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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel approach for synthesis of potent antimicrobial hybrid molecules containing pyrimidine-based imidazole scaffolds

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Abstract This report describes the novel approach for the synthesis and exploration of hybrid molecules containing pyrimidine-based imidazole scaffolds as potent antimicrobial agents. The targeted compounds *N*-(4-arylidene-2-mercapto-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides (**5a–l**) were achieved by the Knoevenagel condensation of a key precursor (**4**) with different aldehydes in good yields having moderate to excellent antimicrobial activity. The structural identification of final products was carried out by known classical spectral techniques like IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. The obtained data indicated that the majority of the tested compounds exhibited good antibacterial activity over antifungal activity, particularly compounds **5j** and **5b** (having MIC values 12.5 μg/mL) showed a comparable effect to a standard antibacterial and antifungal agents.

Keywords Pyrimidine · Imidazole · Antimicrobial activity · MIC · Hybrid molecules

Introduction

The epidemic of resistant pathogens has spurred renewed concern in finding novel antimicrobials. In this pursuit, molecular hybridization serves as an important tool for discovery of new chemical entities. In the past several decades much attention has been given to the design and synthesis of new types of pharmacologically diverse structural hybrid molecules (Vladimir and Alicia, 2009). One shining example is vilazodone, which combined serotonin reuptake inhibitor (SSRI) and 5-HT1A receptor which was a partial agonist and was marketed under the tread name Viibryd (Ding *et al*., 2013). Therefore, in this endeavor of our research group, we have focused on a very unique and efficient synthesis and exploration of antimicrobial activity of hybrid molecules containing pyrimidine with imidazole pharmacophores. Several pyrimidine derivatives have been developed as versatile chemotherapeutic agents and have found wide clinical applications such as antitumor (Diaa and Amira, 2010), antioxidant (Kumar *et al*., 2011), vasodilative (Singh *et al*., 2009; Cho *et al*., 1989), antihypertensive (Alam *et al*., 2010; Atwal *et al*., 1991; Rovnyak *et al*., 1992; Grover *et al*., 1995), and adrenoceptor-selective antagonism (Barrow *et al*., 2000). Also, different pyrimidine derivatives have remarkable pharmaceutical importance because of their biological activity as antitubercular (Virsodia *et al*., 2008), antibacterial (Rostamizadeh *et al*., 2013), and anti-HIV compounds (Wallis *et al*., 1999). Moreover, pyrimidines are important analgesic and anti-inflammatory agents (Sondhia *et al*., 2009).

Imidazole and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases. The imidazolinones are associated with a wide range of therapeutic activities such as anticancer (Baviskar *et al*., 2011), 20HETE (20-hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors (Nakamura *et al*., 2004), carboxypeptidase inhibitors (Pozharskii *et al*., 1997), antiaging agents (Congiu *et al*., 2008), anticoagulants (Venkatesan *et al*., 2008), antiviral (Babizhayev, 2006), antitubercular (Nantermet *et al*., 2004), and antimicrobial (Desai *et al*., 2013a). This group presents in

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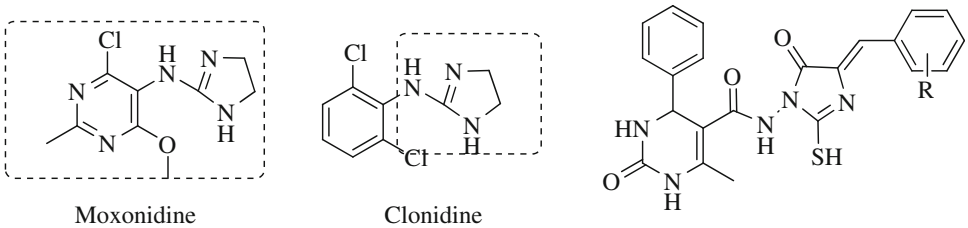


Fig. 1 Structural similarity between marketed drugs and targeted compounds

azoles antifungal which inhibit the accumulation of methylated sterols destroy the composition of the lipid bilayer of membranes. Motivated by the above findings and our previous work (Desai *et al*., 2013b, c), it was thought worthwhile to synthesize new pyrimidine bearing imidazole derivatives (**5a–l)** that contain the aforementioned moieties in a single molecular framework in order to investigate their in vitro antibacterial and antifungal activity. The assumed compounds were characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. These compounds were evaluated for their antimicrobial screening on different strains of bacteria and fungi (Fig. 1).

Results and discussion

Chemistry

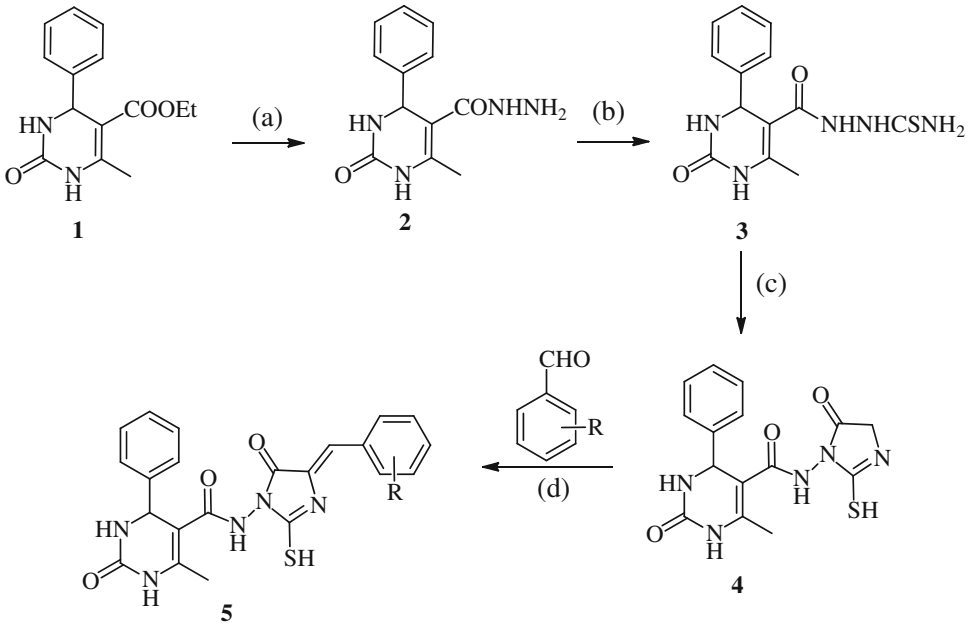
The synthesis of titled compounds (**5a–l)** is outlined in Scheme 1. In a typical experimental procedure, a mixture of benzaldehyde, urea, and ethyl acetoacetate in 1,4-dioxane was heated under reflux in the presence of concentrated HCl to give ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1**), followed by reaction with hydrazine hydrate in 1,4-dioxane in the presence of H_2SO_4 to give 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**2**) (Raval and Akhaja, 2011). The treatment of compound (**2**) with KSCN in acidic medium afforded 2-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide (**3**) (Samshuddin *et al*., 2012). The key precursor *N*-(2-mercapto-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4**) was obtained by the reaction of compound (**3**) with $ClCH_2COOH$ in the presence of anhydrous sodium acetate in glacial acetic acid in reflux conditions. The lone pair of electron on amido group of pyrimidine hydrazinecarbothioamide (**3**) attacks on positively charged methyleneic C atom of the chloroacetic acid to form an intermediate having a new C–N bond with the elimination of HCl molecule. This intermediate undergoes cyclization on loosing H_2O molecule to form an imidazole ring structure (**4**). These conversions are depicted in Scheme 2. Finally, the title compounds *N*-(4-arylidene-2-mercapto-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5a–l**) were afforded by the Knoevenagel condensation reaction of compound (**4**) with different aldehydes in the presence of sodium ethoxide in ethanol. Formation of final products (**5a–l**) was explained based on the literature precedence, and the isomeric ratio of products was presumed to be mainly *Z* in all cases. It was reported that the thermodynamically stable *Z*-isomer predominated with a ratio of *Z*:*E* isomers 10:1 after recrystallization for all arylidene (**5a–l**). The ratio of the two geometrical stereoisomers was readily quantified by ^{1}H NMR as reported in the literature (Ohishi *et al*., 1990).The purity of compounds was checked by TLC as well as by column chromatography. The structure of all the synthesized compounds was established by IR, ^{1}H, ^{13}C NMR, and mass spectral analysis. The result of elemental analysis of the synthesized compounds was in agreement with theoretical values. The outcome of antimicrobial studies of newly synthesized compounds revealed that these compounds have significant antibacterial and antifungal activities.

Antimicrobial screening

From antimicrobial activity data (Table 1), key precursor, imidazole (**4**) showed poor antibacterial activity at MIC $> n$ with aromatic aldehydes. Collectively, compounds (**5a–l**) could be considered as significant to potent active broad-spectrum antimicrobials. Preliminary microbiological screening results showed that compounds **5b** (-2-F-C_6H_4) and **5d** (-2-OH-C_6H_4) exhibited good activity against *Escherichia coli*, while compounds **5f** (-4-Cl-C_6H_4) and **5j** (-2,6-$(Cl)_2$-C_6H_3) demonstrated very good activity against *E. coli.* Compounds **5b** (-2-F-C_6H_4) and **5f** (-4-Cl-C_6H_4) showed good activity against *Staphylococcus aureus*. On installation of -2,6-$(Cl)_2$-C_6H_3 substituent in the compound **5j**, the increment in activity was observed enormously and it exhibited excellent activity against *S. aureus.*

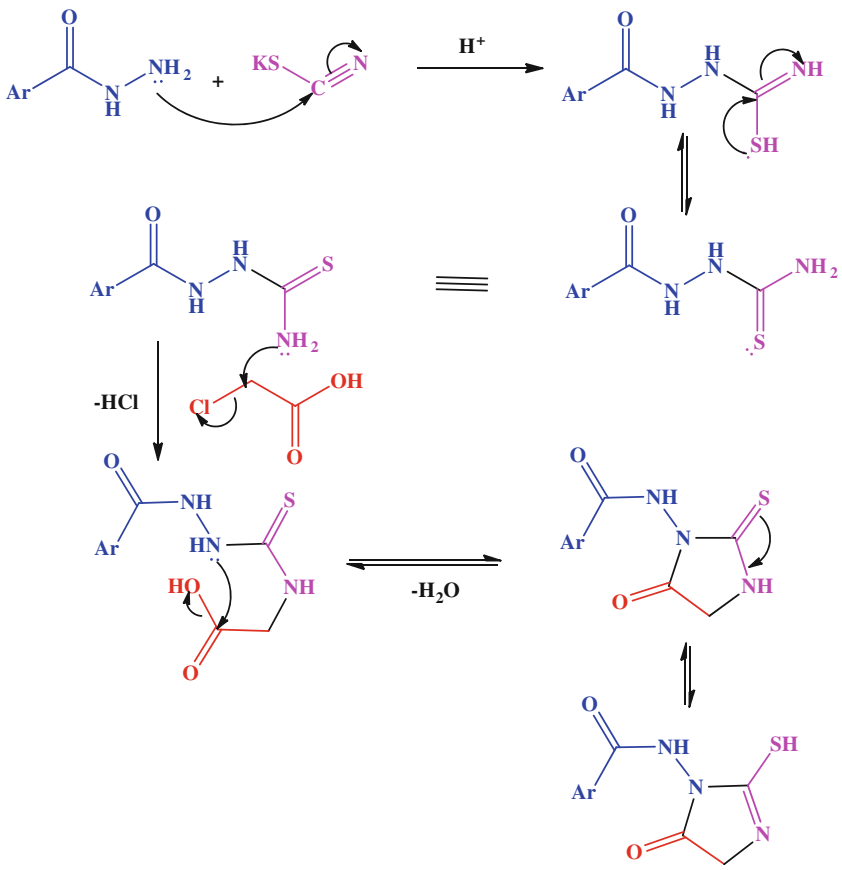
In case of antifungal activity, compound **5j** (-2,6-$(Cl)_2$-C_6H_3) exhibited good activity against *Aspergillus niger*, while compound **5b** (2-F-C_6H_4) demonstrated excellent activity against *Aspergillus clavatus*. In a nutshell, these preliminary screening showed that the series of these novel compounds exhibited significant antibacterial activity in comparison to antifungal activity.

Scheme 1 Reaction scheme. Reagents and conditions: (*a*) $NH_2NH_2H_2O$, Con.H_2SO_4 , 1,4-dioxane, reflux, 4 h; (*b*) KSCN, HCl reflux, 4 h; (*c*) $ClCH_2COOH$, CH_3COONa, CH_3COOH, reflux, 8 h; (*d*) C_2H_5ONa, EtOH, reflux, 6–7 h



Where, R = -H, -2-F, -4-F, -2-OH, -4-OH, -4-Cl, -2-NO_2, -3-NO_2, -4-NO_2, -2,6(Cl)$_2$, -2-OCH_3, -4-OCH_3

Scheme 2 Plausible reaction mechanism



Structure activity relationship (SAR)

Results of antimicrobial activity of final compounds and the precursor (**4**) clearly suggested that the Knoevenagel adduct of imidazolinone was found to be critical for broad spectrum of antimicrobial activity. The substitution pattern was carefully altered to acquire a comprehensible design between the electronic environment and response toward the pathogens. Electron-releasing groups on aromatic ring, such as methyl, methoxy, hydroxy, and electron withdrawing groups from aromatic ring, such as nitro and halogen, are chosen as substituents on the chemical structure of the target compounds. Compounds **5j** and **5b** with electron withdrawing groups (2,6-$(Cl)_2$-C_6H_3 and 2-F-C_6H_4, respectively) represented much lower MIC values than reference drugs against *S. aureus* and *A. clavatus*, respectively. From the data of biological activity, we can presume that, to get most potent antimicrobial agents, compounds must contain electron withdrawing group as substitution. Therefore, the electron withdrawing groups induced a positive effect on the biological activity. Thus, we have discussed and compared antibacterial and antifungal activities based on standard drugs ciprofloxacin and griseofulvin, respectively.

Biological evaluation

Antibacterial assay

The newly synthesized compounds were screened for their antibacterial activity against Gram-positive bacteria [*S. aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442)] and Gram-negative [*E. coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)]. Antibacterial activity was measured as per National Committee for Clinical Laboratory Standards (NCCLS) protocol by Mueller Hinton broth (Becton–Dickinson, USA) (Desai *et al*., 2013b). Standard strains were procured by the Institute of Microbial Technology, Chandigarh. Compounds were primarily screened for their antibacterial activity in six sets against *E. coli*, *S. aureus*, *P. aeruginosa*, and *S. pyogenes* at different concentrations of 1,000, 500, and 250 μg/mL as shown in Table 1. The drugs 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). Synthesized compounds were diluted to 1,000 μg/mL concentration, as a stock solution. A 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 incubated at 37 °C for 24 h for bacteria. Ten μg/mL suspensions were further inoculated on appropriate media, and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture, was considered as MIC for each drug. The highest dilution (lowest concentration) preventing appearance of turbidity was taken as MIC i.e., the amount of growth from the control tube before incubation (which represents the original inoculum) was compared. The test mixture should contain 10^6 CFU/mL organisms. 2 % DMSO and sterilized distilled water was used as negative control, while ampicillin antibiotic (1 U strength) was used as positive control. 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 was significantly affected by the size of inoculum. The standard drug used in the present study was ''Ciprofloxacin'' for evaluating antibacterial activity which showed 25, 25, 50, and 50 μg/mL MIC against *E. coli, P. aeruginosa, S. aureus*, and *S. pyogenes*, respectively. For bacterial growth, in the present protocol, we have used Mueller Hinton broth at 37 °C in aerobic condition for 24 to 48 h.

Antifungal assay

The same compounds were tested for antifungal activity as primary screening in six sets against *Candida albicans*, *A. niger*, and *A. clavatus* at various concentrations of 1,000, 500, 200, and 100 μg/mL as shown in Table 1. Results were recorded in the form of primary and secondary screening. Synthesized compounds were diluted to 1,000 μg/mL concentration, as a stock solution. Those synthesized compounds which were found to be active in this primary screening were further tested 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. Two percentage DMSO and sterilized distilled water was used as negative control, while griseofulvin (1 U strength) was used as positive control. Results of antimicrobial evaluation of derivatives **5a–l** are shown in Table 1. For fungal growth, in the present protocol, we have used Sabourauds dextrose broth at 28 °C in aerobic condition for 48 h.

Materials and methods

General

All reactions except those in aqueous media were carried out by standard techniques with the exclusion of moisture. Melting points were determined on an electrothermal

Table 1 Antimicrobial activity of *N*-(4-arylidene-2-mercapto-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamides

S. no.	-R	Minimum inhibitory concentration (MIC) for bacteria (μg/mL)				Minimum inhibitory concentration (MIC) for fungi (μg/mL)		
		E.c.	*P.a.*	*S.a.*	*S.p.*	*C.a.*	*A.n.*	*A.c.*
4	–	250	250	250	1000	1000	1000	1000
5a	-H	500	250	250	500	500	1,000	1,000
5b	-2-F	**50**	500	**50**	100	**100**	**200**	**12.5**
5c	-4-F	500	200	250	500	1,000	**200**	**200**
5d	-2-OH	**50**	100	250	500	**200**	500	500
5e	-4-OH	100	100	250	500	**200**	1,000	1,000
5f	-4-Cl	**25**	250	**50**	100	1,000	**100**	**200**
5g	-2-NO_2	500	500	1,000	1,000	500	1,000	500
5h	-3-NO_2	500	500	1,000	1,000	1,000	1,000	1,000
5i	-4-NO_2	100	100	250	500	500	1,000	1,000
5j	-2,6-$(Cl)_2$	**25**	100	**12.5**	500	**100**	**50**	**100**
5k	-2-OCH_3	250	200	250	250	500	1,000	1,000
5l	-4-OCH_3	250	250	250	500	1,000	500	500
Ciprofloxacin		25	25	50	50	–	–	–
Griseofulvin		–	–	–	–	500	100	100

Bold values indicate the most active compounds

E.c. Escherichia coli (MTCC-443), *P.a. Pseudomonas aeruginosa* (MTCC-1668), *S.a. Staphylococcus aureus* (MTCC-96), *S.p. Streptococcus pyogenes* (MTCC-442), *C.a. Candida albicans* (MTCC-227), *A.n. Aspergillusniger* (MTCC-282), *A.c. Aspergillusclavatus* (MTCC-1,323)

melting point apparatus and are 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 and 230–400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (% C, H, and N) was carried out using a Perkin-Elmer 2400 CHN analyzer. IR spectra of all compounds have been recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on Bruker Avance II 400 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 recorded on a Shimadzu LCMS 2010 spectrometer. Anhydrous reactions were carried out in ovendried glassware in nitrogen atmosphere. Compound ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1) was prepared according to literature (Gupta *et al*., 2005) method.

*General procedure for the preparation of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**2**) (Raval and Akhaja, 2011)* Compound (**1**) (0.01 mol) was dissolved in 1,4-dioxane (20 mL), and to this hydrazine hydrate (99 %) (0.01 mol) was added followed by the addition of a catalytic amount of conc. H_2SO_4 and allowed to stir for 3 h at 100 °C. After completion of reaction, crude mass was allowed to cool and poured on crushed ice. Product obtained as yellowish precipitate was filtered and dried. Purification was done by crystallization using ethanol (95 %).

*Physical constants and characterization of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**2**)* Light yellow solid, yield: 69 %; m.p.: 195–198 °C; IR (KBr) ν_{max}/cm^{-1}: 3452, 3342 (NH), 3071 (C–H, aromatic), 1513 (C=C), 1685 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.97 (s, 2H, NH_2, D_2O exch.), 2.35 (s, 3H, $–CH_3$), 5.60 (s, 1H, –CH), 5.87 (s, 1H, –NHNH$_2$), 6.05 (s, 1H, –NHCPh), 6.18 (s, 1H, –NHCCH$_3$), 6.94 (d, 2H, Ar–H), 7.23 (d, 2H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.2 ($–CH_3$), 52.9 (–CH), 101.2 (>C<), 114.6–132.4 (C-aromatic), 150.8 (C–CH$_3$), 155.9 (–NHCONH–), 162.5 (–CONHNH$_2$); LCMS (*m/z*): 246 $(M)^+$; Anal. calcd. for $C_{12}H_{14}N_4O_2$: C-58.53, H-5.73, N-22.75; Found: C-58.92, H-5.55, N-22.12 %.

*General procedure for the preparation of 2-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide (**3**) (Samshuddin et al., 2012)* A mixture of 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (**2**) (0.01 mol), potassium thiocyanate(0.015 mol), and hydrochloric acid (5 mL) in water (25 mL) was refluxed for 4 h with stirring. After completion of reaction, the resulting solid thus separated was washed with hot water and recrystallized from ethanol (95 %).

*Physical constants and characterization of 2-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide (**3**)* Light brown solid, yield 83 %; m.p.: 200–202 °C; IR (KBr) ν_{max}/cm^{-1}: 3433, 3367 (NH), 2987 (C–H, aromatic), 1578 (C=C), 1734 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.28 (s, 3H, $–CH_3$), 5.40 (s, 1H, pyrimidine –CH), 6.02 (s, 1H, –NHCPh), 6.24 (s, 1H, –NHCCH$_3$), 6.56 (s, 2H, $–NH_2$), 6.67 (s, 1H, –CONH), 7.34–7.45 (m, 5H, Ar–H), 8.32 (s, 1H, –NHCSNH$_2$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.5 ($–CH_3$), 52.9 (–CH of pyrimidine), 101.2 (>C<), 126.6–140.8 (C-aromatic), 152.4 (–CCH$_3$), 155.9 (–NHCONH–), 161.5 (–CONHNH), 182.5 (–CS); LCMS (*m/z*): 305$(M)^+$; Anal. calcd. for $C_{13}H_{15}N_5O_2S$: C-51.13, H-4.95, N-22.94; Found: C-51.72, H-4.77, N-22.06.

*General procedure for the preparation of N-(2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4**)* A mixture of 2-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl)hydrazinecarbothioamide (**3**) (0.001 mol),

monochloroacetic acid (0.001 mol), and anhydrous sodium acetate (0.002 mol) in glacial acetic acid (30 mL) was refluxed for 8 h. After completion of reaction, the reaction mixture was poured on crushed ice. The resulting solid thus separated was washed with hot water and recrystallized from ethanol.

*Physical constants and characterization of N-(2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4**)* Light orange solid, yield 65 %; m.p.: 262–264 °C; IR (KBr) ν_{max}/cm^{-1}: 3445, 3368 (NH), 3045 (C–H, aromatic), 1545 (C=C), 1734 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.04 (s, 1H, –SH), 2.40 (s, 3H, –CH_3), 4.76 (s, 2H, –CH_2), 5.29 (s, 1H, –CH of pyrimidine), 6.19 (–NHCPh), 6.38 (s, 1H, –NHCCH$_3$), 7.19 (s, 1H, –CONH), 7.29–7.38 (m, 5H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.8 (–CH_3), 48.9 (–CH_2 of imidazole), 53.5 (–CH of pyrimidine), 102.7 (>C<), 128.3–142.4 (Ar–C), 153.6 (–CCH$_3$), 155.7 (–NHCONH–), 157.5 (–CONH), 173.5 (–CS), 178.5 (–CO of imidazole); LCMS (*m/z*): 345 $(M)^+$; Anal. calcd. for $C_{15}H_{15}N_5O_3S$: C-52.16, H-4.38, N-20.28; Found: C-52.07, H-4.73, N-20.55 %.

*General procedure for the preparation of N-(4-benzylidene-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5a–l**)* A solution of *N*-(2-mercapto-5-oxo-4,5-dihydro-1*H*-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**4**) (0.01 mol) in ethanol (25 mL) was taken in a flask equipped with a Dean-Stark apparatus fitted with calcium guard tube. Benzaldehyde (0.01 mol) was slowly added to it with constant stirring, and catalytic amount of sodium ethoxide (0.01 mol) was added along with it. The reaction mixture was refluxed for 6–7 h; after the completion of the reaction, the final product (**5**) was obtained by cooling reaction mass on room temperature, and excess amount of solvent was distilled out. The crude product was filtered off and washed with methanol, dried and recrystallized from ethanol (95 %).

*Physical constants and characterization of compounds (**5a–l**) N-(4-benzylidene-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5a**)* Light brown solid, yield 68 %; m.p.: 272–274 °C; IR (KBr) ν_{max}/cm^{-1}: 3445, 3368 (NH), 3045 (C–H, aromatic), 1545 (C=C), 1734 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.08 (s, 1H, –SH), 2.34 (s, 3H, –CH_3), 5.36 (s, 1H, –CH of pyrimidine), 6.04 (s, 1H, –NHCPh), 6.19 (s, 1H, –CH=), 7.24–7.48 (m, 10H, Ar–H), 7.40 (s, 1H, –CONH), 7.48 (s, 1H, –NHCCH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.3 (–CH_3), 53.2 (–CH of pyrimidine), 102.4 (>C<), 125.4 (–CH=), 125.8 (>C=CH–), 127.7–140.7 (Ar–C), 153.4 (–CCH$_3$), 155.6 (–NHCONH–), 157.6 (–CONH), 165.0 (–CO of imidazole), 182.9 (–C–SH); 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-60.26, H-4.83, N-16.65 %.

*N-(4-(2-fluorobenzylidene)-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5b**)* Light yellow solid, yield 72 %; m.p.: 268–270 °C; IR (KBr) ν_{max}/cm^{-1}: 3467, 3389 (NH), 3034 (C–H, aromatic), 1578 (–C=N), 1556 (C=C), 1738 (C=O), 1245 (C–F); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.19 (s, 1H, –SH), 2.34 (s, 3H, –CH_3), 5.37 (s, 1H, –CH of pyrimidine), 6.10 (s, 1H, –CH=), 6.27 (s, 1H, –NHCPh), 7.21–7.45 (m, 9H, Ar–H), 7.67 (s, 1H, –NHCCH$_3$), 7.78 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.4 (–CH_3), 53.8 (–CH of pyrimidine), 102.4 (>C<), 115.7 (2) (>C–C–F), 125.4 (–CH=), 126.5 (>C=CH–), 128.6–141.9 (Ar–C), 153.5 (–CCH$_3$), 155.7 (–NHCONH–), 158.8 (–CONH), 163.5 (–C–F), 165.7 (–CO of imidazole), 181.9 (–C–SH); LCMS (*m/z*): 451$(M)^+$; Anal. calcd. for $C_{22}H_{18}FN_5O_3S$: C-58.53, H-4.02, N-15.51; Found: C-58.14, H-4.70, N-15.56 %.

*N-(4-(4-fluorobenzylidene)-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5c**)* Light yellow solid, yield 58 %; m.p.: 280–282 °C; IR (KBr) ν_{max}/cm^{-1}: 3456, 3378 (NH), 3023 (C–H, aromatic), 1598 (–C=N), 1545 (C=C), 1745 (C=O), 1222 (C–F); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.24 (s, 1H, –SH), 2.29 (s, 3H, –CH_3), 5.30 (s, 1H, –CH of pyrimidine), 5.98 (s, 1H, –CH=), 6.23 (s, 1H, –NHCPh), 7.15–7.38 (m, 9H, Ar–H), 7.52 (s, 1H, –NHCCH$_3$), 7.60 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.7 (–CH_3), 53.5 (–CH of pyrimidine), 102.8 (>C<), 115.4 (2) (>C–C–F), 125.6 (–CH=), 125.9 (>C=CH–), 128.3–141.5 (Ar–C), 153.2 (–CCH$_3$), 154.9 (–NHCONH–), 158.4 (–CONH), 162.6 (–C–F), 165.4 (–CO of imidazole), 182.4 (–C–SH); LCMS (*m/z*): 451$(M)^+$; Anal. calcd. for$C_{22}H_{18}FN_5O_3S$: C-58.53, H-4.02, N-15.51; Found: C-58.17, H-4.27, N-15.68 %.

*N-(4-(2-hydroxybenzylidene)-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5d**)* Light gray solid, yield 65 %; m.p.: 239–241 °C; IR (KBr) ν_{max}/cm^{-1}: 3423(OH), 3459, 3379 (NH), 3022 (C–H, aromatic), 1563 (–C=N), 1538 (C=C), 1743 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 1H, –SH), 2.43 (s, 3H, –CH_3), 5.28 (s, 1H,OH), 5.43 (s, 1H, –CH of pyrimidine), 6.14 (s, 1H, –CH =), 6.34 (s, 1H, –NHCPh), 7.28–7.53 (m, 9H, Ar–H), 7.72 (s, 1H, –NHCCH$_3$), 7.82 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 18.4 (–CH_3), 54.5

(–CH of pyrimidine), 104.4 (>C<), 124.8 (–CH =), 127.4 (>C=CH–), 129.7–143.5 (Ar–C), 154.5 (–CCH_3), 156.5 (–NHCONH–), 158.4 (>C–OH), 159.9 (–CONH), 167.9 (–CO of imidazole), 182.4 (–C–SH); LCMS (*m/z*): 449$(M)^+$; Anal. calcd. for $C_{22}H_{19}N_5O_4S$: C-58.79, H-4.26, N-15.58; Found: C-58.48, H-4.51, N-15.19 %.

*N-(4-(4-hydroxybenzylidene)-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5e**)* Orange yellow solid, yield 69 %; m.p.: 258-260 °C; IR (KBr) ν_{max}/cm^{-1}: 3434(OH), 3453, 3368 (NH), 3037 (C–H, aromatic), 1557 (–C=N), 1532 (C=C), 1756 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.32 (s, 1H, –SH), 2.48 (s, 3H, –CH_3), 5.34 (s, 1H, OH), 5.48 (s, 1H, –CH of pyrimidine), 6.22 (s, 1H, –CH=), 6.37 (s, 1H, –NHCPh), 7.24–7.49 (m, 9H, Ar–H), 7.67 (s, 1H, –$NHCCH_3$), 7.75 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 18.2 (–CH_3), 54.7 (–CH of pyrimidine), 103.6 (>C<), 124.7 (–CH=), 127.7 (>C=CH-), 130.4–144.7 (Ar–C), 153.6 (–CCH_3), 155.7 (–NHCONH–), 157.6 (>C–OH), 160.4 (CONH), 166.4 (–CO of imidazole), 181.2 (–C–SH); LCMS (*m/z*): 449$(M)^+$; Anal. calcd. for $C_{22}H_{19}N_5O_4S$: C-58.79, H-4.26, N-15.58; Found: C-58.48, H-4.51, N-15.19 %.

*N-(4-(4-chlorobenzylidene)-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5f**)* Light reddish brown solid, yield 80 %; m.p.: 265–267 °C; IR (KBr) ν_{max}/cm^{-1}: 3442, 3353 (NH), 2978 (C–H, aromatic), 1547 (–C=N), 1525 (C=C), 1720 (C=O), 730 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.19 (s, 1H, –SH), 2.34 (s, 3H, –CH_3), 5.32 (s, 1H, –CH of pyrimidine), 6.34 (s, 1H, –CH =), 6.20 (s, 1H, –NHCPh), 7.18–7.37 (m, 9H, Ar–H), 7.56 (s, 1H, –$NHCCH_3$), 7.69 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.9 (–CH_3), 54.4 (–CH of pyrimidine), 102.5 (>C<), 124.4 (–CH=), 127.4 (>C=CH–), 129.2–143.8 (Ar–C), 132.5 (C–Cl), 152.8 (–CCH_3), 155.3 (–NHCONH–), 161.2 (–CONH), 166.8 (–CO of imidazole), 181.8 (–C–SH); LCMS (*m/z*): 467$(M)^+$; Anal. calcd. for $C_{22}H_{18}ClN_5O_3S$: C-56.47, H-3.88, N-14.97; Found: C-56.31, H-3.57, N-14.76 %.

*N-(2-mercapto-4-(2-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5g**)* Orange yellow solid, yield 77 %; m.p.: 139–141 °C; IR (KBr) ν_{max}/cm^{-1}: 3470, 3360 (NH), 2984 (C–H, aromatic), 1545 (–C=N), 1530 (C=C), 1443, 1363 (NO_2), 1745 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.18 (s, 1H, –SH), 2.39 (s, 3H, –CH_3), 5.40 (s, 1H, –CH of pyrimidine), 6.18 (s, 1H, –NHCPh), 6.43 (s, 1H, –CH =), 7.30-8.15 (m, 9H, Ar–H), 7.45 (s, 1H, –CONH), 7.63 (s, 1H, –$NHCCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.8 (–CH_3), 53.6 (–CH of pyrimidine), 102.5 (>C<), 123.9 (2) (>CH–C–NO_2), 125.4 (>C=CH), 126.3 (>C=CH–), 128.4–145.6 (Ar–C), 153.3 (–CCH_3), 155.3 (–NHCONH–), 157.7 (–CONH), 165.3 (–CO of imidazole), 183.7 (–C–SH); LCMS (*m/z*): 478 $(M)^+$; Anal. calcd. for $C_{22}H_{18}N_6O_5S$: C-55.22, H-3.79, N-17.56; Found: C-55.37, H-4.23, N-17.91 %.

*N-(2-mercapto-4-(3-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5h**)* Light yellow solid, yield 58 %; m.p.: 255–257 °C; IR (KBr) ν_{max}/cm^{-1}: 3468, 3349 (NH), 2994 (C–H, aromatic), 1552 (–C=N), 1537 (C=C), 1478, 1349 (NO_2), 1753 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 1H, –SH), 2.47 (s, 3H, –CH_3), 5.43 (s, 1H, –CH of pyrimidine), 6.29 (s, 1H, –NHCPh), 6.48 (s, 1H, –CH=), 7.33–8.23 (m, 9H, Ar–H), 7.37 (s, 1H, –CONH), 7.72 (s, 1H, –$NHCCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.7 (–CH_3), 53.3 (–CH of pyrimidine), 102.9 (>C<), 123.3 (2) (>CH–C–NO_2), 125.3 (>C=CH), 126.6 (>C=CH–), 128.8–145.8 (Ar–C), 153.2 (–CCH_3), 155.5 (–NHCONH–), 157.4 (–CONH), 165.7 (–CO of imidazole), 182.4 (–C–SH); LCMS (*m/z*): 478 $(M)^+$; Anal. calcd. for $C_{22}H_{18}N_6O_5S$: C-55.22, H-3.79, N-17.56; Found: C-55.69, H-4.68, N-17.89 %.

*N-(2-mercapto-4-(4-nitrobenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5i**)* Dark yellow solid, yield 64 %; m.p.: 268–270 °C; IR (KBr) ν_{max}/cm^{-1}: 3467, 3356 (NH), 2978 (C–H, aromatic), 1559 (–C=N), 1530 (C=C), 1458, 1353 (NO_2), 1734 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.14 (s, 1H, –SH), 2.46 (s, 3H, –CH_3), 5.35 (s, 1H, –CH of pyrimidine), 6.26 (s, 1H, –NHCPh), 6.34 (s, 1H, –CH =), 7.28–8.04 (m, 9H, Ar–H), 7.39 (s, 1H, –CONH), 7.59 (s, 1H, –$NHCCH_3$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.5 (–CH_3), 53.3 (–CH of pyrimidine), 102.7 (>C<), 124.8 (2) (>CH–C–NO_2), 125.7 (>C=CH), 125.9 (>C=CH–), 128.7–146.9 (Ar–C), 153.5 (–CCH_3), 155.7 (–NHCONH–), 157.2 (–CONH), 165.4 (–CO of imidazole), 183.4 (–C–SH); LCMS (*m/z*): 478 $(M)^+$; Anal. calcd. for $C_{22}H_{18}N_6O_5S$: C-55.22, H-3.79, N-17.56; Found: C-55.70, H-3.77, N-17.60 %.

*N-(4-(2,6-dichlorobenzylidene)-2-mercapto-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5j**)* Light brown solid, yield 63 %; m.p.: 189–191 °C; IR (KBr) ν_{max}/cm^{-1}: 3439, 3346 (NH), 3067 (C–H, aromatic), 1532 (–C=N), 1534 (C=C), 1735 (C=O), 734 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.04 (s, 1H, –SH), 2.28 (s, 3H, –CH_3), 5.58 (s, 1H, –CH of pyrimidine), 6.11 (s, 1H, –NHCPh), 6.24 (s, 1H, –CH =),6.89 (s, 1H, –CONH),

7.09–7.28 (m, 8H, Ar–H), 7.38 (s, 1H, –NHCCH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 17.3 (–CH$_3$), 53.2 (–CH of pyrimidine), 102.7 (>C<), 120.3 (–CH=), 128.2–140.4 (Ar–C), 132.5 (C–Cl), 142.5 (>C=CH–), 153.5 (–CCH$_3$), 155.7 (–NHCONH–), 158.7 (–CONH), 165.5 (–CO of imidazole), 183.4 (–C–SH); LCMS (*m/z*): 501 (M)$^+$; Anal. calcd. for $C_{22}H_{17}Cl_2N_5O_3S$: C-52.60, H-3.41, N-13.94; Found: C-52.71, H-3.79, N-13.01 %.

*N-(2-mercapto-4-(2-methoxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5k**)* Light gray solid, yield 67 %; m.p.: 223–225 °C; IR (KBr) ν_{max}/cm^{-1}: 3473, 3345 (NH), 2882, 3017 (C–H, aromatic, OCH$_3$), 1543 (–C=N), 1544 (C=C), 1734 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.49 (s, 3H, –CH$_3$), 2.37 (s, 1H, –SH), 3.74 (s, 3H, –OCH$_3$), 5.39 (s, 1H, –CH of pyrimidine), 6.19 (s, 1H, –NHCPh), 6.28 (s, 1H, –CH =), 6.97–7.49 (m, 9H, Ar–H), 7.55 (s, 1H, –NHCCH$_3$), 7.65 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 16.8 (–CH$_3$), 53.7 (–CH of pyrimidine), 57.4 (–OCH$_3$), 103.4 (>C<), 115.7–142.9 (Ar–C), 125.3 (>C=CH), 125.8 (>C=CH–), 153.9 (–CCH$_3$), 155.4 (–NHCONH–), 157.9 (–CONH), 160.4 (>C–OCH$_3$), 165.9 (–CO of imidazole), 182.3 (–C–SH); LCMS (*m/z*): 463 (M)$^+$; Anal. calcd. for $C_{23}H_{21}N_5O_4S$: C-59.60, H-4.57, N-15.11; Found: C-59.67, H-4.53, N-15.03 %.

*N-(2-mercapto-4-(4-methoxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**5l**)* Light orange solid, yield 70 %; m.p.: 278–280 °C; IR (KBr) ν_{max}/cm^{-1}: 3464, 3383 (NH), 2880, 3023 (C–H, aromatic, OCH$_3$), 1567 (–C=N), 1556 (C=C), 1725 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, –CH$_3$), 2.43 (s, 1H, –SH), 3.82 (s, 3H, –OCH$_3$), 5.45 (s, 1H, –CH of pyrimidine), 6.24 (s, 1H, –NHCPh), 6.34 (s, 1H, –CH =), 7.12–7.57 (m, 9H, Ar–H), 7.67 (s, 1H, –NHCCH$_3$), 7.74 (s, 1H, –CONH); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 17.4 (–CH$_3$), 53.3 (–CH of pyrimidine), 58.3 (–OCH$_3$), 103.7 (>C<), 114.8–140.2 (Ar–C), 124.9 (>C=CH), 125.4 (>C=CH–), 153.5 (–CCH$_3$), 155.7 (–NHCONH–), 157.4 (–CONH), 161.2 (>C–OCH$_3$), 165.3 (–CO of imidazole), 182.7 (–C–SH); LCMS (*m/z*): 463 (M)$^+$; Anal. calcd. for $C_{23}H_{21}N_5O_4S$: C-59.60, H-4.57, N-15.11; Found: C-59.94, H-4.01, N-15.23 %.

Conclusion

A very unique and efficient synthesis of new functionalized pyrimidine-based imidazole derivatives is reported with very significant and potent antimicrobial activity. From Table 1, we can presume that the targeted compounds showed potent antibacterial activity as compared to antifungal activity. Structure activity correlation of the obtained results showed that the Knoevenagel adduct installation on imidazolinone ring system with electron withdrawing fluoro and dichloro groups as a substituent increases antibacterial as well as antifungal activities. Efforts are currently being taken up to optimize the lead structure and results of which will be the basis of our future research endeavor. The major advantages of this method are simple experimental and work-up procedures, small amount of catalyst, short reaction time, and high yields. Hence, this study has widened the scope of developing easy method to synthesize functionalized pyrimidine-based imidazole derivatives as promising antimicrobial agents.

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