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Design, synthesis and antimicrobial evaluation of benzimidazole containing 4-thiazolidinone based 5-arylidene derivatives

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In an attempt to design a potent class of antimicrobials, we have synthesized benzimidazole derivatives based on 4-thiazolidinone which possessed 5-arylidenes **5a-o** by using different catalysts under multistep conventional synthesis. Structures of the synthesized compounds have been established based on spectral data and compounds have been screened for their antimicrobial activity. Compound **5j** shows maximum potency against all Gram-positive bacteria with a minimum inhibitory concentration (MIC) in the range of 25-50 µg/mL while moderate activity against Gram-negative bacterial strains is observed with a MIC value of 62.50 µg/mL. Compound **5n** is found to be the most active against fungal strains with a MIC value of 250 µg/mL.

Keywords: Benzimidazole, Thiazolidinone, Arylidene, Antibacterial activity, Antifungal activity

Bacteria undoubtedly play a significant role in the spread of lethal diseases, which becomes a substantial health risk to humans as they are transported to the masses *via* the air[1]. Scientists have long considered it an essential aspect of their research to identify new antimicrobial candidates that could effectively treat these dreaded infections and eliminate antimicrobial resistance[2-4]. Using exhaustive comprehensive drugs, we cannot only reduce the duration of therapy but also delay the emergence of newer drug-resistant strains. It is possible to eliminate the dreaded problem of drug resistance by applying appropriate praxis of available antimicrobial candidates or novel drugs as drug regimens[5-6]. To solve the problem of drug resistance, new drugs or regimens with maximum safety profiles are essential despite some notable advances in antibacterial therapy and several already available inhibitors against drug-resistant Gram-positive and Gram-negative bacteria[7]. The immune-compromised often face life-threatening infections caused by pathogenic fungi as well. There is lack of currently available drugs that treat fungal infections, making research and development of novel antifungal drugs of utmost importance[8-9].

The benzimidazole nucleus is a pharmacophore of high eminence. These molecules exhibit a variety of biological activities, including antiviral, antibacterial, antifungal, antitumor and anticancer, antihypertension and antiparasitic properties, as well as immunosuppressive effects[10-12]. The presence of benzimidazoles directly inhibit DNA and protein synthesis in bacteria, thus having a strong antibacterial effect[13]. As an important structural component of many biomolecules, thiazolidinone is often utilized in the design of new drug molecules due to its unique five-membered aromatic structure containing two heteroatoms[14].

An integrated approach combines two or more pharmacophores into a single molecule. By targeting different active sites of targets, a molecule which contains more than one pharmacophore offers the potential for selectivity, thereby reducing unwanted side effects. Using a multistep reaction, the substituted benzaldehydes were placed with thiazolidinone moiety at the C-2 position with a small linker attached to the benzimidazole ring and investigated their antimicrobial activity. The current work involves using the benzimidazole scaffold as part of a hybrid approach to developing effective antimicrobial agents. For the development of the targeted molecules as antimicrobials, actithiazic acid (antibiotic), ridinilazole (antibiotic), and thiabendazole

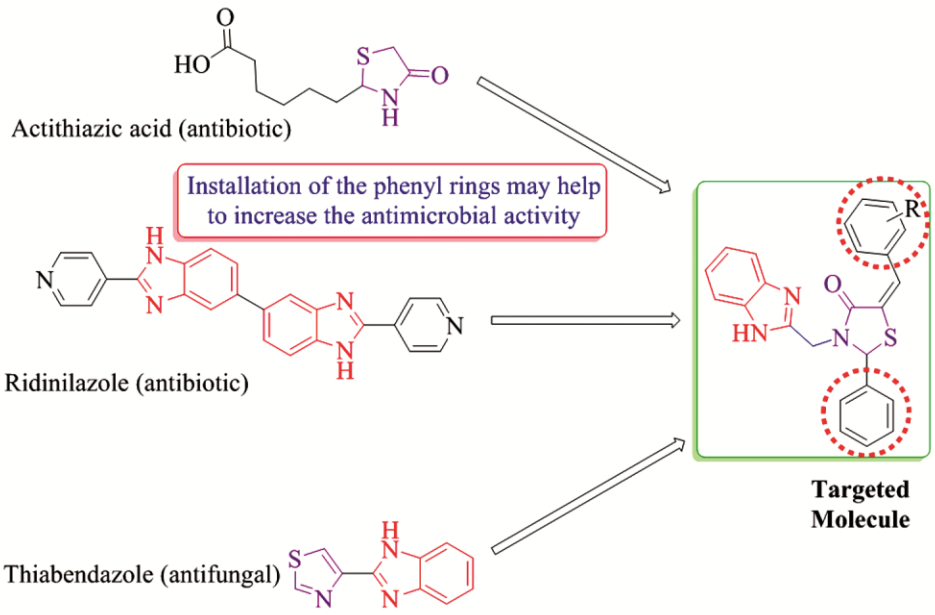


Fig. 1 — An approach for the synthetic design of benzimidazole analogs conjugate 5-arylidene derivatives

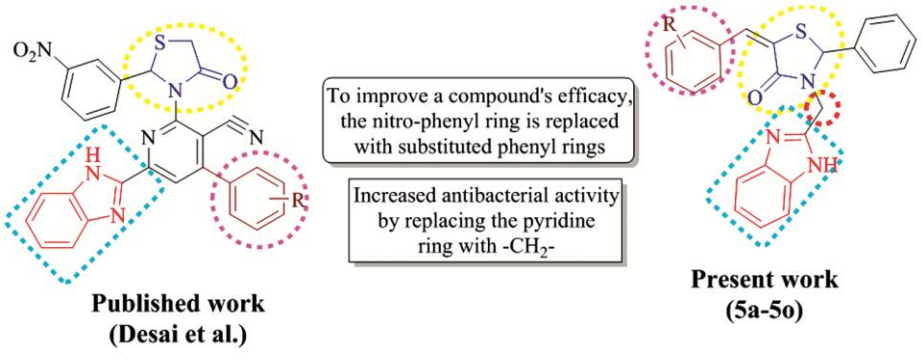


Fig. 2 — Modification of reported work following our previous published work

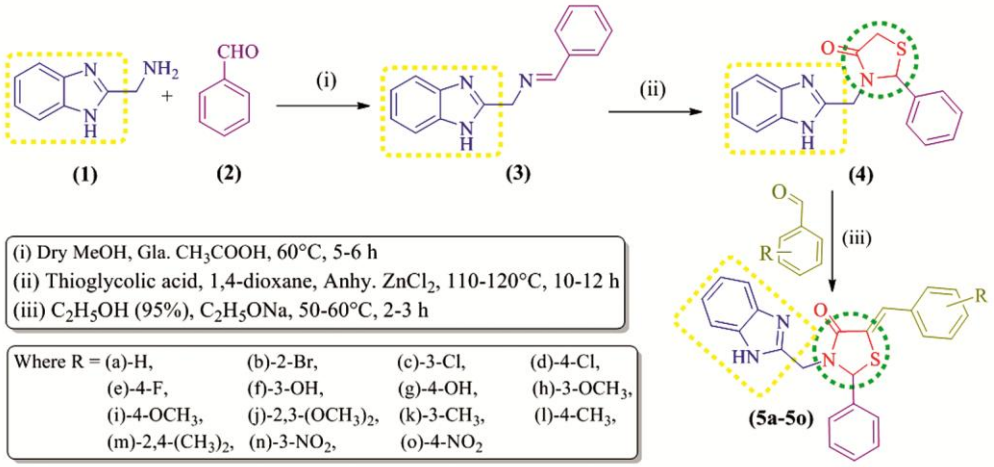
(antifungal) were taken. Benzimidazole is the core pharmacophore of ridinilazole and thiabendazole drugs. The targeted compound was modified by substituted phenyl rings, which may improve its biological properties (Fig. 1).

Novel antimicrobial agents are continuously being developed by our research group. Previously, a series of 6-(1*H*-benzo[*d*]imidazol-2-yl)-2-(2-(3-nitrophenyl)-4-oxothiazolidin-3-yl)-4-arylnicotinonitriles have been synthesized and tested for antimicrobial activity[15]. For enhancing biological activity, the pyridine ring was replaced with a methylene group. To improve the efficiency of the synthesized compounds **5a-o**, the phenyl ring having a nitro group at the *meta* position which was attached to the 2[nd] position of 4-thiazolidinone in our previously synthesized compounds was replaced with a substituted phenyl ring (Fig. 2).

Results and Discussion

Chemistry

The synthesis of the new 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-5-arylidene-2-phenyl-thiazolidin-4-ones is shown in Scheme 1. The synthesis of the targeted compounds was divided into three steps. (1*H*-benzo-[*d*]imidazol-2-yl)methanamine was synthesized according to the procedure described in the literature[16]. *N*-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-1-phenylmethanimine **3** were synthesized by reacting (1*H*-benzo[*d*]imidazol-2-yl)methanamine **1** with benzaldehyde **2** whereas 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-phenylthiazolidin-4-one **4** were synthesized by reacting *N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-phenylmethanimine **3** with thioglycolic acid in presence of anhydrous zinc chloride. Finally, 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-5-arylidene-2-phenyl-thiazolidin-4-ones **5a-o** were synthesized by reacting



Scheme 1 — Synthetic route for newly synthesized compounds **5a-o**

with substituted benzaldehydes in presence of sodium ethoxide.

The formation of Schiff base was initiated by reacting (1*H*-benzo[*d*]imidazol-2-yl)methanamine with benzaldehyde. Based on the IR spectrum, the signal at 1610 cm^{-1} indicates the formation of the C=N bond which was linked between amine and aldehyde. Furthermore, the formation of thiazolidinone from Schiff base at 110-120°C in presence of anhydrous zinc chloride was confirmed by spectral tools. The C–S stretching appearing at 735 cm^{-1} shows the linkage of carbon and sulphur, also converting –N=C< stretching frequency to >N–C< stretching at 1190 cm^{-1} proves the cyclization. Stretching band frequency at 1655 cm^{-1} indicates the appearance of carbonyl group. However, in ^{1}H NMR spectrum peak at δ 3.55 confirms the presence of CH_2– in the thiazolidinone ring. Additionally, ^{13}C NMR has helped to confirm the building of thiazolidinone at δ 172.51 of the carbonyl group and δ 34.88 of –CH_2– carbon has confirmed the formation of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-phenylthiazolidin-4-one **4**.

The final compound was synthesized by refluxing the 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-phenylthiazolidin-4-one **4** with different substituted benzaldehydes using Knoevenagel condensation. In the IR spectra, all previously discussed peaks appeared but additionally there are >C=C< stretching of aliphatic observed at 1562 cm^{-1} which showed the linkage between benzaldehyde and thiazolidinone. Additionally, based on NMR it can be concluded that at δ 7.74 singlet signal of one proton showed the formation of >C=C< between substituted benzaldehydes and thiazolidinone methylene carbon. Also, the appearance of the benzaldehyde ring's protons conformed to different ranges in the ^{1}H NMR spectrum. Disappearing of the δ 3.55 peak confirmed the linkage of the benzaldehyde ring. The addition of carbon signals also confirms the presence of benzaldehyde skeleton. The δ 131.23 signal shows >C=C< formation. The mass spectral analysis also revealed a molecular ion peak which confirmed the molecular weight of compounds **5a-o**.

Antibacterial activity

The comparisons of minimum inhibitory concentrations (MIC) of benzimidazole compounds bearing thiazolidinone against four bacterial strains using the standard drugs, two Gram-positive cocci; *Streptococcus pyogenes* MTCC 442 (*S. pyogenes*), *Staphylococcus aureus* MTCC 96 (*S. aureus*) and two Gram-negative bacteria *Pseudomonas aeruginosa* MTCC 1688 (*P. aeruginosa*) and *Escherichia coli* MTCC 443 (*E. coli*) was carried out. The concentration range was defined by terms such as higher, good, and moderate activity. According to the qualitative assay (Table 1), the most active compound out of the tested compounds was **5j**, which was active against all the Gram positive bacterial strains, when compared to the reference drug.

Compound **5j** showed good to higher activity against all bacteria, except for *P. aeruginosa*. Accordingly, their activity increased due to the presence of benzimidazole and thiazolidinone moieties, respectively. Compounds **5d**, **5j**, **5k** and **5l** showed good activity against *E. coli* with a MIC value of 62.5 µg/mL while other compounds showed

Table 1 — Antimicrobial activity of targeted molecules **5a-o**

Compd	Functional group (-R)	Minimum Inhibition Concentration (MIC)						
		Antibacterial activity				Antifungal activity		
		E.coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 82	*A. clavatus* MTCC 1323
5a	-H	250	250	125	250	1000	>1000	>1000
5b	-2-Br	125	250	100	250	1000	>1000	>1000
5c	-3-Cl	500	250	250	100	1000	>1000	>1000
5d	-4-Cl	62.5	100	125	100	500	>1000	>1000
5e	-4-F	100	100	125	125	1000	>1000	>1000
5f	-3-OH	100	100	125	250	>1000	500	500
5g	-4-OH	100	250	125	125	1000	1000	1000
5h	-3-OCH_3	100	250	250	250	>1000	>1000	>1000
5i	-4-OCH_3	125	250	100	100	500	1000	1000
5j	-2,3(-OCH_3)$_2$	62.5	125	25	50	>1000	>1000	>1000
5k	-3-CH_3	62.5	250	125	100	500	1000	1000
5l	-4-CH_3	62.5	50	125	125	1000	1000	1000
5m	-2,4(-CH_3)$_2$	500	250	250	250	>1000	>1000	>1000
5n	-3-NO_2	125	100	125	62.5	250	>1000	>1000
5o	-4-NO_2	250	100	250	100	500	1000	1000
Chloramphenicol		50	50	50	50	–	–	–
Ciprofloxacin		25	25	50	50	–	–	–
Griseofulvin		–	–	–	–	500	100	100

less activity. Among the compounds tested against *P. aeruginosa*, only compound **5l** presented an equipotent MIC value (50 µg/mL) to chloramphenicol. While only compound **5j** showed higher activity against *S. aureus* with a MIC value of 25 µg/mL. As compared to standard drugs, compound **5j** showed the same MIC value (50 µg/mL) against *S. pyogenes*. A good level of activity was found for compound **5n** against *S. pyogenes* with a MIC value of 62.5 µg/mL whereas other compounds showed a feeble activity. Rest of the compounds showed moderate activity against one or more of the tested bacterial strains.

Antifungal activity

According to Table 1, synthesized compounds **5a-o** were evaluated for their antifungal activity against *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 82, and *Aspergillus clavatus* MTCC 1323 using griseofulvin as a reference drug. Based on antifungal activity, a minimum inhibitory concentration (MIC) was determined. As per Table 1, several compounds having good antifungal activity against *C. albicans* were observed. There was a two-fold decrease in the activity of the compound **5n** against *C. albicans* when compared with griseofulvin. The compounds **5d**, **5i**, **5k**, and **5o** have similar efficacy to standard drugs with a MIC value of 500 µg/mL. Only compound **5f** was moderately effective against *A. niger* and *A. clavatus*.

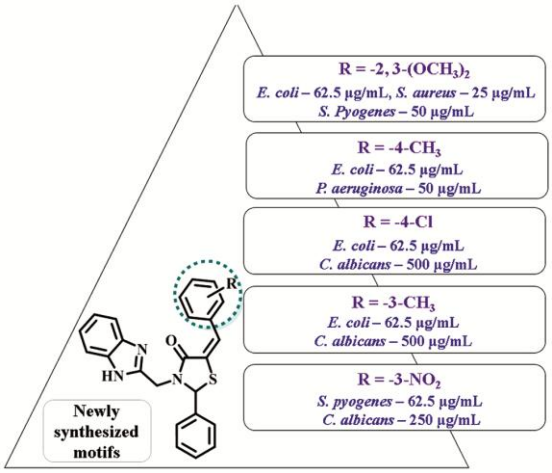


Fig. 3 — Benzimidazole conjugate of 5-arylidene derivatives for the development of new class of antimicrobial agents based on structure-activity relationship (SAR)

Structure activity relationship (SAR)

SAR revealed that among the 3-((1*H*-benzo[*d*] imidazol-2-yl)methyl)-5-substituted arylidene-2-phenylthiazolidin-4-ones **5a-o**, which includes an electron-donating group on its phenyl nucleus, enhanced the biological potency, while an electron-withdrawing substituent caused a significant reduction in potency. Substituting with inductively electron-donating groups, such as dimethoxy showed the most potent antimicrobial effects with a MIC range of 25 to 50 µg/mL (Fig. 3).

Experimental Details

Preparation of *N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-phenylmethanimine, 3

Benzaldehyde **2** (0.01 mol) and compound **1** (0.01 mol) were dissolved in dry methanol (30 mL). A catalytic amount of glacial CH_3COOH was added to the mixture after 10 to 15 min of warming the mixture. Reflux of the reaction mixture at 60°C for 5-6 h was conducted. After cooling at RT, the reaction mixture was filtered to remove the brown crystals that formed. Cold methanol was used to wash the product, and it was dried and purified by recrystallization from ethanol to produce a compound **3**. Yield 74%. Solid. m.p.210–211°C. LCMS: *m/z* 236.21 $[M+H]^+$. Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.51; H, 5.53; N, 17.80%.

Preparation of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-phenylthiazolidin-4-one, 4

A solution of compound **3** (0.01 mole) and thioglycolic acid (0.03 mole) was prepared in 1,4-dioxane (25 mL). After the addition of the catalytic amount of anhy. $ZnCl_2$, the reaction mixture was stirred at 110-120°C for 10-12 h. The reaction mixture was then allowed to cool at RT. In a cooled dil. $NaHCO_3$ solution, the reaction mixture was poured. As a result of the extraction, the light grey product was filtered, washed with dil $NaHCO_3$ solution and then with cold methanol. It was dried and purified by recrystallization from methanol to obtain a compound **4**.Yield 61%. m.p.227–228°C. LCMS: *m/z* 310.13 $[M+H]^+$. Anal. Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.58. Found: C, 65.95; H, 4.82; N, 13.50%.

Preparation of 3-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-5-arylidene-2-phenylthiazolidin-4-ones, 5a-o

As a further step, substituted benzaldehyde (0.01 mol) was added to ethanol (95%) (20 mL) after compound **4** (0.01 mol) was dissolved. The mixture was stirred at 50-60°C for 2-3 h followed by addition of sodium ethoxide in a catalytic amount. Targeted compounds were prepared after the reaction mixture was cooled at RT, washed with cold methanol, dried, and purified by recrystallization from dimethyl formaldehyde followed by filtration and washing.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-benzylidene-2-phenylthiazolidin-4-one, 5a: Yield 83%. m.p.259–260°C. IR (KBr): 3224 (N–H str.), 3099 (C–H str., aromatic), 2981 (C–H str., aliphatic), 1703 (N=C str.), 1647 (C=O str.), 1618 (C=C str., aromatic), 1562 (C=C str., aliphatic), 1284 (N–C str., 2° amine), 1226 (N–C str., 3° amine), 748 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 11.78 (s, 1H of >NH), 8.00 (s, 1H of –C=CH–), 7.61–7.68 (m, 2H of Ar–H), 7.44–7.59 (m, 4H of Benz–H and Ar–H), 7.24–7.42 (m, 6H of Ar–H), 7.11–7.18 (m, 2H of Benz–H), 6.31 (s, 1H of thiazolidinone), 5.06 (s, 2H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 177.52 (>C=O), 157.24 (Benz–C), 142.90 (>C=C<), 140.16 (Benz–C), 138.31 (Ar–C), 136.47 (Benz–C), 133.68 (Ar–C), 129.93 (Ar–C), 129.48 (2) (Ar–C), 128.93 (2) (Ar–C), 128.82 (2) (Ar–C), 128.34 (C_5 of thiazolidinone), 127.43 (Ar–C), 127.37 (2) (Ar–C), 124.15 (Benz–C), 122.61 (Benz–C), 117.30 (Benz–C), 114.29 (Benz–C), 73.63 (C_2 of thiazolidinone), 52.98 ($–CH_2–$); LCMS: *m/z* 398.33 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}N_3OS$: C, 72.52; H, 4.82; N, 10.57. Found: C, 72.48; H, 4.77; N, 10.52%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(2-bromobenzylidene)-2-phenylthiazolidin-4-one, 5b: Yield 76%. m.p.251–252°C. IR (KBr): 3265 (N–H str.), 3031 (C–H str., aromatic), 2959 (C–H str., aliphatic), 1689 (N=C str.), 1643 (C=O str.), 1609 (C=C str., aromatic), 1587 (C=C str., aliphatic), 1311 (N–C str., 2° amine), 1183 (N–C str., 3° amine), 711 (C–S str.), 571 cm^{-1} (C–Br str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.79 (s, 1H of >NH), 7.81 (s, 1H of –C=CH–), 7.54–7.62 (m, 3H of Ar–H and Benz–H), 7.47 (d, *J* = 7.1 Hz, 1H of Benz–H), 7.37–7.45 (m, 3H of Ar–H), 7.24–7.33 (m, 3H of Ar–H), 7.12–7.20 (m, 3H of Ar–H and Benz–H), 6.02 (s, 1H of thiazolidinone), 4.56 (s, 2H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 172.91 (>C=O), 149.65 (Benz–C), 141.14 (Benz–C), 137.22 (Ar–C), 136.34 (Benz–C), 134.32 (Ar–C), 132.30 (Ar–C), 129.67 (>C=*C*<), 129.55 (Ar–C), 129.14 (C_5 of thiazolidinone), 129.05 (Ar–C), 128.85 (Ar–C), 127.87 (Ar–C), 127.78 (Ar–C), 127.72 (Ar–C), 126.40 (Ar–C), 123.89 (Benz–C), 122.47 (Benz–C), 118.45 (Benz–C), 114.45 (Benz–C), 63.62 (C_2 of thiazolidinone), 44.79 ($–CH_2–$); LCMS: *m/z* 477.24 $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}BrN_3OS$: C, 60.51; H, 3.81; N, 8.82. Found: C, 60.45; H, 3.78; N, 8.76%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(3-chlorobenzylidene)-2-phenylthiazolidin-4-one, 5c: Yield 73%. m.p.264–265°C. IR (KBr): 3289 (N–H str.), 3086 (C–H str., aromatic), 2926 (C–H str., aliphatic), 1693 (N=C str.), 1669 (C=O str.), 1606 (C=C str., aromatic), 1577 (C=C str., aliphatic), 1313 (N–C str., 2° amine), 1181 (N–C str., 3° amine), 828 (C–Cl str.), 719 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.07 (s, 1H of >NH), 7.74 (s, 1H of –C=CH–), 7.53–7.62 (m, 3H of Ar–H and Benz–H), 7.37–7.50 (m, 5H of Ar–H and

Benz–H), 7.25–7.35 (m, 3H of Ar–H), 7.10–7.20 (m, 2H of Benz–H), 5.99 (s, 1H of thiazolidinone), 4.55 (s, 2H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.84 (>C=O), 149.65 (Benz–C), 141.14 (Benz–C), 137.51 (Ar–C), 136.37 (Benz–C), 135.77 (Ar–C), 133.88 (Ar–C), 132.19 (>C=*C*<), 131.01 (Ar–C), 129.79 (Ar–C), 129.59 (Ar–C), 129.31 (C_5 of thiazolidinone), 128.86 (2) (Ar–C), 128.66 (Ar–C), 127.82 (2) (Ar–C), 127.71 (Ar–C), 124.21 (Benz–C), 122.47 (Benz–C), 118.34 (Benz–C), 114.44 (Benz–C), 63.62 (C_2 of thiazolidinone), 44.79 ($–CH_2–$); LCMS: *m/z* 432.18 $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}ClN_3OS$: C, 66.74; H, 4.20; N, 9.73. Found: C, 66.69; H, 4.13; N, 9.68%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(4-chlorobenzylidene)-2-phenylthiazolidin-4-one, 5d: Yield 78%. m.p.278–279°C. IR (KBr): 3209 (N–H str.), 3068 (C–H str., aromatic), 2973 (C–H str., aliphatic), 1737 (N=C str.), 1659 (C=O str.), 1625 (C=C str., aromatic), 1580 (C=C str., aliphatic), 1271 (N–C str., 2° amine), 1207 (N–C str., 3° amine), 843 (C–Cl str.), 774 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.17 (s, 1H of >NH), 7.75 (s, 1H of –C=CH–), 7.53–7.59 (m, 3H of Ar–H and Benz–H), 7.47 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.38–7.43 (m, 2H of Ar–H), 7.24–7.36 (m, 5H of Ar–H), 7.09–7.18 (m, 2H of Benz–H), 5.95 (s, 1H of thiazolidinone), 4.54 (s, 1H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.14 (>C=O), 149.68 (Benz–C), 140.11 (Benz–C), 138.16 (Ar–C), 136.08 (Benz–C), 133.62 (Ar–C), 131.38 (Ar–C), 130.31 (>C=*C*<), 129.85 (2) (Ar–C), 129.24 (2) (Ar–C), 128.81 (2) (Ar–C), 128.47 (C_5 of thiazolidinone), 127.68 (2) (Ar–C), 127.39 (Ar–C), 124.33 (Benz–C), 122.54 (Benz–C), 117.43 (Benz–C), 114.34 (Benz–C), 63.61 (C_2 of thiazolidinone), 45.15 ($–CH_2–$); LCMS: *m/z* 432.31 $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}ClN_3OS$: C, 66.74; H, 4.20; N, 9.73. Found: C, 66.67; H, 4.15; N, 9.67%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(4-fluorobenzylidene)-2-phenylthiazolidin-4-one, 5e: Yield 80%. m.p.249–250°C. IR (KBr): 3273 (N–H str.), 3041 (C–H str., aromatic), 2952 (C–H str., aliphatic), 1786 (N=C str.), 1679 (C=O str.), 1644 (C=C str., aromatic), 1551 (C=C str., aliphatic), 1267 (N–C str., 2° amine), 1211 (N–C str., 3° amine), 1149 (C–F str.), 748 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 11.18 (s, 1H of >NH), 7.78 (s, 1H of –C=CH–), 7.63–7.72 (m, 2H of Ar–H), 7.58 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.47 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.38–7.45 (m, 2H of Ar–H), 7.25–7.33 (m, 3H of Ar–H), 7.08–7.17 (m, 4H of Ar–H and Benz–H), 5.95 (s, 1H of thiazolidinone), 4.57 (s, 1H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.03 (>C=O), 161.35 (Ar–C), 149.65 (Benz–C), 141.14 (Benz–C), 137.51 (Ar–C), 136.50 (Benz–C), 131.28 (Benz–C), 130.63 (>C=*C*<), 130.57 (C_5 of thiazolidinone), 128.86 (2) (Ar–C), 128.65 (Ar–C), 127.82 (2) (Ar–C), 127.66 (Ar–C), 124.21 (2) (Ar–C), 122.47 (Benz–C), 118.59 (Benz–C), 116.33 (Benz–C), 116.17 (Benz–C), 114.35 (2) (Ar–C), 63.62 (C_2 of thiazolidinone), 44.79 ($–CH_2–$); LCMS: *m/z* 416.23 $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}FN_3OS$: C, 69.38; H, 4.37; N, 10.11. Found: C, 69.33; H, 4.34; N, 10.05%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(3-hydroxybenzylidene)-2-phenylthiazolidin-4-one, 5f: Yield 71%. m.p.236–237°C. IR (KBr): 3335 (O–H str.), 3215 (N–H str.), 3061 (C–H str., aromatic), 2937 (C–H str., aliphatic), 1722 (N=C str.), 1682 (C=O str.), 1614 (C=C str., aromatic), 1573 (C=C str., aliphatic), 1265 (N–C str., 2° amine), 1251 (N–C str., 3° amine), 1197 (C–O str.), 769 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ δ 10.98 (s,1H of >NH), 8.92 (s, 1H of –OH), 7.79 (s, 1H of –C=CH–), 7.57 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.48 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.38–7.44 (m, 2H of Ar–H), 7.28–7.35 (m, 3H of Ar–H), 7.12–7.26 (m, 4H of Ar–H and Benz–H), 6.96 (s, 1H of Ar–H), 6.89 (d, *J* = 7.7 Hz, 1H of Ar–H), 6.00 (d, *J* = 1.0 Hz, 1H of thiazolidinone), 4.59 (s, 2H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.02 (>C=O), 157.63 (Ar–C), 149.65 (Benz–C), 141.14 (Benz–C), 137.51 (Ar–C), 136.50 (Benz–C), 134.78 (Ar–C), 131.73 (>C=*C*<), 129.81 (Ar–C), 129.69 (C_5 of thiazolidinone), 128.86 (2) (Ar–C), 127.82 (2) (Ar–C), 127.66 (Ar–C), 124.21 (Benz–C), 124.07 (Ar–C), 122.47 (Benz–C), 118.59 (Benz–C), 117.94 (Ar–C), 116.60 (Ar–C), 114.35 (Benz–C), 63.62 (C2 of thiazolidinone), 44.79 ($–CH_2–$); LCMS: *m/z* 414.30 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}N_3O_2S$: C, 69.71; H, 4.63; N, 10.16. Found: C, 69.64; H, 4.59; N, 10.10%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(4-hydroxybenzylidene)-2-phenylthiazolidin-4-one, 5g: Yield 74%. m.p.236–237°C. IR (KBr): 3359 (O–H str.), 3244 (N–H str.), 3044 (C–H str., aromatic), 2959 (C–H str., aliphatic), 1783 (N=C str.), 1677 (C=O str.), 1605 (C=C str., aromatic), 1599 (C=C str., aliphatic), 1286 (N-C str., 2° amine), 1247 (N–C str., 3° amine), 1204 (C–O str.), 736 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.92 (s,1H of >NH), 8.83 (s, 1H of –OH), 7.77 (s, 1H of –C=CH–), 7.58 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.45–7.55 (m, 3H of Ar–H and Benz–H), 7.38–7.43 (m, 2H of Ar–H), 7.24–7.34 (m, 3H of Ar–

H), 7.12–7.18 (m, 2H of Benz–H), 6.98–7.05 (m, 2H of Ar–H), 5.99 (s, 1H of thiazolidinone), 4.56 (s, 2H of –CH_2–); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.03 (>C=O), 159.24 (Ar–C), 149.65 (Benz–C), 141.14 (Benz–C), 137.51 (Ar–C), 136.50 (Benz–C), 131.49 (2) (Ar–C), 131.32 (>C=*C*<), 128.86 (2) (Ar–C), 128.65 (C_5 of thiazolidinone), 127.82 (2) (Ar–C), 127.72 (Ar–C), 127.66 (Ar–C), 124.21 (Benz–C), 122.47 (Benz–C), 118.59 (Benz–C), 116.36 (2) (Ar–C), 114.35 (Benz–C), 63.62 (C2 of thiazolidinone), 44.79 (–CH_2–); LCMS: *m/z* 414.45 $[M+H]^+$. Anal. Calcd for $C_{24}H_{19}N_3O_2S$: C, 69.71; H, 4.63; N, 10.16. Found: C, 69.66; H, 4.60; N, 10.12%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(3-methoxybenzylidene)-2-phenylthiazolidin-4-one, 5h: Yield 69%. m.p.236–237°C. IR (KBr): 3275 (N–H str.), 3072 (C–H str., aromatic), 2934 (C–H str., aliphatic), 2834 (C–H str., –OCH_3), 1715 (N=C str.), 1685 (C=O str.), 1632 (C=C str., aromatic), 1583 (C=C str., aliphatic), 1251 (N–C str., 2° amine), 1210 (N–C str., 3° amine), 781 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 12.10 (s,1H of >NH), 7.78 (s, 1H of –C=CH–), 7.45–7.58 (m, 2H of Benz–H), 7.36–7.43 (m, 3H of Ar–H), 7.23–7.34 (m, 4H of Ar–H), 7.10–7.19 (m, 2H of Benz–H), 7.07 (s, 1H of Ar–H), 6.95 (d, *J* = 7.5 Hz, 1H of Ar–H), 6.00 (s, 1H of thiazolidinone), 4.57 (s, 2H of –CH_2–), 3.82 (s, 3H of –OCH_3); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.02 (>C=O), 159.75 (Ar–C), 149.65 (Benz–C), 141.14 (Benz–C), 137.51 (Ar–C), 136.49 (Benz–C), 134.88 (Ar–C), 131.81 (>C=*C*<), 129.70 (C_5 of thiazolidinone), 129.55 (Ar–C), 128.89 (2) (Ar–C), 127.82 (2) (Ar–C), 127.72 (Ar–C), 125.38 (Ar–C), 124.51 (Benz–C), 122.68 (Benz–C), 118.35 (Benz–C), 115.68 (Ar–C), 114.50 (Benz–C), 113.81 (Ar–C), 63.62 (C_2 of thiazolidinone), 55.28 (–OCH_3), 44.41 (–CH_2–); LCMS: *m/z* 428.41 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}N_3O_2S$: C, 70.24; H, 4.95; N, 9.83. Found: C, 70.19; H, 4.91; N, 9.79%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(4-methoxybenzylidene)-2-phenylthiazolidin-4-one, 5i: Yield 72%. m.p.236–237°C. IR (KBr): 3296 (N–H str.), 3048 (C–H str., aromatic), 2942 (C–H str., aliphatic), 2855 (C–H str., –OCH_3), 1705 (N=C str.), 1654 (C=O str.), 1604 (C=C str., aromatic), 1564 (C=C str., aliphatic), 1235 (N–C str., 2° amine), 1228 (N–C str., 3° amine), 770 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.61 (s, 1H of >NH), 7.77 (s, 1H of –C=CH–), 7.57–7.66 (m, 3H of Ar–H and Benz–H), 7.47 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.38–7.45 (m, 2H of Ar–H), 7.24–7.35 (m, 3H of Ar–H), 7.09–7.18 (m, 2H of Benz–H), 6.98–7.05 (m, 2H of Ar–H), 6.00 (s, 1H of thiazolidinone), 4.55 (s, 2H of –CH_2–), 3.82 (s, 3H of –OCH_3); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.03 (>C=O), 160.19 (Ar–C), 149.65 (Benz–C), 141.14 (Benz–C), 137.51 (Ar–C), 136.49 (Benz–C), 131.86 (2) (Ar–C), 130.92 (>C=*C*<), 128.89 (2) (Ar–C), 128.69 (C_5 of thiazolidinone), 128.41 (Ar–C), 127.82 (2) (Ar–C), 127.72 (Ar–C), 124.51 (Benz–C), 122.68 (Benz–C), 118.35 (Benz–C), 115.01 (2) (Ar–C), 114.50 (Benz–C), 63.62 (C_2 of thiazolidinone), 55.33 (–OCH_3), 44.41 (–CH_2–); LCMS: *m/z* 428.45 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}N_3O_2S$: C, 70.24; H, 4.95; N, 9.83. Found: C, 70.20; H, 4.89; N, 9.81%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(2,3-dimethoxybenzylidene)-2-phenylthiazolidin-4-one, 5j: Yield 61%. m.p.236–237°C. IR (KBr): 3285 (N–H str.), 3012 (C-H str., aromatic), 2934 (C-H str., aliphatic), 2830 (C–H str., –OCH_3), 1751 (N=C str.), 1690 (C=O str.), 1658 (C=C str., aromatic), 1549 (C=C str., aliphatic), 1209 (N–C str., 2° amine), 1233 (N–C str., 3° amine), 751 cm^{-1} (C–S str.); ^{1}H NMR (500 MHz, DMSO–d_6): δ 10.98 (s, 1H of >NH), 7.89 (s, 1H of –C=CH–), 7.59 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.47 (d, *J* = 4.6 Hz, 1H of Benz–H), 7.39–7.45 (m, 2H of Ar–H), 7.21–7.37 (m, 5H of Ar–H), 7.07–7.17 (m, 2H of Benz–H), 7.00 (d, *J* = 5.6 Hz, 1H of Ar–H), 6.03 (s, 1H of thiazolidinone), 4.55 (s, 2H of –CH_2–), 3.88 (s, 6H of –OCH_3); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.14 (>C=O), 149.67 (2) (Benz–C and Ar–C), 148.03 (Ar–C), 140.98 (Benz–C), 136.96 (>C=*C*<), 136.03 (Ar–C), 129.70 (Benz–C), 129.38 (C_5 of thiazolidinone), 128.81 (2) (Ar–C), 127.47 (2) (Ar–C), 127.45 (Benz–C), 124.53 (Ar–C), 124.40 (Benz–C), 123.60 (Ar–C), 123.28 (Ar–C), 122.61 (Ar–C), 118.30 (Ar–C), 114.50 (Benz–C), 114.03 (Benz–C), 63.64 (C_2 of thiazolidinone), 61.18 (–OCH_3), 55.95 (–OCH_3), 44.61 (–CH_2–); LCMS: *m/z* 458.30 $[M+H]^+$. Anal. Calcd for $C_{26}H_{23}N_3O_3S$: C, 68.25; H, 5.07; N, 9.18. Found: C, 68.17; H, 5.00; N, 9.11%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(3-methylbenzylidene)-2-phenylthiazolidin-4-one, 5k: Yield 59%. m.p.236–237°C. IR (KBr): 3270 (N–H str.), 3089 (C–H str., aromatic), 2999 (C–H str., aliphatic), 1716 (N=C str.), 1658 (C=O str.), 1638 (C=C str., aromatic), 1573 (C=C str., aliphatic), 1248 (N–C str., 2° amine), 1275 (N–C str., 3° amine), 737 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.94 (s, 1H of >NH), 7.77 (s, 1H of –C=CH–), 7.59 (d, *J* = 4.6 Hz, 1H of Benz–H), 7.43–7.49 (m, 2H of Benz–H and Ar–H), 7.36–7.41 (m, 2H of Ar–H), 7.07–7.34 (m, 9H of Ar–H and

Benz–H), 5.99 (s, 1H of thiazolidinone), 4.52 (s, 2H of $–CH_2–$), 2.37 (s, 3H of $–CH_3$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.03 (>C=O), 149.67 (Benz–C), 140.14 (Benz–C), 138.77 (Ar–C), 137.52 (Ar–C), 136.51 (Benz–C), 132.06 (Ar–C), 131.84 (>C=*C*<), 129.52 (C_5 of thiazolidinone), 129.47 (Ar–C), 128.83 (Ar–C), 128.34 (2) (Ar–C), 128.28 (2) (Ar–C), 127.55 (Ar–C), 127.39 (2) (Ar–C), 124.24 (Benz–C), 122.53 (Benz–C), 117.45 (Benz–C), 114.25 (Benz–C), 63.61 (C_2 of thiazolidinone), 45.15 ($–CH_2–$), 21.14 ($–CH_3$); LCMS: *m/z* 412.21 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}N_3OS$: C, 72.97; H, 5.14; N, 10.21. Found: C, 72.93; H, 5.08; N, 10.19%.

3-((1*H*-Benzo[d]imidazol-2-yl)methyl)-5-(4-methylbenzylidene)-2-phenylthiazolidin-4-one, 5l: Yield 67%. m.p.236–237°C. IR (KBr): 3235 (N–H str.), 3065 (C–H str., aromatic), 2982 (C–H str., aliphatic), 1758 (N=C str.), 1629 (C=O str.), 1621 (C=C str., aromatic), 1590 (C=C str., aliphatic), 1267 (N–C str., 2° amine), 1223 (N–C str., 3° amine), 739 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.92 (s, 1H of >NH), 7.73 (s, 1H of –C=CH–), 7.58 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.46–7.55 (m, 3H of Ar–H and Benz–H), 7.34–7.44 (m, 4H of Ar–H), 7.24–7.32 (m, 3H of Ar–H), 7.10-7.19 (m, 2H of Benz–H), 5.97 (s, 1H of thiazolidinone), 4.54 (s, 2H of $–CH_2–$), 2.40 (s, 3H of $–CH_3$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.05 (>C=O), 149.67 (Benz–C), 141.07 (Benz–C), 139.98 (Ar–C), 137.56 (Ar–C), 136.49 (Benz–C), 131.64 (Ar–C), 129.54 (>C=*C*<), 128.85 (2) (Ar–C), 128.83 (4) (Ar–C), 128.69 (C_5 of thiazolidinone), 127.55 (2) (Ar–C), 127.39 (Benz–C), 124.14 (Ar–C), 122.48 (Benz–C), 118.59 (Benz–C), 114.33 (Benz–C), 63.60 (C_2 of thiazolidinone), 44.76 ($–CH_2–$), 21.34 ($–CH_3$); LCMS: *m/z* 412.48 $[M+H]^+$. Anal. Calcd for $C_{25}H_{21}N_3OS$: C, 72.97; H, 5.14; N, 10.21. Found: C, 72.92; H, 5.10; N, 10.16%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(2,4-dimethylbenzylidene)-2-phenylthiazolidin-4-one, 5m: Yield 57%. m.p.236–237°C. IR (KBr): 3252 (N–H str.), 3078 (C–H str., aromatic), 2954 (C–H str., aliphatic), 1758 (N=C str.), 1672 (C=O str.), 1634 (C=C str., aromatic), 1602 (C=C str., aliphatic), 1260 (N–C str., 2° amine), 1212 (N–C str., 3° amine), 765 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 11.02 (s, 1H of >NH), 7.79 (s, 1H of –C=CH–), 7.62 (d, *J* = 7.5 Hz, 1H of Ar–H), 7.58 (d, *J* = 6.9 Hz, 1H of Benz–H), 7.47 (d, *J* = 6.9 Hz, 1H of Benz–H), 7.36–7.45 (m, 2H of Ar–H), 7.26–7.35 (m, 3H of Ar–H), 7.24 (s, 1H of Ar–H), 7.10–7.21 (m, 3H of Benz–H and Ar–H), 6.03 (s, 1H of thiazolidinone), 4.57 (s, 2H of $–CH_2–$), 2.39 (s, 3H of $–CH_3$), 2.31 (s, 3H of $–CH_3$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.05 (>C=O), 149.65 (Benz–C), 141.14 (Benz–C), 138.52 (Ar–C), 137.51 (Ar–C), 137.48 (Ar–C), 136.49 (Benz–C), 132.33 (Ar–C), 131.57 (Ar–C), 128.94 (C_5 of thiazolidinone), 128.89 (2) (Ar–C), 127.88 (Ar–C), 127.82 (2) (Ar–C), 127.72 (Ar–C), 127.32 (2) (Ar–C), 125.08 (>C=*C*<), 124.51 (Benz–C), 122.68 (Benz–C), 118.35 (Benz–C), 114.50 (Benz–C), 63.62 (C_2 of thiazolidinone), 44.41 ($–CH_2–$), 21.26 ($–CH_3$), 20.01 ($–CH_3$); LCMS: *m/z* 426.34 $[M+H]^+$. Anal. Calcd for $C_{26}H_{23}N_3OS$: C, 73.38; H, 5.45; N, 9.87. Found: C, 73.35; H, 5.43; N, 9.84%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(3-nitrobenzylidene)-2-phenylthiazolidin-4-one, 5n: Yield 77%. m.p.236–237°C. IR (KBr): 3271 (N–H str.), 3083 (C–H str., aromatic), 2949 (C–H str., aliphatic), 1726 (N=C str.), 1647 (C=O str.), 1605 (C=C str., aromatic), 1546 (C=C str., aliphatic), 1513 (N=O str.), 1279 (N–C str., 2° amine), 1251 (N–C str., 3° amine), 721 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.89 (s, 1H of >NH), 8.45 (s, 1H of Ar–H), 8.17 (d, *J* = 7.2, Hz, 1H of Ar–H), 7.74–7.84 (m, 3H of Ar–H and –C=CH–), 7.59 (d, *J* = 4.6 Hz, 1H of Benz–H), 7.48 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.37–7.46 (m, 2H of Ar–H), 7.25–7.35 (m, 3H of Ar–H), 7.11–7.22 (m, 2H of Benz–H), 5.96 (s, 1H of thiazolidinone), 4.53 (s, 2H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.04(>C=O), 149.67 (Benz–C), 148.53 (Ar–C), 141.43 (Benz–C), 137.51 (Ar–C), 136.21 (Benz–C), 135.18 (Ar–C), 132.71 (Ar–C), 132.29 (>C=*C*<), 129.41 (Ar–C), 129.31 (C_5 of thiazolidinone), 128.81 (2) (Ar–C), 127.76 (Ar–C), 127.72 (2) (Ar–C), 124.48 (Benz–C), 123.89 (Ar–C), 122.88 (Ar–C), 122.65 (Benz–C), 118.58 (Benz–C), 114.51 (Benz–C), 63.64 (C_2 of thiazolidinone), 44.42 ($–CH_2–$); LCMS: *m/z* 443.22 $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}N_4O_3S$: C, 65.15; H, 4.10; N, 12.66. Found: C, 65.11; H, 4.06; N, 12.62%.

3-((1*H*-Benzo[*d*]imidazol-2-yl)methyl)-5-(4-nitrobenzylidene)-2-phenylthiazolidin-4-one, 5o: Yield 82%. m.p.236–237°C. IR (KBr): 3262 (N–H str.), 3076 (C–H str., aromatic), 2958 (C–H str., aliphatic), 1734 (N=C str.), 1651 (C=O str.), 1601 (C=C str., aromatic), 1548 (C=C str., aliphatic), 1534 (N=O str.), 1261 (N–C str., 2° amine), 1237 (N–C str., 3° amine), 777 cm^{-1} (C–S str.); ^{1}H NMR (400 MHz, DMSO–d_6): δ 10.90 (s, 1H of >NH), 8.08 (m, 4H of Ar–H), 7.80 (s, 1H of –C=CH–), 7.58 (d, *J* = 4.5 Hz, 1H of Benz–H), 7.47 (d,

J = 4.5 Hz, 1H of Benz–H), 7.37–7.46 (m, 2H of Ar–H), 7.26–7.36 (m, 3H of Ar–H), 7.13–7.21 (m, 2H of Benz–H), 5.99 (s, 1H of thiazolidinone), 4.55 (s, 2H of $–CH_2–$); ^{13}C NMR (100 MHz, DMSO–d_6): δ 173.03 (>C=O), 149.65 (Benz–C), 148.03 (Ar–C), 141.14 (Benz–C), 137.69 (Ar–C), 137.51 (Ar–C), 136.19 (Benz–C), 130.87 (>C=*C*<), 129.50 (2) (Ar–C), 128.90 (2) (Ar–C), 128.69 (C_5 of thiazolidinone), 127.75 (Ar–C), 127.70 (2) (Ar–C), 124.56 (2) (Ar–C), 124.46 (Benz–C), 122.63 (Benz–C), 118.56 (Benz–C), 114.50 (Benz–C), 63.62 (C_2 of thiazolidinone), 44.41 ($–CH_2–$); LCMS: *m/z* 443.49 $[M+H]^+$. Anal. Calcd for $C_{24}H_{18}N_4O_3S$: C, 65.15; H, 4.10; N, 12.66. Found: C, 65.11; H, 4.06; N, 12.62%.

Conclusion

By synthesizing and screening some novel benzimidazoles bearing 4-thiazolidinone-5-arylidines derivatives, the possibility of synthesizing novel bioactive molecules that will be useful in the development of potent antimicrobial agents have been discussed. *In vitro* antimicrobial activity of the newly synthesized compounds was investigated using a Broth dilution method. The analogs **5d**, **5j**, **5k**, **5l** and **5n** inhibited all the bacterial strains Similarly, analogs **5d**, **5i**, **5k** and **5o** demonstrated good to higher antifungal activity compared to reference drugs. Additionally, compound **5j** inhibited both *S. aureus* and *S. pyogenes* at MIC values 25 µg/mL and 50 µg/mL respectively. To develop effective antimicrobial agents, it was suggested that the final compounds **5a–o** from the SAR studies be modified to increase electronic diversity. The presence of different substituents can also alter biological activity. Having two different pharmacophore scaffolds led to enhanced biological activity.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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