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T3P mediated Synthesis of some new quinoline substituted pyrazole derivatives and its antibacterial studies

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ABSTRACT

*A series of new N-(substituted)-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide derivatives (**5a-h**) have been synthesized by condensing ethyl-3-(dimethylamino)-2-[(phenyl)carbonyl]prop-2-enoate **2** with quinoline-2-yl-hydrazine. Compound **3** is hydrolyzed into **4** which is upon further coupled with different aromatic/aliphatic amines using 50 % prpopyl phosphonic anhydride (T3P) in ethyl acetate as coupling reagent to afford different quinoline substituted pyrazole carboxamide derivatives. All the newly synthesized compounds were screened for their invitro antibacterial studies against Escherichia coli, Bacillus subtilis and Pseudomonas aeruginosa. The results revealed that compounds **5d, 5f,** and **5h** showed good antibacterial activity towards all bacterial strains. These newly synthesized compounds were characterized by NMR, mass spectral, IR spectral study and also by C, H, N analyses.*

Keywords: Ethyl benzoyl acetate, Propyl phosphonic anhydride, Pyrazole, Antibacterial study.

INTRODUCTION

The pyrazole scaffold represents a common motif in many pharmaceutical active and remarkable compounds demonstrating a wide range of pharmacological activities. The most important activities is the anti-inflammatory [1], antibacterial [2], antibacterial [3], herbicidal [4], insecticidal [5] , antidepressant [6], anticonvulsant [7] and other biological activities [8]. Among a large array of medicinally important pyrazole derivatives, 1,5-functionalized pyrazole occupy a unique position and their evaluation as antimicrobial agents has attracted much attention in the past [9]. The incorporation of the aryl system into the pyrazole ring enhances the biological activities to a great extent [10-12]. The presence of different substituent's, both on the pyrazole ring and on the phenyl ring, can greatly modify the biological properties of such molecules [13, 14].

Further quinoline substituted moiety is of great importance to chemists as well as biologists as it is found in a large variety of naturally occurring compounds and also chemically useful molecules having diverse biological activities [15-16]. In view of the above facts about pyrazole derivatives and in continuation of our research on biologically active molecules [17-20], we hereby report the synthesis of some novel 1, 5-disubstituted pyrazole derivatives, their characterization and their antibacterial studies.

Propylphosphonic anhydride (T3P) is a mild water scavenger with low toxicity, they pose no health or environmental threats, and the resulting by-products allow for simple phase extraction instead of cost intensive

chromatography. Its versatility as a reagent in organic synthesis has generated innovative uses for this reagent beyond peptide synthesis [21]. Hence we used T3P as coupling agent in our proposed work.

MATERIALS AND METHODS

2.1 Chemistry

All the Chemicals were procured from Aldrich Co. Reactions were monitored and purity of the products was checked by TLC which was performed on MERCK 60F-254 silica gel plates. Melting points were determined on BUCHI Melting point B-545 instrument. The IR spectra (in KBr pellets) were recorded on NICOLET 6700 FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on BRUKER (400 MHz) spectrometer in DMSO-d_6 solvent. Mass spectra were recorded on LC-MS-Agilent 1200 series with MSD (Ion trap) using 0.1% aqueous TFA in acetonitrile system on XBridge C18 (50X4.6 mm) 3.5 mm column for 10 min duration. The elemental analysis was performed on THERMO Finningan FLASH EA 1112 CHN analyzer. Column chromatography was performed on silica gel (60-120 mesh) supplied by Acme Chemical Co. (India) for compound purification.

2.2 Experimental Section:

2.2.1 Preparation of ethyl-3-(dimethylamino)-2-(phenylcarbonyl) prop-2-enoate (2)

A mixture of Ethylbenzoylacetate **1** (10 g, 0.0520 mol) and N, N dimethyl formamide dimethyl acetal (30.9 g, 0.26 mol) was heated to reflux for 18 h. The excess of acetal was distilled off under reduced pressure and the residue was purified by column chromatography using 60-120 silica gel mesh size using chloroform and methanol as an eluent to give yellow solid. (11 g, 85 %) with melting point 65~70 ^{0}C.

2.2.2 Synthesis of ethyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxylate (3)

To a solution of ethyl-3-(dimethylamino)-2-(phenylcarbonyl) prop-2-enoate **2** (5 g, 0.0204 mol) in absolute ethanol (50 mL) was added quinoline-2-yl-hydrazine (3.5 g, 0.0222 mol) and refluxed for 2 h. After the completion of the reaction, the excess of solvent was evaporated under reduced pressure. The residue was diluted with 1.5N HCl (50 mL) and solid separated was filtered and dried under vacuum. The solid obtained was purified by column chromatography using silica gel 60-120 mesh size and petroleum ether: ethyl acetate as eluent to afford the title compound (6.0 g, 86 %) as a white solid.

(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.5); m.p. 157-159 ^{0}C; IR (KBr, υmax cm-1): 3530, 2835 (Ar-stretch), C=N (1630-stretch of Pyrazole ring), C=C (1535), C-O (1455), C=O (1680-stretch of ester); MS: m/z = 344.3 (M^+); ^{1}H-NMR (DMSO-d_6): δ 8.52-8.50 (d, 1H, *J* = 8.76 Hz, quinoline H), 8.2 (s, 1H, pyrazole-CH), 8.01-7.99 (d, 1H, *J* = 8.08 Hz, Ar-H), 7.78-7.73 (d, 1H, *J* = 8.7 Hz, Ar-H), 7.70-7.68 (t, 1H, *J* = 7.08 Hz, Ar-H), 7.62-7.58 (t, 1H, *J* = 7.96 Hz, Ar-H), 7.47-7.45 (d, 1H, *J* = 8.36 Hz), 7.33-7.30 (m, 5H, Ar-H), 4.15-4.09 (q, 2H), 1.14-1.05 (t, 3H, *J* = 7.12Hz). Anal. Calcd. (Found) for $C_{21}H_{17}N_3O_2$: C 73.45 (73.45), H 4.99 (4.97), N 12.24 (12.20).

2.2.3 Synthesis of 5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxylic acid (4)

To a solution of ethyl 5-phenyl-1-quinolin-2-yl-1*H*-pyrazole-4-carboxylate (5 g, 0.0145 mol) in a mixture of THF (50 mL) and water (30 mL) was added lithium hydroxide (1.12 g, 0.029 mol) at RT. The reaction mixture was stirred at RT for 6 h. After the completion of the reaction, the reaction mixture was concentrated under high vacuum, the residue was acidified with 1.5 N HCl, the solid separated out was filtered and dried under suction to afford the title compound (4.0 g, 88%) as a white solid.

(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.2); m.p. 180-185 ^{0}C; ^{1}H-NMR (DMSO-d_6):12.55 (bs, 1H, -COOH), 8.51-8.49 (d, 1H, *J* = 8.72 Hz, Ar-H), 8.23 (s, 1H, Pyrazole-CH), 8.00-7.98 (d, 1H, *J* = 7.40 Hz, Ar-H), 7.78-7.76 (d, 1H, *J* = 8.72 Hz, Ar-H), 7.71-7.70 (t, 1H, *J* = 5.6 Hz, Ar-H), 7.68-7.61 (m, 1H, Ar-H), 7.45-7.43 (d, 1H, *J* = 8.40 Hz), 7.37-7.28 (m, 5H, Ar-H). ^{13}C-NMR (DMSO-d_6) 163.50, 150.19, 145.75, 145.27, 142.84, 139.24, 130.59, 130.26, 129.69, 128.46, 128.15, 127.87, 127.40, 127.23, 126.83, 117.19, 115.21. MS: m/z = 316.3 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6 mm) 3.5mm. Flow rate 2.0 mL/min.

2.2.4 General procedure for the synthesis of *N*-(Substituted)-5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxamide derivatives (5a-h).

To a solution of 5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxylic acid **4** (0.5g, 0.00158 mol) in dry THF (50 mL) was added Triethyl amine (0.5 mL, 0.00317 mol) followed by 50 % propane phosphonic acid anhydride (T3P) in ethyl acetate (1.5 g, 0.00237 mol) and different aromatic/aliphatic amines (0.00158 mol, 1.0 eq) at RT under nitrogen atmosphere. After the completion, the reaction mixture was concentrated under high vacuum; the residue was basified with 10% $NaHCO_3$ solution and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under high vacuum. The solid obtained was purified by column

chromatography using silica gel 60-120 mesh size and petroleum ether: ethyl acetate as eluent to afford the title compound **(5a-h)** as off white solid.

2.2.4.1 Characterization of Morpholin-4-yl [5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazol-4-yl] methanone (5a)
(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.5) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 8.55-8.52 (d, 1H, *J* = 8.76 Hz, Ar-H), 8.03 (s, 1H, Pyrazole-CH), 8.0 (s, 1H), 7.87-7.85 (d, 1H, *J* = 8.76 Hz, Ar-H), 7.72-7.70 (m, 1H, Ar-H), 7.69-7.68 (m, 1H, Ar-H), 7.45-7.43 (d, 1H, *J* = 8.36 Hz), 7.39-7.34 (m, 3H, Ar-H), 7.33-7.25(m, 2H), 3.55-3.42 (m, 4H), 3.25-2.97 (m, 4H).^{13}C-NMR (DMSO-d_6) 162.86, 150.36, 145.25, 141.16, 140.14, 139.32, 130.56, 129.64, 129.38, 128.64, 128.11, 128.03, 127.91, 127.03, 126.83, 118.31, 116.86, 65.63, 40.12. MS: m/z = 385.2 (M^+) Method: A-0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3065, 2957, 2905 (Ar-stretch), C=N (1618-stretch of Pyrazole ring), C=C (1576), C-O (1425), C=O (1549-stretch of ester); Anal. Calcd. (Found) for $C_{23}H_{20}N_4O_2$: C 71.86 (71.87), H 5.24 (5.25), N 14.57(14.58).

2.2.4.2 Characterization of [5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazol-4-yl](piperazin-1-yl) methanone (5b)
(TLC, Chloroform: methanol, 8:2, R_f = 0.3) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 8.53-8.51 (d, 1H, *J* = 8.65 Hz, Ar-H), 8.02 (s, 1H, Pyrazole-CH), 8.0 (s, 1H), 7.86-7.84 (d, 1H, *J* = 8.75 Hz, Ar-H), 7.76-7.70 (m, 1H, Ar-H), 7.67-7.59 (m, 1H, Ar-H), 7.43-7.41 (d, 1H, *J* = 8.35 Hz), 7.38-7.33 (m, 3H, Ar-H), 7.33-7.25(m, 2H), 3.33-3.15 (m, 4H), 2.50-2.48 (m, 2H), 1.97-1.95 (m, 2H).^{13}C-NMR (DMSO-d_6) 162.68, 150.38, 145.26, 141.03, 140.01, 139.30, 130.54, 129.66, 129.36, 128.54, 128.07, 128.03, 127.91, 127.02, 126.82, 118.59, 116.86, 53.80, 45.17. MS: m/z = 384.2 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3096, 2939, 2789(Ar-stretch), C=N (1640-stretch of Pyrazole ring), C=C (1611), C-O (1451), C=O (1593-stretch of ester); Anal. Calcd. (Found) for $C_{23}H_{21}N_5O$: C 72.04 (72.05), H 5.52 (5.55), N 18.26(18.24).

2.2.4.3 Characterization of (4-methylpiperazin-1-yl)-[5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazol-4-yl] methanone (5c)
(TLC, Chloroform: methanol, 8:2, R_f = 0.38) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 8.54-8.52 (d, 1H, *J* = 8.68 Hz, Ar-H), 8.02 (s, 1H, Pyrazole-CH), 8.0 (s, 1H), 7.87-7.85 (d, 1H, *J* = 8.76 Hz, Ar-H), 7.72-7.69 (m, 1H, Ar-H), 7.62-7.58 (m, 1H, Ar-H), 7.46-7.44 (d, 1H, *J* = 8.36 Hz), 7.38-7.33 (m, 3H, Ar-H), 7.33-7.25(m, 2H), 3.33-3.15 (m, 4H), 2.50-2.48 (m, 2H), 2.06 (s, 3H), 1.97-1.95 (m, 2H).^{13}C-NMR (DMSO-d_6) 162.68, 150.38, 145.26, 141.03, 140.01, 139.30, 130.54, 129.66, 129.36, 128.54, 128.07, 128.03, 127.91, 127.02, 126.82, 118.59, 116.86, 53.80, 45.17, 40.12. MS: m/z = 398.2 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3096, 2939, 2789(Ar-stretch), C=N (1640-stretch of Pyrazole ring), C=C (1611), C-O (1451), C=O (1593-stretch of ester); Anal. Calcd. (Found) for $C_{24}H_{23}N_5O$: C 72.52 (72.53), H 5.83 (5.84), N 17.62(17.62).

2.2.4.4 Characterization of N-cyclohexyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide (5d)
(TLC, Pet ether: Ethyl acetate, 7:3, *Rf* = 0.41) pale yellow solid; ^{1}H-NMR (DMSO-d_6): 8.49-8.47 (d, 1H, *J* = 8.76 Hz, Ar-H), 8.23(s, 1H, Pyrazole-CH), 7.99-7.97 (d, 1H, *J* = 8.00 Hz, Ar-H), 7.800-7.77 (1H, *J* = 8.72 Hz, Ar-H), 7.70-7.66 (m, 1H, Ar-H), 7.59-7.57 (m, 1H), 7.56-7.55(m, 1H), 7.51-7.49 (d, 1H, *J* = 7.84 Hz), 7.37-7.29 (m, 5H), 3.61 (m, 1H), 1.17-1.69 (m, 2H), 1.60-1.50(m, 2H), 1.18-1.18 (m, 1H), 1.18-1.09 (m, 5H).^{13}C-NMR (DMSO-d_6) 160.78, 150.41, 145.32, 143.25, 140.58, 139.22, 130.57, 130.28, 130.16, 128.39, 128.14, 127.91, 127.60, 127.09, 126.77, 119.15, 116.94, 47.57, 32.30, 25.22, 24.55. MS: m/z = 397.2 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3094, 2939, 2759 (Ar-stretch), C=N (1650-stretch of Pyrazole ring), C=C (1651), C-O (1451), C=O (1563-stretch of ester); Anal. Calcd. (Found) for $C_{25}H_{24}N_4O$: C 75.73 (75.74), H 6.10 (6.12), N 14.13(14.14).

2.2.4. 5 Characterization of N-cyclopentyl-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide (5e)
(TLC, Pet ether: Ethyl acetate, 8:2, R_f = 0.34) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 8.50-8.47 (d, 1H, *J* = 8.68 Hz, Ar-H), 8.24(s, 1H, Pyrazole-CH), 7.99-7.97 (d, 1H, *J* = 7.04 Hz, Ar-H), 7.800-7.77 (1H, *J* = 8.76 Hz, Ar-H), 7.68-7.67 (m, 1H, Ar-H), 7.59-7.57 (m, 1H), 7.56-7.55 (m, 1H), 7.51-7.49 (d, 1H, *J* = 7.84 Hz), 7.347.31(m, 5H), 4.12 (m, 1H), 1.78-1.74 (m, 3H), 1.53-1.35, 5H). ^{13}C-NMR (DMSO-d_6) 160.78, 150.41, 145.32, 143.25, 140.58, 139.22, 130.57, 130.28, 130.16, 128.39, 128.14, 127.91, 127.60, 127.09, 126.77, 119.15, 116.94, 47.57, 32.30, 25.22. MS: m/z = 383 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X4.6 mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3094, 2939, 2759 (Ar-stretch), C=N (1650-stretch of Pyrazole ring), C=C (1651), C-O (1451), C=O (1563-stretch of ester); Anal. Calcd. (Found) for $C_{24}H_{22}N_4O$: C 75.37 (75.34), H 5.80 (5.80), N 14.65 (14.66).

2.2.4.6 Characterization of N-(2, 6-dimethylphenyl)-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide (5f)

(TLC, Pet-ether/EtOAc, 7:3, R_f = 0.5) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 9.41(bs, 1H), 8.53-8.50 (d, 1H, *J* = 8.72 Hz, Ar-H), 8.42 (s, 1H, Pyrazole-CH), 7.83-7.81 (d, 1H, *J* =8.72 Hz, Ar-H), 7.72-7.70 (d, 1H, *J* = 7.00Hz, Ar-H), 7.69-7.68 (m, 1H, Ar-H), 7.62-7.58(m, 1H), 7.47-7.45 (d, 1H, *J* = 8.24Hz, Ar-H), 7.38-7.27(m, 5H), 7.07(s, 3H), 2.14 (s, 6H). ^{13}C-NMR (DMSO-d_6) 160.35, 150.35, 145.32, 143.97, 140.49, 139.23, 135.54, 134.88, 130.56, 130.24, 129.86, 128.34, 128.14, 127.88, 127.63, 127.48, 127.13, 126.81, 126.59, 118.61, 117.14, 18.10. MS: m/z = 419.3 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X4.6 mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3394, 3223 (Ar-stretch), C=N (1644-stretch of Pyrazole ring), C=C (1500), C-O (1455), C=O (1597-stretch of ester); Anal. Calcd. (Found) for $C_{27}H_{22}N_4O$: C 77.79 (77.80), H 5.30 (5.31), N 13.39 (13.37).

2.2.4.7 Characterization of N, N-dimethyl-5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxamide (5g)

(TLC, Pet-ether/EtOAc, 1:1, R_f = 0.3) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 8.55-8.52 (d, 1H, *J* = 8.76 Hz, Ar-H), 8.03 (s, 1H, Pyrazole-CH), 8.0 (s, 1H), 7.87-7.85 (d, 1H, *J* = 8.76 Hz, Ar-H), 7.72-7.70 (m, 1H, Ar-H), 7.69-7.68 (m, 1H, Ar-H), 7.45-7.43 (d, 1H, *J* = 8.36 Hz), 7.39-7.34 (m, 3H, Ar-H), 7.33-7.25 (m, 2H), 2.95 (s, 6H).^{13}C-NMR (DMSO-d_6) 162.86, 150.36, 145.25, 141.16, 140.14, 139.32, 130.56, 129.64, 129.38, 128.64, 128.11, 128.03, 127.91, 127.03, 126.83, 118.31, 116.86, 41.9. MS: m/z = 343.3 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3065, 2957, 2905 (Ar-stretch), C=N (1618-stretch of Pyrazole ring), C=C (1576), C-O (1425), C=O (1549-stretch of ester); Anal. Calcd. (Found) for $C_{21}H_{18}N_4O$: C 73.67 (73.67), H 5.30 (5.32), N 16.36 (16.34).

2.2.4.8 Characterization of N, N-diethyl-5-phenyl-1-(quinolin-2-yl)-1*H*-pyrazole-4-carboxamide (5h)

(TLC, Pet-ether/EtOAc, 5:5, R_f = 0.5) pale yellow solid.; ^{1}H-NMR (DMSO-d_6): 8.55-8.52 (d, 1H, *J* = 8.76 Hz, Ar-H), 8.03 (s, 1H, Pyrazole-CH), 8.0 (s, 1H), 7.87-7.85 (d, 1H, *J* = 8.76 Hz, Ar-H), 7.72-7.70 (m, 1H, Ar-H), 7.69-7.68 (m, 1H, Ar-H), 7.45-7.43 (d, 1H, *J* = 8.36 Hz), 7.39-7.34 (m, 3H, Ar-H), 7.33-7.25(m, 2H), 3.23-3.24(m, 4H), 1.15-1.08 (m, 6H). MS: m/z = 371.2 (M^+) Method: A- 0.1%TFA, B-MEOH, Column: XBridge C18 (50 X 4.6mm) 3.5mm. Flow rate 2.0 mL/min. IR (KBr) cm^{-1}: 3065, 2957, 2905 (Ar-stretch), C=N (1618-stretch of Pyrazole ring), C=C (1576), C-O (1425), C=O (1549-stretch of ester); Anal. Calcd. (Found) for $C_{23}H_{22}N_4O$: C 74.57 (74.58), H 5.99 (5.98), N 15.12 (15.11).

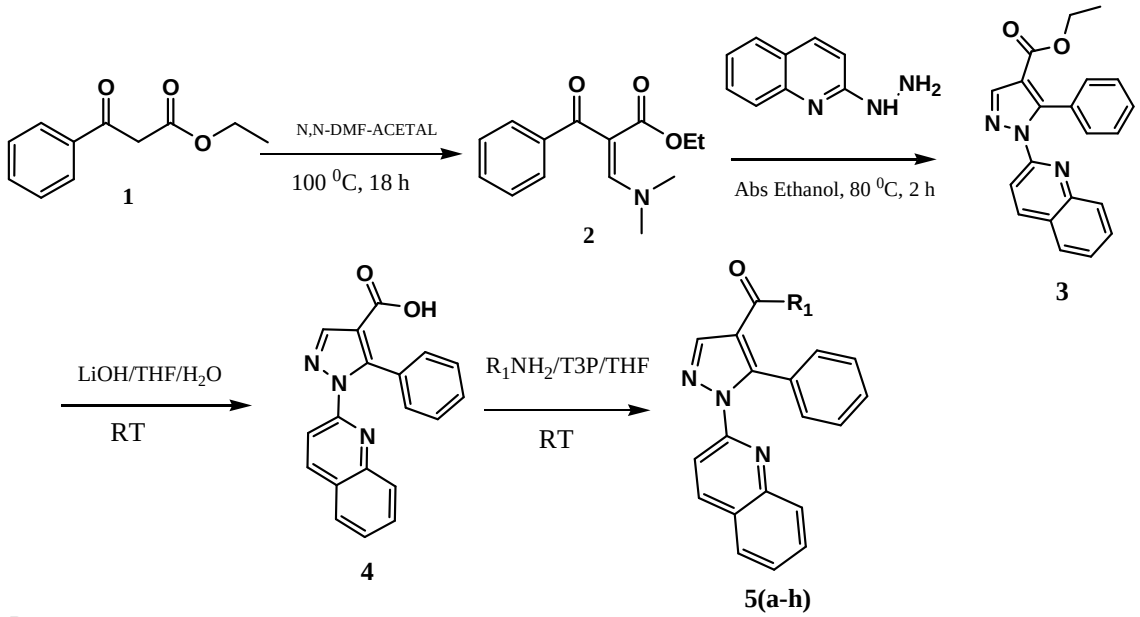
2.3. In vitro antibacterial activity:

The antibacterial activity of the synthesized compounds was done using *Bacillus subtilis* MTCC 441, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. The above activity was examined qualitatively and quantitatively by the presence or absence of inhibition zones and zone diameter. Susceptibility of the test organism to the Organic compound was determined by well plate technique [22-23]. Each strain was inoculated into 10 mL Tryptone soya broth (TSB) in 50 mL conical flask, and was incubated at 37º C till they showed good growth. From the well grown flask 60 µl of the inoculum was spread uniformly on the pre-set media plates. The wells were dug by sterilizing cork borer and organic compound dissolved in DMSO (1 mg/mL and 0.5 mg/mL concentration) were added. The same procedure was repeated for all micro-organisms, the Petri plates were incubated for 24 h at 37^{o}C. Here Dimethyl sulfoxide (DMSO) was used as negative control and Streptomycin as positive controls. The plates were checked for the zone of inhibition, the compounds which showed good zone inhibition, was studied for minimum inhibitory concentration (MIC). MIC was performed at different concentration 1, 10, 25, 50, 100, 500 and 1000 µg/mL. 100 µL of the inoculum was uniformly spread into preset plates and then place sterile filter paper disks (5mm diameter) on the spread plates. The filter paper disk was loaded with 5 µL of the sample of different concentration before starting the experiment aseptically. TSA plates were incubated at 37ºC for 24 h. The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains.

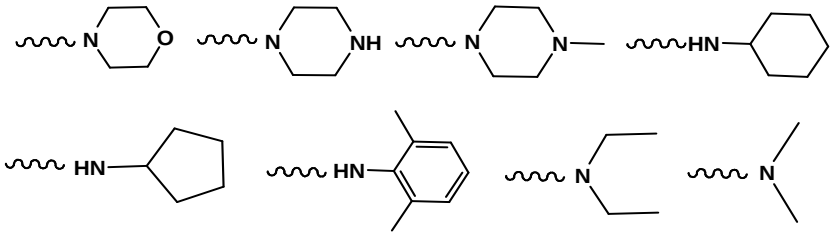
RESULTS AND DISCUSSION

3.1 Chemistry

The key intermediate in the present study is Ethyl -3-(dimethylamino)-2-[phenylcarbonyl] prop-2-enoate **2** and was synthesized by refluxing ethyl benzoylacetate **1** with DMF-acetal using absolute ethanol as solvent. The compound **2** was then treated with quinoline-2-yl-hydrazine to afford cyclised pyrazole carboxylate **3.** Compound **3** is hydrolyzed into **4** which is upon further coupled with different aromatic/aliphatic amines using 50% T3P in ethyl acetate (Propyl phosphonic anhydride) as a coupling agent. The synthetic routes for the compounds (5a-h) were depicted in **Scheme 1**.



Where **R$_1$=**



Scheme-1: Synthetic route for the compounds (5a-h)

Table-1: Characterization data of the compounds (5a-h)

Comp. No	R$_1$	Molecular Formula (Mol. wt.)	Melting point (^{0}C)	Yield (%)
5a	-morpholine	$C_{23}H_{20}N_4O_2$	198-200	86
5b	-piperazine	$C_{23}H_{21}N_5O$	178-182	82
5c	-1-methyl Piperazine	$C_{24}H_{23}N_5O$	156-158	91
5d	-cyclohexyl	$C_{25}H_{24}N_4O$	201-203	93
5e	-cyclopentyl	$C_{24}H_{22}N_4O$	200-202	78
5f	-2,6-$(CH_3)_2$ Ph	$C_{27}H_{22}N_4O$	210-212	95
5g	- dimethyl	$C_{21}H_{18}N_4O$	189-190	88
5h	-diethyl	$C_{23}H_{22}N_4O$	177-179	83

The structures of the pyrazole derivatives were confirmed by recording their IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra analysis. For compound **5a,** the absorption band at 3065, 2957, 2905 cm$^{-1,}$ due to the aromatic stretching of phenyl ring. An absorption band at 1618 cm^{-1} is due to C=N group, band in 1549 is due to carbonyl group C=O of the ester functional group. The ^{1}H NMR of **5a** showed singlet in the region of δ 8.03, which is due to the Pyrzole ring proton. Similarly doublet in the region of δ 8.55-8.52, δ 7.87-7.85 and 7.45-7.43 with coupling constant 8.76, 8.76 and 8.36 respectively is due to quinoline ring protons. Similarly multiplet in the region of δ 7.39-7.34 and δ 7.33-7.25 is due to the phenyl ring protons. Similarly multiplet in the region of 3.55-3.42 and 3.25-2.97 is due to the morpholin ring protons. The mass spectrum of **5a** showed a molecular ion peak at m/z 385.2, which is agreed with the molecular formula $C_{23}H_{20}N_4O_2$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part and the characterization is provided in **Table-1**

3.2. Antibacterial activity

A new series of N-(substituted)-5-phenyl-1-(quinolin-2-yl)-1H-pyrazole-4-carboxamide derivatives (**5a-h**) were synthesized in reasonably good yields. They were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry, IR studies and screened for their antibacterial activity by well plate method. Antibacterial study was assessed by Minimum Inhibitory Concentration (MIC) plate method. The antibacterial screening revealed that, few of the tested compounds showed good inhibition against the tested microbial strains. The compound **5f** and **5h** shows excellent antimicrobial activity against tested strains *Escherichia Coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa* at

concentrations of 1.0 and 0.5 mg/mL compared to standard drug streptomycin. The compound **5f** and **5h** have Cyclopentyl and diethyl group. The compound **5d** shows moderate antibacterial activity against all the tested microbial and which is having cyclohexyl moiety and these groups enhances the activity of the pyrazole ring. Results of antibacterial studies have been presented in **Table -2 and 3**.

Table-2: Antibacterial activity of compounds (5a-h)

Comp. No	*Escherichia coli*		*Bacillus subtilis*		*Pseudomonas aeruginosa*	
Concentration In mg/mL	1	0.5	1	0.5	1	0.5
Streptomycin	17±0.2	15±0.1	20±0.3	17±0.2	16±0.1	13±0.1
Control	00	00	00	00	00	00
5a	-	-	-	-	-	-
5b	05±0.3	03±0.2	04±0.2	02±0.1	06±0.1	04±0.2
5c	-	-	-	-	-	-
5d	08±0.2	05±0.1	07±0.1	05±0.2	07±0.2	04±0.3
5e	-	-	-	-	-	-
5f	10±0.3	08±0.2	07±0.2	05±0.2	07±0.2	04±0.1
5g	06±0.1	04±0.2	05±0.3	04±0.2	05±0.2	03±0.1
5h	11±0.2	09±0.1	10±0.2	07±0.3	11±0.2	08±0.1

Table-3: Minimum Inhibitory concentration (MIC µg/mL) of compounds (5a-h)

Comp. No	*Escherichia coli*	*Bacillus subtilis*	*Pseudomonas aeruginosa*
5b	500	500	500
5d	250	250	250
5f	125	250	125
5g	500	500	500
5h	125	125	125

It has been observed that, derivatization of the active 1H-pyrazole carboxylate into 1H-pyrazole carboxamide leads a number of active compounds. Further, the result obtained clearly indicate that compounds having aliphatic amide linkage have shown pronounced activity; particularly Cyclopentyl and diethyl amide linkage are more active against all the microbial tested, whereas compound bearing aromatic amide linkage is not active.

CONCLUSION

In the present work, a series of some new quinoline substituted pyrazole derivatives were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, mass and elemental analyses. All the compounds were screened for its antibacterial activity. Antibacterial results indicated that the compounds **5d**, **5f** and **5h** showed good antibacterial activity towards all bacterial strains when compared to standard drug streptomycin at a very low concentration of. 1.0 and 0.5 mg/mL. The result of our present study conferred that the aliphatic amide pharmacophore is important for antimicrobial activity of pyrazoles.

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