the first 40 ns of simulation. After that, the interactions changed to Ser159 (S5 subsite) and Arg161, that stayed outside of the binding site. As these news H-bonding interactions are not strong enough, **1e** left out the binding site (SD4).

The H-bonding interactions of **1e** and V170A occurs with Arg123, Arg155, and Ala157 (S4, S2, and S3 subsites, respectively) during the 130 ns of DM simulation. Comparing with WT, the interactions with S2 and S4 subsites were possible due to the appearance of the hydrophobic cavity in the S4 subsite (Figure 6B and SD5).

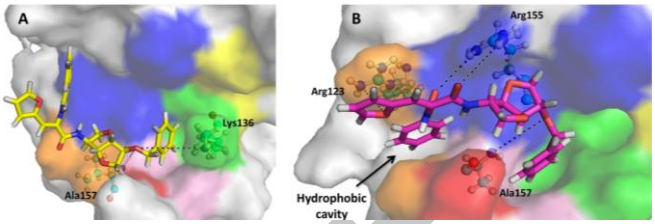


Figure 6. The predicted binding mode and H-bonding interactions (dash line) of **1e** in the active site of (A) WT and (B) V170A. The subsites S1' (Yellow), S1 (Green), S2 (Blue), S3 (Pink), S4 (Orange) and S5 (Red) and the localization of hydrophobic cavity in the S4 subsite are illustrated.

Regarding the binding free energy (ΔG binding), we have evaluated the interaction of **1e** against wild-type and V170A strain using the MM/GBSA method for the last 10 ns of MD simulation (Table 3).

We have observed that ΔG binding values follow the same trend described by residual activity, where **1e** is more active in the V170A (-28.53 ± 1.94 Kcal/mol), followed by the WT (-20.30 ± 1.98 Kcal/mol).

Overall, the nonpolar interactions (ΔEvdw + ΔESASA) determine the affinity of the ligand with the WT and V170A favoring the binding of **1e** with the binding site of WT. In the case of V170A, the increase of nonpolar interactions could be associated with the occurrence of a hydrophobic cavity in the S4 subsite.

Table 3. Binding free energy (ΔG binding) between **1e** and wild-type (WT) and V170A enzymes.

Energy (kcal/mol)	NS3 WT	NS3 V170A
ΔEvdw	-32.55±1.24	-42.39±0.97
ΔEelect	-5.72±1.58	15.83±1.36
ΔEsolv	26.11±1.54	12.77±0.80
ΔESASA	-3.46±0.08	-4.09±0.06
ΔGbinding	-20.30±1.98	-28.53±1.94

We reported a new class of small isosorbide based peptidomimetic compounds that inhibited the HCV NS3/4A protease. The most active compound **1e** tested against the wild-type enzyme was also evaluated in two mutant strains showing a good inhibitory activity in the V170A assay. This is a promising result since this NS3/4Apro mutant is resistant to several HCV inhibitors.

Docking and molecular dynamics studies allowed us to identify the significant interactions between **1e** and wild-type, D168A and V170A strains. To the wild-type NS3/4A, the major interactions occur with S1 and S3 subsites. However, it was observed in D168A strain that the increased flexibility between the S2 and S4 subsites contributed to the loss of inhibitory activity. As for V170A strain, the appearance of the hydrophobic cavity in S4 subsite favored the interactions of **1e** with S2, S3,

and S4 subsites. Thus, these findings reported here may support the search for new HCV NS3/4A protease inhibitors being the compound **1e** a potential prototype for future optimization studies.

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