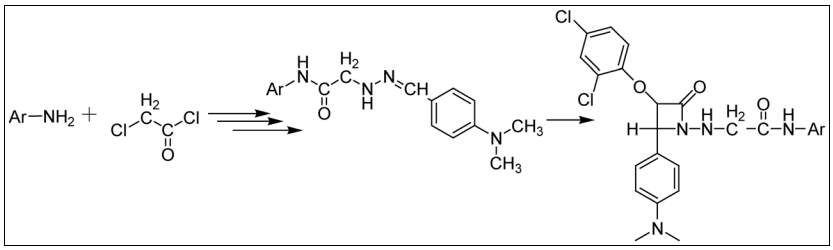
Synthesis and Antimicrobial Evaluation of New Monocyclic β-Lactams

Ramakanth Pagadala,[a] Jyotsna S. Meshram,[a]* Himani N. Chopde,[a] Venkateshwarlu Jetti,[a] Praveen Chidurala,[a] and Uppalaiah Kusampally[b]

[a]Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur-440 033, Maharashtra, India
[b]Department of Chemistry, Osmania University, Hyderabad-500 007, Andhrapradesh, India
*E-mail: drjsmeshram@rediffmail.com

Received December 11, 2010
DOI 10.1002/jhet.973
Published online 26 October 2012 in Wiley Online Library (wileyonlinelibrary.com).



A simple, practical, and efficient approach to synthesize new series of 2-(3-(2,4-dichlorophenoxy)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-ylamino)-*N*-arylacetamide by Staudinger [2 + 2] cycloaddition reaction. The titled compounds were evaluated for their antibacterial and antifungal activity against eight microorganisms. All the newly synthesized compounds are characterized by IR, ^{1}H-NMR, and mass spectroscopic data.

J. Heterocyclic Chem., **49**, 1151 (2012).

INTRODUCTION

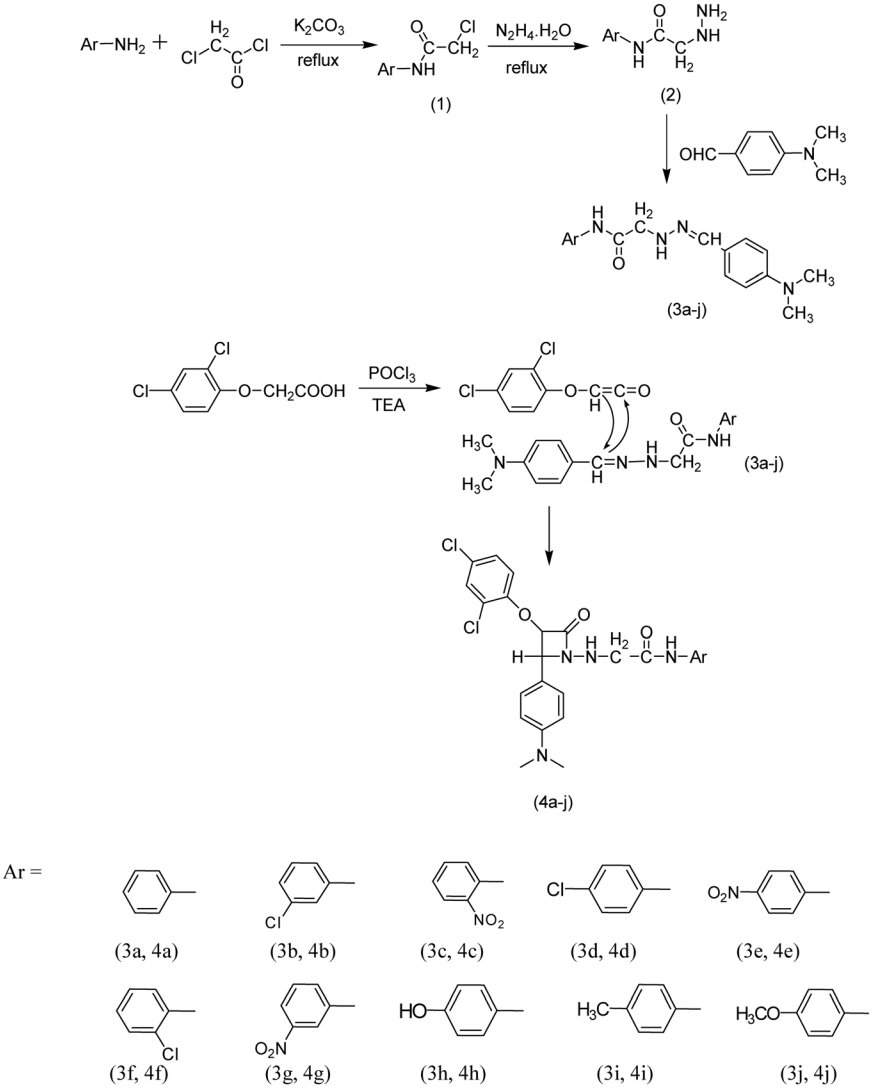
In the past few years, there is an increasing interest in the research area of four-membered heterocycles, the effectiveness of β-lactam heterocycle in various important areas, within many fields of Science, including medicine, biology, and chemistry have been clearly demonstrated [1–7]. In addition to its use in the synthesis of variety of β-lactam antibiotics, the β-lactam skeleton has been recognized as a useful building block by exploiting its strain energy associated with four-member ring [8]. An interesting group of β-lactams are the monocyclic β-lactams, which are molecules that do not contain another ring fused to the β-lactam one. Natural and synthetic azetidinone derivatives occupy a central place among medicinally important compounds due to their diverse and interesting antibiotic activities [9]. Even though they have a long history of development starting from the discovery of Penicillin in 1928, the quest for new synthetic methods and refinement of those already known remains appealing, as does the research into the application of these methods in synthesizing novel biologically active azetidinone derivatives.

The chemistry of small-ring nitrogen heterocycles are of considerable interest not only because of their wide use as important synthetic intermediates but also because of their biological activities such as antibiotic properties. Among them, the four-membered azetidine series, especially azetidin-2-one, has gained enormous attention [10], so functionalization of the azetidin-2-one framework is pivotal for the development of new β-lactam antibiotics [11]. Researchers have shown some other useful biological activities of such compounds, for example, cholesterol absorption inhibition, enzymes inhibition, hypoglycemic, and anticancer activity [12]. Ezetimibe, a monocyclic 2-azetidinone, is clinically used as a cholesterol absorption inhibitor [13]. Because of such a versatile applications, these moieties always attracted the interest of synthetic and medicinal organic chemists [14]. Hence, with these observation, we examined the feasibility and efficiency of an approach to synthesize 2, 4-dichlorophenoxy and *N,N*-dimethylamino group coupled with azetidinone nucleus, which turns to exhibit significant antimicrobial activities.

RESULTS AND DISCUSSION

Chemistry. Preparation of new compounds **4a–j** is depicted on Scheme 1. Reaction course and formation of products were monitored by thin layer chromatography (TLC). 2-Chloro-*N*-arylacetamides (1) were synthesized by various aromatic amines with chloroacetyl chloride. The model reaction was carried out simply treatment of various aromatic amines with chloroacetyl chloride yielded 2-chloro-*N*-arylacetamide (**1**). These compounds, on amination with hydrazine hydrate afforded 2-hydrazinyl-*N*-arylacetamides

Scheme 1. Synthetic route for 2-(3-(2,4-dichlorophenoxy)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-ylamino)-*N*-arylacetamide.



(**2**). The condensation reaction of compound **2** with *N,N*-dimethylaminobenzaldehyde yielded 2-(2-(4-(dimethylamino) benzylidene)hydrazinyl)-*N*-arylacetamide (**3a–j**). Compounds **3a–j**, on reaction with 2,4-dichlorophenoxy acetic acid in the presence of $POCl_3$ and triethylamine afforded azetidinone (**4a–j**). These reactions are summarized in Scheme 1. The end of the reaction was monitored by TLC.

Biological activity. ***Biological screening.*** The synthesized compounds were screened by agar diffusion method [15, 16]. All human pathogenic bacteria *viz. Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Staphylococcus aureus* and fungi *viz. Aspergillus flavus* and *Aspergillus niger*, *Trichoderma viridae* were obtained from the Osmania University, Hyderabad, India. Stock solutions of compounds were diluted in dimethyl sulfoxide (DMSO) to give a final concentration for determining the minimum inhibitory concentration (MIC) value. MIC was defined as the lowest concentration of compound is required for a complete inhibition of the fungal and bacterial growth after incubation time. For antifungal activity, each fungus was spread on Sabouraud's dextrose agar plates. For antibacterial activity, Muller Hinton agar was used. The wells of 6 mm diameter were filled with 0.1 mL of each compound is diluted separately for each test of bacteria and fungi strain. The antibiotic ampicillin and nystatin are used as reference antibacterial and antifungal agents, respectively, for comparison. Inoculated plates were then incubated at 37°C for antibacterial activity for 24 h and 48 h at 28°C for antifungal activity. After incubation, the antimicrobial activity was measured in terms of the zone of inhibition in mm as shown in Table 1. Biological screening results were mentioned in mm, that is, showing diameter of inhibition zone, and these are categorized, as 0–5 mm for mild, 6–12 mm for moderate, and 13–17 mm for efficacy, respectively.

Antibacterial studies. From Table 1, the investigation of antibacterial screening data revealed that all the tested

Table 1

Antimicrobial activities of synthesized compounds.

	Bacteria (MIC at 100 μg/mL)							
	Gram positive			Gram negative		Fungi (MIC at 250 μg/mL)		
Compd.	A	B	C	D	E	F	G	H
4a	+++	+	++	++	+	−	+++	+
4b	−	++	++	+	++	−	++	++
4c	++	+++	+	++	+	+++	+	+++
4d	+	++	−	++	+++	++	−	−
4e	++	+	+++	+++	−	+	++	+
4f	−	+++	+++	++	+	++	−	++
4g	++	−	++	+++	++	++	+++	+
4h	+++	+++	−	+	++	+++	+	+++
4i	+	−	+	++	−	+	++	−
4j	++	+++	+++	++	++	++	+++	++
Ampicillin	+++	++	+++	+++	+++			
Nystatin						+++	+++	+++

Gram positive Bacteria: (A) *Bacillus subtilis*; (B) *Proteus vulgaris*; (C) *Staphylococcus aureus*; Gram negative Bacteria: (D) *Escherichia coli*; (E) *Klebsiella pneumonia*; Fungi: (F) *Aspergillus flavus*; (G) *Aspergillus niger*; (H) *Trichoderma viridae*; inactive = − (inhibition zone < 5 mm); slightly active = + (inhibition zone 5–12 mm); moderately active = ++ (inhibition zone 13–17 mm); highly active = +++ (inhibition zone > 17 mm).

compounds showed moderate to good bacterial inhibition. Compounds **4a** and **4h** active against *B. subtilis*, **4c**, **4f**, **4h**, and **4j** for *Proteus vulgaris*, **4e**, **4f**, and **4j** for *S. aureus*, **4e** and **4j** for *E. coli*, and **4d** for *K. pneumonia* showed very good activity almost equivalent to that of standard against all the bacterial strains. The rest of the compounds were found to be moderately active, slightly active or inactive against the tested microorganisms.

Antifungal studies. The antifungal activity of the compounds was studied with three pathogenic fungi. The results are summarized in Table 1. Nystatin has been used as reference for inhibitory activity against fungi. Compounds **4c** and **4h** for *Aspergillus flavus*, **4a**, **4g**, and **4j** for *Aspergillus niger*, **4c** and **4h** for *Trichoderma viridae* exhibited very good activity almost equivalent to that of standard drug. The rest of the compounds were found to be moderately active, slightly active or inactive against all the fungal strains.

EXPERIMENTAL

General. All the chemicals and solvents were used analytical reagent (AR) grade without further purification. Melting points were taken in an open capillary tube. IR spectra were recorded on a Shimadzu Dr-8031 instrument. ^{1}H-NMR spectra of the titled compounds were recorded on a Bruker-Avance (300 MHz) spectrophotometer using DMSO solvent and tetra methyl silane (TMS) as the internal standard. Elemental analyses were carried out using a PerkinElmer, CHN elemental analyzer model 2400. Electron impact mass spectrometer (EI-MS) spectra were determined on a liquid chromatography quadrupole (LCQ) ion trap mass spectrometer (Thermo Fisher, San Jose, CA), equipped with an electron ionization (EI) source. The reactions were monitored and the purity of products was checked out on precoated TLC plates (Silica gel 60 F254, Merck), visualized the spots under ultraviolet light and iodine chamber.

General procedure for the synthesis of Schiff base (3a-j). A quantity of 0.008 mol of *N,N*-dimethylaminobenzaldehyde, 0.008 mol of 2-hydrazinyl-*N*-arylacetamide (2), and two to three drops of glacial acetic acid in 20 mL of ethanol was refluxed for ~1 h. The reaction was monitored by TLC. After completion of the reaction, the residue was stirred with ice-cold water, filtered, and dried. The air which separates was induced to crystallize by rubbing with glass rod. Solid deposit was collected by filtration and the crude product obtained was purified by *n*-hexane and EtOAc.

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-phenylacetamide (3a). Yield 70%; IR (KBr, cm^{-1}): 3198 (NH), 1608 (CONH), 1552 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.49 (s, 1H, NH), 2.9 (s, 6H, —$N(CH_3)_2$), 3.7 (s, 2H, CH_2), 6.5–7.8 (m, 9H, Ar-H), 8.5 (s, 1H, CONH), 8.8 (s, 1H, —CH═N—); Elemental analysis: Calcd. (found): C, 68.89 (68.82); H, 6.80 (6.69); N, 18.90 (18.85); Mass spectra, *m/z* = 296 (100%).

N-(3-Chlorophenyl)-2-(2-(4-(dimethylamino) benzylidene)-hydrazinyl)acetamide (3b). Yield 75%; IR (KBr, cm^{-1}): 3379 (NH), 1647 (CONH), 1549 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.4 (s, 1H, NH), 2.94 (s, 6H, —$N(CH_3)_2$), 3.6 (s, 2H, CH_2), 6.5–7.6 (m, 8H, Ar-H), 8.2 (s, 1H, CONH), 8.5 (s, 1H, —CH═N—); Elemental analysis: Calcd. (found): C, 61.72 (61.75); H, 5.79 (5.67); N, 16.94 (16.91); Mass spectra, *m/z* = 330 (100%).

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-(2-nitrophenyl)acetamide (3c). Yield 77%; IR (KBr, cm^{-1}): 3317 (NH), 1678 (CONH), 1541 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) ═ 2.43 (s, 1H, NH), 2.89 (s, 6H, —$N(CH_3)_2$), 3.8 (s, 2H, CH_2), 6.7–7.9 (m, 8H, Ar-H), 8.0 (s, 1H, CONH), 8.4 (s, 1H, —CH═N—); Elemental analysis: Calcd. (found): C, 59.81 (59.72); H, 5.61 (5.49); N, 20.52 (20.45); Mass spectra, *m/z* = 341 (100%).

N-(4-Chlorophenyl)-2-(2-(4-(dimethylamino) benzylidene)-hydrazinyl)acetamide (3d). Yield 79%; IR (KBr, cm^{-1}): 3365 (NH), 1637 (CONH), 1521 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.41 (s, 1H, NH), 2.93 (s, 6H, —$N(CH_3)_2$), 3.4 (s, 2H, CH_2), 6.5–7.6 (m, 8H, Ar-H), 8.2 (s, 1H, CONH), 8.5 (s, 1H, —CH═N—); Elemental analysis: Calcd. (found): C, 61.72 (61.67); H, 5.79 (5.72); N, 16.94 (16.98); Mass spectra, *m/z* = 330 (100%).

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-(4-nitrophenyl)acetamide (3e). Yield 68%; IR (KBr, cm^{-1}): 3329 (NH), 1667 (CONH), 1545 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.43 (s, 1H, NH), 2.9 (s, 6H, —$N(CH_3)_2$), 3.7 (s, 2H, CH_2), 6.6–7.9 (m, 8H, Ar-H), 8.1 (s, 1H, CONH), 8.3 (s, 1H, —CH═N—); Mass spectra, *m/z* = 341 (100%).

N-(2-Chlorophenyl)-2-(2-(4-(dimethylamino) benzylidene)-hydrazinyl)acetamide (3f). Yield 72%; IR (KBr, cm^{-1}): 3372 (NH), 1644 (CONH), 1532 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.3 (s, 1H, NH), 2.92 (s, 6H, —$N(CH_3)_2$), 3.8 (s, 2H, CH_2), 6.5–7.6 (m, 8H, Ar-H), 8.4 (s, 1H, CONH), 8.7 (s, 1H, —CH═N—); Mass spectra, *m/z* = 330 (100%).

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-(3-nitrophenyl)acetamide (3g). Yield 70%; IR (KBr, cm^{-1}): 3324 (NH), 1656 (CONH), 1549 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.46 (s, 1H, NH), 2.87 (s, 6H, —$N(CH_3)_2$), 3.75 (s, 2H, CH_2), 6.5–7.9 (m, 8H, Ar-H), 8.1 (s, 1H, CONH), 8.4 (s, 1H, —CH═N—); Mass spectra, *m/z* = 341 (100%).

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-(4-hydroxyphenyl)acetamide (3h). Yield 75%; IR (KBr, cm^{-1}): 3368 (NH), 1666 (CONH), 1558 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.1 (s, 1H, NH), 2.85 (s, 6H, —$N(CH_3)_2$), 3.6 (s, 2H, CH_2), 6.5–7.5 (m, 8H, Ar-H), 8.2 (s, 1H, CONH), 8.3 (s, 1H, —CH═N—), 12.8 (s, 1H, —OH); Mass spectra, *m/z* = 312 (100%).

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-p-tolylacetamide (3i). Yield 75%; IR (KBr, cm^{-1}): 3342 (NH), 1652 (CONH), 1566 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.2 (s, 1H, NH), 2.54 (s, 3H, —CH_3), 2.88 (s, 6H, —$N(CH_3)_2$), 3.65 (s, 2H, CH_2), 6.5–7.6 (m, 8H, Ar-H), 7.9 (s, 1H, CONH), 8.5 (s, 1H, —CH═N—); Mass spectra, *m/z* = 310 (100%).

2-(2-(4-(Dimethylamino)benzylidene)hydrazinyl)-N-(4-methoxyphenyl)acetamide (3j). Yield 78%; IR (KBr, cm^{-1}): 3364 (NH), 1661 (CONH), 1558 (—CH═N—); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.26 (s, 1H, NH), 2.87 (s, 6H, —$N(CH_3)_2$), 3.63 (s, 2H, CH_2), 3.87 (s, 3H, —OCH_3), 6.5–7.6 (m, 8H, Ar-H), 8.2 (s, 1H, CONH), 8.5 (s, 1H, —CH═N—); Mass spectra, *m/z* = 326 (100%).

General procedure for the synthesis of 2-(3-(2,4-dichlorophenoxy)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-ylamino)-*N*-phenylacetamide (4a–j). The appropriate Schiff base (0.02 mol), 2,4-dichlorophenoxy acetic acid (0.02 mol), and triethylamine (0.05 mol) were stirred in anhydrous dichloromethane, while a solution of $POCl_3$ (0.02 mol) in dry dichloromethane was added dropwise. The reaction mixture was stirred for ~14 h. The completion of the reaction was monitored by TLC. The reaction mixture was washed with water and dried over sodium sulphate. The products that were obtained after removing the solvent were purified from ethyl acetate and *n*-hexane.

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-phenylacetamide (4a). Yield 68%; m.p. (°C): 145; IR (KBr, cm^{-1}): 3080 (NH), 1602 (CONH), 1732 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.8 (s, 6H, —$N(CH_3)_2$), 3.2 (s, 1H, NH), 3.6 (s, 2H, CH_2), 5.3 (d, 1H, *J* = 5.4 Hz, CH-Ar), 5.85 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–7.7 (m, 12H, Ar-H), 8.51 (s, 1H, CONH); Elemental analysis: Calcd. (found): C, 60.13 (60.05); H, 4.84 (4.69); N, 11.22 (11.30); Mass spectra, *m/z* = 498 (100%).

N-(3-Chlorophenyl)-2-(3-(2,4-dichlorophenoxy)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-ylamino) acetamide (4b). Yield 69%; m.p. (°C): 138; IR (KBr, cm^{-1}): 3184 (NH), 1662 (CONH), 1741 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.85 (s, 6H, —$N(CH_3)_2$), 3.1 (s, 1H, NH), 3.54 (s, 2H, CH_2), 5.5 (d, 1H, *J* = 5.5 Hz, CH-Ar), 5.83 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–7.8 (m, 11H, Ar-H), 8.4 (s, 1H, CONH); Elemental analysis: Calcd. (found): C, 56.25 (56.18); H, 4.34 (4.28); N, 10.50 (10.49); Mass spectra, *m/z* = 532 (100%).

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-(2-nitrophenyl) acetamide (4c). Yield 65%; m.p. (°C): 168; IR (KBr, cm^{-1}): 3263 (NH), 1670 (CONH), 1734 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.82 (s, 6H, —$N(CH_3)_2$), 3.3 (s, 1H, NH), 3.62 (s, 2H, CH_2), 5.2 (d, 1H, *J* = 5.5 Hz, CH-Ar), 5.78 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–8.0 (m, 11H, Ar-H), 8.6 (s, 1H, CONH); Elemental analysis: Calcd. (found): C, 55.16 (55.22); H, 4.26 (4.19); N, 12.86 (12.68); Mass spectra, *m/z* = 543 (100%).

N-(4-Chlorophenyl)-2-(3-(2,4-dichlorophenoxy)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-ylamino) acetamide (4d). Yield 69%; m.p. (°C): 132; IR (KBr, cm^{-1}): 3198 (NH), 1680 (CONH), 1732 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.87 (s, 6H, —$N(CH_3)_2$), 3.1 (s, 1H, NH), 3.59 (s, 2H, CH_2), 5.4 (d, 1H, *J* = 5.4 Hz, CH-Ar), 5.8 (d, 1H, *J* = 5.1 Hz, CH-OAr), 6.5–7.6 (m, 11H, Ar-H), 8.1 (s, 1H, CONH); Elemental analysis: Calcd. (found): C, 56.25 (56.12); H, 4.34 (4.38); N, 10.50 (10.43); Mass spectra, *m/z* = 532 (100%).

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-(4-nitrophenyl) acetamide (4e). Yield 66%; m.p. (°C): 156; IR (KBr, cm^{-1}): 3248 (NH), 1675 (CONH), 1738 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.85 (s, 6H, —$N(CH_3)_2$), 3.4 (s, 1H, NH), 3.65 (s, 2H, CH_2), 5.2 (d, 1H, *J* = 5.4 Hz, CH-Ar), 5.76 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–8.0 (m, 11H, Ar-H), 8.4 (s, 1H, CONH); Mass spectra, *m/z* = 543 (100%).

N-(2-Chlorophenyl)-2-(3-(2,4-dichlorophenoxy)-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-ylamino) acetamide (4f). Yield 70%; m.p. (°C): 140; IR (KBr, cm^{-1}): 3221 (NH), 1669 (CONH), 1742 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.86 (s, 6H, —$N(CH_3)_2$), 3.2 (s, 1H, NH), 3.56 (s, 2H, CH_2), 5.43 (d, 1H, *J* = 5.5 Hz, CH-Ar), 5.84 (d, 1H, *J* = 5.3 Hz, CH-OAr), 6.5–7.6 (m, 11H, Ar-H), 8.2 (s, 1H, CONH); Mass spectra, *m/z* = 532 (100%).

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-(3-nitrophenyl) acetamide (4g). Yield 64%; m.p. (°C): 160; IR (KBr, cm^{-1}): 3236 (NH), 1672 (CONH), 1733 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.87 (s, 6H, —$N(CH_3)_2$), 3.4 (s, 1H, NH), 3.63 (s, 2H, CH_2), 5.32 (d, 1H, *J* = 5.4 Hz, CH-Ar), 5.74 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–8.0 (m, 11H, Ar-H), 8.1 (s, 1H, CONH); Mass spectra, *m/z* = 543 (100%).

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-(4-hydroxyphenyl) acetamide (4h). Yield 69%; m.p. (°C): 126; IR (KBr, cm^{-1}): 3262 (NH), 1655 (CONH), 1750 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.85 (s, 6H, —$N(CH_3)_2$), 3.2 (s, 1H, NH), 3.6 (s, 2H, CH_2), 5.4 (d, 1H, *J* = 5.3 Hz, CH-Ar), 5.8 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–7.5 (m, 11H, Ar-H), 8.3 (s, 1H, CONH), 12.5 (s, 1H, —OH); Mass spectra, *m/z* = 514 (100%).

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-p-tolylacetamide (4i). Yield 65%; m.p. (°C): 130; IR (KBr, cm^{-1}): 3259 (NH), 1669 (CONH), 1748 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.48 (s, 3H, —CH_3), 2.86 (s, 6H, —$N(CH_3)_2$), 3.1 (s, 1H, NH), 3.72 (s, 2H, CH_2), 5.5 (d, 1H, *J* = 5.5 Hz, CH-Ar), 5.73 (d, 1H, *J* = 5.2 Hz, CH-OAr), 6.5–7.6 (m, 11H, Ar-H), 8.1 (s, 1H, CONH); Mass spectra, *m/z* = 512 (100%).

2-(3-(2,4-Dichlorophenoxy)-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-ylamino)-N-(4-methoxyphenyl) acetamide (4j). Yield 66%; m.p. (°C): 150; IR (KBr, cm^{-1}): 3260 (NH),

1654 (CONH), 1740 (CO, β-lactam); ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) = 2.82 (s, 6H, —$N(CH_3)_2$), 3.4 (s, 1H, NH), 3.69 (s, 2H, CH_2), 3.83 (s, 3H, —OCH_3), 5.28 (d, 1H, J = 5.4 Hz, CH-Ar), 5.68 (d, 1H, J = 5.2 Hz, CH-OAr), 6.4–7.7 (m, 11H, Ar-H), 8.0 (s, 1H, CONH); Mass spectra, m/z = 528 (100%).

CONCLUSIONS

In this article, we have reported a novel series of *N*-substituted azetidinone derivatives were prepared (**4a–j**) and screened their antibacterial activity against five strains of bacteria and antifungal activity against three strains of fungi. All selected penems (**4a–j**) showed superior anti bacterial activity almost equivalent to that of the standard drug. As far as the antifungal screening results are concerned of the compounds displayed good activity. Finally, the titled compounds could be identified as the most biologically active member within this study with an interesting antibacterial and antifungal profile. Consequently, *N*-substituted azetidinone derivatives represent a class that needs further investigation with the hope of finding new antimicrobial agents.

Acknowledgments. The authors are thankful to the Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, for providing the necessary research facilities. And also grateful Indian Institute of Chemical Technology (IICT), Hyderabad for the help in undertaking NMR, Mass spectra. Special thanks are due to the Head, Department of Botany, Osmania University, Hyderabad, for antimicrobial screening.

REFERENCES AND NOTES

[1] Bhalla, A.; Venugopalan, P.; Bhasin, K. K.; Bari, S. S. Tetrahedron 2007, 63, 3195.

[2] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Amino Acids 1999, 16, 321.

[3] Alcaide, B.; Almendros, P. Synlett 2002, 381.

[4] Alcaide, B.; Almendros, P. Chem Soc Rev 2001, 30, 226.

[5] Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. Synlett 2001, 1813.

[6] Ojima, I.; Delaloge, F. Chem Soc Rev 1997, 26, 377.

[7] Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. Heterocycles 1988, 27, 1755.

[8] (a) Manhas, M. S.; Amin, S. G.; Bose, A. K. Heterocycles 1976, 5, 669; (b) Ojima, I. Acc Chem Res 1995, 28, 383; (c) Srirajan, V.; Deshmukh, A. R. A. S.; Bhawal, B. M. Tetrahedron 1996, 52, 5585; (d) Srirajan, V.; Deshmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. Tetrahedron: Asymmetry 1996, 7, 2733; (e) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. Curr Med Chem 2004, 11, 1889; (f) Alcaide, B.; Almendros, P. Curr Med Chem 2004, 11, 1921.

[9] (a) Mukerjee, A. K.; Singh, A. K. Synthesis 1975, 547; (b) Singh, G. S.; Pandeya, S. N. J Chem Engg Data 1987, 32, 278; (c) Mukerjee, A. K.; Singh, A. K. Tetrahedron 1978, 34, 1731.

[10] Cromwell, N. H.; Philips, B. Chem Rev 1979, 79, 331.

[11] (a) Xu, J. ARKIVOC 2009, ix, 21; (b) Ojima, I. Adv Asym Synth 1995, 1, 95; (c) Alcaide, B.; Almendros, P. Org Prep Proc Int 2001, 33, 317; (d) Alcaide, B.; Almendros, P.; Aragonillo, C. Chem Rev 2007, 107, 4437; (e)Brandi, A.; Cicchi, S.; Cordero, F. M. Chem Rev 2008, 108, 3988.

[12] (a) Singh, G. S. Mini Rev Med Chem 2004, 4, 93; (b) Singh, G. S. Mini Rev Med Chem 2004, 4, 69.

[13] Clader, J. W. J Med Chem 2004, 47, 1.

[14] (a) Singh, G. S. Tetrahedron 2003, 59, 7631; (b) Brown, M. J. Heterocycles 1989, 29, 2225; (c) Isaacs, N. S. Chem Soc Rev 1976, 5, 181–189; (d) Mihovilovic, M. D.; Spina, M.; Stanetty, P. ARKIVOC 2005, v, 33; (e) Shirode, N. M.; Kulkarni, K. C.; Gumatse, V. K.; Deshmukh, A. R. A. S. ARKIVOC 2005, i, 53.

[15] Fairbrother, R. W.; Martyn, G. J Clin Pathol 1951, 4, 374.

[16] Gould, J. C.; Bowie, J. H. J Edinb Med 1952, 59, 178.