



Facile synthesis of 3-(1-(4'-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene)indolin-2-ones and 3-(1-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)-5-oxo-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene)indolin-2-ones: β -Lactam derivatives as antimicrobes

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ABSTRACT

A facile synthesis of β -lactam derivatives; 3-(1-(4'-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene)indolin-2-ones (**6a-e**) and 3-(1-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)-5-oxo-2-phenyl-1*H*-imidazol-4(5*H*)-ylidene)indolin-2-ones (**7a-e**) is described herein. The title compounds **6a-e** and **7a-e** were evaluated for their in vitro antimicrobial activity against *Candida albicans* and *Bacillus subtilis* respectively using a two fold serial dilution technique. Investigation revealed that 2-hydroxy phenyl function at β -lactam ring in compounds **6d** and **7d** is a key factor for both antifungal and antibacterial activity, as newly designed compounds **6d** and **7d** exhibited good biological activity with minimum inhibitory concentration (MIC) 12.5 μ g/mL against *Candida albicans* and *Bacillus subtilis* respectively.

1. Introduction

Antimicrobial drugs are effective in the treatment of infections because of their selective toxicity-the ability to kill an invading microorganism without harming the cells of the host. In most instances, the selective toxicity is relative rather than absolute, requiring the concentration of the drug be carefully controlled to attack the microorganism while still being tolerated by the host [1].

Azoles are widely used and studied class of antimicrobials due to their safety profile and high therapeutic index. Among these, Conazolones are a major class of azole based drugs such as Itraconazole, Fluconazole, Voriconazole, Ravuconazole etc. [2-5]. It is also known that members of azole class of antimycotic drugs possess antibacterial properties against some gram positive bacteria [6-7]. Clotrimazole and Econazole have been shown to be effective against *Mycobacterium smegmatis* and *Streptomyces* strains in vitro [8].

During the past decade, imidazole derivatives have occupied a unique place in the field of medicinal chemistry. They have a wide range of biological activities. They are well known analgesics, anti-inflammatory, antiparasitic, antihelminthic, platelet aggregation inhibitors and antiepileptic agents [9-14].

With this view, the present study was designed to evaluate the antimicrobial activity of some new 2'-phenyl-4'-[3'-(2''-oxo-1''*H*-indolidene)-5'-oxo-imidazolyl]-1'-[*p*-1(4-aryl-1-biphenyl)] / 4-aryl-3-chloro azetidinones (**6a-e** and **7a-d**) consisting of

three well established pharmacologically active nuclei-imidazole, azole, and β -lactam [15-19] ring in one molecular union (Scheme 1).

Compounds **6a-e** and **7a-e** were characterized by spectral data and were screened in vitro against clinically isolated strains of *Candida albicans* and *Bacillus subtilis*, following two fold serial dilution technique as recommended by the National Committee for Clinical Laboratory Standard (NCCLS) [20-21].

2. Experimental

2.1. Instrumentation

All the melting points were determined in open capillary tube and are uncorrected. The nitrogen analysis was carried out on CARLO-ERBA EA 1108 elemental analyzer. Homogeneity of the compounds was checked by thin layer chromatography (TLC) using TLC grade silica gel (G) and was developed in an atmosphere of iodine vapors. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer using KBr pellets. ¹H and ¹³C spectra were recorded in CDCl₃ using TMS as an internal standard on a Bruker 200 MHz NMR spectrophotometer respectively. The splitting pattern abbreviations in NMR are as follows: s, singlet; d, doublet; t, triplet; br, broad; m, unresolved multiplet due to the strength of the instrument. Mass spectra were recorded on a Agilent 6520 Mass Spectrometer.

2.2. Synthesis

2.2.1. 4-((2-Oxoindolin-3-ylidene)methyl)-2-phenyloxazol-5(4H)-one (1)

A mixture of isatin (0.03 moles), hippuric acid (0.03 moles), acetic anhydride (20 mL) and anhydrous sodium acetate (0.03 moles) was stirred mechanically for one hour and then refluxed on a water bath for two hours. Subsequently, ethanol (100 mL) was added, and the reaction mixture allowed to stand overnight. A yellow solid which separated out, was filtered off and washed successively with cold water. It was recrystallized from benzene. Yield: 85%. M.p.: 281 °C.

2.2.2. 3-(1-(4'-Amino biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (2)

A mixture of 1 (0.05 mole) and 1,1-diphenyl-4,4-diamine (0.05 mole) in anhydrous pyridine (50 mL) was heated under reflux on a sand bath for 6 hours under anhydrous reaction condition. Subsequently, the reaction mixture was poured in an ice cold water hydrochloric acid solution (100 mL, 2 N). A solid precipitated. It was filtered off and washed with water. After drying in vacuum, it was recrystallized from ethanol (Scheme 1). Yield: 80%. M.p.: 186 °C. FT-IR (KBr, cm⁻¹): 3375-3410 ν(-NH) (amino of benzidine), 3127 ν(N-H) (sec. amide), 3028-3007 ν(Ar-H) (aromatic), 1756 ν(C=O) (sec. amide), 1654 ν(C=N) (imidazole), 1642 ν(C=O) (tertiary amide), 1410 ν(C-N) (imidazole). ¹H NMR (200 MHz, CDCl₃): 5.3 (s, 2H, NH₂), 7.14-7.58 (m, 17H, Ar-H), 7.64 (brs, 1H, CONH). ¹³C NMR (25 MHz, CDCl₃): 175 (1C, carbonyl of indolidene), 169.8 (1C, C-4 of imidazole), 165 (1C, C-2 of imidazole), 142.3 (1C, C-5 of imidazole), 140.8 (1C, C-1 of indolidene), 110, 119.5, 119.7, 122.4, 123.6, 124.1, 128.3, 128.5, 128.6, 128.7, 128.9, 129.2, 129.3, 129.5, 129.6, 129.7, 130.1, 130.4, 133.7, 135.8, 136.5, 138.4, 138.9, 140.2 (24C, Ar-C). ESI-MS (M+1): 456. Anal. Calcd. for C₂₉H₂₀N₄O₂: C, 76.31; H, 4.39; N 12.28. Found: C, 75.69; H, 4.50; N, 12.25%.

2.2.3. 3-((1-Amino-5-oxo-2-phenyl-4,5-dihydro-1H-imidazol-4-yl)methylene)indolin-2-one (3)

A mixture of 1 (0.02 mole) and hydrazine hydrate (0.025 mole) in ethanol (50 mL) was heated under reflux for 4 hours. Ethanol was distilled off and the residual solid thus obtained was washed with water. It was dried with the help of a dryer and recrystallized from dilute methanol as yellow crystals (Scheme 1). Yield: 85%. M.p.: 214 °C. FT-IR (KBr, cm⁻¹): 3400-3485 ν(-NH) (amino), 3130ν(NH) (sec. amide), 3019-3012 ν(Ar-H) (aromatic), 1777 ν(C=O) (sec. amide), 1651 ν(C=O) (tertiary amide), 1647 ν(C=N) (imidazole), 1421 ν(C-N) (imidazole). ¹H NMR (200 MHz, CDCl₃): 4.96 (s, 2H, NH₂), 7.39-7.65 (m, 9H, Ar-H), 7.47 (brs, 1H, CONH). ¹³C NMR (25 MHz, CDCl₃): 170 (1C, C-2 of indolidene), 167.5 (1C, C-5 of imidazole), 144.3 (1C, C-2 of imidazole), 140 (1C, C-4 of imidazole), 135.9 (1C, C-3 of indolidene), 110.2, 122.8, 123.9, 124.3, 128.3, 128.8, 128.9, 130.9, 131.6, 131.7, 133.0, 141.2 (12C, Ar-C). ESI-MS (M+1): 304. Anal. Calc. for C₁₇H₁₂N₄O₂: C, 67.10; H, 3.95; N, 18.42. Found: C, 66.94; H, 4.02; N, 18.38%.

2.2.4. 3-(1-(4'-(Substituted benzylideneamino)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones (4a-e) and 3-(1-(Substituted benzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones (5a-e).

A mixture of imidazole 2/3 (0.02 mole); an appropriate aldehyde (0.02 mole) and acetic acid (1 mL) in absolute alcohol (30 mL), was refluxed for about 8-10 hours. Excess of solvent was removed under pressure. The solid thus obtained,

was washed with cold water and recrystallized from methanol (Scheme 1).

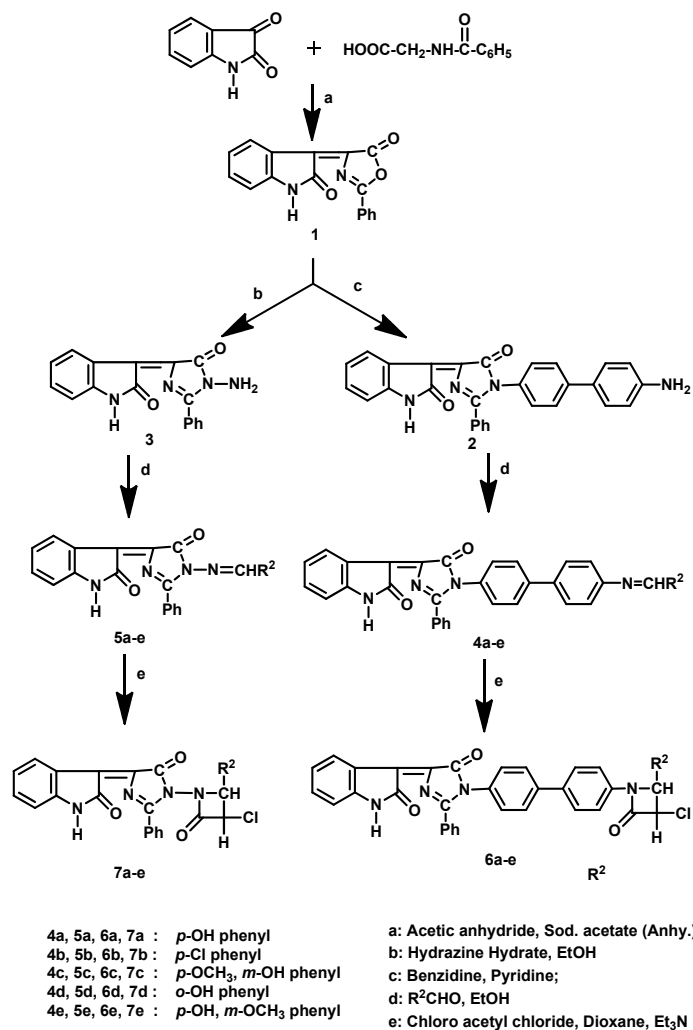
3-(1-(4'-(4-hydroxybenzylideneamino)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (4a): R²= *p*-Hydroxyphenyl: Yield: 70%. M.p.: 226 °C. FT-IR (KBr, cm⁻¹): 3607 ν(OH) (para hydroxyl phenyl), 1769 ν(C=O) (sec. amide), 1670 ν(C=O) (tert. amide), 1635 ν(C=N) (imidazole), 1660 ν(C-N) (imidazole). ¹H NMR (200 MHz, CDCl₃): 4.93 (s, 1H, Ar-OH), 7.18-7.66 (m, 21H, Ar-H), 7.97 (brs, 1H, CONH), 8.65 (s, 1H, N=CH-R). ¹³C NMR (25 MHz, CDCl₃): 168.8, 169.4 (2C, C-5 of imidazole, C-2 of indolidene), 163.7 (1C, C-2 of imidazole), 160.1 (1C, N=CHR²), 139.9, 141.2 (2C, C-4 of imidazole, C-3 of indolidene), 116, 122.8, 123.7, 124.0, 126.7, 127.2, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.2, 129.4, 129.5, 129.7, 129.8, 129.9, 130.3, 130.5, 130.8, 131.1, 134.9, 135.3, 135.8, 138.6, 138.9, 142.5, 144.5 (30C, Ar-C). ESI-MS (M+1): 561. Anal. Calcd. for C₃₆H₂₄N₄O₃: C, 77.14; H, 4.28; N, 10.00. Found: C, 77.10; H, 4.18; N, 9.97%.

3-(1-(4'-(4-chlorobenzylideneamino)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (4b): R²= *p*-Chlorophenyl: Yield: 75%. M.p.: 217 °C. FT-IR (KBr, cm⁻¹): 3365 ν(N-H) (sec. amide), 3010 ν(Ar-H) (aromatic), 1680 ν(C=O) (sec. amide), 1658 ν(N=C) (imidazole), 1650 ν(C=O) (tertiary amide), 690 ν(Ar-Cl) (para substitution). ¹H NMR (200 MHz, CDCl₃): 7.11-7.82 (m, 21H, Ar-H), 7.63 (brs, 1H, CONH), 8.76 (s, 1H, N=CH-R). ¹³C NMR (25 MHz, CDCl₃): 169.6, 171 (2C, C-5 of imidazole, C-2 of indolidene), 164 (C-2 of imidazole), 160.1 (N=CHR²), 137.8, 138.4 (2C, C-4 of imidazole, C-3 of indolidene), 113.8, 121.8, 122.2, 123.1, 127.3, 127.6, 127.8, 127.9, 128.2, 128.5, 128.7, 128.8, 129.0, 129.3, 129.4, 129.6, 129.7, 130.1, 130.4, 130.7, 131.4, 133.9, 134.5, 135.7, 136.2, 136.6, 138.8, 139.0, 139.3, 139.9 (30C, Ar-C). ESI-MS (M+1): 580. Anal. Calcd. for C₃₆H₂₃N₄O₂Cl: C, 74.68; H, 3.98; N, 9.66%. Found: C, 74.68; H, 3.90; N, 9.66%.

3-(1-(4'-(3-hydroxy-4-methoxybenzylideneamino)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (4c): R²= 3-OH, 4-OCH₃-phenyl: Yield: 80%. M.p.: 142 °C. FT-IR (KBr, cm⁻¹): 3523 ν(OH) (3-hydroxy phenyl), 3256 ν(N-H) (sec. amide), 3070 ν(Ar-H) (aromatic), 1672 ν(C=O) (sec. amide), 1649 ν(N=C) (imidazole), 1638 ν(C=O) (tertiary amide). ¹H NMR (200 MHz, CDCl₃): 3.83(-OCH₃), 7.11-7.82 (m, 20H, Ar-H), 7.29 (brs, 1H, CONH), 8.51 (s, 1H, N=CH-R). ¹³C NMR (25 MHz, CDCl₃): 168.4, 168.9 (2C, C-5 of imidazole, C-2 of indolidene), 163.7 (1C, C-2 of imidazole), 159.8 (1C, N=CHR²), 136.1, 137.5 (2C, C-4 of imidazole, C-3 of indolidene), 114.4, 115.9, 116.4, 121.9, 122.2, 123.0, 125.5, 126.9, 127.2, 128.0, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 129.3, 129.6, 130.0, 130.5, 131.7, 132.7, 132.9, 133.2, 133.5, 134.2, 135.6, 135.8, 135.9 (30C, Ar-C), 55.8 (1C, -OCH₃). ESI-MS (M+1): 591. Anal. Calcd. for C₃₇H₂₆N₄O₄: C, 75.25; H, 4.41; N, 9.49. Found: C, 75.21; H, 4.39; N, 9.45%.

3-(1-(4'-(2-hydroxybenzylideneamino)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (4d): R²= *o*-Hydroxyphenyl: Yield: 70%. M.p.: 220 °C. FT-IR (KBr, cm⁻¹): 3373 ν(N-H) (sec. amide), 3056 ν(Ar-H) (aromatic), 3589 ν(Ar-OH), 1677 ν(C=O) (sec. amide), 1643 ν(N=C), 1632 ν(C=O) (tertiary amide). ¹H NMR (200 MHz, CDCl₃): 6.59 (brs, 1H, CONH), 7.06-8.74 (m, 21H, Ar-H), 8.39 (s, 1H, N=CH-R), 10.26 (s, 1H, OH, exchangeable). ¹³C NMR (25 MHz, CDCl₃): 168.9, 169.4 (2C, C-5 of imidazole, C-2 of indolidene), 162.4 (1C, C-2 of imidazole), 160.3 (1C, N=CHR²), 134.9, 135.2 (2C, C-4 of imidazole, C-3 of indolidene), 110.2, 116.8, 120.5, 121.3, 122.4, 122.7, 123.9, 126.9, 127.5, 127.9, 128.1, 128.3, 128.5, 128.6, 128.8, 129.2, 129.4, 129.5, 129.6, 129.8, 130.4, 132.1, 132.5, 135.2, 136.7, 139.3, 139.7, 141.3, 151.0, 161.1 (30C, Ar-C). ESI-MS (M+1): 561. Anal. Calcd. for C₃₆H₂₄N₄O₃: C, 77.14; H, 4.28; N, 10.00. Found: C, 77.00; H, 4.26; N, 9.97%.

3-(1-(4'-(4-hydroxy-3-methoxy-benzylideneamino)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (4e): R²= 4-OH, 3-OCH₃-phenyl: Yield: 77%. M.p.: 214 °C. FT-IR



Scheme 1

(KBr, cm⁻¹): 3610 v (OH) (aromatic), 3369 v (N-H) (sec. amide), 3022 v (C-H) (aromatic), 1668 v (C=O) (sec. amide), 1653 v (N=C) (imidazole), 1645 v (C=O) (tertiary amide). ¹H NMR (200 MHz, CDCl₃): 3.62 (-OCH₃), 6.96-7.77 (m, 20H, Ar-H), 7.89 (brs, 1H, CONH), 8.41 (s, 1H, N=CH-R). ¹³C NMR (25 MHz, CDCl₃): 168.2, 169 (2C, C-5 of imidazole, C-2 of indolidene), 163.6 (1C, C-2 of imidazole), 159.9 (1C, N=CHR²), 115, 115.6, 115.9, 122.3, 122.5, 123.3, 125.4, 127.4, 127.7, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.2, 129.5, 129.6, 130.0, 130.3, 130.8, 131.6, 133.6, 133.8, 136.3, 136.7, 138.5, 139.2, 140.9, 141.4 (30C, Ar-C), 134.9, 135.7 (2C, C-4 of imidazole, C-3 of indolidene), 55.6 (1C, -OCH₃). ESI-MS (M+1): 591. Anal. Calc. for C₃₇H₂₆N₄O₄: C, 75.25; H, 4.41; N, 9.49. Found: C, 75.23; H, 4.46; N, 9.47%.

3-(1-(4-hydroxybenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (5a): R²= *p*-Hydroxy phenyl: Yield: 80%. M.p.: 251 °C. FT-IR (KBr, cm⁻¹): 3412 v(N-H) (sec. amide), 3020 v(Ar-H) (aromatic), 1718 v(C=O) (sec. amide), 1693 v(C=O) (tertiary amide), 1635 v(C=N) (imidazole), 1175 v(C-O stretch) (*p*-hydroxy phenyl). ¹H NMR (200 MHz, CDCl₃): 4.73 (s, 1H, Ar-OH), 7.12-7.66 (m, 13H, Ar-H), 7.92 (brs, 1H, CONH), 8.79 (s, 1H, N=CH-R). ¹³C NMR (25 MHz, CDCl₃): 170.3, 171 (2C, C-5 of imidazole, C-2 of indolidene), 164 (1C, C-2 of imidazole), 154.1 (1C, N=CHR²),

139.8, 140.1 (2C, C-4 of imidazole, C-3 of indolidene), 110.2, 122.5, 123.5, 124.7, 128.3, 128.4, 128.6, 128.7, 128.9, 129.1, 129.4, 129.6, 129.7, 129.9, 130.6, 131.4, 133.8, 141.4 (18C, Ar-C). ESI-MS (M+1): 409. Anal. Calcd. for C₂₄H₁₆N₄O₃: C, 70.59; H, 3.92; N, 13.72. Found: C, 70.61; H, 3.40; N, 13.69%.

3-(1-(4-chlorobenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (5b): R²= *p*-Chlorophenyl: Yield: 70%. M.p.: 220 °C. FT-IR (KBr, cm⁻¹): 3325 v(N-H) (sec. amide), 3090 v(Ar-H) (aromatic), 1670 v(N=C) (imidazole), 1664 v(C=O) (sec. amide), 1633 v(C=O) (tertiary amide), 655 v(Ar-Cl) (*p*-chlorophenyl). ¹H NMR (200 MHz, CDCl₃): 7.32-7.55 (m, 13H, Ar-H), 7.52 (brs, 1H, CONH), 8.33 (s, 1H, N=CH-R). ¹³C NMR (25 MHz, CDCl₃): 168.4, 169.1 (2C, C-5 of imidazole, C-2 of indolidene), 162.7 (1C, C-2 of imidazole), 153 (1C, N=CHR²), 138.5, 138.9 (2C, C-4 of imidazole, C-3 of indolidene), 111, 122.4, 123.5, 124.2, 128.4, 128.6, 128.8, 128.9, 129.0, 129.3, 129.4, 129.5, 130.2, 130.5, 130.7, 131.4, 136.2, 139.8 (18C, Ar-C). ESI-MS (M+1): 428. Anal. Calcd. for C₂₄H₁₅N₄O₂Cl: C, 67.53; H, 3.52; N, 13.14. Found: C, 67.51; H, 3.49; N, 13.12%.

3-(1-(3-hydroxy-4-methoxybenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (5c): R²= 3-OH, 4-OCH₃-phenyl: Yield: 80% M.p.: 283 °C. FT-IR (KBr, cm⁻¹): 3422 v(N-H) (sec. amide), 3085 v(Ar-H) (aromatic), 1676

$\nu(\text{N}=\text{C})$ (imidazole), 1672 $\nu(\text{C}=\text{O})$ (sec. amide), 1648 $\nu(\text{C}=\text{O})$ (tertiary amide). ^1H NMR (200 MHz, CDCl_3): 7.40 (brs, 1 H, CONH), 7.43-7.61 (m, 12H, Ar-H), 8.26 (s, 1H, N=CHR). ^{13}C NMR (25 MHz, CDCl_3): 166.9, 168 (2C, C-5 of imidazole, C-2 of indolidene), 160.7 (1C, C-2 of imidazole), 152.8 (1C, N=CHR²), 137.8, 138.2 (2C, C-4 of imidazole, C-3 of indolidene), 121.0, 121.1, 121.3, 122.7, 122.9, 123.3, 124.1, 128.0, 128.3, 128.4, 128.6, 128.7, 128.8, 129.1, 130.4, 133.7, 135.5, 139.5 (18C, Ar-C). ESI-MS (M+1): 439. Anal. Calcd. for $\text{C}_{25}\text{H}_{18}\text{N}_4\text{O}_4$: C, 68.49; H, 4.11; N, 12.78. Found: C, 68.00; H, 4.00; N, 12.74%.

3-(1-(2-hydroxybenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (5d): R²= *o*-Hydroxyphenyl: Yield: 68% M.p.: 218 °C. FT-IR (KBr, cm^{-1}): 3325 $\nu(\text{N-H})$ (sec. amide), 3090 $\nu(\text{Ar-H})$ (aromatic), 1670 $\nu(\text{N}=\text{C})$ (imidazole), 1664 $\nu(\text{C}=\text{O})$ (sec. amide), 1633 $\nu(\text{C}=\text{O})$ (tertiary amide). ^1H NMR (200 MHz, CDCl_3): 7.38-7.64 (m, 13H, Ar-H), 7.53 (br s, 1 H, CONH), 8.32 (s, 1H, N=CHR). ^{13}C NMR (25 MHz, CDCl_3): 168.1, 168.5 (2C, C-5 of imidazole, C-2 of indolidene), 162.5 (1C, C-2 of imidazole), 153.3 (1C, N=CHR²), 138.4, 139.4 (2C, C-4 of imidazole, C-3 of indolidene), 115.0, 117.5, 118.2, 121.5, 122.4, 123.3, 124.6, 127.6, 128.1, 128.3, 128.4, 128.6, 128.7, 128.8, 129.9, 132.2, 139.4, 140.0 (18C, Ar-C). ESI-MS (M+1): 409. Anal. Calcd. for $\text{C}_{24}\text{H}_{16}\text{N}_4\text{O}_3$: C, 70.59; H, 4.11; N, 13.72. Found: C, 70.60; H, 3.80; N, 13.68%.

3-(1-(4-hydroxy-3-methoxybenzylideneamino)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (5e): R²= 4-OH, 3-OCH₃-phenyl: Yield: 72%. M.p.: 200 °C. FT-IR (KBr, cm^{-1}): 3437 $\nu(\text{N-H})$ (sec. amide), 3079 $\nu(\text{Ar-H})$ (aromatic), 1682 $\nu(\text{N}=\text{C})$ (imidazole), 1675 $\nu(\text{C}=\text{O})$ (sec. amide), 1668 $\nu(\text{C}=\text{O})$ (tertiary amide). ^1H NMR (200 MHz, CDCl_3): 7.41 (br s, 1 H, CONH), 7.49-7.73 (m, 12H, Ar-H), 8.22 (s, 1H, N=CHR). ^{13}C NMR (25 MHz, CDCl_3): 167.4, 168 (2C, C-5 of imidazole, C-2 of indolidene), 161 (1C, C-2 of imidazole), 152.6 (1C, N=CHR²), 137.7, 138.1 (2C, C-4 of imidazole, C-3 of indolidene), 120.8, 120.9, 121.0, 122.4, 122.7, 123.6, 124.1, 127.9, 128.2, 128.4, 128.5, 128.7, 128.8, 129.8, 130.2, 136.3, 136.5, 138.9 (18C, Ar-C). ESI-MS (M+1): 439. Anal. Calcd. for $\text{C}_{25}\text{H}_{18}\text{N}_4\text{O}_4$: C, 68.49; H, 4.02; N, 12.78. Found: C, 68.10; H, 4.05; N, 12.71%.

2.2.5. 3-(1-(4'-(3-Chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones (6a-e) and 3-(1-(3-Chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones (7a-e).

In a solution of compound 4, or 5, (0.01 mole) in dioxan (50 mL) was added chloroacetyl chloride (0.01 mol) and triethylamine (0.01 mol) at 0 °C with stirring. The reaction mixture was left at room temperature for 3 hours, and then refluxed for 10 hours. Excess of solvent was distilled off and the residue was poured onto crushed ice. The solid that separated was collected by filtration and recrystallized from diluted ethanol (Scheme 1).

3-(1-(4'-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (6a): R²= *p*-Hydroxyphenyl: Yield: 85%. M.p.: 202 °C. FT-IR (KBr, cm^{-1}): 3422 $\nu(\text{N-H})$ (indole), 3030 $\nu(\text{Ar-H})$ (aromatic), 1730 $\nu(\text{C}=\text{O})$ (monocyclic β -lactam), 1715 $\nu(>\text{C}=\text{O})$ (sec. amide), 1695 $\nu(>\text{C}=\text{O})$ (tertiary amide), 1645 $\nu(\text{C}=\text{N})$ (imidazole), 1180 $\nu(\text{C-O str})$ (*p*-hydroxyphenyl), 761 $\nu(\text{C-Cl})$ (β -lactam). ^1H NMR (200 MHz, CDCl_3): 4.96 (d, 1H, N-CH-R of β -lactam, $J=8.2$ Hz), 5.19 (s, 1H, Ar-OH), 5.45 (d, 1H, -CHCl, $J=7.1$ Hz), 7.15-7.76 (m, 21H, Ar-H), 8.32 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl_3): 62.5 (1C, CH of β -lactam), 64.4 (1C, CHCl of β -lactam), 110.2, 120.0, 121.5, 121.7, 122.6, 123.2, 125.8, 126.4, 126.9, 128.2, 128.7, 128.9, 129.3, 129.8, 129.9, 130.4, 130.7, 131.5, 131.9, 132.1, 132.3, 132.6, 133.8, 135.7, 136.6, 140.6, 141.8, 142.6, 154.2, 156.5 (30C, Ar-C), 138.6, 139.5 (2C, C-4 of imidazole, C-3 of indolidene), 163.5 (1C, C=O of beta-lactam), 164.7 (1C, C-2 of imidazole), 169.3, 170 (2C, C-5 of imidazole, C-

2 of indolidene). ESI-MS (M+1): 637. Anal. Calcd. for $\text{C}_{38}\text{H}_{25}\text{N}_4\text{O}_4\text{Cl}$: C, 71.64; H, 3.93; N, 8.80. Found: C, 68.10; H, 4.03; N, 8.77%.

3-(1-(4'-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (6b): R²= *p*-Chlorophenyl: Yield: 74%. M.p.: 185 °C. FT-IR (KBr, cm^{-1}): 3395 $\nu(\text{N-H})$ (indole), 3010-3025 $\nu(\text{Ar-H})$ (aromatic), 1790 $\nu(\text{C}=\text{O})$ (sec. amide), 1729 $\nu(>\text{C}=\text{O})$ (monocyclic β -lactam), 1673 $\nu(\text{C}=\text{O})$ (tertiary amide), 1615 $\nu(\text{C}=\text{N})$ (imidazole), 1235 $\nu(\text{C-N})$ (β -lactam), 760 $\nu(\text{C-Cl})$ (β -lactam). ^1H NMR (200 MHz, CDCl_3): 5.02 (d, 1H, N-CH-R of β -lactam, $J=8.6$ Hz), 7.11-5.40 (d, 1H, -CHCl, $J=7.5$ Hz), 7.98-7.72 (m, 21H, Ar-H), 8.25 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl_3): 62.3 (1C, CH of beta-lactam), 64.7 (1C, CHCl of β -lactam), 121, 122.8, 123.8, 124.2, 124.8, 125.0, 127.3, 127.6, 127.8, 128.6, 128.7, 128.9, 129.0, 129.1, 129.6, 129.7, 130.3, 130.6, 130.9, 131.3, 131.4, 131.7, 132.6, 135.7, 137.5, 142.4, 143.4, 144.2, 147.0, 149.3 (30C, Ar-C), 138.9, 139.5 (2C, C-4 of imidazole, C-3 of indolidene), 164.9 (1C, C-2 of imidazole), 165.3 (1C, C=O of beta-lactam), 170.11, 171.5 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 655. Anal. Calcd. for $\text{C}_{38}\text{H}_{24}\text{N}_4\text{O}_3\text{Cl}_2$: C, 69.62; H, 3.66; N, 8.84. Found: C, 69.67; H, 3.49; N, 8.81%.

3-(1-(4'-(3-chloro-2-(3-hydroxy-4-methoxyphenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (6c): R²= 3-OH, 4-OCH₃-phenyl: Yield: 72%. M.p.: 127 °C. FT-IR (KBr, cm^{-1}): 3445 $\nu(\text{N-H})$ (indole), 3415 $\nu(\text{OH})$ (3-hydroxyphenyl), 3019 $\nu(\text{Ar-H})$ (aromatic), 1734 $\nu(>\text{C}=\text{O})$ (monocyclic β -lactam), 1690 $\nu(\text{OCH}_3)$ (*p*-methoxyphenyl), 1681 $\nu(\text{C}=\text{O})$ (sec. amide), 1665 $\nu(\text{C}=\text{O})$ (tertiary amide), 759 $\nu(\text{C-Cl})$ (β -lactam). ^1H NMR (200 MHz, CDCl_3): 3.39 (s, 3H, Ar-OCH₃), 4.91 (s, 1H, Ar-OH), 4.96 (d, 1H, N-CH-R of β -lactam, $J=8.2$ Hz), 5.42 (d, 1H, -CHCl, $J=6.95$ Hz), 7.09-7.69 (m, 20H, Ar-H), 8.19 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl_3): 60.9 (1C, CH of beta-lactam), 63.7 (1C, CHCl of beta-lactam), 119.6, 119.8, 119.9, 120.0, 121.4, 122.8, 123.6, 124.1, 124.8, 127.9, 128.2, 128.6, 128.8, 129.2, 129.3, 129.7, 130.0, 130.5, 131.5, 131.8, 132.3, 132.7, 133.6, 135.6, 136.8, 139.2, 139.7, 140.2, 140.9, 141.2 (30C, Ar-C), 137.2, 138.6 (2C, C-4 of imidazole, C-3 of indolidene), 164.5 (1C, C=O of beta-lactam), 168.3 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 668. Anal. Calcd. for $\text{C}_{39}\text{H}_{27}\text{N}_4\text{O}_5\text{Cl}$: C, 70.22; H, 4.05; N, 8.40. Found: C, 70.09; H, 4.15; N, 8.29%.

3-(1-(4'-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (6d): R²= *o*-Hydroxyphenyl: Yield: 68%. M.p.: 195 °C. FT-IR (KBr, cm^{-1}): 3583 $\nu(\text{OH})$ (*o*-hydroxyphenyl), 3389 $\nu(\text{N-H})$ (indole), 3000 $\nu(\text{Ar-H})$ (aromatic), 1728 $\nu(>\text{C}=\text{O})$ (monocyclic β -lactam), 1669 $\nu(\text{C}=\text{O})$ (sec. amide), 1656 $\nu(\text{C}=\text{O})$ (tertiary amide), 770 $\nu(\text{C-Cl})$ (β -lactam). ^1H NMR (200 MHz, CDCl_3): 4.97 (d, 1H, N-CH-R of β -lactam, $J=8.0$ Hz), 5.40 (d, 1H, -CHCl, $J=7.1$ Hz), 7.49-7.63 (m, 21H, Ar-H), 8.29 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl_3): 62.1 (1C, CH of beta-lactam), 64.3 (1C, CHCl of beta-lactam), 126.4, 126.5, 126.6, 126.7, 126.8, 127.2, 127.5, 127.6, 128.2, 128.6, 128.8, 129.0, 129.3, 130.1, 130.4, 130.9, 131.4, 132.2, 132.4, 132.6, 132.9, 134.5, 136.9, 137.5, 140.1, 142.2, 142.7, 144.8, 149.6, 150.8 (30C, Ar-C), 138.3, 138.9 (2C, C-4 of imidazole, C-3 of indolidene), 165.6 (1C, C=O of beta-lactam), 169.9, 171.2 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 637. Anal. Calcd. for $\text{C}_{38}\text{H}_{25}\text{N}_4\text{O}_4\text{Cl}$: C, 71.64; H, 3.51; N, 8.80. Found: C, 71.71; H, 3.45; N, 8.78%.

3-(1-(4'-(3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (6e): R²= 4-OH, 3-OCH₃-phenyl: Yield: 68%. M.p.: 154 °C. FT-IR (KBr, cm^{-1}): 3514 $\nu(\text{OH})$ (*p*-hydroxyphenyl), 3438 $\nu(\text{N-H})$ (indole), 3011 $\nu(\text{Ar-H})$ (aromatic), 1676 $\nu(\text{C}=\text{O})$ (sec. amide), 1661 $\nu(\text{C}=\text{O})$ (tertiary amide), 1731 $\nu(>\text{C}=\text{O})$ (monocyclic β -lactam), 1686 $\nu(\text{OCH}_3)$ (*p*-methoxyphenyl), 763 $\nu(\text{C-Cl})$ (β -lactam). ^1H NMR (200 MHz, CDCl_3): 4.92 (d, 1H, N-CH-R of β -lactam, $J=8.0$ Hz), 5.46 (d, 1H, -

CHCl, $J=6.8$ Hz), 7.16-7.83 (m, 20H, Ar-H), 8.13 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl₃): 61.2 (1C, CH of beta-lactam), 63.6 (1C, CHCl of beta-lactam), 120.3, 120.5, 120.6, 120.8, 122.1, 122.3, 123.2, 123.9, 124.3, 127.9, 128.5, 128.6, 128.7, 128.8, 129.0, 129.6, 130.0, 130.3, 131.1, 131.5, 132.1, 136.1, 136.4, 136.8, 137.2, 139.3, 140.4, 140.6, 141.8, 144.7 (30C, Ar-C), 137.6, 138.1 (2C, C-4 of imidazole, C-3 of indolidene), 164.2 (1C, C=O of beta-lactam), 168.4, 169.3 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 667. Anal. Calcd. for C₃₉H₂₇N₄O₅Cl: C, 70.22; H, 4.05; N, 8.40. Found: C, 70.30; H, 4.10; N, 8.37%.

3-(1-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetid-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (**7a**): R²= *p*-Hydroxyphenyl: Yield: 60%. M.p.: 229 °C. FT-IR (KBr, cm⁻¹): 3345 ν(N-H) (indole), 3360 ν(OH) (*p*-hydroxyphenyl), 3015 ν(Ar-H) (aromatic), 1729 ν(>C=O) (monocyclic β-lactam), 1684 ν(C=O) (sec. amide), 1655 ν(C=O) (tertiary amide), 1649 ν(C=N) (imidazole), 768 ν(C-Cl) (β-lactam). ^1H NMR (200 MHz, CDCl₃): 4.78 (s, 1H, Ar-OH), 4.88 (d, 1H, N-CH-R of β-lactam, $J=7.9$ Hz), 5.39 (d, 1H, -CHCl, $J=7.1$ Hz), 7.71-7.89 (m, 13H, Ar-H). ^{13}C NMR (25 MHz, CDCl₃): 60.3 (1C, CH of beta-lactam), 64.1 (1C, CHCl of beta-lactam), 110, 114.5, 119.6, 122.3, 124.9, 125.9, 127.9, 128.4, 128.5, 129.6, 130.3, 130.5, 131.1, 131.4, 132.1, 133.9, 154.4, 155.0 (18C, Ar-C), 139.6, 140.6 (2C, C-4 of imidazole, C-3 of indolidene), 144.9 (1C, C-2 of imidazole), 163.8 (1C, C=O of beta-lactam), 168, 168.9 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 485. Anal. Calcd. for C₂₆H₁₇N₄O₄Cl: C, 64.39; H, 3.69; N, 11.57. Found: C, 64.45; H, 3.51; N, 11.55%.

3-(1-(3-chloro-2-(4-chlorophenyl)-4-oxoazetid-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (**7b**): R²= *p*-Chlorophenyl: Yield: 60%. M.p.: 218 °C. FT-IR (KBr, cm⁻¹): 3385 ν(N-H) (indole), 2985 ν(Ar-H) (aromatic), 1733 ν(>C=O) (monocyclic β-lactam), 1689 ν(C=O) (sec. amide), 1675 ν(C=O) (tertiary amide), 1632 ν(C=N) (imidazole), 765 ν(C-Cl) (β-lactam). ^1H NMR (200 MHz, CDCl₃): 5.02 (d, 1H, N-CH-R of β-lactam, $J=8.7$ Hz), 5.44 (d, 1H, -CHCl, $J=7.1$ Hz), 7.19-7.69 (m, 13H, Ar-H), 8.49 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl₃): 60.9 (1C, CH of beta-lactam), 64.5 (1C, CHCl of beta-lactam), 121, 122.3, 122.6, 123.0, 125.2, 126.6, 126.8, 128.3, 128.8, 129.4, 129.7, 129.9, 130.2, 130.4, 130.5, 134.2, 157.6, 158.1 (18C, Ar-C), 140.6, 141.1 (2C, C-4 of imidazole, C-3 of indolidene), 145.3 (1C, C-2 of imidazole), 164.1 (1C, C=O of beta-lactam), 169.9, 171.3 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 503. Anal. Calcd. for C₂₆H₁₆N₄O₃Cl₂: C, 62.03; H, 3.51; N, 11.15. Found: C, 61.98; H, 3.45; N, 11.11%.

3-(1-(3-chloro-2-(3-hydroxy-4-methoxyphenyl)-4-oxoazetid-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (**7c**): R²= 3-OH, 4-OCH₃-phenyl: Yield: 55%. M.p.: 252 °C. FT-IR (KBr, cm⁻¹): 3352 ν(N-H) (indole), 3022 ν(Ar-H) (aromatic), 1716 ν(>C=O) (monocyclic β-lactam), 1670 ν(C=O) (sec. amide), 1658 ν(C=O) (tertiary amide), 1640 ν(C=N) (imidazole), 760 ν(C-Cl) (β-lactam). ^1H NMR (200 MHz, CDCl₃): 3.25 (s, 3H, Ar-OCH₃), 4.95 (s, 1H-Ar-OH), 5.05 (d, 1H, N-CH-R of β-lactam, $J=8.7$ Hz), 7.25-5.45 (d, 1H, -CHCl, $J=7.9$ Hz), 7.85 (m, 12H, Ar-H), 7.88 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl₃): 60.1 (1C, CH of beta-lactam), 63.8 (1C, CHCl of beta-lactam), 119, 119.6, 120.4, 122.1, 125.8, 126.3, 126.9, 128.0, 128.6, 128.9, 129.0, 129.3, 130.3, 130.8, 130.9, 133.7, 146.9, 149.8 (18C, Ar-C), 139.6, 141.2 (2C, C-4 of imidazole, C-3 of indolidene), 144.5 (1C, C-2 of imidazole), 163.6 (1C, C=O of beta-lactam), 169.4, 170.6 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 516. Anal. Calcd. for C₂₇H₁₉N₄O₅Cl: C, 62.97; H, 3.69; N, 10.89. Found: C, 62.85; H, 3.72; N, 10.86%.

3-(1-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetid-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (**7d**): R²= *o*-Hydroxyphenyl: Yield: 68%. M.p.: 249 °C. FT-IR (KBr, cm⁻¹): 3290 ν(N-H) (indole), 3007 ν(Ar-H) (aromatic), 1727 ν(>C=O)

(monocyclic β-lactam), 1663 ν(C=O) (sec. amide), 1649 ν(C=O) (tertiary amide), 1632 ν(C=N) (imidazole), 758 ν(C-Cl) (β-lactam). ^1H NMR (200 MHz, CDCl₃): 4.81 (s, 1H-Ar-OH), 5.42 (d, 1H, -CHCl, $J=7.1$ Hz), 4.99 (d, 1H, N-CH-R of β-lactam, $J=8.4$ Hz), 7.23-7.95 (m, 13H, Ar-H), 8.02 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl₃): 60.3 (1C, CH of beta-lactam), 63.6 (1C, CHCl of beta-lactam), 120.6, 123.5, 123.7, 124.2, 125.6, 125.8, 125.9, 128.2, 129.2, 129.8, 130.1, 130.7, 131.5, 131.7, 132.2, 133.4, 151.6, 152.6 (18C, Ar-C), 139.4, 140.3 (2C, C-4 of imidazole, C-3 of indolidene), 144.2 (1C, C-2 of imidazole), 163.2 (1C, C=O of beta-lactam), 169.1, 170.4 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 486. Anal. Calcd. for C₂₆H₁₇N₄O₄Cl: C, 64.39; H, 3.51; N, 11.57. Found: C, 64.29; H, 3.48; N, 11.53%.

3-(1-(3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetid-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-one (**7e**): R²= 4-OH, 3-OCH₃-phenyl: Yield: 71%. M.p.: 191 °C. FT-IR (KBr, cm⁻¹): 3333 ν(N-H) (indole), 3100 ν(Ar-H) (aromatic), 1717 ν(>C=O) (monocyclic β-lactam), 1666 ν(C=O) (sec. amide), 1660 ν(C=O) (tertiary amide), 1646 ν(C=N) (imidazole), 767 ν(C-Cl) (β-lactam). ^1H NMR (200 MHz, CDCl₃): 3.16 (s, 3H, Ar-OCH₃), 4.43 (s, 1H-Ar-OH), 4.64 (d, 1H, N-CH-R of β-lactam, $J=8.9$ Hz), 7.08-4.99 (d, 1H, -CHCl, $J=8.5$ Hz), 7.60 (m, 12H, Ar-H), 7.71 (brs, 1H, CONH). ^{13}C NMR (25 MHz, CDCl₃): 61.4 (1C, CH of beta-lactam), 64.1 (1C, CHCl of beta-lactam), 119, 122.7, 123.1, 124.2, 126.3, 126.7, 126.8, 128.4, 128.7, 129.1, 129.2, 129.4, 129.5, 129.6, 131, 133.5, 149, 153.5 (18C, Ar-C), 140.7, 141.5 (2C, C-4 of imidazole, C-3 of indolidene), 145 (1C, C-2 of imidazole), 165.7 (1C, C=O of beta-lactam), 170.2, 171.8 (2C, C-5 of imidazole, C-2 of indolidene). ESI-MS (M+1): 515. Anal. Calcd. for C₂₇H₁₉N₄O₅Cl: C, 62.97; H, 3.69; N, 10.89. Found: C, 62.78; H, 3.65; N, 10.80%.

3. Results and discussion

The starting material 2-phenyl-4-(2'-oxo-1'H-3'-indolidene)-1,3-oxazol-5-one (**1**) was prepared by the reaction between isatin, hippuric acid and acetic acid in presence of sodium acetate. The oxazolone **1** on reaction with 1,1-diphenyl-4,4-diamine or hydrazine hydrate in pyridine produced **2** and **3** in moderate yields, respectively. The structure of **2** and **3** has been confirmed by their spectral data. The ^1H NMR spectrum of **2** and **3** showed a broad singlet integrating for two protons at δ 5.30 and δ 4.96 due to -NH₂ group. The IR spectrum of these compounds exhibited two absorption bands due to symmetric and asymmetric stretching frequencies of primary amine between 3375-3425 cm⁻¹ and another band at 3127 and 3130 cm⁻¹ due to >NH absorptions, respectively. The two other bands at 1410 and 1421 cm⁻¹ due to -C-N< were also observed. Compounds **2** and **3** were then subjected to condensation with appropriate aromatic aldehydes in alcohol to give **4a-e** and **5a-e**. These compounds were purified with column chromatography and the yields mentioned are of the major isolable fractions which were characterized by different spectroscopic techniques. The title compounds, 3-(1-(4'-(3-chloro-2-(substituted phenyl)-4-oxoazetid-1-yl)biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones (**6a-e**) and 3-(1-(3-chloro-2-(substituted phenyl)-4-oxoazetid-1-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones (**7a-e**), were obtained by the treatment of **4a-e** and **5a-e** with chloroacetyl chloride in dioxane in presence of triethylamine and were found to have *cis* geometry [22-23]. IR and ^1H NMR spectra of these compounds were well in agreement with the structures assigned.

Out of all tested compounds **6a-e** and **7a-e**, which were screened against *Candida albicans* and *B. subtilis*, as summarized in Table 1, compound **6d** was found to possess interesting antifungal activity (MIC 12.5 μg/mL). The compound contains an ortho hydroxy phenyl function at β-

lactam ring. Similarly, compound **7d** was found to show reasonable degree of antibacterial activity against *Bacillus subtilis* with an MIC value of 12.5 µg/mL, also bears an ortho hydroxyl phenyl function at β-lactam ring.

Table 1. Antimicrobial activities (MIC µg/mL) of compounds **6a-e** and **7a-e**.

Compound	<i>C. albicans</i>	<i>B. subtilis</i>
6a	>100	50
6b	25	50
6c	25	>100
6d	12.5	25
6e	>100	25
7a	50	>100
7b	25	25
7c	>100	50
7d	25	12.5
7e	>100	>100

Based on current findings, it may be suggested that 2-hydroxy phenyl function at β-lactam ring is a key factor for both antifungal and antibacterial activity. Interestingly, when hydroxyl group was substituted at para position the antimicrobial activity was lost. This clearly suggests that the position of the substituent has a greater role than the nature of the substituent or alternatively it seems that an ortho-hydroxyl substituent finds comparatively a better fit at the receptor site than a para-hydroxyl substituent. The loss of activity in other compounds could be explained by the contention that the change in the position of the substituent in the molecules has rendered them inactive.

4. Conclusion

This report comprises a simple synthesis of β-lactam derivatives without protection of other functional group in good yields. In the course of our study for seeking β-lactam derivatives as antimicrobial agents, we found compounds that possessed well in vitro activities against *Bacillus subtilis* and *Candida albicans*. Biological screening data provide a new lead for further structure function studies of compounds. We are currently exploring modifications at this key position to obtain β-lactam with promising antimicrobial activity.

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