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Eco-Friendly Novel Synthesis, Characterization of 2,3-Disubstituted 4-Thiazolidinone Derivatives and their Antimicrobial Evaluations

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A total of nine derivatives of 4-thiazolidinone were synthesized involving the reaction of benzene-1,2-diamine with 4-aminobenzoic acid followed by reaction with substituted benzaldehyde to get the Schiff bases. These synthesized Schiff bases were further reacted with thioglycolic acid to get the desired thiazolidinones (**29-37**). In addition to conventional synthesis, the microwave irradiation method has also been employedfor the synthesis of these compounds which provides not only pollution free and eco-friendly environment but also excellent yields. The results showed that 2-substituted thiazolidinone derivatives exhibit good antibacterial activity. It was also recorded that the compounds containing -Cl, -NO_2 group with thiazolidinone nucleus are more active than other compounds of the synthesized series.

Keywords: 4-Thiazolidinones, Schiff bases, Biological activity, Benzimidazoles, Microwave synthesis.

INTRODUCTION

The impact of infectious diseases caused by bacteria, fungi, viruses and parasites are particularly large in developing countries due to relatively inadequate medicines, emergence of broad drug resistance as well as lack of awareness. There is an urgent need of synchronize plan to fight against bacterial infections which now again became a threat [1-3]. The abuse of the prescriptions as well as insufficient innovative drug development to the condition of antibiotic resistance emergency [4,5].

In recent years, the extensive biological potential of 4-thiazolidinone compounds have been found to be of special interest in the field of medicinal chemistry thus established it as one of the biologically significant scaffolds [6,7]. A wide spectrum of pharmacological activities have been documented against several targets such as antiviral [8] and anti-HIV [9-11], antimicrobial [12-21], anti-inflammatory and analgesic [22-24], anticancer [25,26], antidiuretic [27,28], antiparasitic [29,30], antidiabetic [31,32], antihyperlipidemic (Fig. 1) [33,34]. It has also been documented that the Schiff bases exhibited good antimicrobial potential with broad spectrum of biological activities. It is established that clubbing of 2-substituted benzimidazole and 4-thiazolidinone may lead to a new molecule which is having better activity profile and retains pharmacological property with enhanced selectivity. Investigation of the structure-activity relationship exhibited that the incorporation of (thio) urea-based Schiff bases leads to more potent derivatives with a broader spectrum of antimicrobial activity [35].

With less harmful effects of chemicals on the environment by employing solvent free conditions, greener techniques can be applied to synthesize both well-known chemical compounds by more feasible routes and completely new materials [36]. Many reactions have been performed efficiently and conveniently even with solid reactants in eco-friendly conditions, which also reduces the cost of solvent. In present work, the solvent free

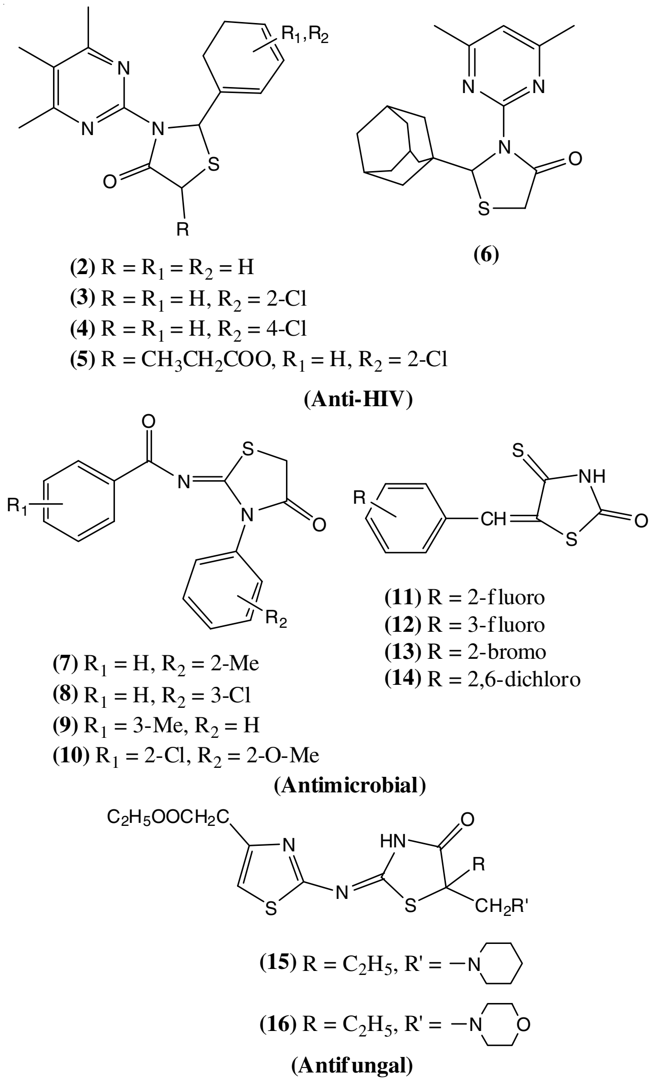


Fig. 1. Biological activities of some 4-thiazolidinone compounds (**2-16**)

synthesis of thiazolidinones is explored. Microwave assisted organic synthesis, a green chemistry methodology, is currently used in the drug synthesis. Microwave-assisted synthesis progresses both improvement in quantity as well as time for research chemists by offering the welfares of extremely reduced reaction times, better yield and pure products [37].

The role of green chemistry is essential to ensure that the next generation of chemicals, materials and energy is more sustainable than the current generation. The eco-friendly chemical processes and products requires the development of novel and cost-effective approaches to prevent pollution of the environment for the present world [38,39]. In view of the above facts, the synthesis of some heterocyclic compounds under green chemistry approach is carried out along with the evaluation of antibacterial and antifungal activity of 2,3-disubstituted 4-thiazolidinone derivatives.

EXPERIMENTAL

All the chemicals and reagents were procured from Himedia Chem. Ltd, S.d-. fine Ltd., E. Merck and Sigma-Aldrich. Melting points were determined using capillary tubes on an electrical melting point apparatus and are uncorrected. The progress of reactions was monitored on thin layer chromatography (TLC) plates (silica gel G) using chloroform with ethanol as mobile phase and the chromatograms were visualized under a UV lamp and iodine vapours. Nuclear Magnetic Resonance (^{1}H & ^{13}C NMR) spectra were determined on Bruker spectrospin DPX-300 MHz in $CDCl_3$. Chemical shift (δ) values are reported in parts per million (ppm) with tetramethylsilane (TMS) as internal reference. The exchangeable protons (OH and NH) are definite by D_2O exchange. Mass spectra were recorded on LC-MS/MS (Perkin-Elmer and LABINDIA, Applied Bio system) model no. API 3000. Infrared spectra be taken on Perkin-Elmer AX-1 spectrometer and values are expressed in cm^{-1}. The purity of the compounds was verified on the basis of elemental analysis using apparatus Perkin-Elmer 2400 elemental analyzer. The microwave irradiated synthesis was performed in scientific microwave oven, catalyst System (operating between 140-700 W).

General procedure for the synthesis of 4-(1*H*-benzo[*d*]-imidazole-2-yl)aniline (19)

Conventional method: Equimolar quantity of *o*-phenylenediamine (0.1 mol, 10.8 g) and *para*-amino benzoic acid (0.1 mol, 13.7 g) were dissolved in ethanol. It was refluxed on water a bath at 70-75 ºC in round bottomed flask for 6 h [40,41]. The completion of the reaction was monitored on TLC by using chloroform and ethanol (7:3) as mobile phase. After cooling, 10% NaOH solution was added gradually with continuous stirring to made alkaline. The crude product was filtered, washed with cold water, decolorized, washed and finally dried. The product was then recrystallized from ethanol. Yield: 65%; m.p: 170-172 ºC; colour: dark brown solid; IR (cm^{-1}, KBr): 3557.37 (N-H *str.*), 1682.38 (C=N), 1618.65 (N-H bend.), 1233.38 (C-N), 3095.28 (arom. C-H *str.*). Anal. calcd. for $C_{13}H_{11}N_3$ (*m.w.* 209.5) C, 74.63; H, 5.30; N, 20.16.

Microwave assisted: Equimolar quantity of *o*-phenylenediamine (0.1 mol, 10.8 g) and *p*-aminobenzoic acid (0.1 mol, 13.7 g) was irradiated in a microwave at 320 W for 4-5 min with solvent ethanol. The completion of the reaction was monitored on TLC by using petroleum ether and ethyl acetate (7:3) as mobile phase. After cooling, 10% NaOH solution was added slowly with stirring to precipitate the product. The product was filtered, washed with cold water and decolorized the product with charcoal. The crude crystalline product was dried and recrystallized with ethanol [42]. The product was dark brown in colour. Yield: 87%, m.p: 170-171 ºC. FT-IR (KBr, ν_{max}, cm^{-1}): 3557.37 (N-H *str.*), 3095.28 (arom. C-H *str.*), 1682.38 (C-N), 1618.65 (N-H bend.), 1233.38 (C=N). Anal. calcd. for $C_{13}H_{11}N_3$ (*m.w.* 209.5): C, 74.63; H, 5.30; N, 20.16.

General procedure for the synthesis of Schiff bases (20-28)

Conventional method: 4-(1*H*-Benzo[*d*]-imidazole-2-yl)-aniline (**19**) (0.1 mol) in 30 mL of ethanol containing a small amount of glacial acetic acid, substituted benzaldehyde (0.1 mol) was added and refluxed for 9-13 h. The completion of reaction was monitored on TLC by using chloroform and ethanol (8:2) as mobile phase. After cooling, the reaction mixture was poured into crushed ice, filtered, washed, dried and recrystallized from ethanol to yield the Schiff bases (**20-28**).

Microwave method: Compound **19** (0.07 mol) in 30 mL of ethanol containing 2-3 drops of glacial acetic acid, substituted benzaldehyde (0.07 mol) was added and the mixture was irradiated in a microwave at 100 W for 2-5 min. The completion of the reaction was monitored by TLC. It was then cooled, poured into crushed ice, filtered, washed, dried and recrystallized from ethanol.

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(2-hydroxyphenyl)thiazolidin-4-one (20): IR (KBr, ν_{max}, cm^{-1}): 3610.35 3094.39 (C-H *str.*), (O-H), 1633.67 (N-H bend.), 1660.43 (C=N imine).

4-((4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylimino)methyl)phenol (21): IR (KBr, ν_{max}, cm^{-1}): 3642.29 (O-H), 1628.78 (C=N imine) , 1522.31 (N-H bend), 1502.91 (arom. C=C *str.*).

4-((4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylimino)methyl)-2-ethoxyphenol (22): IR (KBr, ν_{max}, cm^{-1}): 3634.28 (O-H), 3028.38 (alkane C-H *str.*), 1683.38 (C=N imine), 1612.96 (N-H bend.), 1512.36 (arom. C=C *str.*), 1238.79 (C-O).

5-((4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylimino)methyl)-2-methoxyphenol (23): IR (KBr, ν_{max}, cm^{-1}): 3637.21 (O-H) , 3021.31 (alkane C-H *str.*), 1682.71 (C=N imine), 1611.36 (N-H bend.), 1586.21 (arom. C=C *str.*), 1297.21 (ether C-O *str.* conjugated with Ar ring).

4-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(2-nitrobenzylidene)aniline (24): IR (KBr, ν_{max}, cm^{-1}): 3026.38 (alkane C-H *str.*) , 1681.71 (C=N imine), 1612.36 (N-H bend.), 1572.36 (arom. C=C *str.*), 1494.31 (arom. NO_2).

4-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(3-nitrobenzylidene)aniline (25): IR (KBr, ν_{max}, cm^{-1}): 3063.71 (alkane C-H *str.*), 1681.35 (C=N imine), 1613.35 (N-H bend.), 1583.39 (arom. C=C *str.*), 1434.36 (arom. NO_2).

4-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(4-fluorobenzylidene)aniline (26): IR (KBr, ν_{max}, cm^{-1}): 3063.51 (alkane C-H *str.*), 1662.39 (C=N imine), 1507.36 (N-H bend.), 1475.79 (arom. C=C *str.*), 1217.21 (C-F *str.*).

4-((4-(1*H*-Benzo[*d*]imidazol-2-yl)phenylimino)methyl)-2,6-dimethoxyphenol (27): IR (KBr, ν_{max}, cm^{-1}): 1625.38 (amide N-H bend.), 1584.38 (C=N imine), 1428.32 (arom. C=C *str.*), 1257.38 (ether C-O *str*. (conjugated with Ar ring).

4-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(3-chlorobenzylidene)aniline (28): IR (KBr, ν_{max}, cm^{-1}): 2994.78 (alkane C-H *str.*), 1684.38 (C=N imine), 1594.62 (arom. C=C *str.*), 1545.63 (N-H bend.), 672.38 (C-Cl *str.*).

General procedure for the synthesis of thiazolidinone derivatives (29-37)

Conventional method: Synthesized **Schiff base** (0.01 mol, 20-28) in DMF, 0.01 mol of thioglycolic acid with a pinch of anhydrous $ZnCl_2$ added slowly and refluxed at 120 ºC for 16-18 h . The completion of the reaction was monitored on TLC by using chloroform and ethanol in suitable proportion as mobile phase. DMF was distilled out to yield desire thiazolidinone derivative. The recrystallization was done from ethanol.

Microwave method: A mixture of substituted Schiff base (1.5 g, 0.005 mol, **20-28**) and thioglycolic acid (0.43 g, 0.005 mol) was mixed. A pinch of anhydrous $ZnCl_2$ was added, mixed well and irradiated in microwave oven at 100 W for 7 min and 150 W for 2 min. The completion of the reaction was monitored on TLC using petroleum ether and ethyl acetate (3:4) as mobile phase. The mixture was cooled and the product was recrystallized from ethanol.

The synthesized compounds were characterized by the determination of their physico-chemical properties (Table-1).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(2-hydroxyphenyl) thiazolidin- 4-one (29): IR (KBr, ν_{max}, cm^{-1}): 3623.78 (arom. OH), 3218.20 (arom. N-H *str.*), 1784.29 (C=O *str.*), 1688.35 (C=N imine), 1618.69 (N-H bend.), 1532.89 (arom. C=C), 1198.37 (C-N bend.), 1122.37 (C-O). ^{1}H NMR ($CDCl_3$): 12.569 (s, 1H), 9.686 (s, 1H), 8.207-8.201 (d, *J* = 1.8 Hz, 2H), 7.598-7.592 (*J* = 1.8 Hz), 7.339-7.332 (d, *J* = 2.1 Hz, 2H),

TABLE-1
PHYSICAL DATA OF SYNTHESIZED 4-THIAZOLIDINONE DERIVATIVES (**19-37**) BY CONVENTIONAL METHOD

Compd. code	R (substituent's)	m.f.	m.w.	Colour	m.p. (°C)	Solubility	R_f value
19	–	$C_{13}H_{11}N_3$	209.5	Dark brown	170-171	Ethanol	0.59
20	2-OH	$C_{20}H_{15}N_3O$	313.9	Light yellow	228-230	Ethanol, methanol	0.68
21	4-OH	$C_{20}H_{15}N_3O$	313.8	Dark yellow	240-242	Ethanol	0.65
22	3-OC_2H_5, 4-OH	$C_{22}H_{19}N_3O_2$	357.8	Light brown	210-212	DMSO, ethanol, methanol	0.69
23	4-OCH_3, 3-OH	$C_{21}H_{17}N_3O_2$	343.5	Light yellow	230-232	Ethanol	0.61
24	2-NO_2	$C_{20}H_{14}N_4O_2$	342.7	Dark yellow	250-253	Ethanol	0.64
25	3-NO_2	$C_{20}H_{14}N_4O_2$	343.9	Light brown	212-213	Ethanol	0.62
26	4-F	$C_{20}H_{14}FN_3$	316.2	Dark brown	200-202	Ethanol	0.68
27	3,5-OCH_3, 4-OH	$C_{20}H_{14}ClN_3$	374.1	Off white	240-242	Ethanol	0.52
28	3-Cl	$C_{20}H_{14}ClN_3$	331.7	White	198-200	Ethanol	0.57
29	2-OH	$C_{22}H_{17}N_3O_2S$	387.9	Green	310-312	Ethanol, methanol	0.66
30	4-OH	$C_{22}H_{17}N_3O_2S$	387.6	Brown	298-300	Ethanol	0.63
31	3-OC_2H_5, 4-OH	$C_{24}H_{21}N_3O_3S$	431.9	Light yellow	340-342	Ethanol	0.72
32	4-OCH_3, 3-OH	$C_{23}H_{19}N_3O_3S$	417.8	Brown	330-332	Methanol	0.58
33	2-NO_2	$C_{22}H_{16}N_4O_3S$	416.9	White	325-327	DMSO, ethanol, methanol	0.52
34	3-NO_2	$C_{22}H_{16}N_4O_3S$	416.2	Cream white	250-252	Ethanol, methanol	0.62
35	4-F	$C_{22}H_{16}FN_3OS$	389.9	Brown	320-322	Ethanol	0.63
36	3,5-OCH_3, 4-OH	$C_{24}H_{21}N_3O_4S$	448.2	Brown	270-272	Ethanol, methanol	0.52
37	3-Cl	$C_{22}H_{16}ClN_3OS$	405.9	Black	305-307	Ethanol, methanol	0.72

7.228-7.214 (d, *J* = 4.2 Hz, 2H), 7.094-7.083 (t, *J* = 3.3 Hz, 1H), 7.064-7.052 (d, *J* = 3.6 Hz, 1H), 6.897-6.882 (t, *J* = 4.5 Hz, 1H), 6.834-6.821 (d, *J* = 3.9 Hz, 1H), 6.448 (s, 1H), 3.992-3.986 (d, *J* =1.8 Hz, 1H), 3.906-3.901 (d, *J* = 1.5 Hz, 1H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)2-(4-hydroxyphenyl)thiazolidin-4-one (30): IR (KBr, ν_{max}, cm^{-1}): 3635.62 (arom. OH), 3362.13 (arom. N-H *str.*), 1785.67 (C=O *str.*), 1684.78 (C=N imine), 1607.43 (N-H bend.), 1512.56 (arom. C=C), 1392.93 (C-N bend.), 1193.37 (C-O). ^{1}H NMR (CDCl$_3$): 12.568 (s, 1H), 9.438 (s, 1H), 8.209-8.202 (d, *J* = 2.1 Hz, 2H), 7.786-7.782 (d, *J* = 1.2 Hz, 2H), 7.595-7.591 (d, *J* = 1.2 Hz, 2H), 7.338-7.321 (d, *J* = 5.1 Hz, 2H), 7.338-7.321 (d, *J* = 5.1 Hz, 2H), 7.228-7.221 (d, *J* = 2.1 Hz, 2H), 6.637-6.631 (d, *J* = 1.8 Hz, 1H), 6.442 (s, 1H), 3.993-3.982 (d, *J* = 3.3 Hz, 1H), 3.906-3.901 (d, *J* = 1.5 Hz, 1H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(3-ethoxy-4-hydroxyphenyl)thiazolidin-4-one (31): IR (KBr, ν_{max}, cm^{-1}): 3623.35 (arom. OH), 3367.38 (arom. N-H *str.*), 1784.32 (C=O *str.*), 1686.35 (C=N imine), 1596.31 (N-H bend.), 1522.32 (arom. C=C), 1248.31 (C-O). ^{1}H NMR (CDCl$_3$): 12.484 (s, 1H), 9.834 (s, 1H), 8.204-8.194 (d, *J* = 3.0 Hz, 2H), 7.598-7.594 (d, *J* = 1.2 Hz, 2H), 7.458 (s, 1H), 7.348-7.34 (d, *J* = 1.8 Hz, 1H), 7.336-7.332 (d, *J* = 1.2 Hz, 2H), 7.218-7.214 (d, *J* = 3.6 Hz, 2H), 6.724-6.720 (d, *J* = 1.2 Hz, 1H), 6.448 (s, 1H), 3.992-3.986 (d, *J* = 1.8 Hz, 1H), 3.980-3.974 (d, *J* = 1.8 Hz, 1H), 3.943-3.9484 (d, *J* = 1.5 Hz, 2H), 1.329 (s, 3H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(3-hydroxy-4-methoxyphenyl) thiazolidin-4-one (32): IR (KBr, ν_{max}, cm^{-1}): 3623.35 (arom. OH), 3367.38 (arom. N-H *str.*), 1784.32 (C=O *str.*), 1686.35 (C=N imine), 1596.31 (N-H bend.), 1522.32 (arom. C=C), 1248.31 (C-O). ^{1}H NMR (CDCl$_3$): 12.568 (s, 1H), 9.487 (s, 1H), 8.207-8.202 (d, *J* = 1.5 Hz, 2H), 7.598-7.584 (d, *J* = 4.2 Hz, 2H), 7.409-7.402 (d, *J* = 2.1 Hz, 2H), 7.338-7.326 (d, *J* = 3.6 Hz, 2H), 7.227-7.216 (t, *J* = 3.3 Hz, 2H), 6.862 (s, 1H), 6.704-6.701 (d, *J* = 1 Hz, 1H), 6.447 (s, 1H), 3.982-3.976 (d, *J* = 1.8 Hz, 1H), 3.962-3.954 (d, *J* = 2.4 Hz, 1H), 3.839 (s, 3H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(2-nitrophenyl)thiazolidin-4-one (33): IR (KBr, ν_{max}, cm^{-1}): 3412.72 (arom. N-H *str.*), 1784.32 (C=O *str.*), 1622.37 (C=N imine), 1584.35 (N-H bend.), 1527.47 (arom. C=C), 1407.32 (C-N bend.), 1494.69 (arom. NO$_2$). ^{1}H NMR (CDCl$_3$): 12.562 (s, 1H), 8.208-8.202 (d, *J* = 1.8 Hz, 2H), 7.964-7.960 (d, *J* = 1.2 Hz, 1H), 7.724-7.116 (t, *J* = 2.4 Hz, 1H), 7.592-7.576 (t, *J* = 4.8 Hz, 2H), 7.552-7.542 (t, *J* = 3.3 Hz, 1H), 7.498-7.492 (d, *J* = 1.8 Hz, 1H), 7.338-7.332 (d, *J* = 1.2 Hz, 2H), 7.221-7.2120 (t, *J* = 2.7 Hz, 2H), 6.448 (s, 1H), 3.840-3.836 (d, *J* = 1.2 Hz, 1H), 3.826-3.820 (d, *J* =1.8 Hz, 1H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(3-nitrophenyl)thiazolidin-4-one (34): IR (KBr, ν_{max}, cm^{-1}): 3284.37 (arom. N-H *str.*), 1742.32 (C=O *str.*), 1624.39 (C=N imine), 1574.63 (N-H bend.), 1442.32 (arom. C=C), 1224.25 (C-N) bend.), 15.14.78 (arom. NO$_2$). ^{1}H NMR (CDCl$_3$): 12.562 (s, 1H), 8.207-8.201 (d, *J* = 1.8 Hz, 2H), 8.129-7.960 (s, 1H), 8.079-8.072 (d, *J* = 2.1 Hz, 1H), 7.502-7.742 (d, *J* = 1.8 Hz, 1H), 7.592-7.576 (t, *J* = 4.3 Hz, 1H), 7.572-7568 (d, *J* = 1.2 Hz, 2H), 7.339-7.334 (d, *J* = 1.5 Hz, 2H), 7.229-7.220 (t, *J* = 2.7 Hz, 2H), 6.442 (s, 1H), 3.942-3.931 (d, *J* = 3.3 Hz, 1H), 3.872-3.862 (d, *J* = 3Hz, 1H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(4-fluorophenyl)thiazolidin-4-one (35): IR (KBr, ν_{max}, cm^{-1}): 3312.29 (arom. N-H *str.*), 1793.21 (C=O *str.*), 1680.67 (C=N imine), 1584.29 (N-H bend.), 1443.28 (arom. C=C), 1312.56 (C-F *str.*). ^{1}H NMR (CDCl$_3$): 12.568 (s, 1H), 8.208-8.201 (d, *J* = 2.1 Hz, 2H), 7.597-7.572 (d, *J* = 7.5 Hz, 2H), 7.338-7.331 (d, *J* = 2.1 Hz, 2H), 7.229-7.222 (t, *J* = 2.1 Hz, 2H), 7.219-7.212 (d, *J* = 2.1 Hz, 1H), 7.129-7.121 (d, *J* = 2.4 Hz, 2H), 6.449 (s, 1H), 3.991-3.941 (d, *J* = 1.5 Hz, 1H), 3.872-3.862 (d, *J* = 3.3 Hz, 1H).

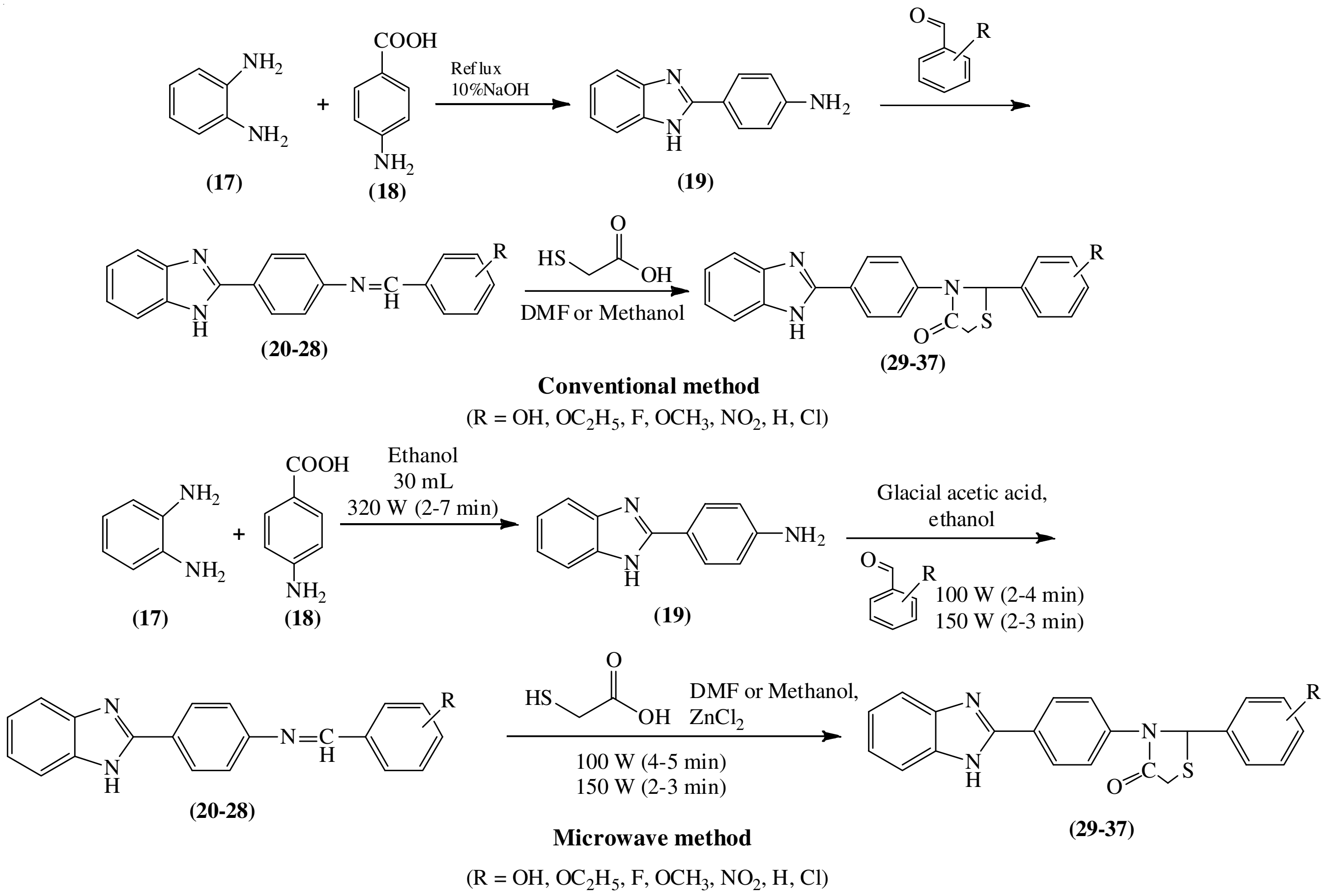
3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(4-hydroxy-3,5-dimethoxyphenyl)thiazolidin-4-one (36): IR (KBr, ν_{max}, cm^{-1}): 3607.71 (arom. OH), 3256.34 (arom. N-H *str.*), 1797.31 (C=O *str.*), 1674.39 (C=N imine), 1582.35 (N-H bend.), 1508.13 (arom. C=C), 1194.35 (ether C-O *str.*). ^{1}H NMR (CDCl$_3$): 12.562 (s, 1H), 8.732 (s, 3H), 8.204-8.196 (d, *J* = 2.4 Hz, 2H), 7.596-7.588 (d, *J* = 2.4 Hz, 2H), 7.336-7.332 (t, *J* = 1.2 Hz, 2H), 7.224-7.212 (t, *J* = 0.6 Hz, 2H), 7.018 (s, 2H), 6.448 (s, 1H), 3.984-3.978 (d, *J* = 1.2 Hz, 1H), 3.842 (s, 1H), 3.822 (s, 1H).

3-(4-(1*H*-Benzo[*d*]imidazol-2-yl)phenyl)-2-(3-chlorophenyl)thiazolidin-4-one (37): IR (KBr, ν_{max}, cm^{-1}): 3376.67 (arom. N-H *str.*), 1678.39 (C=O *str.*), 1607.54 (C=N imine), 1586.78 (N-H bend.), 1472.38 (arom. C=C), 712.38 (C-Cl *str.*). ^{1}H NMR (CDCl$_3$): 12.568 (s, 1H), 8.207-8.202 (d, 2H), 7.597-7.591 (d, *J* = 1.8 Hz, 2H), 7.432 (s, 1H), 7.339-7.329 (d, *J* = 3.3 Hz, 2H) 7.296-7.284 (d, *J* = 3.6 Hz, 1H), 7.270-7.260 (t, *J* = 3.3 Hz, 1H), 7.239-7.231 (d, *J* = 2.4 Hz, 1H), 7.221-7.208 (t, *J* = 3.9 Hz, 1H), 6.447 (s, 1H), 3.994-3.990 (d, *J* = 2.0 Hz, 2H), 3.972-3.963 (d, *J* = 2.1 Hz, 2H).

Antimicrobial activity: Antibacterial activity of the synthesized compounds **19**-**37** in minimum inhibitory concentrations (MICs) was recorded against various pathogenic bacterial strains (Gram-negative and Gram-positive) *viz*. *Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442, *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 741. The synthesized compounds were screened for *in-vitro* antimicrobial activities using the cup plate diffusion method. Both Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*, *Streptococcus pyogenes*) antibacterial species were used in this experiment. Three fungal strains *Candida albcans*, *Aspergillus niger* and *Aspergillus clavatus* were also used to judge the antifungal potential. Solution of each compound at a concentration of 100 µg/0.1 mL in DMSO was prepared and the inhibition zone diameter (IZD) in centimetre was used as the criterion for measuring the microbial activity. Ampicillin and griseofulvin were used as a bacterial and fungal standards, respectively for references to evaluate the efficacy of the tested compounds under the same conditions. DMSO was used as a control (10 mL).

RESULTS AND DISCUSSION

Synthesis of the intermediate and final compounds was performed according to the reactions outlined in **Scheme-I**. Initially, 4-(1*H*-benzo[*d*]imidazole-2-yl)aniline was synthesized by the reaction of benzene-1,2-diamine with 4-aminobenzoic

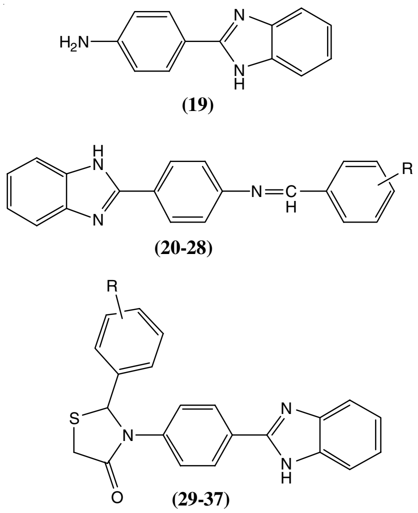


Scheme-I: Conventional and microwave synthesis of 2,3-disubstituted 4-thiazolidinone derivatives

acid. To a solution of 4-(1*H*-benzo[*d*]imidazole-2-yl)aniline in ethanol containing a small amount of glacial acetic acid, substituted benzaldehyde were added and refluxed to get the corresponding Schiff bases. The synthesized Schiff bases in DMF were reacted with thioglycolic acid to get the desired thiazolidinones (**29-37**, Fig. 2). Time required for the synthesis of compounds (**19-37**)and % yield between conventional and green chemistry (microwave irradiation) method (Table-2). The chemical structures of synthesized thiazolidinone molecules (**29-37**) were established by ^{1}H NMR and FT-IR spectral studies. The IR spectrum of 4-(1*H*-benzo[*d*]imidazole-2-yl)aniline (**19**) showed the characteristic IR band at 3557.37cm^{-1}, which indicated the presence of -N-H group and characteristic bands at 1618.65 and 3095.28 cm^{-1} indicated the presence of NH_2 group and C-H (*str.*) in aromatic ring, respectively. Schiff bases (**20-28**) showed the characteristic bands at 1633.67, 1628.78, 1683.38, 1682.71, 1681.71, 1681.35, 1662.39, 1584.38 and 1684.38 cm^{-1} for the presence of C=N (imine) in the compounds **20**, **21**, **22**, **23**, **24**, **25**, **26**, **27** and **28**, respectively. Aromatic C=C *str.* has been observed in these compounds in the range from 1594.62 to 1428.32 cm^{-1}. 3-(4-(1*H*-Benzo[*d*]-imidazol-2-yl)phenyl)-2-(2-hydroxyphenyl)thiazolidin-4-one (**20**) and 4-((4-(1*H*-benzo[*d*]imidazol-2-yl)phenylimino)methyl)-phenol (**21**) showed the presence O-H peak at 3610.35 and 3642.29 cm^{-1}, respectively. The existence of Ar-NO_2 functional group in compounds **24** and **25** was displayed by the existence of

TABLE-2
COMPARISONS OF TIME REQUIRED FOR THE SYNTHESIS OF COMPOUNDS (**19-37**) AND % YIELD BETWEEN CONVENTIONAL AND GREEN CHEMISTRY (MICROWAVE IRRADIATION) METHOD

Compd. code	Microwave irradiation method			Conventional method	
	Time (min)	Power (W)	Yield (%)	Time (h)	Yield (%)
19	4.7	100	87	6	65
20	3.0	125	83	9	57
21	3.2	100	89	13	62
22	2.36	100	76	16	52
23	3.7	100	82	13	54
24	2.0	100	86	17	69
25	3.0	100	82	14	56
26	3.1	150	88	9	69
27	3.2	150	78	21	42
28	4.2	100	89	17	48
29	2	125	87	18	62
30	3.2	100	84	16	56
31	2.8	100	93	12	53
32	2.3	100	82	19	68
33	2.2	125	87	12	61
34	2.6	125	92	10	57
35	2.9	100	89	8	64
36	7.0	100	83	24	59
37	3.6	100	84	22	68



(19)

(20-28)

20: R= 2-OH
21: R= 4-OH
22: R=3-OC_2H_5, 4-OH
23: R= 4-OCH_3, 3-OH
24: R= 2-NO_2
25: R= 3-NO_2
26: R= 4-F
27: R= 3,5-OCH_3, 4-OH
28: R= 3-Cl

(29-37)

29: R= 2-OH
30: R= 4-OH
31: R= 3-OC_2H_5, 4-OH
32: R= 4-OCH_3, 3-OH
33: R= 2-NO_2
34: R= 3-NO_2
35: R= 4-F
36: R= 3,5-OCH_3, 4-OH
37: R= 3-Cl

Fig. 2. Synthesized intermediates (**19-28**) and thiazolidinone analogs (**29-37**)

symmetric Ar-NO_2 stretches in the scale of1434.36-1494.31 cm^{-1}. The IR *str.* vibrations at 1217.21 and 672.38 cm^{-1} in the spectral data of Schiff bases (**26** and **28**) displayed the presence of halogen group (Ar-F and Ar-Cl) on the aromatic nucleus substituted at the *para* and *meta*-position. The impression of IR vibration at 3412.72-3218.20 and 1797.31-1678.39 cm^{-1} in the spectral data of synthesized thiazolidinone derivatives (**29-37**) specified the existence of aromatic (N-H) *str.* and ketone C=O *str.*, respectively. The appearance of IR stretching 1688.35-1607.54 cm^{-1} in the spectral data of synthesized thiazolidinone derivatives **(29-37)** specified the existence of N=CH group. The ^{1}H NMR spectrum of compounds **29-37** showed the signals in between δ 3.820-3.994 ppm confirming the presence of two CH_2 proton present in thiazolidinone ring system. Compound **32** showed singlet at δ 3.839 ppm due to existence of -OCH_3 at the *para*-position.

Antimicrobial activity: Compounds **24**, **25**, **26**, **33**, **34**, and **35** exhibited relatively significant activity against *E. coli* and *S. aureus*. Other compoundsshowed the moderate activity. In antifungal activities, compounds **26** and **35** displayed highest activity against *A. niger*, compound **32** against *A. clavatus* while compounds **25**, **26**, **34** and **35** against C. albicans. Compounds **21**, **22**, **23**, **27**, **28**, **29**, **30**, **31**, **32**, **36** compounds have shown moderate activity. Remaining compounds in antimicrobial screening exhibited weak activity. Most of the compounds containing -NO_2, -F, -Cl and -OCH_3 substitution in thiazolidinone moiety exhibited more activity than the other compounds of the series. Minimum inhibitory concentrations (MICs) of the synthesized compounds are shown in Tables 3 and 4.

Structure activity relationships (SAR): From the structure activity relationship (SAR) of synthesized compounds (Fig. 3), it can be summarized that (i) compounds with halogen atom on cyclic moiety of ring (B) showed better antimicrobial activity in the increasing order of the size of halogen atoms (**35** < **37**); (ii) 4-hydroxy and 3,5-dimethoxy (**36**) substitution in ring B with cyclic moiety significantly decreases the activity; (iii) *p*-substi-tution with ethoxy group has been found to be more active than *ortho*-substitution when the comparison of same substitution at different position on ring B was established; (iv) presence of *para*-methoxy group at cyclic moiety on ring (B) showed better activity as compared to hydroxy being present at *ortho*-position (**30** < **32**); and (v) chloro-substituted cyclic moiety at ring B shows potent antimicrobial activity.

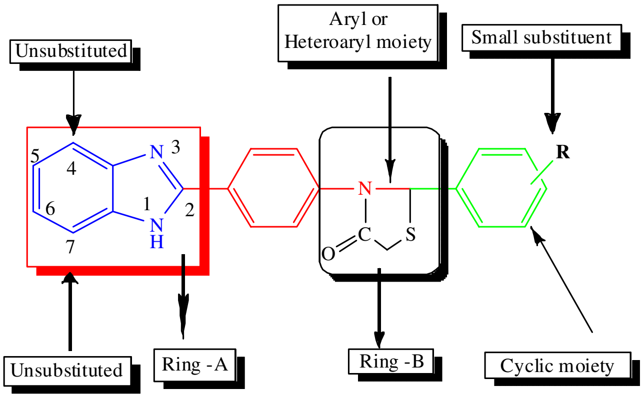


Fig. 3. Structural requirements of benzimidazole and 4-thiazolidinone nucleus with respect to antimicrobial activity

TABLE-3
BIOLOGICAL ACTIVITY DATA OF COMPOUNDS **19** AND **20-28** (SCHIFF BASES)

Compd. code	Minimal inhibitory concentration (MIC) (μg/mL)						
	Tested bacteria				Tested fungi		
	Gram-negative		Gram-positive				
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
19	125	150	150	125	250	250	250
20	150	125	125	200	250	150	225
21	150	100	125	100	100	150	150
22	150	100	100	125	150	250	250
23	125	100	100	125	150	250	68.5
24	72.5	100	75.5	100	95.5	100	75.5
25	75.5	76.5	78.5	100	125	80.5	100
26	78.5	82.5	80.5	85.5	80.5	68.5	100
27	125	150	250	150	125	225	125
28	100	100	125	225	150	250	250
Ampicillin	100	100	250	100	–	–	–
Griseofulvin	–	–	–	–	500	100	100
DMSO (control)	–	–	–	–	–	–	–

TABLE-4
BIOLOGICAL ACTIVITY DATA OF SYNTHESIZED 4-THIAZOLIDINONE DERIVATIVES (**29-37**)

Compd. code	Minimal inhibitory concentration (MIC) (µg/mL)						
	Tested bacteria				Tested fungi		
	Gram-negative		Gram-positive				
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
29	100	200	150	150	500	250	250
30	150	100	125	100	150	150	150
31	150	100	125	125	150	250	125
32	125	100	125	150	125	250	61.5
33	60.5	63.5	62.5	100	76.5	100	70.5
34	65.5	68.5	64.5	87.5	100	100	100
35	68.5	72.6	70.0	75.5	200	65.5	125
36	125	250	250	150	225	225	225
37	100	125	100	150	200	250	250
Ampicillin (10 µg/mL)	100	100	250	100	–	–	–
Griseofulvin	–	–	–	–	500	100	100
DMSO (control)	–	–	–	–	–	–	–

Conclusion

Novel Schiff bases of 4-thiazolidinones and benzimidazole were synthesized and screened for their antimicrobial and antifungal potential. From the results of the antimicrobial activity of the synthesized compounds, it was revealed that the compounds containing -Cl, -NO_2 group with thiazolidinone nucleus are more active than other compounds of the series.It also seems that the presence of -F, -NO_2, -OCH_3, -Cl group increases antibacterial potential. The order of activity with respect to electron withdrawing capacity of the substituents has been observed. It was concluded that the compounds with electron withdrawing substituents showed better antimicrobial activity against almost all the microorganisms under study. The order in this study can be given as: $NO_2 > F > Cl > Br > OCH_3 < OH > CH_3 > OC_2H_5$. The study also provides the opportunity to conduct new lead optimization studies and designing of new thiazolidinone derivatives with improved potency and better spectrum of activity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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