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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial/antimalarial activities of novel naphthalimido *trans*-β-lactam derivatives

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Abstract This paper describes for the first time the synthesis and microbiological assessment of some new β-lactam derivatives containing a 1,8-naphthalimide functional group. These compounds were obtained through a [2 + 2] cyclocondensation (Staudinger reaction) of a ketene derived from 2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl) acetic acid (Alrestatin) and various N-arylimines. The reaction was totally diastereoselective leading exclusively to the formation of *trans*-β-lactam adducts **3a–l**, which were characterized by FT-Infra Red, ^{1}H NMR, ^{13}C NMR, mass spectrometry, elemental analyses, and X-ray crystallography, and then individually evaluated for antibacterial and antimalarial activities. Two of the β-lactams, **3c** and **3l**, afforded IC_{50} values of 3 and 5 μM, respectively, against *Plasmodium falciparum* K1 resistant strain.

Keywords β-Lactam · 1,8-Naphthalimide · Staudinger reaction · Alrestatin · Antimalarial

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Introduction

The β-lactam ring (2-azetidinone) is the important functional group responsible for the incomparable effectiveness of the most widely employed antibacterial agents, such as the penicillins and cephalosporins, (Coates et al. 2005; Morin and Gorman 1982) and as synthetic intermediates and building blocks in organic synthesis (Alcaide et al. 2007; Alcaide et al. 2008). β-Lactams have been investigated for a broad range of biological (Jarrahpour et al. 2016) and pharmacological applications, such as cholesterol absorption inhibitors, (Rosenblum et al. 1998) human cytomegalovirus protease inhibitors, (Mehta et al. 2010) thrombin inhibitors, (Sutton et al. 2004) anti-hyperglycemic, (Goel et al. 2004) anti-tumor, (Chen et al. 2008; Frezza et al. 2008, Banik et al. 2010) anti-HIV, (Sperka et al. 2005) anti-inflammatory analgesic, (Saturnino et al. 2000) anti-malarial, (Ebrahimi et al. 2016; Jarrahpour et al. 2012; Jarrahpour et al. 2014) anti-fungal, (O'Driscoll et al. 2008) anti-proliferative, (O'Boyle et al. 2011) anti-tubercular, (Sharma et al. 2011) anti-oxidant, (Nagarajan et al. 2012),

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and insecticidal activities (Cao et al. 2011), as well as serine-dependent enzyme inhibitors (Konaklieva 2002). Despite the large number of β-lactam compounds that have already been prepared and evaluated for these properties, a dire need still remains for new antibiotic compounds to counter the rapid rise in drug resistance seen among various pathogenic bacteria (Chu et al. 1996). A plethora of synthetic methods have been developed over the last century for the formation of the β-lactam ring, including cyclization reactions, carbene insertion reactions and rearrangement of heterocyclic compounds, Reformatsky reaction, and the Staudinger imine-ketene cycloaddition (Soengas et al. 2011). The most fundamental and versatile method for the synthesis of β-lactams (Singh 2003; Coates et al. 2005) remains the Staudinger imine-ketene cycloaddition reaction, which is used commonly in the pharmaceutical and synthetic chemistry arenas (Southgate 1994).

Cyclic imides have likewise received considerable attention due to their diverse pharmaceutical applications (Zhang and Zhou 2011). In particular, isoquinolinedione (naphthalimide) derivatives are cyclic imides of special interest because of their photophysical and biological properties as free radical scavengers, (Zhang et al. 2011) photoredox anticancer agents, (MacIntyre et al. 2010) fluorescent labels, (Sawa et al. 2006) photosensitizers, (Rogers and Kelly 1999) and medical imaging agents (Alcala et al. 2011). The promising anticancer activity of some naphthalimide-containing compounds is related to the planarity and optimal size of the 1,8-naphthalimide ring that enable for efficient intercalation into duplex DNA (El-Betany and McKeown 2012). In addition, 1,8-naphthalimide derivatives exhibit diverse non-biological applications as fluorescent pigments and dyes, (Stolarski 2009) components in fluorescent sensors for specific metal cations, (Xu et al. 2009) visible pH indicators, (Georgiev et al. 2011) as well as optical switches, (Ferreira et al. 2009) organic luminescent devices, (Jung et al. 2009) coloration of polymers, (Bojinov et al. 2008) light emitting diodes (Bouche et al. 1996) and fluorescence switchers (El-Betany and McKeown 2012). The use of a naphthalimide precursor has been crucial for the development of new anticancer drugs such as Amonafide (Wu et al. 2009) discovered by Brana and Ramos in 2001, (Brana and Ramos 2001) leading to the development of a series of other drug candidates such as mitonafide, elinafide, and bisnafide (Brider and Gellerman 2012; Malviya et al. 1992; Robinson and Castaner 1996). Our interest in the biological applications of β-lactams and naphthalimides led us to assess molecular constructs that contain both bioactive moieties, in terms of their syntheses, as well as investigations into their potential microbiological activities.

Materials and methods

General information

All needed chemicals were purchased from Merck, Fluka and Acros chemical companies and used without further purification. All reagents and solvents were dried prior to use according to standard methods (Armarego and Chai 2003). IR spectra were run on a Shimadzu FT-Infra Red 8300 spectrophotometer using potassium bromide pellets (υ in cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were recorded in dimethylsulfoxide-d_6 (DMSO-d_6) using a Bruker Avance DPX instrument (^{1}H NMR 250 MHz, ^{13}C NMR 62.5 MHz). Chemical shifts are reported in parts per million *(δ)* downfield from tetramethylsilane. All of the coupling constants *(J)* are in hertz *(Hz)*. Splitting patterns are indicated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, dd: doublet of doublet. 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 obtained on a Buchi 510 melting point apparatus and are uncorrected. X-ray data were collected on a Bruker APEX-II CCD diffractometer.

General procedure for the synthesis of Alrestatin

A mixture of 1,8-naphthalic anhydride (1.00 mmol) and glycine (1.10 mmol) was added in DMF (5 mL) and the mixture was stirred at 60 °C for several hours (TLC control in a 2:1 n-hexane:ethyl acetate solvent mixture). After cooling to room temperature, 20 mL water was added and the solid Alrestatin was separated. The product was purified by recrystallization from ethanol and used for the next step (Donkor et al. 1998).

General procedure for the β-lactams preparation (Staudinger reaction)

The appropriate aromatic imine (Schiff base) (1.00 mmol), triethylamine (5.00 mmol), 2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl) acetic acid (1.50 mmol), and tosyl chloride (1.50 mmol) were added to anhydrous CH_2Cl_2 (5 mL) stirred at 0 °C, and the mixture was allowed to warm to room temperature for further stirring for 24 h (TLC control in a 7:3 n-hexane:ethyl acetate solvent mixture). The mixture was then washed twice with 1N aqueous HCl solution (20 mL), and once with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed to produce the product as a crystal, which was then purified by recrystallization from ethyl acetate and acetone in a 3:2 volumetric ratio.

*2-(1-(4-Ethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3a**)*

White solid (Yield 75%); Rf = 0.86 (n-hexane: ethyl acetate = 7:3) Mp: 255–257 °C; IR (KBr, cm^{-1}): 1774 (CO β-lactam), 1704 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6) δ 1.27 (3H, t, $J = 6.7$ Hz, $\underline{CH_3}$), 3.95 (2H, q, $J = 6.7$ Hz, $\underline{CH_2}$), 5.69 (1H, d, $J = 2.7$ Hz, H-4), 5.94 (1H, d, $J = 2.7$ Hz, H-3), 6.91 (2H, d, $J = 9.0$ Hz, ArH), 7.19 (2H, d, $J = 9.0$ Hz, ArH), 7.79–7.89 (4H, m, ArH), 8.24 (2H, d, $J = 9.0$ Hz, ArH), 8.43–8.50 (4H, m, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.2 (CO β-lactam), 162.1 (CO Naph), 155.0, 147.4, 144.8, 134.8, 131.2, 131.1, 130.5, 128.1, 127.4, 127.3, 123.9, 121.5, 118.2, 115.0, (aromatic carbons), 63.4 (C β-lactam), 63.1 (C β-lactam), 58.0 ($\underline{CH_2}$-O), 14.5 ($\underline{CH_3}$); GC-MS $m/z = 507$ [M^+]; Analysis calculated for $C_{29}H_{21}N_3O_6$: C, 68.63; H, 4.17; N, 8.28%. Found: C, 68.20; H, 4.60; N, 8.51%.

*2-(2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3b**)*

White solid (Yield 70%); Rf = 0.91 (n-hexane: ethyl acetate = 7:3); Mp: 272–273 °C; IR (KBr, cm^{-1}): 1766 (CO β-lactam), 1704 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6) δ: 3.69 (3H, s, $\underline{CH_3}$), 5.53 (1H, d, $J = 2.5$ Hz, H-4), 5.90 (1H, d, $J = 2.5$ Hz, H-3), 5.91 (2H, d, $J = 9.0$ Hz, ArH), 7.19 (2H, d, $J = 9.0$ Hz, ArH), 7.43 (2H, d, $J = 8.5$ Hz, ArH), 7.55 (2H, d, $J = 8.5$ Hz, ArH), 7.85 (2H, d, $J = 8.0$ Hz, ArH), 8.43–8.48 (4H, m, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.2 (CO β-lactam), 162.3 (CO Naph), 155.6, 136.0, 134.9, 133.0, 131.2, 130.6, 128.8, 128.7, 127.4, 127.3, 121.5, 118.2, 117.1, 114.4 (aromatic carbons), 63.9 (C β-lactam), 63.4 (C β-lactam), 55.2 ($\underline{CH_3}$–O); GC-MS $m/z = 484$ [M^+, ^{37}Cl], 482 [M^+, ^{35}Cl]; Analysis calculated for $C_{28}H_{19}ClN_2O_4$: C, 69.64; H, 3.97; N, 5.80%. Found: C, 68.24; H, 4.05; N, 5.83%.

*2-(2-(Anthracen-9-yl)-1-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3c**)*

Yellow solid (Yield 80%); Rf = 0.88 (n-hexane: ethyl acetate = 7:3); Mp: 185–187 °C; IR (KBr, cm^{-1}): 1751 (CO β-lactam), 1704 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6) δ: 3.57 (3H, s, $\underline{CH_3}$), 6.73–6.79 (4H, m, ArH and H-4), 6.97 (2H, d, $J = 2.5$ Hz, H-3), 7.09 (2H, d, $J = 8.7$ Hz, ArH), 7.49–7.57 (4H, m, ArH), 7.81–7.90 (2H, m, ArH), 8.16 (2H, d, $J = 7.7$ Hz, ArH), 8.42–8.51 (6H, m, ArH), 8.51(1H, s, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.8 (CO β-lactam), 162.1 (CO Naph), 155.7, 134.9, 131.3, 131.1, 131.0, 130.9, 130.0, 129.8, 129.7, 127.5, 127.4, 127.2, 125.1, 124.1, 122.5, 121.4, 117.7, 114.5 (aromatic carbons), 62.1 (C β-lactam), 55.5 (C β-lactam), 55.0 ($\underline{CH_3}$–O); GC-MS $m/z = 548$ [M^+]; Analysis calculated for $C_{36}H_{24}N_2O_4$: C, 78.82; H, 4.41; N, 5.11%. Found: C, 76.53; H, 4.45; N, 5.81%.

*2-(2-(4-Chlorophenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl)-1H benzo[de]isoquinoline-1,3(2H)-dione (**3d**)*

White solid (Yield 68%); Rf = 0.94 (n-hexane: ethyl acetate = 7:3); Mp: 263–265 °C; IR (KBr, cm^{-1}): 1759 (CO β-lactam), 1705 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6) δ: 2.23 (3H, s, $\underline{CH_3}$), 5.54 (1H, d, $J = 2.5$ Hz, H-4), 5.91 (1H, d, $J = 2.5$ Hz, H-3), 7.13–7.18 (4H, m, ArH), 7.44 (2H, d, $J = 8.5$ Hz, ArH), 7.55 (2H, d, $J = 8.5$ Hz, ArH), 7.87 (2H, t, $J = 7.7$ Hz, ArH), 8.44–8.50 (4H, m, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 168.4 (CO β-lactam), 167.8 (CO Naph), 141.3, 140.1, 140.1, 138.2, 138.2, 136.4, 136.4, 134.8, 134.0, 133.9, 132.6, 132.5, 126.7, 122.0 (aromatic carbons), 68.7 (C β-lactam), 63.3 (C β-lactam), 25.6 ($\underline{CH_3}$); GC-MS $m/z = 468$ [M^+, ^{37}Cl], 466 [M^+, ^{35}Cl]; Analysis calculated for $C_{28}H_{19}ClN_2O_3$: C, 72.30; H, 4.10; N, 6.00%. Found: C, 71.67; H, 3.98; N, 6.11%.

*2-(1-(4-(Diethylamino)phenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3e**)*

Red solid (Yield 69%); Rf = 0.91 (n-hexane: ethyl acetate = 7:3); Mp: 254–256 °C; IR (KBr, cm^{-1}): 1759 (CO β-lactam), 1705 (CO Naph), 1674 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6) δ: 1.02 (6H, t, $J = 7.0$ Hz, $2\underline{CH_3}$), 3.26 (4H, q, $J = 7.0$ Hz, $2\underline{CH_2}$–N), 5.62 (1H, d, $J = 2.5$ Hz, H-4), 5.88 (1H, d, $J = 2.5$ Hz, H-3), 6.62 (2H, d, $J = 8.0$ Hz, ArH), 7.08 (2H, d, $J = 8.0$ Hz, ArH), 7.76–7.83 (2H, m, ArH), 7.86–7.92 (2H, m, ArH), 8.22–8.25 (2H, m, ArH), 8.46–8.52 (4H, m, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.2 (CO β-lactam), 161.6 (CO Naph), 147.4, 145.2, 144.5, 134.8, 131.2, 131.1, 128.0, 127.4, 127.3, 126.1, 123.9, 121.6, 118.6, 111.9 (aromatic carbons), 63.2 (C β-lactam), 57.9 (C β-lactam), 43.6 ($\underline{CH_2}$–N), 12.2 ($\underline{CH_3}$); GC-MS $m/z = 534$ [M^+]; Analysis calculated for $C_{31}H_{26}N_4O_5$: C, 69.65; H, 4.90; N, 10.48%. Found: C, 68.36; H, 4.79; N, 10.80%.

*2-(1-(Naphthalen-1-yl)-2-(naphthalen-2-yl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3f**)*

White solid (Yield 63%); Rf = 0.89 (n-hexane: ethyl acetate = 7:3); Mp: 309–311 °C; IR (KBr, cm−1): 1766 (CO β-lactam), 1704 (CO Naph), 1666 (CO Naph); 1H-NMR (250 MHz, DMSO-d6): 6.10 (1H, d, J = 2.5 Hz, H-4,), 6.38 (1H, d, J = 2.5 Hz, H-3,), 7.41–7.49 (4H, m, ArH), 7.54–7.69 (2H, m, ArH), 7.71–7.74 (1H, m, ArH), 7.78–7.94 (7H, m,

ArH), 8.10 (1H, s, ArH), 8.46–8.59 (5H, m, ArH); 13C-NMR (62.5 MHz, DMSO-d6) δ 164.0 (CO β-lactam), 163.3 (CO Naph), 134.9, 134.3, 133.8, 132.5, 132.4, 131.3, 131.3, 128.5, 127.6, 127.6, 127.5, 127.3, 127.2, 126.6, 126.5, 126.4, 126.3, 126.2, 124.5, 121.5 (aromatic carbons), 62.0 (C β-lactam), 60.0 (C β-lactam); GC-MS $m/z = 518$ [M+]; Analysis calculated for C35H22N2O3: C, 81.07; H, 4.28; N, 5.40%. Found: C, 80.95; H, 4.11; N, 5.53%.

*2-(2-(4-Nitrophenyl)-4-oxo-1-(p-tolyl)azetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3g**)*

White solid (Yield 65%); Rf = 0.94 (n-hexane: ethyl acetate = 7:3); Mp: 290–291 °C; IR (KBr, cm^{-1}): 1774 (CO β-lactam), 1705 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6): 2.24 (3H, s), 5.70 (1H, d, $J = 2.7$ Hz, H-4), 5.95 (1H, d, $J = 2.7$ Hz, H-3), 7.14-7.17 (4H, m, ArH), 7.81 (2H, d, $J = 9.0$ Hz, ArH), 7.88 (2H, t, $J = 8.0$ Hz, ArH), 8.24 (2H, d, $J = 9.0$ Hz, ArH), 8.28 (4H, t, $J = 8.0$ Hz, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 168.4 (CO β-lactam), 167.6 (CO Naph), 152.7, 150.0, 140.1, 140.0, 138.4, 136.5, 136.4, 134.9, 134.3, 133.3, 132.5, 129.2, 126.8, 122.0(aromatic carbons), 68.6 (C β-lactam), 63.2 (C β-lactam), 25.6 ($\underline{CH_3}$); GC-MS $m/z = 477$ [M^+]; Analysis calculated for $C_{28}H_{19}N_3O_5$: C, 70.43; H, 4.01; N, 8.80%. Found: C, 69.32; H, 4.61; N, 8.57%.

*2-(1-(Benzo[d][1,3]dioxol-5-yl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3h**)*

Gray solid (Yield 68%); Rf = 0.90 (n-hexane: ethyl acetate = 7:3); Mp: 242–244 °C; IR (KBr, cm^{-1}): 1766 (CO β-lactam), 1705 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6): 5.67 (1H, d, $J = 2.5$ Hz, H-4), 5.93 (1H, d, $J = 2.5$ Hz, H-3), 5.94–5.98 (2H, m, ArH), 6.59 (2H, d, $J = 7.7$ Hz, ArH), 6.82–6.98 (2H, m, ArH), 7.79–7.91 (4H, m, ArH), 8.22–8.51 (5H, m, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 168.5 (CO β-lactam), 167.5 (CO Naph), 152.8, 152.7, 149.8, 148.9, 140.1, 136.5, 136.4, 133.4, 132.5, 129.1, 126.8, 114.8, 113.8, 106.5, 104.4, 102.4 (aromatic carbons), 87.7 (O–$\underline{CH_2}$–O), 68.5 (C β-lactam), 63.6 (C β-lactam); GC-MS $m/z = 507$ [M^+]; Analysis calculated for $C_{28}H_{17}N_3O_7$: C, 66.27; H, 3.38; N, 8.28%. Found: C, 66.27; H, 4.11; N, 8.57%.

*2-(1-(3,4-Dimethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3i**)*

White solid (Yield 72%); Rf = 0.93 (n-hexane: ethyl acetate = 7:3); Mp: 178–180 °C; IR (KBr, cm-1): 1766 (CO β-lactam), 1704 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6): 3.67 (6H, s), 5.94 (1H, d, $J = 1.0$ Hz, H-4), 5.68 (1H, d, $J = 1.0$ Hz, H-3), 6.51 (1H, d, $J = 8.0$ Hz, ArH), 6.88 (1H, d, $J = 8.0$ Hz, ArH), 7.12 (1H, s, ArH), 7.80–7.91 (4H, m, ArH), 8.24 (2H, d, $J = 8.0$ Hz, ArH), 8.49 (4H, t, $J = 7.0$ Hz, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.2 (CO β-lactam), 162.1 (CO Naph), 149.1, 147.4, 145.4, 144.7, 134.9, 131.2, 131.1, 130.8, 128.1, 127.4, 127.3, 123.9, 121.5, 112.3, 108.2, 102.1 (aromatic carbons), 63.3 (C β-lactam), 58.2 (C β-lactam), 55.7 (O–$\underline{CH_3}$), 55.4 (O–$\underline{CH_3}$); GC-MS $m/z = 523$ [M^+]; Analysis calculated for $C_{29}H_{21}N_3O_7$: C, 66.54; H, 4.04; N, 8.03%. Found: C, 66.83; H, 3.98; N, 8.22%.

*2-(1-(2,4-Dimethoxyphenyl)-2-(2-nitrophenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3j**)*

White solid (Yield 55%); Rf = 0.92 (n-hexane: ethyl acetate = 7:3); Mp: 249–251 °C; IR (KBr, cm^{-1}): 1759 (CO β-lactam), 1697 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6): 3.71 (3H, s), 3.83 (3H, s), 6.41 (1H, d, $J = 2.5$ Hz, H-4), 6.45 (1H, d, $J = 2.5$ Hz, H-3), 6.59–6.61 (1H, m, ArH), 7.56–7.75 (2H, m, ArH), 7.85–8.04 (3H, m, ArH), 8.39–8.56 (6H, m, ArH), 9.50 (1H, s, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 165.2 (CO β-lactam), 163.2 (CO Naph), 151.1, 141.1, 140.6, 138.4, 136.1, 134.5, 131.7, 131.2, 130.8, 130.6, 130.3, 128.8, 127.2, 123.2, 121.7, 119.9, 103.9, 98.7 (aromatic carbons), 68.6 (C β-lactam), 63.5 (C β-lactam), 55.6 (O–$\underline{CH_3}$), 55.1 (O–$\underline{CH_3}$); GC-MS $m/z = 523$ [M^+]; Analysis calculated for $C_{29}H_{21}N_3O_7$: C, 66.54; H, 4.04; N, 8.03%. Found: C, 66.83; H, 4.27; N, 8.22%.

*2-(1-(Benzo[d][1,3]dioxol-5-yl)-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3k**)*

Yellow solid (Yield 80%); Rf = 0.91 (n-hexane: ethyl acetate = 7:3); Mp: 239–241 °C; IR (KBr, cm^{-1}): 1759 (CO β-lactam), 1712 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6): 3.69 (3H, s), 3.73 (3H, s), 5.40 (1H, d, $J = 2.7$ Hz, H-4), 5.95 (1H, d, $J = 2.7$ Hz, H-3), 5.96–6.03 (2H, m, O–$\underline{CH_2}$–O), 6.63 (1H, dd, $J_1 = 8.2$ Hz, $J_2 = 2.0$ Hz, ArH), 6.84–6.95 (2H, m, ArH), 7.04 (1H, dd, $J_1 = 8.2$ Hz, $J_2 = 1.7$ Hz, ArH), 7.12–7.22 (1H, m, ArH), 7.86 (2H, t, $J = 7.7$ Hz, ArH), 8.41–8.54 (3H, m, ArH); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.1 (CO β-lactam), 162.8 (CO Naph), 155.5, 148.9, 148.8, 147.4, 143.4, 134.8, 132.1, 131.2, 128.9, 127.3, 121.5, 118.9, 111.8, 110.5, 109.6, 108.4, 101.1, 99.0 (aromatic carbons), 82.4 (O–$\underline{CH_2}$–O), 63.5 (C β-lactam), 59.3 (C β-lactam), 55.4 (O–$\underline{CH_3}$), 55.3 (O–$\underline{CH_3}$); GC-MS $m/z = 522$ [M^+]; Analysis

calculated for $C_{30}H_{22}N_2O_7$: C, 68.96; H, 4.24; N, 5.36%. Found: C, 68.31; H, 4.35; N, 5.29%.

*2-(1-(2,4-Dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-3-yl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (**3l**)*

Yellow solid (Yield 85%); Rf = 0.92 (n-hexane: ethyl acetate = 7:3); Mp: 191–193 °C; IR (KBr, cm^{-1}): 1755 (CO β-lactam),1705 (CO Naph), 1666 (CO Naph); ^{1}H-NMR (250 MHz, DMSO-d_6): 3.65–3.71 (12H, m, 4 $\underline{CH_3}$), 5.61 (1H, d, J = 2.2 Hz, H-4), 5.87 (1H, d, J = 2.2 Hz, H-3), 6.53 (2H, d, J = 8.7 Hz, ArH), 6.84 (1H, d, J = 8.2 Hz, ArH), 6.93 (1H, d, J = 8.0 Hz, ArH), 7.03 (1H, s, ArH), 7.45 (1H, d, J = 8.2 Hz, ArH), 7.86 (2H, t, J = 7.7 Hz, ArH), 8.47 (4H, d, J = 7.7 Hz, ArH,); ^{13}C-NMR (62.5 MHz, DMSO-d_6) δ 163.2 (CO β-lactam), 163.1 (CO Naph), 158.2, 153.3, 148.6, 148.5, 134.8, 131.2, 130.0, 127.4, 127.3, 127.2, 124.4, 121.5, 118.8, 117.7, 111.6, 110.3, 104.9, 99.4 (aromatic carbons), 63.4 (C β-lactam), 61.7 (C β-lactam), 56.0 (O–$\underline{CH_3}$), 55.7 (O–$\underline{CH_3}$), 55.3 (O–$\underline{CH_3}$), 55.3 (O–CH_3); GC-MS m/z = 538 [M^+]; Analysis calculated for $C_{31}H_{26}N_2O_7$: C, 69.14; H, 4.87; N, 5.20%. Found: C, 68.93; H, 4.50; N, 5.37%.

General procedure for antimalarial activity measurements

The chloroquine-resistant *P. falciparum* strain K1 (Southeast Asia) was in vitro cultured in complete medium consisting of RPMI 1640 (In Vitrogen) 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 (Noedl et al. 2005). 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 post-invasion) at a 0.8% parasitemia and 3% hematocrit in complete medium was added per well. The plates were incubated at 37 °C in presence of 5% CO_2, 85% N_2 and 10% O_2 for 72 h. After culture the plates were frozen at −20 °C. Parasite susceptibility was tested in parallel against chloroquine diphosphate (Sigma-Aldrich) (final concentrations: 6.25–3200 nM). Parasite growth inhibition was quantified using a homemade HRP2 ELISA assay based on pfHRP2 detection. Dose-response curves and drug concentrations inhibiting parasite growth by 50% (IC_{50}) using duplicate-well data for each drug concentration were determined using ICESTIMATOR (Kaddouri et al. 2006; Le Nagard et al. 2011).

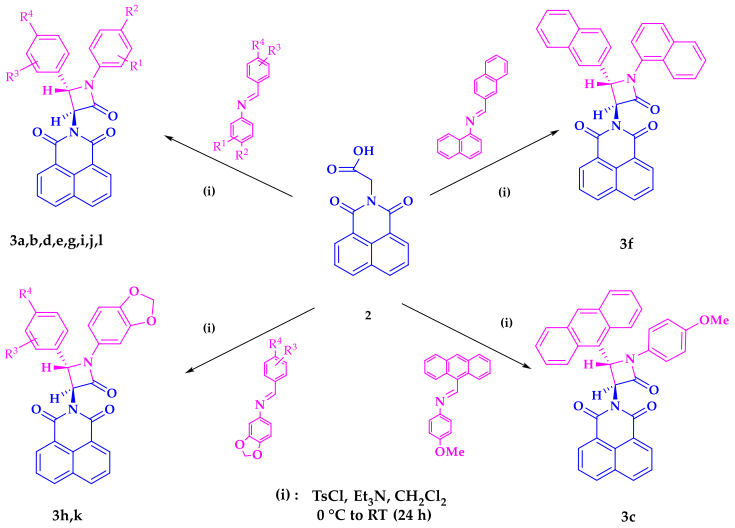
Results and discussion

All new *trans*-β-lactams were synthesized by the reaction between an appropriate aromatic imine and 2-(1,3-dioxo-1H-benzo[de]isoquinolin-2(3H)-yl) acetic acid in the presence of tosyl chloride and triethylamine in anhydrous CH_2Cl_2, stirred at 0 °C to room temperature for 24 h (Scheme 1). The reaction products were purified by recrystallization and fully characterized by spectral and elemental analyses. These experimental conditions afforded exclusively the *trans*-β-lactams **3a–l** in isolated yields varying from 55 to 85%. The *trans* stereochemistry of each new β-lactam compound was assigned from the coupling constants of the two β-lactam ring protons, H-3 and H-4 ($J^{3,4} \leq 2.75$ Hz) (Bandyopadhyay et al. 2012; Banik et al. 2010; Duguet et al. 2010; Wild and Georg 1993; Zarei 2013). X-ray single crystal analysis on 3b and 3c (Fig. 1) (Celik et al. 2015a, 2015b) confirmed the *trans* disubstitution of the β-lactam rings.

Performing the cycloaddition reaction at −78 °C or in different solvents did not lead to improvement in yield or changes in diastereoselectivity, although the use of toluene at reflux had a detrimental effect on the isolated yield.

β-Lactams **3a–l** were evaluated for antimicrobial activities using a standard in vitro microbiological assay. None of the compounds possess significant antimicrobial activities against the Gram-positive *Staphylococcus aureus* or the Gram-negative bacteria *Escherichia coli* or *Pseudomonas aeruginosa*, except for derivative **3f** which has an MIC of 1.5 µg/mL against *S. aureus*. An assessment was subsequently performed for their anticancer activities against a SUM149 breast cancer cell line, but in no case was an IC_{50} lower than 50 µM obtained for the twelve compounds. However, moderate to excellent antimalarial activities were found for some of the compounds against chloroquine-resistant *P. falciparum* K1 strain, as outlined in Table 1. IC_{50} values varying from 3 µM up to 125 µM were obtained. The substituents on the phenyl group at C4 position are responsible for these differences in bioactivity. Indeed, the presence of a nitro group is detrimental, leading to low antimalarial activities (Table 1, compounds **3a**, **3e**, **3g**, **3h**, **3i**) whereas a phenyl group bearing a chloro, a methoxy or an anthracenyl group each gave better in vitro bioactivity (Table 1, compounds **3b**, **3c**, **3d**, **3k**, **3l**). Although the mode of antimalarial action has not yet been identified, the observed anti-*Plasmodium* bioactivity found among just this small library of compounds is intriguing and worthy of further investigation.

Scheme 1 Synthesis of 3-naphthalimido *trans*-β-lactams **3a–l**



Product	R^1	R^2	R^3	R^4	% Yield	Product	R^1	R^2	R^3	R^4	% Yield
3a	H	OEt	H	NO_2	75	**3g**	H	Me	H	NO_2	65
3b	H	OMe	H	Cl	70	**3h**	---	---	H	NO_2	68
3c	H	---	---	---	80	**3i**	3-OMe	OMe	H	NO_2	72
3d	H	Me	H	Cl	68	**3j**	2-OMe	OMe	2-NO_2	H	55
3e	H	NEt_2	H	NO_2	69	**3k**	---	---	3-OMe	OMe	80
3f	---	---	---	---	63	**3l**	2-OMe	OMe	3-OMe	OMe	85

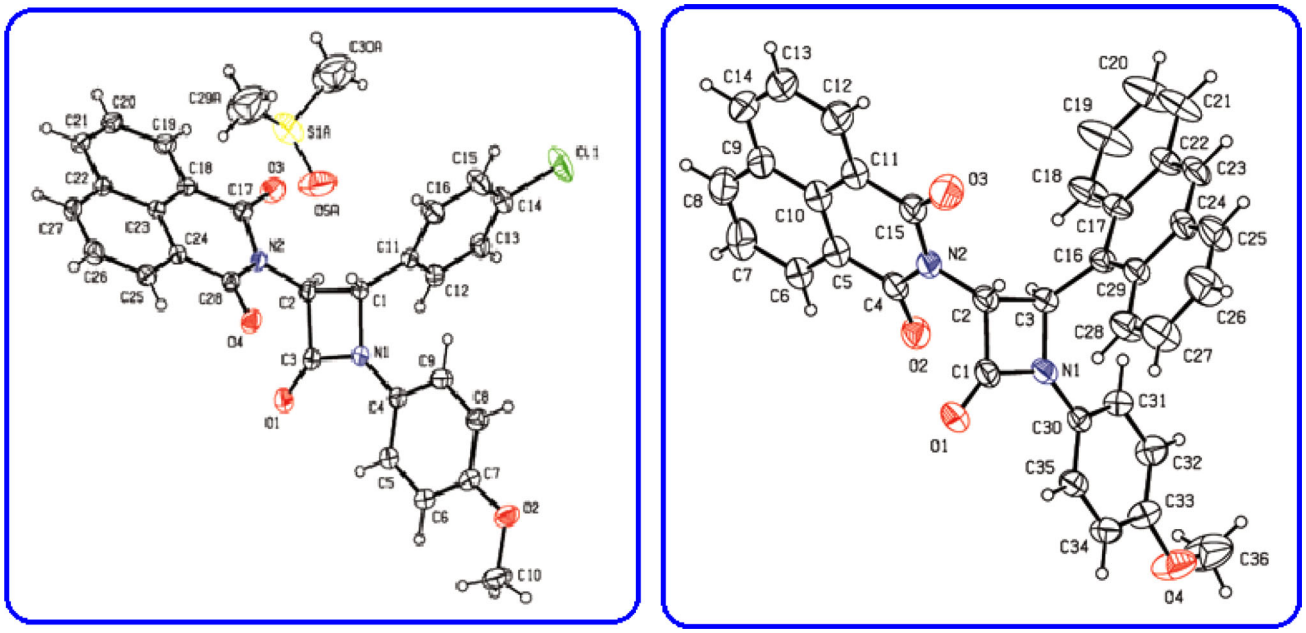


Fig. 1 ORTEP images of the single crystal X-ray structures for 3-naphthalimido *trans*-β-lactams **3b** and **3c**, respectively. (CCDC reference 1044874 and CDCC reference 1048898)

Table 1 Antimalarial activities of *trans*-β-lactams **3a–l** against chloroquine-resistant *P. falciparum* K1 strain

Product	IC_{50} (μM)	Product	IC_{50} (μM)
3a	>125	**3g**	31.17
3b	11.93	**3h**	>125
3c	3.03	**3i**	35.27
3d	8.22	**3j**	NT[b]
3e	44.78	**3k**	24.60
3f	NT[b]	**3l**	5.18
Chl[a]	0.97	–	–

[a] Chl: Chloroquine (reference antibiotic)

[b] NT: Not Tested due to insufficient solubility in DMSO

Conclusion

In this study, we have described the synthesis of a series of naphthalimido-substituted *trans*-β-lactams by a stereoselective ketene-imine cycloaddition (Staudinger reaction). To the best of our knowledge, this is the first time that Alrestatin ketene has been used for the synthesis of 2-azetidinones. This novel ketene afforded good to excellent yields of the desired β-lactams and with exclusive *trans* diastereoselectivity. Additionally we have been able to demonstrate the potent use of such derivatives as antimalarial agents against a chloroquine-resistant strain with an IC_{50} of 3 μM for compound **3c**. Further studies are being focused on the synthesis of additional analogs to enhance anti-*Plasmodium* bioactivity and drug-like properties of the β-lactams, as well as to better understand the basis for the observed antimalarial properties.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

Alcaide B, Almendros P, Aragoncillo C (2007) β-Lactams: versatile building blocks for the stereoselective synthesis of non-β-lactam products. Chem Rev 107:4437–4492

Alcaide B, Aragoncillo C, Almendros P (2008) Comprehensive heterocyclic chemistry III. Taylor ARKARFVSJK (ed.), 111–171

Alcala MA, Kwan SY, Shade CM, Lang M, Uh H, Wang M, Lee YJ (2011) Luminescence targeting and imaging using a nanoscale generation 3 dendrimer in an in vivo colorectal metastatic rat model. Nanomed Nanotechnol Biol Med 7:249–258

Armarego W, Chai C (2003) Purification of laboratory chemicals, 5th edn. Butter Worth, Oxford

Bandyopadhyay D, Cruz J, Banik BK (2012) Novel synthesis of 3-pyrrole substituted β-lactams via microwave-induced bismuth nitrate-catalyzed reaction. Tetrahedron 68:10686–10695

Banik BK, Banik I, Becker FF (2010) Asymmetric synthesis of anticancer β-lactams via Staudinger reaction: Utilization of chiral ketene from carbohydrate. Eur J Med Chem 45:846–848

Bojinov VB, Georgiev NI, Nikolov PS (2008) Synthesis and photophysical properties of fluorescence sensing ester-and amidoamine-functionalized 1,8-naphthalimides. J Photochem Photobiol A 193:129–138

Bouche C-M, Berdague P, Facoetti H, Robin P, Le Barny P, Schott M (1996) Side-chain electroluminescent polymers. Synth Met 81:191–195

Brana M, Ramos A (2001) Naphthalimides as anticancer agents: synthesis and biological activity. Curr Med Chem-Anti-Cancer Agent 1:237–255

Brider T, Gellerman G (2012) A two-step synthesis of medicinally-important 1, 8-naphthalimide peptidyls by solid phase organic synthesis. Tetrahedron Lett 53:5611–5615

Cao XF, Wang YS, Li SW, Chena CS, Ke SY (2011) Synthesis and biological activity of a series of novel N-Substituted β-Lactams derived from natural gallic acid. J Chin Chem Soc 58:35–40

Celik I, Akkurt M, Jarrahpour A, Ameri Rad J, Celik O (2015a) Crystal structure of 2-[4-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-oxoazetidin-3-yl]benzo[de]isoquinoline-1,3-dione dimethyl sulfoxide monosolvate. Acta Crystallogr Sect E 71:o129–o130

Celik I, Akkurt M, Jarrahpour A, Ameri Rad J, Celik O (2015b) Crystal structure of 2-[(3S,4S)-4-(anthracen-9-yl)-1-(4-methoxyphenyl)-2-oxoazetidin-3-yl]-2-aza-2H-phenalene-1,3-dione unknown solvate. Acta Crystallogr Sect E 71:o184–o185

Chen D, Falsetti SC, Frezza M, Milacic V, Kazi A, Cui QC, Long TE, Turos E, Dou QP (2008) Anti-tumor activity of N-thiolated β-lactam antibiotics. Cancer Lett 268:63–69

Chu DT, Plattner JJ, Katz L (1996) New directions in antibacterial research. J Med Chem 39:3853–3874

Coates C, Kabir J, Turos E (2005) β-Lactams. Compounds with Four and Three Carbon-Heteroatom Bonds. Houben-Weyl Met Mol Trans 21.9:609–646

Donkor IO, Abdel-Ghany YS, Kador PF, Mizoguchi T, Bartoszko-Malik A, Miller DD (1998) Synthesis and biological activities of aldose reductase inhibitors bearing acyl benzenesulfonamides as carboxylic acid surrogates. Eur J Med Chem 33:15–22

Duguet N, Donaldson A, Leckie SM, Kallström EA, Campbell CD, Shapland P, Smith AD (2010) Chiral relay in NHC-mediated asymmetric β-lactam synthesis II; asymmetry from NHCs derived from acyclic 1,2-diamines. Tetrahedron: Asymmetry 21:601–616

Ebrahimi E, Jarrahpour A, Heidari N, Sinou V, Latour C, Brunel JM, Turos E (2016) Synthesis and antimalarial activity of new nanocopolymer β-lactams and molecular docking study of their monomers. Med Chem Res 25:247–262

El-Betany AM, McKeown NB (2012) The synthesis and fluorescence properties of macromolecular components based on 1, 8-naphthalimide derivatives and dimers. Tetrahedron Lett 53:808–810

Ferreira R, Remón P, Pischel U (2009) Multivalued logic with a tristable fluorescent switch. J Phys Chem C 113:5805–5811

Frezza M, Garay J, Chen D, Cui C, Turos E, Dou QP (2008) Induction of tumor cell apoptosis by a novel class of N-thiolated β-lactam antibiotics with structural modifications at N1 and C3 of the lactam ring. Int J Mol Med 21:689–695

Georgiev NI, Bojinov VB, Nikolov PS (2011) The design, synthesis and photophysical properties of two novel 1,8-naphthalimide fluorescent pH sensors based on PET and ICT. Dyes Pigm 88:350–357

Goel RK, Mahajan MP, Kulkarni SK (2004) Evaluation of anti-hyperglycemic activity of some novel monocyclic β-lactams. J Pharm Pharm Sci 7:80–83

Jarrahpour A, Ebrahimi E, Khalifeh R, Sharghi H, Sahraei M, Sinou V, Brunel JM (2012) Synthesis of novel β-lactams bearing an anthraquinone moiety, and evaluation of their antimalarial activities. Tetrahedron 68:4740–4744

Jarrahpour A, Ebrahimi E, Sinou V, Latour C, Brunel JM (2014) Diastereoselective synthesis of potent antimalarial cis-β-lactam agents through a [2 + 2] cycloaddition of chiral imines with a chiral ketene. Eur J Med Chem 87:364–371

Jarrahpour A, Shirvani P, Sinou V, Latour C, Brunel JM (2016) Synthesis and biological evaluation of some new β-lactam-triazole hybrids. Med Chem Res 25:149–162

Jung SO, Yuan W, Ju JU, Zhang S, Kim YH, Je JT, Kwon SK (2009) A new orange-light-emitting materials based on (N-naphthyl)-1, 8-naphthalimide for OLED applications. Mol Cryst Liq Cryst 514:45/[375]–54/[384]

Kaddouri H, Nakache S, Houzé S, Mentré F, Le Bras J (2006) Assessment of the drug susceptibility of Plasmodium falciparum clinical isolates from africa by using a Plasmodium lactate dehydrogenase immunodetection assay and an inhibitory maximum effect model for precise measurement of the 50-percent inhibitory concentration. Antimicrob Agents Chemother 50:3343–3349

Konaklieva M (2002) β-Lactams as inhibitors of serine enzymes. Curr Med Chem Anti-Infective Agents 1:215–238

Le Nagard H, Vincent C, Mentré F, Le Bras J (2011) Online analysis of in vitro resistance to antimalarial drugs through nonlinear regression. Comput Meth Prog Bio 104:10–18

MacIntyre MM, Martell JM, Eriksson LA (2010) DFT study of five naphthalimide derivatives: Structures and redox properties. J Mol Struct: Theochem 941:133–137

Malviya VK, Liu P, Alberts DS, Surwit EA, Craig JB, Hannigan EV (1992) Evaluation of amonafide in cervical cancer, Phase II: a SWOG study. Am J Clin Oncol 15:41–44

Mehta PD, Sengar N, Pathak A (2010) 2-Azetidinone - a new profile of various pharmacological activities. Eur J Med Chem 45:5541–5560

Morin RB, Gorman M (eds) (1982) Chemistry and Biology of β-Lactam Antibiotics. Vol 1–3, Academic Press: New York, NY, USA

Nagarajan S, Arjun P, Raaman N, Shah A, Sobhia ME, Das TM (2012) Stereoselective synthesis of sugar-based β-lactam derivatives: docking studies and its biological evaluation. Tetrahedron 68:3037–3045

Noedl H, Bronnert J, Yingyuen K, Attlmayr B, Kollaritsch H, Fukuda M (2005) Simple histidine-rich protein 2 double-site sandwich enzyme-linked immunosorbent assay for use in malaria drug sensitivity testing. Antimicrob Agents Chemother 49:3575–3577

O'Boyle NM, Knox AJ, Price TT, Williams DC, Zisterer DM, Lloyd DG, Meegan MJ (2011) Lead identification of β-lactam and related imine inhibitors of the molecular chaperone heat shock protein 90. Bioorg Med Chem 19:6055–6068

O'Driscoll M, Greenhalgh K, Young A, Turos E, Dickey S, Lim DV (2008) Studies on the antifungal properties of N-thiolated β-lactams. Bioorg Med Chem 16:7832–7837

Robinson K, Castaner J (1996) Bisnafide mesylate: antineoplastic. Drugs Future 21:239–244

Rogers JE, Kelly LA (1999) Nucleic acid oxidation mediated by naphthalene and benzophenone imide and diimide derivatives: consequences for DNA redox chemistry. J Am Chem Soc 121:3854–3861

Rosenblum SB, Huynh T, Afonso A, Davis HR, Yumibe N, Clader JW, Burnett DA (1998) Discovery of 1-(4-fluorophenyl)-(3 R)-[3-(4-fluorophenyl)-(3 S)-hydroxypropyl]-(4 S)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): a designed, potent, orally active inhibitor of cholesterol absorption. J Med Chem 41:973–980

Saturnino C, Fusco B, Saturnino P, Martino GD, Rocco F, Lancelot J-C (2000) Evaluation of analgesic and anti-inflammatory activity of novel. β-lactam monocyclic compounds. Biol Pharm Bull 23:654–656

Sawa M, Hsu T-L, Itoh T, Sugiyama M, Hanson SR, Vogt PK, Wong C-H (2006) Glycoproteomic probes for fluorescent imaging of fucosylated glycans in vivo. Proc Nat Acad Sci USA 103:12371–12376

Sharma R, Samadhiya P, Srivastava SD, Srivastava SK (2011) Synthesis and biological activity of new series of N-[3-(1H-1, 2, 3-benzotriazol-1-yl) propyl]-2-(substituted phenyl)-3-chloro-4-oxo-1-azetidinecarboxamide. Acta Chim Slov 58:110–119

Singh G (2003) Recent progress in the synthesis and chemistry of azetidinones. Tetrahedron 59:7631–7649

Soengas RG, Segade Y, Jiménez C, Rodríguez J (2011) Highly diastereoselective indium-mediated synthesis of β-lactam carbohydrates from imines. Tetrahedron 67:2617–2622

Southgate R (1994) The synthesis of natural β-lactam antibiotics. Contemp Org Synth 1:417–431

Sperka T, Pitlik J, Bagossi P, Tözsér J (2005) β-Lactam compounds as apparently uncompetitive inhibitors of HIV-1 protease. Bioorg Med Chem Lett 15:3086–3090

Stolarski R (2009) Fluorescent naphthalimide dyes for polyester fibres. Fibres Text East Eur 17:91–95

Sutton JC, Bolton SA, Davis ME, Hartl KS, Jacobson B, Mathur A, Seiler SM (2004) Solid-phase synthesis and SAR of 4-carboxy-2-azetidinone mechanism-based tryptase inhibitors. Bioorg Med Chem Lett 14:2233–2239

Wild H, Georg G (1993) The organic chemistry of β-lactams. VCH, New York, NY

Wu A, Xu Y, Qian X (2009) Novel naphthalimide–amino acid conjugates with flexible leucine moiety as side chain: design, synthesis and potential antitumor activity. Bioorg Med Chem 17:592–599

Xu Z, Baek K-H, Kim HN, Cui J, Qian X, Spring DR, Yoon J (2009) Zn^{2+}-triggered amide tautomerization produces a highly Zn^{2+}-selective, cell-permeable, and ratiometric fluorescent sensor. J Am Chem Soc 132:601–610

Zarei M (2013) A facile and effective synthesis of 2-azetidinones via phosphonitrilic chloride. Tetrahedron 69:6620–6626

Zhang Y-Y, Zhou C-H (2011) Synthesis and activities of naphthalimide azoles as a new type of antibacterial and antifungal agents. Bioorg Med Chem Lett 21:4349–4352

Zhang Y, Feng S, Wu Q, Wang K, Yi X, Wang H, Pan Y (2011) Microwave-assisted synthesis and evaluation of naphthalimides derivatives as free radical scavengers. Med Chem Res 20:752–759