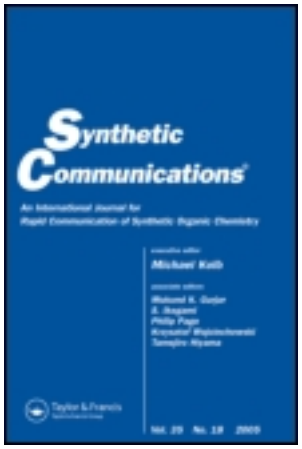

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SOME NOVEL OXADIAZOLYL/AZETIDINYL BENZIMIDAZOLE DERIVATIVES: SYNTHESIS AND IN VITRO BIOLOGICAL EVALUATION

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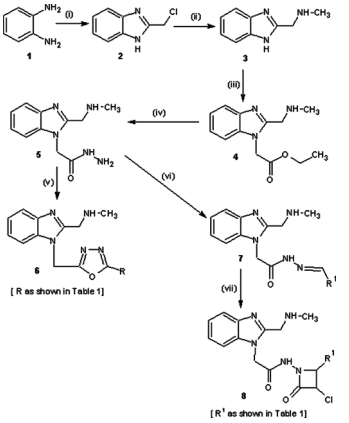
GRAPHICAL ABSTRACT



Abstract *In a wide search program for new and efficient antimicrobial agents, a series of oxadiazole/azetidinone-incorporated benzimidazoles have been synthesized and evaluated against different Gram-positive and Gram-negative bacteria. Derivatives having long alkyl chain on the oxadiazole/azetidinone moiety with three or more carbon atoms have shown less antibacterial activity.*

Keywords Antibacterial activity; azetidin-2-one; *Bacillus subtilis*; benzimidazole; *Escherichia coli*; oxadiazole; *Staphylococcus aureus*

INTRODUCTION

The emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world. Antimicrobial resistance refers

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to microorganisms that have developed the ability to inactivate, exclude, or block the inhibitory or lethal mechanism of the antimicrobial agents.[1] The incidence of antimicrobial resistance has been increasing over the past few decades. Data from the World Health Organization indicated that 50–90% of microbially caused conditions in India and Sri Lanka are resistant to commonly used antimicrobial drugs.[2] In the United States, about 70% of hospital-acquired infections were found to be resistant.[3] Although the judicious use of antibacterial agents is an important in approach to control the emergence of bacterial resistance, the discovery and development of newer agents are desirable for the successful treatment of infections caused by resistant pathogenic bacteria. The study of benzimidazole derivatives has become of much interest in recent years on account of their antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory activities.[4–12] 2-Azetidinones containing benzimidazole derivatives dramatically increase the diversity of certain biological properties such as antibacterial, antifungal, anti-inflammatory, and anthelmintic[13–16] and recently benzimidazole derivatives containing the 2-azetidinone moiety have been reported as antimicrobial agents.[17] In this article the oxadiazolyl and azetidinyl derivatives of benzimidazole have been synthesized by multistep reactions starting with o-phenylenediamine. The activities of these compounds were screened in vitro against the panel of standard Gram-positive and Gram-negative bacteria.

RESULTS AND DISCUSSION

Chemistry

In view of obtaining some potential antibacterial compounds, we have described the syntheses of some benzimidazole derivatives. The relevant step in the synthetic sequence was the initial condensation of o-phenylenediamine 1 with chloroacetic acid[18] to provide 2-(chloromethyl)-1H-benzimidazole **2** in sufficient yields. The subsequent condensation of **2** with alkylamine yielded 1-(1H-benzimidazol-2-yl)-N-methylmethanamine **3** in good yield. This was followed by the chloroacetylation to give ethyl {2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetate **4**. The key intermediate 2-{2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetohydrazide **5** was obtained by the hydrazinolysis of compound **4**. The intermediate **5** was subsequently reacting with appropriate long-chain carboxylic acid in phophoryl chloride to give the respective compounds **6a–l** in excellent yields. The target azetidinones **8a–l** were obtained by the condensation of **5a–l** with various selected aliphatic or aromatic aldehydes furnished Schiff's bases N'-[(1E)-alkylidene/arylidene]-2-{2-[(methylamino) methyl]-1H-benzimidazol-1-yl}acetohydrazide **7a–l** followed by the cycloaddition of **7a–l** with chloroacetyl chloride in the presence of triethylamine catalyst.

The structures of the compounds synthesized were confirmed by the examination of their ^{1}H NMR, ^{13}C NMR, mass spectral (MS), and infrared (IR) spectra. The ^{1}H NMR spectra of the investigated compounds revealed that the characteristic chemical shifts agreed with their proposed structures. The signals due to azetidinone ring protons appeared at about δ 3.70–3.79 ppm as multiplet, δ 5.05–5.10 as doublets (8a–g) and δ 5.00–5.46 as doublets (**8h–l**). Appearance of broad singlets within the range δ 2.0–2.6 ppm corresponds to the one proton of –NH– and confirms the formation of methanamine. The methylene group at position 2 of

2-(chloromethyl)-1H-benzimidazole ring appeared at about δ 4.26–4.32 as a singlet. With the help of ^{1}H NMR spectral data the stereochemistry of the β-lactam ring was observed as *cis*-form. The coupling constants of H-3 and H-4 are 3.1–6.7 Hz for β-lactam (**8a–l**) indicating their *cis*-stereochemistry.[19,20] All the aromatic protons were well separated and observed at the expected regions. The structures of synthesized compounds were further verified by EI-MS spectra (70 eV). The m/z values of molecular ion peaks were in complete agreement with calculated molecular weights for individual compounds. For all compounds investigated the IR spectra were recorded. The C=N groups of oxadiazole rings were observed within the range ν 1733–1716 cm^{-1}, C=O groups showed the vibration at ν 1662–1678 cm^{-1} whereas the aromatic moieties (C=C) appeared between ν 1599 and 1460 cm^{-1}.

Antibacterial Evaluation

The in vitro antibacterial activity was performed using the tube dilution method with different strains of bacteria. Ampicillin and nalidixic acid were used as positive control against bacteria.

Some of compounds **7a–k** and **8a–k** were tested in vitro against *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (MTCC 121), and *Escherichia coli* (ATCC 25922). Compounds **6a** and **6b** showed considerable bactericidal activities against Gram-positive bacteria. Compound **6b** showed significant activity against *S. aureus* but was less active against *B. subtilis*. Other compounds showed intermediate activities against *S. aureus* and *B. subtilis* but most of them were inactive against *E. coli*.

CONCLUSIONS

In conclusion, several benzimidazole derivatives were synthesized starting with o-phenylenediamine. The antibacterial study was undertaken to evaluate the effect of the synthesized compounds on different bacterial strains. As regards the structure–activity relationship of the derivatives, it can be inferred that oxadiazoles are more active than azetidinones. It is also noted that the alkyl side chain on 5-position of oxadiazole ring produced better resistance to bacterial strains than the substituted aryl group on the same position.

More extensive study is needed to confirm these preliminary results and studies involving the mechanism of action are necessary for a complete understanding of their antimicrobial activity and structural modifications on the final investigated compounds to improve their biological activity.

EXPERIMENTAL

All the chemicals and solvents were purchased from Merck (Germany) and were used without further purification. Melting points (mp) were determined in open capillaries and are uncorrected. The purity of the compounds was confirmed by thin-layer chromatography (TLC) performed on Merck silica-gel 60 F254 aluminium sheets, using developing system chloroform/acetone (9:1). Spots were detected by their absorption under ultraviolet (UV) light and by visualization with 10% HCl. Elemental analysis for C, H, and N were carried out by a micro method using the

Table 1. Physical and analytical data of the compounds **2–8**

Compound	R/R^1	Yield (%)	Mp (°C)	Mol. formula	Analysis (%) calculated (found)		
					C	H	N
2	—	82	160–162	$C_8H_7N_2Cl$ (166.60)	57.67 (57.65	4.23 4.21	16.81 16.80)
3	—	85	192–194	$C_9H_{11}N_3$ (161.20)	67.06 (67.05	6.88 6.86	26.072 6.05)
4	—	88	184–186	$C_{13}H_{17}N_3O_2$ (247.29)	63.14 (63.13	6.93 6.90	16.99 16.97)
5	—	79	195–197	$C_{11}H_{15}N_5O$ (233.26)	56.64 (56.62	6.48 6.46	30.02 30.00)
6a	CH_3-	84	201–203	$C_{13}H_{15}N_5O$ (257.29)	60.69 (60.67	5.88 5.87	27.22 27.20)
6b	CH_3CH_2-	81	208–210	$C_{14}H_{17}H_5O$ (271.31)	61.89 (61.87	6.32 6.30	25.81 25.78)
6c	$CH_3(CH_2)_2$-	76	215–217	$C_{15}H_{19}N_5O$ (285.34)	63.14 (63.12	6.71 6.70	24.54 24.52)
6d	$CH_3(CH_2)_3$-	87	220–222	$C_{16}H_{21}N_5O$ (299.37)	64.19 (64.17	7.07 7.05	23.39 23.37)
6e	$CH_3(CH_2)_4$-	78	241–243	$C_{17}H_{23}N_5O$ (313.39)	65.15 (65.14	7.40 7.38	22.35 22.33)
6f	$CH_3(CH_2)_5$-	80	254–256	$C_{18}H_{25}N_5O$ (327.42)	66.03 (66.01	7.70 7.68	21.39 21.37)
6g	$CH_3(CH_2)_6$-	77	280–282	$C_{19}H_{27}N_5O$ (341.45)	66.83 (66.81	7.97 7.96	20.51 20.48)
6h	C_6H_5-	84	198–100	$C_{18}H_{17}N_5O$ (319.36)	67.70 (67.68	5.37 5.35	21.93 21.91)
6i	$C_6H_5CH_3$-	88	183–185	$C_{19}H_{19}N_5O$ (333.38)	68.45 (68.43	5.74 5.72	21.01 21.00)
6j	$C_6H_5CH_3CH_2$-	72	178–180	$C_{20}H_{21}N_5O$ (347.41)	69.14 (69.12	6.09 6.07	20.16 20.14)
6k	$C_6H_5CH_3(CH_2)_2$-	71	184–186	$C_{21}H_{23}N_5O$ (361.44)	69.78 (69.76	6.41 6.39	19.381 9.36)
6l	$C_6H_5CH_3(CH_2)_3$-	75	188–190	$C_{22}H_{25}N_5O$ (375.46)	70.38 (70.37	6.71 6.70	18.65 18.63)
7a	CH_3-	84	232–234	$C_{13}H_{17}N_5O$ (259.30)	60.21 (60.20	6.61 6.59	27.01 26.98)
7b	CH_3CH_2-	74	249–251	$C_{14}H_{19}N_5O$ (273.33)	61.52 (61.50	7.01 7.00	25.62 25.60)
7c	$CH_3(CH_2)_2$-	85	260–262	$C_{15}H_{21}N_5O$ (287.36)	62.70 (62.69	7.37 7.35	24.37 24.35)
7d	$CH_3(CH_2)_3$-	73	273–275	$C_{16}H_{23}N_5O$ (301.38)	63.76 (63.73	7.69 7.68	23.24 23.21)
7e	$CH_3(CH_2)_4$-	71	279–281	$C_{17}H_{25}N_5O$ (315.41)	64.73 (64.72	7.99 7.97	22.20 (22.18)
7f	$CH_3(CH_2)_5$-	84	297–299	$C_{18}H_{27}N_5O$ (329.43)	65.62 (65.60	8.26 8.23	21.26 (21.23)
7g	$CH_3(CH_2)_6$-	81	302–304	$C_{19}H_{29}N_5O$ (343.46)	66.44 (66.41	8.51 8.50	20.39 (20.36)
7h	C_6H_5-	86	203–205	$C_{18}H_{19}N_5O$ (321.37)	67.27 (67.25	5.96 5.94	21.79 (21.77)
7i	$C_6H_5CH_3$-	70	201–203	$C_{19}H_{21}N_5O$ (335.40)	68.04 (68.02	6.31 6.29	20.88 20.86)

(*Continued*)

Table 1. Continued

Compound	R/R^1	Yield (%)	Mp (°C)	Mol. formula	Analysis (%) calculated (found) C	H	N
7j	$C_6H_5CH_3CH_2$-	79	215–217	$C_{20}H_{23}N_5O$ (349.42)	68.74 (68.72	6.63 6.60	20.04 20.01)
7k	$C_6H_5CH_3(CH_2)_2$-	80	230–232	$C_{21}H_{25}N_5O$ (363.45)	69.40 (69.38	6.93 6.91	19.27 19.25)
7l	$C_6H_5CH_3(CH_2)_3$-	85	246–248	$C_{22}H_{27}N_5O$ (377.48)	70.00 (69.97	7.21 7.19	18.55 18.52)
8a	CH_3-	84	187–189	$C_{15}H_{18}N_5O_2Cl$ (335.78)	53.65 (53.62	5.40 5.38	20.86 20.84)
8b	CH_3CH_2-	69	196–198	$C_{16}H_{20}N_5O_2Cl$ (349.81)	54.94 (54.92	5.76 5.74	20.02 20.00)
8c	$CH_3(CH_2)_2$-	77	208–210	$C_{17}H_{22}N_5O_2Cl$ (363.84)	56.12 (56.10	6.09 6.07	19.25 19.22)
8d	$CH_3(CH_2)_3$-	81	220–222	$C_{18}H_{24}N_5O_2Cl$ (377.86)	57.21 (57.19	6.40 6.37	18.53 18.51)
8e	$CH_3(CH_2)_4$-	80	234–236	$C_{19}H_{26}N_5O_2Cl$ (391.89)	58.23 (58.21	6.69 6.68	17.87 17.85)
8f	$CH_3(CH_2)_5$-	83	240–242	$C_{20}H_{28}N_5O_2Cl$ (405.92)	59.18 (59.16	6.95 6.92	17.25 17.23)
8g	$CH_3(CH_2)_6$-	80	261–263	$C_{21}H_{30}N_5O_2Cl$ (419.94)	60.06 (60.04	7.20 7.18	16.68 16.66)
8h	C_6H_5-	79	165–167	$C_{20}H_{20}N_5O_2Cl$ (397.85)	60.38 (60.36	5.07 5.05	17.60 17.59)
8i	$C_6H_5CH_3$-	82	174–176	$C_{21}H_{22}N_5O_2Cl$ (411.88)	61.24 (61.21	5.38 5.36	17.00 16.98)
8j	$C_6H_5CH_3CH_2$-	84	187–189	$C_{22}H_{24}N_5O_2Cl$ (425.91)	62.04 (62.02	5.68 5.66	16.44 16.43)
8k	$C_6H_5CH_3(CH_2)_2$-	68	196–198	$C_{23}H_{26}N_5O_2Cl$ (439.93)	62.79 (62.77	5.96 5.95	15.92 15.90)
8l	$C_6H_5CH_3(CH_2)_3$-	75	200–202	$C_{24}H_{28}N_5O_2Cl$ (453.96)	63.50 (63.48	6.22 6.20	15.43 15.41)

Elementar Vario EL III elemental analyzer. The results of elemental analyses were within ±0.4% of the theoretical values (Table 1).

IR spectra were recorded in KBr on a Perkin-Elmer RX1 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were obtained in a Brucker DRX 300-MHz spectrometer, in $CDCl_3$. Chemical shifts are reported in δ values (ppm) relative to tetramethylsilane (TMS) δ = 0 (1H), as internal standard. Signal multiplicities are represented by the following abbreviations: s (singlet), d (doublet), dd (double doublet), and m (multiplet). For chosen compounds **6**, **7**, and **8** the MS were recorded on a Jeol SX-102 mass spectrometer operating at 70 eV.

Synthesis of 2-(Chloromethyl)-1h-benzimidazole (2)

We heated together the mixture of 5.43 g (0.03 mol) of o-phenylenediamine dihydrochloride, 20 ml of water, and 6.20 ml (0.09 mol) of chloroacetic acid under reflux for 1.5 h, made the cooled reaction mixture distinctly basic by gradual addition

of concentrated ammonia solution, collected the precipitate product, and recrystallized it from 10% aqueous ethanol. Yield 82%, mp 160–162 °C; IR (KBr): 1145 (-C-N), 1455 (-N-CH_2), 1624 (-C=N), 1730 (-C=O ester), 2850 (-C-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.26 (s, 2H, -CH_2), 7.22–7.59 (m, 4H, J = 10.2, 3.4 Hz, Ar-H), 12.18 (s, 1H, NH); MS (*m/z*): 167 [$M^+ + 1$].

Synthesis of 1-(1H-Benzimidazol-2-yl)-N-methylmethanamine (3)

Alkyl/aryl amine (0.202 mol) was added dropwise with stirring to a solution of 2-(chloromethyl)-1H-benzimidazole 2 (0.02 mol) in ethanol and the reaction mixture was refluxed for 4 h. Ethanol was removed, and the solid obtained was washed with chloroform and recrystallized with a chloroform–ethanol mixture. Yield 85%, mp 192–94 °C; IR (KBr): 1624 (-C=N), 1145 (-C-N), 1730 (-C=O ester), 1455 (-N-CH_2), 2850 (-C-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.26 (s, 2H, -CH_2), 7.22–7.59 (m, 4H, *J* = 10.2, 3.4 Hz, Ar-H), 12.18 (s, 1H, NH); MS (*m/z*): 162 [$M^+ + 1$].

Synthesis of Ethyl{2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetate (4)

Ethyl chloroacetate (0.028 mol, 3 ml) was added to a solution of 1-(1H-benzimidazol-2-yl)-N-methylmethanamine 3 (0.028 mol, 4.51 g) in dry acetone (40 ml). Anhydrous K_2CO_3(3 g) was added to this solution, and the reaction mixture was refluxed for 10 h. Acetone was removed, and the residue was crystallized from ethanol. Yield 88%, mp 184–186 °C; IR (KBr): 1150 (-C-N), 1460 (-N-CH_2), 1690 (-C=N), 1735 (-C=O ester), 2882 (-C-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 (t, 3H, *J* = 7.5 Hz, -CH_3), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.13 (q, 2H, *J* = 8.2, 5.6, 1.1 Hz, -CH_2), 4.69 (s, 2H, -CH_2), 7.22–7.59 (m, 4H, *J* = 7.7, 4.2 Hz, Ar-H); MS: [$M^+ + 1$] at *m/z*: 248.

Synthesis of 2-{2-[(Methylamino)methyl]-1H-benzimidazol-1-yl}acetohydrazide (5)

To a solution of compound ethyl {2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetate (**4**) (0.01 mol) dissolved in dry methanol (50 ml), 99% hydrazine hydrate (1 ml) was added, and the mixture was refluxed for 4–5 h. The reaction mixture was cooled, and the solid obtained was filtered and washed with small quantity of cold methanol. Yield 79%, mp 195–197 °C; IR: 1152 (-C-N), 1464 (-N-CH_2), 1695 (-C=N), 1737 (-C=O ester), 2886 (-C-CH_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.22–7.59 (m, 4H, *J* = 8.9, 4.1 Hz, ArH), 8.0 (s, 2H, NH_2); MS: [$M^+ + 1$] at *m/z*: 234.

Synthesis of N-Methyl-1-{1-[(5-alkyl/aryl-1,3,4-oxadiazol-2-yl)methyl]-1H-benzimidazol-2-yl}methanamine (6a–l)

An equimolar mixture of compound 2-{2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetohydrazide (**5**) (0.001 mol) and substituted carboxylic acid in phosphoryl chloride was refluxed for 12–15 h. The reaction mixture was cooled,

Table 2. Spectroscopic data of compounds **6a–l**, **7a–l**, and **8a–l**

Compound	Name	IR (ν cm^{-1})	^{1}H NMR (δ ppm)	MS (m/z $[M^+ + 1]$)
6a	*N*-Methyl-1-{1-[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}methanamine	1150 (-C-N), 1230 (-N-N-), 1460 (-N-CH_2), 1690 (-C=N), 1735 (-C=O), 2882 (-C-CH_3)	2.0 (s, 1H, -NH), 2.62 (s, 3H, -CH_3), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.15–7.60 (m, 4H, $J = 7.5$, 6.9 Hz, Ar-H)	258
6b	1-{1-[(5-Ethyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-*N*-methylmethanamine	1152 (-C-N), 1231 (-N-N-), 1462 (-N-CH_2), 1693 (-C=N), 1738 (-C=O), 2886 (-C-CH_3)	1.26 (t, 3H, $J = 4.3$ Hz, -CH_3), 2.0 (s, 1H, -NH), 2.59 (q, 2H, $J = 5.7$, 2.0 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.20–7.64 (m, 4H, $J = 7.4$, 6.9 Hz, Ar-H)	272
6c	*N*-Methyl-1-{1-[(5-propyl-1,3,4-oxadiazol- 2-yl)methyl]-1*H*-benzimidazol-2-yl}methanamine	1151 (-C-N), 1234 (-N-N-), 1464 (-N-CH_2), 1695 (-C=N), 1739 (-C=O), 2888 (-C-CH_3)	0.90 (t, 3H, $J = 4.3$ Hz, -CH_3), 1.65 (m, 2H, $J = 5.4$, 1.8 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.55 (t, 2H, $J = 5.0$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.20–7.64 (m, 4H, $J = 7.5$, 6.9 Hz, Ar-H)	286
6d	1-{1-[(5-Butyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-*N*-methylmethanamine	1140 (-C-N), 1254 (-N-N-), 1420 (-N-CH_2), 1632 (-C=N), 1725 (-C=O), 2862 (-C-CH_3)	0.90 (t, 3H, $J = 4.5$ Hz, -CH_3), 1.31 (m, 2H, $J = 4.4$, 1.6 Hz, -CH_2), 1.59 (p, 2H, $J = 2.3$, 1.5 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.55 (t, 2H, $J = 2.3$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.20–7.64 (m, 4H, $J = 7.5$, 6.9 Hz, Ar-H)	300
6e	*N*-Methyl-1-{1-[(5-pentyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}methanamine	1142 (-C-N), 1250 (-N-N-), 1418 (-N-CH_2), 1630 (-C=N), 1721 (-C=O), 2860 (-C-CH_3)	0.90 (t, 3H, $J = 4.3$ Hz, -CH_3), 1.29 (p, 2H, $J = 2.3$, 1.5 Hz, -CH_2), 1.31 (m, 2H, $J = 5.2$, 4.3 Hz, -CH_2), 1.59 (p, 2H, $J = 2.2$, 1.5 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.55 (t, 2H, $J = 4.4$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.20–7.64 (m, 4H, $J = 7.5$, 6.3 Hz, Ar-H)	314
6f	1-{1-[(5-Hexyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-*N*-methylmethanamine	1142 (-C-N), 1252 (-N-N-), 1417 (-N-CH_2), 1633 (-C=N), 1724 (-C=O), 2862 (-C-CH_3)	0.88 (t, 3H, $J = 4.3$ Hz, -CH_3), 1.29 (p, 2H, $J = 2.3$, 1.5 Hz, -CH_2), 1.31 (m, 2H, $J = 5.2$, 4.6, Hz, -CH_2), 1.59 (p, 2H, $J = 2.2$, 1.5 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.55 (t, 2H, $J = 4.4$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.20–7.64 (m, 4H, $J = 7.5$, 3.0 Hz, Ar-H)	328
6g	1-{1-[(5-Heptyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}-*N*-methylmethanamine	1152 (-C-N), 1264 (-N-N-), 1421 (-N-CH_2), 1635 (-C=N), 1728 (-C=O), 2870 (-C-CH_3)	0.88 (t, 3H, $J = 4.3$ Hz, -CH_3), 1.29 (p, 2H, $J = 2.3$, 1.2 Hz, -CH_2), 1.31 (m, 2H, $J = 5.2$, 4.6, 0.8 Hz, -CH_2), 1.59 (p, 2H, $J = 2.2$, 1.5 Hz, -CH_2), 2.0 (s, 1H,-NH), 2.55 (t, 2H, $J = 4.6$ Hz,-CH_2), 3.26 (s, 3H,-CH_3), 3.81 (s, 2H,-CH_2), 4.99 (s, 2H,-CH_2), 7.20–7.64 (m, 4H, $J = 7.5$, 3.2 Hz, Ar-H)	342

(*Continued*)

Table 2. Continued

Compound	Name	IR (ν cm^{-1})	^{1}H NMR (δ ppm)	MS (m/z $[M^+ + 1]$)
6h	*N*-Methyl-1-{1-[(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1*H*-benzimidazol-2-yl}methanamine	1144 (-C-N), 1258 (-N-N-), 1418 (-N-CH_2), 1630 (-C=N), 1726 (-C=O), 2862 (-C-CH_3)	2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.22–8.05 (m, 9H, $J = 7.6$, 4.2 Hz, Ar-H)	320
6i	*N*-Methyl-1-(1-{[5-(4-methylphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazol-2-yl)methanamine	1132 (-C-N), 1230 (-N-N-), 1406 (-N-CH_2), 1622 (-C=N), 1714 (-C=O), 2852 (-C-CH_3)	2.0 (s, 1H, -NH), 2.34 (s, 3H, -CH_3), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.29–7.95 (m, 8H, $J = 7.6$, 4.2 Hz, Ar-H)	334
6j	1-(1-{[5-(4-Ethylphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazol-2-yl)-*N*-methylmethanamine	1132 (-C-N), 1232 (-N-N-), 1408 (-N-CH_2), 1627 (-C=N), 1710 (-C=O), 2847 (-C-CH_3)	1.25 (t, 3H, $J = 5.1$ Hz, -CH_3), 2.0 (s, 1H, -NH), 2.50 (q, 2H, $J = 4.5$, 2.3 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.22–8.02 (m, 8H, $J = 7.5$, 3.0 Hz, Ar-H)	348
6k	*N*-Methyl-1-(1-{[5-(4-propylphenyl)-1,3,4-oxadiazol-2-yl]methyl}-1*H*-benzimidazol-2-yl)methanamine	1130 (-C-N), 1229 (-N-N-), 1408 (-N-CH_2), 1625 (-C=N), 1708 (-C=O), 2845 (-C-CH_3)	0.90 (t, 3H, $J = 5.1$ Hz, -CH_3), 1.65 (m, 2H, $J = 6.5$, 2.3, 2.0 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.62 (t, 2H, $J = 4.8$, 2.2 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.22–8.02 (m, 8H, $J = 7.5$, 3.0 Hz, Ar-H)	362
6l	1-(1-((5-(4-Butylphenyl)-1,3,4-oxadiazol-2-yl)methyl)-1*H*-benzimidazol-2--yl)methylmethanamine	1135 (-C-N), 1230 (-N-N-), 1410 (-N-CH_2), 1621 (-C=N), 1714 (-C=O), 2851 (-C-CH_3)	0.90 (t, 3H, $J = 5.1$ Hz, -CH_3), 1.31 (m, 2H, $J = 6.5$, 2.3, 2.0 Hz, -CH_2), 1.59 (m, 2H, $J = 6.5$, 2.3, 1.4 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.62 (t, 2H, $J = 4.8$, 2.2 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.99 (s, 2H, -CH_2), 7.22–8.02 (m, 8H, $J = 7.5$, 3.0 Hz, Ar-H)	376
7a	*N*′-[(1*E*)-Ethylidene]-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetohydrazide	1080 (-C-N), 1250 (-N-N-), 1425 (-N-CH_2), 1660 (-C=N), 1710 (-C=O), 2780 (-C-CH_3)	0.90 (d, $J = 4.5$ Hz,3H, -CH_3), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.24 (q, 1H, $J = 4.2$ Hz, -CH), 7.22–7.59 (m, 4H, $J = 7.2$, 5.7 Hz, Ar-H), 10.58 (s, 1H, -NH)	260
7b	2-{2-[(Methylamino)methyl]-1*H*-benzimidazol-1-yl}-*N*′-[(1*E*)-propylidene]acetohydrazide	1085 (-C-N), 1258 (-N-N-), 1427 (-N-CH_2), 1662 (-C=N), 1713 (-C=O), 2784 (-C-CH_3)	1.01 (t, 3H, $J = 4.1$ Hz, -CH_3), 2.0 (s, 1H, -NH), 2.19 (p, 2H, $J = 6.0$, 2.3 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.50 (t, 1H, $J = 2.4$ Hz, -CH), 7.22–7.59 (m, 4H, $J = 6.5$, 2.3, 2.0 Hz, ArH), 10.58 (s, 1H, -NH)	274
7c	*N*′-[(1*E*)-Butylidene]-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetohydrazide	1086 (-C-N), 1258 (-N-N-), 1429 (-N-CH_2), 1663 (-C=N), 1713 (-C=O), 2786 (-C-CH_3)	0.90 (t, 3H, $J = 4.1$ Hz, -CH_3), 1.30 (q, 2H, $J = 5.5$, 3.7 Hz, -CH_2), 1.44 (m, 2H, $J = 6.5$, 4.5, 1.1 Hz, CH_2), 2.0 (s, 1H, -NH), 2.19 (p, 2H, $J = 6.0$, 2.3 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.50 (t, 1H, $J = 2.4$ Hz,	288

			-CH), 7.22–7.59 (m, 4H, $J = 6.5, 2.3, 2.0$ Hz, Ar-H), 10.58 (s, 1H, -NH)	
7d	2-{2-[(Methylamino)methyl]-1*H*-benzimidazol-1-yl}-*N*′-[(1*E*)-pentylidene]acetohydrazide	1087 (-C-N), 1259 (-N-N-), 1431 (-N-CH_2), 1665 (-C=N), 1715 (-C=O), 2787 (-C-CH_3)	0.90 (t, 3H, $J = 4.1$ Hz, -CH_3), 1.29 (p, 2H, $J = 5.5, 3.7$ Hz,-CH_2), 1.30 (q, 2H, $J = 6.7, 2.3$ Hz, -CH_2), 1.31 (m, 2H, $J = 5.5, 3.7, 2.5$ Hz, -CH_2), 1.44 (m, 2H, $J = 6.5, 4.5, 1.1$ Hz, -CH_2), 2.0 (s, 1H, -NH), 2.19 (p, 2H, $J = 6.0, 2.3$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.50 (t, 1H, $J = 2.4$ Hz, -CH), 7.22–7.59 (m, 4H, $J = 6.5, 2.3, 2.0$ Hz, ArH), 10.58 (s, 1H, -NH)	302
7e	*N*′-[(1*E*)-Hexylidene]-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetohydrazide	1090 (-C-N), 1264 (-N-N-), 1435 (-N-CH_2), 1667 (-C=N), 1717 (-C=O), 2789 (-C-CH_3)	0.90 (t, 3H, $J = 4.1$ Hz, -CH_3), 1.29 (m, 2H, $J = 5.5, 3.7$ Hz, -CH_2), 1.30 (q, 2H, $J = 6.7, 2.3$ Hz, -CH_2), 1.31 (m, 2H, $J = 5.5, 3.7, 2.5$ Hz, -CH_2), 1.44 (m, 2H, $J = 6.5, 4.5, 1.1$ Hz, -CH_2), 2.0 (s, 1H, -NH), 2.19 (p, 2H, $J = 6.0, 2.3$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.50 (t, 1H, $J = 2.4$ Hz, -CH), 7.22–7.59 (m, 4H, $J = 6.5, 2.3, 2.0$ Hz, Ar-H), 10.58 (s, 1H, -NH)	316
7f	*N*′-[(1*E*)-Heptylidene]-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetohydrazide	1094 (-C-N), 1266 (-N-N-), 1438 (-N-CH_2), 1668 (-C=N), 1718 (-C=O), 2790 (-C-CH_3)	0.88 (t, 3H, $J = 4.0$ Hz, -CH_3), 1.29 (m, 2H, $J = 5.5, 3.7$ Hz, -CH_2), 1.30 (q, 2H, $J = 6.7, 2.3$ Hz, -CH_2), 1.31 (m, 2H, $J = 5.5, 3.7, 2.5$ Hz, -CH_2), 1.44 (m, 2H, $J = 6.5, 4.5, 1.1$ Hz, -CH_2), 2.0 (s, 1H, -NH), 2.19 (p, 2H, $J = 6.0, 2.3$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.50 (t, 1H, $J = 2.4$ Hz, -CH), 7.22–7.59 (m, 4H, $J = 6.5, 2.3, 2.0$ Hz,Ar-H), 10.58 (s, 1H, -NH)	330
7g	*N*′-[(1*E*)-Octylidene]-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetohydrazide	1096 (-C-N), 1267 (-N-N-), 1439 (-N-CH_2), 1668 (-C=N), 1720 (-C=O), 2794 (-C-CH_3)	0.88 (t, 3H, $J = 4.0$ Hz, -CH_3), 1.29 (m, 2H, $J = 5.5, 3.7$ Hz, -CH_2), 1.30 (q, 2H, $J = 6.7, 2.3$ Hz, -CH_2), 1.31 (m, 2H, $J = 5.5, 3.7, 2.5$ Hz, -CH_2), 1.44 (m, 2H, $J = 6.5, 4.5, 1.1$ Hz, -CH_2), 2.0 (s, 1H, -NH), 2.19 (p, 2H, $J = 6.0, 2.3$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.50 (t, 1H, $J = 2.4$ Hz, -CH), 7.22–7.59 (m, 4H, $J = 6.5, 2.3, 2.0$ Hz, Ar-H), 10.58 (s, 1H, -NH)	344
7h	2-{2-[(Methylamino)methyl]-1*H*-benzimidazol-1-yl}-*N*′-[(*E*)-phenylmethylidene]acetohydrazide	1087 (-C-N), 1259 (-N-N-), 1431 (-N-CH_2), 1643 (-C=N), 1714 (-C=O), 2774 (-C-CH_3)	2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 8.54 (s, 1H, -CH), 7.22–7.83 (m, 9H, $J = 7.5, 6.5, 3.2$ Hz, Ar-H), 11.07 (s, 1H, -NH)	322

(*Continued*)

Table 2. Continued

Compound	Name	IR (ν cm^{-1})	^{1}H NMR (δ ppm)	MS (m/z $[M^+ + 1]$)
7i	2-{2-[(Methylamino)methyl]-1*H*-benzimidazol-1-yl}-*N*′-[(*E*)-(4-methylphenyl) methylidene]acetohydrazide	1088 (-C-N), 1259 (-N-N-), 1431 (-N-CH_2), 1645 (-C=N), 1715 (-C=O), 2775 (-C-CH_3)	2.0 (s, 1H, -NH), 2.34 (s, 3H, -CH_3), 3.26 (s, 3H, -CH_3), 3.81(s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 8.54 (s, 1H, -CH), 7.22–7.71 (m, 8H, $J = 7.5$, 6.5, 3.2 Hz, Ar-H), 11.07 (s, 1H, -NH)	336
7j	*N*′-[(*E*)-(4-Ethylphenyl) methylidene]-2-{2-[(methylamino) methyl]-1*H*-benzimidazol-1-yl} acetohydrazide	1087 (-C-N), 1256 (-N-N-), 1430 (-N-CH_2), 1645 (-C=N), 1715 (-C=O), 2775 (-C-CH_3)	1.25 (t, 3H, $J = 6.5$ Hz, -CH_3), 2.0 (s, 1H, -NH), 2.60 (q, 2H, $J = 5.4$, 3.4 Hz, -CH_3), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 8.54 (s, 1H, -CH), 7.22–7.78 (m, 8H, $J = 7.5$, 6.5, 3.2 Hz, Ar-H), 11.07 (s, 1H, -NH)	350
7k	*N*′-[(*E*)-(4-Propylphenyl) methylidene]-2-{2-[(methylamino) methyl]-1*H*-benzimidazol-1-yl} acetohydrazide	1091 (-C-N), 1263 (-N-N-), 1435 (-N-CH_2), 1646 (-C=N), 1717 (-C=O), 2779 (-C-CH_3)	0.90 (t, 3H, $J = 3.5$ Hz, -CH_3), 1.65 (m, 2H, $J = 6.5$, 4.4 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.62 (t, 2H, $J = 6.8$, 5.5 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.22–7.78 (m, 8H, $J = 7.5$, 6.5, 3.2 Hz, ArH), 8.54 (s, 1H, -CH), 11.07 (s, 1H, -NH)	364
7l	*N*′-[(*E*)-(4-Butylphenyl)methylidene]-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetohydrazide	1092 (-C-N), 1265 (-N-N-), 1436 (-N-CH_2), 1647 (-C=N), 1720 (-C=O), 2780 (-C-CH_3)	0.90 (t, 3H, $J = 3.5$ Hz, -CH_3), 1.31 (m, 2H, $J = 6.8$, 4.2 Hz, -CH_2), 1.59 (p, 2H, J = 6.5, 3.7 Hz, -CH_2), 2.0 (s, 1H, -NH), 2.62 (t, 2H, $J = 6.8$, 5.5 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 7.22–7.78 (m, 8H, $J = 7.5$, 6.5, 3.2 Hz, Ar-H), 8.54 (s, 1H, -CH), 11.07 (s, 1H, -NH)	378
8a	*N*-(3-Chloro-2-methyl-4-oxoazetidin-1-yl)-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetamide	911 (-C-Cl), 1002 (-C-N), 1270 (-N-N-), 1460 (-N-CH_2), 1688 (-C=N), 1748 (-C=O), 2658 (-C-CH_3)	1.32 (d, 3H, $J = 4.2$ Hz, -CH_3), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 3.95 (p, 1H, $J = 7.5$, 8.1 Hz, -CH), 4.62 (s, 2H, -CH_2), 5.05 (d, 1H, $J = 3.1$ Hz, -CHCl), 7.22–7.59 (m, 4H, $J = 7.8$, 6.6 Hz, Ar-H)	336
8b	*N*-(3-Chloro-2-ethyl-4-oxoazetidin-1-yl)-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetamide	915 (-C-Cl), 1008 (-C-N), 1271 (-N-N-), 1463 (-N-CH_2), 1690 (-C=N), 1749 (-C=O), 2659 (-C-CH_3)	0.90 (t, 3H, $J = 3.6$ Hz, -CH_3), 1.62 (p, 2H, $J = 7.5$, 5.4 Hz, -CH_2), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.7 (q, 1H, $J = 6.6$ Hz, -CH), 3.80 (s, 2H, -CH_2), 4.60 (s, 2H, -CH_2), 5.04 (d, 1H, $J = 3.1$ Hz, -CHCl), 7.22–7.59 (m, 4H, $J = 7.8$, 6.3 Hz, Ar-H)	350
8c	*N*-(3-Chloro-2-oxo-4-propylazetidin-1-yl)-2-{2-[(methylamino)methyl]-	914 (-C-Cl), 1012 (-C-N), 1270 (-N-N-), 1461 (-N-CH_2),	0.90 (t, 3H, $J = 3.6$ Hz, -CH_3), 1.33 (m, 2H, $J = 7.5$, 5.4 Hz, -CH_2), 1.51 (q, 2H, $J = 8.1$, 5.4 Hz, -CH_2), 2.0 (s, 1H, -NH),	364

	1*H*-benzimidazol-1-yl}acetamide	1692 (-C=N), 1746 (-C=O), 2657 (-C-CH_3)	3.26 (s, 3H, -CH_3), 3.7 (q, 1H, J = 6.7, 3.2 Hz, -CH), 3.81 (s, 2H, -CH_2), 4.60 (s, 2H, -CH_2), 5.04 (d, 1H, J = 3.5 Hz, -CHCl), 7.22–7.59 (m, 4H, J = 7.7, 6.5 Hz, Ar-H)	
8d	*N*-(2-Butyl-3-chloro-4-oxoazetidin-1-yl)-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetamide	913 (-C-Cl), 1010 (-C-N), 1268 (-N-N-), 1457 (-N-CH_2), 1690 (-C=N), 1741 (-C=O), 2652 (-C-CH_3)	0.90 (t, 3H, J = 3.6 Hz, -CH_3), 1.33 (q, 2H, J = 7.5, 5.4 Hz,-CH_2), 1.35 (p, 2H, J = 8.1, 5.2 Hz, -CH_2),1.51 (q, 2H, J = 6.5, 3.3 Hz, -CH_2), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.7 (q, 1H, J = 6.7, 3.2 Hz, -CH), 3.81 (s, 2H, -CH_2), 4.60 (s, 2H, -CH_2), 5.04 (d, 1H, J = 3.5 Hz, -CHCl), 7.22–7.59 (m, 4H, J = 7.8, 6.6 Hz, Ar-H)	378
8e	*N*-(3-Chloro-2-oxo-4-pentylazetidin-1-yl)-2-(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	915 (-C-Cl), 1004 (-C-N), 1273 (-N-N-), 1460 (-N-CH_2), 1688 (-C=N), 1744 (-C=O), 2657 (-C-CH_3)	0.88 (t, 3H, J = 3.7 Hz, -CH_3), 1.25 (p, 2H, J = 5.0, 1.8 Hz, -CH_2), 1.31 (q, 2H, J = 7.5, 5.4 Hz, -CH_2), 1.51 (q, 2H, J = 6.5, 3.3 Hz, -CH_2), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.7 (q, 1H, J = 6.7, 3.2 Hz, -CH), 3.81 (s, 2H, -CH_2), 4.60 (s, 2H, -CH_2), 5.04 (d, 1H, J = 3.5 Hz, -CHCl), 7.22 7.59 (m, 4H, J = 7.8, 6.6 Hz, Ar-H)	392
8f	*N*-(3-Chloro-2-hexyl-4-oxoazetidin-1-yl)-2-(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	912 (-C-Cl), 1000 (-C-N), 1270 (-N-N-), 1454 (-N-CH_2), 1682 (-C=N), 1740 (-C=O), 2651 (-C-CH_3)	0.58 (t, 3H, J = 4.2 Hz,-CH_3), 1.25 (p, 2H, J = 5.0, 1.8 Hz, -CH_2), 1.29 (p, 2H, J = 5.0, 1.3, 0.9 Hz, -CH_2), 1.31 (p, 2H, J = 6.4, 3.3 Hz, -CH_2), 1.51 (q, 2H, J = 6.5, 3.3 Hz, -CH_2), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.7 (q, 1H, J = 6.7, 3.2 Hz, -CH), 3.81 (s, 2H, -CH_2), 4.60 (s, 2H, -CH_2), 5.04 (d, 1H, J = 3.5 Hz, -CHCl), 7.22-7.59 (m, 4H, J = 7.8, 6.6 Hz, Ar-H)	406
8g	*N*-(3-Chloro-2-heptyl-4-oxoazetidin-1-yl)-2-(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	918 (-C-Cl), 1005 (-C-N), 1278 (-N-N-), 1465 (-N-CH_2), 1689 (-C=N), 1748 (-C=O), 2659 (-C-CH_3)	0.86 (t, 3H, J = 4.3 Hz, -CH_3), 1.25 (p, 2H, J = 5.0, 1.8 Hz, -CH_2), 1.29 (p, 2H, J = 3.5 Hz, -CH_2), 1.31 (p, 2H, J = 6.4, 3.3 Hz, -CH_2), 1.51 (q, 2H, J = 6.5, 3.3 Hz, -CH_2), 2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.7 (q, 1H, J = 6.7, 3.2 Hz, -CH), 3.81 (s, 2H, -CH_2), 4.60 (s, 2H, -CH_2), 5.04 (d, 1H, J = 3.5 Hz, -CHCl), 7.22–7.59 (m, 4H, J = 7.3, 6.6 Hz, Ar-H)	420
8h	*N*-(3-Chloro-2-oxo-4-phenylazetidin-1-yl)-2-{2-[(methylamino)methyl]-1*H*-benzimidazol-1-yl}acetamide	918 (-C-Cl), 1007 (-C-N), 1279 (-N-N-), 1467 (-N-CH_2), 1690 (-C=N), 1748 (-C=O), 2660 (-C-CH_3)	2.0 (s, 1H, -NH), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 5.0 (d, 1H, J = 4.0 Hz, -CH), 5.44 (d, 1H, J = 4.2 Hz, -CHCl), 7.22–7.65 (m, 9H, J = 8.5, 4.3, 1.2 Hz, Ar-H)	398
8i	*N*-(3-Chloro-2-oxo-4-*p*-tolylazetidin-1-yl)-2-	921 (-C-Cl), 1014 (-C-N), 1284 (-N-N-), 1471 (-N-CH_2),	2.0 (s, 1H, -NH), 2.34 (s, 3H, -CH_3), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.62 (s, 2H, -CH_2), 5.08 (d, 1H, J = 4.0 Hz, -CH),	412

(*Continued*)

Table 2. Continued

Compound	Name	IR (ν cm^{-1})	^{1}H NMR (δ ppm)	MS (m/z $[M^+ + 1]$)
	(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	1695 (-C=N), 1752 (-C=O), 2665 (-C-CH_3)	5.44 (d, 1H, $J = 4.2$ Hz, -CHCl), 7.17–7.65 (m, 8H, $J = 8.5$, 4.3, 1.2 Hz, Ar-H)	
8j	*N*-(3-Chloro-2-(4-ethylphenyl)-4-oxoazetidin-1-yl)-2-(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	920 (-C-Cl), 1014 (-C-N), 1284 (-N-N-), 1470 (-N-CH_2), 1693 (-C=N), 1750 (-C=O), 2663 (-C-CH_3)	1.25 (t, 3H, $J = 3.8$ Hz, -CH_3), 2.0 (s, 1H, -NH), 2.60 (q, 2H, $J = 6.4$, 3.7 Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.82 (s, 2H, -CH_2), 5.08 (d, 1H, $J = 4.0$ Hz, -CH), 5.44 (d, 1H, $J = 4.2$ Hz, -CHCl), 7.05–7.61 (m, 8H, $J = 8.0$, 4.1, 1.2 Hz, Ar-H)	426
8k	*N*-(3-Chloro-2-oxo-4-(4-propylphenyl)azetidin-1-yl)-2-(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	918 (-C-Cl), 1005 (-C-N), 1281 (-N-N-), 1468 (-N-CH_2), 1690 (-C=N), 1749 (-C=O), 2660 (-C-CH_3)	0.90 (t, 3H, $J = 3.5$ Hz, -CH_3), 1.65 (m, 2H, $J = 6.7$ Hz, -CH_2), 2.0 (s, 1H, -NH), 2.62 (t, 2H, $J = 3.2$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.82 (s, 2H, -CH_2), 5.08 (d, 1H, $J = 4.0$ Hz, -CH), 5.44 (d, 1H, $J = 4.2$ Hz,-CHCl), 7.05–7.61 (m, 8H, $J = 8.2$, 4.3, 1.5 Hz, Ar-H)	440
8l	*N*-(2-(4-Butylphenyl)-3-chloro-4-oxoazetidin-1-yl)-2-(2-((methylamino)methyl)-1*H*-benzimidazol-1-yl)acetamide	922 (-C-Cl), 1017 (-C-N), 1288 (-N-N-), 1475 (-N-CH_2), 1699 (-C=N), 1754 (-C=O), 2667 (-C-CH_3)	0.96 (t, 3H, $J = 3.5$ Hz, -CH_3), 2.0 (s, 1H, -NH), 1.82 (m, 2H, $J = 7.5$ Hz, -CH_2), 2.62 (t, 2H, $J = 3.2$ Hz, -CH_2), 3.26 (s, 3H, -CH_3), 3.81 (s, 2H, -CH_2), 4.82 (s, 2H, -CH_2), 5.08 (d, 1H, $J = 4.0$ Hz, -CH), 5.44 (d, 1H, $J = 4.2$ Hz, -CHCl), 7.05–7.61 (m, 8H, $J = 8.7$, 4.3, 1.0 Hz, Ar-H)	454

poured into ice-cold water, and neutralized with 20% $NaHCO_3$ solution. The resultant solid was filtered, washed with water, and recrystallized from ethanol.

Spectroscopic data of the derivatives **6a–l** are given in Table 2.

Synthesis of N′-[(1E)-Alkylidene/arylidene]-2-{2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetohydrazide (7a–l)

Aldehyde (30 mmol) was added to a stirred solution of compound 2-{2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetohydrazide (**5**) (30 mmol) containing four or five drops of glacial acetic acid in methanol (30 ml) and the mixture was refluxed for 5–7 h on a steam bath. Methanol was removed under vacuum, and the resultant semisolid was treated with distilled water (3×10 ml). The separated solid was filtered, dried, and recrystallized from ethanol to give the title compounds.

Spectroscopic data of the derivatives **7a–l** are given in Table 2.

Synthesis of N-(3-Chloro-2-oxo-4-(alkyl/aryl) azetidin-1-yl)-2-(2-((methylamino)methyl)-1H-benzimidazol-1-yl)acetamide (8a–l)

Chloroacetyl chloride (10 mmol) was added dropwise to a stirred solution of compound N′-[(1E)-alkylidene/arylidene]-2-{2-[(methylamino)methyl]-1H-benzimidazol-1-yl}acetohydrazide (**7**) (20 mmol) and triethylamine (10 mmol) in

Table 3. Antibacterial activity of compounds **6a–6l** and **8a–8l** against *Staphylococcus aureus*

	Concentrations					
Compounds	1.0 μg/ml	10 μg/ml	100 μg/ml	200 μg/ml	500 μg/ml	App. MIC μg/ml
6a	+	–	–	–	–	10
6b	+	–	–	–	–	10
6c	++	+	–	–	–	100
6d	++	+	–	–	–	100
6e	+++	+	P	–	–	200
6f	+++	++	+	–	–	200
6g	++	+	P	–	–	200
6h	++	+	–	–	–	100
6i	++	+	–	–	–	100
6j	+++	++	P	–	–	200
8a	+	P	–	–	–	100
8b	+	P	–	–	–	100
8c	++	+	P	–	–	200
8d	++	+	+	–	–	200
8e	+++	++	+	+	–	500
8f	+++	++	+	+	–	500
8h	++	+	+	–	–	200
8i	++	+	+	–	–	200
8l	+++	++	P	P	–	500
Ampicillin	+	–	–	–	–	10

Notes: Total inhibition (no growth of organism), –; poor growth compared to control, P; medium growth compared to control, +; and confluent growth (no inhibition), ++.

Table 4. Antibacterial activity of compounds **6a–6l** and **8a–8l** against *Bacillus subtilis*

	Concentrations					
Compounds	1.0 μg/ml	10 μg/ml	100 μg/ml	200 μg/ml	500 μg/ml	App. MIC μg/ml
6a	+	–	–	–	–	10
6b	++	+	–	–	–	100
6c	++	++	–	–	–	100
6d	+	+	–	–	–	100
6e	++	+	P	–	–	200
6f	++	++	+	–	–	200
6g	++	++	P	–	–	200
6h	++	+	P	–	–	200
6i	+	P	–	–	–	100
8a	++	+	–	–	–	100
8b	++	+	P	–	–	200
8c	++	+	–	–	–	100
8d	+++	++	P	–	–	200
8e	+++	++	P	P	–	500
8f	++	+	+	P	–	500
8h	++	P	–	–	–	100
8i	+++	++	+	–	–	200
Ampicillin	+	–	–	–	–	10

Notes: Total inhibition (no growth of organism), –; poor growth compared to control, P; medium growth compared to control, +; and confluent growth (no inhibition), ++.

Table 5. Antibacterial activity of compounds **6a–6l** and **8a–8l** against *Escherichia coli*

	Concentrations					
Compounds	1.0	10	100	200	500 (μg/ml)	App. MIC (μg/ml)
6a	++	+	–	–	–	100
6b	++	+	–	–	–	100
6c	+++	P	–	–	–	100
6d	+++	++	+	–	–	200
6e	+++	+	P	–	–	200
6g	++	+	P	–	–	200
6h	++	P	P	–	–	200
6i	+++	++	P	–	–	200
6l	+++	++	+	P	–	500
8a	++	+	–	–	–	100
8b	++	P	–	–	–	100
8c	+++	+	P	–	–	200
8f	++	++	+	P	–	500
8g	++	+	P	P	–	500
8h	++	+	+	–	–	200
8i	++	+	+	–	–	200
8k	++	++	+	P	–	500
Nalidixic acid	+	–	–	–	–	10

Notes: Total inhibition (no growth of organism), –; poor growth compared to control, P; medium growth compared to control, +; and confluent growth (no inhibition), ++.

dry dioxane (50 ml) at room temperature. The reaction mixture was stirred for 1 h and then refluxed for 5–10 h. The solid obtained after removal of dioxane was crystallized from aqneous ethanol to give the title compounds.

Spectroscopic data of the derivatives **8a–l** are given in Table 2.

Antibacterial Activity Test

The compounds were added to the medium as dimethylsulfoxide (DMSO) solutions. No inhibition zone was observed in controls (i.e., for DMSO). The concentrations used were as follows: 500, 200, 100, 10 and 1.0 μg/ml. Minimum inhibitory concentration (MIC) values used were determined after incubation at 37 °C for 48 h and determined using tube dilution method according to the standard procedure.[21] Ampicillin and nalidixic acid were used as the antibacterial standard, and DMSO was used both as a solvent and as a control. Antibacterial activity results are presented in Tables 3–5.

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REFERENCES

1. Harrison, P. F.; Lederberg, J. *Antimicrobial Resistance: Issues and Options*; National Academy Press: Washington, D C, 1998.
2. World Health Organization. http://w3.whosea.org/En/section17/section58/section1666_7111.htm
3. Leeb, M. *Nature* (London) **2004**, *43*, 892–893.
4. Goker, H.; Kus, C.; Boykin, D. W.; Yildiz, S.; Altanlar, N. *Bioorg. Med. Chem.* **2002**, *10*, 2589–2596.
5. Guven, O. O.; Erdogan, T.; Goker, H.; Yildiz, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2233–2236.
6. Pawar, N. S.; Dalal, D. S.; Shimpi, S. R.; Mahulikar, P. P. *Eur. J. Pharm. Sci.* **2004**, *21*, 115–118.
7. Desai, K. G.; Desai, K. R. *Bioorg. Med. Chem.* **2006**, *14*, 8271–8279.
8. Rao, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Monforte, P.; Pannecouque, C.; Zappala, M. *Il Farmaco* **2002**, *57*, 819–823.
9. Le, H. T.; Lemaire, L. B.; Gilbert, A. K.; Jolicoeur, F.; Leduc, N.; Lemaire, S. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 146–155.
10. Thakurdesai, P. A.; Wadodkar, S. G.; Chopade, C. T. *Pharmacol. Online* **2007**, *1*, 314–329.
11. A-Kilcigil, G.; Kus, C.; Ozdamar, E. D.; C-Eke, B.; Iscan, M. *Arch. Pharm.* **2007**, *34*, 607–611
12. A-Alagoz, Z.; Kus, C.; Coban, T. *J. Enzyme Inhibit. Med. Chem.* **2005**, *20*, 325–331.
13. Srivastava, S. K.; Srivastava, S.; Srivastava, S. D. *Indian J. Chem.* **1999**, *38B* (2), 183–197.
14. Desai, K. G.; Desai, K. R. *Ind. J. Chem.* **2005**, *44B*, 2093–2096.
15. Lamb, H. M.; Ormrod, D.; Scott, L. J. *Drugs* **2002**, *62* (7), 1041–1089.
16. Mistry, K.; Desai, K. R. *Ind. J. Chem.* **2006**, *45B*, 1762–1766.

17. (a) Ansari, K. F.; Lal, C. *Eur. J. Med. Chem.* **2009**, *44* (10), 4028–4033; (b) Ansari, K. F.; Lal, C. *Eur. J. Med. Chem.* **2009**, *44* (5), 2294–2299; (c) Ansari, K. F.; Lal, C. *J. Chem. Sci.* **2009**, *121* (6), 1017–1025.
18. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Text Book of Practical Organic Chemistry*; ELBS Longman: London, 1998.
19. Lopez, R.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58* (25), 7036–7037.
20. Sharma, A. K.; Mazumdar, S. N.; Mahajan, M. P. *J. Org. Chem.* **1996**, *61* (16), 5506–5509.
21. Frankel, S.; Reitman, S.; Sonnenwirth, A. C. *Gradwol's Clinical Laboratory Methods and Diagnosis: A Textbook on Laboratory Procedures and Their Interpretation*, 7th ed.; Mosby: St. Louis, MO, 1970; vol. 2.