Arabian Journal of Chemistry (2016) 9, S1523–S1531

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Benzothiazole incorporated thiazolidin-4-ones and azetidin-2-ones derivatives: Synthesis and *in vitro* antimicrobial evaluation

Sadaf J. Gilani [a,*], K. Nagarajan [a], Surya P. Dixit [a], M. Taleuzzaman [a], Suroor A. Khan [b]

[a] *Department of Pharmaceutical Chemistry, KIET School of Pharmacy, Ghaziabad 201206, UP, India*
[b] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi 110062, India*

Received 17 January 2012; accepted 2 April 2012
Available online 11 April 2012

KEYWORDS

N-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide;
Benzothiazole;
Thiazolidin-4-ones;
Azetidin-2-ones;
Antimicrobial activity

Abstract In this study, a series of novel thiazolidin-4-ones (**5a–g**) and azetidin-2-ones (**6a–g**) were synthesized from *N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide derivatives of the benzothiazole class. Antimicrobial properties of the title compound derivatives were investigated against one Gram (+) bacteria (*Staphylococcus aureus*), three Gram (−) bacteria (*Escherichia coli*, *Pseudomonas aeruginosa, Klebsiella pneumoniae*) and five fungi (*Candida albicans*, *Aspergillus niger*, *Aspergillus flavus*, *Monascus purpureus* and *Penicillium citrinum)* using serial plate dilution method. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at 12.5–200 μg/mL in DMSO. It has been observed that azetidin-2-ones derivatives are found to be more active than thiazolidin-4-ones derivatives against all pathogenic bacterial and fungal strains.

1. Introduction

Antimicrobial agents are among the most commonly used and misused of all drugs (Nogrady and Weaver, 2005). They reduce or completely block the growth and multiplication of bacteria. This has made them unique for the control of deadly infectious diseases caused by a variety of pathogens (Gilani et al., 2011a,b). Although deaths from bacterial and fungal infections have dropped in the developed world, these are still major causes of death in the developing world. The inevitable consequence of the widespread use of antimicrobial agents has been the emergence of antibiotic-resistant pathogens, fueling an ever-increasing need for new drugs. In the design of new

* Corresponding author. Tel.: +91 9891128162; fax: +91 0120 2675091.
E-mail address: gilanisadaf@gmail.com (S.J. Gilani).

Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2012.04.004
1878-5352

compounds, development of hybrid molecules through the combination of different pharmacophores in one structure may lead to compounds with increased antimicrobial activity.

In addition, the 2-azetdinone ring system, a common structural feature of a number of wide spectrum β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, nocardicins and monobactams, have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases. The azetidin-2-one derivatives have been reported to possess a wide range of biological activities like antibacterial (Patel and Patel, 2011), antifungal (Halve et al., 2007), anti-inflammatory (Gurupadayya et al., 2008), analgesic (Ishwar Bhat et al., 2003), anticonvulsant (Gilani et al., 2009), anticancer (Veinberg and Vorona, 2004), and antitubercular (Kagthara et al., 2000). Similarly, thiazolidin-4-ones are a class of heterocycles which have attracted significant interest in medicinal chemistry and they have a wide range of pharmaceutical and biological activities including antimicrobial (Mohan and Kumar, 2003), anti-inflammatory (Vigorita et al., 2003), analgesic (Kumar et al., 2007), antitubercular (Kucukguzel et al., 2006) and antidiabetic (Pattan et al., 2005). Biocidal activities of Schiff bases have also been well established. These have been attributed to the toxophoric C═N linkage in them. Schiff base acquired broad spectrum biological activities like antibacterial (Iqbal et al., 2007), antifungal (Mishra et al., 2005), antitubercular (Lourenco et al., 2007) and anticonvulsant (Ragavendran et al., 2007).

The rationale for the study includes the designing of the derivatives having some common structural features that are important for the compound to exhibit an antimicrobial activity that includes the following:

1. A lipohilic bicyclic aromatic ring system.
2. Another bulky lipophilic group (e.g. phenyl, *tert* butyl) as a side chain.
3. Two lipophilic domains linked by a spacer of appropriate length with polar center at defined position, for example, naftifine, butenafine, terbinafine, debacarb, penicillins and cephalosporins (Nussbaumer et al., 1994, 1995).

In view of the above mentioned facts and in continuation of our interest in the synthesis of heterocycles containing benzothiazole moiety, to identify new candidates that may be of value in designing new, potent, selective and less toxic antimicrobial agents, we report herein the synthesis and antimicrobial evaluation of some novel structural hybrids incorporating both the benzothiazole moiety with thiazolidin-4-one and azetidin-2-one ring systems through different linkages. This combination was suggested in an attempt to investigate the influence of such hybridization and structural variation on the anticipated antimicrobial activity, hoping to add some synergistic biological significance to the target molecules. The substitution pattern of thiazolidin-4-one (**5a**–**g**) and azetidin-2-one (**6a**–**g**) rings was carefully selected so as to confer different electronic environment to the molecules.

2. Experimental

2.1. General

All the solvents were of AR grade and were obtained from Merck, CDH and S.D. Fine chemicals. Melting points were determined in open capillary tubes and are uncorrected. All the compounds were subjected to elemental analysis (CHN) and the measured values agreed within ±0.4% with the calculated ones. Thin layer chromatography was performed on silica gel G (Merck). The spots were developed in an iodine chamber and visualized with an ultraviolet lamp. The solvent systems used were benzene–acetone (8:2, v/v) and toluene–ethyl acetate–formic acid (5:4:1, v/v). Ashless Whatman No. 1 filter paper was used for vacuum filtration. The spots were developed in an iodine chamber and visualized under an ultraviolet (UV) lamp. The IR spectra were recorded in KBr pellets on a (BIO-RAD FTS 135) WIN-IR spectrophotometer. The FAB mass spectra of all the compounds were recorded on a JEOL SX102/ /DA-600 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. ^{1}H NMR spectra (d, ppm) were recorded in DMSO-d_6 solutions on a Varian-Mercury 300 MHz spectrometer using tetramethylsilane as the internal reference. ^{13}C NMR spectra were recorded in DMSO-d_6 solutions on a Bruker Avance II 400 spectrometer at 400 MHz using tetramethylsilane as the internal reference. 2-Amino-6-chloro-benzothiazole **1** was synthesized by the literature procedure (Gilani et al., 2011b).

2.2. Synthesis of 1-(6-chlorobenzo[d]thiazol-2-yl)urea (2)

To the solution of sodium cyanate in minimum quantity of water, glacial acetic acid (5 mL) was added. This solution was heated with 2-amino-6-chloro-benzothiazole **1** (0.01 mol) in alcohol till the contents of the mixture became turbid and the volume remained half of the original volume. The contents were added to ice cool water. The solid obtained was filtered off, dried and recrystallised from a suitable solvent.

IR (KBr) λ_{max} (cm^{-1}): 3310 (NH), 1628 (C═O), 1560 (C═N), 830 (C–Cl), 645 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.14 (s, 1H, NHC═O), 6.68–6.70 (m, 3H, Ar-H, J = 6 Hz), 6.34 (s, 2H, NH_2).

2.3. Synthesis of N-(6-chlorobenzo[d]thiazol-2-yl)hydrazine carboxamide (3)

To the warm hydrazine hydrate solution of compound **2** in alcohol, conc. NaOH was added and refluxed for 6 h. The reaction mixture was poured into crushed ice and solid obtained was filtered off and dried. The solid collected out was recrystallized from a suitable solvent to get the compound *N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide.

IR (KBr) λ_{max} (cm^{-1}): 3300 (NH), 1660 (C═O), 1588 (C═N), 817 (C–Cl), 657 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.12 (s, 1H, NHC═O), 7.28 (s, 1H, $NHNH_2$), 7.70–7.74 (m, 3H, Ar-H, J = 12 Hz).

2.4. Synthesis of 2-Substituted benzylidene-N-(6-chlorobenzo[d]thiazol-2-yl)hydrazinecarboxamide (4a–g)

To an equimolar methanolic solution of *N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide (**3**) (0.1 mol) and substituted benzaldehyde (0.1 mol), a few drops of glacial acetic acid were added. The mixture was then refluxed on a water bath for 5–6 h. It was then allowed to cool, poured onto crushed ice and recrystallised from methanol.

*2.4.1. 2-Benzylidene-N-(6-chlorobenzo[d]thiazol-2-yl) hydrazinecarboxamide (**4a**)*
IR (KBr) λ_{max} (cm^{-1}): 3318 (NH), 1668 (C═O), 1588 (C═N), 827 (C–Cl), 663 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.12 (s, 1H, NHC═O), 7.90 (s, 1H, N═CH), 7.77–7.781 (m, 8H, Ar-H, J = 12 Hz), 6.10 (s, IH, NH); MS [EI] m/z 330 [M^+], 331 [$M^+ + 1$], 332 [$M^+ + 2$].

*2.4.2. N-(6-Chlorobenzo[d]thiazol-2-yl)-2-(2-chlorobenzyl idene)hydrazinecarboxamide (**4b**)*
IR (KBr) λ_{max} (cm^{-1}): 3314 (NH), 1672 (C═O), 1582 (C═N), 811 (C–Cl), 649 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.10 (s, 1H, NHC═O), 7.92 (s, 1H, N═CH), 7.73–7.77 (m, 7H, Ar-H, J = 12 Hz), 6.14 (s, IH, NH); MS [EI] m/z 365 [M^+], 364 [$M^+ - 1$].

*2.4.3. N-(6-Chlorobenzo[d]thiazol-2-yl)-2-(2,4-dichlorobenzylidene)hydrazinecarboxamide (**4c**)*
IR (KBr) λ_{max} (cm^{-1}): 3320 (NH), 1662 (C═O), 1587 (C═N), 818 (C–Cl), 654 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.11 (s, 1H, NHC═O), 7.94 (s, 1H, N═CH), 7.79–7.83 (m, 6H, Ar-H, J = 12 Hz), 6.12 (s, IH, NH); MS [EI] m/z 401 [$M^+ + 2$]. 399 [M^+], 397 [$M^+ - 2$].

*2.4.4. N-(6-Chlorobenzo[d]thiazol-2-yl)-2-(2-methylbenzy lidene)hydrazinecarboxamide (**4d**)*
IR (KBr) λ_{max} (cm^{-1}): 3311 (NH), 1669 (C═O), 1580 (C═N), 819 (C–Cl), 640 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.09 (s, 1H, NHC═O), 7.97 (s, 1H, N═CH), 7.72–7.76 (m, 7H, Ar-H, J = 12 Hz), 6.13 (s, IH, NH); MS [EI] m/z 346 [$M^+ + 2$], 345 [$M^+ + 1$], 344 [M^+].

*2.4.5. 2-[{2-(6-Chlorobenzo[d]thiazol-2-ylcarbamoyl)hydrazono}methyl]phenyl acetate (**4e**)*
IR (KBr) λ_{max} (cm^{-1}): 3319 (NH), 1664 (C═O), 1589 (C═N), 822 (C–Cl), 644 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.17 (s, 1H, NHC═O), 7.91 (s, 1H, N═CH), 7.75–7.79 (m, 7H, Ar-H, J = 12 Hz), 6.16 (s, IH, NH); MS [EI] m/z 389 [$M^+ + 1$], 388 [M^+], 390 [$M^+ + 2$].

*2.4.6. N-(6-Chlorobenzo[d]thiazol-2-yl)-2-(4-methoxybenzy lidene)hydrazinecarboxamide (**4f**)*
IR (KBr) λ_{max} (cm^{-1}): 3317 (NH), 1662 (C═O), 1586 (C═N), 816 (C–Cl), 654 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.07 (s, 1H, NHC═O), 7.96 (s, 1H, N═CH), 7.77–7.81 (m, 7H, Ar-H, J = 12 Hz), 6.18 (s, IH, NH); MS [EI] m/z 362 [$M^+ + 2$], 361 [$M^+ + 1$], 360 [M^+].

*2.4.7. N-(6-Chlorobenzo[d]thiazol-2-yl)-2-(4-nitrobenzylidene)hydrazinecarboxamide (**4g**)*
IR (KBr) λ_{max} (cm^{-1}): 3323 (NH), 1674 (C═O), 1591 (C═N), 822 (C–Cl), 651 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.17 (s, 1H, NHC═O), 7.98 (s, 1H, N═CH), 7.78–7.82 (m, 7H, Ar-H, J = 12 Hz), 6.20 (s, IH, NH); MS [EI] m/z 377 [$M^+ + 2$], 376 [$M^+ + 1$], 375 [M^+].

*2.5. Synthesis of 1-(6-chlorobenzo[d]thiazol-2-yl)-3-(4-oxo-2-substituted phenylthiazolidin-3-yl)urea (**5a–g**)*

A mixture of **4** (0.01 mol) and thioglycollic acid (0.01 mol) was heated on an oil-bath at 120–125 °C for 12 h. The reaction mixture was cooled and treated with 10% sodium bicarbonate solution. The product was isolated and recrystallised from methanol–dioxane (4:1).

*2.5.1. 1-(6-Chlorobenzo[d]thiazol-2-yl)-3-(4-oxo-2-phenylthia zolidin-3-yl)urea (**5a**)*
IR (KBr) λ_{max} (cm^{-1}): 3216 (NH), 3126 (C–H aromatic), 1726 (C═O thiazolidinone), 1664 (C═O), 1538 (C═C aromatic), 1440 (C–N benzothiazole), 830 (C–Cl), 692 (C–S–C thiazolidinone), 614 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.85 (s, 1H, CONH), 8.05 (s, 1H, NH), 7.65–7.79 (m, 8H, Ar-H), 2.48 (s, 2H, CH_2 thiazolidinone); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 168.8, 153.8, 151.3, 139.2, 132.3, 129.8, 128.6, 127.1, 126.9, 125.8, 121.2, 118.3, 63.8, 35.2 (CH_2 thiazolidinone); MS [EI] m/z 406 [$M^+ + 2$], 405 [$M^+ + 1$], 404 [M^+].

*2.5.2. 1-(6-Chlorobenzo[d]thiazol-2-yl)-3-(2-(2-chloro phenyl)-4-oxothiazolidin-3-yl)urea (**5b**)*
IR (KBr) λ_{max} (cm^{-1}): 3211 (NH), 3120 (C–H aromatic), 1721 (C═O thiazolidinone), 1668 (C═O), 1542 (C═C aromatic), 1438 (C–N benzothiazole), 836 (C–Cl), 696 (C–S–C thiazolidinone), 620 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.83 (s, 1H, CONH), 8.03 (s, 1H, NH), 7.51–7.71 (m,7H, Ar-H), 2.42 (s,2H, CH_2 thiazolidinone); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 168.8, 153.8, 151.3, 134.0, 132.3, 130.1, 129.8, 128.7, 128.5, 126.7, 125.8, 121.2, 118.3, 102.5, 58.7, 35.2 (CH_2 thiazolidinone); MS [EI] m/z 441 [$M^+ + 2$], 439 [M^+], 438 [$M^+ - 1$], 437 [$M^+ - 2$].

*2.5.3. 1-(6-Chlorobenzo[d]thiazol-2-yl)-3-(2-(2,4-dichloro phenyl)-4-oxothiazolidin-3-yl)urea (**5c**)*
IR (KBr) λ_{max} (cm^{-1}): 3214 (NH), 3112 (C–H aromatic), 1730 (C═O thiazolidinone), 1661 (C═O), 1536 (C═C aromatic), 1430 (C–N benzothiazole), 838 (C–Cl), 681 (C–S–C thiazolidinone), 612 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.81 (s, 1H, CONH), 8.01 (s, 1H, NH), 7.59–7.76 (m, 6H, Ar-H), 2.46 (s, 2H, CH_2 thiazolidinone); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 168.8, 153.8, 151.3, 135.4, 134.1, 132.3, 131.5, 130.3, 129.8, 126.8, 125.8, 121.2, 118.3, 100.6, 58.7, 35.2 (CH_2 thiazolidinone); MS [EI] m/z 475 [$M^+ + 2$], 473 [M^+], 471 [M^+-2].

*2.5.4. 1-(6-Chlorobenzo[d]thiazol-2-yl)-3-(4-oxo-2-o-tolylthi azolidin-3-yl)urea (**5d**)*
IR (KBr) λ_{max} (cm^{-1}): 3217 (NH), 3119 (C–H aromatic), 1737 (C═O thiazolidinone), 1667 (C═O), 1531 (C═C aromatic), 1427 (C–N benzothiazole), 842 (C–Cl), 691 (C–S–C thiazolidinone), 618 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.79 (s, 1H,CONH), 8.07 (s, 1H, NH), 7.62–7.71 (m, 6H, Ar-H), 2.44 (s, 2H, CH_2 thiazolidinone), 2.34 (s,3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 168.8, 153.8, 151.3, 139.0, 136.5, 132.3, 130.3, 129.8, 128.6, 127.0, 125.8, 125.6, 121.2, 118.3, 61.3, 35.2 (CH_2 thiazolidinone), 18.4; MS [EI] m/z 420 [$M^+ + 2$], 419 [$M^+ + 1$], 418 [M^+].

*2.5.5. 2-(3-(3-(6-Chlorobenzo[d]thiazol-2-yl)ureido)-4-oxo thiazolidin-2-yl)phenyl acetate (**5e**)*
IR (KBr) λ_{max} (cm^{-1}): 3225 (NH), 3122 (C–H aromatic), 1724 (C═O thiazolidinone), 1674 (C═O), 1540 (C═C aromatic), 1436 (C–N benzothiazole), 844 (C–Cl), 687 (C–S–C thiazolidinone), 622 (C–S–C benzothiazole); ^{1}H NMR (300 MHz,

DMSO-d_6) δ ppm: 11.81 (s, 1H, CONH), 8.00 (s, 1H, NH), 7.62–7.69 (m,7H, Ar-H), 2.60(s,3H, $OCOCH_3$), 2.51 (s, 2H, CH_2 thiazolidinone), 2.31 (s,3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 169.0, 168.8, 153.8, 151.3, 150.0, 132.3, 129.8, 127.5, 127.0, 125.8, 125.4, 123.8, 121.5, 121.2, 118.3, 57.8, 35.2 (CH_2 thiazolidinone), 20.3; MS [EI] *m/z* 464 [$M^+ + 2$], 463 [$M^+ + 1$], 462 [M^+].

*2.5.6. 1-(6-Chlorobenzo[d]thiazol-2-yl)-3-(2-(2-methoxyphenyl)-4-oxothiazolidin-3-yl)urea (**5f**)*

IR (KBr) λ_{max} (cm^{-1}): 3230 (NH), 3127 (C–H aromatic), 1729 (C═O thiazolidinone), 1681 (C═O), 1543 (C═C aromatic), 1441 (C–N benzothiazole), 849 (C–Cl), 693 (C–S–C thiazolidinone), 617 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.77 (s, 1H, CONH), 8.05 (s, 1H, NH), 7.58–7.61 (m, 7H, Ar-H), 3.88 (s, 1H, OCH_3), 2.55 (s, 2H, CH_2 thiazolidinone); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 168.8, 158.3, 153.8, 151.3, 151.3, 132.3, 129.8, 128.1, 127.6, 125.8, 121.2, 120.9, 118.3, 116.5, 112.2, 57.9, 56.1, 35.2 (CH_2 thiazolidinone); MS [EI] *m/z* 436 [$M^+ + 2$], 435 [$M^+ + 1$], 434 [M^+].

*2.5.7. 1-(6-Chlorobenzo[d]thiazol-2-yl)-3-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl) urea (**5g**)*

IR (KBr) λ_{max} (cm^{-1}): 3236 (NH), 3136 (C–H aromatic), 1737 (C═O thiazolidinone), 1691 (C═O), 1551 (C═C aromatic), 1457 (C–N benzothiazole), 1369 (NO_2), 854 (C–Cl), 688 (C–S–C thiazolidinone), 628 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.71 (s, 1H, CONH), 8.08 (s, 1H, NH), 7.46–7.54 (m, 7H, Ar-H), 2.52 (s, 2H, CH_2 thiazolidinone); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 168.8, 153.8, 151.3, 146.3, 145.3, 132.3, 129.8, 129.6, 125.8, 123.8, 121.2, 63.8, 35.2 (CH_2 thiazolidinone); MS [EI] *m/z* 451 [$M^+ + 2$], 450 [$M^+ + 1$], 449 [M^+].

*2.6. 1-(3-Chloro-2-oxo-4-substituted phenylazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2yl)urea (**6a–g**)*

A solution of **4** (0.01 mol) in dioxane (20 mL) was added to a well stirred mixture of chloroacetylchloride (0.012 mol) and triethylamine (Et_3N) (0.012 mol) in dioxane (10 mL) at 0–5 °C. The reaction mixture was then stirred for 8 h, kept for 2 days at room temperature and then treated with cold water. The solid thus obtained was filtered, washed with water and recrystallised from methanol.

*2.6.1. 1-(3-Chloro-2-oxo-4-phenylazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2yl)urea (**6a**)*

IR (KBr) λ_{max} (cm^{-1}): 3250 (NH), 1745 (C═O β lactam ring), 1670 (C═O), 1560 (C═C), 1442 (C–N benzothiazole), 742 (C–Cl), 638 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.41 (s, 1H, CONH), 7.70 (s, 1H, N–CH β lactam ring), 6.61–6.69 (m,8H,Ar-H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 153.8, 151.3, 143.5, 132.3, 129.8, 128.5, 126.9, 126.7, 125.8, 121.2, 118.3, 66.9, 63.7; MS [EI] *m/z* 410 [$M^+ + 3$], 408 [$M^+ + 1$], 407 [M^+].

*2.6.2. 1-(3-Chloro-2-(2-chlorophenyl)-4-oxoazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2yl)urea (**6b**)*

IR (KBr) λ_{max} (cm^{-1}): 3244 (NH), 1752 (C═O β lactam ring), 1673 (C═O), 1566 (C═C), 1447 (C–N benzothiazole), 742 (C–Cl), 643 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.44 (s, 1H, CONH), 7.72 (s, 1H, N–CH β lactam ring), 6.64–6.69 (m, 8H, Ar-H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 153.8, 151.3, 143.5, 132.3, 132.2, 129.8, 128.6, 128.3, 128.1, 126.6, 125.8, 121.2, 118.3, 63.2, 61.8; MS [EI] *m/z* 443 [$M^+ + 3$], 441 [M^+], 439 [M^+-2].

*2.6.3. 1-(3-Chloro-2-(2,4-dichlorophenyl)-4-oxoazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2-yl)urea (**6c**)*

IR (KBr) λ_{max} (cm^{-1}): 3253 (NH), 1758 (C═O β lactam ring), 1677 (C═O), 1568 (C═C), 1456 (C–N benzothiazole), 751 (C–Cl), 647 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.42 (s, 1H, CONH), 7.71 (s, 1H, N–CH β lactam ring), 6.68–6.72 (m, 6H, Ar-H); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 153.8, 151.3, 151.1, 141.6, 133.7, 132.3, 131.1, 129.8, 126.7, 125.8, 121.2, 119.6, 118.3, 63.2, 61.8; MS [EI] *m/z* 477 [$M^+ + 1$], 475 [$M^+ - 1$], 473 [$M^+ - 3$].

*2.6.4. 1-(3-Chloro-2-oxo-4-p-tolylazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2-yl)urea (**6d**)*

IR (KBr) λ_{max} (cm^{-1}): 3261 (NH), 1768 (C═O β lactam ring), 1675 (C═O), 1574 (C═C), 1460 (C–N benzothiazole), 767 (C–Cl), 651 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.46 (s, 1H, CONH), 7.75 (s, 1H, N–CH β lactam ring), 6.58–6.62 (m,7H, Ar-H), 2.37 (s, 3H, CH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 153.8, 151.3, 140.5, 136.4, 132.3, 129.8, 128.8, 125.8, 125.3, 121.2, 118.3, 66.9, 63.7, 21.3; MS [EI] *m/z* 423 [$M^+ + 2$], 422 [$M^+ + 1$], 421 [M^+].

*2.6.5. 4-(3-Chloro-1-(3-(6-chlorobenzo[d]thiazol-2-yl)ureido)-4-oxoazetidin-2-yl)phenyl acetate (**6e**)*

IR (KBr) λ_{max} (cm^{-1}): 3259 (NH), 1772 (C═O β lactam ring), 1681 (C═O), 1577 (C═C), 1454 (C–N benzothiazole), 771 (C–Cl), 656 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.45 (s, 1H, CONH), 7.74 (s, 1H, N–CH β lactam ring), 6.56–6.61 (m,7H,Ar-H), 2.61 (s,3H, $OCOCH_3$); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 169.0, 153.8, 149.3, 140.3, 132.3, 129.8, 126.0, 125.8, 121.4, 121.2, 66.9, 63.7, 20.3; MS [EI] *m/z* 466 [$M^+ + 1$], 465 [M^+], 464 [$M^+ - 1$].

*2.6.6. 1-(3-Chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2-yl)urea (**6f**)*

IR (KBr) λ_{max} (cm^{-1}): 3266 (NH), 1781 (C═O β lactam ring), 1684 (C═O), 1577 (C═C), 1453 (C–N benzothiazole), 773 (C–Cl), 658 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.44 (s, 1H, CONH), 7.73 (s, 1H, N–CH β lactam ring), 6.58–6.67 (m, 7H, Ar-H), 3.85 (s, 1H, OCH_3); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 158.6, 153.8, 151.3, 135.8, 132.3, 129.8, 126.6, 125.8, 121.2, 118.3, 114.1, 66.9, 63.7, 55.8; MS [EI] *m/z* 438 [$M^+ + 1$], 437 [M^+], 436 [$M^+ - 1$].

*2.6.7. 1-(3-Chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)-3-(6-chlorobenzo[d]thiazol-2-yl)urea (**6g**)*

IR (KBr) λ_{max} (cm^{-1}): 3264 (NH), 1784 (C═O β lactam ring), 1676 (C═O), 1580 (C═C), 1457 (C–N benzothiazole), 1374 (NO_2), 776 (C–Cl), 660 (C–S–C benzothiazole); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.43 (s, 1H, CONH), 7.75 (s, 1H, N–CH β lactam ring), 6.55–6.60 (m, 7H, Ar-H); ^{13}C

NMR (400 MHz, DMSO-d_6) δ ppm: 174.5, 163.5 (β lactam ring), 153.8, 151.3, 149.6, 145.9, 132.3, 129.8, 125.8, 123.7, 123.4, 121.2, 66.9, 63.7; MS [EI] m/z 453 [$M^+ + 1$], 452 [M^+],451 [$M^+ - 1$].

2.7. Antimicrobial activity

All the synthesized compounds were tested for their *in vitro* antimicrobial activity against the Gram positive bacteria *Staphylococcus aureus* (ATCC-25923), the Gram-negative bacteria *Escherichia coli* (ATCC-25922), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (ATCC-700603) in the nutrient agar media, and fungi *Candida albicans* (ATCC-2091), *Aspergillus niger* (MTCC-281), *Aspergillus flavus* (MTCC-277), *Monascus purpureus* (MTCC 369) and *Penicillium citrinum* (NCIM-768) in Sabouraud dextrose medium at 200, 100, 50, 25 and 12.5 μg/mL concentrations by using serial plate dilution method. The minimum inhibitory concentrations (MIC's) values were determined by comparison to ofloxacin and ketoconazole as the reference drugs for bacterial and fungal activity, respectively, as shown in Tables 2 and 3. Standard antibiotics ofloxacin and ketoconzole were used as reference drugs at 50, 25 and 12.5 μg/mL concentrations. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of the compounds that inhibited the visible growth of microorganisms on the plate.

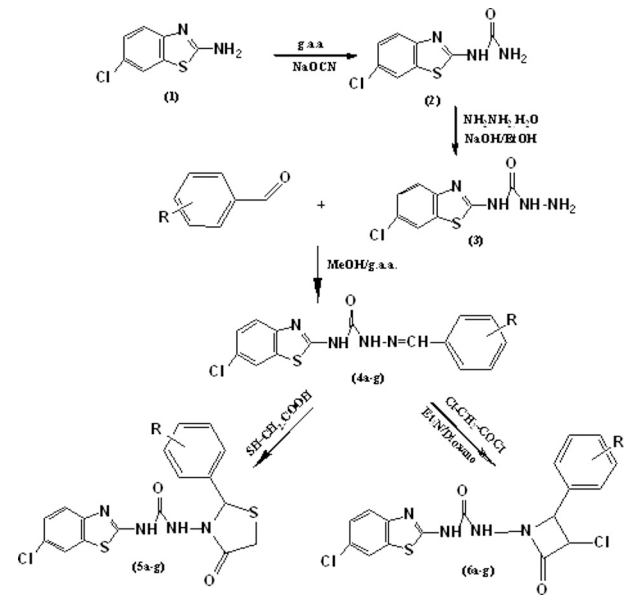
3. Results and discussion

3.1. Chemistry

1-(6-Chlorobenzo[*d*]thiazol-2-yl)-3-(4-oxo-2-substituted phenylthiazolidin-3-yl)urea (**5a–g**) and 1-(3-chloro-2-oxo-4-substituted phenylazetidin-1-yl)-3-(6-chlorobenzo[*d*]thiazol-2yl)urea (**6a–g**) were prepared according to the procedure outlined in Scheme 1. The required 2-substituted benzylidene-*N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazinecarboxamide (**4a–g**) was synthesized by reacting *N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazine carboxamide (**3**) with substituted aromatic aldehyde in ethanol. This salt underwent ring closure by condensation with thioglycollic acid to give the required title compounds (**5a–g**). The synthesis of compounds (**6a–g**) was also accomplished in a single step by reacting the 2-substituted benzylidene-*N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazinecarboxamide (**4a–g**) with chloroacetyl chloride and triethylamine in the presence of dioxane, respectively. The structure of the synthesized compounds was confirmed by elemental analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR & Mass). Physicochemical data for the 2-substituted benzylidene-*N*-(6-chlorobenzo[*d*]thiazol-2-yl)hydrazinecarboxamide derivatives (**4a–g**, **5a–g**, **6a–g**) are given in Table 1.

The IR spectra of compounds **4a–g** showed absorption peaks at 3318 and 1668 cm^{-1} due to N–H, C═O and –N═CH stretching vibrations. The appearance of the stretching of the C═O of thiazolidinone and β-lactam ring at 1726 and 1745 cm^{-1}, respectively, in the spectra of the derivatives, together with the C═O stretching at 1664 and 1670 cm^{-1} confirmed the formation of the compounds **5a–g** and **6a–g**.

The ^{1}H-NMR spectra of compounds **4a–g** revealed a multiplet at δ 7.77–7.81 ppm for the aromatic ring and singlets at δ 6.10 and 7.90 ppm for –NH and –N═CH, respectively.



Scheme 1 Synthetic route for the synthesis of title compounds.

The disappearance of the singlet peak of –N═CH and the presence of a singlet peak at δ 2.48 and 7.70 of –CH_2 of thiazolidinone and –N–CH of β-lactam ring proved that these compounds participated in the cyclisation reaction and formed the desired compounds.

This was further confirmed by ^{13}C–NMR spectrum of the title compounds **5a–g** and **6a–g** which showed peaks at 35.2 and 163.5 ppm suggesting the presence of –CH_2 and –C═O of thiazolidine and β-lactam ring, respectively.

The elemental analysis and molecular ion peaks of compounds **5a–g** and **6a–g** were consistent with the assigned structure.

3.2. Antimicrobial activity

The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **5a–g** and **6a–g** showed good to moderate inhibition at 12.5–200 μg/mL in DMSO. The compounds **5c**, **5d**, **5g**, **6c** and **6f** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active 2,4-dichloro (**5c**), methyl (**5d**), 4-nitro (**5g**) groups attached to the phenyl group at position 2 of the thiazolidin-4-one ring, whereas 2,4-dichlorophenyl (**6c**) and phenoxy group (**6f**) attached at the fourth position of the β-lactam moiety. When these groups were replaced by 2-chlorophenyl (**5b**, **6b**) and acetyl phenyl (**5e**, **6e**), a sharp decrease in activity against most of the strains was observed. Compounds **5a**, **5f**, **6a**, **6d** and **6g** exhibited moderate activity compared to that of standard ofloxacin against all the bacterial strains. Further, the result showed that Gram-negative exhibited better activity than Gram positive organisms.

Compounds **5c**, **5d**, **5f**, **6e** and **6g** showed comparatively good activity against all the fungal strains. The structure of these compounds contains biologically active 2,4-dichlorophenyl (**5c**), methylphenyl (**5d**) and phenoxy (**5f**) groups attached at position 2 of the thiazolidin-4-one ring and acetyl

Table 1 Physical and analytical data of benzothiazole derivatives **4**, **5** & **6a**–**g**.

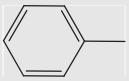
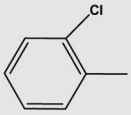
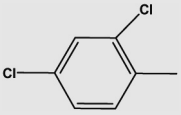
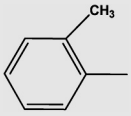
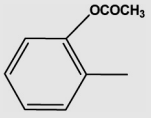
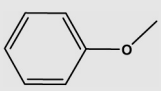
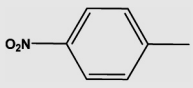
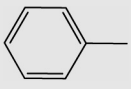
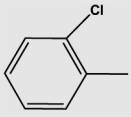
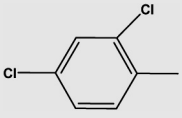
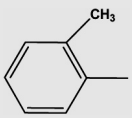
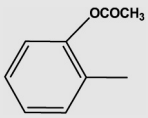
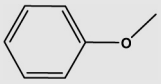
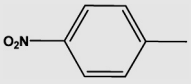
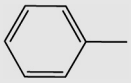
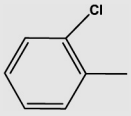
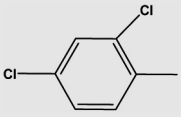
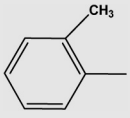
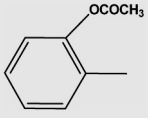
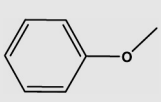
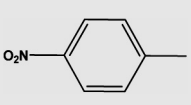
Compound	R	Mol. formula	Yield (%)	M.P. (°C)	Mol. weight	R_f	Analysis % found (calculated)		
							C	H	N
4a		$C_{15}H_{11}ClN_4OS$	84	153	330.79	0.8	54.46 (54.50)	3.35 (3.37)	16.94 (16.63)
4b		$C_{15}H_{10}Cl_2N_4OS$	88	198	365.24	0.6	49.33 (49.38)	2.76 (2.71)	15.34 (15.39)
4c		$C_{15}H_9Cl_3N_4OS$	80	136	399.68	0.7	45.08 (45.11)	2.27 (2.29)	14.02 (14.08)
4d		$C_{16}H_{13}ClN_4OS$	76	149	344.82	0.9	55.73 (55.67)	3.80 (3.76)	16.25 (16.28)
4e		$C_{17}H_{13}ClN_4O_3S$	83	164	388.83	0.6	52.51 (52.54)	3.37 (3.39)	14.41 (14.44)
4f		$C_{16}H_{13}ClN_4O_2S$	79	157	360.82	05	53.26 (53.29)	3.63 (3.57)	15.53 (15.50)
4g		$C_{15}H_{10}ClN_5O_3S$	81	181	375.79	0.8	47.94 (47.78)	2.68 (2.62)	18.64 (18.67)
5a		$C_{17}H_{13}Cl\ N_4O_2S_2$	77	222	404.89	0.7	50.43 (50.46)	3.24 (3.28)	13.84 (13.66)
5b		$C_{17}H_{12}Cl_2N_4O_2S_2$	79	238	439.34	0.6	46.47 (46.49)	2.75 (2.71)	12.75 (12.69)
5c		$C_{17}H_{11}Cl_3N_4O_2S_2$	70	208	473.78	0.8	43.10 (43.14)	2.34 (2.37)	11.83 (11.76)
5d		$C_{18}H_{15}ClN_4O_2S_2$	66	258	418.92	0.7	51.61 (51.58)	3.61 (3.64)	13.37 (13.39)

Table 1 (*continued*)

Compound	R	Mol. formula	Yield (%)	M.P. (°C)	Mol. weight	R_f	Analysis % found (calculated)		
							C	H	N
5e		$C_{19}H_{15}ClN_4O_4S_2$	71	214	462.93	0.9	49.30 (49.34)	3.27 (3.31)	12.10 (12.14)
5f		$C_{18}H_{15}ClN_4O_3S_2$	74	280	434.92	0.6	49.71 (49.67)	3.48 (3.50)	12.88 (12.74)
5g		$C_{17}H_{12}ClN_5O_4S_2$	80	202	449.89	0.8	46.40 (46.43)	3.46 (3.51)	15.03 (15.09)
6a		$C_{17}H_{12}Cl_2N_4O_2S$	71	226	407.27	0.7	50.13 (50.17)	2.97 (2.88)	13.76 (13.64)
6b		$C_{17}H_{11}Cl_3N_4O_2S$	78	232	441.72	0.9	46.22 (46.28)	2.51 (2.54)	12.68 (12.65)
6c		$C_{17}H_{10}Cl_4N_4O_2S$	73	262	476.16	0.5	42.88 (42.79)	2.12 (2.16)	11.77 (11.72)
6d		$C_{18}H_{14}Cl_2N_4O_2S$	76	217	421.30	0.7	51.32 (51.37)	3.35 (3.39)	13.30 (13.34)
6e		$C_{19}H_{14}Cl_2N_4O_4S$	77	238	465.31	0.9	49.04 (49.10)	3.03 (3.07)	12.04 (12.08)
6f		$C_{18}H_{14}Cl_2N_4O_3S$	72	219	437.30	0.8	49.44 (49.47)	3.23 (3.27)	12.81 (12.76)
6g		$C_{17}H_{11}Cl_2N_5O_4S$	75	210	452.27	0.6	45.15 (45.19)	2.45 (2.48)	15.48 (15.51)

(**6e**) and 4-nitrophenyl (**6g**) groups attached at the fourth position of β-lactam ring, respectively. Compounds **5a**, **5b**, **5e**, **5g**, **6a**, **6b** and **6c** showed moderate activity compared to that of the standard against all the fungal strains. All the compounds showed good to moderate activity against all pathogenic fungal strains except compounds **6d** and **6f** having methyl and phenoxy groups attached at the fourth position of the β-lactam nucleus.

Table 2 Antibacterial activity of the title compounds **5** & **6a–g**.

Compounds	Zone of inhibition in mm and MIC (minimum inhibitory concentration) in μg/mL			
	S. aureus	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
5a	13 (100)	17 (50)	19 (50)	19 (50)
5b	5 (< 200)	8 (< 200)	4 (< 200)	8 (< 200)
5c	22 (25)	25 (25)	29 (12.5)	27 (12.5)
5d	22 (25)	30 (12.5)	28 (12.5)	27 (12.5)
5e	3 (< 200)	8 (< 200)	6 (< 200)	7 (< 200)
5f	14 (100)	19 (50)	18 (50)	20 (50)
5g	27 (12.5)	30 (12.5)	27 (12.5)	30 (12.5)
6a	14 (100)	19 (50)	19 (50)	20 (50)
6b	8 (< 200)	7 (< 200)	9 (< 200)	7 (< 200)
6c	22 (25)	29 (12.5)	30 (12.5)	28 (12.5)
6d	12 (100)	17 (50)	19 (50)	18 (50)
6e	4 (< 200)	9 (< 200)	8 (< 200)	7 (< 200)
6f	24 (25)	27 (12.5)	29 (12.5)	30 (12.5)
6g	13 (100)	20 (50)	19 (50)	16 (50)
Ofloxacin	22 (25)	30 (12.5)	27 (12.5)	29 (12.5)

The figures in the table show the zone of inhibition (mm) and the corresponding MIC (μg/mL) values in brackets.

Table 3 Antifungal activity of the title compounds **5** & **6a–g**.

Compound	Zone of inhibition in mm and MIC (minimum inhibitory concentration) in μg/mL				
	C. albicans	*A. niger*	*A. flavus*	*M. purpureus*	*P. citrinum*
5a	19 (50)	19 (50)	14 (100)	13 (100)	19 (50)
5b	18 (50)	11 (100)	14 (100)	20 (50)	17 (50)
5c	28 (12.5)	29 (12.5)	25 (25)	24 (25)	30 (12.5)
5d	29 (12.5)	28 (12.5)	27 (12.5)	21 (25)	23 (25)
5e	19 (50)	14 (100)	20 (50)	20 (50)	15 (50)
5f	22 (25)	24 (25)	29 (12.5)	25 (25)	29 (12.5)
5g	18 (50)	12 (100)	14 (100)	19 (50)	14 (100)
6a	16 (50)	19 (50)	18 (50)	13 (100)	19 (50)
6b	20 (50)	14 (100)	15 (100)	13 (100)	20 (50)
6c	20 (50)	15 (100)	13 (100)	18 (50)	19 (50)
6d	7 (< 200)	8 (< 200)	9 (< 200)	6 (< 200)	7 (< 200)
6e	24 (25)	30 (12.5)	29 (12.5)	26 (12.5)	25 (25)
6f	8 (< 200)	9 (< 200)	8 (< 200)	4 (< 200)	7 (< 200)
6g	30 (12.5)	27 (12.5)	30 (12.5)	22 (25)	29 (12.5)
Ketoconazole	30 (12.5)	28 (12.5)	25 (25)	30 (12.5)	24 (25)

The figures in the table show the zone of inhibition (mm) and the corresponding MIC (μg/mL) values in brackets.

4. Conclusion

- The presence of 2,4-dichloro, methyl and 4-nitro groups attached to the phenyl at position 2 of the thiazolidin-4-ones ring and the presence of 2,4-dichloro and phenoxy groups attached at fourth position of azetidin-2-ones moiety showed good activity against all the bacterial strains.
- Replacing the above substituent with one chloro and acetyl group results in a sharp decrease of antibacterial activity for both thiazolidin-4-ones and azetidin-2-ones nucleus.
- Presence of 2,4-dichloro, methyl and phenoxy groups attached at position 2 of the thiazolidin-4-ones ring and presence of acetyl and nitro groups attached at the fourth position of the β lactam moiety showed increase in activity against all the fungal strains.
- Replacing the above substituent of the β lactam moiety with methyl and phenoxy groups attached at fourth position results in sharp decrease of antifungal activity.
- Further, β lactam derivatives are found to be more active than thiazolidinone derivatives against all pathogenic bacterial and fungal strains. The result also shows that gram-negative exhibited better activity than gram positive organisms.
- Thus, heterocycles accommodating either of the subunits i.e. thiazolidine-4-ones or azetidin-2-ones are expected to prove the therapeutic relevance and their utility in medicinal chemistry and drug development. Ongoing research focuses on the same molecular hybrid template with the incorporation of more effective substituents in search of new specific and effective antimicrobial agents.

Acknowledgements

The authors are thankful to the Head of the Department, Pharmaceutical Chemistry for providing laboratory facilities, Central Drug Research Institute (CDRI) for spectral analysis of the compounds. Authors are also thankful to Dr. Qadir, Head, IGIB, New Delhi for providing bacterial and fungal strains.

References

Gilani, S.J., Alam, O., Khan, S.A., Siddiqui, N., Kumar, H., 2009. Der. Pharm. Lett. 1 (2), 1–8.

Gilani, S.J., Khan, S.A., Alam, O., Siddiqui, N., 2011a. Acta. Pol. Pharm. Drug Res. 68 (2), 205–211.

Gilani, S.J., Khan, S.A., Verma, S.P., Mullick, P., Alam, O., Siddiqui, N., 2011b. J. Enzyme Inhib. Med. Chem. 26 (3), 332–340.

Gurupadayya, B.M., Gopal, M., Padmashali, B., Manohara, Y.N., 2008. Indian J. Pharm. Sci. 70 (5), 572–577.

Halve, A.K., Bhadauria, D., Dubey, R., 2007. Bioorg. Med. Chem. Lett. 17 (2), 341–345.

Iqbal, A., Siddiqui, H.L., Ashraf, C.M., Ahmad, M., Weaver, G.W., 2007. Molecules 12, 245–254.

Ishwar Bhat, K., Mubeen, M., Kalluraya, B., 2003. Indian J. Heterocycl. Chem. 13, 183–184.

Kagthara, P., Teja, S., Rajeev, D., Parekh, H.H., 2000. Indian J. Heterocycl. Chem. 10, 9–12.

Kucukguzel, G., Kocatepe, A., Clercq, E.D., Sahin, F., Gulluce, M., 2006. Eur. J. Med. Chem. 41 (3), 353–359.

Kumar, A., Rajput, C.S., Bhati, S.K., 2007. Bioorg. Med. Chem. 15 (8), 3089–3096.

Lourenco, M.C.S., Souza, M.V.N., Pinheiro, A.C., Ferreira, M.L., Goncalves, R.S.B., Nogueira, T.C.M., Peraltab, M.A., 2007. Arkivoc 15, 181–191.

Mishra, P., Rajak, H., Mehta, A., 2005. J. Gen. Appl. Microbiol. 51, 133–141.

Mohan, J., Kumar, A., 2003. Indian J. Heterocycl. Chem. 12, 189–192.

Nogrady, T., Weaver, F.D., 2005. Medicinal Chemistry: A Molecular & Biochemical Approach. Oxford University Press, p. 559.

Nussbaumer, P., Leitner, I., Stutz, A., 1994. J. Med. Chem. 37, 610–615.

Nussbaumer, P., Leitner, I., Mraz, K., Stutz, A., 1995. J. Med. Chem. 38, 1831–1836.

Patel, N.B., Patel, J.C., 2011. Arabian J. Chem. 4, 403–411.

Pattan, S.R., Suresh, C., Pujar, V.D., Reddy, V.V.K., Rasal, V.P., Koti, B.C., 2005. Indian J. Chem. 44B, 2404–2408.

Ragavendran, J.V., Sriram, D., Patel, S.K., Reddy, I.V., Bharathwajan, N., Stables, J., Yogeeswari, P., 2007. Eur. J. Med. Chem. 42, 146–151.

Veinberg, S., Vorona, K., 2004. Bioorg. Med. Chem. 12, 147–150.

Vigorita, M.G., Ottana, R., Maccari, M.R., Monforte, M.T., Trovato, A., Taviano, M.F., Miceli, N., Luca, G.D., Alcaro, S., Ortuso, F., 2003. Bioorg. Med. Chem. 11 (6), 999–1006.