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ARTICLE

Synthesis and Characterization of Novel (*E*)-4-(4-(((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-amino)phenyl)morpholin-3-one Derivatives

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ABSTRACT

A highly functionalized heterocyclic compounds series were synthesized, characterized and tested for biological evaluation against bacteria and fungus. This novel synthetic route involves Schiff base formation reaction of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with 4-(4-aminophenyl)morpholin-3-one in the presence of base and methanol as a solvent in good yield and high purity. All the synthesized compounds were characterized using IR, ^{1}H NMR and mass spectroscopic techniques. All the compound screened for antimicrobial activity against standard drugs.

KEYWORDS

Schiff base, Pyrazole, Morpholine, Antimicrobial activity.

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INTRODUCTION

Schiff bases or imines are the important molecules that have been extensively studied owing to their broad range of industrial and biomedical applications [1]. The relative ease of their preparation, as well as the facile modification of the electronic and steric factor of the ligands together with their chelating properties toward different metals, have made them attractive targets in the field of medicinal chemistry. Their growing importance stems from their diverse pharmacological properties *e.g.*, antibacterial, antifungal, antimalarial, anti-inflammatory and antiviral [2-4]. Imines have also been found to possess cytotoxic and antiproliferative activity towards several cancer cell lines like leukemia, colorectal adenocarcinoma (Caco-2) and pancreatic cancer (Panc-1) [5-7], where the presence of the azomethine bond (CH=N) is believe to be critical to biological activity [1,2,8]. Inspired by the aforementioned and continuing work on Schiff base compounds and their applications [9-12], the pyrazole nucleus was incorporated into the design and architecture of the imine ligand, with the goal of finding compounds that elicit and enhance bioactivity. The synthesis of two homologous families of *N,N,N-bis*(imino)-pyridine and *N,N-bis*(imino) benzene compounds derived from 3-aminopyrazole was reported, as well as their biological activity was evaluated.

It is expected that the presence of the different substituents on the pyrazole ring, together with the change in the aromatic

system (pyridine, benzene) of the Schiff bases may have an effect in the *in vitro* antibacterial and anticancer activity of these potential chemotherapeutics. Finally, despite the fact that transition metal complexes with *bis*(imino)pyridine ligands, have been extensively used for last two decades as highly active catalyst; especially towards the polymerization of numerous and diverse olefins [13], few reports have been devoted to explore their potential as chemotherapeutics [14]. To the best of our knowledge, this is the first report of pyrazole containing *bis*(imino)pyridine or benzene compounds, coupled with the evaluation of their pharmacological activity.

In order to synthesize more potent stable molecule containing pyrazole moiety, which have significant biological activity, a synthesis and characterization of (*E*)-4-(4-(((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one and their antimicrobial activity were evaluated.

EXPERIMENTAL

All chemicals and solvents were purchased from CDH chemical, Delhi of AR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS probe KBr pallet. ^{1}H NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400 MHz) DMSO-d_6 solvent.

Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

Synthesis of *N*-phenylamino-α-methyl-phenyl azomethine (INT-01): A mixture of phenylhydrazine (1.08 g, 0.01 M) and acetophenone (1.20 g, 0.01 M) in absolute ethanol was refluxed in water bath for 4 h in presence of 1 mL glacial acetic acid. Product obtained after cooling was crystallized from absolute ethanol. Yield: 1.8 g (90 %). m.p. 64 °C.

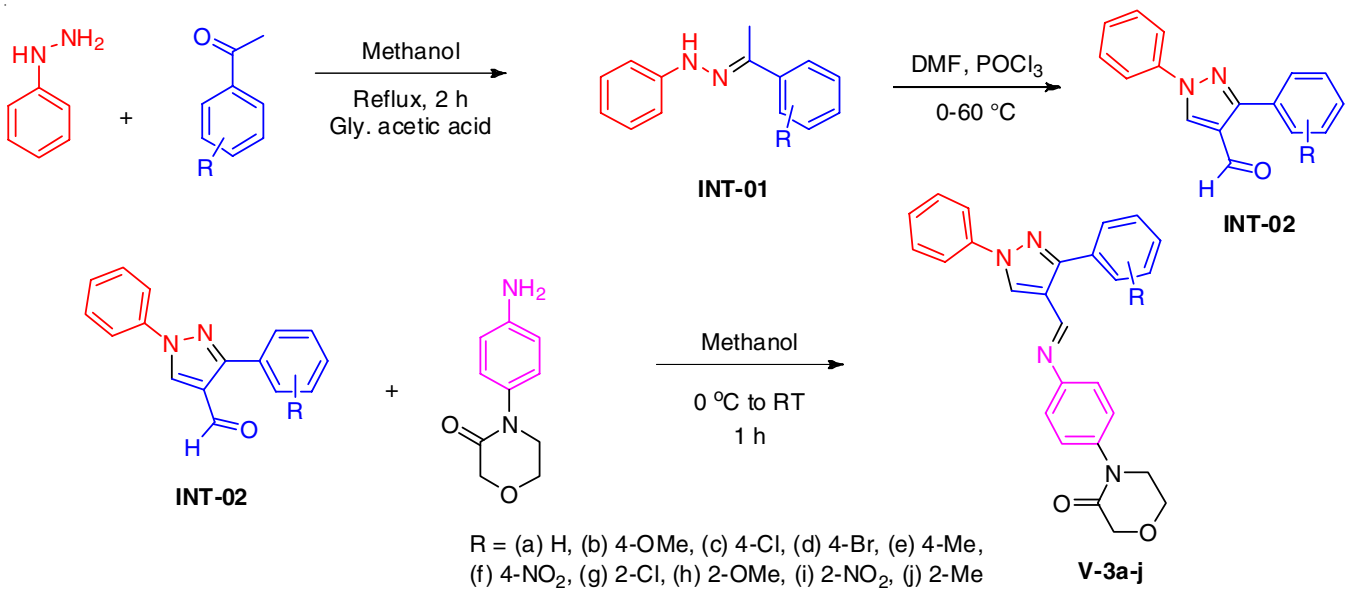
Synthesis of 1-*N*,3-diphenyl-4-formyl pyrazole (INT-2): *N*-Phenylamino-α-methyl-phenyl azomethine (0.84 g, 0.004 M) was added in a mixture of Vilsmeier-Haack reagent (prepared by dropwise addition of 1.2 mL $POCl_3$ in ice cold 10 mL DMF) and refluxed for 6 h. The reaction mixture was poured into crushed ice followed by neutralization using Na_2CO_3 solution. Crude product was isolated and crystallized from methanol. Yield: 2.16 g (87 %), m.p. 125 °C; ($C_{16}H_{12}N_2O$).

General synthesis of Schiff base of pyrazoloaldehyde with 4-(4-aminophenyl)morpholin-3-one (V-3a-j): To a well stirred mixture of methanol and pyarzoloaldehyde (1 mol) was cooled to 0 °C. In this solution, 4-(4-aminophenyl)morpholin-3-one (1.2 mol) was added portionwise. Colour change from yellow to dark red was observed. Reaction mass was poured in to crushed ice. After completion of reaction, product was in good yield (**Scheme-I**).

Spectral data of synthesized compounds

(*E*)-4-(4-(((1,3-Diphenyl-1*H*-pyrazol-4-yl)methylene)-amino)phenyl)morpholin-3-one (V-3a): Yellow solid, yield: 81 %, R_f value: 0.46 (ethyl acetate 8:hexane 2), m.p.: 154-156 °C, IR (KBr, ν_{max}, cm^{-1}): 3056.67 (C-H *str.* arom.), 2868.91 (C-H *str.* aliph.), 1666.18 (C=O *str.* amide), 835.74 (*p*-disub. arom.), 1216.46 (C-O *str.* ethers), 1115.29 (C-N *str.*) 1498.34 (C=C *str.* arom.), 1618.05 (C=N *str.*), ^{1}H NMR ($CDCl_3$), δ ppm: 7.30-8.10 (multiplet, 15H of arom.), 3.70-3.80 (triplet, 2H of –CH_2), 3.95-4.0 (triplet, 2H of –CH_2), 3.20-3.50 (singlet, 2H of –CH_2), MS (*m/z*): 422(M^+), Elemental anal. of $C_{26}H_{22}N_4O_2$ (m.w. 422), calcd. (found) (%): C; 73.92 (73.90), H; 5.25 (5.21), N; 13.26 (13.1).

(*E*)-4-(4-(((3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4- yl)methylene)amino)phenyl)morpholin-3-one (V-3b): Yellow solid, yield: 79 %, R_f value: 0.42 (ethyl acetate:hexane (8:2), m.p.: 170-172 °C, IR (KBr, ν_{max}, cm^{-1}): 3005.66 (C-H *str.* arom.), 2828.83 (C-H *str.* aliph.), 1657.83 (C=O *str.* amide), 837.58 (*p*-disub. arom.), 1225 (C-O *str.* ethers), 1295 (C-N *str.*). ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.10-8.50 (multiplet, 14H of aromatic), 3.70-3.75 (triplet, 2H of -CH_2), 3.90-4.0 (triplet, 2H of -CH_2), 3.80-3.85 (singlet, 2H of -CH_2), 3.10-3.50 (singlet 3H of -CH_3), MS (*m/z*): 452 (M^+). Elemental anal. of $C_{27}H_{24}N_4O_3$ (m.w. 452), calcd. (found) (%): C; 71.67 (71.61), H; 5.35 (5.32), N; 12.38 (12.30).



R = (a) H, (b) 4-OMe, (c) 4-Cl, (d) 4-Br, (e) 4-Me, (f) 4-NO_2, (g) 2-Cl, (h) 2-OMe, (i) 2-NO_2, (j) 2-Me

Scheme-I

(*E*)-4-(4-(((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3c): Dark red, yield: 74 %, R_f value: 0.44 (ethyl acetate:hexane (8:2), m.p.: 152-154 °C, IR (KBr, ν_{max}, cm^{-1}): 3120.66 (C-H *str.* arom.), 2832.80 (C-H *str.* aliph.), 1666.83 (C=O *str.* amide), 855.58 (*p*-disub. arom.), 1228 (C-O *str.* ethers), 1290 (C-N *str.*), 750 (C-Cl *str.* arom.). ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.15-8.55 (multiplet, 14H of arom.), 3.75-3.80 (triplet, 2H of -CH_2), 3.90-4.10 (triplet, 2H of -CH_2), 3.80-3.90 (singlet, 2H of -CH_2), 3.15-3.55 (singlet 3H of -CH_3), MS (*m/z*): 456 (M^+). Elemental anal. of $C_{26}H_{21}N_4O_2Cl$ (m.w. 456), calcd. (found) (%): C; 68.34 (68.31), H; 4.63 (4.60), N; 7.76 (7.72).

(*E*)-4-(4-(((3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3d): Dark red, yield: 85 %, R_f value: 0.42 (ethyl acetate:hexane (8:2), m.p.: 160-162 °C, IR (KBr, ν_{max}, cm^{-1}): 3250.88 (C-H *str.* arom.), 2836.80 (C-H *str.* aliph.), 1656.83 (C=O *str.* amide), 832.50 (*p*-disub. arom.), 1222 (C-O *str.* ethers), 1292 (C-N *str.*), 680 (C-Br *str.* arom.), ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.16-8.56 (multiplet, 14H of arom.), 3.72-3.80 (triplet, 2H of -CH_2), 3.85-4.12 (triplet, 2H of -CH_2), 3.80-3.90 (singlet, 2H of -CH_2), 3.16-3.56 (singlet 3H of -CH_3), MS (*m/z*): 501 (M^+), Elemental anal. of $C_{26}H_{21}N_4O_2Br$ (m.w. 500), calcd. (found) (%): C; 62.28 (62.22), H; 4.22 (4.17), N; 11.17 (11.12).

(*E*)-4-(4-(((1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3e): Red, yield: 82 %, R_f value: 0.48 (ethyl acetate:hexane (8:2), m.p.: 178-180 °C, IR (KBr, ν_{max}, cm^{-1}): 3055.20 (C-H *str.* arom.), 2855.45 (C-H *str.* aliph.), 1665.80 (C=O *str.* amide), 836 (*p*-disub. arom.), 1220 (C-O *str.* ethers), 1290 (C-N *str.*) ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.05-8.55 (multiplet, 14H of arom.), 3.75-3.80 (triplet, 2H of -CH_2), 3.90-4.05 (triplet, 2H of -CH_2), 3.80-3.90 (singlet, 2H of -CH_2), 3.10-3.55 (singlet 3H of -CH_3), MS (*m/z*): 436 (M+). Elemental anal. of $C_{27}H_{24}N_4O_2$ (m.w. 436), calcd. (found) (%): C; 74.29 (74.23), H; 5.54 (5.50), N; 12.84 (12.80).

(*E*)-4-(4-(((3-(4-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3f): Dark yellow, yield: 75 %, R_f value: 0.44 (ethyl acetate:hexane (8:2), m.p.: 180-182 °C, IR (KBr, ν_{max}, cm^{-1}): 3080 (C-H *str.* arom.), 2955.80 (C-H *str.* aliph.), 1645.55 (C=O *str.* amide), 832.69 (*p*-disub. arom.), 1224.25 (C-O *str.* ethers), 1294.11 (C-N *str.*), 1540 & 1385 (NO2- *str.* arom.). ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.02-8.50 (multiplet, 14H of arom.), 3.70-3.80 (triplet, 2H of -CH_2), 3.92-4.05 (triplet, 2H of -CH_2), 3.75-3.90 (singlet, 2H of -CH_2), 3.10-3.56 (singlet 3H of -CH_3), MS (*m/z*): 467 (M+). Elemental anal. of $C_{26}H_{21}N_5O_4$ (m.w. 467), calcd. (found) (%): C; 66.80 (66.74), H; 4.53 (4.50), N; 14.98 (14.92).

(*E*)-4-(4-(((3-(2-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3g): Dark red, yield: 78 %, R_f value: 0.44 (ethyl acetate:hexane (8:2), m.p.: 156-158 °C, IR (KBr, ν_{max}, cm^{-1}): 3122 (C-H *str.* arom.), 2831.70 (C-H *str.* aliph.), 1665.35 (C=O *str.* amide), 854.58 (*p*-disub. arom.), 1221 (C-O *str.* ethers), 1289 (C-N *str.*), 754 (C-Cl *str.* arom.). ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.16-8.55 (multiplet, 14H of arom.), 3.75-3.80 (triplet, 2H of -CH_2), 3.92-4.10 (triplet, 2H of -CH_2), 3.79-3.90 (singlet, 2H of -CH_2), 3.16-3.55 (singlet 3H of -CH_3), MS (*m/z*): 456 (M+). Elemental anal. of $C_{26}H_{21}N_4O_2Cl$ (m.w. 456), calcd. (found) (%): C; 68.34 (68.31), H; 4.63 (4.60), N; 12.26 (12.18).

(*E*)-4-(4-(((3-(2-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3h): Yellow solid, yield: 80 %, R_f value: 0.44 (ethyl acetate:hexane (8:2), m.p.: 144-146 °C, IR (KBr, ν_{max}, cm^{-1}): 3056.35 (C-H *str.* arom.), 2930.85 (C-H *str.* aliph.), 1659.55 (C=O *str.* amide), 831.30 (*p*-disub. arom.), 1221.66 (C-O *str.* ethers), 1292.32 (C-N *str.*). ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.10-8.55 (multiplet, 14H of arom.), 3.70-3.70 (triplet, 2H of –CH_2), 3.90-4.0 (triplet, 2H of -CH_2), 3.80-3.85 (singlet, 2H of -CH_2), 3.10-3.55 (singlet 3H of -CH_3), MS (*m/z*): 452 (M^+). Elemental anal. of $C_{27}H_{24}N_4O_3$ (m.w. 452), calcd. (found) (%): C; 71.67 (71.61), H; 5.35 (5.32), N; 12.38 (12.30).

(*E*)-4-(4-(((3-(2-Nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3i): Dark yellow, yield: 82 %, R_f value: 0.44 (ethyl acetate:hexane (8:2), m.p.: 184-186 °C, IR (KBr, ν_{max}, cm^{-1}): 3076.32 (C-H *str.* arom.), 2952.82 (C-H *str.* aliph.), 1648.52 (C=O *str.* amide), 831.65 (*p*-disub. arom.), 1225.26 (C-O *str.* ethers), 1295.12 (C-N *str.*), 1545 & 1386 (NO_2- *str.* arom.). ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.00-8.50 (multiplet, 14H of arom.), 3.70-3.80 (triplet, 2H of -CH_2), 3.90-4.05 (triplet, 2H of –CH_2), 3.70-3.90 (singlet, 2H of -CH_2), 3.10-3.56 (singlet 3H of -CH_3), MS (*m/z*): 467 (M+). Elemental anal. of $C_{26}H_{21}N_5O_4$ (m.w. 467), calcd. (found) (%): C; 66.80 (66.74), H; 4.53 (4.50), N; 14.98 (14.92).

(*E*)-4-(4-(((1-Phenyl-3-(*o*-tolyl)-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one (V-3j): Red, yield: 86 %, R_f value: 0.46 (ethyl acetate:hexane (8:2), m.p.: 178-180 °C, IR (KBr, ν_{max}, cm^{-1}): 3045.32 (C-H *str.* arom.), 2859.48 (C-H *str.* aliph.), 1664.33 (C=O *str.* amide), 831.69 (*p*-disub. arom.), 1222 (C-O *str.* ethers), 1292 (C-N *str.*), ^{1}H NMR (400 Hz, $CDCl_3$), δ ppm: 7.05-8.50 (multiplet, 14H of arom.), 3.65-3.80 (triplet, 2H of -CH_2), 3.90-4.05 (triplet, 2H of -CH_2), 3.75-3.90 (singlet, 2H of -CH_2), 3.15-3.55 (singlet 3H of -CH_3), MS (*m/z*): 436 (M+). Elemental anal. of $C_{27}H_{24}N_4O_2$ (m.w. 436), calcd. (found) (%): C; 74.29 (74.23), H; 5.54 (5.50), N; 12.84 (12.80).

Antimicrobial evaluation: The minimum inhibitory concentration (MIC) values of the synthesized compounds (**V-3a-j**) were determined by using broth microdilution method with 96 well microdilution plate [15]. The samples were dissolved in DMSO at 1250 µg/mL and were then diluted to achieve concentrations in the range 30 to 500 µg/mL for each compound. Two-fold dilutions of chloroamphenicol and ciprofloxacin, nystatin and greseofulvin (1-32 µg/mL) were used for a positive control.

RESULTS AND DISCUSSION

In present work, we have prepared the synthesis of a series of novel 4-(4-aminophenyl)morpholin-3-ones containing different pyrazole moiety by formation of Schiff base reaction using inorganic base and DMF as solvent at low temperature, resulted in the formation of (*E*)-4-(4-(((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)amino)phenyl)morpholin-3-one derivatives. All synthesized compounds were obtained in good to moderate yields. All the synthesized compounds were characterized by IR, NMR and mass spectrometric techniques.

Antibacterial activity: The results showed that compound **V-3f** was highly active against both Gram positive *S. aureus* and Gram-negative *E. coli*. Compound **V-3j** was highly active against *S. pyogenes* while compounds **V-3i** and **V-3j** were active against *P. aeruginosa* (Table-1).

TABLE-1
ANTIMICROBIAL EVALUATION DATA OF SYNTHESIZED (*E*)-4-(4-(((1,3-DIPHENYL-1*H*-PYRAZOL-4-YL)METHYLENE)AMINO)PHENYL)MORPHOLIN-3-ONE DERIVATIVES (**V-3a-j**)

Compounds and standard drugs	Minimum inhibitory concentration (µg/mL)					
	Antibacterial activity				Antifungal activity	
	Gram+positive bacteria		Gram-negative bacteria			
	S. aureus	*S. pyogenes*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
V-3a	31.25	31.25	15.750	34.625	31.25	32.25
V-3b	15.625	15.625	14.625	40.81	15.660	31.35
V-3c	31.25	62.5	31.25	31.25	62.5	62.5
V-3d	62.5	62.5	31.25	62.5	62.5	62.5
V-3e	15.625	31.25	15.625	62.5	32.25	62.5
V-3f	7.81	31.25	7.81	62.5	32.25	62.5
V-3g	15.625	15.625	14.625	62.5	16.625	62.5
V-3h	15.625	62.5	31.25	31.25	62.5	62.5
V-3i	7.95	7.90	12.625	15.800	32.25	15.655
V-3j	31.25	31.25	31.25	15.680	32.25	18.60
Ciprofloxacin	7.8	7.8	15.625	15.625	–	–
Chloramphenicol	7.8	7.8	7.8	7.8	–	–
Nystatin	–	–	–	–	31.25	31.25
Greseofulvin	–	–	–	–	15.625	15.625

Antifungal activity: The results showed that compounds **V-3a** and **V-3b** were highly active against *C. albicans*, **V-3b** and **V-3i** was highly active against *A. niger* (Table-1).

Conclusion

Synthesis, characterization and biological activity of novel (*E*)-4-(4-(((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)amino)-phenyl)-morpholin-3-one derivatives are sucessfully reported. From activity data, some of the synthesized compounds shows remarkable bioactivity against some bacteria and fungi.

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