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Synthesis, characterization and antimicrobial evaluation of some new N-acetyl pyrazoline derivatives from substituted furan-2-carbaldehyde

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ABSTRACT

A series of 10 new N-acetyl pyrazolines (3a-3j) were synthesized from different chalcones of 5-(3-chloro-4-fluorophenyl) furan-2-carbaldehyde with hydrazine hydrate and acetic acid. The chemical structures of these compounds were confirmed by means of ^1H *NMR,* IR and mass analyses. Newly synthesized compounds were screened in-vitro for their antimicrobial activity against varieties of bacterial strains such Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and fungi strain Aspergillus niger at 40 µg/mL. The resulted of compounds shown that chloro and flouro substituted pyrazoline derivatives are showing quite well activity as compare to the other functional groups.

Keywords: N-acetyl pyrazoline, furan-2-carbaldehyde, chalcone, antimicrobial evaluation

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INTRODUCTION

Infectious diseases caused by bacteria, fungi and other parasite are major threat for health of mankind. With availability of number of drugs in market, the problem is not solved but hastily increases with various cases of multi drug resistance parasites, bacteria and fungi. And this becomes major threat to health of humankind worldwide. So to come out from this budding problem, scientific community all over the world are trying to discover the new affordable and more active compounds which may cross all barrier and rapidly reach to the drug stages. One scientific community is trying to make compounds, which are novel in terms of current available drugs and mode of action. While another community is trying to improve the activity of existing drug scaffold, which may enhance the activity from the parental drug.

1,3-diaryl prop-2-en-1-one very well known as Chalcone, is the molecule which was known from many decades due to its wide range of biological activities such as antimicrobial[1], anti-inflammatory[2], analgesic[3], antiplatelet[4], antiulcerative[5], antimalarial[6], anticancer[7], antiviral[8], antileishmanial[9], antioxidant[10], antitubercular[11], antihyperglycemic[12], immunomodulatory[13], chemical mediators release inhibitors [14], leukotriene B4 inhibitors [15], tyrosinase inhibitors [16] and aldose reductase inhibitors [17] activities. Chalcones belongs to falvanoid family and present in various plant species such as fruits, vegetables, spices, tea etc. Chalcones are intermediate for the synthesis of number of heterocycles for eg. pyridine, pyrimidine, pyrazoline, isooxazoline, flavanoid, benzodiazepine, indazole, azetidinone which also shown various pharmacological activities. Chalcone exist as either E or Z isomer, but E isomer is most stable form and consequently major chalcone are isolated as E isomer. Pyrazoline derivative study has been a developing field within the realm of heterocyclic chemistry for the

part several decades because of its ease of synthesis, wide range of chemical reactivity and broad spectrum of biological activity such as Pyrazole derivatives have been reported to possess diverse biological activities such as antimicrobial [18, 19], antibacterial [20,21], antifungal [22, 23], herbicidal [24], insecticidal [25], anti-inflammatory [26-28], anticonvulsant [29], antitumor [30], anti-oxidant [31,32]

Flourine is the smallest atom than any other halogen series atom. In enzyme receptor interaction, fluorine atom easily interact next to hydrogen. The introduction of fluorine in the compound also increase the lipid solubility which increase the trasport of drug and make ease of absorption in vivo. The strong electron withdrawing inductive effect also Fluorine has been incorporated into well known antibiotic molecule i.e. flouroquinolone. Due to all this reason we choose flouro substitution in our staring material. In this report we synthesized 10 chalcones by taking 5-(3-chloro-4-fluorophenyl)furan-2-carbaldehyde with various acetophenones. And further derivatized them into N-acetyl pyrazoline with use of hydrazine hydrate and acetic acid. The starting compound 5-(3-chloro-4-fluorophenyl)furan-2-carbaldehyde (1) was synthesized by the reaction of diazotized solution of 3-chloro-4-flouro aniline and furfural.

MATERIALS AND METHODS

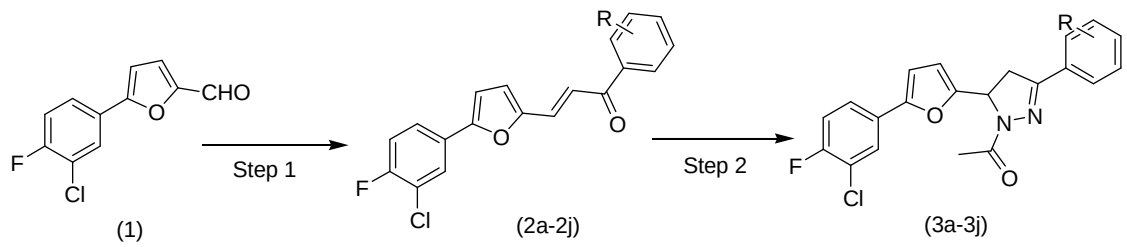
The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 spectrophotometer using KBr disc and ^{1}H NMR spectra in DMSO- d_6 or in $CDCl_3$ (Chemical shift in δ ppm) on Bruker spectrometer (400 MHz) using TMS as an internal standard. The results are in good agreement with the structure assigned. The purity of all compounds was checked by thin layer chromatography using TLC plates of silica gel (E.Merck G254) using Ethyl acetate : Hexane solvent system (7:3). Physical Constants and Spectral data of synthesized compounds (3a-3j) are recorded in Table – 1 and 2 respectively.

General procedure for synthesis of (2E)-3-[5-(3-chloro-4-fluorophenyl)-2-furyl]-1-substituted phenyl prop-2-en-1-ones (2a-2j)

To a well stirred solution of 5-(3-chloro-4-fluorophenyl) furan-2-carbaldehyde (1) (0.01 mole) and substituted acetophenones (0.01 mole) in ethanol (25 ml), 40% KOH solution was added till the solution become basic. The reaction mixture was stirred for 24 hrs at 25^{0}C. Completion of reaction was monitored by TLC. Reaction mass was poured onto crushed ice, acidified using concentrated HCl and filtered the precipitate and crystallized from appropriate solvent.

General procedure for synthesis 1-acetyl-4-[5-(3-chloro-4-fluorophenyl)-2-furyl]-3-substituted phenyl-4,5-dihydro-1H-pyrazoles (3a-3j)

To a solution of 2a-2j(0.01mole) in 25 ml ethanol, hydrazine hydrate (0.01mole) and glacial acetic acid (10 ml) was added and refluxed for 8 hrs. Completion of reaction was monitored by TLC. The reaction mass was poured onto crushed ice and the filtered the product, dried in vacuo and crystallized using an appropriate solvent.



Step-1 *R-C_6H_4-$COCH_3$, 40% NaOH, 24^{0}C, 18 hrs*
Step-2 *Hydrazine hydrate, glacial acetic acid, reflux, 6 hrs*
R = *different substituion*

SCHEME -1

Antimicrobial activity

The antimicrobial activity was assay by using the disc diffusion method. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against four bacterial strains, i.e. two gram +ve baceteria *Staphylococcus epidermidis and Staphylococcus aureus* and two gram –ve bacteria *Escherichia coli and Pseudomonas aeruginosa* and fungi strain *Aspergillus niger*. Standard drug Cephalexin and Greseofulvin were used for the comparison purpose. The obtained results for compounds 3a-3j are recorded Table 3.

TABLE-1 Physical constants 1-acetyl-4-[5-(3-chloro-4-fluorophenyl)-2-furyl substituted phenyl-4,5-dihydro-1H-pyrazoles (3a-3j)

Sr No.	Number of Comp.	R	Molecular Formula	Mol. Weight	Yield	Melting Point (^{0}C)	R_f
1	3a	H	$C_{21}H_{16}ClFN_2O_2$	382	78%	167	0.54
2	3b	4-Cl	$C_{21}H_{15}Cl_2FN_2O_2$	417	68%	177	0.55
3	3c	2-Cl-	$C_{21}H_{15}Cl_2FN_2O_2$	417	65%	182	0.57
4	3d	3-Cl	$C_{21}H_{15}Cl_2FN_2O_2$	417	74%	189	0.53
5	3e	4-OCH_3	$C_{22}H_{18}ClFN_2O_3$	413	78%	190	0.68
6	3f	4-CH_3	$C_{22}H_{18}ClFN_2O_2$	397	70%	175	0.74
7	3g	4-F	$C_{21}H_{15}ClF_2N_2O_2$	401	62%	172	0.48
8	3h	2-Br	$C_{21}H_{21}BrClFN_2O_2$	462	81%	182	0.32
9	3i	4-OH	$C_{21}H_{16}ClFN_2O_2$	399	75%	197	0.36
10	3j	2- NH_2	$C_{21}H_{17}ClFN_3O_2$	398	70%	163	0.57

TABLE-2 Spectroscopic data of 1-acetyl-4-[5-(3-chloro-4-fluorophenyl)-2-furyl]-3-substituted phenyl-4,5-dihydro-1H-pyrazoles (3a-3j)

Sr. No.	Compound No.	IR(KBr) ν(cm^{-1})	^{1}H NMR (δppm)
1	3a	1670 (C=O Str.), 1605 (C=N Str.), 1517 (C=C Str.), 749 (C–Cl), 680(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.25-7.90(5H, m, Ar-H)
2	3b	1660(C=O Str.), 1610(C=N Str.), 1522 (C=C Str.), 755 (C–Cl), 682(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.48(2H,d,Ar-H), 7.90(2H,d,Ar-H)
3	3c	1662(C=O Str.), 1610(C=N Str.), 1525 (C=C Str.), 745 (C–Cl), 684(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.25-7.90(4H, m, Ar-H)
4	3d	1667(C=O Str.), 1608(C=N Str.), 1520 (C=C Str.), 749 (C–Cl), 680(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.25-7.90(4H, m, Ar-H)
5	3e	1670 (C=O Str.), 1602(C=N Str.), 1518 (C=C Str.), 1205 (C-O-C Str.), 749 (C–Cl), 681(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 4.40(3H, s, -OCH_3), 5.60(1H,dd, pyrazoline ring H), 6.48(1H,d, furan-H), 6.80(2H,d, Ar-H) 7.06(1H,d, furan-H), 7.05(1H,dd, Ar-H), 7.15(1H,d, Ar-H), 7.22(1H,s, Ar-H), 8.22(2H,d,Ar-H)
6	3f	1669 (C=O Str.), 1602(C=N Str.), 1515(C=C Str.), 743 (C–Cl), 684(C-F)	2.22(3H,s,Ar-CH_3), 2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.38(2H,d,Ar-H), 7.97(2H,d,Ar-H)
7	3g	1663 (C=O Str.), 1600 (C=N Str.), 1525 (C=C Str.), 749 (C–Cl), 680 (C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.15-7.55(4H, m, Ar-H)
8	3h	1670(C=O Str), 1608 (C=N Str.), 1518 (C=C Str.), 760(C-Br), 749 (C–Cl),683(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d, furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.25-7.87(4H,m,Ar-H)
9	3i	3600–3400 (–OH Str.), 1661(C=O Str.), 1603 (C=N Str.), 1518 (C=C Str.), 749 (C–Cl), 680(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d,furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.17(2H,d,Ar-H), 7.22(1H,s,Ar-H), 7.97(2H,d,Ar-H), 8.25(1H,s,br,-OH)
10	3j	3600–3400 (–NH_2 Str.), 1668 (C=O Str.), 1602(C=N Str.), 1515 (C=C Str.), 749 (C–Cl), 685(C-F)	2.36(3H,s,-$COCH_3$), 3.32(1H,dd, H_a), 3.72(1H,dd, H_b), 5.20(2H,br, -NH_2) 5.60(1H,dd,pyrazoline ring H),6.48(1H,d,furan-H), 7.06(1H,d, furan-H), 7.05(1H,dd,Ar-H), 7.15(1H,d,Ar-H), 7.22(1H,s,Ar-H), 7.25-7.87(4H,m,Ar-H)

Table 3 Antimicrobial screening results of 1-acetyl-4-[5-(3-chloro-4-fluorophenyl)-2-furyl]-3-substituted phenyl-4,5-dihydro-1H-pyrazoles (3a-3j)

Compound No.	R	Zone of inhibiton(in mm)				
		Antibacterial activity				Antifungal activity (%) Activity
		S. aureus	*S.epidermiss*	*E.Coli*	*P.aeruginosa*	*A.niger*
3a	C_6H_5-	72	41	32	71	60
3b	4-Cl-C_6H_4-	54	69	89	84	72
3c	2-Cl-C_6H_4-	77	37	81	77	78
3d	3-Cl-C_6H_4-	80	85	72	82	83
3e	4-OCH_3-C_6H_4-	58	78	63	86	63
3f	4-CH_3-C_6H_4-	71	59	74	68	67
3g	4-F-C_6H_4-	70	71	89	72	70
3h	2-Br-C_6H_4-	69	47	61	66	63
3i	4-OH-C_6H_4-	50	54	79	61	68
3j	4-NH_2-C_6H_4-	81	68	50	39	64
Cephalexin	-	100	100	100	100	-
Griseofulvin	-	-	-	-	-	100

RESULTS AND DISCUSSION

N-acetyl pyrazolines compounds (3a-3j) have been synthesized by the reaction of (2E)-3-[5-(3-chloro-4-fluorophenyl)-2-furyl]-1-substituted phenyl prop-2-en-1-ones (2a-2j) with hydrazine hydrate and acetic acid with 60 to 80% of good yield. The structure of 3a-3j compounds is confirmed by IR, ^{1}HNMR and Mass spectral data analysis. From the results of antimicrobial data, compounds 3c, 3d and 3g were showing excellent active against selected gram positive and negative bacterial strains as compare to standard drug cephalexin, while 3a, 3b, 3e and 3f were moderately active against selected bacterial strains as compare to standard drug. While 3c, 3d and 3g were also shown excellent activity against fungi strain *A.niger* as compare to standard drug griseofulvin. From the structure activity relationship table, we find that phenyl ring substituted with chloro (3c) and flouro (3g) at shown an excellent result compare to standard drug cephalexin at a scale of 40ug/ml.

CONCLUSION

From the antimicrobial results, it worthwhile to say that, newly synthesized pyrazoline derivatives are showing moderate to good activity against bacterial and fungi strains. From the structure activity relationship table and the results we found that, phenyl rings substituted with chloro and flouro 2,3 and 4 position will show good activity as compare to other functional groups. From the obtained data for the newly synthesized pyrazoline derivatives we conclude on that with presence of halogen substitution in pyrazoline derivative will show excellent antimicrobial activity. And will give us path to synthesize more number of compounds with variations of halogen substitution on different ring, which may hope to give a better antimicrobial compound in the true sense.

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