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Structure activity studies of truncated latrunculin analogues with anti-malarial activity

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Abstract

Malarial parasites employ actin dynamics for motility, and any disruption to these dynamics renders the parasites unable to effectively establish infection. Therefore, actin presents a potential target for malarial drug discovery, and naturally occurring actin inhibitors such as latrunculins are a promising starting point. However, the limited availability of the natural product and the laborious route for synthesis of latrunculins have hindered their potential development as drug candidates. In this regard, we recently described novel truncated latrunculins, with superior actin binding potency and selectivity towards *P. falciparum* actin than the canonical latrunculin B. In this paper, we further explore the truncated latrunculin core to summarize the SAR for inhibition of malaria motility. This study helps further understand the binding pattern of these analogues in order to develop them as drug candidates for malaria.

Keywords: Actin inhibitors, heterocycles, latrunculin analogues, malaria, natural products, *P. falciparum.*

Introduction

Malaria is one of the most significant infectious diseases affecting the human population. It is caused by *Plasmodium* parasites and transmitted by *Anopheles* mosquitos. Despite existing drugs, malaria remains a major health burden.[1] The World Health Organisation (WHO) reported 219 million cases of malaria in 2017 (217 million cases in 2016) with a death toll of 435,000.[1] The great majority of disease prevalence and mortality is due to malaria caused by *P. falciparum*. The challenge to reducing the burden of malaria is partly due to the growing resistance of malaria to existing drugs as well as insecticides used for vector control.[2, 3] The current first line therapy for *P. falciparum* malaria is artemisinin combination therapy, most commonly artemether with lumefantrine,[4-6] however, many parasite strains have developed resistance to these, with established resistance to other drugs such as chloroquine and sulfadoxine-pyremethamine.[7, 8] The most advanced malaria vaccine RTS,S has low efficacy (approximately 30% in phase 3 trials) and thus offers only modest protection.[9] This emphasises the need for new drugs with novel modes of action.

Actin is an abundant protein found in eukaryotic cells that reversibly polymerizes between monomeric (G-actin) and filamentous (F-actin) states. The conversion of G-actin to F-actin, leads to the hydrolysis of the tightly bound ATP so as to slowly release Pi. Malarial parasites employ actin dynamics to invade host cells; if actin dynamics is disrupted, the parasites can no longer glide, invade host cells and establish infection,[10-12] making actin inhibitors potential therapeutics to combat this disease. Many natural products belonging to the macrolide family, such as the latrunculins (Figure 1, **A**), jasplakinolide and cytochalasins, are known to bind actin and thereby disrupt its function.[13-15] Latrunculins bind to the G-actin monomer in a 1:1 complex, thereby blocking the ability of actin to polymerize into a growing filament.[16] Latrunculins bind above the ATP binding cleft - between subdomains D2 and D4 of the actin monomer,[14] leading to conformational changes within these domains. The actin monomers can no longer interact with the filament and polymerization is effectively suppressed.[17, 18] Computational analysis revealed that sequence similarity between malarial actin and human actin is sufficient to render homology modelling meaningful, but low enough to allow for selectivity. Studies on actin polymerization, effect of mutations and chimeric actin have been investigated by various groups, which contributes towards exploring actin as a drug target against malaria.[19-21]

We recently explored truncated latrunculin analogues,[22] which demonstrated superior activity and selectivity compared with naturally occurring latrunculins against *Plasmodium* parasites.

Pursuing these outcomes, we set out to further explore the SAR features around the truncated latrunculin core **C** (Figure 1). Our preliminary study highlighted the effect of SAR modifications at the R^1 position;[22] here we explore the effects of substitution at the R^2, R^3 and R^4 positions that further explain the binding interactions of truncated latrunculin analogues in the ATP binding pocket of actin. We combined key functional group modifications to explore additive SAR features, and also synthesised a planar equivalent of the THP ring to understand the importance of chirality and shape in these truncated latrunculin analogues. The activity of the various R^2, R^3 and R^4 modified analogues were compared with our previous lead compound **B**[22] (Figure 1) to further understand SAR. Modifications at the different R regions described herein help establish the binding interaction within the actin binding site and provide further information for the development of these natural product derived anti-malarial compounds with superior potency and selectivity.

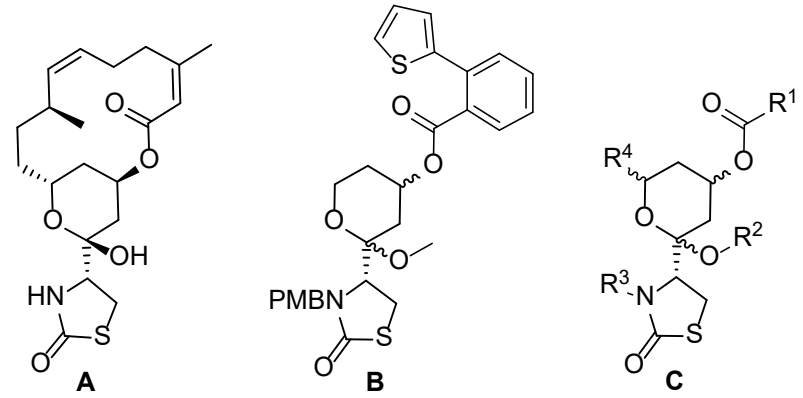

Fig. 1. Structure of latrunculin B (**A**), truncated latrunculin analogue[22] (**B**) and truncated latrunculin core (**C**).

Results and discussion

R^2 modified analogues.

To understand the effect of long chain substitution at the R^2 position, a variety of linear alkyl chain substituents were synthesized while keeping the R^1, R^3 and R^4 substituents consistent with the analogue **B**. These molecules were synthesized following the same route as previously described[23] (Figure 2). *L*-cysteine ethyl ester hydrochloride **1** was successively converted to the *α,β*-unsaturated ketone **6a** (R^3 position with a PMB group) and (but-3-en-1-yloxy)(*tert*-butyl)dimethylsilane (**10a**) was synthesized by TBS protection of but-3-en-1-ol (**9a**)**.** Compounds **6a** and **10a** were then subjected to alkene metathesis followed by deprotection and simultaneous cyclization to obtain the hemiketal **12a**, which was then treated with a selection of different alcohols to yield the R^2 modified intermediates **13(a-c)** (Figure 2). These

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intermediates were then derivatised at the R^1 position with a thiophene benzoate ester, to obtain three R^2 modified analogues **14(a-c)**.

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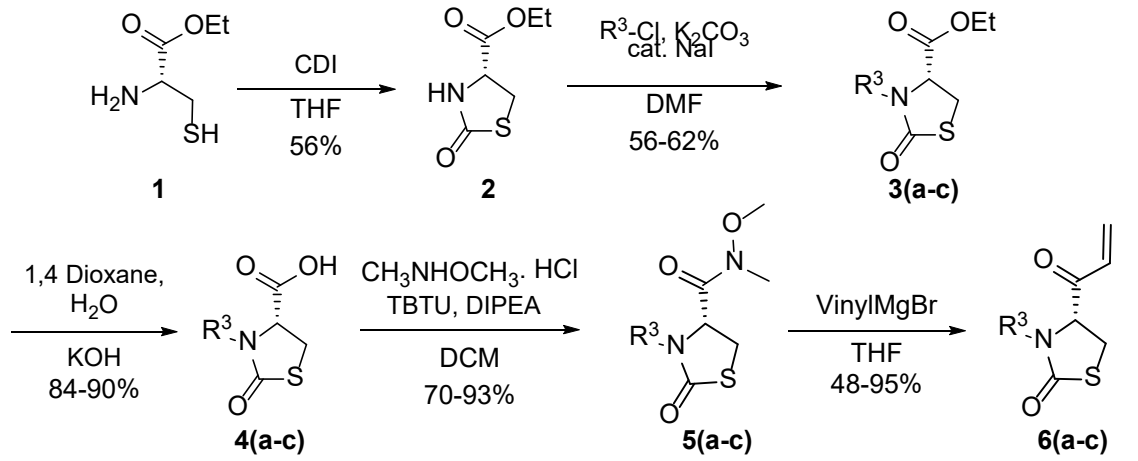

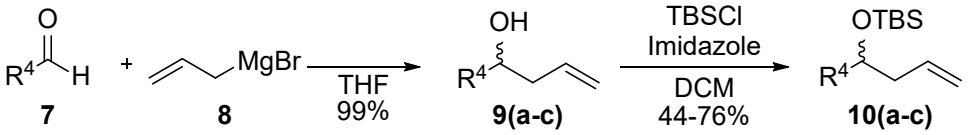

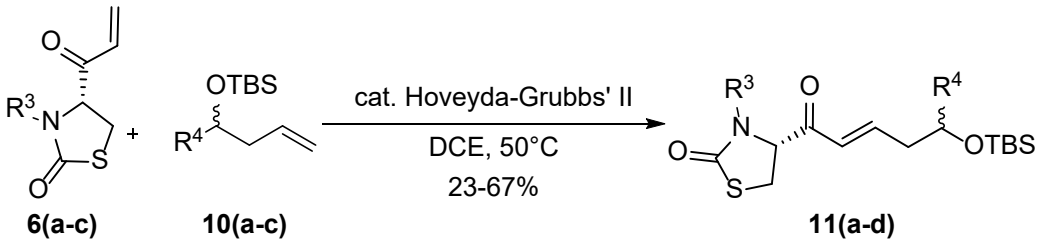

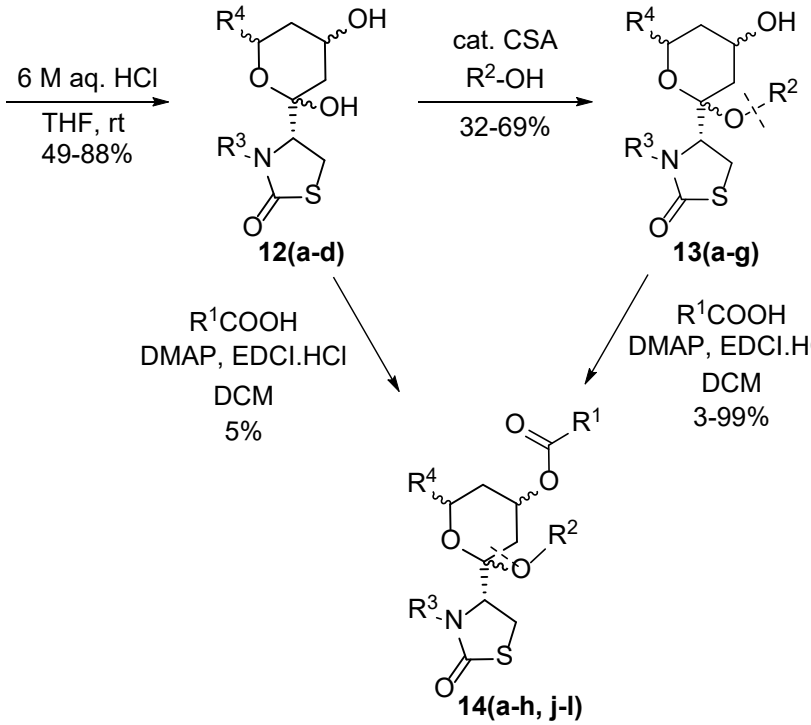

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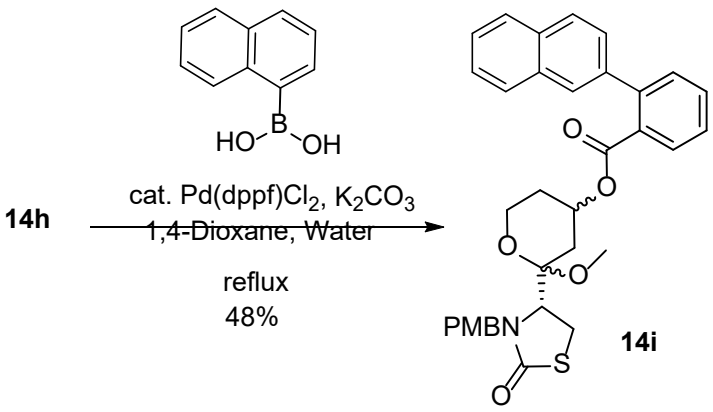

Fig. 2. General procedure for synthesis of R^2 and R^3 modified truncated latrunculin analogues. **3-6** (a: PMB, b: benzyl, c: DMB), **7** (a: phenyl, b: pentyl), **9-10** (a: H, b: phenyl, c: pentyl), **11-12** (a: R^3 benzyl, R^4 H; b: R^3 DMB, R^4 H; c: R^3 PMB, R^4 phenyl; d: R^3 PMB, R^4 pentyl), **13** (a: R^2 ethyl, R^3 DMB, R^4 H; b: R^2 butyl, R^3 PMB, R^4 H; c: R^2 butoxy, R^3 PMB, R^4 H; d: R^2 methyl, R^3 benzyl, R^4 H; e: R^2 methyl, R^3 DMB, R^4 H; f: R^2 methyl, R^3 PMB, R^4 H; g: R^2 methyl, R^3 DMB, R^4 pentyl), **14**(a-l).

Potency of these analogues was determined using a standard *in vitro* growth inhibition assay against *P. falciparum*[24] (Tables 1-3). The R^2 ethoxy analogue **14a** (EC_{50} = 8 μM) demonstrated comparable activity with the previously reported R^2 methoxy analogue **B** (EC_{50} = 7 μM), suggesting the actin binding pocket can accommodate small alkyl chains at this position. However, longer alkyl substituents led to complete loss of activity (**14b** and **14c**). Inactivity of both the butoxy analogue (**14b**) and the 2-methoxyethane analogue (**14c**) suggests that the length of the alkyl chain at R^2 position plays a greater role in potency than the hydrophobicity of the alkyl chain at this position. Thus, the R^2 position can accommodate small alkyl chains and leads to potent truncated latrunculins (**B, 14a**).

Table 1. R^2 analogues of truncated latrunculin and their corresponding activity against *Plasmodium* parasites.

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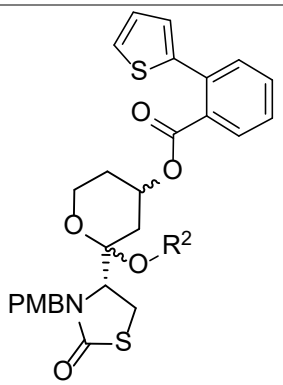
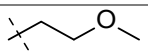
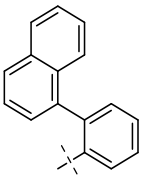
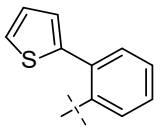
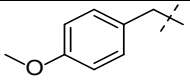
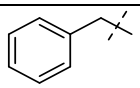
General structure	Compound	R^2	EC_{50} (μM)[a]
	**B**		7±2
	14a		8±3
	14b		>100
	14c		>100

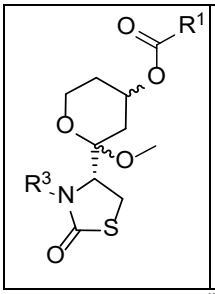
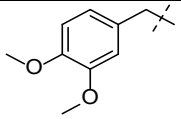
[a]Data are the mean and standard deviation from a duplicate experiment.

R^3 modified analogues.

Previous studies by Sayed *et. al.* on latrunculin derivatives demonstrated that *N*-benzyl substituted latrunculin A was more potent than the canonical latrunculin A in inhibition of actin polymerization.[25] Potency of **B** (truncated latrunculin with PMB group at the R^3 position) also implies the tolerance of a large bulky substituent at the R^3 position. To understand the SAR around this region, we substituted the thiazolidinone nitrogen with a benzyl group and a 3,4-dimethoxybenzyl (DMB) group to obtain compounds **13(d-e)** (Figure 2). Additive SAR was also explored by integrating R^1 modifications to obtain compounds **14(g-j)** (Table 2).

Table 2. R^3 analogues of truncated latrunculin and their corresponding activity against *Plasmodium* parasites as EC_{50} values.

General structure	R^1				
	R^3	**Compound** EC_{50} **(μM)**[a]			
		**14d**[22] 62±1 μM	**14e**[22] 17±3 μM	**14f**[22] 7±0.5 μM	**B**[22] 7±2 μM
		**14g** >100 μM	**14h** 50±3 μM	**14i** 15±2 μM* 17±3 μM#	NC

		NC	NC	NC	**14j** 12±2 μM

*Diastereomer A, #Diastereomer B, [a]Data are the mean and standard deviation from a duplicate experiment. NC- not considered.

P. falciparum growth inhibition assay of R^3 substituted analogues showed that PMB was the most favorable substituent at this position. The R^3 PMB analogues favored the naphthyl (**14f**) and thiophene (**B**) substitution at the R^1 position, although the furan and iodobenzene substitutions were also tolerated.[22] Benzyl substitution at the R^3 position was tolerated but led to decreased potency when compared with the PMB analogues (3-fold decreased potency with an iodobenzene (**14h**) and a 2-fold decreased potency with a naphthyl (**14i**) substituent at the R^1 position). The two diastereomers of compound **14i** were easily separable by column chromatography (arbitrarily assigned as diastereomer A and diastereomer B) and were independently assessed for activity. Both diastereomers had comparable activity (15±2 μM and 17±3 μM, respectively) and hence attempts to configure their exact stereochemistry was not pursued. The R^3 DMB analogue **14j** was also found to retain activity against *P. falciparum* although PMB remained the most preferred substitution at this position. Thus, all the three R^3 substituted analogues were tolerated and gave compounds with superior potency compared with naturally occurring latrunculin B (EC_{50} 44 μM).

R^4 modified analogues.

In order to potentially mimic the macrocycle in the canonical latrunculins, hydrophobic groups such as a phenyl ring and a pentyl chain, were introduced at the R^4 position. The phenyl ring being cyclic and planar would introduce hydrophobic interactions in a rigid manner whereas the flexible alkyl chain could possibly assume the most favorable position within the actin binding site. Phenyl and pentyl aldehydes (**7a-b**) were used to synthesize analogues **12c, 14(k-l)** (Figure 2) and were then tested in growth inhibition assays to determine their potency (Table 3).

Table 3. R^4 analogues of truncated latrunculin and their corresponding activity against *Plasmodium* parasites.

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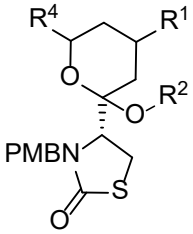
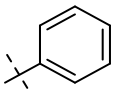
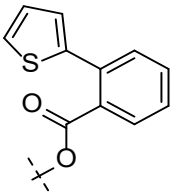
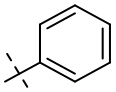
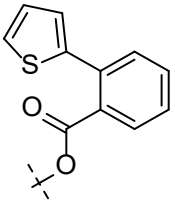
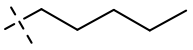
General structure	Compound	R^1	R^2	R^4	EC_{50} (μM)[a]
	**12c**	OH	H[€]		29±3
	14k		H[€]		20±0.6
	14l		Me		13±3[*] 20±1[#]

[*]Diastereomer A, [#]Diastereomer B [a]Data are the mean and standard deviation from a duplicate experiment. [€]When the R^4 position was a benzyl substituent, the R^2 position failed to undergo methyl substitution under the conditions described.

R^4 substituted phenyl hemiketal **12c** showed moderate activity against *Plasmodium* parasites (29 μM), which upon R^1 substitution with a thiophene benzoate group (**14k**) led to a modest improvement in activity; this demonstrates the opportunity afforded by R^1 modification on activity of these truncated latrunculins. The pentyl chain analogue **14l** (with thiophene benzoate group at R^1 position) also showed moderate activity. The two diastereomers of **14l** were separable by chromatography, and one diastereomer showed slightly greater potency over the other. Comparison of activity of compound **B** with compounds **12c** and **14(k-l)** suggests that R^4 substitution with large lipophilic groups, although well tolerated, leads to less potent compounds.

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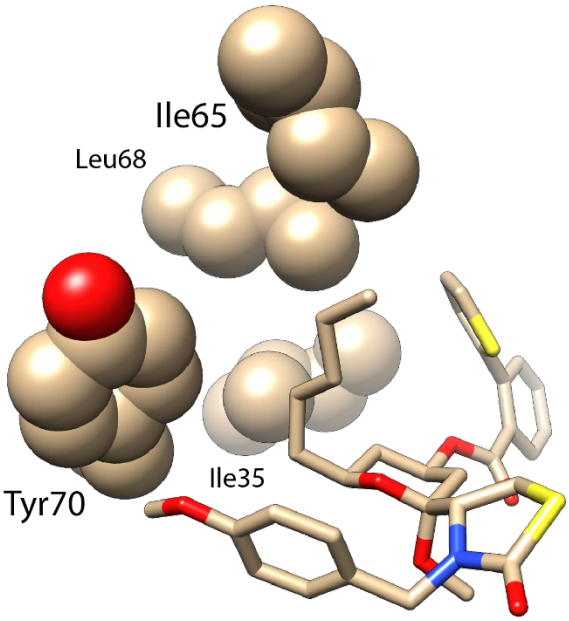


Fig. 3. Model of **14l** in the ligand binding site.

A model of **14l** in the ligand binding site shows the pentyl R^4 group contacts the side chains of several hydrophobic residues, Ile35, Ile65, Leu68 and Tyr70 (Figure 3). The macrocycle alkyl chain contacts these residues in the X-ray crystal structure of latrunculin B in complex with actin (PDB 2q0u).[26] Throughout the molecular dynamics simulation the terminal methyl group of the pentyl group contacts the thiophene of the R^1 group; these two groups appear to form an unconnected surrogate of the latrunculin macrocycle. The hydroxyl of Tyr70 forms a hydrogen bond with the ring-oxygen in both the X-ray crystal structure of latrunculin B and the model of **B** in complex with actin,[22] whereas in the model of **14l** the tyrosine side chain is turned away from the ligand; this could help explain the lack of any improvement in affinity by introduction of the pentyl chain.

Aromatic analogues. To understand the importance of the tetrahydropyran ring and chirality for actin inhibition, aromatic analogues were synthesized. These analogues were prepared using standard procedures[27] as shown in Figure 4. 1-(3-Hydroxyphenyl)ethan-1-one (**15**) was first brominated using copper (II) bromide to yield **16.** Compound **16,** upon treatment with potassium thiocyanate under acidic conditions, led to spontaneous ring closure and dehydroxylation to give **17**. Compound **17** served as a building block, which when subjected to R^1 and R^4 based modifications gave analogues **18** - **19** as shown in Table 4.

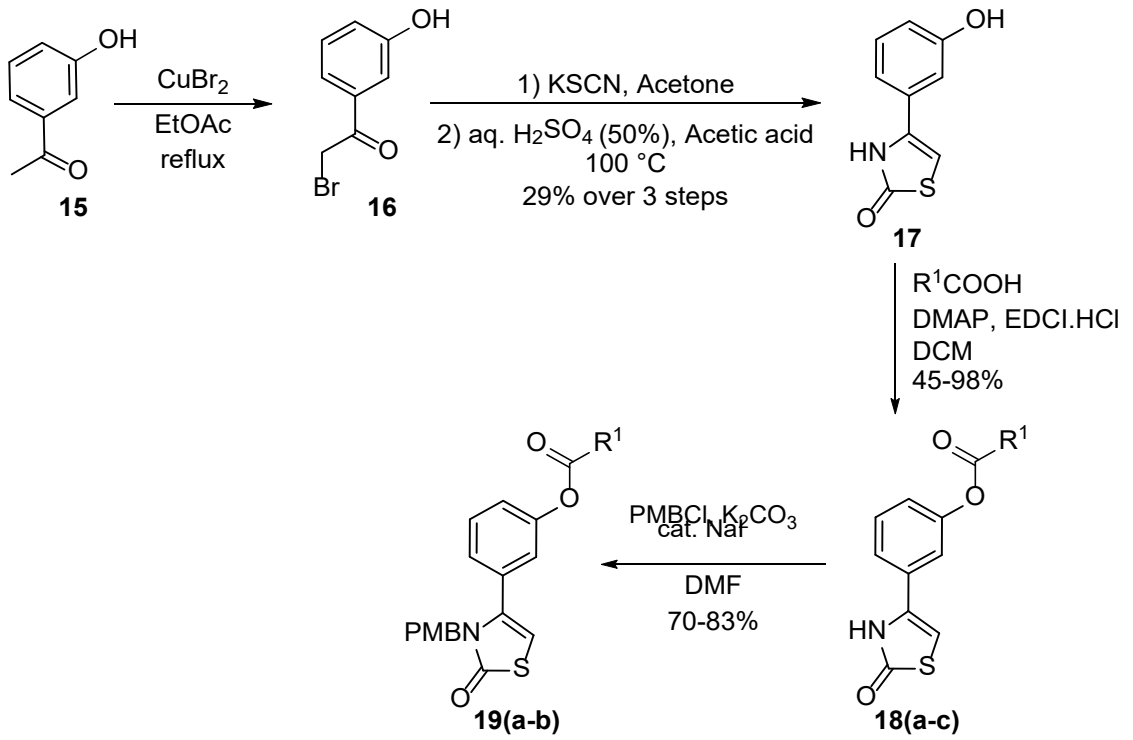
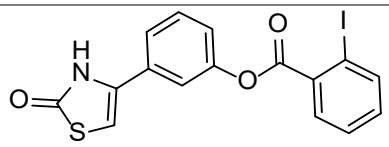
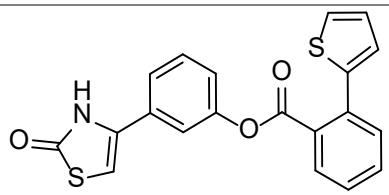
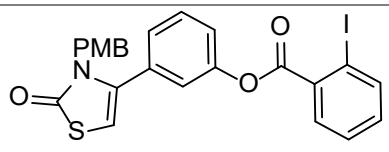
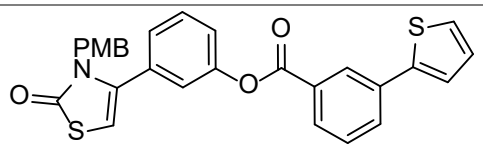


Fig. 4. Synthesis of aromatic analogues.

Table 4. Aromatic analogues of truncated latrunculin and their corresponding activity against *Plasmodium* parasites.

Compound	Structure	EC_{50} (μM)[a]
18a		52±0.22
18b		>100
19a		>100
19b		>100

[a]Data are the mean and standard deviation from a duplicate experiment.

The aromatic analogues when tested against *Plasmodium* parasites were found to be mostly inactive. The only weakly active compound identified in this series was compound **18a** (Table 4). The inactivity of these analogues emphasizes the influence of the 6-membered ring with sp^3 character over the flat sp^2 hybridized aromatic ring. It also suggests that the hydrogen bond acceptor (oxygen) in the THP ring may be important for activity, potentially engaging in the receptor binding.

It should be noted that the novel truncated latrunculin analogues described in this work are an extension of our previous work on R^1 modifications, where we established the selectivity of these analogues for parasite actin over mammalian actin.[22] Since the potent compounds identified in this work are identical in potency with our previous analogues, we did not endeavour to perform such extensive studies at this stage.

On the basis of the findings and analysis described above, a summary of the SAR of truncated latrunculin analogues in this study is illustrated in Figure 5.

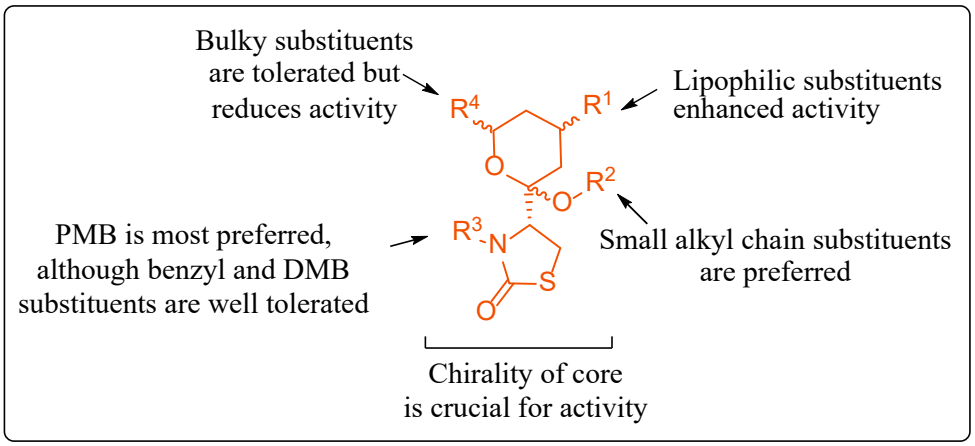


Fig. 5. Summary of the SAR observed with the truncated latrunculin analogues.

Conclusion

With the ongoing increases in the prevalence and geographic spread of *P. falciparum* to first line therapeutics and established resistance to other existing drugs, the need for malarial drug discovery continues to rise. The number of combination therapies available to treat such resistant strains remains underpopulated thereby increasing the need to explore drugs with novel modes of action.

Latrunculins are natural products with actin binding properties that can potentially be used to target various infections including malaria. However, cumbersome synthesis and the lack of selectivity are the major bottleneck limiting their development as anti-malarials. Here we report

the synthesis and biological evaluation of various truncated latrunculin analogues that are not only synthetically more viable, but also present as a more potent inhibitor of malarial actin. Further exploration of SAR from our previously reported truncated latrunculin analogues, helped us to identify additional compounds with greater potency compared with the natural latrunculins. These novel semi-synthetic natural product analogues highlight interesting synthetic organic chemistry that we developed *en route* to our biologically active target molecules. Our success in improving synthetic ease by removing a macrocycle and two Z–double bonds from the natural product while improving the activity, encourages further studies to transform complex natural products to synthetically accessible analogues with improved biological activity.

The SAR discussed in this paper highlights various favorable and unfavorable features of the truncated core, and that the tetrahydropyran ring and chirality are crucial. We reference our SAR interpretation against actin binding and in this context future development of target-engagement studies would be useful to strengthen the association between phenotypic readout and target inhibition. These findings will be crucial for the further development of latrunculin analogues as potential anti-malarial agents.

Experimental section

P. falciparum growth inhibition assay.

The *P. falciparum* growth inhibition assay was performed as previously reported. [22, 24]

Molecular modelling.

A model of **14l** in the ligand binding site was created using the YASARA software (www.yasara.org) using the same approach used earlier;[22] all system parameters were the same as used earlier. The model of **B** in the ligand binding site was manually converted to **14l**, the geometry minimised and 100 ns of molecular dynamics applied before final energy minimisation. Figures were created using the CHIMERA program.[28]

General chemistry experimental.

General. Solvents were of analytical grade or distilled laboratory grade: ethyl acetate (EtOAc); dichloromethane (DCM); dimethyl formamide (DMF); methanol (MeOH); tetrahydrofuran (THF). Analytical TLC was performed on silica gel 60/F_{254} pre-coated aluminium sheets (0.25 mm, Merck). Flash column chromatography was carried out with silica gel 60, 0.63–0.20 mm (70–230 mesh, Merck). ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively. Chemical shifts (δ, ppm) are reported relative to the solvent peak ($CDCl_3$: 7.26 [^{1}H] or 77.16 [^{13}C], DMSO-d_6: 2.50 [^{1}H] or 39.52 [^{13}C]). Proton resonances are annotated as:

chemical shift (ppm), multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J*, Hz), and number of protons. Analytical HPLC was acquired on an Agilent 1260 Infinity analytical HPLC coupled with a G1322A degasser, G1312B binary pump, G1367E high performance autosampler, G4212B diode array detector. Conditions: Zorbax Eclipse Plus C18 Rapid resolution column (4.6 × 100 mm) with UV detection at 254 nm and 214 nm, 30°C; sample was eluted using a gradient of 5 – 100% of solvent B in solvent A where solvent A: 0.1% aq. TFA, and solvent B: 0.1% TFA in CH_3CN (5 to 100% B [9 min], 100% B [1 min]; 0.5 mL/min). Low resolution mass spectrometry was performed on an Agilent 6100 Series Single Quad LCMS coupled with an Agilent 1200 Series HPLC, G1311A quaternary pump, G1329A thermostatted autosampler, and G1314B variable wavelength detector (214 and 254 nm). High resolution MS was performed on a Waters Autospec instrument (for compounds **3** - **20**) or an Agilent 6224 TOF LCMS coupled to an Agilent 1290 Infinity LC. All data were acquired and reference mass corrected via a dual-spray electrospray ionization (ESI) source. LC conditions: Agilent Zorbax SB-C18 Rapid Resolution HT (2.1 × 50 mm, 1.8 µm column), 30°C; sample (5 µL) was eluted using a binary gradient (solvent A: 0.1% aq. HCO_2H; solvent B: 0.1% HCO_2H in CH_3CN; 5 to 100% B [3.5 min], 0.5 mL/min). Purity was determined by HPLC or ^{1}H NMR analysis and was found to be ≥95% for all compounds. Exchangeable protons for some compounds were not observed in the NMR spectra.

General procedure A: Ester hydrolysis

To potassium hydroxide (3 eq.) dissolved in water (0.4 M), was successively added 1,4-dioxane (0.26 M) and the ester (1 eq.). The reaction was allowed to stir for 1 h before being diluted with 3 M aq. HCl. The aqueous layer was then exacted several times with diethyl ether. The combined organic layer was washed with brine, dried with magnesium sulphate and evaporated to dryness to yield the desired product.

General procedure B: Weinreb amide

To the carboxylic acid (1 eq.) dissolved in DCM (0.3 M), was added DIPEA (3 eq.), *N*,*O*-dimethylhydroxylamine hydrochloride (3 eq.) and TBTU (1.5 eq.), and the reaction stirred for 12 h. After the completion of reaction as indicated by TLC analysis, 1 M aq. HCl solution was added and the aqueous layer extracted with DCM (x 3 times). The organic layer was then washed with 0.5 M aq. NaOH solution, dried with sodium sulphate and then evaporated to dryness. Flash chromatography, eluting with 50% EtOAc/petroleum spirits yielded the product.

General procedure C: TBS-protection of alcohol

To the alcohol (1 eq.) dissolved in DMF (0.6 M), *tert*-butyldimethylsilyl chloride (TBSCl) (1.2 eq.) and imidazole (2 eq.) were added and stirred for 12 h. The reaction mixture was then diluted with hexane and washed successively with 5% aq. HCl, saturated sodium bicarbonate, water and brine. Sodium sulphate was used to dry the organic layer and then evaporated to

dryness. Purification was performed by flash chromatography, eluting with 10% DCM/petroleum spirits to yield the product.

General Procedure D: TBS-deprotection and spontaneous ring closure

The TBS-protected alcohol (1 eq.) was dissolved in THF (0.05 M) and 1 M aq. HCl (0.35 M) and stirred for 12 h. The reaction was then quenched with sodium bicarbonate solution and the aqueous layer washed with DCM. The combined organic layer was washed with brine, dried with sodium sulphate and evaporated *in vacuo*. Flash chromatography eluting with 100% diethyl ether yielded the desired product.

General Procedure E: O-Alkylation

The hemiacetal (1 eq.) was dissolved in the corresponding alcohol (0.05 M) and catalytic CSA (0.1 eq.) was added. The reaction was stirred for 12 h before being quenched with sodium bicarbonate solution and extracted repeatedly with DCM. The combined organic layer was washed with brine and dried with sodium sulphate before evaporating to dryness to yield the product.

General Procedure F: EDCI coupling

To the alcohol (1 eq.) dissolved in DCM (0.02 M), was added the carboxylic acid (2.8 eq.), DMAP (3 eq.) and EDCI.HCl (3 eq.). The solution was then stirred at room temperature till the completion of the reaction, as indicated by the TLC analysis. Saturated ammonium chloride solution was then added and the aqueous layer extracted with DCM (x 3). The combined organic layer was then dried with sodium sulphate and evaporated to dryness. Flash chromatography, eluting with 15% EtOAc/petroleum spirits yielded the product.

General procedure G: Suzuki coupling

To the corresponding halide (1 eq.) dissolved in 4:1 ratio of 1,4-dioxane and water (0.05 M), was added potassium carbonate (3 eq.). The solution was degassed to remove all the dissolved oxygen from the solution, before catalytic amount of $Pd(dppf)Cl_2$ (0.05 eq.) was added and the reaction mixture refluxed for 12 h. The reaction was allowed to cool to room temperature and then filtered through celite to remove most of the catalyst. The filtrate was then diluted with EtOAc and washed with brine. The organic layer was dried with sodium sulphate and evaporated to dryness. Flash chromatography, eluting with 15% EtOAc/petroleum spirits yielded the desired product.

Ethyl 3-benzyl-2-oxothiazolidine-4-carboxylate (3b)[29]

To a stirred suspension of (*R*)-ethyl 2-oxothiazolidine-4-carboxylate (500 mg, 2.85 mmol), DMF (13 mL), potassium carbonate (591 mg, 4.3 mmol) and catalytic amount of sodium iodide (21 mg, 0.14 mmol), benzylbromide (0.7 mL, 5.7 mmol) was added drop-wise. The reaction was stirred overnight at room temperature. After the completion of the reaction, diethyl ether was added and the suspension washed with brine (x 3). The organic layer was dried with magnesium sulphate, filtered and evaporated to dryness. Flash chromatography, eluting with

5% EtOAc/petroleum spirits yielded the product as a clear oil (446 mg, 62%).[1]H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 3H), 7.26 – 7.21 (m, 2H), 5.16 (d, *J* = 15.0 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.14 (dd, *J* = 8.6, 3.0 Hz, 1H), 4.05 (d, *J* = 15.0 Hz, 1H), 3.51 (dd, *J* = 11.4, 8.5 Hz, 1H), 3.35 (dd, *J* = 11.4, 3.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

Ethyl 3-(3,4-dimethoxybenzyl)-2-oxothiazolidine-4-carboxylate (3c)

To a stirred suspension of (*R*)-ethyl 2-oxothiazolidine-4-carboxylate (138 mg, 0.72 mmol), DMF (3 mL), potassium carbonate (169 mg, 1.2 mmol) and catalytic amount of sodium iodide (6 mg, 0.036 mmol), 3,4-dimethoxy benzylchloride (220 mg, 1.16 mmol) was added drop-wise. The reaction was stirred overnight at room temperature. After the completion of the reaction, diethyl ether was added and the suspension washed with brine (x 3). The organic layer was dried with magnesium sulphate, filtered and evaporated. Flash chromatography, eluting with 25% EtOAc/petroleum spirits yielded the product as a clear oil (175 mg, 75%). HPLC – rt 6.17 min > 99% purity at 254 nm; HRMS $[M+Na]^+$ 348.0876m/z, found 348.0881 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (m, 3H), 5.08 (d, *J* = 14.7 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.13 (dd, *J* = 8.5, 3.2 Hz, 1H), 3.99 (d, *J* = 14.7 Hz, 1H), 3.87 (d, *J* = 2.9 Hz, 6H), 3.48 (dd, *J* = 11.4, 8.5 Hz, 1H), 3.34 (dd, *J* = 11.4, 3.2 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 170.1, 149.5, 149.1, 128.2, 121.1, 111.7, 111.3, 62.3, 59.5, 56.1, 56.1, 47.9, 29.2, 14.3.

3-Benzyl-2-oxothiazolidine-4-carboxylic acid (4b)

Title compound was prepared from ethyl 3-benzyl-2-oxothiazolidine-4-carboxylate (6.8 g, 27 mmol) using General Procedure A as a white solid (5.5 g, 85%). HPLC – rt 5.30 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 238.0532 m/z, found 238.0531 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 5.23 (d, *J* = 15.0 Hz, 1H), 4.21 (dd, *J* = 8.6, 2.5 Hz, 1H), 4.05 (d, *J* = 15.0 Hz, 1H), 3.56 (dd, *J* = 11.5, 8.6 Hz, 1H), 3.42 (dd, *J* = 11.5, 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 172.9, 135.5, 129.1, 128.4, 128.3, 59.4, 47.9, 29.3.

3-(3,4-Dimethoxybenzyl)-2-oxothiazolidine-4-carboxylic acid (4c)

Title compound was prepared from ethyl 3-(3,4-dimethoxybenzyl)-2-oxothiazolidine-4-carboxylate (1.92 g, 5.9 mmol) according to General Procedure A as a yellow oil (1.58 g, 90%). HPLC – rt 4.65 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 298.0744 m/z, found 298.0758 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 – 6.75 (m, 3H), 5.13 (d, *J* = 14.8 Hz, 1H), 4.20 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.01 (d, *J* = 14.8 Hz, 1H), 3.87 (d, *J* = 1.2 Hz, 6H), 3.53 (dd, *J* = 11.5, 8.6 Hz, 1H), 3.41 (dd, *J* = 11.5, 2.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 171.9, 149.6, 149.2, 128.0, 121.2, 111.7, 111.3, 58.9, 56.2, 56.1, 47.9, 29.2.

3-Benzyl-*N*-methoxy-*N*-methyl-2-oxothiazolidine-4-carboxamide (5b)

Title compound was prepared from 3-benzyl-2-oxothiazolidine-4-carboxylic acid (1 g, 4.2 mmol) according to General Procedure B as a white solid (1.1 g, 93%). HPLC – rt 5.86 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 281.0954 m/z, found 281.0951m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 5H), 5.23 (d, *J* = 14.8 Hz, 1H), 4.40 (dd, *J* = 8.7, 5.2 Hz, 1H), 3.90

(d, *J* = 14.8 Hz, 1H), 3.47 (dd, *J* = 11.3, 8.7 Hz, 1H), 3.32 (s, 3H), 3.20 (s, 3H), 3.16 (dd, *J* = 11.3, 5.2 Hz, 1H; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 169.2, 135.8, 129.0, 128.8, 128.2, 61.3, 57.6, 47.7, 32.6, 28.2.

3-(3,4-Dimethoxybenzyl)-*N*-methoxy-*N*-methyl-2-oxothiazolidine-4-carboxamide (5c)

Title compound was prepared from 3-(3,4-dimethoxybenzyl)-2-oxothiazolidine-4-carboxylic acid (1.58 g, 5.3 mmol) according to General Procedure B (1.26 g, 70%). HPLC – rt 5.32 min > 99% purity at 254 nm; HRMS $[M+Na]^+$ 363.0985 m/z, found 363.1002 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 – 6.76 (m, 3H), 5.14 (d, *J* = 14.6 Hz, 1H), 4.39 (dd, *J* = 8.8, 5.1 Hz, 1H), 3.84 – 3.82 (m, 7H), 3.47 (dd, *J* = 11.3, 8.8 Hz, 1H), 3.39 (s, 3H), 3.22 (s, 3H), 3.16 (dd, *J* = 11.3, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 171.3, 149.5, 149.0, 128.3, 121.4, 112.0, 111.1, 61.4, 57.7, 56.2, 56.1, 47.6, 32.7, 28.3.

4-Acryloyl-3-benzylthiazolidin-2-one (6b)

To 3-benzyl-*N*-methoxy-*N*-methyl-2-oxothiazolidine-4-carboxamide (704 mg, 2.5 mmol) in THF (8mL) at 0 °C, 1.5 M vinylmagnesium bromide (6.8 mL) was added drop wise and stirred overnight. After completion of the reaction, 2 M aq. HCl solution was added and then extracted with DCM (x 3). The combined organic layer was washed with saturated sodium bicarbonate solution, dried with sodium sulphate and evaporated to dryness. Flash chromatography, eluting with a gradient from 10% EtOAc/petroleum spirits to 50% EtOAc/petroleum spirits led to the isolation of the product (589 mg, 95%). HPLC – rt 6.70 min > 92% purity at 254 nm; HRMS $[M+H]^+$ 248.0740 m/z, found 248.0742m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 3H), 7.19 (dd, *J* = 7.3, 1.8 Hz, 2H), 6.48 (dd, *J* = 17.4, 10.4 Hz, 1H), 6.36 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.91 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.16 (d, *J* = 14.9 Hz, 1H), 4.35 (dd, *J* = 9.4, 4.3 Hz, 1H), 3.85 (d, *J* = 14.9 Hz, 1H), 3.53 (dd, *J* = 11.5, 9.4 Hz, 1H), 3.15 (dd, *J* = 11.5, 4.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 172.1, 135.5, 131.9, 131.4, 129.1, 128.7, 128.3, 63.7, 48.0, 27.9.

4-Acryloyl-3-(3,4-dimethoxybenzyl)thiazolidin-2-one (6c)

To 3-(3,4-dimethoxybenzyl)-*N*-methoxy-*N*-methyl-2-oxothiazolidine-4-carboxamide (1.26 g, 3.7 mmol) in THF (25 mL) at -30°C, 1.5 M vinylmagnesium bromide (13 mL) was added drop wise and stirred overnight. After completion of the reaction, 2 M aq. HCl solution was added and then extracted with DCM (x 3). The combined organic layer was washed with saturated sodium bicarbonate solution, dried with sodium sulphate and evaporated to dryness. Flash chromatography, eluting with a gradient from 20% to 50% EtOAc/petroleum spirits led to the isolation of the product (530 mg, 48%). HPLC – rt 5.74 min > 99% purity at 254 nm; LRMS $[M+Na]^+$ 330.1 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 – 6.65 (m, 3H), 6.47 (dd, *J* = 17.4, 10.3 Hz, 1H), 6.35 (dd, *J* = 17.4, 1.3 Hz, 1H), 5.90 (dd, *J* = 10.3, 1.3 Hz, 1H), 5.05 (d, *J* = 14.6 Hz,

1H), 4.34 (dd, *J* = 9.4, 4.6 Hz, 1H), 3.84 – 3.82 (m, 7H), 3.50 (dd, *J* = 11.5, 9.4 Hz, 1H), 3.13 (dd, *J* = 11.5, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 172.1, 149.5, 149.1, 131.8, 131.4, 127.8, 121.4, 111.8, 111.2, 63.7, 56.1, 56.1, 47.9, 27.9

Allylmagnesium bromide (8)

Magnesium (321 mg, 13.2 mmol) and catalytic iodine were added to diethyl ether (20 mL). The reaction mixture was warmed gently before adding allyl bromide (1.04 mL, 6.1 mmol) dropwise. The reaction turns exothermic and was cooled in an ice bath. After the addition of 1-bromopropane was complete, the reaction was stirred for 1 h to obtain the Grignard reagent.

1-phenylbut-3-en-1-ol (9b)[30]

To benzaldehyde (0.20 mL, 2 mmol) in THF (20 mL) at 0 °C was added dropwise 0.6 M allylmagnesium bromide in diethyl ether (4 mmol). The reaction was allowed to slowly warm up to room temperature and left stirring for 8 h. Saturated ammonium chloride solution was used to quench the reaction, followed by extraction with diethyl ether (x 3). The organic layer was then washed with brine, dried with sodium sulphate and evaporated to dryness to obtain the product (290 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 4H), 7.32 – 7.26 (m, 1H), 5.89 – 5.74 (m, 1H), 5.21 – 5.12 (m, 2H), 4.74 (dd, *J* = 7.6, 5.3 Hz, 1H), 2.59 – 2.45 (m, 2H), 2.08 (s, 1H).

Non-1-en-4-ol (9c)[31]

To hexanal (0.25 mL, 2 mmol) in THF (20 mL) at 0 °C was added dropwise 0.6 M allylmagnesium bromide in diethyl ether (7 mL, 4 mmol). The reaction was allowed to slowly warm to room temperature and left stirring for 8 h. Saturated ammonium chloride solution was used to quench the reaction, followed by extraction with diethyl ether (x 3). The organic layer was then washed with brine and dried with sodium sulphate and evaporated to dryness. Flash chromatography, eluting with 10% EtOAc/petroleum spirits afforded the product with minor impurities which was directly used for the next step of TBS-protection.

***tert*-Butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (10b)[32]**

Title compound was prepared from 1-phenylbut-3-en-1-ol (368 mg, 2.48 mmol) according to the General Procedure C. Flash chromatography, eluting with 100% petroleum spirits afforded the product (500 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 4H), 7.22 – 7.20 (m, 1H), 5.78 (m, 1H), 5.08 – 4.94 (m, 2H), 4.68 (dd, *J* = 7.3, 5.2 Hz, 1H), 2.54 – 2.31 (m, 2H), 0.88 (s, 9H), 0.03 (s, 3H), -0.13 (s, 3H).

***tert*-Butyldimethyl(non-1-en-4-yloxy)silane (10c)[33]**

Title compound was prepared from non-1-en-4-ol (380 mg, 2.4 mmol) according to the General Procedure C. Flash chromatography, eluting with 100% petroleum spirits afforded the product (303 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.09 – 4.94 (m, 2H), 3.67 (q, *J* = 5.8 Hz, 1H), 2.28 – 2.13 (m, 2H), 1.51 – 1.13 (m, 9H), 0.88 (s, 11H), 0.04 (d, *J* = 0.8 Hz, 6H).

(*E*)-3-Benzyl-4-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)thiazolidin-2-one (11a)

To of 4-acryloyl-3-benzylthiazolidin-2-one (560 mg, 2.26 mmol) dissolved in DCE (12 mL) was added (but-3-en-1-yloxy)(*tert*-butyl)dimethylsilane (1.27 g, 6.8 mmol) and catalytic Hoveyda-Grubbs' II catalyst (142 mg, 0.23 mmol). The reaction was then heated to 50 °C for 12 h. Upon completion of the reaction, as indicated by TLC analysis, the reaction mixture was filtered through celite to remove the catalyst and then subjected to flash chromatography, eluting with 15% EtOAc/petroleum spirits to obtain the product (150 mg, 67%). HPLC – rt 9.46 min > 81% purity at 254 nm; HRMS $[M+H]^+$ 406.1867m/z, found 406.1856m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 3H), 7.22 – 7.15 (m, 2H), 7.00 (dt, *J* = 15.6, 7.0 Hz, 1H), 6.25 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.14 (d, *J* = 15.0 Hz, 1H), 4.29 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.83 (d, *J* = 14.9 Hz, 1H), 3.72 (t, *J* = 6.1 Hz, 2H), 3.49 (dd, *J* = 11.4, 9.4 Hz, 1H), 3.13 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.46 – 2.37 (m, 2H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 172.2, 148.9, 135.5, 129.0, 128.6, 128.2, 126.3, 63.8, 61.2, 47.9, 36.3, 28.1, 26.0, -5.2.

(*E*)-4-(5-((*tert*-Butyldimethylsilyl)oxy)pent-2-enoyl)-3-(3,4-dimethoxybenzyl)thiazolidin-2-one (11b)

To 4-acryloyl-3-(3,4-dimethoxybenzyl)thiazolidin-2-one (530 mg, 1.7 mmol) dissolved in DCE (9 mL) was added (but-3-en-1-yloxy)(*tert*-butyl)dimethylsilane (643 mg, 3.45 mmol) and catalytic Hoveyda-Grubbs' II catalyst (53 mg, 0.085 mmol). The reaction was then heated to 50 °C for 12 h. Upon completion of the reaction, as indicated by TLC analysis, the reaction mixture was filtered through celite to remove the catalyst and then subjected to flash chromatography, eluting with 15% EtOAc/petroleum spirits to obtain the product (389 mg, 49%). HPLC – rt 8.83 min > 95% purity at 254 nm; HRMS $[M+Na]^+$ 488.1897 m/z, found 488.1916 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dt, *J* = 15.7, 7.0 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.76 – 6.66 (m, 2H), 6.27 (dt, *J* = 15.7, 1.5 Hz, 1H), 5.07 (d, *J* = 14.7 Hz, 1H), 4.27 (dd, *J* = 9.3, 4.7 Hz, 1H), 3.85 (d, *J* = 5.7 Hz, 6H), 3.80 (d, *J* = 14.7 Hz, 1H), 3.73 (t, *J* = 6.1 Hz, 2H), 3.47 (dd, *J* = 11.4, 9.3 Hz, 1H), 3.13 (dd, *J* = 11.4, 4.7 Hz, 1H), 2.43 (qd, *J* = 6.2, 1.4 Hz, 2H), 0.87 (s, 9H), 0.04 (d, *J* = 0.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.9, 172.2, 149.5, 149.1, 148.8, 128.0, 126.3, 121.3, 111.9, 111.2, 64.1, 61.3, 56.1, 56.1, 47.9, 36.4, 28.1, 26.0, -5.2.

(*E*)-4-(5-((*tert*-Butyldimethylsilyl)oxy)-5-phenylpent-2-enoyl)-3-(4-methoxybenzyl)thiazolidin-2-one (11c)

To 4-acryloyl-3-(4-methoxybenzyl)thiazolidin-2-one (743 mg, 3.8 mmol) dissolved in DCE (10 mL) was added *tert*-butyldimethyl((1-phenylbut-3-en-1-yl)oxy)silane (500 g, 1.9 mmol) and catalytic Hoveyda-Grubbs' II catalyst (60 mg, 0.095 mmol). The reaction was then heated to 50 °C for 12 h. Upon completion of the reaction, as indicated by TLC analysis, the reaction mixture was filtered through celite to remove the catalyst and then subjected to flash chromatography, eluting with 25% EtOAc/petroleum spirits to obtain the product as a mixture

of two diastereomers A and B in 1:1 ratio, respectively (340 mg, 35%).HPLC – rt 4.52 min > 96% purity at 254 nm; HRMS $[M+Na]^+$ 534.2105 m/z, found 534.2114 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.20 (m, 10H), 7.07 – 7.03 (m, 4H), 6.96 – 6.94 (m, 2H), 6.87 – 6.77 (m, 4H), 6.11 – 6.10 (m, 2H), 5.04 – 5.01 (m, 2H), 4.82 – 4.79 (m, 2H), 4.19 – 4.16 (m, 2H), 3.79 (s, 6H), 3.75 – 3.62 (m, 2H), 3.44 – 3.33 (m, 2H), 3.05 – 2.96 (m, 2H), 2.67 – 2.49 (m, 4H), 0.87 (d, *J* = 3.5 Hz, 18H), 0.01 (d, *J* = 7.0 Hz, 6H), -0.13 (d, *J* = 3.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 194.7, 159.5, 147.8, 147.7, 144.0, 130.1, 128.4, 127.6, 127.6, 127.5, 127.5, 127.1, 127.0, 125. 8, 125.8, 114.3, 73.8, 63.9, 63.8, 55.4, 47.3, 47.3, 44.3, 44.3, 31.1, 28.0, 28.0, 25.9, 25.9, -4.6, -4.9.

(*E*)-4-(5-((*tert*-Butyldimethylsilyl)oxy)dec-2-enoyl)-3-(4-methoxybenzyl)thiazolidin-2-one (11d)

To 4-acryloyl-3-(4-methoxybenzyl)thiazolidin-2-one (484 mg, 2.13 mmol) dissolved in DCE (7 mL) was added *tert*-butyldimethyl(non-1-en-4-yloxy)silane (303.7 g, 1.18 mmol) and catalytic Hoveyda-Grubbs' II catalyst (37 mg, 0.06 mmol). The reaction was then heated to 50 °C for 12 h. Upon completion of the reaction, as indicated by TLC analysis, the reaction mixture was filtered through celite to remove the catalyst and then subjected to flash chromatography, eluting with 15% EtOAc/petroleum spirits to obtain the product as a single diastereomer and a clear oil (139.5 mg, 23%).

HPLC – rt 5.95 min > 99% purity at 214 nm; HRMS $[M+H]^+$ 506.2755 m/z, found 506.2759 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 14.4, 5.4 Hz, 2H), 7.04 (dtd, *J* = 9.7, 7.4, 2.3 Hz, 1H), 6.83 (dd, *J* = 8.7, 0.8 Hz, 2H), 6.23 (dd, *J* = 15.6, 1.4 Hz, 1H), 5.08 (d, *J* = 14.8 Hz, 1H), 4.26 (ddd, *J* = 9.3, 4.6, 1.8 Hz, 1H), 3.87 – 3.71 (m, 5H), 3.47 (ddd, *J* = 11.6, 9.3, 2.4 Hz, 1H), 3.11 (ddd, *J* = 11.4, 4.6, 0.8 Hz, 1H), 2.48 – 2.24 (m, 2H), 1.45 – 1.19 (m, 8H), 0.93 – 0.80 (m, 12H), 0.09 – -0.02 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.8, 172.1, 159.6, 149.0, 130.1, 127.5, 126.6, 114.4, 71.2, 63.9, 55.4, 47.4, 40.8, 37.5, 32.0, 28.1, 26.0, 25.1, 22.8, 18.2, 14.2, -4.3.

4-(2,4-Dihydroxytetrahydro-2*H*-pyran-2-yl)-3-(3,4-dimethoxybenzyl)thiazolidin-2-one (12b)

Title compound was prepared from (*E*)-4-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)-3-(3,4-dimethoxybenzyl)thiazolidin-2-one (389 mg, 0.835 mmol) according to the General Procedure D. The crude was directly used for the next step of acetal formation.

(4*R*)-4-((2*S*)-2,4-Dihydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (12c)

Title compound was prepared using (*E*)-4-(5-((*tert*-butyldimethylsilyl)oxy)-5-phenylpent-2-enoyl)-3-(4-methoxybenzyl)thiazolidin-2-one (340 mg, 0.66 mmol) according to the General Procedure D as a clear oil and a mixture of two diastereomers A and B in 1:1 ratio, respectively (75 mg, 26%). HPLC – rt (diastereomer A) 6.36 min (46%), (diastereomer B) 6.27 min (38%),

collectively > 84% purity at 254 nm; HRMS $[M+H]^+$ 416.1526 m/z, found 416.1532 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 10H), 6.98 (dd, *J* = 8.5, 6.3 Hz, 4H), 6.80 – 6.75 (m, 2H), 6.74 – 6.67 (m, 2H), 5.13 (d, *J* = 14.5 Hz, 1H), 4.99 – 4.91 (m, 2H), 4.91 – 4.78 (m, 1H), 4.38 (d, *J* = 12.9 Hz, 1H), 4.34 (d, *J* = 12.8 Hz, 1H), 4.31 – 4.22 (m, 2H), 3.76 –3.72 (m, 8H), 3.59 (dd, *J* = 9.4, 1.5 Hz, 1H), 3.41 (dd, *J* = 11.9, 1.6 Hz, 1H), 3.36 – 3.23 (m, 2H), 3.06 (dd, *J* = 40.2, 2.4 Hz, 2H), 2.38 – 2.12 (m, 4H), 1.68 – 1.59 (m, 4H), 1.32 –0.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 173.2, 159.1, 159.0, 141.1, 140.8, 129.7, 129.5, 128.6, 128.5, 128.1, 128.0, 126.7, 126.3, 114.1, 114.0, 101.4, 100.4, 72.4, 71.8, 64.9, 64.8, 64.6, 64.1, 55.3, 55.3, 48.3, 47.6, 42.7, 41.9, 38.3, 37.1, 27.7, 26.9, 26.5, 22.6.

(4*R*)-4-(2,4-Dihydroxy-6-pentyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (12d)

Title compound was prepared using (*E*)-4-(5-((*tert*-butyldimethylsilyl)oxy)dec-2-enoyl)-3-(4-methoxybenzyl)thiazolidin-2-one (139.5 mg, 0.35 mmol) according to the General Procedure D as a clear oil which was directly used for the next step of acetal formation.

4-(2-Ethoxy-4-hydroxytetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (13a)

Title compound was prepared according to General Procedure E using 4-(2,4-dihydroxytetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (100 mg, 0.3 mmol) and EtOH (2 mL) as a milky oil and a mixture of two diastereomers; A and B in 1:0.44 ratio, respectively (47.2 mg, 42%). HPLC – rt (diastereomer A) 6.46 min (64%), (diastereomer B) 6.41 min (24%), collectively > 88% purity at 254 nm; HRMS $[M+Na]^+$ 390.1346 m/z, found 390.1341 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.18 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.85 – 6.82 (m, 3H), 5.19 (d, *J* = 15.6 Hz, 0.5H), 5.01 (d, *J* = 14.3 Hz, 1H), 4.26 – 4.23 (m, 1.5H), 4.16 – 4.01 (m, 2H), 4.01 – 3.89 (m, 1H), 3.91 – 3.65 (m, 7.5H), 3.65 – 3.55 (m, 1H), 3.55 – 3.03 (m, 6.5H), 2.21 (ddd, *J* = 12.5, 4.6, 1.8 Hz, 1H), 2.10 (ddd, *J* = 12.8, 4.7, 1.7 Hz, 0.5H), 1.98 – 1.31 (m, 4.5H), 1.14 (dt, *J* = 14.1, 7.0 Hz, 4.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 173.0, 159.2, 159.1, 130.2, 129.9, 129.7, 129.0, 128.8, 128.1, 114.3, 114.2, 114.2, 114.0, 103.3, 102.4, 64.5, 60.4, 60.3, 59.7, 57.6, 55.4, 55.4, 55.2, 54.8, 47.4, 46.7, 38.1, 37.4, 34.8, 34.6, 26.3, 25.5, 15.4, 15.1.

4-(2-Butoxy-4-hydroxytetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (13b)

Title compound was prepared according to General Procedure E using 4-(2,4-dihydroxytetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (112 mg, 0.33 mmol) and *n*-butanol (4 mL) as a clear oil and a mixture of two diastereomers; A and B in 1:0.4 ratio respectively (57.3 mg, 44%). HPLC – rt (diastereomer A) 7.45 min (70%), (diastereomer B) 7.33 (23%), collectively > 93% purity at 254 nm; HRMS $[M+H]^+$ 396.1839 m/z, found 396.1849 m/z; ^{1}H NMR **(diastereomers A)** (400 MHz, $CDCl_3$) δ 7.22 – 7.18 (m, 2H), 6.85 –

6.77 (m, 2H), 5.01 (d, *J* = 14.4 Hz, 1H), 4.29 (d, *J* = 14.4 Hz, 1H), 4.15 – 4.01 (m, 1H), 3.90 – 3.81 (m, 2H), 3.79 (s, 3H), 3.66 – 3.57 (m, 1H), 3.44 – 3.34 (m, 1H), 3.31 – 3.20 (m, 2H), 3.07 – 3.00 (m, 1H), 2.21 (ddd, *J* = 12.4, 4.6, 1.8 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.60 – 1.43 (m, 4H), 1.43 – 1.23 (m, 2H), 0.91 – 0.88 (m, 3H); ^{1}H NMR **(diastereomers B)** (400 MHz, $CDCl_3$) δ 7.10 – 7.02 (m, 2H), 6.85 – 6.77 (m, 2H), 5.20 (d, *J* = 15.6 Hz, 1H), 4.23 (d, *J* = 15.6 Hz, 1H), 4.15 – 4.01 (m, 1H), 3.99 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.82 – 3.73 (m, 4H), 3.57 – 3.48 (m, 1H), 3.44 – 3.34 (m, 2H), 3.31 – 3.20 (m, 1H), 3.07 – 2.96 (m, 1H), 2.10 (ddd, *J* = 12.7, 4.7, 1.8 Hz, 1H), 1.98 – 1.87 (m, 1H), 1.66 (dd, *J* = 12.6, 10.9 Hz, 1H), 1.60 – 1.43 (m, 3H), 1.43 – 1.23 (m, 2H), 0.91 – 0.85 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.0, 159.2, 159.1, 130.2, 130.0, 129.1, 128.8, 128.2, 114.3, 114.0, 103.2, 102.4, 64.5, 60.3, 60.2, 59.7, 59.4, 59.2, 57.4, 55.4, 55.4, 47.5, 46.6, 38.2, 37.5, 34.8, 34.6, 32.0, 26.3, 25.5, 19.7, 19.7, 14.3, 14.1.

4-(4-Hydroxy-2-(2-methoxyethoxy)tetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (13c)

Title compound was prepared according to General Procedure E using 4-(2,4-dihydroxytetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (112 mg, 0.329 mmol) and 2-methoxyethanol (10 mL) as a clear oil and a mixture of two diastereomers; A and B in 1:1 ratio, respectively (43 mg, 32%). HPLC – rt 5.4 min > 87% purity at 254 nm; HRMS $[M+H]^+$ 398.1632 m/z, found 398.1625m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.7 Hz, 2H), 7.14 – 7.08 (m, 2H), 6.89 – 6.80 (m, 4H), 5.03 (dd, *J* = 14.6, 1.9 Hz, 2H), 4.31 – 4.24 (m, 2H), 4.15 – 4.05 (m, 2H), 3.86 (m, 2H), 3.83 – 3.74 (m, 11H), 3.70 – 3.65 (m, 1H), 3.63 – 3.58 (m, 1H), 3.59 – 3.20 (m, 15H), 2.26 (ddd, *J* = 12.6, 4.6, 2.0 Hz, 1H), 1.95 – 1.88 (m, 2H), 1.67 – 1.58 (m, 1H), 1.56 – 1.40 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 130.2, 130.1, 129.0, 127.5, 114.4, 114.3, 114.2, 114.1, 71.8, 64.5, 64.1, 60.9, 60.6, 60.4, 59.7, 59.5, 59.3, 55.5, 55.4, 47.5, 47.5, 37.4, 35.9, 34.7, 28.1, 25.6.

3-Benzyl-4-(4-hydroxy-2-methoxytetrahydro-2*H*-pyran-2-yl)thiazolidin-2-one (13d)

Title compound was prepared in two steps. In the first step, the starting material, (*E*)-3-benzyl-4-(5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoyl)thiazolidin-2-one (391.6 mg, 0.965 mmol) was converted to the hemiacetal 3-benzyl-4-(2,4-dihydroxytetrahydro-2H-pyran-2-yl)thiazolidin-2-one according to General Procedure D (262.7 mg, 88%). The product obtained was treated with MeOH according to General Procedure E to obtain the title compound as two diastereomers A and B in 1: 0.6 ratios, respectively (157.3 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.17 (m, 8H), 5.29 (d, *J* = 15.8 Hz, 0.6H), 5.06 (d, *J* = 14.5 Hz, 1H), 4.39 (d, *J* = 14.6 Hz, 1H), 4.29 (d, *J* = 15.8 Hz, 0.6H), 4.10 – 3.99 (m, 1.6H), 3.96 (dd, *J* = 8.8, 4.0 Hz, 0.6H), 3.86 (m, 1.6H), 3.83 – 3.76 (m, 1H), 3.60 (ddd, *J* = 13.7, 11.4, 2.4 Hz, 1H), 3.56 – 3.48 (m, 0.6H), 3.44 – 3.15 (m, 3.2H), 3.08 (s, 3H), 2.98 (s, 1.8H), 2.21 (ddd, *J* = 12.5, 4.7, 2.0 Hz, 1H), 2.12 (ddd, *J* = 12.6, 4.7, 1.9 Hz, 0.6H), 1.98 – 1.86 (m, 1.6H), 1.69 (dd, *J* = 12.8, 10.9 Hz, 1H), 1.61 – 1.30 (m, 2.2H).

3-(3,4-dimethoxybenzyl)-4-(4-hydroxy-2-methoxytetrahydro-2*H*-pyran-2-yl)thiazolidin-2-one (13e)

Title compound was prepared from 4-(2,4-dihydroxytetrahydro-2*H*-pyran-2-yl)-3-(3,4-dimethoxybenzyl)thiazolidin-2-one (531 mg, 1.44 mmol) and MeOH (15 mL) according to General Procedure E as a pale yellow oil and a mixture of two diastereomers A and B in 1:0.7 ratio, respectively, over 2 steps (138 mg, 43%). HPLC – rt 5.47 min > 90% purity at 254 nm; HRMS $[M+H]^+$ 384.1475 m/z, found 384.1489 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 – 6.66 (m, 5.1H), 5.21 (d, *J* = 15.4 Hz, 0.7H), 5.03 (d, *J* = 14.3 Hz, 1H), 4.26 (d, *J* = 14.3 Hz, 1H), 4.19 (d, *J* = 15.4 Hz, 0.7H), 4.09 – 3.98 (m, 1.7H), 3.96 (dd, *J* = 7.3, 5.6 Hz, 0.7H), 3.93 – 3.83 (m, 11.9H), 3.83 – 3.74 (m, 1H), 3.62 (ddd, *J* = 13.4, 11.5, 2.3 Hz, 1H), 3.57 – 3.47 (m, 0.7H), 3.39 – 3.18 (m, 3.4H), 3.09 (s, 3H), 3.02 (s, 2.1H), 2.24 – 2.17 (m, 1H), 2.09 – 1.99 (m, 0.7H), 1.99 – 1.85 (m, 2.4H), 1.80 (d, *J* = 5.3 Hz, 1H), 1.66 (dd, *J* = 12.8, 10.9 Hz, 0.7H), 1.59 – 1.38 (m, 2.7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4, 149.2, 148.7, 129.4, 129.2, 121.4, 119.6, 112.0, 112.0, 111.2, 111.1, 110.5, 103.2, 102.5, 64.5, 64.4, 60.5, 60.3, 59.2, 56.9, 56.0, 56.0, 56.0, 47.8, 47.8, 47.6, 47.1, 37.9, 37.3, 34.7, 34.5, 32.5, 31.6, 26.3, 25.4.

4-(4-Hydroxy-2-methoxy-6-pentyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (13g)

Title compound was prepared using (4*R*)-4-(2,4-dihydroxy-6-pentyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (108 mg, 0.26 mmol) and MeOH according to the General Procedure E as a clear oil as a mixture of two diastereomers A and B in 1:0.8 ratio, respectively (30.4 mg, 15% over 2 steps). HPLC – rt 7.48 min > 53% purity at 254 nm; HRMS $[M+H]^+$ 424.2152 m/z, found 424.2157 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 6.80 (m, 7.2H), 5.20 (d, *J* = 15.4 Hz, 0.8H), 5.10 (d, *J* = 14.4 Hz, 1H), 4.27 – 4.21 (m, 1H), 4.25 – 4.18 (m, 0.8H), 4.09 – 4.00 (m, 1.8H), 3.93 (dd, *J* = 8.5, 4.3 Hz, 0.8H), 3.87 – 3.81 (m, 1H), 3.78 – 3.70 (m, 5.4H), 3.62 – 3.46 (m, 1.8H), 3.40 – 3.13 (m, 3.6H), 3.06 (s, 3H), 3.00 (s, 2.4H), 2.46 – 2.37 (m, 1.8H), 2.32 (ddd, *J* = 14.8, 8.2, 7.0 Hz, 1H), 2.20 (ddd, *J* = 12.5, 4.7, 1.7 Hz, 0.8H), 2.13 – 2.05 (m, 1.8H), 2.03 – 0.8(m, 23.4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.1, 130.0, 128.9, 128.7, 128.6, 114.2, 114.1, 103.1, 102.5, 70.4, 70.2, 64.8, 58.9, 57.0, 55.4, 55.4, 53.6, 47.8, 47.6, 47.2, 46.8, 40.6, 40.2, 37.8, 37.1, 36.3, 35.7, 32.0, 32.0, 26.3, 25.6, 25.4, 25.1, 22.8, 22.7, 14.2, 14.1.

2-Ethoxy-2-(3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)tetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14a)

Title compound was prepared using 4-(2-ethoxy-4-hydroxytetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (19.5 mg, 0.053 mmol) and 2-(thiophen-2-yl)benzoic acid (33 mg, 0.16 mmol) according to General Procedure F as a clear oil and a mixture of two diastereomers; A and B in 1:0.5 ratio respectively (80%). HPLC – rt 9.21 min > 97% purity at 254 nm; HRMS $[M+Na]^+$ 576.1485 m/z, found 576.1501 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.81 – 7.73 (m, 1.5H), 7.54 – 7.35 (m, 6H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.09 (ddd, *J* = 8.7, 8.0, 6.0 Hz, 2.5H), 6.99 (dt, *J* = 3.5, 1.1 Hz, 1.5H), 6.91 – 6.80 (m, 3H), 5.29 – 5.17 (m, 2H), 5.01 (d, *J* = 14.4 Hz, 1H), 4.22 (dd, *J* = 15.0, 9.9 Hz, 1.5H), 3.96 (dd, *J* = 8.9, 4.0 Hz, 0.5H), 3.86 – 3.69 (m, 7H), 3.68 – 3.59 (m, 1H), 3.58 – 3.49 (m, 0.5H), 3.49 – 3.02 (m, 6H), 2.09 (ddd, *J* = 12.5, 4.7, 1.7 Hz, 2H), 1.89 (dddd, *J* = 9.6, 7.2, 4.6, 2.8 Hz, 1H), 1.56 – 1.25 (m, 3H), 1.16 (dt, *J* = 15.6, 7.0 Hz, 4.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.1, 168.0, 159.2, 142.2, 134.7, 132.3, 132.2, 131.6, 131.5, 131.2, 131.2, 130.2, 129.8, 129.7, 129.0, 128.8, 128.1, 128.0, 127.3, 126.6, 126.2, 126.0, 114.3, 114.1, 103.2, 102.3, 68.3, 59.9, 59.7, 57.2, 55.4, 55.4, 55.4, 54.9, 47.4, 46.6, 33.7, 33.2, 30.9, 30.8, 27.0, 26.2, 25.3, 15.4, 15.1.

2-Butoxy-2-((*R*)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)tetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14b)

Title compound was prepared using 4-(2-butoxy-4-hydroxytetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (51.3 mg, 0.13 mmol) and 2-(thiophen-2-yl)benzoic acid (79 mg, 0.39 mmol) according to General Procedure F as a clear oil and a mixture of two diastereomers; A and B in 1:0.5 ratio, respectively (38.7 mg, 51%). HPLC – rt 9.79 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 582.1979 m/z, found 582.1991 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 1.5H), 7.54 – 7.37 (m, 6H), 7.21 – 7.19 (m, 2H), 7.13 – 7.06 (m, 2.5H), 6.98 – 6.91 (m, 1.5H), 6.90 – 6.82 (m, 3H), 5.26 – 5.15 (m, 2H), 5.00 (d, *J* = 14.4 Hz, 1H), 4.24 (d, *J* = 14.2 Hz, 1H), 4.21 (d, *J* = 14.9 Hz, 0.5H), 3.98 (dd, *J* = 8.9, 4.0 Hz, 0.5H), 3.86 – 3.81 (m, 1.5H), 3.79 (s, 4.5H), 3.78 – 3.68 (m, 1H), 3.68 – 3.60 (m, 1H), 3.59 – 3.50 (m, 0.5H), 3.43 – 3.17 (m, 4.5H), 3.12 – 2.98 (m, 1.5H), 2.09 (ddd, *J* = 12.5, 4.7, 1.7 Hz, 1H), 1.97 – 1.82 (m, 2H), 1.60 – 1.24 (m, 9H), 0.92 – 0.86 (m, 4.5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 172.8, 168.0, 167.9, 159.2, 159.1, 142.2, 134.7, 134.5, 132.3, 132.2, 131.6, 131.5, 131.2, 131.1, 130.2, 129.8, 129.7, 129.0, 128.8, 128.1, 128.0, 127.3, 126.6, 126.1, 126.0, 114.3, 114.0, 103.1, 102.2, 68.3, 59.74, 59.66, 59.56, 59.32, 57.13, 55.40, 55.36, 47.42, 46.50, 33.70, 33.17, 31.95, 30.84, 30.7, 27.0, 26.2, 25.3, 19.7, 19.6, 14.3, 14.0.

2-((*R*)-3-(4-Methoxybenzyl)-2-oxothiazolidin-4-yl)-2-(2-methoxyethoxy)tetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14c)

Title compound was prepared using 4-(4-hydroxy-2-(2-methoxyethoxy)tetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (40 mg, 0.1 mmol) and 2-(thiophen-2-yl)benzoic acid (62 mg, 0.3 mmol) according to General Procedure F as a clear oil (10.4 mg, 18%). HPLC – rt 8.82 min > 99% purity at 254 nm; HRMS $[M+Na]^+$ 606.1591 m/z, found 606.1608 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.55 – 7.35 (m, 4H), 7.20 (m, 2H), 7.09 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.98 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.85 – 6.81 (m, 2H), 5.30 – 5.14 (m, 1H), 5.01 (d, *J* = 14.4 Hz, 1H), 4.23 (d, *J* = 14.4 Hz, 1H), 3.80 – 3.75 (m, 5H), 3.77 – 3.67 (m, 1H), 3.57 – 3.50 (m, 1H), 3.49 – 3.41 (m, 2H), 3.33 (s, 3H), 3.31 – 3.20 (m, 3H), 2.13 (ddd, *J* = 12.6, 4.7, 1.6 Hz, 1H), 1.89 – 1.85 (m, 1H), 1.50 – 1.28 (m, 2H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 172.9, 167.9, 159.2, 142.2, 134.7, 132.2, 131.6, 131.2, 130.2, 129.9, 129.0, 128.0, 127.4, 126.6, 126.0, 114.1, 103.4, 71.7, 68.2, 59.9, 59.7, 59.7, 59.3, 55.4, 47.5, 33.0, 30.7, 25.4.

2-((*R*)-3-Benzyl-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl furan-2-carboxylate (14g)

Title compound was prepared from 3-benzyl-4-(4-hydroxy-2-methoxytetrahydro-2*H*-pyran-2-yl)thiazolidin-2-one (50 mg, 0.15 mmol) and 2-furoic acid (52 mg, 0.46 mmol) according to the General Procedure F as a clear oil and a mixture of two diastereomers A and B in 1:0.6 ratio, respectively (62.5 mg, 99%). HPLC – rt 7.87 min > 95% purity at 254 nm; HRMS $[M+H]^+$ 418.1319 m/z, found 418.1325 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 6.40 (m, 12.8H), 5.40 – 5.27 (m, 1.6H), 5.24 – 5.19 (m, 0.6H), 5.06 (d, *J* = 14.6 Hz, 1H), 4.35 (d, *J* = 14.5 Hz, 1H), 4.24 (d, *J* = 15.7 Hz, 0.6H), 3.95 – 3.83 (m, 3.2H), 3.64 – 3.61 (m, 1.6H), 3.37 – 3.26 (m, 3.2H), 3.07 (s, 3H), 2.97 (s, 1.8H), 2.26 – 2.18 (m, 1H), 2.18 – 2.06 (m, 0.6H), 2.04 – 2.01 (m, 1.6H), 1.91 – 1.85 (m, 0.6H), 1.76 – 1.65 (m, 1H), 1.72 – 1.41 (m, 1.6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 129.0, 128.8, 128.7, 127.8, 127.7, 127.2, 118.4, 118.3, 112.0, 68.1, 68.0, 60.0, 59.9, 59.6, 56.8, 48.3, 47.7, 47.3, 34.3, 33.7, 31.3, 31.2, 26.2, 25.4.

2-(3-Benzyl-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl 2-iodobenzoate (14h)

Title compound was prepared from 3-benzyl-4-(4-hydroxy-2-methoxytetrahydro-2*H*-pyran-2-yl)thiazolidin-2-one (100 mg, 0.31 mmol) and 2-iodobenzoic acid (230 mg, 0.93 mmol) according to the General Procedure F as a clear oil and a mixture of two diastereomers; A and B in 1:0.7 ratio, respectively (153.6 mg, 89%). HPLC – rt 8.75 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 554.0493 m/z, found 554.0519 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.85 (m, 1.7H), 7.79 – 7.71 (m, 1.7H), 7.42 – 7.35 (m, 1.7H), 7.39 – 7.27 (m, 7.5H), 7.22 – 7.15 (m, 1H), 7.16 – 7.08 (m, 1.7H), 5.43 – 5.33 (m, 1.7H), 5.30 (d, *J* = 15.9 Hz, 0.7H), 5.08 (d, *J* = 14.6 Hz, 1H), 4.42 (d, *J* = 14.6 Hz, 1H), 4.31 (d, *J* = 15.8 Hz, 0.7H), 4.00 (dd, *J* = 7.6, 5.2 Hz, 0.7H), 3.96 – 3.82 (m, 2.7H), 3.79 – 3.70 (m, 1H), 3.66 (dd, *J* = 18.1, 6.5 Hz, 0.7H), 3.46 – 3.23 (m, 3.4H), 3.13 (s, 3H), 3.03 (s, 2.1H), 2.38 (ddd, *J* = 12.4, 4.8, 1.9 Hz, 1H), 2.28 (ddd, *J* = 12.6, 4.7, 1.8 Hz, 0.7H), 2.24 – 2.17 (m, 0.7H), 2.17 – 2.08 (m, 1H), 2.00 (dd, *J* = 12.7, 11.3 Hz, 0.7H), 1.87 – 1.79 (m, 1H), 1.80 – 1.58 (m, 1.7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 166.0, 141.5, 141.4, 137.0, 136.7, 135.0, 132.9, 132.8, 131.2, 131.1, 129.0, 128.8, 128.7, 128.1, 127.8, 127.7, 127.2, 103.3, 102.5, 94.3, 94.2, 69.1, 69.0, 60.1, 59.9, 59.7, 56.9, 48.4, 47.8, 47.7, 47.4, 34.3, 33.7, 31.2, 31.1, 26.3, 25.4.

2-((*R*)-3-Benzyl-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl 2-(naphthalen-1-yl)benzoate (14i*)

Title compound was prepared from 2-(3-benzyl-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl 2-iodobenzoate (87.3 mg, 0.16 mmol) and 1-naphthalene boronic acid (32.6

mg, 0.19 mmol) according to the General Procedure G as a white semisolid as a mixture of two diastereomers with a combined yield of 50%. Diastereomer A was isolated in 27% yield. The proton and carbon NMR spectrum show peak splitting due to axial chirality (1:0.76 ratio). HPLC – rt 4.59 min > 96% purity at 254 nm; HRMS $[M+H]^+$ 554.1996 m/z, found 554.2007 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, 1.76H), 8.00 – 7.91 (m, 3.52H), 7.63 (m, 1.76H), 7.58 – 7.13 (m, 21.12H), 5.23 (d, *J* = 14.6 Hz, 1H), 5.19 (d, *J* = 14.6 Hz, 0.76H), 4.87 – 4.75 (m, 1.76H), 4.15 – 4.02 (m, 1.76H), 3.69 – 3.71 (m, 2.52H), 3.53 – 3.43 (m, 1H), 2.98 – 2.93 (m, 1.76H), 3.22 – 3.16 (m, 3.52H), 2.98 – 2.74 (m, 5.28H), 1.63 – 1.50 (m, 1.76H), 1.49 – 1.40 (m, 1H), 1.37 – 1.23 (m, 0.76H), 0.97 – 0.80 (m, 1.76H), 0.76 – 0.51 (m, 1.76H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.4, 167.2, 167.2, 141.3, 141.3, 140.2, 140.1, 136.5, 136.5, 133.3, 133.2, 132.5, 132.4, 132.1, 131.9, 131.8, 131.8, 131.7, 130.5, 130.5, 128.9, 128.5, 128.3, 127.8, 127.8, 127.6, 127.6, 127.1, 126.3, 126.1, 126.0, 125.9, 125.9, 125.9, 125.6, 125.4, 125.3, 102.1, 102.0, 67.4, 67.3, 59.7, 59.6, 56.7, 56.6, 47.5, 47.2, 41.0, 32.8, 32.3, 30.4, 29.9, 26.1, 24.0, 22.8, 20.9.

2-((*R*)-3-Benzyl-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl 2-(naphthalen-1-yl)benzoate (14i[#])

Title compound was prepared from 2-(3-benzyl-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl 2-iodobenzoate and 1-naphthalene boronic acid according to the General Procedure G as a white semisolid in 50% yield as a mixture of two diastereomers. Diastereomer B was isolated in 21% yield. The proton and carbon NMR spectrum show the peak splitting due to axial chirality (1:0.76 ratio). HPLC – rt 4.24 min > 99% purity at 254 nm; HRMS $[M+Na]^+$ 576.1815 m/z, found 576.1824 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 1.76H), 8.00 – 7.89 (m, 3.52H), 7.63 – 7.57 (m, 1.76H), 7.58 – 7.19 (m, 21.12H), 5.07 (d, *J* = 14.6 Hz, 1H), 4.99 (d, *J* = 14.6 Hz, 0.76H), 4.87 – 4.75 (m, 1.76H), 4.12 – 4.09 (m, 1.76H), 3.69 – 3.58 (m, 1.76H), 3.65 – 3.57 (m, 0.76H), 3.56 – 3.48 (m, 1H), 3.45 – 3.30 (m, 1.76H), 3.22 – 2.76 (m, 3.52H), 2.95 – 2.93 (m, 5.28H), 1.63 – 1.23 (m, 3.52H), 0.97 – 0.51 (m, 3.52H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.0, 172.8, 167.1, 167.0, 141.5, 141.4, 140.2, 140.1, 136.8, 133.3, 133.2, 132.5, 132.4, 132.2, 132.0, 132.0, 131.8, 131.8, 131.7, 131.6, 130.6, 130.4, 128.9, 128.7, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 127.7, 127.1, 126.3, 126.1, 126.0, 126.0, 125.9, 125.8, 125.7, 125.7, 125.6, 125.3, 125.1, 102.7, 102.6, 67.3, 67.2, 59.6, 59.6, 59.5, 59.2, 48.0, 47.9, 47.5, 47.5, 32.5, 32.2, 30.26, 29.6, 24.9, 24.9.

2-(3-(3,4-Dimethoxybenzyl)-2-oxothiazolidin-4-yl)-2-methoxytetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14j)

Title compound was prepared from 3-(3,4-dimethoxybenzyl)-4-(4-hydroxy-2-methoxytetrahydro-2*H*-pyran-2-yl)thiazolidin-2-one (138 mg, 0.36 mmol) and 2-(thiophen-2-yl)benzoic acid (221 mg, 1.08 mmol) according to the General procedure F as a mixture of two diastereomers A and B in 1:1 ratio, respectively (5.6 mg, 3%). HPLC – rt (diastereomer A)

8.52 min (50%), (diastereomer B) 8.60 min (40%), collectively > 90% purity at 254 nm; HRMS $[M+Na]^+$ 592.1434 m/z, found 592.1442 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (ddd, *J* = 7.6, 4.0, 1.3 Hz, 2H), 7.54 – 7.31 (m, 8H), 7.11 – 7.02 (m, 2H), 6.98 (dd, *J* = 3.5, 1.1 Hz, 2H), 6.86 – 6.78 (m, 4H), 6.75 (dd, *J* = 4.2, 2.3 Hz, 2H), 5.29 – 5.12 (m, 3H), 5.03 (d, *J* = 14.3 Hz, 1H), 4.20 (d, *J* = 14.1 Hz, 1H), 4.17 (d, *J* = 15.1 Hz, 1H), 4.00 – 3.71 (m, 16H), 3.71 – 3.59 (m, 1H), 3.60 – 3.50 (m, 1H), 3.41 – 3.15 (m, 4H), 3.09 (s, 3H), 3.01 (s, 3H), 2.12 – 2.02 (m, 1H), 1.93 – 1.74 (m, 3H), 1.68 – 1.28 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 168.1, 149.4, 149.2, 148.7, 148.6, 142.2, 134.6, 134.5, 132.4, 132.2, 131.5, 131.2, 129.8, 129.7, 129.3, 129.2, 128.0, 127.4, 126.6, 126.0, 121.4, 119.6, 112.1, 111.3, 111.1, 110.6, 103.2, 102.4, 68.2, 60.0, 59.9, 59.2, 56.7, 56.1, 56.0, 47.8, 47.7, 47.6, 47.1, 33.5, 33.1, 30.8, 30.7, 26.1, 25.2.

2-Hydroxy-2-(3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-6-phenyltetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14k)

Title compound was prepared using (4*R*)-4-((2*S*)-2,4-dihydroxy-6-phenyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (50 mg, 0.12 mmol) and 2-(thiophen-2-yl)benzoic acid (72 mg, 0.35 mmol) according to the General Procedure F as an off-white solid (4.3 mg, 5%). HPLC – rt 8.93 min > 65% purity at 254 nm; HRMS $[M+H]^+$ 602.1666 m/z, found 602.1656 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.54 – 7.31 (m, 10H), 7.07 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.01 – 6.93 (m, 3H), 6.72 (dd, *J* = 9.1, 2.4 Hz, 2H), 5.42 – 5.35 (m, 1H), 5.16 (d, *J* = 14.5 Hz, 1H), 5.01 (dd, *J* = 12.0, 1.9 Hz, 1H), 4.29 (d, *J* = 14.5 Hz, 1H), 3.74 (s, 3H), 3.54 (dd, *J* = 9.3, 1.8 Hz, 1H), 3.34 – 3.29 (m, 2H), 2.27 – 2.17 (m, 2H), 1.54 – 1.50 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.1, 159.3, 142.3, 140.4, 134.7, 132.2, 131.6, 131.3, 129.9, 129.8, 128.8, 128.6, 128.4, 128.1, 127.4, 126.8, 126.7, 126.1, 114.2, 101.6, 72.3, 68.5, 64.3, 55.4, 47.7, 37.8, 33.0, 26.8.

2-Methoxy-2-(3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-6-pentyltetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14l$^+$)

Title compound was prepared using 4-(4-hydroxy-2-methoxy-6-pentyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (22 mg, 0.05 mmol) and 2-(thiophen-2-yl)benzoic acid (30 mg, 0.15 mmol) according to the General Procedure F (6.3 mg, 20%). HPLC – rt 7.28 min > 74% purity at 254; HRMS $[M+H]^+$ 610.2292 m/z, found 610.2284 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.52 – 7.36 (m, 4H), 7.14 – 7.06 (m, 2H), 7.07 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.98 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.91 – 6.83 (m, 2H), 5.28 – 5.12 (m, 2H), 4.19 (d, *J* = 15.5 Hz, 1H), 3.91 (dd, *J* = 9.6, 3.3 Hz, 1H), 3.80 (s, 3H), 3.53 – 3.49 (m, 1H), 3.38 – 3.21 (m, 2H), 2.98 (s, 3H), 1.97 – 1.88 (m, 1H), 1.87 – 1.77 (m, 1H), 1.52 – 1.15 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 168.2, 159.2, 142.2, 134.5, 132.5, 131.4, 131.1, 129.6, 128.7, 128.6, 128.0, 127.4, 126.6, 126.2, 114.3, 102.4, 69.7, 68.6, 56.7, 55.4, 47.7, 46.7, 36.3, 35.5, 33.4, 31.9, 26.2, 25.0, 22.7, 14.1; $[\alpha]_D^{20}$ = -136.8° (*c* 0.38, MeOH).

2-Methoxy-2-(3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-6-pentyltetrahydro-2*H*-pyran-4-yl 2-(thiophen-2-yl)benzoate (14l[#])

Title compound was prepared using 4-(4-hydroxy-2-methoxy-6-pentyltetrahydro-2*H*-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (22 mg, 0.05 mmol) and 2-(thiophen-2-yl)benzoic acid (30 mg, 0.15 mmol) according to the General Procedure F (8.8 mg, 29%). HPLC – rt 8.89 min > 84% purity at 254 nm; HRMS $[M+H]^+$ 610.2292 m/z, found 610.2232 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.54 – 7.35 (m, 4H), 7.20 – 7.09 (m, 2H), 7.08 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.98 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.89 – 6.83 (m, 2H), 5.26 – 5.14 (m, 1H), 5.09 (d, *J* = 14.4 Hz, 1H), 4.18 (d, *J* = 14.4 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.68 (m, 1H), 3.66 – 3.55 (m, 1H), 3.29 – 3.15 (m, 2H), 3.06 (s, 3H), 2.10 – 2.03 (m, 1H), 1.98 – 1.89 (m, 1H), 1.57 – 1.21 (m, 10H), 0.93 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 168.1, 159.3, 142.2, 134.6, 132.3, 131.5, 131.2, 130.0, 129.8, 128.8, 128.0, 127.4, 126.6, 126.0, 114.1, 103.0, 70.0, 68.6, 58.9, 55.4, 47.6, 47.2, 36.4, 36.2, 32.9, 32.0, 25.5, 25.3, 22.8, 14.2; $[\alpha]_D^{20}$ = +47.2° (*c* 0.53, MeOH).

2-Bromo-1-(3-hydroxyphenyl)ethan-1-one (16)

To 3-hydroxy acetophenone (100 mg, 0.73 mmol) in EtOAc (5 mL) was added copper bromide (195.7 mg, 0.88 mmol) and refluxed for 12 h. The reaction mixture was then cooled to room temperature and diluted with EtOAc and washed with brine. The organic layer was then dried with sodium sulphate and evaporated to dryness. Flash chromatography, eluting with 25% EtOAc/petroleum spirits gave a mixture of the product and the starting material in 1:0.5 ratio which was directly used for the next step.

4-(3-hydroxyphenyl)thiazol-2(3*H*)-one (17)

To potassium thiocyanate (68 mg, 0.7 mmol) in acetone (7 mL), was added 2-bromo-1-(3-hydroxyphenyl)ethan-1-one (106.5 mg, 0.5 mmol) and stirred for 10 min. The solvent was then evaporated *in vacuo* and the residue extracted with EtOAc and brine. The organic layer was dried with sodium sulphate and evaporated to dryness. The crude thus obtained was dissolved in acetic acid (3.5 mL) and 50% aq. H_2SO_4 (0.7 mL). The resulting solution was heated to 100 °C for 12 h. After cooling the solution to room temperature, EtOAc was added. The organic layer was then washed successively with saturated sodium bicarbonate solution, water and brine. The organic layer was dried with sodium sulphate before evaporating to dryness. Flash chromatography, eluting with 25% EtOAc/petroleum spirits gave the product as an off-white solid (28 mg, 29%). HPLC – rt 4.5 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 194.027 m/z, found 194.0274 m/z; ^{1}H NMR (400 MHz, DMSO) δ 9.63 (s, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.05 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 7.00 (t, *J* = 2.0 Hz, 1H), 6.77 (ddd, *J* = 8.1, 2.4, 0.9 Hz, 1H), 6.70 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 172.9, 157.7, 134.1, 131.0, 129.9, 115.8, 115.7, 111.8, 97.9.

3-(2-Oxo-2,3-dihydrothiazol-4-yl)phenyl 2-iodobenzoate (18a)

Title compound was prepared from 4-(3-hydroxyphenyl)thiazol-2(3*H*)-one (27.9 mg, 0.144 mmol) according to the General Procedure F as a white solid (27.6 mg, 45%). HPLC – rt 7.56 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 423.9499 m/z, found 423.9500 m/z; ^{1}H NMR (400 MHz, DMSO) δ 8.12 (dd, *J* = 7.9, 0.9 Hz, 1H), 8.03 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.68 – 7.60 (m, 3H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.33 (ddd, *J* = 8.0, 2.2, 1.0 Hz, 1H), 6.95 (s, 1H); ^{13}C NMR (101 MHz, DMSO) δ 173.3, 165.4, 151.3, 141.5, 134.6, 134.3, 133.3, 131.7, 131.6, 130.7, 129.0, 123.2, 122.4, 118.7, 100.0, 95.6.

3-(2-Oxo-2,3-dihydrothiazol-4-yl)phenyl 2-(thiophen-2-yl)benzoate (18b)

Title compound was prepared from 4-(3-hydroxyphenyl)thiazol-2(3*H*)-one (20 mg, 0.08 mmol) and 2-(thiophen-2-yl)benzoic acid (50 mg, 0.24 mmol) according to the General procedure F (29.8 mg, 98%). HPLC – rt 7.78 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 380.041 m/z, found 380.0417 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.94 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.65 – 7.46 (m, 3H), 7.46 – 7.38 (m, 2H), 7.31 – 7.29 (m, 1H), 7.12 – 7.08 (m, 2H), 7.00 – 6.95 (m, 2H), 6.28 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 167.0, 151.4, 142.0, 134.9, 133.7, 131.9, 131.7, 131.1, 130.9, 130.4, 130.2, 128.2, 127.6, 127.0, 126.3, 122.4, 122.1, 118.1, 99.1.

3-(2-Oxo-2,3-dihydrothiazol-4-yl)phenyl 3-(thiophen-2-yl)benzoate (18c)

Title compound was prepared from 4-(3-hydroxyphenyl)thiazol-2(3*H*)-one (50 mg, 0.26 mmol) and 3-(thiophen-2-yl)benzoic acid (100 mg, 0.77 mmol) according to the General procedure F (70.8 mg, 72%). HPLC – rt 8.16 min > 99% purity at 254 nm; HRMS $[M+H]^+$ 380.041 m/z, found 380.0422 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.43 – 8.38 (m, 1H), 8.15 – 8.07 (m, 1H), 7.88 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.47 – 7.39 (m, 3H), 7.35 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.30 – 7.24 (m, 1H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.35 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.7, 176.2, 151.8, 151.7, 135.3, 133.2, 131.3, 131.2, 130.7, 130.0, 129.5, 129.1, 128.4, 127.6, 125.9, 124.2, 122.5, 122.5, 118.6, 99.4.

3-(3-(4-Methoxybenzyl)-2-oxo-2,3-dihydrothiazol-4-yl)phenyl 2-iodobenzoate (19a)

To a stirred suspension of 3-(2-oxo-2,3-dihydrothiazol-4-yl)phenyl 2-iodobenzoate (32 mg, 0.076 mmol), DMF (0.4 mL), potassium carbonate (18 mg, 0.13 mmol) and catalytic amount of sodium iodide (0.5 mg, 0.004 mmol), 3-methoxy benzylchloride (12 µL, 0.1 mmol) was added drop-wise. The reaction was stirred overnight at room temperature. After the completion of the reaction, diethyl ether was added and the suspension washed with brine (x 3). The organic layer was dried with magnesium sulphate, filtered and evaporated. Flash chromatography, eluting with 15% EtOAc/petroleum spirits yielded the product as a clear oil (34.5 mg, 83% yield). HPLC – rt 8.9 min > 99% purity at 254 nm; LRMS $[M-H]^-$ 541.9 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.98 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.28 – 7.20 (m, 1H),

7.13 – 7.01 (m, 2H), 6.97 – 6.82 (m, 2H), 6.80 – 6.66 (m, 2H), 6.07 (s, 1H), 4.85 (s, 2H), 3.71 (s, 3H).

3-(3-(4-Methoxybenzyl)-2-oxo-2,3-dihydrothiazol-4-yl)phenyl 3-(thiophen-2-yl)benzoate (19b)

To a stirred suspension of 3-(2-oxo-2,3-dihydrothiazol-4-yl)phenyl 3-(thiophen-2-yl)benzoate (50 mg, 0.13 mmol), DMF (3 mL), potassium carbonate (30.5 mg, 0.22 mmol) and catalytic amount of sodium iodide (0.9 mg, 0.0065 mmol), 3-methoxy benzylchloride (21 µL, 0.17 mmol) was added drop-wise and the reaction stirred for 12 h. After the completion of the reaction, diethyl ether was added and the suspension washed with brine (x 3). The organic layer was dried with magnesium sulphate, filtered and evaporated. Flash chromatography, eluting with 1% EtOAc/cyclohexane yielded the product as a clear oil (75 mg, 70%).HPLC – rt 9.41 min > 99% purity at 254 nm; HRMS [M+H]+ 500.0985 m/z, found 500.0995 m/z; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (t, *J* = 1.6 Hz, 1H), 8.11 – 8.05 (m, 1H), 7.89 (ddd, *J* = 7.8, 1.9, 1.1 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.43 (ddd, *J* = 8.0, 6.2, 2.9 Hz, 2H), 7.35 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.07 – 6.95 (m, 2H), 6.96 – 6.89 (m, 2H), 6.76 – 6.70 (m, 2H), 6.07 (s, 1H), 4.88 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 164.8, 159.1, 150.9, 142.9, 136.8, 135.2, 133.0, 131.2, 129.9, 129.9, 129.4, 129.0, 128.7, 128.7, 128.4, 127.5, 126.8, 125.9, 124.2, 122.9, 122.9, 114.0, 99.7, 55.2, 47.0.

Conflicts of interest

The authors have no conflicts to declare.

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