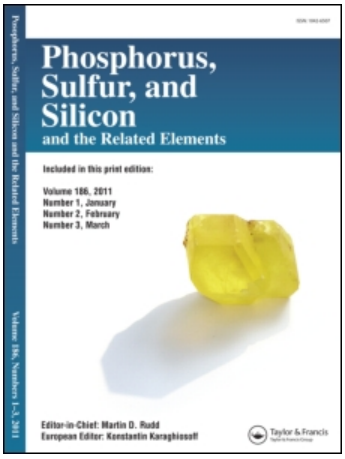

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Synthesis of New *N*-Sulfonyl Monocyclic β-Lactams and the Investigation of Their Antibacterial Activities

Aliasghar Jarrahpour[a]; Mohammad Motamedifar[b]; Maaroof Zarei[a]; Mostafa Mimouni[c]
[a] Department of Chemistry, College of Sciences, Shiraz University, Shiraz, Iran [b] Department of Bacteriology and Virology, Shiraz Medical School, Shiraz University Medical Science, Shiraz, Iran [c] Laboratoire Chimie des Matériaux, Université Mohammed Premier, Oujda, Morocco

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SYNTHESIS OF NEW *N*-SULFONYL MONOCYCLIC β-LACTAMS AND THE INVESTIGATION OF THEIR ANTIBACTERIAL ACTIVITIES

Aliasghar Jarrahpour,[1] Mohammad Motamedifar,[2] Maaroof Zarei,[1] and Mostafa Mimouni[3]

[1]*Department of Chemistry, College of Sciences, Shiraz University, Shiraz, Iran*
[2]*Department of Bacteriology and Virology, Shiraz Medical School, Shiraz University Medical Science, Shiraz, Iran*
[3]*Laboratoire Chimie des Matériaux, Université Mohammed Premier, Oujda, Morocco*

New monocyclic β-lactams 4–6 were synthesized by a ketene-imine [2+2] cycloaddition reaction. The prepared monocyclic β-lactams 4–6 were cleaved by ceric ammonium nitrate (CAN) to give NH-β-lactams 7–9. The NH-β-lactams were converted to N-sulfonyl β-lactams 10–21 by treatment with four different sulfonyl chlorides in the presence of Et_3N and 4-N,N-dimethylaminopyridine (DMAP). Some of these monocyclic β-lactams were active against* Staphylococcus aureus*,* Bacillus subtilis*,* Escherichia coli*, and* Pseudomonas aeruginosa*.

Supplemental materials are available for this article. Go to the publisher's online edition of* Phosphorus, Sulfur, and Silicon and the Related Elements *to view the free supplemental file.

Keywords Antibacterial activity; 2-azetidinones; imines; ketenes; Staudinger reaction; *N*-sulfonyl β-lactams

INTRODUCTION

The class of compounds known as β-lactam antibiotics has served an important and highly successful role in medicine and in pharmaceutical industry.[1] Miracle drugs such as penicillins and cephalosporins have improved the health and life expectancy of humans since their discovery in the early part of the 20th century.[2] However the widespread use of these agents has resulted in an ever increasing number of antibiotic-resistant bacterial strains, and the need for β-lactams with greater potency and broader range has become increasingly important.[3] Following the initial introduction of penicillin during World War II, a variety of classes of β-lactam antibiotics were sequentially identified, including the penams, cephems, clavulanates, monobactams, carbapenems, and trinems.[4,5] In the mid 1970s, a new class of β-lactam antibiotics characterized by a single monocyclic structure, called monocyclic

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Address correspondence to Aliasghar Jarrahpour, Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran. E-mail: jarrah@susc.ac.ir or aliasghar6683@yahoo.com

β-lactams, was introduced.[6] These are molecules that do not contain a ring fused to the β-lactam ring.[7] Some monocyclic β-lactams containing the phthalimido group have shown good antibacterial activity.[8,9] Recently scientists have found that monocyclic β-lactams are also as inhibitors of cytomegalovirus protease,[10,11] inhibitors of thrombin and tryptase,[12,13] cholesterol absorption,[14,15] human leukocyte elastase (HLE),[16,17] porcine pancreatic elastase (PPE),[18] and cysteine protease,[19,20] and are used as anticancer agents.[21,22] In addition to their diverse current uses as pharmaceuticals, β-lactams are of interest as synthetic building blocks[23,24] and in the semisynthesis of Taxol.[25] Selective bond cleavage of the strained β-lactam ring coupled with further interesting synthetic transformations renders these fascinating molecules powerful synthetic building blocks.[26,27] In addition, the existence of the methoxy group on the molecules enhances the various biological activities.[28]

One group of monocyclic β-lactams is the *N*-sulfonyl monocyclic β-lactams.[29,30] Recently, *N*-sulfonyl β-lactams have been shown to be highly useful compounds for medicinal chemistry.[31] Numerous articles can be found throughout the literature describing the preparation and use of *N*-sulfonyl β-lactams (*N*-SO_2R-β-lactams) as intermediates in the synthesis of other target molecules.[32] About 600 *N*-sulfonyl-β-lactams have been examined for biological properties.[33] Konaklieva et al. have synthesized the *N*-sulfonyl-β-lactams and have tested them against some bacteria.[34] It appears that the nature of the substituents has many crucial roles to play in bioactivity (bioavailability and bioselectivity).

As a consequence, a large number of chemical methods for the production of β-lactams have been developed, and the topic has been documented and reviewed several times.[35–37] Ketene–imine cycloaddition (Staudinger reaction) has provided useful and economical entries to β-lactams, mainly due to the ready availability of both Schiff bases and ketenes.[38–40] The Staudinger reaction was the first method by which a 2-azetidinone was synthesized.[41] Ketene–imine cycloaddition is one of the most effective methods that allows us to obtain selectively *cis*-β-lactams.[42–44] Generally, acid chlorides are used as precursors of ketene in the Staudinger reaction.[45–47] *p*-Methoxyphenyl group (PMP) has been used extensively as an *N*-protecting group in β-lactam chemistry. The *N*-PMP-β-lactams were oxidatively cleaved with ceric ammonium nitrate (CAN) into *N*-unsubstituted β-lactams.[48–50]

In this article, we describe the synthesis and antibacterial activities of some new monocyclic β-lactams bearing various sulfonyl groups at position N1.

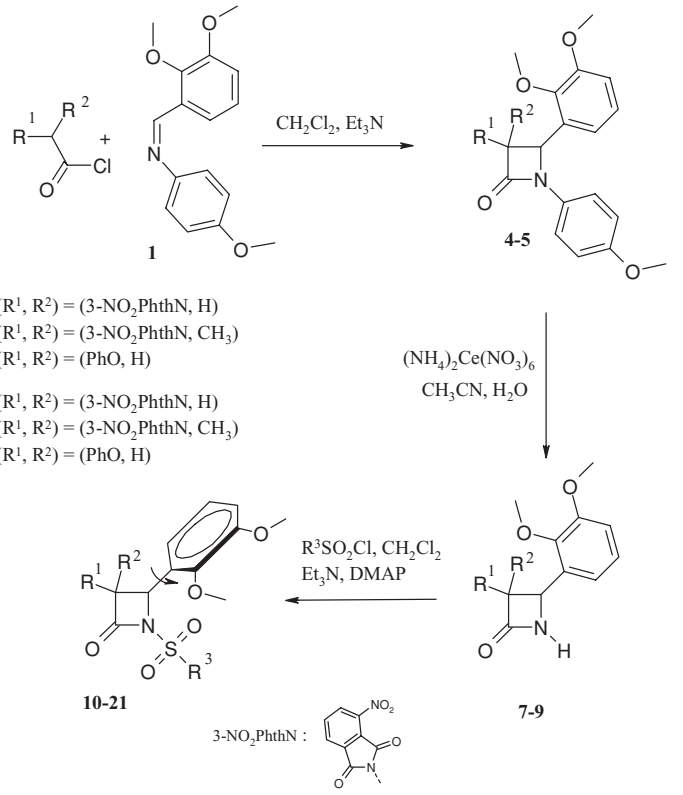
RESULTS AND DISCUSSION

2,3-Dimethoxybenzaldehyde was condensed with *p*-anisidine to give, after recrystallization from cold methanol, the Schiff base, (2,3-dimethoxybenzylidene)-(4-methoxyphenyl)amine **1** as a yellow solid. 3-Nitrophthaloylglycyl chloride **2** and 3-nitrophthaloyl alaninyl chloride **3** were prepared from 3-nitrophthalic anhydride and amino acids glycine and alanine, respectively, in two steps. Monocyclic β-lactams **4–6** were obtained by the [2+2] cycloaddition of imine **1** with ketenes derived from acyl chlorides **2**, **3**, and phenoxyacetyl chloride in the presence of triethylamine in dry dichloromethane at -10°C, respectively. The ^{1}H NMR spectra of **4** and **6** showed doublets for H-3 and H-4 with coupling constants of $J = 4.5$–5.5 Hz, which confirmed the cis stereochemistry for these monocyclic β-lactams. The IR spectra definitely showed the characteristic absorption of carbonyl β-lactam at 1743–1785 cm^{-1} and the ^{13}C NMR spectra exhibited carbonyl function (β-lactam ring) at 163.3–166.5 ppm for β-lactams

4–6. These monocyclic β-lactams were then transformed to *N*-unsubstituted monocyclic β-lactams **7–9** by treatment with ceric ammonium nitrate $(NH_4)_2Ce(NO_3)_6$ called CAN), at −10°C, in a short reaction time and with good yields.

Then the crude products were purified by recrystallization from (hexane:EtOAc, 4:6). The deprotection of the PMP group from these monocyclic β-lactams was confirmed by the presence of NH absorption at 3301–3422 cm^{-1} in their IR spectra. Of course, ^1H NMR spectra showed the NH at 6.33–6.73 ppm for compounds **7–9**. Treatment of *N*-unsubstituted monocyclic β-lactams **7–9** with methanesulfonyl chloride, benzenesulfonyl chloride, *p*-toluenesulfonyl chloride, and 2-naphthalenesulfonyl chloride in the presence of triethylamine and 4-*N*,*N*-dimethylaminopyridine (DMAP) gave the *N*-sulfonyl β-lactams **10–21** (Scheme 1, Table I).

The formation of *N*-SO_2R β-lactams **10–21** was conveniently established from their spectral data. The IR spectra showed the 2-azetidinone carbonyls at 1765–1788 cm^{-1}, S=O absorptions at 1326–1355 cm^{-1} and the NH peaks have been eliminated. TLC monitoring



4: (R^1, R^2) = (3-NO_2PhthN, H)
5: (R^1, R^2) = (3-NO_2PhthN, CH_3)
6: (R^1, R^2) = (PhO, H)

7: (R^1, R^2) = (3-NO_2PhthN, H)
8: (R^1, R^2) = (3-NO_2PhthN, CH_3)
9: (R^1, R^2) = (PhO, H)

10: (R^1, R^2, R^3) = (3-NO_2PhthN, H, CH_3)
11: (R^1, R^2, R^3) = (3-NO_2PhthN, H, C_6H_5)
12: (R^1, R^2, R^3) = (3-NO_2PhthN, H, 4-CH_3-C_6H_4)
13: (R^1, R^2, R^3) = (3-NO_2PhthN, H, 2-naphtalene)
14: (R^1, R^2, R^3) = (3-NO_2PhthN, CH_3, CH_3)
15: (R^1, R^2, R^3) = (3-NO_2PhthN, CH_3, C_6H_5)
16: (R^1, R^2, R^3) = (3-NO_2PhthN, CH_3, 4-CH_3-C_6H_4)
17: (R^1, R^2, R^3) = (3-NO_2PhthN, CH_3, 2-naphtalene)
18: (R^1, R^2, R^3) = (C_6H_5O, H, CH_3)
19: (R^1, R^2, R^3) = (C_6H_5O, H, C_6H_5)
20: (R^1, R^2, R^3) = (C_6H_5O, H, 4-CH_3-C_6H_4)
21: (R^1, R^2, R^3) = (C_6H_5O, H, 2-naphtalene)

Scheme 1 Synthesis of *N*-sulfonyl β-lactams **10–21**.

Table I Monocyclic β-lactams **4–21**

Compounds	R^1	R^2	R^3	Isolated Yield %
4	3-NO_2PhthN	H	—	57
5	3-NO_2PhthN	Me	—	52
6	PhO	H	—	90
7	3-NO_2PhthN	H	—	87
8	3-NO_2PhthN	Me	—	85
9	PhO	H	—	90
10	3-NO_2PhthN	H	Me	78
11	3-NO_2PhthN	H	Ph	80
12	3-NO_2PhthN	H	4-MeAr	85
13	3-NO_2PhthN	H	2-Naphthalene	72
14	3-NO_2PhthN	Me	Me	82
15	3-NO_2PhthN	Me	Ph	80
16	3-NO_2PhthN	Me	4-MeAr	75
17	3-NO_2PhthN	Me	2-Naphthalene	68
18	PhO	H	Me	88
19	PhO	H	Ph	83
20	PhO	H	4-MeAr	84
21	PhO	H	2-Naphthalene	81

in all of the above reactions confirmed the presence of the new compound. All new product structures have been confirmed by elemental analyses and mass spectra (molecular ion).

ANTIMICROBIAL ACTIVITY AND RESULTS

All the synthesized compounds were screened for antimicrobial activity against one Gram-positive, methicillin-resistant strain (*Staphylococcus aureus*), one Gram-negative (*Pseudomonas aeruginosa*), one capsulated Gram-negative (*Kelebsiella pneumonia*), and a Gram-positive spore forming (*Bacillus subtilis*) bacteria using the reported method.[51] (See Supplemental Materials and Table II, available online.)

CONCLUSION AND PERSPECTIVES

A series of new *N*-sulfonyl β-lactams monocyclic Gram-positive and Gram-negative inhibitors was prepared. Improvement in bacteria-based inhibitor potency was observed in comparison to previously disclosed bicyclic β-lactams carrying the "amino(phenyl)acetyl]amino tail" at lactam C-6 of penicillin, for example. Antibacterial activity for several of the C2-substituted inhibitors was examined, with a *N*-sulfonyl β-lactams analog achieving good balance in protein-shifted MIC studies. This first series described here leads us to prepare some analogues containing combined pharmacophores sites able to inhibit HIV-integrase and bacteria.[53] The inclusion of a P atom instead of S will increase the tolerance of the future series.

EXPERIMENTAL

All needed chemicals were purchased from Merck and Fluka chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH_2 and then stored

over molecular sieve 4Å. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.9 MHz). Chemical shifts were reported in ppm (δ) downfield from TMS. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Elemental analyses were run on a Thermo Finnigan Flash EA-1112 series. Melting points were determined in open capillaries with Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was carried out on silica gel 60 Merck (230–270 mesh).

((2,3-Dimethoxybenzylidene)-(4-methoxyphenyl)amine (1)

A mixture of *p*-anisidine (5.00 g, 40.71 mmol) and 2,3-dimethoxy benzaldehyde (6.80 g, 40.71 mmol) was refluxed in ethanol for 5 h. Then the solvent was evaporated under reduced pressure. The crude product was recrystallized from cold methanol to give pure Schiff base **1** as a yellow solid (8.82 g, 80%). mp 66–68°C. IR (KBr) (cm^{-1}): 1618 (C=N). ^{1}H NMR ($CDCl_3$): δ 3.62, 3.70, 3.85 (3 OMe, 3 s, 9H), 6.54–7.74 (ArH, m, 7H), 8.85 (HC=N, s, 1H). ^{13}C NMR ($CDCl_3$) δ 64.4, 64.8 (OMe), 122.8, 123.7, 127.8, 131.4, 133.3, 139.2, 154.4, 158.9, 161.9, 163.1 (aromatic carbons), 167.4 (C=N). MS (m/z,%): 271 (M^+, 11), 256 (8), 241 (14), 149 (29), 134 (15), 128 (6), 123 (100), 121 (36), 92 (19), 77 (30). *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.07; H, 6.44; N, 5.12.

3-Nitrophthaloylglycyl Chloride (2)

3-Nitrophthaloyl glycine was prepared by a reported method.[52] 3-Nitrophthaloylglycyl chloride was obtained by heating 3-nitrophthaloyl glycine (10.0 g, 39.9 mmol) and thionyl chloride (20 mL, 275 mmol) for 2 h. Then the excess of thionyl chloride was removed by distillation, and it was crystallized from light petroleum to give acyl chloride **2** as a light yellow crystal (9.98 g, 93%). It was stable for long periods in a desiccator over $CaCl_2$. mp 116–118°C. IR (KBr) (cm^{-1}): 1735, 1775 (phthalimido, CO), 1805 (COCl).

3-Nitrophthaloylalaninyl Chloride (3)

3-Nitrophthaloyl alanine was prepared by a reported method.[52] 3-Nitrophthaloylalanyl chloride **3** was prepared by the same method as compound **2**. Yield 90%. mp 108–110°C. IR (KBr) (cm^{-1}): 1740, 1785 (phthalimido, CO), 1810 (COCl).

General Procedure for Synthesis of Monocyclic β-Lactams (4–6)

A solution of the corresponding acyl chloride (1.50 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of (2,3-dimethoxybenzylidene)-(4-methoxyphenyl) amine **1** (1.00 mmol) and triethylamine (3.00 mmol) in CH_2Cl_2 (15 mL) at −10°C. The reaction mixture was then allowed to warm to room temperature and stirred overnight. Then it was washed with saturated sodium bicarbonate solution (20 mL) and brine (20 mL), dried (Na_2SO_4), and the solvent was evaporated to give the crude product, which was then purified by column chromatography over silica gel.

2-[2-(2,3-Dimethoxyphenyl)-1-(4-methoxyphen-yl)-4-oxo-azetidin-3-yl]-4-nitroiso-indole-1,3-dione (4). β-Lactam **4** was obtained from Schiff base **1** and acyl chloride **2**. Yield 57% (eluent hexane/EtOAc 6:4). mp 186–188°C. IR (KBr) (cm^{-1}): 1730, 1775 (phth. CO), 1785 (CO, β-lactam). ^1H NMR ($CDCl_3$): δ 3.71, 3.87, 4.52 (3 OMe, 3 s, 9H), 5.28 (H-4, d, 1H, $J = 4.5$ Hz), 5.78 (H-3, d, 1H, $J = 5.5$ Hz), 6.76–8.03 (ArH, m, 10H). ^{13}C NMR ($CDCl_3$): δ 53.9, 55.8, 56.1 (OMe), 58.8 (C-4), 61.2 (C-3), 113.5, 114.7, 118.9, 119.3, 120.9, 123.3, 125.7, 127.7, 131.2, 133.6, 136.2, 147.2, 152.3, 156.8 (aromatic carbons), 161.6 (CO), 164.5 (CO, β-lactam). MS (m/z,%): 503 (M^+, 32), 486 (17), 354 (63), 311 (12), 271 (6), 162 (27), 149 (51), 134 (18), 123 (100), 108 (36), 91 (13), 75 (38). *Anal.* Calcd for $C_{26}H_{21}N_3O_8$: C, 62.03; H, 4.20; N, 8.35. Found: C, 62.18; H, 4.27; N, 8.43.

2-[2-(2,3-Dimethoxyphenyl)-1-(4-methoxyphen-yl)-3-meth-yl-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (5). β-Lactam **5** was obtained from Schiff base **1** and acyl chloride **3**. Yield 52% (eluent hexane/EtOAc 1:1). mp 178–180°C. IR (KBr) (cm^{-1}): 1740, 1778 (phth. CO), 1785 (CO, β-lactam). ^1H NMR ($CDCl_3$): 1.81 (Me, s, 3H), 3.71, 3.80, 3.88 (3 OMe, 3 s, 9H), 5.68 (H-4, s, 1H), 6.69–8.12 (ArH, m, 10H). ^{13}C NMR ($CDCl_3$): 20.4 (Me), 56.5, 56.8, 61.8 (OMe), 63.5 (C-4), 71.5 (C-3), 113.8, 114.3, 115.4, 119.8, 120.7, 124.7, 127.6, 129.6, 131.9, 134.5, 137.0, 146.1, 148.2, 157.4 (aromatic carbons), 166.1 (CO), 166.5 (CO, β-lactam). MS (m/z,%): 517 (M^+, 15), 500 (10), 368 (13), 351 (17), 294 (25), 271 (22), 193 (8), 165 (7), 149 (25), 123 (100), 108 (22), 91 (11), 75 (18). *Anal.* Calcd for $C_{27}H_{23}N_3O_8$: C, 62.67; H, 4.48; N, 8.12. Found: C, 62.59; H, 4.55; N, 8.09.

4-(2,3-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenoxy-2-azetidinone (6). β-Lactam **6** was obtained from Schiff base **1** and phenoxyacetyl chloride. Yield 90% (eluent hexane/EtOAc 7:3). mp 148–150°C. IR (KBr) (cm^{-1}): 1743 (CO β-lactam). ^1H NMR ($CDCl_3$): δ 3.71, 3.81, 3.85 (3 OMe, 3 s, 9H), 5.52 (H-4, d, 1H, $J = 5$ Hz), 5.78 (H-3, d, 1H, $J = 5.1$ Hz), 6.77–7.28 (ArH, m, 12H). ^{13}C NMR ($CDCl_3$): δ 55.8, 56.1, 56.5 (OMe), 78.0 (C-4), 81.8 (C-3), 113.1, 114.8, 116.5, 119.2, 120.6, 122.6, 124.2, 126.8, 129.8, 130.9, 148.0, 152.7,156.8, 157.7 (aromatic carbons), 163.3 (CO, β-lactam). MS (m/z,%): 405 (M^+, 34), 374 (10), 312 (12), 256 (100), 241 (8), 213 (16), 163 (15), 148 (38), 134 (19), 123 (65), 108 (23), 77 (55). *Anal.* Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 70.96; H, 5.68; N, 3.52.

General Procedure for Synthesis of *N*-Unsubstituted (NH)-β-Lactams (7–9)

A solution of $(NH_4)_2Ce(NO_3)_6$ (CAN) (3.00 mmol) in water (15 mL) was added dropwise to a solution of each of β-lactams **4**–**6** (1.00 mmol) in CH_3CN (25 mL) at –10°C. The mixture was stirred at this temperature for 45 min. Then, water (30 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL) and washed with a saturated solution of $NaHCO_3$ (40 mL). The aqueous layer of $NaHCO_3$ was extracted again with EtOAc (15 mL), and all organic layers were combined and washed with 10% $NaHSO_3$ (2 × 30 mL), $NaHCO_3$ (20 mL), and brine (20 mL), and dried over sodium sulfate. After filtration and evaporation of the solvent in vacuo, the crude product was purified by recrystallization from hexane:EtOAc, 4:6 to afford the products.

2-[2-(2,3-Dimethoxyphenyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (7). (87%). mp 106–108°C. IR (KBr) (cm^{-1}): 1736, 1778 (phth, CO), 1790 (CO, β-lactam), 3422 (NH). ^1H NMR ($CDCl_3$): δ 3.52, 3.62 (2 OMe, 2 s, 6H), 5.20 (H-4, dd,

1H, $J = 10.0, 5.0$ Hz), 5.61 (H-3, d, 1H, $J = 5.2$ Hz), 6.61 (NH, brs, 1H), 6.89–8.07 (ArH, m, 6H). ^{13}C NMR ($CDCl_3$): δ 58.5, 59.3 (OMe), 59.7 (C-4), 61.0 (C-3), 111.9, 116.8, 118.9, 122.7, 126.7, 129.9, 134.6, 143.8, 151.3, 160.2 (aromatic carbons), 163.2 (CO), 164.2 (CO, β-lactam). MS (m/z,%): 397 (M^+, 16), 354 (11), 298 (16), 237 (8), 205 (39), 192 (15), 166 (30), 148 (25), 119 (11), 103 (36), 91 (13), 75 (100), 43 (50). *Anal.* Calcd for $C_{19}H_{15}N_3O_7$: C, 57.43; H, 3.81; N, 10.58. Found: C, 57.57; H, 3.87; N, 10.51.

2-[2-(2,3-Dimethoxyphenyl)-3-methyl-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (8). (85%). mp 124–126°C. IR (KBr) (cm^{-1}): 1730, 1770 (Phth, CO), 1785 (CO, β-lactam), 3410.1 (NH). ^{1}H NMR ($CDCl_3$): δ 1.92 (Me, s, 3H), 3.57, 3.72 (2 OMe, 2 s, 6H), 5.11 (H-4, d, 1H, $J = 4.5$ Hz), 6.33 (NH, brs, 1H), 6.66–7.99 (ArH, m, 6H). ^{13}C NMR ($CDCl_3$): δ 20.6 (Me), 57.2, 60.3 (OMe), 62.2 (C-4), 73.8 (C-3), 114.1, 117.3, 120.5, 125.3, 130.4, 137.4, 146.3, 153.4, 163.4, 166.2 (aromatic carbons), 169.5 (CO), 171.2 (CO, β-lactam). MS (m/z,%): 411 (M^+, 17), 368 (13), 351 (13), 321 (7), 246 (17), 219 (32), 177 (46), 166 (33), 148 (45), 133 (12), 103 (46), 75 (100), 55 (30). *Anal.* Calcd for $C_{20}H_{17}N_3O_7$: C, 58.39; H, 4.17; N, 10.21. Found: C, 58.43; H, 4.30; N, 10.29.

4-(2,3-Dimethoxyphenyl)-3-phenoxy-2-azetidin-one (9). (90%). mp 116–118°C. IR (neat)(cm^{-1}): 1761 (CO, β-lactam), 3301 (NH). ^{1}H NMR ($CDCl_3$): δ 3.71, 3.79 (2 OMe, 2 s, 6H), 5.14 (H-4, dd, 1H, $J = 8.3, 4.3$ Hz), 5.29 (H-3, d, 1H, $J = 4.6$ Hz), 6.73 (NH, br s, 1H), 6.85–7.83 (ArH, m, 8H). ^{13}C NMR ($CDCl_3$): δ 57.1, 61.1 (OMe), 82.0 (C-4), 83.6 (C-3), 112.8, 113.6, 116.4, 122.8, 124.3, 129.7, 138.4, 147.6, 152.5, 157.6 (aromatic carbons), 168.1 (CO, β-lactam). MS (m/z,%): 299 (M^+, 28), 268 (14), 256 (32), 238 (9), 206 (7), 165 (23), 134 (12), 105 (20), 93 (37), 77 (100), 43 (21). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.16; H, 5.79; N, 4.60.

Typical Procedure for Synthesis of *N*-Sulfonyl-β-lactams (10–21)

To a solution of *N*-unsubstituted-β-lactams **7–9** (1.00 mmol), separately, in dry CH_2Cl_2 (10 mL) cooled to -10°C, triethylamine (1.5 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (0.1 mmol) were added. A solution of the corresponding sulfonyl chloride (1.5 mmol) in dry CH_2Cl_2 (5 mL) was slowly added to the resulting mixture. After stirring at -10°C for 1 h, the reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed with brine (10 mL) and dried over sodium sulfate. The solvent was evaporated at reduced pressure, and the crude products were purified by column chromatography over silica gel (hexane:EtOAc, 2:8) to give the *N*-sulfonyl-β-lactams as oil.

2-[2(2,3-Dimethoxyphenyl)-1-methanesulfonyl-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (10). (78%). β-Lactam **10** was obtained by the reaction of β-lactam **7** and methanesulfonyl chloride. IR (neat) (cm^{-1}): 1330 (S=O), 1735, 1775 (phth., CO), 1785 (CO, β-lactam). ^{1}H NMR (DMSO): δ 3.44 (SO_2Me, s, 3H), 4.48, 4.50 (2 OMe, 2 s, 6H), 5.04 (H-4, d, 1H, $J = 4.5$ Hz), 5.60 (H-3, d, 1H, $J = 5.5$ Hz), 6.81–8.23 (ArH, m, 6H). ^{13}C NMR (DMSO): δ 31.8 (SO_2Me), 56.0, 59.1 (OMe), 60.3 (C-4), 61.6 (C-3), 106.9, 113.5, 118.5, 124.6, 127.9, 129.4, 132.6, 137.1, 144.7, 151.6 (aromatic carbons), 161.8 (CO), 164.7 (CO, β-lactam). MS (m/z,%): 475 (M^+, 22), 444 (11), 353 (33), 314 (9), 284 (6), 243 (13), 166 (44), 121 (48), 94 (53), 75 (100), 51 (67). *Anal*. Calcd for $C_{20}H_{17}N_3O_9S$: C, 50.53; H, 3.60; N, 8.84. Found: C, 50.61; H, 3.72; N, 8.76.

2-[1-Benzenesulfonyl-2-(2,3-dimethoxyphenyl)-4-oxoazetidin-3-yl]-4-nitroisoindole-1,3-dione (11). (80%). β-Lactam **11** was obtained by the reaction of β-lactam **7** and benzenesulfonyl chloride. IR (neat) (cm^{-1}): 1350 (S=O), 1738, 1778

(phth., CO), 1788 (CO, β-lactam). ^{1}H NMR (DMSO): δ 3.67, 3.77 (2 OMe, 2 s, 6H), 5.37 (H-4, d, 1H, $J = 5.5$ Hz), 5.59 (H-3, d, 1H, $J = 5.5$ Hz), 6.77–8.12 (ArH, m, 11H). ^{13}C NMR (DMSO): δ 54.1, 55.8 (OMe), 59.6 (C-4), 60.6 (C-3), 106.9, 114.1, 120.9, 123.6, 125.8, 128.2, 129.9, 133.1, 134.5, 136.8, 138.9, 144.8, 147.4, 152.3 (aromatic carbons), 161.4 (CO), 164.0 (CO, β-lactam). MS (m/z,%): 537 (M^+, 28), 506 (37), 476 (15), 396 (10), 354 (32), 305 (24), 215 (11), 158 (31), 141 (18), 121 (25), 77 (100), 75 (39). *Anal*. Calcd for $C_{25}H_{19}N_3O_9S$: C, 55.86; H, 3.56; N, 7.82. Found: C, 55.93; H, 3.64; N, 7.78.

2-[2-(2,3-Dimethoxyphenyl)-4-oxo-1-(toluene-4-sulfon-yl)-azetidin-3-yl]-4-nitroiso-indole-1,3-dione (12). (85%). β-Lactam **12** was obtained by the reaction of β-lactam **7** and 4-toluenesulfonyl chloride. IR (neat) (cm^{-1}): 1346 (S=O), 1743, 1775 (phth, CO), 1780 (CO, β-lactam).^{1}H NMR (DMSO): δ 2.06 (Me, s, 3H), 3.01, 3.07 (2 OMe, 2 s, 6H), 5.12 (H-4, d, 1H, $J = 6.1$ Hz), 5.58 (H-3, d, 1H, $J = 6.5$ Hz), 6.37–8.15 (ArH, m, 10H). ^{13}C NMR (DMSO): δ 21.2 (Me), 45.5, 52.3 (OMe), 55.2 (C-4), 60.9 (C-3), 107.0, 110.5, 113.1, 117.6, 119.0, 122.4, 125.9, 127.3, 129.6, 133.7, 142.2, 147.6, 151.4, 156.3 (aromatic carbons), 161.9 (CO), 164.7 (CO, β-lactam). MS (m/z,%): 551 (M^+, 19), 536 (13), 490 (8), 354 (26), 229 (18), 197 (28), 149 (33), 137 (41), 121 (100), 91 (44), 75 (65), 41 (37). *Anal*. Calcd for $C_{26}H_{21}N_3O_9S$: C, 56.62; H, 3.84; N, 7.62. Found: C, 56.72; H, 3.96; N, 7.64.

2-[2-(2,3-Dimethoxyphenyl)-1-(naphthalene-2-sulfonyl)-4-oxo-azetidin-3-yl]-4-nitro-isoindole-1,3-dione (13). (72%). β-Lactam **13** was obtained by the reaction of β-lactam **7** and naphthalene-2-sulfonyl chloride. IR (neat) (cm^{-1}): 1355 (S=O), 1740, 1775 (phth, CO), 1785 (CO, β-lactam). ^{1}H NMR (DMSO): δ 3.04, 3.12 (2 OMe, 2 s, 6H), 5.15 (H-4, d, 1H, $J = 5.5$ Hz), 5.75 (H-3, d, 1H, $J = 4.8$ Hz), 6.45–8.15 (ArH, m, 13H). ^{13}C NMR (DMSO): δ 53.1, 55.8 (OMe), 56.5 (C-4), 60.7 (C-3), 107.1, 109.2, 113.5, 120.2, 122.3, 122.9, 123.7, 124.3, 126.7, 127.7, 128.8, 129.0, 129.4, 132.9, 137.2, 139.9, 142.6, 145.6, 147.4, 150.8, 151.6, 157.0 (aromatic carbons), 161.8 (CO), 164.7 (CO, β-lactam). MS (m/z,%): 587 (M^+, 31), 526 (7), 460 (22), 355 (17), 233 (15), 207 (31), 191 (19), 149 (27), 143 (14), 127 (100), 103 (15), 75 (98). *Anal.* Calcd for $C_{29}H_{21}N_3O_9S$: C, 59.28; H, 3.60; N, 7.15. Found: C, 59.21; H, 3.65; N, 7.12.

2-[2-(2,3-Dimethoxyphenyl)-1-methanesulfonyl-3-methyl-4-oxoazetidin-3-yl]-4-nitroisoindole-1,3-dione (14). (82%). β-Lactam **14** was obtained by the reaction of β-lactam **8** and methanesulfonyl chloride. IR (neat) (cm^{-1}): 1333 (S=O), 1730, 1773 (Phth, CO), 1783 (CO, β-lactam). ^{1}H NMR (DMSO): δ 1.69 (Me, s, 3H), 2.69 (SO_2Me, s, 3H), 3.62, 3.76 (2 OMe, 2 s, 6H), 5.11 (H-4, s, 1H), 6.56–8.01 (ArH, m, 6H). ^{13}C NMR (DMSO): δ 18.2 (Me), 36.5 (Me), 58.7, 59.3 (OMe), 69.8 (C-4), 71.4 (C-3), 111.6, 117.5, 118.0, 122.2, 125.8, 127.4, 132.5, 135.0, 143.8, 150.9, 160.9, 163.7 (aromatic carbons), 166.7 (CO), 168.2 (CO, β-lactam). MS (m/z,%): 489 (M^+, 23), 458(18), 428(9), 368(29), 298(14), 246(37), 243(17), 165(12), 121(52), 94(23), 75(100), 43(35). Anal. Calcd for $C_{21}H_{19}N_3O_9S$: C, 51.53; H, 3.91; N, 8.59; found: C, 51.46; H, 4.02; N, 8.63.

2-[1-Benzenesulfonyl-2-(2,3-dimethoxyphenyl)-3-methyl-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (15). (80%). β-Lactam **15** was obtained by the reaction of β-lactam **8** and benzenesulfonyl chloride. IR (neat) (cm^{-1}): 1338.0 (S=O), 1740, 1772 (phth, CO), 1787 (CO, β-lactam). ^{1}H NMR (DMSO): δ 1.72 (Me, s, 3H), 3.73, 3.80 (2 OMe, 2 s, 6H), 5.19 (H-4, s, 1H), 6.58–8.03 (ArH, m, 11H). ^{13}C NMR (DMSO): δ 20.7 (Me), 56.0, 58.2 (OMe), 67.6 (C-4), 73.3 (C-3), 115.0, 120.9, 125.9, 128.3, 129.5, 130.7, 131.3, 132.2, 137.1, 138.4, 143.5, 147.3, 154.2, 162.8, 165.3 (aromatic carbons), 167.5 (CO), 171.3 (CO, β-lactam). MS (m/z,%): 551 (M^+, 30), 536 (16), 490 (15), 368

(22), 305 (27), 246 (14), 182 (7), 177 (35), 143 (14), 141 (28), 77 (100), 75 (47). *Anal.* Calcd for $C_{26}H_{21}N_3O_9S$: C, 56.62; H, 3.84; N, 7.62. Found: C, 56.70; H, 3.94; N, 7.55.

2-[2-(2,3-Dimethoxyphenyl)-3-methyl-4-oxo-1-(toluene-4-sulfonyl)-azetidin-3-yl]-4-nitroisoindole-1,3-dione (16). (75%). β-Lactam **16** was obtained by the reaction of β-lactam **8** and 4-toluenesulfonyl chloride. IR (neat) (cm^{-1}): 1329 (S=O), 1737, 1770 (phth., CO), 1782 (CO, β-lactam). ^1H NMR (DMSO): δ 1.78 (Me, s, 3H), 2.46 (MePh, s, 3H), 3.57, 3.66 (2 OMe, 2 s, 6H), 5.71 (H-4, s, 1H), 6.84–8.19 (ArH, m, 10H). ^{13}C NMR (DMSO): δ 18.0 (Me), 21.5 (MePh), 55.2, 56.0 (OMe), 60.5 (C-4), 70.7 (C-3), 107.1, 118.7, 123.4, 125.9, 126.2, 128.2, 129.2, 130.7, 133.9, 137.2, 144.7, 146.3, 149.6, 152.0 (aromatic carbons), 161.2 (CO), 165.8 (CO, β-lactam). MS (m/z,%): 565 (M^+, 25), 550 (33), 534 (19), 410 (20), 368 (27), 319 (18), 246 (28), 197 (12), 155 (8), 91 (24), 75 (100), 43 (31). *Anal.* Calcd for $C_{27}H_{23}N_3O_9S$: C, 57.34; H, 4.10; N, 7.43. Found: C, 57.38; H, 4.18; N, 7.49.

2-[2-(2,3-Dimethoxyphenyl)-3-methyl-1-(naphthalene-2-sulfonyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (17). (68%). β-Lactam **17** was obtained by the reaction of β-lactam **8** and naphthalene-2-sulfonyl chloride. IR (neat) (cm^{-1}): 1336 (S=O), 1740, 1776 (phth, CO), 1785 (CO, β-lactam). ^1H NMR (DMSO): δ 2.05 (Me, s, 3H), 3.00, 3.10 (2 OMe, 2 s, 6H), 5.72 (H-4, s, 1H), 6.85–8.70 (ArH, m, 13H). ^{13}C NMR (DMSO): δ 31.0 (Me), 55.2, 56.0 (OMe), 56.3 (C-4), 60.4 (C-3), 107.1, 109.5, 119.2, 122.7, 124.2, 124.4, 126.7, 127.7, 128.3, 128.8, 129.9, 130.7, 133.6, 137.3, 141.1, 145.9, 147.8, 149.6, 150.4, 152.7, 156.7 (aromatic carbons), 162.8 (CO), 165.7 (CO, β-lactam). MS (m/z,%): 601 (M^+, 18), 586 (8), 570 (27), 410 (26), 335 (24), 246 (36), 219 (33), 191 (14), 127 (100), 75 (82). *Anal.* Calcd for $C_{30}H_{23}N_3O_9S$: C, 59.90; H, 3.85; N, 6.98. Found: C, 59.97; H, 3.93; N, 7.05.

4-(2,3-Dimethoxyphenyl)-1-methanesulfonyl-3-phenoxy-azetidin-2-one (18). (88%). β-Lactam **18** was obtained by the reaction of β-lactam **9** and methanesulfonyl chloride. IR (neat) (cm^{-1}): 1326 (S=O), 1768 (CO, β-lactam). ^1H NMR (DMSO): δ 2.05 (Me, s, 3H), 3.73, 3.78 (2 OMe, 2 s, 6H), 5.33 (H-4, d, 1H, $J = 4.8$ Hz), 5.68 (H-3, d, 1H, $J = 5.0$ Hz), 6.82–7.67 (ArH, m, 8H). ^{13}C NMR (DMSO): δ 29.8 (Me), 59.4, 59.7 (OMe), 80.1 (C-4), 82.0 (C-3), 106.1, 11.7, 114.8, 121.6, 128.6, 138.2, 143.5, 151.1, 155.8, 156.3 (aromatic carbons), 165.8 (CO, β-lactam). MS (m/z,%): 377 (M^+, 38), 346 (13), 316 (6), 298 (13), 256 (63), 243 (18), 120 (11), 93 (75), 77 (100), 43 (29). *Anal.* Calcd for $C_{18}H_{19}NO_6S$: C, 57.28; H, 5.07; N, 3.71. Found: C, 57.19; H, 5.21; N, 3.73.

1-Benzenesulfonyl-4-(2,3-dimethoxyphenyl)-3-phenoxy-azetidin-2-one (19). (83%). β-Lactam **19** was obtained by the reaction of β-lactam **9** and benzenesulfonyl chloride. IR (neat) (cm^{-1}): 1330 (S=O), 1765 (CO, β-lactam). ^1H NMR (DMSO): δ 3.63, 3.71 (2 OMe, 2 s, 6H), 5.37 (H-4, d, 1H, $J = 5.5$ Hz), 5.56 (H-3, d, 1H, $J = 5.8$ Hz), 6.61–7.70 (ArH, m, 13H). ^{13}C NMR (DMSO): δ 59.5, 61.2 (OMe), 78.2 (C-4), 82.1 (C-3), 107.0, 113.6, 116.4, 123.1, 126.5, 127.9, 128.8, 130.2, 134.7, 139.1, 143.7, 148.2, 152.5, 157.0 (aromatic carbons), 167.3 (CO, β-lactam). MS (m/z,%): 439 (M^+, 16), 408 (19), 346 (10), 305 (9), 298 (22), 256 (58), 182 (21), 134 (15), 93 (69), 77 (100), 75 (37). *Anal.* Calcd for $C_{23}H_{21}NO_6S$: C, 62.86; H, 4.82; N, 3.19. Found: C, 62.92; H, 5.01; N, 3.16.

4-(2,3-Dimethoxyphenyl)-3-phenoxy-1-(toluene-4-sulfonyl)-azetidin-2-one (20). (84%). β-Lactam **20** was obtained by the reaction of β-lactam **9** and 4-toluene sulfonyl chloride. IR (neat) (cm^{-1}): 1327 (S=O), 1772 (CO, β-lactam). ^1H NMR (DMSO): δ 2.04 (Me, s, 3H), 3.75, 3.82 (2 OMe, 2 s, 6H), 5.70 (H-4, d, 1H, $J = 6.3$ Hz), 5.95 (H-3, d, 1H, $J = 7.5$ Hz), 6.82–7.68 (ArH, m, 12H). ^{13}C NMR (DMSO): δ 22.3 (Me), 56.0, 56.9 (OMe), 61.4 (C-4), 61.8 (C-3), 108.0, 114.5, 116.6, 123.1, 126.7, 128.3, 130.6, 132.0,

135.9, 140.1, 146.7, 151.7, 153.0, 157.3 (aromatic carbons), 165.1 (CO, β-lactam). MS (m/z,%): 453 (M^+, 23), 438 (15), 422 (26), 319 (16), 256 (68), 229 (7), 197 (19), 134 (7), 121 (100), 93 (43), 91 (29), 77 (79). *Anal*. Calcd for $C_{24}H_{23}NO_6S$: C, 63.56; H, 5.11; N, 3.09. Found: C, 63.48; H, 5.19; N, 3.05.

4-(2,3-Dimethoxyphenyl)-1-(naphthalene-2-sulfonyl)-3-phenoxy-azetidin-2-one (21). (81%). β-Lactam **21** was obtained by the reaction of β-lactam **9** and naphthalene-2-sulfonyl chloride. IR (neat) (cm^{-1}): 1329 (S=O), 1769 (CO, β-lactam). ^{1}H NMR (DMSO): δ 3.19, 3.55 (2 OMe, 2 s, 6H), 5.08 (H-4, d, 1H, J = 4.8 Hz), 5.75 (H-3, d, 1H, J = 5.2 Hz), 6.71–8.73 (ArH, m, 15H). ^{13}C NMR (DMSO): δ 56.1, 57.8 OMe), 65.6 (C-4), 68.0 (C-3), 116.3, 117.7, 119.4, 123.0, 124.9, 126.1, 127.7, 128.0, 128.6, 129.1, 129.5, 131.2, 133.2, 136.4, 140.5, 143.3, 148.1, 150.6, 151.5, 156.3, 158.9 (aromatic carbons), 166.8 (CO, β-lactam). MS (m/z,%): 489 (M^+, 35), 458 (22), 396 (14), 355 (41), 256 (37), 233 (10), 191 (13), 134 (29), 127 (100), 93 (75), 77 (54). *Anal.* Calcd for $C_{27}H_{23}NO_6S$: C, 66.24; H, 4.74; N, 2.86. Found: C, 66.17; H, 4.91; N, 2.89.

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