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Synthesis of Novel *N*-Sulfonyl Monocyclic β-Lactams as Potential Antibacterial Agents

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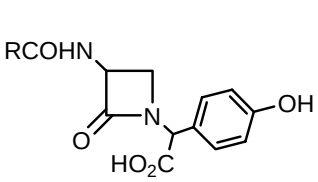
Abstract— New *cis* monocyclic β-lactams were synthesized by [2+2] Staudinger cycloaddition reactions of the imine (3,4-dimethoxybenzylidene)-(4-methoxyphenyl)-amine and ketenes derived from different acyl chlorides and Et_3N. These monocyclic β-lactams were then cleaved by ceric ammonium nitrate (CAN) to give NH-monocyclic β-lactams, which in turn were converted to *N*-sulfonyl monocyclic β-lactams by treatment with four different sulfonyl chlorides in the presence of Et_3N and 4,4-dimethyl-aminopyridine (DMAP).

Keywords: 2-Azetidinones, N-Sulfonyl β-lactams, Ketene, Imine, CAN, DMAP

Introduction

Even more than 70 years after the discovery of penicillin, β-lactam antibiotics remain as one of the most important contributions of science to Humanity [1]. The β-lactam skeleton is the common structural element of the widely used penicillins, cephalosporins, thienamycine, nocardicins, aztreonam and carumonam [2]. The first member of this class of compounds was synthesized by Staudinger in 1907 [3], but until the discovery of penicillin by Fleming in 1929, the importance of β-lactams as antibiotics was not recognized [4]. Widespread use of β-lactam antibiotics exerts selective pressure on bacteria and permits the proliferation of resistant organisms [5]. A comparison of current antibiograms with those from previous decades shows an alarming increase in bacterial resistance to

β-lactam antibiotics [6]. Consequently, because of the growing resistance of bacteria towards β-lactam antibiotics and the need for medicines with a more specific antibacterial activity several synthetic and semi-synthetic β-lactam antibiotics have been developed by the pharmaceutical industry [7]. An interesting group of β-lactams are the monocyclic β-lactams, which are molecules that do not contain another ring fused to the β-lactam one. In the late 1970s and early 1980s, the first classes of monocyclic β-lactams antibacterial agents were isolated from natural sources [8]. The discovery of the nocardicins, **1,** and monobactams, **2**, demonstrated for the first time that β-lactams do not require a conformationally constrained bicyclic structure to have antibacterial properties [9], suggesting that the biological activity was strictly correlated to the presence of a suitably functionalized 2-azetidinone ring [10]. In addition to the monobactams and nocardicins, some other monocyclic β-lactams such as compounds **3** [11], **4** [12]**,** and **5** [13] have also shown good antibacterial activity. Cyclic sulfonamides have been shown to be highly useful heterocycles in medicinal chemistry [13]. The sulfonamido group, in addition to its antibacterial activity, shows potent anti-HIV and latent leishmanicidal activities [15]. Numerous articles can be found through out the literature describing the preparation and use of *N*-sulfonyl β-lactams as intermediates in synthesis [16]. About 600 *N*-sulfonyl β-lactams have been examined for biological properties [17]. Turos and coworkers [18] synthesized the *N*-sulfonyl monocyclic β-lactams **6** and have tested them against some bacteria. Recently, it has been reported that monocyclic β-lactams have novel biological activities such as cytomegalovirus protease inhibitors [19], thrombin and tryptase inhibitors [20], cholesterol absorption inhibitors [21], human leukocyte elastease (HLE) inhibitors [22], porcine pancereatic elastease (PPE) inhibitors [23] and anticancer activities [24]. Besides their biological activities, the importance of β-lactams as synthetic intermediates has been widely recognized in organic synthesis [25] for example in the semisynthesis of Taxol [26].



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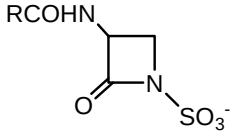

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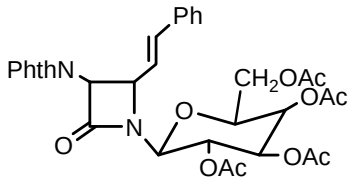

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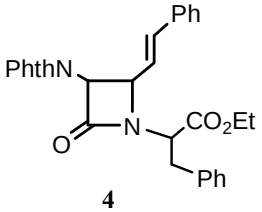

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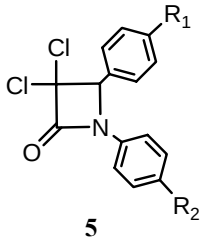

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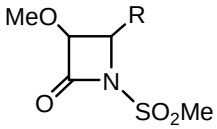

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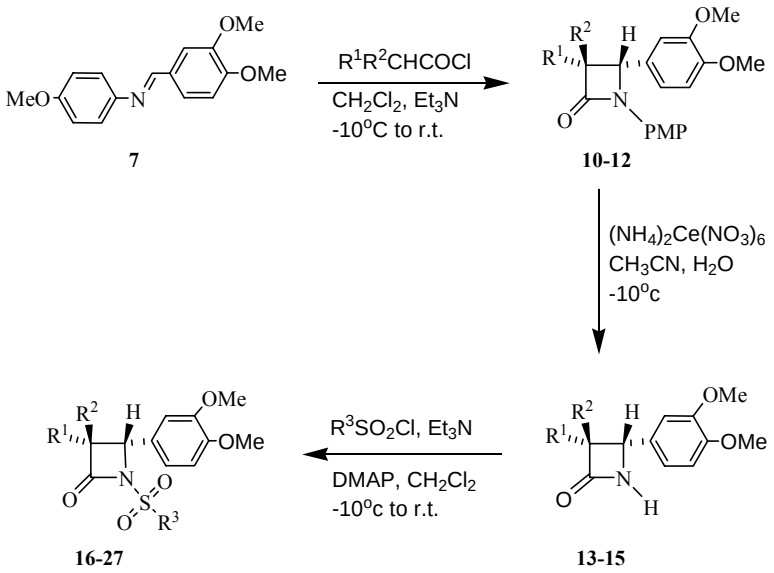
The β-lactam moiety is accessible by several synthetic methods and the topic has been reviewed several times [27]. Stereoselection at positions 3 and 4 of the 2-azetidinone ring is obviously of utmost importance with the perspective of its participation in biologically or pharmacologically-active molecules [28]. The most popular method for the preparation of the β-lactam ring involves the classical ketene-imine (Staudinger) reaction [29] that leads to β-lactams with *cis* selectivity [30]. In this paper, we describe the synthesis of some new monocyclic β-lactams bearing different sulfonyl groups at their N1-positions.

Results and Discussion

Aldimine **7** was prepared in quantitative yield by condensation of *p*-methoxyaniline and 3,4-dimethoxybenzaldehyde in refluxing ethanol. The formation of the Schiff base **7** was readily established from its spectral data. Treatment of **7** with ketenes derived from the acyl chlorides 3-nitrophthaloylglycyl chloride (**8**), 3-nitrophthaloylalaninyl chloride (**9**) and phenoxyacetyl chloride in the presence of triethylamine afforded cis-2-azetidinones **10-12** (Scheme 1). The presence of these new compounds was confirmed by t.l.c. monitoring. The IR spectra showed the β-lactam carbonyl at 1755.0-1786.6 cm^{-1}. The indicated *cis* stereochemistry for these monocyclic β-lactams was deduced from analysis of their ^{1}H-NMR spectra. The coupling constant of H-3 and H-4 is *J*= 5.2-5.3 Hz for β-lactam **10** and *J*= 5.6-5.8 Hz for β-lactam **12**, which are indicative of their *cis* stereochemistry. In addition, ^{13}C-NMR spectroscopic data of β-lactams **10-12** definitely showed the lactam CO (C2) signal at 161.8-166.8 ppm, whereas C-3 resonated at around 63.2-70.2 ppm and C-4 at 59.8-63.8 ppm.

Scheme 1



Monocyclic β-lactams **10-12** were then converted to *N*-unsubstituted β-lactams **13-15** by reaction with ceric ammonium nitrate (CAN) at –10°C. In this reaction, the quinone released was removed by forming the corresponding bisulfite adduct, which can be washed out with water after workup with aqueous $NaHSO_3$solution [31]. The IR spectra of the *N*-unsubstituted β-lactams **13-15** exhibited the characteristic NH absorption at 3290.3-3380.0 cm^{-1} and the 2-azetidinone carbonyl at 1762.5-1785.0 cm^{-1}. Furthermore, the ^{1}H-NMR spectra showed the NH peaks at 6.55-6.60 ppm and H-4 as a doublet of doublet peak at 5.04 ppm for **13**, 4.77 ppm for **15** and a doublet peak at 4.6 ppm for **14**, that confirmed the NH-β-lactam structures for **13-15**. *N*-Sulfonyl monocyclic β-lactams **16-27** were obtained by reaction of *N*-unsubstituted β-lactams **13-15** with methanesulfonyl chloride, benzenesulfonyl chloride, *p*-tolouenesulfonyl chloride and 2-naphthalenesulfonyl chloride, respectively, in the presence of 4,4-dimethylaminopyridine (DMAP) and Et_3N (see Table 1). The IR spectra showed the β-lactam carbonyls at 1766.4-1788.1 cm^{-1}, S=O absorptions (strong peaks) at 1328.5-1336.2 cm^{-1} and the

disappearance of the NH peaks. Other spectroscopic and analytical data were consistent with the indicated structures of the *N*-sulfonyl moncyclic β-lactams **16**-**27**.

Conclusions

In summary, new *cis*-monocyclic β-lactams **10**-**12** bearing N1-*p*-methoxyphenyl (PMP) groups were obtained with high stereoselectivity using classical Staudinger methodology. These β-lactams were oxidatively cleaved to NH-β-lactams **13**-**15** by reaction with ceric ammonium nitrate. A novel series of monocyclic β-lactams containing sulfonamidos groups at N1 were then synthesized from the NH-β-lactams **13**-**15** and the appropriate sulfonyl chlorides. The coexistence of a β-lactam ring and a sulfonamido group may make these valuable compounds for study of antimicrobial activities.

Table 1. Monocyclic β-lactams

Compound	R^1	R^2	R^3	Yield%
10	3-NO_2Phth	H	-	60
11	3-NO_2Phth	Me	-	58
12	PhO	H	-	97
13	3-NO_2Phth	H	-	79
14	3-NO_2Phth	Me	-	88
15	PhO	H	-	83
16	3-NO_2Phth	H	Me	78
17	3-NO_2Phth	H	Ph	85
18	3-NO_2Phth	H	4-MeAr	88
19	3-NO_2Phth	H	2-naphthalene	73
20	3-NO_2Phth	Me	Me	79
21	3-NO_2Phth	Me	Ph	76
22	3-NO_2Phth	Me	4-MeAr	83
23	3-NO_2Phth	Me	2-naphthalene	82
24	PhO	H	Me	83
25	PhO	H	Ph	86
26	PhO	H	4-MeAr	74
27	PhO	H	2-naphthalene	72

Acknowledgments

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Experimental

General

All required chemicals were purchased from the Merck and Fluka chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH_2 and then stored over 4Å

molecular sieves. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ (compounds **7**, **10-15**) or DMSO-d_6 (compounds **16-27**) using a Bruker Avance DPX instrument (operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts were reported in ppm (δ) downfield from TMS. All of the coupling constants (*J*) are in Hertz. The mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography (t.l.c.) was carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kieselgel (230-270 mesh).

Synthesis of (3,4-dimethoxybenzylidene)-(4-methoxyphenyl)amine (**7**):

A mixture of *p*-methoxyaniline (5.00 g, 40.71 mmol) and 3,4-dimethoxybenzaldehyde (6.80 g, 40.71 mmol) was refluxed in ethanol for 4 hours. After cooling the solution the precipitate formed was filtered off and washed with ethanol to give pure Schiff base **7** as a yellow solid (10.46 g, 95%). m.p. 128-130 ^{o}C; IR (KBr, cm^{-1}) 1620.1 (C=N); ^{1}H-NMR δ 3.85, 4.01, 4.02 (3 OMe, 3 s, 9H), 6.87-7.72 (ArH, m, 7H), 8.40 (HC=N, s, 1H); ^{13}C-NMR δ 64.59, 65.11 (OMe), 117.90-160.88 (aromatic carbons), 167.15 (C=N); MS (m/e) 272, 271 (M^{+}), 257, 256, 240, 154, 134, 115, 77.

Synthesis of 3-nitrophthaloylglycyl chloride (**8**):

3-Nitrophthaloylglycine was prepared by a reported method [32]. 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 hours, the excess of thionyl chloride was removed by distillation and the residue was crystallized from light petroleum to give acyl chloride **8** as a light yellow crystalline solid (10.65 g, 93 %). It was stable for long periods when stored in a dessicator over $CaCl_2$; m.p. 116-118 ^{o}C; IR (KBr, cm^{-1}) 1735, 1775 (phthalimido, CO), 1805 (COCl).

Synthesis of 3-nitrophthaloylalaninyl chloride (**9**):

3-Nitrophthaloylalanine was prepared by a reported method [32]. 3-Nitrophthaloylalanyl chloride (**9**) was prepared by the same method as compound **8**. Yield 90 %; m.p. 108-110 ^{o}C; IR (KBr, cm^{-1}) 1740, 1785 (phthalimido, CO), 1810 (COCl).

General procedure for synthesis of monocyclic β-lactams **10-12:**

A solution of the corresponding acyl chloride (1.50 mmol) in dry CH_2Cl_2 (10 mL) was slowly added to a solution of (3,4-dimethoxybenzylidene)-(4-methoxyphenyl) amine (**7**, 1.00 mmol) and triethylamine (3.00 mmol) in CH_2Cl_2 (15 mL) at –10 ^{o}C. The reaction mixture was then allowed to warm to room temperature, stirred overnight and then it was washed with saturated sodium bicarbonate solution (20 mL), 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-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl]-4-nitroisoindole-1,3-dione (**10**). β-Lactam **10** was obtained as a light brown solid from Schiff base **7** and acyl chloride **8**. Yield 60 % (eluent hexane/EtOAc 5:5); m.p. 198-200 ^{o}C; IR (KBr, cm^{-1}) 1735.0, 1770.0 (phth. CO), 1778.0 (CO β-lactam); ^{1}H-NMR δ 3.65, 3.74, 3.78 (3 OMe, 3 s, 9H), 5.33 (H-4, d, 1H, *J*=5.2), 5.53 (H-3, d, 1H, *J*=5.3), 6.64-8.01 (ArH, m, 10H); ^{13}C-NMR δ 55.80, 56.10, 56.39 (OMe), 61.16 (C-4), 63.29 (C-3), 109.12-156.96 (aromatic carbons), 161.20 (CO), 163.52 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-methyl-4-oxo-azetidin-3-yl]-4-nitroiso indole-1,3-dione (**11**)**.** β-Lactam **11** was obtained as a light brown solid from Schiff base **7** and acyl chloride **9**. Yield 58 % (eluent hexane/EtOAc 4:6); m.p. 181-183 ^{o}C; IR (KBr, cm^{-1}) 1735.0, 1775.7 (phth. CO), 1786.6 (CO β-lactam); ^{1}H-NMR δ 1.82 (Me, s, 3H), 3.73, 3.75, 3.82 (3 OMe, 3 s, 9H), 5.69 (H-4, s, 1H), 6.74-8.07 (ArH, m, 10H); ^{13}C-NMR δ 20.41 (Me), 56.51, 56.81, 61.85 (OMe), 63.84 (C-4), 70.20 (C-3), 113.81-157.45 (aromatic carbons), 166.01 (CO), 166.82 (CO, β-lactam).

4-(3,4-Dimethoxyphenyl)-1-(4-methoxyphenyl)-3-phenoxy-2-azetidinone (**12**). β-Lactam **12** was obtained as a light yellow solid from Schiff base **7** and phenoxyacetyl chloride. Yield 97 %; m.p. 158-160 ^{o}C; IR (KBr, cm^{-1}) 1755.0 (CO, β-lactam); ^{1}H-NMR δ 3.62, 3.72, 3.76 (3 OMe, 3 s, 9H), 5.44 (H-4, d, 1H, *J*=5.8), 5.71 (H-3, d, 1H, *J*=5.6), 6.68-7.37 (ArH, m, 12H); ^{13}C-NMR δ 54.36, 54.72, 55.09 (OMe), 59.85 (C-4), 66.50 (C-3), 113.65-156.25 (aromatic carbons), 161.87(CO, β-lactam).

General procedure for synthesis of N-unsubstituted β-lactams **13-15**:

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 the β-lactams **10**-**12** (1.00 mmol) in CH_3CN (25mL) at –10 ^{o}C. The mixture was stirred at this temperature for 45 minutes, 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 successively with 10 % $NaHSO_3$ (2×30 mL), $NaHCO_3$ (20 mL), brine (20 mL) and then dried over sodium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by recrystalization from 4:6 hexane-EtOAc to afford the products **13**-**15**, respectively.

2-[2-(3,4-Dimethoxyphenyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (**13**). β-Lactam **13** was prepared by deprotection of β-lactam **10**. Brown solid (79 %); m.p. 117-119 ^{o}C; IR (KBr, cm^{-1}) 1735.0, 1770.2 (phth., CO), 1785.0 (CO, β-lactam), 3380.5 (NH); ^{1}H-NMR δ 3.61, 3.75 (2 OMe, 2 s, 6H), 5.04 (H-4, dd, 1H, *J*=12.2, 3.5), 5.53 (H-3, d, 1H, *J*=5.5), 6.55 (NH, br s, 1H), 6.97-8.63 (ArH, m, 6H); ^{13}C-NMR δ 55.44, 55.85 (OMe), 60.81 (C-4), 63.16 (C-3), 110.08-150.07 (aromatic carbons), 163.36 (CO), 164.49 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-3-methyl-4-oxoazeti- din-3-yl]-4-nitroisoindole-1,3-dione (**14**)**.** β-Lactam **14** was prepared by deprotection of β-lactam **11**. Brown solid (88 %); m.p. 113-115 ^{o}C; IR (KBr, cm^{-1}) 1735.0, 1775.0 (phth., CO), 1790.0 (CO, β-lactam), 3310.0 (NH); ^{1}H-NMR δ 1.63 (Me, s, 3H), 3.22, 3.83 (2 OMe, 2 s, 6H), 4.69 (H-4, d, 1H, *J*=7.3), 6.57 (NH, br s, 1H), 7.23-8.63 (ArH, m, 6H);

^{13}C-NMR δ 16.51 (Me), 49.72, 50.02 (OMe), 64.52 (C-4), 69.88 (C-3), 117.20-164.45 (aromatic carbons), 167.05 (CO), 171.85 (CO, β-lactam).

4-(3,4-Dimethoxyphenyl)-3-phenoxy-2-azetidinone (**15**). β-Lactam **15** was prepared by deprotection of β-lactam **12**. Red oil (83 %); IR (neat, cm^{-1}) 1762.5 (CO, β-lactam), 3290.3 (NH); ^{1}H-NMR δ 3.67, 3.79 (2 OMe, 2 s, 6H), 4.77 (H-4, dd, 1H, *J*=13.5, 5.2), 5.27 (H-3, d, 1H, *J*=8.2), 6.60 (NH, br s, 1H), 6.67-7.88 (ArH, m, 8H); ^{13}C-NMR δ 56.80, 60.80 (OMe), 81.68 (C-4), 82.95 (C-3), 111.25-157.16 (aromatic carbons), 167.81 (CO, β-lactam).

Typical procedure for synthesis of N-sulfonyl-β-lactams **16-27**:

To a solution of *N*-unsubstituted β-lactams **13-15** (1.00 mmol), separately, in dry CH_2Cl_2 (10 mL) cooled to –10 ^{o}C was added triethylamine (1.5 mmol) and 4-*N*,*N*-dimethylaminopyridine (DMAP) (0.1 mmol). A solution of corresponding sulfonyl chloride (1.5 mmol) in dry CH_2Cl_2 (5 mL) was slowly added to the resulting mixture. After stirring at –10 ^{o}C for one hour, 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 in reduced pressure to give the *N*-sulfonyl β-lactams **16-27**.

2-[2-(3,4-Dimethoxyphenyl)-1-methanesulfonyl-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (**16**). β-Lactam **16** was obtained by reaction of β-lactam **13** and methanesulfonyl chloride as a red oil (78 %); IR (neat, cm^{-1}) 1331.7 (S=O), 1735.0, 1776.2 (phth., CO), 1785.0 (CO, β-lactam); ^{1}H-NMR δ 3.54 (SO_2Me, s, 3H), 4.48, 4.55 (2 OMe, 2 s, 6H), 5.14 (H-4, d, 1H, *J*=5.5), 5.60 (H-3, d, 1H, *J*=5.0), 6.88-8.13 (ArH, m, 6H); ^{13}C-NMR δ 31.82 (Me), 56.03, 59.12 (OMe), 60.26 (C-4), 61.65 (C-3), 106.92-151.61 (aromatic carbons), 161.81(CO), 164.73 (CO, β-lactam).

2-[1-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (**17**). β-Lactam **17** was obtained by reaction of β-lactam **13** and benzenesulfonyl chloride as a red oil (85 %); IR (neat, cm^{-1}) 1331.7 (S=O), 1735.0, 1776.2 (phth., CO), 1785 (CO, β-lactam); ^{1}H-NMR δ 3.77, 3.78 (2 OMe, 2 s, 6H), 5.39 (H-4, d, 1H, *J*=5.2), 5.48 (H-3, d, 1H, *J*=5.6), 6.87-8.10 (ArH, m, 11H); ^{13}C-NMR δ 55.13, 55.89 (OMe), 59.91 (C-4), 61.59 (C-3), 107.88-152.72 (aromatic carbons), 161.47(CO), 164.71 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-4-oxo-1-(toluene-4-sulfonyl)-azetidin-3-yl]-4-nitroisoindole-1,3-dione (**18**) β-Lactam **18** was obtained by reaction of β-lactam **13** and 4-toluenesulfonyl chloride as a red oil (88 %); IR (neat, cm^{-1}) 1330.9 (S=O), 1737.5, 1777.3 (phth., CO), 1787.2 (CO, β-lactam); ^{1}H-NMR δ 2.16 (MePh, s, 3H), 3.21, 3.37 (2 OMe, 2 s, 6H), 5.02 (H-4, d, 1H, *J*=5.1), 5.48(H-3, d, 1H, *J*=5.0), 6.48-8.08 (ArH, m, 10H); ^{13}C-NMR δ 23.20 (MePh), 46.47, 52.56 (OMe), 56.22 (C-4), 60.09 (C-3), 108.04-156.12 (aromatic carbons), 161.85 (CO), 164.75 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-1-(naphthalene-2-sulfonyl)-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione (**19**). β-Lactam **19** was obtained by reaction of β-lactam **13** and naphthalene-2-sulfonyl chloride as a red oil (73 %); IR (neat, cm^{-1}) 1336.2 (S=O), 1741.2, 1775.6 (phth., CO), 1784.9 (CO, β-lactam);

^{1}H- NMR δ 3.04, 3.22 (2 OMe, 2 s, 6H), 5.05 (H-4, d, 1H, *J*=5.5), 5.67 (H-3, d, 1H, *J*=5.8), 6.55-8.05 (ArH, m, 13H); ^{13}C-NMR δ 53.45, 55.68 (OMe), 56.55 (C-4), 61.67 (C-3), 106.12-156.47 (aromatic carbons), 161.65 (CO), 164.77 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-1-methanesulfonyl-3-methyl-4-oxo-azetidin-3-yl]-4-nitroisoindole-1,3-dione **(20)**. β-Lactam **20** was obtained by reaction of β-lactam **14** and methanesulfonyl chloride as a red oil (79 %); IR (neat, cm^{-1}) 1331.9 (S=O), 1736.9, 1777.0 (phth., CO), 1788.1 (CO, β-lactam); ^{1}H-NMR δ 1.49 (Me, s, 3H), 2.63 (SO_2Me, s, 3H), 3.52, 3.68 (2 OMe, 2 s, 6H), 5.22(H-4, s, 1H), 6.76-8.11 (ArH, m, 6H); ^{13}C-NMR δ 19.16 (Me), 32.46 (SO_2Me), 59.66, 59.97 (OMe), 69.80 (C-4), 70.39 (C-3), 112.57-163.70 (aromatic carbons), 166.76 (CO), 168.14 (CO, β-lactam).

2-[1-Benzenesulfonyl-2-(3,4-dimethoxyphenyl)-3-methyl-4-oxo-azetidin-3-yl]-4-nitroisoindole1,3-dione (**21**). β-Lactam **21** was obtained as a red oil (76 %) by reaction of β-lactam **14** and benzenesulfonyl chloride. IR (neat, cm^{-1}) 1329.2 (S=O), 1739.1, 1778.1 (phth., CO), 1786.3 (CO, β-lactam); ^{1}H-NMR 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 δ 20.74 (Me), 55.97, 58.15 (OMe), 67.64 (C-4), 73.33 (C-3), 114.99-165.27 (aromatic carbons), 167.51 (CO), 171.35 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-3-methyl-4-oxo-1-(toluene-4-sulfonyl)-azetidin-3-yl]-4-nitroisoindole-1,3-dione (**22**). β-Lactam **22** was obtained by reaction of β-lactam **14** and 4-toluenesulfonyl chloride as a red oil (83 %). IR (neat, cm^{-1}) 1335.1 (S=O), 1740.0, 1777.0 (phth., CO), 1788.1 (CO, β-lactam); ^{1}H-NMR δ 1.58 (Me, s, 3H), 2.36 (MePh, s, 3H), 3.48, 3.55 (2 OMe, 2 s, 6H), 5.70 (H-4, s, 1H), 6.88-8.16 (ArH, m, 10H); ^{13}C-NMR δ 18.98 (Me), 20.48 (MePh), 55.18, 55.86 (OMe), 60.57 (C-4), 70.03 (C-3), 108.14-152.97 (aromatic carbons), 161.22 (CO), 165.85 (CO, β-lactam).

2-[2-(3,4-Dimethoxyphenyl)-3-methyl-1-(naphthalene-2-sulfonyl)-4-oxo-azetidin-3-yl]-4-nitro-isoindole-1,3-dione (**23**). β-Lactam **23** was obtained by reaction of β-lactam **14** and naphthalene-2-sulfonyl chloride as a red oil (82 %). IR (neat, cm^{-1}) 1333.1 (S=O), 1738.4, 1776.9 (phth., CO), 1787.1 (CO, β-lactam); ^{1}H-NMR δ 2.15 (Me, s, 3H), 3.06, 3.19 (2 OMe, 2 s, 6H), 5.62 (H-4, s, 1H), 6.74-8.75 (ArH, m, 13H); ^{13}C-NMR δ 30.55 (Me), 56.13, 56.88 (OMe), 57.35 (C-4), 60.42 (C-3), 107.32-156.60 (aromatic carbons), 165.32 (CO), 167.66 (CO, β-lactam).

4-(3,4-Dimethoxyphenyl)-1-methanesulfonyl-3-phenoxy-azetidin-2-one (**24**). β-Lactam **24** was obtained by reaction of β-lactam **15** and methanesulfonyl chloride as a red oil (83 %). IR (neat, cm^{-1}): 1332.2 (S=O), 1766.4 (CO, β-lactam); ^{1}H-NMR δ 2.15 (SO_2Me, s, 3H), 3.83, 3.98 (2 OMe, 2 s, 6H), 5.35 (H-4, d, 1H, *J*=5.8), 5.60 (H-3, d, 1H, *J*=4.1), 6.72-7.87 (ArH, m, 8H); ^{13}C-NMR δ 26.83 (SO_2Me), 59.62, 59.87 (OMe), 81.32 (C-4), 82.52 (C-3), 107.14-163.31 (aromatic carbons), 165.83 (CO, β-lactam).

1-Benzenesulfonyl-4-(3,4-dimethoxyphenyl)-3-phenoxy-azetidin-2-one (**25**). β-lactam **25** was obtained by reaction of β-lactam **15** and benzenesulfonyl chloride as a red oil (86 %); IR (neat, cm^{-1}): 1328.5 (S=O), 1772.0 (CO, β-lactam); ^{1}H-NMR δ 3.60, 3.69 (2 OMe, 2 s, 6H), 5.17 (H-4, d, 1H, *J*=6.5), 5.46

(H-3, d, 1H, *J*=4.8), 6.55-7.75 (ArH, m, 13H); ^{13}C-NMR δ 59.30, 60.21 (OMe), 78.49 (C-4), 82.43 (C-3), 108.15-156.75 (aromatic carbons), 157.52 (CO, β-lactam).

4-(3,4-Dimethoxyphenyl)-3-phenoxy-1-(toluene-4-sulfonyl)-azetidin-2-one (**26**). β-Lactam **26** was obtained by reaction of β-lactam **15** and 4-toluenesulfonyl chloride as a red oil (74 %); IR (neat, cm^{-1}) 1329.8 (S=O), 1769.3 (CO, β-lactam); ^{1}H-NMR δ 2.14 (MePh, s, 3H), 3.68, 3.80 (2 OMe, 2 s, 6H), 5.74 (H-4, d, 1H, *J*=6.0), 5.90 (H-3, d, 1H, *J*=5.5), 6.62-7.65 (ArH, m, 12H); ^{13}C-NMR δ 22.06 (MePh), 56.10, 56.72 (OMe), 61.43 (C-4), 61.65 (C-3), 108.24-157.77 (aromatic carbons), 165.06 (CO, β-lactam).

4-(3,4-Dimethoxyphenyl)-1-(naphthalene-2-sulfonyl)-3-phenoxy-azetidin-2-one (**27**). β-Lactam **27** was obtained by reaction of β-lactam **15** and naphthalene-2-sulfonyl chloride as a red oil (72 %); IR (neat, cm^{-1}) 1332.1 (S=O), 1770.1 (CO, β-lactam); ^{1}H-NMR δ 3.29, 3.64 (2 OMe, 2 s, 6H), 5.18 (H-4, d, 1H, *J*=5.0), 5.85 (H-3, d, 1H, *J*=5.6), 6.85-8.65 (ArH, m, 15H); ^{13}C-NMR δ 55.89, 57.06 (OMe), 65.60 (C-4), 68.11 (C-3), 118.34-158.84 (aromatic carbons), 166.79 (CO, β-lactam).

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