Synthesis and Antimicrobial Studies of Novel Imidazole Containing Bisazetidinones and Bisthiazolidinone Derivatives

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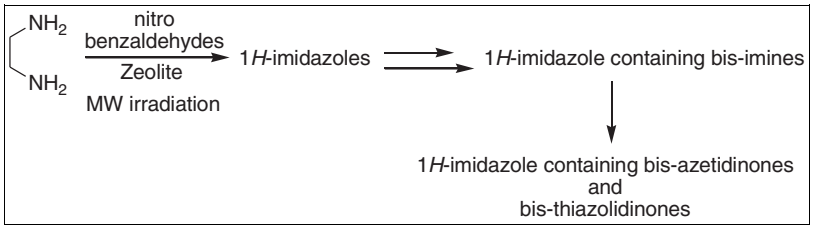

A simple, practical, and efficient approach to new series of imidazole containing bisazetidinones (**7a–j** and **9a–j**) was prepared by Staudinger [2 + 2] cycloaddition reaction, and bisthiazolidinones (**8a–j** and **10a–j**) were obtained by cyclization of bisimines with thioglycolic acid. The bisimines (**5a–j** and **6a–j**) were synthesized by the condensation of 3-(1-(3-aminobenzyl)-4, 5-dihydro-1H-imidazol-2-yl) aniline (**3**, **4**) with a series of different substituted aromatic aldehydes. All the newly synthesized target compounds were evaluated for their *in vitro* antimicrobial activity against two Gram-positive bacteria and two Gram-negative bacteria. Additionally, these synthesized compounds were tested for their antifungal activities. Few compounds showed very good antibacterial and antifungal activity.

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INTRODUCTION

Heterocyclic compounds are an integral part of a huge number of natural and synthetic compounds and play important roles in the biological systems [1]. The structural features of multiple target drugs [2], which are proven to be more effective and economical, demand the presence of various ligating sites along with the presence of hydrophobic moieties in the molecule. The compounds with the imidazole ring system have many pharmacological properties and play important roles in biochemical processes [3]. The applications of imidazoles in medicinal chemistry [4] or natural chemistry products, or alkaloids [5,6] or of 1, 3-disubstituted imidazole salts as ionic liquids [7,8] are also well known. Because of these multiple biological applications, the development of an efficient synthesis of imidazole containing derivatives is still required with more attention even though a few examples of the synthesis and applications of optically active imidazole derivatives have been published [9–13]. In view of this, the chemistry of imidazole containing β-lactams has received significant attention because of their selective functionalization [14] and their biological activities, especially as antimicrobial agents compared with single imidazole or beta lactam rings [15]. Furthermore, thiazolidinone derivatives are found to possess a wide spectrum of biological activities [16]. The Schiff bases are characterized by the -N═CH- (imine) group, which is important for elucidating the mechanism of transamination and racemization reactions in biological systems [17] and are also known to have biological activities such as antimicrobial [18], antifungal [19], antitumor [20], and herbicidal [21]. They have been studied extensively as a class of ligand [22–24] and have been known to coordinate with metal ions through the azomethine nitrogen atom. So, we now developed a novel series of imidazole containing bisimine derivatives, which is found to be new, facile, and convenient methodology. Efforts have been made to exploring such new aspects of β-lactam chemistry using enantiomerically pure β-lactams as versatile intermediates for organic syntheses [25]. The activity of the prominent antibiotics such as penicillins, cephalosporins, and carbapenems is attributed to the presence of 2-azetidinone ring in them. Some other types of biological activities have been reported by the compounds containing 2-azetidinone ring [26] such as antibacterial activity including the antifungal, antitubercular, antitumor, cholesterol absorption inhibition, and enzyme inhibition activity. Extensive efforts have been made on monocyclic β-lactam compounds to improve their biological activities [27], but at the same time, small effort has been drawn to those of bis-β-lactams.

However, it is surprising to note that reports are not available in the literature for the synthesis of imidazole containing bisazetidinones and bisthiazolidinone. Bis-β-lactams serve as an important intermediate for the synthesis [28] of synthetically useful compounds such as bisazetidines, enantiomerically pure diamines, peptides, amino alcohols, polyamino alcohols, polyamino ethers, and polyamines. Bisazetidines are shown to exhibit various biological

activities. Recently, we have published a zeolite-promoted one-pot synthesis of 1H-imidazoles (Figure 1) under microwave irradiation in the absence of solvent [29]. In continuation of our efforts, in this paper we wish to report our results in the Staudinger [2 + 2] cycloaddition of imidazole containing different substituted bisimines to ketene for the synthesis of bisazetidinones and thioglycolic acid, bisimines in ethanol afforded bisthiazolidinones.

RESULTS AND DISCUSSION

Chemistry. Imidazole containing aromatic bisamines (**3** and **4**) was prepared from **1**, **2**, and **3**, taking inspiration from previously reported by the respective authors [30]. Briefly, **1**, **2**, **3**, and zinc powder were stirred with hydrazine glyoxylate at room temperature to furnish aromatic bisamines (**3**, **4**) (yield = 70–76%). A first family of compounds was prepared from **3** and **4**. This precursor could be readily obtained by the condensation of different substituted aromatic aldehydes, in refluxing ethanol, to afford, respectively, bisimines (**5a–j** and **6a–j**) (Scheme 1).

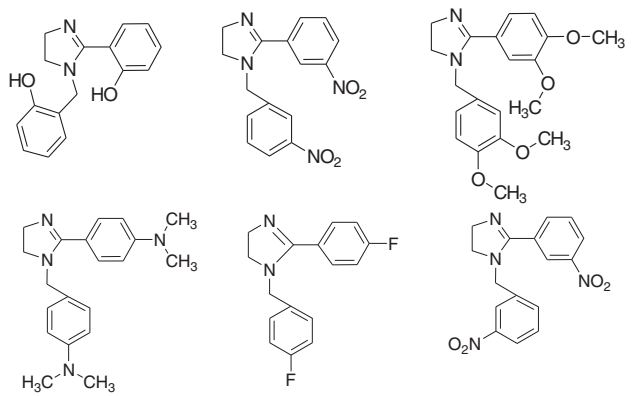


Figure 1. Structures of imidazoles reported our recent publication [29].

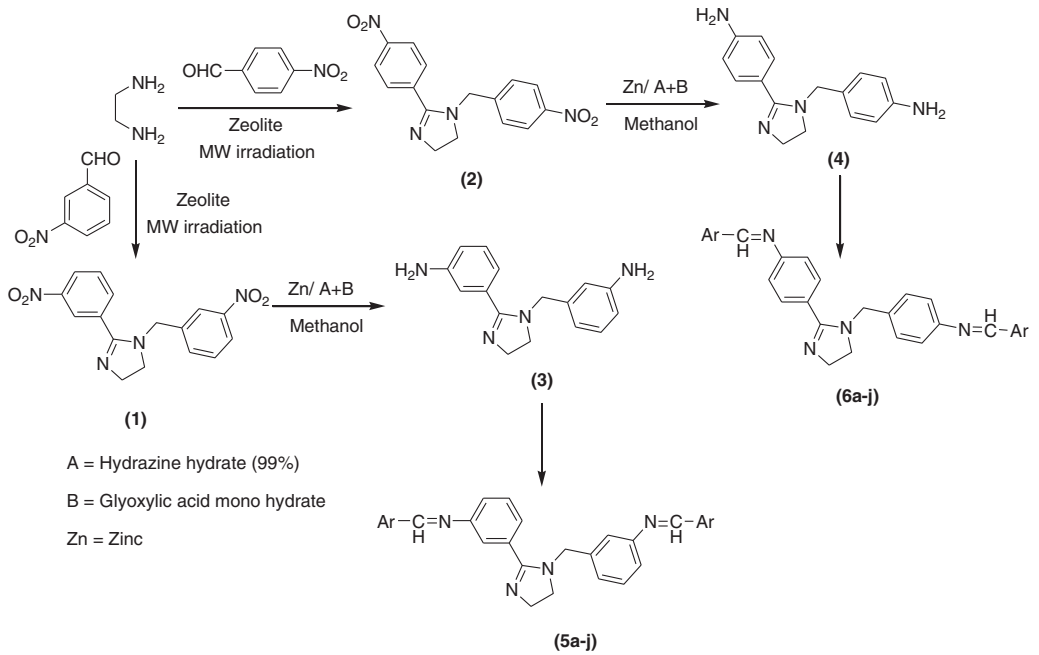
A second family of imidazole containing bisazetidinones (**7a–j** and **9a–j**) was synthesized by [2 + 2] cycloaddition (Staudinger reaction) reaction of ketene, generated *in situ* from chloroacetyl chloride using triethylamine and bisimines, and a series of bisthiazolodinones were prepared from **5a–j** and **6a–j**. Substituted bisimines on cyclization with thioglycolic acid in ethanol afforded corresponding bisthiazolodinones (**8a–j** and **10a–j**). The executed synthetic strategy is highlighted in Scheme 2. The substituents of the compounds are given in Table 1.

All newly synthesized compounds 5**a–d** to **10a–d** were fully characterized by elemental analyses and their IR, ^{1}H NMR, and mass spectral data stated in experimental section. All the compounds were obtained in excellent yield as solids melting in the range 146–264°C.

Biological activity

In vitro biological screening. The newly synthesized compounds **7a–d** to **10a–d** were tested *in vitro* on a panel of selected Gram-positive (*Bacillus subtilis*, *Proteu vulgaris*, and *Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Klebsiella pneumonia*) bacterial and fungal strains (*Aspergillus flavus*, *Aspergillus niger*, and *Trichoderma viridae*) (Tables 2 and 3). The activity of compounds **7d** (H), **8a** (D, F), **8d** (A), **9d** (B, G), **10a** (B, F), and **10c** (D) against selected set of bacterial and fungal strains could not

Scheme 1. Synthesis of substituted bisimines.



Scheme 2. Synthesis of imidazole containing bisazetidinone and bisthiazolodinone.

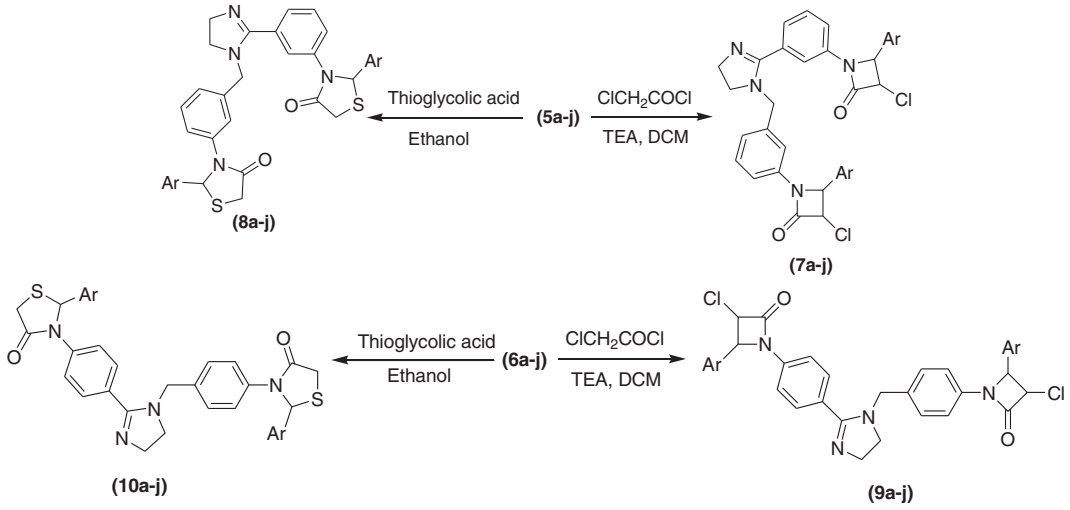


Table 1

Substituent of compounds **5a–j** to **10a–j**.

Compound	Substituent Ar
5a–10a	*p*-$(CH_3)_2NC_6H_4$
5b–10b	*p*-$OCH_3C_6H_4$
5c–10c	*p*-OHC_6H_4
5d–10d	*p*-ClC_6H_4
5e–10e	*p*-$NO_2C_6H_4$
5f–10f	*o*-ClC_6H_4
5g–10g	o-OHC_6H_4
5h–10h	*m*-ClC_6H_4
5i–10i	*m*-$NO_2C_6H_4$
5j–10j	C_6H_5

be precisely determined because the minimum inhibitory concentrations (MICs) were generally higher than the standard used in our *in vitro* screen. These compounds could be considered as antibacterially and antifungally inactive.

Antibacterial studies. From Tables 2 and 3 the investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition to compare with Ampicillin standard drug. The compounds **7b**, **8b**, **9a**, **9b**, and **10b** active against *B. subtilis*, **7a** and **8b** for *P. vulgaris*, **7a** for *S. aureus*, **7c**, **8c**, **9b**, and **10d** for *E. coli*, and **7b**, **8b**, **9a**, and **10b** for *K. pneumonia* showed very good activity almost equivalent to that of standard against all the bacterial strains. The

Table 2

Antibacterial and antifungal activity of bisazetidinone derivatives (zone of inhibition in mm).

	Bacteria (MIC at 100 μg/mL)							
	Gram + Ve			Gram − Ve		Fungi (MIC at 250 μg/mL)		
Compound	A	B	C	D	E	F	G	H
7a	++	+++	+++	++	++	+++	++	+++
7b	+++	++	++	++	+++	++	++	++
7c	++	+	++	+++	++	++	+++	++
7d	++	++	+	++	+	++	++	−
9a	+++	+	++	++	+++	+++	+++	+
9b	+++	++	++	+++	++	+++	++	++
9c	+	++	+	++	++	+++	++	++
9d	++	−	++	+	+	++	−	+
Ampicillin	+++	++	+++	+++	+++			
Nystatin						++ +	+++	+++

MIC, minimum inhibitory concentration.
Gram + ve Bacteria: A, *Bacillus subtilis*; B, *Proteus vulgaris*; C, *Staphylococcus aureus*.
Gram − ve 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).

Table 3

Antibacterial and antifungal activity of bisthiazolidinone derivatives (zone of inhibition in mm).

	Bacteria (MIC at 100 μg/mL)					Fungi (MIC at 250 μg/mL)		
	Gram + Ve			Gram – Ve				
Compound	A	B	C	D	E	F	G	H
8a	++	–	+	–	+	–	++	+
8b	+++	+++	++	++	+++	++	+++	++
8c	++	++	+	+++	+	++	+	++
8d	–	++	++	+	++	+	+	++
10a	++	–	++	+	+	–	+	+
10b	+++	+	+	++	+++	++	–	++
10c	+	++	++	–	+++	+	+++	+
10d	+	++	–	+++	+	++	+++	–
Ampicillin	+++	++	+++	+++	+++			
Nystatin						+++	+++	+++

MIC, minimum inhibitory concentration.
Gram + ve Bacteria: A, *Bacillus subtilis*; B, *Proteus vulgaris*; C, *Staphylococcus aureus*.
Gram – ve Bacteria: D, *Escherichia coli*; E, *Klebsiella pneumonian*.
Fungi: F, *Aspergillus flavus*; G, *Aspergillus niger*; H, *Trichoderma viridae*.
Inactive, – (inhibition zone < 5 mm); Slightly active, + (inhibition zone 5–10 mm); moderately active, ++ (inhibition zone 11–16 mm); Highly active, +++ (inhibition zone > 17 mm).

compounds **7a**, **7c**, **7d**, **8a**, **8c**, **9d**, and **10a** showed moderate active against *B. subtilis*, **7b**, **7c**, **7d**, **8c**, **8d**, **9a**, **9b**, **10c**, and **10d** for *P. vulgaris*, **7b**, **8b**, **8d**, **9c**, **9d**, **10a**, and **10c** for *S. aureus*, **7a**, **7b**, **7d**, **8b**, **9a**, **9c**, and **10b** for *E. coli*, and **7a**, **8d**, **9b**, and **9c** for *K. pneumonia*.

Antifungal studies. The antifungal activity of the compounds was studied with three pathogenic fungi. The results are summarized in Tables 2 and 3. Nystatin has been used as reference for inhibitory activity against fungi. All the compounds showed good antifungal activity. The compounds **7a**, **8a**, and **9a** showed activity against all the three fungi. In addition to this, the compounds **7c**, **9a**, **10c**, and **10d** also exhibited good activity against *A. niger*, whereas **7b**, **7c**, **8c**, **9b**, and **9c** showed moderate activity, and the compounds **7d**, **8c**, and **9d** also showed moderate activity against fungi *T. viridae* and *A. flavus*, respectively, whereas the remaining compounds showed less activity compared with Nystatin.

CONCLUSION

In summary, the newly synthesized series of imidazole containing bisazetidinone and bisthiazolidinone derivatives screened *in vitro* against Gram-positive and Gram-negative bacteria have shown promising activity to compare with standard drug Ampicillin. Most of the compounds among the 36 novel compounds (prepared in this study) were screened against eight microbes for antibacterial activity, and they revealed that moderate to good bacterial inhibition is almost equivalent to that of the standard. As far as the antifungal screening results, these compounds displayed good activity to evaluate with standard drug is Nystatin. To summarize from all the experimental data, the titled compounds could be identified as the most biologically active members with potential antibacterial and antifungal profile. Consequently, imidazole containing bisazetidinones and bisthiazolidinones represents a class that needs further investigation with the hope of finding new antimicrobial agents.

EXPERIMENTAL

Materials. All the chemicals and solvents were obtained from AR grade and were used without further purification. Melting points were taken in an open capillary tube. Elemental analyses were carried out using a Perkin-Elmer (Maryland, US), CHN elemental analyzer model 2400. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-Avance (Switzerland) (300 MHz), Varian-Gemini (Switzerland) (200 MHz) spectrophotometer using DMSO solvent and TMS as the internal standard. Electron ionization mass spectrometry were determined on an LCQ ion trap mass spectrometer (Thermo Fisher, San Jose, CA, USA), equipped with an electron ionization source. The reactions were monitored, and the purity of products was checked out on pre-coated TLC plates (Silica gel 60 F254, Merck, India Scientific Co, Nagpur, Maharashtra, India), visualizing the spots under ultraviolet light and iodine chamber.

Biological screening. Antimicrobial activity of all synthesized compounds was determined by agar diffusion method [31,32]. All human pathogenic bacteria, viz. *B. subtilis*, *E. coli*, *K. pneumonia*e, *P. vulgaris*, and *S. aureus*, and fungi, viz. *A. flavus*, *A. niger*, and *T. viridae*, were obtained from the Osmania University, Hyderabad, India. Stock solutions of compounds were diluted in dimethyl sulfoxide (1% DMSO) to give a final concentration ranging from 50 to 500 μg/mL for determining the MIC value. MIC was defined as the lowest concentration of compound 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 dilution separately for each test of fungi and bacterial strain. The antibiotics Nystatin (30 μg/mL) and Ampicillin (10 μg/mL) are used as reference antifungal and antibacterial agents, respectively, for comparison. Inoculated plates were then incubated at 37°C for antibacterial activity for 24 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 Tables 2 and 3. Biological screening results were mentioned in mm for inhibition zone; that is, these are categorized as 0–5 mm for mild, 6–12 mm for moderate, and 13–17 mm for efficacy, respectively.

Synthesis of bisimines. General procedure for the preparation of bisimine (**5a–j** to **6a–j**): A quantity of (0.008 mol) aldehyde, (0.004 mol) bisamines (**3** and **4**), and 20 mL of ethanol was refluxed for ~2h. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was set on one side to cool. The air that separates may be induced to crystallize by rubbing with glass rod. Collect the solid deposit by filtration, and the crude product was re-crystallized from methanol.

4-((3-(1-(3-(4-(Dimethylamino)benzylideneamino) benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenylimino) methyl)-N,N-dimethylaniline (5a). m.p.: 190–195°C, IR (KBr, cm^{-1}): 1670 (-C═N-), 1630 (-C═N-); ^{1}H NMR: δ = 2.90 (d, 2H, Ar-CH); 3.10 (s, 12H, (Ar-N$(CH_3)_2)_2$); 4.10 (d, 2H, Ar-CH_2); 5.70 (d, 2H, Ar-CH); 6.70–6.80 (m, 5H, Ar-CH); 7.20 (d, 2H, Ar-CH); 7.40 (s, 1H, Ar-CH); 7.60 (d, 2H, Ar-CH); 7.70–7.80 (m, 7H, Ar-CH); 8.40 (s, 1H, N═CH); 8.60 (s, 1H, N═CH); MS ($C_{34}H_{36}N_6$): *m/z* = 528 (M+, 100%). Elemental analysis: Calcd (found): C, 77.24 (76.90); H, 6.86 (6.20); N, 15.90 (15.40).

N-(4-Methoxybenzylidene)-3-(1-(3-(4-methoxybenzylideneamino) benzyl)-4,5-dihydro-1H-imidazol-2-yl)aniline (5b). m.p.: 160–164°C, IR (KBr, cm^{-1}): 1620 (-C═N-), 1640 (-C═N-); ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 3.90 (s, 6H, (Ar-$OCH_3)_2$) 4.10 (d, 2H, Ar-CH_2); 5.60 (d, 2H, Ar-CH); 6.80 (s, 1H, Ar-CH); 7.00–7.10 (m, 4H, Ar-CH); 7.20–7.40 (m, 6H, Ar-CH); 7.60–7.80 (m, 5H, Ar-CH); 8.50 (s, 1H, N═CH); 8.70 (s, 1H, N═CH); MS ($C_{32}H_{30}N_4O_2$): *m/z* = 502 (M+, 100%). Elemental analysis: Calcd (found): C, 76.47 (76.50); H, 6.02 (6.10); N, 11.15 (11.19).

4-((3-(1-(3-(4-Hydroxybenzylideneamino)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenylimino)methyl)phenol (5c). m.p.: 172–176°C, IR (KBr, cm^{-1}): 1610 (-C═N-), 1630 (-C═N-), 2990 (Ar-OH), 3110 (Ar-OH); ^{1}H NMR: δ = 2.40 (d, 2H, Ar-CH); 3.80 (d, 2H, Ar-CH_2); 5.70 (d, 2H, Ar-CH); 6.70–6.80 (m, 5H, Ar-CH); 7.30–7.70 (m, 6H, Ar-CH); 7.90–8.30 (m, 5H, Ar-CH); 8.70 (s, 1H, N═CH); 8.90 (s, 1H, N═CH); 9.20 (s, 2H, (Ar-$OH)_2$); MS ($C_{30}H_{26}N_4O_2$): *m/z* = 474 (M+, 100%). Elemental analysis: Calcd (found): C, 75.93 (75.98); H, 5.52 (5.58); N, 11.81 (11.86).

N-(4-Chlorobenzylidene)-3-(1-(3-(4-chlorobenzylideneamino) benzyl)-4,5-dihydro-1H-imidazol-2-yl)aniline (5d). m.p.: 146–150°C, IR (KBr, cm^{-1}): 1620 (-C═N-), 1650 (-C═N-); ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 4.10 (d, 2H, Ar-CH_2); 5.60 (d, 2H, Ar-CH); 6.70 (s, 1H, Ar-CH); 6.90–7.50 (m, 15H, Ar-CH); 8.50 (s, 1H, N═CH); 8.80 (s, 1H, N═CH); MS ($C_{30}H_{24}N_4Cl_2$): *m/z* = 510 (M+, 95%). Elemental analysis: Calcd (found): C, 70.45 (70.50); H, 4.73 (4.78); N, 10.95 (10.88).

***4-((4-(1-(4-(4-(Dimethylamino)benzylideneamino) benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenylimino) methyl)-N,N-*dimethylaniline (6a).** m.p.: 182–186°C, IR (KBr, cm^{-1}): 1630 (-C═N-), 1650 (-C═N-); ^{1}H NMR: δ = 2.60 (d, 2H, Ar-CH); 3.20 (s, 12H, (Ar-N$(CH_3)_2)_2$); 4.20 (d, 2H, Ar-CH_2); 5.50 (d, 2H, Ar-CH); 6.60–6.80 (m, 4H, Ar-CH); 7.40 (d, 2H, Ar-CH); 7.70(d, 2H, Ar-CH); 7.80–7.90 (m, 8H, Ar-CH); 8.90 (s, 2H, (N═$CH)_2$); MS ($C_{34}H_{26}N_6$): *m/z* = 528 (M+, 100%). Elemental analysis: Calcd (found): C, 77.24 (77.28); H, 6.86 (6.90); N, 15.90 (15.93).

N-(4-Methoxybenzylidene)-4-(1-(4-(4-methoxybenzylideneamino) benzyl)-4,5-dihydro-1H-imidazol-2-yl)aniline (6b). m.p.: 174–179°C, IR (KBr, cm^{-1}): 1610 (-C═N-), 1650 (-C═N-); ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 3.80 (s, 6H, (Ar-$OCH_3)_2$) 4.30 (d, 2H, Ar-CH_2); 5.50 (d, 2H, Ar-CH); 6.80–6.90 (m, 4H, Ar-CH); 7.30 (d, 2H, Ar-CH); 7.40 (d, 2H, Ar-CH); 7.60–7.80 (m, 8H, Ar-CH); 8.90 (s, 2H, (N═$CH)_2$); MS ($C_{32}H_{30}N_4O_2$): *m/z* = 502 (M+, 100%). Elemental analysis: Calcd (found): C, 76.47 (76.42); H, 6.02 (6.05); N, 11.15 (11.10).

4-((4-(1-(4-(4-Hydroxybenzylideneamino)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenylimino)methyl)phenol (6c). m.p.: 165–170°C, IR (KBr, cm^{-1}): 1630 (-C═N-), 1640 (-C═N-), 2920 (Ar-OH), 3120 (Ar-OH); ^{1}H NMR: δ = 2.90 (d, 2H, Ar-CH); 4.20 (d, 2H, Ar-CH); 5.70 (d, 2H, Ar-CH); 6.60–6.70 (m, 4H, Ar-CH); 7.10 (d, 2H, Ar-CH); 7.30 (d, 2H, Ar-CH); 7.50–7.80 (m, 8H, Ar-CH); 8.70 (s, 2H, (N═$CH)_2$); 9.80 (s, 2H, (Ar-$OH)_2$); MS ($C_{30}H_{26}N_4O_2$): *m/z* = 474 (M+, 95%). Elemental analysis: Calcd (found): C, 75.93 (75.98); H, 5.52 (5.60); N, 11.81 (11.77).

N-(4-Chlorobenzylidene)-4-(1-(4-(4-chlorobenzylideneamino) benzyl)-4,5-dihydro-1H-imidazol-2-yl)aniline (6d). m.p.: 161–165°C, IR (KBr, cm^{-1}): 1650 (-C═N-), 1670 (-C═N-); ^{1}H NMR: δ = 2.70 (d, 2H, Ar-CH); 4.10 (d, 2H, Ar-CH_2); 5.80 (d, 2H, Ar-CH); 6.70–6.80 (m, 4H, Ar-CH); 7.50 (d, 2H, Ar-CH); 7.60 (d, 2H, Ar-CH); 7.70–7.90 (m, 8H, Ar-CH); 9.10 (s, 2H, (N═CH)$_2$); MS ($C_{30}H_{24}N_4Cl_2$): *m/z* = 510 (M+, 95%). Elemental analysis: Calcd (found): C, 70.45 (70.48); H, 4.73 (4.76); N, 10.95 (10.90).

General procedure for the preparation of bisazetidinones. A solution of chloroacetyl chloride/phenylacetyl chloride (0.02 mol) in dry dichloromethane was added drop wise to a well-stirred solution of appropriate bisschiff base (0.01 mol) and triethylamine (0.04 mol) in anhydrous dichloromethane (50 mL). After the addition had been completed, the solution 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 sulfate. The products that were obtained after removing the solvent were purified from ethyl acetate and n-hexane.

3-Chloro-1-(3-(1-(3-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)-4-(4-(dimethylamino)phenyl)azetidin-2-one (7a). m.p.: 240–246°C, IR (KBr, cm^{-1}): 1370 (-C-N-), 1730 (-C═O β-lactam); ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 3.10 (s, 12H, (N$(CH_3)_2)_2$); 4.20 (d, 2H, Ar-CH2); 5.20 (d, 2H, Ar-CH); 5.50 (d, 2H, Ar-CH); 5.90 (d, 2H, Ar-CH); 6.70 (m, 4H, Ar-CH); 7.10–7.20 (m, 5H, Ar-CH); 7.30 (d, 2H, Ar-CH); 7.40 (t, 3H, Ar-CH); 7.90 (d, 2H, Ar-CH); MS ($C_{38}H_{38}N_6Cl_2O_2$): *m/z* = 680 (M +, 95%). Elemental analysis: Calcd (found): C, 66.96 (66.92); H, 5.62 (5.58); N, 12.33 (12.29).

3-Chloro-1-(3-(1-(3-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-methoxyphenyl)azetidin-2-one (7b). m.p.: 223–228°C, IR (KBr, cm^{-1}): 1320 (-C-N-), 1785 (-C═O β-lactam); ^{1}H NMR: δ = 2.90 (d, 2H, Ar-CH); 3.80 (s, 6H, (Ar-$OCH_3)_2$); 4.30 (d, 2H, Ar-CH2); 5.10 (d, 2H, Ar-CH); 5.40 (d, 2H, Ar-CH); 5.80 (d, 2H,

Ar-CH); 6.90 (m, 4H, Ar-CH); 7.10–7.30 (m, 7H, Ar-CH); 7.60 (t, 3H, Ar-CH); 7.80 (d, 2H, Ar-CH); MS ($C_{36}H_{32}N_4Cl_2O_4$): $m/z = 654$ (M+, 95%). Elemental analysis: Calcd (found): C, 65.96 (65.99); H, 4.92 (4.98); N, 8.55 (8.60).

3-Chloro-1-(4-(1-(3-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-hydroxyphenyl)azetidin-2-one (7c). m.p.: 213–218°C, IR (KBr, cm^{-1}): 1360 (-C-N-), 1765 (-C═O β-lactam); ^{1}H NMR: δ = 2.70 (d, 2H, Ar-CH); 3.90 (d, 2H, Ar-CH2); 4.90 (d, 2H, Ar-CH); 5.30 (d, 2H, Ar-CH); 5.70 (d, 2H, Ar-CH); 6.70 (m, 4H, Ar-CH); 7.10–7.20 (m, 7H, Ar-CH); 7.50 (t, 3H, Ar-CH); 7.90 (d, 2H, Ar-CH); 9.50 (s, 2H, (Ar-OH)2); MS ($C_{34}H_{28}N_4Cl_2O_4$): $m/z = 626$ (M+, 100%).

3-Chloro-1-(3-(1-(3-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-chlorophenyl) azetidin-2-one (7d). m.p.: 208–213°C, IR (KBr, cm^{-1}): 1350 (-C-N-), 1770 (-C═O β-lactam); ^{1}H NMR: δ = 2.90 (d, 2H, Ar-CH); 4.10 (d, 2H, Ar-CH2); 5.30 (d, 2H, Ar-CH); 5.60 (d, 2H, Ar-CH); 5.90 (d, 2H, Ar-CH); 7.10 (s, 1H, Ar-CH); 7.20 (d, 2H, Ar-CH); 7.40–7.50 (m, 11H, Ar-CH); 7.80 (d, 2H, Ar-CH); MS ($C_{34}H_{26}N_4Cl_4O_2$): $m/z = 664$ (M+, 100%).

3-Chloro-1-(4-(1-(4-(3-chloro-2-(4-(dimethylamino)phenyl)-4-oxoazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-(dimethylamino)phenyl)azetidin-2-one (9a). m.p.: 210–215°C, IR (KBr, cm^{-1}): 1380 (-C-N-), 1760 (-C═O β-lactam); ^{1}H NMR: δ = 2.90 (d, 2H, Ar-CH); 3210 (s, 12H, $(N(CH_3)_2)_2$); 4.30 (d, 2H, Ar-CH_2); 5.10 (d, 2H, Ar-CH); 5.30 (d, 2H, Ar-CH); 5.80 (d, 2H, Ar-CH); 6.60–6.70 (m, 4H, Ar-CH); 6.80 (d, 2H, Ar-CH); 7.10–7.20 (m, 4H, Ar-CH); 7.30–7.40 (m, 4H, Ar-CH); 8.10 (d, 2H, Ar-CH); MS ($C_{38}H_{38}N_6Cl_2O_2$): $m/z = 680$ (M+, 100%).

3-Chloro-1-(4-(1-(4-(3-chloro-2-(4-methoxyphenyl)-4-oxazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-methoxyphenyl) azetidin-2-one (9b). m.p.: 241–246°C, IR (KBr, cm^{-1}): 1340 (-C-N-), 1760 (-C═O β-lactam); ^{1}H NMR: δ = 2.70 (d, 2H, Ar-CH); 3.60 (s, 6H, (Ar–OCH_3)$_2$); 4.20 (d, 2H, Ar-CH_2); 5.10 (d, 2H, Ar-CH); 5.40 (d, 2H, Ar-CH); 5.80 (d, 2H, Ar-CH); 6.40–6.50 (m, 4H, Ar-CH); 6.90 (d, 2H, Ar-CH); 7.20–7.30 (m, 4H, Ar-CH); 7.50–7.60 (m, 4H, Ar-CH); 7.80 (d, 2H, Ar-CH); MS ($C_{36}H_{32}N_4Cl_2O_4$): $m/z = 654$ (M+, 100%).

3-Chloro-1-(4-(1-(4-(3-chloro-2-(4-hydroxyphenyl)-4-oxazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-hydroxyphenyl) azetidin-2-one (9c). m.p.: 195–199°C, IR (KBr, cm^{-1}): 1310 (-C-N-), 1770 (-C═O β-lactam); ^{1}H NMR: δ = 2.50 (d, 2H, Ar-CH); 3.80 (d, 2H, Ar-CH_2); 4.70 (d, 2H, Ar-CH); 5.20 (d, 2H, Ar-CH); 5.60 (d, 2H, Ar-CH); 6.60–6.70 (m, 4H, Ar-CH); 6.80 (d, 2H, Ar-CH); 7.10–7.20 (m, 4H, Ar-CH); 7.30–7.40 (m, 4H, Ar-CH); 7.90 (d, 2H, Ar-CH); 9.80 (s, 2H, (Ar-OH)$_2$); MS ($C_{34}H_{28}N_4Cl_2O_4$): $m/z = 626$ (M+, 100%). Mass spectra, $m/z = 626.00$(100%). Elemental analysis: Calcd (found): C, 65.08 (65.15); H, 4.50 (4.53); N, 8.93 (8.97).

3-Chloro-1-(4-(1-(4-(3-chloro-2-(4-chlorophenyl)-4-oxazetidin-1-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl)-4-(4-chlorophenyl) azetidin-2-one (9d). m.p.: 190–194°C, IR (KBr, cm^{-1}): 1350 (-C-N-), 1740 (-C═O β-lactam); ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 3.90 (d, 2H, Ar-CH_2); 5.30 (d, 2H, Ar-CH); 5.60 (d, 2H, Ar-CH); 5.90 (d, 2H, Ar-CH); 6.60–6.70 (m, 4H, Ar-CH); 6.90 (d, 2H, Ar-CH); 7.10–7.30 (m, 4H, Ar-CH); 7.60–7.70 (m, 4H, Ar-CH); 8.20 (d, 2H, Ar-CH); MS ($C_{34}H_{26}N_4Cl_4O_2$): $m/z = 664$ (M+, 100%). Elemental analysis: Calcd (found): C, 61.46 (61.43); H, 3.94 (3.98); N, 8.43 (8.48).

General procedure for the preparation of bisthiazolidinones. A mixture of bisimine (0.002 mol) and thioglycolic acid (0.004 mol) was dissolved in ethanol (10 mL), and the reaction mixture was refluxed for 14–16 h. The completion of the reaction was monitored by TLC. After the completion of reaction, it was poured in ice cold water, and the solid precipitate was separated out. Collect the solid deposit by filtration, and the crude product was purified from ethyl acetate and n-hexane.

2-(4-(Dimethylamino)phenyl)-3-(3-(1-(3-(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl)phenyl) thiazolidin-4-one (8a). m.p.: 241–246°C, IR (KBr, cm^{-1}): 650 (C-S-C, 4-thiazolidinone),790 (1, 2 disubtituted benzene ring), 1270 (C-N), 1640 (C═O, thiazolidinone), ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 3.20 (s, 12H, $(N(CH_3)_2)_2$); 3.90 (m, 4H, Ar-CH_2); 4.30 (d, 2H, Ar-CH); 5.50 (d, 2H, Ar-CH); 6.10 (d, 2H, Ar-CH); 6.70 (m, 4H, Ar-CH); 6.90–7.10 (m, 5H, Ar-CH); 7.20 (d, 2H, Ar-CH); 7.40 (d, 2H, Ar-CH); 7.60 (s, 1H, Ar-CH); 7.70 (s, 1H, Ar-CH); 7.80 (s, 1H, Ar-CH); MS ($C_{38}H_{40}N_6O_2S_2$): $m/z = 676$ (M+, 100%). Elemental analysis: Calcd (found): C, 67.43 (67.47); H, 5.96 (5.99); N, 12.48 (12.46).

2-(4-Methoxyphenyl)-3-(3-(1-(3-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (8b). m.p.: 220–225°C, IR (KBr, cm^{-1}): 650 (C-S-C, 4-thiazolidinone), 730 (1, 2 disubtituted benzene ring), 1260 (C-N), 1610 (C═O, thiazolidinone), ^{1}H NMR: δ = 2.50 (d, 2H, Ar-CH); 3.70 (s, 6H, (Ar-OCH_3)$_2$); 3.90 (m, 4H, Ar-CH_2); 4.20 (d, 2H, Ar-CH); 5.60 (d, 2H, Ar-CH); 6.10 (s, 1H, Ar-CH); 6.80 (m, 4H, Ar-CH); 7.10 (s, 1H, Ar-CH); 7.20 (d, 2H, Ar-CH); 7.40 (d, 2H, Ar-CH); 7.60 (d, 2H, Ar-CH); 7.70–7.80 (m, 5H, Ar-CH); MS ($C_{36}H_{34}N_4O_4S_2$): $m/z = 650$ (M+, 100%). Elemental analysis: Calcd (found): C, 66.44 (66.46); H, 5.27 (5.30); N, 8.61 (8.65).

2-(4-Hydroxyphenyl)-3-(3-(1-(3-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (8c). m.p.: 232–238°C, IR (KBr, cm^{-1}): 630 (C-S-C, 4-thiazolidinone), 770 (1, 2 disubtituted benzene ring), 1280 (C-N), 1630 (C═O, thiazolidinone), 3030 (Ar-OH); ^{1}H NMR: δ = 2.80 (d, 2H, Ar-CH); 4.10 (m, 4H, Ar-CH_2); 4.30 (d, 2H, Ar-CH); 5.70 (d, 2H, Ar-CH); 6.20 (d, 2H, Ar-CH); 6.60 (m, 4H, Ar-CH); 7.10–7.30 (m, 6H, Ar-CH); 7.50–7.70 (m, 5H, Ar-CH); 9.90 (s, 2H, (Ar-OH)$_2$); MS ($C_{34}H_{30}N_4O_4S_2$): $m/z = 622$ (M+, 100%). Elemental analysis: Calcd (found): C, 65.57 (65.60); H, 4.86 (4.83); N, 9.00 (9.05).

2-(4-Chlorophenyl)-3-(3-(1-(3-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (8d). m.p.: 215–220°C, IR (KBr, cm^{-1}): 660 (C-S-C, 4-thiazolidinone), 750 (1, 2 disubtituted benzene ring), 1220 (C-N), 1680 (C═O, thiazolidinone), ^{1}H NMR: δ = 2.70 (d, 2H, Ar-CH); 3.80 (m, 4H, Ar-CH_2); 4.10 (d, 2H, Ar-CH); 5.70 (d, 2H, Ar-CH); 6.30 (d, 2H, Ar-CH); 7.10–7.20 (m, 7H, Ar-CH); 7.30–7.40 (m, 6H, Ar-CH); 7.60 (d, 2H, Ar-CH); 7.90 (s, 1H, Ar-CH); MS ($C_{34}H_{28}Cl_2N_4O_2S_2$): $m/z = 658$ (M+, 100%).

2-(4-(Dimethylamino)phenyl)-3-(4-(1-(4-(2-(4-(dimethylamino) phenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (10a). m.p.: 218–222°C, IR (KBr, cm^{-1}): 610 (C-S-C, 4-thiazolidinone), 770 (1, 2 disubtituted benzene ring), 1290 (C-N), 1680 (C═O, thiazolidinone); ^{1}H NMR: δ = 2.70 (d, 2H, Ar-CH); 3.10 (s, 12H, $(N(CH_3)_2)_2$); 3.40 (m, 4H, Ar-CH_2); 4.30 (d, 2H, Ar-CH); 5.60 (d, 2H, Ar-CH); 6.50 (d, 2H, Ar-CH); 6.60–6.70 (m, 4H, Ar-CH); 6.80 (d, 2H, Ar-CH); 7.10 (m, 4H, (Ar-CH)); 7.20–

7.30 (m, 5H, Ar-CH); 7.80 (d, 2H, Ar-CH); MS ($C_{38}H_{40}N_6O_2S_2$): $m/z = 676$ (M+, 100%). Elemental analysis: Calcd (found): C, 67.43 (67.40); H, 5.96 (5.98); N, 12.42 (12.48).

2-(4-Methoxyphenyl)-3-(4-(1-(4-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (10b). m.p.: 236–240°C, IR (KBr, cm^{-1}): 610 (C-S-C, 4-thiazolidinone), 770 (1, 2 disubtituted benzene ring), 1230 (C-N), 1660 (C═O, thiazolidinone), ^1H NMR: $\delta = 2.60$ (d, 2H, Ar-CH); 3.50 (s, 6H, (Ar-OCH_3)$_2$); 3.70 (m, 4H, Ar-CH2); 4.30 (d, 2H, Ar-CH); 5.80 (d, 2H, Ar-CH); 6.30 (d, 2H, Ar-CH); 6.60–6.70 (m, 6H, Ar-CH); 7.30–7.40 (m, 5H, Ar-CH); 7.90–8.10 (m, 6H, Ar-CH); MS ($C_{36}H_{34}N_4O_4S_2$): $m/z = 650$ (M+, 100%).

2-(4-Hydroxyphenyl)-3-(4-(1-(4-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (10c). m.p.: 252–258°C, IR (KBr, cm^{-1}): 670 (C-S-C, 4-thiazolidinone), 720 (1, 2 disubtituted benzene ring), 1250 (C-N), 1610 (C═O, thiazolidinone), 3020 (Ar-OH); ^1H NMR: $\delta = 2.80$ (d, 2H, Ar-CH); 3.80 (m, 4H, Ar-CH2); 4.10 (d, 2H, Ar-CH); 5.60 (d, 2H, Ar-CH); 6.10 (d, 2H, Ar-CH); 6.70 (m, 4H, Ar-CH); 6.90 (d, 2H, Ar-CH); 7.20–7.30 (m, 5H, Ar-CH); 7.70–7.80 (m, 6H, Ar-CH); 9.80 (s, 2H, (Ar-OH)$_2$); MS ($C_{34}H_{30}N_4O_4S_2$): $m/z = 622$ (M+, 100%).

2-(4-Chlorophenyl)-3-(4-(1-(4-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)benzyl)-4,5-dihydro-1H-imidazol-2-yl) phenyl)thiazolidin-4-one (10d). m.p.: 223–229°C, IR (KBr, cm^{-1}): 680 (C-S-C, 4-thiazolidinone), 750 (1, 2 disubtituted benzene ring), 1270 (C-N), 1640 (C═O, thiazolidinone); ^1H NMR: $\delta = 2.60$ (d, 2H, Ar-CH); 4.20 (m, 4H, Ar-CH_2); 4.40 (d, 2H, Ar-CH); 5.50 (d, 2H, Ar-CH); 6.30 (d, 2H, Ar-CH); 6.80 (d, 2H, Ar-CH); 7.10–7.20 (m, 4H, Ar-CH); 7.40–7.50 (m, 9H, Ar-CH); 7.90 (d, 2H, Ar-CH); MS ($C_{34}H_{28}Cl_2N_4O_2S_2$): $m/z = 658$ (M+, 100%). Elemental analysis: Calcd (found): C, 61.91 (61.94); H, 4.28 (4.32); N, 8.49 (8.54).

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