[BIL]-Mediated Efficient Synthesis of Novel 4-thiazolidinone derivatives and their Bioevaluation

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Ionic liquids (ILs) have attracted interest as environmentally benign media for catalysis, synthesis, separation, adjustable physical and chemical properties.[1-6] ILs include numerous exclusive properties, such as extensive liquid range, nonvolatility, low toxicity, high thermal stability, noncombustible, excellent solubility, and recyclability.[7] ILs act as "neoteric solvents" for a wide range of industrial and chemical processes.[8] In recent times, ILs have been originating to be valuable as environmental friendly media for countless organic revolutions.[9] Thus, the introduction of a dynamic, inexpensive, mild, and environmental friendly catalyst for significant cyclization reaction superior to analogues of pharmaceutical and biological prominence is in demand.

Multicomponent reactions (MCRs) are significant role in rapid and elegant synthesis of heterocyclic compounds from simple building blocks. MCRs are exhibit high atom-economy, simple experimental procedure and high selectivity protocol due to the construction of C-C and C-X (X= hetero atom) in one-pot.[10] MCRs in the drug discovery process offer a number of advantages over traditional approaches.[11] Furthermore, MCRs achieve the several advantages such as minimizes cost, time, effort and byproduct which are extremely agreeable with the goals of green and sustainable chemistry.[12]

The emergence of highly resistant eukaryotic microorganisms fungi to drugs in the past decades has challenged the research group's world over to design, synthesize and evaluate the new molecules.[12] Fungi are vital opportunistic pathogens of humans and are becoming drug-resistant to the approved compounds most prominent of them include *Cryptococcus neoformans* and species of *Candida* and *Aspergillus*. The *Candida albicans* could cause superficial or invasive infections or both in immune compromised individuals.[13] The other factors that have contributed to drug resistance are the frequently used more-invasive medical procedures and the treatment with broad-spectrum antibiotics. In many cases, it is not the AIDS or cancer itself but the mycoses that are lethal to these patients. Another serious fungal infection are caused mostly by *Candida albicans*, *Cryptococcus neoformans* and *Aspergillus fumigates* with *Candida albicans* being the most common agent of fungal blood stream infections.[14] Therefore, it is necessary to find new and efficacious drugs to solve these problems.

The human body has a complex system of natural enzymatic and non-enzymatic antioxidant defenses which counteract the harmful effects of free radicals and other oxidants. Reactive oxygen species (ROS) are essential for an organism's essential activities, such as the regulation of cell proliferation, intracellular signaling and synthesis of biologically active compounds and energy. However, excessive production of ROS causes oxidative stress and chronic diseases such as cardiovascular disease, Alzheimer's disease, rheumatoid arthritis, ageing, heart diseases and cancer. ROS are known to directly interact with all types of

biomolecules, including proteins, lipids and DNA, resulting in oxidative cellular damage.[15] another important aspect regarding the antioxidant activity is the lipophilicity of the compounds. It is well established in the literature that the lipophilic compounds exhibit good antioxidant behavior in lipid systems.[16]

4-Thiazolidinones has been act as a fascination scaffolds (magical nucleus) and represents an significant group of heterocyclic compound with a extensive range of noteworthy biological activity such as anti-convulsant,[13] anti-inflammatory,[14] antimicrobial,[15] anti-viral,[16] antitumor,[17] antidiabetic,[18] antituberculosis,[19] antiparasitic,[20] analgesic,[21] antidiarrhoeal,[22] antiarthritic[23] cardiovascular activity[24] anti-HIV,[25] and FSH agonist.[26] Furthermore, 4-thiazolidinones are also exhibits excellent activity against various cancer cell line including, breast cancer JSP-1 inhibitor,[27] (MCF-7),[28] tumor necrosis factor (TNFα),[29] antiapoptotic biocomplex (Bcl-XL-BH3),[30] integrin avb3 receptor,[31] antiproliferative activity against Reh and Nalm6 cells,[32] Cyclin B/CDK1 inhibitor[33] and HT29 colon cancer cell line[34] and Some of the representative biologically active 4-thiazolidinone scaffolds are shown in **Fig. 1**.

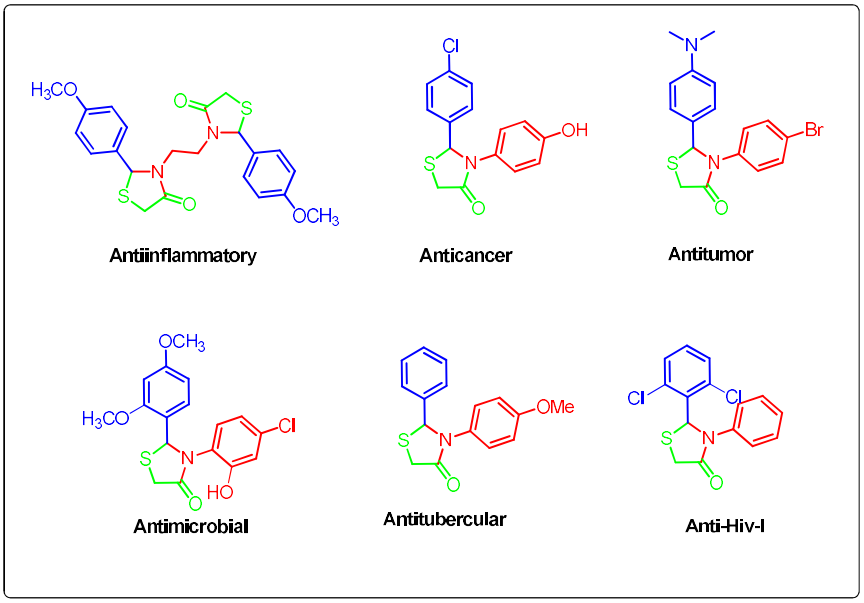


Fig. 1. Some biologically important 4-thiazolidinones

Because of its broad spectrum of biological activities, numerous preparative routes have been developed for the preparation of 4-thiazolidinone scaffolds. Due to this in recent year several catalytic protocol have been developed such as DIPEA,[35] DBSA,[36] nano-Fe_3O_4@SiO_2,[37] montmorillonite K-10,[38] silica gel,[39] acetic acid,[40] *N*-methyl pyridinium tosylate,[41] ammonium persulfate,[42] $SnCl_2$,[43] Cd-Zr_4- $[PO_4]_6$[44] $Bi[SCH_2COOH]_3$[45] ionic liquid [bmim]OH,[46] silica supported Co Fe_2O_4@SiO_2/$PrNH_2$[47] and $Y[OTf]_3$[48] and acid catalysed.[49] However, the above reported protocol advocates prolonged heating, hazardous solvent, tedious work-up procedure, separation and recycling of catalyst. Moreover, many of these schemes utilize organic solvents as the reaction medium. Hence, a protocol which overcomes these demerits invites a lot of attention for the researcher. Hence, the further innovation toward contemporary reaction with easy isolation of product, reusability of catalyst, perhaps with minimal or no waste is highly attractive. Recently, BIL was widely used as catalysts in different research area. The combination of BIL with cation to give the formation of novel ionic liquids.[50] The large number of functionalized ILs has been considered for diverse

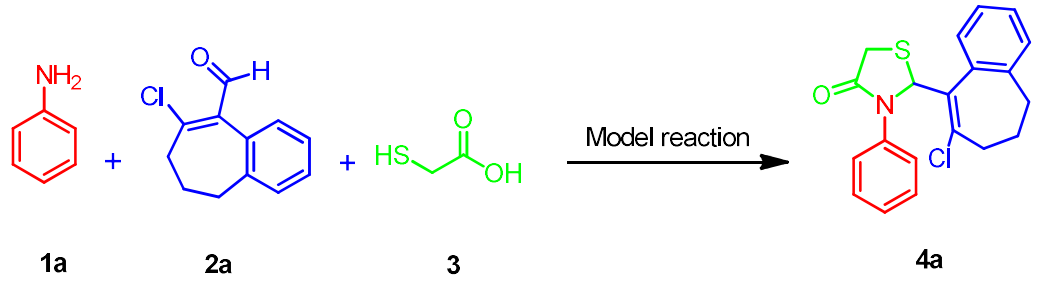
purposes.[51] ILs have been deemed as environment friendly substitutes and recyclable for volatile organic solvents attributing to their good-looking thermal and chemical stability, negligible vapour pressure, high ionic conductance and non-flammability. Due to this wide range of applications, they are used as a suitable solvent for wide array of synthetic protocols.

As per our investigation, the existential of this work is to begin a rapid and efficient synthetic protocol for obtaining 4-thiazolidinone derivatives under ecofriendly conditions. As an extension of emerging economic and efficient strategy to develop pharmaceutically and biologically significant molecules, herein, we reported synthesis of library of novel 4-thiazolidinone derivatives promoted by synergistic effect of ionic liquid without any added catalyst in good to excellent yields.

RESULTS AND DISCUSSION

Chemistry

To achieve optimized conditions protocol based on the reaction of aniline (**1a**), 8-chloro-6,7-dihydro-5H-benzo[7]annulene-9-carbaldehyde (**2a**) (1 mmol), and thioglycolic acid (**3**) (1 mmol) as model reaction (**Scheme 1**), we checked temperatures and solvents, catalyst loading and the results of this study are summarized in **Table 1**.



Scheme 1. Standard model reaction

The model reaction carried out in MeOH and EtOH (**Table 1**, entry 1, and 2) was completed in 50 min with the yield of 56 and 50%, respectively. Whereas, in *tert*-BuOH (**Table 1**, entry 3), a lower yield (45%) was obtained in 50 min. In H_2O decreased yields (32%) of the product **4a** were obtained (**Table 1**, entries 4). Conducting the reaction in Toluene, THF, CH_3CN and DMF (**Table 1**, entries 5-8), slightly improve the yield of the product. However, when the model reaction was carried out under a solvent-free condition with 20 mol% [BIL], a significant increase in the yield was observed (**Table 1**). Therefore it proved that the solvent-free condition is best suited for the transformation. Therefore, it can be thought that [BIL] is green and a superior solvent and catalyst compared to the others shown in **Table 1**.

Table 1. Optimizations of the reaction conditions for the synthesis of 4-thiazolidinone derivatives **3a**[a]

Entry	Solvent	Temp (°C)	Yield[b] (%)
1	EtOH	Reflux	56
2	MeOH	Reflux	50
3	*Tert*-BuOH	Reflux	45
4	H_2O	Reflux	32
5	Toluene	Reflux	62
6	THF	Reflux	59
7	CH_3CN	Reflux	52
8	DMF	Reflux	56
9	**Solvent-free**	**80**	**89**

[a]Reaction conditions: aniline **1a** (1 mmol), aldehyde **2a** (1 mmol), thioglycolic acid **3** (1 mmol) [BIL] (20 mol%) stirred at 80 °C. [b]Isolated yields. Bold values are for highlighting the good result.

In the next step we examine the efficiency of ionic liquid [BIL] for the synthesis of 4-thiazolidinone derivatives. When change in concentration of [BIL] on model reaction suggest that much more effect on yield of final product. The catalyst loading study suggest that 20 mol% of [BIL] catalyst are best for the synthesis of final product in 90% yields (**Table 2**).

Furthermore, we also studied the effect of temperature on the model reaction at different temperatures. According to this study better results of the desired product when reaction carried at 80 °C (**Table 3**, entry 3). Detailed reaction conditions are shown in **Table 3.**

Table 2. Effect of catalyst concentration[a]

Entry	Catalyst (mol %)	Time (min)	Yield[b] (%)
1	5	100	61
2	10	80	70
3	15	60	81
4	20	50	89
5	25	50	89

[a]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3** (1 mmol) and [BIL] at 80 °C. [b]Isolated yield.

Table 3. Temperature effect on the synthesis of **3a**[a]

Entry	Temp °C	Time[b] (min)	Yield[c]
1	50	100	61
2	60	60	75
3	70	30	81
4	80	30	89

[a]Reaction conditions: **1a** (2 mmol) and **2** (1 mmol) in the presence of [BIL] 20 mol% at 80 °C. [b]Reaction progress monitored by TLC. [c]Isolated yield.

A extremely superlative method to economic and greener preparation is recovery and recyclability of a ionic liquid. Therefore we have to check the efficiency of catalyst after recover from the reaction media during the work-up procedure.

Table 4. Reusability of [BIL] ionic liquid for model reaction

Entry	Run	Time[a] (min)	Yield[b]
1	Fresh	30	89
2	2	30	89
3	3	30	84
4	4	30	81
5	5	30	81

[a]Reaction progress monitered by TLC. [b]Isolated yield.

When reaction is completed, then reaction mass was pour on ice cold water to obtained fine crystal of final 4-thiazolidinone derivatives. In the last step removal H_2O from filtrate using reduced pressure to gave viscous liquid, which is on cooling to give pure ionic liquid. Recovered catalysts were reused for next four repeated cycles without considerable loss in catalytic efficiency (**Table 4**).

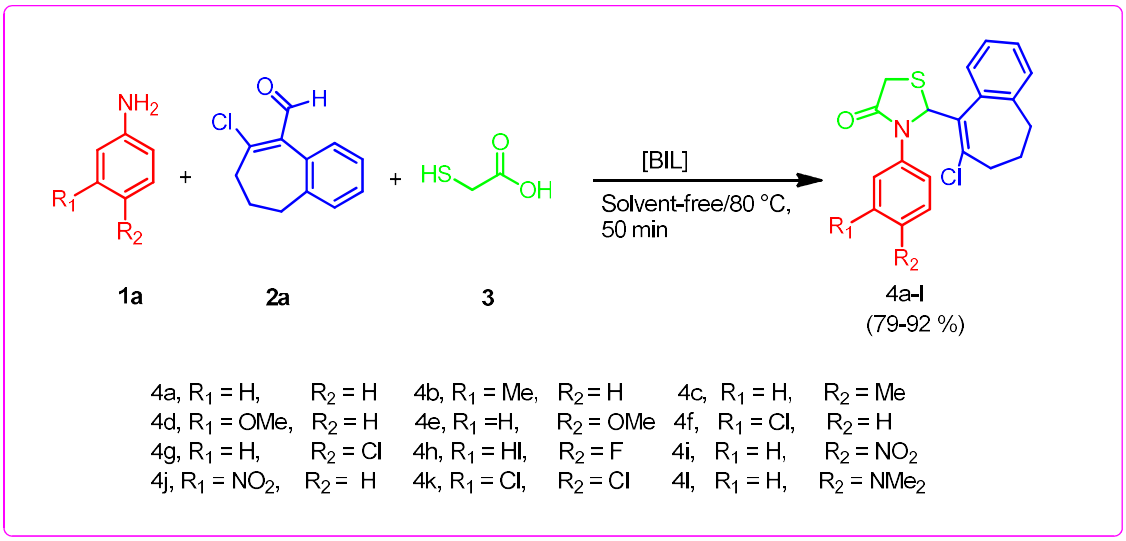
Comparison of [BIL] (IL) catalyst with previous reported protocol

We have proved the comparison study of the [BIL] with other reported catalysts for the preparation of 4-thiazolidinone derivative. The comparison results proved that [BIL] is better catalyst in terms of excellent yield and reusability with less reaction time (**Table 5**, **entry 10**). In conclusion [BIL] is found to be a facile and environmentally benign protocol for the synthesis of 4-thiazolidinone derivatives.

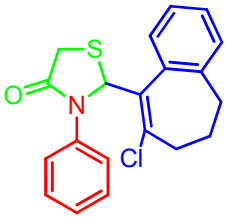
Table 5. Comparative Catalytic Performance of the [BIL] (IL) with Other Previously Reported Catalysts

Entry	Catalyst	Time (min)	Yield (%)	solvent/condition	Ref.
1	$HClO_4$-SiO_2	5 h	85	PhMe/100	54
2	H_2SO_4-SiO_2	5 h	55	PhMe/100	54
3	TfOH-SiO_2	5 h	72	PhMe/100	54
4	[bmim][BF_4]	1.7 h	82	80 °C	55
5	[MOEMIM]TFA	9 h	90	80 °C	55
6	[bmim][PF_6]	9 h	80	80 °C	55
7	Silica gel, DCM	6 h	96	DCM/RT	39
8	$Bi(SCH_2COOH)_3$	2 h	90	Solvent-free/80 °C	56
9	[BIL]	**50 min**	**89**	Solvent-free/80 °C	**Present work**

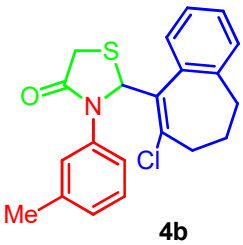
The structural identification of synthesized **4f** compound was established by ^{1}H and ^{13}C NMR spectral analysis. ^{1}H NMR spectra the peak observed at 2.25 δ ppm for the CH_3 group. The two distinct doublet of a doublet at 3.96-3.86 ppm due to the -CH_2 protons of 4-thiazolidinone scaffold, this different peak suggest that the both the -CH_2 protons are magnetically different. The peak appeared as a singlet at δ 6.02 ppm due the presence of C-H proton of the 4-thiazolidinone scaffold. In ^{13}C NMR spectra peak appeared at around 33.3, 64.9 and 170.8 ppm (CH, CH_2 and C=O respectively, due to the presence of 4-thiazolidinone ring in the synthesized compounds.



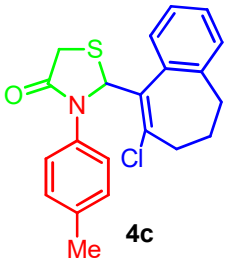
Scheme 2. Substrate scope for the synthesis of 4-Thiazolidinones derivatives using [BIL] catalyst.



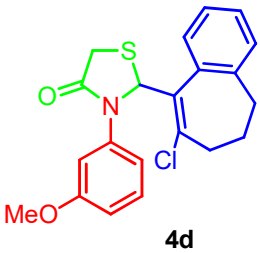
4a



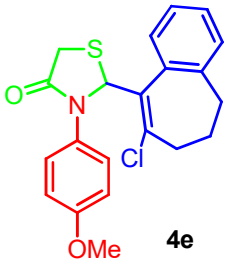
4b



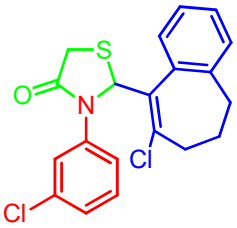
4c



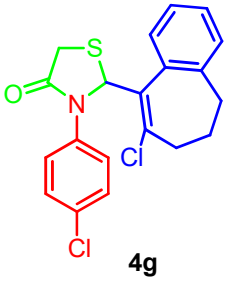
4d



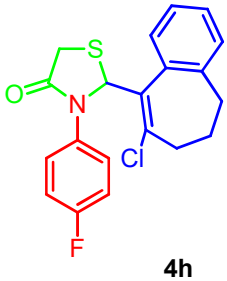
4e



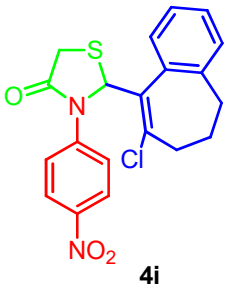
4f



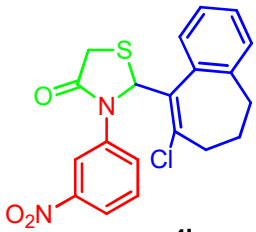
4g



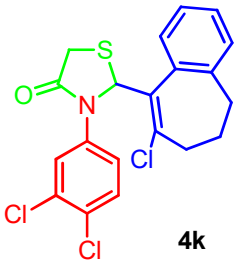
4h



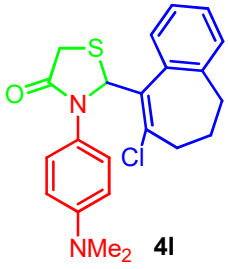
4i



4j



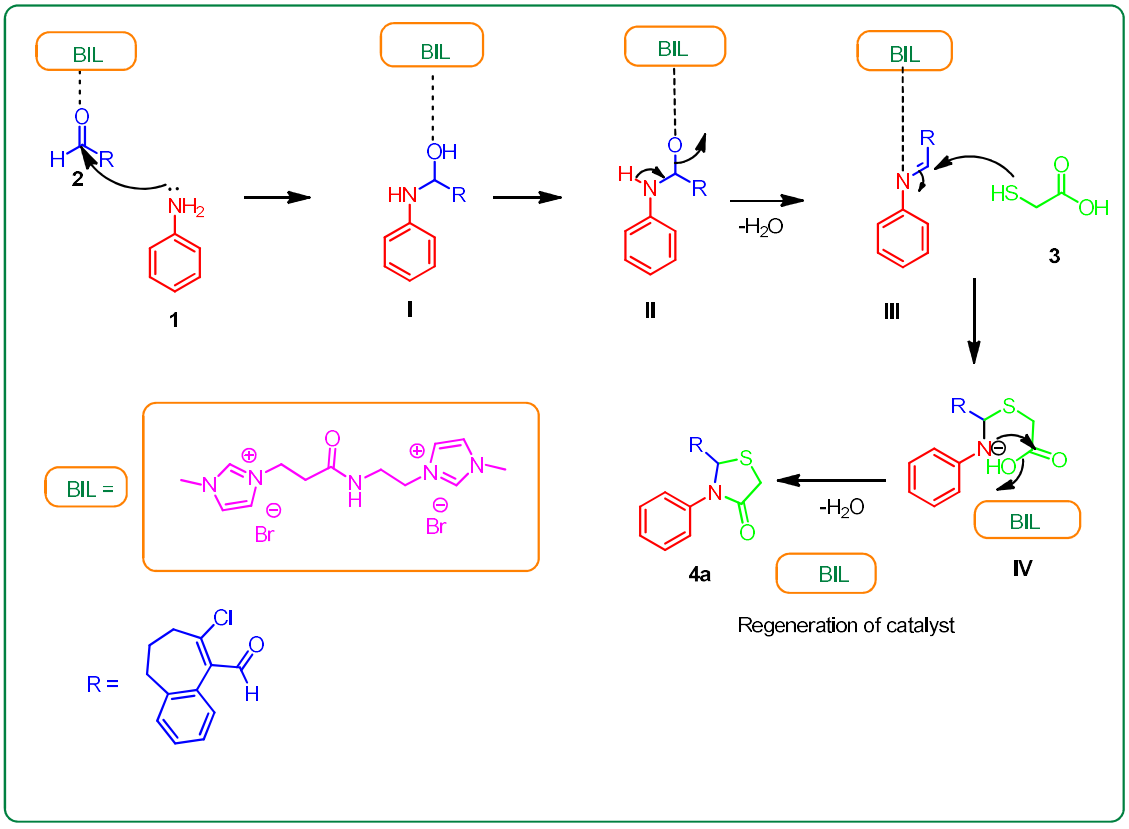
4k



4l

Plausible Reaction Mechanism

Reaction mechanism cycle for the preparation of 4-thiazolidinone analogues employing [BIL]is catalyst. In first step aldehyde activated by [BIL]followed by nucleophilic substitution of aniline results formation intermediate **I**. In next step removal of water molecules from intermediates **I** with the help of [BIL]to give imine product **II**. In the third step intermediate **III** react with **3** afforded cycloaddition product **IV**. Further intramolecular cyclization to form final product **4a** *via* removal of H_2O molecule and regeneration of catalyst. Details reaction mechanism is presented in **Scheme 3.**



Scheme 3. Reaction mechanism cycle for the preparation of compounds **4a**.

Experimental section

Materials and methods

All chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC) with a flame ionization detector (FID) with a capillary column (30 m 0.25 mm 0.25 lm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. Products were purified by column chromatography on 100–200 mesh silica gel. The 1H NMR spectra were recorded on 400 MHz spectrometers using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded at 100 MHz and chemical shifts were reported in parts per million (d) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (J) values were reported in hertz (Hz). The splitting patterns of the proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) in 1H NMR spectroscopic analysis. The products were confirmed by ^{1}H and ^{13}C NMR spectroscopy analysis.

Preparation of [BIL]

General Procedure for the Synthesis of [BIL] are given in supporting information.

General Procedure for Synthesis of 4-thiazolidinone derivatives (4a-l)

A mixture of aryl anilines (**1a-i**), aldehyde (**2a**) 1 mmol, thioglycolic acid (**3a**) 1 mmol and ionic liquid 2 mmol [BIL] was stirred at 80 ºC temperature for 50 min. The progress of the reaction was monitored by thin layer chromatography (*n*-Hexane/EtOAc 8:2). Further, addition of ice cold water (10 mL) was added to it and stirred for 10 min and filtered. The obtained solid was filtered, washed with cold water to remove the ionic liquid. The obtained crude compounds were recrystallized using ethanol. The synthesized compound is confirmed by MP, ^{1}H NMR and ^{13}C NMR spectra.

/4a/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-phenylthiazolidin-4-one:

The cyclocondensation reaction of **1a, 2a** and **3** in ionic liquid for 40 min to give product **7a**. White solid; Mp: 208-210 °C; Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.59 – 7.35 (m, 4H), 7.35-7.15 (m, 5H), 5.43 (s, 1H), 3.88 (q, J = 12.5 Hz, 2H), 2.78 (t, J = 6.3 Hz, 2H), 2.24 (t, J = 6.4 Hz, 2H) and 1.96 (dd, J = 12.7, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.92, 145.13, 142.25, 140.46, 137.97, 134.37, 131.51, 130.68, 129.34, 128.81, 127.74, 123.79, 66.14, 39.39, 36.99, 36.47 and 27.51.

***/4b/*2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(m-tolyl)thiazolidin-4-one:**
The compound **4b** was obtained *via* cyclocondensation of **1b**, **2a** and **3** as white solid; Mp: 180-184 °C; Yield: 89%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.46-7.26 (m, 3H), 7.25-7.03 (m, 5H), 5.42 (s, 1H), 3.82 (q, J = 12.4 Hz, 2H), 2.81 (t, J = 5.7 Hz, 2H), 2.47-2.23 (m, 5H), 2.01-1.77 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.91, 145.11, 142.19, 140.44, 139.73, 134.36, 131.99, 131.73, 130.67, 128.79, 125.46, 123.81, 66.12, 39.38, 36.98, 36.46, 27.50 and 23.09.

/4c/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(p-tolyl)thiazolidin-4-one:
The compound **4c** was obtained *via* oxidative cyclocondensation of **1c**, **2a** and **3** as white solid; Mp: 184-186 °C ; Yield: 84%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.43 – 7.11 (m, 8H), 5.42 (s, 1H), 3.53 (q, J = 12.4 Hz, 2H), 2.78 (t, J = 6.3 Hz, 2H), 2.44 (s, 3H), 2.28 (t, J = 6.5 Hz, 2H) and 1.95 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 177.21, 145.41, 142.54, 140.75, 138.86, 136.93, 134.66, 133.02, 130.97, 129.09, 124.47, 124.07, 66.43, 39.68, 37.28, 36.76, 27.80 and 23.32.

/4d/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(3-methoxyphenyl)thiazolidin-4-one:
The compound **4d** was obtained *via* cyclocondensation of **1d**, **2a** and **3** as white solid; Mp: 180-182 °C; Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.42 (t, J = 7.5 Hz, 1H), 7.17-6.84 (m, 7H), 5.39 (s, 1H), 3.95-3.79 (m, 5H), 2.61 (t, J = 5.8 Hz, 2H), 2.22 (t, J = 6.4 Hz, 2H), 1.87 (p, J = 6.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.92, 163.46, 145.12, 142.25, 140.49, 134.36, 132.38, 130.68, 128.80, 123.78, 119.74, 115.20, 113.67, 66.13, 57.93, 39.39, 36.99, 36.47 and 27.50.

/4e/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(4-methoxyphenyl)thiazolidin-4-one:

The compound **4e** was obtained *via* cyclocondensation of **1e**, **2a** and **3** as white solid; Mp: 176-178 °C; Yield: 85%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.40-7.14 (m, 6H), 7.07 (d, J = 7.5 Hz, 2H), 5.43 (s, 1H), 3.93 (s, 3H), 3.55 (q, J = 12.4 Hz, 2H), 2.79 (t, J = 6.3 Hz, 2H), 2.29 (t, J = 6.5 Hz, 2H), 1.98 (dd, J = 12.8, 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 178.18, 161.10, 146.39, 143.51, 141.72, 135.63, 133.60, 131.94, 130.07, 129.62, 125.05, 118.81, 67.40, 59.20, 40.66, 38.25, 37.73 and 28.77.

/4f/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(3-chlorophenyl)thiazolidin-4-one:

The compound **4f** was obtained *via* cyclocondensation of **1f**, **2b** and **3** as yellow solid; Mp: 168-170 °C; Yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.46-7.34 (m, 4H), 7.34-7.19 (m, 4H), 5.48 (s, 1H), 3.88 (q, J = 12.5 Hz, 2H), 2.88 (t, J = 5.7 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H) and 2.13 – 1.88 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.31, 144.51, 141.64, 139.83, 135.03, 133.75, 130.41, 130.07, 128.19, 126.76, 126.30, 123.99, 123.17, 65.52, 38.78, 36.38, 35.86 and 26.89.

/4g/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(4-chlorophenyl)thiazolidin-4-one:

The compound **4g** was obtained *via* cyclocondensation of **1g**, **2c** and **3** as brown solid; Mp: 170-172 °C; Yield: 91%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.59-7.48 (m, 3H), 7.31 (tt, J = 4.7, 3.1 Hz, 3H), 7.04 (d, J = 7.5 Hz, 2H), 5.45 (s, 1H), 3.92 (q, J = 12.4 Hz, 2H), 2.40 (t, J = 6.2 Hz, 2H), 2.27 (t, J = 6.5 Hz, 2H) and 1.93 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 177.20, 145.41, 142.53, 140.74, 137.96, 134.65, 134.44, 131.80, 130.96, 129.09, 127.99, 124.07, 66.42, 39.68, 37.27, 36.75, 27.79.

/4h/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(4-fluorophenyl)thiazolidin-4-one:

The compound **4h** was obtained *via* cyclocondensation of **1h**, **2c** and **3** as white solid; Mp: 174-176 °C; Yield: 88%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.32 (ddd, J = 8.7, 6.9, 3.3 Hz, 3H), 7.27-7.04 (m, 5H), 5.40 (s, 1H), 3.80 (q, J = 12.5 Hz, 2H), 2.78 (t, J = 5.7 Hz, 2H), 2.34 (t, J = 6.8 Hz, 2H) and 1.91 (td, J = 6.7, 3.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.59, 162.65, 160.54, 144.80, 141.93, 140.13, 135.54, 134.04, 130.36, 128.67-128.38, 123.46, 118.54, 118.33, 65.81, 39.07, 36.67, 36.15 and 27.18.

/4i/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(4-nitrophenyl)thiazolidin-4-one:

The compound **4h** was obtained *via* cyclocondensation of **1i**, **2d** and **3** as white solid; Mp: 150-152 °C; Yield: 79%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.32 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.34 – 7.07 (m, 4H), 5.39 (s, 1H), 3.51 (q, J = 12.5 Hz, 2H), 2.75 (t, J = 6.3 Hz, 2H), 2.25 (t, J = 6.5 Hz, 2H) and 1.93 (p, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.60, 146.43, 145.50, 144.81, 141.94, 140.14, 134.04, 130.37, 128.49, 127.86, 123.40, 65.82, 39.08, 36.68, 36.16, 27.19.

/4j/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(3-nitrophenyl)thiazolidin-4-one:

The compound **4j** was obtained *via* cyclocondensation of **7j**, **8g** and **9** as yellow solid; Mp: 162-164 °C; Yield: 92%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.34-8.07 (m, 2H), 7.77-7.42 (m, 2H), 7.32-7.08 (m, 4H), 5.37 (s, 1H), 3.51 (q, J = 12.5 Hz, 2H), 2.74 (t, J = 6.3 Hz, 2H), 2.24 (t, J = 6.5 Hz, 2H) and 1.91 (p, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.31, 150.05, 144.51, 141.64, 140.20, 139.84, 133.76, 132.76, 130.49, 130.07, 128.19, 123.11, 122.85, 65.52, 38.78, 36.38, 35.86 and 26.90.

/4k/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(3,4-dichlorophenyl)thiazolidin-4-one:

The compound **4k** was obtained *via* cyclocondensation of **7k**, **8c** and **9** as white solid; Mp: 172-174 °C; Yield: 90%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.51-7.00 (m, 7H), 5.40 (s, 1H), 3.80 (q, J = 12.4 Hz, 2H), 2.80 (t, J = 5.7 Hz, 2H), 2.34 (t, J = 6.8 Hz, 2H) and 1.91 (td, J = 6.7, 3.3 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 176.91, 145.14, 142.24, 140.61, 140.44, 134.33, 132.56, 130.67, 128.77, 124.44, 124.25, 123.77, 66.12, 39.38, 36.98, 36.46 and 27.49.

/4l/2-(8-chloro-6,7-dihydro-5H-benzo[7]annulen-9-yl)-3-(4-(dimethylamino)phenyl)thiazolidin-4-one:

The compound **4l** was obtained cyclocondensation of **7l**, **8c** and **9** as white solid; Mp: 178-180 °C; Yield: 86%; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.47 (dd, J = 7.0, 2.1 Hz, 1H), 7.38 – 7.24 (m, 3H), 7.13 (d, J = 7.5 Hz, 2H), 6.97 (d, J = 7.5 Hz, 2H), 5.48 (s, 1H), 3.87 (q, J = 12.4 Hz, 2H), 3.08 (s, 6H), 2.64 (t, J = 6.1 Hz, 2H), 2.31 (t, J = 6.3 Hz, 2H) and 1.95 (t, J = 6.2 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 177.50, 154.21, 145.71, 142.83, 141.04, 134.95, 131.26, 130.43, 129.64, 129.39, 124.37, 120.04, 66.72, 44.39, 39.98, 37.57, 37.05 and 28.09.

3.1. Biological activity

3.1.1. In vitro Anti-mycobacterial act Antifungal evaluation

All the synthesized 4-thiazolidinone was evaluated for their *in vitro* antifungal activity. The antifungal activity was screened 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 all synthesized 4-thiazolidinone were analyzed using standard agar dilution method as per CLSI guidelines.[31] 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 the standard antifungal drugs (**Table 6**).

Table 6. *In vitro* antifungal and antioxidant activity of compounds **4a-l** MIC in (µg/mL)

Entry	R_1	R_2	Antifungal activity MIC (µg/mL)					DPPH IC_{50}
			CA	*FO*	*AF*	*AN*	*CN*	(µg/mL)
4a	H	H	100	100	50	50	200	30.12
4b	Me	H	150	125	100	100	125	21.32

4c	H	Me	100	100	125	100	150	17.40
4d	OMe	H	100	100	50	100	150	19.20
4e	H	OMe	50	50	50	50	75	16.50
4f	Cl	H	25	25	50	50	50	18.52
4g	H	Cl	25	25	25	25	25	16.47
4h	H	F	6.25	6.25	6.25	12.5	6.25	16.50
4i	H	NO_2	25	25	50	50	75	23.54
4j	NO_2	H	25	25	25	25	25	25.41
4k	Cl	Cl	8.25	8.25	8.25	12.5	8.25	16.70
4l	H	NMe_2	50	50	75	100	50	22.12
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

CA, Candida Albicans; FO, Fusarium Oxysporum; *AF*, *Aspergillus Flavus; AN, Aspergillus Niger* and *CN*, *Cryptococcus Neoformans.* BHT: Butylated hydroxy toluene; MA: Micanazole, FA: Fluconazole, NT: *Not tested, Note:* No activity was observed.*

The antifungal activity data suggest (**Table 6**), many of the synthesized 4-thiazolidinone conjugates were exhibits promising antifungal activity. Some compounds were less active while some of them were found to be a wide range activity against all fungal strains. Compound **4f** (R_1 = Cl) with MIC values 25 µg/mL, exhibited equivalent activity compared to the standard drug miconazole against the fungicidal strain *C. albicans* and *Fusarium Oxysporum.* Compounds **4g** in which (R_2 = -Cl) showed excellent activity with MIC values 25 µg/mL against the strain *C. albicans, Fusarium Oxysporum*, *Aspergillus Flavus*, *Aspergillus Niger* and *Cryptococcus Neoformans* fungicidal strains. Compounds **7i** in which (R_2 = -Cl) exhibits superior activity against the *C. albicans and Fusarium Oxysporum*. Compounds **4h** in which (R_2 = -F) MIC values 5.25 µg/mL, exhibited prominent activity against the fungicidal strain such as *C. albicans, Fusarium Oxysporum*, *Aspergillus Flavus, Aspergillus Niger* and *Cryptococcus Neoformans*. The **4i** 4-thiazolidinone in which (R_3 = -NO_2) MIC values 25 µg/mL, exhibited equipotent activity against the fungicidal strain *C. albicans and Fusarium Oxysporum*, *respectively* compared to the standard drug Butylated hydroxy toluene. Compounds **4K** in which (R_1 and R_2= -Cl) showed excellent activity with MIC values 8.25 µg/mL against the strain *C. albicans, Fusarium Oxysporum*, *Aspergillus Flavus*, *Aspergillus Niger* and *Cryptococcus Neoformans* fungicidal strains.

2.2.2. Antioxidant Activity:

Quinoline-sulfamethaoxazole incorporated substituted 4-Thiazolidinones hybrids were screened for their *in vitro* free radical scavenging activity against free radicals. All the synthesized compounds provide evidence that **4a-l** showed a concentration dependent anti-radical activity resulting from reduction of DPPH radicals to their non-radical forms and were measured using the 2,2 diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay.[32] Butylated hydroxytoluene (BHT) are used for standard drugs for the comparison of antioxidant activity and the all results are displays in **Table 6**.

According to the DPPH assay, compounds **4a** (R_1 & R_2 = -H) (IC_{50}= 30.12 μg/mL), **4b** (R_1 = -Me) (IC_{50}= 21.32 μg/mL), **4c** (R_2 = -Me) (IC_{50}= 17.40 μg/mL), **4d** (R_1 = -OMe) (IC_{50}= 19.20 μg/mL), **4e** (R_1 = -OMe) (IC_{50}= 16.50 μg/mL), **4f** (R_2 = -Cl) (IC_{50}= 18.52 μg/mL), **4g** (R_3 = -Cl) (IC_{50}= 16.52 μg/mL), **4h** (R_1 = -F) (IC_{50}= 16.47 μg/mL), **4i** (R_1 = -NO_2) (IC_{50}= 23.54 μg/mL), **4j** (R_2= -NO2) (IC_{50}= 25.41 μg/mL) **4k** (R_1 & R_2 = -Cl) (IC_{50}= 16.70 μg/mL) and **4k** (R_3 = -NMe2) (IC_{50}= 22.12 μg/mL) show excellent to moderate antioxidant activity compared to the standard antioxidant drug BHT (IC_{50}= 16.45 μg/mL). From the synthesized compounds, **4e**, **4g**, **4h** and **4i** exhibits excellent antioxidant activity when compared with standard IC_{50} value range are 16.50-16.70 μg/mL.

Antifungal activity

The 4-thiazolidinone conjugates **4a-l** were screened for *in vitro* (**Table 6**) against the five human pathogenic fungal strains, as *Candida albicans* (NCIM 3471), *Aspergillus Flavus* (NCIM 539), *Fusarium oxysporum* (NCIM 1332), *Cryptococcus neoformons* (NCIM 576) and *Aspergillus niger* (NCIM 1196) as compared with standard reference drug fluconazole and miconazole. The minimum inhibitory concentration (MIC) values were determined using the standard agar method.

4. Conclusions

In conclusion, an environmentally efficient protocol has been established for the synthesis of functionalized 4-thiazolidinone derivatives using an inexpensive and recoverable [BIL] catalytic solvent-free in 50 min. This, to the best of our knowledge, has no examples.

Most of the synthesized compounds exhibit antifungal activity against *fungal* strain. Five compounds (**4g**, **4h**, **4i**, **4j** and **4k)** of the series displays exhibited promising activity against with MIC range 25, 12.5 and 6.25 μg/mL, respectively. The antifungal activity results most of the synthesized 4-thiazolidinone derivatives displays **4e, 4g, 4h and 4i** promising radical activity. The synthesized 4-thiazolidinone conjugates **4a-l** analyzed by ^{1}H NMR and ^{13}C NMR analysis methods.

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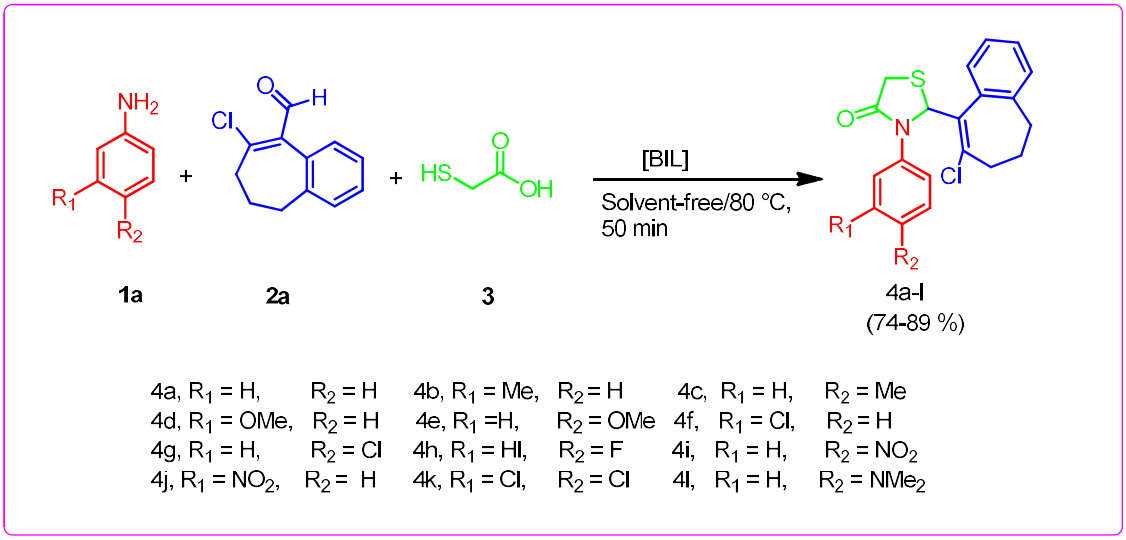

- **BIL** as a greener and environmentally friendly catalyst
- Reusable and recyclable catalyst without loss in catalytic activity
- Synthesis of novel 4-thiazolidinone derivatives
- Imidazole functionalized ionic liquid
- Most of the compounds shows more selective and excellent antifungal activity
- Compounds **4g, 4h, 4i, 4j and 4k** displays excellent antifungal activity

  Compounds **4e, 4g, 4h and 4i** showed very good antioxidant activity