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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization and in vitro antimicrobial evaluation of some novel hydrazone derivatives bearing pyrimidinyl and pyrazolyl moieties as a promising heterocycles

Raj Kamal · Vipan Kumar · Vikas Bhardwaj · Vikas Kumar · Kamal Rai Aneja

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Abstract In the present investigation, ten new 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3a–j**) having pyrimidinyl and pyrazolyl moieties were synthesized. Structures of all compounds were confirmed by their spectral and elemental data. Most of the tested compounds were found to be significantly more effective against bacterial strains *Staphylococcus aureus, Bacillus subtilis* and *Pseudomonas aeruginosa* than the reference drug ciprofloxacin. All the newly synthesized compounds were found to be more potent antifungal agents than reference drug against *Candida albicans,* whereas except **3e** all other compounds also shown good activity against *Saccharomyces cerevisiae*.

Keywords Hydrazones · Pyrimidine · Pyrazole · Antimicrobial activity · Antibacterial activity · Antifungal activity

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Introduction

Hydrazones possess an azomethine –NHN=CH group which are considered as derivatives of aldehydes and ketones in which the oxygen atom has been replaced by the $=NNH_2$ group. The literature studies on hydrazones have shown that these derivatives possess a wide variety of biological activities such as anticonvulsant (Ragavendran *et al*., 2007), antioxidant (Abdel-Wahab *et al*., 2011), antidepressant (De-Oliveira *et al*., 2011), analgesic (Gokce *et al*., 2009), anti-inflammatory (Gokce *et al*., 2009), antiplatelet (Verma *et al*., 2014), antimalarial (Melnyk *et al*., 2006), antimicrobial (Padmini *et al*., 2013; Abdel-Wahab *et al*., 2011), antimycobacterial (Sriram *et al*., 2005), anticancer (Al-Said *et al*., 2011; Altintop *et al*., 2012), vasodilator (Rollas and Kucukguzel, 2007; Singh and Raghav, 2011), antiviral (El-Sabbagh and Rady, 2009), anti-HIV (Vicini *et al*., 2009), antitumor (Cui *et al*., 2010), and antihypertensive (Bakale *et al*., 2014) activities. The metal complexes of hydrazones have potential applications, such as catalysts (Pouralimardan *et al*., 2007), and luminescent probes (Basu *et al*., 2007).

Pyrimidine ring is a prominent scaffold in the area of drug discovery. Pyrimidine and its derivatives make a core structure of number of well-established marketed drugs such as pyrantelembonate, flucytosine, broxuridine, 5-iododeoxyuridine, tetroxoprim, metioprim, trimethoprim, fluorouracil, azathioprine, cytarabine, uramustine, gemcitabine, amicetin, bleomycin, capromycin, buspirone, prazocin, acetiamine and retrovir. Indeed, pyrimidine based derivative have shown diverse biological and pharmacological applications such as antimicrobial (Gupta *et al*., 2013), antioxidant (El-Gazzar *et al*., 2009), antimalarial (Agarwal *et al*., 2005), anticancer (Xie *et al*., 2009), analgesic (El-Gazzar *et al*., 2009), anti-inflammatory (El-Gazzar *et al*., 2009),

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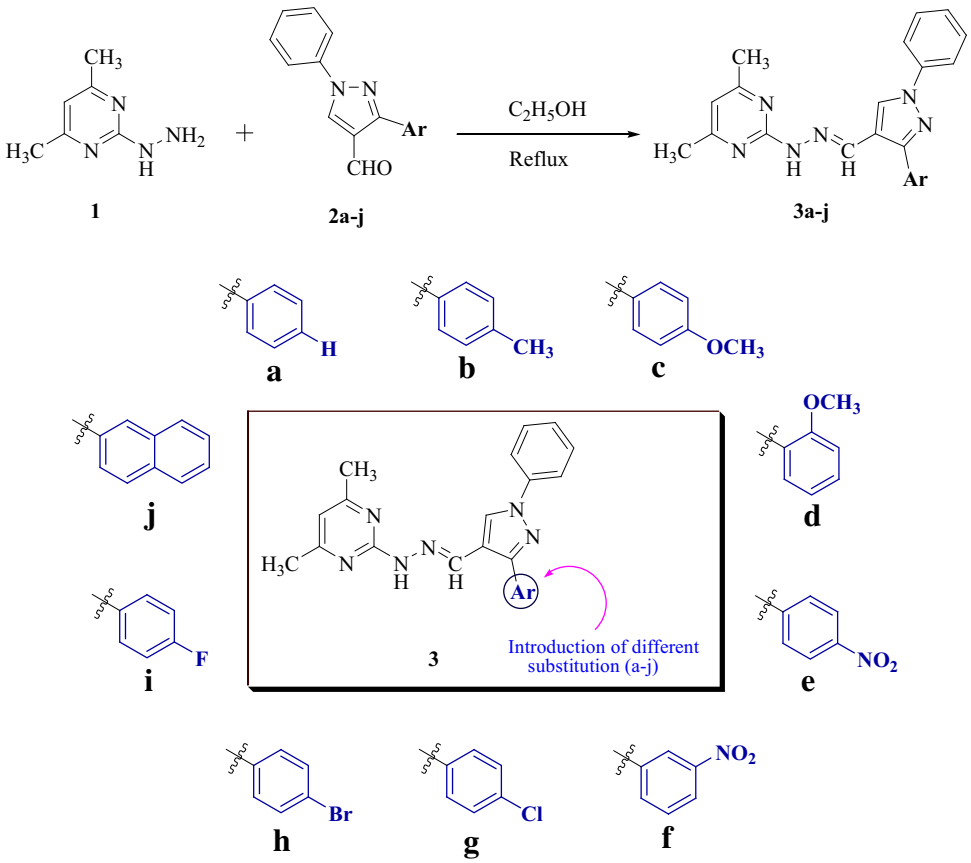

Scheme 1 Synthesis and structure of 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazines (**3a–j**)

anti-HIV-1 (Singh *et al.*, 2013), antitumor (Gangjee *et al.*, 2012), anti-depressive (Wang *et al.*, 2012), anticonvulsant (Wang *et al.*, 2012), anti-neoplastic (Patel *et al.*, 2012) and herbicides (Li *et al.*, 2006). Second, pyrazole structure also has occupied a significant position in the medical research due to wide spectrum of biological and pharmacological properties such as antibacterial (Perez-Fernandez *et al.*, 2014; Mert *et al.*, 2014), antidepressant (Abdel-Aziz *et al.*, 2009), antioxidant (Bandgar *et al.*, 2009; Padmaja *et al.*, 2011), antifungal (Mert *et al.*, 2014), anti-inflammatory (Alegaon *et al.*, 2014), antiviral (Ouyang *et al.*, 2008; Kelekci *et al.*, 2007), anticancer (Kumar *et al.*, 2013; Balbi *et al.*, 2011), hypoglycaemic (Bauer *et al.*, 1968), antipyretic (Pasin *et al.*, 2010), anthelmintic (Sharma and Jain, 2012) and selective enzyme inhibitory (Nayak *et al.*, 2013; Khloya *et al.*, 2014; El-Sayed *et al.*, 2011) activities. The pyrazole ring is present as the core in a variety of leading drugs such as celebrex, tartrazine, deracoxib, mepiprazole, sildenafil (viagra), lonazlac, rimonabant and difenamizole.

In view of all the above observations, this study is aimed to design and synthesize novel structural entities that incorporate pyrimidinyl, pyrazolyl and hydrazone moiety into a single molecular structure, and to evaluate their potential for antimicrobial activities. Consequently, prompted from the findings described above, we herein report the synthesis and antimicrobial evaluation of ten new 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazines (**3a–j**).

Results and discussion

Synthesis

Synthesis of all new 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethyl pyrimidin-2-yl)hydrazines (**3a–j**) was accomplished according to the general synthetic route as shown in Scheme 1. First, the starting material 1-(4,6-dimethylpyrimidin-2-yl)-hydrazine (**1**) was synthesized by the condensation of urea and acetylacetone. The condensed product was treated with phosphorus oxychloride for chlorination, followed by hydrazine monohydrate according to reported procedure (Kosolapoff and Roy, 1961). 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde derivatives (**2**) were synthesized by the *Vilsmeier–Haack* reaction of hydrazone of substituted acetophenone and phenyl hydrazine by reported procedure (Kira *et al.*, 1969). Finally, the required hydrazone analogues **3a–j** were easily accessible in high yields (88–96 %) (Table 1) simply by refluxing the 1-(4,6-dimethylpyrimidin-2-yl)-hydrazine

Table 1 Yield (%) and melting point (°C) of 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazines (**3a–j**)

Entry	Compound	Yield (%)	Melting point[a] (°C)
1	**3a**	94	232–234
2	**3b**	96	208–210
3	**3c**	91	224–226
4	**3d**	89	184–186
5	**3e**	96	234–236
6	**3f**	88	134–136
7	**3g**	93	220–222
8	**3h**	92	226–228
9	**3i**	88	242–244
10	**3j**	90	228–230

[a] Melting points are taken in open capillary may be incorrect

with appropriate 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde derivative **2a–j** in ethanol for 4–5 min.

All the newly synthesized hydrazones gave satisfactory analyses for the proposed structure, which were confirmed on the basis of their spectral (IR, ^{1}H NMR and ^{13}C NMR) and Elemental analytical data (Fig. 1). Melting points are given in Table 1. The IR spectra of compounds **3a–j** exhibited characteristic absorption band in the range 3,070–3,217 cm^{-1} due to NH stretching. The ^{1}H NMR spectra of compounds **3a–j** showed characteristic singlets due to C(5) proton of pyrazolyl group and C(5) proton of pyrimidinyl group, in the range of δ 8.65–9.01 ppm and δ 6.45–6.72 ppm, respectively. One more singlet corresponding to six protons is also appearing in the range of δ 2.30–2.39 ppm due to presence of two methyl substituents at C(4) and C(6) position of pyrimidinyl group. Two more singlets, one due to methylene proton (–N=C–H) and another due to exchangeable (N–H) proton also appeared in the ^{1}H NMR spectra of all the compounds in the range of δ 8.27–8.68 ppm and δ 7.66–7.95 ppm in $CDCl_3$, respectively. The value of exchangeable proton (N–H) has been shifted to δ 10.94–11.81 ppm if we used DMSO as solvent instead of $CDCl_3$. These two peaks show the presence of azomethine –NHN=CH moiety and hence gave the successful formation of desired product. All aromatic protons appeared in the expected region of δ 6.95–8.70 ppm. The structures of the compounds **3a–j** were further established by ^{13}C NMR spectrum, which showed characteristic signals for C=N in the range of δ 134.31–139.73 ppm. Elemental analysis is also in good agreement with the expected data.

Pharmocology

In vitro anti-bacterial activities

All ten newly synthesized hydrazones and a well-known commercially available antibiotic ciprofloxacin, as a reference drug, were subjected to in vitro for their anti-bacterial studies against two Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). These bacterial strains were chosen as they are the known pathogens of human body. All the tested compounds possessed variable but good antibacterial activity against both Gram-positive strains (*S. Aureus* and *B. subtilis*) and one Gram-negative strain, *P. aeruginosa*. However, none of the 10 derivatives depicted to have significant antibacterial effect on another Gram-negative bacterial strain i.e. *E. coli*. This is attributed to intrinsic resistance of the Gram-negative bacterial membrane which functions as a barrier and prevents penetration of the derivative molecules. The results for the antibacterial evaluation for all the tested compounds are summarized in Tables 2 and 3.

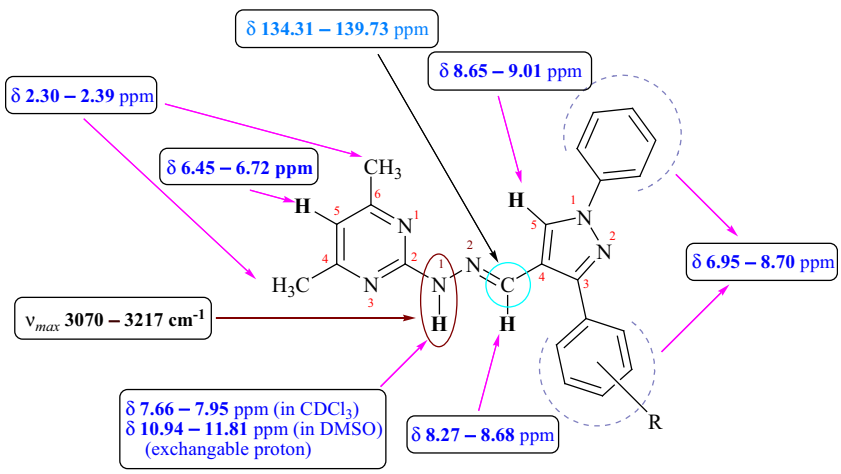

Fig. 1 Overview of spectral data for 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazines (**3a–j**)

Table 2 In vitro antibacterial activities of compounds **3a–j**

Compound[a]	Diameter of growth of inhibition zone (mm)[b]			
	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	22	22	10	20
3b	22	21	12	21
3c	23	23	10	**22**
3d	23	25	10	**22**
3e	17	15	–	18
3f	20	–	–	15
3g	21	15	–	20
3h	20	17	14	19
3i	**25**	14	–	18
3j	**27**	20	13	20
Ciprofloxacin	24	26.6	25	22

– no activity

[a] Concentration 4.0 mg/mL

[b] Values including diameter of the well (8 mm) are means of three replicates

Table 3 Minimum inhibitory concentration (μg/mL) of compounds **3a–j**

Compound	Gram-positive bacteria		Gram-negative bacteria	
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	25	25	nt	25
3b	25	25	nt	25
3c	25	25	nt	25
3d	25	12.5	nt	25
3e	50	nt	nt	50
3f	25	nt	nt	nt
3g	25	nt	nt	25
3h	25	50	nt	25
3i	12.5	nt	nt	50
3j	12.5	25	nt	25
Ciprofloxacin	6.25	6.25	6.25	12.5

nt not tested

On the basis of maximum inhibitory activity reported in Table 2 and Fig. 2, nine compounds, out of ten, exhibited good activity by showing effective zone of inhibition ranging from 20.0 to 27.0 mm against *B. subtilis*, whereas the zone of inhibition shown by ciprofloxacin is 24.0 mm. Compounds **3a**, **3b**, **3c**, **3d** and **3j** have shown almost good range of zone of inhibition from 20.0 to 25.0 mm against *S. aureus*, whereas the reference value is 26.6 mm in this case. All the compounds except **3f** showed good zone of inhibition ranging from 18.0 to 22.0 mm, whereas the zone of inhibition shown by ciprofloxacin was 22.0 mm against Gram-negative strain, *P. aeruginosa*.

From these findings, it was observed that compounds **3a**, **3b**, **3c** and **3d** were highly active against all of the evaluating bacterial strains except *E. coli* and compounds **3i** and **3j** were found to be more effective against *B. subtilis* even than the reference drug. Rest of the compounds also showed fair activity against all the bacterial strains except *E. coli.*

Compounds showing promising antibacterial activities were selected for Minimum inhibitory concentration (MIC) studies (Table 3; Fig. 3). All compounds possessed fairly good activity having MIC values of 12.5–50.0 μg/mL against all the tested bacteria strains except *E. coli*, whereas MIC value of standard drug for *B. subtilis, S. aureus and E. Coli* was 6.25 μg/mL and for *P. Aeruginosa* was 12.5 μg/mL. Out of compounds **3a–j**, compound **3i** and **3j** showed lowest MIC values 12.5 μg/mL against *B. subtilis* and compound **3d** showed lowest MIC value 12.5 μg/mL against *S. aureus.* Compounds **3d** and **3j** were found to be most active against all the bacteria strains except *E. Coli.*

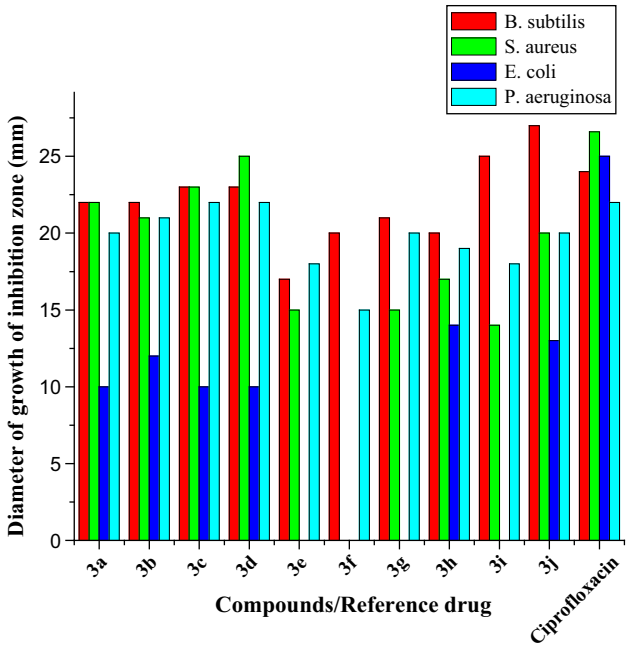

Fig. 2 Comparison of growth of inhibition of compounds **3a–j** and reference drug for antibacterial activity

Table 4 In vitro antifungal activities of compounds **3a–j**

Compound[a]	Diameter of growth of inhibition zone (mm)[b]	
	Candida albicans	*Saccharomyces cerevisiae*
3a	22	16
3b	**27**	15
3c	20	16
3d	24	18
3e	23	–
3f	20	15
3g	23	**19**
3h	21	16
3i	21	18
3j	**31**	15
Amphotericin-B	16.6	19.3

– no activity

[a] Concentration 4.0 mg/mL

[b] Values including diameter of the well (8 mm) are means of three replicates

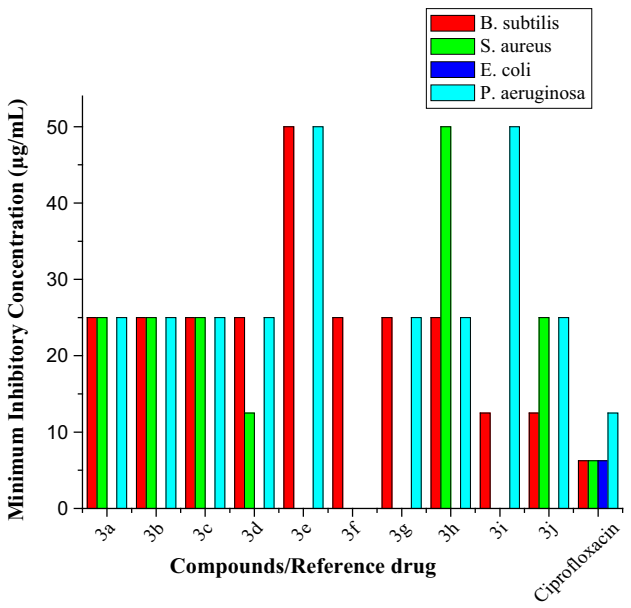

Fig. 3 Comparison of MIC of compounds **3a–j** and reference drug for antibacterial activity

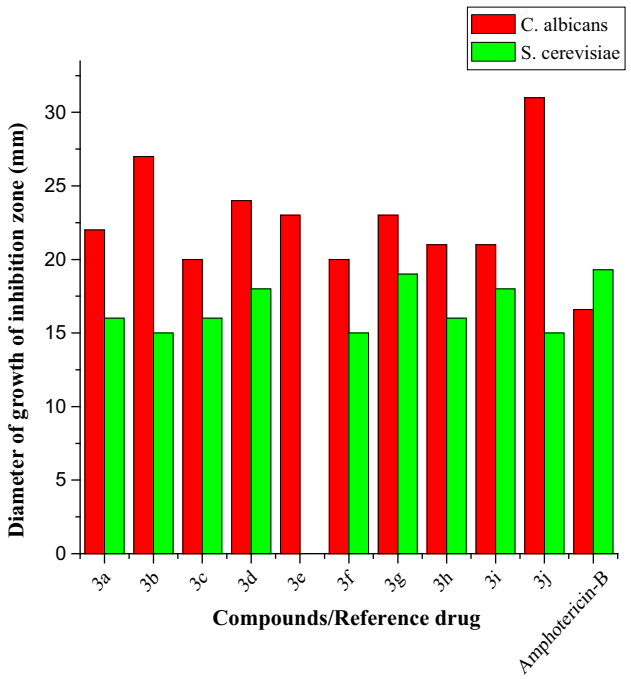

Fig. 4 Comparison of growth of inhibition of compounds **3a–j** and reference drug for antifungal activity

In vitro anti fungal activities

All ten hydrazone derivatives **3a–j** were also evaluated in vitro for their antifungal activity against two yeast, *Candida albicans* and *Saccharomyces cerevisiae*. Antifungal drug Amphotericin-B was used, as reference, for the comparison of activities shown by the compounds **3a–j**. All the tested compounds showed remarkable growth of inhibition zone against *C. albicans*, whereas except compound **3e**, other derivatives showed moderate growth of inhibition

Table 5 Minimum inhibitory concentration (μg/mL) of compounds **3a–j**

Compound	*Candida albicans*	*Saccharomyces cerevisiae*
3a	25	50
3b	**12.5**	nt
3c	25	50
3d	25	50
3e	25	nt
3f	25	nt
3g	25	50
3h	25	50
3i	25	50
3j	**6.25**	nt
Amphotericin-B	12.5	12.5

nt not tested

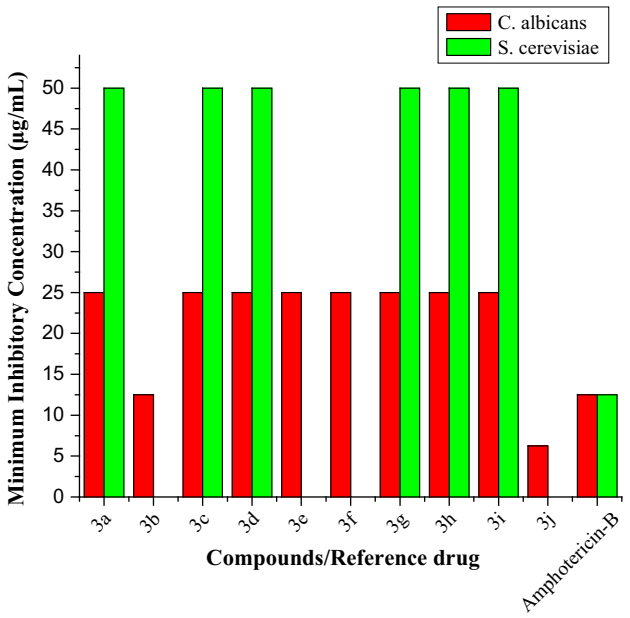

Fig. 5 Comparison of MIC of compounds **3a–j** and reference drug for antifungal activity

zone against *S. cerevisiae*. The results are summarized in Table 4 and Fig. 4.

After careful analysis of results, it was observed that compound **3b** and **3j** exhibited remarkable activity against *C. albicans* by showing zone of inhibition of 27 and 31.0 mm with a MIC value of 12.5 and 6.25 μg/mL, respectively, whereas the reference drug showed the zone of inhibition of 16.6 mm with MIC value 12.5 μg/mL. Other tested compounds showed good activities with MIC values of 6.25–25.0 μg/mL against *C. albicans* and fair activity against *S. cerevisiae* shown in Table 5 and Fig. 5.

Conclusion

We report herein the synthesis, structural elucidation and antimicrobial activities of ten novel 2-((3-aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethyl pyrimidin-2-yl)hydrazine (**3a–j**). The structures are fully supported by spectroscopic data and elemental analysis. Taking all the biological data into consideration, it can be concluded that all the tested compounds showed good activities against bacterial strains *S. aureus, B. subtilis* and *P. aeruginosa.* However, all the tested compounds were found to be almost ineffective against *E. coli*. Compounds **3i** and **3j** were found to be better inhibitors for the growth of *B. subtilis* than the reference drug ciprofloxacin. All the ten synthesized compounds were found to be more potent then reference antifungal drug, amphotericin-B, to inhibit the growth of *C. albicans*. Compound **3b** and **3j** were more effective antifungal compounds against *C. albicans*. Except compound **3e**, all tested compounds exhibited good activities against *S. cerevisiae*. It is hoped that these studies can have good effect in medicinal area to further efforts towards the development of novel and effective antimicrobial agents.

Experimental

Melting points were taken in open capillaries in an electrical apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II instrument at 400 MHz and 100 MHz, respectively. Elemental analyses were carried out in Euro vector EA 3000 instrument.

2-((3-Aryl-1-phenyl-1*H*-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3**)

General procedure

To the ethanolic solution of 1-(4,6-dimethylpyrimidin-2-yl), hydrazine (**1**, 0.01 mol) was added appropriate 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde derivative (**2**, 0.01 mol), and the solution was refluxed for 4–5 min. The solvent was evaporated in vacuo to half its volume and cooled to room temperature. The solid obtained was filtered and re-crystallized with ethanol to get the target compound **3**.

*2-((1,3-Diphenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)hydrazine (**3a**)* IR (ν_{max} cm^{-1}, KBr): 3,217 cm^{-1} (–NH str.); ^{1}H NMR (δ ppm, $CDCl_3$, 400 MHz): 8.79 (s, 1H, C(5)H-pyrazole), 8.68 (s, 1H, N=

C–H), 7.95 (s, 1H, N–H), 7.79–7.81 (m, 2H, Ar–H), 7.64–7.66 (m, 2H, Ar–H), 7.41–7.49 (m, 5H, Ar–H), 7.29–7.33 (t, 1H $J = 7.4$ Hz, Ar–H), 6.51 (s, 1H, C(5)–H-pyrimidine), 2.39 (s, 6H, CH_3); ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz): 168.29 (C-4, C-6-pyrimidine), 159.37 (C-2-pyrimidine), 152.43 (C-3-pyrazole), 139.63 (C=N), 135.47 (Ar), 132.44 (Ar), 129.50 (C-5-pyrazole), 128.72 (Ar), 128.58 (Ar), 128.49 (Ar), 126.86 (Ar), 126.41 (Ar), 119.13 (Ar), 116.83 (C-5-pyrimidine), 112.58 (C-4-pyrazole), 23.9 (CH_3); Anal. Calculated for $C_{22}H_{20}N_6$ (C, H, N): C 71.72, H 5.47, N 22.81; Found: C 71.57, H 5.47, N 22.60.

*2-((1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl)-hydrazine (**3b**)* IR (ν_{max} cm^{-1}, KBr): 3,183 cm^{-1} (–NH str.); ^1H NMR (δ ppm, $CDCl_3$, 400 MHz): 8.75 (s, 1H, C(5)H-pyrazole), 8.66 (s, 1H, N=C–H), 7.95 (s, 1H, N–H), 7.78–7.82 (m, 2H, Ar–H), 7.52–7.54 (d, 2H, $J = 8.0$ Hz, Ar–H), 7.44–7.48 (m, 2H, Ar–H), 7.25–7.32 (m, 3H, Ar–H), 6.50 (s, 1H, C(5)–H-pyrimidine), 2.41 (s, 3H, CH_3). 2.39 (s, 6H, CH_3); ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz): 168.30 (C-4, C-6-pyrimidine), 159.52 (C-2-pyrimidine), 152.51 (C-3-pyrazole), 139.70 (C=N), 138.38 (Ar), 135.56 (Ar), 129.58 (C-5-pyrazole), 129.49 (Ar), 129.42 (Ar), 128.47 (Ar), 126.78 (Ar), 126.29 (Ar), 119.12 (Ar), 116.76 (C-5-pyrimidine), 112.56 (C-4-pyrazole), 24.01 (CH_3), 21.35 (CH_3); Anal. Calculated for $C_{23}H_{22}N_6$ (C, H, N): C 72.23, H 5.80, N 21.97; Found: C 72.16, H 5.87, N 21.97.

*2-((3-(4-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3c**)* IR (ν_{max} cm^{-1}, KBr): 3,225 cm^{-1} (–NH str.); ^1H NMR (δ ppm, DMSO, 400 MHz): 11.81 (s, 1H, N–H), 9.01 (s, 1H, C(5)H-pyrazole), 8.35 (s, 1H, N=C–H), 7.92–7.94 (d, 2H, $J = 7.76$ Hz, Ar–H) 7.68–7.71 (d, 2H, $J = 8.7$ Hz, Ar–H), 7.50–7.54 (m, 2H, Ar–H), 7.25–7.32 (t, 1H, $J = 7.4$ Hz, Ar–H), 7.03–7.06 (d, 2H, $J = 8.7$ Hz, Ar–H), 6.72 (s, 1H, C(5)–H-pyrimidine), 3.85 (s, 3H, OCH_3), 2.43 (s, 6H, CH_3); ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz): 168.31 (C-4, C-6-pyrimidine), 159.94 (Ar), 159.49 (C-2-pyrimidine), 152.29 (C-3-pyrazole), 139.70 (C=N), 135.52 (Ar), 129.85 (C-5-pyrazole), 129.49 (Ar), 126.75 (Ar), 126.32 (Ar), 125.00 (Ar), 119.09 (Ar), 116.61 (Ar), 114.19 (C-5-pyrimidine), 112.59 (C-4-pyrazole), 55.40 (OCH_3), 24.01 (CH_3); Anal. Calculated for $C_{23}H_{22}N_6O$ (C, H, N, O): C 69.33, H 5.57, N 21.09, O 4.02; Found: C 69.18, H 5.98, N 20.92, O 3.92.

*2-((3-(2-Methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3d**)* IR (ν_{max} cm^{-1}, KBr): 3,172 cm^{-1} (–NH str.); ^1H NMR (δ ppm, $CDCl_3$, 400 MHz): 8.83 (s, 1H, C(5)H-pyrazole), 8.65 (s, 1H, N=C–H), 7.77–7.79 (m, 2H, Ar–H), 7.66 (s, 1H, N–H), 7.38–7.51 (m, 4H, Ar–H), 7.26–7.30 (m, 1H, Ar–H), 6.97–7.07 (m, 1H, Ar–H), 6.95–6.97 (d, 1H $J = 8.2$ Hz, Ar–H), 6.45 (s, 1H, C(5)–H-pyrimidine), 3.73 (s, 3H, OCH_3), 2.35 (s, 6H, CH_3). ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz): 168.20 (C-4, C-6-pyrimidine), 159.54 (C-2-pyrimidine), 156.88 (Ar), 150.20 (C-3-pyrazole), 139.73 (C=N), 136.95 (Ar), 131.68 (Ar), 130.27 (Ar), 129.40 (C-5-pyrazole), 126.61 (Ar), 125.38 (Ar), 121.43 (Ar) 120.99 (Ar), 119.04 (Ar), 118.38 (Ar), 112.27 (C-5-pyrimidine), 111.17 (C-4-pyrazole), 55.52 (OCH_3), 23.93 (CH_3); Anal. Calculated for $C_{23}H_{22}N_6O$ (C, H, N, O): C 69.33, H 5.57, N 21.09, O 4.02; Found: C 69.86, H 5.84, N 21.25, O 3.04.

*2-((3-(4-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3e**)* IR (ν_{max} cm^{-1}, KBr): 3,140 cm^{-1} (–NH str.); ^1H NMR (δ ppm, DMSO, 400 MHz): 11.12 (s, 1H, N–H), 8.83 (s, 1H, C(5)H-pyrazole), 8.34 (s, 1H, N=C–H), 8.31 (s, 4H, Ar–H), 7.93–7.95 (d, 2H, $J = 8.2$ Hz, Ar–H), 7.50–7.54 (t, 2H, $J = 7.6$ Hz, Ar–H), 7.34–7.38 (t, 1H, $J = 7.4$, Ar–H), 6.56 (s, 1H, C(5)–H-pyrimidine), 2.36 (s, 6H, CH_3); ^{13}C NMR (δ ppm, DMSO, 100 MHz): 167.13 (C-4, C-6-pyrimidine), 159.27 (C-2-pyrimidine), 153.19 (C-3-pyrazole), 148.10 (Ar), 146.79 (Ar), 138.97 (C=N), 138.85 (Ar), 133.85 (Ar), 129.30 (C-5-pyrazole), 129.21 (Ar), 128.13 (Ar), 126.80 (Ar), 123.21 (Ar), 118.53 (C-5-pyrimidine), 111.35 (C-4-pyrazole), 23.44 (CH_3); Anal. Calculated for $C_{22}H_{19}N_7O_2$ (C, H, N, O): C 63.91, H 4.63, N 23.72, O 7.74; Found: C 63.82, H 4.90, N 23.58, O 7.71.

*2-((3-(3-Nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3f**)* IR (ν_{max} cm^{-1}, KBr): 3,070 cm^{-1} (–NH str.); ^1H NMR (δ ppm, DMSO, 400 MHz): 11.04 (s, 1H, N–H), 8.92 (s, 1H, C(5)H-pyrazole), 8.69–8.70 (t, 1H, $J = 1.92$ Hz, Ar–H), 8.50–8.53 (m, 1H, Ar–H), 8.31 (s, 1H, N=C–H), 8.26–8.29 (m, 1H, Ar–H), 7.98–8.00 (m, 2H, Ar–H), 7.77–7.81 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.52–7.56 (t, 2H, $J = 7.8$ Hz, Ar–H), 7.35–7.39 (t, 1H, $J = 7.4$ Hz, Ar–H), 6.56 (s, 1H, C(5)–H-pyrimidine), 2.30 (s, 6H, CH_3); ^{13}C NMR (δ ppm, DMSO, 100 MHz): 167.13 (C-4, C-6-pyrimidine) 159.63 (C-2-pyrimidine), 148.09 (C-3-pyrazole), 147.84 (Ar), 138.91 (C=N), 134.88 (Ar), 134.22 (Ar), 133.38 (Ar), 129.78 (Ar), 129.45 (C-5-pyrazole), 128.36 (Ar), 126.85 (Ar), 122.73 (Ar), 118.58 (Ar), 118.12 (Ar), 113.05 (C-5-pyrimidine), 111.31 (C-4-pyrazole), 23.45 (CH_3); Anal. Calculated for $C_{22}H_{19}N_7O_2$ (C, H, N, O): C 63.91, H 4.63, N 23.72, O 7.74; Found: C 63.14, H 4.63, N 23.46, O 8.77.

*2-((3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3g**)* IR (ν_{max} cm^{-1}, KBr): 3,217 cm^{-1} (–NH str.); ^1H NMR (δ ppm, $CDCl_3$, 400 MHz): 8.65 (s, 1H, C(5)H-pyrazole),

8.44 (s, 1H, N=C–H), 7.93 (s, 1H, N–H), 7.80–7.83 (m, 2H, Ar–H), 7.64–7.67 (m, 2H, Ar–H), 7.44–7.52 (m, 4H, Ar–H), 7.33–7.37 (t, 1H, $J = 7.4$ Hz, Ar–H), 6.56 (s, 1H, C(5)–H-pyrimidine), 2.43 (s, 6H, CH_3); ^{13}C NMR (δ ppm, $CDCl_3$, 100 MHz; 163.10 (C-4, C-6-pyrimidine), 154.17 (C-2-pyrimidine), 145.93 (C-3-pyrazole), 134.31 (C=N), 129.40 (Ar), 125.77 (Ar), 124.59 (Ar), 124.31 (C-5-pyrazole), 123.69 (Ar), 121.79 (Ar), 121.42 (Ar), 118.98 (Ar), 113.92 (Ar), 111.64 (C-5-pyrimidine), 107.51 (C-4-pyrazole), 18.78 (CH_3); Anal. Calculated for $C_{22}H_{19}N_6Cl$ (C, H, N): C 65.59, H 4.75, N 20.86; Found: C 65.19, H 4.85, N 21.04.

*2-((3-(4-Bromophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3h**)* IR (ν_{max} cm^{-1}, KBr): 3,209 cm^{-1} (–NH str.); ^{1}H NMR (δ ppm, DMSO, 400 MHz): 10.94 (s, 1H, N–H), 8.76 (s, 1H, C(5)H-pyrazole), 8.28 (s, 1H, N=C–H), 7.92–7.94 (m, 2H, Ar–H), 7.83–7.86 (m, 2H, Ar–H), 7.62–7.65 (m, 2H, Ar–H), 7.48–7.52 (m, 2H, Ar–H), 7.31–7.35 (t, 1H, $J = 7.4$ Hz, Ar–H), 6.53 (s, 1H, C(5)–H-pyrimidine), 2.33 (s, 6H, CH_3). ^{13}C NMR (δ ppm, DMSO, 100 MHz): 167.06 (C-4, C-6-pyrimidine), 159.61 (C-2-pyrimidine), 149.45 (C-3-pyrazole), 139.02 (C=N), 134.04 (Ar), 131.54 (Ar), 131.17 (Ar), 130.16 (C-5-pyrazole), 129.27 (Ar), 126.94 (Ar), 126.49 (Ar), 121.65 (Ar), 118.41 (Ar), 117.77 (C-5-pyrimidine), 111.19 (C-4-pyrazole), 23.51 (CH_3); Anal. Calculated for $C_{22}H_{19}N_6Br$ (C, H, N): C 59.07, H 4.78, N 18.79; Found: C 59.24, H 4.90, N 18.22.

*2-((3-(4-Fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3i**)* IR (ν_{max} cm^{-1}, KBr): 3,209 cm^{-1} (–NH str.); ^{1}H NMR (δ ppm, DMSO, 400 MHz): 10.97 (s, 1H, N–H), 8.81 (s, 1H, C(5)H-pyrazole), 8.27 (s, 1H, N=C–H), 7.92–7.97 (m, 4H, Ar–H), 7.49–7.53 (m, 2H, Ar–H), 7.31–7.35 (t, 1H, $J = 7.4$ Hz, Ar–H), 7.25–7.29 (m, 2H, Ar–H), 6.55 (s, 1H, C(5)–H-pyrimidine), 2.33 (s, 6H, CH_3); ^{13}C NMR (δ ppm, DMSO, 100 MHz; 167.08 (C-4, C-6-pyrimidine), 162.16 (d, ^{3}J, 245 Hz) (Ar), 159.63 (C-2-pyrimidine), 149.70 (C-3-pyrazole), 139.07 (C=N), 134.18 (Ar), 130.39 (d, ^{1}J, 8 Hz) (Ar), 129.35 (C-5-pyrazole), 128.77 (Ar), 126.96 (Ar), 126.48 (Ar), 118.43 (Ar), 117.61 (C-5-pyrimidine), 115.17 (d, ^{2}J, 21 Hz) (Ar), 111.18 (C-4-pyrazole), 23.50 (CH_3); Anal. Calculated for $C_{22}H_{19}N_6F$ (C, H, N): C 68.38, H 4.96, N 21.75; Found: C 68.12, H 5.08, N 21.68.

*2-((3-(Naphthalen-3-yl)-1-phenyl-1H-pyrazol-4-yl)-methylene)-1-(4,6-dimethylpyrimidin-2-yl) hydrazine (**3j**)* IR (ν_{max} cm^{-1}, KBr): 3,148 cm^{-1} (–NH str.); ^{1}H NMR (δ ppm, DMSO, 400 MHz): 11.12 (s, 1H, N–H), 8.90 (s, 1H, C(5)H-pyrazole), 8.44 (s, 1H, Ar–H), 8.42 (s, 1H, N=C–H), 7.95–8.07 (m, 6H, Ar–H), 7.52–7.58 (m, 4H, Ar–H), 7.34–7.38 (t, 1H, $J = 7.4$ Hz, Ar–H), 6.58 (s, 1H, C(5)–H-pyrimidine), 2.34 (s, 6H, CH_3); ^{13}C NMR (δ ppm, DMSO, 100 MHz): 167.15 (C-4, C-6-pyrimidine), 159.27 (C-2-pyrimidine), 150.58 (C-3-pyrazole), 139.12 (C=N), 134.98 (Ar), 132.89 (Ar), 132.60 (Ar), 129.74 (Ar), 129.43 (C-5-pyrazole), 128.36 (Ar), 127.92 (Ar), 127.45 (Ar), 127.41 (Ar), 127.01 (Ar), 126.59 (Ar), 126.36 (Ar), 126.21 (Ar), 125.99 (Ar), 118.54 (Ar), 117.85 (C-5-pyrimidine), 111.29 (C-4-pyrazole), 23.41 (CH_3); Anal. Calculated for $C_{26}H_{22}N_6$ (C, H, N): C 74.62, H 5.30, N 20.08; Found: C 75.80, H 4.49, N 19.70.

Biological assay

Test microorganisms

Total six microbial strains were selected on the basis of their clinical importance in causing diseases in humans. Two Gram-positive bacteria (*Staphylococcus aureus* MTCC 96 and *Bacillus subtilis* MTCC 121), two Gram-negative bacteria (*Escherichia coli* MTCC 1652 and *Pseudomonas aeruginosa* MTCC 741), and two yeast (*Candida albicans* MTCC 227 and *Saccharomyces cerevisiae* MTCC 170) were screened for evaluation of antibacterial and antifungal activity of the chemical compounds. All the microbial cultures were procured from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology (IMTECH), Chandigarh. The bacteria were sub-cultured on nutrient agar (NA) whereas yeast on malt extract agar (MEA) plates.

In vitro antimicrobial assay

The antimicrobial activity and MIC value of 10 chemical compounds were evaluated by the agar well-diffusion assay. The inoculum suspensions of the test microorganisms were prepared by using 16-h-old cultures adjusted to 10^8 cfu/ml by referring the 0.5 McFarland standards. 20 ml of agar medium (NA and MEA) was poured into each Petri plate and plates were swabbed with 100 µl inocula of the test microorganisms and kept for 15 min for adsorption. Using sterile cork borer of 8 mm diameter, wells were bored into the seeded agar plates and these were loaded with a 100 µl volume with concentration of 4.0 mg/ml of each compound reconstituted in the dimethylsulphoxide (DMSO). All the plates were incubated at 37 °C for 24 h. Antimicrobial activity of each compound was evaluated by measuring the zone of growth inhibition against the test organisms with zone reader (HiAntibiotic zone scale). DMSO was used as a negative control, whereas Ciprofloxacin and Amphotericin-B were used as positive control for bacteria and yeast, respectively. This procedure was

performed in three replicate plates for each organism (Aneja *et al.*, 2011 Chandak *et al.*, 2013; Sharma *et al.*, 2012, Pundeer *et al.*, 2012).

Determination of minimum inhibitory concentration (MIC) of chemical compounds

MIC is the lowest concentration of an antimicrobial compound that will inhibit the visible growth of a microorganism after incubation. MIC of the various compounds against bacterial and yeast strains was tested through a modified agar well-diffusion method (Aneja *et al.*, 2011; Mady *et al.*, 2014; sneha *et al.*, 2014; Singh *et al.*, 2014). In this method, a two-fold serial dilution of each chemically synthesized compound was prepared by first reconstituting the compound in DMSO followed by dilution in sterile distilled water to achieve a decreasing concentration range of 4–0.0625 mg/ml. A 100 µl volume of each dilution was introduced into wells (in triplicate) in the agar plates already seeded with 100 µl of standardized inoculum (10^8 cfu/ml) of the test microbial strain. All test plates were incubated aerobically at 37 °C for 24 h and observed for the inhibition zones. MIC, taken as the lowest concentration of the chemical compound that inhibited the growth of the microbe, has shown by a clear zone.

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