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# Synthesis, characterization and biological evaluation of some novel carboxamide derivatives of pyrazole

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**ABSTRACT**

*A novel series of Carboxamide derivative of N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide have been synthesized by using different aromatic acid chloride in very good yield. The structures of the synthesized compounds have been characterized by using IR, $^1$H NMR and Mass spectroscopy. All the prepared new NCEs were screened for anti microbial activity and anti fungal activity.*

**Keywords:** Pyrazole, Morpholine, Carboxamide derivatives, Antimicrobial activity

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## INTRODUCTION

Heterocyclic compounds are one of the main groups of organic compounds possessing wide range of applications in various areas of science and high technologies. Many heterocyclic compounds are natural compounds that can also be formed by biosynthesis [1]. Synthesis of pyrazole and its N-substituted analogues has been a topic of regular interest because of the wide applications in pharmaceutical as well as in agrochemical industry and dye industries [2-3]. The pyrazole ring system is a useful structural moiety found in numerous biologically active compounds. Pyrazole is useful structural unit in the field of the medicinal chemistry [4-6] and has been reported to exhibit a variety of biological activities such as analgesic [7], anti-inflammatory [8], antipyretic [9], antibacterial [10,], antifungal [11], anti-cancer [12], anti tubercular [13-14], and anti allergic [15] etc.

In recent years, the number of life-threatening infections caused by multi-drug resistant Gram-positive and Gram negative pathogen bacteria have reached at higher level in many countries around the world [16-17]. A number of antifungal azoles were discovered in the last three decades and are introduced in clinical practice up till now [18]. A number of clinical survey in the United States and worldwide have independently described the emergence of vancomycin resistance in methicillin-resistance Staphylococcus aureus (MRSA) isolates and other human pathogen Gram-negative isolates [19]. Infections caused by these microorganisms pose a serious challenge to the medical community and need for an effective therapy has led to a search for novel antibacterial agents. Literatures report that pyrazole compounds, among their numerous pharmacological properties, possess also antimicrobial activity [20-21].

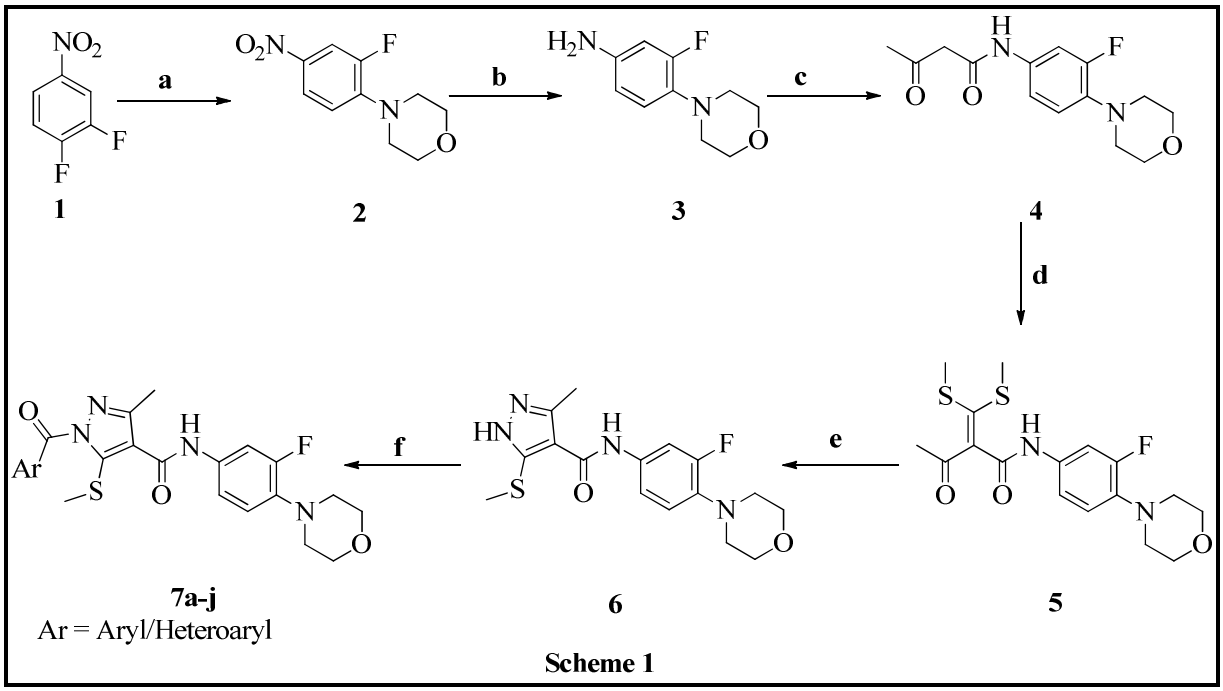
Motivated by all these fact, we aimed the synthesis of a series of novel afore-mentioned findings and as a continuation of our research to develop novel series of carboxamide derivative of N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide.

## EXPERIMENTAL SECTION

All chemicals were purchased from commercial suppliers and used without further purification. The progress of the reaction was monitored by analytical TLC on precoated plates (silica gel 60, F254) and visualized with UV light. Melting points were determined using open capillary tube and are uncorrected. Flash column chromatography was performed with silica gel (60-120 mesh). NMR spectra ($^1$H at 400 MHz) were recorded using DMSO-d$^6$ as a solvent

and chemical shifts are expressed in parts per million (ppm) related to internal TMS. Infrared spectra were determined on a Shimadzu FT-IR. The specifications of the LC/MS are as follows: electrospray (+) ionization, mass range 100-800 Da, 20-V cone voltage, and X terra MS C18 column (2.1 mm x 50 mm x 3.5 µm).

**SCHEME-1**




**Scheme 1**

**Preparation of 4-(2-fluoro-4-nitrophenyl) morpholine (2)**

To a stirred solution of morpholine (30.1g, 345.7mmol) and potassium carbonate (43.4g, 314.3mmol) in N,N-Dimethylformamide (150 ml), 3,4-difluoro nitrobenzene **1** (50.0 g, 314.3mmol) was added at room temperature within 1 hour. The reaction mixture was stirred at room temperature for 3 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into water (750 ml) and stirred for 1 hour. The solid product was filtered and washed with excess of water and dried to yield 4-(2-fluoro-4-nitrophenyl) morpholine **2** (66.0g, 93% yield) as a yellow color solid.

**Preparation of 3-fluoro-4-morpholinoaniline (3)**

To a stirred solution of 4-(2-fluoro-4-nitrophenyl)morpholine **2** (65g, 287.3mmol) in acetone (130 ml) and water (325 ml), sodium dithionite (301.14 g, 1149.4mmol) was added into the reaction mixture lot wise within 2 hours and the reaction mixture was stirred at room temperature for 5 hours. The progress of the reaction was monitored by TLC. The solid product thus separated was filtered and washed with water and dried to yield 3-fluoro-4-morpholinoaniline **3** (40.6g, 72% yield) as a brown color solid.

**Preparation of N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide (4)**

The reaction mixture containing 3-fluoro-4-morpholinoaniline **3** (38g, 193.7 mmol), ethylacetoacetate (27.7g, 213.0 mmol) and catalytic amount of sodium hydroxide (3.8g, 10%) was refluxed in toluene (380 ml) for 30 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture than cooled to room temperature and then toluene layer washed with water (190 ml). The toluene layer was distilled under vacuum by rotary evaporation. The crude material was purified by column chromatography (EtOAc/Hexane, 4:6) to yield N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide **4** (35.8g, 66 yield) as a creamish solid.

**Preparation of 2-(bis(methylthio)methylene)-N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide (5) (ketene dithioacetal derivative)**

To a stirred solution of N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide **4** (32g, 114.2 mmol) in N,N-Dimethylformamide (100 ml), dried potassium carbonate (17.36g, 125.6 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. To this reaction mixture carbon disulfide (17.15g, 228.3 mmol) was added and the reaction mixture was stirred for additional 2 hours. Then the reaction mixture was cooled to 0-5°C and methyl iodide (34.05g, 239.8mmol) was added within 30 minutes and stirred it for 3 hours at room temperature. The progress of the reaction was monitored by TLC. After completion of reaction, the mixture was poured into water (500 ml) and stirred it for 30 minutes. The precipitated solid material was filtered and washed with water and

dried to afford 2-(bis (methylthio) methylene)-N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide **5** (ketene dithioacetal derivative) (34.2g, 78% yield) as a yellow color solid which was used directly for the next stage.

**Preparation of N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (6)**

To a stirred solution of 2-(bis (methylthio) methylene)-N-(3-fluoro-4-morpholino phenyl) -3-oxobutanamide **5** (ketene dithioacetal derivative) (32g, 83.2 mmol) and hydrazine hydrate (8.3g, 166.4 mmol) in isopropyl alcohol (160 mL) was refluxed for 4 hours. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and water (160 mL) was added. The reaction mixture was stirred for 1 hour at room temperature. The precipitated solid material was filtered, washed with water, dried and crystallized from isopropyl alcohol to afford N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide **6** (21.8g, 75% yield) as a yellow color solid.

**General procedure for the preparation of N-(3-fluoro-4-morpholinophenyl)-3-methyl-1-(aroyl)-5-(methylthio) -1H-pyrazole-4-carboxamide (7a-j)**

To a stirred solution of N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide **6** (2.8 mmol) and triethylamine (4.3 mmol) in dichloromethane (5 mL) at room temperature, a solution of different substituted aromatic acid chloride (3.1 mmol) in dichloromethane (5ml) was added. The reaction mixture was stirred at room temperature for 1 hour. The progress of the reaction was monitored by TLC. After completion of reaction, organic layer was washed with water (10 ml). Organic layer and aqueous layer were separated. Organic layer was concentrated in vacuum by rotary evaporator to afford crude material which was crystallized in acetone to give pure N-(3-fluoro-4-morpholinophenyl)-3-methyl-1-(aroyl)-5-(methylthio)-1H-pyrazole-4-carboxamide **7a-j** as a white to off white color solid compound in 48-92% yield.

**Table-1: Physical data for the product 7a-j**

| Sr. No. | Compound Code | Ar | M.P. (°C) | Yield (%) | M. F. | M. Wt. |
|---|---|---|---|---|---|---|
| 1 | 7a | 4-Nitro phenyl | 189-191 | 54 | $C_{23}H_{22}FN_5O_5S$ | 499.51 |
| 2 | 7b | Thiophene | 230-232 | 85 | $C_{21}H_{21}FN_4O_3S_2$ | 460.54 |
| 3 | 7c | 5-Chloro thiophene | 220-222 | 89 | $C_{21}H_{20}ClFN_4O_3S_2$ | 494.99 |
| 4 | 7d | 4-Methyl phenyl | 199-201 | 90 | $C_{24}H_{25}FN_4O_3S$ | 468.54 |
| 5 | 7e | 2-Methoxy phenyl | 141-143 | 68 | $C_{24}H_{25}FN_4O_4S$ | 484.54 |
| 6 | 7f | 3-Methoxy phenyl | 156-158 | 73 | $C_{24}H_{25}FN_4O_4S$ | 484.54 |
| 7 | 7g | 4-Methoxy phenyl | 187-189 | 81 | $C_{24}H_{25}FN_4O_4S$ | 484.54 |
| 8 | 7h | m-Phenoxy phenyl | 120-122 | 92 | $C_{29}H_{27}FN_4O_4S$ | 546.61 |
| 9 | 7i | 2-pyridyl | 192-194 | 48 | $C_{22}H_{22}FN_5O_3S$ | 455.51 |
| 10 | 7j | 4-pyridyl | 201-203 | 56 | $C_{22}H_{22}FN_5O_3S$ | 455.51 |

**N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1-(4-nitrophenyl)-1H-pyrazole-4-carboxamide (7a)**

Yield: 54 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.536 (s,3H), 2.912 (s,3H), 2.997-3.019 (t,4H), 3.852-3.974 (t,4H), 6.912-6.957 (t, 1H), 7.212-7.235 (dd, 1H), 7.472-7.497 (m, 2H), 7.543-7.582 (dd, 1H), 8.165-8.188 (m, 2H), 10.259 (s, 1H) ppm; MS: m/z 499.3 $(M+1)^+$; IR Cm$^{-1}$: 3338.78, 2955.87, 2875.86, 1701.22, 1598.99, 1513.62, 1277.29, 1122.57

**N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1-(thiophene-2-carbonyl)-1H-pyrazole-4-carboxamide (7b)**

Yield: 85 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.589 (s,3H), 2.953 (s,3H), 3.052-3.079 (t,4H), 3.872-3.892 (t,4H), 6.916-6.962 (t, 1H), 7.102-7.124 (m, 1H), 7.210-7.238 (dd, 1H), 7.5437.587 (dd, 1H), 7.760-7.879 (m, 2H), 10.322 (s, 1H) ppm MS: m/z 460.2 $(M+1)^+$ ; IR Cm$^{-1}$: 3338.78, 3259.70, 2956.87, 1685.79, 1595.13, 1508.33, 1246.02, 1114.86

**1-(5-chlorothiophene-2-carbonyl)-N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (7c)**

Yield: 89 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ=2.658 (s,3H), 2.709 (s,3H), 2.955-2.977 (t,4H), 3.728-3.750 (t,4H), 7.019-7.065 (t, 1H), 7.316-7.337 (d, 1H), 7.379-7.390 (t, 1H), 7.556-7.598 (dd, 1H), 8.139-8.150 (d, 1H), 10.256 (s, 1H) ppm MS: m/z 495.0 $(M(Cl^{35})+1)^+$ 497.2 $(M(Cl^{37})+1)^+$; IR Cm$^{-1}$: 3259.70, 2858.51, 1687.71, 1593.20, 1516.05, 1244.09, 1116.78

**N-(3-fluoro-4-morpholinophenyl) -3-methyl-1-(4-methyl benzoyl)-5-(methyl thio)-1H-pyrazole-4-carboxamide (7d)**

Yield: 90 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ=2.456 (s,3H), 2.573 (s,3H), 2.940 (s, 3H), 3.058-3.082 (t,4H), 3.870-3.893 (t,4H), 6.906-6.951 (t, 1H), 7.216-7.241 (dd, 1H), 7.264-7.301 (t, 2H), 7.548-7.589 (dd, 1H), 7.896-7.918 (d, 2H), 8.388 (s, 1H) ppm; MS: m/z 469.2 $(M+1)^+$; IR Cm$^{-1}$: 3338.78, 3260.72, 2875.86, 1695.58, 1598.90,

1508.21, 1271.62, 1122.28

**N-(3-fluoro-4-morpholinophenyl)-1-(2-methoxybenzoyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (7e)**
Yield: 68 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.574 (s,3H), 2.936 (s,3H), 3.983 (s, 3H), 2.993-3.016 (t,4H), 3.805-3.830 (t,4H), 6.903-7.075 (m, 2H), 7.218-7.246 (m, 2H), 7.466-7.586 (m, 2H), 7.834-7.856 (m, 1H), 10.254 (s, 1H) ppm; MS: m/z 484.2 $(M+1)^+$; IR Cm$^{-1}$: 3338.78, 2875.86, 1701.22, 1598.99, 1516.05, 1273.02, 1122.57

**N-(3-fluoro-4-morpholinophenyl)-1-(3-methoxybenzoyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (7f)**
Yield: 73 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.409 (s,3H), 2.890 (s,3H), 3.975 (s, 3H), 3.048-3.070 (t,4H), 3.862-3.887 (t,4H), 6.908-7.055 (m, 2H), 7.200-7.225 (dd, 1H), 7.434-7.458 (t, 1H), 7.540-7.772 (m, 3H), 10.250 (s, 1H) ppm; MS: m/z 484.1 $(M+1)^+$; IR Cm$^{-1}$: 3338.78, 2875.86, 1701.22, 1598.99, 1516.05, 1273.02, 1122.57

**N-(3-fluoro-4-morpholinophenyl)-1-(4-methoxybenzoyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (7g)**
Yield: 81 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.540 (s,3H), 2.891 (s,3H), 3.982 (s, 3H), 3.052-3.076 (t,4H), 3.869-3.891 (t,4H), 6.904-6.948 (t, 1H), 7.132-7.156 (d, 2H), 7.210-7.235 (dd, 1H), 7.543-7.580 (dd, 1H), 7.965-7.986 (d, 2H), 10.248 (s, 1H) ppm; MS: m/z 484.1 $(M+1)^+$; IR Cm$^{-1}$: 3338.78, 3259.70, 2956.87, 2875.86, 1697.99, 1598.99, 1513.23, 1271.54, 1114.21

**N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1-(4-phenoxybenzoyl)-1H-pyrazole-4-carboxamide (7h)**
Yield: 92 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ=2.494 (s,3H), 2.934 (s,3H), 3.056-3.078 (t,4H), 3.869-3.890 (t,4H), 6.902-6.947 (t, 1H), 7.042-7.062 (d, 2H), 7.133-7.169 (t, 1H), 7.201-7.223 (d, 1H), 7.263-7.292 (d, 1H), 7.350-7.389 (t, 2H), 7.439-7.479 (t, 1H), 7.530-7.569 (dd, 1H), 7.629 (s, 1H) 7.720-7.740 (d, 1H), 8.289 (s, 1H) ppm MS: m/z 547.1 $(M+1)^+$; IR Cm$^{-1}$: 3263.56, 2856.58, 1699.29, 1641.42, 1591.27, 1489.05, 1120.94, 1120.64

**N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1-picolinoyl-1H-pyrazole-4-carboxamide (7i)**
Yield: 48 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.575 (s,3H), 2.890 (s,3H), 3.048-3.072 (t,4H), 3.970-3.794 (t,4H), 6.900-6.944 (t, 1H), 7.116-7.230 (dd, 1H), 7.542-7.603 (m, 2H), 7.963-7.985 (m, 1H), 8.021-8.045 (dd, 1H), 8.626-8.639 (dd, 1H), 8.280 (s, 1H) ppm MS: m/z 455.1 $(M+1)^+$; IR Cm$^{-1}$: 3338.78, 3268.23, 2872.68, 1701.22, 1585.46, 1513.21, 1271.25, 1113.78

**N-(3-fluoro-4-morpholinophenyl)-1-isonicotinoyl-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide (7j)**
Yield: 56 %. $^1$H NMR (400 MHz, DMSO-d$^6$): δ = 2.611 (s,3H), 2.960 (s,3H), 3.061-3.093 (t,4H), 875-3.899 (t,4H), 6.913-6.965 (t, 1H), 7.222-7.246 (dd, 1H), 7.543-7.584 (dd, 1H), 7.961-7.973 (d, 2H), 8.709-8.872 (d, 2H), 8.267c (s, 1H) ppm MS: m/z 455.1 $(M+1)^+$; IR Cm$^{-1}$: 3338.65, 3254.85, 2872.68, 1703.51, 1585.46, 1513.21, 1271.25, 1113.78

## RESULTS AND DISCUSSION

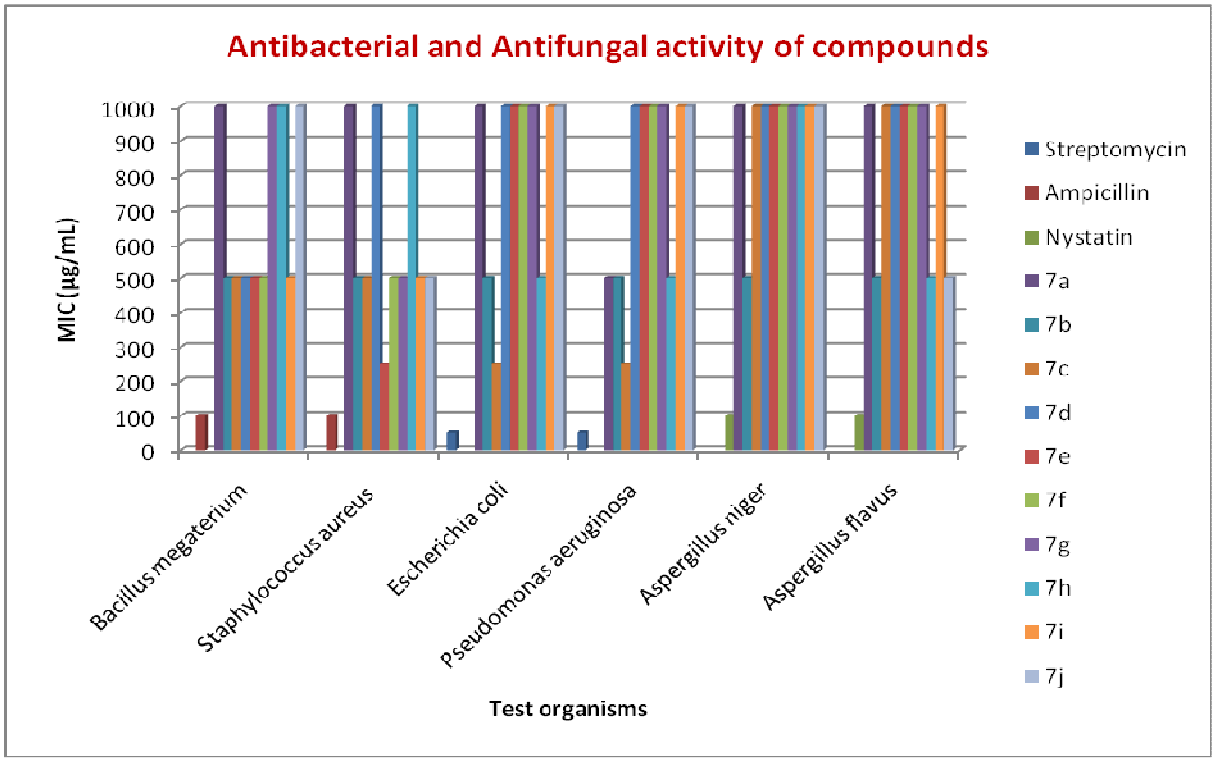
The synthesis of N-(3-fluoro-4-morpholinophenyl)-3-methyl-1-(aroyl)-5-(methylthio)-1H-pyrazole-4-carboxamide is outlined in **scheme-1**. 3,4-difluoro nitrobenzene is reacted with morpholine in the presence of base to give 4-(2-fluoro-4-nitrophenyl) morpholine, which is reduced with sodium dithionite to affords N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide. This amino compound is reacted with ethylacetoacetate in the presence of catalytic amount of sodium hydroxide to afford actoacetamide derivatives, which on reaction with carbon disulfide in the presence of potassium carbonate, followed by methyl iodide to yield of 2-(bis(methylthio)methylene)-N-(3-fluoro-4-morpholinophenyl)-3-oxobutanamide 5 (ketene dithioacetal derivative). Ketene dithioacetal derivatives cyclized with hydrazine hydrate to give pyrazole derivative as N-(3-fluoro-4-morpholinophenyl)-3-methyl-5-(methylthio)-1H-pyrazole-4-carboxamide, which on reaction with different acid chloride in the presence of triethylamine to afford N-(3-fluoro-4-morpholinophenyl)-3-methyl-1-(aroyl)-5-(methylthio)-1H-pyrazole-4-carboxamide.

**Antimicrobial activity**
The *in vitro* antimicrobial activity of all the synthesized compounds was carried out by broth micro dilution method. Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. The appropriate inoculum size for standard MIC is 104 to 105 CFU/ml.

**Table-2: Antibacterial and antifungal activity of N-(3-fluor-4-morpholinophenyl)-3-methyl-1-(aroyl)-5-(methylthio)-1H-pyrazole-4-carboxamide derivatives (7a-j)**

| Compounds | Antibacterial MIC (µg/mL) | | | | Antifungal MIC (µg/mL) | |
|---|---|---|---|---|---|---|
| | *B. megaterium* MTCC2444 | *S. aureus* MTCC737 | *E. coli* MTCC1687 | *P. aeruginosa* MTCC3541 | *A. niger* MTCC282 | *A. flavus* MTCC418 |
| Streptomycin | | | 50 | 50 | | |
| Ampicillin | 100 | 100 | | | | |
| Nystatin | | | | | 100 | 100 |
| 7a | 1000 | 1000 | 1000 | 500 | 1000 | 1000 |
| 7b | 500 | 500 | 500 | 500 | 500 | 500 |
| 7c | 500 | 500 | 250 | 250 | 1000 | 1000 |
| 7d | 500 | 1000 | 1000 | 1000 | 1000 | 1000 |
| 7e | 500 | 250 | 1000 | 1000 | 1000 | 1000 |
| 7f | 500 | 500 | 1000 | 1000 | 1000 | 1000 |
| 7g | 1000 | 500 | 1000 | 1000 | 1000 | 1000 |
| 7h | 1000 | 1000 | 500 | 500 | 1000 | 500 |
| 7i | 500 | 500 | 1000 | 1000 | 1000 | 1000 |
| 7j | 1000 | 500 | 1000 | 1000 | 1000 | 500 |

**Figure-1: Antibacterial and antifungal activity chart**




Minimal bactericidal concentration showed that, some of the newly synthesized compound showed little improved bactericidal activity. All compounds displayed moderate to poor activity against all bacterial strains compared to standard drug. Compounds **7b** (Thiophene) is broad spectrum drug which can inhibit the growth of gram positive, gram negative bacteria and fungi. It is observed that **7c** (5-Chloro thiophene) displayed good activity against *Escherichia coli* & *Pseudomonas aeruginosa* but moderate activity against *Bacillus megaterium* & *Staphylococcus aureus*.

Compound **7b** (Thiophene)**, 7e** (2-Methoxy phenyl)**, 7f** (3-Methoxy phenyl) and **7i** (2-pyridyl) is active against gram positive bacteria and **7c** (5-Chloro thiophene) is active against only gram negative bacteria, while all other derivatives showed moderate to poor activity.

Minimal fungicidal activity showed that compound **7b** (Thiophene) displayed good activity against *Aspergillus niger* and *Aspergillus flavus.* Compound **7h** (m-Phenoxy phenyl) showed moderate activity against *Aspergillus flavus* and poor activity against *Aspergillus niger*. Similarly Compound **7j** (4-pyridyl) showed moderate activity against *Aspergillus flavus* and poor activity against *Aspergillus niger*, while remaining all possessed poor activity against all fungal stains.

## CONCLUSION

An efficient method for preparing carboxamide derivatives of pyrazole was described and the structure of synthesized compounds was determine by IR, $^1$H NMR and Mass spectroscopic analysis and evaluated for their in vitro antimicrobial activity by broth dilution method.

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## REFERENCES

[1] Menpara, K.; Pansuriya, D.; Kachhadiya, N.; Menpara, J.; Ladva, K. *J. Appl. Chem.,* **2014**, *3*, 535–540.
[2] Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.,* **2003**, *44*, 6737–6740.
[3] Thakare, N. R.; Dhawas, A. K.; Ganoskar, P. S.; Kale, P. D. *J. Chem. Pharm. Res.,* **2012**, *4*, 3329–3332.
[4] Sharmat, S.; Srivastava, V. K.; Kumar, A. *Indian J. Chem.,* **2002**, *41B*, 2647–2654.
[5] Sawhney, S. N.; Bhutani, S.; Vir, D. *Indian J. Chem.,* **1989**, *28(B)*, 667.
[6] A. Dandia, V. Sehgal, P. S. *Indian J. Chem.,* **1993**, *32(B)*, 1288.
[7] Sauzem, P. D.; Machado, P.; Rubin, M. A.; Anna, S. S.; Faber, H. B.; Souza, A. H. De; Mello, C. F.; Beck, P.; Burrow, R. A.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *Eur. J. Med. Chem.,* **2008**, *43*, 1237–1247.
[8] Ashish Kumar Tewari, Priyanka Srivastava, Ved Prakash Singh, Amit Singh, Raj Kumar Goel, C. G. M. *Chem. Pharm. Bull.,* **2010**, *58* (5), 634–638.
[9] Souza, F. R.; Souza, V. T.; Ratzlaff, V.; Borges, L. P.; Oliveira, M. R.; Bonacorso, H. G.; Zanatta, N.; Martins, M. a P.; Mello, C. F. *Eur. J. Pharmacol.,* **2002**, *451*, 141–147.
[10] Thumar, N. J.; Patel, M. P. *Saudi Pharm. J.,* **2011**, *19*, 75–83.
[11] Tandon, V. K.; Yadav, D. B.; Chaturvedi, A. K.; Shukla, P. K. *Bioorganic Med. Chem. Lett.,* **2005**, *15* (13), 3288–3291.
[12] arag, A. M.; Ali, K. a K.; El-Debss, T. M. a; Mayhoub, A. S.; Amr, A. G. E.; Abdel-Hafez, N. a.; Abdulla, M. M. *Eur. J. Med. Chem.,* **2010**, *45* (12), 5887–5898.
[13] Manfredini, S.; Bazzanini, R.; Baraldi, G.; Guarneri, M.; Simoni, D.; Marongiu, M. E.; Pani, A.; Tramontano, E.; Colla, P. La. *J. Med. Chem.,* **1992**, *35*, 917–924.
[14] Nayak, N.; Ramprasad, J.; Dalimba, U. *Bioorg. Med. Chem. Lett.,* **2015**, *25*, 5540–5545.
[15] Parsia, M. T. Di; Suiirez, C.; Vitolo, M. J.; Victor E. Mdrquez. *J. Med. Chem.,* **1981**, *24*, 117–119.
[16] Berber, I.; C. Cokmus; E. Atalan. *Microbiology.,* **2003**, *72*, 54–59.
[17] Mitscher, L. A.; S.P. Pillai; E.J. Gentry; Shankel, D. M. *Med. Res. Rev.,* **1999**, *19*, 477.
[18] Patil, A.; Jadhav, R.; Raundal, H.; Sharma, L.; Badgujar, R.; Bobade, V. *J. Chem. Pharm. Res.,* **2014**, *6*, 218–223.
[19] Lee, V. J.; Hecker, S. J. *J. Med. Res. Rev.,* **1999**, *19*, 521–542.
[20] Pimerova, E. V.; E.V.Voronina. *Pharm. Chem. J.,* **2001**, *35*, 18–20.
[21] Chornous, V. A.; M.K. Bratenko; M.V. Vovk. *Pharm. Chem. J.,* **2001**, *35*, 26–28.