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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Microwave-assisted synthesis and antimicrobial screening of new imidazole derivatives bearing 4-thiazolidinone nucleus

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**Abstract** A new series of compounds 2-((1-(4-(4-arylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl) ethylidene)hydrazono)thiazolidin-4-ones (**4a–o**) have been synthesized under conventional and microwave irradiation method. All compounds were characterized by IR, $^{1}$H NMR, $^{13}$C NMR and mass spectra. Newly synthesized compounds were screened for their antibacterial and antifungal activities on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus pyogenes*, *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* by bioassays, namely serial broth dilution. The synthesized compounds showed potent antimicrobial activity against tested microorganisms. Compounds **4h**, **4j**, **4m** and **4n** were the most potent amongst tested compounds.

**Keywords** Imidazole · 4-Thiazolidinone · Antibacterial activity · Antifungal activity · MIC

## Introduction

The exploitation of microwaves for assisting different organic reactions has blossomed into an important tool in synthetic organic chemistry. In the present programme, our aim is to develop an efficient procedure for the synthesis of new heterocyclic systems containing imidazole and 4-thiazolidinone derivatives. Owing to the timeless ease of workability and eco-friendliness, microwaves provide alternative to environmentally unacceptable procedures (Desai *et al.*, 2011). Microwave energy offers numerous benefits in performing synthesis including increased reaction rates, yield enhancements and cleaner chemistries. Owing to greater selectivity, rapid transfers of energy, significant practical simplicity and pure product, microwave-assisted reactions have greater advantage over conventional methods. Toxicity of conventional method prompted us to explore other green processes. Reactions without using solvent usually with close vessel in Synthos-3000, Anton Paar microwave reaction system are currently popular amongst the synthetic chemists to create eco-friendly atmosphere.

The pharmacological interest of the imidazole ring has been established—nitroimidazoles being extensively used in therapy against amoebic, trichomonal, giardial and anaerobic infections or as hypoxic cell radiosensitizers (Nair and Nagarajan, 1983). Metronidazole and substituted imidazoles are well-tolerated drugs that are potentially active against leishmania, but their use in the treatment of cutaneous and visceral leishmaniasis has produced conflicting results (Gangneux *et al.*, 1999). Clotrimazole is an antifungal drug commonly used in the treatment of fungal infections such as vaginal yeast, oral thrush and ringworm. The imidazole moiety which incorporates both *p*-excessive and *p*-deficient characteristics has proven to be a master key in the range of drug target families (Abdel-Meguid *et al.*, 1994; Muller, 2003).

Compounds incorporating the imidazole scaffold are known as inhibitors of p38 MAPK (Laufer *et al.*, 2004), JNK (Lisnock *et al.*, 2002), B-Raf kinase (Takle *et al.*, 2006), transforming growth factor $\beta$-1 (TGF-$\beta$1) type 1 receptor kinase (Laping *et al.*, 2002) and acyl-CoA: cholesterol O-acyl transferase (ACAT) (Riddell *et al.*, 1996). Imidazoles substituted with 2-arylamino functionality have

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been reported to have potent and selective agonist activity at $\alpha_2$-adrenoceptors (Clarke and Harris, 2002). Further, the chemistry of thiazolidinone ring system is of considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities (Desai *et al.*, 2012a; Dandia *et al.*, 2011). The thiazolidinone nucleus also appears frequently in the structure of various natural products, notably thiamine, compounds possessing cardiac and glycemic benefits such as troglitazone (Ghazzi *et al.*, 1997) and many metabolic products of fungi and primitive marine animals, including 2-(aminoalkyl)-thiazole-4-carboxylic acids (Ulrich *et al.*, 1987). Numerous thiazolidinone derivatives have shown significant bioactivities such as antidiarrhoeal (Diurno *et al.*, 1997), anticonvulsant (Ragab *et al.*, 1997), antimicrobial (Ravichandran *et al.*, 2011), antidiabetic (Norisada *et al.*, 2004), antihistaminic (Previtera *et al.*, 1994), anticancer (Havrylyuk *et al.*, 2009), anti-HIV (Rawal *et al.*, 2005), cardioprotective (Kato *et al.*, 1999a), $Ca^{2+}$ channel blocker (Knutsen *et al.*, 2007), PAF antagonist (Tanabe *et al.*, 1991), antiischemic (Raghubir *et al.*, 2011), COX inhibitory (Ottana *et al.*, 2002), DPP-IV inhibitor (Sakashita *et al.*, 2006), non-peptide thrombin receptor antagonist (Kato *et al.*, 1999b), tumour necrosis factor-α antagonist (Voss *et al.*, 2003) and nematicidal activities. Certain commercially available drugs containing imidazole and 4-thiazolidinone nucleus are shown in Fig. 1.

In view to the above findings and in continuation of our research program (Desai *et al.*, 2012b, c) to find new antimicrobial agents for the treatment of infectious diseases, herein we would like to report the microwave-assisted synthesis and in vitro antimicrobial activity profile of a series 2-((1-(4-(4-arylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene)hydrazono)thiazolidin-4-ones (**4a**–**o**). Structures of synthesized compounds were assigned on the basis of IR, $^1$H-NMR, $^{13}$C-NMR and mass spectral data. These compounds were evaluated for their antibacterial and antifungal screening on different strains of bacteria and fungi.

## Results and discussion

### Chemistry

The synthetic pathways to obtain the intermediate and target compounds in this study are depicted in Scheme 1. Compounds 4-(arylidene)-2-methyloxazol-5(4*H*)-ones (**1a**–**o**) were prepared in an excellent yield in one step by Perkin condensation of *N*-acetyl glycine, different substituted aldehydes and acetic anhydride in the presence of anhydrous sodium acetate. The condensation reaction was carried out in microwave at 300 W intermittently at 30 s intervals for 3–5 min. In the second step, intermediate (**1**) was reacted with *p*-aminoacetophenone in glacial acetic acid (5 mL), an equivalent amount of fused sodium acetate was irradiated by 200 W intermittently at 30 s interval for 3–5 min to furnish product 1-(4-acetylphenyl)-4-(arylidene)-2-methyl-1*H*-imidazol-5(4*H*)-ones (**2a**–**o**). The key intermediates (**3a**–**o**) were synthesized through condensation of equimolar amounts of compounds (**2a**–**o**), thiosemicarbazide and catalytic amount of DMF (4 mL), and irradiated at 300 W intermittently at 30 s intervals for 4–6 min. This Schiff base (**3a**) was characterized by IR and NMR spectra. IR spectra showed strong absorption bands at 3,413 and 3,378 $cm^{-1}$ due to primary amine group. Absorption band at 1,323 $cm^{-1}$ over the range was due to C=S stretching vibration. The characteristic signals in $^1$H NMR of compound (**3a**) displayed singlet at $\delta = 8.57$ ppm integrating two protons of the primary amine and proton of secondary amine appeared as a singlet at $\delta = 7.00$ ppm. $^{13}$C NMR spectra displayed a signal at 181.7 ppm assignable to thiocarbamoyl carbon (C=S). The mass spectrum of (**3a**) showed a molecular ion peak at $m/z = 377$ ($M^+$) corresponding to a molecular formula $C_{20}H_{19}N_5OS$. Moreover, the aforementioned schiff bases (**3a**–**o**) were cyclized to (**4a**–**o**) through their reaction with ethyl bromoacetate, sodium acetate (0.08 mol) and catalytic amount of DMF was irradiated at 200 W intermittently at 30 s intervals for 4–7 min. Compound (**4a**) showed strong

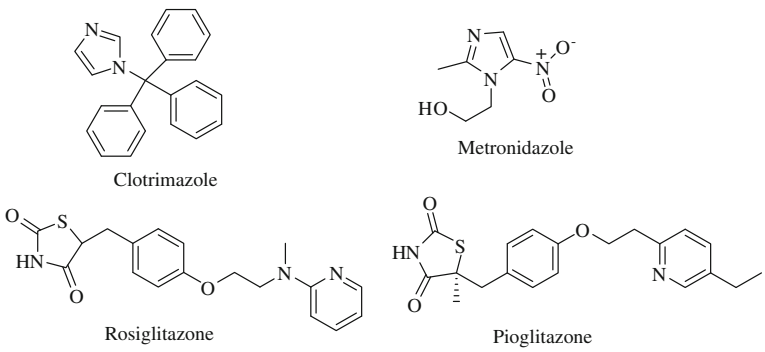
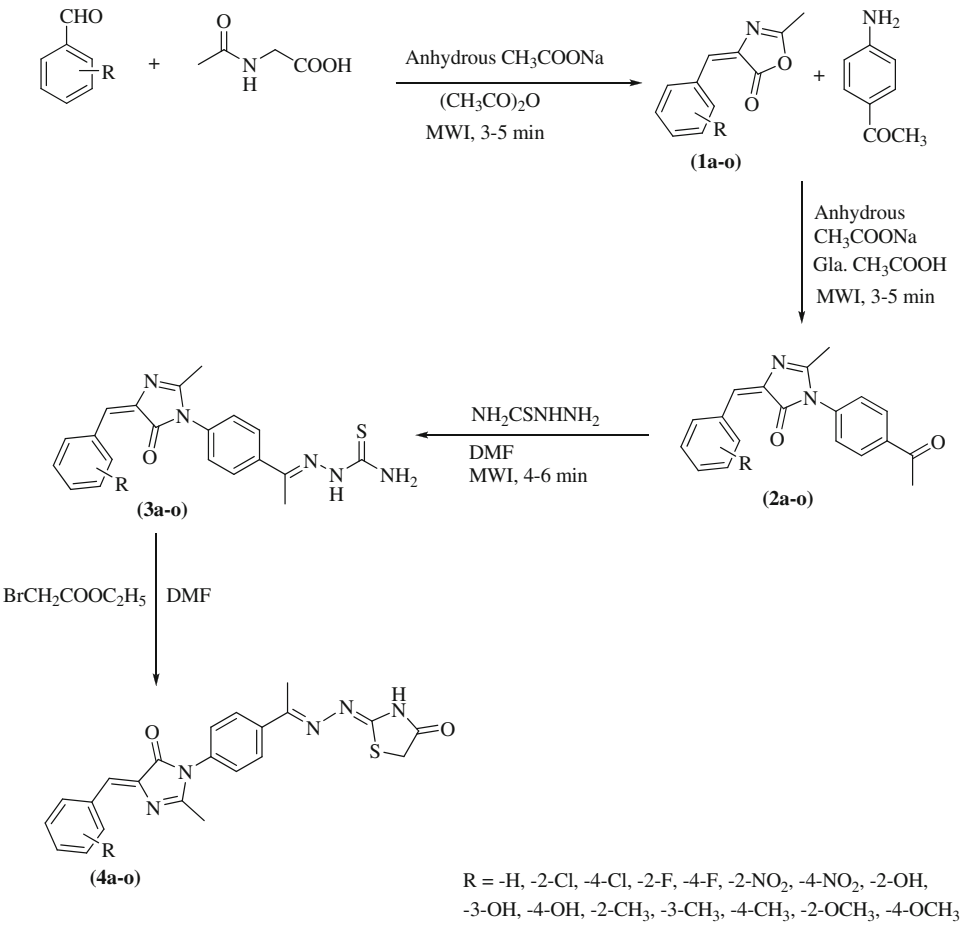



**Fig. 1** Commercially available drugs containing imidazoline and thiazolidinone nucleus

**Scheme 1** Synthetic route for the preparation of title compounds (**4a–o**)




absorption bands at 1,680 and 1,713 $cm^{-1}$ due to carbonyl group in IR spectra. Absorption band which appeared at 3,351 $cm^{-1}$ was due to stretching vibration corresponding to secondary amine. In addition to this, $^{1}H$ NMR spectra revealed the appearance of singlet peak at $\delta = 3.91$ ppm integrating two protons of the thiazolidine ring. The characteristic signal of compound (**3a**) displayed singlet at $\delta = 8.51$ ppm integrating proton of the secondary amine. $^{13}C$ NMR confirmed the proposed structure by the appearance of signal at $\delta = 176.5$ ppm due to carbonyl carbon as well as the appearance of signal around $\delta = 38.4$ ppm assignable to methylene group of the thiazolidine ring. Moreover, the mass spectrum of (**4a**) showed a molecular ion peak at $m/z = 417$ ($M^+$) corresponding to a molecular formula $C_{22}H_{19}N_5O_2S$.

## Antimicrobial activity

All the newly synthesized compounds were evaluated against Gram-positive bacteria (*Staphylococcus aureus*, *Staphylococcus pyogenes*), Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*) and fungi (*Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*) strains. Individual minimum inhibitory concentration (MIC, μg/mL) values of tested compounds (**4a–o**) against the test microbes are listed in Tables 1 and 2 along with MIC values of reference compounds ampicillin (for bacteria) and griseofulvin (for fungi). The results revealed that a majority of the synthesized compounds showed varying degrees of inhibition against the test panel of species. The obtained antimicrobial activity of tested compounds could be correlated to the structural variations and modifications. Precursors (**2a–o**) showed poor antibacterial activity against all tested bacterial strains, amongst which compounds **2j**, **2m** and **2o** showed poor activity (MIC = 1,000 μg/mL against *E. coli* and *S. aureus*). Intermediates (**2a–o**) reacted with thiosemicarbazide to produce key scaffold (**3a–o**). Again, these intermediates were tested against different bacterial strains and were found to have mild to poor antibacterial activity. Intermediate compounds **3h**, **3j**, **3m** and **3o** displayed mild activity (MIC = 500 μg/mL against *P. aeruginosa*, *S. aureus* and *S. pyogenes*), whereas **3i** and **3l** exhibited poor activity (MIC = 1,000 μg/mL against *E. coli* and *S. pyogenes*). Now, schiff bases (**3a–o**) were reacted to ethyl bromoacetate to afford cyclized final compounds (**4a–o**), which in turn, was found to have broad spectrum antibacterial activity. Compounds (**4a–o**) were displayed significant to potent activities. Compound **4f** (2-$NO_2$) and **4h** (2-OH) showed

**Table 1** Results of antibacterial screening of compounds (**4a–o**)

| Sr. no. | –R | Minimum inhibitory concentration (MIC) for bacteria (μg/mL) ± SD | | | |
|---|---|---|---|---|---|
| | | *E. coli* MTCC 443 | *P. aeruginosa* MTCC 1688 | *S. aureus* MTCC 96 | *S. pyogenes* MTCC 442 |
| **4a** | –H | 1,000 ± 2.08* | 500 ± 3.12 | 250 ± 1.86** | 1,000 ± 4.86** |
| **4b** | –2-Cl | 500 ± 3.28 | 100 ± 2.16* | 500 ± 1.12* | 250 ± 2.62 |
| **4c** | –4-Cl | 1,000 ± 1.18* | 250 ± 2.88** | 250 ± 1.67 | 100 ± 1.14 |
| **4d** | –2-F | 250 ± 2.08** | 500 ± 4.98 | 500 ± 3.86 | 100 ± 2.12* |
| **4e** | –4-F | 250 ± 1.06** | 250 ± 3.70* | 100 ± 3.12* | 500 ± 2.62 |
| **4f** | –2-$NO_2$ | 100 ± 1.86* | 500 ± 2.08 | 250 ± 1.04** | 100 ± 1.12** |
| **4g** | –4-$NO_2$ | 500 ± 0.70* | 100 ± 2.32* | 250 ± 2.36* | 250 ± 3.86* |
| **4h** | –2-OH | 100 ± 1.22** | 25 ± 2.18*** | 250 ± 3.78* | 100 ± 3.78 |
| **4i** | –3-OH | 250 ± 4.16* | 250 ± 3.78 | 100 ± 1.60** | 250 ± 4.60* |
| **4j** | –4-OH | 50 ± 2.18 | 100 ± 2.14 | 50 ± 1.82* | 50 ± 1** |
| **4k** | –2-$CH_3$ | 250 ± 4.40* | 250 ± 3.46* | 25 ± 1.08** | 25 ± 2.36 |
| **4l** | –3-$CH_3$ | 500 ± 2.62 | 250 ± 3.04 | 100 ± 1.04 | 100 ± 1.62*** |
| **4m** | –4-$CH_3$ | 50 ± 1.18* | 250 ± 2.32* | 12.5 ± 1.64*** | 25 ± 2.68 |
| **4n** | –2-$OCH_3$ | 250 ± 1.12** | 50 ± 1.60 | 50 ± 2.04 | 100 ± 2.72 |
| **4o** | –4-$OCH_3$ | 250 ± 2.64* | 100 ± 1.28* | 500 ± 4.50*** | 50 ± 4.16** |
| | Ampicillin | 250 ± 2.68 | 100 ± 0.98 | 100 ± 1.24 | 100 ± 1.04 |

All values are presented as mean of 6 experiments (n = 6). All significant differences are considered from control value 0.00. 2 % DMSO used as control and its antibacterial activity is nil or zero

*SD* standard deviation

*** $P < 0.001$ extremely significant, ** $P < 0.01$ moderately significant, * $P < 0.05$ significant

**Table 2** Results of antifungal screening of compounds (**4a–o**)

| Sr. no. | –R | Minimum inhibitory concentration (MIC) for fungi (μg/mL) ± SD | | |
|---|---|---|---|---|
| | | *C. albicans* MTCC 227 | *A. niger* MTCC 282 | *A. clavatus* MTCC 1323 |
| **4a** | –H | 1,000 ± 2.56* | 500 ± 1.48 | 500 ± 2.62 |
| **4b** | –2-Cl | 1,000 ± 1.64 | 1,000 ± 3.02* | 1,000 ± 1.36 |
| **4c** | –4-Cl | 500 ± 4.16* | 500 ± 2.86* | 250 ± 1.48 |
| **4d** | –2-F | 1,000 ± 1.84* | 500 ± 1.56* | 500 ± 1.36* |
| **4e** | –4-F | 500 ± 2.68* | 500 ± 1** | 500 ± 3.62** |
| **4f** | –2-$NO_2$ | 500 ± 1.42** | 500 ± 1.62 | 500 ± 3.68 |
| **4g** | –4-$NO_2$ | 500 ± 3.62 | 250 ± 1.60 | 100 ± 2.15* |
| **4h** | –2-OH | 100 ± 2.64* | 50 ± 1.18*** | 100 ± 3.20 |
| **4i** | –3-OH | 500 ± 2.68 | 250 ± 1.38 | 250 ± 2.56** |
| **4j** | –4-OH | 50 ± 1.78* | 50 ± 1.52* | 100 ± 2.16** |
| **4k** | –2-$CH_3$ | 500 ± 4.72* | 100 ± 2.02** | 250 ± 1.72 |
| **4l** | –3-$CH_3$ | 500 ± 2.56** | 250 ± 3.08* | 100 ± 2.64 |
| **4m** | –4-$CH_3$ | 250 ± 2.88** | 12.5 ± 1.08*** | 50 ± 2.56 |
| **4n** | –2-$OCH_3$ | 500 ± 2.60** | 100 ± 2.36 | 25 ± 1.86** |
| **4o** | –4-$OCH_3$ | 500 ± 2.04 | 250 ± 1.72* | 250 ± 4.04 |
| | Griseofulvin | 500 ± 0.58 | 100 ± 1.16 | 100 ± 1.10 |

All values are presented as mean of 6 experiments ($n = 6$). All significant differences are considered from control value 0.00. 2 % DMSO used as control and its antifungal activity is nil or zero

*SD* standard deviation

*** $P < 0.001$ extremely significant, ** $P < 0.01$ moderately significant, * $P < 0.05$ significant

inhibition at MIC = 100 μg/mL, while compounds **4j** (4-OH) and **4m** (4-$CH_3$) found to have excellent inhibition at MIC = 50 μg/mL against *E. coli* as compared to standard ampicillin (MIC = 250 μg/mL). Compound **4n** (2-$OCH_3$) displayed inhibition at MIC = 50 μg/mL, whereas compound **4h** (2-OH) exhibited excellent inhibition at MIC = 25 μg/mL against *P. aeruginosa* as compared to standard ampicillin (MIC = 100 μg/mL). Compounds **4j** (4-OH) and **4n** (2-$OCH_3$) displayed very good inhibition at MIC = 50 μg/mL, while compounds **4k** (2-$CH_3$) showed excellent inhibition at MIC = 25 μg/mL and compound **4m** (4-$CH_3$) showed highest inhibition at MIC = 12.5 μg/mL against *S. aureus* as compared to standard ampicillin (MIC = 100 μg/mL). Compounds **4j** (4-OH) and **4o** (4-$OCH_3$) exhibited inhibition at MIC = 50 μg/mL, while compounds **4k** (2-$CH_3$) and **4m** (4-$CH_3$) exhibited excellent inhibition at MIC = 25 μg/mL against *S. pyogenes* as compared to standard ampicillin (MIC = 100 μg/mL).

MIC values of antifungal activity observed similar pattern as antibacterial activity. Intermediates (**2a–o**) showed poor activity against all fungal strains. Compounds **2h** and **2j** showed poor inhibitory effect (MIC = 1,000 μg/mL against *C. albicans* and *A. clavatus*). Same as antibacterial activity schiff bases (**3a–o**) exhibited mild antifungal activity against almost all fungal strains. Compounds **2m** and **2n** exhibited mild activity (MIC = 500 μg/mL and MIC = 250 μg/mL against *A. niger* and *A. clavatus* respectively). To pursue broad spectrum of activity against all fungal strain, schiff bases were cyclized to final compounds **4a–o** which exhibited desired results. Compound **4m** (4-$CH_3$) showed inhibition at MIC = 250 μg/mL, whereas compound **4h** (2-OH) and **4j** (4-OH) displayed excellent activity at MIC = 100 μg/mL and 50 μg/mL, respectively, as compared to griseofulvin (MIC = 500 μg/mL). Compounds **4h** (2-OH) and **4j** (4-OH) displayed activity at MIC = 50 μg/mL, while compound **4m** (4-$CH_3$) showed highest inhibition at MIC = 12.5 μg/mL as compared to standard griseofulvin (MIC = 100 μg/mL). Compound **4m** (4-$CH_3$) found to have very good inhibitory action at MIC = 50 μg/mL, while compound **4n** (2-$OCH_3$) showed excellent activity at MIC = 25 μg/mL as compared to standard griseofulvin (MIC = 100 μg/mL).

### Structure activity relationship

The structure–activity relationships (SAR) of compounds **4a–o** were determined on the basis of results presented in Tables 1 and 2. SAR studies revealed that the presence of thiazolidine ring was essential for broad range of antimicrobial activity. From activity data, it is clear that final compound **4a** without substitution did not display significant antimicrobial activity against any tested microbial strains. Compounds containing electron-donating substitutions in basic skeleton led to increase in antimicrobial activity. Compound **4m** containing 4-$CH_3$ group showed highest inhibition at MIC = 12.5 μg/mL against bacterial strain *S. aureus* and fungal strain *A. niger*. In general, compounds containing electron releasing groups such as –OH, –$CH_3$ and –$OCH_3$ led to increase in activity. This is attributed to higher hydrophilic nature and smaller size—which diminish ring strain—of the group. In contrast, antimicrobial activity vanished when we employed electron-withdrawing groups such as –Cl, –F and –$NO_2$ on benzene ring. This may be attributed to their hydrophobicity and size of the group. Owing to large size of group, ring strain increased and made compound less stable and active. In general, compounds come out as compounds exhibiting more noteworthy antimicrobial activity.

## Conclusion

In summary, we have developed a new, efficient and environmentally benign methodology towards the synthesis of 2-((1-(4-(4-arylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene)hydrazono)thiazolidin-4-ones (**4a–o**). This synthetic strategy allows the assimilation of two promising bioactive nuclei in a single scaffold through an easy way. Reviewing the antimicrobial activity data, it has been concluded that the presence of electron-donating group emerged as active in both antibacterial and antifungal screening. Hence, there is enough scope for further study in the developing these as good lead compounds. Further studies on these compounds and optimization of their structures leading to novel analogues with superior biological properties are ongoing in our laboratory.

## Experimental

### *General*

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. TLC on silica gel plates (Merck, 60, $F_{254}$) was used for purity checking and reaction monitoring. Column chromatography on silica gel (Merck, 70–230 mesh and 230–400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (% C, H, N) was carried out using a Perkin-Elmer 2400 CHN analyzer. IR spectra of all compounds were recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr. $^1$H NMR spectra were recorded on Varian Gemini 300 MHz and $^{13}$C NMR spectra on Varian Mercury-400, 100 MHz in DMSO-$d_6$ as a solvent

and tetramethylsilane (TMS) as an internal standard. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Synthos-3000, Anton Paar reaction system was used for microwave synthesis. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere.

General procedure for preparation 4-(arylidene)-2-methyloxazol-5(4*H*)-ones (**1a**–**o**)

*Conventional method*

A mixture of different substituted aromatic aldehydes (0.25 mol), *N*-acetyl glycine, acetic anhydride (0.30 mol) and anhydrous sodium acetate (0.25 mol) was taken and mixed thoroughly. The mixture was stirred at room temperature for 20 min. Upon completion of reaction the vessel was cooled, ethanol was added and the mixture was kept overnight in the refrigerator. The crystalline product obtained was filtered and washed with ice cold alcohol and then with boiling water. Crude product was recrystallized from benzene.

*Microwave method*

A mixture of different substituted aromatic aldehydes (0.25 mol), *N*-acetyl glycine, acetic anhydride (0.30 mol) and anhydrous sodium acetate (0.25 mol) was taken in a reaction vessel and mixed thoroughly. The mixture was irradiated under microwave for 3–5 min at 300 W with constant shaking and intermittent radiation of 30 s interval. Upon completion of reaction, the vessel was cooled, ethanol was added and the mixture was kept overnight in the refrigerator. The crystalline product obtained was filtered and washed with ice cold alcohol and then with boiling water. Crude product was recrystallized from benzene.

General procedure for preparation 1-(4-acetylphenyl)-4-(arylidene)-2-methyl-1*H*-imidazol-5(4*H*)-ones (**2a**–**o**)

*Conventional method*

A homogeneous mixture of different oxazolones (**1a**–**o**) (0.01 mol) and 4-amino acetophenone (0.01 mol) in glacial acetic acid (5 mL) an equivalent amount of fused sodium acetate was added and refluxed for 14 h. The product formed was washed with water and crystallized from ethanol.

*Microwave method*

A homogeneous mixture of different oxazolones (**1a**–**o**) (0.01 mol) and 4-amino acetophenone (0.01 mol) in glacial acetic acid (5 mL), an equivalent amount of fused sodium acetate was introduced into microwave reaction vessel equipped with a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction mixture was irradiated by 200 W intermittently at 30 s interval for 3–5 min. The solid formed was washed with water and crystallized from ethanol.

*1-(4-Acetylphenyl)-4-benzylidene-2-methyl-1H-imidazol-5(4H)-one (**2a**)*

Yield: 65 %; m.p.: 177–179 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,064 (C–H, aromatic), 2,921, 3,002 (C–H), 1,712 (C=O), 1,682 (C=O), 1,571 (C=N), 1,514 (C=C), 964 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 7.23–7.89 (m, 9H, Ar–H), 7.42 (s, 1H, CH=C); LCMS (*m*/*z*): 304 ($M^+$); Anal. Calcd. For $C_{19}H_{16}N_2O_2$: C-74.98, H-5.30, N-9.20; Found: C-74.90, H-5.22, N-9.26 %.

*1-(4-Acetylphenyl)-4-(2-chlorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2b**)*

Yield: 68 %; m.p.: 194–196 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,057 (C–H, aromatic), 2,937, 3,011 (C–H), 1,715 (C=O), 1,691 (C=O), 1,575 (C=N), 1,511 (C=C), 976 (C–H bending), 745 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.06 (s, 3H, $CH_3$), 2.51 (s, 3H, $CH_3$), 7.26–7.91 (m, 8H, Ar–H), 7.44 (s, 1H, CH=C); LCMS (*m*/*z*): 338 ($M^+$); Anal. Calcd. For $C_{19}H_{15}ClN_2O_2$: C-67.36, H-4.46, N-7.27; Found: C-67.30, H-4.40, N-7.32 %.

*1-(4-Acetylphenyl)-4-(4-chlorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2c**)*

Yield: 66 %; m.p.: 155–157 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,043 (C–H, aromatic), 2,931, 3,006 (C–H), 1,710 (C=O), 1,688 (C=O), 1,570 (C=N), 1,518 (C=C), 982 (C–H bending), 765 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 7.28–7.93 (m, 8H, Ar–H), 7.42 (s, 1H, CH=C); LCMS (*m*/*z*): 338 ($M^+$); Anal. Calcd. For $C_{19}H_{15}ClN_2O_2$: C-67.36, H-4.46, N-7.27; Found: C-67.41, H-4.52, N-7.20 %.

*1-(4-Acetylphenyl)-4-(2-fluorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2d**)*

Yield: 69 %; m.p.: 186–188 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,056 (C–H, aromatic), 2,924, 3,016 (C–H), 1,713 (C=O), 1,682 (C=O), 1,571 (C=N), 1,513 (C=C), 976 (C–H bending), 760 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.01 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 7.14–7.92 (m, 8H, Ar–H), 7.47 (s, 1H, CH=C); LCMS (*m*/*z*): 322 ($M^+$); Anal. Calcd. For $C_{19}H_{15}FN_2O_2$: C-70.80, H-4.69, N-8.69; Found: C-70.84, H-4.62, N-8.64 %.

*1-(4-Acetylphenyl)-4-(4-fluorobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2e**)*

Yield: 63 %; m.p.: 188–190 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,062 (C–H, aromatic), 2,936, 3,013 (C–H), 1,718 (C=O), 1,688 (C=O), 1,578 (C=N), 1,519 (C=C), 1,152 (C–F), 982 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.54 (s, 3H, $CH_3$), 7.12–7.90 (m, 8H, Ar–H), 7.43 (s, 1H, CH=C); LCMS (*m*/*z*): 322 ($M^+$); Anal. Calcd. For $C_{19}H_{15}FN_2O_2$: C-70.80, H-4.69, N-8.69; Found: C-70.73, H-4.74, N-8.74 %.

*1-(4-Acetylphenyl)-4-(2-nitrobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2f**)*

Yield: 60 %; m.p.: 167–169 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,068 (C–H, aromatic), 2,927, 3,010 (C–H), 1,711 (C=O), 1,684 (C=O), 1,574 (C=N), 1,521 (C=C), 1,487, 1,352 ($NO_2$), 1,157 (C–F), 967 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.10 (s, 3H, $CH_3$), 2.57 (s, 3H, $CH_3$), 7.21–8.24 (m, 8H, Ar–H), 7.41 (s, 1H, CH=C); LCMS (*m*/*z*): 349 ($M^+$); Anal. Calcd. For $C_{19}H_{15}N_3O_4$: C-65.32, H-4.33, N-12.03; Found: C-65.39, H-4.28, N-12.08 %.

*1-(4-Acetylphenyl)-4-(4-nitrobenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2g**)*

Yield: 66 %; m.p.: 148–150 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,057 (C–H, aromatic), 2,935, 3,005 (C–H), 1,715 (C=O), 1,687 (C=O), 1,572 (C=N), 1,528 (C=C), 1,481, 1,357 ($NO_2$), 1,151 (C–F), 972 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.07 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 7.22–8.27 (m, 8H, Ar–H), 7.43 (s, 1H, CH=C); LCMS (*m*/*z*): 349 ($M^+$); Anal. Calcd. For $C_{19}H_{15}N_3O_4$: C-65.32, H-4.33, N-12.03; Found: C-65.27, H-4.38, N-11.98 %.

*1-(4-Acetylphenyl)-4-(2-hydroxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2h**)*

Yield: 68 %; m.p.: 166–170 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,411 (O–H), 3,047 (C–H, aromatic), 2,930, 3,003 (C–H), 1,712 (C=O), 1,687 (C=O), 1,574 (C=N), 1,528 (C=C), 1,486, 1,351 ($NO_2$), 983 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.09 (s, 3H, $CH_3$), 2.52 (s, 3H, $CH_3$), 6.71–7.95 (m, 8H, Ar–H), 7.46 (s, 1H, CH=C), 9.14 (s, 1H, OH); LCMS (*m*/*z*): 320 ($M^+$); Anal. Calcd. For $C_{19}H_{16}N_2O_3$: C-71.24, H-5.03, N-8.74; Found: C-71.20, H-5.11, N-8.80 %.

*1-(4-Acetylphenyl)-4-(3-hydroxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2i**)*

Yield: 67 %; m.p.: 206–208 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,417 (O–H), 3,054 (C–H, aromatic), 2,924, 3,010 (C–H), 1,716 (C=O), 1,681 (C=O), 1,579 (C=N), 1,522 (C=C), 1,481, 1,355 ($NO_2$), 975 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.05 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 6.68–7.92 (m, 8H, Ar–H), 7.42 (s, 1H, CH=C), 9.13 (s, 1H, OH); LCMS (*m*/*z*): 320 ($M^+$); Anal. Calcd. For $C_{19}H_{16}N_2O_3$: C-71.24, H-5.03, N-8.74; Found: C-71.18, H-5.09, N-8.69 %.

*1-(4-Acetylphenyl)-4-(4-hydroxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2j**)*

Yield: 64 %; m.p.: 194–196 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,422 (O–H), 3,061 (C–H, aromatic), 2,921, 3,004 (C–H), 1,717 (C=O), 1,685 (C=O), 1,582 (C=N), 1,520 (C=C), 1,480, 1,357 ($NO_2$), 980 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.03 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 6.65–7.97 (m, 8H, Ar–H), 7.42 (s, 1H, CH=C), 9.13 (s, 1H, OH); LCMS (*m*/*z*): 320 ($M^+$); Anal. Calcd. For $C_{19}H_{16}N_2O_3$: C-71.24, H-5.03, N-8.74; Found: C-71.28, H-4.98, N-8.81 %.

*1-(4-Acetylphenyl)-2-methyl-4-(2-methylbenzylidene)-1H-imidazol-5(4H)-one (**2k**)*

Yield: 69 %; m.p.: 116–118 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,075 (C–H, aromatic), 2,927, 3,012 (C–H), 1,712 (C=O), 1,681 (C=O), 1,587 (C=N), 1,528 (C=C), 1,484, 1,353 ($NO_2$), 981 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.06 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 7.01–7.94 (m, 8H, Ar–H), 7.44 (s, 1H, CH=C); LCMS (*m*/*z*): 318 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_2O_2$: C-75.45, H-5.70, N-8.80; Found: C-75.52, H-5.77, N-8.74 %.

*1-(4-Acetylphenyl)-2-methyl-4-(3-methylbenzylidene)-1H-imidazol-5(4H)-one (**2l**)*

Yield: 64 %; m.p.: 154–156 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,067 (C–H, aromatic), 2,920, 3,006 (C–H), 1,718 (C=O), 1,688 (C=O), 1,582 (C=N), 1,524 (C=C), 1,480, 1,358 ($NO_2$), 977 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 2.57 (s, 3H, $CH_3$), 7.07–7.96 (m, 8H, Ar–H), 7.43 (s, 1H, CH=C); LCMS (*m*/*z*): 318 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_2O_2$: C-75.45, H-5.70, N-8.80; Found: C-75.40, H-5.64, N-8.85 %.

*1-(4-Acetylphenyl)-2-methyl-4-(4-methylbenzylidene)-1H-imidazol-5(4H)-one (**2m**)*

Yield: 65 %; m.p.: 184–186 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,047 (C–H, aromatic), 2,926, 3,016 (C–H), 1,715 (C=O), 1,683 (C=O), 1,580 (C=N), 1,528 (C=C), 1,481, 1,356 ($NO_2$), 973 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$),

7.14–7.98 (m, 8H, Ar–H), 7.42 (s, 1H, CH=C); LCMS (*m/z*): 318 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_2O_2$: C-75.45, H-5.70, N-8.80; Found: C-75.49, H-5.75, N-8.74 %.

*1-(4-Acetylphenyl)-4-(2-methoxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2n**)*

Yield: 67 %; m.p.: 177–179 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,053 (C–H, aromatic), 2,921, 3,011 (C–H), 1,710 (C=O), 1,681 (C=O), 1,587 (C=N), 1,520 (C=C), 1,486, 1,351 ($NO_2$), 984 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.57 (s, 3H, $CH_3$), 3.56 (s, 3H, $OCH_3$), 6.91–7.94 (m, 8H, Ar–H), 7.43 (s, 1H, CH=C); LCMS (*m/z*): 334 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_2O_3$: C-71.84, H-5.43, N-8.38; Found: C-71.88, H-5.48, N-8.45 %.

*1-(4-Acetylphenyl)-4-(4-methoxybenzylidene)-2-methyl-1H-imidazol-5(4H)-one (**2o**)*

Yield: 68 %; m.p.: 165–167 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,068 (C–H, aromatic), 2,928, 3,007 (C–H), 1,715 (C=O), 1,685 (C=O), 1,592 (C=N), 1,528 (C=C), 1,482, 1,356 ($NO_2$), 980 (C–H bending); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.53 (s, 3H, $CH_3$), 3.58 (s, 3H, $OCH_3$), 6.94–7.91 (m, 8H, Ar–H), 7.47 (s, 1H, CH=C); LCMS (*m/z*): 334 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_2O_3$: C-71.84, H-5.43, N-8.38; Found: C-71.79, H-5.38, N-8.34 %.

General procedure for the preparation 2-(1-(4-(4-(arylidene)-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene)hydrazinecarbothioamides (**3a**–**o**)

*Conventional method*

A mixture of compounds 1-(4-acetylphenyl)-4-(arylidene)-2-methyl-1*H*-imidazol-5(4*H*)-ones (**2a**–**o**) (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (40 mL) was heated under reflux for 1 h. The solid formed was washed with cold methanol and crystallized from ethanol.

*Microwave method*

A mixture of compounds 1-(4-acetylphenyl)-4-(arylidene)-2-methyl-1*H*-imidazol-5(4*H*)-ones (**2a**–**o**) (0.01 mol) and thiosemicarbazide (0.01 mol) and catalytic amount of DMF (4 mL) was introduced into microwave reaction vessel equipped using a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction mixture was irradiated by 300 W intermittently at 30 s intervals for 4–6 min. The solid formed was washed with cold methanol and crystallized from ethanol.

*2-(1-(4-(4-Benzylidene-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3a**)*

Yield: 64 %; m.p.: 176–178 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,413, 3,378 ($NH_2$), 3,231 (NH), 3,074 (C–H, aromatic), 2,928, 3,010 (C–H), 1,689 (C=O), 1,572 (C=N), 1,518 (C=C), 1,323 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.06 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 7.00 (s, 1H, NH), 7.29–7.89 (m, 9H, Ar–H), 7.34 (s, 1H, CH=C), 8.57 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.5, 21.3, 114.4, 124.7, 127.4, 128.2, 128.7, 129.4, 130.3, 133.4, 135.4, 135.7, 147.2, 166.7, 170.5, 181.7; LCMS (*m/z*): 377 ($M^+$); Anal. Calcd. For $C_{20}H_{19}N_5OS$: C-63.64, H-5.07, N-18.55; Found: C-63.69, H-5.12, N-18.61 %.

*2-(1-(4-(4-(2-Chlorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3b**)*

Yield: 62 %; m.p.: 191–193 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,422, 3,371 ($NH_2$), 3,235 (NH), 3,070 (C–H, aromatic), 2,921, 3,017 (C–H), 1,686 (C=O), 1,578 (C=N), 1,520 (C=C), 1,327 (C=S), 746 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 7.02 (s, 1H, NH), 7.25–7.87 (m, 8H, Ar–H), 7.65 (s, 1H, CH=C), 8.54 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.3, 21.7, 108.3, 124.8, 126.4, 127.8, 129.1, 129.3, 129.6, 130.1, 133.3, 133.6, 134.2, 135.7, 147.2, 166.4, 170.6, 181.3; LCMS (*m/z*): 411 ($M^+$); Anal. Calcd. For $C_{20}H_{18}ClN_5OS$: C-58.32, H-4.40, N-17.00; Found: C-58.38, H-4.47, N-17.08 %.

*2-(1-(4-(4-(4-Chlorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3c**)*

Yield: 60 %; m.p.: 168–170 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,427, 3,362 ($NH_2$), 3,230 (NH), 3,062 (C–H, aromatic), 2,931, 3,011 (C–H), 1,681 (C=O), 1,582 (C=N), 1,527 (C=C), 1,330 (C=S), 751 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.00 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 7.05 (s, 1H, NH), 7.32 (s, 1H, CH=C), 7.38–7.88 (m, 8H, Ar–H), 8.54 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.5, 21.3, 114.2, 124.7, 128.5, 129.1, 129.7, 130.7, 133.5, 133.6, 133.8, 135.4, 147.2, 166.1, 170.8, 181.5; LCMS (*m/z*): 411 ($M^+$); Anal. Calcd. For $C_{20}H_{18}ClN_5OS$: C-58.32, H-4.40, N-17.00; Found: C-58.28, H-4.35, N-16.85 %.

*2-(1-(4-(4-(2-Fluorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3d**)*

Yield: 63 %; m.p.: 156–158 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,417, 3,366 ($NH_2$), 3,243 (NH), 3,052 (C–H, aromatic), 2,917, 3,006 (C–H), 1,691 (C=O), 1,574 (C=N), 1,533 (C=C), 1,328 (C=S), 1,151 (C–F stretching); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 7.03 (s, 1H, NH), 7.16–7.88 (m, 8H, Ar–H), 8.09 (s, 1H, CH=C), 8.55 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.7, 21.4, 108.4, 115.2, 123.3, 124.4, 124.8, 128.3, 129.3, 129.7, 130.5, 133.2, 135.7, 147.4, 161.7, 166.6, 170.3, 181.6; LCMS (*m/z*): 395 ($M^+$); Anal. Calcd. For $C_{20}H_{18}FN_5OS$: C-60.74, H-4.59, N-17.71; Found: C-60.80, H-4.65, N-17.75 %.

*2-(1-(4-(4-(4-Fluorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3e**)*

Yield: 61 %; m.p.: 167–169 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,412, 3,354 ($NH_2$), 3,251 (NH), 3,077 (C–H, aromatic), 2,922, 3,004 (C–H), 1,682 (C=O), 1,570 (C=N), 1,526 (C=C), 1,333 (C=S), 1,145 (C–F stretching); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 7.01 (s, 1H, NH), 7.19–7.91 (m, 8H, Ar–H), 7.82 (s, 1H, CH=C), 8.53 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.3, 21.5, 114.3, 115.8, 124.7, 129.3, 130.5, 130.8, 131.2, 133.3, 135.8, 147.7, 162.7, 166.4, 170.6, 181.8; LCMS (*m/z*): 395 ($M^+$); Anal. Calcd. For $C_{20}H_{18}FN_5OS$: C-60.74, H-4.59, N-17.71; Found: C-60.69, H-4.55, N-17.64 %.

*2-(1-(4-(2-Methyl-4-(2-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3f**)*

Yield: 65 %; m.p.: 184–186 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,417, 3,340 ($NH_2$), 3,264 (NH), 3,065 (C–H, aromatic), 2,927, 3,008 (C–H), 1,689 (C=O), 1,577 (C=N), 1,517 (C=C), 1,483, 1,355 ($NO_2$), 1,325 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.10 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 7.08 (s, 1H, NH), 7.68–8.32 (m, 8H, Ar–H), 7.91 (s, 1H, CH=C), 8.58 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.6, 21.3, 108.6, 123.6, 124.8, 127.4, 127.6, 128.6, 129.4, 130.8, 133.2, 134.5, 135.7, 147.2, 147.9, 166.7, 170.7, 181.4; LCMS (*m/z*): 422 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_6O_3S$: C-56.86, H-4.29, N-19.89; Found: C-56.80, H-4.34, N-19.95 %.

*2-(1-(4-(2-Methyl-4-(4-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3g**)*

Yield: 62 %; m.p.: 134–136 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,423, 3,338 ($NH_2$), 3,272 (NH), 3,058 (C–H, aromatic), 2,932, 3,014 (C–H), 1,691 (C=O), 1,581 (C=N), 1,510 (C=C), 1,487, 1,352 ($NO_2$), 1,330 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.08 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 7.09 (s, 1H, NH), 7.52 (s, 1H, CH=C), 7.80–8.24 (m, 8H, Ar–H), 8.58 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.5, 21.8, 114.6, 123.4, 124.3, 129.2, 129.5, 130.2, 133.6, 135.1, 141.3, 147.4, 147.7, 166.7, 170.2, 181.7; LCMS (*m/z*): 422 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_6O_3S$: C-56.86, H-4.29, N-19.89; Found: C-56.92, H-4.22, N-19.88 %.

*2-(1-(4-(4-(2-Hydroxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3h**)*

Yield: 60 %; m.p.: 178–180 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,422 (OH), 3,417, 3,357 ($NH_2$), 3,259 (NH), 3,064 (C–H, aromatic), 2,928, 3,010 (C–H), 1,683 (C=O), 1,576 (C=N), 1,515 (C=C), 1,334 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.03 (s, 3H, $CH_3$), 2.32 (s, 3H, $CH_3$), 7.05 (s, 1H, NH), 7.62 (s, 1H, CH=C), 6.72–7.88 (m, 8H, Ar–H), 8.53 (s, 2H, $NH_2$), 9.15 (s, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.3, 21.4, 108.5, 116.3, 116.8, 121.3, 124.5, 128.8, 129.1, 129.3, 130.1, 133.5, 135.7, 147.2, 157.4, 166.6, 170.5, 181.5; LCMS (*m/z*): 393 ($M^+$); Anal. Calcd. For $C_{20}H_{19}N_5O_2S$: C-61.05, H-4.87, N-17.80; Found: C-61.00, H-4.82, N-17.88 %.

*2-(1-(4-(4-(3-Hydroxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3i**)*

Yield: 64 %; m.p.: 190–192 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,428 (OH), 3,416, 3,364 ($NH_2$), 3,252 (NH), 3,072 (C–H, aromatic), 2,922, 3,007 (C–H), 1,687 (C=O), 1,583 (C=N), 1,520 (C=C), 1,339 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.07 (s, 3H, $CH_3$), 2.30 (s, 3H, $CH_3$), 7.02 (s, 1H, NH), 7.32 (s, 1H, CH=C), 6.64–7.93 (m, 8H, Ar–H), 8.59 (s, 2H, $NH_2$), 9.12 (s, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.5, 21.7, 112.3, 114.6, 115.4, 121.3, 124.3, 129.6, 130.3, 130.7, 133.7, 135.6, 139.3, 147.2, 158.4, 166.7, 170.2, 181.7; LCMS (*m/z*): 393 ($M^+$); Anal. Calcd. For $C_{20}H_{19}N_5O_2S$: C-61.05, H-4.87, N-17.80; Found: C-61.11, H-4.92, N-17.74 %.

*2-(1-(4-(4-(4-Hydroxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3j**)*

Yield: 61 %; m.p.: 166–168 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,421 (OH), 3,413, 3,356 ($NH_2$), 3,263 (NH), 3,083 (C–H, aromatic), 2,929, 3,013 (C–H), 1,684 (C=O), 1,580 (C=N), 1,517 (C=C), 1,333 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.06 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 7.07 (s, 1H, NH), 7.36 (s, 1H, CH=C), 6.64–7.88 (m, 8H, Ar–H), 8.54 (s, 2H, $NH_2$), 9.15 (s, 1H, OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.7, 21.3, 114.6, 116.1, 124.6, 127.6, 129.3, 130.6, 130.9, 133.2, 135.6, 147.4, 157.8, 166.3, 170.8, 181.3; LCMS *(m/z)*: 393 ($M^+$); Anal. Calcd. For $C_{20}H_{19}N_5O_2S$: C-61.05, H-4.87, N-17.80; Found: C-61.09, H-4.81, N-17.84 %.

*2-(1-(4-(2-Methyl-4-(2-methylbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3k**)*

Yield: 64 %; m.p.: 188–190 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,418, 3,354 ($NH_2$), 3,261 (NH), 3,075 (C–H, aromatic), 2,924, 3,003 (C–H), 1,688 (C=O), 1,575 (C=N), 1,512 (C=C), 1,337 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.03 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 2.50 (s, 3H, $CH_3$), 7.02 (s, 1H, NH), 6.19–7.88 (m, 8H, Ar–H), 8.05 (s, 1H, CH=C), 8.54 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.6, 19.4, 21.4, 108.4, 124.7, 125.4, 126.6, 127.4, 127.9, 129.5, 130.6, 133.5, 135.7, 136.1, 136.4, 147.5, 166.7, 170.8, 181.3; LCMS (*m/z*): 391 ($M^+$); Anal. Calcd. For $C_{21}H_{21}N_5OS$: C-64.43, H-5.41, N-17.89; Found: C-64.51, H-5.34, N-17.82 %.

*2-(1-(4-(2-Methyl-4-(3-methylbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3l**)*

Yield: 60 %; m.p.: 216–218 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,412, 3,338 ($NH_2$), 3,248 (NH), 3,066 (C–H, aromatic), 2,937, 3,011 (C–H), 1,681 (C=O), 1,572 (C=N), 1,518 (C=C), 1,330 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$), 7.00 (s, 1H, NH), 7.06–7.87 (m, 8H, Ar–H), 7.38 (s, 1H, CH=C), 8.54 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.3, 21.5, 21.8, 114.5, 124.6, 125.7, 126.8, 128.1, 128.6, 129.2, 130.6, 133.5, 135.4, 135.7, 138.4, 147.3, 166.6, 170.7, 181.3; LCMS (*m/z*): 391 ($M^+$); Anal. Calcd. For $C_{21}H_{21}N_5OS$: C-64.43, H-5.41, N-17.89; Found: C-64.38, H-5.47, N-17.94 %.

*2-(1-(4-(2-Methyl-4-(4-methylbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3m**)*

Yield: 63 %; m.p.: 205–207 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,410, 3,345 ($NH_2$), 3,239 (NH), 3,060 (C–H, aromatic), 2,931, 3,009 (C–H), 1,687 (C=O), 1,579 (C=N), 1,525 (C=C), 1,335 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 7.02 (s, 1H, NH), 7.14–7.89 (m, 8H, Ar–H), 7.81 (s, 1H, CH=C), 8.52 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.4, 21.1, 21.7, 114.2, 124.4, 128.5, 128.9, 129.6, 130.7, 132.3, 133.7, 137.6, 135.4, 147.3, 166.5, 170.4, 181.6; LCMS (*m/z*): 391 ($M^+$); Anal. Calcd. For $C_{21}H_{21}N_5OS$: C-64.43, H-5.41, N-17.89; Found: C-64.48, H-5.48, N-17.93 %.

*2-(1-(4-(4-(2-Methoxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3n**)*

Yield: 64 %; m.p.: 188–190 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,417, 3,349 ($NH_2$), 3,238 (NH), 3,058 (C–H, aromatic), 2,927, 3,009 (C–H), 1,683 (C=O), 1,581 (C=N), 1,522 (C=C), 1,329 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.07 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 3.57 (s, 3H, $CH_3$), 7.03 (s, 1H, NH), 6.94–7.88 (m, 8H, Ar–H), 7.62 (s, 1H, CH=C), 8.56 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.4, 21.7, 56.3, 108.5, 114.6, 120.7, 124.4, 128.3, 128.5, 129.6, 130.7, 133.7, 135.4, 147.3, 159.4, 166.5, 170.4, 181.6; LCMS (*m/z*): 407 ($M^+$); Anal. Calcd. For $C_{21}H_{21}N_5O_2S$: C-61.90, H-5.19, N-17.19; Found: C-61.84, H-5.25, N-17.14 %.

*2-(1-(4-(4-(4-Methoxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamide (**3o**)*

Yield: 61 %; m.p.: 167–169 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,414, 3,342 ($NH_2$), 3,239 (NH), 3,061 (C–H, aromatic), 2,925, 3,005 (C–H), 1,689 (C=O), 1,586 (C=N), 1,525 (C=C), 1,332 (C=S); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 3.55 (s, 3H, $CH_3$), 7.02 (s, 1H, NH), 6.92–7.88 (m, 8H, Ar–H), 7.36 (s, 1H, CH=C), 8.53 (s, 2H, $NH_2$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 16.2, 21.5, 55.4, 114.3, 114.6, 124.6, 127.6, 129.3, 130.4, 130.7, 133.1, 135.6, 147.7, 159.8, 166.2, 170.6, 181.3; LCMS (*m/z*): 407 ($M^+$); Anal. Calcd. For $C_{21}H_{21}N_5O_2S$: C-61.90, H-5.19, N-17.19; Found: C-61.95, H-5.13, N-17.26 %.

General procedure for the preparation 2-((1-(4-(4-arylidene-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene)hydrazono)thiazolidin-4-ones (**4a**–**o**)

*Conventional method*

A mixture of compounds **3a**–**o** (0.01 mol), ethyl bromoacetate (0.01 mol) and sodium acetate (0.08 mol) in ethanol (40 mL) was heated under reflux for 1–3 h. The solid formed was washed with cold methanol and crystallized from ethanol. The crystal was purified by column chromatography using n-hexane:ethyl acetate (7:3) as eluent to afford the title compounds.

*Microwave method*

A homogeneous mixture of 2-(1-(4-(4-(arylidene)-2-methyl-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)phenyl)ethylidene) hydrazinecarbothioamides (**3a**–**o**) (0.01 mol), ethyl bromoacetate (0.01 mol), sodium acetate (0.08 mol) and catalytic amount of DMF was introduced into microwave reaction vessel equipped with a magnetic stirrer (Synthos-3000). The vessel was sealed and the reaction mixture is irradiated by 200 W intermittently at 30 s intervals for 4–7 min. The solid formed was washed with cold methanol and crystallized from DMF. The crystal was purified by column chromatography using n-hexane:ethyl acetate (7:3) as eluent to afford the title compounds. Reaction conditions and yield of the final compounds **4a**–**o** are depicted in Table 3.

*2-((1-(4-(4-Benzylidene-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene)hydrazono) thiazolidin-4-one (**4a**)*

Yield: 56 %; m.p.: 173–175 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,351 (NH), 3,057 (C–H, aromatic), 2,926, 2,861 (C–H), 1,680, 1,713 (C=O), 1,581 (C=N), 1,511 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.92 (s, 3H, $CH_3$), 3.91 (s, 2H, $CH_2$), 7.23–7.89 (m, 9H, Ar–H), 7.92 (s, 1H, CH=C), 8.51 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.8, 21.8, 38.4, 113.7, 124.2, 127.4, 127.6, 128.2, 128.7, 129.3, 131.4, 135.4, 135.7, 141.2, 158.4, 166.4, 170.3, 176.5; LCMS (*m/z*): 417 ($M^+$); Anal. Calcd. For $C_{22}H_{19}N_5O_2S$: C-63.29, H-4.59, N-16.78; Found: C-63.36, H-4.53, N-16.73 %.

*2-((1-(4-(4-(2-Chlorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4b**)*

Yield: 52 %; m.p.: 185–187 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,343 (NH), 3,059 (C–H, aromatic), 2,923, 2,864 (C–H), 1,692, 1,709 (C=O), 1,582 (C=N), 1,522 (C=C), 744 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.01 (s, 3H, $CH_3$), 2.95 (s, 3H, $CH_3$), 3.92 (s, 2H, $CH_2$), 7.21–7.88 (m, 8H, Ar–H), 7.98 (s, 1H, CH=C), 8.52 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.4, 21.7, 38.2, 108.7, 124.3, 126.8, 127.4, 127.9, 129.3, 129.6, 129.8, 131.2, 133.6, 134.7, 135.2, 141.6, 158.4, 166.7, 170.7, 176.4; LCMS (*m/z*): 451 ($M^+$); Anal. Calcd. For $C_{22}H_{18}ClN_5O_2S$: C-58.47, H-4.01, N-15.50; Found: C-58.53, H-4.06, N-15.44 %.

*2-((1-(4-(4-(4-Chlorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene)hydrazono) thiazolidin-4-one (**4c**)*

Yield: 50 %; m.p.: 165–167 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,363 (NH), 3,064 (C–H, aromatic), 2,926, 2,878 (C–H), 1,681, 1,717 (C=O), 1,582 (C=N), 1,509 (C=C), 751 (C–Cl); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.06 (s, 3H, $CH_3$), 2.93 (s, 3H, $CH_3$), 3.97 (s, 2H, $CH_2$), 7.31–7.89 (m, 8H, Ar–H), 7.96 (s, 1H, CH=C), 8.56 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.5, 21.1, 38.6, 114.2, 124.3, 127.5, 128.6, 129.2, 129.3, 131.7, 133.8, 135.2, 133.8, 141.7, 158.2, 166.6, 170.4, 176.6; LCMS (*m/z*): 451 ($M^+$); Anal. Calcd. For $C_{22}H_{18}ClN_5O_2S$: C-58.47, H-4.01, N-15.50; Found: C-58.42, H-3.93, N-15.56 %.

*2-((1-(4-(4-(2-Fluorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4d**)*

Yield: 57 %; m.p.: 193–195 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,357 (NH), 3,071 (C–H, aromatic), 2,932, 2,862 (C–H), 1,681, 1,710 (C=O), 1,575 (C=N), 1,517 (C=C), 1,148 (C–F); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.03 (s, 3H, $CH_3$), 2.95 (s, 3H, $CH_3$), 3.96 (s, 2H, $CH_2$), 7.14–7.88 (m, 8H, Ar–H), 7.94 (s, 1H, CH=C), 8.53 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.1, 21.6, 38.7, 108.4, 115.2, 123.3, 124.2, 124.6, 127.2, 128.5, 129.6, 129.8, 131.4, 135.2, 141.6, 158.2, 161.7, 166.7, 170.4, 176.7; LCMS (*m/z*): 435 ($M^+$); Anal. Calcd. For $C_{22}H_{18}FN_5O_2S$: C-60.68, H-4.17, N-16.08; Found: C-60.61, H-4.23, N-16.14 %.

*2-((1-(4-(4-(4-Fluorobenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4e**)*

Yield: 51 %; m.p.: 173–175 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,348 (NH), 3,061 (C–H, aromatic), 2,928, 2,861 (C–H), 1,698, 1,720 (C=O), 1,581 (C=N), 1,522 (C=C), 1,158 (C–F); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.05 (s, 3H, $CH_3$), 2.94 (s, 3H, $CH_3$), 3.91 (s, 2H, $CH_2$), 7.12–7.91 (m, 8H, Ar–H),

**Table 3** Reaction conditions and yield for compounds **4a–o**

| Comp. | –R | Reaction time | | Yield (%) | | Solvent system for TLC |
|---|---|---|---|---|---|---|
| | | Microwave method (min) | Conventional method (h) | Microwave method | Conventional method | |
| **4a** | –H | 5 | 1 | 56 | 50 | Chloroform:methanol (4:1) |
| **4b** | –2-Cl | 4 | 1 | 52 | 45 | Chloroform:methanol (4:1) |
| **4c** | –4-Cl | 4 | 1 | 50 | 47 | Chloroform:methanol (4:1) |
| **4d** | –2-F | 4 | 3 | 57 | 42 | Chloroform:methanol (4:1) |
| **4e** | –4-F | 7 | 2 | 51 | 49 | *n*-hexane:ethyl acetate (7:3) |
| **4f** | –2-$NO_2$ | 5 | 2 | 55 | 48 | *n*-hexane:ethyl acetate (7:3) |
| **4g** | –4-$NO_2$ | 6 | 3 | 53 | 45 | *n*-hexane:ethyl acetate (7:3) |
| **4h** | –2-OH | 6 | 1 | 50 | 43 | *n*-hexane:ethyl acetate (7:3) |
| **4i** | –3-OH | 4 | 3 | 56 | 45 | *n*-hexane:ethyl acetate (7:3) |
| **4j** | –4-OH | 4 | 3 | 51 | 42 | *n*-hexane:ethyl acetate (7:3) |
| **4k** | –2-$CH_3$ | 4 | 1 | 53 | 46 | *n*-hexane:ethyl acetate (7:3) |
| **4l** | –3-$CH_3$ | 7 | 2 | 55 | 48 | Chloroform:methanol (4:1) |
| **4m** | –4-$CH_3$ | 5 | 2 | 52 | 43 | Chloroform:methanol (4:1) |
| **4n** | –2-$OCH_3$ | 7 | 2 | 51 | 46 | *n*-hexane:ethyl acetate (7:3) |
| **4o** | –4-$OCH_3$ | 5 | 1 | 54 | 50 | *n*-hexane:ethyl acetate (7:3) |

7.91 (s, 1H, CH=C), 8.57 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.6, 21.7, 38.2, 114.3, 115.3, 124.7, 127.4, 129.7, 130.4, 131.3, 131.7, 135.2, 141.5, 158.3, 162.5, 166.6, 170.4, 176.7; LCMS (*m*/*z*): 435 ($M^+$); Anal. Calcd. For $C_{22}H_{18}FN_5O_2S$: C-60.68, H-4.17, N-16.08; Found: C-60.73, H-4.12, N-16.02 %.

*2-((1-(4-(2-Methyl-4-(2-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4f**)*

Yield: 55 %; m.p.: 195–197 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3,356 (NH), 3,071 (C–H, aromatic), 2,927, 2,862 (C–H), 1,682, 1,707 (C=O), 1,581 (C=N), 1,517 (C=C), 1,481, 1,357 ($NO_2$); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.01 (s, 3H, $CH_3$), 2.93 (s, 3H, $CH_3$), 3.96 (s, 2H, $CH_2$), 7.72–8.25 (m, 8H, Ar–H), 7.95 (s, 1H, CH=C), 8.53 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.4, 21.7, 38.8, 108.1, 123.6, 124.7, 127.4, 127.5, 127.6, 128.6, 129.7, 131.8, 134.5, 135.5, 141.3, 147.9, 158.7, 166.5, 170.2, 176.8; LCMS (*m*/*z*): 462 ($M^+$); Anal. Calcd. For $C_{22}H_{18}N_6O_4S$: C-57.13, H-3.92, N-18.17; Found: C-57.20, H-3.98, N-18.12 %.

*2-((1-(4-(2-Methyl-4-(4-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4g**)*

Yield: 53 %; m.p.: 166–168 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3,352 (NH), 3,064 (C–H, aromatic), 2,932, 2,864 (C–H), 1,687, 1,714 (C=O), 1,587 (C=N), 1,511 (C=C), 1,481, 1,364 ($NO_2$); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.07 (s, 3H, $CH_3$), 2.97 (s, 3H, $CH_3$), 3.92 (s, 2H, $CH_2$), 7.70–8.23 (m, 8H, Ar–H), 7.96 (s, 1H, CH=C), 8.51 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.2, 21.7, 38.2, 114.4, 123.6, 124.7, 127.3, 129.1, 129.5, 131.8, 135.3, 141.3, 141.8, 147.3, 158.4, 166.8, 170.7, 176.4; LCMS (*m*/*z*): 462 ($M^+$); Anal. Calcd. For $C_{22}H_{18}N_6O_4S$: C-57.13, H-3.92, N-18.17; Found: C-57.08, H-3.86, N-18.23 %.

*2-((1-(4-(4-(2-Hydroxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4h**)*

Yield: 50 %; m.p.: 189–191 °C; IR (KBr) $\nu_{max}$/cm$^{-1}$: 3,415 (O–H), 3,355 (NH), 3,072 (C–H, aromatic), 2,945, 2,863 (C–H), 1,684, 1,712 (C=O), 1,585 (C=N), 1,519 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.04 (s, 3H, $CH_3$), 2.97 (s, 3H, $CH_3$), 3.95 (s, 2H, $CH_2$), 6.73–7.85 (m, 8H, Ar–H), 7.91 (s, 1H, CH=C), 8.56 (s, 1H, $D_2O$ exch., NH), 9.14 (s, 1H, $D_2O$ exch., OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.5, 21.3, 38.5, 108.6, 113.1, 116.7, 116.8, 121.3, 124.7, 127.6, 128.8, 129.2, 129.5, 131.6, 135.3, 141.7, 157.4, 158.6, 166.8, 170.5, 176.8; LCMS (*m*/*z*): 433 ($M^+$); Anal. Calcd. For $C_{22}H_{19}N_5O_3S$: C-60.96, H-4.42, N-16.16; Found: C-61.06, H-4.37, N-16.12 %.

*2-((1-(4-(4-(3-Hydroxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene)hydrazono) thiazolidin-4-one (**4i**)*

Yield: 56 %; m.p.: 223–225 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,417 (O–H), 3,355 (NH), 3,061 (C–H, aromatic), 2,926, 2,876 (C–H), 1,681, 1,704 (C=O), 1,582 (C=N), 1,511 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.08 (s, 3H, $CH_3$), 2.94 (s, 3H, $CH_3$), 3.91 (s, 2H, $CH_2$), 6.68–7.89 (m, 8H, Ar–H), 7.93 (s, 1H, CH=C), 8.52 (s, 1H, $D_2O$ exch., NH), 9.13 (s, 1H, $D_2O$ exch., OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.4, 21.7, 38.5, 112.3, 113.8, 114.6, 115.6, 121.4, 124.2, 127.7, 129.4, 130.7, 131.8, 135.3, 139.5, 141.5, 158.2, 158.6, 166.6, 170.8, 176.4; LCMS (*m/z*): 433 ($M^+$); Anal. Calcd. For $C_{22}H_{19}N_5O_3S$: C-60.96, H-4.42, N-16.16; Found: C-60.88, H-4.47, N-16.21 %.

*2-((1-(4-(4-(4-Hydroxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene)hydrazono) thiazolidin-4-one (**4j**)*

Yield: 51 %; m.p.: 184–186 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,412 (O–H), 3,351 (NH), 3,078 (C–H, aromatic), 2,921, 2,862 (C–H), 1,685, 1,705 (C=O), 1,580 (C=N), 1,512 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.08 (s, 3H, $CH_3$), 2.94 (s, 3H, $CH_3$), 3.91 (s, 2H, $CH_2$), 6.65–7.87 (m, 8H, Ar–H), 7.95 (s, 1H, CH=C), 8.54 (s, 1H, $D_2O$ exch., NH), 9.16 (s, 1H, $D_2O$ exch., OH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.6, 21.3, 38.6, 113.2, 114.7, 116.1, 124.6, 127.4, 127.7, 129.4, 130.9, 131.5, 135.2, 141.7, 157.8, 158.4, 166.8, 170.7, 176.6; LCMS (*m/z*): 433 ($M^+$); Anal. Calcd. For $C_{22}H_{19}N_5O_3S$: C-60.96, H-4.42, N-16.16; Found: C-60.90, H-4.36, N-16.11 %.

*2-((1-(4-(2-Methyl-4-(2-methylbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4k**)*

Yield: 53 %; m.p.: 170–172 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,348 (NH), 3,068 (C–H, aromatic), 2,927, 2,874 (C–H), 1,681, 1,706 (C=O), 1,581 (C=N), 1,516 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.06 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 2.91 (s, 3H, $CH_3$), 3.94 (s, 2H, $CH_2$), 7.01–7.86 (m, 8H, Ar–H), 7.96 (s, 1H, CH=C), 8.51 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.6, 21.2, 19.4, 38.8, 108.4, 113.3, 124.2, 125.5, 126.6, 127.4, 127.8, 127.9, 129.1, 131.5, 135.8, 136.1, 136.4, 141.4, 158.2, 166.8, 170.5, 176.4; LCMS (*m/z*): 431 ($M^+$); Anal. Calcd. For $C_{23}H_{21}N_5O_2S$: C-64.02, H-4.91, N-16.23; Found: C-64.08, H-4.97, N-16.18 %.

*2-((1-(4-(2-Methyl-4-(3-methylbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene)hydrazono) thiazolidin-4-one (**4l**)*

Yield: 55 %; m.p.: 183–185 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,344 (NH), 3,065 (C–H, aromatic), 2,923, 2,875 (C–H), 1,682, 1,714 (C=O), 1,582 (C=N), 1,515 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.03 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 2.92 (s, 3H, $CH_3$), 3.96 (s, 2H, $CH_2$), 7.08–7.86 (m, 8H, Ar–H), 7.92 (s, 1H, CH=C), 8.57 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.8, 21.6, 21.8, 38.7, 114.6, 124.8, 125.7, 126.8, 127.3, 128.1, 128.6, 129.5, 131.2, 135.3, 135.8, 138.4, 141.1, 158.8, 166.6, 170.3, 176.5; LCMS (*m/z*): 431 ($M^+$); Anal. Calcd. For $C_{23}H_{21}N_5O_2S$: C-64.02, H-4.91, N-16.23; Found: C-63.97, H-4.85, N-16.29 %.

*2-((1-(4-(2-Methyl-4-(4-methylbenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene)hydrazono) thiazolidin-4-one (**4m**)*

Yield: 52 %; m.p.: 165–167 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,342 (NH), 3,055 (C–H, aromatic), 2,924, 2,872 (C–H), 1,684, 1,708 (C=O), 1,581 (C=N), 1,516 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.00 (s, 3H, $CH_3$), 2.94 (s, 3H, $CH_3$), 3.77 (s, 3H, $OCH_3$), 3.98 (s, 2H, $CH_2$), 7.14–7.89 (m, 8H, Ar–H), 7.97 (s, 1H, CH=C), 8.54 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.2, 21.1, 21.4, 38.3, 114.2, 124.6, 127.2, 128.5, 128.9, 129.4, 131.1, 132.3, 135.5, 137.6, 141.3, 158.6, 166.2, 170.6, 176.1; LCMS (*m/z*): 431 ($M^+$); Anal. Calcd. For $C_{23}H_{21}N_5O_2S$: C-64.02, H-4.91, N-16.23; Found: C-64.08, H-4.96, N-16.17 %.

*2-((1-(4-(4-(2-Methoxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4n**)*

Yield: 51 %; m.p.: 190–192 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,352 (NH), 3,064 (C–H, aromatic), 2,934, 2,873 (C–H), 1,682, 1,715 (C=O), 1,586 (C=N), 1,512 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.02 (s, 3H, $CH_3$), 2.90 (s, 3H, $CH_3$), 3.74 (s, 3H, $OCH_3$), 3.95 (s, 2H, $CH_2$), 6.90–7.88 (m, 8H, Ar–H), 7.92 (s, 1H, CH=C), 8.51 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.2, 21.5, 38.7, 56.3, 108.5, 114.6, 120.7, 124.6, 127.7, 128.3, 128.5, 129.2, 131.8, 135.3, 141.5, 158.8, 159.4, 166.5, 170.2, 176.8; LCMS (*m/z*): 447 ($M^+$); Anal. Calcd. For $C_{23}H_{21}N_5O_3S$: C-61.73, H-4.73, N-15.65; Found: C-61.80, H-4.68, N-15.70 %.

*2-((1-(4-(4-(4-Methoxybenzylidene)-2-methyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)phenyl)ethylidene) hydrazono)thiazolidin-4-one (**4o**)*

Yield: 54 %; m.p.: 165–167 °C; IR (KBr) $\nu_{max}/cm^{-1}$: 3,362 (NH), 3,061 (C–H, aromatic), 2,944, 2,871 (C–H), 1,683, 1,701 (C=O), 1,586 (C=N), 1,513 (C=C); $^1$H NMR (300 MHz, DMSO-$d_6$, $\delta$, ppm): 2.00 (s, 3H, $CH_3$), 2.92 (s, 3H, $CH_3$), 3.75 (s, 3H, $OCH_3$), 3.97 (s, 2H, $CH_2$), 6.92–7.91 (m, 8H, Ar–H), 7.94 (s, 1H, CH=C), 8.58 (s, 1H, $D_2O$ exch., NH); $^{13}$C NMR (100 MHz, DMSO-$d_6$, $\delta$, ppm): 13.1, 21.4, 38.6, 55.4, 114.3, 114.7, 124.3, 127.2, 127.6, 129.6, 130.4, 131.3, 135.4, 141.8, 159.8, 158.3, 166.8, 170.2, 176.8; LCMS (*m/z*): 447 ($M^+$); Anal. Calcd. For $C_{23}H_{21}N_5O_3S$: C-61.73, H-4.73, N-15.65; Found: C-61.67, H-4.78, N-15.60 %.

## Biological evaluation

### Antibacterial assay

The newly synthesized compounds (**4a–o**) were screened for their antibacterial activity against Gram-positive bacteria (*S. aureus* (MTCC-96), *S. pyogenes* (MTCC-442)) and Gram-negative bacteria (*E. coli* (MTCC-443), *P. aeruginosa* (MTCC-1688)). All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh. The activity of compounds was determined as per National Committee for Clinical Laboratory Standards (NCCLS) protocol using Mueller–Hinton Broth (Becton–Dickinson, USA) (Finegold and Garrod, 1995; Desai *et al.*, 2012d, e). Compounds were screened for their antibacterial activity as primary screening in six sets against *E. coli*, *S. aureus*, *P. aeruginosa* and *S. pyogenes* at different concentrations of 1,000, 500 and 250 μg/mL. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25 and 12.5 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Inoculum size for test strain was adjusted to $10^6$ CFU/mL (Colony Forming Unit per milliliter) by comparing the turbidity (turbidimetric method). Mueller–Hinton Broth was used as nutrient medium to grow and dilute the compound suspension for test bacteria. 2 % DMSO was used as a diluent/vehicle to obtain the desired concentration of synthesized compounds and standard drugs to test upon standard microbial strains. Synthesized compounds were diluted to 1,000 μg/mL concentration, as a stock solution. The control tube containing no antibiotic was immediately subcultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of test organisms. The tubes were then put for incubation at 37 °C for 24 h for bacteria. 10 μg/mL suspensions were further inoculated on an appropriate media and growth was noted after 24 and 48 h. The highest dilution (lowest concentration) preventing appearance of turbidity was considered as minimum inhibitory concentration (MIC, μg/mL), i.e. the amount of growth from the control tube before incubation (which represents the original inoculum) was compared. A set of tubes containing only seeded broth and solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth. The result of this is greatly affected by the size of inoculum. The test mixture should contain $10^6$ CFU/mL organisms. Standard drug used in the present study was 'ampicillin' for evaluating antibacterial activity which showed 250, 100, 100 and 100 μg/mL MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes*, respectively.

### Antifungal assay

The same compounds (**4a–o**) were tested for antifungal activity as primary screening in six sets against *C. albicans*, *A. niger* and *A. clavatus* at various concentrations of 1,000, 500 and 250 μg/mL. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50 and 25 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Griseofulvin was used as a standard drug for antifungal activity, which showed 500, 100 and 100 μg/mL MIC against *C. albicans*, *A. niger* and *A. clavatus*, respectively. For fungal growth, in the present protocol, we have used Sabourauds dextrose broth at 28 °C in aerobic condition for 48 h.

### Statistical analysis

Standard deviation value was expressed in terms of ±SD. On the basis of calculated value, by means of one-way ANOVA method followed by independent two sample *t* test, it has been observed that differences below 0.001 level were considered as statistically significant.

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