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SYNTHESIS OF 1-((1-((5-PHENYL-1,3,4-OXADIAZOL-2-YL)METHYL)-1H-PYRAZOL-3-YL)METHYL)PIPERAZINE

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ABSTRACT
Synthesis of 1-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-pyrazol-3-yl)methyl)piperazine were synthesis by condensation of ethyl 2-(3-((piperazin-1-yl)methyl)-1H-pyrazol-1-yl)acetate with hydrazine hydrate and polyposparic acid to obtain2-(3-((piperazin-1-yl)methyl)-1H-pyrazol-1-yl)acetohydrazide in excelent yield. The structurer of these newly synthesis compound were charactrised by H^1-NMR, C^{13}-NMR, Mass and IR elemental analysis.

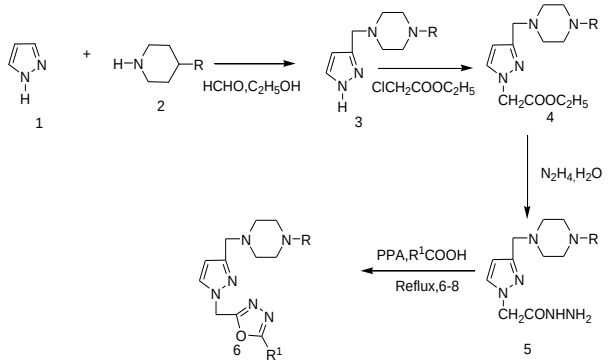
KEYWORD: Pyrozole, Manich bases, 1,3,4 oxadiazole,.

INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their immense biological andpharmacological potency. Various biologically active synthetic compounds have five membered nitrogen containingheterocyclic ring in their structures. Many compounds bearing pyrazoles and their reduced forms pyrazolinesconstitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities such as antimicrobial[1,2], antiviral[3], anti-inflammatory[4,5], antidepressant[6], antitubercular[7], antiamoebic[8], analgesic[9] activities. Literature survey reveals several synthetic protocols for the synthesis of these compoundsand the presence of this core in any molecule plays a key role in enhancing the activity. On the other hand, coumarinand its derivatives represent one of the important class of heterocyclic compounds possessing a wide range of biological activities. These include antibacterial[10], antifungal[11,12], antitumor[13,14], herbicidal, antiinflammatory[15] activities. Coumarins are oxygen containing heterocycles widely distributed in nature. They arealso used as additives in food, perfumes, agrochemicals, pharmaceuticals and in the preparation of insecticides, optical brighteners, dispersed fluorescent and dye lasers. Chalcones are 1,3-diaryl-2-propen-1-ones are natural or synthetic compounds prepared by claisen-schmidtcondensation of aromatic aldehydes with acetophenones in presence of base and alcohol as solvent medium.[16,17] These compounds found application in the synthesis of various heterocyclic compounds. Keeping in view of the above interesting pharmacological features, we hereby report the synthesis and antimicrobialactivity of a series of new pyrazoline derivatives.

MATERIALS AND METHODS

All the chemicals were used as receivedwithout further purification. Melting points were determined in open capillary tubes in Buchi 530 circulating oil apparatus and are not corrected. Reactions were carried out usinghousehold micro oven (power consumption 1200 W, microwave frequency 2450 MHz) andmonitored by thin layer chromatography (TLC) on silica gel plates (60 F254) visualizing withultraviolet light or iodine spray. 1H NMR spectra were determined in DMSO-*d*6 solution on JOEL AL300Spectrometers. Proton chemical shifts arerelative to tetramethylsilane as internalstandard and expressed in ppm.



R	H	H	H	H	H	H
R^1	C_6H_5	$C_6H_4CH_3$	$C_6H_4C_2H_5$	C_6H_4Cl	C_6H_4Br	$C_6H_4NO_2$

Experimental section

Chemicals and reagents used in the current study were of analytical grade. The reactions were monitored by thinlayer chromatography (TLC) on Merck pre-coated silica GF254 plates. Melting points were determined usinga Mettler Toledo FP62 capillary melting point apparatus (Mettler-Toledo, Greifensee, Switzerland) and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum One series FT-IR apparatus (Version5.0.1) (Perkin Elmer, Norwalk, CT, USA), using potassium bromide pellets; the frequencies were expressedin cm^{-1}. The ^{1}H- and ^{13}C-NMR spectra were recorded with a Varian Mercury-400 FT-NMR spectrometer.

(Varian, Palo Alto, CA, USA), using tetramethylsilane as the internal reference, with chloroform-$CDCl_3$ as solvent, the chemical shifts were reported in parts per million (ppm) and coupling constants (*J*) were given in hertz (Hz). Elemental analyses were performed on a LECO 932 CHNS instrument (Leco-932, St. Joseph, MI, USA) and analyses for C, H, and N were within 0.4% of the theoretical values.

General procedure for the synthesis of compounds (3)

pyrazole (1) (2 mmol, 235 mg) was dissolved in 20 mL of ethanol-water (1:1) solution and formaldehyde 37% (3mmol) and substituted piperazine (2) (2 mmol) were added. The mixture was stirred at room temperature and the reaction was controlled by TLC in benzene: methanol (9:1) and toluene: ethyl acetate: diethylamine (75:25:1). At the end of the reaction, the precipitate was filtrated, dried and recrystallized using an appropriate solvent.

Yield: 45%: mp 179.7^{0}C. IR (KBr) √ in cm^{-1}: 3130 (N-H), 3095-2756 (C-H). 1H-NMR (CDCl3): *δ* 7.45-6.15 (bs, 2H, pyrazole C-H), 3.79 (s, 2H, C-CH2 -N), 3.20 (t, 4H, piperazine H3, H5, *J* = 4.8), 2.68(t, 4H, piperazine H2, H6, *J* = 4.8). Anal. Calc. for$C_8H_{14}N_4$: C, 57.81; H, 8.45; N, 33.65%, found: C, 57.81; H, 8.49; N, 33.71%, m/z: 166.5

ethyl 2-(3-((piperazin-1-yl)methyl)-1H-pyrazol-1-yl)acetate (4)

An equimolar mixture of 1-((1H-pyrazol-3-yl)methyl) piperazine (3) and chloro ethyl acetate were dissolved in dimethyl formamide solvent and to this reaction mixture anhydrous K_2CO_3 was added and the reaction mixture was stirred at room temperature (35^{0}C) for 8 hours and the progress of the reaction was monitered by TLC using cyclohexane and ethylacetate solvent mixture (7:3) as eluent the reaction mixture was kept over night. After completion of the reaction the solvent was evaporated on rota-evaporater. The gummy solid was seperated and it was recrystalised from -2-propanol-petrolium ether (80^{0}c) solvent mixture. The crystaline solid was found to be -1-((1H-pyrazol-3-yl)methyl)piperazine. with a yield of 75% and mp 143-145^{0}C.

Yield: 55%: mp 185.7^{0}C. IR (KBr) √ in cm−1: 3150 (N-H), 3095-2782 (C-H). 1H-NMR (CDCl3): *δ* 6.45-7.65 (m, 2H, pyrazole), 3.85 (s, 2H, C-CH2 -N), 3.25 (t, 4H, piperazine H3, H5, *J* = 4.8), 2.70(t, 4H, piperazine H2, H6, *J* = 4.8), 1.29 (t,3H, J=13.2Hz, CH_3 of ethyl group), 4.13 (q, 2H, J=13.2Hz, CH_2 of ethyl group),. Anal. Calc. for $C_{12}H_{20}N_4O_2$: C, 57.12; H, 7.99; N, 22.21, O; 12.68%, found: C, 57.51; H, 7.85; N, 22.50, O; 12.55%, m/z: 252238.

2-(3-((piperazin-1-yl)methyl)-1H-pyrazol-1-yl)acetohydrazide (5)

A solution of 4 (0.01mol) and hydrazine hydrate (0.015) in ethanol (20ml) was refluxed for 5 hours. The reaction mixture was cooled and poured in to icecold water with stirring. The seperated solid was filtered, washed with water and recrystalised from ethanol.

Yield: 50%: mp 180.7^{0}C. IR (KBr) √ in cm^{-1}: 3160 (N-H), 3070-2780 (C-H). 1H-NMR (CDCl3): *δ*, 6.25-7.50 (m, 2H, pyrazole), 3.80 (s, 2H, C-CH2 -N), 3.25 (t, 4H, piperazine H3, H5, *J* = 4.8), 2.70 (t, 4H, piperazine H2, H6, *J* = 4.8), 4.28 (s, 2H,-NH_2), 4.36 (s,2H N-CH_2-C =O), 4.98 (s,1 H,-N-NH), Anal. Calc. for $C_{10}H_{18}N_6O$: C, 50.40; H, 7.61; N, 35.27, O; 6.71%, found: C, 50.75; H, 6.94; N, 34.95O; 6.71%, m/z: 238.36.

1-((1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-1H-pyrazol-3-yl)methyl)piperazine 6(a)

A mixture of 2-(3-((piperazin-1-yl)methyl)-1H-pyrazol-1-yl)acetohydrazide (5) (0.01 mol) and substituted corboxilic acid (0.01 mol) was heated at 100−120^{o}C in presence of excess polyphosphoric acid (PPA) for 4−5 h. After cooling, the mixture was poured into crushed ice and neutralized with 5% aq. NaHCO3 solution. The precipitated solid was filtered and purified using column chromatography (petroleum ether: ethyl acetate, 9:1).

Yield: 60%: mp 190.7^{0}C. IR (KBr) √ in cm^{-1}: 3150 (N-H), 3050-2750 (C-H). 1H-NMR (CDCl3): *δ*, 6.25-7.50 (m, 2H, pyrazole), 7.35-7.45(m, 5H, phenyl group), 3.80 (s, 2H, C-CH2 -N), 3.25 (t, 4H, piperazine H3, H5, *J* = 4.8), 2.70(t, 4H, piperazine H2, H6, *J* = 4.8), Anal. Calc. for $C_{17}H_{20}N_6O$: C, 62.95; H, 6.21; N, 25.91%, O: 4.95found: C, 62.93; H, 6.15; N, 25.50, O: 4.93%, m/z: 373.45

Anti-Bacterial Activity

The anti bacterial activity of synthesized compounds was studied by the disc diffusion method against the following pathogenic organisms. The gram-positive bacteria screened were staphylococcus aureus NCCS 2079. The gram negative bacteria screened were Escherichia coli NCCS 2065 and pseudomonas aeruginosa NCCS 2200.

The synthesized compounds were used at the concentration of 250 µglml and 500µglml using DMSO as a solvent the Cefaclor 10µglml disc was used as a standard. (Himedia, Laboratories Ltd, Mumbai). The test

results presented in the table -1, suggest that **6d,6e,6f** exhibit high activity against the tested bacteria, the rest of the compounds were found to be moderate active against the tested microorganisms.

Antifungal activity

Compounds were treatd at the concentrations of 500µglm and 1000µglml using DMSO as solvent. The standard used was Clotrimazole 50µglml against both organisms. The test results were presented in the table-2.

Table 1: Antibacterial activity by disc diffusion method of pyrazole linked 1,3,4 oxadiazole 6(a.f).

Compound	Zone of inhibition (mm)			
	Staphylococcus aureus	Bacillus cereus	Escherichia coli	Pseudomonas aeruginosa
6a	16	18	13	12
6b	14	11	15	10
6c	13	12	10	09
6d	16	17	12	11
6e	18	16	15	17
6f	11	14	13	12
Cefaclor	19	22	19	20

Table 2: Antifungal activity by disc diffusion method for pyrazole linked1,3,4 oxadiazole 6(a-f).

Compound	Zone of inhibition (mm)	
	Asperigillus niger	Candida albicans
6a	14	16
6b	15	13
6c	17	15
6d	18	17
6e	23	21
6f	15	13
Clotrimazole	25-30	25-30

CONCLUSIONS

1. Further more the substitution of mannich bases showed better activities.
2. pyrazole linked mannich bases showed better antibacterial activity.
3. 1,3,4 oxadiazole and its derivatives were found to play an important role in medicinal chemistry as herbicidal, fungicidal, bacterial, anti-inflammatory.

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