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ORIGINAL RESEARCH

Synthesis and biological evaluation of some new β-lactam-triazole hybrids

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Abstract *A series of novel* β-lactams was synthesized from different imines and a special ketene derived from *N*-endo-5-norbornene-2,3-dicarboxyloylglycine **1** via the [2 + 2] ketene imine cycloaddition. Then, β-lactams **3a–h** were treated with 1-azido-4-nitrobenzene **4** to afford β-lactam-triazole hybrids **5a–h**. Of the twenty-three β-lactams tested against chloroquine-resistant *P. falciparum* K14 strain, **3a** and **3d** showed $IC_{50} < 20$ μM, while **3j**, **3m**, **5a–5f** exhibited $IC_{50} < 50$. These newly synthesized β-lactams were also tested against *S. aureus*, *E. coli*, *P. aeruginosa, C. albicans* and *C. glabrata* and showed no activity below 125 μg/mL.

Keywords β-Lactam · *N*-endo-5-norbornene-2,3-dicarboxyloylglycine · Triazole hybrids · *P. falciparum*

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Introduction

The azetidine-2-one ring system is the key of biological activities in β-lactam antibiotics which are a large group of antibiotics, such as penicillins (Marchand-Brynaert and Brulé, 2008), cephalosporins (Alcaide *et al.*, 2008), nocardicins, carbapenems and monobactams (Palomo *et al.*, 2001; Alcaide *et al.*, 2007; Deshmukh *et al.*, 2004; Halve *et al.*, 2007), that have been widely used as chemotherapeutic agents for treating microbial diseases (Georg, 1993; Halve *et al.*, 2007). In addition, it possess many other pharmacological activities such as human cytomegalovirus protease inhibitors (Borthwick *et al.*, 1998), LHRH antagonists (Guillon *et al.*, 2007), cholesterol absorption inhibitors (Burnett, 2004), anticancer agents (Banik *et al.*, 2010; O'Boyle *et al.*, 2010), antihyperglycemic (Goel *et al.*, 2004), antimalarial (Jarrahpour *et al.*, 2012), anti-HIV (Sperka *et al.*, 2005), anti-inflammatory and analgesic activities (Saturnino *et al.*, 2000).

Azoles are the widest group of antifungal drugs. They are first-line drugs in the treatment of fungal infections, because of their high therapeutic index. Besides their antifungal activity (Rezaei *et al.*, 2009), they show different potential activities such as antibacterial (Bagihalli *et al.*, 2008), antitubercular (Wujec *et al.*, 2008), antiproliferative (Manfredini *et al.*, 2000), anti-HIV (Akhtar *et al.*, 2007) and antiviral (Holla *et al.*, 2001).

However, the development of drug resistance for the common antimicrobials has encouraged considerable research efforts in the development of new drugs using different approaches (Dondorp *et al.*, 2009; Schlitzer, 2007) of which the molecular hybridization approach (Meunier, 2007; Muregi and Ishih, 2010) is quite an attractive strategy. Molecular hybridization is the logical design of new chemical entities by the combination of two

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distinct known bioactive pharmacophores into a single molecule (Claudio *et al.*, 2007; Walsh and Bell, 2009). These two pharmacophores are usually picked out based on their observed synergetic pharmacological activities. The two most important profits of molecular hybridization are increasing therapeutic efficacy and improving the bioavailability profile (Claudio *et al.*, 2007). Hybrid compounds can be assembled by linking pharmacophore subunits directly or with spacer agents.

There are some reports of β-lactam-azole hybrid displaying good antimicrobial activities (Kumar *et al.*, 2012; Raj *et al.*, 2013; Vatmurge *et al.*, 2008). Based on these observations and in continuation of our interest for the synthesis of new bioactive β-lactams, we report herein the synthesis of some novel β-lactam-triazole hybrids and their in vitro antibacterial, antifungal and antimalarial evaluation.

Experimental section

Materials

Chemical materials and solvents were obtained from Merck, Fluka and Aldrich chemical companies. Solvents were dried and purified by standard procedures. Melting points were determined in open capillary tubes in Thermo Fisher scientific IA9200 apparatus and are not corrected. FTIR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250 (^{1}H-NMR 250 MHz, ^{13}C-NMR 62.9 MHz) spectrometer in $CDCl_3$ or DMSO-d_6 solvents using TMS as an internal standard. Chemical shifts were reported in ppm (δ) downfield from TMS. All of the coupling constants (J) are in Hertz. Mass spectra were obtained on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. The determination of the prepared products and reaction monitoring were carried out on silica gel 254 analytical sheets obtained from Fluka. Column chromatography was carried out by silica gel 60 Merck (230-270).

Synthesis of *N*-endo-5-norbornene-2,3-dicarboxyloylglycine 1

To endo-5-norbornene-2,3-dicarboxylic anhydride (16.41 g, 100.0 mmol) dissolved in DMF (30 mL) was added glycine (7.50 g, 100.0 mmol). The reaction mixture was refluxed for 24 h, cooled to room temperature, diluted with ethyl acetate (70 mL) and washed with saturated aqueous ammonium chloride solution (5 × 50 mL). The organic phase was dried on anhydrous Na_2SO_4, filtered and evaporated in vacuo. The residue was recrystallized (five times) from ethyl acetate giving N-5-norbornene-2,3-dicarboxyloylglycine as a white crystalline solid (yield 61 %, 13.5 g); mp: 149–151 °C.

General procedure for the preparation of Schiff bases 2a–q

A mixture of aldehyde (9 mmol) and aromatic amine (9 mmol) was refluxed in ethanol (20 mL) for 3–5 h. Then, the solvent was evaporated under vacuum and crude oily and solid Schiff bases were obtained. Crude solid Schiff bases were filtered and washed with ethanol to afford pure solid Schiff bases.

N-(4-chlorobenzylidene)-4-methoxyaniline ***(2a)*** Light silver crystal (yield 95 %, 2.1 g); mp: 121–123 °C; IR (KBr, cm-1): 1620 (C=N) (Barbarotto *et al.*, 2009).

N1-(2,3-dimethoxybenzylidene)-N4,N4-dimethylbenzene-1,4-diamine ***(2b)*** Olive solid (yield 92 %, 2.3 g); mp: 229–230 °C; IR (KBr, cm^{-1}): 1630 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.97 (CH_3, s, 6H), 3.80, 3.84 (2 OCH_3, s, 6H), 6.72 (ArH, d, 2H, $J = 8.62$ Hz), 6.84–7.13 (ArH, m, 3H), 7.71 (ArH, d, 2H, $J = 8.56$ Hz), 7.96 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 39.9 (CH_3), 55.4, 55.6 ($2OCH_3$), 110.5, 115.8, 116.9, 117.2, 118.5, 122.8, 138.4, 144.6, 147.3, 151.96 (aromatic carbons), 160.8 (C=N).

N-(2-chlorobenzylidene)-2-(3,4-dimethoxyphenyl)ethanamine ***(2c)*** Red oil (yield 93 %, 2.5 g); IR (KBr, cm^{-1}): 1643 (C=N) (Weinbach and Hartung, 1950).

N-(2-chlorobenzylidene)-4-isopropylaniline ***(2d)*** Gray oil (yield 94 %, 2.2 g); IR (KBr, cm^{-1}): 1626 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.14 (CH_3, d, 6H, $J = 6.95$ Hz), 2.81 (CH, m, 1H), 7.07–7.29 (ArH, m, 8H), 8.12 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 18.8 (CH_3), 26.5 (CH), 115.9, 121.8, 121.9, 123.3, 124.7, 126.7, 128.1, 130.7, 142.1, 144.2 (aromatic carbons), 150.96 (C=N).

N-(3,4-dimethoxybenzylidene)benzo[d][1,3]dioxol-5-amine ***(2e)*** Brown solid (yield 96 %, 2.4 g); mp: 119.9–121 °C; IR (KBr, cm^{-1}): 1627 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 3.87, 3.91 ($2OCH_3$, 2 s, 6H), 5.91 (CH_2, s, 2H), 6.73 (ArH, d, 2H, $J = 7.83$ Hz), 6.77 (ArH, d, 1H, $J = 8.41$ Hz), 6.82 (ArH, s, 1H), 6.86 (ArH, s, 1H), 7.21 (ArH, dd, 1H, $J = 8.36$, $J = 7.58$ Hz), 8.27 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 56.0, 56.1 ($2OCH_3$), 101.4 (CH_2), 101.6, 108.3, 110.5, 115.1, 129.0, 129.8, 134.7, 137.0, 145.9, 148.3, 156.8 (aromatic carbons), 158.34 (C=N).

N1-(4-isopropylbenzylidene)-N4,N4-dimethylbenzene-1,4-diamine ***(2f)*** Yellow solid (yield 95 %, 2.3 g); mp: 99–100 °C; IR (KBr, cm^{-1}): 1627 (C=N) (Gawinecki and Muzalewski, 1984).

4-(((3,4-Dimethoxyphenethyl)imino)methyl)-N,N-dimethylaniline ***(2g)*** Yellow solid (yield 97 %, 2.7 g); mp:

114–116 °C; IR (KBr, cm^{-1}): 1635 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.94 (CH_2–Ph, t, 2H, $J = 7.26$ Hz), 3.00 (CH_3, s, 6H), 3.75 (CH_2–N, m, 2H), 3.79, 3.83 ($2OCH_3$, s, 6H), 6.66 (ArH, d, 2H, $J = 7.42$ Hz), 6.76 (ArH, s, 3H), 7.59 (ArH, d, 2H, $J = 8.05$ Hz), 7.96 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 37.2 (CH_2–Ph), 40.2 (CH_3), 55.7, 55.8 ($2OCH_3$), 62.9 (CH_2–N), 111.1, 111.6, 112.5, 120.8, 129.7, 132.7, 147.2, 148.5, −152.2 (aromatic carbons), 161.5 (C=N).

N-(3,4-dimethoxybenzylidene)-2,4-dimethoxyaniline ***(2h)*** Green oil (yield 91 %, 2.4 g); IR (KBr, cm^{-1}): 1632 (C=N) (Adib *et al.*, 2011).

N-(anthracen-9-ylmethylene)benzo[d][1,3]dioxol-5-amine ***(2i)*** Brown solid (yield 85 %, 2.5 g); mp: 114.9–118.2 °C; IR (KBr, cm^{-1}): 1620 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 6.05 (CH_2, s, 2H), 6.91–7.04 (ArH, m, 3H), 7.47–7.60 (ArH, m, 4H), 8.02 (ArH, d, 2H, $J = 6.95$ Hz), 8.53 (ArH, s, 1H), 8.69 (ArH, d, 2H, $J = 9.16$ Hz), 9.64 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 101.5 (CH_2), 102.0, 108.5, 114.9, 124.7, 125.4, 127.2, 129.0, 130.5, 131.3, 146.4, 147.1, 148.4 (aromatic carbons), 158.0 (C=N).

N1-(4-(dimethylamino)benzylidene)-N4,N4-dimethylbenzene-1,4-diamine ***(2j)*** Olive solid (yield 90 %, 2.2 g); mp: 237.5–239 °C; IR (KBr, cm^{-1}): 1633 (C=N) (Neuvonen *et al.*, 2006).

2-(3,4-Dimethoxyphenyl)-N-(4-isopropylbenzylidene) ethanamine ***(2k)*** Red oil (yield 97 %, 2.7 g); IR (KBr, cm^{-1}): 1643. (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.16 (CH_3, d, 6H, $J = 7.04$), 2.85 (CH, m, 1H), 3.10 (CH_2–Ph, t, 2H, $J = 8.25$ Hz), 3.69 (CH_2–N, m, 2H), 3.75, 3.87 ($2OCH_3$, s, 6H), 6.62–6.67 (ArH, m, 3H), 7.43 (ArH, d, 2H, $J = 8.31$ Hz), 7.54 (ArH, d, 2H, $J = 7.98$ Hz), 8.26 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 20.5 (CH_3), 28.0 (CH), 35.0 (CH_2–Ph), 55.1, 55.5 ($2OCH_3$), 62.3 (CH_2–N), 110.8, 111.1, 124.5, 127.1, 133.1, 133.9, 146.4, 148.3, 153.4 (aromatic carbons), 160.4 (C=N).

N-(2,3-dimethoxybenzylidene)-2-(3,4 dimethoxyphenyl) ethanamine ***(2l)*** Red oil (yield 89 %, 2.6 g); IR (KBr, cm^{-1}): 1638 (C=N) (Bian *et al.*, 2006).

N-(4-chlorobenzylidene)-2-(3,4-dimethoxyphenyl)ethanamine ***(2m)*** Orange solid (yield 90 %, 2.5 g); mp: 108.2–109.8 °C IR (KBr, cm^{-1}): 1628 (C=N) (Tiwari *et al.*, 2006).

2-((Benzo[d][1,3]dioxol-4-ylimino)methyl)-6-(morpholinomethyl) phenol ***(2n)*** Brown solid (yield 92 %, 2.8 g); mp: 133.7–135 °C; IR (KBr, cm^{-1}): 1610 (C=N), 3322–3498 (OH); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 2.60 (CH_2–N, t, 4H), 3.74 (CH_2, s, 2H), 3.74 (CH_2–O, t, 4H), 5.94 (CH_2–2O, s, 2H), 6.74–7.43 (ArH, m, 6H), 8.52 (HC=N, s, 1H), 13.61 (OH, brs, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 53.5 (C-14), 56.4 (C-13), 66.8 (C-15), 101.5 (C-12), 101.7, 108.5, 115.4, 118.6, 119.2, 124.4, 131.2, 134.2, 142.8, 146.8, 148.5, 159.5 (aromatic carbons), 160.24 (C=N).

3-Methoxy-N-(3-methoxybenzylidene)aniline ***(2o)*** Black oil (yield 91 %, 2.0 g); IR (KBr, cm^{-1}): 1626 (C=N) (Smith *et al.*, 1988).

N-(2,3-dimethoxybenzylidene)-4-isopropylaniline ***(2p)*** Red oil (yield 96 %, 2.4 g); IR (KBr, cm^{-1}): 1689 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.15 (CH_3, d, 6H, $J = 7.42$), 2.79 (CH, m, 1H), 3.65, 3.72 ($2OCH_3$, s, 6H), 6.85–7.12 (ArH, m, 3H), 7.32 (ArH, d, 2H, $J = 7.85$ Hz), 7.44 (ArH, d, 2H, $J = 8.68$ Hz), 8.52 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 22.2 (CH_3), 30.7 (CH), 57.3, 57.8 ($2OCH_3$), 112.4, 114.8, 121.1, 122.5, 129.6, 143.2, 145.1, 153.2, 155.2 (aromatic carbons), 161.0 (C=N).

N1-(2,3-dimethoxybenzylidene)-N4,N4-diethylbenzene-1,4-diamine ***(2q)*** Brown solid (yield 95 %, 2.7 g); mp: 96–98 °C; IR (KBr, cm^{-1}): 1612 (C=N); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.13 (CH_3, t, 6H, $J = 8.25$ Hz), 3.52 (CH_2, q, 4H), 3.64, 3.71 ($2OCH_3$, s, 6H), 6.72–6.75 (ArH, d, 2H, $J = 8.24$ Hz), 6.92–7.21 (ArH, m, 3H), 7.38 (ArH, d, 2H, $J = 7.37$ Hz), 8.15 (HC=N, s, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 13.3 (CH_3), 49.8 (CH_2), 56.4, 57.1 ($2OCH_3$), 114.4, 114.9, 115.8, 122.7, 124.1, 139.2, 141.4, 151.8, 154.3 (aromatic carbons), 159.4 (C=N).

General procedure for the synthesis of monocyclic β-lactams 3a–q

A mixture of Schiff base (7.0 mmol), triethylamine (35.0 mmol), N-5-norbornene-2,3-dicarboxyloylglycine (10.5 mmol) and tosyl chloride (10.5 mmol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature for 24 h. Then, it was washed with HCl 1 N (30 mL), saturated $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried on anhydrous Na_2SO_4 and filtered, and the solvent was evaporated to give crude product. It was filtered off and purified by column chromatography.

2-(2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione ***(3a)*** White solid (yield 74 %, 2.3 g); mp: 264–267 °C. IR (KBr, cm^{-1}): 1704 (CO imide), 1755 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.47 (1H,

d, $J = 8.8$ Hz, H-11), 1.68 (1H, d, $J = 8.8$ Hz, H-11), 3.27–3.30 (2H, m, H-6 and H-7), 3.35–3.37 (2H, m, H-5 and H-8), 3.67 (3H, s OCH_3), 4.82 (1H, d, $J = 2.52$ Hz, H-4), 4.99 (1H, d, $J = 2.52$ Hz, H-3), 6.11–6.21 (2H, 2m, H-9 and H-10), 6.69 (2H, d, $J = 8.95$ Hz, ArH), 7.08–7.19 (4H, m, ArH), 7.26 (2H, d, $J = 8.46$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 45.3, 45.8 (C-5, C-10), 47.1, 47.9 (C-6, C-9), 52.1 (C-11), 55.4 (OCH_3), 59.4 (C-4), 62.7 (C-3), 114.4, 118.9, 127.3, 129.6, 134.5, 134.8, 140.3, 144.6, 147.8, 148.2, 155.3 (C-9, C10 and aromatic carbons), 161.7 (CO, β-lactam), 177.0, 177.3 (CO, imide); EIMS $m/z = 450$ [M^+, ^{37}Cl], 448 [M^+, ^{35}Cl]; Anal. Calcd for $C_{25}H_{21}ClN_2O_4$: C, 66.89; H, 4.72; N, 6.24. Found: C, 66.95; H, 4.81; N, 6.30.

*2-(2-(2,3-Dimethoxyphenyl)-1-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3b**)* Orange solid (yield 73 %, 2.5 g);mp: 191–193 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.51, 1.47 (1H, d, $J = 8.8$ Hz, H-11), 1.71 (1H, d, $J = 8.84$ Hz, H-11), 2.84 (6H, s, NCH_3), 3.30–3.31 (2H, m, H-6 and H-7), 3.38–3.39 (2H, m, H-5 and H-8), 3.80, 3.85 (6H, 2 s, $2OCH_3$), 4.99 (1H, d, $J = 2.52$ Hz, H-4), 5.42 (1H, d, $J = 2.52$ Hz, H-3), 6.18–6.24 (2H, 2m, H-9 and H-10), 6.57 (2H, d, $J = 8.68$ Hz, ArH), 6.79–6.87 (2H, m, ArH), 6.96 (1H, d, $J = 7.89$ Hz, ArH), 7.15 (2H, d, $J = 7.10$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 40.8 (NCH_3), 45.0, 45.2 (C-6, C-7), 46.7, 46.8 (C-5, C-18), 52.0 (C-11), 54.9, 56.7 ($2OCH_3$), 60.9 (C-4), 61.8 (C-3), 112.9, 118.5, 118.8, 124.6, 127.6, 129.4, 134.3, 134.8, 147.0, 147.7, 152.7 (C-9, C10 and aromatic carbons), 160.8 (CO, β-lactam), 176.2, 176.4 (CO, imide); MS $m/z = 487$ [M^+]; Anal. Calcd for $C_{38}H_{29}N_3O_5$: C, 68.98; H, 6.00; N, 8.62. Found: C, 69.32; H, 5.67; N, 8.54.

*2-(2-(2-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3c**)* White solid (yield 86 %, 3.0 g); mp: 197–199 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1758 (CO β-lactam); 1H-NMR (250 MHz, CDCl3) δ (ppm): 1.34 (1H, d, $J = 9.00$ Hz, H-11), 1.49 (1H, d, $J = 9.00$ Hz, H-11), 2.90 (2H, t, $J = 7.58$ Hz, H-13), 3.03–3.08 (2H, m, H-6 and H-7), 3.19–3.23 (2H, m, H-5 and H-8), 3.32, 4,03 (2H, 2m, H-12), 3.80, 3.86 (6H, 2 s, $2OCH_3$), 4.93 (1H, d, $J = 5.21$ Hz, H-4), 5.22 (1H, d, $J = 5.21$ Hz, H-3), 6.69–6.80 (2H, 2m, H-9 and H-10), 7.25–7.42 (7H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ(ppm): 30.2 (C-13), 42.6 (C-12), 44.5, 44.8 (C-6, C-7), 45.3, 45,9 (C-5, C-18), 51.2 (C-11), 55.8, 55.9 ($2OCH_3$), 58.8 (C-4), 59.4 (C-3), 111.3, 111.4, 120.5, 128.6, 129.2, 129.6, 129.7, 130.2, 131.4, 133.4, 133.7, 147.8 -149.0 (C-9, C10 and aromatic carbons 164.25 (CO, β-lactam), 175.71, 175.79 (CO, imide); MS $m/z = 506$ [M^+]; Anal. Calcd for $C_{28}H_{27}ClN_2O_5$: C, 66.33; H, 5.37; N, 5.53. Found: C, 65.86; H, 5.48; N, 5.44.

*2-(2-(2-Chlorophenyl)-1-(4-isopropylphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3d**)* White solid (yield 82 %, 2.6 g); mp: 200–202 °C; IR (KBr, cm^{-1}): 1704 (CO imide) 1782 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.17 (6H, d, $J = 6.69$ Hz, H-13), 1.54 (1H, d, $J = 8.34$ Hz, H-11), 1.74 (1H, d, $J = 8.34$, Hz H-11), 2.84 (1H, m, H-12), 3.35–3.36 (2H, m, H-6 and H-7), 3.39–3.42 (2H, m, H-5 and H-8), 4.88 (1H, d, $J = 2.52$ Hz, H-4), 5.65 (1H, d, $J = 2.52$ Hz, H-3), 6.18–6.26 (2H, 2m, H-9 and H-10), 7.14 (2H, d, $J = 6.79$ Hz, ArH), 7.21–7.43 (6H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 23.9 (C-13), 33.6 (C-12), 45.0, 45.2 (C-6, C-7), 45.7, 46.0 (C-5, C-8), 52.2 (C-11), 56.3 (C-4), 62.0 (C-3), 117.4, 126.9, 127.1, 127.6, 129.7, 130.0, 132.4, 133.5, 134.6, 134.9, 145.2 (C-9, C10 and aromatic carbons), 161.2 (CO, β-lactam), 175.9, 176.3 (CO, imide); MS $m/z = 461$ [M^+]; Anal. Calcd for $C_{25}H_{21}ClN_2O_4$: C, 70.35; H, 5.47; N, 6.08. Found: C, 69.97; H, 5.68; N, 6.26.

*2-(1-(Benzo[d][1,3]dioxol-5-yl)-2-(2,3-dimethoxyphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3e**)* Cream solid (yield 78 %, 2.6 g); mp: 178–180 °C; IR (KBr, cm^{-1}): 1712 (CO imide) 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.52 (1H, d, $J = 8.85$ Hz, H-11), 1.72 (1H, d, $J = 8.85$ Hz, H-11), 3.31–3.33 (2H, m, H-6 and H-7), 3.38–3.42 (2H, m, H-5 and H-8), 3.80, 3.86 (6H, 2 s, $2OCH_3$), 4.91 (1H, d, $J = 2.52$ Hz, H-4), 4.96 (1H, d, $J = 2.52$ Hz, H-3), 5.88 (2H, q, $J = 2.26$ Hz, H-12), 6.15–6.27 (2H, 2m, H-9 and H-10), 6.61 (2H, d, $J = 2.68$ Hz, ArH), 6.71 (1H, s, ArH), 6.82 (2H, s, ArH), 6.95 (2H, d, $J = 1.26$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 45.2, 45.2 (C-6, C-7), 45.7, 45.8 (C-5, C-18), 52.0 (C-11), 55.9, 56.0 ($2OCH_3$), 60.3 (C-4), 62.8 (C-3), 100.0 (C-12), 101.2, 108.2, 110.4, 111.6, 118.9, 128.0, 131.8, 134.5, 134.7, 144.3, 147.8, 149.6, 149.8 (C-9, C10 and aromatic carbons), 161.2 (CO, β-lactam), 176.2, 176.4 (CO, imide); MS $m/z = 488$ [M^+]; Anal. Calcd for $C_{27}H_{24}N_2O_7$: C, 66.39; H, 4.95; N, 5.73. Found: C, 65.74; H, 4.87; N, 6.07.

*2-(1-(4-(Dimethylamino)phenyl)-2-(4-isopropylphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3f**)* Yellow solid (yield 62 %, 2.0 g); mp: 268–269 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1743 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.21 (6H, d, $J = 6.79$ Hz, H-13), 1.53 (1H, d, $J = 9.00$ Hz, H-11), 1.73 (1H, d, $J = 9.00$ Hz, H-11), 2.87 (7H, s, H-12 and NCH_3), 3.30–3.33 (2H, m, H-6 and H-7), 3.40–3.43

(2H, m, H-5 and H-8), 4.91 (1H, d, $J = 2.52$ Hz, H-4), 5.05 (1H, d, $J = 2.52$ Hz, H-3), 6.18–6.29 (2H, 2m, H-9 and H-10), 6.64 (2H, d, $J = 9.00$ Hz, ArH), 7.18 (6H, q, $J = 3.00$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 23.8 (C-13), 33.8 (C-12), 40.8 (NCH_3), 45.2 (C-6, C-7), 45.7 (C-5, C-8), 52.0 (C-11), 59.8 (C-4), 62.7 (C-3), 112.9, 119.0, 125.9, 127.3, 133.4, 134.5, 134.7, 147.7, 149.5 (C-9, C10 and aromatic carbons), 160.7 (CO, β-lactam), 176.2, 176.5 (CO, imide); MS $m/z = 469$ [M^+]; Anal. Calcd for $C_{29}H_{31}N_3O_3$: C, 74.18; H, 6.65; N, 8.95. Found: C, 73.97; H, 5.88; N, 9.13.

*2-(1-(3,4-Dimethoxyphenethyl)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3g**)* Orange solid (yield 71 %, 2.5 g); mp: 145–146 °C; IR (KBr, cm^{-1}): 1697 (CO imide), 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.62 (1H, d, $J = 9.16$ Hz, H-11), 1.72 (1H, d, $J = 9.16$ Hz, H-11), 2.87 (2H, m, H-13), 2.95 (6H, s, NCH_3), 3.06, 3,68 (2H, 2m, H-12), 3.28–3.30 (2H, m, H-6 and H-7), 3.33–3.42 (2H, m, H-5 and H-8), 3.80, 3.86 (6H, 2 s, $2OCH_3$), 4.42 (1H, d, $J = 2.36$ Hz, H-4), 4.76 (1H, d, $J = 2.36$ Hz, H-3), 6.10–6.21 (2H, 2m, H-9 and H-10), 6.64–6.77 (5H, m, ArH), 6.88 (2H, d, $J = 8.68$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 30.6 (C-13), 40.4 (NCH_3), 42.0 (C-12), 45.1, 45.2 (C-6, C-7), 45.7 (C-5, C-18), 51.9 (C-11), 56.7, 56.9 ($2OCH_3$), 60.9 (C-4), 62.4 (C-3), 111.1, 112.0, 112.5, 120.7, 127.5, 131.2, 134.3, 134.7, 147.5, 148.7, 150.8 (C-9, C10 and aromatic carbons), 164.4 (CO, β-lactam), 176.2, 176.5 (CO, imide); MS $m/z = 515$ [M^+]; Anal. Calcd for $C_{30}H_{33}N_3O_5$: C, 69.88; H, 6.45; N, 8.15. Found: C, 69.62; H, 6.32; N, 8.36.

*2-(1-(2,4-Dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3h**)* Golden solid (yield 45 %, 1.6 g); mp: 267–268.5 °C; IR (KBr, cm^{-1}): 1704 (CO imide), 1743 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ1.54 (2H, t, $J = 9.16$ Hz, H-11), 3.28–3.35 (2H, m, H-6 and H-7,), 3.42–3.44 (2H, m, H-5 and H-8), 3.66, 3.68 (12H, 2 s, $4OCH_3$), 4.78 (1H, d, $J = 2.52$ Hz, H-4), 5.20 (1H, d, $J = 2.52$ Hz, H-3), 5.97–6.26 (2H, 2m, H-9 and H-10), 6.46–7.35 (6H, m, ArH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (ppm): 44.5, 44.6 (C-6, C-7), 45.2, 45.7 (C-5, C-8), 52.4 (C-11), 55.5, 55.9, 56.3, 56.4 ($4OCH_3$), 60.4 (C-4), 62.9 (C-3), 100.0, 101.2, 108.2, 110.4, 111.6, 118.9, 131.8, 134.7, 144.3, 147.8, 149.6, 149.8 (C-9, C10 and aromatic carbons), 161.2 (CO, β-lactam), 176.7, 176.9 (CO, imide); MS $m/z = 504$ [M^+, ^{37}Cl], 448 [M^+, ^{35}Cl]; Anal. Calcd for $C_{28}H_{28}N_2O_7$: C, 66.66; H, 5.59; N, 5.55. Found: C, 66.51; H, 5.36; N, 5.75.

*2-(2-(Anthracen-9-yl)-1-(benzo[d][1,3]dioxol-5-yl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3i**)* Green solid (yield 64 %, 2.4 g); mp: 257–259 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1751 (CO β-lactam); ^{1}H-NMR 250 MHz (DMSO-d_6) δ (ppm): 1.54 (1H, d, $J = 6.9$ Hz, H-11), 1.73 (1H, d, $J = 6.9$ Hz, H-11), 3.30–3.38 (2H, m, H-6 and H-7), 3.46–3.50 (2H, m, H-5 and H-8), 5.68 (1H, d, $J = 2.84$ Hz, H-4), 5.78 (3H, m, H-3 and H-12), 5.88–5.96 (2H, 2m, H-9 and H-10), 6.38–6.50 (2H, m, ArH), 6.77 (1H, d, $J = 3.15$ Hz, ArH), 7.44–7.55 (4H, m, ArH), 8.03 (2H, d, $J = 8.68$ Hz, ArH), 8.31 (2H, d, $J = 8.53$ Hz, ArH), 8.51 (1H, s, ArH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (ppm): 44.4, 45.1, (C-6, C-7), 45.3, 45.9 (C-5, C-8), 51.6 (C-11), 55.9 (C-4), 61.0 (C-3), 99.4 (C-12), 108.3, 109.7, 123.1, 125.1, 126.9, 127.3, 128.5, 129.4, 129.6, 130.4, 131.5, 134.7, 134.8, 144.5, 148.0 (C-9, C10 and aromatic carbons), 160.9 (CO, β-lactam), 174.9, 175.7 (CO, imide); MS $m/z = 528$ [M^+]; Anal. Calcd for $C_{33}H_{24}N_2O_5$: C, 74.99; H, 4.58; N, 5.30. Found: C, 74.02; H, 3.98; N, 5.60.

*2-(1,2-Bis(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3j**)* Brownish solid (yield 65 %, 2.1 g); mp: 263.4–263.8 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1743 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.46 (1H, d, $J = 8.37$ Hz, H-11), 1.66 (1H, d, $J = 8.37$ Hz, H-11), 2.78, 2.86 (12H, 2 s, NCH_3), 3.23–3.25 (2H, m, H-6 and H-7), 3.32–3.35 (2H, m, H-5 and H-8), 4.83 (1H, d, $J = 2.84$ Hz, H-4), 5.91 (1H, d, $J = 2.84$ Hz, H-3), 6.09–6.20 (2H, 2m, H-9 and H-10), 6.50 (2H, d, $J = 8.53$ Hz, ArH), 6.57 (2H, d, $J = 8.53$ Hz, ArH), 7.03–7.19 (4H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 39.4, 39.8 (NCH_3), 44.1, 44.2 (C-6, C-7), 44.7, 44.8 (C-5, C-8), 50.9 (C-11), 58.9 (C-4), 61.7 (C-3), 111.7, 112.0, 118.0, 122.0, 126.0, 130.6, 132.2, 133.4, 133.7, (C-9, C10 and aromatic carbons), 160.0 (CO, β-lactam), 175.2, 175.4 (CO, imide); MS $m/z = 470$ [M^+]; Anal. Calcd for $C_{28}H_3N_4O_3$: C, 71.47; H, 6.43; N, 11.91. Found: C, 72.97; H, 6.74; N, 11.43.

*2-(1-(3,4-Dimethoxyphenethyl)-2-(4-isopropylphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3k**)* Yellow solid (yield 67 %, 2.4 g); mp: 165–168 °C; IR (KBr, cm^{-1}): 1704 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.22, (6H, s, H-15), 1.52 (1H, d, $J = 8.88$ Hz, H-11), 1.72 (1H, d, $J = 8.88$ Hz, H-11), 2.81–2.93 (3H, m, H-13 and H-14), 3.06, 3,70 (2H, 2m, H-12), 3.26–3.31 (2H, m, H-6 and H-7), 3.37–3.42 (2H, m, H-5 and H-8), 3.78, 3.86 (6H, 2 s, $2OCH_3$), 4.44 (1H, d, $J = 2.36$ Hz, H-4), 4.75 (1H, d, $J = 2.36$ Hz, H-3), 6.12–6.20 (2H, 2m, H-9

and H-10), 6.66–7.27 (7H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 23.9 (C-15), 30.5 (C-13), 30.8 (C-14), 42.2 (C-12), 45.1, 45.2 (C-6, C-7), 46.7 (C-5, C-18), 52.0 (C-11), 55.7, 55.9 ($2OCH_3$), 59.9 (C-4), 62.5 (C-3), 111.1, 111.9, 120.7, 126.4, 127.1, 131.1, 132.8, 134.4, 134.7, 147.6, 148,8, 149.7 (C-9, C10 and aromatic carbons), 164.3 (CO, β-lactam), 176.2, 176.5 (CO, imide); MS $m/z = 514$ [M^+]; Anal. Calcd for $C_{31}H_{34}N_2O_5$: C, 72.35; H, 6.66; N, 5.44. Found: C, 72.54; H, 6.87; N, 4.93.

2-(1-(3,4-Dimethoxyphenethyl)-2-(2,3-dimethoxyphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione ***(3l)*** Yellow solid (yield 86 %, 3.2 g); mp: 90.1–91 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.34 (1H, d, $J = 8.21$ Hz, H-11), 1.49 (1H, d, $J = 8.21$ Hz, H-11), 2.83–2.91 (2H, m, H-13), 3.02–3.11 (2H, m, H-6 and H-7), 3.18–3.22 (2H, m, H-5 and H-8), 3.33, 3,96 (2H, 2m, H-12), 3.71, 3.80, 3.84 (12H, 3 s, $4OCH_3$), 4.97 (1H, d, $J = 5.37$ Hz, H-4), 5.13 (1H, d, $J = 5.37$ Hz, H-3), 6.11–6.31 (2H, 2m, H-9 and H-10), 6.69–7.05 (6H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 33.2 (C-13), 42.3 (C-12), 44.6, 44.7 (C-6, C-7), 45.4, 45,8 (C-5, C-18), 51.9 (C-11), 55.7, 55.7, 55.8, 55.9 ($4OCH_3$), 59.2 (C-4), 60.4 (C-3), 111.3, 111.4, 112.3, 120.4, 123.3, 126.9, 130.5, 133.5, 133.7, 134.6, 147.7, 149.0, 152.4 (C-9, C10 and aromatic carbons), 164.2 (CO, β-lactam), 175.8, 176.0 (CO, imide); MS $m/z = 532$ [M^+]; Anal. Calcd for $C_{30}H_{32}ClN_2O_7$: C, 67.66; H, 6.06; N, 5.26. Found: C, 68.12; H, 5.68; N, 5.13.

2-(2-(4-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione ***(3m)*** White solid (yield 84 %, 3.0 g); mp: 160.5–162 °C; IR (KBr, cm^{-1}): 1712 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.53 (1H, d, $J = 8.68$ Hz, H-11), 1.74 (1H, d, $J = 8.68$ Hz, H-11), 2.80–2.92 (2H, m, H-13), 3.09, 3,73 (2H, 2m, H-12), 3.30–3.32 (2H, m, H-6 and H-7), 3.38–3.43 (2H, m, H-5 and H-8), 3.80, 3.86 (6H, 2 s, $2OCH_3$), 4.42 (1H, d, $J = 2.36$ Hz, H-4), 4.71 (1H, d, $J = 2.36$ Hz, H-3), 6.10–6.20 (2H, 2m, H-9 and H-10), 6.64–6.73 (3H, m, ArH), 6.90 (2H, d, $J = 8.53$ Hz, ArH), 7.27 (2H, d, $J = 8.53$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 33.6 (C-13), 42.3 (C-12), 45.2 (C-6, C-7), 45.7 (C-5, C-18), 52.0 (C-11), 55.7, 55.9 ($2OCH_3$), 59.5 (C-4), 62.5 (C-3), 111.2, 112.0, 120.6, 127.8, 129.2, 130.9, 134.2, 134.4, 134.7, 134.8, 147.6, 148.8 (C-9, C10 and aromatic carbons), 164.0 (CO, β-lactam), 176.1, 176.4 (CO, imide); MS $m/z = 506$ [M^+]; Anal. Calcd for $C_{28}H_{27}ClN_2O_5$: C, 66.33; H, 5.37; N, 5.53. Found: C, 67.07; H, 5.12; N, 5.28.

2-(1-(Benzo[d][1,3]dioxol-5-yl)-2-(2-hydroxy-3-(morpholinomethyl)phenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione ***(3n)*** Orange solid (yield 59 %, 2.2 g); mp: 250–251.6 °C; IR (KBr, cm^{-1}): 1704 (CO imide), 1758.9 (CO β-lactam), 3260–3540.9 (OH); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.53 (1H, d, $J = 8.53$ Hz, H-11), 1.73 (1H, d, $J = 8.53$ Hz, H-11), 2.55(4H, s, H-14) 3.33–3.36 (2H, m, H-6 and H-7), 3.41–3.447 (2H, m, H-5 and H-8), 3.67 (2H, s, H-13), 3.77 (4H, t, $J = 4.26$ Hz, H-15), 4.99 (1H, d, $J = 2.36$ Hz, H-4), 5.39 (1H, d, $J = 2.36$ Hz, H-3), 5.89 (2H, d, $J = 2.21$ Hz, H-12), 6.16–6.29 (2H, 2m, H-9 and H-10), 6.64–7.27 (6H, m, ArH), 10.20 (brds, 1H, OH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 46.7, 46.8 (C-6, C-7), 46.9 (C-5, C-18), 51.8 (C-11), 53.1 (C-14), 55.8 (C-13), 59.9 (C-4), 62.2 (C-3), 99.9 (C-12), 101.3, 108.3, 110.4, 110.7, 110.8, 116.9, 121.0, 124.4, 128.8, 129.2, 146.0, 147.4, 149.5 (C-9, C10 and aromatic carbons), 162.2 (CO, β-lactam), 176.2, 176.6 (CO, imide); MS $m/z = 543$ [M^+]; Anal. Calcd for $C_{30}H_{29}N_3O_7$: C, 66.29; H, 5.38; N, 7.73. Found: C, 67.04; H, 4.92; N, 7.12.

2-(1,2-Bis(3-methoxyphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione ***(3o)*** Yellow solid (yield 57 %, 1.8 g); mp: 267–-268.5 °C; IR (KBr, cm^{-1}): 1704 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ(ppm): 1.52 (1H, d, $J = 7.74$ Hz, H-11), 1.72 (1H, d, $J = 7.74$ Hz, H-11), 3.31–3.34 (2H, m, H-6 and H-7), 3.36–3.43 (2H, m, H-5 and H-8), 3.71, 3.75 (6H, 2 s, $2OCH_3$), 4.94 (1H, d, $J = 2.52$ Hz, H-4), 5.06 (1H, d, $J = 2.52$ Hz, H-3), 5.18–6.28 (2H, 2m, H-9 and H-10), 6.57–7.30 (8H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 45.2, 45.3 (C-6, C-7), 46.7 (C-5, C-8), 52.0 (C-11), 55.2 ($2OCH_3$), 59.9 (C-4), 62.6 (C-3), 103.3, 108.6, 109.6, 110.4, 111.6, 114.1, 118.1, 129.8, 130.5, 134.5, 134.7, 138.2, 160.0, 160.3 (C-9, C10 and aromatic carbons), 161.5 (CO, β-lactam), 176.2, 176.4 (CO, imide); MS $m/z = 444$ [M^+, ^{37}Cl]; Anal. Calcd for $C_{26}H_{24}N_2O_5$: C, 70.26; H, 5.44; N, 6.30. Found: C, 69.66; H, 5.12; N, 7.18.

2-(2-(3,4-Dimethoxyphenyl)-1-(4-isopropylphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione ***(3p)*** White solid (yield 88 %, 3.0 g); mp: 189–190.8 °C; IR (KBr, cm^{-1}): 1704 (CO imide), 1766 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.15 (6H, d, $J = 6.95$, H-13), 1.52 (1H, d, $J = 8.84$ Hz, H-11), 1.72 (1H, d, $J = 8.84$ Hz, H-11), 2.78–2.87 (1H, m, H-12), 3.28–3.33 (2H, m, H-6 and H-7), 3.36–3.44 (2H, m, H-5 and H-8), 3.81, 3.87 (6H, 2 s, $2OCH_3$), 5.02 (1H, d, $J = 2.36$ Hz, H-4), 5.44 (1H, d, $J = 2.36$ Hz, H-3), 6.18–6.27 (2H, 2m, H-9 and H-10), 6.81–7.22 (7H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 23.9 (C-13), 30.6 (C-12), 45.1, 45.2 (C-6, C-7), 46.7 (C-5, C-18), 52.0 (C-11), 55.0, 55.7 ($2OCH_3$), 60.9 (C-4), 61.9 (C-3), 112.7,

117.3, 118.4, 124.7, 126.9, 129.2, 134.3, 134.8, 135.0, 144.8, 148.9, 152.75 (C-9, C10 and aromatic carbons), 161.5 (CO, β-lactam), 176.1, 176.4 (CO, imide); MS *m/z* = 486 [M^+]; Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 70.89; H, 6.45; N, 5.39.

*2-(1-(4-(Diethylamino)phenyl)-2-(2,3-dimethoxyphenyl)-4-oxoazetidin-3-yl)-3a,4,7,7a-tetrahydro-1H-4,7-methanoisoindole-1,3(2H)-dione (**3q**)* Brown oil (yield 90 %, 3.2 g); IR (KBr, cm^{-1}): 1712 (CO imide), 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.10 (6H, t, *J* = 3.47 Hz, H-13), 1.36 (1H, d, *J* = 7.58 Hz, H-11), 1.52 (1H, d, *J* = 7.58 Hz, H-11), 3.05–3.13 (2H, m, H-6 and H-7), 3.23–3.39 (6H, m, H-5, H-8 and H-12), 3.85, 3.87 (6H, 2 s, $2OCH_3$), 5.37 (1H, d, *J* = 3.47 Hz, H-4), 5.52 (1H, d, *J* = 3.47 Hz, H-3), 6.56–6.61 (2H, 2m, H-9 and H-10), 6.87–7.30 (7H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 12.4 (C-13), 44.3 (C-12), 44.5, 44.7 (C-6, C-7), 45.4 (C-5, C-18), 51.8 (C-11), 55.6, 56.3 ($2OCH_3$), 58.3 (C-4), 60.4 (C-3), 112.0, 112.2, 118.5, 121.2, 123.2, 126.1, 126.7, 133.8, 144.7, 147.2, 152.1 (C-9, C10 and aromatic carbons), 160.3 (CO, β-lactam), 175.7, 175.9 (CO, imide); MS *m/z* = 515 [M^+].

General procedure for the synthesis of β-lactam-triazole hybrids 5a–h

A mixture of *p*-nitrophenyl azide (1 mmol) and an appropriate β-lactam **3a**–**h** (1 mmol) in 10–15 mL of anhydrous toluene was refluxed till the completion of the reaction (TLC monitoring). The solvent was removed under reduced pressure, and the precipitate was filtered off, washed with toluene and dried in air.

*6-(2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano [1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione (**5a**)* Olive solid (yield 74 %, 0.4 g); mp: 275 °C decomposed; IR (KBr, cm^{-1}): 1589 (N=N), 1712 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ 1.18 (1H, d, *J* = 10.26 Hz, H-11), 1.86 (1H, d, *J* = 10.26 Hz, H-11), 3.09–3.15 (2H, m, H-5 and H-8), 3.20–3.24 (2H, m, H-6 and H-7), 3.66 (3H, s, OCH_3), 3.84, 4.79 (2H, 2d, *J* = 8.68 Hz, H-9 and H-10), 4.91 (1H, d, *J* = 2.52 Hz, H-4), 5.11 (1H, d, *J* = 2.52 Hz, H-3), 6.66 (2H, d, *J* = 9.00 Hz, ArH), 6.90 (2H, d, *J* = 9.79 Hz, ArH), 7.01–7.21 (6H, m, ArH), 8.03 (2H, d, *J* = 8.37 Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 32.0 (C-11), 37.1, 37.9 (C-5, C-8), 47.1, 47.5 (C-6, C-7), 53.4 (C-9), 55.4 (OCH_3), 59.0 (C-4), 62.9 (C-3), 82.6 (C-10), 114.4, 118.9, 120.7, 125.3, 127.3, 129.7, 130.0, 1340, 135.1, 142.6, 156.7, 157.6 (aromatic carbons), 160.4 (CO, β-lactam), 175.3, 176.0 (CO, imide); Anal. Calcd for $C_{31}H_{25}ClN_6O_6$: C, 60.74; H, 4.11; N, 13.71. Found: C, 61.22; H, 4.41; N, 13.48.

*6-(2-(2,3-Dimethoxyphenyl)-1-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano[1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione (**5b**)* Golden solid (yield 78 %, 0.5 g); mp: 228 °C decomposed; IR (KBr, cm^{-1}): 1596 (N=N), 1712 (CO imide), 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.36 (1H, d, *J* = 11.05 Hz, H-11), 1.59 (1H, d, *J* = 11.05 Hz, H-11), 2.89 (6H, s, NCH_3), 3.10–3.19 (2H, m, H-5 and H-8), 3.31–3.40 (2H, m, H-6 and H-7), 3.67, 3.76 (6H, 2 s, OCH_3), 4.01, 4.85 (2H, 2d, *J* = 9.04 Hz, H-9 and H-10), 5.10 (1H, d, *J* = 2.68 Hz, H-4), 5.61 (1H, d, *J* = 2.68 Hz, H-3), 6.62 (2H, d, *J* = 7.10 Hz, ArH), 6.81–7.22 (5H, m, ArH), 7.36 (2H, t, *J* = 9.63 Hz, ArH), 8.23 (2H, m, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 35.6 (C-11), 40.7 (NCH_3), 42.6, 43.7 (C-5, C-8), 45.4, 45.6 (C-6, C-7), 55.1 (C-9), 54.8, 56.7 ($2OCH_3$), 60.8 (C-4), 62.0 (C-3), 83.2 (C-10), 112.9, 113.4, 113.6, 118.2, 118.9, 124.7, 126.0, 127.1, 128.8, 142.4, 144.4, 146.6, 148.0, 152.6 (aromatic carbons), 160.2 (CO, β-lactam), 174.6, 175.1 (CO, imide); Anal. Calcd for $C_{34}H_{33}N_7O_7$: C, 62.66; H, 5.10; N, 15.05. Found: C, 62.31; H, 4.66; N, 14.77.

*6-(2-(2-Chlorophenyl)-1-(3,4-dimethoxyphenethyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8 methano [1,2,3] triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione (**5c**)* Brown solid (yield 71 %, 0.5 g); mp: 225 °C decomposed; IR (KBr, cm^{-1}): 1596 (N=N), 1712 (CO imide), 1766 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.10 (1H, d, *J* = 10.58 Hz, H-11), 1.40 (1H, d, *J* = 10.58 Hz, H-11), 2.90–2.96 (2H, m, H-13), 2.97–3.23 (4H, m, H-5, H-8, H-6 and H-7), 3.80, 3.85 (6H, 2 s, $2OCH_3$), 3.38, 4.07 (2H, 2m, H-12), 4.26, 4.76 (2H, 2d, *J* = 9.79 Hz, H-9 and H-10), 5.01 (1H, d, *J* = 2.68 Hz, H-4), 5.41 (1H, d, *J* = 2.68 Hz, H-3), 6.62–7.49 (9H, m, ArH), 8.25 (2H, dt, *J* = 9.47, *J* = 3.15 Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 33.2 (C-11), 35.2 (C-13), 41.7, 42.8 (C-5, C-8), 43.7 (C-12), 44.8, 45.0 (C-6, C-7), 54.9 (C-9), 56.7 ($2OCH_3$), 56.9 (C-4), 59.3 (C-3), 82.8 (C-10), 111.4, 113.3, 120.5, 125.8, 126.1, 127.2, 129.0, 129.5, 129.8, 130.0, 130.5, 131.1, 131.6, 143.7, 144.2, 149.1 (aromatic carbons), 163.4 (CO, β-lactam), 173.8, 174.2 (CO, imide); Anal. Calcd for $C_{34}H_{31}ClN_6O_7$: C, 60.85; H, 4.66; N, 12.52. Found: C, 61.41; H, 4.38; N, 12.16.

*6-(2-(2-Chlorophenyl)-1-(4-isopropylphenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano [1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione (**5d**)* Olive solid (yield 78 %, 0.5 g); mp: 175 °C decomposed; IR (KBr, cm^{-1}): 1596 (N=N), 1712 (CO imide), 1766 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.20 (6H,

d, $J = 6.16$ Hz, H-13), 1.37 (1H, d, $J = 11.21$ Hz, H-11), 1.60 (1H, d, $J = 11.21$ Hz, H-11), 2.89 (1H, m, H-12), 3.14–3.21 (2H, m, H-5 and H-8), 3.34–3.43 (2H, m, H-6 and H-7), 3.97, 4.84 (2H, 2d, $J = 8.68$ Hz, H-9 and H-10), 5.06 (1H, d, $J = 2.68$ Hz, H-4), 5.84 (1H, d, $J = 2.68$ Hz, H-3), 7.13–7.42 (10H, m, ArH), 8.20 (2H, d, $J = 9.47$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 23.9 (C-13), 33.6 (C-11), 35.7 (C-12), 42.8, 43.6 (C-5, C-8), 45.5, 45.6 (C-6, C-7), 55.2 (C-9), 56.3 (C-4), 62.1 (C-3), 83.0 (C-10), 113.5, 117.5, 125.3, 126.0, 127.0, 127.3, 127.9, 128.2, 129.0, 130.1, 132.1, 133.1, 134.5, 142.5, 144.2, 145.7 (aromatic carbons), 160.5 (CO, β-lactam), 174.2, 175.1 (CO, imide); Anal. Calcd for $C_{33}H_{29}ClN_6O_5$: C, 63.41; H, 4.68; N, 13.44. Found: C, 64.19; H, 4.83; N, 12.95.

6-(1-(Benzo[d][1,3]dioxol-5-yl)-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano[1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione ***(5e)*** Yellow solid (yield 63 %, 0.4 g); mp: 206.5 °C decomposed; IR (KBr, cm^{-1}):1596 (N=N), 1712 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR δ 250 MHz (DMSO-d_6): 1.07 (1H, d, $J = 11.05$ Hz, H-11), 1.61 (1H, d, $J = 11.05$ Hz, H-11), 3.05–3.18 (2H, m, H-5 and H-8), 3.43–3.54 (2H, m, H-6 and H-7), 3.62, 3.69 (6H, 2 s, OCH_3), 3.72, 4.79 (2H, 2d, $J = 8.84$ Hz, H-9, H-10), 5.09 (1H, d, $J = 2.52$ Hz, H-4), 5.33 (1H, d, $J = 2.52$ Hz, H-3), 5.94 (2H, d, $J = 3.63$ Hz, H-12), 6.59 (1H, d, $J = 8.37$ Hz, ArH), 6.86 (3H, t, ArH), 6.99–7.09 (2H, m, ArH), 7.25 (2H, d, $J = 8.37$ Hz, ArH), 8.27 (2H, d, $J = 8.37$ Hz, ArH); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (ppm): 34.7 (C-11), 42.0, 42.8 (C-5, C-8), 45.1, 45.2 (C-6, C-7), 55.1 (C-9), 55.3 (OCH_3), 59.1 (C-4), 62.1 (C-3), 83.0 (C-10), 99.3 (C-12), 101.2, 108.4, 110.2, 111.7, 111.8, 113.3, 119.3, 126.1, 126.2, 127.9, 131.1, 141.5, 143.8, 144.2, 148.9, 149.0 (aromatic carbons), 161.0 (CO, β-lactam), 175.3, 175.9 (CO, imide); Anal. Calcd for $C_{33}H_{28}ClN_6O_9$: C, 60.73; H, 4.32; N, 12.88. Found: C, 59.98; H, 4.35; N, 13.45.

6-(1-(4-(Dimethylamino)phenyl)-2-(4-isopropylphenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano[1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione ***(5f)*** Golden solid (yield 68 %, 0.4 g); mp: 223 °C decomposed; IR (KBr, cm^{-1}): 1596 (N=N), 1704 (CO imide), 1751 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.21 (6H, d, $J = 6.95$ Hz, H-13), 1.34 (1H, d, $J = 10.74$ Hz, H-11), 1.57 (1H, d, $J = 10.74$ Hz, H-11), 2.87 (7H, s, H-12 and NCH_3), 3.08–3.14 (2H, m, H-5 and H-8), 3.31–3.37 (2H, m, H-6 and H-7), 3.99, 4.79 (2H, 2d, $J = 8.84$ Hz, H-9 and H-10), 5.11 (1H, d, $J = 2.52$, H-4), 5.33 (1H, d, $J = 2.52$, H-3), 6.59 (2H, d, $J = 7.74$ Hz, ArH), 7.14–7.33 (8H, m, ArH), 8.20 (2H, d, $J = 9.32$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 23.9 (C-13), 33.5 (C-12), 33.8 (C-11), 42.2, 43.0 (C-5, C-8), 445.1, 45.2 (C-6, C-7), 6.7 (NCH_3), 52.0 (C-9), 59.9 (C-4), 62.5 (C-3), 82.3 (C-10), 111.1, 111.9, 120.7, 126.3, 127.1, 131.1, 132.8, 134.4, 134.7, 147.6, 148.8, 149.7 (aromatic carbons), 164.3 (CO, β-lactam), 176.2, 176.5 (CO, imide); Anal. Calcd for $C_{35}H_{35}N_7O_5$: C, 66.34; H, 5.57; N, 15.47. Found: C, 65.67; H, 5.12; N, 14.76.

6-*(1-(3,4-Dimethoxyphenethyl)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano[1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dion*e ***(5g)*** Olive solid (yield 62 %, 0.4 g); mp: 223 °C decomposed; IR (KBr, cm^{-1}): 1596 (N=N), 1704 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.35 (1H, d, $J = 11.37$ Hz, H-11), 1.58 (1H, d, $J = 11.37$ Hz, H-11), 2.82–2.92 (2H, m, H-13), 2.95 (6H, s, NCH_3), 3.10–3.17 (2H, m, H-5 and H-8), 3.30–3.36 (2H, m, H-6 and H-7), 3.34, 3.86 (2H, 2m, H-12), 3,78, 3.86 (2H, 2 s, $2OCH_3$), 3.95, 4.74 (2H, 2d, $J = 9.47$ Hz, H-9 and H-10), 4.66 (1H, d, $J = 2.21$ Hz, H-4), 4.97 (1H, d, $J = 2.21$ Hz, H-3), 6.62–6.76 (5H, m, ArH), 6.92 (2H, d, $J = 8.5$ Hz, ArH), 7.30 (2H, d, $J = 9.47$ Hz, ArH), 8.23 (2H, d, $J = 8.53$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 33.6 (C-11), 35.5 (C-13), 40.3 ($2NCH_3$), 42.2, 42.7 (C-5, C-8), 43.6 (C-12), 45.3, 45.6 (C-6, C-7), 55.1 (C-9), 55.8, 55.9 ($2OCH_3$), 59.7 (C-4), 62.6 (C-3), 82.9 (C-10), 111.2, 111.8, 112.3, 113.5, 120.8, 121.5, 126.0, 127.9, 130.9, 142.4, 144.2, 147.6, 148.8, 151.0 (aromatic carbons), 163.7 (CO, β-lactam), 174.3, 175.5 (CO, imide); Anal. Calcd for $C_{36}H_{37}N_7O_7$: C, 63.61; H, 5.49; N, 14.42. Found: C, 62.97; H, 4.82; N, 13.76.

6-(1-(2,4-Dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-3-yl)-1-(4-nitrophenyl)-1,4,4a,7a,8,8a-hexahydro-4,8-methano[1,2,3]triazolo[4,5-f]isoindole-5,7(3aH,6H)-dione ***(5h)*** Brown solid (yield 71 %, 0.5 g); mp: 163 °C decomposed; IR (KBr, cm^{-1}):1596 (N=N), 1712 (CO imide), 1758 (CO β-lactam); ^{1}H-NMR (250 MHz, $CDCl_3$) δ (ppm): 1.35 (1H, d, $J = 11.05$ Hz, H-11), 1.59 (1H, d, $J = 11.05$ Hz, H-11), 3.14–3.21 (2H, m, H-5 and H-8), 3.34–3.39 (2H, m, H-6 and H-7), 3.68, 3.70, 3.73, 3.74, 3.78, 3.80 (12H, 6 s, OCH_3), 4.01, 4.79 (2H, 2d, $J = 8.84$ Hz, H-9, H-10,), 5.02 (1H, d, $J = 2.53$ Hz, H-4), 5.43 (1H, d, $J = 2.53$ Hz, H-3), 6.36–6.46 (2H, m, ArH), 6.60 (1H, s, ArH), 6.71–6.86 (2H, m, ArH), 6.96 (1H, d, $J = 9.32$ Hz, ArH), 7.27–7.36 (2H, m, ArH), 8.06 (2H, d, $J = 8.21$ Hz, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (ppm): 31.9 (C-11), 37.1, 37.9 (C-5, C-8), 47.1, 47.5 (C-6, C-7), 55.0 (C-9), 55.5, 55.7, 55.8 ($4OCH_3$), 61.9 (C-4), 62.8 (C-3), 82.9 (C-10), 99.8, 104.7, 108.9, 111.2, 113.5, 119.3, 120.7, 125.1, 125.9, 142.3, 149.3, 149.4, 153.8, 153.9 (aromatic carbons), 159.3 (CO, β-lactam), 175.5, 175.7 (CO, imide); Anal. Calcd for $C_{34}H_{32}N_6O_9$: C, 61.07; H, 4.82; N, 12.57. Found: C, 61.30; H, 4.94; N, 11.75.

Scheme 1 Synthesis of *N*-endo-5-norbornene-2,3-dicarboxyloylglycine

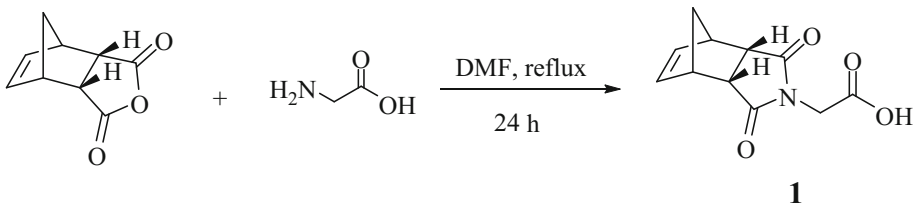
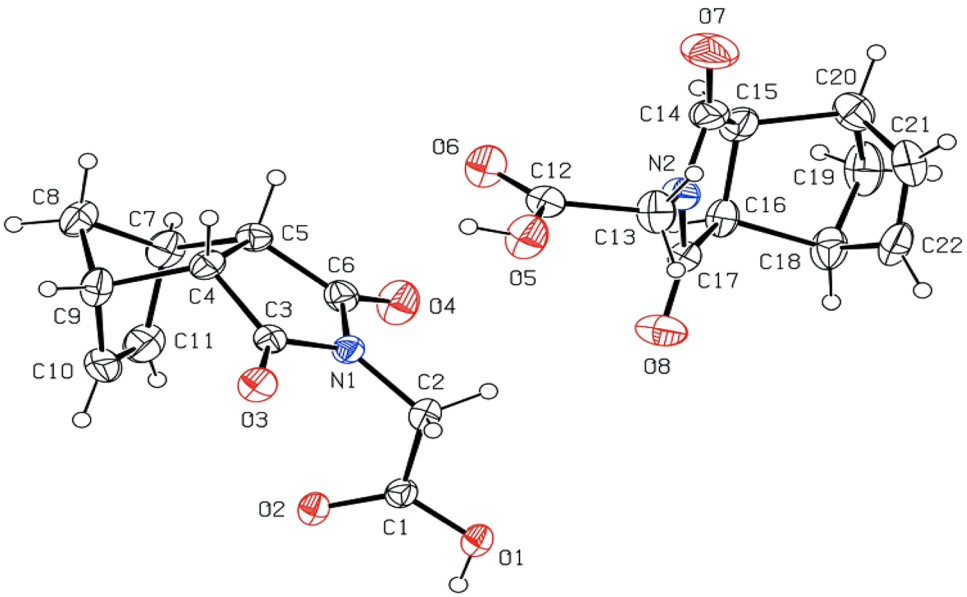
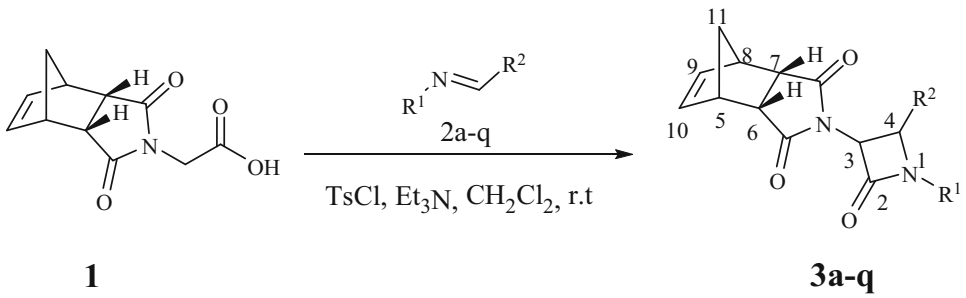


Fig. 1 X-ray crystal structures of two conformers A and B of **1**



Scheme 2 Synthesis of β-lactams **3a–q**

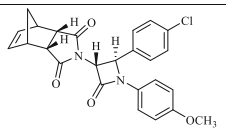
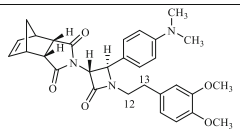
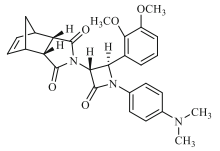
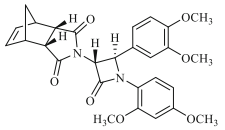
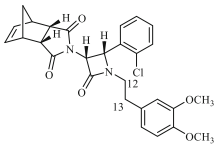
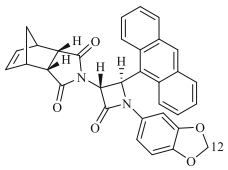
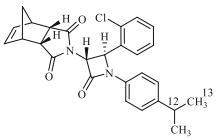
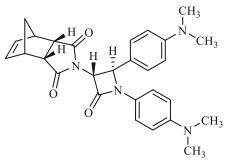
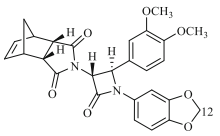
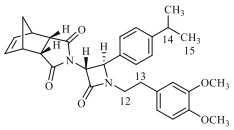
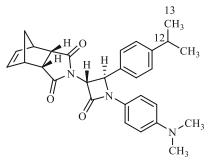
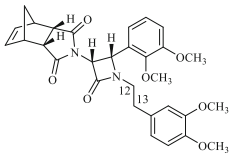
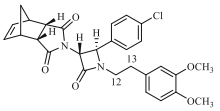
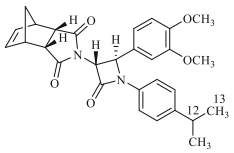
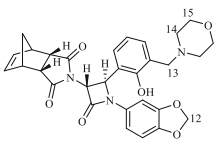
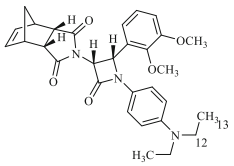
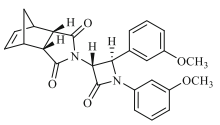


General procedure for the determination of MICs against bacteria

Antimicrobial activity of the compounds was studied by the determination of minimal inhibitory concentrations (MICs) according to the NCCLS guidelines M7-A2 using the microbroth dilution methods. The bacteria strains were grown on trypticase soy agar (Becton–Dickinson) at 37 °C for 24 h. Inocula were prepared in TCE (tryptone 0.1 %, NaCl 8 %, wt/vol) by adjusting the turbidity at 623 nm to obtain 1–3 10^5 CFU/mL.

Antimicrobial activities of the compounds were determined by using a broth microdilution method performed in sterile 96-well microplates. All compounds were solubilized in methanol at a concentration of 5 mg/mL and were transferred to each microplate well (in all cases, concentrations of the desired molecules in methanol do not exceed 2 % of the total proportion), in order to obtain a twofold serial dilution in 100 µL of broth, and 100 µL of inocula containing 2–6 10^5 CFU of each bacteria and yeast was added to each well. A number of wells were reserved for positive controls, inoculum viability and solvent effect. After 24 h of incubation, MIC was defined for each agent from duplicate observations as the lowest concentration of compound allowing no visible growth.

Table 1 Structures of β-lactams **3a–q**

β-lactam	Structure	Yield (%) (*cis/trans* (%))	β-lactam	Structure	Yield (%) (*cis/trans* (%))
3a		74(0/100)	**3g**		71(0/100)
3b		73(0/100)	**3h**		45(0/100)
3c		86(100/0)	**3i**		64(0/100)
3d		82(0/100)	**3j**		65(0:100)
3e		78(0/100)	**3k**		67(0/100)
3f		62(0/100)	**3l**		86(100/0)
3m		84(0/100)	**3p**		88(0/100)
3n		59(0/100)	**3q**		90(100/0)
3o		57(0/100)			

General procedure for antimalarial activity measurements

The chloroquine-resistant *P. falciparum* strain K14 (Southeast Asia) was cultured in vitro in a complete medium consisting of RPMI 1640 (Invitrogen) supplemented with 27.5 mM $NaHCO_3$, 20 mg/L gentamycin and 10 % human serum. Parasites were grown at 37 °C in human O red blood cells at a 6 % hematocrit under a 5 % CO_2, 10 % O_2 and 85 % N_2 atmosphere. Cultures were

synchronized by sorbitol treatments. Stock solutions of lactam derivatives were prepared in sterile DMSO (10 mM), and later dilutions were with complete culture medium. Increasing concentrations of lactam derivatives (100 µL/well, top concentration = 50 µM) were distributed in a 96-well plate; DMSO (0.5 % vol/vol, top concentration) was distributed for control. Then, 100 µL from a culture containing >95 % ring (0–20 h postinvasion) at a 0.8 % parasitemia and 3 % hematocrit in complete medium was added per well along with 1.0 µCi of 3H-hypoxanthine with a specific activity of 14.1 Ci/mmol (PerkinElmer, Courtaboeuf, France). Parasites were grown for 42 h at 37 °C. Plates were then freeze-thawed and harvested on filters. Dried filters were moistened in scintillation liquid mixture (Microscint O; PerkinElmer) and counted in a Top Count Microbeta counter (PerkinElmer). Percentage growth inhibition was calculated from the parasite-associated radioactivity. In the absence of lactam derivatives, 100 % 3H-hypoxanthine incorporation was determined from a control grown. The concentration of drug giving 50 % inhibition of label incorporation (IC_{50}) was determined by nonlinear regression analysis of log-based dose–response curve (Riasmart; Packard). Each concentration was estimated from independent experiments in triplicate.

Results and discussion

Chemistry

The precursor *N*-endo-5-norbornene-2,3-dicarboxyloylglycine **1** was prepared according to a reported procedure (Biagini *et al.*, 1995) (Scheme 1).

The X-ray crystallography of **1** showed two conformers: A, the norbornene and carboxylic acid groups lie to the same side of the heterocycle, and B, they lie on opposite sides (Akkurt *et al.*, 2013) (Fig. 1).

The β-lactams **3a–q** were synthesized by Staudinger reaction of appropriately functionalized Schiff bases **2a–q** with ketene derived from **1**, prepared in situ from *N*-endo-5-norbornene-2,3-dicarboxyloylglycine and *p*-toluenesulfonyl chloride in the presence of triethylamine (Scheme 2; Table 1).

The desired hybrids **5a–h** were synthesized using the 1,3-dipolar cycloaddition reaction (Tarabara *et al.*, 2009) of 1-azido-4-nitrobenzene **4** (prepared by using a literature procedure) (Kamalraj *et al.*, 2008) and β-lactams **3a–h** (Scheme 3; Table 2).

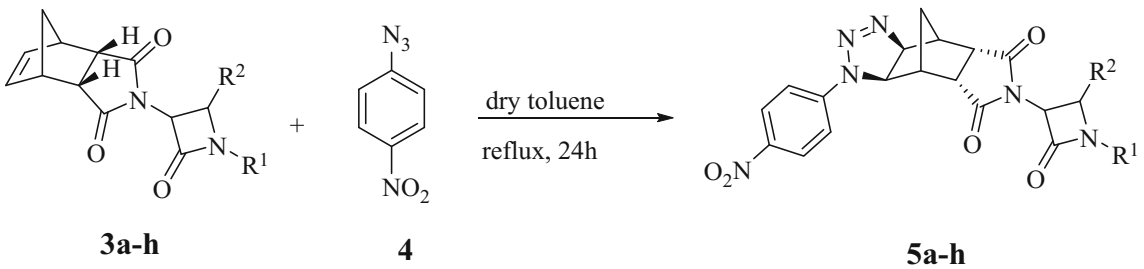
The *cis* or *trans* stereochemistry of the products **3a–q** and **5a–h** was assigned on the basis of observed coupling constant between β-lactam ring hydrogens. The structure assigned to the hybrids **5** was confirmed based on spectral data and analytical evidences.

Due to the presence of asymmetrically substituted triazole fragment in the molecules **5a–h**, their ^{1}H-NMR spectra are somewhat different from the **3a–h** spectra and are affected by the nonequivalent triazole fragment protons (H-9, H-10) that resonate in the regions 3.72–4.26 and 4.76–4.85 ppm. Their vicinal coupling constant 8.68–9.79 Hz is similar to the systems bearing *exo*-oriented triazole fragment (Shea and Kim, 1992). Furthermore, the position of the bridge proton signals (H-11) that are nonequivalent is another evidence of a preferential *exo* orientation of the synthesized triazole ring.

Biological evaluations

These newly synthesized β-lactams and their triazole hybrids were evaluated for their biological activities. Firstly, no significant antimicrobial efficiency against Gram-positive *S. aureus* (ATCC 25923) and Gram-negative bacteria *E. coli* (ATCC 25922) or *P. aeruginosa* (ATCC 27853) and fungi such as *C. albicans* (ATCC 90028) and *C. glabrata* (ATCC 90030) with MICs values less than 125 µg/mL have been encountered. Nevertheless, moderate-to-good antimalarial activities have been obtained against chloroquine-resistant *P. falciparum* K14 strain as outlined in Table 3 with IC_{50} varying from 15 to 50 µM.

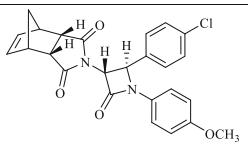
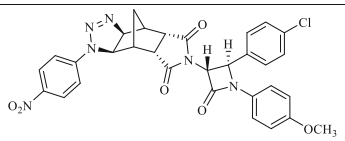
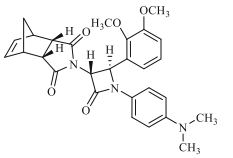
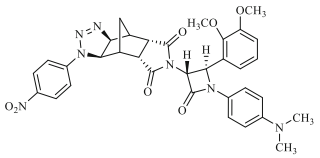
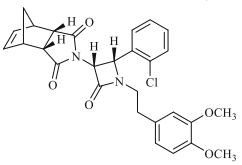
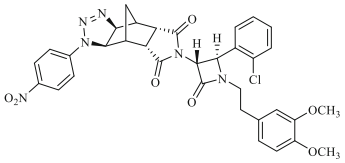
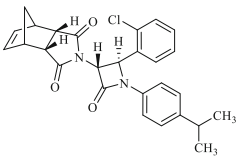
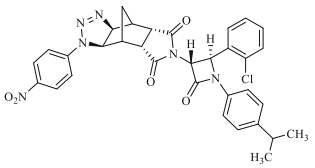
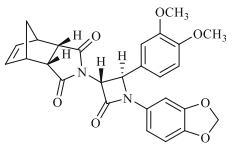
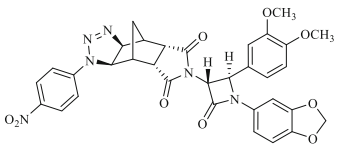
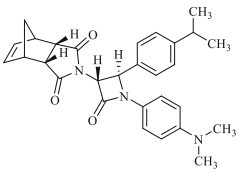
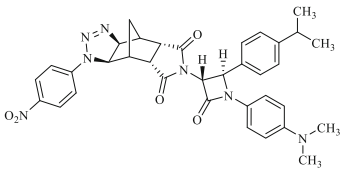
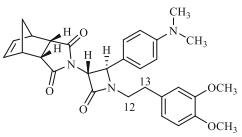
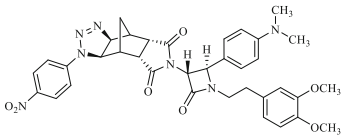
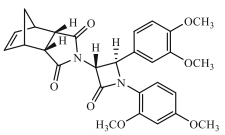
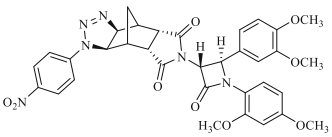
There is no clear structure–activity relationship (SAR) dealing with our antimalarial activities results. Nevertheless, most of the compounds demonstrating a potent



3a-h **4** **5a-h**

Scheme 3 Synthesis of β-lactam-triazole hybrids **5a–h**

Table 2 Structures of β-lactam-triazole hybrids **5a–h**

β-lactam	Structure	β-lactam	Structure	Yield(%) (*cis/trans* (%))
3a		**5a**		74(0/100)
3b		**5b**		78(0/100)
3c		**5c**		71(0/100)
3d		**5d**		78(0/100)
3e		**5e**		63(0/100)
3f		**5f**		68(0/100)
3g		**5g**		62(0/100)
3h		**5h**		71(0/100)

antimalarial activity possess a chlorophenyl moiety suggesting a positive effect of this halogen group with respect to the mechanism of action involved against the *P. falciparum* K14 strain.

Changing the isopropyl tertiary carbon in **3f** to nitrogen in **3j** enhances the biological activity as well as enlarging in **3m** the carbon space between the nitrogen β-lactam ring and the aryl group by two carbons. Substitution of the chlorine group in **3m** by an isopropyl one in **3g** decreased dramatically the biological activity encountered demonstrating the important role of a chlorine atom in such molecules.

Finally, adding a triazole moiety to **3a**, **3g** and **3h** did not lead to a significant enhancement of the biological activity, whereas the presence of this group in **5b–5f** structure leads to a decrease in activity for **5d** with respect

Table 3 Antimalarial activities of β-lactams **3a–3q** and triazole hybrids **5a–5h**

Compound	IC_{50} (μM) *P. falciparum* K14	Compound	IC_{50} (μM) *P. falciparum* K14
Chloroquine	11	**3l**	>50
3a	17.93	**3m**	22.11
3b	>50	**3p**	>50
3c	>50	**3q**	>50
3d	15.0	**5a**	27.2
3e	>50	**5b**	34.6
3f	>50	**5c**	21.6
3g	>50	**5d**	42.6
3h	>50	**5e**	48.9
3i	>50	**5f**	34.2
3j	22.5	**5g**	>50
3k	>50	**5h**	>50

to **3d** but to a three times improvement for all the other compounds.

Conclusion

A series of novel β-lactams and their triazole conjugates were synthesized via the [2 + 2] ketene imine cycloaddition *reaction.* *N*-endo-5-norbornene-2,3-dicarboxyloylglycine was the source of a special ketene used in these syntheses. These derivatives demonstrated moderate-to-good IC_{50} values varying from 15 to 50 μM against *P. falciparum* K14-resistant strain. A rapid analysis of our data has clearly demonstrated that the presence of a chlorophenyl group associated with a *p*-methoxyphenyl substituent on the β-lactam ring enhances the antimalarial activity. Otherwise, it has been recently reported that azole derivatives could be inhibitors of Falcipain-2, a papain family cysteine protease and important hemoglobinase of erythrocytic *Plasmodium falciparum* parasites (Kumar *et al.*, 2014a, b). In this context, further studies are now under current investigation to elucidate the mechanism of action involved by our molecules against Falcipain-2 in order to improve their structure–activity relationships.

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