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SYNTHESIS, CHARACTERIZATION, ANTI BACTERIAL AND ANTIFUNGAL ACTIVITY OF SOME NOVEL PYRAZOLE DERIVATIVE

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Abstract: A series of carboxamide derivative N-(2,4-dimethylphenyl)-3-oxobutanamide was prepared by reaction of 2,4 dimethyl aniline with ethyl acetoacetate in presence of catalytic amount Sodium hydroxide in Toluene at reflux temperature to afford a good yield of Int-1. The Int-1 upon reaction with Dimethyl sulfide in presence of K_2CO_3 followed by reaction with methyl iodide in DMF solvent was converted to 2-(bis (methylthio) methylene)-N-(2,4-dimethylphenyl)-3-oxobutanamide(Int-2). The cyclisation of Int-2 using hydrazine in IPA solvent resulted in N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide(Int-3) as the main scaffold. The reaction of Int-3 with various substituted aromatic and aliphatic acid chloride derivatives resulted in substituted pyrazole derivate **P1-P17**. The structures of synthesized compounds are characterized by IR, LCMS and 1H-NMR. All compounds are screening for antifungal and antibacterial activity. Overall, Compound P-1, 2, 5, 6, 7, 8, 9 and 17 showed good to moderate antibacterial activity.

Keywords: Pyrazole**,** Acid chloride, Carboxamide derivatives, Antibacterial, Anti fungal activity

Introduction:

Pyrazole is the important members of heterocyclic compound with two adjacent nitrogens in a five-member ring system. Among the two nitrogen atoms; one is basic and the other is neutral in nature. These are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. The aromatic nature arises from the four π electrons and the unshared pair of electrons on the –NH nitrogen.

Pyrazole and its derivatives, a class of well-known nitrogen heterocycles, inhabit a prime position in medicinal chemistry for their diverse biological activities. Pyrazole analogues have found use as building blocks in organic synthesis

for designing pharmaceutical legends for metal catalysis.

Pyrazole derivatives were reported to show a broad spectrum of biological activity including antimicrobial[1-6], anti-inflammatory[7-9], antihypertensive[10], anti-tumor[11-13], anti tuberculosis[14], antiviral[15, 16]. Due to its wide range of biological activity, pyrazole has received a considerable interest in the field of drug discovery and therefore pyrazole ring constitutes a relevant synthetic target in the pharmaceutical industry. In fact, such a heterocyclic moiety represents the core structure of a number of drugs.

Substitution of the heterocyclic moieties on the pyrazole ring is having potential biological activity, for the synthesis of substituted pyrazole derivatives through the condensation reaction of hydrazine derivatives[17]. The generality of this reaction was extended for various mercapto heterocyclic compounds. In the present communication synthesis, characterization and the biological activity of various pyrazole substituted with heterocyclic moieties are reported. Based on this hypothesis, 17 novels substituted pyrazole derivatives were designed synthesized and evaluated for antifungal and antibacterial activity.

MATERIALS AND METHOD:

Chemicals used in the present research work were procured from Spectrochem, SD fine chemicals, Sigma Aldrich and Alfa-Aesar. The progress of reactions and the purity of the products formed was checked by thin layer chromatography (TLC) using silica gel plates and examined under the ultraviolet lamp. The structures of synthesized compounds were corroborated by using different spectral techniques- FT-IR, 1H-NMR and mass/LCMS spectra. The FT-IR spectra were scanned on Shimadzu IR Affinity-I FT-IR spectrophotometer in range of 400-4000 cm-1 using potassium bromide (KBr) powder. The NMR spectra were recorded at 400 MHz (1H-NMR), on a commercial Bruker Advance II instrument, in deuterated dimethylsulphoxide-d6 as a solvent. The chemical shift values were noted as δ ppm using tetramethylsilane as an internal standard.

GENERAL PROCEDURE

Procedure for preparation of N-(2,4-dimethylphenyl)-3-oxobutanamide (Int-1)

To a stirred solution of 2,4-dimethylaniline (25.0 g 206.4 mmol), ethyl acetoacetate (29.55 g, 227.1 mmol) in Toluene (250 mL) and the catalytic amount of sodium hydroxide (2.5 g 10%) was added, the reaction mass was refluxed for 24 hrs. The reaction progress was monitored by TLC using Ethyl acetate: Hexane (1:1) as mobile phase, after completion of reaction, cool the reaction mass and water was added, separate the layer and organic layer was distilled out under reduced pressure. The crude material was purified by purified by column chromatography by using 20% ethyl acetate in hexane to get pure intermediate N-(2,4-dimethylphenyl)-3-oxobutanamide (**int-1**) (26.25 g, 62.59% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.12 (s,3H), 2.25 (s,3H), 2.35 (s,3H), 3.75 (s,2H), 7.01-7.03 (d, *J*=10.4 Hz, 1H), 7.07 (s,1H), 7.21-7.25 (d, *J*=7.6 Hz, 1H), 10.01 (s,1H); MS-Ms: m/z 205.8 $(M+H)^+$.

2-(bis (methylthio) methylene)-N-(2,4-dimethylphenyl)-3-oxobutanamide (Int-2)

To a stirred solution of N-(2,4-dimethylphenyl)-3-oxobutanamide (int-1) (25 g, 121.80 mmol) in DMF (150 mL), dried K_2CO_3 (20.18 g, 146.26 mmol) was added and the reaction mixture was stirred for 2 hrs at 25-35°C, to this reaction mixture carbon disulfide (18.55 g, 243.70 mmol) was added and the reaction mixture was stirred for 2 hrs. Then the reaction

mixture was cooled to 0-5°C and methyl iodide (58.51 g, 243.70 mmol) was added within 30 minutes and stirred for 3 hrs at 25-35°C. The progress of the reaction was monitored by TLC by using Ethyl acetate: hexane (5:5) as a mobile phase. After completion of the reaction, the mixture was poured into water (700 mL) and stirred for 30 minutes. The solid precipitated was filtered, washed with water and dried to afford 2-(bis (methylthio) methylene)-N-(2, 4-dimethylphenyl)-3-oxobutanamide (**Int-2**) (24.55 g, 65.17% yield) as a yellow colored solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.13 (s,3H), 2.25 (s,3H), 2.35 (s,3H), 2.85 (s, 6H), 7.01-7.04 (d, *J*=11.2 Hz, 1H), 7.07 (s,1H), 7.21-7.25 (d, *J*=7.6 Hz, 1H), 10.40 (s,1H), MS-Ms: m/z 205.8 $(M+H)^+$.

N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (Int-3)

To a stirred solution of N-(3,5-bis(trifluoromethyl) phenyl)-2-cyano-3,3-bis(methylthio) acrylamide (int-2) (23.0 g, 74.41mmol) in IPA (115mL), hydrazine hydrate (9.06 g, 161.7 mmol) was added and reaction mass was heated to reflux temperature for 4 hrs. The progress of the reaction was monitored by TLC by using Methanol: MDC (0.5:9.5) as a mobile phase. After completion of the reaction, the reaction mixture was cooled to 25-35°C and water (200 mL) was added. The reaction mixture was stirred for 1 hr. at 25-35°C. The precipitated solid material was filtered, washed with water, dried and crystallization from IPA to afford N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (**int-3**) (14.10 g, 68.88% yield) as a yellow colored solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.13 (s,3H), 2.25 (s,3H), 2.35 (s,3H), 2.47 (s,3H), 2.53 (s, 3H), 7.01-7.03 (d, *J*=11.2 Hz, 1H), 7.08 (s,1H), 7.21-7.25 (d, *J*=7.6 Hz, 1H), 9.76 (s,1H), 13.5 (s,1H),; MS-Ms: m/z 275.8 $(M+H)^+$.

General procedure for the preparation of N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P1-P17)

To a solution of N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (int-3) (1.81 mmol) and Triethylamine (0.75 g 2.42 mmol) in Dichloromethane (10 mL) at 25-35°C, a solution of different aromatic and aliphatic acid chloride (2.66 mmol) in Dichloromethane (20 mL) was added. The reaction mixture was stirred at 25-35°C for 1 hr. The progress of the reaction was monitored by TLC using Methanol: MDC (0.5:9.5) as a mobile phase. After completion of reaction water (50 mL) was added in the reaction mass, separate organic layer dried with sodium sulphate and distilled out under reduced pressure to get the crude material. Crude martial was further crystallized acetone to give the desired product (P1-P17) as a white to off-white solid material with 31.97%-86.75% yield.

REPRESENTATIVE SPECTRAL DATA

1-Benzoyl-N-(2, 4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P1)

Yield: 65.31%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.22 (s,3H), 2.27 (s,3H), 2.40 (s,3H), 2.76 (s,3H), 7.00-7.028 (d, *J*=11.2 Hz, 1H), 7.07 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 7.54-7.58 (m,2H), 7.66-7.70 (m,1H); 7.95-7.97 (m,2H), 9.56 (s,1H); MS-LCMs: m/z 380.17 $(M+H)^+$,: IR cm^{-1}: 3217, 1701,1631, 1577, 1085.

N-(2, 4-dimethylphenyl)-1-hexanoyl-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P2)

Yield: 60.45%. ^{1}H-NMR (400 MHz, DMSO-d_6):

δ=0.87-0.90 (m,3H), 1.31-1.35 (m,4H), 1.65-1.69 (m,2H), 2.20(s,3H), 2.26 (s,3H), 2.53 (s,3H), 2.67 (s,3H), 3.07-3.11 (t, *J*=8 Hz, 2H), 6.99-7.01 (d, *J*=8 Hz, 1H), 7.06(s,1H), 7.25-7.27 (t, *J*=7.6 Hz, 1H), 9.48 (s,1H),; MS-LCMs: m/z 374.22 $(M+H)^+$,: IR cm^{-1}: 3388, 2594, 1735,1666, 1556, 974.

N-(2, 4-dimethylphenyl)-1-hexanoyl-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P3)

Yield: 46.63%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=0.85-0.88 (m,3H), 1.27-1.32 (m,8H), 1.64-1.68 (m,2H), 2.20(s,3H), 2.26 (s,3H), 2.53 (s,3H), 2.67 (s,3H), 3.07-3.11 (t, *J*=8 Hz, 2H), 6.99-7.01 (d, *J*=8 Hz, 1H), 7.06 (s,1H), 7.25-7.27 (t, *J*=7.6 Hz, 1H), 9.48 (s,1H),; MS-LCMs: m/z 374.22 $(M+H)^+$,: IR cm^{-1}: 3388, 2594, 1735,1666, 1556, 974.

1-(4-chlorobenzoyl)-N-(2, 4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P4)

Yield: 31.97%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.21 (s,3H), 2.27 (s,3H), 2.41 (s,3H), 2.70 (s,3H), 7.02-7.03 (d, *J*=11.2 Hz, 1H), 7.08 (s,1H), 7.25-7.29 (d, *J*=8.0 Hz, 1H), 7.59-7.63 (d, *J*=8.0 Hz, 2H), 7.82-7.84 (d, *J*=11.2 Hz, 2H), 9.56 (s,1H),; MS-LCMs: m/z 414.21 $(M+H)^+$,: IR cm^{-1}: 3312, 2272, 1704,1635, 1582, 1085.

1-(4-bromobenzoyl)-N-(2, 4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P5)

Yield: 31.97%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.20 (s,3H), 2.26 (s,3H), 2.41(s,3H), 2.76 (s,3H), 7.01-7.028 (d, *J*=11.2 Hz, 1H), 7.07 (s,1H), 7.27-7.30 (d, *J*=8.0 Hz, 1H), 7.58-7.62 (d, *J*=8.0 Hz, 2H), 7.83-7.85 (d, *J*=11.2 Hz, 2H), 9.57 (s,1H),; MS-LCMs: m/z 458.37 $(M+H)^+$,: IR cm^{-1}: 3315, 2281, 1701,1634, 1582, 1081.

1-(3-bromobenzoyl)-N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P6)

Yield: 63.80%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.21 (s, 3H), 2.27 (s, 3H), 2.41(s, 3H), 2.75 (s, 3H), 7.01-7.03 (d, *J*=11.2 Hz, 1H), 7.07 (s, 1H), 7.26-7.29 (d, *J*=7.6 Hz, 1H), 7.51-7.55 (m, 1H), 7.83-7.88 (m, 1H), 8.10-8.15 (m, 2H), 9.56 (s, 1H),; MS-Ms: m/z 458.37 $(M+H)^+$,: IR cm^{-1}: 3317, 2284, 1701,1634, 1582, 1082.

1-(4-fluorobenzoyl)-N-(2, 4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P7)

Yield: 42.95%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.23 (s,3H), 2.29 (s,3H), 2.41 (s,3H), 2.70 (s,3H), 7.03-7.04 (d, *J*=11.2 Hz, 1H), 7.08 (s,1H), 7.25-7.28 (d, *J*=7.6 Hz, 1H), 7.61-7.68 (m, 2H), 7.82-7.84 (m, 2H), 9.57 (s,1H),; MS-Ms: m/z 398.21 $(M+H)^+$,: IR cm^{-1}: 3315, 2271, 1704,1635, 1582, 1210.

N-(2,4-dimethylphenyl)-1-(3-methoxybenzoyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P8)

Yield: 49.08%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.23 (s,3H), 2.29 (s,3H), 2.41 (s,3H), 2.73 (s,3H), 3.71 (s. 3H), 7.02-7.04 (d, *J*=10.8 Hz, 1H), 7.09 (s,1H), 7.25-7.28 (d, *J*=7.6 Hz, 1H), 7.62-7.66 (m, 2H), 7.81-7.84 (d, *J*=11.2 Hz, 2H), 9.57 (s,1H),; MS-Ms: m/z 409.8 $(M+H)^+$,: IR cm^{-1}: 3315, 2271, 1704,1635, 1582.

N-(2,4-dimethylphenyl)-3-methyl-1-(4-methylbenzoyl)-5-(methylthio)-1H-pyrazole-4-carboxamide (P9)

Yield: 45.48%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.20 (s,3H), 2.25 (s,3H), 2.35 (s, 3H), 2.42 (s,3H), 2.76 (s,3H), 7.03-7.04 (d, *J*=11.0 Hz, 1H), 7.09 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 7.59-7.63 (d, *J*=8.0 Hz, 2H), 7.83-7.85 (d, *J*=11.2 Hz, 2H), 9.60 (s,1H),; MS-Ms: m/z 393.8 $(M+H)^+$,: IR cm^{-1}: 3315, 2281, 1701,1634, 1582.

1-acetyl-N-(2,4-dimethylphenyl)-3-methyl-

5-(methylthio)-1H-pyrazole-4-carboxamide (P10)

Yield: 86.75%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.20 (s,3H), 2.26 (s,3H), 2.41 (s,3H), 2.63 (s,3H), 2.85 (s,3H), 7.03-7.04 (d, *J*=11.0 Hz, 1H), 7.09 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 9.58 (s,1H),; MS-Ms: m/z 317.9 $(M+H)^+$,: IR cm^{-1}: 3315, 2281, 1715,1634, 1582.

N-(2,4-dimethylphenyl)-3-methyl-1-(3-methylbenzoyl)-5-(methylthio)-1H-pyrazole-4-carboxamide (P11)

Yield: 57.38%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=2.21 (s, 3H), 2.27 (s, 3H), 2.34 (s,3H), 2.41(s, 3H), 2.75 (s, 3H), 7.02-7.04 (d, *J*=11.2 Hz, 1H), 7.07 (s, 1H), 7.26-7.29 (d, *J*=7.6 Hz, 1H), 7.51-7.55 (m, 1H), 7.83-7.88 (m, 1H), 8.10-8.15 (m, 2H), 9.56 (s, 1H),; MS-LCMs: m/z 393.9 $(M+H)^+$,: IR cm^{-1}: 3313, 2286, 1701,1634, 1582..

N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1-pivaloyl-1H-pyrazole-4-carboxamide (P12)

Yield: 58.21%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=1.20 (s, 9H), 2.20 (s,3H), 2.25 (s,3H), 2.42 (s,3H), 2.76 (s,3H), 7.03-7.04 (d, *J*=11.0 Hz, 1H), 7.09 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 9.59 (s,1H),; MS-Ms: m/z 359.8 $(M+H)^+$,: IR cm^{-1}: 3315, 2281, 1702,1634, 1583.

N-(2,4-dimethylphenyl)-3-methyl-1-(3-methylbutanoyl)-5-(methylthio)-1H-pyrazole-4-carboxamide (P13)

Yield: 32.17%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=0.91-0.92 (d, *J*=8.0 Hz, 6H), 1.98-2.01 (m, 1H), 2.20 (s,3H), 2.26 (s,3H), 2.42 (s,3H), 2.76 (s,3H), 7.03-7.05(d, *J*=11.0 Hz, 1H), 7.09 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 9.58 (s,1H),; MS-Ms: m/z 359.8 $(M+H)^+$,: IR cm^{-1}: 3315, 2283, 1704,1634, 1582.

N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1-(thiophene-2-carbonyl)-1H-pyrazole-4-carboxamide (P14)

Yield: 64.30%. ^{1}H-NMR (400 MHz, DMSO-d_6): 2.20 (s, 3H), 2.26 (s, 3H), 2.42 (s, 3H), 2.76 (s, 3H), 7.02-7.04 (d, *J*=11.0 Hz, 1H), 7.09 (s, 1H), 7.28-7.31 (d, *J*=8.0 Hz, 1H), 7.35-7.38 (m, 1H). 8.01-8.04 (m, 1H), 8.15-8.18 (m, 1H), 9.60 (s, 1H); MS-Ms: m/z 385.8 $(M+H)^+$,: IR cm^{-1}: 3315, 2281, 1701,1634, 1582.

N-(2,4-dimethylphenyl)-1-(furan-2-carbonyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P15)

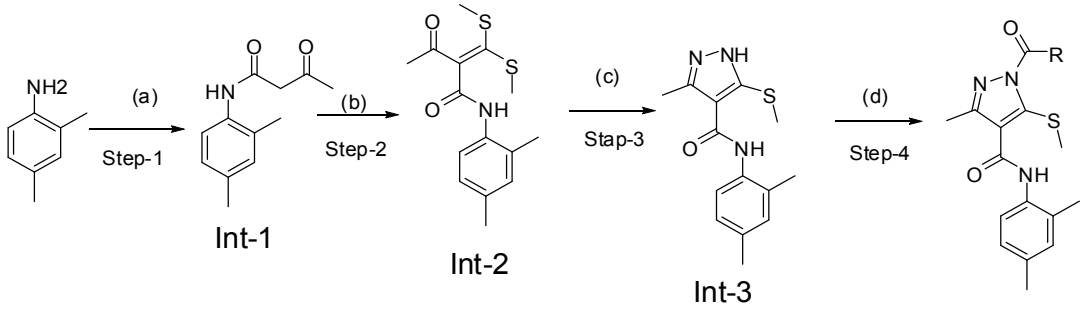
Yield: 63.35%. ^{1}H-NMR (400 MHz, DMSO-d_6): 2.20 (s, 3H), 2.26 (s, 3H), 2.42 (s, 3H), 2.76 (s, 3H), 6.83-6.85 (m, 1H), 7.02-7.04 (d, *J*=11.0 Hz, 1H), 7.09 (s, 1H), 7.28-7.31 (d, *J*=8.0 Hz, 1H), 8.06-8.09 (m, 2H), 9.59 (s, 1H); MS-Ms: m/z 369.8 $(M+H)^+$,: IR cm^{-1}: 3317, 2281, 1705,1634, 1585.

1-acryloyl-N-(2,4-dimethylphenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P16)

Yield: 86.93%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ= 2.21 (s,3H), 2.28 (s,3H), 2.42 (s,3H), 2.76 (s,3H), 5.78-5.80 (d, *J*=7.2 Hz, 1H), 6.00-6.02 (d, *J*=7.6 Hz, 1H), 6.31 (m, 1H), 7.03-7.05(d, *J*=11.0 Hz, 1H), 7.09 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 9.58 (s,1H),; MS-Ms: m/z 329.9 $(M+H)^+$,: IR cm^{-1}: 3315, 2283, 1704,1634, 1582.

N-(2,4-dimethylphenyl)-1-isobutyryl-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (P17)

Yield: 57.39%. ^{1}H-NMR (400 MHz, DMSO-d_6): δ=1.09-1.11 (d, *J*=8.0 Hz, 6H), 2.20 (s,3H), 2.26 (s,3H), 2.42 (s,3H), 2.60-2.63 (m, 1H), 2.76 (s,3H), 7.03-7.05(d, *J*=11.0 Hz, 1H), 7.09 (s,1H), 7.28-7.30 (d, *J*=8.0 Hz, 1H), 9.58 (s,1H),; MS-Ms: m/z 345.8 $(M+H)^+$,: IR cm^{-1}: 3317, 2278, 1705,1634, 1582.



a) Ethylacetoacetae ,sodium hydroxide, Toluene reflux (b) i. CS_2, K_2CO_3, DMF, RT: ii. MeI, 0-10°C to RT; (c) NH_2NH_2, IPA, Reflux 4 hrs (d) Acid chloride, TRA, MDC

Figure: 1: General Synthesis scheme

Table 1: Physical constants of synthesized compounds

Sr No	Compound code	R	Yield (%)	Mol. Formula	Mol. weight
1.	P-1	-Ph	65.31	$C_{21}H_{21}N_3O_2S$	379.14
2.	P-2	$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$	60.45	$C_{20}H_{27}N_3O_2S$	373.18
3.	P-3	$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_3$	46.63	$C_{22}H_{31}N_3O2S$	401.21
4.	P-4	4-Cl-Ph	31.97	$C_{21}H_{20}ClN_3O_2S$	413.10
5.	P-5	4-Br-Ph	39.73	$C_{21}H_{20}BrN_3O_2S$	457.05
6.	P-6	3-Br-Ph	63.80	$C_{21}H_{20}BrN_3O_2S$	457.05
7.	P-7	4-F-Ph	42.95	$C_{21}H_{20}FN_3O_2S$	397.13
8.	P-8	3-OMe-Ph	49.08	$C_{22}H_{23}N_3O_3S$	409.15
9.	P-9	4-Me-Ph	45.48	$C_{22}H_{23}N_3O_2S$	393.15
10.	P-10	$-CH_3$	86.75	$C_{16}H_{19}N_3O_2S$	317.12
11.	P-11	3-Me-Ph	57.38	$C_{22}H_{23}N_3O_2S$	393.15
12.	P-12	$-C(CH_3)_3$	58.21	$C_{19}H_{25}N_3O_2S$	359.17
13.	P-13	$-CH_2-CH(CH_3)_2$	32.17	$C_{19}H_{25}N_3O_2S$	359.17
14.	P-14	-2-Thiophene	64.30	$C_{19}H_{19}N_3O_2S_2$	385.09
15.	P-15	-2-Furan	63.35	$C_{19}H_{19}N_3O_3S$	369.11
16.	P-16	$-CH=CH_2$	86.93	$C_{17}H_{19}N_3O_2S$	329.12
17.	P-17	$-C(CH_3)_2$	57.39	$C_{18}H_{23}N_3O_2S$	345.15

RESULTS AND DISCUSSION:

BIOLOGICAL EVALUATION

Synthesized compounds were evaluated for their in vitro antibacterial and antifungal activity. For evaluation of antibacterial activity, the representative strains of Gram-negative bacteria (Escherichia Coli, Pseudomonas Aeruginosa) and Gram-positive bacteria (Staphylococcus Aureus, Streptococcus Pyogenus) were used. For antifungal activity, Candida Albicans, Aspergillus Niger and Aspergillus Clavatus were used. All standard strains were procured from Institute of Microbial Technology, Chandigarh, and Punjab, India. The Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin were used as standard antibacterial drugs for the comparison. Nystatin and Greseofulvin were used as standard antifungal drugs. The agar diffusion and broth dilution test methods were followed and each test compounds were dissolved in Dimethyl Sulfoxide (DMSO). Muller Hinton Broth was used as a nutrient medium to grow and dilute the drug suspension for the test bacteria. Inoculums size for the test strain was adjusted to 108 Cfu/mL by comparing the turbidity. The synthesized compounds and standard drugs were dissolved in DMSO, adjusted the concentration to 2000 µg/mL and then, used as stock solution. Serial dilutions were prepared for primary and secondary screening for the test compounds. The test compound tubes were incubated for 24 hrs at 37ºC. The

turbidity produced in each tube was recorded by UV/Visible spectrophotometer. The turbidity produced by the Broth (without inoculums) was considered as 100% transparency. The minimum inhibitory concentration (MIC) was noted as the minimum concentration of the test substance, which completely inhibits the growth of the microorganism i.e. 100% transparency.

RESULTS AND DISCUSSION:

In the present study, seventeen novel carboxamide pyrazole derivatives were synthesized in reasonably good yield. The presence of characteristic peaks in FR-IR, NMR and Mass spectra confirmed the structure of titled compound derivatives. All synthesized compounds were evaluated for antibacterial and antifungal activity. The test results of antimicrobial activity are mentioned in Table 2, Table 3 and in Graph 1 and Graph 2.

(1) Antibacterial evaluation: Compounds **P-6, 7, 8, 10, 15** and **17** were found to be equipotent while **P-2 and P-5** were found to be more potent to Ampicillin (MIC=100 μg/mL) against *E.Coli* (MTCC 443). Compound **P-2** found to be more potent and found to be equipotent to Ciprofloxacin (MIC=25 μg/mL) for E.Coli. Compound **P-1, 3, 4, 5, 11** and **14** were found to be equipotent to Ampicillin (MIC=100 μg/mL) while Compound **P-17** was found to be equipotent to Chloramphenicol (MIC=50μg/mL) against P.Aeruginosa (MTCC 1688). Compounds **P-2, 5, 9, 14** and **16** were found to be equipotent; Compound **P-3, 4, 8, 10, 13, 15 and P-17** were found to be more potent to Ampicillin, while Compound **P-1, 6** and **7** were found to be significantly potent to Ampicillin against S.Aureus (MTCC 96). Compounds **P-6, 7, 8** and **15** were found to possess equivalent potency while compound **P-9** was found to possess more potency compared Ampicillin against Pyogenus (MTCC 442). Overall, Compound **P-1, 2, 5, 6, 7, 8, 9** and **17** showed good to moderate potential antibacterial activity.

Table 2: Antibacterial Activity, Minimum Inhibition Concentration. (MIC[a])
(MIC)[a]: Minimum Inhibitory concentration in µg/mL

ANTIBACTERIAL ACTIVITY TABLE				
MINIMUM INHIBITION CONCENTRATION				
CODE	**E.COLI**	**P.AERUGINOSA**	**S.AUREUS**	**S.PYOGENUS**
NO.	**MTCC 443**	**MTCC 1688**	**MTCC 96**	**MTCC 442**
P-1	125	**100**	**50**	250
P-2	**25**	125	**250**	250
P-3	250	**100**	**125**	250
P-4	125	**100**	**125**	125
P-5	**62.5**	**100**	**250**	**50**
P-6	**100**	250	**25**	**100**
P-7	**100**	125	**62.5**	**100**
P-8	**100**	**62.5**	**125**	**100**
P-9	500	250	**250**	**62.5**
P-10	**100**	250	**100**	250
P-11	500	**100**	250	250
P-12	500	500	500	500
P-13	500	250	**125**	250
P-14	250	**100**	**250**	250
P-15	**100**	250	**100**	**100**
P-16	250	250	**250**	250
P-17	**100**	**50**	**125**	125
Standard drugs	MICROGRAMME/mL			
GENTAMYCINE	0.05	1	0.25	0.5
AMPICILLIN	100	100	250	100
CHLORAMPHENICOL	50	50	50	50
CIPROFLOXACIN	25	25	50	50
NORFLOXACIN	10	10	10	10

(2) Antifungal evaluation: Compounds **P-5, 7, 8, 10, 11, 12** and **16** were found to be equipotent while Compound **P-1, 3, 6, 9, 13, 14** and **P-15** were found to be more potent to Greseofulvin (MIC=500 μg/mL) against C.Albicans (MTCC 227). All other synthesized compounds were found to be less potent than standard drugs against A.Niger (MTCC 282) and A.Clavatus (MTCC 1323).

CONCLUSION:

The novel pyrazole compounds synthesized in reasonably good yield using commercial grade raw materials. The structures of synthesized compounds were confirmed by FT-IR, mass and ^{1}H-NMR. The synthesized compounds were evaluated for potential biological activities. All synthesized compounds were found to possess reasonably good antimicrobial activity and Compound **P-1, 2, 5, 6, 7, 8, 9** and **17** showed good to moderate potential antibacterial activity.

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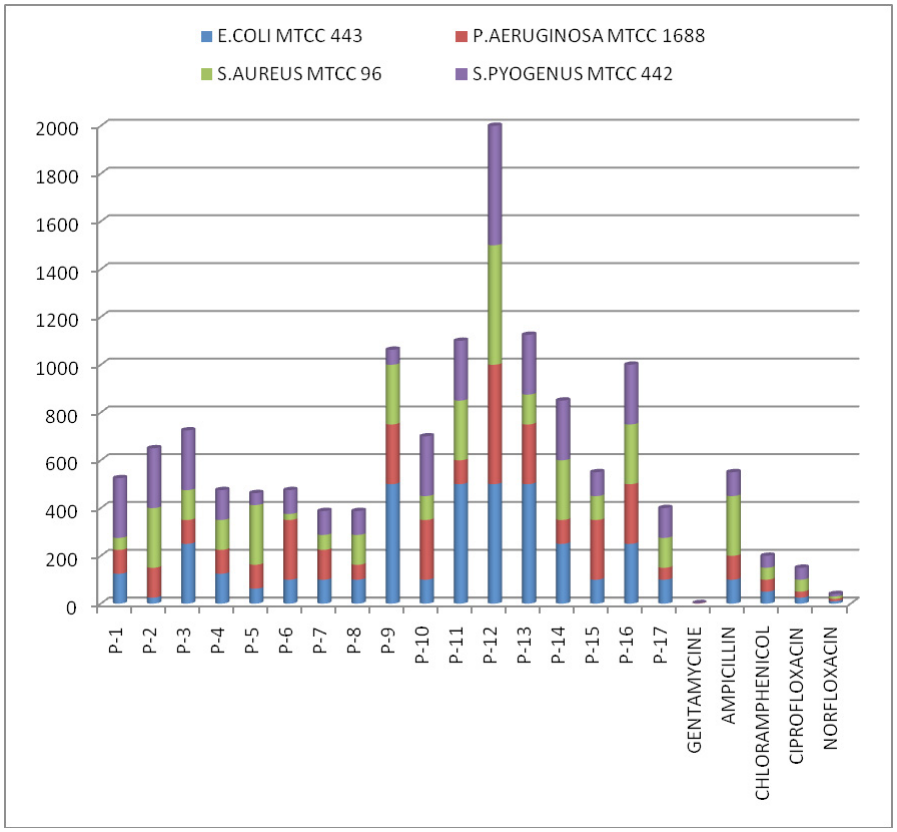
REFERENCES:

1. S. Bondock, W. Fadaly, M. A. Metwally, Eur. *J. Med. Chem*., **2010,** 45, 3692-3701.
2. S. Radi, S. Salhi, A. Radi, *Letters in Drug Design & Discovery*, **2010**,7, 27-30.
3. S. K. Sahu, M. Banerjee, A. Samantray, C. Behera, M.A. Azam, *Tropical J. Pharm. Research*, **2008,** 7(2): 961-968.
4. N. RaoJyothi, K.V. Sujith, B. Kalluraya, Saudi Chem. Soc,

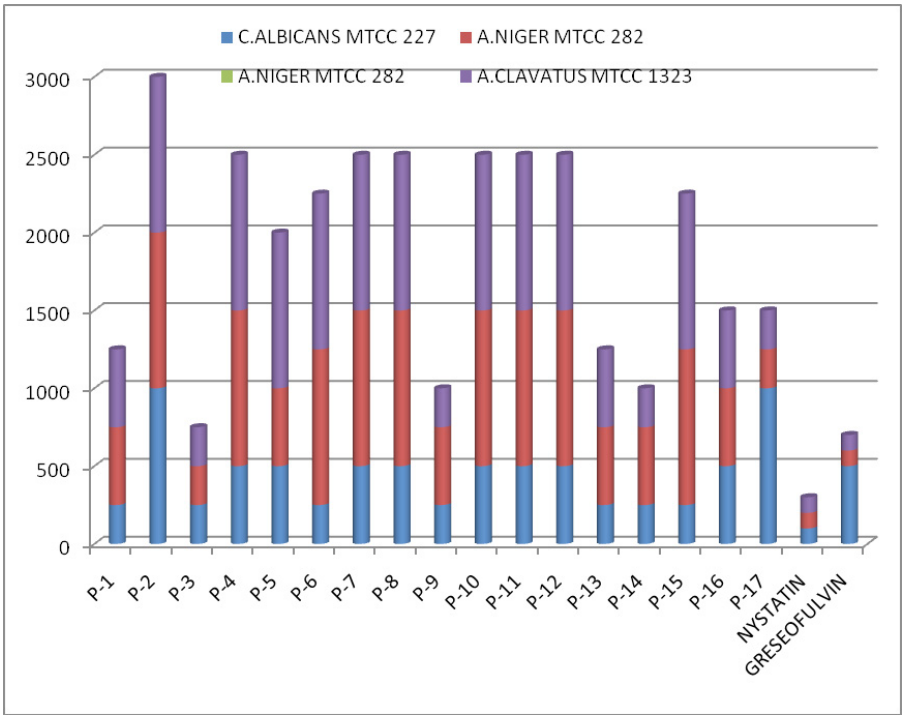
Table 3: Antifungal activity, Minimum Fungicidal Concentration (MIC)[b]
(MIC)[b]: Minimum Inhibitory concentration in µg/mL

ANTIFUNGAL ACTIVITY TABLE			
MINIMAL INHIBITION CONCENTRATION			
CODE NO.	C.ALBICANS MTCC 227	A.NIGER MTCC 282	A.CLAVATUS MTCC 1323
P-1	**250**	500	500
P-2	1000	1000	1000
P-3	**250**	250	250
P-4	**500**	1000	1000
P-5	**500**	500	>1000
P-6	**250**	1000	>1000
P-7	**500**	1000	1000
P-8	**500**	1000	1000
P-9	**250**	500	250
P-10	**500**	1000	1000
P-11	**500**	1000	1000
P-12	**500**	1000	1000
P-13	**250**	500	500
P-14	**250**	500	250
P-15	**250**	1000	1000
P-16	**500**	500	500
P-17	1000	250	250
Standard drugs	MICROGRAMME/mL		
NYSTATIN	100	100	100
GRESEOFULVIN	500	100	100

Graph 1: Antibacterial Activity, Minimum Inhibition Concentration (Graphical form)



Graph 2: Antifungal activity, Minimum Fungicidal Concentration (Graphical Form)



2008,12(3), 347.

5. N.D. Argade, B. K. Kalrale, C.H. Gill, *E-Journal Chemistry*,**2008**, 5 (1): 120-129.
6. M. Kuntal, K.Yadvendra, *Bioorganic & Medicinal Chemistry Letters*,**2009**, 19, 2688-2692.
7. M.Abdul-Aziz, O. M. Aly, Eur. *J. Med. Chem*.**2009**, 44, 3068-3076.
8. F. F. Barsoum, A. S. Girgis, , Eur. *J. Med. Chem*. ,**2009**,44, 2172-2177.
9. A. A. Bekhit, H. M. A. Ashour, Y. S. A. Ghany, A. El-Din, A, Bekhit, A, Baraka, Eur *J. Med. Chem*., **2008**. 43, 456-463.
10. M. Bonesi, M. R. Loizzo, G. A. Statti, S. Michel, F. Tillequin, Menichini, *Bioorg. Med. Chem. Lett*, **2010**, 20, 1990-1993.
11. P.-Ch. Lv., H.-L. Zhu, H.-Q. Li, J. Sun, Y. Zhou,.Bioorg. *Med. Chem*.**2010**, 18 4606-4614.
12. M. S., Christodoulou, L. Sandra, K. M. Kasiotis, S. A. Harotounian, *Bioorg. Med. Chem.*, **2010**, 18, 4338-4350.
13. R. Lin, G. Chiu, Y. Yu, P. J. Connolly, S. Li, Y. Lu, M. Adams, A. R. Fuentes-Pesquera, S. L. Emanuel, L. M. Greenberger, *Bio org. Med. Chem. Lett*, **2007**,17, 4557-4561.
14. D. Jia, Inorganica *ChimicaActa*, **2010**, 363, 289-464.
15. Singaravelmohan, SarkkariAnanthan , *IJSPR*,**2010**, 1(9), 391--396.
16. Sh. R. Pattan, P. A. Rabara, J. S. Pattan, A. A. Bukitagar, V. S. Wakale, D. S. Musmade, *Indian Journal of Chemistry*, **2009**, 48 B, 1453-1456.
17. G. A. Idrees, O. M. Aly, A. A. G. El-Din, AbuoRahma, M.F. Radwan, *Eur. J. Med. Chem*.,**2009**, 44, 397-402.
18. Abu Elmaati, T. M.; El-Taweel, F. M. *J. Heterocyclic Chem*., 2004, **41**, 109-134.
19. N.M Thumar, A.A kaneria, M.Vadodariya, K.Ladva, *journal chem. and pharmaceutical research*,**2017**,9, 340-347.