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Original Article

SYNTHESIS, CHARACTERIZATION, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITIES OF SUBSTITUTED PYRAZOLINES FROM FURYL-FLUORENYL CHALCONE

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ABSTRACT

Objective: Pyrazolines are nitrogen-containing heterocyclic compounds with five-membered rings. They are fairly widely known, which is what sparked people's interest in this area of research to begin with. It has been shown that there are several ways to accomplish their synthesis. It has come to light that a great number of pyrazoline derivatives exhibit a wide variety of biological features.

Methods: The pyrazoline derivatives and the modified chalcone serve as the foundation for this research. Methods such as elemental analysis, infrared spectroscopy, nuclear magnetic resonance (^{1}H and ^{13}C), and mass spectrometry were used in order to analyze the structures of the produced compounds.

Results: The synthesis of chalcone (Furyl-Fluorenyl derivative) and the substituted pyrazolines was successful and analyzed enough by sophisticated techniques including NMR and Mass Spectrometry. The antibacterial and antioxidant capabilities of the compounds that were produced were also investigated and found the significant potential of the compounds.

Conclusion: The antibacterial and antioxidant capabilities of the compounds that were produced were also investigated and found the significant potential of the compounds.

Keywords: Pyrazolines, Chalcone, Antioxidant, Antimicrobial, NMR

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INTRODUCTION

A Various types of chemicals are being used in the medical field today. Organic molecules in especially has a significant function in medicine. The majority of organic compounds come from natural sources. Also these are derived from synthetic methods. Common pharmaceutical compounds such as atorvastatin, pluticasone, clopidogrel, chloroform, prednisolone, isoprenaline, sulfadiazine, fluorouracil, and align, aspirin, and paracetamol are all derived from organic compounds. This research investigates chalcones and their derivatives, which have been naturally occurring bioactive organic substances. This article is about natural organic products such as chalcones and their derivatives.

Chalcones are derivatives of the open-chain organic compounds and commonly is known as α, β-unsaturated ketones (trans-1,3-tire-2-propane-1-ones). These are directly linked to the ketoethylenic bond with two aryl groups (Ph–CO–CH = CH-Ph). They are naturally called flavonoids and are responsible for the pigmentation of plant flowers [1-3]. The chalcones are produced by the Claisen-Schmidt condensation method [4]. Due to the α, β-unsaturated carbonyl group contained in chalcones [5]. They have a lot of biological activity and can be used as good intermediates as in the synthesis of a number of heterocyclic compounds. [6]. The heterocyclic compounds of Isoxazoles [7], 2-Aminopyrimidines [8], Thiazines [9], Oxazines [10], Pyrazoline [11], N-Acyl pyrazoline [12], 2-Amino-3-cyanopyridines [13], 3-Cyanopyridines [14], Barbitones [15], 1,4-Diazepine [16], 1,4-Benzothiazepines [17] and Benzo[1,5]thiazepine [18] have been synthesized from chalcones have been synthesized from chalcones.

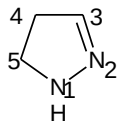


Fig. 1: General structure of pyrazoline

The heterocyclic compound of pyrazoline (fig. 1) is a five-member ring compound with two adjacent nitrogen atoms and three carbon atoms within the ring [19, 20]. The reaction of chalcones and hydrazine or phenylhydrazines within medium of acetic acid yields pyrazoline [21].

Pyrazole derivatives are used in a variety of biological functions because of their wide range of immunity, as can be seen from various studies [22-35]. They are employed as starting molecules for the development of novel medications. They we planned to the synthesis, characterization and biological evaluation of substituted pyrazolines based on recent literature studies. The structures of the compounds were determined by IR, ^{1}H, and ^{13}C NMR spectral data, and also elemental studies. The biological evaluation of obtained compounds was explained and given with in the discussion thread.

MATERIALS AND METHODS

Sigma Aldrich chemicals were used to synthesize of title compounds without purified. The compounds were generated by using the reporting method [11], which is elaborated in Schemes 1 and 2. Thin-layer chromatography was used to confirm the reaction completion. The melting points were determined in an open capillary tube without an uncorrected. The IR spectra of the prepared compounds being read using a Shimadzu IR spectrometer with a KBr disc, and the values were expressed in cm^{-1}. The ^{1}H and ^{13}C-NMR spectra have been obtained on Broker (400MHz) spectro-instrument using the TMS as an internal standard (chemical changes in ppm) with the DMSO-D6 act as a solvent. The calculated values for C, H, N and S correspond to the values observed in the elemental analysis.

Synthesis of chalcone

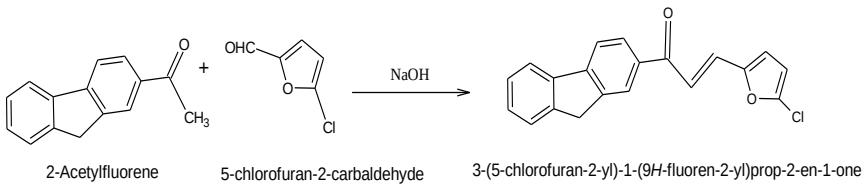
Synthesis of 3-(5-Chlorofuran-2-yl)-1-(9*H*-fluoren-2-yl)prop-2-en-1-one (C01)

The ethanolic NaOH solution of 2-Acetylfluorene (0.01 mol) was added to 5-chlorofuran-2-carbaldehyde (0.01 ml). The mixture was stirred for 3 h and then cooled for 24 h. Thin-layer chromatography technique was used for checking purity. The cooled mixture is then

placed in a solution of crushed ice and HCl acid. The resulting solid products have been precipitated and washed with water and recrystallized with ethanol.

3-(5-Chlorofuran-2-yl)-1-(9*H*-fluoren-2-yl)prop-2-en-1-one

$C_{20}H_{13}ClO_2$; m. p 145 °C; IR (KBr, λ_{max} in cm^{-1}): 3046 (C-H), 2957, 2854 (C-H), 1721 (C=O) 1612 (C-C), 1458 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 7.47 (d, 1H, *J*=15.2Hz), 7.98 (d, 1H, *J*=14.8Hz), 8.00 (d, 1H, *J*=1.2Hz, $C_{1'''}H$), 7.80-7.77 (m, 1H, $C_{3'''}H$), 7.81 (d, 1H, *J*=7.2Hz, $C_{4'''}H$), 7.66-7.23 (m, 4H, $C_{5'''}H$-$C_{8'''}H$), 7.01 (d, 1H, *J*=7.6Hz, $C_{4''}H$), 6.81 (d, 1H, *J*=7.6Hz, $C_{3''}H$), 3.74 (s, 2H, $C_{9'''}H$));^{13}C NMR (100 MHz, $CDCl_3$, δ (ppm)): 191.04 (C1), 151.83 (C2''), 144.34 (C10'''), 142.13 (C13'''), 139.62 (C12'''), 139.60 (C11'''), 138.71 (C5''), 137.11 (C2'''), 126.09 (C7'''), 126.07 (C3), 125.46 (C6'''), 125.35 (C8'''), 125.11 (C3'''), 124.46 (C1'''), 123.03 (C3''), 122.57 (C4'''), 122.09 (C5'''), 121.49 (C2), 114.11 (C4''), 35.36 (C9'''); MS (EI): m/z 320 [M+]; Elemental analysis-calcd: C, 74.89; H, 4.05 (%); found: C, 74.89; H, 4.08 (%).



Scheme 1: Method for synthesis of chalcone

Method for synthesis of substituted pyrazoline derivative 3-(5-Chlorofuran-2-yl)-1-(9*H*-fluoren-2-yl)prop-2-en-1-one (FP01)

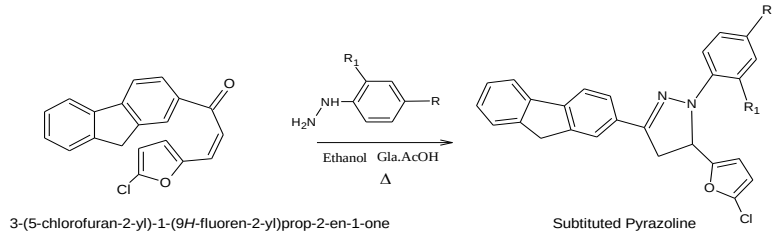
A 3-(5-Chlorofuran-2-yl)-1-(9*H*-fluoren-2-yl)prop-2-en-1-one (0.005 mol) has been mixed with phenylhydrazine (0.005 mol) and heated under reflux for 4 h with 25 ml glacial acetic acid. Thin-layer chromatography technique was used for checking purity. The cooled mixture is then placed in a solution of crushed ice. The resulting solid products have been precipitated and washed with water and recrystallize with ethanol. The same procedure was used to synthesis of FP02–FP04 (table 1).

5-(5-Chlorofuran-2-yl)-3-(9*H*-fluoren-2-yl)-1-phenyl-4,5-dihydro-1*H*-pyrazole

$C_{26}H_{19}ClN_2O$; m. p 178 °C; IR (KBr, λ_{max} in cm^{-1}): 3043 (C-H), 2932, 2813 (C-H), 1699 (C=O) 1613 (C-C), 1418 (C-H); ^{1}H-NMR (400 MHz, $CDCl_3$, δ (ppm)): 7.91 (d, 1H, J=1.6Hz, C1'''H) 7.88 (d, 1H, J=8.8Hz, C4'''H), 7.77-7.71 (m, 2H, C3'''H and C5'''H), 7.55-7.50 (m, 1H, C3'H and C5'H), 7.46-7.39 (m, 2H, C6'''H and C8'''H) 7.39-7.36 (m, 1H, C2'H and C6'H), 7.33-7.29 (m, 1H, C7'''H), 7.26-7.22 (m, 1H, C4'H) 6.54 (d, 1H, J=7.6Hz, C4''H), 6.43 (d, 1H, J=9.6Hz, C3''H), 5.88 (dd,1H, J=18, 8.8 Hz Py-Hx), 3.97 (dd, 1H, J=12.4, 9.2 Hz, Py-Ha), 3.78 (s, 2H, C9'''H) 3.73 (dd,1H, J=12.4, 8.8 Hz, Py-Hb); 13C NMR (100 MHz, CDCl3, δ (ppm)): 194.62 (C1), 151.37 (C2''), 143.12(C10'''), 142.20 (C1'), 142.13 (C13'''), 139.73 (C11'''), 139.62 (C12'''), 138.77 (C5''), 136.91(C2'''), 129.23(C3'and C5'), 126.12(C7'''), 125.36(C6'''), 125.35(C8'''), 124.44(C4'''), 124.22(C4'), 123.92 (C1'''), 122.12 (C5'''), 119.32(C3'''), 118.83(C3''), 117.63 (C2'and 6'), 108.54(C4''), 75.83(C3), 36.13 (C2) and 35.45 (C9'''); MS (EI): m/z 410 [M+]; Elemental analysis-calcd: C, 76.01; H, 4.62; N, 6.82 (%); found: C, 75.99; H, 4.66; N, 6.81(%)

5-(5-Chlorofuran-2-yl)-1-(4-chlorophenyl)-3-(9*H*-fluoren-2-yl)-4,5-dihydro-1*H*-pyrazole

$C_{26}H_{18}Cl_2N_2O$; m. p 181 °C; IR (KBr, λ_{max} in cm^{-1}): 3038 (C-H), 2923, 2819 (C-H), 1705 (C=O) 1614 (C-C) and 1443 (C-H); 1H NMR (400 MHz, $CDCl_3$, δ (ppm)): 7.90 (d, 1H, J=1.6Hz, C1'''H), 7.88 (d, 1H, J=7.6Hz, C4'''H), 7.74 (d, 1H, J=1.6Hz, C3'''H), 7.72 (d, 1H, J=7.2Hz, C5'''H), 7.54 (d, 2H, J=7.6Hz, C3'H and C5'H), 7.46-7.37 (m, 2H, C6'''H and C8'''H), 7.32 (d, 2H, J=7.2Hz, C2'H and C6'H), 7.29 (d, 1H, J=1.6Hz, C7'''H), 6.52 (d, 1H, J=7.6Hz, C3'''H), 6.43 (d, 1H, J=7.2Hz C4''H), 5.86 (dd,1H, J=18, 9.2 Hz Py-Hx), 3.96 (dd, 1H, J=5.2, 1.6 Hz, Py-Ha), 3.78 (s, 2H, C9'''H), 3.74 (dd,1H, J=12, 8 Hz, Py-Hb); 13C NMR (100 MHz, CDCl3, δ (ppm)): 192.12 (C1), 152.24 (C2''), 145.16 (C10'''), 142.43 (C13'''), 140.67 (C1'), 139.95(C11'''), 139.59 (C12'''), 139.11 (C5''), 138.87(C4'), 137.11(C2'''), 129.09 (C3'andC5'), 126.19(C7'''), 125.46 (C6'''), 125.14(C8'''), 124.46(C4'''), 124.12 (C1'''), 122.09 (C5'''), 119.29 (C3'''), 119.13 (C3''), 118.67 (C2'and C6'), 109.63 (C4''), 78.81 (C3), 35.97 (C2), 35.36 (C9'''); MS(EI): m/z 445 [M+]; Elemental analysis-calcd: C, 70.12; H, 4.04; N, 6.29 (%); found: C, 70.12; H, 4.04; N, 6.29 (%)



Scheme 2: Method for synthesis of pyrazoline derivatives

Table 1: Pyrazoline derivatives

Radical	FP01	FP02	FP03	FP04
R	Cl	Br	NO_2	NO_2
R_1	H	H	H	NO_2

5-(5-Chlorofuran-2-yl)-3-(9*H*-fluoren-2-yl)-1-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazole

$C_{26}H_{18}ClN_3O_3$; m. p 211 °C; IR (KBr, λ_{max} in cm^{-1}): 3049 (C-H), 2951, 2849(C-H), 1702 (C=O) 1613 (C-C), 1434 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 8.3 (d, 2H, *J*=7.6Hz, $C_{3'}H$ and $C_{5'}H$), 7.90 (d, 1H, *J*=1.2Hz, $C_{1'''}H$), 7.88 (d, 1H, *J*=7.6Hz, $C_{4'''}H$), 7.74 (d, 1H, *J*=1.2Hz, $C_{3'''}H$), 7.72 (d, 1H, *J*=7.6Hz,$C_{5'''}H$), 7.62 (d, 2H, *J*=7.2Hz, $C_{2'}H$ and $C_{6'}H$), 7.46-7.29 (m, 3H, $C_{6'''}H$, $C_{7'''}H$ and $C_{8'''}H$), 6.79 (d, 1H, *J*=7.6Hz $C_{3''}H$), 6.41 (d, 1H, *J*=7.2Hz, $C_{4''}H$), 5.92 (dd,1H, *J*=12.8, 9.2Hz Py-H_x), 3.97 (dd, 1H, *J*=12.8, 9.2 Hz, Py-H_a), 3.78 (s, 2H, $C_{9'''}H$), 3.71 (dd,1H, *J*=12.4, 8.8Hz, Py-H_b);^{13}C NMR (100 MHz, CDCl3, δ (ppm)): 191.34 (C1),

151.97 (C2''), 145.35 (C1'), 144.65 (C10'''), 142.45 (C13'''), 141.98 (C4'), 139.65 (C5''), 139.65 (C12'''), 138.93 (C11'''), 136.89 (C2'''), 126.23 (C7'''), 125.91 (C1'''), 125.77 (C3'and C5'), 125.73 (C6'''), 125.23 (C8'''), 124.97 (C4'''), 122.54 (C5'''), 119.13 (C3'''), 118.87 (C3''), 116.44 (C2'and C6'), 108.64 (C4''), 75.12 (C3), 36.23 (C2), 36.18 (C9'''); MS(EI): m/z 471 [M+]; Elemental analysis-calcd: C, 68.51; H, 3.95; N, 9.22 (%); found: C, 68.49; H, 3.97; N, 9.21 (%)

5-(5-Chlorofuran-2-yl)-1-(2,4-dinitrophenyl)-3-(9*H*-fluoren-2-yl)-4,5-dihydro-1*H*-pyrazole

$C_{26}H_{17}ClN_4O_5$; m. p 213 °C; IR (KBr, λ_{max} in cm^{-1}): 3051 (C-H), 2953, 2852 (C-H), 1736 (C=O) 1639 (C-C) and 1456 (C-H); ^{1}H NMR (400 MHz, $CDCl_3$, δ (ppm)): 9.25 (d, 1H, *J*=1.2Hz, C_3'H), 8.76-8.73 (m, 1H, C_5'H), 7.99 (d, 1H, *J*=1.2Hz, C_1'''H), 7.89 (d, 1H, *J*=7.6Hz, C_4'''H), 7.78 (d, 1H, *J*=7.6Hz, C_6'H), 7.74-7.71 (m, 2H, C_3'''H and C_5'''H),7.47-7.37 (m, 2H, C_6'''H and C_8'''H), 7.33-7.29 (m, 1H, C_7'''H), 6.75 (d, 1H, *J*=7.6Hz C_3''H), 6.61 (d, 1H, *J*=2.8Hz, C_4''H), 5.89 (dd,1H, *J*=17.6, 8.8Hz Py-H_x), 3.80 (s, 2H, C_9'''H,) 4.03 (dd, 1H, *J*=12.8, 9.2Hz, Py-H_a), 3.75 (dd,1H, *J*=14, 10.4Hz, Py-H_b); ^{13}C NMR (100 MHz, CDCl3, δ (ppm)): 193.17(C1), 152.47(C2''), 146.28(C10'''), 142.65(C13'''), 139.93(C11'''), 139.68(C12'''), 138.70 (C2'), 138.13(C1'), 138.04(C4'), 137.71(C5''), 136.97(C2'''), 129.97(C5'), 126.56(C7'''), 126.16(C6'''), 125.23(C8'''), 125.12(C4'''), 123.88(C3'), 123.12(C1'''), 122.32(C5'''), 121.48(C5''), 119.93(C3''), 119.35(C3'''), 109.69(C4''), 76.13(C3), 37.32(C2) and 36.32(C9'''); MS(EI): m/z 500 [M+]; Elemental analysis-calcd: C, 62.34; H, 3.39; N, 11.18 (%); found: C, 62.34; H, 3.39; N, 11.19 (%)

Method of biological activity

Antimicrobial activity

In vitro antimicrobial activities of the synthesized compounds were screened using the Kirby-Bauer disc diffusion method [36] and the results are shows in table 2. The compound's antibacterial activity was assessed on bacteria such as *B. subtilis*, *S. aureus*, *S. typhi*, and *E. coli*. The antibacterial activity of *ciprofloxacin* was employed as a standard. *Fluconazole* is being used as an antifungal drug against *Candida albicans*. Standard and evaluated components have been prepared at different concentrations using DMSO. After 24 h of the incubation period of 35-37 °C, the inhibition zone of antibacterial activity was compared with that of the standard compound of *ciprofloxacin*. Similarly, after 48 h at a temperature of 25 °C the results of antifungal activity have been obtained by comparing the zone inhibition with the standard.

Antioxidant activity

The compound's antioxidant activity has been assessed using the DPPH method [37]. A solution of DPPH (0.1 mmol, 2 ml) was mixed with various concentrations of the synthesized or standard compounds (2 ml). The resultant solution was then kept in the dark for 20 min before incubating at 37 °C. At 517 nm, the absorbance of the solution was measured. AA and BHA were used as positive controls. The percentage of inhibition was calculated using the equation of (blank OD−sample OD/blank OD)×100. Table 3 shows the results of antioxidants for the synthesized compounds.

RESULTS AND DISCUSSION

The schemes−1 and 2 describes the synthesis of chalcone (Furyl-Fluorenyl derivative) and the synthesis of substituted pyrazolines. The required starting material of chalcone (schme-1) was synthesized from 2-Acetylfluorene. The substituted pyrazolines (FP01-FP04) were synthesized using chalcone of Furyl-Fluorenyl derivative (schem-1) and phenylhydrazine or substituted phenylhydrazine such as 4-Chlorophenylhydrazine, 4-Nitrophenylhydrazine, and 2,4-Dinitrophenylhydrazine. The elemental analysis, IR, NMR and mass spectral methods were used to confirm the structure of compounds and the spectrum values were compared to the previously published values. The value of the IR spectra of C-C, C-H, C = O and other functional groups in the synthesized pyrozolines is corresponds to the reported values. ^{1}H and ^{13}C-NMR spectroscopy reported the existence of hydrogens and carbons in the synthesized compounds. Since the hydrogen atoms in the synthesized compounds are so close together, hydrogens are appears doublet and multiplet in the ^{1}HNMR spectrum. ^{13}C-NMR data's of all the prepared compounds were within the literature value. However, small variations are found depending on the other atoms attached to the carbons. The pyrozoline carbons are numbered C1=N, C-2, and C-3 based on the resulting signals of ^{13}C NMR spectral data. Also, three types of carbon skeletons are joined in the pyrazoline ring system, namely as a fluorenyl ring, 4-(subtitued) phenyl ring and furyl ring. The values of the aromatic carbons of all the rings correspond to the reported literary values. The methylene carbon is located at C-9. The value of the molecular ion [M^+] in the mass spectrum is equal to the molecular weight of the prepared compounds. Kirby-Bauer disc diffusion is used to study antimicrobial activity. The inhibition zone was compared to the standard. Table 2 shows the result of the antimicrobial activity of synthesized compounds. The newly synthesized compounds were highly effective against a variety of bacteria. Due to dinitrosubstitution, FP04 showed great antifungal activity when compared to other compounds. Table 3 shows the result of antioxidant activity. The calculated IC_{50} values are given in table 3. The FP04 is the most active compound with an IC_{50} value of 19.76µg/ml, whereas AA and BHA had IC50 values of 8.64 and 6.96µg/ml, respectively.

Table 2: Antimicrobial activity of the synthesized compounds

Sample code	Zone of inhibition (mm) of synthesized compounds																			
	Antibacterial activity																Antifugal activity			
	Bacillus subtilis				*Staphylococcus aureus*				*Salmonella typhi*				*Escherichia coli*				*Candida albicans*			
	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std
F01	10	7	-	18	11	8	4	14	16	8	4	21	13	8	4	18	18	11	8	25
FP01	12	9	4	24	18	7	3	19	15	9	4	18	16	9	4	19	19	13	11	24
FP02	11	8	5	16	19	8	4	21	17	8	3	19	12	7	3	17	17	14	8	21
FP03	12	9	6	17	13	7	6	24	18	9	3	21	14	8	5	17	16	9	7	19
FP04	18	11	6	20	21	11	6	24	21	12	8	24	15	7	6	19	23	16	9	26

Std–Standard (Ciprofloxacin); *Average of three independent determinations

Table 3: Antioxidant activity of synthesized compounds

Compound	Concentration (µg/ml)					IC_{50} (µg/ml)*
	20	40	60	80	100	
F01	62.27	67.91	72.45	76.81	78.77	43.39
FP01	43.81	51.25	63.92	69.72	77.50	33.84
FP02	66.59	71.01	75.25	79.11	81.51	70.42
FP03	46.58	54.06	65.83	71.23	78.72	27.39
FP04	61.30	68.38	75.32	80.91	85.45	19.76
BHT	57.52	64.44	71.99	82.10	93.93	6.96
AA	57.47	64.37	76.70	87.81	98.09	8.64

*Average of three independent determinations

CONCLUSION

A serious substituted pyrazoline derivative was synthesized and elemental and spectral analysis confirmed the compounds' structures. Antimicrobial activity against selected bacteria and fungi was proved by newly synthesized compounds. The compound FP04 illustrated significant antioxidant activity. Finally 5-(5-Chlorofuran-2-yl)-1-(2,4-dinitrophenyl)-3-(9*H*-fluoren-2-yl)-4,5-dihydro-1*H*-pyrazole has been shown to have antifungal and antioxidant activity.

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Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Rudrapal M, Khan J, Dukhyil AAB, Alarousy RMII, Attah EI, Sharma T. Chalcone scaffolds, bioprecursors of flavonoids: chemistry, bioactivities, and pharmacokinetics. Molecules. 2021;26(23):7177. doi: 10.3390/molecules26237177, PMID 34885754.
2. Raut NA, Dhore PW, Saoji SD, Kokare DM. Selected bioactive natural products for diabetes mellitus. Stud Nat Prod Chem. 2016;48:287-322. doi: 10.1016/B978-0-444-63602-7.00009-6.
3. Stavenga DG, Leertouwer HL, Dudek B, van der Kooi CJ. Coloration of flowers by flavonoids and consequences of pH dependent absorption. Front Plant Sci. 2020;11:600124. doi: 10.3389/fpls.2020.600124, PMID 33488645.
4. Dong F, Jian C, Zhenghao F, Kai G, Zuliang L. Synthesis of chalcones via claisen–schmidt condensation reaction catalyzed by acyclic acidic ionic liquids. Cat Commun. 2008;9(9):1924-7. doi: 10.1016/j.catcom.2008.03.023.
5. Banoth RK, Thatikonda A. A review on natural chalcones an update. Int J Pharm Sci Res. 2019;5:546-55. doi: 10.13040/IJPSR.0975-8232.11(2).546-55.
6. Jawad AM, Salih MNM, Helal TA, Obaid NH, Aljamali NM. Review on chalcone (preparation, reactions, medical and bio applications). Int J Chem Synth Chem React. 2019;5(1):16-27.
7. Panda SS, Chowdary PVR, Jayashree BS. Synthesis, antiinflammatory and antibacterial activity of novel indolyl-isoxazoles. Indian J Pharm Sci. 2009;71(6):684-7. doi: 10.4103/0250-474X.59554, PMID 20376225.
8. Selvakumar D, Venkatesan J, Pandeya S. Synthesis and biological evaluation of 4,6-diaryl substituted-4,5-dihydro-2-amino pyrimidines. Indian J Pharm Sci. 2007;69(4). doi: 10.4103/0250-474X.36954.
9. BR, Murthy MS, Basha Shaik A. Design, facile synthesis, and biological evaluation of novel 1,3-thiazine derivatives as potential anticonvulsant agents. Asian J Pharm Clin Res 2015;9(5). doi: 10.22159/ajpcr.2016.v9i5.13676.
10. Sharma A, Khaturia S, Singh HL. Synthesis of new schiff base of 1,3-oxazine and 1,3-Thiazine derivatives derived from 4-phenyl substituted chalcones and evaluation of their antibacterial activity. Asian J Chem. 2021;33(3):531-6. doi: 10.14233/ajchem.2021.23050.
11. Kavitha R, Nagoor Meeran M, Sureshjeyakumar RP. Synthesis, characterization and antimicrobial activity of substituted pyrazolines. Chem Sci Trans. 2015;4(4):1001-6. doi: 10.7598/cst2015.1118.
12. Thirunarayanan G, Sekar KG. Solvent-free one-pot cyclization and acetylation of chalcones: synthesis of some 1-acetyl pyrazoles and spectral correlations of 1-(3-(3,4-dimethyl phenyl)-5-(substituted phenyl)-4,5-dihydro-1H-pyrazole-1-yl) ethanones. J Saudi Chem Soc. 2016;20(6):661-72. doi: 10.1016/j.jscs.2013.12.002.
13. Drabu S, Kumar N. Synthesis and biological screening of substituted 2-aminocyanopyridines. Asian J Chem. 2007;19(6):4957-9.
14. Karthikeyan V, Sivakumar K, Gokuldass A, Mohana Sundaram S. Studies on larvicidal activity of leucas aspera, vitex negundo and eucalyptus against culex quinquefasciatus collected from coovum river of Chennai, India. Asian J Pharm Sci Clin Res. 2012;5(3):1-4.
15. Venkatesh T, Bodke YD. Synthesis, the antimicrobial and antioxidant activity of chalcone derivatives containing thiobarbitone nucleus. Med Chem Los Angeles. 2016;6(7):7. doi: 10.4172/2161-0444.1000383.
16. Kaoua R, Bennamane N, Bakhta S, Benadji S, Rabia C, Nedjar Kolli B. Synthesis of substituted 1,4-diazepines and 1,5-benzodiazepines using an efficient heteropolyacid-catalyzed procedure. Molecules. 2010 Dec 28;16(1):92-9. doi: 10.3390/molecules16010092, PMID 21189457, PMCID PMC6259285.
17. Bhat KI, Kumar A. Synthesis and anti-inflammatory activity of some novel 1,5-benzodiazepine derivatives. Asian J Pharm Clin Res. 2016;9(4):63-6.
18. Mohanasundaram S, Doss VA, Haripriya G, Varsha M, Daniya S, Madhankumar. GC-MS analysis of bioactive compounds and comparative antibacterial potentials of aqueous, ethanolic and hydroethanolic extracts of Senna alata L. against enteric pathogens. Int J Res Pharm Sci. 2017;8(1):22-7.
19. Biswajit D. Pyrazoline hydroxylic [review]. IJPSR. 2016;12(6):2570-88. doi: 10.13040/IJPSR.0975-8232.12(5).2570-88.
20. Yusuf M, Jain P. Synthetic and biological studies of pyrazolines and related heterocyclic compounds. Arab J Chem. 2014;7(5):553-96. doi: 10.1016/j.arabjc.2011.09.013.
21. Mohanasundaram S, Rangarajan N, Sampath V, Porkodi K, Dass Prakash MV, Monicka N. GC-MS identification of anti-inflammatory and anticancer metabolites in edible milky white mushroom (Calocybe indica) against human breast cancer (MCF-7) cells. Res J Pharm Technol. 2021;14(8):4300-6.
22. Jain SK, Singhal R. A review on pyrazoline derivatives as antimicrobial agent. Int J Pharm Pharm Sci 2020;12:15-24. doi: 10.22159/ijpps.2020v12i6.37456.
23. Patel MR, Dodiya BL, Ghetiya RM, Joshi KA, Vekariya PB, Bapodara AH. Synthesis and antimicrobial evaluation of pyrazoline derivatives. Int J Chem Tech Res. 2011;3(2):967-74.
24. Mohanasundaram S, Doss VA, Maddisetty P, Magesh R, Sivakumar K, Subathra M. Pharmacological analysis of a hydroethanolic extract of Senna alata (L.) for *in vitro* free radical scavenging and cytotoxic activities against Hep G2 cancer cell line. Pak J Pharm Sci. 2019;32(3):931-4.
25. Kumar AK, Jayaroopa P. Pyrazoles: synthetic strategies and their pharmaceutical application-an overview. Int J Pharm Tech Res. 2013;5(4):1473-86.
26. Kumar AK, Pyrazolines GM. Versatile molecules of synthetic and pharmaceutical applications-a review. Int J Chem Tech Res. 2015;8(1):313-22.
27. Surendra Kumar R, Arif IA, Ahamed A, Idhayadhulla A. Anti-inflammatory and antimicrobial activities of novel pyrazole analogues. Saudi J Biol Sci. 2016;23(5):614-20. doi: 10.1016/j.sjbs.2015.07.005. PMID 27579011.
28. Revanasiddappa BC, Kumar MV, Kumar H. Synthesis and antioxidant activity of novel pyrazoline derivatives. Hygeia JD Med 2018;10(1):43-9. doi: 10.15254/H.J.D.Med.10.2018.177.
29. Patel P, Gor D, Patel PS. Design, synthesis and pharmacological evaluation of new series of pyrazolines based thiazolidine-4-one derivatives. Chem Sci Trans. 2016;2(4):1089-93.
30. Rahaman SA, Ragjendra Prasad Y, Bhuvaneswari K, Phani K. Synthesis and antihistaminic activity of novel pyrazoline derivatives. Int J Chem Technol Research. 2010;2(1):16-20.
31. Mohanasundaram S, Rangarajan N, Sampath V, Porkodi K, Pennarasi M. GC-MS and HPLC analysis of antiglycogenolytic and glycogenic compounds in kaempferol 3-O–gentiobioside containing senna alata L. leaves in experimental rats. Translational Metab Syndr Research. 2021;4:10-7.
32. Slilveri S, Basaboina N, Vamaraju HB, Raj S. Design, synthesis, molecular docking, ADMET studies and biological evaluation of pyrazoline incorporated 1,2,3 triazole benzene sulphonamides. Int J Pharm Pharm Sci. 2019;11:6-15.

33. Rangarajan N, Sangeetha R, Mohanasundaram S, Sampath, Porkodi K, Dass Prakash MV. Additive inhibitory effect of the peels of citrus limon and citrus sinensis against amylase and glucosidase activity. IJRPS 2021;11(4):6876-80. doi: 10.26452/ijrps.v11i4.3661.
34. Sadashiva R, Naral D, Kudva J, Madan Kumar S, Byrappa K, Mohammed Shafeeulla R. Synthesis, structure characterization, *in vitro* and *in silico* biological evaluation of a new series of thiazole nucleus integrated with pyrazoline scaffolds. J Mol Struct. 2017;1145:18-31. doi: 10.1016/j.molstruc.2017.05.066.
35. Ahmad A, Husain A, Khan SA, Mujeeb M, Bhandari A. Synthesis, antimicrobial and antitubercular activities of some novel pyrazoline derivatives. J Saudi Chem Soc. 2016;20(5):577-84. doi: 10.1016/j.jscs.2014.12.004.
36. Sankar A, Pandimuthu G, Nithya G, Ravikumar R, Meeran NM. Synthesis, characterization and antimicrobial activity of substituted pyrazole-based heterocyclic compounds. Pharm Chem. 2016;8(19):345-9.
37. Meeran MN, Hussain AZ. Synthesis, characterization and DPPH scavenging assay of isatin-related spiro heterocyclic compounds. Indian J Pharm Sci. 2017;79(4):641-5. doi: 10.4172/pharmaceutical-sciences.1000273.