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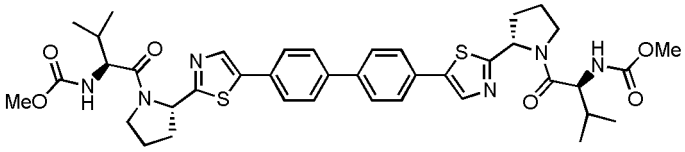
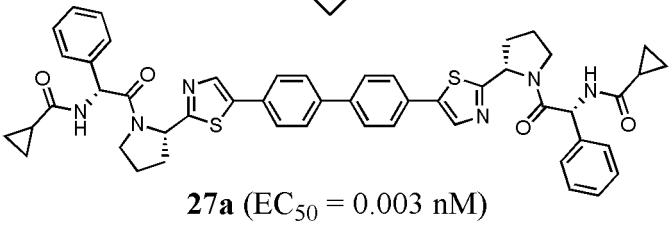


8 (EC_{50} = 56.3 nM)

Lead Optimization



27a (EC_{50} = 0.003 nM)

A Novel, Potent, and Orally Bioavailable Thiazole HCV NS5A Inhibitor for the Treatment of Hepatitis C Virus

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ABSTRACT

A medicinal chemistry program based on the small-molecule HCV NS5A inhibitor daclatasvir has led to the discovery of dimeric phenylthiazole compound **8**, a novel and potent HCV NS5A inhibitor. The subsequent SAR studies and optimization revealed that the cycloalkyl amide derivatives **27a**-**29a** exhibited superior potency against GT1b with GT1b EC_{50} values at picomolar concentration. Interestingly, high diastereospecificity for HCV inhibition was observed in this class with the (1*R*,2*S*,1'*R*,2'*S*) diastereomer displaying the highest GT1b inhibitory activity. The best inhibitor **27a** was found to be 3-fold more potent (GT1b EC_{50} = 0.003 nM) than daclatasvir (GT1b EC_{50} = 0.009 nM) against GT1b, and no detectable in vitro cytotoxicity was observed (CC_{50} > 50 μM). Pharmacokinetic studies demonstrated that compound **27a** had an excellent pharmacokinetic profiles with a superior oral exposure and desired bioavailability after oral administration in both rats and dogs, and therefore it was selected as a developmental candidate for the treatment of HCV infection.

Keywords: HCV; discovery; SAR; NS5A inhibitor; phenylthiazole; inhibitory activity

1. Introduction

Hepatitis C virus (HCV), first discovered in 1989, is a positive sense single stranded RNA virus that causes inflammation of the liver.[1] At least six major genotypes, including multiple subtypes within each genotype, of HCV have been described and genotype 1 is the most common infection worldwide.[2] HCV, chronically infected more than 170 million people worldwide, can lead to liver fibrosis, liver cancer and liver failure.[3] Traditional dual therapy (pegylated interferon plus ribavirin) produces relatively low rates of sustained virological response (SVR) for Genotype 1, historically the most difficult-to-treat genotype.[4] Telaprevir and boceprevir (Figure 1), approved by US Food and Drug Administration (FDA) in 2011, were the first oral NS3 protease inhibitors used with pegylated interferon and ribavirin to treat genotype 1 chronic hepatitis C.[5] Treatment with a telaprevir- or boceprevir-based triple therapy has resulted in an improved SVR rate in genotype 1 patients, when compared with pegylated interferon plus ribavirin therapy. [5c-e, 6] These triple therapies, however, have significant limitations due to side effects and unfavorable tolerability, especially in patients with difficult-to-treat liver cirrhosis.[5c-e, 6a-e, 7] The selling of telaprevir and boceprevir was stopped on 2014 and 2015, respectively, because highly efficacious and better tolerated direct-acting antiviral drugs (DAAs) were approved by

FDA since 2013.[8]

Insert Figure 1

A great advance has been recently made in treating chronic hepatitis C (CHC) due to newly approved DAAs (Figure 2), such as the NS3/4A protease inhibitors simeprevir,[9] paritaprevir,[10] grazoprevir,[11] and glecaprevir,[12,13] the NS5A inhibitors ledipasvir,[14] ombitasvir,[15] daclatasvir,[16] elbasvir[11c-g, 17] velpatasvir,[18] and pibrentasvir,[13,19,20] the NS5B polymerase inhibitors sofosbuvir[18c-f, 21] and dasabuvir[22]. A number of DAAs, with or without ribavirin, have been approved and those all-oral, interferon-free regimens[23], which have higher antiviral efficacy and fewer dose-related adverse effects as well as lower risk of resistant strains have been marketed.[24] For the currently approved combination products, the NS5A inhibitors are the most commonly used DAAs combined with an NS5B polymerase inhibitor and/or an NS3/4A protease inhibitor for effectively treating treatment-naive and treatment-experienced patients who have HCV genotype 1 to 6. Within a treatment period of 12 weeks, new combination drugs have a cure rate of over 90% and no significant effects, with most recent treatments only requiring 8 weeks of therapy in multiple genotypes for treatment-naïve non-cirrhotic populations. Unfortunately, the

high prices of the medications have caused a heavy barrier to most people to access that care even in high-income countries. Therefore many research groups have been working toward the development of a new effective, safe, and cheap treatment for HCV infection. The primary object of our research effort was to identify chemically novel, potent, and orally bioavailable HCV NS5A inhibitor with lower cost and shorter duration of therapy.

Insert Figure 2

As mentioned above, several NS5A inhibitors have been successfully developed and approved for the treatment of HCV infection, such as ledipasvir, ombitasvir, daclatasvir, elbsvir, velpatasvir, and pibrentasvir (Figure 2). In this paper, daclatasvir was selected as a basis for further structural modification in our new drug discovery program since it has been reported to exert strong potency against HCV in a cell-based HCV replicon assay. It is important to note that the scaffold of daclatasvir consisted of two symmetrical imidazole rings, which play a crucial role for the strong potency of HCV. In a preliminary study, we observed that the replacement of the two imidazole rings of daclatasvir with the hydrophobic thiazole rings has led to the discovery of the dimeric phenylthiazole compound **8** as our initial lead of new HCV

NS5A inhibitor (Figure 3). Surprisingly, compound **8** was found to possess moderate GT1b inhibitory activity with a GT1b EC_{50} of 56.3 nM, although it was much less potent than daclatasvir (GT1b EC_{50} = 0.009 nM) against GT1b. This interesting result prompted us to further investigate this new class of HCV NS5A inhibitors.

Insert Figure 3

In an attempt to improve the GT1b potency of the lead compound **8**, a series of structurally related dimeric phenylthiazole derivatives **9**-**57** have been designed, synthesized, and evaluated for their inhibitory activity against GT1b in our anti-HCV screening program. The detailed SAR and pharmacokinetic studies were described. Among these compounds, the best inhibitor **27a** (Figure 4) was identified as a highly potent (GT1b EC_{50} = 0.003 nM) and orally bioavailable HCV NS5A inhibitor. It appeared to be the most promising developmental candidate for the treatment of HCV infection. In this paper, we described the discovery and optimization of a novel class of dimeric phenylthiazole derivatives as potent HCV NS5A inhibitors via a medicinal chemistry program based on the scaffold of compound **8**.

Insert Figure 4

2. Results and discussion

2.1. Chemistry

The synthetic procedures for this class of dimeric phenylthiazole derivatives **8**-**57** are presented in Schemes 1-4. The key intermediate **6** was prepared according to the synthetic method shown in Scheme 1 beginning from the commercially available 2-amino-4'-bromoacetophenone hydrochloride **1**. Neutralization of the hydrochloride salt **1** with DIPEA in CH_2Cl_2 at room temperature followed by coupling reaction of its corresponding free base with N-Boc-*L*-proline in the presence of HOBt·H_2O/EDC led to the formation of amide **2** in 90% yield. Reaction of **2** with Lawesson's reagent gave the phenylthiazole **3** in 78% yield,[25] which was reacted with bis(pinacolato)diboron in the presence of $Pd(PPh_3)_4$ and potassium acetate to give the corresponding organoboron compound **4** in 99% yield.[26] The dimeric phenylthiazole compound **5** was then prepared by reacting the organoboron compound **4** with **3** under $PdCl_2$(dppf) catalysis using Suzuki coupling reaction in 47% yield.[27] Acidic deprotection of **5** with trifluoroacetic acid in CH_2Cl_2 at room temperature gave the key intermediate **6** in 99% yield.

Insert Scheme 1

Exploration of the substituents on the pyrrolidine nitrogen in this class of dimeric phenylthiazole compounds has been done (Schemes 2-4). The synthetic procedures for a series of alkyl carbamate derivatives (1*S*,2*S*,1'*S*,2'*S*) **8-17** are presented in Scheme 2 (synthetic method A). The L form amino acid derivatives (**III**) that were not commercially available were prepared by reacting the corresponding amino acid **(I)** with the substituted chloroformate **(II)** at room temperature in the presence of sodium carbonate and 1.0 M aqueous sodium hydroxide solution.[28] Subsequent peptide coupling reaction of the pyrrolidine nitrogen of intermediate **6** with compound **(III)** in the presence of HOBt·H_2O/EDC in DMF at room temperature gave the desired coupling product (1*S*,2*S*,1'*S*,2'*S*) **8-17** as a single diastereomer in 54-86% yields following flash column purification. This result indicated that no racemization occurred during the coupling reaction.

Insert Scheme 2

The synthetic procedures for the carbamate derivatives **18a,b**, sulfonamide derivatives

19a,b, and a variety of substituted amide derivatives **20a,b - 49a,b** are presented in Scheme 3 (synthetic method B). The *N*-Boc protected phenylglycine derivative **7** was prepared by coupling the intermediate **6** with *N*-Boc-D-phenylglycine at room temperature in the presence of HOBt·H_2O/EDC in 75% yield. Acidic deprotection of **7** with trifluoroacetic acid at room temperature gave the amine intermediate, which underwent substitution reaction with methyl chloroformate in the presence of triethylamine to provide the methyl carbamate derivative (1*R*,2*S*,1'*R*,2'*S*) **18a** and its corresponding diastereomer (1*R*,2*S*,1'*S*,2'*S*) **18b**. In addition, reaction of the amine intermediate with methanesulfonyl chloride gave the methyl sulfonamide derivative (1*R*,2*S*,1'*R*,2'*S*) **19a** and its corresponding diastereomer (1*R*,2*S*,1'*S*,2'*S*) **19b**. Similarly the substituted amide derivatives (1*R*,2*S*,1'*R*,2'*S*) **20a-49a** and (1*R*,2*S*,1'*S*,2'*S*) **20b-49b** were also prepared by deprotection of **7** with trifluoroacetic acid followed by reactions with a variety of acyl chloride in the presence of trimethylamine in 10-55% yield. These results may be due to the rapid racemization at the C_1 position of the (*R*)-phenylglycine moiety during the reaction process.

Insert Scheme 3

The cyclopropyl amide derivatives (1*R*,2*S*,1'*R*,2'*S*) **50-57** were prepared as shown in

Scheme 4 (synthetic method A). The D form amino acids **(IV)** were acylated with cyclopropyl carbonyl chloride at room temperature in the presence of sodium carbonate and 1.0 M aqueous sodium hydroxide solution to give the corresponding amide intermediate **(V)** in excellent yields.[28] Peptide coupling reaction of **6** with **(V)** in the presence of HOBt·H_2O/EDC in DMF at room temperature gave the desired cyclopropyl amide derivatives (1*R*,2*S*,1'*R*,2'*S*) **50-57** as a single diastereomer in 51-69% yields.

Insert Scheme 4

2.2. ***Biological evaluation***

The dimeric phenylthiazole compounds **8-57** described herein were evaluated for GT1b inhibitory activity using an *in vitro* assay system that is suitable for monitoring anti-HCV activities of compounds. This system is composed of a human hepatocarcinoma cell line (Huh-7) supporting multiplication of a GT1b replicon.[29] While there are several genotypes in HCV, our assay employed genotype 1b replicon. We examined compounds' ability to inhibit the replication of subgenomic HCV RNA in a GT1b replicon cell system. In addition, all target compounds were also tested for their cytotoxicity toward human Huh-7 cells. Details of this SAR investigation

has been done on GT1b and will be described herein.

Daclatasvir is a potent HCV NS5A inhibitor, which showed excellent GT1b inhibitory activity (GT1b EC_{50} = 0.009 nM) in a HCV genotype 1b subgenomic replicon assay. In our efforts to identify a new generation inhibitor possessing greater GT1b potency relative to daclatasvir, we first examined the role of the two imidazole rings in daclatasvir (Table 1). Surprisingly, the replacement of the two imidazole rings in daclatasvir with the thiazole rings led to the discovery of a dimeric phenylthiazole compound **8** as our initial lead of new HCV NS5A inhibitor, which showed moderate GT1b inhibitory activity (GT1b EC_{50} = 56.3 nM) in a HCV genotype 1b subgenomic replicon assay. Although compound **8** was much less potent than daclatasvir against GT1b, it was found to possess low cytotoxicity (CC_{50} > 50 μM) and high therapeutic index (CC_{50}/GT1b EC_{50}), and worthy of further optimization. Having shown that the imidazole rings can be replaced by the thiazole rings, a series of structurally related dimeric phenylthiazole derivatives have been synthesized and evaluated for their GT1b inhibitory activities (Table 1). Modifications of the two methyl groups on the carbamate moiety (R_1) and the isopropyl groups at the C-1 and C-1' position (R_2) of the compound **8** led to the following general conclusions. The replacement of the two methyl groups on the carbamates of **8** with either the ethyl (**9)** or phenyl group

(**10**) significantly reduced GT1b inhibitory activity (GT1b EC_{50} = 327.1 and 2815.6 nM, respectively). This effect might be due to their strict steric requirement at this position in the binding site. Since it appeared that retention of the methyl carbamate group was nevertheless beneficial, we turned our attention to the exploration of the SAR around the alkyl substituents (R_2) at the C-1 and C-1' position of the compound. Replacing the two isopropyl groups at the C-1 and C-1' position of **8** with the methyl groups (**11**) moderately reduced activity against GT1b (GT1b EC_{50} = 158.5 nM); however, the ethyl derivative **12** had GT1b inhibitory activity (GT1b EC_{50} = 56.6 nM) comparable to that of **8**. In an effort to further improve the GT1b inhibitory activity, we extended the alkyl substituents at the C-1 and C-1' position of **8**. Replacement of the two isopropyl groups with either a *n*-propyl (**13**), *n*-butyl (**14**), *i*-butyl (**15**), or *t*-butyl (**16**) resulted in a general reduction in activity (GT1b EC_{50} = 123-471 nM) against GT1b. Importantly, the phenyl derivative **17**, when compared to its corresponding isopropyl derivative **8**, provided a significant improvement in GT1b inhibitory activity (GT1b EC_{50} = 40.9 nM), and demonstrated the best GT1b potency in this series of dimeric phenylthiazole compounds.

Insert Table 1

We next investigated the stereochemical requirements for GT1b inhibitory activity in the methyl carbamate series (compounds **17**, **18a**, and **18b**). Results are shown in Table 2. Interestingly, the (1*R*,2*S*,1'*R*,2'*S*) diastereomer **18a** (GT1b EC_{50} = 0.19 nM) was found to be significantly more potent than the corresponding diastereomers (1*S*,2*S*,1'*S*,2'*S*) **17** (GT1b EC_{50} = 40.9 nM) and (1*R*,2*S*,1'*S*,2'*S*) **18b** (GT1b EC_{50} = 107.9 nM) against GT1b, demonstrating the critical stereochemical requirement at C-1 and C-1' position for a R absolute configuration to display strong GT1b inhibitory activity in this series. It seems that the stereochemistry (1*R*,2*S*,1'*R*,2'*S*) of this class of dimeric phenylthiazole compounds optimally fits to a binding pocket of NS5A. With these results, the methyl carbamate derivative (1*R*,2*S*,1'*R*,2'*S*) **18a** was chosen for further SAR study based on its strong GT1b potency.

Insert Table 2

In an attempt to improve the GT1b potency of the lead compound **18a**, we explored the possibility of replacing the carbamate group at the C-1 and C-1' position of **18a** with other functional groups. The results are shown in Table 3 and are compared to **18a**. Replacement of the carbamate group with the sulfonamide, compound **19a**, resulted in a significant reduction in GT1b inhibitory activity (GT1b EC_{50} = 3.4 nM).

Encouragingly, the methyl amide derivative **20a** (GT1b EC_{50} = 0.02 nM) was found to be 10-fold more potent than the corresponding methyl carbamate derivative **18a** (GT1b EC_{50} = 0.19 nM) against GT1b. We also investigated the stereochemical comparison for GT1b inhibitory activity (Table 3). As expected, the stereochemically unfavorable (1*R*,2*S*,1'*S*,2'*S*) diastereomers **18b**-**20b** were found to be significantly less potent than their corresponding (1*R*,2*S*,1'*R*,2'*S*) diastereomers **18a**-**20a** against GT1b, respectively.

Insert Table 3

Having achieved excellent GT1b potency with amide derivatives, we investigated the SAR around the alkyl substituents on the amide moiety of this class of dimeric phenylthiazole compounds (Table 4). A variety of substituted amide derivatives (1*R*,2*S*,1'*R*,2'*S*) **21a**-**49a** and their corresponding (1*R*,2*S*,1'*S*,2'*S*) diastereomers **21b**-**49b** were prepared in an attempt to increase potency against GT1b. The results are shown in Table 4 and are compared to the methyl amide derivatives **20a** and **20b**. In (1*R*,2*S*,1'*R*,2'*S*) isomer series, increasing the chain length of the alkyl substituent on the amide from methyl (**20a**) to ethyl (**21a**) and *n*-propyl (**22a**) generally retained the GT1b inhibitory activity. The *n*-butyl amide derivative **23a** showed a slight

reduction in potency against GT1b. Further extension of the side chain to *n*-pentyl (**24a**) resulted in a further reduction in GT1b inhibitory activity. More importantly, the isopropyl amide derivative **25a** exhibited superior GT1b potency (GT1b EC_{50} = 0.009 nM), which was comparable to that of daclatasvir. Surprisingly, the *t*-butyl amide derivative **26a** was considerably less active than **20a** against GT1b.

We further investigated varying the substituents on the amide by changing from alkyl to cycloalkyl group in this series in an effort to increase GT1b potency (Table 4). Interestingly, the cycloalkyl amide derivatives **27a-29a** were found to be significantly more potent (GT1b EC_{50} < 0.01 nM) than the corresponding alkyl amide derivatives **22a-24a** against GT1b. This is possibly due to their drastically conformational change and steric requirement at this position in the binding site. It is worth noting that the cyclopropyl amide derivative **27a** was found to be 3-fold more potent (GT1b EC_{50} = 0.003 nM) than daclatasvir (GT1b EC_{50} = 0.009 nM) in GT1b inhibitory activity, and no apparent cellular cytotoxicity was observed (CC_{50} > 50 μM). Therefore compound **27a** was chosen for further pharmacokinetic study based on its GT1b potency. However, the bulky cyclohexyl amide derivative **30a** displayed a significant reduction in GT1b inhibitory activity (GT1b EC_{50} = 0.25 nM).

Although compound **30a** showed weak GT1b inhibitory activity, we also investigated replacing the cyclohexyl rings of **30a** with aryl or heteroaryl rings on the amide (Table 4). Intriguingly, aromatization of the cyclohexyl ring of **30a** (**31a**) induced a drastic decrease in GT1b inhibitory activity; however, the corresponding benzyl amide derivative **32a** had GT1b inhibitory activity comparable to **30a**. More interestingly, when the phenyl ring on the amide of **31a** was replaced with a 4-pyridinyl (**33a**), a dramatic improvement in GT1b inhibitory activity was observed. Moving the nitrogen atom to the 3-position (3-pyridinyl amide derivative **34a**) caused a loss in GT1b inhibitory activity, indicating that this nitrogen atom is not tolerated at this position, and the 2-pyridinyl amide derivative **35a** exhibited a further reduction in GT1b inhibitory activity. In addition, the 2- and 3-furanyl amide derivatives, **36a** and **37a**, exhibited excellent GT1b inhibitory activity (GT1b EC_{50} = 0.07 and 0.08 nM, respectively), which were almost comparable to that of 4-pyridinyl amide derivative **33a** (GT1b EC_{50} = 0.011 nM). Surprisingly, the 2- and 3-thienyl amide derivatives, **38a** and **39a**, were considerately less potent than the corresponding 2- and 3-furanyl amide derivatives, **36a** and **37a** against GT1b.

We next tried to seek a more attractive structure for optimization instead of the aryl and heteroaryl amides, thus several different types of heterocyclic and

amino-substituted alkyl amide derivatives **40a-49a** were also synthesized and examined. Interestingly, the morpholyl, pyrrolidyl, piperidyl, and pyrrolyl amide derivatives **40a-43a** were found to possess excellent GT1b inhibitory activity with GT1b EC_{50} values ranging from 0.016 - 0.035 nM. However, the amino-substituted alkyl amide derivatives **44a-49a** were about 100-fold less potent than **40a-43a**. Further investigation will be required to explore this unexpected result.

On the other hand, we also investigated the stereochemical comparison for GT1b inhibitory activity in the amide series (Table 4). Interestingly, high diastereospecificity for HCV inhibition was observed with the (1*R*,2*S*,1'*R*,2'*S*) diastereomer displaying the highest GT1b inhibitory activity. However, the stereochemically unfavorable (1*R*,2*S*,1'*S*,2'*S*) diastereomers **21b-49b** were found to be significantly less potent than their corresponding (1*R*,2*S*,1'*R*,2'*S*) diastereomers **21a-49a** against GT1b in the amide series.

Insert Table 4

Modifications of the alkyl substituents (R) at both the C-1 and C-1' position of the dimeric phenylthiazole derivatives are shown in Table 5 and are compared to the best

inhibitor **27a**. Replacement of the phenyl groups at both the C-1 and C-1' position of **27a** with either a methyl (**50**), ethyl (**51**), *n*-propyl (**52**), *n*-butyl (**53**), *i*-propyl (**54**), *i*-butyl (**55**), *t*-butyl (**56**), cyclohexyl (**57**) significantly reduced GT1b inhibitory activity. This is probably due to the fact that the strongest hydrophobic interaction could be provided by the phenyl rings at both the C-1 and C-1' position in the binding site. With these results, we observed that the isobutyl analogue of the amide (**55**) bestowed the best GT1b potency (GT1b EC_{50} = 27.1 nM) in this series. However, the bulky cyclohexyl analogue of the amide (**57**) was found to be devoid of GT1b inhibitory activity (GT1b EC_{50} > 50 μM). The underlying cause of this effect is still unknown and deserves further research.

Insert Table 5

To evaluate the cytotoxicity of this class of dimeric phenylthiazole derivatives, all target compounds **8-57** were tested for their cytotoxic effect toward human Huh-7 cell lines. Very encouragingly, compounds **8-57** were found to display no detectable cytotoxicity at the highest concentration of 50 μM (CC_{50} > 50 μM).

2.3. Pharmacokinetic studies

Following extensive SAR studies, the cyclopropyl amide derivative **27a** was then selected for animal pharmacokinetic evaluation since it appeared to demonstrate the most potent inhibitory activity (GT1b EC_{50} = 0.003 nM) against GT1b in this novel class of compounds. The pharmacokinetic parameters of **27a** were determined in rats and dogs and the data are summarized in Table 6 and 7. There were no deaths and no treatment-related effects on body weight or clinical observations. After intravenous (1.0 mg/kg) and oral (5.0 mg/kg) administration in rats, the compound was characterized by a low plasma clearance (CL) of 1.1 mL/min/kg, a moderate volume of distribution (*Vss*) of 1.3 L/kg, a long oral half-life ($t_{1/2}$) of 20.4 h, and an acceptable bioavailability of 22% which resulted in a good oral exposure (AUC) of 14539 ng/mL×h. In addition, compound **27a** was dosed both intravenously (0.1 mg/kg) and orally (0.5 mg/kg) in dogs, similarly it had a low plasma clearance of 1.3 mL/min/kg, a moderate volume of distribution of 1.6 L/kg, a long oral half-life ($t_{1/2}$) of 21.4 h, and a reasonable bioavailability of 23.3%, leading to a good oral exposure of 1622 ng/mL×h. These significant results demonstrated that compound **27a** had an excellent GT1b potency and favorable pharmacokinetic properties with acceptable bioavailability after oral dosing in both rats and dogs. Therefore, it appeared to be the most promising preclinical candidate for further development as anti-HCV agent

Insert Table 6

Insert Table 7

Furthermore, drug resistance studies have been carried out to elucidate how compound **27a** works in the HCV RNA replication.[30] The resistance profile showed that the N terminus of NS5A is the region responsible for the **27a**-mediated inhibition of HCV replicon activity.[30] It may be possible that **27a** exerts GT1b inhibitory activity by directly binding to the N terminus of NS5A due to similar resistance profile to daclatasvir, a NS5A inhibitor, resulting in the drug resistance mutations within the N terminus of NS5A.[31] Of course, there is still a need to clarify the binding site and molecular mechanism of action of this class of NS5A inhibitors. Importantly, these findings from this study provide very useful information to develop novel anti-HCV agents.

3. Conclusions

In summary, a novel class of dimeric phenylthiazole derivatives was designed, synthesized, and identified as potent HCV NS5A inhibitors based on daclatasvir scaffold. We have developed the SAR for the substituent on the (*S*)-pyrrolidine and have shown that the

(*R*)-phenylglycine moiety is sufficient for good potency against GT1b, and the potency increases in the order SO_2 < CO_2 < CO for the linker from the methyl substituent to the (*R*)-phenylglycine. In these studies, it was demonstrated that the stereochemistry at the C-1 and C-1' position of the phenylglycine moieties plays a very important role in affecting their GT1b inhibitory activities of this class of dimeric phenylthiazole compounds. The stereochemically preferred (1*R*,2*S*,1'*R*,2'*S*) diastereomers were found to be significantly more potent than the corresponding (1*R*,2*S*,1'*S*,2'*S*) and (1*S*,2*S*,1'*S*,2'*S*) diastereomers against GT1b. Furthermore, modifications of the substituent at the amide group on the (*R*)-phenylglycine moiety resulted in an interesting pattern of GT1b inhibitory activity. Several compounds described in this work exhibited superior potency against GT1b with GT1b EC_{50} values at picomolar concentration. The cyclopropyl amide derivative **27a** was found to be the best inhibitor of GT1b replicon (GT1b EC_{50} = 0.003 nM), which showed promising pharmacokinetic properties and bioavailability after oral administration in both rats and dogs. Previous drug resistance studies demonstrated that compound **27a** is likely to inhibit HCV replication by directly binding to HCV NS5A. On the basis of these encouraging results, compound **27a** was selected as a preclinical candidate for the treatment of HCV infection. Further SAR and mechanistic studies on this class of compounds are currently under active investigation and will be reported in due course.

4. Experimental

4.1. General procedures

All commercial chemicals and solvents are reagent grade and were used without further treatment unless otherwise noted. ^{1}H NMR spectra were obtained with a Varian Mercury-300 or a Varian Mercury-400 spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) and were reported relative to the solvent peak or TMS. Coupling constants (*J*) are reported in hertz (Hz). Splitting patterns are described by using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. LC/MS data were measured on an Agilent MSD-1100 ESI-MS/MS System. All tested compounds were detected at UV 254nm unless otherwise stated. Column chromatography was performed with silica gel (Merck Kieselgel 60, 230-400 mesh). Reactions were monitored by TLC using Merck 60 F_{254} silica gel glass backed plates and visualized under ultraviolet irradiation (254 nm and 360 nm) or by spraying with phosphomolybdic acid reagent (Aldrich) followed by heating at 80 ^{o}C. Melting points were determined on an Electrothermal IA9000 Series Digital Melting Point Apparatus. Purity of the final compounds was determined on a Hitachi 2000 series HPLC system with a reverse phase C_{18} column (Agilent ZORBAX Eclipse XDB-C18 5 μm, 4.6 mm x 150 mm), operating at 25 ^{o}C. Mobile phase A was acetonitrile. Mobile phase B was 10 mM

NH_4OAc aqueous solution containing 0.1% formic acid. The gradient system started from A/B (10%/90%) at 0 min to A/B (90%/10%) at 45 min. The flow rate of the mobile phase was 0.5 mL/min, and the injection volume of the sample was 5 μL. Peaks were detected at 254 nm. The purity of all tested compounds is >95% purity.

4.1.1. N-[2-(4-Bromophenyl)-2-oxoethyl]-1-(tert-butoxycarbonyl)-L-prolinamide (2)

A solution of *N*-Boc-L-proline (5.16 g, 24 mmol) and hydroxybenzotriazole monohydrate ($HOBt \cdot H_2O$, 3.67 g, 24 mmol) in 200 mL CH_2Cl_2 was stirred at room temperature for 10 minutes, then treated with *N*-ethyl-*N'*-(3-dimethylaminopropyl) carbodiimide hydrochloride ($EDC \cdot HCl$, 4.6 g, 24 mmol). The resulting mixture was stirred at room temperature for 30 minutes and then treated with a yellow solution formed by stirring 2-amino-4-bromoacetophenone hydrochloride (5.0 g, 20 mmol) and *N*,*N'*-diisopropylethylamine (DIPEA, 2.58 g, 20 mmol) in 150 mL CH_2Cl_2 at room temperature for 10 minutes. The resulting mixture was stirred at room temperature overnight and then filtered through Celite to remove the precipitate. The filtrate was partitioned between CH_2Cl_2 and water. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated via vacuo. The residue was purified by column chromatography (ethyl acetate : hexane = 2 : 5) to yield pure product **2** as a yellow solid (7.39 g, 90% yield): mp 130-131 ^oC; ^1H NMR

(300MHz, $CDCl_3$) (1 : 2 mixture of rotomers) δ 1.45 (s, 9H), 1.83-2.00 (m, 2H), 2.14 (br s, 4/3H), 2.22 (br s, 2/3H), 3.38 (br s, 2/3H), 3.48 (br s, 4/3H), 4.28 (br s, 1/3H), 4.35 (br s, 2/3H), 4.69 (d, *J* = 4.5 Hz, 2H), 7.02 (br s, 2/3H), 7.51 (br s, 1/3H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 2H); LC/MS (ESI) *m/z*: 411.3 $[M + H]^+$, 433.0 $[M + Na]^+$.

4.1.2. tert-Butyl (2S)-2-[5-(4-bromophenyl)-1,3-thiazol-2-yl]pyrrolidine-1-carboxylate (3)

To a solution of the kitoamide substrate **2** (25.26 g, 61.42 mmol) in THF (300 mL), Lawesson's reagent (37.21 g, 92.11 mmol) was added. The resulting mixture was refluxed for 6 hours, cooled to room temperature, and then concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate : hexane = 1 : 2) to get the product **3** as a yellow solid (19.6 g, 78% yield): mp 84-85 ^oC; ^1H NMR (400MHz, $CDCl_3$) (4 : 5 mixture of rotomers) δ 1.33 (s, 5H), 1.47 (s, 4H), 1.94 (br s, 2H), 2.22 (br s, 8/9H), 2.27 (br s, 10/9H), 3.43-3.60 (m, 2H), 5.08 (s, 5/9H), 5.19 (s, 4/9H), 7.36 (d, *J* = 6.4 Hz, 2H), 7.47 (d, *J* = 6.4 Hz, 2H), 7.80 (s, 1H); LC/MS (ESI) *m/z*: 409.0 $[M + H]^+$, 431.0 $[M + Na]^+$.

4.1.3. tert-Butyl

(2S)-2-{5-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1,3-thiazol-2-yl}pyrrolidine-1-carboxylate (4)

A flask charged with $Pd(PPh_3)_4$ (0.49 g, 0.43 mmol), potassium acetate (2.09 g, 21.37 mmol), bis(pinacolato)diboron (5.16 g, 17.1 mmol), compound **3** (3.50 g, 8.55 mmol) and 1,4-dioxane (100 mL) was flushed with nitrogen. The reaction mixture was stirred at 80^{o}C for 6 hours. After cooling to ambient air temperature, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate : hexane = 1 : 2) to give the product **4** as a yellow solid (3.88 g, 99% yield): mp 138-140 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (4 : 5 mixture of rotomers) δ 1.27 (s, 17H), 1.41 (s, 4H), 1.86-1.93 (m, 2H), 1.60-2.22 (m, 2H), 3.37-3.57 (m, 2H), 5.04 (s, 5/9H), 5.16 (s, 4/9H), 7.21 (s, 4/9H), 7.28 (s, 5/9H), 7.46 (s, 2H), 7.75 (s,2H); LC/MS (ESI) *m/z*: 457.2 $[M + H]^{+}$.

4.1.4. di-tert-Butyl (2S,2'S)-2,2'-(biphenyl-4,4'-diyldi-1,3-thiazole-5,2-diyl)dipyrrolidine-1-carboxylate (5)

A flask charged with $PdCl_2$(dppf) (0.48 g, 0.59 mmol), potassium carbonate (5.87 g, 42.5 mmol), compound **3** (3.75 g, 9.16 mmol), compound **4** (3.88 g, 8.5 mmol) and 1,2-dimethoxyethane (100 mL) was flushed with nitrogen. The reaction mixture was

stirred at 80 ^{o}C over 24 hours. After cooling to ambient air temperature, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (ethyl acetate : hexane = 1 : 2) to give the product **5** as a white solid (2.66 g, 47% yield): mp 188-190 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (4 : 5 mixture of rotomers) δ 1.37 (s, 10H), 1.51 (s, 8H), 1.95-2.04 (m, 4H), 2.27-2.35 (m, 4H), 3.46-3.65 (m, 4H), 5.13 (s, 10/9H), 5.24 (s, 8/9H), 7.63 (s, 8H), 7.90 (s,2H); LC/MS (ESI) *m/z*: 658.8 $[M + H]^+$.

4.1.5. 5,5'-Biphenyl-4,4'-diylbis{2-[(2S)-pyrrolidin-2-yl]-1,3-thiazole} (6)

Trifluoroacetic acid (5 equiv) was introduced to the solution of compound **5** (2.66 g, 4.04 mmol) in CH_2Cl_2 (40 mL) at ice-bath. The resulting mixture was stirred at room temperature for 2 hours, and then cooled with ice-bath. The saturated $NaHCO_3$ (aq) was introduced to neutralized the reaction mixture until the pH reached to 8. The resulting mixture was partitioned between CH_2Cl_2 and water. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (100% ethyl acetate, then methanol : CH_2Cl_2 = 1 : 20) to give pure product **6** as a yellow solid (1.83 g, 99% yield): mp 247-249 ^{o}C; ^{1}H NMR (300MHz, DMSO-d_6) δ 2.04-2.23 (m, 8H), 3.33-3.41 (m, 4H), 5.12 (t, J = 5.9 Hz, 2H), 7.85 (d, J = 6.3 Hz, 4H), 7.82 (d, J =

6.3 Hz, 4H), 8.40 (s, 2H), 9.60 (br s, 2H); LC/MS (ESI) *m/z*: 459.0 $[M + H]^+$.

4.1.6. di-tert-Butyl (biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate (7)

A suspended mixture of *N*-Boc-D-phenylglycine (2.21 g, 8.8 mmol) and hydroxybenzotriazole monohydrate ($HOBt \cdot H_2O$, 1.35 g, 8.8 mmol) in DMF (30 mL) was stirred at room temperature for 10 minutes. Then, EDC (1.68 g, 8.8 mmol) was added and the clear solution was continuously stirred for 30 minutes. To the former solution, compound **6** (1.83 g, 4.0 mmol) was added. The resulting mixture was stirred at room temperature overnight and then partitioned between ethyl acetate and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (methanol : CH_2Cl_2 = 1 : 20) to yield the pure product **7** as a white solid (2.77 g, 75% yield): mp 113-115 ^oC; ^1H NMR (300MHz, $CDCl_3$) δ 2.06 (s, 18H), 3.33-3.43 (m, 4H), 3.60-3.68 (m, 4H), 3.89-3.99 (m, 4H), 5.39-5.49 (m, 2H), 7.28-7.44 (m, 14H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.59-7.68 (m, 4H), 8.00 (s, 2H), 9.99 (br s, 2H); LC/MS (ESI) *m/z*: 925.3 $[M + H]^+$.

4.2. Chemistry

Synthetic Method A: General procedure for the synthesis of compounds **8-17** and **50-57**

A suspended mixture of *N*-substituted amino acid (2.2 equiv) and hydroxybenzotriazole monohydrate (HOBt·H_2O, 2.2 equiv) in DMF was stirred at room temperature for 10 minutes. Then, EDC (2.2 equiv) was added and the clear solution was continuously stirred for 30 minutes. To the former solution, compound **6** (1 equiv) was added. The resulting mixture was stirred at room temperature overnight and then partitioned between ethyl acetate and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (methanol : CH_2Cl_2 = 1 : 20) to afford the desired product.

Synthetic Method B: General procedure for the synthesis of compounds **18a-49a** and **18b-49b**

Trifluoroacetic acid (5 equiv) was introduced to the solution of compound **7** (1 equiv) in CH_2Cl_2 at ice-bath. The resulting mixture was stirred at room temperature for 2 hours, and then cooled with ice-bath. The saturated $NaHCO_3$ (aq) was introduced to neutralized the reaction mixture until the pH reached to 8. The resulting mixture was partitioned between CH_2Cl_2 and water. The combined organic layers were dried

over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was used as starting material in next step without further purification. Acid chloride (2.4 equiv) and triethylamine (2.4 equiv) were added sequentially to the solution of the crude product in DMF with ice-bath. The resulting mixture was stirred at ice-bath and monitored by TLC until reaction completed. The reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated via vacuo. The residue was purified by thin-layer chromatography (methanol : CH_2Cl_2 : ethyl acetate = 0.1 : 8 : 1) to afford two desired products.

4.2.1. Methyl [(2S)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate (8)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-L-valine according to the general procedure of the synthetic method A in 71% yield: mp 197-199 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 0.94 (d, *J* = 6.6 Hz, 6H), 1.04 (d, *J* = 6.6 Hz, 6H), 2.06-2.13 (m, 4H), 2.21-2.31 (m, 4H), 2.40-2.45 (m, 2H), 3.68 (s, 6H), 3.77-3.86 (m, 4H), 4.21-4.30 (m,

0.2H), 4.40 (dd, J = 5.7, 8.7 Hz, 1.8H), 5.43 (d, *J* = 9.3 Hz, 2H), 5.52 (d, *J* = 5.7 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 4H), 7.62 (d, *J* = 8.4 Hz, 4H), 7.87 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 773.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{40}H_{49}N_6O_6S_2$ $[M + H]^+$ 773.3155, found 773.3158; HPLC t_R = 39.35 min, 95.7%.

4.2.2. Ethyl [(2S)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(ethoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate (9)

The title compound was obtained from compound **6** and *N*-(ethoxycarbonyl)-L-valine according to the general procedure of the synthetic method A in 70% yield: mp 196-178 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 0.95 (d, *J* = 6.6 Hz, 6H), 1.04 (d, *J* = 6.6 Hz, 6H), 1.25 (t, *J* = 7.2 Hz, 6H), 1.98-2.19 (m, 4H), 2.22-2.33 (m, 4H), 2.42-2.48 (m, 2H), 3.60-3.66 (m, 0.2H), 3.76-3.89 (m, 3.8H), 4.12 (q, *J* = 7.2 Hz, 4H), 4.27-4.29 (m, 0.2H), 4.40 (dd, J = 5.6, 9.8 Hz, 1.8H), 5.20 (br s, 0.2H), 5.41 (d, *J* = 9.6 Hz, 1.8H), 5.53 (d, *J* = 5.6 Hz, 2H), 7.59 (d, *J* = 6.3 Hz, 4H), 7.62 (d, *J* = 6.3 Hz, 4H), 7.86 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 801.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{42}H_{53}N_6O_6S_2$ $[M + H]^+$ 801.3468, found 801.3467; HPLC t_R = 43.75 min, 96.8%.

4.2.3. Phenyl [(2S)-3-methyl-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-3-methyl-2-[(phenoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-1-oxobutan-2-yl]carbamate (10)

The title compound was obtained from compound **6** and *N*-(phenoxycarbonyl)-L-valine according to the general procedure of the synthetic method A in 57% yield: mp 139-140 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 1.03 (d, *J* = 6.8 Hz, 6H), 1.09 (d, *J* = 6.6 Hz, 6H), 1.95-2.17 (m, 4H), 2.19-2.30 (m, 4H), 2.41-2.45 (m, 2H), 3.60-3.65 (m, 0.2H), 3.78-3.89 (m, 3.6H), 3.89-4.00 (m, 0.2H), 4.30 (dd, *J* = 6.0, 9.0 Hz, 0.2H), 4.46 (dd, *J* = 6.0, 9.0 Hz, 1.8H), 5.42 (d, *J* = 9.2 Hz, 0.2H), 5.55 (d, *J* = 9.2 Hz, 1.8H), 5.81 (d, *J* = 9.0 Hz, 0.2H), 5.98 (d, *J* = 9.0 Hz, 1.8H), 7.14 (d, *J* = 7.6 Hz, 4H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.35 (dd, *J* = 7.2, 7.6 Hz, 4H), 7.60 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 8.4 Hz, 4H), 7.89 (s, 1.8H), 7.91 (s, 0.2H); LC/MS (ESI) *m/z*: 897.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{53}N_6O_6S_2$ $[M + H]^+$ 897.3468, found 897.3460; HPLC t_R = 48.64 min, 95.9%.

4.2.4. Methyl {(2S)-1-[(2S)-2-{5-[4'-(2-{(2S)-1-[N-(methoxycarbonyl)-L-alanyl]pyrrolidin-2-yl}-1,

3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-1-oxopropan-2-yl}carbamate (11)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-L-alanine according to the general procedure of the synthetic method A in 75% yield: mp 144-146 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 1.43 (d, *J* = 6.9 Hz, 6H), 2.09-2.36 (m, 6H), 2.38-2.45 (m, 2H), 3.68 (s, 6H), 3.63-3.80 (m, 4H), 4.56-4.62 (m, 2H), 5.45 (d, *J* = 7.5 Hz, 0.2H), 5.53 (d, *J* = 7.5 Hz, 1.8H), 5.72 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 4H), 7.62 (d, *J* = 8.4 Hz, 4H), 7.88 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 717.0 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{36}H_{41}N_6O_6S_2$ $[M + H]^+$ 717.2529, found 717.2528; HPLC t_R = 30.19 min, 96.6%.

4.2.5. Dimethyl (biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(2S)-1-oxobutane-1,2-diyl]})biscarbamate (12)

The title compound was obtained from compound **6** and (2*S*)-2-[(methoxycarbonyl)amino]butanoic acid according to the general procedure of the synthetic method A in 68% yield: mp 122-123 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 1.00 (t, *J* = 7.5 Hz, 6H), 1.68-1.76 (m, 2H), 1.83-1.96 (m, 2H), 2.02-2.35 (m, 6H), 2.40-2.50 (m, 2H), 3.68 (s, 6H), 3.66-3.87 (m, 4H), 4.35-4.45

(m, 0.2H), 4.51 (dd, *J* = 7.6, 13.4 Hz, 1.8H), 5.51-5.56 (m, 4H), 7.58 (d, *J* = 8.4 Hz, 4H), 7.62 (d, *J* = 8.4 Hz, 4H), 7.89 (s, 1.8H), 7.94 (s, 0.2H); LC/MS (ESI) *m/z*: 745.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{38}H_{45}N_6O_6S_2$ $[M + H]^+$ 745.2842, found 745.2839; HPLC t_R = 34.49 min, 95.2%.

4.2.6. Methyl [(2S)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]pentanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-1-oxopentan-2-yl]carbamate (13)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-L-norvaline according to the general procedure of the synthetic method A in 65% yield: mp 130-131 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 0.97 (t, *J* = 7.2 Hz, 6H), 1.37-1.50 (m, 4H), 1.52-1.84 (m, 4H), 2.03-2.35 (m, 6H), 2.41-2.48 (m, 2H), 3.51 (s, 0.6H), 3.68 (s, 5.4H), 3.65-3.87 (m, 4H), 4.40-4.50 (m, 0.2H), 4.56 (dt, *J* = 4.8, 8.2 Hz, 1.8H), 5.35 (br s, 0.2H), 5.47 (d, *J* = 8.7 Hz, 1.8H), 5.52 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 8.4 Hz, 4H), 7.87 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 773.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{40}H_{49}N_6O_6S_2$ $[M + H]^+$ 773.3155, found 773.3156; HPLC t_R = 39.13 min, 100.0%.

4.2.7. Methyl [(2S)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]hexanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-1-oxohexan-2-yl]carbamate (14)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-L-norleucine according to the general procedure of the synthetic method A in 62% yield: mp 127-128 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 0.90 (t, *J* = 7.2 Hz, 6H), 1.26-1.40 (m, 8H), 1.60-1.67 (m, 2H), 1.69-1.84 (m, 2H), 2.10-2.19 (m, 2H), 2.22-2.31 (m, 4H), 2.44-2.46 (m, 2H), 3.51 (s, 0.6H), 3.68 (s, 5.4H), 3.61-3.86 (m, 4H), 4.42 (br s, 0.2H), 4.55 (dt, *J* = 5.2, 8.0 Hz, 1.8H), 5.36 (br s, 0.2H), 5.49 (d, *J* = 8.8 Hz, 1.8H), 5.52 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 4H), 7.62 (d, *J* = 8.4 Hz, 4H), 7.88 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 801.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{42}H_{53}N_6O_6S_2$ $[M + H]^+$ 801.3468, found 801.3466; HPLC t_R = 44.01 min, 100.0%.

4.2.8. Methyl [(2S)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-

4-methyl-1-oxopentan-2-yl]carbamate (15)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-L-leucine according to the general procedure of the synthetic method A in 64% yield: mp 172-174 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 0.97 (d, *J* = 6.6 Hz, 6H), 1.03 (d, *J* = 6.6 Hz, 6H), 1.47-1.62 (m, 4H), 1.75-1.81 (m, 2H), 2.11-2.18 (m, 2H), 2.20-2.33 (m, 4H), 2.43-2.49 (m, 2H), 3.49 (s, 0.6H), 3.68 (s, 5.4H), 3.71-3.76 (m, 2H), 3.85 (q, *J* = 8.8 Hz, 2H), 4.45 (br t, *J* = 9.6 Hz, 0.2H), 4.60 (dt, *J* = 4.0, 9.6 Hz, 1.8H), 5.28 (d, *J* = 8.8 Hz, 0.2H), 5.41 (d, *J* = 8.8 Hz, 1.8H), 5.51 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 4H), 7.63 (d, *J* = 8.4 Hz, 4H), 7.87 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 801.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{42}H_{53}N_6O_6S_2$ $[M + H]^+$ 801.3468, found 801.3461; HPLC t_R = 43.41 min, 100.0%.

4.2.9. Methyl [(2S)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-3,3-dimethyl-1-oxobutan-2-yl]carbamate (16)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-3-methyl-L-valine according to the general procedure of the

synthetic method A in 54% yield: mp 238-240 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 9 mixture of rotomers) δ 0.99 (s, 1.8H), 1.04 (s, 16.2H), 2.02-2.11 (m, 2H), 2.17-2.33 (m, 4H), 2.43-2.49 (m, 2H), 3.69 (s, 5.4H), 3.74 (s, 0.6H), 3.80-3.85 (m, 2H), 3.88-3.94 (m, 2H), 4.25 (d, *J* = 9.6 Hz, 0.2H), 4.40 (d, *J* = 9.6 Hz, 1.8H), 5.41-5.52 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 4H), 7.63 (d, *J* = 8.0 Hz, 4H), 7.87 (s, 1.8H), 7.95 (s, 0.2H); LC/MS (ESI) *m/z*: 801.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{42}H_{53}N_6O_6S_2$ $[M + H]^+$ 801.3468, found 801.3473; HPLC t_R = 44.21 min, 98.8%.

4.2.10. Dimethyl (biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate (17)

The title compound was obtained from compound **6** and *N*-(methoxycarbonyl)-L-phenylglycine according to the general procedure of the synthetic method A in 86% overall yield: mp 119-121 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.94-2.08 (m, 4H), 2.15-2.17 (m, 0.4H), 2.21-2.31 (m, 1.6H), 2.37-2.41 (m, 2H), 3.39-3.46 (m, 2H), 3.55 (s, 1.2H), 3.64 (s, 4.8H), 3.65-3.74 (m, 1.6H), 3.89-3.96 (m, 0.4H), 5.05 (d, *J* = 6.4 Hz, 0.4H), 5.28 (d, *J* = 7.2 Hz, 0.4H), 5.48 (d, *J* = 7.6 Hz, 1.6H), 5.57 (d, *J* = 8.0 Hz, 1.6H), 6.18 (d, *J* = 7.6 Hz, 1.6H), 6.22 (d, *J* = 7.2 Hz, 0.4H), 7.34-7.47 (m, 8H), 7.54 (d, *J* = 8.4 Hz, 4H), 7.63-7.68 (m, 6H),

7.85 (s, 1.6H), 7.99 (s, 0.4H); LC/MS (ESI) *m/z*: 841.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{45}N_6O_6S_2$ $[M + H]^+$ 841.2842, found 841.2843; HPLC t_R = 40.69 min, 97.5%.

4.2.11. Dimethyl (biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate (18a)

The title compound was obtained from compound **7** and methyl chloroformate according to the general procedure of the synthetic method B in 51% overall yield: mp 132-134 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.88-1.93 (m, 2H), 2.01-2.24 (m, 4H), 2.34-2.38 (m, 2H), 3.18 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.62 (s, 4.8H), 3.64 (s, 1.2H), 3.75-3.85 (m, 2.4H), 5.45-5.53 (m, 3.6H), 5.67 (d, *J* = 8.0 Hz, 0.4H), 6.02 (d, *J* = 7.6 Hz, 0.4H), 6.26 (d, *J* = 7.6 Hz, 1.6H), 7.00-7.13 (m, 2H), 7.33-7.49 (m, 8H), 7.60-7.68 (m, 8H), 7.84 (s, 0.4H), 7.89 (s, 1.6H); LC/MS (ESI) *m/z*: 841.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{45}N_6O_6S_2$ $[M + H]^+$ 841.2842, found 841.2843; HPLC t_R = 40.73 min, 96.5%.

4.2.12. Methyl [(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-ox

o-1-phenylethyl]carbamate (18b)

The title compound was obtained from compound **7** and methyl chloroformate according to the general procedure of the synthetic method B in 26% overall yield: mp 203-204 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.88-2.48 (m, 8H), 3.18 (dd, *J* = 9.4, 16.6 Hz, 1H), 3.83-3.46 (m, 1H), 3.54 (s, 0.6H), 3.62 (s, 2.4H), 3.64 (s, 3H), 3.67-3.93 (m, 2H), 5.04 (d, *J* = 6.8 Hz, 0.2H), 5.28 (d, *J* = 7.2 Hz, 0.2H), 5.45-5.53 (m, 2.6H), 5.57 (dd, *J* = 2.4, 8.0 Hz, 0.8H), 5.67 (d, *J* = 8.0 Hz, 0.2H), 6.03 (d, *J* = 7.6 Hz, 0.2H), 6.19 (d, *J* = 7.6 Hz, 0.8H), 6.23 (d, *J* = 7.6 Hz, 0.2H), 6.26 (d, *J* = 7.6 Hz, 0.8H), 6.99-7.13 (m, 1H), 7.32-7.68 (m, 17H), 7.85 (s, 1H), 7.89 (s, 0.8H), 7.99 (s, 0.2H); LC/MS (ESI) *m/z*: 841.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{45}N_6O_6S_2$ $[M + H]^+$ 841.2842, found 841.2845; HPLC t_R = 40.75 min, 95.8%.

4.2.13.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dimethanesulfonamide (19a)

The title compound was obtained from compound **7** and methanesulfonyl chloride according to the general procedure of the synthetic method B in 45% overall yield: mp 149-150 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.91-2.10

(m, 2H), 2.11-2.38 (m, 4H), 2.41-2.49 (m, 2H), 2.61 (s, 1.2H), 2.62 (s, 4.8H), 3.13 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.77-3.84 (m, 2.4H), 5.32 (d, *J* = 7.2 Hz, 1.6H), 5.36 (d, *J* = 7.2 Hz, 0.4H), 5.48 (d, *J* = 7.2 Hz, 1.6H), 5.58 (d, *J* = 7.2 Hz, 0.4H), 5.92 (d, *J* = 7.2 Hz, 2H), 7.03-7.14 (m, 1H), 7.33-7.49 (m, 9H), 7.52-7.78 (m, 8H), 7.88 (s, 2H); LC/MS (ESI) *m/z*: 881.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{44}H_{45}N_6O_6S_4$ $[M + H]^+$ 881.2283, found 881.2287; HPLC t_R = 39.29 min, 97.7%.

4.2.14.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Methylsulfonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]methanesulfonamide (19b)

The title compound was obtained from compound **7** and methanesulfonyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 173-175 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.92-2.46 (m, 8H), 2.61 (s, 0.6H), 2.68 (s, 2.4H), 2.69 (s, 2.4H), 2.75 (s, 0.6H), 3.13 (dd, *J* = 9.4, 16.6 Hz, 1H), 3.31-3.35 (m, 0.8H), 3.55-3.68 (m, 1H), 3.70-3.84 (m, 1H), 3.90-3.95 (m, 0.2H), 4.96 (d, *J* = 7.2 Hz, 0.2H), 5.19 (d, *J* = 7.6 Hz, 0.2H), 5.31-5.37 (m, 1.6H), 5.47 (d, *J* = 7.6 Hz, 1H), 5.58 (d, *J* = 8.0 Hz, 1H), 5.91-5.98 (m, 2H), 7.02-7.14 (m, 1H), 7.34-7.79 (m, 17H), 7.84 (s, 1H), 7.88 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI)

m/z: 881.1 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{44}H_{45}N_6O_6S_4$ $[M + H]^+$ 881.2283, found 881.2286; HPLC t_R = 39.20 min, 98.4%.

4.2.15.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})diacetamide (20a)

The title compound was obtained from compound **7** and acetyl chloride according to the general procedure of the synthetic method B in 40% overall yield: mp 197-199 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.89-1.94 (m, 2H), 1.96 (s, 4.8H), 1.98 (s, 1.2H), 2.06-2.46 (m, 6H), 3.18 (dd, *J* = 9.3, 16.2 Hz, 1.6H), 3.75-3.87 (m, 2.4H), 5.47 (d, *J* = 7.8 Hz, 1.6H), 5.72 (d, *J* = 7.8 Hz, 0.4H), 5.80 (d, *J* = 7.2 Hz, 2H), 6.76 (d, *J* = 7.0 Hz, 0.4H), 7.01-7.15 (m, 2.6H), 7.27-7.48 (m, 9H), 7.60-7.67 (m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 809.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{45}N_6O_4S_2$ $[M + H]^+$ 809.2944, found 809.2946; HPLC t_R = 32.58 min, 99.6%.

4.2.16.

N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-(Acetylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}acetamide (20b)

The title compound was obtained from compound **7** and acetyl chloride according to the general procedure of the synthetic method B in 12% overall yield: mp 230-232 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.96 (overlapped s, 3H), 1.99 (overlapped s, 3H), 1.88-2.46 (m, 8H), 3.18 (dd, *J* = 9.3, 16.2 Hz, 1H), 3.63-3.43 (m, 0.8H), 3.65-3.88 (m, 2.2H), 5.04 (d, *J* = 7.2 Hz, 0.2H), 5.47 (d, *J* = 7.2 Hz, 0.8H), 5.55 (d, *J* = 7.5 Hz, 1H), 5.71-5.81 (m, 2H), 6.78 (d, *J* = 7.5 Hz, 0.2H), 6.96-7.22 (m, 2.8H), 7.32-7.82 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 809.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{45}N_6O_4S_2$ $[M + H]^+$ 809.2944, found 809.2946; HPLC t_R = 33.96 min, 98.8%.

4.2.17.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dipropanamide (21a)

The title compound was obtained from compound **7** and propanoyl chloride according to the general procedure of the synthetic method B in 45% overall yield: mp 151-152 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.10 (t, *J* = 7.5 Hz, 6H), 1.88-2.37 (m, 12H), 3.19 (dd, *J* = 9.3, 16.5 Hz, 1.6H), 3.75-3.88 (m, 2.4H), 5.47 (d, *J* = 6.9 Hz, 1.6H), 5.72 (d, *J* = 6.9 Hz, 0.4H), 5.81 (d, *J* = 7.5 Hz, 2H), 6.68 (d, *J* = 7.2 Hz, 0.4H), 6.99 (d, *J* = 7.5 Hz, 1.6H), 7.03-7.16 (m, 1H), 7.30-7.48 (m, 9H), 7.60-7.67

(m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 837.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{48}H_{49}N_6O_4S_2$ $[M + H]^+$ 837.3257, found 837.3255; HPLC t_R = 37.36 min, 98.1%.

4.2.18.

N-{(1R)-2-Oxo-1-phenyl-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-phenyl-2-(propanoylamino)acetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]ethyl}propanamide (21b)

The title compound was obtained from compound **7** and propanoyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 208-210 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.02-1.18 (m, 6H), 1.88-2.38 (m, 12H), 3.19 (dd, *J* = 9.0, 16.2 Hz, 1H), 3.38-3.42 (m, 0.8H), 3.66-3.88 (m, 2.2H), 5.04 (d, *J* = 7.2 Hz, 0.2H), 5.48 (d, *J* = 7.2 Hz, 0.8H), 5.57 (d, *J* = 7.5 Hz, 1H), 5.71-5.82 (m, 2H), 6.67 (d, *J* = 7.8 Hz, 0.2H), 6.90-7.19 (m, 2.8H), 7.32-7.66 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 837.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{48}H_{49}N_6O_4S_2$ $[M + H]^+$ 837.3257, found 837.3255; HPLC t_R = 37.87 min, 96.1%.

4.2.19.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo

-1-phenylethane-2,1-diyl]})dibutanamide (22a)

The title compound was obtained from compound **7** and butanoyl chloride according to the general procedure of the synthetic method B in 52% overall yield: mp 125-127 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.86 (t, *J* = 7.6 Hz, 4.8H), 0.90 (t, *J* = 7.6 Hz, 1.2H), 1.56-1.66 (m, 4H), 1.87-2.02 (m, 2H), 2.03-2.23 (m, 8H), 2.33-2.36 (m, 2H), 3.20 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.75-3.79 (m, 0.4H), 3.86 (t, *J* = 9.0 Hz, 2H), 5.47 (d, *J* = 5.6 Hz, 1.6H), 5.72 (d, *J* = 8.4 Hz, 0.4H), 5.77 (d, *J* = 7.2 Hz, 0.4H), 5.81 (d, *J* = 7.2 Hz, 1.6H), 6.68 (d, *J* = 7.2 Hz, 0.4H), 6.96 (d, *J* = 7.2 Hz, 1.6H), 7.00-7.15 (m, 2H), 7.31-7.39 (m, 5H), 7.45-7.47 (m, 3H), 7.60-7.66 (m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 865.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{53}N_6O_4S_2$ $[M + H]^+$ 865.3570, found 865.3571; HPLC t_R = 41.09 min, 100.0%.

4.2.20.

N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-(Butanoylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}butanamide (22b)

The title compound was obtained from compound **7** and butanoyl chloride according to the general procedure of the synthetic method B in 19% overall yield: mp 209-211 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.80-0.89 (m, 6H),

1.43-1.66 (m, 4H), 1.87-2.39 (m, 12H), 3.20 (dd, *J* = 9.6, 16.4 Hz, 1H), 3.39-3.42 (m, 0.8H), 3.63-3.88 (m, 2.2H), 5.05 (d, *J* = 8.0 Hz, 0.2H), 5.47 (d, *J* = 8.0 Hz, 0.8H), 5.56 (d, *J* = 8.0 Hz, 1H), 5.71-5.82 (m, 2H), 6.69 (d, *J* = 7.6 Hz, 0.2H), 6.91-7.13 (m, 2.8H), 7.28-7.66 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 865.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{53}N_6O_4S_2$ $[M + H]^+$ 865.3570, found 865.3572; HPLC t_R = 41.43 min, 97.2%.

4.2.21.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dipentanamide (23a)

The title compound was obtained from compound **7** and pentanoyl chloride according to the general procedure of the synthetic method B in 45% overall yield: mp 112-113 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.77 (t, *J* = 7.6 Hz, 4.8H), 0.82 (t, *J* = 7.6 Hz, 1.2H), 1.15-1.28 (m, 4H), 1.45-1.55 (m, 4H), 1.67-1.95 (m, 2H), 2.01-2.19 (m, 8H), 2.27-2.43 (m, 2H), 3.13 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.68-3.70 (m, 0.4H), 3.80 (t, *J* = 7.6 Hz, 2H), 5.40 (d, *J* = 8.0 Hz, 1.6H), 5.66 (d, *J* = 8.0 Hz, 0.4H), 5.74 (d, *J* = 7.6 Hz, 2H), 6.64 (d, *J* = 7.2 Hz, 0.4H), 6.92 (d, *J* = 7.2 Hz, 1.6H), 6.96-7.24 (m, 2H), 7.29-7.36 (m, 5H), 7.39-7.46 (m, 3H), 7.53-7.63 (m, 8H), 7.81 (s, 1.6H), 7.83 (s, 0.4H); LC/MS (ESI) *m/z*: 893.3 $[M + H]^+$; HRMS (*m/z*): calcd

for $C_{52}H_{57}N_6O_4S_2$ $[M + H]^+$ 893.3883, found 893.3886; HPLC t_R = 44.77 min, 99.0%.

4.2.22.

N-{(1R)-2-Oxo-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-(pentanoylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-1-phenylethyl}pentanamide (23b)

The title compound was obtained from compound **7** and pentanoyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 208-210 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.62-0.80 (m, 6H), 1.11-1.27 (m, 4H), 1.40-1.55 (m, 4H), 1.82-2.29 (m, 12H), 3.13 (dd, *J* = 9.6, 16.4 Hz, 1H), 3.32-3.35 (m, 0.8H), 3.57-3.82 (m, 2.2H), 4.98 (d, *J* = 7.2 Hz, 0.2H), 5.40 (d, *J* = 7.2 Hz, 0.8H), 5.49 (d, *J* = 7.6 Hz, 1H), 5.65-5.75 (m, 2H), 6.61 (d, *J* = 7.5 Hz, 0.2H), 6.84-7.07 (m, 2.8H), 7.23-7.59 (m, 17H), 7.79 (s, 1H), 7.84 (s, 0.8H), 7.91 (s, 0.2H); LC/MS (ESI) *m/z*: 893.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{57}N_6O_4S_2$ $[M + H]^+$ 893.3883, found 893.3886; HPLC t_R = 45.23 min, 95.6%.

4.2.23.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dihexanamide (24a)

The title compound was obtained from compound **7** and hexanoyl chloride according to the general procedure of the synthetic method B in 41% overall yield: mp 143-144 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.81 (t, *J* = 7.2 Hz, 4.8H), 0.85 (t, *J* = 7.2 Hz, 1.2H), 1.17-1.34 (m, 8H), 1.54-1.61 (m, 4H), 1.89-2.08 (m, 2H), 2.11-2.23 (m, 8H), 2.33-2.46 (m, 2H), 3.20 (dd, *J* = 9.6, 16.4 Hz, 1.6H), 3.75-3.79 (m, 0.4H), 3.86 (t, *J* = 7.6 Hz, 2H), 5.47 (d, *J* = 8.0 Hz, 1.6H), 5.72 (d, *J* = 8.0 Hz, 0.4H), 5.77 (d, *J* = 7.2 Hz, 0.4H), 5.80 (d, *J* = 7.2 Hz, 1.6H), 6.69 (d, *J* = 7.2 Hz, 0.4H), 6.98 (d, *J* = 7.2 Hz, 1.6H), 7.00-7.15 (m, 2H), 7.31-7.39 (m, 5H), 7.43-7.47 (m, 3H), 7.60-7.66 (m, 8H), 7.88 (s, 1.6H), 7.89 (s, 0.4H); LC/MS (ESI) *m/z*: 921.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{61}N_6O_4S_2$ $[M + H]^+$ 921.4196, found 921.4192; HPLC t_R = 48.62 min, 100.0%.

4.2.24.

N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-(Hexanoylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}hexanamide (24b)

The title compound was obtained from compound **7** and hexanoyl chloride according to the general procedure of the synthetic method B in 11% overall yield: mp 192-194 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.81-0.95 (m, 6H),

1.10-1.38 (m, 8H), 1.51-1.64 (m, 4H), 1.90-2.43 (m, 12H), 3.20 (dd, *J* = 9.0, 16.6 Hz, 1H), 3.38-3.44 (m, 0.8H), 3.66-3.89 (m, 2.2H), 5.07 (d, *J* = 7.6 Hz, 0.2H), 5.48 (d, *J* = 7.6 Hz, 0.8H), 5.58 (d, *J* = 7.2 Hz, 1H), 5.72-5.82 (m, 2H), 6.71 (d, *J* = 7.6 Hz, 0.2H), 6.94-7.23 (m, 2.8H), 7.36-7.64 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.98 (s, 0.2H); LC/MS (ESI) *m/z*: 921.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{61}N_6O_4S_2$ $[M + H]^+$ 921.4196, found 921.4192; HPLC t_R = 49.21 min, 97.2%.

4.2.25.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis(2-methylpropanamide) (25a)

The title compound was obtained from compound **7** and 2-methylpropanoyl chloride according to the general procedure of the synthetic method B in 51% overall yield: mp 138-140 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.06 (d, *J* = 7.2 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.82-2.44 (m, 10H), 3.21 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.74-3.79 (m, 0.4H), 3.86 (t, *J* = 7.5 Hz, 2H), 5.47 (d, *J* = 7.5 Hz, 1.6H), 5.71-5.79 (m, 2.4H), 6.74 (d, *J* = 7.2 Hz, 0.4H), 6.99-7.14 (m, 3.6H), 7.30-7.39 (m, 5H), 7.43-7.47 (m, 3H), 7.59-7.65 (m, 8H), 7.89 (s, 2H); LC/MS (ESI) *m/z*: 865.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{53}N_6O_4S_2$ $[M + H]^+$ 865.3570, found 865.3568; HPLC t_R = 40.65 min, 99.9%.

4.2.26.

2-Methyl-N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(2-methylpropanoyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]propanamide (25b)

The title compound was obtained from compound **7** and 2-methylpropanoyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 239-241 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.09-1.16 (m, 12H), 1.82-2.51 (m, 10H), 3.20 (dd, *J* = 9.3, 16.2 Hz, 1H), 3.39-3.43 (m, 0.8H), 3.62-3.89 (m, 2.2H), 5.07 (d, *J* = 7.8 Hz, 0.2H), 5.48 (d, *J* = 7.8 Hz, 0.8H), 5.58 (d, *J* = 7.8 Hz, 1H), 5.73-5.80 (m, 2H), 6.72 (d, *J* = 7.2 Hz, 0.2H), 6.95-7.22 (m, 2.8H), 7.31-7.66 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 865.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{53}N_6O_4S_2$ $[M + H]^+$ 865.3570, found 865.3568; HPLC t_R = 41.49 min, 99.1%.

4.2.27.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})bis(2,2-dimethylpropanamide) (26a)

The title compound was obtained from compound **7** and 2,2-dimethylpropanoyl

chloride according to the general procedure of the synthetic method B in 43% overall yield: mp 128-130 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.16 (s, 14.4H), 1.18 (s, 3.6H), 1.89-2.36 (m, 8H), 3.22 (dd, *J* = 9.3, 16.5 Hz, 1.6H), 3.77-3.90 (m, 2.4H), 5.47 (d, *J* = 7.5 Hz, 1.6H), 5.70-5.76 (m, 2.4H), 6.90 (d, *J* = 7.2 Hz, 0.4H), 6.99-7.15 (m, 2H), 7.22 (d, *J* = 7.2 Hz, 1.6H), 7.33-7.48 (m, 8H), 7.60-7.67 (m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 893.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{57}N_6O_4S_2$ $[M + H]^+$ 893.3883, found 893.3881; HPLC t_R = 47.46 min, 98.0%.

4.2.28.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(2,2-Dimethylpropanoyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]-2,2-dimethylpropanamide (26b)

The title compound was obtained from compound **7** and 2,2-dimethylpropanoyl chloride according to the general procedure of the synthetic method B in 20% overall yield: mp 250-252 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.16 (s, 9H), 1.18 (s, 9H), 1.89-2.34 (m, 8H), 3.20 (dd, *J* = 9.3, 16.6 Hz, 1H), 3.39-3.46 (m, 0.8H), 3.66-3.90 (m, 2.2H), 5.47 (d, *J* = 5.9 Hz, 1H), 5.56 (d, *J* = 4.8 Hz, 1H), 5.69-5.76 (m, 2H), 6.69-7.23 (m, 3H), 7.33-7.66 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 893.4 $[M + H]^+$; HRMS (*m/z*): calcd for

$C_{52}H_{57}N_6O_4S_2$ $[M + H]^+$ 893.3883, found 893.3881; HPLC t_R = 47.67 min, 98.8%.

4.2.29.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dicyclopropanecarboxamide (27a)

The title compound was obtained from compound **7** and cyclopropanecarbonyl chloride according to the general procedure of the synthetic method B in 54% overall yield: mp 151-152 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.65-0.75 (m, 4H), 0.87-0.97 (m, 4H), 1.38-1.46 (m, 2H), 1.89-2.48 (m, 8H), 3.18 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.75-3.79 (m, 0.4H), 3.86 (t, *J* = 9.0 Hz, 2H), 5.47 (d, *J* = 7.6 Hz, 1.6H), 5.71 (d, *J* = 7.6 Hz, 0.4H), 5.81 (d, *J* = 7.4 Hz, 0.4H), 5.85 (d, *J* = 7.4 Hz, 1.6H), 6.99-7.16 (m, 2H), 7.28-7.53 (m, 10H), 7.60-7.69 (m, 8H), 7.87 (s, 1.6H), 7.89 (s, 0.4H); LC/MS (ESI) *m/z*: 861.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{49}N_6O_4S_2$ $[M + H]^+$ 861.3257, found 861.3253; HPLC t_R = 39.50 min, 100.0%.

4.2.30.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Cyclopropylcarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]cyclopropanecarboxamide (27b)

The title compound was obtained from compound **7** and cyclopropanecarbonyl chloride according to the general procedure of the synthetic method B in 20% overall yield: mp 229-231 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.64-0.78 (m, 4H), 0.88-0.97 (m, 4H), 1.38-1.44 (m, 2H), 1.89-2.38 (m, 8H), 3.19 (dd, *J* = 9.4, 16.6 Hz, 1H), 3.39-3.45 (m, 0.8H), 3.70-3.77 (m, 1.2H), 3.86 (t, *J* = 7.6 Hz, 1H), 5.07 (d, *J* = 8.0 Hz, 0.2H), 5.48 (d, *J* = 8.0 Hz, 0.8H), 5.58 (d, *J* = 7.2 Hz, 1H), 5.72 (d, *J* = 7.6 Hz, 0.2H), 5.81 (d, *J* = 7.6 Hz, 0.8H), 5.85 (d, *J* = 7.6 Hz, 1H), 7.01-7.27 (m, 3H), 7.29-7.66 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 861.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{49}N_6O_4S_2$ $[M + H]^+$ 861.3257, found 861.3253; HPLC t_R = 39.81 min, 100.0%.

4.2.31.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dicyclobutanecarboxamide (28a)

The title compound was obtained from compound **7** and cyclobutanecarbonyl chloride according to the general procedure of the synthetic method B in 52% overall yield: mp 167-169 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.76-2.37 (m, 20H), 2.95-3.03 (m, 2H), 3.20 (dd, *J* = 9.3, 16.2 Hz, 1.6H), 3.75-3.89 (m, 2.4H), 5.47 (d, *J* = 7.8 Hz, 1.6H), 5.72-5.81 (m, 2.4H), 6.58 (d, *J* = 7.5 Hz, 0.4H), 6.89 (d, *J*

= 7.5 Hz, 1.6H), 7.00-7.15 (m, 2H), 7.27-7.41 (m, 5H), 7.46-7.48 (m, 3H), 7.60-7.67 (m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 889.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{53}N_6O_4S_2$ $[M + H]^+$ 889.3570, found 889.3577; HPLC t_R = 43.21 min, 100.0%.

4.2.32. N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Cyclobutylcarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]cyclobutanecarboxamide (28b)

The title compound was obtained from compound **7** and cyclobutanecarbonyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 221-223 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.83-2.51 (m, 20H), 2.95-3.08 (m, 2H), 3.20 (dd, *J* = 9.3, 18.0 Hz, 1H), 3.39-3.44 (m, 0.8H), 3.65-3.75 (m, 1.2H), 3.87 (t, *J* = 7.2 Hz, 1H), 5.07 (d, *J* = 5.7 Hz, 0.2H), 5.47 (d, *J* = 5.7 Hz, 0.8H), 5.62 (d, *J* = 6.9 Hz, 1H), 5.75-5.81 (m, 2H), 6.60 (d, *J* = 7.2 Hz, 0.2H), 6.84 (d, *J* = 7.2 Hz, 0.8H), 6.89 (d, *J* = 7.5 Hz, 1H), 7.00-7.18 (m, 1H), 7.36-7.72 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.98 (s, 0.2H); LC/MS (ESI) *m/z*: 889.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{53}N_6O_4S_2$ $[M + H]^+$ 889.3570, found 889.3577; HPLC t_R = 43.59 min, 98.4%.

4.2.33.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dicyclopentanecarboxamide (29a)

The title compound was obtained from compound **7** and cyclopentanecarbonyl chloride according to the general procedure of the synthetic method B in 44% overall yield: mp 137-138 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.51-1.88 (m, 18H), 2.03-2.44 (m, 6H), 2.47-2.60 (m, 2H), 3.21 (dd, *J* = 9.0, 16.5 Hz, 1.6H), 3.75-3.89 (m, 2.4H), 5.47 (d, *J* = 7.8 Hz, 1.6H), 5.71-5.81 (m, 2.4H), 6.69 (d, *J* = 7.5 Hz, 0.4H), 6.98-7.24 (m, 3.6H), 7.27-7.40 (m, 5H), 7.45-7.47 (m, 3H), 7.60-7.66 (m, 8H), 7.87 (s, 1.6H), 7.90 (s, 0.4H); LC/MS (ESI) *m/z*: 917.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{57}N_6O_4S_2$ $[M + H]^+$ 917.3883, found 917.3886; HPLC t_R = 46.47 min, 100.0%.

4.2.34.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Cyclopentylcarbonyl)amino]-2-phenyl acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-y l}-2-oxo-1-phenylethyl]cyclopentanecarboxamide (29b)

The title compound was obtained from compound **7** and cyclopentanecarbonyl chloride according to the general procedure of the synthetic method B in 10% overall

yield: mp 260-262 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.49-2.43 (m, 24H), 2.47-2.60 (m, 2H), 3.20 (dd, *J* = 9.3, 16.2 Hz, 1H), 3.34-3.43 (m, 0.8H), 3.65-3.87 (m, 2.2H), 5.08 (d, *J* = 5.9 Hz, 0.2H), 5.46 (d, *J* = 5.9 Hz, 0.8H), 5.40 (d, *J* = 6.9 Hz, 1H), 5.71-5.81 (m, 2H), 6.69 (d, *J* = 7.2 Hz, 0.2H), 6.92-7.13 (m, 2.8H), 7.31-7.71 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 917.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{57}N_6O_4S_2$ $[M + H]^+$ 917.3883, found 917.3886; HPLC t_R = 46.91 min, 100.0%.

4.2.35.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dicyclohexanecarboxamide (30a)

The title compound was obtained from compound **7** and cyclohexanecarbonyl chloride according to the general procedure of the synthetic method B in 55% overall yield: mp 136-138 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.11-1.45 (m, 8H), 1.66-1.93 (m, 14H), 2.03-2.21 (m, 6H), 2.23-2.36 (m, 2H), 3.21 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.75-3.77 (m, 0.4H), 3.87 (t, *J* = 7.4 Hz, 2H), 5.47 (d, *J* = 7.6 Hz, 1.6H), 5.71-5.80 (m, 2.4H), 6.69 (d, *J* = 7.2 Hz, 0.4H), 6.99-7.14 (m, 3.6H), 7.31-7.46 (m, 8H), 7.60-7.66 (m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 945.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{61}N_6O_4S_2$ $[M + H]^+$ 945.4196, found 945.4191;

HPLC t_R = 49.81 min, 100.0%.

4.2.36.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Cyclohexylcarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]cyclohexanecarboxamide (30b)

The title compound was obtained from compound **7** and cyclohexanecarbonyl chloride according to the general procedure of the synthetic method B in 12% overall yield: mp 261-263 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.08-1.46 (m, 8H), 1.63-1.93 (m, 14H), 2.03-2.47 (m, 8H), 3.22 (dd, *J* = 9.6, 16.4 Hz, 1H), 3.40-3.42 (m, 0.8H), 3.65-3.89 (m, 2.2H), 5.08 (d, *J* = 8.0 Hz, 0.2H), 5.47 (d, *J* = 8.0 Hz, 0.8H), 5.55 (d, *J* = 7.6 Hz, 1H), 5.71-5.80 (m, 2H), 6.71 (d, *J* = 7.2 Hz, 0.2H), 6.95-7.13 (m, 2.8H), 7.33-7.64 (m, 17H), 7.86 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 945.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{61}N_6O_4S_2$ $[M + H]^+$ 945.4196, found 945.4191; HPLC t_R = 50.19 min, 100.0%.

4.2.37.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dibenzamide (31a)

The title compound was obtained from compound **7** and benzoyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 160-162 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 2.04-2.37 (m, 8H), 3.24 (dd, *J* = 9.0, 16.2 Hz, 1.6H), 3.79-3.88 (m, 0.4H), 3.90 (t, *J* = 7.6 Hz, 2H), 5.51 (d, *J* = 7.6 Hz, 1.6H), 5.78 (d, *J* = 7.6 Hz, 0.4H), 5.97 (d, *J* = 6.8 Hz, 2H), 7.00-7.08 (m, 1H), 7.22-7.26 (m, 1H), 7.28-7.50 (m, 12H), 7.52-7.68 (m, 10H), 7.79-7.87 (m, 6H), 7.89 (s, 1.6H), 7.90 (s, 0.4H); LC/MS (ESI) *m/z*: 933.1 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{49}N_6O_4S_2$ $[M + H]^+$ 933.3257, found 933.3261; HPLC t_R = 46.85 min, 95.1%.

4.2.38.

N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-(Benzoylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}benzamide (31b)

The title compound was obtained from compound **7** and benzoyl chloride according to the general procedure of the synthetic method B in 39% overall yield: mp 280-282 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.84-2.26 (m, 8H), 3.19 (dd, *J* = 9.6, 16.4 Hz, 1H), 3.38-3.43 (m, 1H), 3.66-3.73 (m, 1H), 3.82-3.93 (m, 1H), 5.06 (d, *J* = 7.6 Hz, 0.2H), 5.45 (d, *J* = 7.6 Hz, 0.8H), 5.51 (d, *J* = 7.6 Hz, 1H), 5.68 (d, *J* = 7.2 Hz, 0.2H), 5.73 (d, *J* = 7.2 Hz, 0.2H), 5.88 (d, *J* = 7.2 Hz, 0.8H), 5.90 (d, *J* = 7.2

Hz, 0.8H), 6.94-7.22 (m, 2H), 7.30-7.75 (m, 28H), 7.80 (s, 1H), 7.83 (s, 0.8H), 7.91 (s, 0.2H); LC/MS (ESI) *m/z*: 933.1 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{49}N_6O_4S_2$ $[M + H]^+$ 933.3257, found 933.3261; HPLC t_R = 47.25 min, 95.6%.

4.2.39.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis(2-phenylacetamide) (32a)

The title compound was obtained from compound **7** and phenylacetyl chloride according to the general procedure of the synthetic method B in 40% overall yield: mp 132-134 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.85-2.48 (m, 8H), 3.18 (dd, *J* = 9.3, 16.5 Hz, 1.6H), 3.54 (s, 3.2H), 3.55 (s, 0.8H), 3.67-3.78 (m, 0.4H), 3.84 (t, *J* = 9.5 Hz, 2H), 5.44 (d, *J* = 7.8 Hz, 1.6H), 5.69 (d, *J* = 7.8 Hz, 0.4H), 5.74 (d, *J* = 7.5 Hz, 0.4H), 5.78 (d, *J* = 7.5 Hz, 1.6H), 6.80 (d, *J* = 6.6 Hz, 0.4H), 6.99-7.10 (m, 3.6H), 7.15-7.48 (m, 18H), 7.58-7.69 (m, 8H), 7.89 (s, 2H); LC/MS (ESI) *m/z*: 961.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{58}H_{53}N_6O_4S_2$ $[M + H]^+$ 961.3570, found 961.3572; HPLC t_R = 45.03 min, 100.0%.

4.2.40.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(phenylacetyl

)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrol idin-1-yl}ethyl]-2-phenylacetamide (32b)

The title compound was obtained from compound **7** and phenylacetyl chloride according to the general procedure of the synthetic method B in 14% overall yield: mp 180-182 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.88-2.44 (m, 8H), 3.18 (dd, *J* = 9.4, 16.3 Hz, 1H), 3.32-3.45 (m, 1H), 3.49 (s, 0.4H), 3.54 (s, 1.6H), 3.58 (s, 2H), 3.66-3.86 (m, 2H), 5.03 (d, *J* = 7.8 Hz, 0.2H), 5.45 (d, *J* = 7.8 Hz, 0.8H), 5.53 (d, *J* = 7.8 Hz, 1H), 5.73 (d, *J* = 7.2 Hz, 1H), 5.77 (d, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 6.9 Hz, 0.2H), 6.91-7.08 (m, 2.8H), 7.18-7.69 (m, 27H), 7.84 (s, 1H), 7.90 (s, 0.8H), 7.96 (s, 0.2H); LC/MS (ESI) *m/z*: 961.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{58}H_{53}N_6O_4S_2$ $[M + H]^+$ 961.3570, found 961.3572; HPLC t_R = 45.47 min, 100.0%.

4.2.41.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dipyridine-4-carboxamide (33a)

The title compound was obtained from compound **7** and pyridine-4-carbonyl chloride according to the general procedure of the synthetic method B in 35% overall yield: mp 169-171 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.93-2.49 (m, 8H), 3.21 (dd, *J* = 9.2, 16.4 Hz, 1.6H), 3.74-3.82 (m, 0.4H), 3.88 (t, *J* = 7.8 Hz,

2H), 5.51 (d, *J* = 7.4 Hz, 1.6H), 5.73 (d, *J* = 7.4 Hz, 0.4H), 5.91 (d, *J* = 7.0 Hz, 1.6H), 5.95 (d, *J* = 7.0 Hz, 0.4H), 6.97-7.17 (m, 1H), 7.21-7.26 (m, 1H), 7.34-7.46 (m, 6H), 7.54-7.76 (m, 14H), 7.83 (s, 1.6H), 7.87 (s, 0.4H), 7.91 (d, *J* = 14.4 Hz, 2H), 8.71 (d, *J* = 10.0 Hz, 4H); LC/MS (ESI) *m/z*: 935.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{47}N_8O_4S_2$ $[M + H]^+$ 935.3162, found 935.3165; HPLC t_R = 37.23 min, 98.7%.

4.2.42. N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(pyridin-4-yl carbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]pyridine-4-carboxamide (33b)

The title compound was obtained from compound **7** and pyridine-4-carbonyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 167-169 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.93-2.49 (m, 8H), 3.22 (dd, *J* = 9.0, 16.6 Hz, 1H), 3.42-3.44 (m, 0.8H), 3.65-3.96 (m, 2.2H), 5.10 (d, *J* = 7.6 Hz, 0.2H), 5.51 (d, *J* = 7.6 Hz, 0.8H), 5.57 (d, *J* = 7.2 Hz, 0.8H), 5.72-5.75 (m, 0.4H), 5.89-5.98 (m, 1.8H), 6.99-7.24 (m, 2H), 7.27-7.43 (m, 6H), 7.55-7.73 (m, 14H), 7.85-7.99 (m, 4H), 8.14 (d, *J* = 8.4 Hz, 2H), 8.69 (d, *J* = 8.4 Hz, 2H); LC/MS (ESI) *m/z*: 935.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{47}N_8O_4S_2$ $[M + H]^+$ 935.3162, found 935.3165; HPLC t_R = 36.12 min, 95.5%.

4.2.43.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dipyridine-3-carboxamide (34a)

The title compound was obtained from compound **7** and pyridine-3-carbonyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 154-156 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.91-2.38 (m, 8H), 3.22 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.80-3.87 (m, 0.4H), 3.89 (t, *J* = 7.8 Hz, 2H), 5.51 (d, *J* = 7.4 Hz, 1.6H), 5.75 (d, *J* = 7.4 Hz, 0.4H), 5.94-5.99 (m, 2H), 7.01-7.09 (m, 1H), 7.22-7.27 (m, 1H), 7.31-7.43 (m, 8H), 7.55-7.68 (m, 10H), 7.87-7.90 (m, 4H), 8.07 (dd, *J* = 2.4, 5.6 Hz, 2H), 8.69 (d, *J* = 4.8 Hz, 2H), 9.03 (d, *J* = 2.4 Hz, 2H); LC/MS (ESI) *m/z*: 935.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{47}N_8O_4S_2$ $[M + H]^+$ 935.3162, found 935.3167; HPLC t_R = 36.67 min, 96.4%.

4.2.44.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(pyridin-3-ylcarbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]pyridine-3-carboxamide (34b)

The title compound was obtained from compound **7** and pyridine-3-carbonyl chloride

according to the general procedure of the synthetic method B in 30% overall yield: mp 155-157 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.91-2.37 (m, 8H), 3.23 (dd, *J* = 9.2, 16.4 Hz, 1H), 3.42-3.46 (m, 0.8H), 3.65-3.92 (m, 2.2H), 5.10 (d, *J* = 7.6 Hz, 0.2H), 5.51 (d, *J* = 7.6 Hz, 0.8H), 5.58 (d, *J* = 7.2 Hz, 0.8H), 5.72-5.74 (m, 0.4H), 5.92-5.99 (m, 1.8H), 7.02-7.25 (m, 2H), 7.30-7.44 (m, 8H), 7.53-7.68 (m, 10H), 7.82-7.90 (m, 4H), 8.06-8.11 (m, 2H), 8.68-8.72 (m, 2H), 9.04 (s, 2H); LC/MS (ESI) *m/z*: 935.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{47}N_8O_4S_2$ $[M + H]^+$ 935.3162, found 935.3167; HPLC t_R = 37.28 min, 95.5%.

4.2.45.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dipyridine-2-carboxamide (35a)

The title compound was obtained from compound **7** and pyridine-2-carbonyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 147-149 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.91-2.37 (m, 8H), 3.28 (dd, *J* = 9.3, 16.5 Hz, 1.6H), 3.79-3.81 (m, 0.4H), 3.93 (t, *J* = 7.4 Hz, 2H), 5.54 (d, *J* = 7.8 Hz, 1.6H), 5.83 (d, *J* = 7.8 Hz, 0.4H), 5.99 (d, *J* = 7.8 Hz, 2H), 7.02-7.24 (m, 2H), 7.31-7.43 (m, 8H), 7.57-7.60 (m, 10H), 7.72-7.84 (m, 2H), 7.87 (s, 1.6H), 7.88 (s, 0.4H), 8.12 (d, *J* = 8.1 Hz, 2H), 8.54 (d, *J* = 4.2 Hz, 2H), 9.07 (d, *J* =

8.1 Hz, 0.4H), 9.33 (d, *J* = 8.1 Hz, 1.6H); LC/MS (ESI) *m/z*: 935.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{47}N_8O_4S_2$ $[M + H]^+$ 935.3162, found 935.3160; HPLC t_R = 47.63 min, 100.0%.

4.2.46.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(pyridin-2-yl carbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]pyridine-2-carboxamide (35b)

The title compound was obtained from compound **7** and pyridine-2-carbonyl chloride according to the general procedure of the synthetic method B in 27% overall yield: mp 153-155 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.93-2.39 (m, 8H), 3.26 (dd, *J* = 9.0, 16.2 Hz, 1H), 3.46-3.53 (m, 0.8H), 3.65-3.96 (m, 2.2H), 5.14 (d, *J* = 6.6 Hz, 0.2H), 5.54 (d, *J* = 6.6 Hz, 0.8H), 5.60 (d, *J* = 7.2 Hz, 0.8H), 5.74 (d, *J* = 7.2 Hz, 0.2H), 5.83 (d, *J* = 7.5 Hz, 0.2H), 5.94 (d, *J* = 7.5 Hz, 0.8H), 5.99 (d, *J* = 7.5 Hz, 1H), 7.03-7.11 (m, 2H), 7.35-7.42 (m, 8H), 7.46-7.64 (m, 10H), 7.71-8.03 (m, 4H), 8.13 (d, *J* = 7.6 Hz, 2H), 8.54 (d, *J* = 3.0 Hz, 2H), 9.08 (d, *J* = 7.6 Hz, 0.4H), 9.33 (dd, *J* = 3.0, 7.6 Hz, 1.6H); LC/MS (ESI) *m/z*: 935.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{47}N_8O_4S_2$ $[M + H]^+$ 935.3162, found 935.3160; HPLC t_R = 47.56 min, 96.5%.

4.2.47.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})difuran-2-carboxamide (36a)

The title compound was obtained from compound **7** and furan-2-carbonyl chloride according to the general procedure of the synthetic method B in 55% overall yield: mp 128-130 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.90-2.52 (m, 8H), 3.22 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.75-3.81 (m, 0.4H), 3.89 (t, *J* = 7.6 Hz, 2H), 5.52 (d, *J* = 8.0 Hz, 1.6H), 5.77 (d, *J* = 8.0 Hz, 0.4H), 5.95 (d, *J* = 8.0 Hz, 2H), 6.44 (s, 1.6H), 6.54 (m, 0.4H), 7.00-7.15 (m, 3H), 7.19-7.26 (m, 1H), 7.33-7.47 (m, 8H), 7.54-7.68 (m, 10H), 7.84 (d, *J* = 12.4 Hz, 2H), 7.88 (s, 1.6H), 7.89 (s, 0.4H); LC/MS (ESI) *m/z*: 913.0 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_6S_2$ $[M + H]^+$ 913.2842, found 913.2843; HPLC t_R = 43.53 min, 97.6%.

4.2.48.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Furan-2-ylcarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]furan-2-carboxamide (36b)

The title compound was obtained from compound **7** and furan-2-carbonyl chloride

according to the general procedure of the synthetic method B in 14% overall yield: mp 240-242 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.92-2.49 (m, 8H), 3.23 (dd, *J* = 9.4, 16.6 Hz, 1H), 3.44-3.46 (m, 0.8H), 3.65-3.96 (m, 2.2H), 5.11 (d, *J* = 7.0 Hz, 0.2H), 5.52 (d, *J* = 7.2 Hz, 0.8H), 5.59 (d, *J* = 7.0 Hz, 0.8H), 5.71 (d, *J* = 7.2 Hz, 0.2H), 5.78 (d, *J* = 7.6, 0.2H), 5.91 (d, *J* = 7.6 Hz, 0.8H), 5.95 (d, *J* = 7.2 Hz, 1H), 6.42-6.54 (m, 2H), 6.99-7.17 (m, 3H), 7.22-7.24 (m, 1H), 7.35-7.48 (m, 8H), 7.54-7.69 (m, 10H), 7.82-7.98 (m, 4H); LC/MS (ESI) *m/z*: 913.1 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_6S_2$ $[M + H]^+$ 913.2842, found 913.2843; HPLC t_R = 43.56 min, 98.3%.

4.2.49.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})difuran-3-carboxamide (37a)

The title compound was obtained from compound **7** and furan-3-carbonyl chloride according to the general procedure of the synthetic method B in 50% overall yield: mp 175-177 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.90-1.93 (m, 2H), 2.04-2.51(m, 6H), 3.21 (dd, *J* = 9.4, 16.6 Hz, 1.6H), 3.74-3.82 (m, 0.4H), 3.88 (t, *J* = 7.6 Hz, 2H), 5.50 (d, *J* = 7.6 Hz, 1.6H), 5.75 (d, *J* = 7.6 Hz, 0.4H), 5.93 (d, *J* = 6.8 Hz, 2H), 6.64 (s, 2H), 6.99-7.21 (m, 2H), 7.33-7.42 (m, 8H), 7.52-7.79 (m,

12H), 7.89 (s, 1.6H), 7.90 (s, 0.4H), 7.92 (s, 2H); LC/MS (ESI) *m/z*: 913.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_6S_2$ $[M + H]^+$ 913.2842, found 913.2846; HPLC t_R = 41.15 min, 96.9%.

4.2.50.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Furan-3-ylcarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]furan-3-carboxamide (37b)

The title compound was obtained from compound **7** and furan-3-carbonyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 58-260 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.90-2.35 (m, 8H), 3.21 (dd, *J* = 9.2, 16.4 Hz, 1H), 3.40-3.47 (m, 0.8H), 3.65-3.91 (m, 2.2H), 5.09 (d, *J* = 5.1 Hz, 0.2H), 5.50 (d, *J* = 6.9 Hz, 0.8H), 5.58 (d, *J* = 5.1 Hz, 0.8H), 5.69 (d, *J* = 6.9 Hz, 0.2H), 5.75 (d, *J* = 7.2, 0.2H), 5.89 (d, *J* = 7.2 Hz, 0.8H), 5.94 (d, *J* = 7.2 Hz, 1H), 6.61 (s, 0.4H), 6.64 (s, 1.6H), 7.01-7.22 (m, 2H), 7.28-7.42 (m, 8H), 749-7.67 (m, 12H), 7.87-7.98 (m, 4H); LC/MS (ESI) *m/z*: 913.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_6S_2$ $[M + H]^+$ 913.2842, found 913.2846; HPLC t_R = 41.92 min, 97.4%.

4.2.51.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dithiophene-2-carboxamide (38a)

The title compound was obtained from compound **7** and thiophene-2-carbonyl chloride according to the general procedure of the synthetic method B in 49% overall yield: mp 168-170 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.90-2.37 (m, 8H), 3.21 (dd, *J* = 9.3, 16.2 Hz, 1.6H), 3.78-3.91 (m, 2.4H), 5.51 (d, *J* = 7.8 Hz, 1.6H), 5.75 (d, *J* = 7.8 Hz, 0.4H), 5.93 (d, *J* = 6.9 Hz, 2H), 7.01-7.09 (m, 3H), 7.21-7.26 (m, 1H), 7.27-7.47 (m, 8H), 7.52-7.67 (m, 14H), 7.89 (s, 1.6H), 7.90 (s, 0.4H); LC/MS (ESI) *m/z*: 945.1 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_4S_4$ $[M + H]^+$ 945.2385, found 945.2387; HPLC t_R = 45.55 min, 99.6%.

4.2.52.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(thiophen-2-ylcarbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]thiophene-2-carboxamide (38b)

The title compound was obtained from compound **7** and thiophene-2-carbonyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 282-284 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers)

δ 1.90-2.40 (m, 8H), 3.21 (dd, *J* = 9.3, 15.9 Hz, 1H), 3.42-3.45 (m, 0.8H), 3.66-3.91 (m, 2.2H), 5.09 (d, *J* = 7.5 Hz, 0.2H), 5.50 (d, *J* = 6.9 Hz, 0.8H), 5.58 (d, *J* = 7.5 Hz, 0.8H), 5.69 (d, *J* = 6.9 Hz, 0.2H), 5.75 (d, *J* = 8.1 Hz, 0.2H), 5.88 (d, *J* = 8.1 Hz, 0.8H), 5.94 (d, *J* = 6.9 Hz, 1H), 6.91-7.09 (m, 3H), 7.15-7.24 (m, 1H), 7.32-7.45 (m, 8H), 7.51-7.70 (m, 14H), 7.87 (s, 1H), 7.90 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 945.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_4S_4$ $[M + H]^+$ 945.2385, found 945.2387; HPLC t_R = 46.09 min, 99.1%.

4.2.53.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})dithiophene-3-carboxamide (39a)

The title compound was obtained from compound **7** and thiophene-3-carbonyl chloride according to the general procedure of the synthetic method B in 44% overall yield: mp 158-160 ^oC; ^1H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.90-2.37 (m, 8H), 3.23 (dd, *J* = 9.3, 16.5 Hz, 1.6H), 3.78-3.92 (m, 2.4H), 5.51 (d, *J* = 7.5 Hz, 1.6H), 5.77 (d, *J* = 7.5 Hz, 0.4H), 5.94 (d, *J* = 7.2 Hz, 2H), 7.00-7.09 (m, 1H), 7.20-7.25 (m, 1H), 7.27-7.48 (m, 12H), 7.54-7.68 (m, 12H), 7.89 (s, 2H); LC/MS (ESI) *m/z*: 945.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_4S_4$ $[M + H]^+$ 945.2385, found 945.2380; HPLC t_R = 44.41 min, 98.8%.

4.2.54.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(thiophen-3-ylcarbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]thiophene-3-carboxamide (39b)

The title compound was obtained from compound **7** and thiophene-3-carbonyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 279-281 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.91-2.36 (m, 8H), 3.22 (dd, *J* = 9.0, 16.5 Hz, 1H), 3.44-3.47 (m, 0.8H), 3.66-3.92 (m, 2.2H), 5.11 (d, *J* = 6.9 Hz, 0.2H), 5.51 (d, *J* = 6.6 Hz, 0.8H), 5.58 (d, *J* = 6.9 Hz, 0.8H), 5.71 (d, *J* = 6.6 Hz, 0.2H), 5.77 (d, *J* = 7.2 Hz, 0.2H), 5.90 (d, *J* = 7.2 Hz, 0.8H), 5.95 (d, *J* = 7.2 Hz, 1H), 7.01-7.10 (m, 1H), 7.22-7.40 (m, 12H), 7.54-7.68 (m, 13H), 7.85-7.98 (m, 2H); LC/MS (ESI) *m/z*: 945.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{45}N_6O_4S_4$ $[M + H]^+$ 945.2385, found 945.2380; HPLC t_R = 44.81 min, 95.5%.

4.2.55.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dimorpholine-4-carboxamide (40a)

The title compound was obtained from compound **7** and morpholine-4-carbonyl

chloride according to the general procedure of the synthetic method B in 40% overall yield: mp 139-141 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.96-2.40 (m, 8H), 3.09 (d, *J* = 9.6, 16.4 Hz, 1.6H), 3.28 (t, *J* = 14.1 Hz, 8H), 3.56 (t, *J* = 14.4 Hz, 8H), 3.64-3.80 (m, 2.4H), 5.40 (d, *J* = 6.4 Hz, 1.6H), 5.48 (d, *J* = 6.4 Hz, 0.4H), 5.60-5.68 (m, 2H), 5.96 (d, *J* = 6.8 Hz, 0.4H), 6.08 (d, *J* = 6.8 Hz, 1.6H), 6.93-7.00 (m, 1H), 7.07-7.25 (m, 1H), 7.27-7.60 (m, 16H), 7.77 (s, 0.4H), 7.81 (s, 1.6H); LC/MS (ESI) *m/z*: 951.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{55}N_8O_6S_2$ $[M + H]^+$ 951.3686, found 951.3691; HPLC t_R = 34.13 min, 99.4%.

4.2.56.

N-[(1R)-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-[(Morpholin-4-ylcarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]morpholine-4-carboxamide (40b)

The title compound was obtained from compound **7** and morpholine-4-carbonyl chloride according to the general procedure of the synthetic method B in 18% overall yield: mp 168-170 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.89-2.36 (m, 8H), 3.16 (d, *J* = 9.4, 16.6 Hz, 1H), 3.27-3.43 (m, 9H), 3.60-3.65 (m, 8H), 3.71-3.78 (m, 1H), 3.84-3.88 (m, 1H), 5.04 (d, *J* = 6.8 Hz, 0.2H), 5.47 (d, *J* = 7.2 Hz, 1H), 5.55 (d, *J* = 6.8 Hz, 0.8H), 5.68-5.75 (m, 2.2H), 6.03 (d, *J* = 6.8 Hz, 0.8H),

6.15 (d, *J* = 6.4 Hz, 1H), 7.00-7.16 (m, 2H), 7.32-7.67 (m, 16H), 7.87 (s, 1H), 7.91 (s, 0.8H), 7.98 (s, 0.2H); LC/MS (ESI) *m/z*: 951.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{55}N_8O_6S_2$ $[M + H]^+$ 951.3686, found 951.3691; HPLC t_R = 35.33 min, 100.0%.

4.2.57.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dipyrrolidine-1-carboxamide (41a)

The title compound was obtained from compound **7** and pyrrolidine-1-carbonyl chloride according to the general procedure of the synthetic method B in 46% overall yield: mp 90-92 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.25-1.56 (m, 8H), 1.90-2.36 (m, 8H), 3.05-3.12 (m, 2H), 3.26 (br s, 8H), 3.59-3.83 (m, 2H), 5.36-5.42 (m, 2H), 5.66-5.75 (m, 4H), 6.77-7.17 (m, 2H), 7.29-7.43 (m, 16H), 7.84 (s, 2H); LC/MS (ESI) *m/z*: 919.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{55}N_8O_4S_2$ $[M + H]^+$ 919.3788, found 919.3787; HPLC t_R = 37.99 min, 98.6%.

4.2.58.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(pyrrolidin-1-ylcarbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]pyrrolidine-1-carboxamide (41b)

The title compound was obtained from compound **7** and pyrrolidine-1-carbonyl chloride according to the general procedure of the synthetic method B in 15% overall yield: mp 260-262 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.77-1.80 (m, 8H), 1.98-2.29 (m, 8H), 3.11 (dd, J = 9.6, 16.8 Hz, 1H), 3.22-3.36 (m, 9H), 3.58-3.83 (m, 2H), 4.98 (br s, 0.2H), 5.32 (d, *J* = 7.6 Hz, 0.2H), 5.41 (d, *J* = 8.0 Hz, 0.8H), 5.48 (d, *J* = 7.6 Hz, 0.8H), 5.60-5.73 (m, 4H), 6.94-7.10 (m, 2H), 7.24-7.57 (m, 16H), 7.79 (s, 1H), 7.83 (s, 0.8H), 7.90 (s, 0.2H); LC/MS (ESI) *m/z*: 919.2 [M + H]$^{+}$; HRMS (*m/z*): calcd for $C_{52}H_{55}N_8O_4S_2$ [M + H]$^{+}$ 919.3788, found 919.3787; HPLC t_R = 40.10 min, 100.0%.

4.2.59.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})dipiperidine-1-carboxamide (42a)

The title compound was obtained from compound **7** and piperidine-1-carbonyl chloride according to the general procedure of the synthetic method B in 53% overall yield: mp 133-135 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.52 (br s, 12H), 1.89-2.85 (m, 8H), 3.12-3.23 (m, 2H), 3.32 (br s, 8H), 3.65-3.91 (m, 2H), 5.47 (d, *J* = 7.6 Hz, 1.6H), 5.64-5.79 (m, 2.8H), 6.07 (d, *J* = 7.2 Hz, 1.6H), 6.98-7.16 (m, 2H), 7.31-7.49 (m, 8H), 7.61-7.66 (m, 8H), 7.90 (s, 2H); LC/MS (ESI) *m/z*: 947.2

$[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{59}N_8O_4S_2$ $[M + H]^+$ 947.4101, found 947.4104; HPLC t_R = 44.38 min, 99.2%.

4.2.60.

N-[(1R)-2-Oxo-1-phenyl-2-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2S)-2-phenyl-2-[(piperidin-1-ylcarbonyl)amino]acetyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]piperidine-1-carboxamide (42b)

The title compound was obtained from compound **7** and piperidine-1-carbonyl chloride according to the general procedure of the synthetic method B in 13% overall yield: mp 248-250 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.52 (br s, 12H), 1.90-2.36 (m, 8H), 3.14-3.43 (m, 10H), 3.65-3.90 (m, 2H), 5.05 (br s, 0.2H), 5.48 (d, *J* = 7.6 Hz, 0.8H), 5.56 (d, *J* = 7.2 Hz, 0.8H), 5.63-5.78 (m, 2.4H), 5.95 (d, *J* = 7.6 Hz, 0.8H), 6.06 (d, *J* = 7.2 Hz, 1H), 7.00-7.14 (m, 2H), 7.29-7.64 (m, 16H), 7.86 (s, 1H), 7.91 (s, 0.8H), 7.97 (s, 0.2H); LC/MS (ESI) *m/z*: 947.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{54}H_{59}N_8O_4S_2$ $[M + H]^+$ 947.4101, found 947.4104; HPLC t_R = 44.91 min, 99.4%.

4.2.61.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo

-1-phenylethane-2,1-diyl]})bis[3-(1H-pyrrol-1-yl)propanamide] (43a)

The title compound was obtained from compound **7** and 3-(1*H*-pyrrol-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 25% overall yield: mp 127-129 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.83-2.30 (m, 8H), 2.45-2.61 (m, 4H), 3.10 (dd, *J* = 9.4, 16.2 Hz, 1.6H), 3.67-3.71 (m, 0.4H), 3.76 (t, *J* = 7.8 Hz, 2H), 4.09 (t, *J* = 6.8 Hz, 4H), 5.38 (d, *J* = 7.6 Hz, 1.6H), 5.60 (d, *J* = 7.6 Hz, 0.4H), 5.67 (d, *J* = 7.2 Hz, 2H), 5.94 (s, 3.2H), 5.98 (s, 0.8H), 6.45 (s, 3.2H), 6.51 (s, 0.8H), 6.65 (br d, *J* = 8.0 Hz, 0.4H), 6.91-7.03 (m, 3.6H), 7.27-7.40 (m, 8H), 7.48-7.59 (m, 8H), 7.83 (m, 2H); LC/MS (ESI) *m/z*: 967.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{55}N_8O_4S_2$ $[M + H]^+$ 967.3788, found 967.3789; HPLC t_R = 42.79 min, 95.6%.

4.2.62.

N-{(1R)-2-Oxo-1-phenyl-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-phenyl-2-{[3-(1H-pyrrol-1-yl)propanoyl]amino}acetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]ethyl}-3-(1H-pyrrol-1-yl)propanamide (43b)

The title compound was obtained from compound **7** and 3-(1*H*-pyrrol-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 25% overall yield: mp 141-143 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers)

δ 1.83-2.32 (m, 8H), 2.43-2.62 (m, 4H), 3.10 (dd, *J* = 9.2, 16.8 Hz, 1H), 3.30-3.35 (m, 0.8H), 3.60-3.69 (m, 1.2H), 3.76 (t, *J* = 8.0 Hz, 1H), 4.02-4.13 (m, 4H), 4.98 (br s, 0.2H), 5.38 (d, *J* = 8.0 Hz, 0.8H), 5.47 (d, *J* = 7.6 Hz, 0.8H), 5.65-5.69 (m, 2.2H), 5.92 (s, 0.4H), 5.94 (s, 1.6H), 5.98 (s, 2H), 6.40 (s, 0.4H), 6.45 (s, 1.6H), 6.49 (s, 1.6H), 6.51 (s, 0.4H), 6.85-7.03 (m, 4H), 7.29-7.41 (m, 8H), 7.46-7.73 (m, 8H), 7.78 (m, 0.2H), 7.81 (s, 0.8H), 7.83 (s, 0.8H), 7.92(s, 0.2H); LC/MS (ESI) *m/z*: 967.2 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{55}N_8O_4S_2$ $[M + H]^+$ 967.3788, found 967.3789; HPLC t_R = 42.90 min, 99.5%.

4.2.63.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis[3-(dimethylamino)propanamide] (44a)

The title compound was obtained from compound **7** and *N*,*N*-dimethyl-β-alanyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 153-155 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.83-2.20 (m, 6H), 2.14 (overlapped s, 9.6H), 2.18 (overlapped s, 2.4H), 2.22-2.53 (m, 8H), 3.18 (dd, *J* = 9.0, 16.2 Hz, 1.6H), 3.57-3.77 (m, 0.4H), 3.82 (t, *J* = 9.0 Hz, 2H), 4.63 (s, 2H), 5.38 (d, *J* = 7.2 Hz, 1.6H), 5.66 (d, *J* = 7.2 Hz, 0.4H), 5.77 (d, *J* = 7.6 Hz, 2H), 6.94-7.05 (m, 2H), 7.22-7.44 (m, 8H), 7.53-7.59 (m, 8H), 7.66 (m,

0.4H), 7.82 (s, 1.6H), 8.89 (d, *J* = 7.4 Hz, 1.6H), 9.20 (d, *J* = 7.4 Hz, 0.4H); LC/MS (ESI) *m/z*: 923.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{59}N_8O_4S_2$ $[M + H]^+$ 923.4101, found 923.4103; HPLC t_R = 21.45 min, 97.2%.

4.2.64.

3-(Dimethylamino)-N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-{[3-(dimethylamino) propanoyl]amino}-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1, 3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}propanamide (44b)

The title compound was obtained from compound **7** and *N*,*N*-dimethyl-β-alanyl chloride according to the general procedure of the synthetic method B in 29% overall yield: mp 187-189 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.90-2.76 (m, 26H), 3.21-3.24 (m, 1H), 3.52-3.91 (m, 3H), 4.70 (s, 2H), 5.09 (br s, 0.2H), 5.46 (d, *J* = 7.2 Hz, 0.8H), 5.58 (d, *J* = 7.6 Hz, 0.8H), 5.72-5.84 (m, 2.2H), 7.01-7.22 (m, 2H), 7.26-7.62 (m, 16H), 7.73 (m, 0.2H), 7.84 (s, 0.8H), 7.89 (s, 0.8H), 7.98 (s, 0.2H), 8.96 (d, *J* = 7.2 Hz, 0.8H), 9.15-9.27 (m, 1.2H); LC/MS (ESI) *m/z*: 923.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{52}H_{59}N_8O_4S_2$ $[M + H]^+$ 923.4101, found 923.4103; HPLC t_R = 21.48 min, 96.8%.

4.2.65.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis[3-(diethylamino)propanamide] (45a)

The title compound was obtained from compound **7** and *N*,*N*-diethyl-β-alanyl chloride according to the general procedure of the synthetic method B in 30% overall yield: mp 74-75 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.88 (t, *J* = 7.2 Hz, 12H), 1.94-2.64 (m, 22H), 3.20 (dd, *J* = 8.6, 16.4 Hz, 1.6H), 3.57-3.71 (m, 0.8H), 3.84 (t, *J* = 8.8 Hz, 1.6H), 4.63 (s, 2H), 5.40 (d, *J* = 7.5 Hz, 1.6H), 5.63 (d, *J* = 7.5 Hz, 0.4H), 5.75 (d, *J* = 7.5 Hz, 2H), 6.96-7.05 (m, 2H), 7.22-7.44 (m, 8H), 7.53-7.66 (m, 8H), 7.79 (m, 0.4H), 7.82 (s, 1.6H), 9.48 (d, *J* = 7.5 Hz, 1.6H), 9.66 (d, *J* = 7.5 Hz, 0.4H); LC/MS (ESI) *m/z*: 979.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{67}N_8O_4S_2$ $[M + H]^+$ 979.4727, found 979.4729; HPLC t_R = 22.69 min, 97.7%.

4.2.66.

3-(Diethylamino)-N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-{[3-(diethylamino)propanoyl]amino}-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}propanamide (45b)

The title compound was obtained from compound **7** and *N*,*N*-diethyl-β-alanyl chloride according to the general procedure of the synthetic method B in 25% overall yield: mp 169-171 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 0.81-0.98

(m, 12H), 1.86-2.67 (m, 22H), 3.20 (dd, *J* = 9.6, 16.4 Hz, 1H), 3.45-3.57 (m, 1H), 3.68-3.85 (m, 2H), 4.63 (s, 2H), 5.00 (d, *J* = 7.6 Hz, 0.2H), 5.38 (d, *J* = 7.6 Hz, 0.8H), 5.58 (d, *J* = 7.6 Hz, 0.8H), 5.64 (d, *J* = 7.6 Hz, 0.2H), 5.74-5.97 (m, 2H), 6.84-7.11 (m, 2H), 7.19-7.55 (m, 16H), 7.66 (s, 0.2H), 7.77 (s, 0.8H), 7.82 (s, 0.8H), 7.91 (s, 0.2H), 9.48-9.58 (m, 1.8H), 9.66 (d, *J* = 7.5 Hz, 0.2H); LC/MS (ESI) *m/z*: 979.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{67}N_8O_4S_2$ $[M + H]^+$ 979.4727, found 979.4729; HPLC t_R = 23.39 min, 98.3%.

4.2.67.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis[3-(pyrrolidin-1-yl)propanamide] (46a)

The title compound was obtained from compound **7** and 3-(pyrrolidin-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 22% overall yield: mp 82-84 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.68-2.88 (m, 32H), 3.24-3.32 (m, 2H), 3.66-3.95 (m, 2H), 5.46 (d, *J* = 7.6 Hz, 1.6H), 5.70 (d, *J* = 7.6 Hz, 0.4H), 5.81 (d, *J* = 7.6 Hz, 1.6H), 5.86 (d, *J* = 7.6 Hz, 0.4H), 7.04-7.22 (m, 2H), 7.31-7.56 (m, 8H), 7.61-7.66 (m, 8H), 7.75 (m, 0.4H), 7.89 (s, 1.6H), 9.28 (d, *J* = 7.2 Hz, 1.6H), 9.66 (d, *J* = 7.2 Hz, 0.4H); LC/MS (ESI) *m/z*: 975.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{63}N_8O_4S_2$ $[M + H]^+$ 975.4414, found

975.4419; HPLC t_R = 22.97 min, 98.5%.

4.2.68.

N-{(1R)-2-Oxo-1-phenyl-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-phenyl-2-{[3-(pyrrolidin-1-yl)propanoyl]amino}acetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]ethyl}-3-(pyrrolidin-1-yl)propanamide (46b)

The title compound was obtained from compound **7** and 3-(pyrrolidin-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 21% overall yield: mp 121-123 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.66-2.87 (m, 32H), 3.13-3.33 (m, 1H), 3.51-3.95 (m, 3H), 5.10 (d, *J* = 7.4 Hz, 0.2H), 5.46 (d, *J* = 7.4 Hz, 0.8H), 5.58 (d, *J* = 7.5 Hz, 0.8H), 5.70 (d, *J* = 7.5 Hz, 0.2H), 5.76-5.87 (m, 2H), 7.03-7.19 (m, 2H), 7.30-7.66 (m, 16H), 7.76 (s, 0.2H), 7.84 (s, 0.8H), 7.89 (s, 0.8H), 7.98 (s, 0.2H), 9.23 (d, *J* = 7.2 Hz, 1H), 9.36 (d, *J* = 6.9 Hz, 0.8H), 9.61 (br s, 0.2H); LC/MS (ESI) *m/z*: 975.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{56}H_{63}N_8O_4S_2$ $[M + H]^+$ 975.4414, found 975.4419; HPLC t_R = 23.07 min, 98.1%.

4.2.69.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})bis[3-(piperidin-1-yl)propanamide] (47a)

The title compound was obtained from compound **7** and 3-(piperidin-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 28% overall yield: mp 107-108 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.31-1.61 (m, 16H), 1.85-2.55 (m, 20H), 3.23 (dd, *J* = 9.2, 16.8 Hz, 1.6H), 3.30-3.58 (m, 0.4H), 3.67-3.78 (m, 0.4H), 3.87 (t, *J* = 8.0 Hz, 1.6H), 5.40 (d, *J* = 7.6 Hz, 1.6H), 5.63 (d, *J* = 7.6 Hz, 0.4H), 5.75 (d, *J* = 7.6 Hz, 1.6H), 5.78 (d, *J* = 7.6 Hz, 0.4H), 6.98-7.17 (m, 2H), 7.24-7.45 (m, 8H), 7.53-7.59 (m, 8H), 7.68 (m, 0.4H), 7.82 (s, 1.6H), 9.52 (d, *J* = 7.4 Hz, 1.6H), 9.77 (d, *J* = 7.4 Hz, 0.4H); LC/MS (ESI) *m/z*: 502.3 $[M + 2H]^{2+}$; HPLC t_R = 22.93 min, 98.4%.

4.2.70.

N-{(1R)-2-Oxo-1-phenyl-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-phenyl-2-{[3-(piperidin-1-yl)propanoyl]amino}acetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]ethyl}-3-(piperidin-1-yl)propanamide (47b)

The title compound was obtained from compound **7** and 3-(piperidin-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 24% overall yield: mp 174-175 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.39-1.62 (m, 16H), 1.92-2.74 (m, 20H), 3.27-3.40 (m, 1H), 3.51-3.59 (m, 1H), 3.62-3.95 (m, 2H), 5.11 (d, *J* = 7.4 Hz, 0.2H), 5.45 (d, *J* = 7.4 Hz, 0.8H), 5.59 (d, *J* =

8.0 Hz, 0.8H), 5.68 (d, *J* = 8.0 Hz, 0.2H), 5.77-5.86 (m, 2H), 7.04-7.14 (m, 2H), 7.29-7.68 (m, 16H), 7.75 (s, 0.2H), 7.84 (s, 0.8H), 7.88 (s, 0.8H), 7.98 (s, 0.2H), 9.58 (d, *J* = 7.2 Hz, 1H), 9.67 (d, *J* = 7.2 Hz, 0.8H), 9.84 (br s, 0.2H); LC/MS (ESI) *m/z*: 502.3 $[M + 2H]^{2+}$; HPLC t_R = 23.24 min, 96.9%.

4.2.71.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis[3-(morpholin-4-yl)propanamide] (48a)

The title compound was obtained from compound **7** and 3-(morpholin-4-yl)propanoyl chloride according to the general procedure of the synthetic method B in 31% overall yield: mp 117-118 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.83-2.21 (m, 6H), 2.29-2.63 (m, 18H), 3.19 (dd, *J* = 9.3, 15.9 Hz, 1.6H), 3.52-3.68 (m, 8.4H), 3.84 (t, *J* = 7.4 Hz, 2H), 5.39 (d, *J* = 7.5 Hz, 1.6H), 5.64 (d, *J* = 7.5 Hz, 0.4H), 5.73 (d, *J* = 7.8 Hz, 2H), 6.95-7.15 (m, 2H), 7.26-7.42 (m, 8H), 7.53-7.60 (m, 8H), 7.65 (m, 0.4H), 7.83 (s, 1.6H), 9.18 (d, *J* = 7.5 Hz, 1.6H), 9.38 (d, *J* = 7.5 Hz, 0.4H); LC/MS (ESI) *m/z*: 504.2 $[M + 2H]^{2+}$; HPLC t_R = 21.86 min, 98.0%.

4.2.72.

3-(Morpholin-4-yl)-N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-{[3-(morpholin-4-yl)

propanoyl]amino}-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1, 3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}propanamide (48b)

The title compound was obtained from compound **7** and 3-(morpholin-4-yl)propanoyl chloride according to the general procedure of the synthetic method B in 26% overall yield: mp 201-203 ^{o}C; ^{1}H NMR (300MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.86-2.73 (m, 24H), 3.18 (dd, *J* = 9.4, 16.9 Hz, 1H), 3.40-3.86 (m, 11H), 5.00 (d, *J* = 7.5 Hz, 0.2H), 5.38 (d, *J* = 7.5 Hz, 0.8H), 5.52 (d, *J* = 7.5 Hz, 0.8H), 5.63-5.74 (m, 2.2H), 6.98-7.17 (m, 2H), 7.27-7.59 (m, 16H), 7.65 (s, 0.2H), 7.78 (s, 0.8H), 7.83 (s, 0.8H), 7.91 (s, 0.2H), 9.18 (d, *J* = 7.2 Hz, 1H), 9.26 (d, *J* = 7.2 Hz, 0.8H), 9.38 (d, *J* = 7.2 Hz, 0.2H); LC/MS (ESI) *m/z*: 504.2 $[M + 2H]^{2+}$; HPLC t_R = 22.01 min, 97.1%.

4.2.73.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo -1-phenylethane-2,1-diyl]})bis[3-(4-methylpiperazin-1-yl)propanamide] (49a) The title compound was obtained from compound **7** and 3-(4-methylpiperazin-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 28% overall yield: mp 91-93 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.80 (br s, 8H), 1.91-2.60 (m, 30H), 3.10-3.24 (m, 2H), 3.67-3.71 (m, 0.4H), 3.87 (t, *J* = 7.6 Hz, 1.6H), 5.40 (d, *J* = 7.6 Hz, 1.6H),

5.62 (d, *J* = 7.6 Hz, 0.4H), 5.73 (d, *J* = 7.6 Hz, 1.6H), 5.77 (d, *J* = 7.6 Hz, 0.4H), 6.99-7.09 (m, 2H), 7.25-7.42 (m, 8H), 7.51-7.59 (m, 8H), 7.67 (m, 0.4H), 7.82 (s, 1.6H), 9.25 (d, *J* = 7.2 Hz, 1.6H), 9.47 (d, *J* = 7.2 Hz, 0.4H); LC/MS (ESI) *m/z*: 517.8 $[M + 2H]^{2+}$; HPLC t_R = 20.58 min, 98.9%.

4.2.74.

3-(4-Methylpiperazin-1-yl)-N-{(1R)-2-[(2S)-2-{5-[4'-(2-{(2S)-1-[(2S)-2-{[3-(4-methylpiperazin-1-yl)propanoyl]amino}-2-phenylacetyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}propanamide

(49b)

The title compound was obtained from compound **7** and 3-(4-methylpiperazin-1-yl)propanoyl chloride according to the general procedure of the synthetic method B in 29% overall yield: mp 171-173 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 4 mixture of rotomers) δ 1.78 (br s, 8H), 1.91-2.66 (m, 30H), 3.21 (dd, *J* = 9.6, 16.0 Hz, 1H), 3.43-3.45 (m, 0.8H), 3.58 (br s, 0.2H), 3.67-3.90 (m, 2H), 5.02 (br s, 0.2H), 5.39 (d, *J* = 7.6 Hz, 0.8H), 5.51 (d, *J* = 8.0 Hz, 0.8H), 5.61 (d, *J* = 8.0 Hz, 0.2H), 5.69 (d, *J* = 7.6 Hz, 1H), 5.73 (d, *J* = 7.6 Hz, 0.8H), 5.77 (d, *J* = 7.6 Hz, 0.2H), 6.99-7.09 (m, 2H), 7.27-7.55 (m, 16H), 7.67 (s, 0.2H), 7.78 (s, 0.8H), 7.83 (s, 0.8H), 7.91 (s, 0.2H), 9.19-9.29 (m, 1.8H), 9.46 (d, *J* = 7.2 Hz, 0.2H); LC/MS (ESI) *m/z*:

517.8 $[M + 2H]^{2+}$; HPLC t_R = 20.81 min, 99.4%.

4.2.75.

N-{(2R)-1-[(2S)-2-{5-[4'-(2-{(2S)-1-[N-(Cyclopropylcarbonyl)-D-alanyl]pyrrolidin-2-yl}-1,3-thiazol-5-yl)biphenyl-4-yl]-1,3-thiazol-2-yl}pyrrolidin-1-yl]-1-oxopropan-2-yl}cyclopropanecarboxamide (50)

The title compound was obtained from compound **6** and *N*-(cyclopropylcarbonyl)-D-alanine according to the general procedure of the synthetic method A in 69% yield: mp 143-145 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.69-0.75 (m, 4H), 0.87-0.99 (m, 4H), 1.25-1.29 (m. 2H), 1.41 (d, *J* = 18.4 Hz, 6H), 2.04-2.53 (m, 8H), 3.71-3.82 (m, 2.5H), 3.91-4.01 (m, 1.5H), 4.76-4.79 (m, 0.5H), 4.86-4.90 (m, 1.5H), 5.45 (d, *J* = 8.0 Hz, 1.5H), 5.81 (d, *J* = 8.0 Hz, 0.5H), 6.32 (d, *J* = 7.8 Hz, 0.5H), 6.65 (d, *J* = 7.8 Hz, 0.5H), 6.73 (d, *J* = 7.8 Hz, 1H), 7.58-7.67 (m, 8H), 7.88 (s, 1.5H), 7.93 (s, 0.5H); LC/MS (ESI) *m/z*: 737.3 $[M + H]^{+}$; HRMS (*m/z*): calcd for $C_{40}H_{45}N_6O_4S_2$ $[M + H]^{+}$ 737.2944, found 737.2938; HPLC t_R = 28.47 min, 95.4%.

4.2.76.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(2R)-1-oxo

butane-1,2-diyl]})dicyclopropanecarboxamide (51)

The title compound was obtained from compound **6** and (2*R*)-2-[(cyclopropylcarbonyl)amino]butanoic acid according to the general procedure of the synthetic method A in 65% yield: mp 138-139 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.65-0.77 (m, 4H), 0.80-1.01 (m, 10H), 1.27-1.42 (m, 2H), 2.02-2.41 (m, 8H), 3.61-3.75 (m, 6.5H), 4.03-4.10 (m, 1.5H), 4.64-4.68 (m, 0.5H), 4.81-4.86 (m, 1.5H), 5.46 (d, *J* = 8.0 Hz, 1.5H), 5.84 (d, *J* = 8.0 Hz, 0.5H), 6.33 (d, *J* = 8.4 Hz, 0.5H), 6.56 (d, *J* = 8.4 Hz, 0.5H), 6.77 (d, *J* = 8.4 Hz, 1H), 7.56-7.66 (m, 8H), 7.87 (s, 1.5H), 7.93 (s, 0.5H); LC/MS (ESI) *m/z*: 965.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{42}H_{49}N_6O_4S_2$ $[M + H]^+$ 765.3257, found 765.3255; HPLC t_R = 32.11 min, 97.4%.

4.2.77.

N-[(2R)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2R)-2-[(Cyclopropylcarbonyl)amino]pentanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-1-oxopentan-2-yl]cyclopropanecarboxamide (52)

The title compound was obtained from compound **6** and *N*-(cyclopropylcarbonyl)-D-norvaline according to the general procedure of the synthetic method A in 58% yield: mp 290-292 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 3

mixture of rotomers) δ 0.57-0.79 (m, 4H), 0.81-0.99 (m, 10H), 1.20-1.57 (m, 8H), 1.66-1.80 (m, 2H), 2.03-2.45 (m, 8H), 3.60-3.77 (m, 2.5H), 4.09-4.15 (m, 1.5H), 4.71-4.74 (m, 0.5H), 4.85-4.92 (m, 1.5H), 5.46 (d, *J* = 8.0 Hz, 1.5H), 5.85 (d, *J* = 8.0 Hz, 0.5H), 6.62 (d, *J* = 8.4 Hz, 0.5H), 6.78 (d, *J* = 8.4 Hz, 0.5H), 7.19 (d, *J* = 8.4 Hz, 1H), 7.54-7.66 (m, 8H), 7.86 (s, 1.5H), 7.92 (s, 0.5H); LC/MS (ESI) *m/z*: 793.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{44}H_{53}N_6O_4S_2$ $[M + H]^+$ 793.3570, found 793.3567; HPLC t_R = 35.93 min, 100.0%.

4.2.78.

N-[(2R)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2R)-2-[(Cyclopropylcarbonyl)amino]hexanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-1-oxohexan-2-yl]cyclopropanecarboxamide (53)

The title compound was obtained from compound **6** and *N*-(cyclopropylcarbonyl)-D-norleucine according to the general procedure of the synthetic method A in 55% yield: mp 136-138 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.54-0.70 (m, 4H), 0.83-1.09 (m, 10H), 1.26-1.53 (m, 10H), 1.69-1.83 (m, 4H), 2.02-2.44 (m, 8H), 3.60-3.76 (m, 2.5H), 4.11-4.18 (m, 1.5H), 4.67-4.70 (m, 0.5H), 4.83-4.90 (m, 1.5H), 5.47 (d, *J* = 8.0 Hz, 1.5H), 5.87 (d, *J* = 8.0 Hz, 0.5H), 6.79 (d, *J* = 8.4 Hz, 0.5H), 6.92 (d, *J* = 8.4 Hz, 0.5H), 7.37 (d, *J* = 8.4 Hz,

1H), 7.54-7.66 (m, 8H), 7.86 (s, 1.5H), 7.92 (s, 0.5H); LC/MS (ESI) *m/z*: 821.4 [M + H]$^+$; HRMS (*m/z*): calcd for $C_{46}H_{57}N_6O_4S_2$ [M + H]$^+$ 821.3883, found 821.3885; HPLC t_R = 40.15 min, 100.0%.

4.2.79.

N-[(2R)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2R)-2-[(Cyclopropylcarbonyl)amino]-3-methyl butanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]cyclopropanecarboxamide (54)

The title compound was obtained from compound **6** and *N*-(cyclopropylcarbonyl)-D-valine according to the general procedure of the synthetic method A in 63% yield: mp 143-145 ^oC; ^1H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.67-0.79 (m, 4H), 0.84-1.02 (m, 14H), 1.17-1.30 (m, 4H), 1.37-1.43 (m, 2H), 2.06-2.41 (m, 8H), 3.63-3.74 (m, 2.5H), 4.11-4.15 (m, 1.5H), 4.59 (t, *J* = 8.4 Hz, 0.5H), 4.69 (t, *J* = 8.4 Hz, 1.5H), 5.46 (d, *J* = 7.4 Hz, 1.5H), 5.84 (d, *J* = 7.4 Hz, 0.5H), 6.14 (d, *J* = 9.2 Hz, 0.5H), 6.29 (d, *J* = 9.2 Hz, 0.5H), 6.38 (d, *J* = 9.2 Hz, 1H), 7.52-7.66 (m, 8H), 7.84 (s, 1.5H), 7.93 (s, 0.5H); LC/MS (ESI) *m/z*: 793.3 [M + H]$^+$; HRMS (*m/z*): calcd for $C_{44}H_{53}N_6O_4S_2$ [M + H]$^+$ 793.3570, found 793.3576; HPLC t_R = 35.49 min, 95.5%.

4.2.80.

N-[(2R)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2R)-2-[(Cyclopropylcarbonyl)amino]-4-methyl pentanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrrolidin -1-yl}-4-methyl-1-oxopentan-2-yl]cyclopropanecarboxamide (55)

The title compound was obtained from compound **6** and *N*-(cyclopropylcarbonyl)-D-leucine according to the general procedure of the synthetic method A in 60% yield: mp 284-286 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.53 (d, *J* = 6.4 Hz, 1H), 0.58 (d, *J* = 8.4 Hz, 1H), 0.61-0.71 (m, 2H), 0.88-1.01 (m, 12H), 1.21-1.26 (m, 2H), 1.30-1.39 (m, 2H), 1.48-1.54 (m, 2H), 1.60-1.78 (m, 4H), 2.00-2.46 (m, 10H), 3.57-3.76 (m, 2.5H), 4.09-4.18 (m, 1.5H), 4.68-4.72 (m, 0.5H), 4.93-4.97 (m, 1.5H), 5.44 (d, *J* = 7.6 Hz, 1.5H), 5.91 (d, *J* = 7.6 Hz, 0.5H), 6.53 (d, *J* = 8.8 Hz, 0.5H), 6.69 (d, *J* = 8.8 Hz, 0.5H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.55-7.66 (m, 8H), 7.86 (s, 1.5H), 7.91 (s, 0.5H); LC/MS (ESI) *m/z*: 821.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{57}N_6O_4S_2$ $[M + H]^+$ 821.3883, found 821.3884; HPLC t_R = 39.36 min, 100.0%.

4.2.81.

N-[(2R)-1-{(2S)-2-[5-(4'-{2-[(2S)-1-{(2R)-2-[(Cyclopropylcarbonyl)amino]-3,3-dime thylbuttanoyl}pyrrolidin-2-yl]-1,3-thiazol-5-yl}biphenyl-4-yl)-1,3-thiazol-2-yl]pyrroli

din-1-yl}-3,3-dimethyl-1-oxobutan-2-yl]cyclopropanecarboxamide (56) The title compound was obtained from compound **6** and *N*-(cyclopropylcarbonyl)-3-methyl-D-valine according to the general procedure of the synthetic method A in 51% yield: mp 161-162 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.70-0.79 (m, 4H), 0.91-1.04 (m, 4H), 1.07 (s, 18H), 1.41-1.45 (m, 2H), 2.03-2.44 (m, 8H), 3.65-3.74 (m, 2.5H), 4.11-4.18 (m, 1.5H), 4.74 (d, *J* = 9.6 Hz, 0.5H), 4.80 (d, *J* = 9.6 Hz, 1.5H), 5.46 (d, *J* = 6.8 Hz, 1.5H), 5.87 (d, *J* = 6.8 Hz, 0.5H), 6.19 (d, *J* = 9.6 Hz, 0.5H), 6.30 (d, *J* = 9.6 Hz, 1.5H), 7.56-7.66 (m, 8H), 7.88 (s, 1.5H), 7.95 (s, 0.5H); LC/MS (ESI) *m/z*: 821.3 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{46}H_{57}N_6O_4S_2$ $[M + H]^+$ 821.3883, found 821.3881; HPLC t_R = 41.75 min, 98.5%.

4.2.82.

N,N'-(Biphenyl-4,4'-diylbis{1,3-thiazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-1-cyclohexyl-2-oxoethane-2,1-diyl]})dicyclopropanecarboxamide (57)

The title compound was obtained from compound **6** and (2*R*)-cyclohexyl[(cyclopropylcarbonyl)amino]ethanoic acid according to the general procedure of the synthetic method A in 61% yield: mp 167-169 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$) (1 : 3 mixture of rotomers) δ 0.59-0.76 (m, 4H), 0.88-1.38 (m, 18H), 1.65-1.92 (m, 10H), 2.07-2.40 (m, 8H), 3.63-3.77 (m, 2.5H), 4.10-4.18 (m,

1.5H), 4.62-4.73 (m, 2H), 5.47 (d, *J* = 7.2 Hz, 1.5H), 5.78 (d, *J* = 7.2 Hz, 0.5H), 6.20 (d, *J* = 8.8 Hz, 0.5H), 6.29 (d, *J* = 8.8 Hz, 0.5H), 6.68 (d, *J* = 8.8 Hz, 1H), 7.52-7.66 (m, 8H), 7.86 (s, 1.5H), 7.92 (s, 0.5H); LC/MS (ESI) *m/z*: 873.4 $[M + H]^+$; HRMS (*m/z*): calcd for $C_{50}H_{61}N_6O_4S_2$ $[M + H]^+$ 873.4196, found 873.4199; HPLC t_R = 45.05 min, 97.4%.

4.3. Biology

Huh-7 cells containing HCV subgenomic replicons (Ava5) were provided by Apath, LLC (St. Louis, MO). The reporter-based HCV subgenomic replicon, Ava5-EG(D4AB)SEAP, has previously been described.[29] Cell culture reagents were obtained from Life Technologies (Gaithersburg, MD). Cell viability was determined by the MTS assay that was essentially as described.

4.3.1. Subgenomic HCV inhibitory assay

In 96-well plates, Ava5-EG(D4AB)SEAP cells were seeded at a density of 7×10^3 cells per well. After incubation at 37 ^oC for 1 day, cells were treated with various drugs at final 10 μM. Two days later, culture medium was replaced with fresh phenol red-free DMEM/10% FBS containing the same concentration of drugs and cells were incubated for one more day. Culture supernatants were collected from

each well and SEAP activities were measured using Phospha-Light assay kit (Tropix, Foster City, CA), according to the manufacturer's instruction.

4.4. Pharmacokinetic analysis of 27a in Sprague-Dawley rats

The SD rats for the pharmacokinetic study were obtained from BioLASCO Taiwan Co., Ltd. (Ilan, Taiwan, ROC), and housed in the animal facility at the National Health Research Institutes, Taiwan, ROC. The animal studies were performed according to committee approved procedures. Male rats, each weighing 330–380 g (9–10 weeks old), were quarantined for 1 week before use. The animals were surgically implanted with a jugular-vein cannula 1 day before treatment, and were fasted before treatment. The compound was given to the rats (n = 3) as an intravenous (1.0 mg/kg) or oral (5.0 mg/kg) dose prepared in a mixture of dosing vehicles. The volume of the dosing solution given was adjusted according to the body weight recorded before the drug was administered. At 0 (immediately before dosing), 2, 5 (intravenous only), 15 and 30 min and 1, 2, 4, 6, 8 and 24 h after dosing, a blood sample (~150 mL) was taken from each animal via the jugular-vein cannula and stored in ice (0–4 ^{o}C). The processing of the plasma and analysis by high performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) was carried out as described. The plasma concentration data were analyzed with a standard

non-compartmental method.

4.5. Pharmacokinetic analysis of 27a in Beagle dogs

The Beagle dogs for the pharmacokinetic study were obtained from NARC (Japan). The animal studies were performed at the National Health Research Institutes (NHRI) according to committee approved procedures. Male dogs, 9–10 months old, were bred in NHRI animal facility. The compound was given to the dogs (n = 3) as an intravenous (0.1 mg/kg) or oral (0.5 mg/kg) dose prepared in a mixture of dosing vehicles. The volume of the dosing solution given was adjusted according to the body weight recorded before the drug was administered. At 0 (immediately before dosing), 2, 5 (intravenous only), 15 and 30 min and 1, 2, 4, 6, 8 and 24 h after dosing, a blood sample (~150 mL) was taken from each animal via the jugular-vein cannula and stored in ice (0–4 ^{o}C). The processing of the plasma and analysis by high performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) was carried out as described. The plasma concentration data were analyzed with a standard non-compartmental method.

5. Notes

The authors declare no competing financial interest.

Appendix A. Supplementary data

^{1}H NMR and ESMS spectra for all target compounds, elemental analysis data for test compounds (PDF).

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(28) Na_2CO_3 (0.5 equiv.) was added to the NaOH aqueous solution (1.0 M, 1 equiv.) of amino acids (1 equiv.) and the resulting solution was cooled with ice-water bath. The chloroformates **(II)** (1.1 equiv.) or cyclopropanecarbonyl chloride (1.1 equiv.) was added drop-wise over 15 min, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was washed with ether (x3), and the aqueous phase was cooled with ice-water bath and

acidified with concentrated HCl to a pH region of 1-2, and extracted with CH_2Cl_2 (x3). The organic phase was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the desired product **(III)** or **(V)**.

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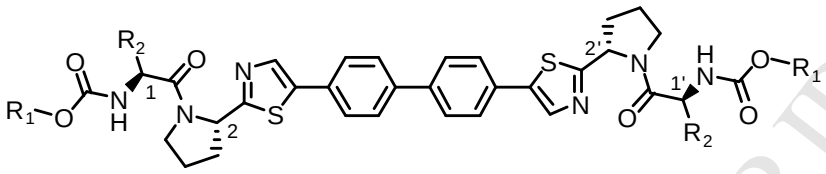
Table 1. GT1b inhibitory activity for the dimeric phenylthiazole compounds (1*S*,2*S*,1'*S*,2'*S*)

8-17

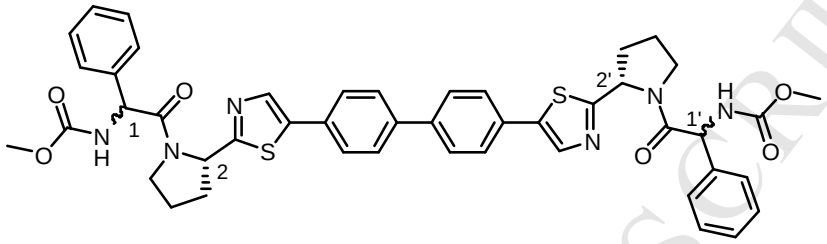


Compound	R_1	R_2	Prep[a]	GT1b EC_{50} (nM)[b]
daclatasvir	-	-	-	0.009
8	Me	*i*-Pr	A	56.3
9	Et	*i*-Pr	A	327.1
10	Ph	*i*-Pr	A	2815.6
11	Me	Me	A	158.5
12	Me	Et	A	56.6
13	Me	*n*-Pr	A	123.1
14	Me	*n*-Bu	A	236.5
15	Me	*i*-Bu	A	179.0
16	Me	*t*-Bu	A	470.8
17	Me	Ph	A	40.9

[a] Method of preparation : see Scheme 2 (method A).

[b] Mean of triplicate well values. All experiments were performed at least twice; GT1b EC_{50} stands for 50% effective concentration. The genotype 1b subgenomic replicon cells were applied to evaluate the inhibitory activity of the compounds.

Table 2. GT1b inhibitory activity for the dimeric phenylthiazole compound (1*S*,2*S*,1'*S*,2'*S*) **17** and its corresponding diastereomers (1*R*,2*S*,1'*R*,2'*S*) **18a** and (1*R*,2*S*,1'*S*,2'*S*) **18b**

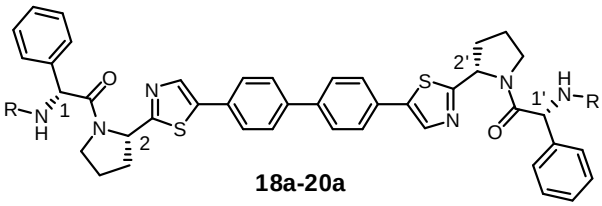


Compound	Stereochemistry				Prep[a]	GT1b EC_{50} (nM)[b]
	1	2	1'	2'		
17	S	S	S	S	A	40.9
18a	R	S	R	S	B	0.19
18b	R	S	S	S	B	107.9

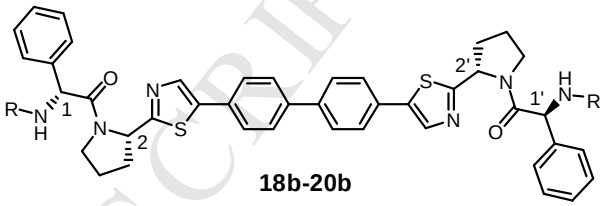
[a] Method of preparation : see Scheme 2 (method A) and Scheme 3 (method B).

[b] Mean of triplicate well values. All experiments were performed at least twice; GT1b EC_{50} stands for 50% effective concentration. The genotype 1b subgenomic replicon cells were applied to evaluate the inhibitory activity of the compounds.

Table 3. GT1b inhibitory activity for the dimeric phenylthiazole compounds (1*R*,2*S*,1'*R*,2'*S*) **18a-20a** and their corresponding diastereomers (1*R*,2*S*,1'*S*,2'*S*) **18b-20b**



18a-20a



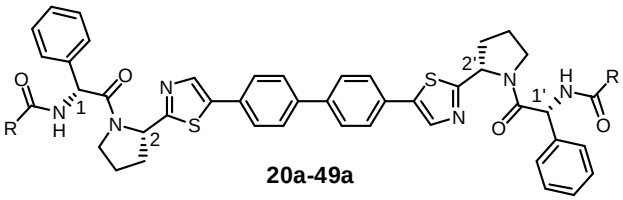
18b-20b

R	Prep[a]	Compound	GT1b EC_{50} (nM)[b]	Compound	GT1b EC_{50} (nM)[b]
CO_2Me	B	**18a**	0.19	**18b**	107.9
SO_2Me	B	**19a**	3.4	**19b**	149.3
COMe	B	**20a**	0.02	**20b**	0.59

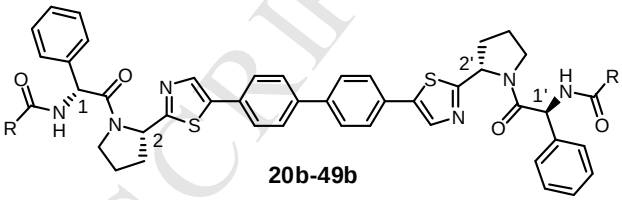
[a] Method of preparation : see Scheme 3 (method B).

[b] Mean of triplicate well values. All experiments were performed at least twice; GT1b EC_{50} stands for 50% effective concentration. The genotype 1b subgenomic replicon cells were applied to evaluate the inhibitory activity of the compounds.

Table 4. GT1b inhibitory activity for the dimeric phenylthiazole compounds (1*R*,2*S*,1'*R*,2'*S*) **20a-49a** and their corresponding diastereomers (1*R*,2*S*,1'*S*,2'*S*) **20b-49b**

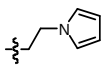
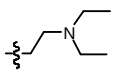
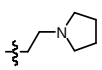
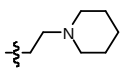


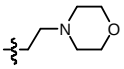
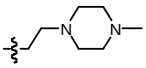
20a-49a



20b-49b

R	Prep[a]	Compound	GT1b EC_{50} (nM)[b]	Compound	GT1b EC_{50} (nM)[b]
-	-	daclatasvir	0.009	-	-
Me	B	**20a**	0.02	**20b**	0.59
Et	B	**21a**	0.016	**21b**	0.85
n-Pr	B	**22a**	0.013	**22b**	0.77
n-Bu	B	**23a**	0.031	**23b**	7.6
n-Pent	B	**24a**	0.063	**24b**	2.37
i-Pr	B	**25a**	0.009	**25b**	0.31
t-Bu	B	**26a**	1.35	**26b**	52.0
Cyclopropyl	B	**27a**	0.003	**27b**	1.5
Cyclobutyl	B	**28a**	0.007	**28b**	0.45

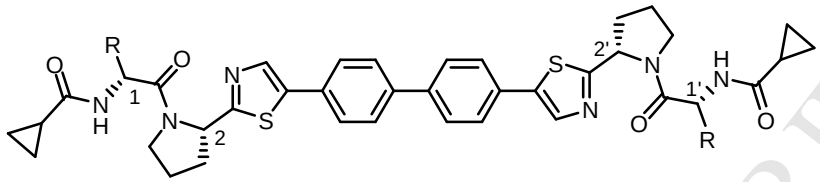
Cyclopentyl	B	**29a**	0.006	**29b**	1.1
Cyclohexyl	B	**30a**	0.25	**30b**	39.8
Ph	B	**31a**	20.8	**31b**	271.9
Benzyl	B	**32a**	0.13	**32b**	2.87
4-Pyridinyl	B	**33a**	0.011	**33b**	0.37
3-Pyridinyl	B	**34a**	0.13	**34b**	2.1
2-Pyridinyl	B	**35a**	46.3	**35b**	2635.9
2-Furanyl	B	**36a**	0.07	**36b**	1.7
3-Furanyl	B	**37a**	0.08	**37b**	0.63
2-Thienyl	B	**38a**	1.43	**38b**	109.8
3-Thienyl	B	**39a**	0.53	**39b**	122.3
Morpholyl	B	**40a**	0.02	**40b**	1.13
Pyrrolidyl	B	**41a**	0.035	**41b**	1.3
Piperidyl	B	**42a**	0.016	**42b**	1.9
	B	**43a**	0.017	**43b**	0.23
	B	**44a**	2.5	**44b**	6.9
	B	**45a**	1.0	**45b**	22.4
	B	**46a**	4.0	**46b**	22.6
	B	**47a**	0.89	**47b**	15.6

	B	**48a**	0.20	**48b**	2.6
	B	**49a**	7.2	**49b**	101.8

[a] Method of preparation : see Scheme 3 (method B).

[b] Mean of triplicate well values. All experiments were performed at least twice; GT1b EC_{50} stands for 50% effective concentration. The genotype 1b subgenomic replicon cells were applied to evaluate the inhibitory activity of the compounds.

Table 5. GT1b inhibitory activity for the dimeric phenylthiazole compounds (1*R*,2*S*,1'*R*,2'*S*) **50-57**



Compound	R	Prep[a]	GT1b EC_{50} (nM)[b]
27a	Ph	B	0.003
50	Me	A	115.4
51	Et	A	433.4
52	*n*-Pr	A	91.7
53	*n*-Bu	A	358.0
54	*i*-Pr	A	731.9
55	*i*-Bu	A	27.1
56	*t*-Bu	A	1603.0
57	Cyclohexyl	A	>50000

[a] Method of preparation : see Scheme 4 (method A).

[b] Mean of triplicate well values. All experiments were performed at least twice; GT1b EC_{50} stands for 50% effective concentration. The genotype 1b subgenomic

replicon cells were applied to evaluate the inhibitory activity of the compounds.

Table 6. Pharmacokinetic parameters of compound **27a** following intravenous administration[a] to Sprague-Dawley rats[b] and Beagle dogs[b]

PK parameters	Species	
	Sprague-Dawley rat	Beagle dog
Dose (mg/kg)	1.0	0.1
CL (mL/min/kg)	1.1	1.3
V_{ss} (L/kg)	1.3	1.6
$t_{1/2}$ (h)	18.3	19.2
AUC (ng/mL×h)	16268	1387

[a] Compound was formulated as a solution in DMA/propylene glycol (20/80, v/v).

[b] n = 3.

Table 7. Pharmacokinetic parameters of compound **27a** following oral administration[a] in Sprague-Dawley rats[b] and Beagle dogs[b]

PK parameters	Species	
	Sprague-Dawley rat	Beagle dog
Dose (mg/kg)	5.0	0.5
C_{max} (ng/mL)	305	94.9
T_{max} (h)	3.3	2.5
$t_{1/2}$ (h)	20.4	21.4
AUC (ng/mL×h)	14539	1622
bioavailability (%)	22	23.3

[a] Compound was formulated as a solution in DMA/propylene glycol (20/80, v/v).

[b] n = 3.

Figure Legends

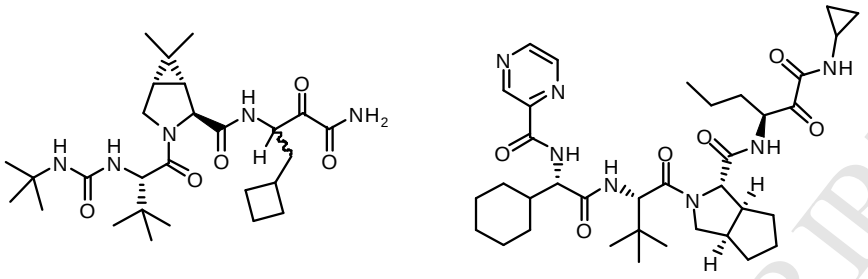
Figure 1. First generation direct-acting antivirals: NS3 protease inhibitors Boceprevir and Telaprevir.

Figure 2. Second generation direct-acting antivirals: Simeprevir, Paritaprevir, Grazoprevir, Glecaprevir, Ledipasvir, Ombitasvir, Daclatasvir, Elbasvir, Velpatasvir, Pibrentasvir, Sofosbuvir and Dasabuvir.

Figure 3. Rational drug design and a new HCV NS5A inhibitor **8**.

Figure 4. Lead Optimization.

Figure 1



Boceprevir **Telaprevir**

NS3 protease inhibitors

Figure 2

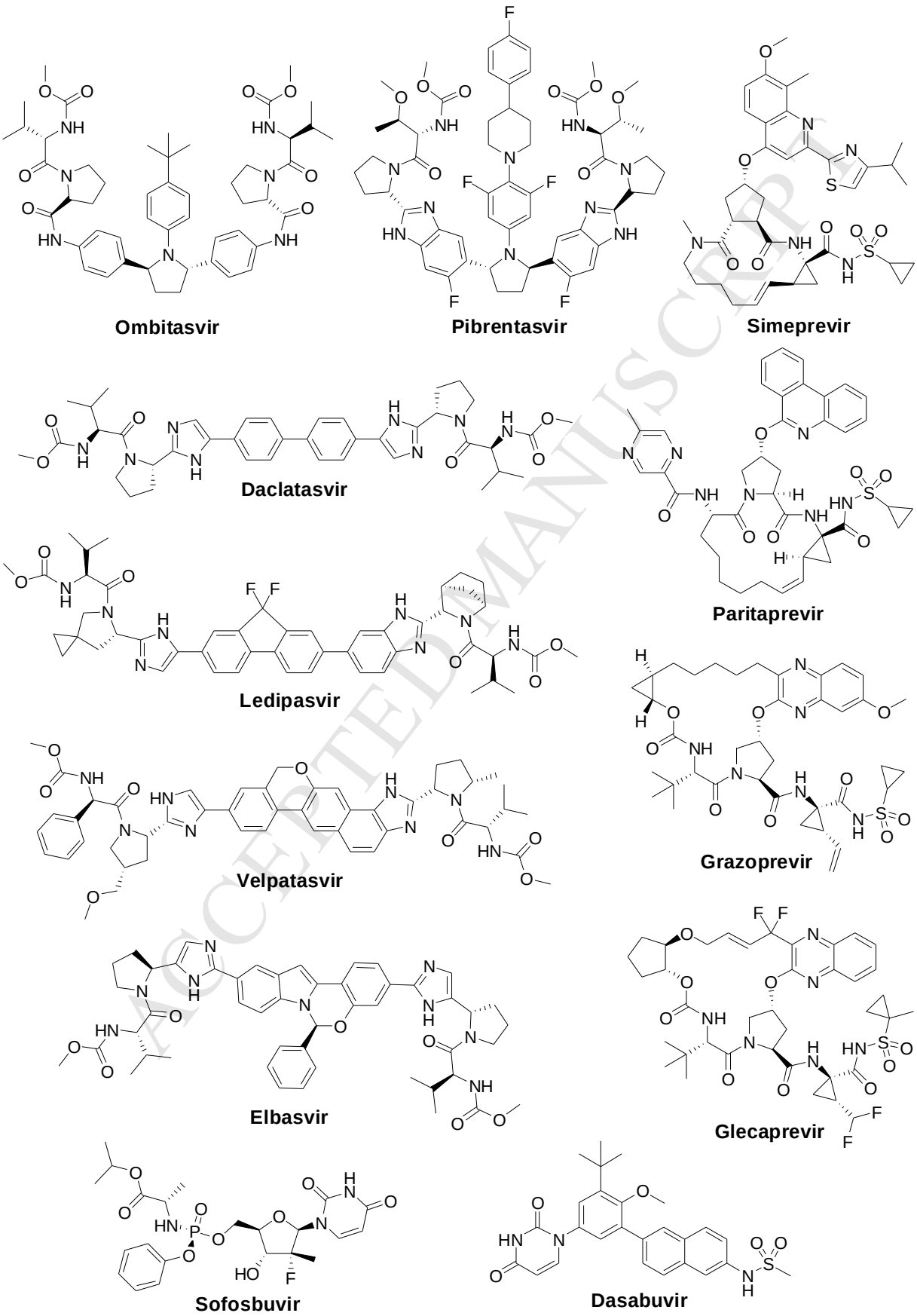
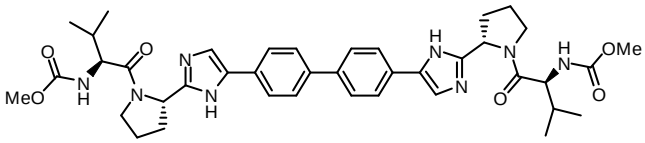
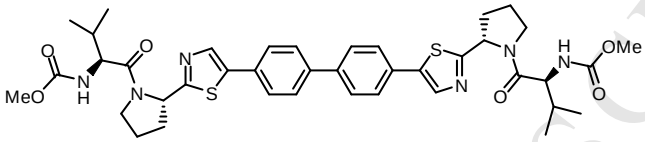


Figure 3



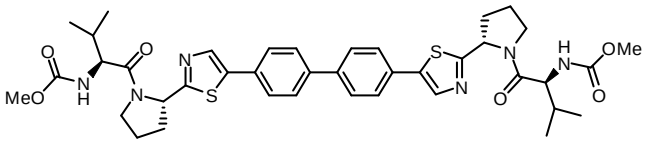
Daclatasvir



8

GT1b EC_{50} = 56.3 nM

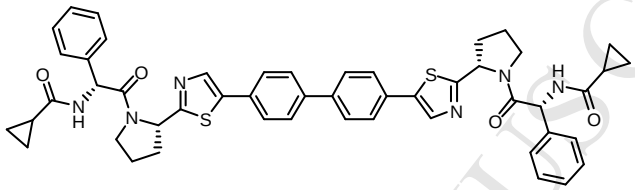
Figure 4



8

GT1b EC_{50} = 56.3 nM

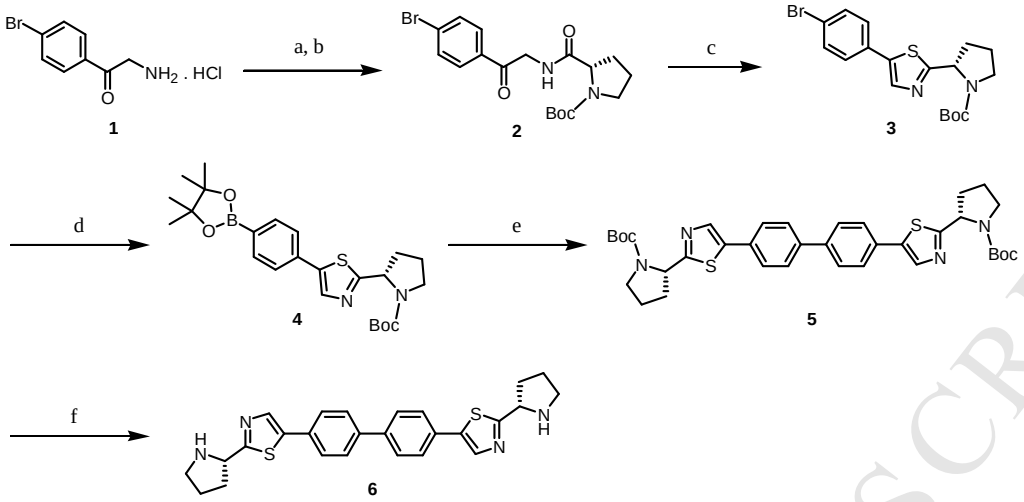
Lead Optimization



27a

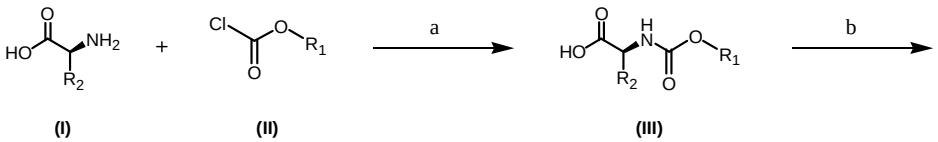
GT1b EC_{50} = 0.003 nM

Scheme 1[a]

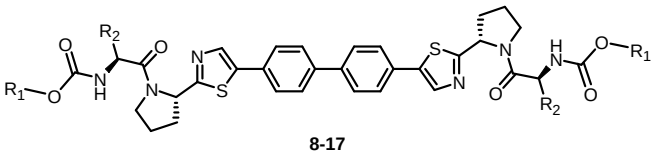


[a] Reagents and conditions: (a) DIPEA, CH_2Cl_2, RT, 10 min; (b) N-Boc-*L*-proline, HOBt·H_2O, EDC, CH_2Cl_2, RT, overnight, 90%; (c) Lawesson's reagent, THF, reflux, 6 h, 78%; (d) bis(pinacolato)diboron, $Pd(PPh_3)_4$, KOAc, 1,4-dioxane, 80 ℃, 6 h, 99%; (e) **3**, $PdCl_2$(dppf), K_2CO_3, 1,2-dimethoxyethane, 80 ℃, 18 h, 47%; (f) TFA, CH_2Cl_2, RT, 1 h, 99%.

Scheme 2[a]



(I) **(II)** **(III)**

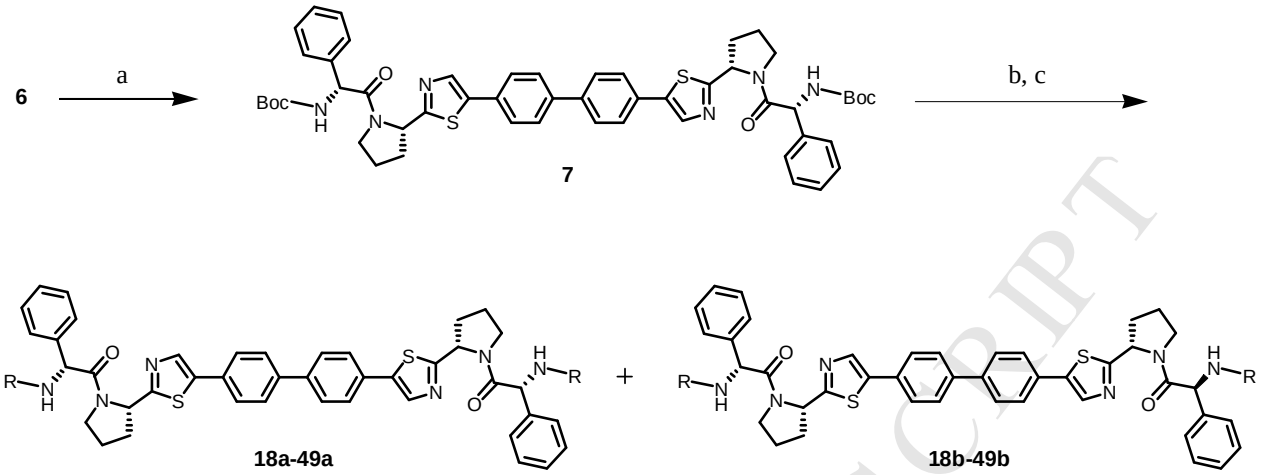


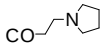
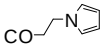
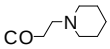
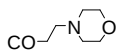
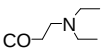
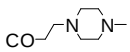
8-17

compd	R_1	R_2
8	Me	*i*-Pr
9	Et	*i*-Pr
10	Ph	*i*-Pr
11	Me	Me
12	Me	Et
13	Me	*n*-Pr
14	Me	*n*-Bu
15	Me	*i*-Bu
16	Me	*t*-Bu
17	Me	Ph

[a] Reagents and conditions (synthetic method A): (a) Na_2CO_3, 1.0 M NaOH (aq), RT, 3 h; (b) **6**, HOBt·H_2O, EDC, DMF, RT, overnight, 54-86%.

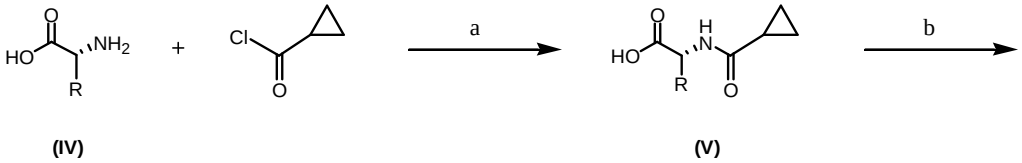
Scheme 3[a]



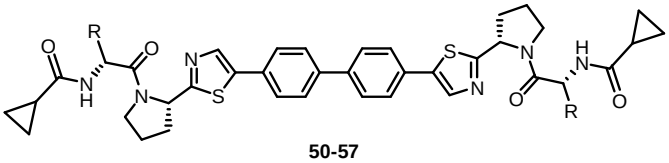
compd	R	compd	R	compd	R	compd	R	compd	R
18	COOMe	**26**	CO-*t*-Bu	**34**	CO-3-Py	**42**	CO-piperidyl	**46**	
19	SO_2Me	**27**	CO-cyclopropyl	**35**	CO-2-Py				
20	CO-Me	**28**	CO-cyclobutyl	**36**	CO-2-furyl	**43**		**47**	
21	CO-Et	**29**	CO-cyclopentyl	**37**	CO-3-furyl				
22	CO-*n*-Pr	**30**	CO-cyclohexyl	**38**	CO-2-thienyl	**44**		**48**	
23	CO-*n*-Bu	**31**	CO-Ph	**39**	CO-3-thienyl				
24	CO-*n*-Pent	**32**	CO-Bn	**40**	CO-morpholyl	**45**		**49**	
25	CO-*i*-Pr	**33**	CO-4-Py	**41**	CO-pyrrolidyl				

[a] Reagents and conditions (synthetic method B): (a) N-Boc-*D*-phenylglycine, HOBt·H_2O, EDC, DMF, RT, overnight, 75%; (b) TFA, CH_2Cl_2, RT, 1 h; (c) R-Cl, Et_3N, DMF, 0 ℃ to RT, 20 min, 10-55%.

Scheme 4[a]



(IV) **(V)**



50-57

compd	R
50	Me
51	Et
52	n-Pr
53	n-Bu
54	i-Pr
55	i-Bu
56	t-Bu
57	Cyclohexyl

[a] Reagents and conditions (synthetic method A): (a) Na_2CO_3, 1.0 M NaOH (aq), RT, 3 h; (b) **6**, HOBt·H_2O, EDC, DMF, RT, overnight, 51-69%.

Highlights:

A novel class of dimeric phenylthiazole derivatives was designed, synthesized, and identified as potent HCV NS5A inhibitors based on daclatasvir scaffold.

Several compounds described in this work exhibited superior GT1b potency with GT1b EC_{50} values at picomolar concentration.

Compound **27a** was found to be the best HCV inhibitor, which showed promising pharmacokinetic properties and oral bioavailability in both rats and dogs.