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Studies about newly synthesized quinoxaline fused 1,2,4-triazine derivatives

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ABSTRACT

*Some new pyrazoline derivatives were synthesized by using following synthetic sequences (i) Preparation of (E)-1-(4-aminophenyl)-3-(furan-2yl) prop-2-en-1-one (**3a-b**) by the reaction between p-NH_2-aminoacetophenone (**1**) and heterocyclic aldehydes**(2a-b)** (ii) Preparation of (E)-1-(4-((E-)-4-chlorobenzylideneamino) phenyl)-3-(furan-2-yl) prop-2-en-1-one and (E)-1-(4-((E-)-4-chlorobenzylideneamino) phenyl)-3-(thiophene-2-yl) prop-2-en-1-one**(5a-b)** by the reaction of **3a-b**with p-Cl-benzaldehyde (**4**). (iii) Preparation of new pyrazoline derivatives **7a-h**was by the cyclysationreaction between **5a-b** with semicarbazide, thiosemicarbazide, phenylhydrazine and benzhydrazide**(6a-d)** in alcohol medium.The structures of the synthesizedcompounds were confirmed by using UV, IR,^{1}H-NMR, and ^{13}C-NMR spectral data. The invitro antimicrobial activity of synthesized compounds were evaluated against selective bacteria and fungus and preliminary results showed that most of the compounds showed moderate to good activity*

Keywords: Pyrazolines, Chalcones, Schiff bases, Anti-microbial activity, Furan2-aldehyde.

INTRODUCTION

Pyrazolines are well known nitrogen-containing 5-membered heterocyclic compounds and their synthesis [1], characterization and studies have been developing field within the realm of the heterocyclic chemistry for the past several decades.The numerous pyrazoline derivatives have been found to possess prominent biological activities, such as antimicrobial [2-5],antibacterial [6], antifungal [7], anticancer [8], anti-inflammatory [9], analgesic [10]and antidepressantactivities [11-12].Particularly 2-Pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), azolid/ tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric). The changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents with improved potency and lesser toxicity.We are highly promoted by these reports and also with continuation of our work on biologically important heterocyclic compounds, we planned to synthesize some bioactivepyrazoline entitieswith compact structure and evaluated their biological activity.

MATERIALS AND METHODS

General: Chemicals were procured from E. Merck (India), S. D. Fine Chemicals (India) and reagent/solvents were used without distillation procedure. Melting points were taken in open capillary tubes and are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (ν in cm^{-1}) and NMR spectra were recorded

on a Bruker spectrometer DPX-300MHz (Bruker, Germany) by using $CDCl_3$ or DMSO as solvent with tetramethylsilane (TMS) as an internal standard. All the spectral data are consistent with the assigned structures of the desired product and the progress of the reactions was monitored on silica gel G plates using iodine vapour as visualizing agent.

1. Synthesis of (E)-1-(4-aminophenyl)-3-(furan-2yl) prop-2-en-1-one (3a-b):
A mixture of 4-NH_2-Acetophenone (0.01mol) and furan-2-aldehyde/thiophene-2-aldehyde (0.01 mol) was stirred in ethanol (40 ml). To this reaction mixture an aqueous solution of NaOH (10 ml) was added and this was stirred for 3-4 hr continuously at room temperature. The progress of the reaction was monitored by using TLC-technique. After completion of the reaction, the mixture was poured in crushed ice and acidified with dilute HCl. The solid separated was filtered and recrystallized from ethanol.

2. Synthesis of (E)-1-(4-((E-)-4-chlorobenzylideneamino) phenyl)-3-(furan-2-yl) prop-2-en-1-one/ (5a-b):
A mixture of (E)-1-(4-aminophenyl)-3-(furan-2yl) prop-2-en-1-one (3a-b) (0.01moles) and substituted 4-chlorobenzaldehyde (0.01 mole) was refluxed for 5-6 hr in distilled ethanol (40 mL). The progress of the reaction was monitored by using TLC-technique. After completion of the reaction indicated by TLC, the mixture was kept for overnight in refrigerator. The solid formed was filtered off, washed with water, dried and recrystalyzed from ethanol.

3. Synthesis of pyrazoline derivatives (7a-h):
(E)-1-(4-((E-)-4-chlorobenzylideneamino) phenyl)-3-(furan-2-yl) prop-2-en-1-one (5a-b) (0.01 mol) with semicarbazide/thiosemicarbazide/phenylhydrazine/benzhydrazide (0.01 mol) were refluxed in ethanol with NaOH by using round bottom flask. The reaction mixture was refluxed for 4-5 hrs and the progress of the reaction was monitored by TLC. After completion of the reaction, the content were cooled and poured into crushed ice, the solid obtained was filtered, washed with water and recrystalyzed from ethanol.

Spectral data of some selective pyrazoline derivatives were given below:

(E)–3-(4-(4-chlorobenzyledineamino)phenyl-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (7a):UV-Vis(DMSO, nm): 203.72, 233.14, 280.00, 357.10., IR (KBr, cm^{-1}): 3409.63, 3260.96, (NH bands), 2827.86, 2984.31(Ar-C-H), 1617.52, 1559.98 (C=N); ^{1}H-NMR ($CDCl_3$, δppm), 3.35-3.40 (dd,1H,), 3.53-3.60 (dd,1H), 4.00 (NH_2),5.54-5.58 (dd,1H), 6.30-6.73 (m,3Ar-H), 7.30-7.70 (8Ar-H), 8.81 (s, CH=N). ^{13}C-NMR ($CDCl_3$, δppm), 39.23 (C-4 of pyrazoline), 53.38 (C-5 of pyrazoline), 108.90-140.88 (13Ar-C), 141.91 (C-Cl), 148.54 (N-C=C), 152.80 (N=C of pyrazoline), 153.10 (C-connected with furan), 155.76 ($CONH_2$), 161.10 (CH=N, imine).

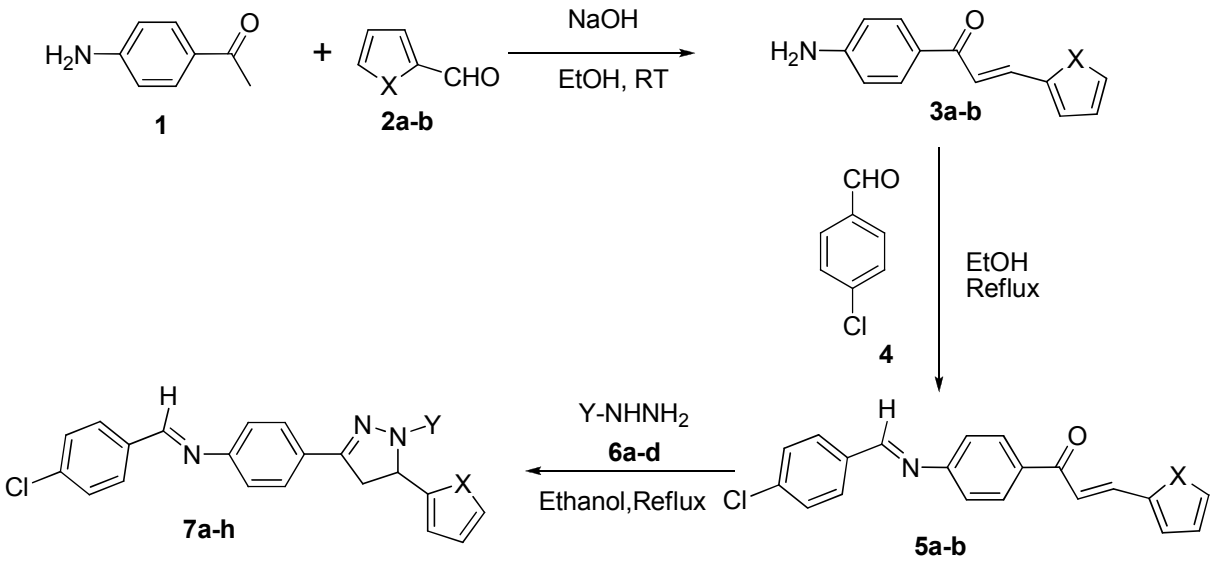
(E)–N-(4-chlorobenzyledine)-4-(5-furan-2-yl)-1-phenyl-4,5-dihydro-1H-pyrazole-1-3-yl) aniline (7c):UV-Vis(DMSO, nm): 203.72, 235.10, 284.00, 355.10., IR (KBr, cm^{-1}): 3353.33, 3160.15, (NH bands), 2827.00, 2884.31 (Ar-C-H), 1619.52, 1561.05 (C=N); ^{1}H-NMR ($CDCl_3$, δppm), 3.30-3.69 (dd,1H,), 3.73-3.79 (dd,1H), 6.31-6.35 (dd,1H), 6.68-7.84 (m,16Ar-H), 7.91 (s, CH=N); ^{13}C-NMR ($CDCl_3$, δppm), 4.17 (C-4 of pyrazoline), 60.54 (C-5 of pyrazoline), 112.80-133.92 (18Ar-C), 135.82 (C-Cl), 140.79 (N-C=C), 144.24 (C-connected with furan), 147.27, 148.07 (N=C of pyrazoline), 151..29 (CH=N, imine).

(E)–3-(4-(4-chlorobenzyledineamino)phenyl-5-(thiophene-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide (7f):UV-Vis(DMSO, nm): 203.72, 233.14, 276.10, 345.13., IR (KBr, cm^{-1}): 3409.63, 3260.96, (NH bands), 2800.21, 2950.31 (Ar-C-H), 1612.02, 1559.98 (C=N); ^{1}H-NMR ($CDCl_3$, δppm), 3.20-3.28 (dd,1H,), 3.72-3.78 (dd,1H), 1.63 (NH_2),5.42-5.46 (dd,1H), 6.69-7.83 (m, 11Ar-H), 7.95 (s, CH=N). ^{13}C-NMR ($CDCl_3$, δppm), 42.86 (C-4 of pyrazoline), 58.89 (C-5 of pyrazoline), 113.96-135.70 (11Ar-C), 136.72 (C-Cl), 142.55 (C-connected with furan), 144.27 (N-C=C), 149.38 (N=C of pyrazoline), 175.74 ($CSNH_2$), 156.65 (CH=N, imine).

(E)–N-(4-chlorobenzyledine)-4-(5-thiophene-2-yl)-1-phenyl-4,5-dihydro-1H-pyrazole-1-3-yl) aniline (7g):UV-Vis(DMSO, nm): 203.72, 235.10, 284.00, 355.10., IR (KBr, cm^{-1}): 3353.33, 3160.15, (NH bands), 2827.00, 2884.31 (Ar-C-H), 1619.52, 1561.05 (C=N); ^{1}H-NMR ($CDCl_3$, δppm), 2.92-3.10 (dd,1H,), 3.40-3.51 (dd,1H), 3.95-4.22 (dd,1H), 6.61-7.89 (m,16Ar-H), 8.62 (s, CH=N);^{13}C-NMR ($CDCl_3$, δppm), 43.17 (C-4 of pyrazoline), 60.00 (C-5 of pyrazoline), 113.25-133.30 (18Ar-C), 137.09 (C-Cl), 140.79 (N-C=C), 151.51 (N=C of pyrazoline), 166.11 (CH=N, imine).

RESULTS AND DISCUSSION

The synthesis of chalcones (**3a-b**) from p-NH_2-aminoacetophenone**1**and heterocyclic aldehyde**2a-b**was performed according to the Claisen-Schmidt condensation reaction. The obtained chalcone derivatives reacted with p-Cl-benzaldehyde (**4**) producedschiff bases (**5a-b**) and these products were cyclyzedbyusing semicarbazide,thiosemicarbazide, phenylhydrazine and benzhydrazide(**6a-d**) afforded corresponding pyrazoline derivatives (**7a-h**, **scheme-1**).



Scheme-1. Synthesis of pyrazoline derivatives

The formation of final product explained based on the formation of hydrazone intermediate and subsequent addition of N-H bond to the olefinic bond of the propenone moiety and detailed analytical data given in **table-1**. The formation of chalcone was confirmed based on the UV-Vis spectra by the increasedλ_{max} values from 348.93 to 369.20 nm of carbonyl group due to extended conjugation in chalcones and schiff base was confirmed the appearance new λ_{max} value around 280.0nm because of the formation of C=N chromophor. The formation of pyrazoline was identified the appearance of new absorption band around 420 nm and this may be due to C=O or C=S present in the pyrazoline moiety. The IR- stretching frequency of C=O group in the P-NH_2-aminoacetophenone appeared at 1644.92$cm^{-1}$and this value decreased towards 1601.24cm^{-1} in chalcone was confirmed the formation of chalcone and this is due to single bond character of C=O by the conjugation. The disappearance of weak doublet peak of NH_2group around 3325.03$cm^{-1}$and further appearance of new band at 1604cm^{-1} due to C=N bond formation ofschiff base. The appearance ofsome new bands around 1555-1590 cm^{-1}were confirmed that the C=N bond formation in pyrazoline molecules.The^{1}H-NMR spectra of products showed characteristics ABX system due to geminal-vicinal coupling between 4-CH_2 and 5-CH protons from the pyrazoline ring. The high field doubletdoublet at δ 3.35-3.40and 3.53-3.63δppm due to H_A and H_B protons attached with C-4 of pyrazoline ring and low field doubletdoubletaround 5.54-5.58δppmdue to Hxattached with C-5.The imine (CH=N) proton appeared at 8.81δppmand multiplets signals around7.30-7.70δppmwas assigned to various aromatic protons.The ^{13}C-NMR spectra of all compounds were showed some characteristic carbon signals and these are in good agreement with the proposed structures. The C4 and C5 carbon of pyrazoline ring resonated at 39.23-40.51 and 53.38-54.25δppm respectively in all the compounds. The appearance of signal around 161.01δppm in all the compounds due to imine carbon and several signals around 113.3–162.0δppm were assigned to the various aromatic carbons. We have taken some selective compounds 7b,7c,7d,7f,7g forantimicrobial activity, Among these compounds, 7c,7d 7f, 7g were showed moderate to very good activity against Staphylococcus aureus and Escherichia coli bacteria. .The above said compounds showed moderate activity against Aspergillusnigerfungi and both the case 7b was inactive.

Table-1: Physical data of synthesized compounds7a-h

Comp.code	X	Y	Yield (%)	Mp (ºC)	R_f value
7a	S	$CONH_2$	80	160-162	0.50
7b	S	$CSNH_2$	82	120-124	0.45
7c	S	C_6H_5	75	170-172	0.45
7d	S	C_6H_5CO	80	200-204	0.50
7e	O	$CONH_2$	75	180-182	0.55
7f	O	$CSNH_2$	70	210-212	0.50
7g	O	C_6H_5	70	140-144	0.50
7h	O	C_6H_5CO	65	156-158	0.45

3:2 ml hexane and ethylacetate used as eluents

Table-2:Antimicrobial data of synthesized compounds 7b,7c,7d,7f and 7g.

S. No.	Sample	**Zone of Inhibition** (mm in diameter, 20 µg/disc)		
		Escherichia coli	***Staphylococcus aureus***	***Aspergillus niger***
1	**PC***	**13**	**18**	**14**
2	**NC**	**-**	**-**	**-**
3	**7b**	**-**	**09**	**-**
4	**7c**	**14**	**11**	**12**
5	**7d**	**13**	**11**	**14**
6	**7f**	**18**	**13**	**14**
7	**7g**	**20**	**22**	**15**

** Gentamicin (10 µg) for Bacteria, * Ketoconazole (10 µg) for Fungi*

CONCLUSION

In the present report, we synthesized a series of new pyrazoline derivatives obtained in moderate to goodyield.All the synthesized compounds were characterized by using UV-Vis, IR, ^{1}H-NMR,^{13}C-NMR spectroscopy and obtained results are well supported for our proposedstructures. From the results of antimicrobial data, compounds 7c,7d, 7f and 7g shown good activity against bacterial pathogens while the above compounds were found moderate active against fungi pathogens.

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