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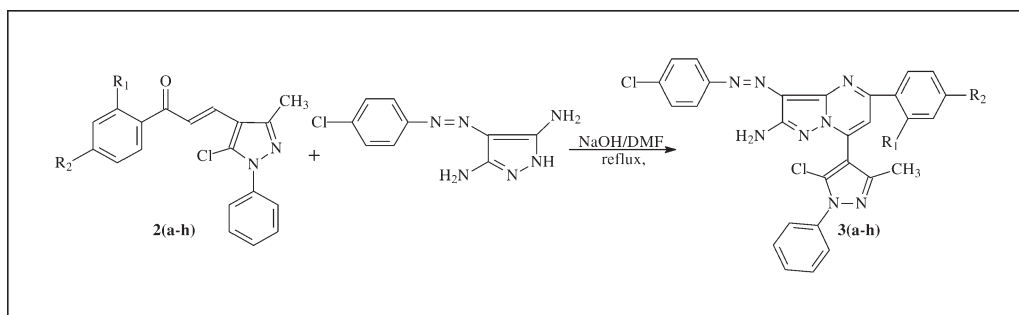
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A novel series of pyrazolo [1,5-a] pyrimidines were synthesized by the condensation of substituted chalcones with 5-amino pyrazole in presence of dimethyl formamide. All the synthesized products were characterized by the spectral analysis. Further, all newly synthesized compounds were screened for their antimicrobial activity. Most of the compounds showed potent activity.

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INTRODUCTION

Pyrazole nucleus has wide applications in medicinal chemistry. The ring system plays an important role in many biological processes, and many therapeutic agents contain pyrazole moiety. Several pyrazoles with antimicrobial, antiviral, and anticancer properties have been reported [1]. Certain alkyl pyrazoles have shown significant antiallergic, anti-inflammatory, and antiarthritic properties [2,3]. Many pyrazole-fused heterocyclic compounds have been to exhibit biological activity and widely used studied in pesticide and medicine [4–6]. Pyrazolopyrimidines are of considerable chemical and pharmacological importance as purine analogues [7,8], and have antitumor, antileukemic activities. Pyrazolo [1,5-a] pyrimidines useful properties, as antimetabolites in purine biochemical reactions [9–11]. These interesting biological activities reported for pyrazolopyrimidines have stimulated chemists to develop new class of these compounds.

RESULTS AND DISCUSSION

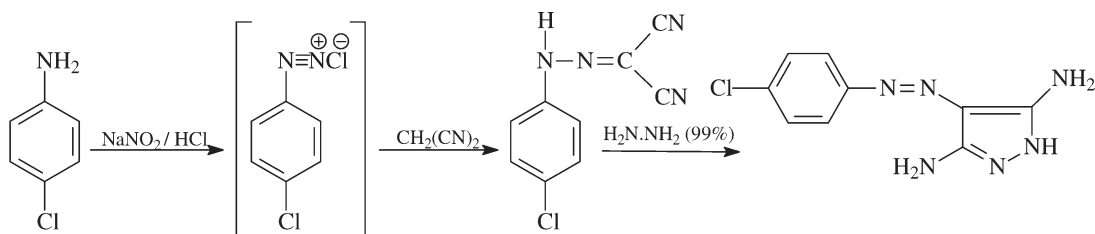
In continuation of our work on the synthesis of some new bioactive heterocyclic compounds [12–15], herein we report a new series of pyrazolo [1,5-a] pyrimidines by the condensation of chalcones with the 5-amino pyrazole in dimethyl formamide (DMF).

The starting 5-amino pyrazole was prepared in two steps from the corresponding amine by the diazotization and then treatment with malononitrile followed by reaction with hydrazine hydrate [16] (Scheme 1), while the novel α,β -unsaturated carbonyl compounds **2(a–h)** were prepared in the presence of base by conventional Claisen–Schmidt condensation of substituted acetophenones and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde (Scheme 2). Finally, the synthesis of pyrazolo [1,5-a] pyrimidines **3(a–h)** were attempted by the reacting 5-amino pyrazole with α,β -unsaturated carbonyl compounds (chalcones) using NaOH in presence of DMF as reaction solvent (Scheme 3).

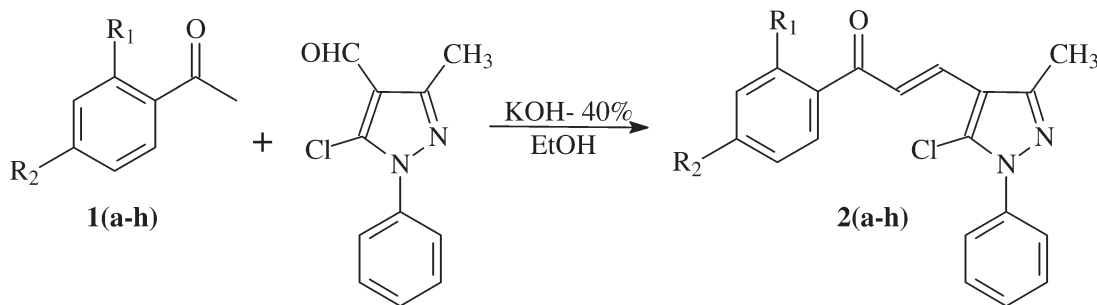
The formation of products were assumed to proceed through the Micheal-type addition of the ring nitrogen in 5-amino pyrazole (which is more active) to the activated double bond followed by intramolecular cyclization [17,18] with the elimination of water and dehydrogenation. The structures of compounds were appropriately established by the spectroscopic and analytical methods.

The results of the antimicrobial screening data are given in Table 1. In comparison with reference drugs, compounds **3a**, **3b**, and **3c** showed effective activity against all the tested microbes. Compounds **3a** and **3b** showed near to par activity against *Bacillus subtilis*. Only the compound **3a** was showed potent activity against *Escherichia coli* than standard penicillin drug.

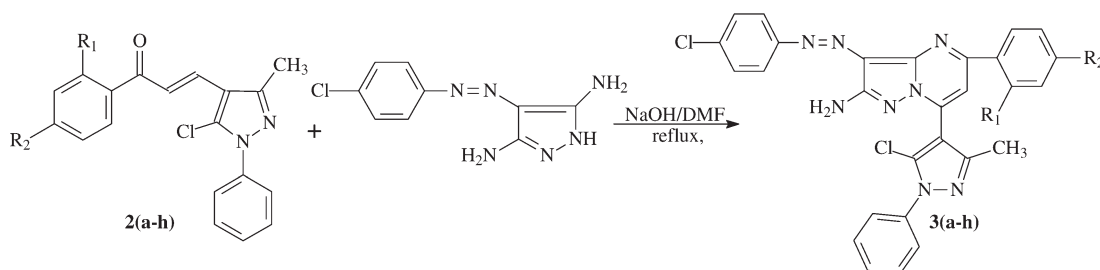
Scheme 1. Synthesis of 5-amino pyrazole.



Scheme 2. Synthesis of chalcones.



Scheme 3. Synthesis of pyrazolo [1,5-a] pyrimidines.



Compound **3b** showed stronger activity against *Aspergillus flavus* than reference Nystatin drug. On the other hand, compounds **3(d-h)** displayed moderate antimicrobial activity.

Table 1

Antimicrobial activity of synthesized compounds **3(a-h)**.

Product	A	B	C	D
3a	25	27	17	15
3b	22	26	16	18
3c	22	27	16	15
3d	18	15	14	12
3e	20	18	11	10
3f	18	21	12	11
3g	14	16	10	8
3h	16	20	12	15
Reference1	24	28	NA	NA
Reference2	NA	NA	18	16

Zone of inhibitions are expressed in mm.

A = *Escherichia coli*, B = *Bacillus subtilis*, C = *Fusarium moniliformae*, D = *Aspergillus flavus*, Reference 1 = Penicillin, Reference 2 = Nystatin, NA = Not Applicable.

As far as the antimicrobial results are concerned only the three compounds displayed very good activity. Pyrazolo [1,5-a] pyrimidines carrying *p*-chloro phenyl, *p*-hydroxy phenyl, and *p*-methoxy phenyl at C₅-position emerged as active in both antibacterial and antifungal screening. The substitution of *o*-hydroxy phenyl may increase the antimicrobial activity against various pathogens. When we compared the activity of substituted compounds with a nonsubstituted compound (**3g**), the substituted compounds showed higher activity.

CONCLUSIONS

In summary, we have designed and synthesized some novel pyrazolo [1,5-a] pyrimidines by the condensation of substituted chalcones with 5-amino pyrazole in presence of a base (solid sodium hydroxide) in dimethylformamide. The preliminary *in vitro* antimicrobial screening of this series revealed that compounds **3a**, **3b**, and **3c** showed potent activity when compared with standard drug. Therefore, the present study is useful drugs in

medicinal investigation against bacterial and fungal diseases.

EXPERIMENTAL

Melting points were uncorrected and determined in an open capillary tube. IR spectra were recorded on FTIR Shimadzu spectrometer. ^1H NMR spectra were recorded in DMSO- d_6 on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

General procedure for the synthesis of chalcone derivatives 2(a-h). A mixture of substituted acetophenone **1** (1 mmol), 5-chloro-3-methyl-1-phenyl-1H-pyrazole-4-carbaldehyde (1 mmol) and NaOH (2 mmol) were dissolved in ethanol (20 mL) solution. The reaction mixture was heated for 2 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were poured in ice cold water and then acidified by dil. HCl. The solid obtained was filtered and washed with cold water. Then crude product was crystallized from acetic acid to give the corresponding product **2**.

1-(4-chloro-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2a). Color, Dark yellow; Yield, 81%; IR (KBr): 1648 ($>\text{C}=\text{O}$), 1598 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.36 (s, 3H, CH_3), δ 7.05–8.22 (m, 11H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 357 (M^+), 359 ($\text{M}+2$), 361 ($\text{M}+4$); Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OCl}_2$: C, 63.88; H, 3.95; N, 7.84%. Found: C, 63.96; H, 3.83; N, 7.98%.

1-(4-hydroxy-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2b). Color, Yellow; Yield, 78%; IR (KBr): 1652 ($>\text{C}=\text{O}$), 1608 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.31 (s, 3H, CH_3), δ 5.58 (s, 1H, OH), δ 7.11–8.29 (m, 11H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 338 (M^+), 340 ($\text{M}+2$); Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: C, 67.36; H, 4.46; N, 8.27%. Found: C, 67.48; H, 4.35; N, 8.36%.

1-(4-methoxy-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2c). Color, Yellow; Yield, 80%; IR (KBr): 1651 ($>\text{C}=\text{O}$), 1602 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.34 (s, 3H, CH_3), δ 3.32 (s, 3H, OCH_3), δ 7.08–8.21 (m, 11H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 352 (M^+), 354 ($\text{M}+2$); Anal. Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2\text{Cl}$: C, 68.09; H, 4.86; N, 7.94%. Found: C, 68.02; H, 4.97; N, 7.82%.

1-(4-fluoro-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2d). Color, Yellow; Yield, 76%; IR (KBr): 1648 ($>\text{C}=\text{O}$), 1615 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.36 (s, 3H, CH_3), δ 7.12–8.26 (m, 11H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 340 (M^+), 342 ($\text{M}+2$); Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OFCl}$: C, 69.97; H, 4.14; N, 8.22%. Found: C, 66.91; H, 4.27; N, 8.35%.

1-(4-nitro-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2e). Color, Reddish yellow; Yield, 75%; IR (KBr): 1646 ($>\text{C}=\text{O}$), 1599 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.31 (s, 3H, CH_3), δ 7.06–8.21 (m, 11H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 368 (M^+), 370 ($\text{M}+2$); Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_3\text{O}_3\text{Cl}$: C, 61.71; H, 4.38; N, 11.63%. Found: C, 61.84; H, 4.31; N, 11.72%.

1-(4-bromo-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2f). Color, Yellow; Yield, 78%; IR (KBr): 1652 ($>\text{C}=\text{O}$), 1605 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ

Table 2

Yields and physical data of synthesized products **3(a-h)**.

Entry	Product	R ₁	R ₂	Time (h)	Yield (%)	M.P. (°C)
1	3a	H	Cl	4	72	173–175
2	3b	H	OH	4	68	210–212
3	3c	H	OCH_3	4	70	188–190
4	3d	H	F	5	68	166–168
5	3e	H	NO_2	5	65	225–227
6	3f	H	Br	4	60	194–196
7	3g	H	H	5	65	152–154
8	3h	OH	H	5	66	178–180

2.36 (s, 3H, CH_3), δ 7.10–8.29 (m, 11H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 400 (M^+), 402 ($\text{M}+2$), 404 ($\text{M}+4$); Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{OClBr}$: C, 56.81; H, 3.51; N, 6.97%. Found: C, 56.72; H, 3.62; N, 6.91%.

1-(phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2g). Color, Pale yellow; Yield, 76%; IR (KBr): 1650 ($>\text{C}=\text{O}$), 1595 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.32 (s, 3H, CH_3), δ 7.06–8.28 (m, 12H, Ar-H + $\text{CH}=\text{CH}$) ppm; M.S. (m/z): 322 (M^+), 324 ($\text{M}+2$); Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{OCl}$: C, 70.72; H, 4.68; N, 8.68%. Found: C, 70.84; H, 4.56; N, 8.75%.

1-(2-hydroxy-phenyl)-3-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-propenone (2h). Color, Yellow; Yield, 78%; IR (KBr): 1652 ($>\text{C}=\text{O}$), 1606 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.36 (s, 3H, CH_3), δ 7.05–8.22 (m, 11H, Ar-H + $\text{CH}=\text{CH}$), δ 10.82 (s, 1H, OH) ppm; M.S. (m/z): 338 (M^+), 340 ($\text{M}+2$); Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_2\text{Cl}$: C, 67.36; H, 4.46; N, 8.27%. Found: C, 67.48; H, 4.52; N, 8.18%.

Typical procedure for the synthesis of pyrazolo [1,5-a] pyrimidines 3(a-h). A mixture of **2a** (1 mmol), 5-amino pyrazole (1 mmol), and 1–2 pellets of NaOH were dissolved in DMF (15 mL). The reaction mixture was refluxed for the period as shown in Table 2. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with diethyl ether (2 \times 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , and the solvent was evaporated under reduced pressure. The crude product was recrystallized from aqueous acetic acid to give the product **3a**. Similarly, other analogues of this were synthesized by using the same procedure.

2-Amino-3-(4-chloro-phenylazo)-5-(4-chloro-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-pyrazolo [1,5-a] pyrimidine (3a). Color, Brown; IR (KBr): 3256 ($-\text{NH}_2$), 1616 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.26 (s, 3H, CH_3), δ 5.21 (bs, 2H, NH_2), δ 7.12–8.28 (m, 13H, Ar-H), δ 8.34 (s, 1H, 6H-of pyrimidine) ppm; ^{13}C NMR (DMSO- d_6): δ 10, 101, 112, 118 (2 \times C), 120, 121 (2 \times C), 124, 126, 127 (2 \times C), 128 (2 \times C), 129 (2 \times C), 130 (2 \times C), 131, 132, 133, 135, 136, 138, 151, 158, 163, 166 ppm; M.S. (m/z): 573 (M^+), 575 ($\text{M}+2$), 577 ($\text{M}+4$), 579 ($\text{M}+6$); Anal. Calcd for $\text{C}_{28}\text{H}_{19}\text{N}_8\text{Cl}_3$: C, 58.60; H, 3.34; N, 19.53%. Found: C, 58.56; H, 3.42; N, 19.64%.

2-Amino-3-(4-chloro-phenylazo)-5-(4-hydroxy-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-pyrazolo [1,5-a] pyrimidine (3b). Color, Brown; IR (KBr): 3251 ($-\text{NH}_2$), 1618 ($-\text{C}=\text{N}$); ^1H NMR (DMSO- d_6): δ 2.29 (s, 3H, CH_3), δ 5.25

(bs, 2H, NH₂), δ 5.68 (s, 1H, OH), δ 7.08–8.21 (m, 13H, Ar-H), δ 8.32 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m/z*): 555 (M⁺), 557 (M+2), 559 (M+4); Anal. Calcd for C₂₈H₂₀N₈OCl₂: C, 60.55; H, 3.63; N, 20.17%. Found: C, 60.42; H, 3.71; N, 20.11%.

2-Amino-3-(4-chloro-phenylazo)-5-(4-methoxy-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3c). Color, Dark brown; IR (KBr): 3322 (–NH₂), 1616 (–C=N); ¹H NMR (DMSO-*d*₆): δ 2.26 (s, 3H, CH₃), δ 5.28 (bs, 2H, NH₂), δ 3.38 (s, 1H, OH), δ 7.05–8.25 (m, 13H, Ar-H), δ 8.38 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m/z*): 569 (M⁺), 571 (M+2), 573 (M+4); Anal. Calcd for C₂₉H₂₂N₈OCl₂: C, 61.17; H, 3.89; N, 19.68%. Found: C, 61.31; H, 3.76; N, 19.76%.

2-Amino-3-(4-chloro-phenylazo)-5-(4-fluoro-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3d). Color, Brown; IR (KBr): 3286 (–NH₂), 1618 (–C=N); ¹H NMR (DMSO-*d*₆): δ 2.21 (s, 3H, CH₃), δ 5.32 (bs, 2H, NH₂), δ 7.11–8.28 (m, 13H, Ar-H), δ 8.32 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m/z*): 557 (M⁺), 559 (M+2), 561 (M+4); Anal. Calcd for C₂₈H₁₉N₈FCl₂: C, 60.33; H, 3.44; N, 20.10%. Found: C, 60.42; H, 3.38; N, 20.24%.

2-Amino-3-(4-chloro-phenylazo)-5-(4-nitro-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3e). Color, Brown; IR (KBr): 3318 (–NH₂), 1617 (–C=N); ¹H NMR (DMSO-*d*₆): δ 2.26 (s, 3H, CH₃), δ 5.25 (bs, 2H, NH₂), δ 7.15–8.31 (m, 13H, Ar-H), δ 8.41 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m/z*): 584 (M⁺), 586 (M+2), 588 (M+4); Anal. Calcd for C₂₈H₁₉N₈O₂Cl₂: C, 56.16; H, 3.25; N, 21.57%. Found: C, 56.28; H, 3.18; N, 21.66%.

2-Amino-3-(4-chloro-phenylazo)-5-(4-bromo-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3f). Color, Reddish brown; IR (KBr): 3338 (–NH₂), 1615 (–C=N); ¹H NMR (DMSO-*d*₆): δ 2.24 (s, 3H, CH₃), δ 5.18 (bs, 2H, NH₂), δ 7.11–8.26 (m, 13H, Ar-H), δ 8.35 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m/z*): 618 (M⁺), 620 (M+2), 622 (M+4), 624 (M+6); Anal. Calcd for C₂₈H₁₉N₈Cl₂Br: C, 54.39; H, 3.10; N, 18.12%. Found: C, 54.32; H, 3.21; N, 18.23%.

2-Amino-3-(4-chloro-phenylazo)-5-(phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3g). Color, Brown; IR (KBr): 3352 (–NH₂), 1618 (–C=N); ¹H NMR (DMSO-*d*₆): δ 2.28 (s, 3H, CH₃), δ 5.28 (bs, 2H, NH₂), δ 7.05–8.21 (m, 14H, Ar-H), δ 8.31 (s, 1H, 6H-of pyrimidine) ppm; M.S. (*m/z*): 539 (M⁺), 541 (M+2), 543 (M+4); Anal. Calcd for C₂₈H₂₀N₈Cl₂: C, 62.35; H, 3.74; N, 20.77%. Found: C, 62.46; H, 3.68; N, 20.66%.

2-Amino-3-(4-chloro-phenylazo)-5-(4-hydroxy-phenyl)-7-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4yl)-pyrazolo [1,5-a] pyrimidine (3h). Color, Brown; IR (KBr): 3238 (–NH₂), 1616 (–C=N); ¹H NMR (DMSO-*d*₆): δ 2.21 (s, 3H, CH₃), δ 5.22 (bs, 2H, NH₂), δ 7.11–8.28 (m, 13H, Ar-H), δ 8.38 (s, 1H, 6H-of pyrimidine), δ 11.56 (s, 1H, OH) ppm; M.S. (*m/z*): 555 (M⁺), 557 (M+2), 559 (M+4); Anal. Calcd for C₂₈H₂₀N₈OCl₂: C, 60.55; H, 3.63; N, 20.17%. Found: C, 60.62; H, 3.68; N, 20.24%.

Antimicrobial activity. The antimicrobial activities of the synthesized compounds **3(a–h)** were determined by agar well diffusion method [19]. The compounds were evaluated for antibacterial activity against *Escherichia coli* (MTCC 2939)

and *Bacillus subtilis* (MTCC 1789). The antifungal activity was evaluated against *Fusarium moniliformae* (MTCC 156) and *Aspergillus flavus* (MTCC 2501) were procured from Institute of Microbial technology (IMTech), Chandigarh, India. The antibiotic penicillin (25 µg/mL) and nystatin (25 µg/mL) was used as reference drug for antibacterial and antifungal activity, respectively. Dimethyl sulphoxide (1%, DMSO) was used a control with out compound.

The culture strains of bacteria were maintained on nutrient agar slant at 37 ± 0.5°C for 24 h. The antibacterial activity was evaluated using nutrient agar plate seeded with 0.1 mL of respective bacterial culture strain suspension prepared in sterile saline (0.85%) of 10⁵ CFU/mL dilutions. The wells of 6 mm diameter were filled with 0.1 mL of compound solution at fixed concentration 25 µg/mL separately for each bacterial strain. All the plates were incubated at 37 ± 0.5°C for 24 h. Zone of inhibition of compounds in mm were noted.

For antifungal activity, all the culture strains of fungi maintained on potato dextrose agar (PDA) slant at 27 ± 0.2°C for 24–48 h, until sporulation. Spore of strains were transferred into 5 mL of sterile distilled water containing 1% Tween-80 (to suspend the spore properly). The spores were counted by haemocytometer (10⁶ CFU/mL). Sterile PDA plate was prepared containing 2% agar; 0.1 mL of each fungal spore suspension was spread on each plate and incubated at 27 ± 0.2°C for 12 h. After incubation well prepared using sterile cork borer and each agar well was filled with 0.1 mL of compound solution at fixed concentration 25 µg/mL. The plates were kept in refrigerator for 20 min for diffusion and then incubated at 27 ± 0.2°C for 24–28 h. After incubation, zone of inhibition of compounds were measured in mm along with standard.

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