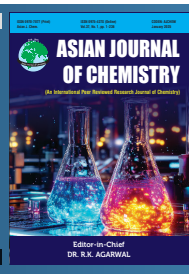
Asian Journal of Chemistry; Vol. 37, No. 2 (2025), 455-464

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2025.33177



Facile Synthesis of New Substituted 4-Thiazolidinones Conjugates containing Quinoline-Sulfamethoxazole Motifs and their Bioevaluation

NAWAJ ALI BEG[1,*] and MAQDOOM FAROOQUI[2]

[1]Department of Chemistry, Maulana Azad Post Graduate & Research Centre, Aurangabad-431001, India
[2]Department of Chemistry, Dr. Rafiq Zakaria College for Women, Aurangabad-431001, India

*Corresponding author: E-mail: nawaja91@gmail.com

Received: 11 December 2024; *Accepted*: 20 January 2025; *Published online*: 31 January 2025; AJC-21898

Difunctional Brönsted acidic ionic liquid [DBN][HSO_4] mediated synthesis of quinoline-sulfamethoxazole blended 4-thiazolidinones derivatives (**7a-l**) by reacting 4-amino-*N*-(5-methylisoxazol-3-yl) benzenesulfonamide (**4**), 2-chloro-3-formyl quinoline (**5a-l**) and mercapto acetic acid (**6**) in promising yields at 80 ºC. All the newly synthesized quinoline-sulfamethaoxazole incorporated 4-thiazolidinones derivatives were explored for their *in vitro* antifungal and antioxidant activity. The novel compounds, 4-thiazolidinones hybrids were evaluated against various fungal strains and compounds **7g**, **7h**, **7i**, **7j** and **7k** displays promising antifungal activity. Furthermore, all the synthesized 4-thiazolidinones conjugates were evaluated for antioxidant activity and almost all derivatives (**7b-l**) exhibit excellent radical activity. Using [DBN][HSO_4] protocol providing economical as well as environmental advantages and its applicable for divergent functional groups.

Keywords: Ionic liquid, 4-Thiazolidinones, Quinoline, Sulfamethaoxazole, Antifungal activity.

INTRODUCTION

Ionic liquids (ILs) are gaining attention as a good greener media for synthesis, catalysis, separation, variable chemical and physical properties [1-6]. ILs have many unique properties such as non-volatility, widespread liquid range, low toxicity, high thermal stability, excellent solubility, recyclability and non-combustible [7]. ILs act as "neoteric solvents" for a extensive span of chemical and industrial operations. Currently, ionic liquids offer a cost-effective and eco-friendly protocol for unrestricted organic transformations [8]. Thus, the account of a mild, cost-effective, dynamic and environmentally greener catalyst for extensive cyclic ring formation reaction various biological and pharmaceutical prominence is in demand.

Multicomponent reactions (MCRs) display simple experimental route, extreme selectivity pathway and high atom-economy due to the production of carbon-hetero (C-X) and carbon-carbon (C-C) in one-pot [9]. MCRs are applicable for variety of the new drug discovery process and it gives better results over the traditional pathways [10]. In addition to MCRs complete the numerous compensation including time, cost reducing, effluents and side product which are enormously pleasant with the goals of clean and green chemistry [11].

The exponential growth of highly resistant eukaryotic microorganisms, particularly fungi, to pharmaceuticals has posed a significant challenge to the global research community, prompting the need to propose, assess, and develop innovative bioactive compounds [12]. Fungi are important human pathogens and are appropriate drug-resistant to the accepted products most prominent of them include species of *Candida*, *Cryptococcus neoformans* and *Aspergillus*. The *Candida albicans* could cause superficial or activity infections or both in individuals with low immunity [13]. In additional factors that have contribute to drug resistance are the regularly used more-invasive medicinal route and the treatment with divergent antibiotics. An additional hazardous fungal infectivity are caused frequently by *Cryptococcus neoformans* and *Aspergillus fumigates* combined with *Candida albicans* being the majority general driving force of fungal blood stream infections [14]. Hence, it is essential to discover novel and effective drugs to resolve the issues.

The non-enzymatic antioxidant defenses were found in human body and complex system of natural enzymatic which

counter the damaging special effects of oxidants and free radicals. The lipophilicity is an additional significant characteristic concerning the antioxidant activity of the bioactive molecules. It is well recognized that the lipophilic compounds demonstrate high-quality antioxidant behaviour in lipid systems [15].

In last few years, the 4-thiazolidinones motif has been received enormous attention among scientists due to prominent potency including anti-convulsant [16], anti-inflammatory [17], antimicrobial [18], antiviral [19], antitumor [20], antidiabetic [21], antituberculosis [22], antiparasitic [23], analgesic [24], antidiarrhoeal [25], antiarthritic [26], cardiovascular activity [27], anti-HIV [28] and FSH agonist [29]. In addition, 4-thiazolidinones derivatives are also displays promising bioactivity against diverse cancer cell line include breast cancer JSP-1 inhibitor [30], (MCF-7) [31], antiapoptic biocomplex (BCl-XL-BH_3) [32], tumor necrosis factor (TNFα) [33], antiproliferative activity against Reh and Nalm6 cells [34], integrin avb3 receptor [35], cycline B/CDK1 inhibitor [36] and HT29 colon cancer cell line [37] and Some representative structures of bioactive 4-thiazolidinone conjugates are displays in Fig. 1.

Sulfonamides are found in many bioactive molecules, natural products and pharmaceuticals. In addition, sulfonamides show various biological activity including, antitumor, anticonvalsant, HIV inhibitors protease and antifungal agents [38], for treating erectile dysfunction [39], some of malaria strain, herbicides, uterine and urinary infections, dyes [40]. Isoxazole conjugates extensively exist in diverse natural products [41]. 5-Methylisoxazole exists in many drugs parecoxib, valdecoxib and leflunomide used in the market. They exhibit antiviral, anticancer, analgesic, antibacterial, antinociceptive, anticonvulsant and immunomodulating activity [42]. The propose of sulfamethaoxazole incorporated substituted 4-thiazolidinones hybrids are mostly divided into three different sections as shown in Fig. 2. The main core moiety of the design approach that is 4-thiazolidinone bioactive unit. It used to improve the biological activity as they display drug alike properties. The second part isoxazole linkage with sulfonamides which is accountable for medicinal activity. Aryl group part with varied substitutuents, which is accountable for the control of lipophilicity as well as it involvement of extremely strong biological part because of presence of polyfunctional group.

Due to its divergent medicinal activities, several preparative pathways have been established for the synthesis of 4-thiazolidinone motifs. Due to this current years numerous catalytic routes have been established including DIPEA [43], DBSA [44], nano-Fe_3O_4@SiO_2 [45], montmorillonite K-10 [46], silica gel [47], acetic acid [48], *N*-methyl pyridinium tosylate [49], $SnCl_2$ [50], ammonium persulfate [51], Cd-Zr_4-$[PO_4]_6$ [52], $Bi[SCH_2COOH]_3$ [53], ionic liquid [bmim]OH [54], silica supported $CoFe_2O_4$@SiO_2/$PrNH_2$ [55] and $Y[OTf]_3$ [56] and acid catalyzed [57]. However, the previous report some disadvantages such as dangerous solvent, prolonged heating, tedious work-up procedure, recycling and separation of catalyst. Moreover, numerous of such methods promotes organic solvents as the reaction medium. Hence, a newer route which overcomes these drawbacks invites a bundle of consideration for the investigator. Therefore, the additional improvement toward contemporary reaction with reusability of catalyst, painless isolation of compounds, without waste is highly good-looking. Recently, 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) ionic liquids signifi-

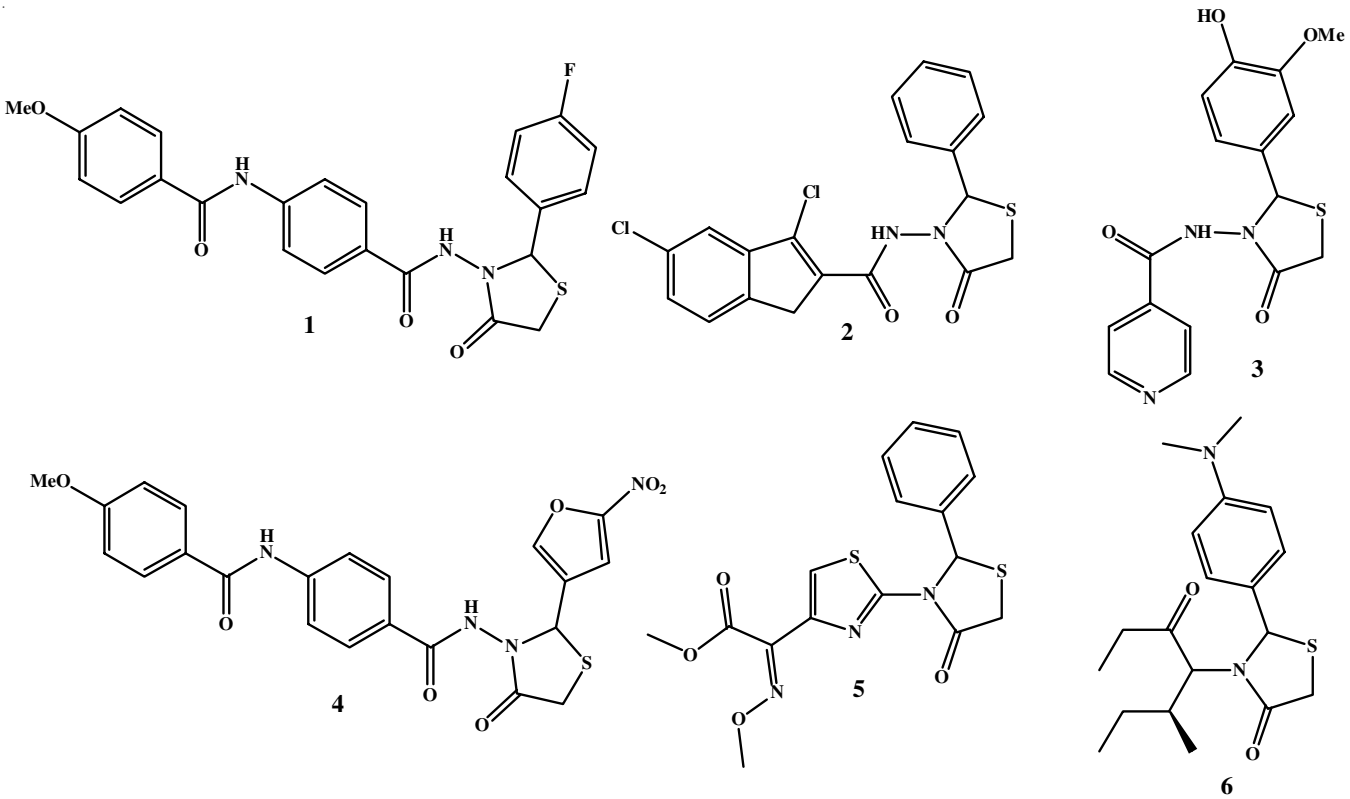


Fig. 1. Reported 4-thiazolidinone hybrids act as biological activity

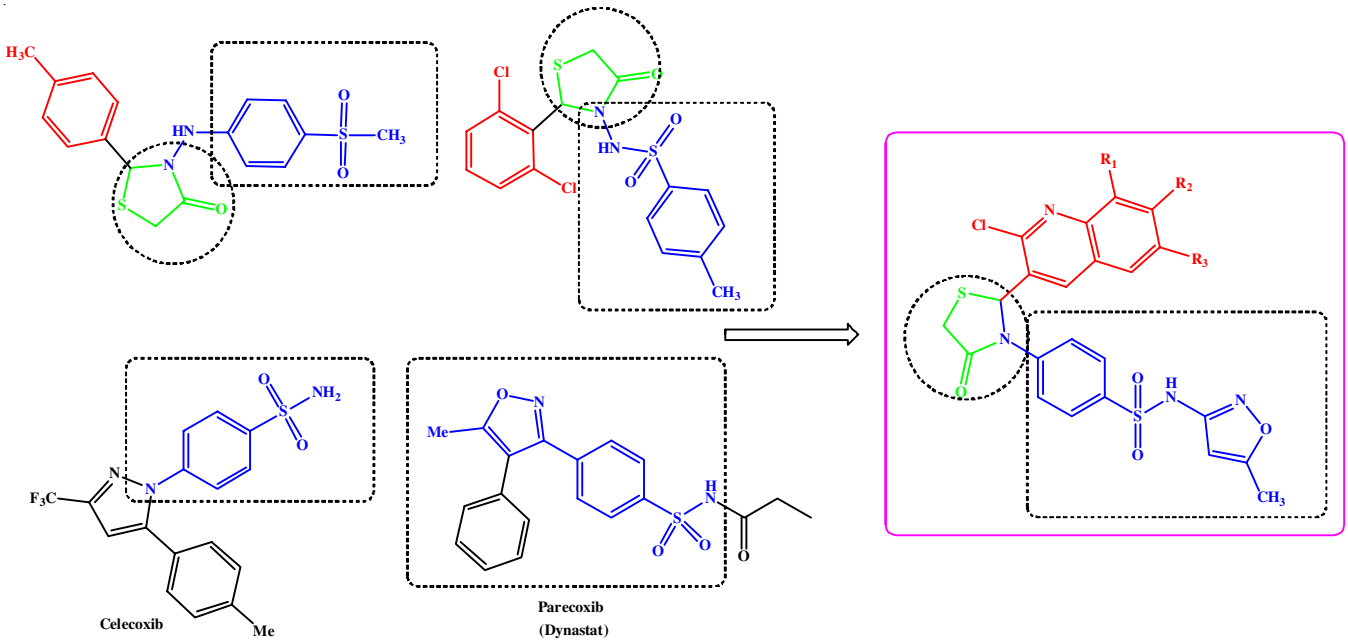


Fig. 2. Molecular design approach for the preparation of novel 4-thiazolidinones hybrids bearing sulfamethoxazole scaffolds

cantly utilized as catalyst in various research fields. The amalgamation of DBN with cation to produce the development of newer ionic liquids [58]. The number of polyfunctional ILs has been considered for large range of applications. These ILs have been displays excellent properties due to the recyclability, volatility, negligible vapour pressure, chemical and thermal stability, eco-friendly, non-flammability and high ionic conductance. The preparation of the above IL through constructing with to these -SO_3H supported acidic ionic liquid [59].

From all the known facts, the necessity of current work is to develop clean and greener pathway for synthesis of 4-thiazolidinone conjugates. As an expansion of promising efficient and economic approach to enlarge biologically and pharmaceutically remarkable molecules, herein, we reported synthesis of 4-thiazolidinone conjugates using novel ionic liquid to give excellent yields.

EXPERIMENTAL

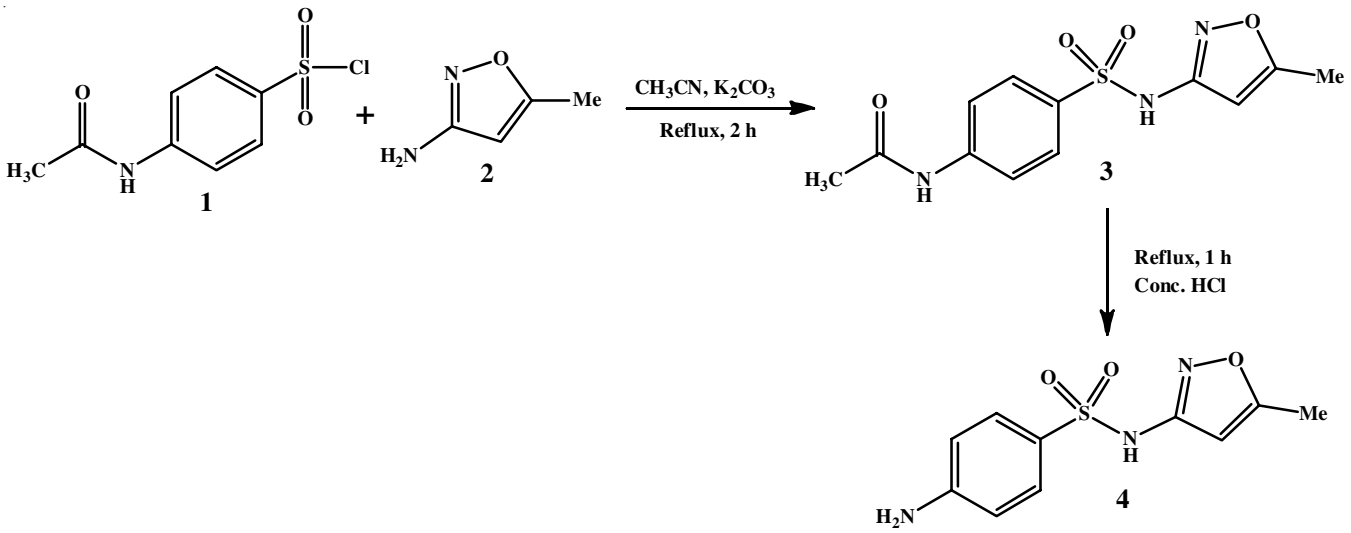
All chemicals used were of laboratory grade and used as such. The melting points were determined in open capillaries and are uncorrected. The progress of the reaction was monitored by thin layer chromatography on Merck silica plates and visualized with UV/iodine light. ^{1}H NMR spectra were recorded using the Bruker AvIII HD-400 MHz spectrometer at 400 MHz using DMSO solvent and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on a Waters UPLCTQD (ESI-MS and APCI-MS) instrument and mass spectra were recorded on a CHNS automated analyzer.

General procedure for the synthesis of 4-amino-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (4a): Reaction of *N*-acetylsulfanilyl chloride (**1**) (5mmol), 3-amino-5-methylisoxazole (**2**) (5 mmol) K_2CO_3 (2.5 mmol) and ethanenitrile (15 mL) refluxed for 2 h followed by acid hydrolysis to give *N*-acylation intermediate (**3**). The improvement of reaction were checked by TLC. After completion of reaction the mixture was quench using ice chilled water to give products. After the washing with distilled water followed by recrystallization using ethanol afford titled compounds (**Scheme-I**).

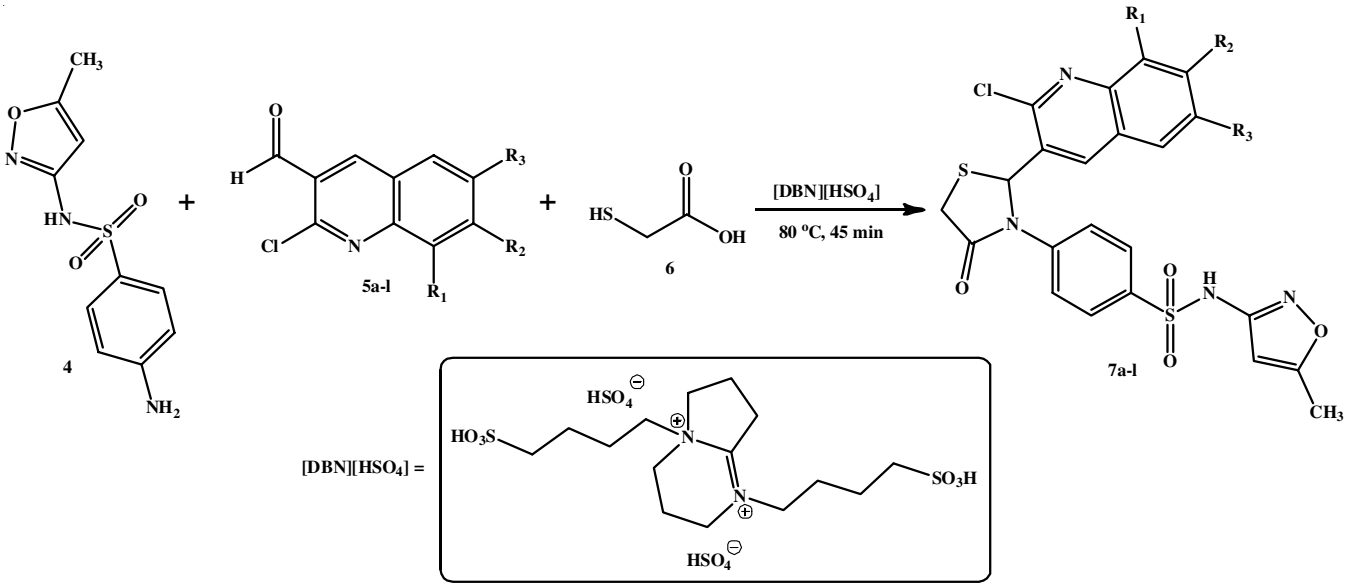
General procedure for the synthesis of sulfamethaoxazole incorporated substituted 4-thiazolidinones hybrid (7a): Reaction of 4-amino-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**4**) (1 mmol), 2-chloro-3-formylquinoline aldehyde (**5a**) (1 mmol) and mercapto acetic acid (**6**) (1 mmol) using [DBN]-[HSO_4] as catalyst at 80 ºC for 40 min. The progress reaction was optimized by using TLC and *n*-hexane-ethyl acetate (8:2) solvent system. After the reaction completion, the reaction mixture was extracted using ethyl acetate and washed with brine and 5% $NaHCO_3$ solutions. The removal of organic solvents from organic layer using rotavapor to give crude final compounds (**Scheme-II**). In final step, purification and crystallization thiazolidinone product **7** using ethanol to give 93% yield of titled product.

4-(2-(2-Chloroquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-((5-methylsoxazol-3-yl)benzenesulfonamide (7a): White solid; m.p.: 208-210 ºC; yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.96-7.85 (m, 2H, Ar-H), 7.84-780 (m, 2H, Ar-H), 7.54-7.50 (m, 2H, Ar-H), 7.40-7.38 (s, 1H, NH), 7.23-7.13 (m, 2H, Ar-H), 6.57 (s, 1H, S-CH-N), 6.17 (s, 1H, -C = CH), 3.68 (d, 1H, CH_2, J = 12 Hz), 3.64 (d, 1H, CH_2, J = 12 Hz) and 2.22 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.90, 160.20, 148.99, 143.23, 135.87, 132.70, 132.67, 130.85, 130.77, 129.30, 127.47, 125.19, 124.08, 116.20, 115.98, 115.60, 99.44, 52.53, 36.90 and 14.22; MS (ESI-qTOF): calcd. for $C_{22}H_{18}ClN_4O_4S_2$ $[M+H]^+$, 501.5242: found: 501.5270.

4-(2-(2-Chloro-8-methylquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7b): White solid; m.p.: 224-226 ºC; yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.09-8.07 (m, 2H, Ar-H), 7.84 (s, 1H, NH), 7.43-7.40 (m, 2H, Ar-H), 7.29-7.22 (m, 4H, Ar-H),



Scheme-I: Synthesis of 4-amino-N-(5-methylisoxazol-3-yl)benzenesulfonamide (**4**) from N-acetylsulfanilyl chloride (**1**) and 3-aino-5-methylisoxazole (**2**), respectively



7a, R_1 = H, R_2 = H, R_3 = H
7b, R_1 = CH_3, R_2 = H, R_3 = H
7c, R_1 = H, R_2 = CH_3, R_3 = H
7d, R_1 = H, R_2 = H, R_3 = CH_3
7e, R_1 = OCH_3, R_2 = H, R_3 = H
7f, R_1 = H, R_2 = OCH_3, R_3 = H
7g, R_1 = H, R_2 = H, R_3 = OCH_3
7h, R_1 = Cl, R_2 = H, R_3 = H
7i, R_1 = H, R_2 = Cl, R_3 = H
7j, R_1 = H, R_2 = H, R_3 = Cl
7k, R_1 = H, R_2 = H, R_3 = F
7l, R_1 = H, R_2 = H, R_3 = OCH_2CH_3

Scheme-II: Synthesis of novel quinoline based 4-thiazolidinones hybrids bearing sulfamethaoxazole scaffolds **7a-l**

6.99 (s, 1H, S-CH-N), 6.50 (s, 1H, -C = CH), 3.82 (d, 1H, CH_2, J = 12 Hz), 3.79 (d, 1H, CH_2, J = 12 Hz), 2.58 (s, 3H, -CH_3) and 2.37 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 174.24, 160.26, 149.21, 143.19, 139.68, 132.69, 130.83, 130.74, 129.56, 129.35, 127.37, 125.17, 124.09, 116.18, 115.96, 115.60, 98.50, 52.51, 36.27, 20.48 and 14.83; MS (ESI-qTOF): calcd. for $C_{23}H_{19}ClN_4O_4S_2$ $[M+H]^+$, 516.3250: found: 516.3293.

4-(2-(2-Chloro-7-methylquinolin-3-yl)-4-oxothiazolidin-3-yl)-N-(5-methylisoxazol-3-yl)benzenesulfonamide (7c): White solid; m.p.: 234-236 ºC; yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.22-8.20 (m, 2H, Ar-H), 7.78 (s, 1H, NH), 7.62-7.57 (m, 3H, Ar-H), 7.62-7.57 (m, 3H, Ar-H), 7.55-7.39 (m, 3H, Ar-H), 6.60 (s, 1H, S-CH-N), 6.54 (s, 1H, -C = CH), 3.91 (d, 1H, CH_2, J = 12 Hz), 3.87 (d, 1H, CH_2, J = 12 Hz), 2.63 (s, 3H, -CH_3) and 2.49 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 174.94, 162.46, 160.91, 150.34, 149.87, 148.39, 144.48, 144.03, 140.36, 130.24, 130.19, 130.03, 128.09, 126.36, 125.06, 124.76, 116.30, 98.04, 53.09, 36.31, 20.52 and 15.15; MS (ESI-qTOF): calcd. for $C_{23}H_{19}ClN_4O_4S_2$ $[M+H]^+$, 516.3250: found: 516.3293.

4-(2-(2-Chloro-6-methylquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7d): Yellow solid; m.p.: 210-212 ºC; yield: 81%; ^{1}H NMR

(400 MHz, DMSO-d_6, δ ppm): 8.28-8.26 (m, 2H Ar-H), 8.13-8.02 (m, 2H, Ar-H), 7.78 (s, 1H, NH), 7.63-7.61 (m, 2H, Ar-H), 7.53-7.52 (m, 2H, Ar-H), 6.50 (s, 1H, S-CH-N), 6.40 (s, 1H, -C = CH), 4.08 (d, 1H, CH_2, J = 12 Hz), 4.05 (d, 1H, CH_2, J = 12 Hz), 2.63 (s, 3HH, -CH_3), 2.49 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.04, 165.63, 148.04, 144.84, 141.52, 139.77, 136.35, 132.87, 128.68, 128.19, 127.66, 127.28, 124.28, 124.10, 123.97, 118.71, 99.44, 53.13, 41.56, 36.59, 31.58, 19.86 and 14.85; MS (ESI-qTOF): calcd. for $C_{23}H_{19}ClN_4O_4S_2$ [M+H]$^+$, 516.3260: found: 516.3297.

4-(2-(2-Chloro-8-methoxyquinolin-3-yl)-4-oxothiazolidin-3-yl-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7e): White solid; m.p.: 236-238 ºC; yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.16-8.14 (m, 2H, Ar-H), 7.84 (s, 1H, NH), 7.52 (s, 1H, Ar-H), 7.38-7.20 (m, 4H, Ar-H), 6.87-6.85 (m, 2H, Ar-H), 6.83 (s, 1H, S-CH-N), 6.58 (s, 1H, -C = CH), 3.98 (d, 1H, CH_2, J = 12 Hz), 3.88 (d, 1H, CH_2, J = 12 Hz), 2.51 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 177.85, 160.29, 150.80, 149.31, 147.77, 143.86, 143.39, 141.09, 135.23, 129.56, 129.40, 127.43, 125.73, 124.44, 121.99, 115.67, 98.26, 52.45, 36.34 and 15.17; MS (ESI-qTOF): calcd. for $C_{23}H_{19}ClN_4O_5S_2$ [M+H]$^+$, 531.3260: found: 531.3297.

4-(2-(2-Chloro-7-methoxyquinolin-3-yl)-4-oxothiazolidi-3-yl)-N-(95-methylisoxazol-3-yl)benzenesulfonamide (7f): White solid; m.p.: 232-234 ºC; yield: 78%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.24-8.22 (m, 2H, Ar-H), 7.94 (s, 1H, NH), 7.62-7.58 (m, 2H, Ar-H), 7.52 (s, 1H, Ar-H), 7.49-7.43 (m, 4H, Ar-H), 6.93 (s,1H, S-CH-N), 6.64 (s, 1H, -C = CH), 4.09 (s, 3H, -OCH_3); 4.05 (d, 1H, CH_2, J = 12 Hz), 4.01 (d, 1H, CH_2, J = 12 Hz), 2.60 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 175.43, 160.33, 150.82, 149.34, 146.83, 143.28, 141.11, 138.25, 135.89, 132.22, 130.75, 129.41, 127.47, 125.38, 122.01, 115.67, 99.77, 52.62, 35.71 and 15.18; MS (ESI-qTOF): calcd. for $C_{23}H_{19}ClN_4O_5S_2$ [M+H]$^+$, 531.2023: found: 531.2043.

4-(2-(2-Chloro-6-methoxyquinolin-3-yl)-4-oxothiazolidi-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7g): White solid; m.p.: 245-247°C; Yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.23-8.22 (m, 2H, Ar-H), 7.94-7.93 (m, 2H, Ar-H), 7.69-7.68 (m, 2H, Ar-H), 7.56 (s, 1H, NH), 7.49-7.47 (m, 3H, Ar-H), 7.11-7.10 (m, 1H, Ar-H), 6.93 (s, 1H, S-CH-N), 6.63 (s, 1H, -C = CH), 4.07 (d, 1H, CH_2, = 12 Hz), 4.01 (d, 1H, CH_2, J = 12 Hz), 2.60 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.09, 160.22, 149.05, 148.73, 147.78, 143.87, 143.42, 138.53, 135.90, 129.58, 129.33, 127.55, 125.74, 124.45, 124.10, 115.67, 99.78, 52.46, 35.98 and 15.75; MS (ESI-qTOF): calcd. for $C_{23}H_{19}ClN_4O_5S_2$ [M+H]$^+$, 531.2958: found: 531.2998.

4-(2-(2,8-Dichloroquinolin-3-yl)-4-oxothiazolidi-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7h): Red solid; m.p.: 234-236 ºC; yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.08-8.07 (m, 2H, Ar-H), 7.87 (s, 1H, NH), 7.62-7.60 (m, 2H, Ar-H), 7.57 (s, 1H, Ar-H), 7.56-7.29 (m, 3H, Ar-H), 6.57 (s, 1H, S-CH-N), 6.51 (s, 1H, -C = CH), 3.88 (d, 1H, CH_2, J = 12 Hz), 3.83 (d, 1H, CH_2, J = 12 Hz), 2.43 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.24, 165.27, 139.71, 136.46, 133.82, 133.77, 130.20, 129.82, 128.06, 127.61, 123.80, 123.70, 123.23, 122.85, 122.78, 118.65, 99.08, 53.07, 41.53, 36.65, 31.51 and 14.13; MS (ESI-qTOF): calcd. for $C_{22}H_{16}Cl_2N_4O_4S_2$ [M+H]$^+$, 535.2841: found: 531.2824.

4-(2-(2,7-Dichloroquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7i): White solid; m.p.: 225-227 ºC; yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.14-8.13 (m, 2H, Ar-H), 8.01 (s, 1H, NH), 7.90 (s, 1H, Ar-H), 7.69-7.67 (s, 1H, Ar-H), 7.50-7.48 (m, 2H, Ar-H), 7.37-7.35 (m, 2H, Ar-H), 6.81 (s, 1H, S-CH-N), 6.57 (s, 1H, -C = CH), 3.93 (d, 1H, CH_2, J = 12 Hz), 3.90 (d, 1H, CH_2, J = 12 Hz), 2.49 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 177.44, 166.14, 142.02, 140.42, 135.73, 130.81, 130.59, 130.50, 128.64, 128.20, 124.43, 124.16, 123.79, 119.34, 116.78, 116.56, 99.97, 54.01, 42.21, 37.97, 32.13 and 15.94; MS (ESI-qTOF): calcd. for $C_{22}H_{16}Cl_2N_4O_4S_2$ [M+H]$^+$, 535.0512: found: 535.0526.

4-(2-(2,6-Dichloroquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7j): Yellow solid; m.p.: 246-248 ºC; yield: 74%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.22-8.20 (m, 2H, Ar-H), 8.10-8.08 (m, 1H, Ar-H), 8.02 (s, 1H, NH), 7.79-7.74 (m, 2H, Ar-H), 7.73 (m, 1H, Ar-H), 7.58-7.43 (m, 2H, Ar-H), 6.89 (s, 1H, S-CH-N), 6.64 (s, 1H, -C = CH), 4.02 (d, 1H, CH_2, J = 12 Hz), 3.95 (d, 1H, CH_2, J = 12 Hz), 2.57 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.22, 164.09, 158.09, 157.55, 150.39, 148.56, 144.54, 143.47, 138.67, 132.67, 132.97, 130.35, 126.84, 125.21, 115.05, 114.85, 112.97, 102.40, 53.27, 37.13 and 15.38; MS (ESI-qTOF): calcd. for $C_{22}H_{16}Cl_2N_4O_4S_2$ [M+H]$^+$, 535.0833: found: 535.0893.

4-(2-(2-Chloro-6-fluoroquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7k): White solid; m.p.: 224-226 ºC; yield: 81%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.24-8.22 (m, 2H, Ar-H), 7.98-7.97 (m, 2H, Ar-H), 7.57 (s, 1H, NH), 7.43-7.32 (m, 2H, Ar-H), 6.81 (s, 1H, Ar-H), 6.81 (s, 1H, S-CH-N), 6.13 (s, 1H, -C = CH), 5.47 (s, 1H, -C = CH), 3.93 (d, 1H, CH_2, J = 12 Hz), 3.90 (d, 1H, CH_2, J = 12 Hz) and 2.47 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 177.09, 164.57, 158.06, 150.33, 149.12, 143.39, 139.23, 136.02, 132.90, 131.68, 126.66, 124.42, 124.08, 114.98, 114.79, 112.92, 102.34, 53.05, 37.35, 15.34; MS (ESI-qTOF): calcd. for $C_{22}H_{18}ClFN_4O_4S_2$ [M+H]$^+$, 519.2642: found: 519.2621.

4-(2-(2-Chloro-6-ethoxyquinolin-3-yl)-4-oxothiazolidin-3-yl)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7l): Yellow solid; m.p.: 218-220 ºC; yield: 80%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.11-8.10 (m, 2H, Ar-H), 7.91-7.83 (m, 2H, Ar-H), 7.56-7.55 (m, 2H, Ar-H), 7.48 (s, 1H, NH), 7.33-7.32 (m, 2H, Ar-H), 7.03-7.02 (m, 1H, Ar-H), 6.78 (s, 1H, S-CH-N), 6.53 (s, 1H, -C = CH), 4.18-4.14 (m, 2H, CH_2), 3.91 (d, 1H, CH_2, J = 12 Hz), 3.87 (d, 1H, CH_2, J = 12 Hz), 2.46 (s, 3H, -CH_3), 1.53 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.70, 164.53, 157.97, 150.25, 143.13, 141.25, 137.07, 135.87, 132.80, 129.92, 129.33, 129.13, 126.17, 124.86, 114.88, 112.81, 102.25, 54.02, 36.98, 36.98, 16.95, 15.23; MS (ESI-qTOF): calcd. for $C_{24}H_{21}ClN_4O_5S_2$ [M+H]$^+$, 545.2732: found: 545.2772.

Biological activity

Antifungal evaluation: All the synthesized 4-thiazolidinones (**7a-l**) were screened for their *in vitro* antifungal activity. The antifungal activity was evaluated against various fungal strains such as *Fusarium oxysporum* (NCIM 1332), *Aspergillus flavus* (NCIM 539), *C. albicans* (NCIM 3471), *C. neoformans* (NCIM 576) and *Aspergillus niger* (NCIM 1196), minimum inhibitory concentration (MIC, µg/mL) values of synthesized 4-thiazolidinone were analyzed using standard agar dilution method asper CLSI guidelines [30]. All the experiments performed in triplicates and mean reading is taken as a final reading 5% DMSO was used as a negative control along with fluconazole and miconazole as standard antifungal drugs.

RESULTS AND DISCUSSION

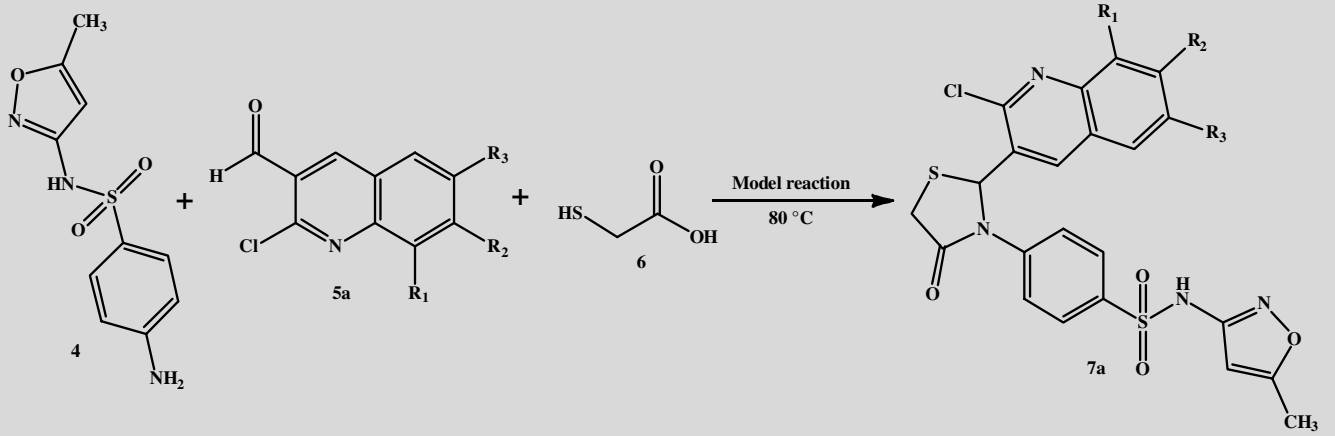
The reactants *viz*. 4-amino-*N*-(5-methylisoxazol-3-yl)-benenesulfonamide (**4**) were synthesized from *N*-acetylsulfanilyl chloride (**1**) with 3-amino-5-methyl-isoxazole (**2**) to give *N*-acylation products **3** by treating with acid hydrolysis as shown in **Scheme-I**. Then, the desired 4-thiazolidinone hybrids bearing sulfamethaoxazole scaffolds (**7a-l**) were synthesized by cycloaddition reaction of synthesized 4-amino-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (**4**), aryl aldehydes **(5a-I)** and mercapto acetic acid (**6**). This reaction was carried out in toluene as a solvent for 12h at reflux temperature resulted into the corresponding sulfamethaoxazole incorporated substituted 4-thiazolidinone conjugates (**7a-l**) in excellent yields (**Scheme-II**).

Intially, the reaction was performed in the presence of DBN ionic liquid 20 mol% under reflux condition using various solvents (Table-1). When ethanol and methanol, utilized as solvents for model reactions (Table-1, entries 1 and 2), yielded 52% and 61% after 50 min, respectively, whereas *tert*.-BuOH resulted in a lower yield of 48% (Table-1, entry 3). Similarly, results are also found when reaction was performed using THF and water (Table-1, entries 4-5). Using polar solvents like DMF and CH_3CN (Table-1, entries 6-8), the results does not much improved the yield of the product. Surprisingly, when the model reaction was performed without any solvent in the presence of 20 mol% [DBN][HSO_4] catalyst afford promising yield of 4-thiazolidinones. Therefore, above results represents that solvent-free protocol is the best conditions for the synthesis of 4-thiazolidnones hybrids.

The performance of [DBN][HSO_4] as catalyst for the synthesis of 4-thiazolidinone hybrids was further evaluated. Altering the catalyst concentration demonstrates a significantly greater impact on the percentage yield of the final product. The catalyst loading study shows that 20 mol % of [DBN][HSO_4] are optimal for the transformation of product in 93% of yield (Table-2). In addition, the optimum temperature for the representative reaction at differnt temperatures were also investigation. Based on the results shown in Table-3, the screening study suggests that excellent results were obtained at 80 ºC (entry 3).

An enormously excellent method to greener and economic production, recyclability and recovery of a ionic liquid. Therefore, it is essential to assess the efficiency of the catalyst after it has been separated from the reaction. After the catalyst was

TABLE-1
OPTIMIZATIONS OF THE REACTION CONDITIONS FOR THE SYNTHESIS OF 4-THIAZOLIDINONE DERIVATIVES **7a**[a]



Entry	Solvent	Temp. (°C)	Yield (%)
1	EtOH	Reflux	61
2	MeOH	Reflux	52
3	*tert*-BuOH	Reflux	48
4	THF	Reflux	40
5	H_2O	Reflux	53
6	Toulene	Reflux	50
7	DMF	Reflux	52
8	CH_3CN	Reflux	54
9	Solvent-free	80	93

[a]Reaction conditions: Quinoline aldehyde **1a** (1 mmol), 4-amino-N-(5-methylisoxazol-3-yl)benenesulfonamide **2** (1 mmol), mercapto acetic acid 3 (1 mmol) and (20 mol%) [DBN][HSO_4] stirred at 80 °C

TABLE-2
EFFECT OF CATALYST CONCENTRATION ON THE SYNTHESIS OF **7a**[a]

Entry	Catalyst (mol%)	Time (min)	Yield (%)
1	5	80	62
2	10	60	71
3	15	50	82
4	20	40	93
5	25	40	93

[a]Reaction conditions: **1a** (**1** mmol), **2** (1 mmol) and [DBN][HSO_4] at 80 °C

TABLE-3
TEMPERATURE EFFECT ON THE SYNTHESIS OF **7a**[a]

Entry	Temp. (°C)	Time[b] (min)	Yield (%)
1	60	100	65
2	70	70	83
3	80	40	93
4	90	40	93

[a]Reaction conditions: **1a** (1 mmol) and **2** (1 mmol) at 80 °C using 20 mol% [DBN][HSO_4] °C. [b]Reaction progress optimized using TLC

recovered, it was employed for four successive cycles without any reduction in its efficacy (Table-4).

TABLE-4
REUSABILITY OF [DBN][HSO_4] CATALYST FOR REPRESENTATIVE REACTION

Entry	Run	Time[a] (min)	Yield (%)
1	Fresh	40	93
2	2	40	93
3	3	40	85
4	4	40	82
5	5	40	80

[a]Reaction progress monitored by TLC

Comparative study: The efficiency of [DBN][HSO_4] as catalyst is compared with other reported catalysts for the synthesis of 4-thiazolidinone derivatives. The comparison study suggests that [DBN][HSO_4] ionic liquids results prominent yield, easily reusable and less reaction time (Table-5, entry 10). Thus, it is concluded that [DBN][HSO_4] is promising and greener pathway for the synthesis of 4-thiazolidinone conjugates.

The formation of compound **7a** has been established by ^{1}H NMR. ^{13}C NMR and HRMS analysis. In ^{1}H NMR spectrum of product **7a**, the CH_2 proton of 4-thiazolidinone motif was observed two different doublet of a doublet at δ 3.64 and 3.68 ppm, due to both the magnetically non-equivalent protons. The singlet peak observed at δ 6.57 ppm due C-H proton of 4-thiazolidinone ring. In ^{13}C NMR spectrum, 4-thiazolidinone ring formation was also established by the peaks observed at around 36.90 (CH_2), 52.33 (CH) and 176.90 (C = O) ppm. Further, the synthesis of **7a** products has been also confirmed by HRMS and calcd. for $C_{12}H_{18}ClN_4O_4S_2$ $[M+H]^+$, 501.3540: found: 501.3586.

Plausible mechanism: Plausible reaction mechanism for the synthesis of 4-thiazolidinone conjugates using [DBN][HSO_4] ionic liquid as a catalyst is shown in **Scheme-III**. Initially, aryl aldehyde bind with [DBN][HSO_4] to give intermediate **I**. In next step, inter-mediate **I** was converted to **II**, which upon dehydration to give imine **III**. The formation of intermediate **IV** results with the reaction of intermediate **III** with mercapto acetic acid, which then converted to intermediate **V** through intramolecular cyclization. In last step, the removal of H_2O molecule using [DBN][HSO_4] to results in the formation of titled 4-thiazolidinone conjugates **3a**.

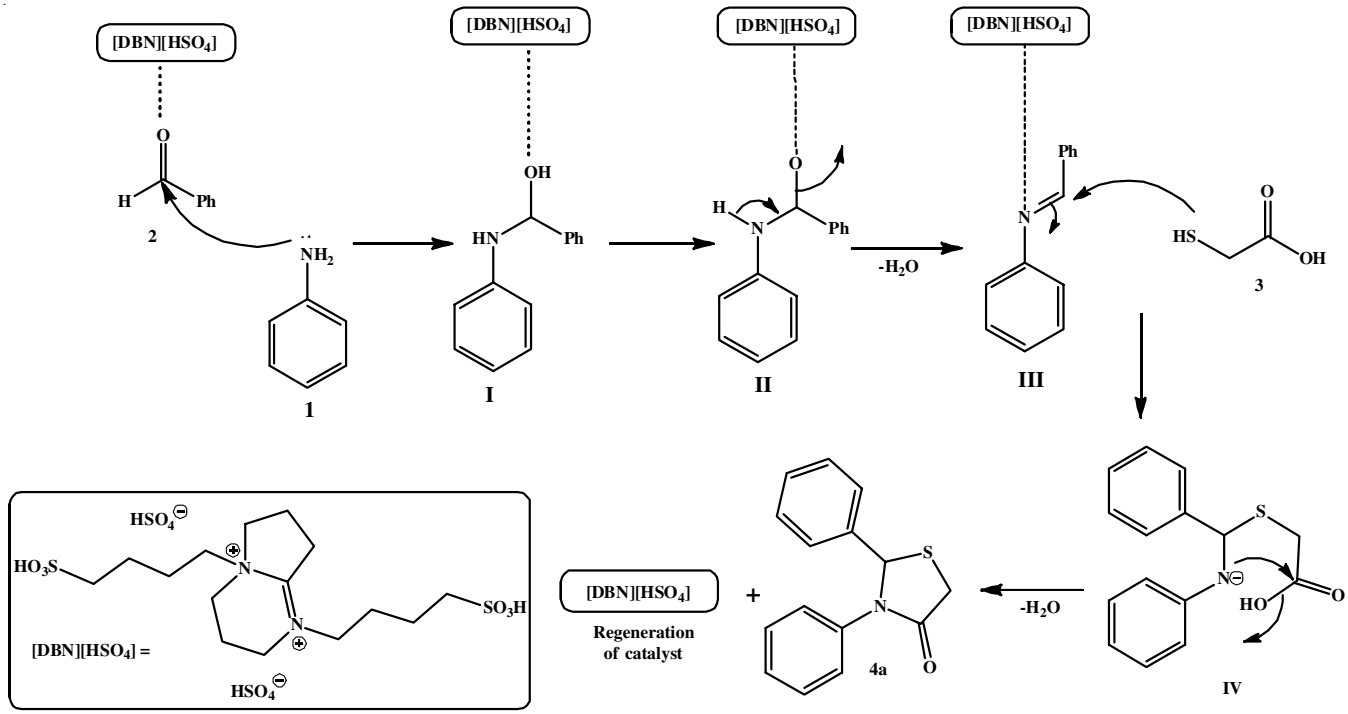
Biological activity

Antifungal activity: The antifungal activity data (Table-6) suggestted that several synthesized 4-thiazolidinone conjugates exhibit promising antifungal activity. Certain compounds exhibited reduced activity, whereas others demonstrated a broad spectrum of effectiveness against all fungal strains. Compound **7g** (R_3 = -OMe) with MIC values 25 µg/mL, exhibited equivalent activity compared to the standard drug miconazole against the fungicidal strain *C. albicans*, *F. oxysporum* and *A. flavus*. Compound **7h** in which (R_1 = -Cl) showed excellent activity with MIC values 25 µg/mL against the strain *C. albicans*, *F. oxysporum* and *A. flavus* fungicidal strains and compound **7i** in which (R_2 = -Cl) exhibits superior activity against *C. albicans* and *F. oxysporum*. Compounds **7j** in which (R_3 = -Cl) MIC values 25 µg/mL, exhibited prominent activity against the fungicidal strain *C. albicans*, *F. oxysporum*, *A. flavus*, *A. niger* and *C. neoformans*. Compound **7k** (R_3 = -F), MIC values 6.25 and 12.5 µg/mL, exhibited equipotent activity against the fungicidal strains *C. albicans*, *C. neoformans*, *F. oxysporum*, *A. flavus* and *A. niger*, respectively compared to the standard drugs fluconazole and miconazole.

Antioxidant activity: Quinoline-sulfamethaoxazole incorporated substituted 4-thiazolidinones hybrids were also screened for their *in vitro* free radical scavenging activity against free radicals. All the synthesized compounds provide evidence that compounds **7a-l** showed a concentration dependent anti-

TABLE-5
COMPARATIVE CATALYTIC PERFORMANCE OF [DBN][HSO_4] WITH OTHER REPORTED CATALYSTS

Entry	Catalyst	Time (h)	Yield (%)	Condition	Ref.
1	[bmim][PF_6]	9	80	80 °C	[43]
2	[bmim][BF_4]	1.7	82	80 °C	[43]
3	[MOEMIM]TFA	9	90	80 °C	[43]
4	$HClO_4$-SiO_2	5	85	PhMe/100	[44]
5	TfOH-SiO_2	5	72	PhMe/100	[44]
6	H_2SO_4-SiO_2	5	55	PhMe/100	[44]
7	Silica gel, DCM	6	96	DCM/RT	[36]
8	$Bi(SCH_2COOH)_3$	2	90	70 °C	[40]
10	[DBN][HSO_4]	40 min	93	Solvent free/80 °C	Present work



Scheme-III: Mechanism reaction for the synthesis of 4-thiazolidinone (**3a**)

TABLE-6
In vitro ANTIFUNGAL AND ANTIOXIDANT ACTIVITY DATA OF SYNTHESIZED COMPOUNDS **7a-l**

Entry	R_1	R_2	R_3	MIC (µg/mL)					DPPH IC_{50} (µg/mL)
				Candida albicans	*Fusarium oxysporum*	*Aspergillus flavus*	*Aspergillus niger*	*Cryptococcus neoformans*	
7a	H	H	H	100	100	50	50	200	35.20
7b	Me	H	Me	150	125	100	100	*	24.52
7c	H	Me	H	100	100	125	*	*	22.40
7d	H	H	Me	100	100	50	100	150	18.20
7e	OMe	H	H	50	50	50	50	75	17.50
7f	H	OMe	H	50	50	50	50	50	20.41
7g	H	H	OMe	25	25	25	50	75	16.80
7h	Cl	H	H	25	25	50	25	75	28.20
7i	H	Cl	H	25	25	50	50	75	24.54
7j	H	H	Cl	25	25	25	25	25	26.41
7k	H	H	F	6.25	6.25	6.25	12.5	6.25	20.12
7l	H	H	-OEt	50	50	75	100	50	23.12
BHT	–	–	–	NT	NT	NT	NT	NT	16.47
MA	–	–	–	25	25	25	25	25	NT
FA	–	–	–	6.25	6.25	6.25	12.5	6.25	NT

BHT = Butylated hydroxy toluene; MA = Micanazole, FA = Fluconazole, NT = Not tested, Note: *No activity was observed.

oxidant species and measured it by DPPH radical scavenging assay. Butylated hydroxytoluene (BHT) was used for conventional drug to compare the antioxidant activity. Based on the results (Table-6), it was found that the synthesized compounds show excellent to moderate bioactivity compared to the standard antioxidant drug BHT (IC_{50} = 16.45 µg/mL). From the synthesized compounds, **7b-l** exhibits lower antioxidant activity when compared with standard IC_{50} value range are 16.80-35.20 µg/mL.

Conclusion

The synthesis, characterization and the biological activity of substituted 4-thiazolidinone conjugates (**7a-l**) containing quinoline-sulfamethoxazole motifs were successfully accomplished in the presence of 20 mol% of [DBN][HSO_4] as a catalyst at 80 ºC, which serve as one of the best method. Five compounds (**7g**, **7h**, **7i**, **7j** and **7k**) of the series displays exhibited promising activity against with MIC range 25, 12.5 and 6.25 µg/L, respectively, however compounds **7b-l** displayed moderate radical activity.

ACKNOWLEDGEMENTS

One of the authors NAB, are thankful to CSIR-HRDG, New Delhi India for awarding the SRF fellowship. The authors are also thankful to the management of Maulana Azad Post

Graduate & Research Centre, Aurangabad India for providing excellent laboratory facilities.

CONFLICT OF INTEREST

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

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