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ORIGINAL PAPER

Synthesis of some new monocyclic β-lactams as antimalarial agents

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Abstract A series of new monocyclic β-lactams bearing several methoxy groups and possessing a similar meticillin structure was prepared by the ketene–imine [2+2] cycloaddition reaction (Staudinger reaction). The cycloaddition reaction was found to be totally diastereoselective for **3a-l** (electron donating phenoxy ketenes) and **3u** leading exclusively to the formation of *cis*-β-lactams while **3m-o, 3q-s,** and **3v-x** were formed as *trans* diastereomer. β-lactams **3p, 3t,** and **3y** were found to be a mixture of *cis*/*trans* diastereomers. Compounds **3a-x** were tested against chloroquine-resistant *p. falciparum* K14 strain and showed low to excellent activities with IC_{50} varying from 5 to 50 μM.

Keywords B-lactam · Meticillin · Staudinger reaction · *P. falciparum* · Dimethoxyaniline

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Introduction

Due to their important biological activities, β-lactams are one of the best known and most extensively studied classes of antibiotics [1]. These classes of drugs have revolutionized treatment in medicine [2]. The azetidinone ring is responsible for the antibacterial and other biological activities and variable side chains that account for the major differences in their chemical and pharmacological properties [3]. 2-Azetidinones are susceptible to ring cleavage reactions, due to ring strain. This property has been discussed by some research groups who have utilized the β-lactam as a synthon for a wide variety of compounds [4, 5]. Bacteria have enhanced their resistance against the most common antibacterial drugs. In particular, meticillin-resistant staphylococci represent one of the most challenging and threatening diseases globally [6, 7]. Meticillin is insensitive to beta-lactamase enzymes secreted by many penicillin-resistant bacteria. The presence of the ortho-dimethoxyphenyl group directly attached to the side chain carbonyl group of the penicillin nucleus facilitates the β-lactamase resistance, since those enzymes are relatively intolerant of side-chain steric hindrance. Movement of one of the methoxy groups to the para position or replacing one of them by a hydrogen results in an analog sensitive to β-lactamase. Putting in a methylene between the aromatic ring and 6-APA likewise produces a β-lactamase sensitive agent. These findings provide strong support for the hypothesis that resistance to enzyme degradation is based on differential steric hindrance [8, 9]. In this context, we have envisioned the synthesis of 2-azetidinones bearing methoxy groups at different positions to mimic meticillin structure.

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Experimental section

General

All required chemicals were purchased from the Merck, Fluka, Aldrich and Acros chemical companies. Dichloromethane and triethylamine were dried by distillation over CaH_2 and then stored over 4Å molecular sieves. IR spectra were run on a Shimadzu FT-IR 8300 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 using a Bruker Avance DPX instrument (operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts were reported in ppm (δ) downfield from TMS. All values of the coupling constants (*J*) are in Hertz. The mass spectra were recorded on a Shimadzu GC–MS QP 1000 EX instrument. Melting points were determined in open capillaries with a Buchi 510 melting point apparatus and are not corrected. Thin-layer chromatography was carried out on silica gel F254 analytical sheets obtained from Fluka. Column chromatography was performed on Merck Kieselgel (230–270 mesh).

General procedure for the synthesis of Schiff bases 1a-p

A mixture of dimethoxyaniline (20.00 mmol) and a substituted benzaldehyde (20.00 mmol) was refluxed in ethanol (25 mL) for 2–4 h. After cooling the solution, the precipitate formed was filtered off and washed with ethanol to give pure Schiff bases as colored solids or crystals in excellent yields.

General procedure for the synthesis of β-lactams 3a-y

A solution of pure or crude Schiff base (1.0 eq.) was stirred with the corresponding substituted acetic acid (1.5 eq.), *p*-toluenesulfonyl chloride (1.5 eq.) and triethylamine (4–5 eq.) in dry CH_2Cl_2 at room temperature. After 24 h, the mixture was washed with HCl 1 N, saturated sodium bicarbonate solution and brine, dried over sodium sulfate and the solvent was evaporated to give the crude product which was then purified by recrystallization from EtOAc, EtOH and MeOH.

*1-(3,4-Dimethoxyphenyl)-4-(2-nitrophenyl)-3-phenoxyazetidin-2-one (**3a**)*

Yield 65 %; mp: 183–185 °C; IR (KBr) cm^{-1}: 1751 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.76, 3.80 (OMe, s, 6H), 5.62 (H-4, d, H, $J = 5.25$), 6.08 (H-3, d, 1H, $J = 5.25$), 6.44–8.16 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 56.05, 59.23 (2 OCH_3), 68.12 (C-4), 82.14 (C-3), 102.27, 108.27, 111.27, 116.37122.76, 125.38138.78, 129.23, 129.30, 129.46, 130.13, 13073, 130.88, 133.96, 146.41, 148.18, 149.66, 157.18 (aromatic carbons), 163.37 (CO, β-lactam); Anal. calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 62.42; H, 4.04; N, 5.68; GC–MS (*m/z*) = 420 [M$^+$].

*1-(3,4-Dimethoxyphenyl)-4-(3-nitrophenyl)-3-phenoxyazetidin-2-one (**3b**)*

Yield: 80 %; mp: 144–146 °C; IR (KBr) cm^{-1}: 1766 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.78,3.83 (OMe, s, 6H), 5.49 (H-4, d, 1H, $J = 4.80$), 5.64 (H-3, d, 1H, $J = 4.80$), 6.43–8.24 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 56.04, 56.06 (2 OCH_3), 61.15 (C-4), 81 (C-3), 102.61, 108.32, 111.27, 115.40, 122.61, 123.29, 123.83, 128.80, 129.49, 130.89, 133.88, 135.37, 146.52, 148.18, 149.68, 156.38 (aromatic carbons), 162.02 (CO, β-lactam); Anal. calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66;. Found: C, 65.51; H, 4.66; N, 5.83; GC–MS (*m/z*) = 420 [M$^+$].

*1-(3,4-Dimethoxyphenyl)-4-(4-nitrophenyl)-3-phenoxyazetidin-2-one (**3c**)*

Yield: 79 %; mp: 131–133 °C; IR (KBr) cm^{-1}: 1755 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.72,3.77 (OMe, s, 6H), 5.41 (H-4, d, 1H, $J = 4.85$), 5.56 (H-3, d, 1H, $J = 4.85$), 6.29–8.08 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 56, 56.04 (2 OCH_3), 61.19 (C-4), 81.16 (C-3), 102.49, 108.27, 111.21, 115.40, 122.63, 123.58, 128.98, 129.48, 130.20, 140.46, 146.48, 148.11, 149.62, 156.45 (aromatic carbons), 161.98 (CO, β-lactam); Anal. calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C, 64.39; H, 4.71; N, 7.23; GC–MS (*m/z*) = 420 [M$^+$].

*1-(2,4-Dimethoxyphenyl)-4-(3,4-dimethoxyphenyl)-3-phenoxyazetidin-2-one (**3d**)*

Yield: 45 %; mp: 116–118 °C; IR (KBr) cm^{-1}: 1758 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.64–3.70 (OMe, s, 12H), 5.51 (H-3, 4, s, 2H, $J = 4.35$), 6.30–7.59 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.48, 55.55, 55.68, 55.86 (4 OCH_3), 64.94 (C-4), 82.01 (C-3), 99.64, 104.46, 110.44, 111.22, 115.51, 117.75, 121.19, 121.88, 125.30, 126.44, 128.78, 129.20, 130.89, 148.47, 148.90, 153.00, 157.02, 158.89 (aromatic carbons), 164.58 (CO, β-lactam); Anal. calcd. for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C,68.47; H, 5.93; N, 3.73; GC–MS (*m/z*) = 420 [M$^+$].

*1,4-Bis(3,4-dimethoxyphenyl)-3-phenoxyazetidin-2-one (**3e**)*

Yield: 75 %; mp: 123–125 °C; IR (KBr) cm^{-1}: 1755 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.69–3.76 (OMe, s, 12H), 5.23 (H-4, d, 1H, $J = 4.70$), 5.48 (H-3, d, 1H, $J = 4.70$), 6.50–7.29 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.77–56.00 (4 OCH_3), 62.20 (C-4), 81.06 (C-3), 102.52, 108.73,

110.72, 110.86, 111.1, 115.57, 120.97, 122.15, 124.97, 129.28, 130.85, 146.07, 148.88, 149.31 (aromatic carbons), 162.65 (CO, β-lactam); Anal. calcd. for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C,68.75; H, 5.56; N, 2.90.

*1-(2,4-Dimethoxyphenyl)-4-(2-methoxyphenyl)-3-phenoxyazetidin-2-one (**3f**)*

Yield: 50 %; mp: 108–110 °C; IR (KBr) cm^{-1}: 1743 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.66–3.72 (OMe, d, 9H), 5.58 (H-4, dd, 1H, $J = 2.62$), 5.61 (H-3, dd, 1H, $J = 2.12$), 6.36–7.72 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 55.15–55.50 (3 OCH_3), 65.06 (C-4), 82.15 (C-3), 99.74, 104.49, 113.74, 113.85, 115.66, 117.89, 120.12, 120.78, 125.17, 128.94, 129.18, 135.79, 152.80, 157.08, 158.77, 159.23 (aromatic carbons), 167.55 (CO, β-lactam); Anal. calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 70.73; H, 5.88; N, 3.98; GC–MS (*m/z*) = 405 [M^+].

*1-(2,4-Dimethoxyphenyl)-4-(3-methoxyphenyl)-3-phenoxyazetidin-2-one (**3 g**)*

Yield: 20 %; mp: 98–100 °C; IR (KBr) cm^{-1}: 1747 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.61, 3.68, 3.73 (OMe, t, 9H), 5.56 (H-4, m, 1H), 6.13 (H-3, t, 1H), 6.35–7.82 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 55.12, 55.49, 55.55 (3 OCH_3), 59.59 (C-4), 82.16 (C-3), 99.75, 104.56, 109.91, 115.64, 118.44, 120.13, 121.64, 122.66, 124.88, 128.10, 128.93, 152.68, 157.22, 157.27, 158.53 (aromatic carbons), 164.78 (CO, β-lactam); Anal. calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C,70.50; H, 5.44; N, 3.32; GC–MS (*m/z*) = 405 [M^+].

*1-(2,4-Dimethoxyphenyl)-4-(2-nitrophenyl)-3-phenoxyazetidin2-one (**3 h**)*

Yield: 75 %; mp: 128–130 °C; IR (KBr) cm^{-1}: 1743 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.50, 3.71 (OMe, s, 6H), 6.36 (H-4, d, 1H, $J = 5.11$), 5.66 (H-3, d, 1H, $J = 5.11$), 6.31–8.01 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 55.42, 55.54 (2 OCH_3), 61.77 (C-4), 83.28 (C-3), 99.72, 104.75, 116.23, 122.45, 124.09, 124.81, 128.79, 128.90, 129.37, 130.88, 132.07, 133.43, 151.80, 157.24, 158.52 (aromatic carbons), 164.67 (CO, β-lactam); Anal. calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C,62.42; H, 4.04; N, 5.68; GC–MS (*m/z*) = 420 [M^+].

*1-(2,4-Dimethoxyphenyl)-4-(3-nitrophenyl)-3-phenoxyazetidin-2-one (**3i**)*

Yield: 80 %; mp: 131–133 °C; IR (KBr) cm^{-1}: 1758 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.63, 3.69 (OMe, s, 6H), 5.60 (H-3, d, 1H, $J = 2.59$), 6.30 (H-4, d, 1H, $J = 2.42$), 6.40–8.14 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 54.43, 54.45 (2 OCH_3), 63.16 (C-4), 80.1 (C-3), 98.52, 103.64, 114.25, 116.33, 120.60, 121.23, 121.43, 122.21, 122.34, 122.65, 123.89, 127.97, 128.35, 133.15, 135.84, 146.84, 151.41, 155.40, 157.96 (aromatic carbons), 162.86 (CO, β-lactam); Anal. calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.79; N, 6.66. Found: C,65.93; H, 5.88; N, 5.86; GC–MS (*m/z*) = 420 [M^+].

*1-(3,4-Dimethoxyphenyl)-4-(2-methoxyphenyl)-3-phenoxyazetidin-2-one (**3j**)*

Yield 77 %; mp: 168–170 °C; IR (KBr) cm^{-1}: 1755 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.69–3.77 (OMe, s, 9H), 5.49 (H-4, d, 1H, $J = 4.82$), 5.73 (H-3, d, 1H, $J = 4.82$), 6.48–7.32 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 55.15, 55.95, 56.03 (3 OCH_3), 56.46 (C-4), 81.08 (C-3), 102.35, 108.66, 110.03, 111.24, 115.73, 120.42, 120.62, 121.91, 128.23, 129.01, 129.48, 130.93, 145.98, 149.37, 157.16, 157.30 (aromatic carbons), 162.92 (CO, β-lactam); Anal. calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 70.43; H, 5.75; N, 3.79; GC–MS (*m/z*) = 405 [M^+].

*1-(3,4-Dimethoxyphenyl)-4-(3-methoxyphenyl)-3-phenoxyazetidin-2-one (**3 k**)*

Yield 65 %; mp: 114–116 °C; IR (KBr) cm^{-1}: 1745 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.65–3.75 (OMe, s, 9H), 5.25 (H-4, d, 1H, $J = 4.81$), 5.48 (H-3, d, 1H, $J = 4.81$), 6.46–7.27 (ArH, m, 12H); ^{13}C-NMR ($CDCl_3$) δ 55.25, 55.92, 56.01 (3 OCH_3), 62.19 (C-4), 81.15 (C-3), 102.51, 108.71, 111.21, 113.61, 114.33, 115.74, 120.56, 122.18, 129.25, 129.42, 130.79, 134.30, 146.09, 149.35, 157.00, 159.57 (aromatic carbons), 162.59 (CO, β-lactam); Anal. calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 70.14; H, 5.91; N, 5.27; GC–MS (*m/z*) = 405 [M^+].

*1-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-3-phenoxyazetidin-2-one (**3 l**)*

Yield: 50 %; mp: 123–125 °C; IR (KBr) cm^{-1}: 1745 (CO, β-lactam); ^{1}H-NMR ($CDCl_3$) δ 3.65–3.75 (OMe, s, 12H), 5.24 (H-4, d, 1H, $J = 4.72$), 5.44 (H-3, d, 1H, $J = 4.72$), 6.48–7.61 (ArH, 12 m, H); ^{13}C-NMR ($CDCl_3$) δ 55.17-61.92 (4 OCH_3), 68.12 (C-4), 81.16 (C-3), 102.53, 108.75, 111.15, 113.84, 115.67, 122.11, 124.46, 128.78, 129.25, 129.43, 130.88, 145.99, 149.30,156.99, 159.85 (aromatic carbons), 162.70 (CO, β-lactam); Anal. calcd. for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C,70.90; H, 5.26; N, 5.97.

*2-(1-(2,4-Dimethoxyphenyl)-2-(2-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3 m**)*

Yield: 85 %; mp: 227–229 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1750-1780 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.47, 3.72 (OMe, d, 6H), 5.21 (H-2, d, 1H, J = 2.32), 6.10 (H-3, d, 1H, J = 1.98), 5.97–8.36 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.59, 59.99 (2 OCH_3), 62.43 (C-3), 62.90 (C-2), 99.76, 104.86, 123.55, 123.78, 124.01, 124.49, 124.73, 125.00, 126.62, 128.77, 128.80, 130.27, 130.87, 131.23, 133.38, 134.28, 134.43, 152.30, 158.72 (aromatic carbons), 162.80, 163.18 (2 CO, Phth), 166.96 (CO, β-lactam); Anal. calcd. for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88. Found: C, 57.53; H, 3.38; N, 10.97; GC–MS (*m/z*) = 473 [M^+].

*2-(1-(2,4-Dimethoxyphenyl)-2-(3-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3n**)*

Yield: 65 %; mp: 220–218 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1760–1775 (CO, Phth); ^{1}H-NMR (DMSO) δ 3.62, 3.71 (OMe, s, 6H), 5.26 (H-2, d, 1H, J = 2.50), 5.81 (H-3, d, 1H, J = 2.50), 6.45–8.36 (ArH, m, 11H); ^{13}C-NMR (DMSO) δ 55.34, 55.70 (2 OCH_3), 61.84 (C-3), 62.02 (C-2), 99.61, 105.26, 117.07, 121.91, 123.12, 123.43, 124.56, 130.10, 131.41, 133.09, 134.32, 139.74, 147.81, 152.74, 158.49 (aromatic carbons), 162.12 (2 CO, Phth), 166.66 (CO, β-lactam); Anal. calcd. for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88. Found: C, 63.28; H, 4.17; N, 6.75.

*2-(1-(2,4-Dimethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3o**)*

Yield: 60 %; mp: 186–188 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1770–1782 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.64, 3.77 (OMe, s, 6H), 5.27 (H-2, d, 1H, J = 2.65), 5.76 (H-3, d, 1H, J = 2.65), 6.38–8.21 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.56-55.60 (2 OCH_3), 62.64 (C-3), 63.40 (C-2), 99.83, 104.85, 123.86, 124.24, 124.81, 126.99, 131.64, 134.66, 144.74, 147.96, 152.88, 159.07 (aromatic carbons), 162.04 (2 CO, Phth), 166.76 (CO, β-lactam); Anal. calcd. for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88. Found: C, 62.37; H, 3.87; N, 10.84.

*2-(1-(2,4-Dimethoxyphenyl)-2-(2-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3**p**)*

Mixture of *cis* and *trans*, yield 75 %; mp: 179–181 °C; IR (KBr) cm^{-1}: 1716 (CO, β-lactam), 1758–1770 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.55–3.73 (OMe, s, 18H), *trans*: 5.31 (H-4, d, H, J = 2.70), 5.82 (H-3, d, 1H, J = 2.70), *cis*: 5.74 (H-4, d, 1H, J = 5.44), 5.95 (H-3, d, 1H, J = 5.44), 6.33–8.08 (ArH, m, 22H); ^{13}C-NMR ($CDCl_3$) δ 55.01, 55.77 (3 OCH_3), 59.033, 60.40 (C-4), 60.58, 61.11 (C-3), 99.83, 104.61, 109.01, 110.38, 118.77, 120.22, 120.46, 123.13, 123.55, 124.70, 125.43, 125.47, 127.05, 127.82, 129.23, 131.31, 131.84, 134.06, 134.46, 153.40, 157.14, 158.63, 158.75 (aromatic carbons), 163.13 (2 CO, β-lactam); Anal. calcd. for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.22; H, 4.90; N, 6.18; GC–MS (*m/z*) = 458 [M^+].

*2-(1-(2,4-Dimethoxyphenyl)-2-(3-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3q**)*

Yield: 60 %; mp: 118–120 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1750–1770 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.59, 3.68, 3.69 (OMe, s, 9H), 5.22 (H-2, d, 1H, J = 2.54), 5.57 (H-3, d, 1H, J = 2.54), 6.32–7.82 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.17, 55.49, 55.72 (3 OCH_3), 63.90 (C-3), 68.13 (C-2), 99.84, 104.62, 111.63, 114.03, 117.90, 118.8, 123.70, 125.15, 128.79, 129.95, 130.90, 131.78, 134.46, 138.67, 153.61, 158.96, 159.99 (aromatic carbons), 162.78,166.91 (2 CO, Phth), 167.76 (CO, β-lactam); Anal. calcd. for: $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.51; H, 4.86; N, 7.94; GC–MS (*m/z*) = 458 [M^+].

*2-(1-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3**r**)*

Yield: 85 %; mp: 184–186 °C; IR (KBr) cm^{-1}: 1716 (CO, β-lactam), 1755–1775 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.63, 3.65 (OMe, s, 9H), 5.19 (H-2, d, 1H, J = 2.55), 5.53 (H-3, d, 1H, J = 2.55), 6.28–7.76 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.21, 55.44, 55.70 (3 OCH_3), 62.54 (C-3), 63.58 (C-2), 99.76, 104.56, 114.22, 117.75, 123.61, 125.24, 127.71, 128.79, 131.69, 134.45, 153.63, 158.92, 159.76 (aromatic carbons), 162.86 (2 CO, Phth), 166.92 (CO, β-lactam); Anal. calcd. for: $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.02; H, 4.81; N, 5.93; GC–MS (*m/z*) = 458 [M^+].

*2-(1-(3,4-Dimethoxyphenyl)-2-(2-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3 s**)*

Yield: 25 %; mp: 203–205 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1755, 1762 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.55, 3.85 (OMe, s, 6H), 5.32 (H-2, d, 1H, J = 2.62), 5.93 (H-3, d, 1H, J = 2.62), 6.05–8.12 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.92,56.08 (2 OCH_3), 57.62 (C-3), 62.24 (C-2), 102.72, 108.65, 111.31, 123.53, 123.61, 123.69, 125.02, 125.77, 127.56, 129.52, 129.62, 131.24, 131.74, 131.99, 133.77, 134.24, 134.32, 134.42, 134.58, 149.66 (aromatic carbons), 161.95 (2 CO, Phth), 166.95 (CO, β-lactam); Anal. calcd. for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88. Found: C, 62.11; H, 3.86; N, 8.64.

*2-(1-(3,4-Dimethoxyphenyl)-2-(3-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3**t**)*

Mixture of *cis* and *trans*, yield: 50 %; mp: 148–150 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1755–1770 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.73, 3.83 (OMe, s, 6H), *trans*: 5.21 (H-2, d, 1H, $J = 2.56$), 5.41 (H-3, d, 1H, $J = 2.56$), *cis:* 5.48 (H-2, d, 1H, $J = 5.59$), 5.70 (H-3, d, 1H, $J = 5.59$), 6.30–8.19 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.97-60.28 (2 OCH_3), 60.48 (C-3), 62.56 (C-2), 102.40, 102.77, 107.89, 108.59, 111.22, 121.49, 122.40, 123.52, 123.70, 123.91, 124.13, 129.64, 130.29, 130.69, 130.86, 131.51, 131.94, 133.39, 134.60, 134.76, 138.31, 146.41, 148.81, 149.56 (aromatic carbons), 160.03,161.02 (2 CO, Phth), 166.72 (CO, β-lactam); Anal. calcd. for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88. Found: C, 62.94; H, 4.11; N, 8.64.

*2-(1-(3,4-Dimethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3u**)*

Yield: 58 %; mp: 244–246 °C; IR (KBr) cm^{-1}: 1716 (CO, β-lactam), 1762–1775 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.78, 3.85 (OMe, s, 6H), 5.47 (H-2, d, 1H, $J = 5.63$), 5.70 (H-3, d, 1H, $J = 5.63$), 6.34-8.02 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 56.12 (2 OCH_3), 58.78 (C-3), 60.39 (C-2), 102.43, 107.86, 111.25, 123.74, 123.79, 128.36, 130.80, 130.90, 134.69, 140.00, 146.49, 147.86,149.78 (aromatic carbons), 159.8 (2 CO, Phth), 166.60 (CO, β-lactam); Anal. calcd. for $C_{25}H_{19}N_3O_7$: C, 63.42; H, 4.05; N, 8.88. Found: C, 62.80; H, 4.36; N, 6.65; GC–MS (*m/z*) = 458, 473 [M^+].

*2-(1-(3,4-Dimethoxyphenyl)-2-(2-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (**3v**)*

Yield: 45 %; mp: 208–210 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1751–1760 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.59, 3.77, 3.83 (OMe, s, 9H), 5.57 (H-2, d, 1H, $J = 2.55$), 5.70 (H-3, d, 1H, $J = 2.55$), 6.53–7.58 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.05, 56.07 (3 OCH_3), 57.71 (C-3), 57.93 (C-2), 102.40, 108.23, 109.23, 111.20, 120.33, 120.49, 123.26, 128.82, 129.35, 131.26, 131.68, 13413, 145.91, 149.45, 156.55 (aromatic carbons), 161.55 (2 CO, Phth), 166.33 (CO, β-lactam); Anal. calcd. for: $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C, 66.67; H, 4.93; N, 6063; GC–MS (*m/z*) = 458 [M^+].

*2-(1-(3,4-Dimethoxyphenyl)-2-(3-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3**w**)*

Yield: 70 %; mp: 183–185 °C; IR (KBr) cm^{-1}: 1720 (CO, β-lactam), 1760–1770 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.77–3.84 (OMe, s, 9H), 5.29 (H-2, 3, d, 2H, $J = 2.63$), 6.54–7.89 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.31, 55.88, 56.03 (3 OCH_3), 61.45 (C-3), 62.60 (C-2), 102.59, 108.88, 111.26, 111.77, 114.41, 118.44, 123.80, 130.51, 131.02, 131.68, 134.25, 134.57, 137.47, 146.04, 149.30 (aromatic carbons), 160.36, 161.57 (2 CO, Phth), 166.8 (CO, β-lactam); Anal. calcd. for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C,66.40; H, 4.70; N, 6.32; GC–MS (*m/z*) = 458 [M^+].

*2-(1-(3,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)isoindoline-1,3-dione (3**x**)*

Yield: 80 %; mp: 186–188 °C; IR (KBr) cm^{-1}: 1716 (CO, β-lactam), 1755–1775 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.73–3.76 (OMe, s, 9H), 5.19 (H-2, d, 1H, $J = 2.57$), 5.22 (H-3, d, 1H, $J = 2.57$), 6.50–7.81 (ArH, m, 11H); ^{13}C-NMR ($CDCl_3$) δ 55.10-56.02 (3 OCH_3), 61.16 (C-3), 62.75 (C-2), 102.44, 108.93, 111.23, 113.89, 114.74, 123.75, 127.60, 128.52, 131.02, 131.67, 134.25, 134.54, 145.95, 149.26 (aromatic carbons), 160.18, 161.70 (2 CO, Phth), 166.85 (CO, β-lactam); Anal. calcd. for $C_{26}H_{22}N_2O_6$: C, 68.11; H, 4.84; N, 6.11. Found: C,67.02; H, 4.81; N, 5.93; GC–MS (*m/z*) = 458 [M^+].

*2-(1-(2,4-Dimethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-4-nitroisoindoline-1,3-dione (3**y**)*

Mixture of *cis* and *trans*, yield: 80 %; mp: 190–192 °C (*trans*), 194–196 °C (*cis*); IR (KBr) cm^{-1}: 1735 (CO, β-lactam), 1785–1787 (CO, Phth); ^{1}H-NMR ($CDCl_3$) δ 3.55, 3.69 (OMe, s, 6H), *trans*: 5.20 (H-2, d, 1H, $J = 1.70$), 5.70 (H-3, d, 1H, $J = 2.07$), *cis*: 5.72 (H-2, d, 1H, $J = 5.56$), 5.88 (H-3, d, 1H, $J = 5.56$), 6.29–8.13 (ArH, m, 10H); ^{13}C-NMR ($CDCl_3$) δ 55.54 (2 OCH_3), 62.72 (C-3), 63.02 (C-2), 99.71, 104.85, 117.29, 124.26, 124.70, 127.06, 127.62, 129.19, 133.57, 136.13, 144.29, 145.23, 148.02, 152.77, 159.14 (aromatic carbons), 161.10 (2 CO, Phth), 164.28 (CO, β-lactam); Anal. calcd. for $C_{25}H_{18}N_4O_9$: C, 57.92; H, 3.50; N, 10.81. Found: C,56.28; H, 4.48; N, 9.91; GC–MS (*m/z*) = 518 [M^+].

General procedure for dephthaloylation of monocyclic β-lactams

Method A

A mixture of monocyclic β-lactam **3n** (1.50 mmol), methanol (25.00 mL) and 0.12 mL (2.55 mmol) of hydrazine hydrate was refluxed for 1 h. After evaporation of the solvent, $CHCl_3$ (20.00 mL) was added and 2,3-dihydrophthalazine-1,4-dione formed was filtered. The filtrate was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate and

the solvent was evaporated to give the crude product of 3-amino azetidin-2-one. Compounds xxxx were treated by this method.

Method B

A mixture of monocyclic β-lactam **3o** (1.00 mmol), CH_2Cl_2 (25.00 mL) and methylhydrazine (0.05 mL,1.10 mmol)was stirred for 3 days. Then the methylphthalhydrazide formed was filtered. The filtrate was washed with saturated sodium bicarbonate, solution, brine and dried over sodium sulfate and the solvent was evaporated to give the crude product of 3-amino-azetidin-2-one **4d** which was then purified by column chromatography. β-Lactams xxxx were obtained by this method.

*3-Amino-1-(2,4-dimethoxyphenyl)-4-(4-nitrophenyl) azetidin-2-one (**4d**)*

Yield: 42 %; mp:138–140 °C; IR (KBr) cm^{-1}: 1745 (CO, β-lactam), 3290, 3379 (NH_2); ^{1}H-NMR ($CDCl_3$) δ 1.99 (NH_2, s, 2H), 3.62, 3.75 (OMe, s, 6H), 4.10 (H-3, d, 1H, $J = 1.82$), 5.10 (H-4, d, 1H, $J = 1.50$), 6.34–8.18 (ArH, m, 7H); ^{13}C-NMR ($CDCl_3$) δ 55.39, 55.50 (2 OCH_3), 68.74 (C-3), 70.46 (C-4), 98.61-158.72 (aromatic carbons), 168.23 (CO, β-lactam); Anal. calcd. for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found: C, 57.29; H, 4.48; N, 12.46.

General procedures for the synthesis of amido β-lactams (5a-c, 5d)

Method A

A mixture of oxalyl dichloride (0.17 mL, 2.00 mmol), 2,6-dimethoxybenzoic acid (1.50 mmol), CH_2Cl_2 (25 mL) was stirred for 30 min. Then $E_{t3}N$ (0.50 mL) and the crude of 3-amino-azetidin-2-one (1.5 mmol) from **3n** were added and the mixture was stirred overnight. Then it was washed with HCl 1 N, saturated sodium bicarbonate solution, brine and dried over sodium sulfate. The solvent was evaporated under vaccum to afford the crude amide **5a** which was then purified by column chromatography.

*N-(1-(2,4-Dimethoxyphenyl)-2-(3-nitrophenyl)-4-oxoazetidin-3-yl)-2,6-dimethoxybenzamide (**5a**)*

Yield: 15 %; mp: 87–89 °C; IR (KBr) cm^{-1}: 1672 (CO, Amide), 1755 (CO, β-lactam), 2941 (NH); ^{1}H-NMR ($CDCl_3$) δ 3.56–3.79 (OMe, s, 12H), 4.80 (H-3, dd, 1H, $J = 1.99, 5.56$), 5.34 (H-2, d, 1H, $J = 1.82$), 6.31–8.07 (ArH, m, 10H), 8.22 (NH); Anal. calcd. for $C_{26}H_{25}N_3O_8$: C, 61.53; H, 4.97; N, 8.28. Found: C, 59.53; H, 4.38; N, 8.97.

*N-(1-(2,4-Dimethoxyphenyl)-2-(2-methoxyphenyl)-4-oxoazetidin-3-yl)-2,6-dimethoxybenzamide (5**b**)*

Mixture of *cis* and *trans*. yield: 30 %; mp: 110–112 °C; IR (KBr) cm^{-1}: 1687 (CO, Amide), 1755 (CO, β-lactam), 2950 (NH); ^{1}H-NMR ($CDCl_3$) δ 3.61–3.84 (OMe, s, 15H), 5.03, 5.13 (H-3, dd, 1H, $J = (2.25, 8.96), (2.50, 9.77)$), 5.41, 5.50 (H-2, d, 1H, $J = 2.21, 2.25$), 6.30–7.92 (ArH, m, 10H), 8.25, 8.36 (NH, d); Anal. calcd. for $C_{27}H_{28}N_2O_7$: C, 65.84; H, 5.73; N, 5.69. Found: C, 63.46; H, 6.42; N, 5.11.

*N-(1-(2,4-Dimethoxyphenyl)-2-(4-methoxyphenyl)-4-oxoazetidin-3-yl)-2,6-dimethoxybenzamide (**5c**)*

Yield: 20 %; mp: 82-84 °C; IR (KBr) cm^{-1}: 1677 (CO, Amide), 1758 (CO, β-lactam), 2931 (NH); ^{1}H-NMR ($CDCl_3$) δ 3.61–3.80 (OMe, s, 15H), 4.79 (H-3, dd, 1H, $J = 2.10, 8.13$), 5.18 (H-2, d, 1H, $J = 1.88$), 6.30–8.19 (ArH, m, 10H), 8.19 (NH, d, 1H, $J = 2.00$); Anal. calcd. for $C_{27}H_{28}N_2O_7$: C, 65.84; H, 5.73; N, 5.69. Found: C, 64.54; H, 4.93; N, 6.12.

Method B

A mixture of 2,6-dimethoxybenzoic acid (1.10 mmol), TsCl (1.10 mmol), Et_3N (1.10 mmol) and CH_2Cl_2 (25.00 mL) was stirred for 3 h. Then an excess amount of Et_3N (0.5 mL) and 3-amino-1-(2,4-dimethoxyphenyl)-4-(4-nitrophenyl)azetidin-2-one **4d** (1 mmol) was added and the mixture was stirred overnight. Then the mixture was washed with HCl 1 N, saturated sodium bicarbonate solution, brine and dried over sodium sulfate. The solvent was evaporated under vaccum to afford the crude amide **5d** which was then purified by column chromatography.

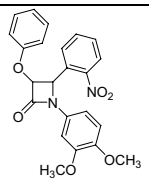
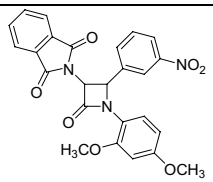
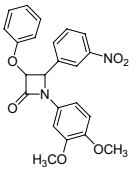
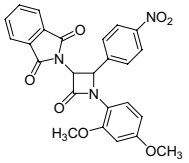
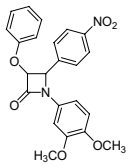
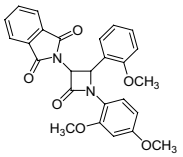
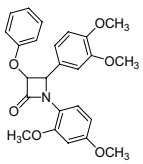
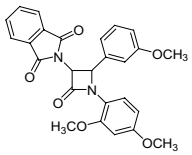
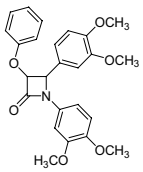
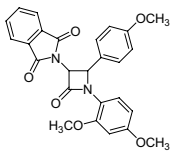
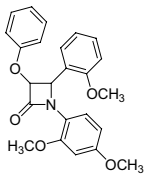
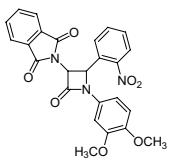
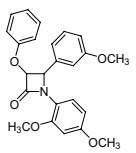
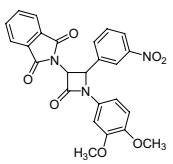
*N-(1-(2,4-Dimethoxyphenyl)-2-(4-nitrophenyl)-4-oxoazetidin-3-yl)-2,6-dimethoxybenzamide (**5d**)*

Yield: 50 %; mp: 84–86 °C; IR (KBr) cm^{-1}: 1688 (CO, Amide), 1758 (CO, β-lactam), 2941 (NH); ^{1}H-NMR ($CDCl_3$) δ 3.62, 3.77, 3.84 (OMe, s, 12H), 4.86 (H-3, dd, 1H, $J = 1.97, 5.4$), 5.44 (H-2, d, 1H, $J = 1.82$), 6.38–7.70 (ArH, m, 10H), 8.18 (NH, d, $J = 8.65$); ^{13}C-NMR ($CDCl_3$) δ 55.48, 55.55, 56.07 (4 OCH_3), 66.34 (C-3), 66.66 (C-4), 98.76–157.69 (aromatic carbons), 158.87 (CO, amide), 163.30 (CO, β-lactam); Anal. calcd. for $C_{26}H_{25}N_3O_8$: C, 61.53; H, 4.97; N, 8.28. Found: C, 59.72; H, 5.16; N, 8.05.

Results and discussion

Schiff bases **1a-p** were prepared from dimethoxyanilines and substituted bezaldehydes in refluxing ethanol. Then

Table 1 Synthesis of 2-azetidinones **3a-y**

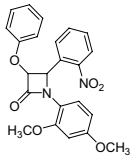
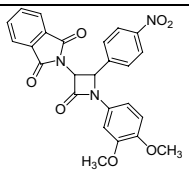
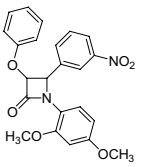
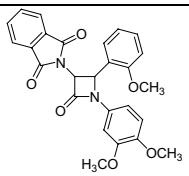
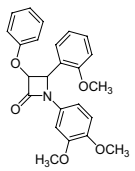
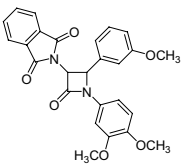
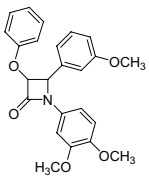
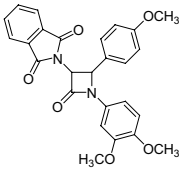
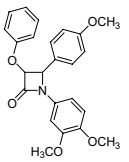
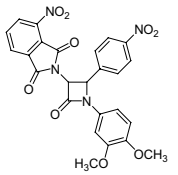
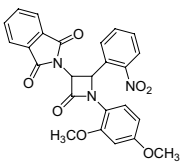
β-lactam	Structure	Yield (%)[a] *cis/trans* (%)	β-lactam	Structure	Yield (%)[a] *cis/trans* (%)
3a		65 (100:0)	**3n**[b]		65 (0:100)
3b		80 (100:0)	**3o**		60 (0:100)
3c[b]		79 (100:0)	**3p**		75 (50:50)
3d[b]		45 (100:0)	**3q**[b]		60 (0:100)
3e[b]		75 (100:0)	**3r**		85 (0:100)
3f		50 (100:0)	**3s**		25 (0:100)
3g[b]		20 (100:0)	**3t**		50 (60:40)

a mixture of Schiff base, triethylamine, substituted acetic acid **2** and tosyl chloride in dry CH_2Cl_2 was stirred at room temperature for 24 h to give 2-azetidinones **3a-y** (Table 1) by the ketene–imine [2+2] cycloaddition reaction (Staudinger reaction) (Scheme 1) [12–18].

TLC monitoring confirmed the presence of the expected new products and the structures of the cycloadducts have been additionally characterized by spectral analyses. For example, the IR spectrum of compound **3a** indicated a characteristic absorption band of a β-lactam carbonyl moiety at 1751 cm^{-1}.

The ^{1}H-NMR spectrum of **3a** exhibited the signals of the methoxy protons as two singlets at 3.76 and 3.80 ppm, the β-lactam ring protons H-3 and H-4 as two doublets at

Table 1 continued

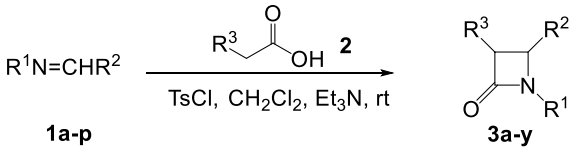
β-lactam	Structure	Yield (%)[a]	β-lactam	Structure	Yield (%)[a]
3h[b]		80 (100:0)	**3u**[b]		58 (100:0)
3i		80 (100:0)	**3v**		45 (0:100)
3j		77 (100:0)	**3w**		70 (0:100)
3k		65 (100:0)	**3x**[b]		80 (0:100)
3l[b]		50 (100:0)	**3y**		80 (70:30)
3m		85 (0:100)			

6.08, 5.62 and aromatic protons as multiplets at 6.44–8.16. Furthermore, the ^{13}C-NMR spectrum exhibited the C-3, and C-4 (β-lactam ring) at 82.14, 68.12 and the β-lactam carbonyl at 163.37. The stereochemistries of these 2-azetidinones were either *cis* or *trans* due to the coupling constants of H-3 and H-4 of the β-lactam ring. The *cis* geometry was assigned for the coupling constants larger than 3 Hz and the *trans* geometry for those lower than 3 Hz [19]. The monocyclic β-lactams, **3a-e**, **3h**, **3j-l, 3u**, **were** obtained as *cis* isomer, whereas derivatives 3**m, 3n**, **3o**, **3q-r** and **3v-x**, were isolated as *trans* isomer and 3**p**, **3t and** 3**y** as a mixture of *cis* and *trans* isomers. On the other hand, 3-phthalimido β-lactams **3n, 3r** and **3p** were converted to 3-amido-2-azetidinones **5a-c** by the procedure outlined in Scheme 2 [20].

Moreover, **3o** was converted into 3-amido β-lactam **5d** as shown in Scheme 3 [21]. In these reactions, the free 3-amino azetidin-2-ones reacted with 2,6-dimethoxybenzoic acid in the presence of tosyl chloride as acid activator at room temperature to afford the amido β-lactam.

Antimalarial activity of β-lactams 3a-x

Low to excellent antimalarial activities have been obtained against chloroquine-resistant *p. falciparum* K14 strain as outlined in Table 2 for all derivatives with IC_{50} varying from



1a-p 3a-y

3a R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 2-NO$_2$C$_6$H$_4$, R^3 = PhO

3b R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 3-NO$_2$C$_6$H$_4$, R^3 = PhO

3c R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 4-NO$_2$C$_6$H$_4$, R^3 = PhO

3d R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 3,4-DiMeOC$_6$H$_3$, R^3 = PhO

3e R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 3,4-DiMeOC$_6$H$_3$, R^3 = PhO

3f R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 2-MeOC$_6$H$_4$, R^3 = PhO

3g R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 3-MeOC$_6$H$_3$, R^3 = PhO

3h R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 2-NO$_2$C$_6$H$_4$, R^3 = PhO

3i R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 3-NO$_2$C$_6$H$_4$, R^3 = PhO

3j R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 2-MeOC$_6$H$_4$, R^3 = PhO

3k R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 3-MeOC$_6$H$_4$, R^3 = PhO

3l R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 4-MeOC$_6$H$_4$, R^3 = PhO

3m = R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 2-NO$_2$C$_6$H$_4$, R^3 = PhthN

3n = R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 3-NO$_2$C$_6$H$_4$, R^3 = PhthN

3o = R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 4-NO$_2$C$_6$H$_4$, R^3 = PhthN

3p = R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 2-MeOC$_6$H$_4$, R^3 = PhthN

3q = R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 3-MeOC$_6$H$_4$, R^3 = PhthN

3r = R^1 = 2,4-DiMeOC$_6$H$_3$, R^2 = 4-MeOC$_6$H$_4$, R^3 = PhthN

3s = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 2-NO$_2$C$_6$H$_4$, R^3 = PhthN

3t = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 3-NO$_2$C$_6$H$_4$, R^3 = PhthN

3u = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 4-NO$_2$C$_6$H$_4$, R^3 = PhthN

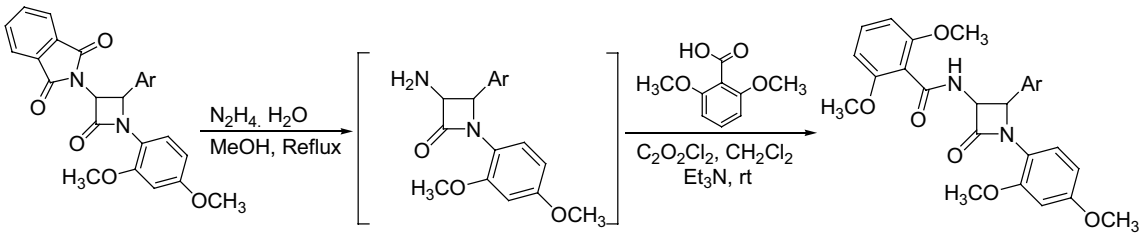
3v = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 2-MeOC$_6$H$_4$, R^3 = PhthN

3w = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 3-MeOC$_6$H$_4$, R^3 = PhthN

3x = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 4-MeOC$_6$H$_4$, R^3 = PhthN

3y = R^1 = 3,4-DiMeOC$_6$H$_3$, R^2 = 4-NO$_2$C$_6$H$_4$, R^3 = 3-NO$_2$PhthN

Scheme 1 Synthesis of β-lactams **3a-y**



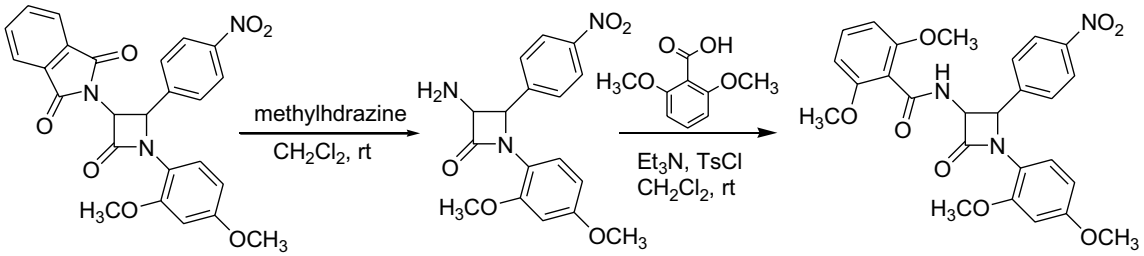
3n, 3p, 3r **4a-c** **5a-c**

5a: Ar = 3-NO$_2$C$_6$H$_4$ (15%)
5b: Ar = 2-MeOC$_6$H$_4$ (30%)
5c: Ar = 4-MeOC$_6$H$_4$ (20%)

Scheme 2 Synthesis of 3-amido β-lactams **5a-c**

5 to up to 50 μM. It is also noteworthy that the best derivatives **3c** and **3i** present a phenoxy group attached to the lactam moiety, whereas their corresponding parent derivatives **3t** and **3u** bearing a 1H-isoindole-1,3(2H)-dione are poorly active suggesting closely structure activity relationships.

Moreover, **3a** and **3b** isomers of compound 3**c** differing only by the position (ortho, meta) of the nitro group are quite low active. On the other hand, parent derivative **3l** of **3c** remains quite interesting since the replacement of a nitro group by a methoxy moiety led to an IC_{50} of 25 μM. In conclusion, a strong influence of the structure of the considered lactam derivative on the mechanism of action is underlined suggesting the importance of the phenoxy moiety and the position of aromatic substituents. Nevertheless, it is actually difficult to conclude on such weak differences since the target of these derivatives remains unknown.



3o **4d** **5d**

Scheme 3 Synthesis of 3-amido β-lactam **5d**

Table 2 Antimalarial activity of compounds **3a-x** against chloroquine-resistant *p. falciparum* K14 strain

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
3a	42	**3m**	31.5
3b	29	**3n**	40
3c	5.25	**3o**	>50
3d	30	**3p**	36.5
3e	36.5	**3q**	46
3f	24.11	**3r**	>50
3g	26.71	**3s**	45
3h	21	**3t**	>50
3i	13.25	**3u**	>50
3j	50	**3v**	28
3k	28.59	**3w**	47
3l	25	**3x**	>50

In conclusion, these new β-lactam derivatives are easily prepared and appear as new potent antimalarial agents. Works are now under process to investigate their biological mechanism of action and will be reported in due course.

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