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$SOCl_2$ CATALYZED CYCLIZATION OF CHALCONES: SYNTHESIS AND SPECTRAL STUDIES OF SOME BIO-POTENT ^1H PYRAZOLES

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ABSTRACT. Some aryl-aryl ^1H pyrazoles have been synthesised by cyclization of aryl chalcones and hydrazine hydrate in the presence of $SOCl_2$. The yields of the pyrazoles are more than 85%. These pyrazoles are characterized by their physical constants and spectral data. The infrared, NMR spectral group frequencies of these pyrazolines have been correlated with Hammett substituent constants, F and R parameters. From the results of statistical analyses the effects of substituent on the spectral frequencies have been studied. The antimicrobial activities of all synthesised pyrazolines have been studied using Bauer-Kirby method.

KEY WORDS: $SOCl_2$, ^1H Pyrazolines, IR spectra, NMR spectra, Hammett substituent constants, Antimicrobial activities

INTRODUCTION

The prominent nitrogen containing five membered heterocyclic compounds, such as pyrazolines are extensive important synthons [1] in the synthetic organic chemistry and drug designing. Pyrazoline refers to both the classes of simple aromatic ring organic compounds of the heterocyclic series characterized by a five membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and the unsubstitued parent compound. These pyrazolines have played an important role in the development of theoretical heterocyclic chemistry and organic synthesis. So these compounds with pharmacological effects on humans are classified as alkaloid, although they are rare in nature. Many pyrazoline shows various pharmacological-multipronged properties [2, 3]. Some pyrazoline derivatives are used as pesticides [4], fungicides [5], antibacterial [6], antifungal [7], antiamoebic [8], and antidepressant activity [9] and insecticides. Heterocyclic of the type 3-hetaryl-^{1}H-4,5-dihydropyrazoles arouse particular interest because the properties determined by the pyrazoline fragment are combined with the features of the hetarene [9, 10]. Therefore, it should be noted that 3-(4-hydroxy-3-coumarinyl)-1H-4,5-dihydropyrazolesare structural analogs of 3-substituted 4-hydroxy-coumarins some representatives of which are effective blood anticoagulants. The pyrazoline function is quite stable, and has inspired chemists to utilize the mentioned stable fragment in bioactive moieties to synthesize new compounds possessing biological activity. Some pyrazoline related compounds possess anticonvulsant activity and was evaluated by medicinal bio-chemistry researchers [11]. The antidepressant activities of these compounds were evaluated by the "Porsolt Behavioural Despair Test" on Swiss-Webster mice [12]. The α,β-unsaturated ketones can play the role of versatile precursors in the synthesis of the corresponding pyrazoline derivatives [13, 14]. The reaction of hydrazine and its derivatives with α,β-unsaturated ketones and α,β-epoxy ketones is one of the preparative methods for the synthesis of pyrazolines and pyrazoles derivatives [15]. Alternatively, the reaction of substituted

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hydrazine with α,β-unsaturated ketones has been reported to form regioselective pyrazolines [16]. The synthesis of pyrazoline rings from chalcone derivatives containing anisole and the 3,4-methylenedioxyphenyl ring by the conventional method using acetic acid was reported with low yields [17]. Some 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazoline derivatives have been synthesized by the reaction of 1-thiocarbamoyl-3,5-diaryl-2-pyrazoline derivatives with phenacetylbromide in ethanol. The structural elucidations of the compounds were performed by IR, ^{1}HNMR and mass spectral data and elemental analysis [18]. Semicarbazide (hydrochloride) and thiosemicarbazide on reaction with α,β-unsaturated ketones of the ferrocene series in excess of *t*-But-OK gave 1-carbamoyl and 1-thiocarbamoyl (ferrocenyl)-4,5-dihydropyrazoles. Ten new fluorine-containing 1-thiocarbamoyl-3,5-diphenyl-2-pyrazolines have been synthesized in 80-85% yields by a microwave- promoted solvent–free condensation of 2,4-dichloro-5-fluoro chalcones with thiosemicarbazide over potassium carbonate [19]. Nanoparticles of 1-phenyl-3-naphthyl-5-(dimethylamino) phenyl)-2-pyrazolines ranging from tens to hundreds of nanometres have been prepared by the reprecipitation method [20]. Five new 1,3,5-triphenyl-2-pyrazolines have been synthesized by reacting 1,3-diphenyl-2-propene-1-one with phenyl hydrazine hydrochloride and another five new 3-(2"-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazoline have been synthesized by reacting 1-(2'-hydroxylnaphthyl)-3-phenyl-2-propene-1-one with phenyl hydrazine hydrochloride [21]. Also some new 1,3,5-triphenyl-2-pyrazolines have been synthesized by reacting 1,3-diphenyl-2-propene-1-one with phenyl hydrazine hydrochloride and another five new 3-(2"-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazoline have been synthesized by reacting 1-(2'-hydroxylnaphthyl)-3-phenyl-2-propene-1-one with phenyl hydrazine hydrochloride [22]. The effect of substituents on the group frequencies have been studied, through UV-Vis, IR, ^{1}H and ^{13}C NMR spectra of ketones [23], unsaturated ketones [24-28], acyl bromides-esters [29] and naphthyl and 5-bromo-2-thienyl pyrazolines [30] by spectral analysts and organic chemists. The effect of substituents on the infrared, proton and carbon-13 group frequencies of pyrazoline derivatives are not been studied so far. Hence, the authors have taken efforts to synthesise some pyrazoline derivatives by cyclization of 5-chloro-2-thienyl chalcones and hydrazine hydrate in the presence of $SOCl_2$ and to study the spectral linearity and also the antimicrobial activities.

EXPERIMENTAL

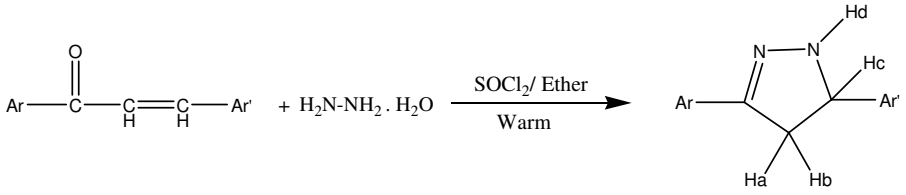
All chemicals used were procured from Sigma-Aldrich and E-Merck. Melting points of all pyrazoles were determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected. Infrared spectra (KBr, 4000-400 cm^{-1}) were recorded on Bruker (Thermo Nicolet) Fourier transform spectrophotometer. The NMR spectra of all pyrazolines were recorded on Bruker Avance III 500 MHz spectrometer operating at 500 MHz for recording ^{1}H spectra and 125.46 MHz for ^{13}C spectra in DMSO solvent using TMS as internal standard. Mass spectra were recorded on Shimadzu spectrometer using chemical ionization technique.

Synthesis of chalcones

An appropriate equi-molar quantities of 2-acetyl-5-chlorothiophene (2 mmol), substituted benzaldehydes (2 mmol) and silica: H_2SO_4 (0.4 g) were taken in borosil tube and tightly capped. The mixture was subjected to microwave heated for 8-10 min in a microwave oven (LG Grill, Intellowave, Microwave Oven, 160-800 W) and then cooled to room temperature. The organic layer was separated with dichloromethane and the solid product was obtained on evaporation. The solid, on recrystallization with benzene-hexane mixture gave glittering solid. The insoluble catalyst was recycled by washing the solid reagent remained on the filter by ethyl acetate (8 mL) followed by drying in an oven at 100 °C for 1 h and it was made reusable for further reactions.

Synthesis of pyrazolines derivatives: [^{1}H-3-(substituted aryl)-5-(substituted phenyl)-2-pyrazolines]

An appropriate equi-molar quantities of substituted styryl aryl ketones (2 mmol), hydrazine hydrate (2 mmol) and $SOCl_2$ (0.5 mL) was warmed (60 °C,) in (15 mL) of diethylether for 30 min (Scheme 1) in water bath. The progress of the reaction was monitored by TLC. The reaction mixture was cooled, and poured into cold water. The precipitate was filtered, dried and subjected to column chromatography using hexane and ethyl acetate (3:1) as eluent. The yield, analytical and mass spectral data are presented in Table 1. The IR and NMR spectral data are given in Table 2.



(1-50)

Scheme 1. Synthesis of pyrazolines.

Table 1. Analytical, yield, physical constants and mass spectral data of 3,5-disubstituted ^1H pyrazoline derivatives.

Entry	Ar	Ar′	M.F.	M.W.	Yield (%)	M.p. (°C)	Mass (m/z)
1	Ph	Ph	$C_{15}H_{14}N_2$	222	85	199-200 (199)[31]	---
2	Ph	4-ClPh	$C_{15}H_{13}ClN_2$	256	85	218-219 (217)[31]	---
3	Ph	4-OCH_3Ph	$C_{16}H_{16}N_2O$	252	83	214-215 (212-214)[32]	---
4	Ph	4-CH_3Ph	$C_{16}H_{16}N_2$	236	83	184-185 (183-184)[32]	---
5	Ph	4-NO_2Ph	$C_{15}H_{13}N_3O_2$	267	85	235-236 (234-236)[32]	---
6	4-BrPh	Ph	$C_{15}H_{13}BrN_2$	301	84	215-215 (215)[31]	---
7	4-BrPh	4-ClPh	$C_{15}H_{12}BrClN_2$	335	85	250-251 (248-250)[31]	---
8	4-BrPh	4-CH_3Ph	$C_{15}H_{15}BrN_2$	315	84	245-246 (244-245)[31]	---
9	4-ClPh	Ph	$C_{15}H_{13}ClN_2$	256	85	220-221 (217)[31]	---
10	4-ClPh	4-ClPh	$C_{15}H_{12}Cl_2N_2$	291	85	231-232 (230-232)[31]	---
11	4-ClPh	4-OCH_3Ph	$C_{16}H_{15}ClN_2O$	286	85	222-223 (220-222)[31]	---
12	4-ClPh	4-CH_3Ph	$C_{15}H_{15}ClN_2$	271	84	237-238 (236-237)[32]	---
13	4-ClPh	4-NO_2Ph	$C_{15}H_{12}ClN_3O_2$	302	83	234-235 (233-234)[32]	---
14	4-CH_3Ph	Ph	$C_{16}H_{16}N_2$	236	85	184-185	---

						(183-184)[31]	
15	4-CH_3Ph	4-ClPh	$C_{15}H_{15}ClN_2$	270	85	237-238 (236-237)[31]	---
16	4-CH_3Ph	4-CH_3Ph	$C_{17}H_{18}N_2$	250	84	237-238 (236-237)[31]	---
17	3-CH_3-4-OHPh	Ph	$C_{16}H_{16}N_2O$	252	85	182-182 (182)[31]	---
18	3-CH_3-4-OHPh	2-ClPh	$C_{16}H_{15}N_2OCl$	286	84	142-143 (142)[33]	---
19	3-CH_3-4-OHPh	4-ClPh	$C_{16}H_{15}N_2OCl$	286	82	141-142 (141)[33]	---
20	3-CH_3-4-OHPh	4-FPh	$C_{16}H_{15}N_2OF$	270	83	145-146 (144)[33]	---
21	3-CH_3-4-OHPh	4-N$(CH_3)_2$Ph	$C_{18}H_{21}N_3O$	295	80	162-163 (162-163)[33]	---
22	3-CH_3-4-OHPh	4-OCH_3Ph	$C_{17}H_{18}N_2O_2$	282	80	149-150 (149)[33]	---
23	3-CH_3-4-OHPh	3-NO_2Ph	$C_{16}H_{15}N_3O_3$	297	82	151-152 (151)[33]	---
24	3-CH_3-4-OHPh	2,6-Cl_2Ph	$C_{16}H_{14}N_2OCl$	321	81	141-142 (141)[33]	---
25	3-CH_3-4-OHPh	3,4-$(OCH_3)_2$Ph	$C_{18}H_{20}N_2O_3$	312	80	121-122 (121)[33]	---
26	3-CH_3-4-OHPh	3,4,5-$(OCH_3)_3$Ph	$C_{19}H_{22}N_2O_4$	342	80	103-104 (103)[33]	---
27	3-CH_3-4-OHPh	2-Furyl	$C_{14}H_{14}N_2O_2$	242	83	163-164 (163)[33]	---
28	1-Naphthyl	1-Naphthyl	$C_{23}H_{18}N_2$	322	80	196-197 (195-196)[34]	---
29	Ph	2-Thienyl	$C_{15}H_{14}N_2S$	242	85	260-262 (260-262)[35]	---
30	Ph	2-Naphthyl	$C_{20}H_{16}N_2$	272	85	247-248 (247-248)[36]	---
31	Biphenyl	Ph	$C_{21}H_{18}N_2$	312	85	102-103 (102)[37]	---
32	Biphenyl	2-ClPh	$C_{21}H_{17}ClN_2$	322	83	114-115 (114)[37]	---
33	Biphenyl	4-ClPh	$C_{21}H_{17}ClN_2$	322	81	124-125 (124))[37]	---
34	Biphenyl	4-N$(CH_3)_2$Ph	$C_{23}H_{23}N_3$	341	84	166-167 (166)[37]	---
35	Biphenyl	4-OCH_3Ph	$C_{22}H_{20}N_2O$	328	85	158-159 (158)[37]	---
36	Biphenyl	4-CH_3Ph	$C_{22}H_{20}N_2$	312	84	164-165 (164)[37]	---
37	Biphenyl	3,4-$(OCH_3)_2$Ph	$C_{23}H_{22}N_2O_2$	358	85	128-129 (128)[37]	---
38	Biphenyl	2,4,6-$(OCH_3)_2$Ph	$C_{24}H_{24}N_2O_3$	388	82	190-191 (190)[37]	---
39	5-Cl-2-Th	Ph	$C_{13}H_{11}ClN_2S$	262	85	79-82	262[M^+], 264[M^{2+}], 227, 185, 145, 117, 77, 69, 55
40	5-Cl-2-Th	3-BrPh	$C_{13}H_{11}BrClN_2S$	341	84	80-83	341[M^+], 343[M^{2+}], 305, 261, 223, 185,

							155, 117, 79, 77, 69, 55
41	5-Cl-2-Th	3-Cl Ph	$C_{13}H_{10}Cl_2N_2S$	297	80	88-92	297[M^+], 299[M^{2+}], 261, 179, 185, 117, 111,77, 69, 55
42	5-Cl-2-Th	2-F Ph	$C_{13}H_{10}ClFN_2S$	280	81	86-91	280[M^+], 282[M^{2+}], 261, 185, 163, 117, 95, 77, 69, 55
43	5-Cl-2-Th	4-F Ph	$C_{13}H_{10}ClN_2S$	280	83	74-79	280[M^+], 282[M^{2+}], 261, 185, 163, 117, 95, 77, 69, 55
44	5-Cl-2-Th	4-OHPh	$C_{13}H_{11}ClN_2OS$	278	85	83-86	278[M^+], 280[M^{2+}], 261, 243, 185, 161, 117, 93, 77, 69, 55
45	5-Cl-2-Th	2-OCH_3Ph	$C_{14}H_{13}ClN_2OS$	293	82	66-70	293[M^+], 295[M^{2+}], 261, 257, 185, 175, 117, 107, 77, 69, 55
46	5-Cl-2-Th	4-OCH_3Ph	$C_{14}H_{13}ClN_2OS$	293	84	68-72	293[M^+], 295[M^{2+}], 261, 257, 185, 175, 117, 107, 77, 69, 55
47	5-Cl-2-Th	2-CH_3Ph	$C_{14}H_{13}ClN_2S$	277	84	82-86	277[M^+], 279[M^{2+}], 261, 241,185,117, 159, 91, 77, 69, 55
48	5-Cl-2-Th	4-CH_3Ph	$C_{14}H_{13}ClN_2S$	277	82	68-72	277[M^+], 279[M^{2+}], 261, 241,185,117, 159, 91, 77, 69, 55
49	5-Cl-2-Th	4-NO_2Ph	$C_{14}H_{10}ClN_3OS$	307	84	208-212	307[M^+], 309[M^{2+}], 261, 190, 185, 122, 117, 77, 69, 55
50	5-Cl-2-Th	3-OC_6H_5	$C_{19}H_{15}ClN_2OS$	354	84	70-75	354[M^+], 356[M^{2+}], 319, 277 ,261, 237, 185, 169, 93, 77, 69, 55

Table 2. IR and NMR spectral data of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives(entries **39-50**).

Entry	X	IR		^{1}H				^{13}C
		νC=N	νC-Cl	δH_a (*dd*)	δH_b (*dd*)	δH_c (*dd*)	δH_d (*s*)	δC=N
39	H	1645.22	792.95	2.770, *J* = 21 Hz	2.962, *J* = 21 Hz	4.005, *J* = 14 Hz	7.126	155.43
40	3-Br	1653.96	781.83	2.931, *J* = 18 Hz	3.177, *J* = 18 Hz	4.085, *J* = 12 Hz	7.140	155.54
41	3-Cl	1653.18	785.57	2.788, *J* = 21 Hz	2.968, *J* = 21 Hz	4.057, *J* = 14 Hz	7.131	155.19
42	2-F	1652.42	790.30	2.790, *J* = 21 Hz	2.975, *J* = 21 Hz	4.038, *J* = 15 Hz	7.112	155.23
43	4-F	1651.82	789.11	2.770, *J* = 21 Hz	2.964, *J* = 21 Hz	4.063, *J* = 14 Hz	7.181	155.29
44	4-OH	1647.36	786.42	2.893, *J* = 21 Hz	3.044, *J* = 21 Hz	3.858, *J* = 16 Hz	7.026	158.80
45	2-OCH_3	1646.77	789.75	2.995, *J* = 17 Hz	3.158, *J* = 17 Hz	3.905, *J* = 20 Hz	7.099	155.65
46	4-OCH_3	1653.19	794.08	2.745, *J* = 21 Hz	2.935, *J* = 21 Hz	3.983, *J* = 14 Hz	7.117	155.41
47	2-CH_3	1647.32	788.02	2.756, *J* = 21 Hz	2.932, *J* = 21 Hz	4.216, *J* = 14 Hz	7.106	155.60
48	4-CH_3	1652.48	788.26	2.753, *J* = 21 Hz	2.936, *J* = 21 Hz	3.979, *J* = 14 Hz	7.014	155.43
49	4-NO_2	1648.72	783.88	2.939, *J* = 22 Hz	3.125, *J* = 22 Hz	4.078, *J* = 14 Hz	6.787	155.86
50	3-OC_6H_5	1654.46	784.40	2.791, *J* = 21 Hz	2.958, *J* = 21 Hz	4.061, *J* = 14 Hz	7.138	155.21

RESULTS AND DISCUSSION

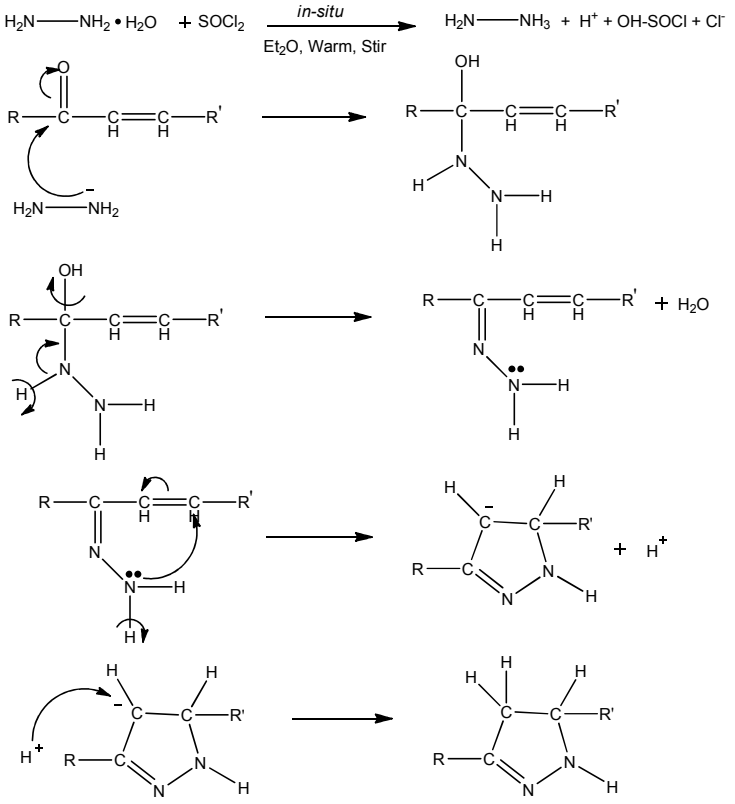
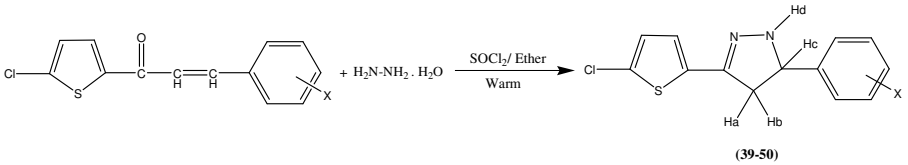


Figure 1. The proposed general mechanism for synthesis of 3,5-diaryl-^{1}*H*-pyrazolines.



(39-50)

X=H, 3-Br, 3–Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5

Scheme 2. Synthesis of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives.

In our organic chemistry research laboratory, we attempted to synthesize aryl pyrazoline derivatives by cycloaddition of chalcones and hydrazine hydrate using vigorous acidic catalyst $SOCl_2$ except acid or base or its salt in warming condition. Hence, we have synthesised the pyrazoline derivatives by the reaction between 2 mmol of chalcones and 2 mmol of hydrazine hydrate, 0.5 mL of $SOCl_2$ and 15 mL of diethyl ether in water bath warming at 60 °C (Scheme

1). During the course of this reaction the acidic $SOCl_2$ catalyses for the cycloaddition reaction between chalcone and hydrazine hydrate. The catalyst $SOCl_2$ abstracts water and it produce H^+ and Cl^- ions *in-situ* from the hydrazine hydrate. The hydrazine molecule attacks the carbonyl carbon of the chalcones and further rearranges leads to the formation of pyrazoline molecule. The yield of the reaction is more than 80%. The proposed general mechanism of this reaction is given in Figure 1. Further we investigated this reaction with equimolar quantities of the styryl 5-chloro-2-thienyl ketone with hydrazine hydrate (Scheme 2). In this reaction the obtained yield is 85%.

IR spectral study

The synthesized pyrazoline derivatives are shown in Scheme 1. The infrared νC=N and C-Cl stretching frequencies (cm^{-1}) of the pyrazolines (entries 39-50) have been recorded and are presented in Table 2. These data are [24-29, 38, 39] with Hammett substituent constants and Swain-Lupton's [40] parameters. In this correlation the structure parameter Hammett equation employed is as shown in equation (1).

$$\nu = \rho\sigma + \nu_o \quad (1)$$

where ν_o is the frequency for the parent member of the series.

The observed νC=N and C-Cl stretching frequencies (cm^{-1}) are correlated with various Hammett substituent constants, F and R parameters through single and multi-regression analyses including Swain-Lupoton's [40] parameters. The results of statistical analysis of single parameter correlation are shown in Table 3. The correlation of νC=N (cm^{-1}) frequencies of pyrazolines with Hammett σ_R substituent constants is found to be satisfactory with negative ρ value. The remaining constants were failing in correlation with positive ρ values. This implies that there is a normal substituent effect operates in all systems. This is due to the absence of inductive and resonance effects of the substituent and is associated with the conjugated structure shown in (Figure 2). In short some of the single parameter correlations of νC=N (cm^{-1}) frequencies with Hammett substituent constants of resonance and inductive effects fail. So, we think that it is worthwhile to seek the multi regression analysis and which produce a satisfactory correlation with Resonance, Field and Swain-Lupton's [40] constants. The corresponding equations are given in (2 and 3).

$$\nu C{=}N(cm^{-1}) = 1648.25(\pm1.904) + 5.472(\pm4.280)\,\sigma_I - 2.083(\pm4.243)\,\sigma_R \quad (2)$$
$$(R = 0.932,\ n = 12,\ P > 90\%)$$

$$\nu C{=}N(cm^{-1}) = 1657.07(\pm3.568) - 3.260(\pm6.674)F + 2.036(\pm2.925)R \quad (3)$$
$$(R = 0.957,\ n = 12,\ P > 95\%)$$

The correlation of νC-Cl (cm^{-1}) frequencies of pyrazolines with Hammett σ, σ_I, σ_R, F and R parameters were found to be satisfactory except σ^+ constants. All correlations produce negative ρ values. The remaining constants were fails in correlation with negative ρ values. The fail in correlation with σ^+ is due to the absence of polar effects of the substituent and is associated with the conjugated structure shown in (Figure 2). Also the authors observed the worth full multi-regression analysis and which produce a satisfactory correlation with Resonance, Field and Swain-Lupton's [40] constants. The corresponding equations are given in (4 and 5).

$$\nu C\text{-}Cl(cm^{-1}) = 788.92(\pm1.964) - 8.018(\pm4.417)\,\sigma_I - 5.387(\pm4.379)\,\sigma_R \quad (4)$$
$$(R = 0.967,\ n = 12,\ P > 95\%)$$

$$\nu C\text{-}Cl(cm^{-1}) = 788.34(\pm1.718) - 5.566(\pm3.848)F - 5.615(\pm2.987)R \quad (5)$$
$$(R = 0.930,\ n = 12,\ P > 90\%)$$

Table 3. Results of statistical analysis of infrared νC=N and C-Cl (cm^{-1}) modes of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives (entries **39-50**) with Hammett σ, σ^+, σ_I, σ_R constants and F and R parameters.

Frequency	Constants	r	I	ρ	s	n	Correlated derivatives
νC=N	σ	0.833	1650.30	3.026	3.17	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ^+	0.811	1650.55	0.690	3.34	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_I	0.834	1648.75	5.480	3.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_R	0.913	1649.77	-2.570	3.31	10	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.835	1648.94	4.330	3.14	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.814	1650.85	1.336	3.33	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
νC-Cl	σ	0.998	788.25	-6.112	3.08	12	H, 3-Br, 3–Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ^+	0.837	787.63	-2.517	3.56	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_I	0.945	790.16	-7.191	3.42	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_R	0.926	786.71	-4.177	3.70	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.937	789.28	-3.921	3.68	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.943	786.62	-4.633	3.46	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5

r = correlation co-efficient; ρ = slope; I = intercept; s = standard deviation; n = number of substituents.

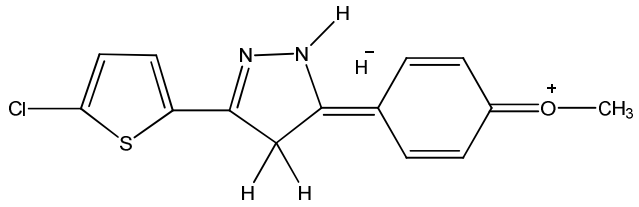


Figure 2. The resonance – conjugative structure.

^{1}H NMR spectral study

The ^{1}H NMR spectra of twelve pyrazoline derivatives under investigation have been recorded in deuteraated dimethyl sulphoxide solution employing tetramethylsilane (TMS) as internal standard. The signals of the pyrazoline ring protons have been assigned. They have been calculated as AB or AA' systems, respectively. The chemical shifts (ppm) of H_a are at higher fields than those of H_b, H_c and H_d in this series of pyrazolines. This is due to the deshielding of protons which are in different chemical as well as magnetic environment. These H_a protons gave an AB pattern and the H_b proton doublet of doublet in most cases was well separated from the signals H_c and the aromatic protons. The assigned chemical shifts (ppm) of the pyrazoline ring H_a, H_b, H_c and H_d protons are presented in Table 2.

In nuclear magnetic resonance spectra, the ^{1}H or the ^{13}C chemical shifts (δ) (ppm) depend on the electronic environment of the nuclei concerned. These chemical shifts have been correlated with reactivity parameters. Thus the Hammett equation may be used in the form as shown in (6).

$$\text{Log } \delta = \text{Log } \delta_0 + \rho\sigma \quad (6)$$

where δ_0 is the chemical shift of the corresponding parent compound.

The assigned H_a, H_b, H_c and H_d proton chemical shifts (ppm) of pyrazoline ring have been correlated [24-29, 38-42] with various Hammett sigma constants. The results of statistical analysis are presented in Table 4. The H_a proton chemical shifts (ppm) with Hammett substituent constants and F and R parameters fail in correlation except σ values. All correlations gave positive ρ values. This shows that the normal substituent effect operates in all systems. The failure in correlation is associated with the conjugative structure shown in Figure 2.

Table 4. Results of statistical analysis of ^{1}H NMR δH_a, δH_b, δH_c and δH_d and ^{13}C NMR δC=N (ppm) of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives with Hammett substituent constants σ, σ^+, σ_I, σ_R, F and R parameters(entries **39-50**).

Chemical shifts	Constants	r	I	ρ	s	n	Correlated derivatives
δ_{Ha} (ppm)	σ	0.915	2.854	0.036	0.09	10	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ^+	0.715	2.829	0.025	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_I	0.840	2.777	0.155	0.08	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_R	0.701	2.824	0.007	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.826	2.795	0.086	0.08	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.808	2.820	-0.021	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
δ_{Hb} (ppm)	σ	0.825	3.007	0.065	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ^+	0.728	3.015	0.047	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5

	σ_I	0.904	2.954	0.176	0.08	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_R	0.807	3.019	0.029	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.729	2.974	0.105	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.805	3.007	-0.005	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
δ_{Hc} (ppm)	σ	0.950	4.019	0.130	0.08	11	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ^+	0.905	4.035	0.086	0.08	11	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_I	0.907	4.017	0.029	0.09	9	3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 4-NO_2, 3-OC_6H_5
	σ_R	0.840	4.072	0.160	0.08	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.805	4.026	0.019	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.846	4.061	0.125	0.08	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
δ_{Hd} (ppm)	σ	0.837	7.088	-1.108	0.10	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ^+	0.818	7.076	-0.055	0.10	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_I	0.917	7.106	-0.086	0.10	11	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 3-OC_6H_5
	σ_R	0.756	7.011	-0.250	0.09	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.810	7.095	-0.039	0.10	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.825	7.060	-0.077	0.10	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
δCN (ppm)	σ	0.934	155.77	-0.958	0.97	10	H,3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 3-OC_6H_5
	σ^+	0.709	155.46	-0.038	0.23	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5

	σ_I	0.806	155.48	-0.062	0.23	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	σ_R	0.731	155.55	0.306	0.22	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	F	0.794	155.51	-0.123	0.23	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5
	R	0.709	155.45	-0.060	0.23	12	H, 3-Br, 3-Cl, 2-F, 4-F, 4-OH, 2-OCH_3, 4-OCH_3, 2-CH_3, 4-CH_3, 4-NO_2, 3-OC_6H_5

r = correlation co-efficient; ρ = slope; I = intercept; s = standard deviation; n = number of substituents.

The results of statistical analysis of H_b proton chemical shifts (ppm) with Hammett substituents are shown in Table 4. The H_b proton chemical shifts with Hammett $\sigma_I$constants give satisfactory correlation. The remaining Hammett substituent constants, F and R parameters were failed in correlation. This is due to the absence of inductive and resonance effect of substituents and it is associated with the conjugative structure shown in Figure 2.

The results of statistical analysis of H_c proton chemical shifts (ppm) with Hammett substituents are presented in Table 4. The H_c proton chemical shifts with Hammett σ, σ^+ and σ_I constants gave satisfactory correlation. The remaining σ_R, F and R parameters fail in correlation. All correlations produce positive ρ values. This means that the normal substituent effect operates in all systems. This failure in correlation is associated with conjugative structure shown in Figure 2.

The results of statistical analysis of H_d proton chemical shifts (ppm) with Hammett substituents are presented in Table 4. The H_c proton chemical shifts with Hammett σ_I constants gave satisfactory correlation. The remaining σ, σ^+, σ_R, F and R parameters fail in correlation. This failure in correlation is associated with conjugative structure shown in Figure 2.

In view of the inability of the Hammett σ constants to produce individually satisfactory correlation, the authors think that it is worthwhile to seek multiple correlations involving either σ_I andσ_R constants or F and R parameters [40]. The correlation equations for H_a–H_d protons are given in (7-14).

$$\delta Ha(ppm) = 2.781(\pm0.051) + 0.157(\pm0.116)\sigma_I + 0.016(\pm0.011)\sigma_R \quad (R = 0.941, n = 12, P > 90\%) \quad (7)$$

$$\delta Ha\ (ppm) = 2.794(\pm0.048) + 0.084(\pm0.109)F - 0.006(\pm0.084)R \quad (R = 0.926, n = 12, P > 90\%) \quad (8)$$

$$\delta H_b(ppm) = 2.968(\pm0.052) + 0.185(\pm0.117)\sigma_I + 0.057(\pm0.116)\sigma_R \quad (R = 0.946, n = 12, P > 90\%) \quad (9)$$

$$\delta H_b(ppm) = 2.974(\pm0.050) + 0.103(\pm0.112)F + 0.002(\pm0.087)R \quad (R = 0.929, n = 12, P> 90\%) \quad (10)$$

$$\delta Hc(ppm) = 4.056(\pm0.054) + 0.055(\pm0.121)\sigma_I + 0.169(\pm0.120)\sigma_R \quad (R = 0.942, n = 12, P > 90\%) \quad (11)$$

$$\delta Hc\ (ppm) = 4.042(\pm0.046) + 0.059(\pm0.013)F + 0.136(\pm0.080)R \quad (R = 0.949, n = 12, P> 90\%) \quad (12)$$

$$\delta H_d(ppm) = 7.082(\pm0.019) + 0.069(\pm0.044)\sigma_I - 0.003(\pm0.044)\ \sigma_R \quad (R = 0.946, n = 12, P > 90\%) \quad (13)$$

$$\delta H_d(ppm) = 7.095(\pm0.017) + 0.054(\pm0.039)F + 0.031(\pm0.030)R \quad (14)$$
$$(R = 0.946, n = 12, P > 90\%)$$

^{13}C NMR spectra

Organic chemists and researchers [24-29, 38-42] have made extensive study of ^{13}C NMR spectra for a large number of different ketones, styrenes, styryl ketones and keto-epoxides. They have studied linear correlation of the chemical shifts (ppm) of C_α, C_β and CO carbons with Hammett σ constants in alkenes, alkynes, acid chlorides and styrenes. In the present study, the chemical shifts (ppm) of pyrazoline ring C=N carbon, have been assigned and are presented in Table 2. Attempts have been made to correlate the δC=N chemical shifts (ppm) with Hammett substituent constants, field and resonance parameters, with the help of single and multi-regression analyses to study the reactivity through the effect of substituents.

The chemical shifts (ppm) observed for the δC=N have been correlated [24-29, 38-42] with Hammett constants and the results of statistical analysis are presented in Table 4. The δC=N chemical shifts (ppm) give satisfactory correlation with Hammett σ constants except 3-Br and 4-substituents. When these are included in the correlation they reduce the correlation co-efficient considerably. The remaining Hammett σ^+, σ_I, σ_R, F and R parameters fail in correlation. This is due to the reason stated earlier with resonance conjugative structure shown in Figure 2.

In view of inability of some of the σ constants to produce individually satisfactory correlation, the authors think that it is worthwhile to seek multiple correlation involving all σ_I, σ_R, F and R parameters [40]. The correlation equations are given in (15 and 16).

$$\delta C{=}N\ (ppm) = 155.68(\pm0.637) - 0.393(\pm1.432)\sigma_I - 0.568(\pm1.420)\sigma_R \quad (15)$$
$$(R = 0.914, n = 12, P > 90\%)$$

$$\delta C{=}N\ (ppm) = 155.60(\pm0.525) - 0.575(\pm1.176)F - 0.116(\pm0.913)R \quad (16)$$
$$(R = 0.939, n = 12, P > 90\%)$$

Microbial activities

Pyrazoline derivatives possess a wide range of biological activities [4, 6, 8, 10-12, 43, 44]. These multipronged activities are associated with different pyrazoline rings. Hence, it is intended to examine their activities against respective microbes-bacterial and fungal strains.

Antibacterial sensitivity assay

The antibacterial screening effect of synthesized pyrazoline is shown in Figure 3 (Plates 1-10). The antibacterial activities of all the synthesized pyrazolines have been studied against three gram positive pathogenic strains *Micrococcousluteus*, *Bacillus substilis*, *Staphylococcus aureus* and two gram negative strains *Escherichia coli* and *Klebsiella species*. The disc diffusion technique was followed using the Kirby-Bauer [45] method, at a concentration of 250 µg/mL with ampicillin taken as the standard drug. The measured zone of inhibition is shown in Table 5 and the clustered column chart is shown in Figure 4. All the compounds showed high activity against *Escherichia coli. M*oderate activity was observed against *Micrococcusluteus* and *Klebsilla pneumoniae.* The pyrazoline containing substituents 4-F, 2-CH_3 and 4-NO_2 have shown high antibacterial activity against all the strains. The rest of the compounds displayed lesser antibacterial activity against all the strains. However the activities of the test compounds are less than that of standard antibacterial agent used.

Table 5. Antibacterial activity of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives(entries **39-50**).

Entry	X	Zone of Inhibition (mm)				
		Gram positive bacteria			Gram negative bacteria	
		Bacillus substilis	*Micrococcus luteus*	*Staphylococcus aureus*	*Escherichia coli*	*Klebsilla pneumoniae*
39	H	6	7	7	6	6
40	3-Br	7	7	8	8	7
41	3-Cl	7	8	6	6	6
42	2-F	7	8	-	8	6
43	4-F	7	9	6	7	7
44	4-OH	7	8	-	8	7
45	2-OCH_3	7	8	8	6	8
46	4-OCH_3	6	7	6	6	6
47	2-CH_3	6	8	6	7	-
48	4-CH_3	7	7	-	7	8
49	4-NO_2	8	6	-	8	8
50	3-OC_6H_5	6	9	-	6	7
Standard	Ampicillin	22	20	12	10	9
Control	DMSO	-	-	-	-	-

Antifungal sensitivity assay

Antifungal sensitivity assay was performed using Kirby-Bauer [45] disc diffusion technique. PDA medium was prepared and sterilized as above. It was poured (ear bearing heating condition) in the petri-plate which was already filled with 1 mL of the fungal species. The plate was rotated clockwise and counter clock-wise for uniform spreading of the species. The discs were impregnated with the test solution. The test solution was prepared by dissolving 15 mg of the pyrazoline in 1 mL of DMSO solvent (250 µg/L). The medium was allowed to solidify and kept for 24 h. Then the plates were visually examined and the diameter values of zone of inhibition were measured. Triplicate results were recorded by repeating the same procedure.

The antifungal activities of substituted pyrazoline synthesized in the present study are shown in Figure 5 for plates (1-4) and the zone of inhibition values of the effect is given in Table 6. The clustered column chart, shown in Figure 6 reveals that all the compounds have moderate antifungal activity against *Aspergillius niger*, *Mucor species*, *Trichoderma viridie.* The pyrazoline containing 3-Cl, 2-OCH_3 and 2-OCH_3 substituents have shown higher antifungal activity than those with the other substituents present in the series.

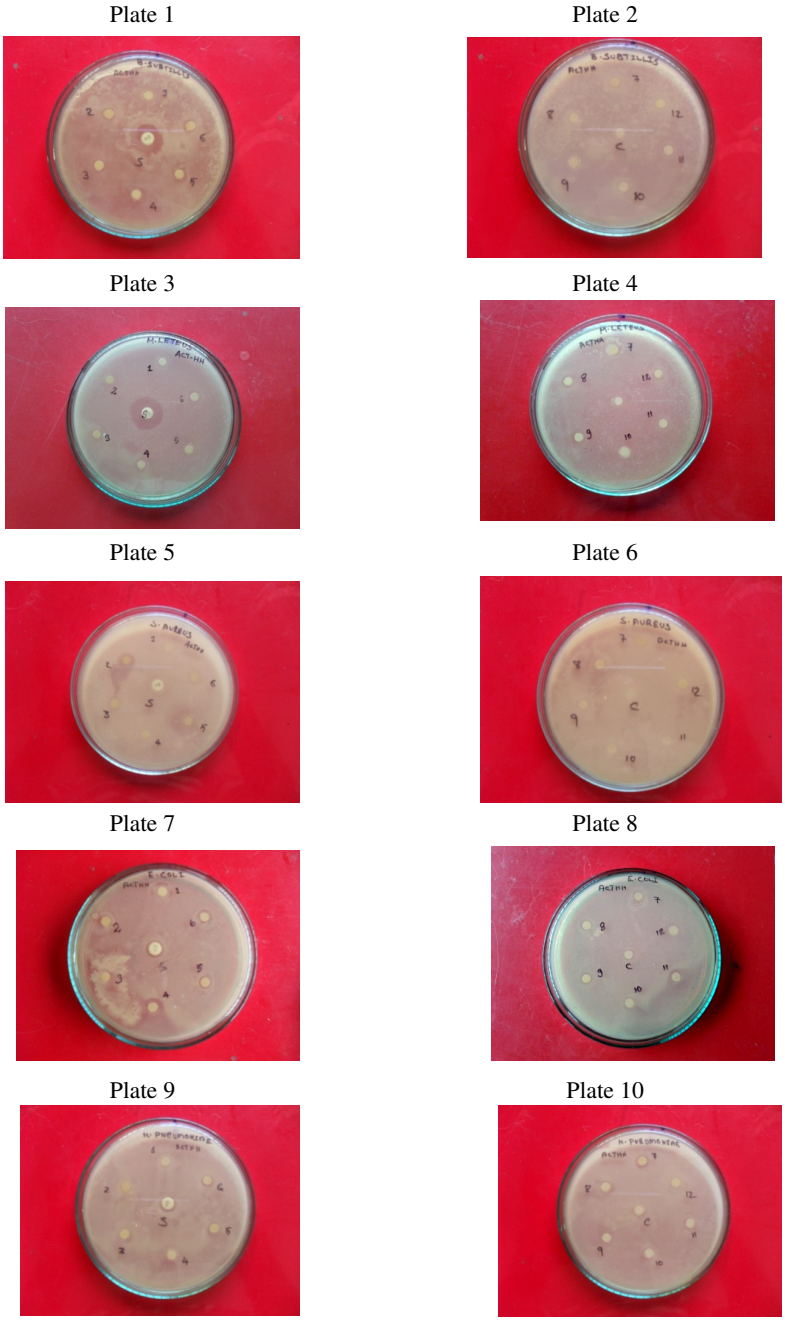


Figure 3. Antibacterial activities of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives-petri-dishes.

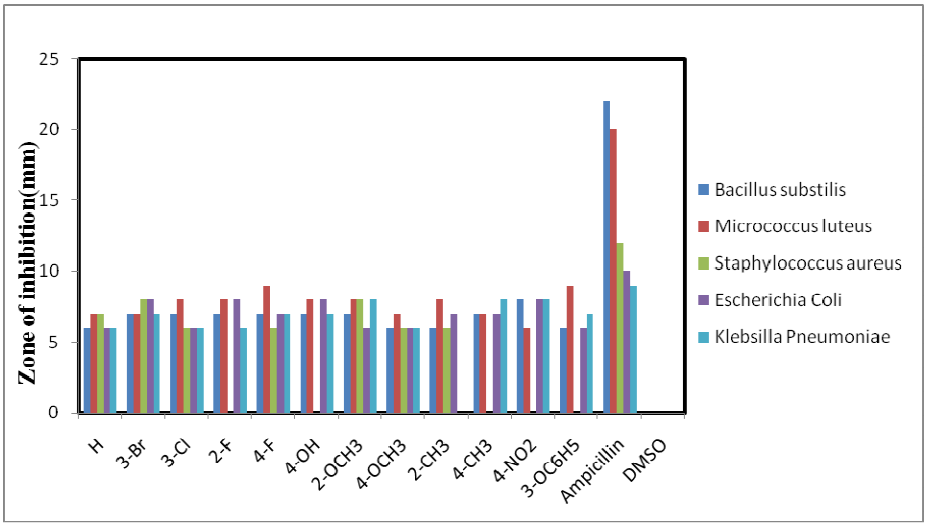


Figure 4. Antibacterial activities of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^1H-pyrazoline derivatives-clustered column chart.

Table 6. Antifungal activity of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^1H-pyrazoline derivatives (entries **39-50**).

Entry	X	*Zone of inhibition(mm)*		
		Aspergillius niger	*Mucor species*	*Trichoderma viride*
39	H	7	8	9
40	3-Br	8	7	6
41	3-Cl	6	8	8
42	2-F	6	6	7
43	4-F	7	-	8
44	4-OH	-	6	7
45	2-OCH_3	7	9	7
46	4-OCH_3	11	7	8
47	2-CH_3	10	6	-
48	4-CH_3	7	-	6
49	4-NO_2	-	8	-
50	3-OC_6H_5	6	7	7
Standard	Miconazole	9	18	15
Control	DMSO	-	-	-

Plate 1

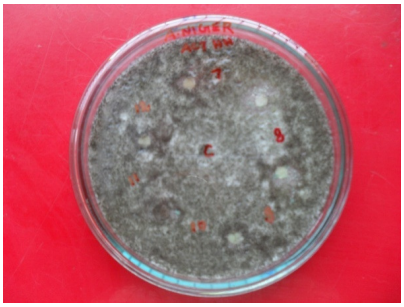


Plate 2

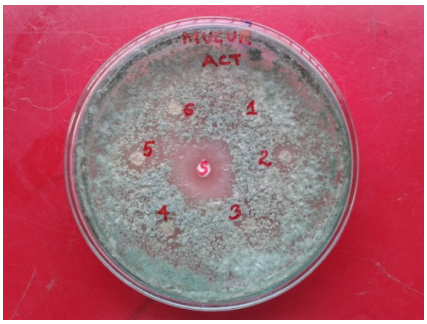


Plate 3

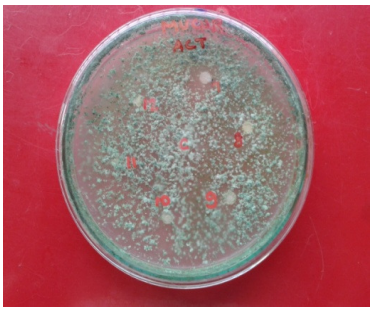


Plate 4

Plate 5

Plate 6

Figure 5. Antifungal activities of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-[1]*H*-pyrazoline derivatives-petri-dishes.

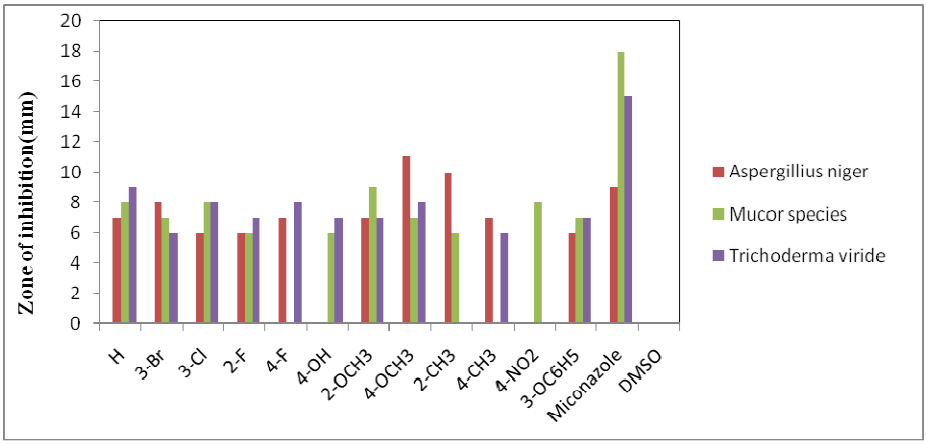


Figure 6. Antifungal activities of 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-^{1}*H*-pyrazoline derivatives-clustered column chart.

CONCLUSION

We have synthesized some aryl ^{1}H pyrazolines including 3-(5-chlorothiophen-2-yl)-4,5-dihydro-5-(substituted phenyl)-1H-pyrazoline derivatives by cyclization of aryl chalcones and hydrazine hydrate in the presence of $SOCl_2$. The yields of the pyrazoles are more than 85%. These pyrazoles are characterized by their physical constants and spectral data. The infrared, NMR spectral group frequencies of these pyrazolines have been correlated with Hammett substituent constants, F and R parameters. From the results of statistical analyses the effects of substituent on the spectral frequencies have been studied. The antimicrobial activities of all synthesised pyrazolines have been studied using Bauer-Kirby method.

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