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Thermal and Microwave-Assisted Synthesis of New Highly Functionalized Bis-β-lactams from Available Compounds via Bisketene as an Intermediate

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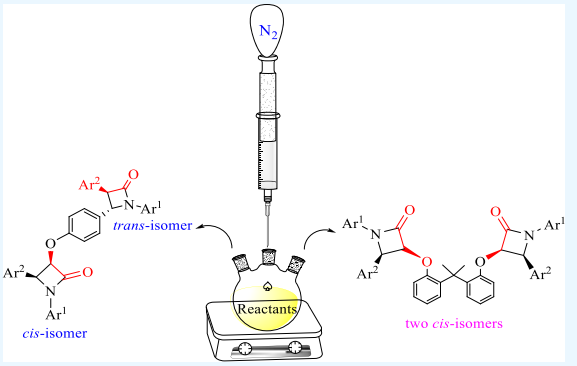
ABSTRACT: The synthesis of highly functionalized bis-β-lactams containing aromatic rings was achieved by thermal and microwave-assisted methods starting from easily available 2-(4-hydroxyphenyl)acetic acid and 2,2′-(propane-2,2-diyl)diphenol precursors. The approach to these valuable heterocyclic scaffolds involved formal [2π + 2π] cycloadditions between Schiff bases and novel bisketenes, which were generated in situ, followed by an electrocyclic reaction of zwitterionic intermediates. Reactions carried out under microwave irradiation were clean and gave high yields with significantly reduced reaction times. Interestingly, in the thermal method, the reaction proceeded in a stereospecific manner, and only the *trans*−*cis* or *cis*−*cis* isomers were formed. However, under the microwave conditions, the reaction proceeded stereoselectively, and other possible isomers such *trans*−*trans* and *cis*−*trans* isomers were formed in addition to the product formed under thermal conditions. More interestingly, when the two compounds that did not produce any products under thermal conditions were reacted under microwave conditions, one formed the *trans*−*cis* isomer and the other formed the *cis*−*trans* and *trans*−*trans* isomers as two products .



INTRODUCTION

The importance of heterocyclic compounds has been known to humans for a long time, so the synthesis of this family of compounds has been on the agenda of many chemists and pharmacists. Various articles about the preparation and application of heterocyclic compounds are published in the literature every day.[1−4] These compounds are widely used in various industries such as pharmaceuticals, food industries, pesticides, and herbicides.[5−12] One interesting heterocycle is the four-membered heterocycle of β-lactams, where the ring plays a key and effective role in the action of drugs.[13−16] β-Lactams, also called azitidine 2-ones, are quaternary cyclic amides that contain a nitrogen atom attached to a carbonyl group. Antimicrobial, antitumor, anti-inflammatory, antiseizure, antibiotic, anticancer, and antiviral properties have been reported for this family.[17,18] In addition, the β-lactam ring acts as a synthon for the synthesis of amino acid derivatives, peptides, polyamino alcohols, and esters.[19] Penicillins, cephalosporins, and carbapenems are some of the drugs known as antibiotics that have β-lactam rings.[20−22] Several methods have been reported for the synthesis of β-lactams.[23−26] Among the available methods for the preparation of β-lactams, the reactions of ketenes with imines are well documented and are mostly used mainly due to their simplicity.[27−29] Ketenes are highly active compounds that are formed and consumed as intermediates in some reactions. Their lifespans are very short, and there are only a few that can be stored in the refrigerator.[30−32] Some ketenes that are stable, have relatively good shelf lives, and can be stored in the refrigerator include diphenylketene, chlorocarbonylphenylketene, and ketenes with two bulky groups.[33,34] Ketenes react with many nucleophiles due to their high activity and form dimers if there is no other reactant in the medium.[35] Ketenes also participate in [2 + 2] cycloaddition reactions with various compounds, such as imines and alkenes, and rarely participate in [2 + 4] reactions. Although many papers have been published in the literature on the syntheses of β-lactams[36,37] and bis-β-lactams,[38] less attention has been paid to the simultaneous synthesis of bis-β-lactams in a one-pot reaction. In synthetic methods, a β-lactam ring is usually synthesized first, and then this β-lactam is the used as a starting material in the synthesis of the bis-β-lactam. The interesting point is that the simultaneous construction of two β-lactam rings gives rise to numerous geometric isomers. Therefore, it is very important to fine-tune the conditions and use precursor materials with

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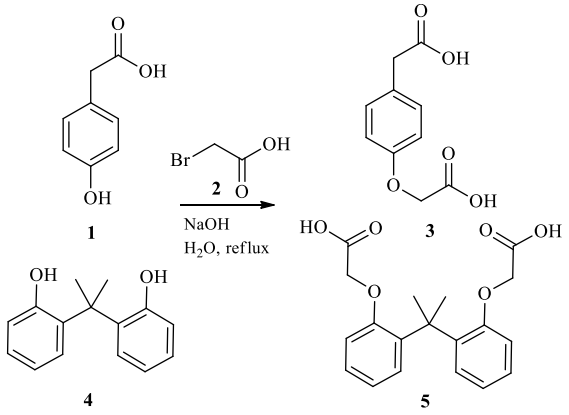
tuned electronic and spatial properties to perform the desired products. According to the above explanation, in view of the importance of azitidine 2-ones in the treatment of infectious diseases and other diseases, and as part of our program that involves the synthesis of new heterocyclic compounds,[17,39−47] we became interested in making novel bis-β-lactams. Here, we now report the preparation of new highly functional bis-β-lactams.

RESULTS AND DISCUSSION

To achieve the goal designed in this project, the desired dicarboxylic acids (**3** or **5**) were prepared using a modified procedure from the reaction of 2-(4-hydroxyphenyl) acetic acid **1** or 2,2′-(propane-2,2-diyl)diphenol **4**, respectively, with 2-bromoacetic acid in the presence of sodium hydroxide under reflux conditions in aqueous media.[48] Then, the solution was cooled and acidified with hydrochloric acid. The resulting solid was filtered and recrystallized from boiling water (Scheme 1).

Scheme 1. Synthesis of Dicarboxylic Acids 3 and 5



There are various procedures for activating carboxylic acids, and we used Mukaiyama's reagent to prepare bis-β-lactams from dicarboxylic acid and imines **6** in the presence of Et_3N in CH_2Cl_2 (Scheme 2).[35,46] To optimize the reaction conditions, we selected the reaction of 2-(4-(carboxymethoxy)phenyl)-acetic acid **3** with diphenylmethanimine **6** as a the model reaction. Treating imine **6** with bisketene **8**, which was generated in situ from compound **3** and carboxylic acids activators (such as Mukaiyama reagent), resulted products that were characterized as bis-β-lactams **9** on the basis of spectral data (Scheme 2). Several parameters were examined to obtain the product with the highest efficiency. To achieve this goal, we changed the following conditions: the acid activating agents, the time before the addition of Schiff base **6** (t_1), and the time interval from the addition of Schiff base **6** to the completion of the reaction (t_2). In the first experiment, compound **3** was reacted with the Mukaiyama reagent in CH_2Cl_2 for 8 h under reflux conditions. To the reaction mixture were then added imine **6** and Et_3N, and reflux continued for 10 h. The bis-β-lactam **9a** was obtained in a 55% yield. (Table 1, entry 1). Refluxing **3**, **6**, and **7** in CH_2Cl_2 with Et_3N as a base for 16 h was quite effective, and product **9a** was obtained in a 65% yield (Table 1, entry 2). Compound **9a** was synthesized in a 67% yield when the reaction was performed at a temperature of 50 °C for 5 h (Table 1, entry 3).

When the reaction was performed under microwave irradiation, the reaction time significantly decreased from hours to 15 min. The reaction of **3**, **6**, and **7** in the microwave at 100 °C for 15 or 25 min led to the production of compound **9** in a 75% or 78% yields, respectively (Table 1, entry 4 or 5, respectively). Solvents such as dichloromethane, toluene, and chloroform were used for the in situ generation of the mentioned ketene and its [2π + 2π] cycloaddition reaction with aromatic imine **6**. When the reaction was performed in dichloromethane, the corresponding bis-β-lactam **9** was obtained in an 83% yield (Table 1, entry 5). Using chloroform and toluene instead of dichloromethane reduced the yields of the product to 50% and 35%, respectively (Table 1, entries 6 and 7, respectively). Additionally, the reaction was performed in CH_2Cl_2 in the presence of benzenesulfonyl chloride as an activating reagent (Table 1, entry 8), but the efficiency was lower than that of the reaction in dichloromethane.

Using the optimal conditions, the different bis-β-lactams (**9a−9j** and **11a−f**, Tables 2 and 3) were synthesized in thermal and microwave conditions from the reaction of dicarboxylic acids **3** and **5** with various imines in the presence the Mukaiyama reagent and Et_3N.

As shown in Table 3, under thermal conditions, compounds **9a−9i** were formed only as *trans−cis* isomers and compounds **11a−11e** were formed only as *cis−cis* isomers, and in two cases

Scheme 2. Synthesis of Bis(β-Lactam) from Bisketene as an Intermediate

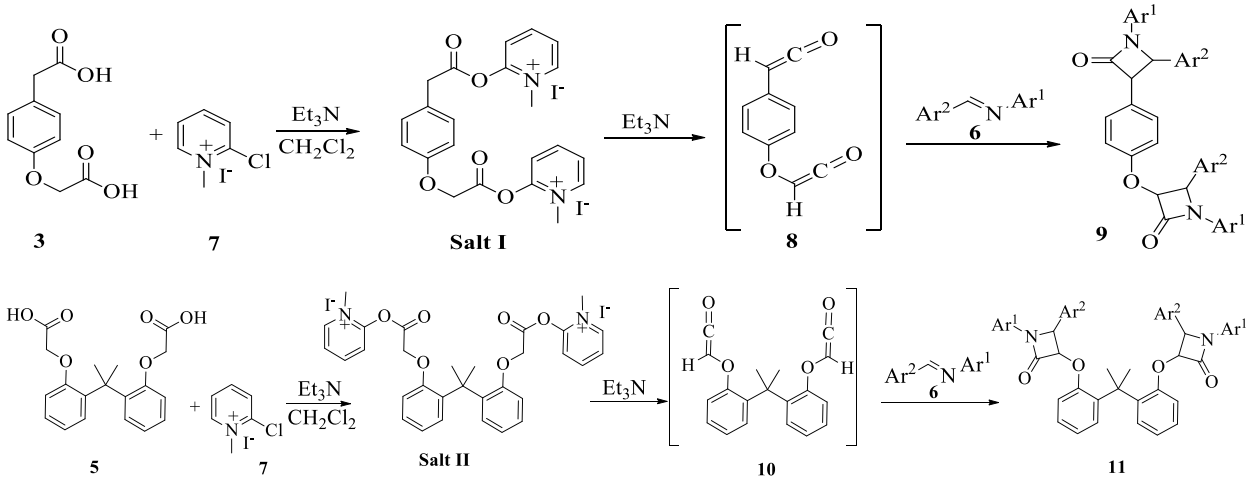


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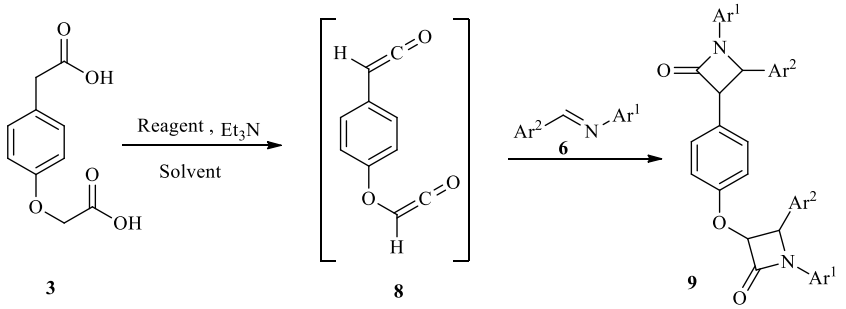
Table 1. Optimization of Reaction Conditions for the Synthesis of 9a as the Model Reaction



entry	product	solvent	reagent	condition	t_1 (h)	t_2 (h)	yield (%)
1	**9a**	CH_2Cl_2	Mukaiyama	reflux	8	10	55
2	**9a**	CH_2Cl_2	Mukaiyama	reflux	16	0	65
3	**9a**	CH_2Cl_2	Mukaiyama	50 °C	5	0	67
4	**9a**	CH_2Cl_2	Mukaiyama	MW, 100 °C	25 min	0	78
5	**9a**	CH_2Cl_2	Mukaiyama	MW, 100 °C	15 min	0	75
6	**9a**	$CHCl_3$	Mukaiyama	MW, 100 °C	15 min	0	50
7	**9a**	toluene	Mukaiyama	MW, 100 °C	20 min	0	35
8	**9a**	CH_2Cl_2	benzenesulfonyl chloride	MW, 100 °C	20 min	0	65

Table 2. Synthesis of Bis-β-lactams 9 and 11 at 50 °C

entry	product	acid	Ar^1	Ar^2	yield (*trans–cis*)	yield (*cis–trans*)	yield (*cis–cis*)	yield (*trans–trans*)
1	**9a**	**3**	4-BrC_6H_4	Ph	65	0	0	0
2	**9b**	**3**	Ph	4-$NO_2C_6H_4$	0	0	0	0
3	**9c**	**3**	4-ClC_6H_4	Ph	49	0	0	0
4	**9d**	**3**	Ph	4-ClC_6H_4	55	0	0	0
5	**9e**	**3**	Ph	4-BrC_6H_4	58	0	0	0
6	**9f**	**3**	4-BrC6H4	4-MeC_6H_4	48	0	0	0
7	**9g**	**3**	4-MeC_6H_4	4-ClC_6H_4	58	0	0	0
8	**9h**	**3**	Ph	Ph	67	0	0	0
9	**9i**	**3**	4-BrC_6H_4	2,4-$Cl_2C_6H_3$	31	0	0	0
10	**9j**	**3**	4-BrC_6H_4	4-$OMeC_6H_4$	0	0	0	0
11	**11a**	**5**	4-BrC_6H_4	2,4-$Cl_2C_6H_3$	0	0	61	0
12	**11b**	**5**	Ph	4-$NO_2C_6H_4$	0	0	0	0
13	**11c**	**5**	4-BrC_6H_4	4-MeC_6H_4	0	0	63	0
14	**11d**	**5**	4-MeC_6H_4	2,4-$Cl_2C_6H_3$	0	0	51	0
15	**11e**	**5**	Ph	4-ClC_6H_4	0	0	58	0
16	**11f**	**5**	4-ClC_6H_4	4-MeC_6H_4	0	0	44	0

Table 3. Preparation of Bis-β-lactams 9 and 11 under Microwave Irradiation

entry	product	acid	Ar^1	Ar^2	yield (*trans–cis*)	yield (*cis–trans*)	yield (*cis–cis*)	yield (*trans–trans*)
1	**9a**	**3**	4-BrC_6H_4	Ph	75	0	0	12
2	**9b**	**3**	Ph	4-$NO_2C_6H_4$	60	0	0	0
3	**9c**	**3**	4-ClC_6H_4	Ph	65	0	0	18
4	**9d**	**3**	Ph	4-ClC_6H_4	70	0	0	12
5	**9e**	**3**	Ph	4-BrC_6H_4	63	10	0	0
6	**9f**	**3**	4-BrC_6H_4	4-MeC_6H_4	71	0	0	13
7	**9g**	**3**	4-MeC_6H_4	4-ClC_6H_4	73	13	0	0
8	**9h**	**3**	Ph	Ph	69	15	0	0
9	**9i**	**3**	4-BrC_6H_4	2,4-$Cl_2C_6H_3$	71	0	0	10
10	**9j**	**3**	4-BrC_6H_4	4-$OMeC_6H_4$	77	0	0	0
11	**11a**	**5**	4-BrC_6H_4	2,4-$Cl_2C_6H_3$	0	0	71	0
12	**11b**	**5**	Ph	4-$NO_2C_6H_4$	61	0	0	21
13	**11c**	**5**	4-BrC_6H_4	4-MeC_6H_4	6	11	66	4
14	**11d**	**5**	4-MeC_6H_4	2,4-$Cl_2C_6H_3$	8	10	69	3
15	**11e**	**5**	Ph	4-ClC_6H_4	5	0	65	11
16	**11f**	**5**	4-ClC_6H_4	4-MeC_6H_4	8	4	70	5

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no product was obtained (entries 2 and 12). Table 3 shows the products formed under microwave conditions. As can be seen from Table 3, the number of formed isomers increased relative to that for the thermal conditions such that all possible isomers were formed for compounds **11c**, **11d**, and **11f**.

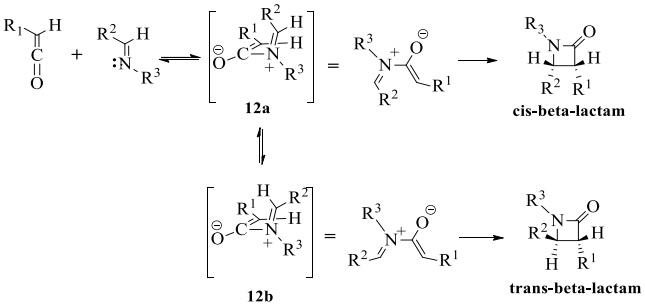
The structure of the products was fully characterized using the IR, ^{1}H NMR, and ^{13}C NMR spectra along with the elemental analysis data. The IR spectra of these compounds showed absorption bands at 1735−1760 and 1740−1766 cm^{-1} for compounds **9** and **11**, respectively, due to the carbonyl group. ^{1}H NMR spectroscopy is commonly used to distinguish between *cis*- and *trans*-isomers of *β*-lactams because the H−H coupling constant is larger (J = 4−6 Hz) in the *cis* -isomer than in the *trans*-isomer (J = 2−3 Hz). The ^{1}H NMR spectrum of **9a** (*trans*−*cis* isomer) exhibited two doublets at δ 4.41 and 5.33 ppm ($^3J_{HH}$ = 2.6 Hz) for the vicinal methine protons of the *β*-lactam without an oxygen atom and two doublets at δ 5.41 and 5.54 ppm ($^3J_{HH}$= 4.2 Hz) for the vicinal methine protons of the *β*-lactam containing oxygen atom, along with a multiplet at δ 6.89−7.56 ppm for the aromatic ring protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **9a** showed 26 distinct resonances, in agreement with the suggested structure; the partial assignment of these resonances is given in the Experimental Section. Characteristic ^{13}C NMR signals of the two carbonyl groups appeared at δ 170.93 and 167.56 ppm, and signals for the CH groups appeared at δ 72.65, 68.85, 67.95, and 67.24 ppm, respectively. The ^{1}H NMR and ^{13}C NMR spectroscopic data of compounds **9a−j** and **11a−f** are presented in the Experimental Section and the Supporting Information.

A reasonable mechanism for the formation of bisketenes is shown in Scheme 2. In this mechanism, salt **I** or **II** is first formed as an intermediate from the reaction of dicarboxylic acid **3** or **5** with Mukaiyama reagent **7** in the presence of Et_3N and then converted to the corresponding bisketene by an elimination reaction.

The stereochemistry in the cycloaddition reaction between the ketene and the imine involves the initial attack of the nitrogen atom of the imine on the C1 of the ketene to form the zwitterionic intermediate **12a**, which is in equilibrium with **12b**. The intermediate **12a** can be rapidly converted to *cis*-*β*-lactam by an electrocylic ring closure reaction via a conrotatory mode. *trans*-*β*-Lactam is also formed as a product from the less-crowded intermediate **12b** by the same electrocylic ring closure reaction. On the basis of research reports recorded in the literature so far,[49,50] the origin of the relative stereoselectivity can be explained as follows: (1) The ring closure step is most likely the intramolecular nucleophilic addition of enolate to the imine moiety, which is clearly influenced by the electronic effect of ketenes and imine substituents. (2) Electron-donating substituents on the ketene and electron-withdrawing substituents on the imine accelerate the direct ring closure, leading to a preference for *cis*-isomer formation, while electron-withdrawing substituents on the ketene and electron-donating substituents on the imine slow the direct ring closure, leading to a preference for *trans*-isomer formation. Finally, (3) the electronic effect of the substituents on the isomerization is a minor factor in terms of influencing the stereoselectivity.

According to the important points mentioned above and as shown in Scheme 4, one of the ketenes in bisketene **8** has an oxygen atom that acts as an electron donor group and causes the formation of *cis*-*β*-lactam under thermal conditions, while

Scheme 3. Plausible Mechanism for Formation of *trans*- and *cis*-*β*-Lactams from Ketene



the other ketene, which lacks an oxygen atom, produces *trans*-*β*-lactam. Bisketene **10**, in which both ketenes have oxygen atoms, also produces *cis*-*β*-lactams.

Under the microwave conditions, each ketene produces the same product created under thermal conditions as the major product, and the other *β*-lactam isomers are created as minor products. Therefore, it can be said that the reactions of the two ketenes are stereospecific in thermal conditions and stereoselective in microwave conditions.

CONCLUSIONS

In conclusion, a successful short route toward highly functionalized bis-*β*-lactams was achieved by thermal and microwave-assisted methods starting from easily accessible precursors. The reactions were performed via the formal [2π + 2π] cycloaddition of Schiff bases and novel bisketenes, which were generated in situ. Reactions performed under microwave irradiation were better than those performed under thermal conditions, and the products were formed in high yields with much shorter reaction times. Under thermal conditions, the reactions proceeded in a stereospecific manner; under the microwave conditions, the reactions proceeded stereoselectively.

EXPERIMENTAL SECTION

General Considerations. IR spectra were recorded on a commercial Spectrophotometer (Bruker Tensor 27 FT-IR). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 AVANCE III NMR Magnet spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) using DMSO-d_6 and $CDCl_3$ as solvents with TMS as the internal standard. ^{13}C NMR data are reported with complete proton decoupling. Elemental analysis (CHNS) was performed on a Costech-ECS 4010 CHNSO analyzer, and melting points were recorded on an Electrothermal-9200 system. Data are reported as follows: chemical shift δ_H and δ_C (ppm), coupling constants J (Hz), integration, and multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). Solvents for the reaction were distilled prior to use. Toluene, dichloromethane, *n*-hexane, and ethyl acetate were dried before used, and triethylamine (Et_3N) was dried over sodium wire. Column chromatography was carried out using 40 Å Sigma-Aldrich silica gel.

Modified Procedure for Synthesis of 2-(4-(Carboxymethoxy)phenyl)acetic Acid (3). A solution of sodium hydroxide (6g, 150 mmol) in 100 mL of water was slowly added to of 2-(4-hydroxyphenyl)acetic acid (7.6 g, 50 mmol) in 100 mL of water under stirring. Then, to this mixture was added a solution of 2-bromoacetic (6.95 g, 50 mmol mmol) in 30 mL of water, and the mixture heated for 24 h at

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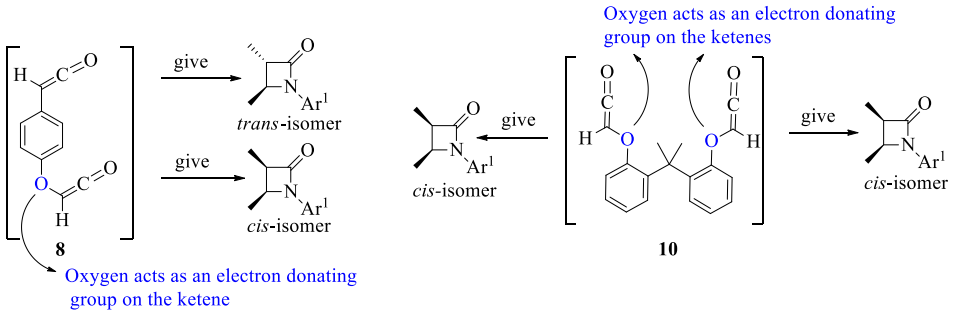
Scheme 4. Effect of Oxygen as an Electron-Donating Group on Ketene and the Product Formation Process



120−125 °C (oil bath temperature). The resulting solution was cooled, diluted with water, acidified with HCl, and allowed to remain at room temperature for 1 h. The formed precipitate was filtered and dissolved in a sodium bicarbonate solution, and the unreacted precursor was extracted with CH_2Cl_2. The aqueous layer was acidified and left at room temperature for 2 h. The formed solid was filtered, and 2-(4-(carboxymethoxy)-phenyl)acetic acid was obtained as the pure form after crystallization from boiling water. mp 179−181 °C. IR (ν_{max}, cm^{-1}): 1763 (C═O), 2750−3300 (OH).

General Procedure for Preparation of Imines (6a). Distilled aniline (50 mmol, 4.56 mL) was added to a solution of distilled benzaldehyde (50 mmol, 5.1 mL) in 10 mL of toluene. The mixture was heated under reflux for 7 h at 110 °C in the presence of calcium sulfate. The mixture was filtered to separate the calcium sulfate, then the solvent was evaporated. The *N*-benzylideneaniline was obtained as the pure form by crystallization from hexane.

Two Procedures for the Preparation of *β*-Lactams (9a). *Procedure A.* *N*-Benzylideneaniline **6a** (0.83 g, 4.58 mmol) and triethylamine (1.28 mL, 9.18 mmol) were added to a mixture of 2-(4-(carboxymethoxy)phenyl)acetic acid **3** (0.4 g, 1.91 mmol) and Mukaiyama's reagent (1.03 g, 4.04 mmol) in anhydrous dichloromethane (25 mL). Then the reaction mixture was heated under a nitrogen atmosphere for 5 h at 50 °C. After cooling, the solution was washed with water, a 5% HCl aqueous solution, and again with water. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude products were purified by column chromatography (silica gel, *n*-hexane/EtOAc, 10:3).

Procedure B. A microwave vial was charged with the imine **6a** (0.07 g, 0.4 mmol), 2-(4-(carboxymethoxy)phenyl)acetic acid **3** (0.04 g, 0.2 mmol), Mukaiyama's reagent (0.11 g, 0.2 mmol), triethylamine (0.11 mL, 0.8 mmol) and dichloro-methane. The reaction mixture was heated for 15 min in the microwave at 100 °C. After the completion of the reaction, the mixture was concentrated in vacuo and purified by column chromatography (silica gel, *n*-hexane/EtOAc, 10:3).

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-oxo-4-phenylazetidin-3-yl)oxy)phenyl)-4-phenylazetidin-2-one (**9a** trans−cis).* Yellow solid, 72.3 mg, 75%. mp 113−116 °C. Anal. Calcd for $C_{36}H_{26}Br_2N_2O_3$ (694.41): C, 62.27%; H, 3.77%; N, 4.03%. Found: C, 61.95%; H, 4.05%; N, 3.96%. IR (ν_{max}, cm^{-1}): 1748 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.89−7.56 (m, 23H, Ph), 4.41 (d, J = 2.6 Hz, 1H, CH), 5.33 (d, J = 2.6 Hz, 1H, CH), 5.41 (d, J = 4.2 Hz, 1H, CH), 5.54 (d, J = 4.2 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 170.93, 167.56, 161.37, 142.32, 141.39, 140.78, 140.28, 137.38, 137.33, 134.42, 134.36, 134.27, 133.84, 133.46, 133.39, 132.35, 131.56, 124.75, 124.29, 121.74, 120.95, 120.87, 72.65, 68.85, 67.95, 67.24.

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-oxo-4-phenylazetidin-3-yl)oxy)phenyl)-4-phenylazetidin-2-one (**9a** trans−trans).* Yellow solid, 11.57 mg, 12%. mp 100−102 °C. Anal. Calcd for $C_{36}H_{26}Br_2N_2O_3$ (694.41): C, 62.27%; H, 3.77%; N, 4.03%. Found: C, 62.19%; H, 3.95%; N, 4.27%. IR (ν_{max}, cm^{-1}): 1749 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.90−7.47 (m, 23H, Ph), 4.26 (d, J = 2.6 Hz, 1H, CH), 4.90 (d, J = 2.6 Hz, 1H, CH), 5.03 (d, J = 1.6 Hz, 1H, CH), 5.54 (broad peak, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.81, 162.34, 156.04, 136.86, 136.35, 135.79, 134.89, 132.25, 132.16, 129.64, 129.45, 128.94, 128.89, 128.86, 128.41, 126.43, 125.84, 119.18, 118.78, 117.60, 116.88, 116.02, 87.49, 64.70, 64.67, 64.16.

*4-(4-Nitrophenyl)-3-(4-(((2-(4-nitrophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)-1-phenylazetidin-2-one (**9b** trans−trans).* White solid, 60.7 mg, 60%. mp 150−152 °C. Anal. Calcd for $C_{36}H_{26}N_4O_7$ (696.61): C, 69%; H, 4.18%; N, 8.94%. Found: C, 68.76%; H, 4.05%; N, 9.08%. IR (ν_{max}, cm^{-1}): 1737 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.89−7.50 (m, 22H, Ph), 4.38 (d, J = 2.7 Hz, 1H, CH), 5.27 (d, J = 2.7 Hz, 1H, CH), 5.81 (d, J = 4.9 Hz, 1H, CH), 5.92 (d, J = 4.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.89, 163.08, 156.43, 137.29, 136.98, 136.96, 133.52, 132.66, 130.41, 129.88, 129.69, 129.54, 129.23, 129.17, 128.83, 128.80, 128.52, 125, 124.48, 117.58, 117.49, 116.06, 81.10, 63.62, 61.70, 60.56.

*1-(4-Chlorophenyl)-3-(4-(((1-(4-chlorophenyl)-2-oxo-4-phenylazetidin-3-yl)oxy)phenyl)-4-phenylazetidin-2-one (**9c** trans−cis).* Yellow solid, 54.6 mg, 65%. mp 198−200 °C: Anal. Calcd For $C_{36}H_{26}Cl_2N_2O_3$ (605.51): C, 71.41%; H, 4.33%; N, 4.63%. Found: C, 71.46%; H, 3.99%; N, 4.39%. IR (ν_{max}, cm^{-1}): 1756 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.86−7.45 (m, 22H, Ph), 4.37 (d, J = 2.6 Hz, 1H, CH), 5.26 (d, J = 2.6 Hz, 1H, CH), 5.79 (d, J = 4.9 Hz, 1H, CH), 5.92 (d, J = 4.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.09, 163.31, 156.51, 137.58, 136.25, 135.93, 133.16, 129.82, 129.60, 129.15, 129.07, 129.04, 128.79, 128.65, 128.53, 128.41, 128.17, 127.60, 126.81, 119.26, 119.16, 116.09, 81.36, 63.95, 62.56, 61.48.

*1-(4-Chlorophenyl)-3-(4-(((1-(4-chlorophenyl)-2-oxo-4-phenylazetidin-3-yl)oxy)phenyl)-4-phenylazetidin-2-one (**9c** trans−trans).* Yellow solid, 15.1 mg, 18%. mp 213-215 °C. Anal. Calcd for $C_{36}H_{26}Cl_2N_2O_3$ (605.51): C, 71.41%; H, 4.33%; N, 4.63%. Found: C, 71.34%; H, 4.70%; N, 4.86%. IR (ν_{max}, cm^{-1}): 1754 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.89−7.57 (m, 22H, Ph), 4.42 (d, J = 2.6 Hz, 1H, CH), 5.33 (d, J = 2.6 Hz, 1H, CH), 5.41 (d, J = 3.3 Hz, 1H, CH), 5.55 (d, J = 3.3 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ

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166.16, 162.78, 156.63, 137.59, 136.26, 135.59, 135.55, 129.74, 129.67, 129.61, 129.51, 129.09, 128.91, 128.73, 128.66, 128.18, 127.60, 126.82, 119.67, 119.19, 116.13, 116.09, 86.84, 64.09, 63.24, 62.54.

*4-(4-Chlorophenyl)-3-(4-(((2-(4-chlorophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)-1-phenylazetidin-2-one (**9d** trans−cis).* White solid, 58.8 mg, 70%. mp 171−172 °C. Anal. Calcd for $C_{36}H_{26}Cl_2N_2O_3$ (605.51): C, 71.41%; H, 4.33%; N, 4.63%. Found: C, 71.30%; H, 4.20%; N, 4.96%. IR (ν_{max}, cm^{-1}): 1755 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.71−7.31 (m, 22H, Ph), 4.06 (d, J = 2.6 Hz, 1H, CH), 4.73 (d, J = 2.6 Hz, 1H, CH), 5.31 (d, J = 4.9 Hz, 1H, CH), 5.46 (d, J = 4.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165,.40, 162.62, 156.60, 137.20, 136.62, 135.94, 134.79, 134.56, 131.14, 129.60, 129.49, 129.31, 129.23, 128.86, 128.55, 128.37, 127.25, 124.93, 124.33, 117.54, 117.17, 116.27, 81.13, 64.46, 63.27, 61.30.

*4-(4-Chlorophenyl)-3-(4-(((2-(4-chlorophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)-1-phenylazetidin-2-one (**9d** trans−trans).* White solid, (10.0 mg, 12%). mp 185−187 °C. Anal. Calcd for $C_{36}H_{26}Cl_2N_2O_3$ (605.51): C, 71.41%; H, 4.33%; N, 4.63%. Found: C, 71.81%; H, 4.14%; N, 4.75%. IR (ν_{max}, cm^{-1}): 1756 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.90−7.47 (m, 22H, Ph), 4.21 (d, J = 2.5 Hz, 1H, CH), 4.90 (d, J = 2.5 Hz, 1H, CH), 5.04 (broad peak 1H, CH), 5.11 (d, J = 3.2 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.40, 162.11, 156.68, 137.16, 136.58, 135.91, 135.26, 134.60, 133.95, 130.93, 129.83, 129.62, 129.29, 128.92, 128.43, 127.85, 127.26, 124.93, 124.36, 117.60, 117.17, 116.02, 87.20, 68018, 64.57, 63.30.

*4-(4-Bromophenyl)-3-(4-(((2-(4-bromophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)-1-phenylazetidin-2-one (**9e** trans−cis).* White solid, 60.7 mg, 63%. mp 180−183 °C. Anal. Calcd for $C_{36}H_{26}Br_2N_2O_3$ (694.41): C, 62.27%; H, 3.77%; N, 4.03%. Found: C, 62.51%; H, 3.66%; N, 4.24%. IR (ν_{max}, cm^{-1}): 1756 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.89−7.49 (m, 22H, Ph), 4.83 (d, J = 2.6 Hz, 1H, CH), 5.27 (d, J = 2.6 Hz, 1H, CH), 5.81 (d, J = 4.8 Hz, 1H, CH), 5.92 (d, J = 4.8 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.88, 163.08, 156.44, 137.31, 137.02, 136.98, 133.51, 132.69, 130.43, 129.88, 129.69, 129.54, 129.24, 129.19, 128.84, 128.81, 128.54, 124.98, 124.45, 117.57, 117.49, 116.06, 81.12, 63.61, 61.66, 60.55.

*4-(4-Bromophenyl)-3-(4-(((2-(4-bromophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)-1-phenylazetidin-2-one (**9e** cis−trans).* White solid, 9.6 mg, 10%. mp 170−172 °C. Anal. Calcd for $C_{36}H_{26}Br_2N_2O_3$ (694.41): C, 62.27%; H, 3.77%; N, 4.03%. Found: C, 62.25%; H, 4.02%; N, 3.63%. IR (ν_{max}, cm^{-1}): 1735 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.71−7.31 (m, 22H, Ph), 4.40 (d, J = 2.6 Hz, 1H, CH), 5.33 (d, J = 2.6 Hz, 1H, CH), 5.42 (d, J = 4.2 Hz, 1H, CH), 5.54 (d, J = 4.2 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.96, 162.60, 156.61, 137.31, 137.01, 136.60, 134.97, 134.07, 133.52, 129.79, 129.69, 129.64, 129.61, 129.56, 128.82, 128.64, 125.13, 124.47, 118, 117.51, 116.06, 116.04, 86.44, 63.78, 62.26, 61.58.

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)oxy)phenyl)-4-(p-tolyl)azetidin-2-one (**9f** trans−cis).* White solid, 71.2 mg, 71%. mp 148−149 °C. Anal. Calcd for $C_{38}H_{30}Br_2N_2O_3$ (722.46): C, 63.17%; H, 4.19%; N, 3.88%. Found: C, 63.26%; H, 4.36%; N, 3.40%. IR (ν_{max}, cm^{-1}): 1756 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.87−7.58 (m, 20H, Ph), 4.34 (d, J = 2.6 Hz, 1H, CH), 5.20 (d, J = 2.6 Hz, 1H, CH), 5.73 (d, J = 4.8 Hz, 1H, CH), 5.87 (d, J = 4.8 Hz, 1H, CH), 2.24(s, 3H, CH_3), 2.3(s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.20, 163.38, 156.61, 138.48, 138.30, 136.66, 136.32, 134.52, 132.69, 132.47, 130.15, 130.08, 129.49, 129.17, 128.50, 126.78, 125.82, 119.58, 119.49, 116.64, 116.13, 116.09, 81.40, 64.02. 63.99, 61.36, 22.88, 21.21.

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)oxy)phenyl)-4-(p-tolyl)azetidin-2-one (**9f** trans−trans).* White solid, 13.0 mg, 13%. mp 125−128 °C. Anal. Calcd for $C_{38}H_{30}Br_2N_2O_3$ (722.46): C, 63.17%; H, 4.19%; N, 3.88%. Found: C, 62.98%; H, 4.19%; N, 3.55%. IR (ν_{max}, cm^{-1}): 1752(C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.88−7.45 (m, 20H, Ph), 4.38 (d, J = 2.6 Hz, 1H, CH), 5.27 (d, J = 2.6 Hz, 1H, CH), 5.36 (d, J = 1.5 Hz, 1H, CH), 5.50 (d, J = 1.5 Hz, 1H, CH), 2.31(s, 3H. CH_3), 2.33(s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.87, 162.76, 156.59, 139.05, 138.49, 136.28, 135.60, 134.53, 132.51, 130.24, 130.16, 129.73, 129.59, 129.50, 128.84, 128.66, 128.10, 127.56, 126.79, 119.65, 119.16, 116.03, 88.79, 64.11, 63.12, 62.43, 21.27, 21.21.

*4-(4-Chlorophenyl)-3-(4-(((2-(4-chlorophenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl)oxy)phenyl)-1-(p-tolyl)azetidin-2-one (**9g** trans−cis).* White solid, 64.2 mg, 73%. mp 134−136 °C. Anal. Calcd for $C_{38}H_{30}C_{l2}N_2O_3$ (633.56): C, 72.04%; H, 4.77%; N, 4.42%. Found: C, 71.87%; H, 4.80%; N, 4.14%. IR (ν_{max}, cm^{-1}): 1735 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.82−7.42 (m, 20H, Ph), 4.15 (d, J = 2.6 Hz, 1H, CH), 4.82 (d, J = 2.6 Hz, 1H, CH), 5.39 (d, J = 4.8 Hz, 1H, CH), 5.58 (d, J = 4.8 Hz, 1H, CH), 2.32 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.18, 163.32, 156.60, 136.06, 134.73, 134.66, 134.50, 134.17, 133.94, 131.23, 129.77, 129.69, 129.55, 128.79, 128.56, 128.52, 128.46, 128.42, 127.23, 117.47, 117.10, 116.23, 81.09, 64.43, 63.24, 61.25, 20.97, 20.93.

*4-(4-Chlorophenyl)-3-(4-(((2-(4-chlorophenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl)oxy)phenyl)-1-(p-tolyl)azetidin-2-one (**9g** cis−trans).* White solid, 11.4 mg, 13%. mp 150−152 °C. Anal. Calcd for $C_{38}H_{30}Cl_2N_2O_3$ (633.56): C, 72.04%; H, 4.77%; N, 4.42%. Found: C, 72.30%; H, 4.51%; N, 4.35%. IR (ν_{max}, cm^{-1}) 1749 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.61−7.73 (m, 20H, Ph), 4.37 (d, J = 2.9 Hz, 1H, CH), 5.47 (d, J = 2.9 Hz, 1H, CH), 5.96 (d, J = 4.7 Hz, 1H, CH), 5.58 (d, J = 4.7 Hz, 1H, CH), 2.27 (s, 6H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.39, 162.92, 156.50, 134.78, 134.48, 134.43, 134.16, 133.90, 133.48, 130.37, 130.20, 129.90, 129.52, 129.40, 129.01, 128.97, 128.46, 127.93, 117.48, 117.42, 116.18, 116.04, 81.23, 63.01, 62.98, 59.48, 20.96, 20.94.

*3-(4-(((2-Oxo-1,4-diphenylazetidin-3-yl)oxy)phenyl)-1, 4-diphenylazetidin-2-one (**9h** trans−cis).* White solid, 51.4 mg, 69%. mp 160−163 °C. Anal. Calcd for $C_{36}H_{28}N_2O_3$ (536.62): C, 80.58%; H, 5.26%; N, 5.22%. Found: C, 80.30%; H, 5.53%; N, 5.2%. IR (ν_{max}, cm^{-1}): 1756 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.81−7.43 (m, 24H, Ph), 4.19 (d, J = 2.6 Hz, 1H, CH), 4.87 (d, J = 2.6 Hz, 1H, CH), 5.44 (d, J = 4.8 Hz, 1H, CH), 5.60 (d, J = 4.8 Hz, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.71, 162.87, 156.66, 137.48, 136.90, 130.46, 129.30, 129.19, 129.10, 128.86, 128.85, 128.67, 128.51, 128.50, 128.45, 128.13, 128.85, 124.69, 124.08, 117.62, 117.21, 116.35, 81.25, 64.44, 36.90, 62.03.

*3-(4-(((2-Oxo-1, 4-diphenylazetidin-3-yl) oxy) phenyl)-1,4-diphenylazetidin-2-one (**9h** cis−trans).* White solid, 11.17 mg, 15%. mp 152−153 °C. Anal. Calcd for $C_{36}H_{28}N_2O_3$ (536.62): C, 80.58%; H, 5.26%; N, 5.22%. Found: C, 80.35%; H, 5.25%; N, 5.55%. IR (ν_{max}, cm^{-1}): 1754 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.88−7.48 (m, 24H, Ph), 4.34 (d, J = 2.5 Hz, 1H, CH), 5.23 (d, J = 2.5 Hz, 1H,

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CH), 5.77 (d, J = 4.7 Hz, 1H, CH), 5.90 (d, J = 4.7 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.74, 166.25, 157.83, 138.90, 138.08, 137.55, 130.44, 129.63, 129.54, 129.30, 129.22, 129.17, 128.94, 128.48, 128.33, 127.58, 126.80, 124.33, 120.17, 117.50, 115.57, 115.23, 70.27, 66.09, 63.97, 56.39.

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-4-oxoazetidin-3-yl)oxy)phenyl)-4-(2,4-dichlorophenyl)azetidin-2-one (**9i** trans−cis).* Yellow solid, 82.0 mg, 71%. mp 201−203 °C. Anal. Calcd for $C_{36}H_{22}Br_2Cl_4N_2O_3$ (832.19): C, 51.96%; H, 2.66%; N, 3.37%. Found: C, 51.73%; H, 2.49%; N, 3.1%. IR (ν_{max}, cm^{-1}): 1763 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.88−7.88 (m, 18H, Ph), 4.43 (d, J = 4.2 Hz, 1H, CH), 5.54 (d, J = 4.2 Hz, 1H, CH), 5.60 (d, J = 2 Hz, 1H, CH), 5.67 (d, J = 2 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.77, 163.32, 156.46, 136.42, 136.09, 134.43, 134.29, 134.06, 133.48, 132.87, 132.65, 129.98, 129.75, 129.55, 128.96, 128.83, 128.53, 128.01, 119.88, 119.59, 119.53, 117.22, 117.02, 116.48, 116.23, 116.09, 81.51, 63.29, 63.26, 59.67.

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-(2, 4-dichlorophenyl)-4-oxoazetidin-3-yl)oxy)phenyl)-4-(2,4-dichlorophenyl)azetidin-2-one (**9i** trans−trans).* Yellow solid, 11.5 mg, 10%. mp 212−215 °C. Anal. Calcd for $C_{36}H_{22}Br_2Cl_4N_2O_3$ (832.19): C, 51.96%; H, 2.66%; N, 3.37%. Found: C, 51.66%; H, 3.01%; N, 3.67%. IR (ν_{max}, cm^{-1}): 1761 (C═O). ^{1}H NMR (500 MHz; $CDCl_3$): δ 6.79−7.41 (m, 18H, Ph), 4.19 (d, J = 2.7 Hz, 1H, CH), 4.81 (d, J = 2.7 Hz, 1H, CH), 5.39 (d, J = 2.9 Hz, 1H, CH), 5.52 (d, J = 2.9 Hz, 1H, CH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.71, 163.23, 156.50, 137.20, 136.86, 134.44, 134.38, 134.21, 133.98, 133.49, 130.37, 130.02, 129.94, 129.84, 129.56, 129.46, 128.95, 128.91, 128.51, 127.97, 125.21, 124.68, 117.83, 117.47, 116.20, 116.06, 81.14, 63.07, 59.49, 58.01.

*1-(4-Bromophenyl)-3-(4-(((1-(4-bromophenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)oxy)phenyl)-4-(4-methoxyphenyl)azetidin-2-one (**9j** trans−cis).* Yellow solid, 80.6 mg, 77%. mp 132−135 °C. Anal. Calcd for $C_{38}H_{30}Br_2N_2O_5$ (754.46): C, 60.49%; H, 4.01%; N, 3.71%. Found: C, 60.59%; H, 4.40%; N, 3.85%. IR (ν_{max}, cm^{-1}): 1751(C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.85−7.91 (m, 20H, Ph), 4.34 (d, J = 2.3 Hz, 1H, CH), 5.19 (d, J = 2.3 Hz, 1H, CH), 5.72 (d, J = 4.6 Hz, 1H, CH), 5.86 (d, J = 4.6 Hz, 1H, CH), 3.70 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.55, 162.76, 156.44, 137.07, 134.88, 134.55, 134.22, 133.64, 133.45, 132.78, 130.41, 130.23, 130.05, 129.51, 129.19, 129.14, 128.80, 128.60, 128.56, 117.54, 117.49, 116.03, 81.11, 63.58, 63.56, 61.62, 61.55, 60.49.

*1-(4-Bromophenyl)-3-(2-(2-(2-(((1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-4-oxoazetidin-3-yl)oxy)phenyl)propan-2-yl)phenoxy)-4-(2,4-dichlorophenyl)azetidin-2-one (**11a** cis−cis).* White solid, 131.5 mg, 71%. mp 219−221 °C. Anal. Calcd for $C_{45}H_{32}Br_2Cl_4N_2O_4$ (966.37): C, 55.93%; H, 3.34%; N, 2.90%. Found: C, 55.84%; H, 3.64%; N, 2.95%. IR (ν_{max}, cm^{-1}): 1740 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.89−7.50 (m, 22H, Ph), 5.94 (d, J = 5.1 Hz, 2H, 2CH), 5.97 (d, J = 5.1 Hz, 2H, 2CH), 1.53 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.54, 154.82, 144.75, 136.14, 135.81, 134.47, 134.22, 132.85, 130.22, 129.55, 128.08, 127.86, 119.83, 119.49, 117.18, 116.96, 115.48, 81.75, 58.26, 31.02, 29.97.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(4-(4-nitrophenyl)-1-phenylazetidin-2-one) (**11b** trans−cis).* White solid, 88.9 mg, 61%. mp 226−227 °C. Anal. Calcd for $C_{45}H_{36}N_4O_8$ (760.79): C, 71.04%; H, 4.77%; N, 7.36%. Found: C, 71.34%; H, 4.32%; N, 7.33%. IR (ν_{max}, cm^{-1}): 1741 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.99−7.72 (m, 26H, Ph), 5.40 (broad peak, 1H, CH), 5.44 (d, J = 1.7 Hz, 1H, CH), 5.73 (d, J = 4.8 Hz, 1H, CH), 5.87 (d, J = 4.8 Hz, 1H, CH), 1.53 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.50, 162.96, 154.92, 154.73, 144.87, 144.09, 135.95, 135.64, 133.20, 132.08, 129.81, 129.73, 129.65, 129.58, 129.12, 128.96, 128.89, 128.87, 128.66, 128.60, 12854, 12817, 128.06, 127.77, 127.59, 122.34, 119.65, 119.24, 115.16, 115.10, 87.09, 81.34, 63.31, 61.46, 31.05, 30.26, 28.83.

*4-(4-Nitrophenyl)-3-(2-(2-(2-(((2-(4-nitrophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)propan-2-yl)phenoxy)-1-phenylazetidin-2-one (**11b** trans−trans).* White solid, 30.6 mg, 21%. mp 197−199 °C. Anal. Calcd for $C_{45}H_{36}N_4O_8$ (760.79): C, 71.04%; H, 4.77%; N, 7.36%. Found: C, 71.11%; H, 4.42%; N, 7.09%. IR (ν_{max}, cm^{-1}): 1763 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.74−7.54 (m, 26H, Ph), 5.39 (d, J = 1.7 Hz, 2H, 2CH), 5.43 (d, J = 1.7 Hz, 2H, 2CH), 1.56 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.94, 154.95, 144.65, 135.66, 135.63, 132.08, 129.74, 129.64, 129.55, 128.83, 128.10, 127.59, 125.95, 119.62, 115.15, 87.07, 63.25, 30.98, 30.26.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(1-(4-bromophenyl)-4-(p-tolyl)azetidin-2-one) (**11c** trans−cis).* White solid, 11.1 mg, 6%. mp 213-214 °C. Anal. Calcd for $C_{47}H_{40}Br_2N_2O_4$ (856.64): C, 65.90%; H, 4.71%; N, 3.27%. Found: C, 66.01%; H, 4.55%; N, 3.35%. IR (ν_{max}, cm^{-1}): 1767 (C═O). ^{1}H NMR (300 MHz; DMSO-d_6): δ 6.65−7.57 (m, 24H, Ph), 5.33 (d, J = 1.7 Hz, 1H, CH), 5.39 (d, J = 1.7 Hz, 1H, CH), 5.68 (d, J = 4.5 Hz, 1H, CH), 5.82 (d, J = 4.5 Hz, 1H, CH), 1.50 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.33 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.65, 162.98, 155.57, 154.98, 145.25, 144.31, 140.84, 138.96, 138.21, 136.37, 136.07, 132.67, 132.59, 132.19, 132.06, 130.22, 129.38, 129.13, 128.52, 128.07, 127.90, 127.74, 127.51, 119.96, 119.56, 116.87, 116.58, 115.26, 115.13, 115.04, 87.81, 81.58, 63.19, 61.51, 31.22, 31.14, 3.99, 22.87, 21.27.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(1-(4-bromophenyl)-4-(p-tolyl)azetidin-2-one) (**11c** cis−trans).* White solid, 18.0 mg, 11%. mp 180−182 °C. Anal. Calcd for $C_{47}H_{40}Br_2N_2O_4$ (856.64): C, 65.90%; H, 4.71%; N, 3.27%. Found: C, 66.10%; H, 4.41%; N, 3.51%. IR (ν_{max}, cm^{-1}): 1765 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.70−7.42 (m, 24H, Ph), 4.99 (d, J = 2.2 Hz, 1H, CH), 5.08 (d, J = 2.2 Hz, 1H, CH), 5.35 (d, J = 4.9 Hz, 1H, CH), 5.54 (d, J = 4.9 Hz, 1H, CH), 1.59 (s, 6H, $2CH_3$), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.34, 162.81, 155, 154.92, 144.80, 144.53, 144.50, 139.39, 138.73, 135.93, 132.19, 132.01, 130.23, 129.23, 129.07, 129.06, 129.03, 128.82, 128.06, 127.91, 127.58, 126.37, 119.19, 119.17, 117.40, 117.31, 115.41, 115.37, 114.82, 114.79, 87.80, 81.71, 64.15, 62.03, 30.91, 30.38, 28.95, 21.30, 21.27.

*1-(4-Bromophenyl)-3-(2-(2-(2-(((1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl) oxy)phenyl) propan-2-yl)-phenoxy)-4-(p-tolyl)azetidin-2-one (**11c** trans−trans).* White solid, (6.5 mg, 4%). mp 226−227 °C. Anal. Calcd for $C_{47}H_{40}Br_2N_2O_4$ (856.64): C, 65.90%; H, 4.71%; N, 3.27%. Found: C, 65.66%; H, 4.78%; N, 3.11%. IR (ν_{max}, cm^{-1}): 1766 (C═O). ^{1}H NMR (300 MHz; $CDCl_3$): δ 6.65−7.30 (m, 24H, Ph), 4.88 (d, J = 1.7 Hz, 2H, 2CH), 4.96 (d, J = 1.7 Hz, 2H, 2CH), 1.50 (s, 3H, CH_3), 1.5 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$). ^{13}C NMR δ_C (75 MHz, $CDCl_3$): δ 162.80, 154.97, 144.69, 139.38, 135.94, 132.18, 132, 130.91, 130.22, 128.82,

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127.94, 126.37, 119.18, 117.40, 114.87, 87.81, 64.13, 30.38, 28.95, 21.29.

*1-(4-Bromophenyl)-3-(2-(2-(2-(((1-(4-bromophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)oxy)phenyl)propan-2-yl)-phenoxy)-4-(p-tolyl)azetidin-2-one (**11c** cis−cis).* White solid, 108.3 mg, 66%. mp 198−200 °C. Anal. Calcd for $C_{47}H_{40}Br_2N_2O_4$ (856.64): C, 65.90%; H, 4.71%; N, 3.27%. Found: C, 65.92%; H, 4.98%; N, 3.49%. IR (ν_{max}, cm^{-1}): 1761 (C═O). ^1H NMR (500 MHz; $CDCl_3$): δ 6.81−7.38 (m, 24H, Ph), 5.37 (d, J = 4.6 Hz, 2H, 2CH), 5.54 (d, J = 4.6 Hz, 2H, 2CH), 1.28 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.48, 163.64, 156.03, 154.92, 144.79, 144.39, 143.62, 138.25, 138.22, 136.34, 132.66, 132.17, 132.08, 132, 130.17, 129.37, 129.13, 128.51, 127.87, 127.78, 127.71, 127.50, 122.10, 119.58, 116.59, 115.79, 115.24, 115.15, 115.09, 114.49, 81.52, 67.91, 67.54, 61.40, 31.06, 30.27, 28.83, 22.86, 21.20.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(4-(2,4-dichlorophenyl)-1-(p-tolyl)azetidin-2-one) (**11d** cis−trans).* White solid, 16.04 mg, 10%. mp 212−214 °C. Anal. Calcd for $C_{47}H_{38}Cl_4N_2O_4$ (836.63): C, 67.47%; H, 4.58%; N, 3.35%. Found: C, 67.56%; H, 4.30%; N, 3.44%. IR (ν_{max}, cm^{-1}): 1764 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.72−7.58 (m, 22H, Ph), 5.38 (broad peak, 1H, CH), 5.41 (d, J = 2.3 Hz, 1H, CH), 5.73 (d, J = 6.1 Hz, 1H, CH), 5.85 (d, J = 6.1 Hz, 1H, CH), 1.54 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.94, 162.43, 154.96, 154.67, 144.81, 144.17, 144.12, 135.11, 134.61, 134.37, 134.21, 134.17, 134, 133.38, 132.81, 132.20, 132.03, 130.41, 130.19, 130.12, 129.58, 129.53, 129.12, 128.62, 128.58, 128.49, 128.13, 128.08, 127.77, 121.85, 118.02, 117.54, 115.17, 115.14, 86.78, 81.16, 62.37, 60.52, 31.08, 30.95, 28.84, 22.86, 20.92.

*4-(2,4-Dichlorophenyl)-3-(2-(2-(2-(((2-(2,4-dichlorophenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl)oxy)phenyl)propan-2-yl)-phenoxy)-1-(p-tolyl)azetidin-2-one (**11d** cis−cis).* Yellow solid, 110.6 mg, 69%. mp 198−200 °C. Anal. Calcd for $C_{47}H_{38}Cl_4N_2O_4$ (836.63): C, 67.47%; H, 4.58%; N, 3.35%. Found: C, 67.45%; H, 4.71%; N, 3.33%. IR (ν_{max}, cm^{-1}): 1754 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.72−7.56 (m, 22H, Ph), 5.72 (d, J = 4.6 Hz, 2H, 2CH), 5.85 (d, J = 4.6 Hz, 1H, CH), 1.56 (s, 6H, $2CH_3$), 2.24 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.91, 154.65, 143.83, 134.59, 134.15, 133.37, 132.80, 130.43, 130.21, 129.55, 128.65, 127.86, 121.45, 120.15, 117.51, 115.12, 114.49, 81.14, 60.50, 31.08, 30.95, 20.95.

*4-(2,4-Dichlorophenyl)-3-(2-(2-(2-(((2-(2,4-dichlorophenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl)oxy)phenyl)propan-2-yl)-phenoxy)-1-(p-tolyl)azetidin-2-one (**11d** trans−trans).* Yellow solid, 4.8 mg, 3%. mp 219−220 °C. Anal. Calcd for $C_{47}H_{38}Cl_4N_2O_4$ (836.63): C, 67.47%; H, 4.58%; N, 3.35%. Found: C, 67.47%; H, 4.22%; N, 3.48%. IR (ν_{max}, cm^{-1}): 1762 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.73−8.03 (m, 22H, Ph), 5.38 (d, J = 1.6 Hz, 2H, 2CH), 5.41 (d, J = 1.6 Hz, 1H, CH), 1.58 (s, 6H, $2CH_3$), 2.23 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.68, 162.44, 156.29, 154.98, 148.77, 146.38, 144.96, 144.63, 139.07, 136.92, 136.73, 136.03, 135.11, 134.37, 134.19, 134.15, 133.96, 133.26, 132.18, 132.08, 130.14, 130.08, 129.58, 129.56, 129.46, 129.13, 128.87, 128.14, 128.09, 125.95, 122, 120.95, 118, 115.14, 86.73, 81.38, 67.90, 62.31, 31, 30.27, 28.84, 22.87, 20.98.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(4-(2,4-dichlorophenyl)-1-(p-tolyl)azetidin-2-one) (**11d** trans−cis).* Yellow solid, 12.8 mg, 8%. mp 235−237 °C. Anal. Calcd for $C_{47}H_{38}Cl_4N_2O_4$ (836.63): C, 67.47%; H, 4.58%; N, 3.35%. Found: C, 67.44%; H, 4.67%; N, 3.49%. IR (ν_{max}, cm^{-1}): 1758 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.47−7.89 (m, 22H, Ph), 5.73 (d, J = 4.7 Hz, 2H, 2CH), 5.86 (d, J = 2.3 Hz, 2H, 2CH), 1.56 (s, 6H, $2CH_3$), 2.24 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.36, 155.72, 143.83, 134.58, 134.16, 130.43, 130.20, 129.53, 128.64, 128.56, 127.97, 127.90, 121.45, 120.14, 117.52, 115.11, 114.43, 81.11, 67.78, 31.09, 30.27, 20.93.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(4-(4-chlorophenyl)-1-phenylazetidin-2-one) (**11e** trans−cis).* White solid, 7.0 mg, 5%. mp 201−204 °C. Anal. Calcd for $C_{45}H_{36}Cl_2N_2O_4$ (739.68): C, 73.07%; H, 4.91%; N, 3.79%. Found: C, 72.80%; H, 5.06%; N, 3.78%. IR (ν_{max}, cm^{-1}): 1760 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.65−7.61 (m, 26H, Ph), 5.42 (broad peak, 1H, CH), 5.44 (d, J = 2 Hz, 1H, CH), 5.75 (d, J = 4.6 Hz, 1H, CH), 5.86 (d, J = 4.6 Hz, 1H, CH), 1.54 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.24, 162.79, 154.93, 154.62, 144.83, 144.20, 144.15, 140.84, 137, 136.64, 135.06, 134.04, 133.43, 132.71, 130.43, 129.86, 129.78, 129.64, 129.57, 128.64, 128.10, 127.80, 127.74, 125.09, 124.95, 117.98, 117.55, 115.4, 115.05, 114.34, 86.72, 81.11, 62.34, 60.54, 31.10, 30.27, 28.84.

*4-(4-Chlorophenyl)-3-(2-(2-(2-(((2-(4-chlorophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)propan-2-yl) phenoxy)-1-phenylazetidin-2-one (**11e** trans−trans).* White solid, 15.5 mg, 11%. mp 168−171 °C. Anal. Calcd for $C_{45}H_{36}Cl_2N_2O_4$ (739.68): C, 73.07%; H, 4.91%; N, 3.79%. Found: C, 73.36%; H, 5.20%; N, 3.78%. IR (ν_{max}, cm^{-1}): 1758 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.47−7.60 (m, 26H, Ph), 5.41 (d, J = 1.7 Hz, 2H, 2CH), 5.43 (d, J = 1.7 Hz, 2H, 2CH), 1.57 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.77, 154.94, 144.65, 136.63, 135.05, 134.02, 132.08, 129.78, 129.63, 129.59, 129.13, 128.14, 125.09, 117.97, 115.11, 86.70, 62.31, 30.26, 28.83.

*4-(4-Chlorophenyl)-3-(2-(2-(2-(((2-(4-chlorophenyl)-4-oxo-1-phenylazetidin-3-yl)oxy)phenyl)propan-2-yl)-phenoxy)-1-phenylazetidin-2-one (**11e** cis−cis).* White solid, 92.1 mg, 65%. mp 216−217 °C. Anal. Calcd for $C_{45}H_{36}Cl_2N_2O_4$ (739.68): C, 73.07%; H, 4.91%; N, 3.79%. Found: C, 72.85%; H, 5.09%; N, 4.07%. IR (ν_{max}, cm^{-1}): 1760 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.66−7.68 (m, 26H, Ph), 5.76 (d, J = 4.1 Hz, 2H, 2CH), 5.87 (d, J = 4.3 Hz, 2H, 2CH), 1.56 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.16, 163.26, 155.97, 154.63, 144.38, 134.44, 138.92, 137.01, 133.42, 132.95, 132.74, 132.18, 132.07, 130.45, 129.86, 129.43, 129.16, 128.86, 128.38, 127.91, 127.86, 127.80, 124.94, 124.10, 121.45, 120.12, 117.54, 115.12, 114.49, 114.21, 81.14, 78.17, 64.99, 60.56, 31.08, 30.27, 29.48.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(1-(4-chlorophenyl)-4-(p-tolyl)azetidin-2-one) (**11f** cis−trans).* Yellow solid, 5.9 mg, 4%. mp 200−202 °C. Anal. Calcd for $C_{47}H_{40}Cl_2N_2O_4$ (767.74): C, 73.53%; H, 5.25%; N, 3.65%. Found: C, 73.38%; H, 5.28%; N, 3.93%. IR (ν_{max}, cm^{-1}): 1763 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.72−7.44 (m, 24H, Ph), 5.34 (broad peak, 1H, CH), 5.40 (d, J = 2.1 Hz, 1H, CH), 5.69 (d, J = 4.6 Hz, 1H, CH), 5.83 (d, J = 4.6 Hz, 1H, CH), 1.53 (s, 6H, $2CH_3$), 2.22 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.58, 162.93, 154.96, 154.95, 144.77, 144.19, 138.99, 138.19, 135.99, 135.67, 132.62, 132.18, 132.07, 130.22, 129.78, 129.71, 129.35, 129.13, 128.90, 128.81, 128.52, 128.25, 128.06, 127.78, 127.53, 127.37,

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119.64, 119.22, 115.27, 115.09, 87.10, 81.53, 63.21, 61.40, 31.08, 30.94, 30.27, 22.87, 21.20.

*1-(4-Chlorophenyl)-3-(2-(2-(2-(((1-(4-chlorophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)oxy)phenyl)propan-2-yl)-phenoxy)-4-(p-tolyl)azetidin-2-one (**11f** trans−trans).* Yellow solid, 7.6 mg, 5%. mp 174−175 °C. Anal. Calcd for $C_{47}H_{40}Cl_2N_2O_4$ (767.74): C, 73.53%; H, 5.25%; N, 3.65%. Found: C, 73.61%; H, 5.04%; N, 3.37%. IR (ν_{max}, cm^{-1}): 1760 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.72−7.43 (m, 24H, Ph), 5.34 (d, J = 1.7 Hz, 1H, CH), 5.40 (d, J = 1.7 Hz, 1H, CH), 1.56 (s, 6H, $2CH_3$), 2.33 (s, 6H, $2CH_3$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 162.94, 154.98, 144.63, 138.98, 135.69, 132.64, 132.09, 130.23, 130.04, 129.72, 128.80, 128.12, 127.55, 119.64, 115.13, 87.10, 63.21, 30.88, 29.16, 21.28.

*3,3′-((Propane-2,2-diylbis(2,1-phenylene))bis(oxy))bis(1-(4-chlorophenyl)-4-(p-tolyl)azetidin-2-one) (**11f** trans−cis).* Yellow solid, 11.8 mg, 8%. mp 188−190 °C. Anal. Calcd for $C_{47}H_{40}Cl_2N_2O_4$ (767.74): C, 73.53%; H, 5.25%; N, 3.65%. Found: C, 73.64%; H, 5.35%; N, 3.85%. IR (ν_{max}, cm^{-1}): 1767 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.66−7.74 (m, 24H, Ph), 5.33 (d, J = 2.2 Hz, 1H, CH), 5.39 (d, J = 2.2 Hz, 1H, CH), 5.69 (d, J = 4.6 Hz, 1H, CH), 5.83 (d, J = 4.6 Hz, 1H, CH), 1.55 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.38, 162.93, 156.08, 154.93, 140.84, 138.96, 138.19, 137.95, 135.67, 132.62, 130.22, 129.79, 129.71, 129.38, 129.07, 129, 128.78, 128.53, 128.10, 128.08, 127.91, 127.74, 127.54, 121.64, 119.62, 119.21, 115.13, 115.08, 114.51, 114.30, 87.07, 81.56, 63.20, 61.43, 31.10, 30.99, 30.27, 22.88, 21.27.

*1-(4-Chlorophenyl)-3-(2-(2-(2-(((1-(4-chlorophenyl)-2-oxo-4-(p-tolyl)azetidin-3-yl)oxy)phenyl)propan-2-yl)-phenoxy)-4-(p-tolyl)azetidin-2-one (**11f** cis−cis).* Yellow solid, 103.0 mg, 70%. mp 220−222 °C. Anal. Calcd for $C_{47}H_{40}Cl_2N_2O_4$ (767.74): C, 73.53%; H, 5.25%; N, 3.65%. Found: C, 73.30%; H, 5.00%; N, 3.27%. IR (ν_{max}, cm^{-1}): 1754 (C═O). ^1H NMR (300 MHz; DMSO-d_6): δ 6.65−7.72 (m, 24H, Ph), 5.34 (broad peak, 1H, CH), 5.40 (d, J = 4.4 Hz, 1H, CH), 5.68 (d, J = 4.8 Hz, 1H, CH), 5.83 (d, J = 4.8 Hz, 1H, CH), 1.51 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.33 (s, 3H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): δ 163.61, 162.95, 154.96, 154.85, 144.82, 144.31, 140.92, 138.99, 138.23, 135.98, 135.66, 132.60, 132.07, 130.22, 129.78, 129.71, 129.38, 129.12, 128.80, 128.53, 128.09, 127.90, 127.75, 127.52, 119.64, 119.23, 115.25, 115.12, 115.5, 114.35, 87.10, 81.55, 63.22, 61.42, 30.99, 30.27, 28.83, 22.87, 21.22.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c03902.

^1H NMR and ^{13}C NMR spectra of new bis-β-lactams (PDF)

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Notes

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