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DESIGN, SYNTHESIS AND *IN-VITRO* ANTI-INFLAMMATORY, ANTIMICROBIAL ACTIVITIES OF SOME NOVEL MANNICH BASES OF PYRAZOLE-1-CARBOTHIOAMIDE DERIVATIVES

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ABSTRACT:
A novel series of Mannich Bases of Pyrazole-1-Carbothioamide Derivatives **(7a-g)** was synthesized by first cyclocondensation of chalcones **(3a-g)** with thiosemicarbazide to obtained 5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide**(5a-g)**, which further refluxed with 4-chloroaniline **(6)** and formaldehyde in methanol for 6-10 hrs. to afford Mannich Bases of Pyrazole-1-Carbothioamide derivatives i.e. 4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide **(7a-g)**. The structural identification of products is reported by IR and ^{1}H-NMR spectral data as well as analytical and physical data and also the synthesized compounds were screened for their *in-vitro* anti-inflammatory and antimicrobial activity.

KEYWORDS: Chalcones; Pyrazoles; carbothioamide; *in-vitro* anti-inflammatory, antimicrobial activity.

INTRODUCTION

Discovery of heterocyclic nucleus continuously attracted attention of organic chemists due to their various biological activities. The recent literature survey revealed that Pyrazole-1-Carbothioamide and Mannich Bases are familiar class of heterocyclic moieties possessing a wide variety of biological activities and their utility in medicine is very much established. Among Pyrazoles, 2-pyrazolines are widely used as useful precursor in organic synthesis and having various biological activities [I, II]. Many Pyrazole-1-Carbothioamide derivatives possess widespread pharmacological and biological activities, such asantimicrobial [III, IV], anti-inflammatory[V],antiviral[VI], antioxidant[VII], anticonvulsant[VIII-X], anticancer[XI]and hypotensive[XII].
Several medicinally useful Mannich base has been reviewed by various scientist [XIII-XV].

It has wide application in organic synthesis and many drug molecules [XVI]. Along with this Mannich bases also possess biological activities like antibacterial[XVII], antifungal[XVIII], anti-inflammatory[XIX], anticancer[XX], anticonvulsant[XXI], anthelmintic[XXII], antitubercular[XXIII], analgesic[XXIV], anti-HIV[XXV],antimalarial[XXVI], antiviral [XXVII].

In continuation of the our research work [XXVIII, XXIX], the synthesis of some novel series of Mannich Bases of Pyrazole-1-Carbothioamide Derivatives i.e. 4-(((4-chlorophenyl)amino) methyl)-5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide are reported herein.

MATERIALS AND METHODS

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Perkin–Elmer spectrometer.^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel $60F_{254}$ with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm). Physical constants and analytical data of all the compoundsreported in this paper.

General procedure for the synthesis of 1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one(Chalcone)[XIV] (3a-g).

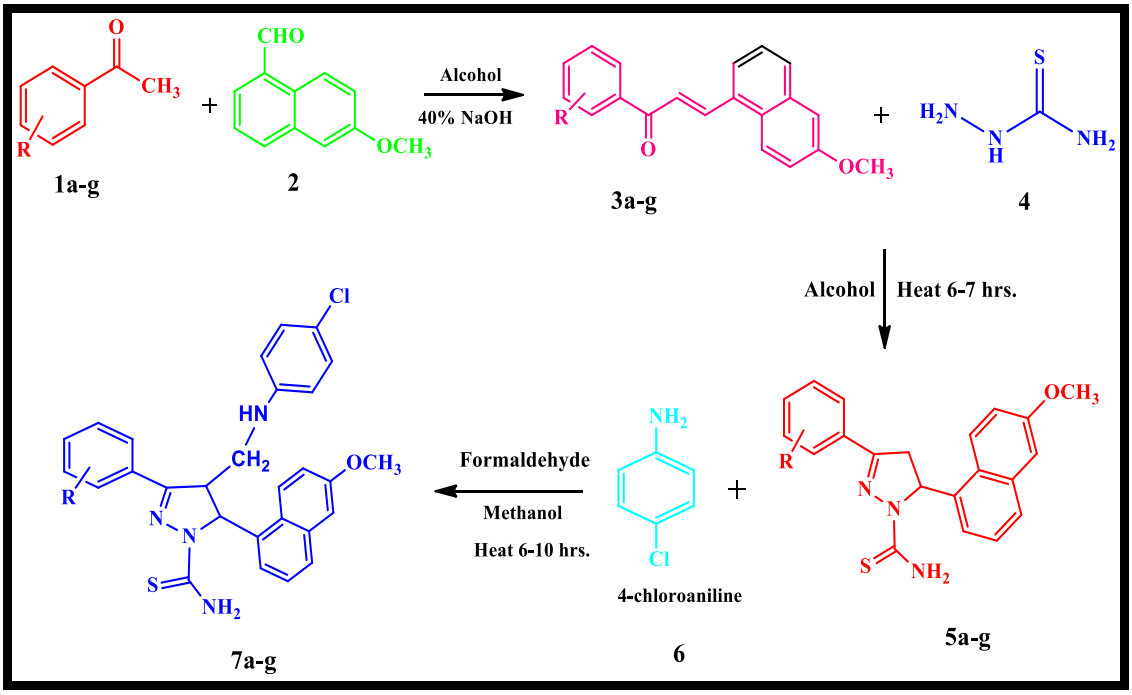
A mixture of substituted acetophenone**(1a-g)**(0.01mol) and 6-methoxy-1-naphthaldehyde (**2)**(0.01mol) was stirred in ethanol (30 ml) and thensodium hydroxide solution (15 ml, 0.02 mol) was added to it. The reaction mixture was kept overnight at room temperature and then it was poured on crushed ice and acidified with dilute hydrochloric acid. The Chalcone i.e. [1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one] **(3a-g)** precipitate out as solid. Then it was filtered, dried and purified by crystallization from acetic acid. Percentage yield and physical constants were recorded.

General procedure for the synthesis of`5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (5a-g)

A mixture of 1-(4-substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one **(3a-g)**(0.01mole) and thiosemicarbazide (0.02mole) in 50 mL ethanolwas reflux for 6-8 hrs., excess ethanol was distilled and the resulting solution was keptovernight at room temperature and then it was poured on crushed ice,the precipitate of 5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide**(5a-g)** separated out. Then it was filtered, dried and purified by crystallization from acetic acid. Percentage yield and physical constants were recorded.

General Procedure for Synthesis ofMannich basesof Pyrazole-1-Carbothioamide (7a-g)

In a clean & dry round bottom flask a solution of compounds 5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide**(5a-g)**(0.01mol) in methanol (30ml), formaldehyde (0.02mol) and corresponding 4-chloroaniline (0.02mol) were added. The reaction-mixture was refluxed for 6 -10 h. The solvent was distilled off and the residue was poured into ice water. The precipitate solid was filtered off, dried and recrystallized from ethanol. Percentage yield and physical constants were recorded.



Scheme-1:4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

RESULT AND DISCUSSION

In the present research paper, some novel Mannich Bases of Pyrazole-1-Carbothioamide derivatives**(7a-g)** are synthesized by reacting different substituted acetophenones **(1a-g)** with 6-methaoxy-1-napthaldehyde **(2)** in alcoholic sodium hydroxide to obtained Chalcones **(3a-g)** as an intermediate, which on further reacting with thiosemicarbazide**(4)** to obtained5-(6-methoxynaphthalen-1-yl)-3-(Substitutedphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide **(5a-g).** Further it is refluxed with 4-chloroaniline **(6)**and formaldehyde in methanol for 6-10 hrs.to afford Mannich Bases of Pyrazole-1-Carbothioamide derivativesi.e. 4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-(Substituted phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide**(7a-g).**Structure of synthesized Mannich bases of Pyrazole-1-Carbothioamide derivativeswas confirmed on the basis of Spectral data (IR, ^{1}H NMR, mass and elemental analysis) anddeterminefor*in-vitro* anti-inflammatory, antimicrobial activities. From spectral andanalytical data it is full agreement with the synthesized products. The IR spectrum of **7a-g** exhibited absorption peak at 3132, 3230, 3435 cm^{-1}it is due to (NH, NH_2).Further on explaining^{1}H NMR (DMSO) spectrums;it appears an additional peak at δ 6.55-6.45 ppm was assigned due to CH_2 of Mannich base of Pyrazole-1-Carbothioamide derivatives. The antimicrobial and *in-vitro* anti-inflammatory data revealed that most of synthesized derivative are promising to moderately active.

Spectral data of compounds

(7a):4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield: 80%, M.P. 155 ^{0}C. Elemental analysis Cal. for$C_{28}H_{25}Cl_2N_4OS$;C, 67.12; H, 5.03; N, 11.18; O, 3.19; found:C, 67.02; H, 5.13; N, 11.10; O, 3.15:IR (KBr pellets Cm^{-1}): 3132, 3230, 3435 cm−1 (NH, NH_2), 3052 (Aromatic C-H stretching), Aliphatic C-H (2833), 1650 (>C=O), 1610 (C=N, pyrazoline ring), 1510 (C=C), 1166 (C=S), 1152 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.65-8.40 (m, 6H, Ar-H), 7.66-7.52(5H, m, Ar-H),7.20 (bs, 2H, NH_2), 6.92-6.76(4H, m, Ar-H), 6.55-6.40(2H, d, CH_2), 5.26(1H, s, HN-Ar), 5.20-5.10(1H, d, -CH), 3.85 (s, 3H, OCH_3), 3.35-3.22(1H, m, -CH).; Mass (m/z): 501.04 (M+1).

(7b):3-(4-chlorophenyl)-4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield: 80%, M.P. 162^{0}C. Elemental analysis Cal. for$C_{28}H_{24}Cl_2N_4OS$;C, 62.80; H, 4.52; N, 10.46; O, 2.99; found:C, 62.70; H, 4.45; N, 10.40; O, 2.91:IR (KBr pellets Cm^{-1}):3134, 3234, 3440 cm−1 (NH, NH_2), 3046 (Aromatic C-H stretching), Aliphatic C-H b(2824), 1655 (>C=O), 1608 (C=N, pyrazoline ring), 1505 (C=C), 1167 (C=S),1150 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.62-8.42 (m, 6H, Ar-H), 7.63-7.53(4H, m, Ar-H), 7.24 (bs, 2H, NH_2),6.91-6.66(4H, m, Ar-H), 6.50-6.42(2H, d, CH_2), 5.30(1H, s, HN-Ar), 5.25-5.18(1H, d, -CH), 3.83 (s, 3H, OCH_3), 3.31-3.18(1H, m, -CH).; Mass (m/z): 535.49 (M+1).$C_{28}H_{24}Cl_2N_4OS$, C, 62.80; H, 4.52; Cl, 13.24; N, 10.46; O, 2.99; S, 5.99

(7c):3-(4-bromophenyl)-4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield:82%, M.P. 160^{0}C. Elemental analysis Cal. for $C_{28}H_{24}BrClN_4OS$;C, 57.99; H, 4.17; N, 9.66; O, 2.76; found:C, 57.90; H, 4.11; N, 9.59; O, 2.70: IR (KBr pellets Cm^{-1}): 3130, 3230, 3436 cm−1 (NH, NH_2),3045 (Aromatic C-H stretching), Aliphatic C-H (2815), 1650 (>C=O), 1620 (C=N, pyrazoline ring), 1510 (C=C), 1162 (C=S),1155 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.60-8.38 (m, 6H, Ar-H), 7.65-7.55(4H, m, Ar-H), 7.27 (bs, 2H, NH_2), 6.90-6.62(4H, m, Ar-H), 6.54-6.45(2H, d, CH_2), 5.28(1H, s, HN-Ar), 5.23-5.10(1H, d, -CH), 3.85 (s, 3H, OCH_3),3.29-3.16(1H, m, -CH).; Mass (m/z): 578.05(M+1).

(7d):4-(((4-chlorophenyl)amino)methyl)-3-(4-fluorophenyl)-5-(6-methoxynaphthalen-1-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield:75%, M.P. 170^{0}C. Elemental analysis Cal. for$C_{28}H_{24}ClFN_4OS$;C, 64.79; H, 4.66; N, 10.79; O, 3.08; found:C, 64.68; H, 4.61; N, 10.70; O, 3.12:IR (KBr pellets Cm^{-1}):3134, 3232, 3436 cm−1 (NH, NH_2),3042 (Aromatic C-H stretching), Aliphatic C-H (2826), 1645 (>C=O), 1610 (C=N, pyrazoline ring), 1518 (C=C), 1167 (C=S),1140 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.54-8.47 (m, 6H, Ar-H), 7.60-7.42(4H, m, Ar-H), 7.18 (bs, 2H, NH_2), 6.92-6.65(4H, m, Ar-H), 6.55-6.42(2H, d, CH_2), 5.21(1H, s, HN-Ar), 5.27-5.21(1H, d, -CH), 3.82 (s, 3H, OCH_3),3.30-3.15(1H, m, -CH).; Mass (m/z): 519.03(M+1).

(7e):4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-(p-tolyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield: 85%, M.P. 156^{0}C. Elemental analysis Cal. for $C_{29}H_{27}ClN_4OS$;C, 67.62; H, 5.28; N, 10.88; O, 3.11; found:C, 67.55; H, 5.21; N, 10.78; O, 3.01: IR (KBr pellets Cm^{-1}): 3125, 3227, 3430 cm−1 (NH, NH_2), 3032 (Aromatic C-H streaching), Aliphatic C-H (2810), 1640 (>C=O), 1623 (C=N, pyrazoline ring), 1525 (C=C),1160 (C=S), 1135 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.60-8.41 (m, 6H, Ar-H), 7.61-7.52(4H, m, Ar-H), 7.20 (bs, 2H, NH_2), 6.87-6.54(4H, m, Ar-H), 6.61-6.41(2H, d, CH_2), 5.23(1H, s, HN-Ar), 5.21-5.12(1H, d, -CH), 3.74 (s, 3H, OCH_3),3.35-3.22(1H, m, -CH), 2.71 (s, 3H, -CH_3); Mass (m/z): 514.16 (M+1).

(7f):4-(((4-chlorophenyl)amino)methyl)-5-(6-methoxynaphthalen-1-yl)-3-(4-methoxy phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield: 72%, M.P. 155^{0}C. Elemental analysis Cal. for $C_{29}H_{27}ClN_4O_2S$;C, 65.59; H, 5.12; N, 10.55; O, 6.03; found:C, 65.50; H, 5.02; N, 10.45; O, 6.14: IR (KBr pellets Cm^{-1}): 3140, 3237, 3438 cm−1 (NH, NH_2), 3030 (Aromatic C-Hstreaching), Aliphatic C-H (2820), 1635 (>C=O), 1640 (C=N, pyrazoline ring), 1530 (C=C), 1170 (C=S),1145 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.62-8.47 (m, 6H, Ar-H), 7.60-7.55(4H, m, Ar-H), 7.15 (bs, 2H, NH_2), 6.91-6.75(4H, m, Ar-H), 6.57-6.45(2H, d, CH_2), 5.25(1H, s, HN-Ar), 5.19-5.07(1H, d, -CH), 3.84 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3),3.28-3.10(1H, m, -CH).; Mass (m/z): 531.07 (M+1).

(7g):4-(((4-chlorophenyl)amino)methyl)-3-(2,4-dichlorophenyl)-5-(6-methoxynaphthalen-1-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide

Yield: 65%, M.P. 160^{0}C. Elemental analysis Cal. for $C_{28}H_{23}Cl_3N_4OS$;C, 59.01; H, 4.07; N, 9.83; O, 2.81; found:C, 59.12; H, 4.01; N, 9.73; O, 2.70:IR (KBr pellets Cm^{-1}): 3133, 3238, 3440 cm−1 (NH, NH_2), 3052 (Aromatic C-H streaching), Aliphatic C-H (2830), 1640 (>C=O), 1608 (C=N, pyrazoline ring), 1535 (C=C), 1165 (C=S),1144 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) 8.60-8.47 (m, 6H, Ar-H), 7.61-7.56 (4H, m, Ar-H), 7.22 (bs, 2H, NH_2), 6.93-6.65(3H, m, Ar-H), 6.51-6.45(2H, d, CH_2), 5.27(1H, s, HN-Ar), 5.20-5.08(1H, d, -CH), 3.81 (s, 3H, OCH_3),3.30-3.20(1H, m, -CH).; Mass (m/z): 569.93(M+1).

Biological activity:

In-vitro anti-inflammatory activity[30,31].

The standard drug and synthesized Mannich bases of Pyrazole-1-Carbothioamide derivatives**(7a-g)** was dissolve in minimum amount of dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, pH 7.4). Final concentration of DMF in all solutions was less than 2.0%. Test solution (1 ml) containing different concentration of drugs was mixed with 1 ml of 1% mM albumin solution in phosphate buffer and incubated at 27±1^{0}C in BOD incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 60±1 ^{0}C in water bath for 10 min. After cooling, the turbidity was measured at 660nm (UV-Visible Shimadzu Spectrophotometer). Percentage of inhibition of denaturation was calculated from control where no drug was added. Each experiment was done in triplicate and average was taken. The ibuprofen was used as standard drug. Results are tabulated in **Table 1.**

$$\% \text{ of inhibition } = \left(\frac{Vt}{Vc} - 1 \right) X\ 100$$

Where, Vt = Mean absorbance value of test group.

Vc = Mean absorbance value of control group

TABLE 1- ANTI-INFLAMMATORY ACTIVITY OF SYNTHESIZED COMPOUNDS(7a-g)

Sr. No.	Compounds	Mean absorbance value ± SEM	Inhibition of denaturation (in %)
1	Control	0.0850	-
2	Ibuprofen	0.162 ± 0.008	90.58
3	7a	0.102 ± 0.002	20.00
4	7b	0.115 ± 0.002	35.29
5	7c	0.134 ± 0.002	57.64
6	7d	0.141 ± 0.007	65.88
7	7e	0.102 ± 0.002	20.00
8	7f	0.115 ± 0.002	35.29
9	7g	0.110 ± 0.002	30.19

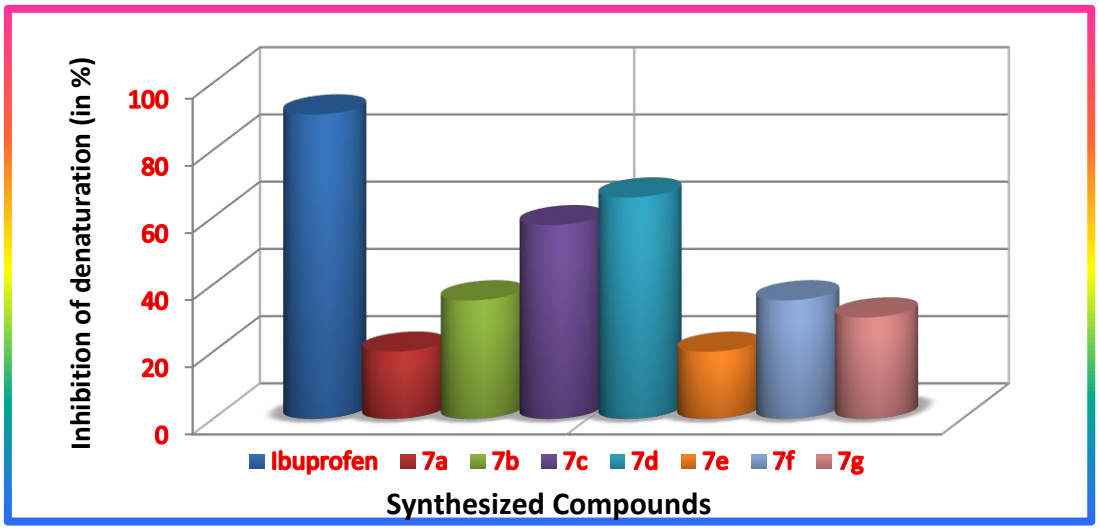


Fig. 1 Anti-inflammatory activity of the synthesized compounds

Antimicrobial activity

The newly synthesized Mannich base of Pyrazole-1-Carbothioamide derivatives were screened for their antibacterial activity against *E. coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis* by disc diffusion method[32, 33]using penicillin as standard and antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *penicillium chrysogenum*, *Fusarium moneliforme*, by poison plate method[34]using Griseofulvin as reference standard and DMSO as control solvent.From antibacterial screening results it indicates that some of the compounds shows significant antibacterial property and some of the compounds are moderately activity. The data of antifungal activity revealed that some Mannich base of Pyrazole-1-Carbothioamide derivativespossess promising and some compounds show no antifungal activity. The results are shown in **Table 1 and 2** respectively.

TABLE 2-ANTIBACTERIAL SCREENING RESULTS OF THE COMPOUNDS**(7a-g)**

Sr. No.	**Entry**	Diameter of growth inhibition zone (mm)			
		E. coli	***Salmonella typhi***	***Staphylococcus aureus***	***Bacillus subtilis***
1	**7a**	09	11	14	12
2	**7b**	14	18	22	18
3	**7c**	16	15	13	10
4	**7d**	18	20	14	18
5	**7e**	08	09	16	14
6	**7f**	15	15	18	20
7	**7g**	11	08	11	16
8	**DMSO**	-ve	-ve	-ve	-ve
9	**Penicillin**	22	25	35	38
-ve no antibacterial activity					

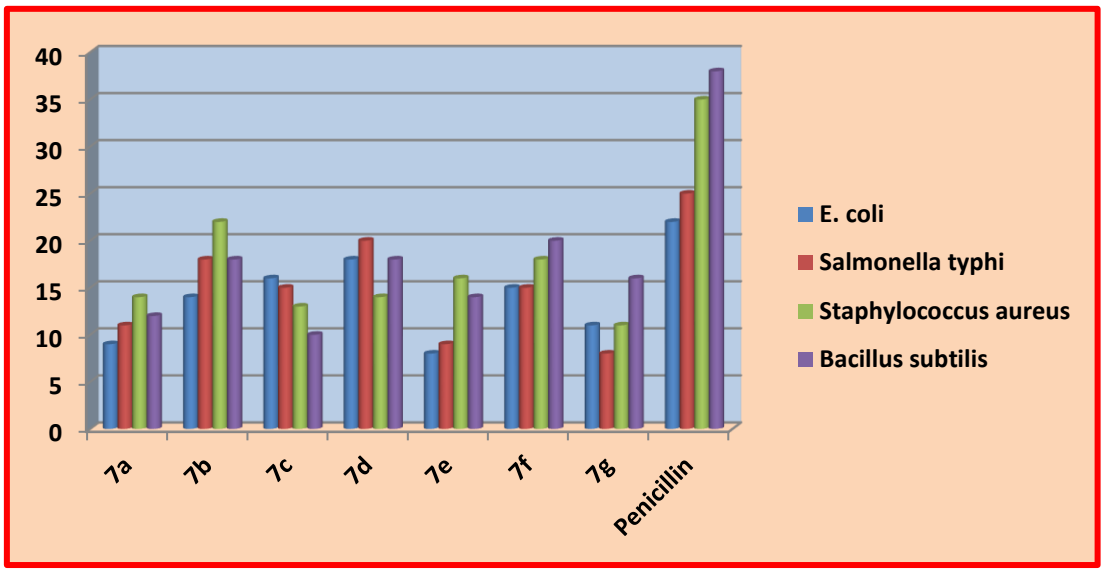


Fig.-2 Flow Chart For Antibacterial Screening

TABLE 3-ANTIFUNGAL SCREENING RESULTS OF THE COMPOUNDS **7a-g.**

Sr. No.	**Entry**	Diameter of growth inhibition zone (mm)			
		Asp. Niger	***Asp. Flavus***	***Pen. chrysogenum***	***Fusarium Moneliforme***
1	**7a**	-ve	-ve	RG	RG
2	**7b**	+ve	-ve	-ve	-ve
3	**7c**	-ve	-ve	-ve	-ve
4	**7d**	-ve	+ve	-ve	-ve
5	**7e**	-ve	RG	+ve	RG
6	**7f**	RG	-ve	-ve	-ve
7	**7g**	-ve	-ve	RG	-ve
8	**DMSO**	+ve	+ve	+ve	+ve
9	**Griseofulvin**	-ve	-ve	-ve	-ve
-ve -No growth Antifungal activity present , +ve -Growth Antifungal activity absent RG -Reduced growth					

CONCLUSION

In the above paper we have synthesized some novel Mannich bases of Pyrazole-1-Carbothioamide derivatives and evaluated for *In-vitro* anti-inflammatory, antibacterial and antifungal activities. From *In-vitro* anti-inflammatoryand antimicrobial data it can be conclude that tested compounds **7b, 7c, 7d, and 7f** were found to possess moderately active. From the above results it suggest that Mannich bases of Pyrazole-1-Carbothioamide derivatives can be considered as a promising lead molecule for modern chemist who is working under this area for developing as good anti-inflammatoryand antimicrobial agents.

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CONFLICT OF INTEREST: The author declares no conflict of interest.

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