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NEW THIAZOLIDINONE AND TRIAZINETHIONE CONJUGATES DERIVED FROM AMINO-β-LACTAMS

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Abstract - Thioureas 3a-s, generated from amino-β-lactams 1a-c, were used to achieve two different cyclizations: (i) condensation with ethyl bromoacetate which resulted in the formation of a variety of iminothiazolidinones 4a/a'-n, and (ii) condensation with aqueous formaldehyde and methylamine which resulted in the formation of triazinethiones 5a-g. The condensation of thioureas 3b-f, 3h and 3m-s (R^1 = cyclohexyl, *exo*-norbornyl, aryl, R^2 = β-lactam) with ethyl bromoacetate proceeded with high regioselectivity leading exclusively to the formation of a single regioisomer A of iminothiazolidinones 4b-n. However, the cyclization of thiourea 3a (R^1 = *n*-hexyl, R^2 = β-lactam) with ethyl bromoacetate led to the formation of a mixture of two regioisomers A (minor) and B (major) of the iminothiazolidinones 4a/a' in the ratio 23:77. Furthermore, condensation of thioureas 3d, 3g, 3i-l and 3n with aqueous formaldehyde and methylamine, furnished triazinethiones 5a-g.

INTRODUCTION

Monocyclic β-lactams occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities.[1-3] Consequently their synthesis has been of considerable interest to the synthetic community over the past five decades.[4-6] The potential of β-lactams as intermediates for the access to α- and β-amino acid derived peptides, has helped research on this topic to achieve significant attention.[7-10] Enantiopure 3-amino-β-lactams are the key intermediates for the

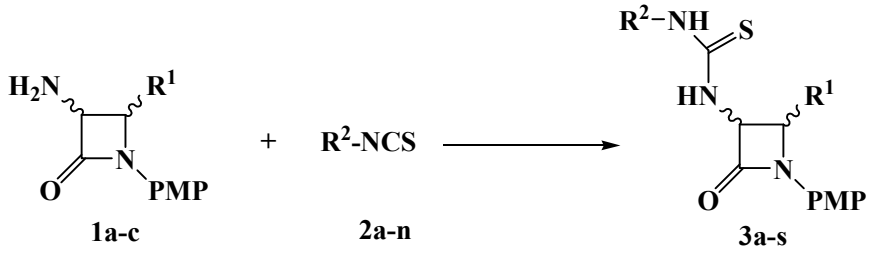
synthesis of peptides and peptidomimetics. A variety of 3-amino-β-lactams with excellent enantiopurities can be obtained based on chiral ester enolate – imine cyclocondensations.[8,10-13] Their hydrolysis affords the corresponding α,β-diamino acids.[14] This creates the foundation for the applications of these β-lactams to the asymmetric synthesis of non-protein amino acids, peptides, dipeptide isosters and peptidomimetics that are not easily prepared by conventional methods. α,β-Diamino acids are frequently found to be components of peptide antibiotics including lavendomycin and glumamycin.[15]

On the other hand, the amino functionality in enantiopure 3-amino-β-lactams represents a good point for extension of the β-lactam class and provides new possibilities in asymmetric synthesis and the development of methods for preparation of diverse substances potentially with a broad spectrum of activity.[1,6,16,17] Thioureas,[18,19] thiazolidinone[20-35] and triazine[36,37] moieties represent building blocks for the generation of new compounds with possible pharmacological and biological application in the areas of antibacterial, antifungal, herbicidal, and pesticidal activity. Thioureas have attracted much attention due to their pharmaceutical and pesticidal activity. A variety of thiourea derivatives and their metal complexes exhibit analgetic,[38] anti-inflamatory,[39] antimicrobial,[40] anticancer,[38] and antifungal[41] activities. Furthermore, thioureas are important building blocks in the synthesis of heterocycles, e.g. iminothiazolidinones and triazinethiones, that posses a broad spectrum of biological activity. The former group, beside antibacterial and antifungal properties, have a special importance as nonsteroidal anti-inflamatory drugs (*NSAID's*) and in contrast with the majority of *NSAID's*, they cause only minor disturbance of the gastrointestinal system.[26,30]

RESULTS AND DISCUSSION

We employed the chiral ester lithium enolate-imine condensation strategy,[13,42,43] to the asymmetric synthesis of *trans*-3-amino-β-lactams **1a-c**.[11,12] This synthetic methodology is generally used for the formation of the azetidin-2-one nucleus and is also known as the β-lactam synthon method.[44,45] Treatment of *trans*-3-amino-β-lactams **1a-c** with a variety of isothiocyanates **2a-n** in acetonitrile provided the corresponding thioureas **3a-s** (Scheme 1).

Thioureas **3a-s** were subjected to two different cyclizations: (i) condensation with ethyl bromoacetate in the presence of sodium carbonate[29,34] which resulted in the formation of a variety of iminothiazolidinones **4a-n** (Scheme 2), and (ii) condensation with aqueous formaldehyde and methylamine[36,46,47] which led to the formation of triazinethiones **5a-g** (Scheme 5). Iminothiazolidinones **4a-n** were isolated in 45-98 % yields, when the reaction mixtures were heated in acetonitrile at 40-60 °C for 6 h. Crude products were purified by column chromatography on silica gel, followed by crystallization.

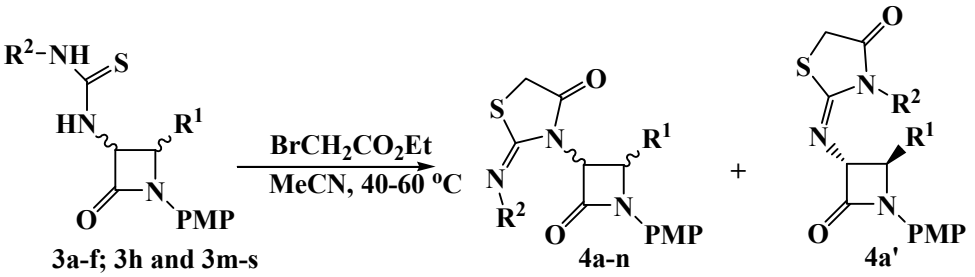


(3*R*,4*R*)-1a: R^1 = Ph
(3*S*,4*S*)-1b: R^1 = Ph
(3*R*,4*R*)-1c: R^1 = Fc
PMP = 4-MeO-C_6H_4
Ph = Phenyl
Fc = Ferrocenyl

2a: R^2 = *n*-hexyl
2b: R^2 = cyclohexyl
2c: R^2 = norbornyl
2d: R^2 = Ph
2e: R^2 = 2-Cl-C_6H_4
2f: R^2 = 4-Cl-C_6H_4
2g: R^2 = 2-F-C_6H_4
2h: R^2 = 4-F-C_6H_4
2i: R^2 = 4-CF_3-C_6H_4
2j: R^2 = 4-CF_3O-C_6H_4
2k: R^2 = PMP
2l: R^2 = 4-N_3-C_6H_4
2m: R^2 = 4-NO_2-C_6H_4
2n: R^2 = 4--NC-C_6H_4

(3*R*,4*R*)-3a: 54%; R^1 = Ph; R^2 = *n*-hexyl
(3*R*,4*R*)-3b: 72%; R^1 = Ph; R^2 = cyclohexyl
(3*R*,4*R*)-3c: 94%; R^1 = Ph; R^2 = norbornyl
(3*R*,4*R*)-3d: 96%; R^1 = Ph; R^2 = Ph
(3*S*,4*S*)-3e: 98%; R^1 = Ph; R^2 = Ph
(3*R*,4*R*)-3f: 94%; R^1 = Ph; R^2 = 2-Cl-C_6H_4
(3*R*,4*R*)-3g: 94%; R^1 = Ph; R^2 = 4-Cl-C_6H_4
(3*R*,4*R*)-3h: 66%; R^1 = Ph; R^2 = 2-F-C_6H_4
(3*R*,4*R*)-3i: 89%; R^1 = Ph; R^2 = 4-F-C_6H_4
(3*R*,4*R*)-3j: 97%; R^1 = Ph; R^2 = 4-CF_3-C_6H_4
(3*R*,4*R*)-3k: 84%; R^1 = Ph; R^2 = 4-CF_3O-C_6H_4
(3*R*,4*R*)-3l: 99%; R^1 = Ph; R^2 = PMP
(3*R*,4*R*)-3m: 85%; R^1 = Ph; R^2 = 4-N_3-C_6H_4
(3*R*,4*R*)-3n: 81%; R^1 = Ph; R^2 = 4-NO_2-C_6H_4
(3*R*,4*R*)-3o: 97%; R^1 = Ph; R^2 = 4-NC-C_6H_4
(3*R*,4*R*)-3p: 72%; R^1 = Fc; R^2 = cyclohexyl
(3*R*,4*R*)-3q: 96%; R^1 = Fc; R^2 = Ph
(3*R*,4*R*)-3r: 88%; R^1 = Fc; R^2 = 2-Cl-C_6H_4
(3*R*,4*R*)-3s: 81%; R^1 = Fc; R^2 = 4-NO_2-C_6H_4

Scheme 1

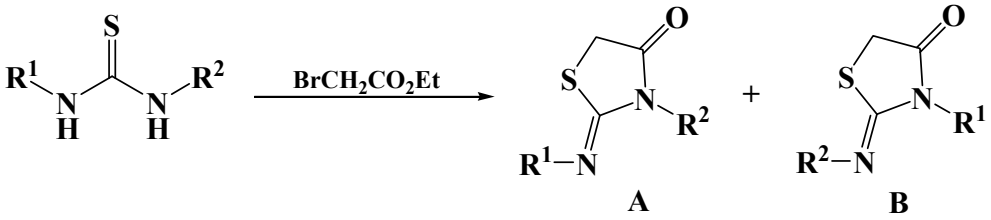


(3*R*,4*R*)-3a: R^1 = Ph; R^2 = *n*-hexyl
(3*R*,4*R*)-3b: R^1 = Ph; R^2 = cyclohexyl
(3*R*,4*R*)-3c: R^1 = Ph; R^2 = norbornyl
(3*R*,4*R*)-3d: R^1 = Ph; R^2 = Ph
(3*S*,4*S*)-3e: R^1 = Ph; R^2 = Ph
(3*R*,4*R*)-3f: R^1 = Ph; R^2 = 2-Cl-C_6H_4
(3*R*,4*R*)-3h: R^1 = Ph; R^2 = 2-F-C_6H_4
(3*R*,4*R*)-3m: R^1 = Ph; R^2 = 4-N_3-C_6H_4
(3*R*,4*R*)-3n: R^1 = Ph; R^2 = 4-NO_2-C_6H_4
(3*R*,4*R*)-3o: R^1 = Ph; R^2 = 4-NC-C_6H_4
(3*R*,4*R*)-3p: R^1 = Fc; R^2 = cyclohexyl
(3*R*,4*R*)-3q: R^1 = Fc; R^2 = Ph
(3*R*,4*R*)-3r: R^1 = Fc; R^2 = 2-Cl-C_6H_4
(3*R*,4*R*)-3s: R^1 = Fc; R^2 = 4-NO_2-C_6H_4

(3*R*,4*R*)-4a/4a': 67% (4a:4a'=23:77); R^1 = Ph; R^2 = *n*-hexyl
(3*R*,4*R*)-4b: 77%; R^1 = Ph; R^2 = cyclohexyl
(3*R*,4*R*)-4c: 99%; R^1 = Ph; R^2 = norbornyl
(3*R*,4*R*)-4d: 73%; R^1 = Ph; R^2 = Ph
(3*S*,4*S*)-4e: 62%; R^1 = Ph; R^2 = Ph
(3*R*,4*R*)-4f: 92%; R^1 = Ph; R^2 = 2-Cl-C_6H_4
(3*R*,4*R*)-4g: 90%; R^1 = Ph; R^2 = 2-F-C_6H_4
(3*R*,4*R*)-4h: 45%; R^1 = Ph; R^2 = 4-N_3-C_6H_4
(3*R*,4*R*)-4i: 96%; R^1 = Ph; R^2 = 4-NO_2-C_6H_4
(3*R*,4*R*)-4j: 84%; R^1 = Ph; R^2 = 4-NC-C_6H_4
(3*R*,4*R*)-4k: 70%; R^1 = Fc; R^2 = cyclohexyl
(3*R*,4*R*)-4l: 67%; R^1 = Fc; R^2 = Ph
(3*R*,4*R*)-4m: 57%; R^1 = Fc; R^2 = 2-Cl-C_6H_4
(3*R*,4*R*)-4n: 70%; R^1 = Fc; R^2 = 4-NO_2-C_6H_4

Scheme 2

The construction of the iminothiazolidinone ring relies on the reaction of thioureas with α-halo esters or acids in the presence of an inorganic base in a polar solvent. For unsymmetrical thioureas ($R^1 \neq R^2$, Scheme 3), regiocontrol in the cyclization step is influenced by electronic factors that predispose electron-withdrawing substituents (e.g. aryl or heteroaryl) to maintain conjugative stabilization with the imine nitrogen (e.g. R^1 in structure **A**, Scheme 3).[29] This electronic preference allows the regioselective cyclization of a thiourea bearing one alkyl and one aryl substituent or two aryl groups having significantly different electronic properties.[29,48,49] However, for substituents with no difference in electronic properties (e.g. $R^1 = R^2$ = alkyl) the reaction of an unsymmetrical thiourea with an α-halo ester or acid could be expected to proceed with minimal regioselectivity.[29]



Scheme 3

In our strategy to construct iminothiazolidinone ring we used unsymmetrical thioureas **3a-f**, **3h** and **3m-s** (R^1 = alkyl, aryl; R^2 = β-lactam) in the reaction with ethyl bromoacetate in acetonitrile at 40-60 °C, in the presence of sodium carbonate. The cyclization led exclusively to the formation of a single regioisomer **A** in the cases of iminothiazolidinones **4b-n**, (R^1 = cyclohexyl, *exo*-norbornyl, aryl; R^2 = β-lactam), whereas with less sterically hindered substances, R^1 = *n*-hexyl, the formation of **A** (minor) and **B** (major) iminothiazolidinone regioisomers **4a** (minor) and **4a'** (major) in the ratio 23:77 was observed. When the mixture of **4a/4a'** (in the ratio 23:77) was further subjected to prolonged heating (24 h) at 60 °C in acetonitrile and in the presence of sodium carbonate, the ratio of **4a/4a'** remained the same. Determination of the isomer ratio **4a** and **4a'** is based on the ^{1}H NMR spectra (Figure 1) and HPLC analyses. The structures of regioisomers **4a/a'-n** were determined by ^{1}H and ^{13}C NMR spectra analysis. The resonances of *n*-hexyl and β-lactam *C3-*H_a and *C4-*H_b protons allowed us to identify each regioisomer. In **4a'** the $CH_2(CH_2)_4CH_3$ protons appeared as a triplet resonating at higher chemical shift (3.75 ppm) than the same protons of **4a** (3.16 ppm). The chemical shifts are in accordance with the observation made by Ottanà and coworkers,[26] for $CH_2CH_2CH_3$ protons in the 2-imino-4-thiazolidinone regioisomers that they investigated. The β-lactam *C3-*H_a and *C4-*H_b protons of **4a'** appear as two well-separated dublets at 4.97 and 4.54 ppm, whereas for **4a** they appear as two very close dublets at 5.38 and 5.36 ppm, respectively (Figure 1, **I**). When ^{1}H NMR spectra was recorded in DMSO-d_6 the close doublets for the β-lactam *C3-*H_a and *C4-*H_b protons of **4a** are well-separated and appear at 5.42 and 5.25 ppm, respectively (Figure 1, **II**).

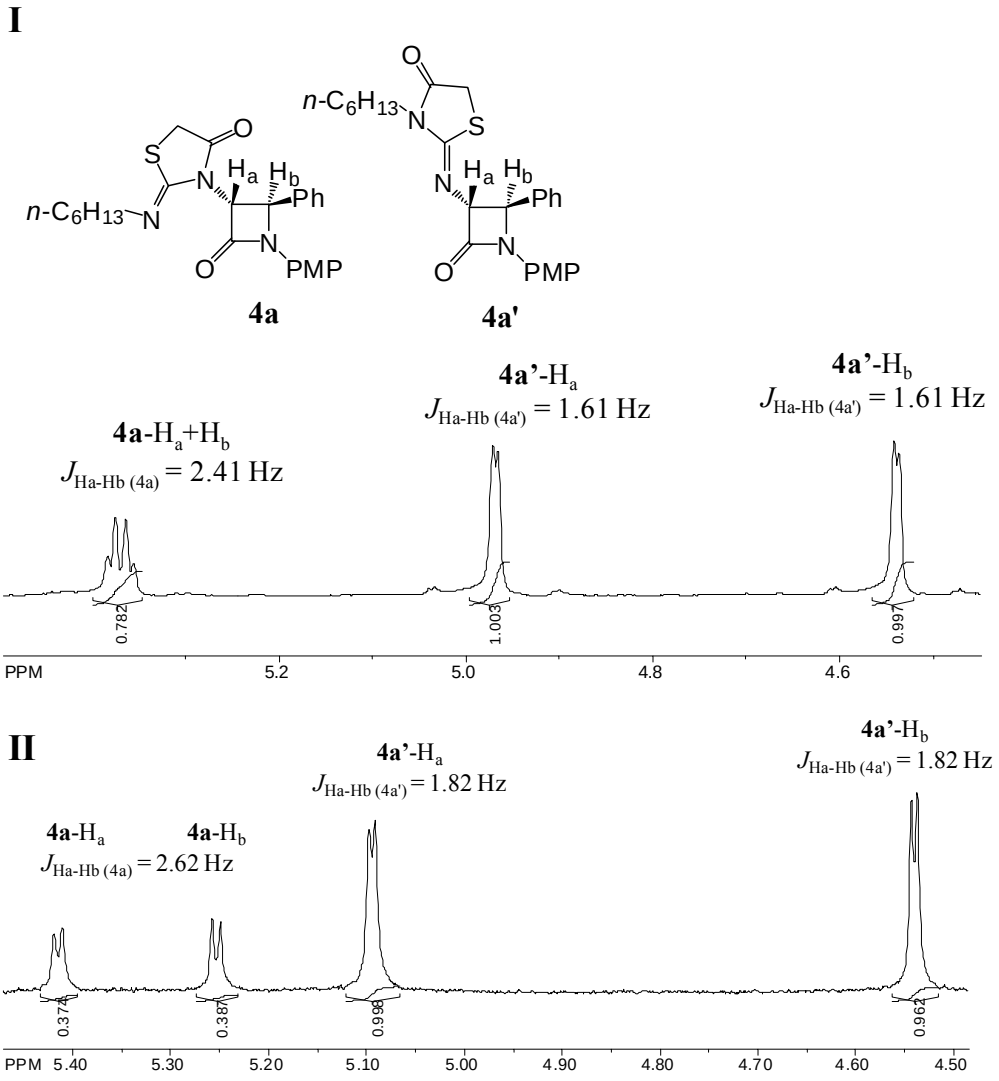
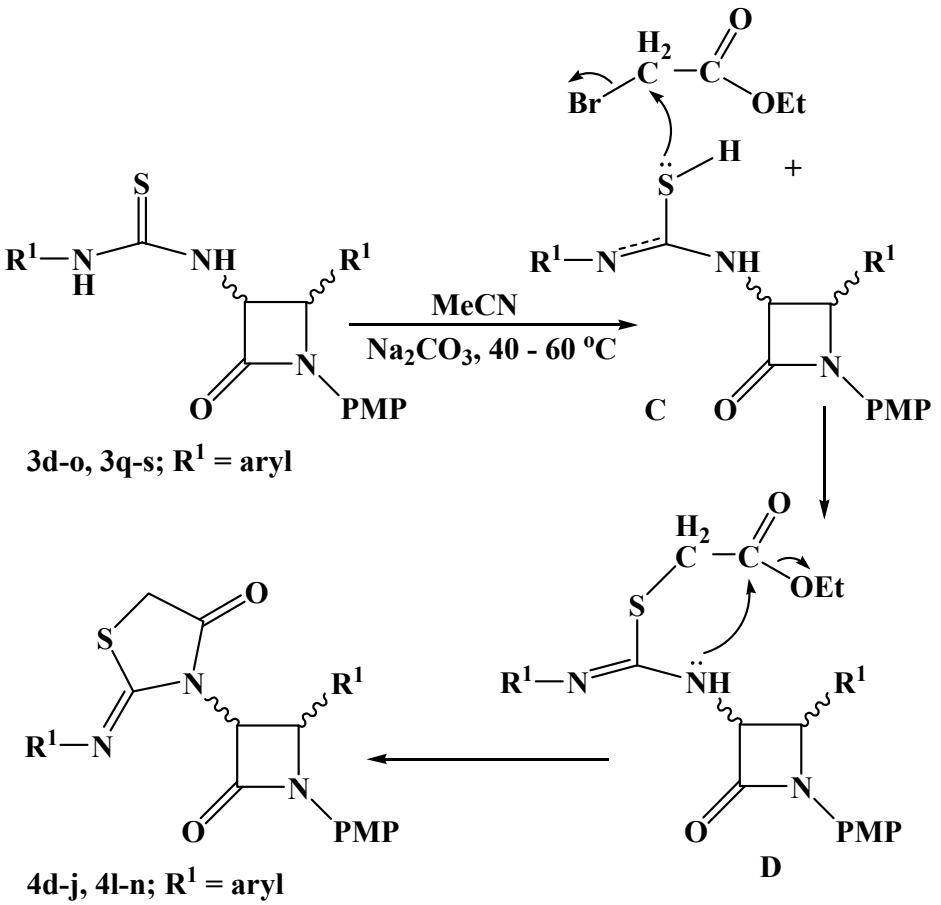


Figure 1 ^{1}H NMR spectra recorded in $CDCl_3$ (**I**) and DMSO-d_6 (**II**) of the β-lactam *C3-H*$_a$ and *C4-H*$_b$ protons in the mixture of iminothiazolidinone regioisomers **4a** and **4a'**

^{1}H NMR spectra analysis for iminothiazolidinones **4b-n**, (R^1 = cyclohexyl, *exo*-norbornyl, aryl; R^2 = β-lactam), revealed the formation of a single regioisomer **A**. The *CH* protons for **4b,c** appear as multiplets at 3.15 (cyclohexyl) and 3.09 (*exo*-norbornyl) ppm. The β-lactam *C3-H*$_a$ and *C4-H*$_b$ protons appear as very close doublets at 5.37 and 5.35 ppm for **4b** and 5.35 and 5.30 ppm for **4c**, respectively. ^{1}H NMR spectra analysis for iminothiazolidinones **4d-n**, (R^1 = aryl; R^2 = β-lactam), reveals the presence of a single set of doublets for the β-lactam *C3-H*$_a$ and *C4-H*$_b$ protons appearing in the area between 5.40-5.60 ppm, with exception of **4k** (R^1 = cyclohexyl; R^2 = β-lactam) where a single multiplet peak for the cyclohexyl *CH* proton is also observed at 3.16 ppm.

The formation of a single regioisomer **A** (Scheme 3) in the cases of the iminothiazolidinones **4d-j** and **4l-n** (Scheme 4) originated from the condensation of ethyl bromoacetate with the sulphur atom of the most

stable arylimino thiol intermediate **C**, generated from thioureas **3d-o** and **3q-s** (R^1 = aryl; R^2 = β-lactam), by delocalization of the lone pair on the nitrogen bearing aryl substituent on the adjacent thiocarbonyl group and followed by intramolecular cyclization of thus formed intermediate **D** (Scheme 4).



Scheme 4

However, with $R^1 = R^2$ = alkyl the reaction might be expected to proceed with minimal regioselectivity. When thioureas **3b-c** and **3p**, bearing sterically hindered alkyls (R^1 = cyclohexyl, *exo*-norbornyl; R^2 = β-lactam), are employed in the condensation with ethyl bromoacetate, we believe that the reaction proceeds *via* intermediate **E** (Figure 2) caused by delocalization of the lone pairs involving both nitrogens adjacent to the thiocarbonyl group. Furthermore, intermediate **E**, proceeds to intermediate **D**, leading to the formation of a single regioisomer **A** (Scheme 3) in the cases of iminothiazolidinones **4b**,**c** and **4k**. The condensation of thiourea **3a** (R^1 = *n*-hexyl; R^2 = β-lactam) with ethyl bromoacetate led to the formation of a mixture of two regioisomers **A** (minor) and **B** (major) of **4a/4a'** in the ratio 22:77. With the less sterically hindered alkyl compound (R^1 = *n*-hexyl), the condensation proceeded *via* intermediate **E**, followed by intramolecular cyclization with minimal regioselectivity *via* intermediates **D** (minor) and **F** (major) (Figure 2).

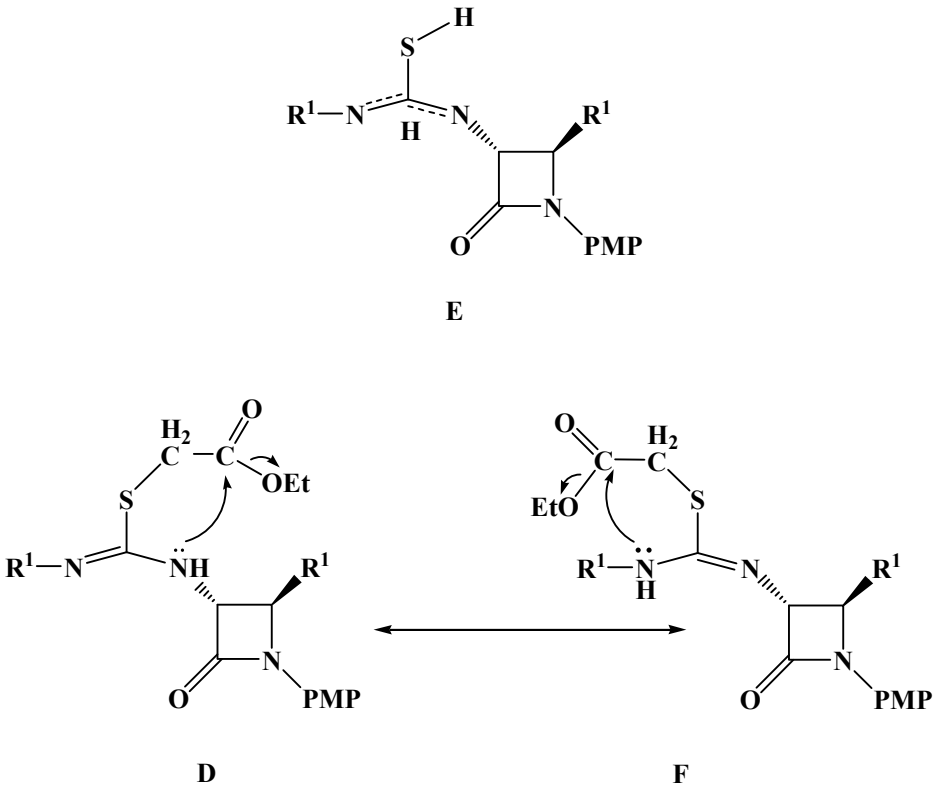
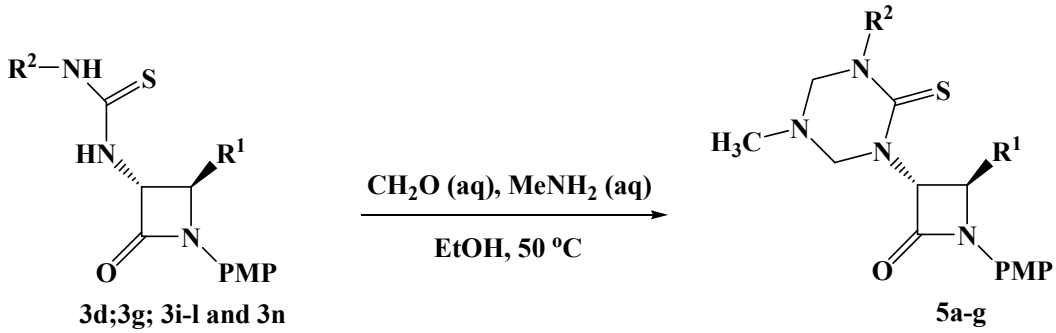


Figure 2 Intermediates **D**, **E** and **F**

Furthermore, a variety of triazinethiones **5a-g** (Scheme 5) were prepared from the corresponding thioureas **3d**, **3g**, **3i-l** and **3n** in a reaction with aqueous formaldehyde and methylamine. The reaction mixture was heated in ethanol at 50 °C for 48 h and the crude products were purified by column chromatography on silica gel.



(3*R*,4*R*)-3d: R^1 = Ph; R^2 = Ph
(3*R*,4*R*)-3g: R^1 = Ph; R^2 = 4-Cl-C_6H_4
(3*R*,4*R*)-3i: R^1 = Ph; R^2 = 4-F-C_6H_4
(3*R*,4*R*)-3j: R^1 = Ph; R^2 = 4-CF_3-C_6H_4
(3*R*,4*R*)-3k: R^1 = Ph; R^2 = 4-CF_3O-C_6H_4
(3*R*,4*R*)-3l: R^1 = Ph; R^2 = PMP
(3*R*,4*R*)-3n: R^1 = Ph; R^2 = 4-NO_2-C_6H_4

(3*R*,4*R*)-5a: 30%; R^1 = Ph; R^2 = Ph
(3*R*,4*R*)-5b: 27%; R^1 = Ph; R^2 = 4-Cl-C_6H_4
(3*R*,4*R*)-5c: 15%; R^1 = Ph; R^2 = 4-F-C_6H_4
(3*R*,4*R*)-5d: 24%; R^1 = Ph; R^2 = 4-CF_3-C_6H_4
(3*R*,4*R*)-5e: 29%; R^1 = Ph; R^2 = 4-CF_3O-C_6H_4
(3*R*,4*R*)-5f: 13%; R^1 = Ph; R^2 = PMP
(3*R*,4*R*)-5g: 36%; R^1 = Ph; R^2 = 4-NO_2-C_6H_4

Scheme 5

The reaction proceeded very slow. It needed 48 h to produce yields of 12-35% of triazinethiones **5a-g**. We believe that the basic aqueous-ethanolic media caused by an excess of methyl amine at elevated temperature (50 °C) created conditions that promoted β-lactam ring hydrolysis thus reducing the yields of the triazinethiones.

CONCLUSION

In summary, the amino functionality in enantiopure 3-amino-β-lactams represents a good point for extension of the β-lactam class and provides new possibilities in asymmetric synthesis and the development of methods for preparation of diverse substances potentially with a broad spectrum of pharmacological and biological application. To the best of our knowledge for the first time, we report the synthesis of new thiazolidinone and triazinethione conjugates derived from amino-β-lactams.

Thioureas **3a-s** (Scheme 1), generated from amino-β-lactams **1a-c**, were employed in two different cyclizations: (i) condensation with ethyl bromoacetate which resulted in the formation of a variety of iminothiazolidinones **4a/a'-n** (Scheme 2), and (ii) condensation with aqueous formaldehyde and methylamine which led to the formation of triazinethiones **5a-g** (Scheme 5).

EXPERIMENTAL

Melting points were determined on a Reichert Thermovar 7905 apparatus and are not corrected. The IR spectra were recorded on a Perkin Elmer Spectrum RX I FT-IR System spectrometer (KBr pellets technique). The ^{1}H and ^{13}C NMR spectra (in $CDCl_3$, CD_3OD and DMSO-d_6 at rt) were measured on a Bruker AV 300 and/or AV 600 spectrometer, δ in ppm relative to tetramethylsilane as the internal reference. Microanalyses were performed on a Perkin Elmer 2400 Series II CHNS/O Analyzer. Optical rotations: Optical Activity Automatic Polarimeter AA-10 in a 1 dm cell; *c* in g/100 mL. HPLC analyses were performed on a Knauer HPLC System supplied with Knauer UV/VIS WellChrom Diode Array Detector K-2800 using Macherey-Nagel 5μm Kromasil C18 4.0 × 250 mm HPLC column operated at a rt and a flow rate 1 mL/min; linear gradient of water containing 0.1% formic acid (solvent A) and MeOH (solvent B); 60% A + 40% B, 10 min; 40% A + 60% B, 5 min; 5% A + 95% B, 10 min. LC-MS spectra were recorded on a Waters LC-MS System equipped with a binary solvent pump (Waters 515 HPLC Pump), an autosampler (Waters 2767 Sample Manager, volume injection set to 20 μL), Waters 2996 Photodiode Array Detector and Waters Micromass ZQ Detector (2040 Da) with electrospray ionization (ESI) using Waters SunFire™, C18, 3.5 μm, 4.6 x 75 mm HPLC column operated at rt and a flow rate 3 mL/min; linear gradient of water containing 0.05% formic acid (solvent A) and MeCN (solvent B); 50% A + 50% B, 2.50 min; 5% A + 95% B, 0.90 min; 5% A + 95% B, 0.10 min; 50% A + 50% B, 1.50 min. Operating conditions of the ESI interface in positive ion mode were: source temperature 120 °C,

desolvation temperature 350 °C, cone gas flow 50 L/h, desolvation gas flow 700 L/h, capillary voltage 3000 V. Column chromatography was performed on a Merck's silica gel 60, 70-230 mesh, 60 Å at rt. Thin layer and preparative thin layer chromatographies were carried out on Merck's TLC aluminium sheets, 20 × 20 cm, silica gel 60 F_{254} and PLC plates, 20 × 20 cm, silica gel 60 F_{254}, 2 mm, respectively. Electrospray mass spectra (ESI-MS) of positive ions were performed on a Waters Q-TOF Premier mass spectrometer. Aqueous sodium formate was used for calibration. Acetonitrile-water (0.1% formic acid) sample solutions were injected at a flow rate 5 μL/min. Needle voltage was 2.0 kV and sample cone voltage varied from 20 to 40 V. Desolvation gas flow was at 600 L/h and desolvating temperature was varied from 80 and 150 ºC.

trans-3-Amino-β-lactams **1a-c** were prepared according to the literature.[11,12]

Preparation of thiuoreas 3a-s

General Procedure. – To a solution of a *trans*-3-amino-β-lactam (**1a-c**; 1.0 equiv) in MeCN (1.0 mL) was added dropwise a solution of an isothiocyanate (**2a-n**; 1.10 equiv) in MeCN (1.0 mL). The reaction mixture was stirred at rt for 24 h, followed by evaporation to dryness. Crude thioureas **3a-s** were purified by preparative thin layer chromatography or by silica gel column chromatography, using a mixture of EtOAc-petroleum ether (bp 40-70 ºC) in ratio 1:1 or 1:2 as eluent.

***N*-(*n*-Hexyl)-*N'*-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3a)**

Prepared from **1a** (40.0 mg, 1.49×10^{-1} mmol) and **2a** (23.50 mg, 25.0 μL, 1.64×10^{-1} mmol). Evaporation of the solvent and purification of the residue by means of preparative thin layer chromatography with EtOAc-petroleum ether (1:2) as the eluent, furnished thiourea **3a** as a yellow oil; yield: 33.0 mg (54%); $[\alpha]_D^{20}$ +68.03 (*c* 0.15, CH_2Cl_2); IR (KBr): 3249, 2924, 2853, 1730, 1652, 1498, 1468, 1446, 1409, 1342, 1246, 1228, 1184, 1026, 924, 829, 760, 706, 689, 556, 454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J_1 = J_2 = 6.32$ Hz, CH_3, *n*-hexyl), 1.26-1.37 (m, 8H, 4xCH_2, *n*-hexyl), 1.60 (m, 2H, CH_2N, *n*-hexyl), 3.70 (s, 3H, OCH_3, PMP), 4.96 (bs, 1H, C4, β-lactam), 5.33 (bs, 1H, C3, β-lactam), 6.65 (d, 2H, $J = 8.46$ Hz, PMP), 7.08 (d, 2H, $J = 8.82$ Hz, PMP), 7.29-7.45 (m, 7H, 5H-Ph and 2H-NHCSNH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.00 (C6, *n*-hexyl), 22.52 (C5, *n*-hexyl), 26.56 (C4 and C3, *n*-hexyl), 28.79 (C2, *n*-hexyl), 31.43 (C1, *n*-hexyl), 55.25 (OCH_3, PMP), 64.70 (C4, β-lactam), 68.84 (C3, β-lactam), 114.19 (C3 and C5, PMP), 118.92 (C2 and C6, PMP), 126.58 (C2 and C6, Ph), 128.78 (C4, Ph), 128.91 (C3 and C5, Ph), 129.94 (C1, Ph), 135.60 (C1, PMP), 156.52 (C4, PMP), 164.73 (CO), 180.76 (CS). HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{29}N_3O_2S$: 412.2059; found: 412.2049.

***N*-(Cyclohexyl)-*N'*-[*trans*-(3*R*,4*R*)-1-(4-metoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3b)**

Prepared from **1a** (90.0 mg, 3.35×10^{-1} mmol) and **2b** (52.10 mg, 50.6 μL, 3.69×10^{-1} mmol).

Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent, furnished thiourea **3b** as a white solid; yield: 99.0 mg (72%); mp 95-98 °C; $[\alpha]_D^{20}$ –60.58 (*c* 0.40, CH_2Cl_2); IR (KBr): 3678, 3651, 3630, 3292, 3062, 2931, 2853, 1732, 1612, 1516, 1453, 1396, 1300, 1248, 1177, 1145, 1067, 1030, 971, 945, 891, 863, 828, 797, 778, 751, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.84-0.87 (m, 1H, cyclohexyl), 1.20-1.27 (m, 2H, cyclohexyl), 1.37-1.39 (m, 2H, cyclohexyl), 1.61-1.73 (m, 3H, cyclohexyl), 2.04 (d, 2H, *J* = 10.08 Hz, cyclohexyl), 3.69 (s, 3H, OCH_3, PMP), 4.07 (bs, 1H, C1, cyclohexyl), 4.91 (s, 1H, C4, β-lactam), 5.30 (bs, 1H, C3, β-lactam), 6.63 (bs, 2H, PMP), 7.06 (d, 2H, *J* = 7.08 Hz, PMP), 7.32-7.38 (m, 6H, 5H-Ph and 1H-NH-β-lactam), 7.43 (bs, 1H, NHCS); ^{13}C NMR (150 MHz, $CDCl_3$): δ 24.65, 24.68 (C3 and C5, cyclohexyl), 25.39 (C4, cyclohexyl), 32.61, 32.68 (C2 and C6, cyclohexyl), 55.25 (OCH_3, PMP), 55.40 (C1, cyclohexyl), 64.84 (C4, β-lactam), 68.78 (C3, β-lactam), 114.18 (C3 and C5, PMP), 118.89 (C2 and C6, PMP), 126.61 (C2 and C6, Ph), 128.77 (C4, Ph), 128.90 (C3 and C5, Ph), 129.93 (C1, Ph), 135.59 (C1, PMP), 156.51 (C4, PMP), 164.66 (CO), 181.77 (CS). Anal. Calcd for $C_{23}H_{27}N_3O_2S$: C, 67.45; H, 6.64; N, 10.26; S, 7.83. Found: C, 67.46; H, 6.92; N, 9.90; S, 7.62.

_N_-(_exo_-Norbornyl)-_N'_-[_trans_-(3_R_,4_R_)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3c)

Prepared from **1a** (70.0 mg, 2.61×10^{-1} mmol) and **2c** (44.0 mg, 2.87×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3c** as a white solid; yield: 103.0 mg (94%); mp 95-98 °C; $[\alpha]_D^{20}$ –39.29 (*c* 0.28, CH_2Cl_2); IR (KBr): 3651, 3630, 3294, 2953, 2870, 1735, 1511, 1248, 828, 750, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (m, 1H, norbornyl), 1.13-1.55 (m, 6H, norbornyl), 1.72 (m, 1H, norbornyl), 1.81-1.91 (m, 1H, norbornyl), 2.32 (m, 2H, norbornyl), 3.69 (s, 3H, OCH_3, PMP), 4.92 (bs, 1H, C4, β-lactam), 5.35 (bs, 1H, C3, β-lactam), 6.63 (d, 2H, *J* = 8.04 Hz, PMP), 7.06 (d, 2H, *J* = 8.67 Hz, PMP), 7.33-7.42 (m, 7H, 5H-Ph and 2H-N<u>H</u>CSN<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.27 (C3, norbornyl), 28.14 (C4, norbornyl), 40.28 (C6 and C7, norbornyl), 42.18 (C2 and C5, norbornyl), 55.25 (OCH_3, PMP), 64.75 (C1, norbornyl), 64.82 (C4, β-lactam), 68.90 (C3, β-lactam), 114.16 (C3 and C5, PMP), 118.88 (C2 and C6, PMP), 126.62 (C2 and C6, Ph), 128.74 (C4, Ph), 128.88 (C3 and C5, Ph), 129.95 (C1, Ph), 135.62 (C1, PMP), 156.46 (C4, PMP), 164.59 (CO), 182.04 (CS). Anal. Calcd for $C_{24}H_{27}N_3O_2S$: C, 68.38; H, 6.46; N, 9.97; S, 7.61. Found: C, 68.74; H, 6.66; N, 9.57; S, 7.48.

_N_-Phenyl-_N'_-[_trans_-(3_R_,4_R_)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3d)

Prepared from **1a** (50.0 mg, 1.86×10^{-1} mmol) and **2d** (27.70 mg, 24.2 μL, 2.05×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3d** as a white solid; yield: 72.0 mg, (96%); mp 91-

95 °C; $[\alpha]_D^{20}$ –47.36 (*c* 0.78, CH_2Cl_2); IR (KBr): 3651, 3630, 3234, 1735, 1513, 1248, 1029, 828, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3, PMP), 4.96 (d, 1H, J = 1.65 Hz, C4, β-lactam), 5.27 (dd, 1H, J_1 = 1.44 Hz, J_2 = 5.01 Hz, C3, β-lactam), 6.65 (d, 2H, J = 8.94 Hz, PMP), 6.68 (m, 1H, NH-β-lactam), 7.08 (d, 2H, J = 8.94 Hz, PMP), 7.33-7.45 (m, 10H, 5H-PhN and 5H-Ph-β-lactam), 8.33 (bs, 1H, PhNH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.26 (OCH_3, PMP), 64.58 (C4, β-lactam), 69.14 (C3, β-lactam), 114.16 (C3 and C5, PMP), 118.84 (C2 and C6, PMP), 125.26 (C2 and C6, PhN), 126.72 (C2 and C6, Ph-β-lactam), 127.42 (C4, PhN), 128.71 (C4, Ph-β-lactam), 128.82 (C3 and C5, Ph-β-lactam), 130.06 (C3 and C5, PhN), 130.12 (C1, Ph-β-lactam), 135.83 (C1, PMP), 136.16 (C1, PhN), 156.38 (C4, PMP), 163.22 (CO), 181.38 (CS). Anal. Calcd for $C_{23}H_{21}N_3O_2S$: C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.64; H, 5.17; N, 10.22; S, 8.19.

_N_-Phenyl-_N'_-[*trans*-(3*S*,4*S*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3e)

Prepared from **1b** (30.0 mg, 1.12×10^{-1} mmol) and **2d** (16.60 mg, 15.4 μL, 1.23×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3e** as a white solid; yield: 44.0 mg, (98%); mp 91-95 °C; $[\alpha]_D^{20}$ +48.22 (*c* 0.80, CH_2Cl_2); IR (KBr): 3651, 3630, 3234, 1735, 1513, 1248, 1029, 828, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H, OCH_3, PMP), 4.98 (d, 1H, J = 1.65 Hz, C4, β-lactam), 5.27 (dd, 1H, J_1 = 1.65 Hz, J_2 = 5.82 Hz, C3, β-lactam), 6.66 (d, 2H, J = 8.94 Hz, PMP), 6.69 (m, 1H, NH-β-lactam), 7.10 (d, 2H, J = 8.91 Hz, PMP), 7.30-7.44 (m, 10H, 5H-PhN and 5H-Ph-β-lactam), 8.43 (bs, 1H, NH-Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.27 (OCH_3, PMP), 64.56 (C4, β-lactam), 69.13 (C3, β-lactam), 114.20 (C3 and C5, PMP), 118.88 (C2 and C6, PMP), 125.19 (C2 and C6, PhN), 126.73 (C2 and C6, Ph-β-lactam), 127.37 (C4, PhN), 128.71 (C4, Ph-β-lactam), 128.82 (C3 and C5, Ph-β-lactam), 130.03 (C3 and C5, PhN), 130.13 (C1, Ph-β-lactam), 135.84 (C1, PhN), 136.21 (C1, PMP), 156.41 (C4, PMP), 163.23 (CO), 181.32 (CS). Anal. Calcd for $C_{23}H_{21}N_3O_2S$: C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.49; H, 5.18; N, 10.29; S, 8.09.

_N_-(2-Chlorophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3f)

Prepared from **1a** (91.0 mg, 3.39×10^{-1} mmol) and **2e** (63.30 mg, 49.5 μL, 3.73×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3f** as a white solid; yield: 139.0 mg, (94%), mp 75-77 °C; $[\alpha]_D^{20}$ –37.95 (*c* 0.32, CH_2Cl_2); IR (KBr): 3678, 3651, 3631, 3234, 2930, 1735, 1512, 1389, 1299, 1248, 1171, 1137, 1030, 827, 751, 733, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H, OCH_3, PMP), 4.92 (d, 1H, J = 1.68 Hz, C4, β-lactam), 5.28 (dd, 1H, J_1 = 1.53 Hz, J_2 = 6.29 Hz, C3, β-lactam), 6.64 (d, 2H, J = 9.00 Hz, PMP), 7.07 (d, 2H, J = 9.00 Hz, PMP), 7.29-7.40 (m, 7H, 5H-Ph-β-lactam and

2H-ClPh), 7.47 (dd, 1H, J_1 = 1.43 Hz, J_2= 7.96 Hz, ClPh), 7.65 (d, 1H, J = 6.30 Hz, NH-β-lactam), 7.75 (dd, 1H, J_1 = 1.35 Hz, J_2 = 7.94 Hz, ClPh), 8.15 (bs, 1H, NHCS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.27 (OCH_3, PMP), 64.93 (C4, β-lactam), 69.00 (C3, β-lactam), 114.17 (C3 and C5, PMP), 118.94 (C2 and C6, PMP), 126.73 (C2 and C6, Ph), 127.48 (C4, ClPh), 127.84 (C5, ClPh), 127.98 (C6, ClPh), 128.72 (C4, Ph), 128.79 (C3 and C5, Ph), 129.50 (C2, ClPh), 129.93 (C1, Ph), 130.35 (C3, ClPh), 134.05 (C1, ClPh), 135.67 (C1, PMP), 156.49 (C4, PMP), 163.53 (CO), 181.75 (CS). Anal. Calcd for $C_{23}H_{20}N_3O_2SCl$: C, 63.08; H, 4.60; N, 9.59; S, 7.32. Found: C, 63.44; H, 4.98; N, 9.34; S, 7.55.

_N_-(4-Chlorophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3g)

Prepared from **1a** (40.0 mg, 1.49 × 10^{-1} mmol) and **2f** (28.0 mg, 1.64 × 10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3g** as a yellow solid; yield: 61.0 mg, (94%); mp 80-84 °C; $[\alpha]_D^{20}$ +27.74 (*c* 0.14, CH_2Cl_2); IR (KBr): 3630, 3568, 1742, 1498, 1468, 1438, 1250, 1094, 824, 733, 683 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 3.68 (s, 3H, OCH_3, PMP), 5.15 (d, 1H, J = 1.98 Hz, C4, β-lactam), 5.26 (d, 1H, J = 1.92 Hz, C3, β-lactam), 6.70 (m, 2H, 2H-PhCl), 6.78 (d, 2H, J = 8.97 Hz, PMP), 7.19 (d, 2H, J = 8.97 Hz, PMP), 7.28-7.50 (m, 7H, 5H-Ph, 2H-PhCl); ^{13}C NMR (75 MHz, CD_3OD): δ 55.85 (OCH_3, PMP), 65.01 (C4, β-lactam), 70.24 (C3, β-lactam), 115.29 (C3 and C5, PMP), 120.25 (C2 and C6, PMP), 126.90 (C2 and C6, PhCl), 127.75 (C2 and C6, Ph), 129.61 (C4, Ph), 129.94 (C3 and C5, Ph), 130.00 (C3 and C5, PhCl), 131.82 (C1, Ph), 131.85 (C4, PhCl), 138.05 (C1, PMP), 138.58 (C1, PhCl), 158.01 (C4, PMP), 165.98 (CO), 183.21 (CS). HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{23}H_{20}N_3O_2SCl$: 438.1043; found: 438.1060.

_N_-(2-Fluorophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3h)

Prepared from **1a** (90.0 mg, 3.35 × 10^{-1} mmol) and **2g** (56.50 mg, 46.2 μL, 3.69 × 10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3h** as a yellow solid; yield: 98.0 mg, (66%); mp 99-102 °C; $[\alpha]_D^{20}$ –34.98 (*c* 0.46, CH_2Cl_2); IR (KBr): 3678, 3651, 3630, 3226, 2952, 2835, 1732, 1514, 1455, 1388, 1300, 1251, 1178, 1138, 1101, 1067, 1030, 827, 754, 698 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.67 (s, 3H, OCH_3, PMP), 4.92 (bs, 1H, C4, β-lactam), 5.29 (bs, 1H, C3, β-lactam), 6.61 (d, 2H, J = 8.58 Hz, PMP), 7.03 (d, 2H, J = 8.64 Hz, PMP), 7.16-7.26 (m, 3H, 1H-NH-β-lactam and 2H-FPh), 7.34-7.36 (m, 5H, Ph), 7.69-7.76 (m, 2H, FPh), 8.31 (bs, 1H, NHCS); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.28 (OCH_3, PMP), 64.82 (C4, β-lactam), 69.00 (C3, β-lactam), 114.20 (C3 and C5, PMP), 116.58 (d, J = 19.94 Hz, C3, FPh), 118.97 (C2 and C6, PMP), 124.89 (d, J = 3.79 Hz, C5, FPh,), 126.74 (C2 and C6, Ph), 127.21 (C6, FPh), 128.32 (d, J = 7.28 Hz, C4, FPh,), 128.74 (C4, Ph), 128.80 (C3 and C5, Ph), 129.94 (C1, Ph),

135.68 (C1, PMP), 135.75 (C1, FPh), 156.13 (d, J = 249.15 Hz, C2, FPh,), 156.51 (C4, PMP), 163.49 (CO), 181.89 (CS). Anal. Calcd for $C_{23}H_{20}N_3O_2SF$: C, 65.54; H, 4.78; N, 9.97; S, 7.61. Found: C, 65.51; H, 4.82; N, 9.95; S, 7.85.

_N_-(4-Fluorophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3i)

Prepared from **1a** (100.0 mg, 3.73×10^{-1} mmol) and **2h** (62.8 mg, 4.10×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3i** as a yellow solid; yield: 140.0 mg, (89%); mp 89-93 °C; $[\alpha]_D^{20}$ –12.82 (*c* 0.16, CH_2Cl_2); IR (KBr): 3220, 2953, 1734, 1511, 1455, 1249, 1217, 1152, 1067, 1029, 882, 750, 697, 538, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 3H, OCH_3, PMP), 4.94 (bs, 1H, C4, β-lactam), 5.34-5.36 (m, 1H, C3, β-lactam), 6.58 (d, 2H, J = 8.70 Hz, PMP), 7.00 (d, 2H, J = 8.79 Hz, PMP), 7.08 (t, 2H, $J_1 = J_2$ = 8.40 Hz, FPh), 7.27-7.35 (m, 7H, 5H-Ph-β-lactam and 2H-FPh), 7.43 (m, 1H, NH-β-lactam), 8.53 (bs, 1H, FPh-NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.19 (OCH_3, PMP), 64.53 (C4, β-lactam), 68.99 (C3, β-lactam), 114.09 (C3 and C5, PMP), 116.73 (d, J = 22.94 Hz, C3 and C5, FPh), 118.81 (C2 and C6, PMP), 126.59 (C2 and C6, Ph-β-lactam), 127.83 (d, J = 8.30 Hz, C2 and C6, FPh), 128.78 (C4, Ph-β-lactam), 128.91 (C3 and C5, Ph-β-lactam), 129.92 (C1, Ph-β-lactam), 132.22 (d, J = 3.10 Hz, C1, FPh), 135.69 (C1, PMP), 156.41 (C4, PMP), 161.41 (d, J = 247.91 Hz, C4, FPh), 163.66 (CO), 181.80 (CS). HRMS: m/z $[M+H]^+$ calcd for $C_{23}H_{20}N_3O_2SF$: 422.1339; found: 422.1325.

_N_-(4-Trifluoromethylphenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]-thiourea (3j)

Prepared from **1a** (50.0 mg, 1.86×10^{-1} mmol) and **2i** (41.5 mg, 2.05×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3j** as a yellow solid; yield: 85.6 mg, (97%); mp 105-107 °C; $[\alpha]_D^{20}$ +43.71 (*c* 0.11, CH_2Cl_2); IR (KBr): 3461, 2925, 1744, 1513, 1468, 1326, 1249, 1109, 1067, 827, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.69 (s, 3H, OCH_3, PMP), 5.10 (bs, 1H, C4, β-lactam), 5.26-5.27 (m, 1H, C3, β-lactam), 6.66 (d, 2H, J = 8.94 Hz, PMP), 7.08 (d, 2H, J = 8.91 Hz, PMP), 7.37 (s, 5H, Ph-β-lactam), 7.57 (s, 4H, CF_3Ph), 7.78 (bs, 1H, NH-β-lactam), 8.69 (bs, 1H, CF_3Ph-NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.28 (OCH_3, PMP), 64.31 (C4, β-lactam), 68.70 (C3, β-lactam), 114.29 (C3 and C5, PMP), 119.09 (C2 and C6, PMP), 123.53 (d, J = 273.45 Hz, CF_3), 123.86 (C2 and C6, CF_3Ph), 126.49 (d, J = 3.79 Hz, C3 and C5, CF_3Ph), 126.61 (C2 and C6, Ph-β-lactam), 127.88 (d, J = 33.31 Hz, C4, CF_3Ph), 128.97 (C4, Ph-β-lactam), 129.01 (C3 and C5, Ph-β-lactam), 129.76 (C1, Ph-β-lactam), 135.45 (C4, PMP), 140.55 (d, J = 1.41 Hz, CF_3Ph), 156.74 (C1, PMP), 164.17 (CO), 181.36 (CS). Anal. Calcd for $C_{24}H_{20}N_3O_2SF_3$: C, 61.14; H, 4.28; N, 8.91; S, 6.80. Found: C, 61.33; H, 4.63; N, 8.78; S, 6.57.

_N_-(4-Trifluoromethoxyphenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3k)

Prepared from **1a** (67.0 mg, 2.50×10^{-1} mmol) and **2j** (45.0 mg, 2.75×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3k** as a yellow solid; yield: 102.2 mg, (84%); mp 92-94 °C; $[\alpha]_D^{20}$ +22.43 (*c* 0.22, CH_2Cl_2); IR (KBr): 3220, 2926, 1744, 1513, 1469, 1256, 1204, 1150, 827, 761, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3, PMP), 4.95 (d, 1H, J = 1.68 Hz, C4, β-lactam), 5.44 (m, 1H, C3, β-lactam), 6.56 (d, 2H, J = 8.94 Hz, PMP), 6.66-6.78 (m, 2H, CF_3OPh), 6.97 (d, 2H, J = 8.94 Hz, PMP), 7.24 (d, 2H, J = 8.49 Hz, CF_3OPh), 7.36 (s, 5H, Ph-β-lactam), 7.83 (m, 1H, NH-β-lactam), 8.99 (bs, 1H, CF_3OPh-NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.11 (OCH_3, PMP), 64.46 (C4, β-lactam), 68.77 (C3, β-lactam), 114.01 (C3 and C5, PMP), 118.80 (C2 and C6, PMP), 120.39 (CF_3O), 122.14 (C2 and C6, CF_3OPh), 126.46 (C2 and C6, Ph-β-lactam), 127.03 (C3 and C5, CF_3OPh), 128.81 (C4, Ph-β-lactam), 128.92 (C3 and C5, Ph-β-lactam), 132.52 (C1, Ph-β-lactam), 135.08 (C1, CF_3OPh), 135.53 (C4, PMP), 147.55 (d, J = 8.31 Hz, CF_3OPh), 156.41 (C1, PMP), 164.00 (CO), 181.56 (CS). Anal. Calcd for $C_{24}H_{20}N_3O_3SF_3$: C, 59.13; H, 4.14; N, 8.62; S, 6.58. Found: C, 59.22; H, 4.54; N, 8.37; S, 6.31.

_N_-(4-Methoxyphenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3l)

Prepared from **1a** (40.0 mg, 1.49×10^{-1} mmol) and **2k** (27.10 mg, 23.0 μL, 1.64×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3l** as a yellow solid; yield: 63.6 mg, (99%); mp 96-100 °C; $[\alpha]_D^{20}$ +47.69 (*c* 0.13, CH_2Cl_2); IR (KBr): 3650, 3630, 1735, 1654, 1560, 1509, 1246, 1028, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3, PMP-2), 3.77 (s, 3H, OCH_3, PMP-1), 4.91 (d, 1H, J = 1.80 Hz, C4, β-lactam), 5.25 (dd, 1H, J_1 = 1.74 Hz, J_2 = 6.69 Hz, C3, β-lactam), 6.62 (d, 2H, J = 9.06 Hz, PMP-2), 6.95 (d, 2H, J = 8.88 Hz, PMP-1), 7.05 (d, 2H, J = 9.03 Hz, PMP-1), 7.22 (d, 2H, J = 8.82 Hz, PMP-2), 7.33-7.38 (m, 6H, 5H-Ph-β-lactam and 1H-NH-β-lactam), 8.09 (bs, 1H, PMP-2-NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.23 (OCH_3, PMP-2), 55.53 (OCH_3, PMP-1), 64.71 (C4, β-lactam), 69.30 (C3, β-lactam), 114.11 (C3 and C5, PMP-1), 115.32 (C3 and C5, PMP-2), 118.77 (C2 and C6, PMP-1), 126.69 (C2 and C6, PMP-2), 127.80 (C2 and C6, Ph-β-lactam), 128.28 (C1, PMP-2), 128.67 (C4, Ph-β-lactam), 128.80 (C3 and C5, Ph-β-lactam), 130.17 (C1, Ph-β-lactam), 135.99 (C1, PMP-1), 156.32 (C4, PMP-1), 159.11 (C4, PMP-2), 163.14 (CO), 181.96 (CS). Anal. Calcd for $C_{24}H_{23}N_3O_3S$: C, 66.49; H, 5.35; N, 9.69; S, 7.40. Found: C, 66.79; H, 5.76; N, 9.39; S, 7.13.

_N_-(4-Azidophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3m)

Prepared from **1a** (51.0 mg, 1.91×10^{-1} mmol) and **2l** (37.0 mg, 2.10×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3m** as a yellow solid; yield: 71.0 mg, (85%); mp 190-193 °C; $[\alpha]_D^{20}$ +58.08 (*c* 0.21, CH_2Cl_2); IR (KBr): 3630, 3386, 2123, 2088, 1742, 1654, 1638, 1511, 1468, 1439, 1420, 1289, 1248, 1182, 987, 827, 760, 740, 711, 683, 513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3, PMP), 4.97 (d, 1H, J = 1.86 Hz, C4, β-lactam), 5.29-5.32 (m, 1H, C3, β-lactam), 6.62 (d, 2H, J = 9.00 Hz, PMP), 7.02-7.06 (m, 4H, 2H-PMP and 2H-N_3Ph), 7.32 (d, 2H, J = 8.73 Hz, N_3Ph), 7.36 (m, 5H, Ph), 7.43 (m, 1H, NH-β-lactam), 8.51 (bs, 1H, NHCS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.24 (OCH_3, PMP), 64.51 (C4, β-lactam), 68.99 (C3, β-lactam), 114.15 (C3 and C5, PMP), 118.87 (C2 and C6, PMP), 120.23 (C2 and C6, N_3Ph), 126.61 (C2 and C6, Ph), 126.99 (C3 and C5, N_3Ph), 128.82 (C4, Ph), 129.91 (C3 and C5, Ph), 129.94 (C1, Ph), 133.08 (C1, N_3Ph), 135.66 (C1, PMP), 138.98 (C4, N_3Ph), 156.46 (C4, PMP), 163.63 (CO), 181.56 (CS). HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{23}H_{20}N_6O_2S$: 467.1266; found: 467.1263.

N-(4-Nitrophenyl)-*N'*-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3n)

Prepared from **1a** (80.0 mg, 2.98×10^{-1} mmol) and **2m** (59.4 mg, 23.28×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3n** as a yellow solid; yield: 107.0 mg, (81%); mp 120-122 °C; $[\alpha]_D^{20}$ +30.95 (*c* 0.58, CH_2Cl_2); IR (KBr): 3677, 3651, 3630, 3327, 3064, 2933, 2834, 1730, 1598, 1513, 1454, 1440, 1401, 1330, 1111, 1030, 848, 828, 750, 698 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.70 (s, 3H, OCH_3, PMP), 5.21 (bs, 2H, 1H-C4-β-lactam and 1H-C3-β-lactam), 6.68 (d, 2H, J = 8.82 Hz, PMP), 7.10 (d, 2H, J = 8.82 Hz, PMP), 7.38 (bs, 5H, Ph), 7.74 (d, 2H, J = 8.88 Hz, NO_2Ph), 8.11 (m, 3H, 2H-NO_2Ph and 1H-NH-β-lactam), 9.05 (bs, 1H, NHCS); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.33 (OCH_3, PMP), 64.15 (C4, β-lactam), 68.38 (C3, β-lactam), 114.41 (C3 and C5, PMP), 119.28 (C2 and C6, PMP), 122.09 (C2 and C6, NO_2Ph), 124.61 (C3 and C5, NO_2Ph), 126.59 (C2 and C6, Ph), 127.69 (C4, Ph), 129.10 (C3 and C5, Ph), 129.51 (C1, Ph), 135.15 (C1, PMP), 144.00 (C1, NO_2Ph), 144.15 (C4, NO_2Ph), 157.01 (C4, PMP), 164.51 (CO), 180.99 (CS). Anal. Calcd for $C_{23}H_{20}N_4O_4S$: C, 61.59; H, 4.49; N, 12.49; S, 7.15. Found: C, 61.50; H, 4.58; N, 12.44; S, 7.40.

N-(4-Cyanophenyl)-*N'*-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-phenylazetidin-3-yl]thiourea (3o)

Prepared from **1a** (85.0 mg, 3.17×10^{-1} mmol) and **2n** (56.1 mg, 3.49×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3o** as a yellow solid; yield: 131.0 mg, (97%); mp 123-126 °C; $[\alpha]_D^{20}$ +14.05 (*c* 0.50, CH_2Cl_2); IR (KBr): 3319, 2949, 2225, 1725, 1605, 1510, 1404, 1302, 1251, 1147, 1033, 945, 824,

742, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 3H, OCH_3, PMP), 5.16 (d, 1H, J = 1.80 Hz, C4, β-lactam), 5.23 (bs, 1H, C3, β-lactam), 6.67 (d, 2H, J = 9.03 Hz, PMP), 7.10 (d, 2H, J = 9.00 Hz, PMP), 7.38 (bs, 5H, Ph), 7.55 (d, 2H, J = 8.82 Hz, CNPh), 7.65 (d, 2H, J = 8.76 Hz, CNPh), 8.00 (bs, 1H, NH-β-lactam), 8.89 (bs, 1H, NHCS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.31 (OCH_3, PMP), 64.18 (C4, β-lactam), 68.41 (C3, β-lactam), 108.19 (CN), 114.34 (C3 and C5, PMP), 118.58 (C4, CNPh), 119.18 (C2 and C6, PMP), 122.91 (C2 and C6, CNPh), 126.57 (C2 and C6, Ph), 129.05 (C3 and C5, Ph), 129.55 (C1, Ph), 129.61 (C4, Ph), 132.99 (C3 and C5, CNPh), 135.19 (C1, PMP), 142.12 (C1, CNPh), 156.89 (C4, PMP), 164.52 (CO), 181.01 (CS). HRMS: m/z $[M+Na]^+$ calcd for $C_{24}H_{20}N_4O_2S$: 451.1205; found 451.1209.

_N_-(Cyclohexyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-ferrocenylazetidin-3-yl]thiourea (3p)

Prepared from **1c** (36.6 mg, 9.72×10^{-2} mmol) and **2b** (15.10 mg, 14.6 μL, 1.07×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3p** as a brown solid; yield: 36.0 mg, (72%); mp 86-87 °C; $[\alpha]_D^{20}$ +287.08 (c 0.02, CH_2Cl_2); IR (KBr): 3294, 2925, 2850, 1726, 1512, 1464, 1450, 1298, 1247, 1178, 1029, 1001, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.83-0.92 (m, 1H, cyclohexyl), 1.11-1.44 (m, 5H, cyclohexyl), 1.59-1.63 (m, 1H, cyclohexyl), 1.68-1.78 (m, 2H, cyclohexyl), 2.04-2.17 (m, 2H, cyclohexyl), 3.75 (s, 3H, OCH_3, PMP), 4.10-4.20 (m, 4H, Fc), 4.22 (s, 5H, Fc), 4.50 (d, J = 0.84 Hz, 1H, C4, β-lactam), 5.30 (bs, 1H, C3, β-lactam), 6.19 (bs, 1H, NH-cyclohexyl), 6.65 (d, 2H, J = 6.93 Hz, PMP), 7.07 (d, 2H, J = 8.01 Hz, PMP), 7.45 (bs, 1H, NHCS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.78, 24.82 (C3 and C5, cyclohexyl), 25.41 (C4, cyclohexyl), 32.52, 32.79 (C2 and C6, cyclohexyl), 55.26 (OCH_3, PMP), 55.40 (C1, cyclohexyl), 60.99 (C4, β-lactam), 66.09 (C3, β-lactam), 66.67, 68.23, 68.89, 68.98, 70.22, 82.75 (Fc), 114.03 (C3 and C5, PMP), 119.88 (C2 and C6, PMP), 129.45 (C1, PMP), 156.60 (C4, PMP), 166.54 (CO), 175.35 (CS). Anal. Calcd for $C_{27}H_{31}N_3O_2SFe$: C, 62.67; H, 6.04; N, 8.12; S, 6.20. Found: C, 63.00; H, 6.45; N, 7.73; S, 6.39.

_N_-Phenyl-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-ferrocenylazetidin-3-yl]thiourea (3q)

Prepared from **1c** (55.0 mg, 1.46×10^{-1} mmol) and **2d** (21.80 mg, 20.0 μL, 1.61×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3q** as a brown solid; yield: 71.0 mg, (96%); mp 123-126 °C; $[\alpha]_D^{20}$ –116.05 (c 0.10, CH_2Cl_2); IR (KBr): 3651, 3630, 3227, 2953, 1734, 1514, 1248, 1034, 693 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3, PMP), 4.15-4.22 (m, 9H, Fc), 4.56 (bs, 1H, C4, β-lactam), 4.83 (bs, 1H, C3, β-lactam), 6.01 (bs, 1H, NH-β-lactam), 6.70 (d, 2H, J = 8.46Hz, PMP), 7.13 (d, 2H, J = 8.46 Hz, PMP), 7.26-7.42 (m, 5H, Ph), 8.38 (bs, 1H, NH-Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.33 (OCH_3, PMP), 60.39 (C4, β-lactam), 66.73 (C3, β-lactam), 68.24, 68.71, 68.84, 68.98,

70.07, 83.42 (Fc), 114.14 (C3 and C5, PMP), 120.03 (C2 and C6, PMP), 125.68 (C2 and C6, Ph), 127.26 (C4, Ph), 129.76 (C1, Ph), 129.82 (C3 and C5, Ph), 136.59 (C1, PMP), 156.59 (C4, PMP), 164.79 (CO), 181.69 (CS). Anal. Calcd for $C_{27}H_{25}N_3O_2SFe$: C, 63.41; H, 4.93; N, 8.22; S, 6.27. Found: C, 63.86; H 4.77; N, 7.98; S, 5.97.

_N_-(2-Chlorophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-ferrocenylazetidin-3-yl]-thiourea (3r)

Prepared from **1c** (22.0 mg, 5.80×10^{-2} mmol) and **2e** (10.90 mg, 8.50 μL, 6.40×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished thiourea **3r** as a brown solid; yield: 28.0 mg, (88%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3, PMP), 4.10-4.21 (m, 9H, Fc), 4.55 (d, 1H, J = 1.02 Hz, C4, β-lactam), 4.74 (d, 1H, J = 1.80 Hz, C3, β-lactam), 6.07 (d, 1H, J = 7.29 Hz, NH-β-lactam), 6.68 (d, 2H, J = 8.97 Hz, PMP), 7.07 (d, 2H, J = 8.97 Hz, PMP), 7.20-7.26 (m, 1H, ClPh), 7.35-7.40 (m, 1H, ClPh), 7.45-7.48 (m, 1H, ClPh), 7.70-7.76 (m, 1H, ClPh), 8.36 (bs, 1H, NHCS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.31 (OCH_3, PMP), 60.73 (C4, β-lactam), 66.41 (C3, β-lactam), 66.66, 68.17, 68.86, 70.04, 83.32 (Fc), 114.05 (C3 and C5, PMP), 120.07 (C2 and C6, PMP), 127.82 (C4, ClPh), 128.35 (C5, ClPh), 128.93 (C6, ClPh), 129.42 (C2, ClPh), 130.18 (C3, ClPh), 130.57 (C1, ClPh), 134.12 (C1, PMP), 156.65 (C4, PMP), 165.02 (CO), 182.02 (CS); HRMS: m/z $[M+Na]^+$ calcd for $C_{27}H_{24}N_3O_2SClFe$: 568.0525; found 568.0504.

_N_-(4-Nitrophenyl)-_N'_-[*trans*-(3*R*,4*R*)-1-(4-methoxyphenyl)-2-oxo-4-ferrocenyl-azetidin-3-yl]-thiourea (3s)

Prepared from **1c** (21.0 mg, 5.58×10^{-2} mmol) and **2m** (11.5 mg, 6.14×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished thiourea **3s** as a brown solid; yield: 25.0 mg, (81%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H, OCH_3, PMP). 4.17-4.23 (m, 9H, Fc), 4. 41 (bs, 1H, C4, β-lactam), 5.08 (bs, 1H, C3, β-lactam), 6.01 (bs, 1H, NH-β-lactam), 6.69 (d, 2H, J = 8.82 Hz, PMP), 7.13 (d, 2H, J = 8.79 Hz, PMP), 7.74 (d, 2H, J = 9.00 Hz, NO_2Ph), 8.11 (d, 2H, J = 8.55 Hz, NO_2Ph), 9.14 (bs, 1H, NHCS); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.34 (OCH_3, PMP), 60.49 (C4, β-lactam), 65.60 (C3, β-lactam), 66.48, 68.61, 68.92, 69.54, 70.13, 81.77 (Fc), 114.27 (C3 and C5, PMP), 120.13 (C2 and C6, PMP), 122.53 (C2 and C6, NO_2Ph), 124.37 (C3 and C5, NO_2Ph), 135.58 (C1, PMP), 144.93 (C1, NO_2Ph), 144.24 (C4, NO_2Ph), 157.13 (C4, PMP), 163.55 (CO), 181.03 (CS). LRMS: m/z $[M+H]^+$ calcd for $C_{27}H_{24}N_4O_4SFe$: 557.09; found 557.09.

Preparation of iminothiazolidinones 4a-n

General Procedure. – To a stirred suspension of anhydrous sodium carbonate (2.0 equiv) in MeCN (1.0

mL), a solution of a thiourea (**3a-f; 3h** and **3m-s**; 1.0 equiv) in MeCN (3.0 mL) was added dropwise. Thereafter, a solution of ethyl bromoacetate (1.1 equiv) in MeCN (1.0 mL) was added and the mixture was stirred at 40-60 °C for 6h. The reaction mixture was then cooled, filtered and evaporated to dryness. Crude iminothiazolidinone (**4a-n**) was purified by silica gel column chromatography using a mixture of EtOAc-pethroleum ether (bp 40-70 °C) in the ratio 1:1 or 1:2.

2-(*n*-Hexyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4a) / 2-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-imino-3-(*n*-hexyl)thiazolidin-4-one (4a')

Prepared from **3a** (33.0 mg, 8.00×10^{-2} mmol), ethyl bromoacetate (14.70 mg, 10.0 μL, 8.80×10^{-2} mmol) and Na_2CO_3 (17.0 mg, 1.60×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished a mixture of isomers **4a**/**4a'**; yield: 24.0 mg, (67%); IR (KBr): 3440, 3032, 2930, 2858, 1748, 1732, 1652, 1634, 1515, 1456, 1386, 1299, 1247, 1181, 1141, 1068, 1033, 830, 794, 750, 700, 524, 485 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, 3H, J_1 = 6.47 Hz, J_2 = 7.22 Hz, CH_3, *n*-hexyl, **4a**), 0.88 (t, 3H, $J_1 = J_2$ = 6.47 Hz, CH_3, *n*-hexyl, **4a'**), 1.07-1.06 (m, 2H, *n*-hexyl, **4a** and **4a'**), 1.26-1.40 (m, 2 x 6H, *n*-hexyl, **4a** and **4a'**), 1.61-1.65 (m, 2H, *n*-hexyl, **4a** and **4a'**), 3.17 (t, 2H, $J_1 = J_2$ = 6.41 Hz , C1, *n*-hexyl, **4a**), 3.74 (s, 2 x 3H, OCH_3, PMP, **4a** and **4a'**), 3.78 (m, 2H, C1, *n*-hexyl, **4a'**), 3.80 (d, 2H, J = 5.34 Hz, CH_2, thiazolidinone, **4a'**), 3.87 (s, 2H, CH_2, thiazolidinone, **4a**), 4.54 (d, 1H, J = 1.61 Hz, C3, β-lactam, **4a'**), 4.97 (d, 1H, J = 1.61 Hz, C4, β-lactam, **4a'**), 5.37 (m, 2H, C3 and C4, β-lactam, **4a**), 6.77-6.81 (m, 2 x 2H, PMP, **4a** and **4a'**), 7.21 (d, 2H, J = 9.12 Hz, PMP, **4a**), 7.26 (d, 2H, J = 8.91 Hz, PMP, **4a'**), 7.36-7.38 (m, 2 x 5H, Ph, **4a** and **4a'**); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.99 (C6, *n*-hexyl, **4a'**), 14.04 (C6, *n*-hexyl, **4a**), 22.48 (C5, *n*-hexyl, **4a**), 22.51 (C5, *n*-hexyl, **4a'**), 26.44 (C4, *n*-hexyl, **4a'**), 26.91 (C3, *n*-hexyl, **4a**), 27.00 (C3, *n*-hexyl, **4a'**), 30.37 (C4, *n*-hexyl, **4a**), 31.31 (C2, *n*-hexyl, **4a**), 31.50 (C2, *n*-hexyl, **4a'**), 32.70 (CH_2, thiazolidinone, **4a**), 32.94 (CH_2, thiazolidinone, **4a'**), 43.14 (C1, *n*-hexyl, **4a'**), 51.75 (C1, *n*-hexyl, **4a**), 55.36 (OCH_3, PMP, **4a**), 55.39 (OCH_3, PMP, **4a'**), 59.32 (C4, β-lactam, **4a**), 64.21 (C4, β-lactam, **4a'**), 65.80 (C3, β-lactam, **4a**), 76.34 (C3, β-lactam, **4a'**), 114.20 (C3 and C5, PMP, **4a**), 114.30 (C3 and C5, PMP, **4a'**), 118.66 (C2 and C6, PMP, **4a** and **4a'**), 126.20 (C2 and C6, Ph, **4a'**), 126.31 (C2 and C6, Ph, **4a**), 128.69 (C4, Ph, **4a'**), 128.81 (C4, Ph, **4a**), 129.12 (C3 and C5, Ph, **4a'**), 129.19 (C3 and C5, Ph, **4a**), 130.87 (C1, Ph, **4a'**), 131.12 (C1, Ph, **4a**), 136.43 (C1, PMP, **4a**), 136.70 (C1, PMP, **4a'**), 148.62 (C=N, thiazolidinone, **4a**), 156.22 (C4, PMP, **4a** and **4a'**), 157.30 (C=N, thiazolidinone, **4a'**), 161.84 (CO, β-lactam, **4a**), 163.31 (CO, β-lactam, **4a'**), 170.09 (CO, thiazolidinone, **4a**), 171.39 (CO, thiazolidinone, **4a'**). ^1H-NMR and RP-HPLC analysis of isomeric mixture showed the ratio of **4a'**/**4a** to be 77:23 (**4a'**, 18.18 min and **4a**, 18.37 min). LC-MS: *m/z* $[M+H]^+$ calcd for $C_{25}H_{29}N_3O_3S$: 452.20; found 452.20 (**4a'**,

2.35 min) and 452.20 (**4a**, 2.50 min); HRMS: *m*/*z* $[M+H]^+$ calcd. for $C_{25}H_{29}N_3O_3S$ (**4a**/**4a'**): 452.2008; found 452.1991.

2-(Cyclohexyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4b)

Prepared from **3b** (20.0 mg, 4.90×10^{-2} mmol), ethyl bromoacetate (9.02 mg, 6.00 μL, 5.40×10^{-2} mmol) and Na_2CO_3 (10.5 mg, 9.80×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-petroleum ether (1:2) as the eluent furnished **4b** as a white solid; yield: 17.0 mg, (77%); mp 61-64 °C; $[\alpha]_D^{20}$ +13.37 (*c* 0.22, CH_2Cl_2); IR (KBr): 3630, 3504, 3032, 2928, 2852, 1764, 1724, 1654, 1513, 1452, 1350, 1298, 1245, 1141, 1112, 1069, 1029, 990, 892, 828, 740, 698, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.80-1.09 (m, 2H, cyclohexyl), 1.12-1.44 (m, 6H, cyclohexyl), 1.48-1.69 (m, 2H, cyclohexyl), 3.15 (bs, 1H, cyclohexyl), 3.75 (s, 3H, OCH_3, PMP), 3.88 (s, 2H, CH_2, thiazolidinone), 5.35 (d, 1H, J = 2.52 Hz, C4, β-lactam), 5.37 (d, 1H, J = 2.55 Hz, C3, β-lactam), 6.79 (d, 2H, J = 9.00 Hz, PMP), 7.22 (d, 2H, J = 8.97 Hz, PMP), 7.36 (bs, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.22, 23.40 (C3 and C5, cyclohexyl), 25.56 (C4, cyclohexyl), 32.64 (C2, cyclohexyl), 32.82 (CH_2, thiazolidinone), 33.04 (C6, cyclohexyl), 55.40 (OCH_3, PMP), 59.25 (C4, β-lactam), 60.30 (C1, cyclohexyl), 65.88 (C3, β-lactam), 114.20 (C3 and C5, PMP), 118.63 (C2 and C6, PMP), 126.32 (C2 and C6, Ph), 128.79 (C4, Ph), 129.17 (C3 and C5, Ph), 131.22 (C1, Ph), 136.46 (C1, PMP), 146.26 (C=N, thiazolidinone), 156.12 (C4, PMP), 161.89 (CO, β-lactam), 170.10 (CO, thiazolidinone). Anal. Calcd for $C_{25}H_{27}N_3O_3S$: C, 66.79; H, 6.05; N, 9.35; S, 7.13. Found: C, 66.49; H, 5.96; N, 9.39; S, 7.40.

2-(*exo*-Norbornyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4c)

Prepared from **3c** (38.0 mg, 9.00×10^{-2} mmol), ethyl bromoacetate (16.50 mg, 11.0 μL, 9.90×10^{-2} mmol) and Na_2CO_3 (19.0 mg, 1.80×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4c** as a white solid; yield: 41.0 mg, (99%); mp 72-75 °C; $[\alpha]_D^{20}$ +20.90 (*c* 0.34, dichloromethane); IR (KBr): 3630, 2953, 2867, 1763, 1725, 1648, 1513, 1394, 1361, 1246, 1144, 1030, 966, 794, 698, 513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.74-1.61 (m, 8H, norbornyl), 1.94 (dd, 1H, J_1 = 3.18 Hz, J_2 = 12.31 Hz, norbornyl), 2.04 (d, 1H, J = 3.06 Hz, norbornyl), 3.09 (d, 1H, J = 5.99 Hz, norbornyl), 3.74 (s, 3H, OCH_3, PMP), 3.87 (s, 2H, CH_2, thiazolidinone), 5.29-5.35 (m, 2H, 1H-C4-β-lactam and 1H-C3-β-lactam), 6.78 (d, 2H, J = 8.97 Hz, PMP), 7.22 (d, 2H, J = 8.97 Hz, PMP), 7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.14 (C3, norbornyl), 28.82 (C4, norbornyl), 32.89 (CH_2, thiazolidinone), 34.96, 35.04 (C6 and C7, norbornyl), 35.73 (C5, norbornyl), 43.78 (C2, norbornyl), 55.42 (OCH_3, PMP), 59.21 (C4, β-lactam), 64.58 (C1, norbornyl), 65.85 (C3, β-lactam), 114.21 (C3 and C5, PMP), 118.51 (C2 and C6, PMP), 126.28 (C2 and

C6, Ph), 128.80 (C4, Ph), 129.20 (C3 and C5, Ph), 131.28 (C1, Ph), 136.48 (C1, PMP), 146.51 (C=N, thiazolidinone), 156.12 (C4, PMP), 161.98, (CO, β-lactam), 169.95 (CO, thiazolidinone). Anal. Calcd for $C_{26}H_{27}N_3O_3S$: C, 67.66; H, 5.90; N, 9.10; S, 6.95. Found: C, 68.00; H, 6.22; N, 8.98; S, 6.65.

2-Phenylimino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]thiazolidin-4-one (4d)

Prepared from **3d** (34.0 mg, 8.40×10^{-2} mmol), ethyl bromoacetate (15.50 mg, 10.5 μL, 9.30×10^{-2} mmol) and Na_2CO_3 (18.0 mg, 1.68×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **4d** as a white solid; yield: 27.0 mg, (73%); mp 65-68 °C; $[\alpha]_D^{20}$ +51.57 (*c* 0.50, CH_2Cl_2); IR (KBr): 3630, 3569, 1655, 1509, 1247, 828, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3, PMP), 3.90 (s, 2H, CH_2, thiazolidinone), 5.46 (d, 1H, J = 2.40 Hz, C4, β-lactam), 5.55 (d, 1H, J = 2.28 Hz, C3, β-lactam), 6.76 (d, 2H, J = 8.88 Hz, PMP), 6.91 (d, 2H, J = 7.32 Hz, PMP), 7.11 (m, 1H, PhN), 7.23-7.41 (m, 9H, 4H-PhN and 5H-Ph-β-lactam). ^{13}C NMR (150 MHz, $CDCl_3$): δ 32.57 (CH_2, thiazolidinone), 55.39 (OCH_3, PMP), 59.74 (C4, β-lactam), 66.02 (C3, β-lactam), 114.32 (C3 and C5, PMP), 119.03 (C2 and C6, PMP), 121.05 (C2 and C6, Ph-β-lactam), 124.94 (C2 and C6, PhN), 126.41 (C4, PhN), 129.01 (C4, Ph-β-lactam), 129.17 (C3 and C5, Ph-β-lactam), 129.29 (C3 and C5, PhN), 130.81 (C1, Ph-β-lactam), 136.19 (C1, PMP), 146.80 (C1, PhN), 151.63 (C=N, thiazolidinone), 156.38 (C4, PMP), 161.43 (CO, β-lactam), 170.39 (CO, thiazolidinone). Anal. Calcd for $C_{25}H_{21}N_3O_3S$: C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.98; H, 4.85; N, 9.29; S, 7.28.

2-Phenylimino-3-[*trans*-(3'*S*,4'*S*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]thiazolidin-4-one (4e)

Prepared from **3e** (26.5 mg, 6.60×10^{-2} mmol), ethyl bromoacetate (12.0 mg, 8.00 μL, 7.20×10^{-2} mmol) and Na_2CO_3 (14.0 mg, 1.31×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4e** as a brown solid; yield: 18.0 mg, (62%). mp 65-68 °C; $[\alpha]_D^{20}$ –51.70 (*c* 0.50, CH_2Cl_2); IR (KBr): 3630, 3569, 1655, 1509, 1247, 828, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3, PMP), 3.89 (s, 2H, CH_2, thiazolidinone), 5.46 (d, 1H, J = 2.64 Hz, C4, β-lactam), 5.55 (d, 1H, J = 2.61 Hz, C3, β-lactam), 6.77 (d, 2H, J = 9.06 Hz, PMP), 6.91 (d, 2H, J = 8.37 Hz, PMP), 7.10 (m, 1H, PhN), 7.22-7.44 (m, 9H, 4H-PhN and 5H-Ph-β-lactam); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.57 (CH_2, thiazolidinone), 55.38 (OCH_3, PMP), 59.73 (C4, β-lactam), 65.99 (C3, β-lactam), 114.30 (C3 and C5, PMP), 119.02 (C2 and C6, PMP), 121.04 (C2 and C6, Ph-β-lactam), 124.93 (C2 and C6, PhN), 126.40 (C4, PhN), 129.00 (C4, Ph-β-lactam), 129.17 (C3 and C5, Ph-β-lactam), 129.28 (C3 and C5, PhN), 130.78 (C1, Ph-β-lactam), 136.16 (C1, PMP), 146.79 (C1, PhN), 151.64 (C=N, thiazolidinone), 156.36 (C4, PMP), 161.44 (CO, β-lactam),

170.40 (CO, thiazolidinone). Anal. Calcd for $C_{25}H_{21}N_3O_3S$: C, 67.70; H, 4.77; N, 9.47; S, 7.23. Found: C, 67.92; H, 4.85; N, 9.51; S, 7.19.

2-(2-Chlorophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4f)

Prepared from **3f** (60.0 mg, 1.37×10^{-1} mmol), ethyl bromoacetate (25.20 mg, 17.0 μL, 1.51×10^{-1} mmol) and Na_2CO_3 (29.0 mg, 2.74×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4f** as a yellow solid; yield: 60.0 mg, (92%), mp 80-83 °C; $[\alpha]_D^{20}$ +109.14 (*c* 0.50, CH_2Cl_2); IR (KBr): 3449, 2930, 1763, 1637, 1584, 1513, 1473, 1455, 1364, 1247, 1181, 1144, 1030, 828, 794, 755, 742, 697, 515 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, OCH_3, PMP), 3.93 (d, 2H, J = 0.86 Hz, CH_2, thiazolidinone), 5.54 (d, 1H, J = 2.65 Hz, C4, β-lactam), 5.70 (d, 1H, J = 2.65 Hz, C3, β-lactam), 6.75 (d, 2H, J = 8.90 Hz, PMP), 6.97-7.08 (m, 2H, ClPh), 7.17-7.20 (m, 1H, ClPh), 7.22 (d, 2H, J = 9.08 Hz, PMP), 7.33-7.42 (m, 6H, 5H-Ph and 1H-ClPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.82 (CH_2, thiazolidinone), 55.34 (OCH_3, PMP), 59.48 (C4, β-lactam), 65.81 (C3, β-lactam), 114.23 (C3 and C5, PMP), 119.16 (C2 and C6, PMP), 121.37 (C4, ClPh), 125.84 (C5, ClPh), 126.44 (C2 and C6, Ph), 127.43 (C6, ClPh), 128.98 (C4, Ph), 129.24 (C3 and C5, Ph), 129.99 (C3, ClPh), 130.60 (C1, Ph), 135.27 (C1, ClPh), 136.04 (C1, PMP), 144.11 (C1, ClPh), 153.75 (C=N, thiazolidinone), 156.33 (C4, PMP), 161.11 (CO, β-lactam), 170.19 (CO, thiazolidinone). Anal. Calcd for $C_{25}H_{20}N_3O_3SCl$: C, 62.82; H, 4.22; N, 8.79; S, 6.71. Found: C, 62.98; H, 4.58; N, 8.35; S, 6.85.

2-(2-Fluorophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4g)

Prepared from **3h** (75.0 mg, 1.78×10^{-1} mmol), ethyl bromoacetate (32.70 mg, 22.0 μL, 1.96×10^{-1} mmol) and Na_2CO_3 (38.0 mg, 3.56×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4g** as a white solid; yield: 74.0 mg, (90%); mp 82-85 °C; $[\alpha]_D^{20}$ +83.61 (*c* 0.42, CH_2Cl_2); IR (KBr): 3630, 3504, 2932, 1763, 1637, 1605, 1513, 1491, 1364, 1247, 1222, 1176, 1145, 1029, 829, 754, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 3H, OCH_3, PMP), 3.93 (s, 2H, CH_2, thiazolidinone), 5.54 (bs, 2H, 1H-C4-β-lactam and 1H-C3-β-lactam), 6.76 (d, 2H, J = 8.97 Hz, PMP), 7.05-7.08 (m, 4H, FPh), 7.23 (d, 2H, J = 8.94 Hz, PMP), 7.36-7.41 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.82 (CH_2, thiazolidinone), 55.36 (OCH_3), 59.48 (C4, β-lactam), 65.89 (C3, β-lactam), 114.25 (C3 and C5, PMP), 116.26 (d, J = 19.61 Hz, C3, FPh), 119.13 (C2 and C6, PMP), 122.43 (d, J = 1.33 Hz, C6, FPh), 124.35 (d, J = 3.89 Hz, C5, FPh), 125.97 (d, J = 7.29 Hz, C4, FPh), 126.42 (C2 and C6, Ph), 128.98 (C4, Ph), 129.26 (C3 and C5, Ph), 130.63 (C1, Ph), 134.70 (d, J = 12.22 Hz, C1, FPh), 136.05 (C1, PMP), 152.24 (d, J = 274.42 Hz, C2,

FPh), 154.14 (C=N, thiazolidinone), 156.35 (C4, PMP), 161.13 (CO, β-lactam), 170.27 (CO, thiazolidinone). Anal. Calcd for $C_{25}H_{20}N_3O_3SF$: C, 65.06; H, 4.37; N, 9.10; S, 6.95. Found: C, 65.38; H, 4.64; N, 8.77; S, 6.83.

2-(4-Azidophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4h)

Prepared from **3m** (57.0 mg, 1.28×10^{-1} mmol), ethyl bromoacetate (23.50 mg, 16.0 μL, 1.41×10^{-1} mmol) and Na_2CO_3 (27.0 mg, 2.57×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4h** as brown solid; yield: 28.0 mg, (45%); mp 87-90 °C; $[\alpha]_D^{20}$ +60.84 (*c* 0.26, CH_2Cl_2); IR (KBr): 3651, 3631, 2931, 2116, 1763, 1654, 1637, 1512, 1499, 1364, 1247, 1029, 829, 794, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3, PMP), 3.91 (s, 2H, CH_2, thiazolidinone), 5.44 (d, 1H, J = 2.61 Hz, C4, β-lactam), 5.53 (d, 1H, J = 2.61 Hz, C3, β-lactam), 6.77 (d, 2H, J = 8.97 Hz, PMP), 6.92 (m, 4H, N_3Ph), 7.23 (d, 2H, J = 8.97 Hz, PMP), 7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.61 (CH_2, thiazolidinone), 55.36 (OCH_3, PMP), 59.70 (C4, β-lactam), 65.98 (C3, β-lactam), 114.29 (C3 and C5, PMP), 118.94 (C2 and C6, PMP), 119.72 (C2 and C6, N_3Ph), 122.60 (C3 and C5, N_3Ph), 126.36 (C2 and C6, Ph), 129.02 (C4, Ph), 129.28 (C3 and C5, Ph), 130.72 (C1, Ph), 136.07 (C1, N_3Ph), 136.54 (C1, PMP), 143.62 (C4, N_3Ph), 151.97 (C=N, thiazolidinone), 156.37 (C4, PMP), 161.35 (CO, β-lactam), 170.23 (CO, thiazolidinone). HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{25}H_{20}N_6O_3S$: 507.1215; found 507.1220.

2-(4-Nitrophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4i)

Prepared from **3n** (20.0 mg, 4.50×10^{-2} mmol), ethyl bromoacetate (8.18 mg, 5.50 μL, 4.90×10^{-2} mmol) and Na_2CO_3 (9.50 mg, 8.90×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4i** as a yellow solid; yield: 21.0 mg, (96%); mp 180-182 °C; $[\alpha]_D^{20}$ +75.26 (*c* 0.40, CH_2Cl_2); IR (KBr): 3630, 3448, 2937, 1745, 1638, 1512, 1458, 1370, 1347, 1250, 1180, 1154, 1026, 861, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.72 (s, 3H, OCH_3, PMP), 3.96 (s, 2H, CH_2, thiazolidinone), 5.43 (d, 1H, J = 2.64 Hz, C4, β-lactam), 5.53 (d, 1H, J = 2.64 Hz, C3, β-lactam), 6.77 (d, 2H, J = 9.03 Hz, PMP), 7.01 (d, 2H, J = 9.00 Hz, 4-NO_2Ph), 7.22 (d, 2H, J = 9.03 Hz, PMP), 7.41 (s, 5H, Ph), 8.17 (d, 2H, J = 9.00 Hz, 4-NO_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.73 (CH_2, thiazolidinone), 55.36 (OCH_3, PMP), 59.73 (C4, β-lactam), 66.00 (C3, β-lactam), 114.34 (C3 and C5, PMP), 118.93 (C2 and C6, PMP), 121.72 (C2 and C6, 4-NO_2Ph), 125.13 (C3 and C5, 4-NO_2Ph), 126.34 (C2 and C6, Ph), 129.18 (C4, Ph), 129.36 (C3 and C5, Ph), 130.54 (C1, Ph), 135.83 (C1, PMP), 144.71 (C4, 4-NO_2Ph), 152.63 (C=N, thiazolidinone), 154.00 (C1, 4-NO_2Ph), 156.49 (C4, PMP), 160.91 (CO, β-lactam), 170.02 (CO, thiazolidinone). Anal. Calcd for $C_{25}H_{20}N_4O_5S$: C, 61.47; H,

4.13; N, 11.47; S, 6.56. Found: C, 61.93; H, 4.48; N, 10.97; S, 6.25.

2-(4-Cyanophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-thiazolidin-4-one (4j)

Prepared from **3o** (70.0 mg, 1.63×10^{-1} mmol), ethyl bromoacetate (30.10 mg, 20.0 μL, 1.80×10^{-1} mmol) and Na_2CO_3 (35.0 mg, 3.27×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4j** as a yellow solid; yield: 64.0 mg, (84%); mp 91-94 °C; $[\alpha]_D^{20}$ +53.29 (*c* 0.54, CH_2Cl_2); IR (KBr): 3504, 2934, 2224, 1763, 1636, 1595, 1513, 1455, 1366, 1299, 1247, 1182, 1145, 1028, 828, 793, 744, 698, 550, 514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.73 (s, 3H, OCH_3, PMP), 3.95 (s, 2H, CH_2, thiazolidinone), 5.41 (d, 1H, J = 2.61 Hz, C4, β-lactam), 5.52 (d, 1H, J = 2.61 Hz, C3, β-lactam), 6.77 (d, 2H, J = 9.03 Hz, PMP), 6.98 (d, 2H, J = 8.58 Hz, CNPh), 7.22 (d, 2H, J = 9.03 Hz, PMP), 7.40-7.42 (m, 5H, Ph), 7.58 (d, 2H, J = 8.58 Hz, CNPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.69 (CH_2, thiazolidinone), 55.37 (OCH_3, PMP), 59.71 (C4, β-lactam), 65.99 (C3, β-lactam), 108.32 (CN), 114.32 (C3 and C5, PMP), 118.81 (C4, CNPh), 118.93 (C2 and C6, PMP), 121.97 (C2 and C6, CNPh), 126.34 (C2 and C6, Ph), 129.17 (C4, Ph), 129.36 (C3 and C5, Ph), 130.56 (C1, Ph), 133.41 (C3 and C5, CNPh), 135.85 (C1, PMP), 150.75 (C1, CNPh), 153.68 (C=N, thiazolidinone), 156.46 (C4, PMP), 160.95 (CO, β-lactam), 170.04 (CO, thiazolidinone). HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{25}H_{20}N_4O_3S$: 491.1154; found 491.1150.

2-Cyclohexylimino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-ferrocenylazetidin-3'-yl]-thiazolidin-4-one (4k)

Prepared from **3p** (31.0 mg, 6.00×10^{-2} mmol), ethyl bromoacetate (11.0 mg, 8.0 μL, 6.60×10^{-2} mmol) and Na_2CO_3 (13.0 mg, 1.20×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4k** as a brown solid; yield: 23.0 mg, (70%); mp 79-81 °C; $[\alpha]_D^{20}$ –174.90 (*c* 0.10, CH_2Cl_2); IR (KBr): 3630, 2929, 2853, 1762, 1654, 1648, 1513, 1389, 1351, 1298, 1245, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11-1.19 (m, 1H, cyclohexyl), 1.23-1.39 (m, 4H, cyclohexyl), 1.46-1.51 (m, 1H, cyclohexyl), 1.63-1.69 (m, 4H, cyclohexyl), 3.14-3.18 (m, 1H, cyclohexyl), 3.77 (s, 3H, OCH_3, PMP), 3.93 (d, 2H, J = 1.98 Hz, CH_2, thiazolidinone), 4.17 (s, 5H, Fc), 4.21-4.31 (m, 4H, Fc), 5.28 (d, 1H, J = 2.73 Hz, C4, β-lactam), 5.79 (d, 1H, J = 2.73 Hz, C3, β-lactam), 6.83 (d, 2H, J = 8.97 Hz, PMP), 7.29 (d, 2H, J = 8.94 Hz, PMP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.63, 23.81 (C3 and C5, cyclohexyl), 25.55 (C4, cyclohexyl), 32.50 (CH_2, thiazolidinone), 33.04, 33.28 (C2 and C6, cyclohexyl), 55.41 (OCH_3, PMP), 55.65 (C1, cyclohexyl), 60.78 (C4, β-lactam), 63.31 (C3, β-lactam), 66.38, 68.21, 68.67, 69.25, 69.77, 83.79 (Fc), 114.14 (C3 and C5, PMP), 119.69 (C2 and C6, PMP), 130.81 (C1, PMP), 146.85 (C=N, thiazolidinone), 156.40 (C4, PMP), 162.16 (CO, β-lactam), 170.52 (CO, thiazolidinone). HRMS: *m*/*z* $[M+H]^+$ calcd for

$C_{29}H_{31}N_3O_3SFe$: 558.1514; found 558.1500.

2-Phenylimino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-ferrocenylazetidin-3'-yl]-thiazolidin-4-one (4l)

Prepared from **3q** (14.0 mg, 2.73×10^{-2} mmol), ethyl bromoacetate (5.03 mg, 3.50 μL, 3.01×10^{-2} mmol) and Na_2CO_3 (6.00 mg, 5.47×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4l** as a brown solid; yield: 10.0 mg, (67%); mp 75-79 °C; $[\alpha]_D^{20}$ –123.08 (*c* 0.07, CH_2Cl_2); IR (KBr): 3630, 3448, 1752, 1637, 1511, 1246, 829 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3, PMP), 3.94 (d, 2H, J = 7.05 Hz, CH_2, thiazolidinone), 4.19 (s, 5H, Fc), 4.24 (s, 2H, Fc), 4.31 (s, 1H, Fc), 4.35 (s, 1H, Fc), 5.39 (d, 1H, J = 2.34 Hz, C4, β-lactam), 5.97 (d, 1H, J = 2.34 Hz, C3, β-lactam), 6.81 (d, 2H, J = 8.82 Hz, PMP), 7.00 (d, 2H, J = 7.62 Hz, PMP), 7.15 (m, 1H, Ph), 7.28-7.35 (m, 4H, Ph); ^{13}C NMR (150 MHz, $CDCl_3$): δ 32.45 (CH_2, thiazolidinone), 55.43 (OCH_3, PMP), 56.55 (C4, β-lactam), 63.36 (C3, β-lactam), 66.35, 68.45, 68.77, 69.55, 70.03, 83.19 (Fc), 114.28 (C3 and C5, PMP), 120.25 (C2 and C6, PMP), 121.07 (C2 and C6, Ph), 124.99 (C4, Ph), 129.29 (C3 and C5, Ph), 130.49 (C4, PMP), 147.09 (C1, Ph), 152.30 (C=N, thiazolidinone), 156.74 (C4, PMP), 161.81 (CO, β-lactam), 170.91 (CO, thiazolidinone). HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{29}H_{25}N_3O_3SFe$: 574.0864; found 574.0865; Anal. Calcd for $C_{29}H_{25}N_3O_3SFe$: C, 63.17; H, 4.57; N, 7.62; S, 5.81. Found: C, 62.89; H, 4.61; N, 7.51; S, 5.48.

2-(2-Chlorophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-ferrocenylazetidin-3'-yl]-thiazolidin-4-one (4m)

Prepared from **3r** (28.0 mg, 5.13×10^{-2} mmol), ethyl bromoacetate (9.42 mg, 6.50 μL, 5.64×10^{-2} mmol) and Na_2CO_3 (11.0 mg, 1.03×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4m** as a brown solid; yield: 17.0 mg, (57%); mp 220-223 °C; $[\alpha]_D^{20}$ –67.95 (*c* 0.18, CH_2Cl_2); IR (KBr): 3630, 3449, 2927, 1752, 1630, 1585, 1513, 1378, 1356, 1246, 1175, 1444, 1029, 824, 795, 758, 692, 481 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3, PMP), 3.98 (d, 2H, J = 14.45 Hz, CH_2, thiazolidinone), 4.18 (s, 5H, Fc), 4.23 (s, 2H, Fc), 4.28 (s, 1H, Fc), 4.37 (s, 1H, Fc), 5.67 (s, 1H, C4, β-lactam), 5.92 (d, 1H, J = 1.98 Hz, C3, β-lactam), 6.81 (d, 2H, J = 8.70 Hz, PMP), 7.03 (d, 1H, J = 7.50 Hz, ClPh), 7.08 (t, 1H, $J_1 = J_2 = 7.44$ Hz, ClPh), 7.22 (t, 1H, $J_1 = J_2 = 7.38$ Hz, ClPh), 7.30 (d, 2H, J = 8.70 Hz, PMP), 7.41 (d, 1H, J = 7.86 Hz, ClPh); ^{13}C NMR (150 MHz, $CDCl_3$): δ 32.85 (CH_2, thiazolidinone), 55.40 (OCH_3, PMP), 55.99 (C4, β-lactam), 63.51 (C3, β-lactam), 66.51, 68.43, 68.69, 69.31, 69.91, 83.53 (Fc), 114.22 (C3 and C5, PMP), 120.51 (C2 and C6, PMP), 121.50 (C4, ClPh), 125.88 (C5, ClPh), 126.59 (C2, ClPh), 127.52 (C6, ClPh), 130.08 (C3, ClPh), 130.27 (C1, PMP), 144.34 (C1, ClPh), 154.24 (C=N, thiazolidinone), 156.75 (C4, PMP), 161.47 (CO, β-lactam), 170.52 (CO, thiazolidinone). LRMS: *m*/*z* $[M+H]^+$ calcd for

$C_{29}H_{24}N_3O_3SClFe$: 586.07; found 586.07.

2-(4-Nitrophenyl)imino-3-[*trans*-(3'*R*,4'*R*)-1'-(4'-methoxyphenyl)-2'-oxo-4'-ferrocenylazetidin-3'-yl]thiazolidin-4-one (4n)

Prepared from **3s** (20.0 mg, 3.59×10^{-2} mmol), ethyl bromoacetate (6.60 mg, 4.50 μL, 3.95×10^{-2} mmol) and Na_2CO_3 (7.60 mg, 7.19×10^{-2} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:2) as the eluent furnished **4n** as a brown solid; yield: 14.9 mg, (70%); mp 101-103 °C; $[\alpha]_D^{20}$ –88.65 (*c* 0.11, CH_2Cl_2); IR (KBr): 3631, 3449, 2926, 1752, 1654, 1638, 1584, 1511, 1340, 1245, 828, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3, PMP), 4.01 (d, 2H, J = 0.72 Hz, CH_2, thiazolidinone), 4.19 (s, 5H, Fc), 4.27 (t, 2H, $J_1 = J_2$ = 1.68 Hz, Fc), 4.30 (d, 1H, J = 1.62 Hz, Fc), 4.34 (d, 1H, J = 1.47 Hz, Fc), 5.35 (d, 1H, J = 2.67 Hz, C4, β-lactam), 5.93 (d, 1H, J = 2.67 Hz, C3, β-lactam), 6.81 (d, 2H, J = 8.97 Hz, PMP), 7.11 (d, 2H, J = 8.88 Hz, NO_2Ph), 7.28 (d, 2H, J = 8.22 Hz, PMP), 8.22 (d, 2H, J = 8.88 Hz, NO_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.65 (CH_2, thiazolidinone), 55.41 (OCH_3, PMP), 56.55 (C3, β-lactam), 63.50 (C4, β-lactam), 66.24, 68.54, 68.74, 69.69, 69.95, 82.96 (Fc), 114.29 (C3 and C5, PMP), 120.10 (C2 and C6, PMP), 121.74 (C2 and C6, NO_2Ph), 125.27 (C3 and C5, NO_2Ph), 130.23 (C1, PMP), 144.82 (C4, NO_2Ph), 152.85 (C=N, thiazolidinone), 154.47 (C1, NO_2Ph), 156.82 (C4, PMP), 161.28 (CO, β-lactam), 170.45 (CO, thiazolidinone). HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{29}H_{24}N_4O_5SFe$: 597.0895; found 597.0900.

Preparation of triazinethiones 5a-g

General procedure. – To a stirred solution of a thiourea (**3d**, **3g**, **3i-l** and **3n**; 1 equiv) in absolute EtOH (10 mL), aqueous solutions of formaldehyde (37%) (5 equiv) and methylamine (40%) (2 equiv) were added dropwise. The reaction mixture was heated at 50 °C for 48 h, then cooled, filtered and evaporated to dryness. Crude products **5a-g** were purified by silica gel column chromatography using a mixture of EtOAc-pethroleum ether (bp 40-70 °C) in the ratio 1:1.

1-Phenyl-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5a)

Prepared from **3d** (70.0 mg, 1.73×10^{-1} mmol) and aqueous solutions of formaldehyde (26.0 mg, 63.0 μL, 8.67×10^{-1} mmol) and methylamine (10.80 mg, 30.0 μL, 3.47×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5a** as a white solid; yield: 24.0 mg, (30%); mp 155-158 °C; $[\alpha]_D^{20}$ +336.13 (*c* 0.01, CH_2Cl_2); IR (KBr): 3631, 3463, 2949, 1736, 1655, 1638, 1586, 1521, 1498, 1298, 1259, 1137, 1028, 833, 754, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H, NCH_3, triazinethione), 3.73 (s, 3H, OCH_3, PMP), 4.51 (m, 2H, CH_2, triazinethione), 4.64 (d, 2H, J = 12.04 Hz, CH_2, triazinethione), 5.02 (d, 1H, J = 1.98 Hz,

C4, β-lactam), 6.32 (d, 1H, *J* = 1.98 Hz, C3, β-lactam), 6.78 (d, 2H, *J* = 8.94 Hz, PMP), 7.22-7.46 (m, 12H, 5H-PhN, 5H-Ph-β-lactam and 2H-PMP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.83 (NCH_3, triazinethione), 55.38 (OCH_3, PMP), 62.22 (C4, β-lactam), 67.49 (C4, triazinethione), 72.62 (C6, triazinethione), 74.02 (C3, β-lactam), 114.31 (C3 and C5, PMP), 118.89 (C2 and C6, PMP), 126.51 (C2 and C6, Ph, β-lactam), 127.56 (C4, PhN), 127.96 (C2 and C6, PhN), 128.56 (C4, Ph, β-lactam), 128.88 (C3 and C5, PhN), 129.43 (C3 and C5, Ph, β-lactam), 130.48 (C1, Ph, β-lactam), 135.92 (C1, PMP), 144.46 (C1, PhN), 156.37 (C4, PMP), 162.54 (CO, β-lactam), 179.81 (CS, triazinethione). Anal. Calcd for $C_{26}H_{26}N_4O_2S$: C, 68.10; H, 5.71; N, 12.22; S, 6.99. Found: C, 67.75; H, 5.50; N, 12.27; S, 6.90.

1-(4-Chlorophenyl)-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5b)

Prepared from **3g** (46.0 mg, 1.05×10^{-1} mmol) and aqueous solutions of formaldehyde (15.80 mg, 38.0 μL, 5.25×10^{-1} mmol) and methylamine (8.17 mg, 23.0 μL, 2.63×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5b** as a yellow solid; yield: 14.0 mg, (27%); mp 150-153 °C; $[\alpha]_D^{20}$ +312.50 (*c* 0.02, CH_2Cl_2); IR (KBr): 3650, 3630, 2924, 1735, 1654, 1560, 1508, 1458, 1245, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H, NCH_3, triazinethione), 3.74 (s, 3H, OCH_3, PMP), 4.45-4.67 (m, 4H, triazinethione), 5.00 (d, 1H, *J* = 2.01 Hz, C4, β-lactam), 6.27 (d, 1H, *J* = 1.86 Hz, C3, β-lactam), 6.65 (d, 2H, *J* = 8.79 Hz, PMP), 6.73-6.80 (m, 4H, ClPh), 7.18 (d, 2H, *J* = 8.55 Hz, PMP), 7.32-7.37 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.87 (NCH_3, triazinethione), 55.42 (OCH_3, PMP), 62.25 (C4, β-lactam), 67.61 (C4, triazinethione), 72.61 (C6, triazinethione), 74.06 (C3, β-lactam), 114.37 (C3 and C5, PMP), 118.94 (C2 and C6, PMP), 126.52 (C2 and C6, Ph), 128.69 (C4, Ph), 128.97 (C2 and C6, ClPh), 129.44 (C3 and C5, Ph), 129.70 (C3 and C5, ClPh), 130.46 (C1, Ph), 133.35 (C4, ClPh), 135.88 (C1, PMP), 142.92 (C1, ClPh), 156.46 (C4, PMP), 162.38 (CO, β-lactam), 179.93 (CS, triazinethione). HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{25}N_4O_2SCl$: 515.1284; found: 515.1287.

1-(4-Fluorophenyl)-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5c)

Prepared from **3i** (230 mg, 5.46×10^{-1} mmol) and aqueous solutions of formaldehyde (82.0 mg, 198 μL, 2.73 mmol) and methylamine (42.20 mg, 118 μL, 1.36 mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5c** as a yellow solid; yield: 40.0 mg, (15%); mp 167-170 °C; $[\alpha]_D^{20}$ +53.57 (*c* 0.06, CH_2Cl_2); IR (KBr): 3651, 3630, 2950, 1736, 1512, 1484, 1438, 1298, 1260, 1220, 1154, 1136, 1029, 835, 681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H, NCH_3, triazinethione), 3.73 (s, 3H, OCH_3, PMP), 4.45-4.67 (m, 4H, triazinethione), 5.01 (d, 1H, *J* = 2.13 Hz, C4, β-lactam), 6.29 (d, 1H, *J* = 2.10 Hz, C3, β-lactam),

6.78 (d, 2H, *J* = 8.97 Hz, PMP), 6.99 (m, 3H, FPh), 7.18-7.37 (m, 8H, 1H-FPh, 2H-PMP and 5H-Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.84 (NCH_3, triazinethione), 55.40 (OCH_3, PMP), 62.21 (C4, β-lactam), 67.55 (C4, triazinethione), 72.71 (C6, triazinethione), 74.09 (C3, β-lactam), 114.34 (C3 and C5, PMP), 116.38 (d, *J* = 22.83 Hz, C3 and C5, FPh), 118.91 (C2 and C6, PMP), 126.50 (C2 and C6, Ph), 128.65 (C4, Ph), 128.94 (C3 and C5, Ph), 129.75 (d, *J* = 8.67 Hz, C2, C6, FPh), 130.46 (C1, Ph), 135.89 (C1, PMP), 140.39 (d, *J* = 3.27 Hz, C1, FPh), 156.42 (C4, PMP), 161.50 (d, *J* = 247.60 Hz, C4, FPh), 162.42 (CO, β-lactam), 180.12 (CS, triazinethione). HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{26}H_{25}N_4O_2SF$: 499.1580; found: 499.1587.

1-(4-Trifluoromethylphenyl)-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5d)

Prepared from **3j** (60.0 mg, 1.27×10^{-1} mmol) and aqueous solutions of formaldehyde (19.10 mg, 46.0 μL, 6.36×10^{-1} mmol) and methylamine (9.88 mg, 27.0 μL, 3.18×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5d** as a yellow solid; yield: 16.0 mg, (24%); mp 149-152 °C; $[\alpha]_D^{20}$ +80.65 (*c* 0.09, CH_2Cl_2); IR (KBr): 3753, 3631, 2953, 1736, 1612, 1542, 1512, 1490, 1329, 1298, 1258, 1128, 1066, 833, 523 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (s, 3H, NCH_3, triazinethione), 3.74 (s, 3H, OCH_3, PMP), 4.48-4.69 (m, 4H, triazinethione), 5.02 (d, 1H, *J* = 2.07 Hz, C4, β-lactam), 6.26 (d, 1H, *J* = 2.01 Hz, C3, β-lactam), 6.78 (d, 2H, *J* = 9.12 Hz, PMP), 6.80 (d, 2H, *J* = 9.03, CF_3Ph), 7.26 (d, 2H, *J* = 9.60 Hz, PMP), 7.32-7.44 (m, 5H, Ph), 7.65 (d, 2H, *J* = 8.31 Hz, CF_3Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.85 (NCH_3, triazinethione), 55.41 (OCH_3, PMP), 62.23 (C4, β-lactam), 67.68 (C4, triazinethione), 72.46 (C6, triazinethione), 73.94 (C3, β-lactam), 114.36 (C3 and C5, PMP), 118.92 (C2 and C6, PMP), 123.76 (d, *J* = 272.06 Hz, CF_3), 126.50 (C2 and C6, Ph), 126.60 (d, *J* = 3.81 Hz, C3 and C5, CF_3Ph), 128.62 (C2 and C6, CF_3Ph), 128.70 (C4, Ph), 128.96 (C3 and C5, Ph), 129.52 (d, *J* = 32.94 Hz, C4, CF_3Ph), 130.40 (C1, Ph), 135.82 (C1, PMP), 147.44 (d, *J* = 1.25 Hz, C1, CF_3Ph), 156.47 (C4, PMP), 162.22 (CO, β-lactam), 179.72 (CS, triazinethione). LRMS: *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{25}N_4O_2SF_3$: 527.17; found 527.17.

1-(4-Trifluoromethoxyphenyl)-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5e)

Prepared from **3k** (70.0 mg, 1.44×10^{-1} mmol) and aqueous solutions of formaldehyde (21.60 mg, 52.0 μL, 7.18×10^{-1} mmol) and methylamine (11.10 mg, 31.0 μL, 3.59×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5c** as a white solid; yield: 22.7 mg, (29%); mp 169-172 °C; $[\alpha]_D^{20}$ –10.27 (*c* 0.10, CH_2Cl_2); IR (KBr): 3752, 3467, 2951, 1739, 1654, 1587, 1513, 1486, 1439, 1393, 1298, 1260, 1162, 1136, 1029, 834, 752, 682, 525 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H, NCH_3, triazinethione),

3.73 (s, 3H, OCH_3, PMP), 4.46-4.67 (m, 4H, triazinethione), 5.02 (d, 1H, J = 2.16 Hz, C4, β-lactam), 6.26 (d, 1H, J = 2.13 Hz, C3, β-lactam), 6.78 (d, 2H, J = 9.06 Hz, PMP), 6.79 (d, 2H, J = 9.03, CF_3OPh), 7.21-7.38 (m, 9H, 5H-Ph, 2H-PMP and 2H-CF_3OPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.83 (NCH_3, triazinethione), 55.39 (OCH_3, PMP), 62.22 (C4, β-lactam), 67.62 (C4, triazinethione), 72.59 (C6, triazinethione), 74.04 (C3, β-lactam), 114.34 (C3 and C5, PMP), 118.91 (C2 and C6, PMP), 121.81 (C2 and C6, CF_3OPh), 122.06 (CF_3O), 126.48 (C2 and C6, Ph), 128.66 (C4, Ph), 128.94 (C3 and C5, Ph), 129.61 (C3 and C5, CF_3OPh), 130.43 (C1, Ph), 135.86 (C1, PMP), 142.79 (C1, CF_3OPh), 147.96 (C4, CF_3OPh), 156.44 (C4, PMP), 162.32 (CO, β-lactam), 179.92 (CS, triazinethione). Anal. Calcd for $C_{27}H_{25}N_4O_3SF_3$: C, 59.77; H, 4.64; N, 10.33; S, 5.91. Found: C, 59.54; H, 4.93; N, 10.40; S, 5.77.

1-(4-Methoxyphenyl)-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5f)

Prepared from **3l** (51.0 mg, 1.18×10^{-1} mmol) and aqueous solutions of formaldehyde (17.70 mg, 43.0 μL, 5.88×10^{-1} mmol) and methylamine (9.13 mg, 25.0 μL, 2.94×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5f** as a yellow solid; yield: 7.2 mg, (13%); mp 160-162 °C; $[\alpha]_D^{20}$ +126.90 (*c* 0.04, CH_2Cl_2); IR (KBr): 3651, 3469, 1742, 1686, 1654, 1560, 1511, 1388, 1246, 1166, 1029, 829, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.83 (s, 3H, NCH_3, triazinethione), 3.74 (s, 3H, OCH_3, PMP-1), 3.80 (s, 3H, OCH_3, PMP-2), 4.45-4.66 (m, 4H, triazinethione), 5.01 (d, 1H, J = 1.89 Hz, C4, β-lactam), 6.32 (d, 1H, J = 1.92 Hz, C3, β-lactam), 6.79 (d, 2H, J = 8.79 Hz, PMP-1), 6.91 (d, 2H, J = 8.85 Hz, PMP-2), 7.15 (d, 2H, J = 8.82 Hz, PMP-2), 7.24-7.38 (m, 7H, 2H-PMP-1 and 5H-Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.89 (NCH_3, triazinethione), 55.40 (OCH_3, PMP-2), 55.43 (OCH_3, PMP-1), 62.30 (C4, β-lactam), 67.47 (C4, triazinethione), 72.83 (C6, triazinethione), 74.18 (C3, β-lactam), 114.35 (C3 and C5, PMP-1), 114.66 (C3 and C5, PMP-2), 118.93 (C2 and C6, PMP-1), 126.65 (C2 and C6, PMP-2), 128.07 (C2 and C6, Ph), 128.60 (C4, Ph), 128.93 (C3 and C5, Ph), 130.67 (C1, Ph), 130.83 (C1, PMP-2), 135.96 (C1, PMP-1), 156.40 (C4, PMP-1), 159.83 (C4, PMP-2), 163.17 (CO, β-lactam), 180.93 (CS, triazinethione). HRMS: *m*/*z* $[M+H]^+$ calcd for $C_{27}H_{28}N_4O_3S$: 489.1960; found: 489.1980.

1-(4-Nitrophenyl)-3-[*trans*-(3'*R*,4'*R*)-1'-(4-methoxyphenyl)-2'-oxo-4'-phenylazetidin-3'-yl]-5-methylhexahydro-2-thioxo-1,3,5-triazine (5g)

Prepared from **3n** (50.0 mg, 1.11×10^{-1} mmol) and aqueous solutions of formaldehyde (16.70 mg, 40.0 μL, 5.57×10^{-1} mmol) and methylamine (6.92 mg, 20.0 μL, 2.23×10^{-1} mmol). Evaporation of the solvent and purification of the residue over a silica gel column using EtOAc-petroleum ether (1:1) as the eluent furnished **5g** as a yellow solid; yield: 21.0 mg, (36%); mp 166-168 °C; $[\alpha]_D^{20}$ +360.82 (*c* 0.02, CH_2Cl_2); IR (KBr): 3630, 3569, 2931, 1752, 1736, 1593, 1513, 1458, 1347, 1300, 1247, 1066, 827, 696

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.85 (s, 3H, NCH_3, triazinethione), 3.74 (s, 3H, OCH_3, PMP), 4.51 (d, 1H, J = 12.28 Hz, CH_2, triazinethione), 4.56 (s, 2H, CH_2, triazinethione), 4.68 (d, 1H, J = 12.07 Hz, CH_2, triazinethione), 5.04 (d, 1H, J = 2.10 Hz, C4, β-lactam), 6.21 (d, 1H, J = 2.01 Hz, C3, β-lactam), 6.79 (d, 2H, J = 9.00 Hz, PMP), 7.25 (d, 2H, J = 8.94 Hz, PMP), 7.31-7.36 (m, 5H, Ph), 7.44 (d, 2H, J = 8.91 Hz, NO_2Ph), 8.25 (d, 2H, J = 8.88 Hz, NO_2Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.84 (NCH_3, triazinethione), 55.40 (OCH_3, PMP), 62.11 (C4, β-lactam), 67.84 (CH_2, C4, triazinethione), 72.34 (C6, triazinethione), 73.86 (C3, β-lactam), 114.36 (C3 and C5, PMP), 118.91 (C2 and C6, PMP), 126.51 (C2 and C6, Ph, β-lactam), 127.56 (C4, PhN), 127.96 (C2 and C6, PhN), 124.79 (C2 and C6, NO_2Ph), 126.45 (C3 and C5, NO_2Ph), 128.79 (C4, Ph), 129.01 (C2 and C6, Ph), 129.17 (C3 and C5, Ph), 130.30 (C1, Ph), 135.73 (C1, PMP), 146.33 (C1, NO_2Ph), 149.93 (C4, NO_2Ph), 156.49 (C4, PMP), 162.00 (CO, β-lactam), 179.55 (CS, triazinethione). Anal. Calcd for $C_{26}H_{25}N_5O_4S$: C, 62.01; H, 5.00; N, 13.91; S, 6.37. Found: C, 62.17; H, 5.13; N, 14.07; S, 6.46.

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