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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW 1-SUBSTITUTED-3-METHYL-4-(HYDRAZONO)-2-PYRAZOLIN-5-ONE

SABIR HUSSAIN[*], JYOTI SHARMA and MOHAMMAD AMIR[a]

Department of Chemistry, Govt. R. R. College, ALWAR (Raj.) INDIA
[a]Department of Pharmaceutical Chemistry, Jamia Hamdard, NEW DELHI, INDIA

ABSTRACT

Various-1-carbothioamide-3-methyl-4-(hydrazono)-2-pyrazolin-5-one **(2a-f)**, 1-(pyridine-4-ylcarbonyl)-3-methyl-4-(hydrazono)-2-pyrazolin-5-one **(3a-f)**, 1-(5-chloro-6-fluoro-1, 3-benzothiazole-2-yl)thiocarbamoyl-3-methyl-4-(hydrazono)-2-pyrazolin-5-one**(4a-f)** and 1-[(1, 2, 4-triazole-4-yl) carbothioamide]-3-methyl 4(hydrazono)-2-pyrazolin-5-one **(5a-f)** were synthesized and evaluated for their antimicrobial activities. The compounds showed significant antibacterial and antifungal activity.

Keywords: Pyrazoline derivatives, Antibacterial activity, Antifungal activity.

INTRODUCTION

Amoebiasis is a protozoan infection caused by intestinal parasite *Entamoeba histolytica*. The prevalence of amoebic colitis and liver abscess is greater in developing regions such as Central and South America than in the industrialized world. It is the third most common cause of death from parasitic diseases after malaria and schistosomiasis. It is estimated that 40-50 million cases of amoebic colitis and liver abscess due to *E. histolytica* occur worldwide and result in 100 000 deaths[1-3]. Amoebic abscesses of the brain are a dreadful complication of *E. histolytica* infection[4]. The cornerstones of amoebic liver abscess treatment are nitroimidazoles such as metronidazole. However, metronidazole is mutagenic and has been associated with serious side effects and some *E. histolytica* strains resistant to this drug have also begun to appear[5-8]. Therefore, it is desirable to search for new lead molecules, which can be effectively used against amoebiasis. In drug designing programs, an essential component of the search for new leads is the synthesis of molecules, which is novel yet resembles known biologically active molecules by virtue of the presence of critical

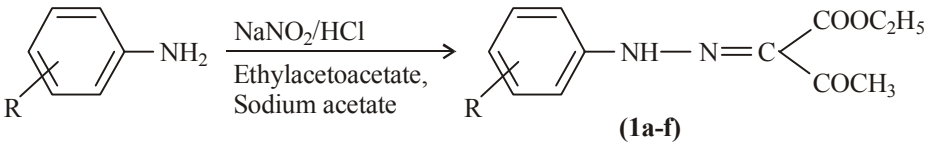
[*]Author for correspondence; E-mail: sabir_zhirka@rediffmail.com

structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules[9,10]. Pyrazoles and their reduced forms, pyrazolines, are well known nitrogen containing heterocyclic compounds, and various procedures have been developed for their syntheses[10]. The interest of scientists in such compounds has been stimulated by their various promising pharmacological properties[11]. 2-Pyrazoline derivatives have been reported to exhibit various pharmacological activities such as antibacterial, antifungal, antimicrobial and antidepressant[12-16].

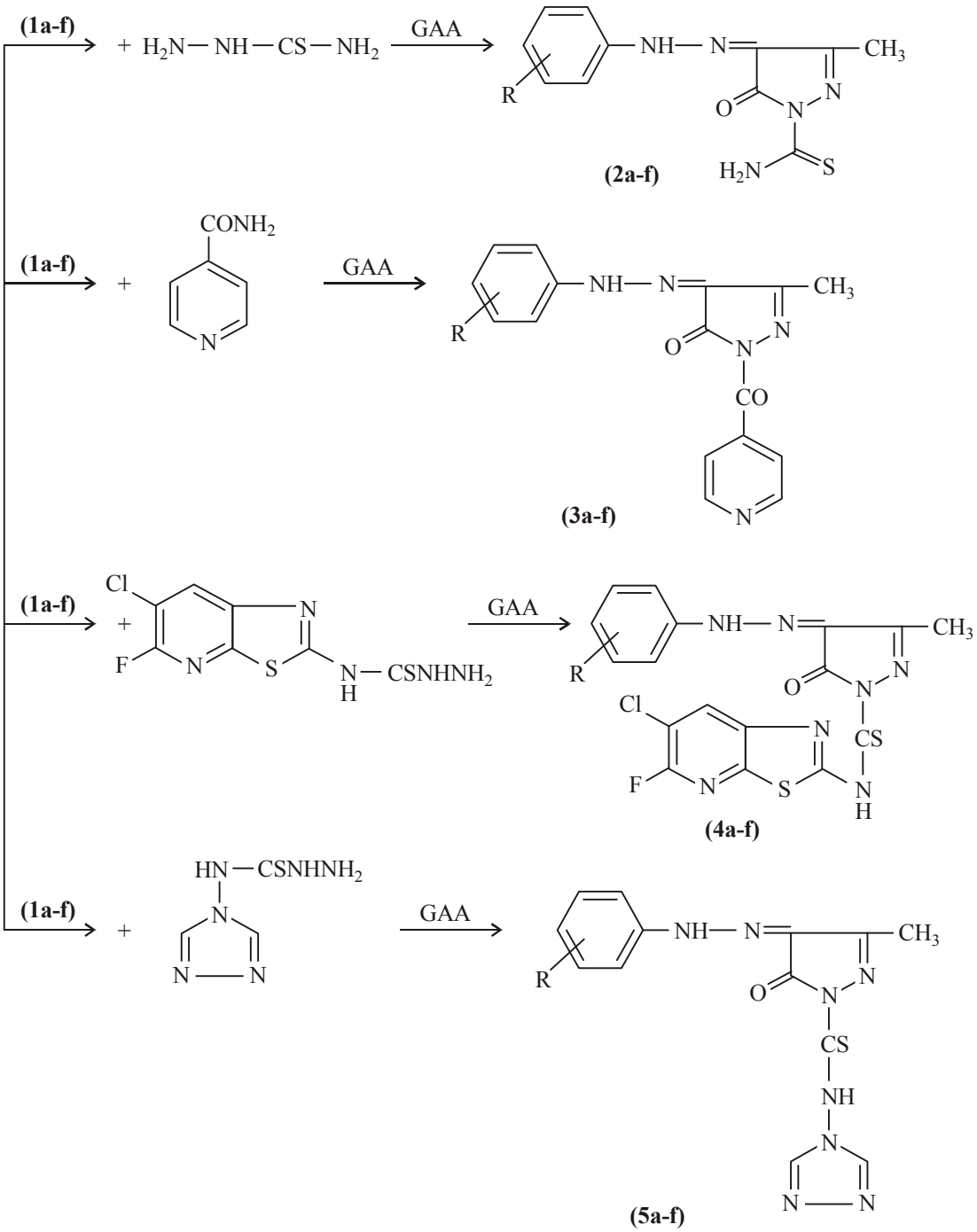
In view of the potential biological activities[17-24] of hydrazono-2-pyrazolin-5-one, we report herein the synthesis of some new 1-(substituted)-3-methyl-4-(hydrazono)-2-pyrazolin-5-ones. The synthesis involves treatment of ethyl acetoacetate with different diazonium salts in the presence of sodium acetate, when ethyl 2-[(substituted phenyl) hydrazono]-3-oxobutanoate **(1a-f)** are obtained. The later, on treatment with thiosemicarbazide, isonicotinic acid hydrazide, N-(5-chloro-6-fluro-1, 3-benzothiazole-2-yl) hydrazine carbothioamide and N-4H-1,2,4-triazol-4-ylhydrazine carbothioamide furnished 1-(substituted)-3-mehtyl 4-(hydrazono)-2-pyrazolin-5-one **(Scheme 1)**. The structures of the various compounds were assigned on the basis of IR and ^{1}H NMR spectral data.

EXPERIMENTAL

Reactions were conducted in oven dried glass wear. All the chemicals were purchased from Aldrich chemical company (USA). Analytical thin layer chromatography was performed on precoated silica gel 60 F_{254} plates and column chromatography was accomplished using silica gel, 60 Å (200-400 mesh) and basic alumina. Elemental analyses were performed at Central Drug Research Institute, Lucknow, using Heraeus Vario EL III analyzer, and the results were within 0.3% of the theoretical values. Electronic spectra were recorded in methanol on a Shimadzu UV-1601 PC UV-Visible spectrophotometer. IR spectra on KBr disks were recorded on a Perkin-Elmer model 1620 FT-IR spectrophotometer. ^{1}H NMR spectra were taken in $CDCl_3$ at ambient temperature using a Bruker Spectrospin DPX-300 MHz spectrophotometer with TMS as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Chemical shift values are given in ppm. The physical data of the compounds prepared are presented in Table 1.



(1a-f)

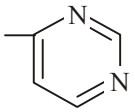

(1a-f)
+ H2N—NH—CS—NH2
GAA
NH—N=
CH3
R
O
N
N
H2N
S
(2a-f)
(1a-f)
CONH2
N
(3a-f)
(1a-f)
Cl
F
N
S
N—CSNHNH2
H
(4a-f)
(1a-f)
HN—CSNHNH2
(5a-f)

Scheme 1

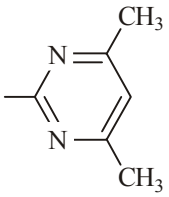
Where

R = (a) m-Cl, p-F

(b) $-SO_2NH_2$

(c) p-SO_2NH 

(d) m-COOH, p-OH

(e) p-SO_2NH 

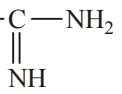
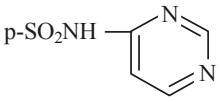
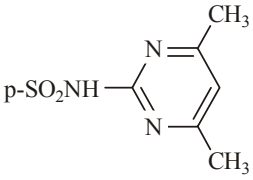
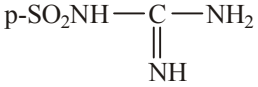
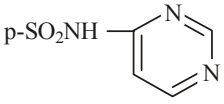
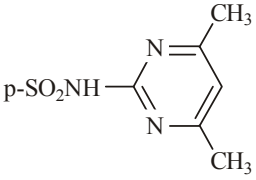
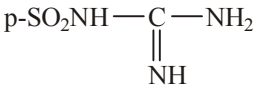
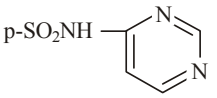
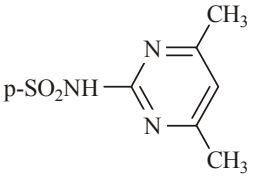
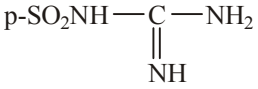
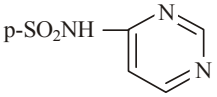
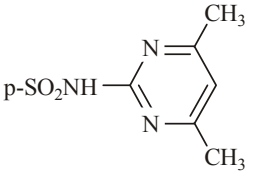
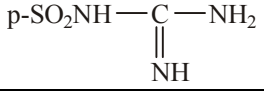
(f) p-SO_2NH 

Table 1: Physical data of the synthesized compounds

Compd.	R	M.P (°C)	Yield (%)	Mol. Formula	N (%)	
					Found	Calcd.
2a	m-Cl, p-F	239	60	$C_{11}H_9N_5OSClF$	22.43	22.32
2b	p-SO_2NH_2	206	48	$C_{11}H_{12}N_6O_3S$	24.82	24.69
2c	p-SO_2NH 	204	55	$C_{15}H_{14}N_8O_3S_2$	26.86	26.78
2d	m-COOH, p-OH	245	60	$C_{12}H_{11}N_5O_4S$	22.05	21.80
2e	p-SO_2NH 	277	44	$C_{17}H_{18}N_8O_3S_2$	25.23	25.10
2f	p-SO_2NH 	285	56	$C_{12}H_{14}N_8O_3S_2$	29.47	29.30
3a	m-Cl, p-F	212	62	$C_{16}H_{11}ClFN_5O_2$	19.56	19.47
3b	p-SO_2NH_2	207	59	$C_{16}H_{14}N_6O_4S$	21.90	21.75
3c	p-SO_2NH 	241	60	$C_{20}H_{16}N_8O_4S$	24.21	24.13
3d	m-COOH, p-OH	267	67	$C_{17}H_{13}N_5O_5$	19.37	19.07

Cont…

Compd.	R	M.P (°C)	Yield (%)	Mol. Formula	N (%)	
					Found	Calcd.
3e		290	77	$C_{22}H_{20}N_8O_4S$	22.70	22.75
3f		292	58	$C_{17}H_{16}N_8O_4S$	26.20	26.15
4a	m-Cl, p-F	222	65	$C_{20}H_{16}N_6OS_2Cl_2F_2$	15.96	15.87
4b	p-SO_2NH_2	252	63	$C_{20}H_{19}N_7O_3S_3ClF$	17.82	17.63
4c		278	65	$C_{24}H_{21}N_9O_3S_3ClF$	19.98	19.88
4d	m-COOH, p-OH	281	70	$C_{21}H_{18}N_6O_4S_2ClF$	15.79	15.65
4e		218	65	$C_{26}H_{25}N_9O_3S_3ClF$	19.17	19.04
4f		288	66	$C_{21}H_{21}N_9O_3S_3ClF$	21.18	21.08
5a	m-Cl, p-F	284	77	$C_{13}H_{10}N_8OSClF$	29.50	29.43
5b	p-SO_2NH_2	278	58	$C_{13}H_{13}N_9O_3S_2$	30.96	30.94
5c		260	51	$C_{17}H_{15}N_{11}O_3S_2$	31.89	31.73
5d	m-COOH, p-OH	273	68	$C_{14}H_{12}N_8O_4S$	28.93	28.85
5e		280	62	$C_{19}H_{19}N_{11}O_3S_2$	31.12	30.04
5f		284	55	$C_{14}H_{15}N_{11}O_3S_2$	34.38	34.28

Synthesis of ethyl 2-[(substituted phenyl) hydrazono]-3-oxobutanoate (1a-f)

Substituted aniline (0.05 mol) was dissolved in dil HCl (40 mL, 1 : 1). The contents were stirred and cooled (0-2°C) and a cold solution of sodium nitrite (6.0 g in 15 mL of water) was added to it slowly maintaining the temperature between 0-2°C. The cold diazotized solution was added dropwise to a well cooled and stirred mixture of ethyl acetoacetate (0.05 mol) and sodium acetate (4 g, dissolved in 5 mL of 50% ethanol). The stirring was continued for 1.5 h and crystals separated were filtered, washed with water, dried and crystallized from ethanol to yield **(1a-f)**. IR (KBr) (**1a-f)**: 3386-3418 cm^{-1}, NH stretching, 2982-2993 cm^{-1}, CH stretching, 1686-1705 cm^{-1}, C=O stretching and 1571-1583 cm^{-1}, C=C stretching vibration of aromatic rings; ^{1}H NMR ($CDCl_3$): (**1a)**: δ 1.25 (s, 3H, CH_3), 4.29 (q, for OCH_2 protons), δ 2.39 (s, indicating the presence of $COCH_3$), δ 8.24 (s, 1H, NH) and 6.85-8.0 (complex m, for Ar-H); (**1f)**: δ 1.24 (s, 3H, CH_3), 4.28 (q, for OCH_2 protons), 6.85-8.0 (complex m, for Ar-H).

Synthesis of 1-carbothioamide-3-methyl-4-(hydrazono)-2-pyrazolin-5-one (2a-f)

Ethyl 2-[(substituted phenyl) hydrazono]-3-oxobutanoate **(1a-f) (**0.001 mol) and thiosemicarbazide (0.001 mol) were dissolved in glacial acetic acid (10 mL) and the solution was refluxed for 20 h. The resulting solid was purified by repeated washing with acetic acid and crystallization from acetic acid to get **(2a-f).** IR (KBr) **(2a-f)**: 2968-3161 cm^{-1} (CH stretching), 1682-1690 cm^{-1}, C=O stretching of pyrazoline ring, 1566-1597 cm^{-1} (C=N), 1043-1070 cm^{-1} (C=S); ^{1}H NMR ($CDCl_3$) **(2a)**: δ 2.16 (s, 3H, CH_3), 11.53 (s, 1H, NH); **(2b)**: δ 2.16 (s, 03H, CH_3), 11.53 (s, 1H, NH) and 6.75-7.16 (complex m, 4H, Ar-H).

Synthesis of 1-isonicotinyl-3-methyl-4-(hydrazono)-2-pyrazolin-5-one (3a-f)

Ethyl 2-[(substituted phenyl) hydrazono]-3-oxobutanoate (**1a-f)** (0.001 mol) and 2 isonicotinic acid hydrazide (0.001 mol) were dissolved in glacial acetic acid (10 mL) and the solution was refluxed for 20 h. The resulting solid was filtered, washed with acetic acid and recrystallized from acetic acid to obtain **(3a –f)**. IR (KBr) **(3a-f)**: 1657-1673 cm^{-1} (C=N), 1682-1691 cm^{-1} (C=O) of pyrazoline ring), ^{1}H NMR ($CDCl_3$) (**3d)**: δ 2.18 (s, 3H, CH_3), 11.16 (s, 1H, NH), 7.85-7.90 (m, 4H, pyridyl), δ 12.40 (s, 1H, COOH); **(3e)**: δ 2.16 (s, 3H, CH_3), 11.08 (s, 1H, NH), 7.85-7.92 (m, 4H pyridyl), 7.10-7.70 (complex m, 4H, Ar-H).

Synthesis of 1-(5-chloro-6-fluoro-1, 3-benzothiazole-2-yl) thiocarbamoyl-3-methyl-4 (substituted phenyl hydrazono)-2-pyrazolin-5-one (4a-f)

Ethyl 2-[(substituted phenyl) hydrazono]-3-oxobutanoate **(1a-f)** (0.001 mol**)** and 5-chloro-6-fluoro-1,3-benzothiazole-2-yl-thiosemicarbazide (0.001 mol) were dissolved in

glacial acetic acid (10 mL) and the solution was refluxed for 20 h. The resulting solid was filtered, washed with acetic acid and recrystallized from acetic acid to obtain **(4a-f)**. IR (KBr) **(4a-f)**: 1041-1078 cm^{-1} (C=S), 1512-1569 cm^{-1} (C=N), 2965-3188 cm^{-1} (CH stretching), 1656-1678 cm^{-1} (C=O stretching of pyrazoline ring); ^1H NMR ($CDCl_3$) **(4b)**: δ 2.38 (s, 3H, CH_3), δ 10.63 (s, 1H, NH), δ 6.87-6.95 (complex m, 6H, Ar-H) ^1H NMR ($CDCl_3$) **4d**: δ 2.38 (s, 3H, CH_3), δ 10.63 (s, 1H, NH), δ 6.72-6.81 (complex m, 5H, Ar-H), δ 12.32 (s, 1H, COOH).

Synthesis of 1-[(1, 2, 4-triazol-4-yl) carbothioamide]-3-methyl-4-(substituted phenyl hrdrazono)-2-pyrazolin-5-one (5a-f)

Ethyl 2-[(substituted phenyl) hydrazono]-3-oxobutanoate **(1a-f)** (0.001 mol) and N-4H-1,2,4-triazol-4-ylhydrazine (0.001 mol) were dissolved in glacial acetic acid (10 mL) and solution was refluxed for 20 h. The reaction mixture was cooled and the compound separated was filtered and washed with acetic acid. It was further purified by recrystallization from acetic acid to get **(5a-f)**. IR (KBr) **(5a-f)**: 2948-3109 cm^{-1} (CH stretching), 1666-1685 cm^{-1}, C=O stretching of pyrazoline ring, 1560-1613 m^{-1} (C=N), 974-1076 (C=S); ^1H NMR ($CDCl_3$) **(5a):** δ 2.16 (s, 3H, CH_3), 11.53 (s, 1H, NH), δ 6.68-6.80 (complex m, 5H, Ar-H), **(5d)**: δ 2.40 (s, 3H, CH_3), δ 10.68 (s, 1H, NH), δ 6.72-6.80 (complex m, 5H, Ar-H), δ 12.40 (s, 1H, COOH).

RESULTS AND DISCUSSION

Spectral characterization of the compounds

The IR spectrum of the compounds **(1a-f)** showed peaks at 3386-3418 cm^{-1}, NH stretching; 2982-2993 cm^{-1}, CH stretching; 1686-1705 cm^{-1}, C=O stretching and 1571-1583 cm^{-1}, C=C stretching vibrations of aromatic rings. The ^1H NMR spectrum of the compound **(1a)** showed a singlet at δ 1.25 for CH_3 and a quartet at δ 4.29 for OCH_2 protons of ethoxy group. A singlet at δ 2.39 was observed indicating the presence of $COCH_3$ protons. A signal of NH proton was observed as a singlet at δ 8.24. In the aromatic region, a multiplet of four protons was observed at δ 6.85-8.0 indicating the presence of phenyl protons. The ^1H NMR spectrum of the compound **(1f)** showed a singlet at δ 1.24 for CH_3 and a quartet at δ 4.28 for OCH_2 protons of ethoxy group. A multiplet for four aromatic protons was observed at δ 6.85-8.0.

The IR spectrum of the compounds **(2a-f)** showed peaks at 2968-3161 cm^{-1}, CH stretching; 1682-1690 cm^{-1}, C=O stretching of pyrazoline ring; 1566-1597 cm^{-1}, C=N stretching and 1043-1070 cm^{-1}, C=S stretching. The NMR spectrum of the compound **(2a)**

showed a singlet for CH_3 protons at δ 2.12. The NH proton was obtained as a singlet at δ 11.62. The ^{1}H NMR spectrum of the compound **(2b)** showed a singlet at δ 2.16, showing the presence of methyl protons. A multiplet was observed at δ 6.75-7.16 indicating the presence of 4 aromatic protons. Furthermore, the singlet for NH proton was observed at δ 11.53. The ^{1}H NMR spectrum of the compound **(2c)** showed a singlet at δ 2.27, indicating the presence of methyl protons. A complex multiplet was obtained at δ 6.85-7.21 indicating the presence of 6 aromatic protons. A singlet was observed at δ 11.47 indicating the presence of NH proton.

The IR spectrum of the compounds **(3a-f)** showed peaks at 1682-1691 cm^{-1}, C=O stretching of pyrazoline ring and 1657-1673 cm^{-1}, C=N stretching. The ^{1}H NMR spectrum of the compound **(3d)** showed a singlet at δ 2.18, indicating the presence of methyl protons attached to the pyrazoline ring. A multiplet was obtained at δ 7.85-7.88 indicating the presence of 4 pyridyl protons. The singlet of NH proton was also observed at δ 11.16. Furthermore, the singlet for COOH proton was observed at δ 12.40. The ^{1}H NMR spectrum of the compound **(3e)** showed a singlet at δ 2.16, indicating the presence of methyl protons attached to the pyrazoline ring. A multiplet was obtained at δ 7.85-7.92 indicating the presence of 4 pyridyl protons. The singlet of NH proton was also observed at δ 11.08. A complex multiplet was observed at δ 7.10-7.70 ppm indicating the presence of 5 aromatic protons.

The IR spectrum of the compounds **(4a-f)** showed peaks at 2965-3188 cm^{-1}, CH stretching; 1656-1678 cm^{-1}, C=O stretching of pyrazoline ring; 1512-1569 cm^{-1}, C=N stretching and 1041-1078 cm^{-1}, C=S stretching. The ^{1}H NMR spectrum of the compound **(4b)** showed a singlet at δ 2.38, indicating the presence of methyl protons attached to the pyrazoline ring. The singlet of NH proton was also observed at δ 10.63. A complex multiplet was observed at δ 6.87-6.95 indicating the presence of 6 aromatic protons. The ^{1}H NMR spectrum of the compound **(4d)** showed a singlet at δ 2.38, indicating the presence of methyl protons attached to the pyrazoline ring. A complex multiplet was obtained at δ 6.72-6.81 indicating the presence of 5 aromatic protons. The singlet of NH proton was also observed at δ 10.63. The singlet for COOH proton was observed at δ 12.32.

The IR spectrum of the compounds **(5a-f)** showed peaks at 2948-3109 cm^{-1}, CH stretching; 1685-1666 cm^{-1}, C=O stretching of pyrazoline ring; 1560-1613 cm^{-1}, C=N stretching and 974-1076 cm^{-1}, C=S stretching. The NMR spectrum of the compound **(5a)** showed a singlet at δ 2.16, indicating the presence of methyl protons attached to the pyrazoline ring. The singlet of NH proton was also observed at δ 11.53. A complex multiplet

was observed at δ 6.68-6.80 indicating the presence of 5 aromatic protons. The ^{1}H NMR spectrum of the compound **(5d)** showed a singlet at δ 2.40, indicating the presence of methyl protons attached to the pyrazoline ring. A complex multiplet was obtained at δ 6.72-6.80 indicating the presence of 5 aromatic protons. The singlet of NH proton was also observed at δ 10.68. A singlet for COOH proton was observed at δ 12.40.

Antimicrobial Activity

Compounds **(2a-f, 3a-f, 4a-f** and **5a-f)** have been evaluated for their *in vitro* anti-microbial activity against *Staphylococcus aureus* (*S. aureus*, ATCC-29737), as an example of gram-positive bacteria, *Escherchia coli* (*E. coli*, ATCC-8739) as an example of gram-negative bacteria and *Aspergilus niger* (*A. niger*) as a representative of fungi using cup plate technique. DMF was run as a control and test was performed at 200, 100, 50, 25 µg/mL concentration. Ofloxacin and ketoconazole was used as a standard drug. The micro dilution susceptibility test in nutrient agar media (Hi-Media) and Sabroaud's dextrose agar media were used for determination of antibacterial and antifungal activities, respectively. The minimal inhibitory concentration (MICs, µgmL^{-1}) of the tested compounds are recorded in Table 2.

Table 2: Antimicrobial activities of the compound

Compound	MIC (µg / mL)		
	S. aureus	***E. coli***	***A. niger***
Ofloxacin	10.0	12.5	--
Ketoconazole	--	--	12.5
2a	50	50	100
2b	100	200	100
2c	200	200	200
2d	100	200	100
2e	200	100	100
2f	100	100	100
3a	25	50	50
3b	50	100	100

Cont...

Compound	MIC (µg / mL)		
	S. aureus	***E. coli***	*A. niger*
3c	100	200	100
3d	50	50	50
3e	100	100	100
3f	100	100	200
4a	100	200	100
4b	200	200	100
4c	100	200	100
4d	100	50	100
4e	200	200	200
4f	100	200	100
5a	50	100	100
5b	100	200	100
5c	200	200	200
5d	100	100	100
5e	200	200	100
5f	100	200	100

Out of all the synthesized pyrazolines derivatives of the series, compound **(3a)** having chloro and fluoro group at 3rd and 4th position, respectively of the phenyl ring exhibited remarkable antibacterial activity (MIC 25 µgmL^{-1}), against *S. aureus* (gram-positive bacteria), whereas the compound **(3d)** having COOH, OH group at meta & para position, respectively of the phenyl ring showed MIC 50 µgmL^{-1} against *S. aureus*, *E. coli*, as compared with the broad spectrum antibiotics ofloxacin (MIC 10.0 µgmL^{-1} against *S. aureus* and 12.5 µgmL^{-1} against *E. coli*). In case of the antifungal activity, only the compounds **(3a)** having 3-chloro, 4-fluoro and **(3d)** having COOH, OH group at meta and para positions of the phenyl ring, respectively, show moderate activity (MIC 50 µgmL^{-1}) against fungus *A. niger*, as compared with the standard drug ketoconazole (MIC 12.5 µg mL^{-1}). The compound **(5a)** having 3-chloro, 4-fluoro group on the phenyl ring was found

active (MIC 50 μgmL^{-1}) against *S. aureus*, whereas the compounds **(4d)** showed moderate activity (MIC 50 μgmL^{-1}) against *E. coli* (gram-negative bacteria).

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