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Chemical and pharmacological evolution of some synthesized chalcones and hetrocyclic compounds

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ABSTRACT

Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. With centuries medicinal chemistry had emerged as a magnanimous field of science getting a facelift from the available natural compounds for synthesis of newer and complex molecules possessing medicinal activity while the transit from the earth to a synthetically furnished laboratory. Medicinal chemistry or pharmaceutical chemistry is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Chalcones is a generic term given to compounds bearing the 1,3-diarylprop2-en-1-one, which can be functionlized in the propane chain by the presence of olefinic, keto and/or hydroxyl group. Chalcones belongs to the flavonoid family. Chemically chalcones consisted of open chain flavonoids in which the two aromatic rings are joined by a three carbon a,ß-unsaturated carbonyl system (Dhar, 1981). Microorganisms are a heterogeneous group of several distinct classes of living beings. They were classified under third kingdom, the Prostita. Based on differences in cellular organization and biochemistry, the kingdom prostita has been divided into two groups, Prokaryotes and Eukaryotes. Bacteria and blue green algae are prokaryotes while fungi, other algae, slime moulds and protozoa are eukaryotes. Anti-fungal drugs are among the most frequently prescribed preparations because of their fungal activity. They are widely used for the treatment of the fungal diseases such as Candidiasis and Apergillosis. These agents prevent from fungal infection. Anti-oxidant drugs are among the most frequently prescribed preparations prevent Oxidation.

Keywords— *Synthesis, Chalcone, Hetrocyclic compound, Antioxidant, Antifungal*

1. INTRODUCTION

Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. With centuries medicinal chemistry had emerged as a magnanimous field of science getting a facelift from the available natural compounds for synthesis of newer and complex molecules possessing medicinal activity while the transit from the earth to a synthetically furnished laboratory. Medicinal chemistry or pharmaceutical chemistry is a discipline at the intersection of chemistry and pharmacology involved with designing, synthesizing and developing pharmaceutical drugs. Medicinal chemistry involves the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also includes the study of existing drugs, their biological properties and their quantitative structural-activity relationships (QSAR).

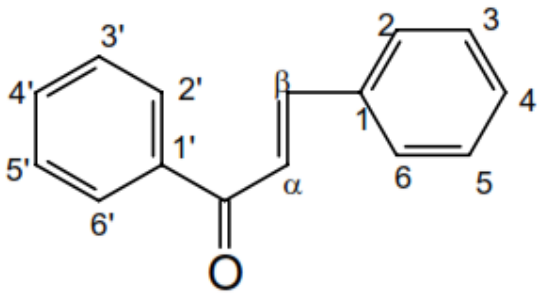
Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals. During the early stages of medicinal chemistry development, scientists were primarily concerned with the isolation of medicinal agents found in plants. Today, scientists in this field are also equally concerned with the creation of new synthetic drug compounds. Medicinal chemistry is almost always geared toward drug discovery and development. The focus on development of new synthetic drug compounds has resulted in the incorporation of many other disciplines, such as biochemistry, combinatorial chemistry, chemical biology, phytochemistry, pharmacology, enzymology, pharmacognosy, statistics, physical chemistry and molecular biology into medicinal chemistry. In this view medicinal chemists are also trying to speed up drug discovery process for finding the lead molecule (Thomas *et al.* 1998).

1.1 Chalcones

Chalcones is a generic term given to compounds bearing the 1,3-diarylprop2-en-1-one**,** which can be functionlized in the propane chain by the presence of olefinic, keto and/or hydroxyl group. Chalcones belongs to the flavonoid family. Chemically chalcones consisted of open chain flavonoids in which the two aromatic rings are joined by a three carbon *a,ß*-unsaturated carbonyl system

(Dhar, 1981). Pharmacological properties of chalcones are due to the presence of both a,ß-unsaturation and an aromatic ring. Chalcones considered as precursors of flavonoids and isoflavonoids are abundant in plants (Ni *et al.* 2004; Nowakowska, 2007; Dimmock *et al.* 1999).

1.2 General structure of chalcone



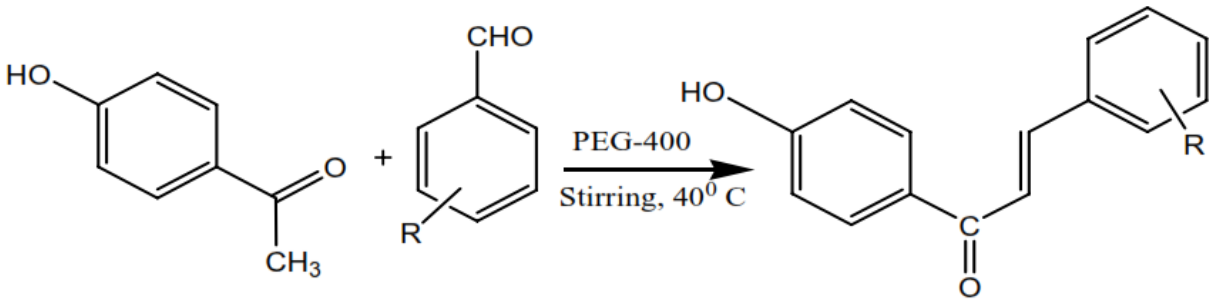
Chalcones are one of the major classes of natural products which occur widely in nature particularly in colored flowers and wide spread distribution in fruits, vegetables, spices and tea. Various natural or synthetic chalcones have been found to posses diverse biological activites (Di Carlo *et al.* 1999).

All the chalcones give dark red coloration with concentrated sulphuric acid wilson test) and violet red coloration with alcoholic ferric chloride solution. Chalcones on heating with traces of iodine in dimethylsulphoxide (DMSO) for two hours give the corresponding flavones. Chalcones were converted into the corresponding flavonols by their oxidation using hydrogen peroxide in methanolic sodium hydroxide solution and these flavonols showed characteristic greenish yellow fluorescence in ethanolic solution as well as with concentrated sulphuric acid.

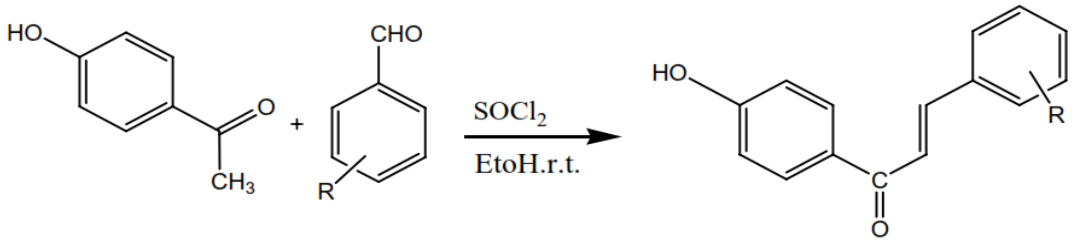
1.3 General methods of synthesis of chalcones

Chalcones are well known intermeadiates for synthesizing various heterocyclic compounds. They can be obtained by the acid or base catalyzed aldol condensation of acetophenones with benzaldehydes (Guida *et al.* 1997).

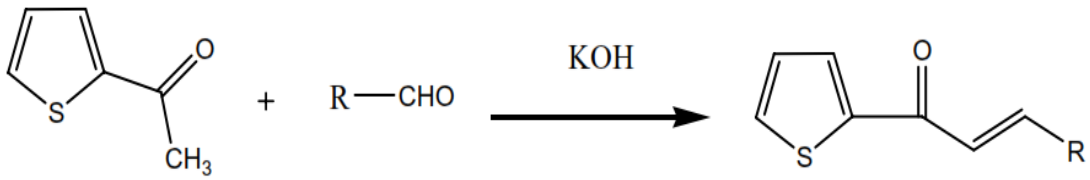
1) Claisen–Schmidt condensation between 4-hydroxy acetophenone and benzaldehyde was carried out in the presence of a base catalyst was stirred in PEG-400 as a recyclable solvent form 4' -hydroxy chalcones (Sreedhar *et al.* 2010).



2) Stirred mixture of 4-hydroxy acetophenone and various benzaldehyde in the presence of thionylchloride in absolute ethnol form substituted 4'-hydroxy chalcones (Eddarir, 2003).



A mixture of 2-acetyl thiophene substituted aldehydes was stirred in ethnol then an aqueous solution of KOH was added to form chalcones (Romanelli *et al.* 2011).



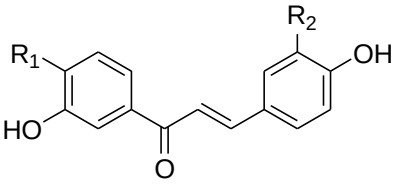
2. LITERATURE REVIEW

Antioxidant Activity

Oxidative damage to various tissues by free radicals have been implicated as the cause of diverse diseases. Plants produce a variety of antioxidants against molecular damage from reactive oxygen species (ROS), and phenolics compose the major class of plant-

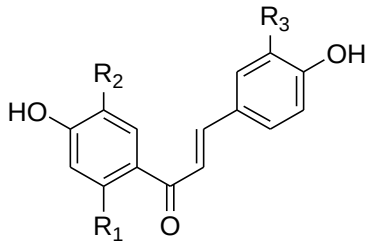
derived antioxidants. Among the various phenolic compounds, the flavonoids are perhaps the most important group. They have the property to scavenge free radicals and to prevent lipid peroxidation (Morel *et al.* 1993).

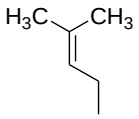
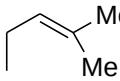
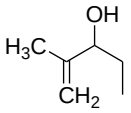
3, 4-Dihydroxy chalcones, such as butein (**10**) and okanin (**57**), are particularly effective antioxidants in the range of concentrations 0.025–0.1%, as judged by induction period measurements (Dziedzic and Hudson 1983). Some synthetic chalcones and some structurally related compounds were investigated for their cytotoxic, tumour reducing and antioxidant activities by Anto *et al.* found that dihydroxy chalcone (**58**) which was found to be the most active tumour reducing agent was also found to be the most potent inhibitor of lipid peroxidation. It could be inferred from this study that substitution of electron donating groups at the ortho or para positions of the benzene ring could increase the tumour reducing and antioxidant activity of the chalcones (Anto *et al.* 1995).



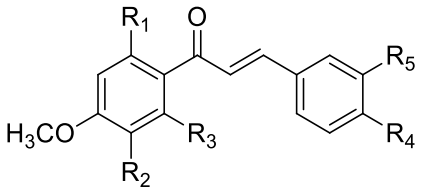
Comp.	R_1	R_2
(57)	OH	OH
(58)	H	H

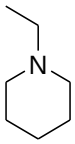
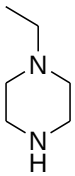
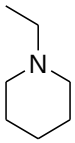
Broussochalcone A (BCA), isolated from *Broussonetia papyrifera Vent.* inhibited iron-induced lipid peroxidation in rat brain homogenate in a concentration-dependent manner with an IC_{50} of 0.63 ± 0.03 µM which indicated that BCA (**59**) was a powerful antioxidant with versatile free radical-scavenging activity. On the other hand, BCA suppressed NO production concentration-dependently, with an IC_{50} of 11.3 µM in LPS-activated macrophages (Cheng *et al.* 2001). In search for new cancer chemopreventive agents some new compounds were isolated from the roots and stolons of licorice (Glycyrrhiza glabra) which were tested in an authentic peroxynitrite anti-oxidant assay in which isoliquiritigenin **(60)**, and paratocarpin B **(61)** were found to be the most potent anti-oxidant agents (Chin *et al.* 2007).



Comp.	R_1	R_2	R_3
(59)	OH		OH
(60)	OH	H	H
(61)	H		

A series of 2'-hydroxy-chalcones were synthesized and tested for their antioxidant and lipoxygenase inhibitory activity and an extensive structure-relationship study revealed that among the tested compounds chalcone **62** possess an appealing pharmacological profile combining high antioxidant and lipid peroxidation activity with potent soybean LOX inhibition (Detsi *et al.* 2009).

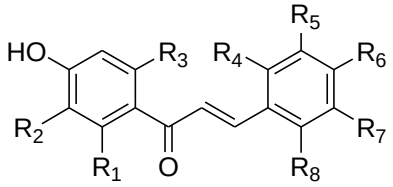


Comp.	R_1	R_2	R_3	R_4	R_5
(62)	OH	H	OCH_3	Cl	H
(63)	OCH_3		OH	Br	H
(64)	OCH_3		OH	Cl	H
(65)	OCH_3		OH	H	Cl

A novel series of nitrogen-containing chalcones were synthesized and screened for anti-inflammatory related activities such as inhibition of cyclo-oxygenase 2 (COX-2), trypsin and β-glucuronidase. The results of the studies reveal that the chalcones with N-methyl piperazine methyl **(63)** and piperidine methyl **(64)** substitution seems to be important for inhibition of β-glucuronidase whereas the chalcones with piperidine methyl **(65)** substitution were observed as effective inhibitors of COX-2 (Bandgar *et al.* 2010).

Tyrosinase Inhibitor

Tyrosinase (monophenol monooxygenase), also known as polyphenol oxidase (Whitaker, 1995), is a copper-containing enzyme widely distributed in nature. It catalyzes two reactions involving molecular oxygen in the melanin biosynthesis pathway: the hydroxylation of monophenols to o-phenols (monophenolase activity), and the oxidation of the o-phenols to *o*-quinones (diphenolase activity) (Seo *et al.* 2003). Isoliquiritigenin **(60)** can inhibit both mono- and diphenolase tyrosinase activities with IC_{50} was 8.1 µM, when tyrosine was used as substrate, suggesting that chalcones may serve as candidates for skin-lightening agents (Nerya *et al.* 2003). Different tetrahydroxychalcones, the commercially available Butein **(10)** and other three which were synthesized and evaluated for the contribution of the different functional groups of the tetrahydroxychalcones to their inhibitory potency on tyrosinase, with a view to optimizing the design of whitening agents and showed that a 2,4-substituted resorcinol subunit on ring B contributed the most to inhibitory potency and found two very active tyrosinase inhibitors, **66** and **67** with IC_{50} of 0.2 and 0.02µM, respectively (Khatib *et al.* 2004). A series of hydroxychalcones were synthesized and examined for their tyrosinase inhibitory activity and the results showed that **68** exhibited high inhibitory effects on tyrosinase with respect to L-tyrosine as a substrate. Kinetic study revealed that **68** acts as a competitive inhibitor of tyrosinase with Ki value of 3.1 µM (Jun *et al.* 2007).

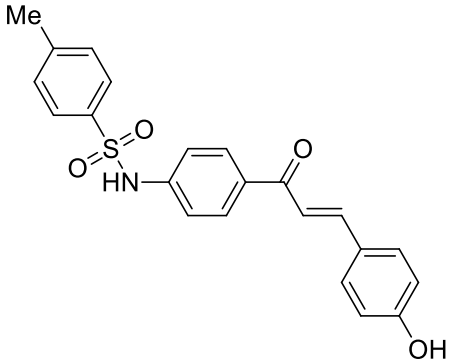


Comp.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
(66)	H	OH	H	OH	H	OH	H	H
(67)	H	OH	H	H	OH	H	OH	H
(68)	OH	H	OH	H	H	OH	H	OH

The 4'-(p-toluenesulfonylamino)-4-hydroxychalcone (TSAHC) **(69)**, which bears inhibitory chemotypes for both α-glucosidase and tyrosinase, was evaluated for tyrosinase activity and depigmenting ability relative to compounds designed to only target tyrosianse activity and showed that TSAHC significantly decreased three main tyrosinase related protein in melanin biosynthesis, tyrosinase, TRP-1 and TRP-2 (Seo *et al.* 2010).

3. RESEARCH ENVISAGED

Pyrazole derivatives have aroused considerable interest of chemists due to their versatile practical applications as well as their wide range of biochemical properties. Pyrazole have been reported to posses a broad spectrum of biological activities namely , antifungal, antioxidant, activities. Some pyrazole derivatives are also showing CNS depressant and analgesic activities in animal models. Due to its wide range of biological activity pyrazole ring constitutes a relavent synthetic target in pharmaceutical industry. (Nowakowska, 2007; Dimmock et al. 1999; Batovska and Todorova, 2010).



The stability and broad range of promising pharmacological properties inspired chemists to synthesize and study more chalcone derivatives since structural modifications can lead to different bioactivity. Extensive literature survey revealed that pyrazole derivatives in particular has received a considerable interest in recent years. In the present work the effort is made to develop a convenient method for the synthesis of substituted chalcones.

Understanding the importance of chalcones for their antimicrobial activity, some novel substituted chalcone derivatives were synthesized by structural modification on the chalcone rings. Finally the synthesized compounds were screened for their antimicrobial activity and other activities. Based on these findings, our main objective of the study:

- To establish the method for the synthesis of the proposed compounds.
- To characterize the synthesized compounds by physical constants like melting point, thin layer chromatography, molecular weight, molecular formula.
- To confirm the structures of the synthesized compounds by spectral analysis like IR, ^{1}H NMR, Mass spectra and elemental analysis.
- To evaluate the antimicrobial activity, anti-inflammatory and analgesic activities of the synthesized compounds.

4. PLAN OF WORK

The work was planned as follows;

A. Synthesis and physicochemical studies

- Synthesis of chalcone derivatives
- Synthesis of 2-pyrazoline derivatives
- Synthesis of semicarbazide derivatives

- Characterization of synthesized compounds by following physicochemical methods
  - ✓ Physical constant (colour, mp)
  - ✓ Thin layer chromatography (TLC)
  - ✓ Infrared spectroscopy (IR)
  - ✓ Nuclear magnetic resonance spectroscopy
  - ✓ Mass spectrometry (MS)
  - ✓ Elemental Analysis

B. Biological evaluation

- ➢ Antioxidant activities of synthesized compounds
- ➢ Antifungal activities of synthesized compounds

5. EXPERIMENTAL WORK

All the other chemicals used were obtained from Sigma-Aldrich, Spectrochem and High Media.

Synthesis of Designed Compounds

The structures of synthesized compounds were determined using melting points, infrared spectroscopy (IR), ^{1}H nuclear magnetic resonance spectroscopy (^{1}H-NMR) and elementary analysis. The melting point of the synthesized compounds were determined using an open capillary and are uncorrected.

IR spectra were refcorded on a FT-IR Shimadzu DZU 8400S spectrophotometer in KBr disks and Elemental analysis were done on a Perkin-Elmer 2400C, H, N analyzer and values were found to be within the acceptable limits of the calculated values.
The ^{1}H-NMR spectra of the synthesized compounds in $CDCl_3$/DMSO were recorded at 400 MHz by Bruker Advance II 400 NMR spectrometer. Chemical shift values are given in scale using tetramethylsilane (TMS) as an internal standard. Significant ^{1}H-NMR data are written in order: number of protons, multiplicity (b, broad; s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet), coupling constants in Hertz, assignment. The FAB mass spectra (at room temperature) were recorded on TOF MS ES$^+$ mass spectrometer. All these above analysis were done at SAIF, Punjab University, Chandigarh. Progress of reaction and purity of synthesized compounds was ascertained by thin layer chromatography (A) using Silica gel G and Iodine vapors as detecting agent.

Chemistry

The synthesis of the designed compounds (**2a-2p, 3a-3p**) was performed in a manner as outlined in Figure .

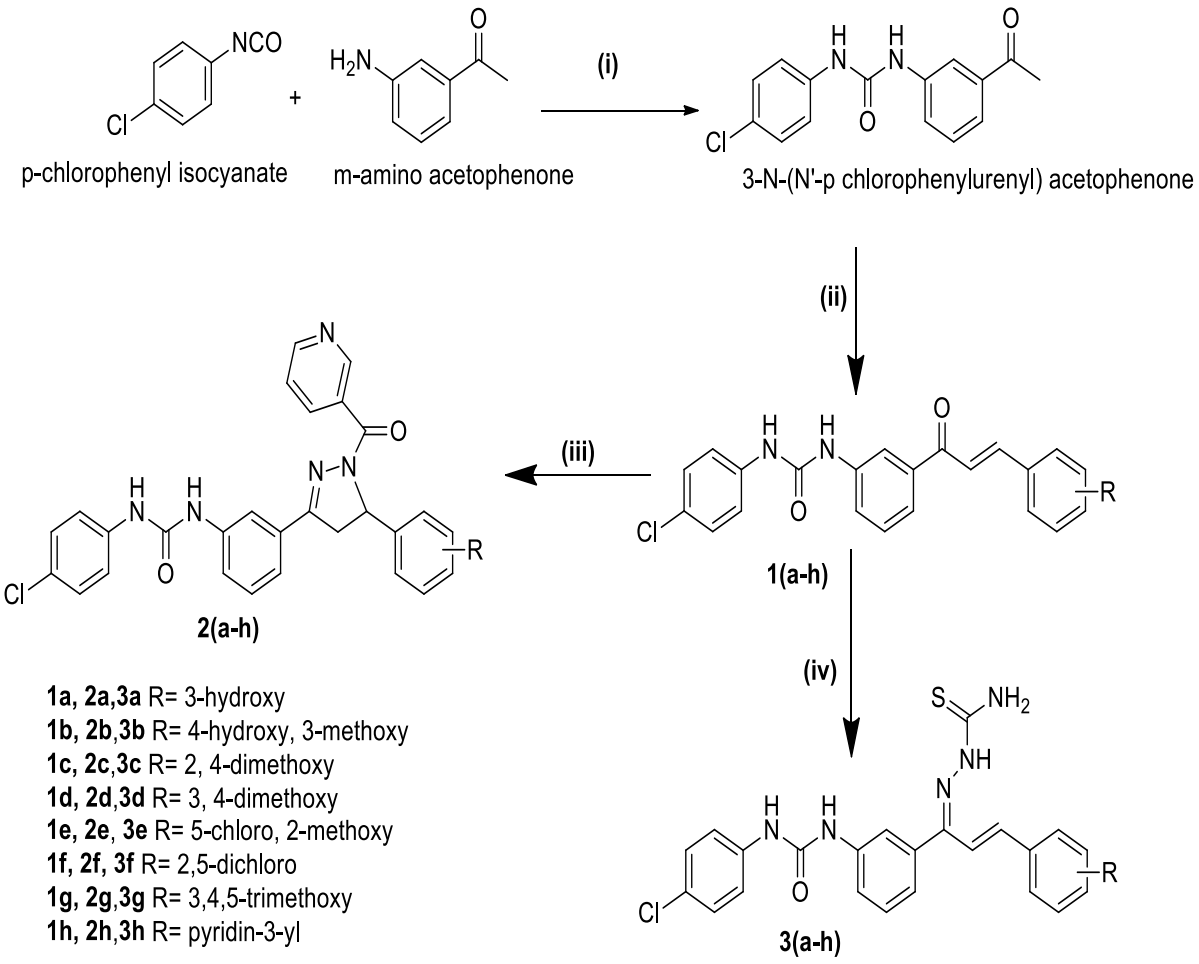


Fig. : The synthesis of the designed compounds 1a-1h, 2a-2h, 3a-3h (i) Me_2CO, rt, 6 hr (ii) substituted benzaldehyde, methanolic NaOH, stirred at room temperature, 24 hr (iii) *n*-butanol, reflux (iv) thiosemicarbazide, EtOH, AcOH, reflux.

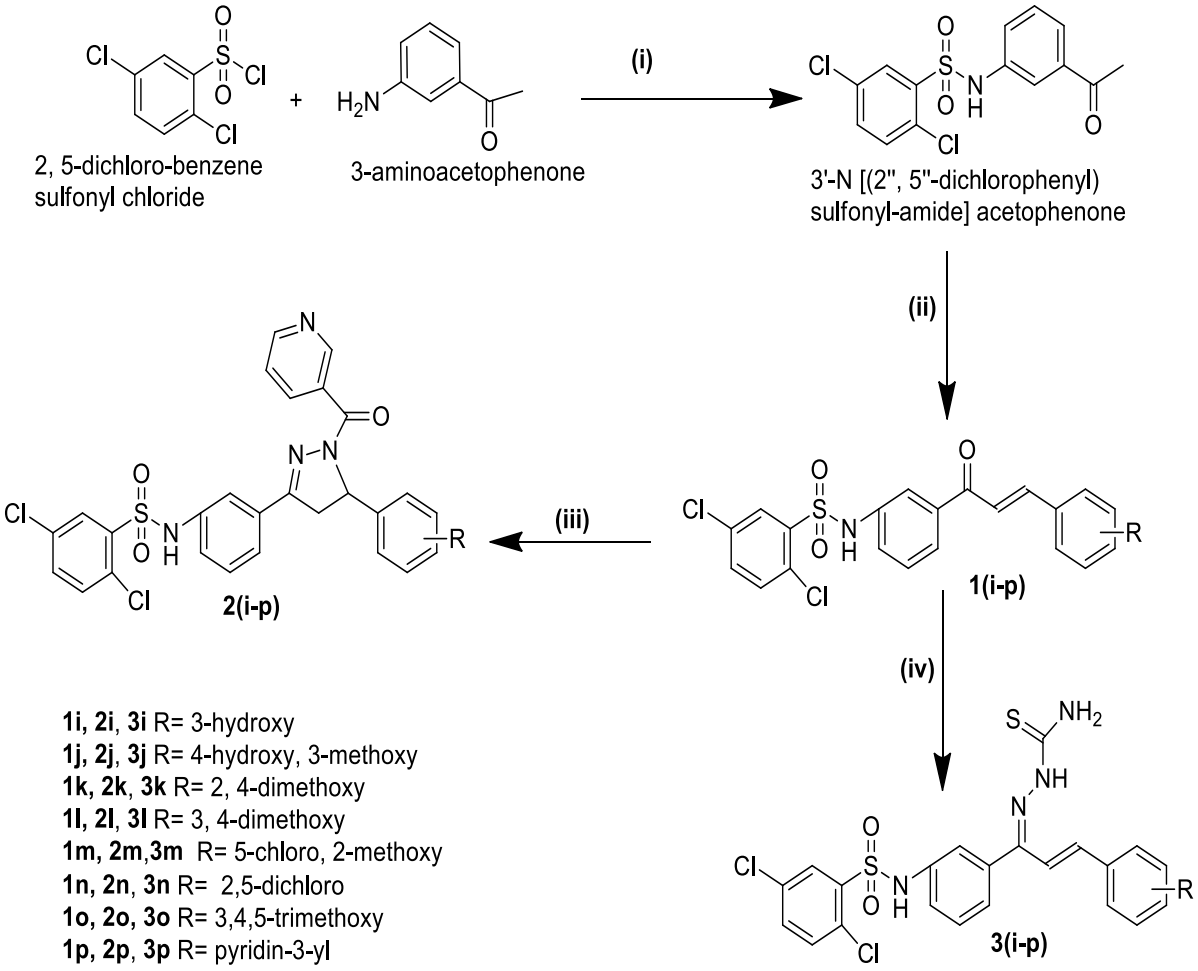
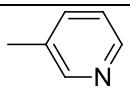
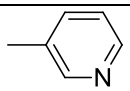


Fig. : The synthesis of the designed compounds 1i-1p, 2i-2p, 3i-3p (i) $CHCl_3$, rt, 3-6 hrs (ii) substituted benzaldehyde, methanolic NaOH, stirred at room temperature, 24 hr (iii) *n*-butanol, reflux (iv) thiosemicarbazide, EtOH, AcOH, reflux.

Table : Different substitutions on new synthesized substituted Chalcones and pyrazolines compounds (1a- 1p, 2a-2p, 3a-3p)

S.No	Comp. No.		R_2	R_3	R_4	R_5
1	**2a**	**3a**	-	OCH_3	-	-
2	**2b**	**3b**	-	OCH_3	OH	-
3	**2c**	**3c**	OCH_3	-	OCH_3	-
4	**2d**	**3d**	-	OCH_3	OCH_3	-
5	**2e**	**3e**	OCH_3	-	-	Cl
6	**2f**	**3f**	Cl	-	-	Cl
7	**2g**	**3g**	-	OCH_3	OCH_3	OCH_3
8	**2h**	**3h**				
9	**2i**	**3i**	-	OCH_3	-	-
10	**2j**	**3j**	-	OCH_3	OH	-
11	**2k**	**3k**	OCH_3	-	OCH_3	-
12	**2l**	**3l**	-	OCH_3	OCH_3	-
13	**2m**	**3m**	OCH_3	-	-	Cl
14	**2n**	**3n**	Cl	-	-	Cl
15	**2o**	**3o**	-	OCH_3	OCH_3	OCH_3
17	**2p**	**3p**				

Synthesis of intermediates

Synthesis 3-N-(N'-p-chlorophenylurenyl)acetophenone

Synthesis of methyl ketone derivative was carried out by making *m*-amino acetophenone react with the *p*-chlorophenyl isocyanate. A mixture of the *m*-aminoacetophenone (2.7 g, 20 mmol) and *p*-chlorophenyl isocyanate (3 g, 20 mmol) was dissolved in dry acetone (100 mL). The mixture was stirred for 6-7 hr at room temperature, filtered, and the crude compound urenylacetophenone was recrystallized using ethanol (Sonmez *et al.*, 2011).

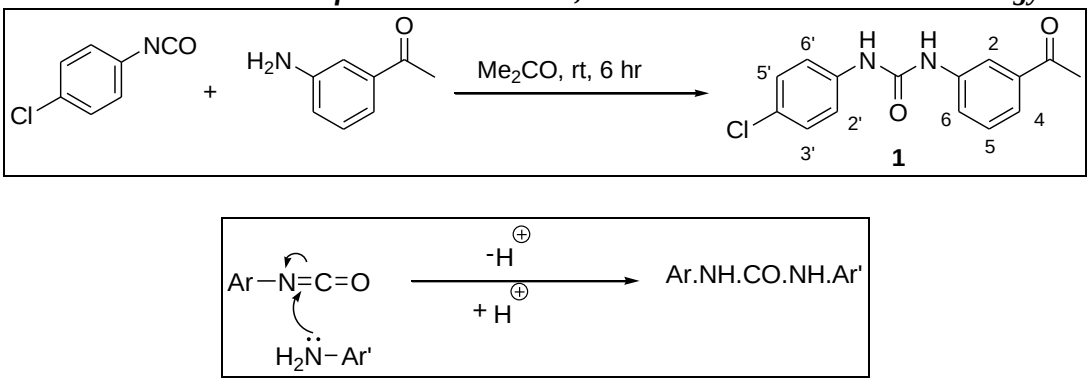


Figure : Scheme for synthesis of *3-N-(N'-p-chlorophenylurenyl)acetophenone*

Yield 3.3 g, 58%, White solid; mp 272-274 °C; IR(KBr) ν_{max} /cm^{-1} 3372 (N-H), 3056 (ArC-H), 2962 2872 (C-H), 1711 ($COCH_3$), 1645 (C=O), 1614, 1534, 1461 (Ar C=C), 1515, 1290, 1185 (ArC-N), 1147 (Ar-Cl) 756, 687 (Ar); ^{1}H-NMR (DMSO-d_6, 400 MHz): δ_H 9.12 (br s, 1H, NH), 8.91 (br s, 1H, NH); 8.18 (1H, s, H-2), 7.78 (1H, d, *J* 5.9, H-6), 7.53 (3H, m, H-4, 2', 6'), 7.30 (1H, t, *J* 6.30, H-5), 7.21 (2H, d, *J* 6.65, H-3', 5'), 2.53 (s, 3H, 3-$COCH_3$).

Synthesis of 3'-N [(2'', 5''-dichlorophenyl) sulfonyl-amide] acetophenone

The intermediate compound 3'-N[(2'',5''-dichlorophenyl) sulfonyl-amide] acetophenone was synthesized adopting the procedure described by Leon *et al*. (2007) with some modifications (Figure).

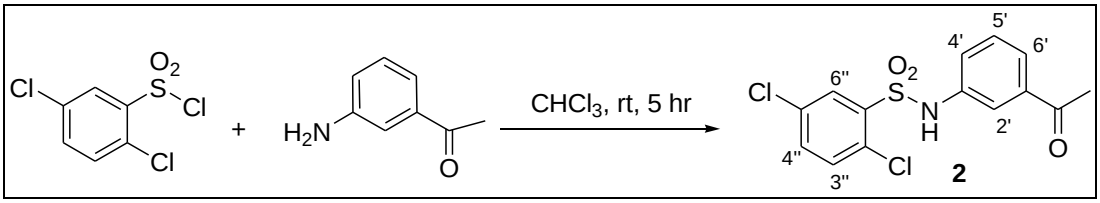


Figure : Scheme for synthesis of 3'-N[(2'',5''-dichlorophenyl) sulfonyl-amide] acetophenone

A mixture of 3-aminoacetophenone (2.7 g, 20 mmol) and 2, 5-dichloro-benzene sulfonyl chloride (4.9 g, 20 mmol) in 5 mL of chloroform was stirred at room temperature (rt) for 3–6 hr. The resulting precipitate was washed with acetone, filtered, and the crude material obtained was recrystallized in acetonitrile to give pure compound 3'-N[(2'',5''-dichlorophenyl) sulfonyl-amide] acetophenone.. Yield 3.6 g, 52%, Brown crystals; mp 230–232 °C; IR 3216 (N-H); 1667 (C=O); 1715 ($COCH_3$), 1337, 1270 (SO_2), 1142 (Ar-Cl), 3060 (Ar-H), 2967 (C-H), 1584, 1461, 1357, 1297, 1273, 1166, 993, 852, 819, 795, 720 (Ar); ^{1}H-NMR: δ_H 11.38 (s, 1H, NH), 7.94 (1H, s, H-6´´), 7.70 (1H, d, *J* 8.44, H-3´´), 7.25-7.44 (3H, m, H-2´, 5´, 6'), 7.71 (d, 1H, *J* 6.42, H-4´´), 6.94 (1H, d, *J* 8.91, H4'), 2.51 (s, 3H, CH_3CO).

General method of synthesis of chalcone derivatives (1a-1p)

Chalcones are synthesized by Claisen-Schmidt condensation (Furniss *et al.*, 1989; Kumar *et al.*, 2010) of aldehyde and ketone by base catalyzed or acid catalyzed followed by dehydration to yield chalcones .

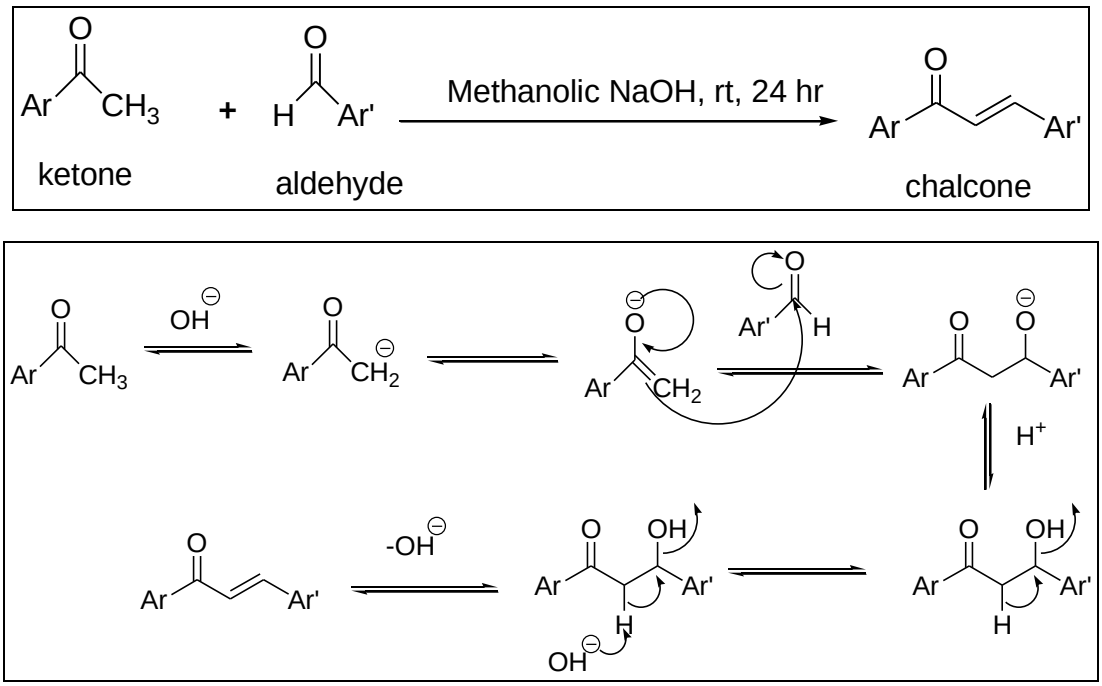


Figure : Mechanism of reaction for synthesis of chalcone derivatives (1a-1p)

Synthesis of trisubstituted pyrazolines (2a-2p)

General method for synthesis of 1, 3, 5-trisubstituted pyrazolines (2a-2p)

1,3,5-trisubstituted pyrazolines (**2a-2p**) were synthesized according to the scheme depicted in Figure 4.6 (Ozdemir *et al.*, 2008). In this method, chalcone and nicotinic acid hydrazide were refluxed in *n*-butanol in order to synthesize the desired product (Kini and Gandhi, 2008). Factors such as the structure and position of the substituents have profoundly influenced the rate of the reaction. The generally accepted interpretation of this reaction, involves the initial formation of an aryl hydrazone with subsequent nucleophilic attack of nitrogen upon the carbon-carbon double bond at β position. Hence the electropositive nature of β carbon may control the overall rate of the reaction. The electropositive nature of β carbon is controlled by the aromatic ring directly connected to it. Halogens being electron withdrawing in nature significantly increase the positive character of β carbon lead to faster reaction while electron donating alkyl and alkoxy groups contributed for slower reaction.

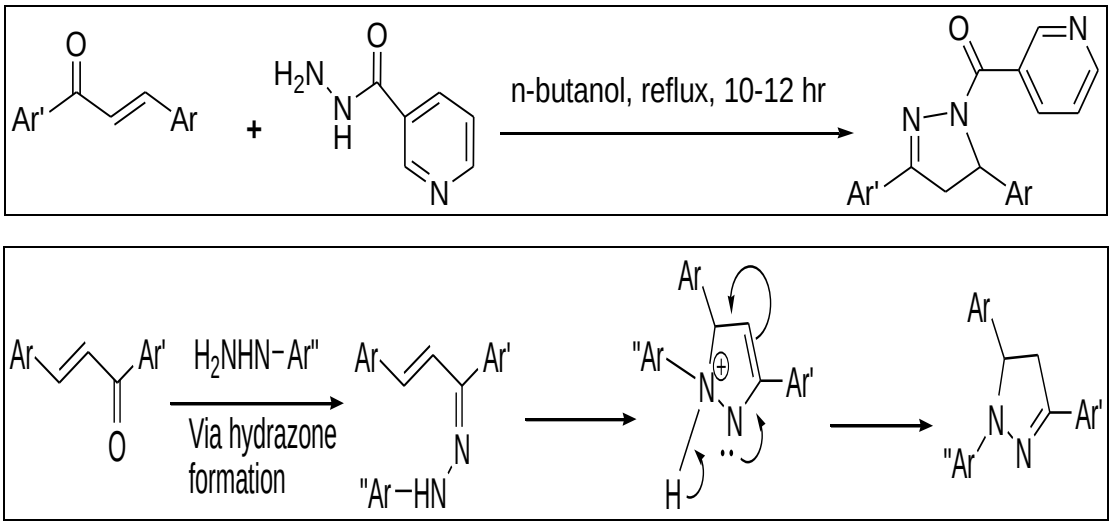
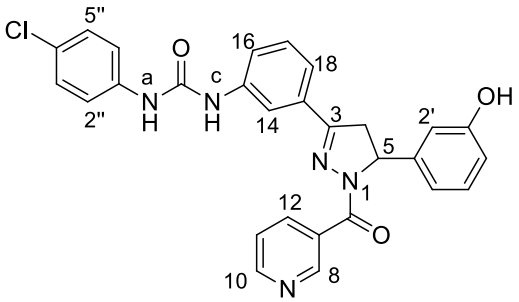


Figure : Scheme and mechanism of reaction for synthesis of compounds (2a-2p)

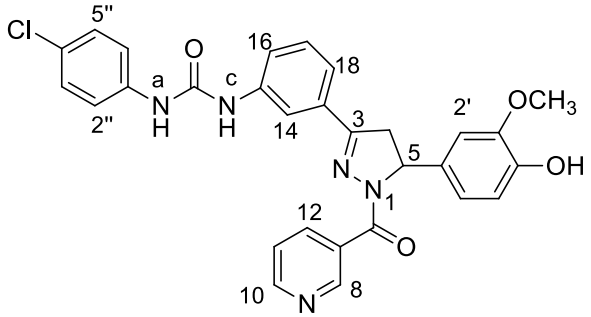
To the solution of the appropriate chalcone **1a-1p** (4 mmole) in 10 mL of *n*-butanol, (0.55 g, 4 mmole) of nicotinic acid hydrazide was added and the reaction mixture was refluxed for 8–10 hr. The excess of solvent was removed under reduced pressure and the reaction mixture was cooled on an ice bath. The products precipitated out at low temperature were washed five times with 50 mL distilled water, reconstituted in minimum amount of methanol and dried under reduced pressure. This product was further purified by crystallization from the ethanol-DMF mixture (1:1). Purity of the products was checked by TLC using mixture of acetone and petroleum ether (40:60 V/V) as mobile phase.

a-(4"-chlorophenyl)-c-(3-(5"-(3'-hydroxyphenyl)-1-nicotinoyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)urea (2a)



Synthesized by method from chalcone **1a** (4 mmol) and nicotinic acid hydrazide (4 mmol) after 14 hrs reflux; Yield 67%, Pale yellow solid; mp 165-167°C; IR (KBr) ν_{max}/cm^{-1} 3414 (O-H), 1665 (N-C=O), 1596 (Ar C=C), 1260, 1092 (C–O), 1215 (C-N), 1108 (C–Cl), 3045, 2956 (C-H), 1502, 1465, 922, 816, 798 (Ar); ^{1}H-NMR, δ 10.02 (1H, s, 3'-OH), 9.15 (1H, br s, NH), 8.96 (1H, br s, NH), 9.02 (1H, s, 8-H), 8.73 (1H, d, *J* 3.7, 10-H), 8.25 (2H, t, *J* 6.50, H-12, 14), 7.80 (1H, d, *J* 6.70, H-16), 7.45-7.58 (6H, m, H-11, 17, 18, 3", 5", 6"), 7.10 (2H, dd, H-5', 6'), 6.85 (2H, dd, H-2', 4'), 5.95 (1H, dd, *J 12.1* and 6.8, H-5), 3.83 (1H, dd, *J 17.7* and 11.6, 4-H_y), 3.18 (1H, dd, *J 17.1* and 4.3, 4-H_x); FAB-MS *m/z*: 511.54 $[M+H]^+$; Analysis Calcd. (%) for $C_{28}H_{22}ClN_5O_3$: C, 65.69; H, 4.33; N, 13.68;Found: C, 65.38; H, 4.18; 13.85;

a-(4"-chlorophenyl)-c-(3-(5"-(4'-hydroxy,3'-methoxyphenyl)-1-nicotinoyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)urea (2b)



Synthesized by method from chalcone **1b** (1.29 g, 4 mmol) and nicotinic acid hydrazide (0.55 g, 4 mmol); Yield 0.97 g, 55%, Pale yellow powder; mp 135-137°C; IR (KBr) ν_{max}/cm^{-1} 3221 (O-H), 1665 (N-C=O), 1596 (Ar C=C), 1260, 1092 (C–O), 1215 (C-N), 1108 (C–Cl), 3045, 2956 (C-H), 1502, 1465, 922, 816, 798 (Ar); ^{1}H-NMR, δ 10.05 (1H, s, 4'-OH), 9.10 (1H, br s, NH), 8.96 (1H, br s, NH), 9.07 (1H, s, 8-H), 8.71 (1H, d, *J* 3.9, 10-H), 8.16 (1H, d, *J* 7.2, 12-H), 7.68 (1H, d, *J* 7.6, H-11), 7.48-7.58 (5H, m, H-17, 18, 2", 5", 6"), 7.40 (1H, d, *J* 4.2, H-4''), 6.87-6.94 (3H, m, H-2', 5', 6'), 5.93 (1H, dd, *J 12.3* and 6.2, H-5), 3.89 (1H, dd, *J 17.5* and 11.6, 4-H_y), 3.83 (3H, s, OCH_3-3'), 3.10 (1H, dd, *J 17.8* and 4.8, 4-H_x); FAB-MS *m/z*: 541.31 $[M+H]^+$; Analysis Calcd. (%) for $C_{29}H_{24}ClN_5O_4$: C, 64.27; H, 4.46; N, 12.92; Found: C, 64.36; H, 4.26; N, 12.71

Synthesis of trisubstituted pyrazolines (2a-2p)

General method for synthesis of 1, 3, 5-trisubstituted pyrazolines (2a-2p)

1,3,5-trisubstituted pyrazolines (**2a-2p**) were synthesized according to the scheme depicted in Figure 4.6 (Ozdemir *et al.*, 2008). In this method, chalcone and nicotinic acid hydrazide were refluxed in *n*-butanol in order to synthesize the desired product (Kini and Gandhi, 2008). Factors such as the structure and position of the substituents have profoundly influenced the rate of the reaction. The generally accepted interpretation of this reaction, involves the initial formation of an aryl hydrazone with subsequent nucleophilic attack of nitrogen upon the carbon-carbon double bond at β position. Hence the electropositive nature of β carbon may control the overall rate of the reaction. The electropositive nature of β carbon is controlled by the aromatic ring directly connected to it. Halogens being electron withdrawing in nature significantly increase the positive character of β carbon lead to faster reaction while electron donating alkyl and alkoxy groups contributed for slower reaction.

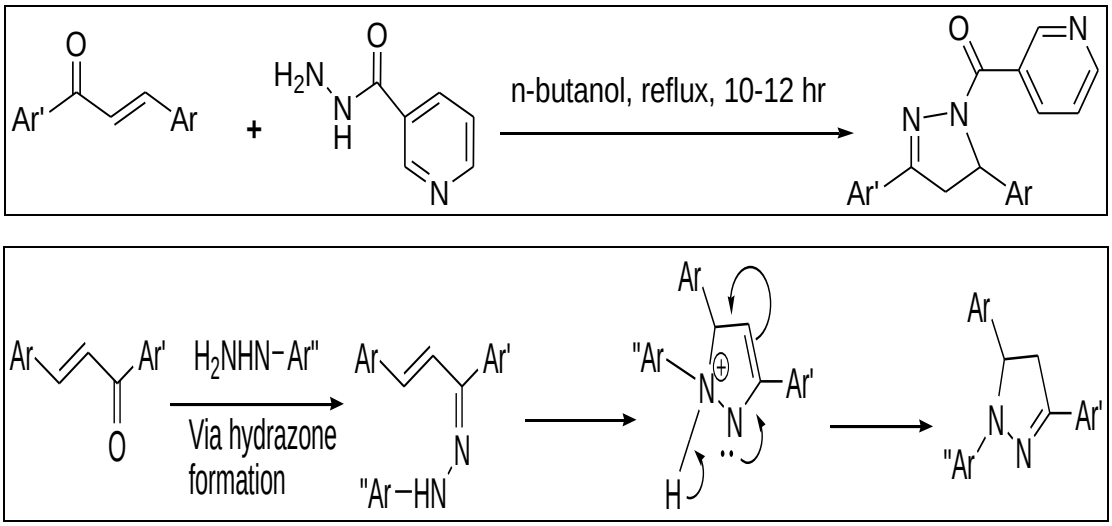
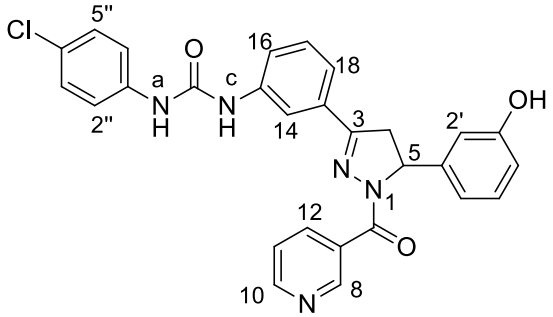


Figure . Scheme and mechanism of reaction for synthesis of compounds (2a-2p)

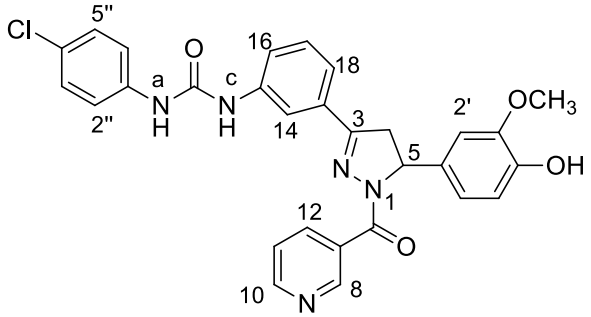
To the solution of the appropriate chalcone **1a-1p** (4 mmole) in 10 mL of *n*-butanol, (0.55 g, 4 mmole) of nicotinic acid hydrazide was added and the reaction mixture was refluxed for 8–10 hr. The excess of solvent was removed under reduced pressure and the reaction mixture was cooled on an ice bath. The products precipitated out at low temperature were washed five times with 50 mL distilled water, reconstituted in minimum amount of methanol and dried under reduced pressure. This product was further purified by crystallization from the ethanol-DMF mixture (1:1). Purity of the products was checked by TLC using mixture of acetone and petroleum ether (40:60 V/V) as mobile phase.

a-(4"-chlorophenyl)-c-(3-(5"-(3'-hydroxyphenyl)-1-nicotinoyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)urea (2a)



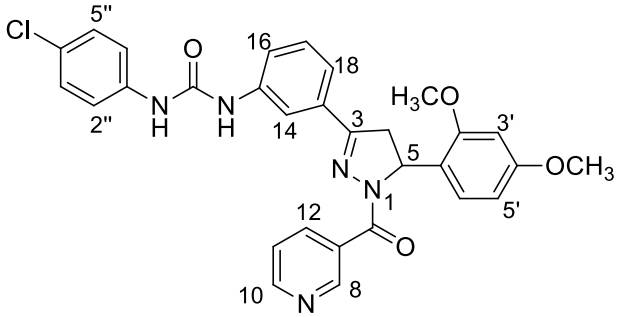
Synthesized by method from chalcone **1a** (4 mmol) and nicotinic acid hydrazide (4 mmol) after 14 hrs reflux; Yield 67%, Pale yellow solid; mp 165-167°C; IR (KBr) ν_{max}/cm^{-1} 3414 (O-H), 1665 (N-C=O), 1596 (Ar C=C), 1260, 1092 (C–O), 1215 (C-N), 1108 (C–Cl), 3045, 2956 (C-H), 1502, 1465, 922, 816, 798 (Ar); ^{1}H-NMR, δ 10.02 (1H, s, 3'-OH), 9.15 (1H, br s, NH), 8.96 (1H, br s, NH), 9.02 (1H, s, 8-H), 8.73 (1H, d, *J* 3.7, 10-H), 8.25 (2H, t, *J* 6.50, H-12, 14), 7.80 (1H, d, *J* 6.70, H-16), 7.45-7.58 (6H, m, H-11, 17, 18, 3", 5", 6"), 7.10 (2H, dd, H-5', 6'), 6.85 (2H, dd, H-2', 4'), 5.95 (1H, dd, *J 12.1* and 6.8, H-5), 3.83 (1H, dd, *J 17.7* and 11.6, 4-H_y), 3.18 (1H, dd, *J 17.1* and 4.3, 4-H_x); FAB-MS *m/z*: 511.54 $[M+H]^+$; Analysis Calcd. (%) for $C_{28}H_{22}ClN_5O_3$: C, 65.69; H, 4.33; N, 13.68;Found: C, 65.38; H, 4.18; 13.85;

a-(4"-chlorophenyl)-c-(3-(5"-(4'-hydroxy,3'-methoxyphenyl)-1-nicotinoyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)urea (2b)



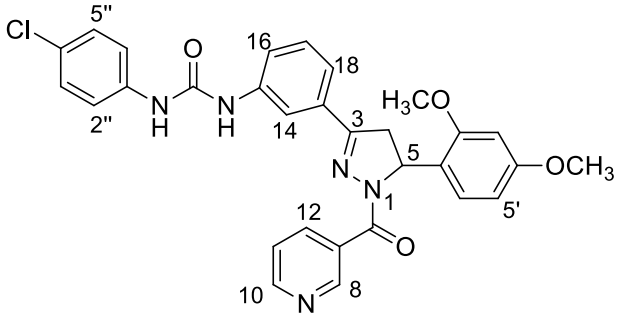
Synthesized by method from chalcone **1b** (1.29 g, 4 mmol) and nicotinic acid hydrazide (0.55 g, 4 mmol); Yield 0.97 g, 55%, Pale yellow powder; mp 135-137°C; IR (KBr) ν_{max}/cm^{-1} 3221 (O-H), 1665 (N-C=O), 1596 (Ar C=C), 1260, 1092 (C–O), 1215 (C-N), 1108 (C–Cl), 3045, 2956 (C-H), 1502, 1465, 922, 816, 798 (Ar); ^{1}H-NMR, δ 10.05 (1H, s, 4'-OH), 9.10 (1H, br s, NH), 8.96 (1H, br s, NH), 9.07 (1H, s, 8-H), 8.71 (1H, d, *J* 3.9, 10-H), 8.16 (1H, d, *J* 7.2, 12-H), 7.68 (1H, d, *J* 7.6, H-11), 7.48-7.58 (5H, m, H-17, 18, 2", 5", 6"), 7.40 (1H, d, *J* 4.2, H-4''), 6.87-6.94 (3H, m, H-2', 5', 6'), 5.93 (1H, dd, *J 12.3* and 6.2, H-5), 3.89 (1H, dd, *J 17.5* and 11.6, 4-H_y), 3.83 (3H, s, OCH_3-3'), 3.10 (1H, dd, *J 17.8* and 4.8, 4-H_x); FAB-MS *m/z*: 541.31 $[M+H]^+$; Analysis Calcd. (%) for $C_{29}H_{24}ClN_5O_4$: C, 64.27; H, 4.46; N, 12.92; Found: C, 64.36; H, 4.26; N, 12.71

a-(4"-chlorophenyl)-c-(3-(5-(2',4'-dimethoxyphenyl)-1-nicotinoyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)urea (2c)



Synthesized by method above from chalcone **1c** (4 mmol) and nicotinic acid hydrazide (4 mmol); Yield 69%, Light yellow solid; mp 156-159°C; IR (KBr) ν_{max}/cm^{-1} 3294 (N-H), 1668 (N-C=O), 1591 (Ar C=C), 1560 (C=N), 1262, 1096 (C–O), 1210 (C-N), 1102 (C–Cl), 3041, 2954 (C-H), 1501, 1467, 922, 815, 798 (Ar); ^{1}H-NMR, δ 9.12 (1H, br s, NH), 8.91 (1H, br s, NH), 9.02 (1H, s, 8-H), 8.70 (1H, d, *J* 3.9, 10-H), 8.26 (1H, d, *J* 7.2, 12-H), 8.18 (2H, dd, *J 12.3* H-12, 14), 7.85 (1H, d, *J* 6.70, H-16), 7.68-7.75 (3H, m, H-18, 2", 6"), 7.50-7.60 (4H, m, H-11, 17, 3",6"), 7.08 (1H, d, *J* 6.54, H-6'), 6.60 (2H, t, *J* 6.54, H-5', 3'), 5.95 (1H, dd, *J 12.3* and 6.2, H-5), 3.88 (1H, dd, *J 17.5* and 11.6, 4-H_y), 3.70 (6H, s, OCH_3-2',4'), 3.11 (1H, dd, *J 17.5* and 4.6, 4-H_x); FAB-MS *m/z*: 556.31 $[M+H]^+$; Analysis Calcd. (%) for $C_{30}H_{26}ClN_5O_4$: C, 64.80; H, 4.71; N, 12.60; Found: C, 64.39; H, 4.17; N, 12.25

a-(4"-chlorophenyl)-c-(3-(5-(2',4'-dimethoxyphenyl)-1-nicotinoyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)urea (2d)



Synthesized by method above from chalcone **1d** (4 mmol) and nicotinic acid hydrazide (4 mmol); Yield 69%, yellow solid; mp 151-153°C; IR (KBr) ν_{max}/cm^{-1} 3298 (N-H), 3045, 2953 (C-H), 1660 (N-C=O), 1599 (Ar C=C), 1561 (C=N), 1256, 1084 (C–O), 1227 (C-N), 1127 (C–Cl), 1501, 798 (Ar); ^{1}H-NMR, δ 9.10 (1H, br s, NH), 8.91 (1H, br s, NH), 9.08 (1H, s, 8-H), 8.76 (1H, d, *J* 3.9, 10-H), 8.20 (1H, d, *J* 7.2, 12-H), 8.18 (2H, dd, *J 12.3* H-12, 14), 7.80 (1H, d, *J* 6.70, H-16), 7.58-7.63 (3H, m, H-18, 2", 6"), 7.48-7.53 (4H, m, H-11, 17, 3",6"), 7.11 (1H, d, *J* 6.54, H-6'), 6.60 (2H, t, *J* 6.54, H-5', 3'), 5.91 (1H, dd, *J 12.3* and 6.2, H-5), 3.81 (1H, dd, *J 17.5* and 11.6, 4-H_y), 3.72 (6H, s, OCH_3-3',4'), 3.18 (1H, dd, *J 17.5* and 4.6, 4-H_x); FAB-MS *m/z*: 556.16 $[M+H]^+$; Analysis Calcd. (%) for $C_{30}H_{26}ClN_5O_4$: C, 64.80; H, 4.71; N, 12.60; Found: C, 64.72; H, 4.19; N, 12.23

6. RESULTS AND DISCUSSION

All the synthesized substituted chalcone and pyrazoline derivatives remitted in products with good yield. Purity of all the synthesized compounds was checked by their melting point as well as TLC. The structure of synthesized compounds has been established and confirmed by spectral and elemental data obtained viz, FT-IR, ^{1}HNMR and Mass. The synthesized compounds were screened for , Antioxidant ,Antifungal activity.

Antioxidant Activity

Nitric oxide Scavenging Activity:

Among all the compounds tested, **B05** and **B06** showed moderate antioxidant activity and remaining compounds showed mild activity as compared to that of standard Ascorbic acid .

Antioxidant activity data of synthesized compounds

S.No.	Compound	Conc. µg/ml	Absorbannce at 546 nm	% Antioxidant Activity	IC_{50} µg/ml
1.	1g	**100**	**0.475**	**52.8**	**329.1**
2.	1h	**100**	**0.287**	**22.7**	**1017.8**
3.	1j	**100**	**0.468**	**26.9**	**386.1**
4.	1k	**100**	**0.562**	**21.6**	**328.2**
5.	1l	**100**	**0.330**	**30.8**	**540.4**
6.	1m	**100**	**0.386**	**43.9**	**1175.4**
7.	1o	**100**	**0.370**	**39.3**	**590.2**
8.	1p	**100**	**0.464**	**45.6**	**1059.3**

DPPH (2,2-diphenyl-1-picrayl hydrazyl) reduction method

Antioxidant activity of synthesized compounds by DPPH method

Sl.No	Compound	% Inhibition	IC50 ± SEM DPPH Method
1	1g	19.97 – 85.95	47.47 ± 2.473
2	1h	3.07-64.92	186.36 ± 2.285
3	1j	7.4 - 48.75	>500
4	1k	10.47 - 68.37	57.27 ± 1.375
5	1l	10.42 - 82.58	>500
6	1m	15.37 - 75.28	145.57 ± 2.862
7	1o	4.1 - 76.37	87.19 ± 1.845
8	1p	5.37 – 73.12	83.53 ± 2.476
STD	Ascorbic acid	44.95 - 87.5	16.8 ± 0.95

Antifungal activity

All the synthesized compounds (**1a-1p, 2a-2p, 3a-3p)** have been evaluated for their antifungal activity against *A .niger*, *R. oryzae* and *A. Jlavus.* The results of this evaluation is compared to that of fluconazole (1000 pg/mL) as a standard drug at a dose level of 0.05 mL and 0.1 mL. The antifungal activity data of synthesized compounds (**1a-1p, 2a-2p, 3a-3p)** is presented in.

Antifungal activity of synthesized compounds (2a-2p, 3a-3p)

Compounds	Zone of inhibition (in mm)					
	A.niger		*R.oryzae*		*A.flavus*	
	50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
2a	16	18	19	21	17	19
2b	17	18	18	20	21	22
2c	18	19	17	19	20	23
2d	16	19	17	19	17	22
2e	18	19	16	19	16	18
2f	18	19	17	20	18	20
2g	17	19	18	20	18	23
2h	18	20	22	24	17	22
2i	18	20	20	23	16	18
2j	16	17	17	18	16	18
2k	19	21	16	18	17	19
2l	19	20	19	21	18	20
2m	20	21	20	22	19	22
2o	23	27	21	26	20	22
2p	20	24	20	25	18	21
3a	17	20	19	21	18	20
3b	18	20	17	18	21	24
3c	17	18	17	18	17	21
3d	18	18	18	19	17	18
3e	16	20	17	18	17	18
3f	16	19	18	21	19	21
3g	17	20	18	22	17	20

3h	18	20	17	19	18	21
3i	20	23	18	20	17	22
3j	18	19	17	19	17	19
3k	16	19	16	17	18	19
3l	18	19	17	20	19	20
3m	18	20	19	22	18	19
3o	18	20	18	20	17	19
3p	20	23	20	22	18	20
STD#	25	28	23	27	24	28
Control	-	-	-	-	-	-

**Average of triplicate ± Standard deviation # Clotrimazole*

- no zone of inhibition

It is observed from the table 5.2 that all the compounds exhibited considerable inhibitory action specially against *A. niger* and *R. oryzae.* However, their action has been found to be very weak against *A. flavus.* Compounds **2m, 2o, 2p, 3i** and **3p** have shown high potency specially against *A. niger, R. oryzae* and *A. flavus.*

7. SUMMARY AND CONCLUSION

With increasing resistance to available antimicrobial drugs, intensive drug discovery efforts aimed at developing new antimicrobial drugs or modifying existing agents are ongoing. In this context, chalcones and Pyrazoline are promising candidates, as these individually possess multifarious pharmacological profiles including antimicrobial activities with different mode of action. The substitution on these two pharmacophores into novel scaffolds and evaluation of their biological activities have not yet been reported.

The strategy to synthesis of designed compounds **2a-2p** and **3a-3p** has been shown in Fig.

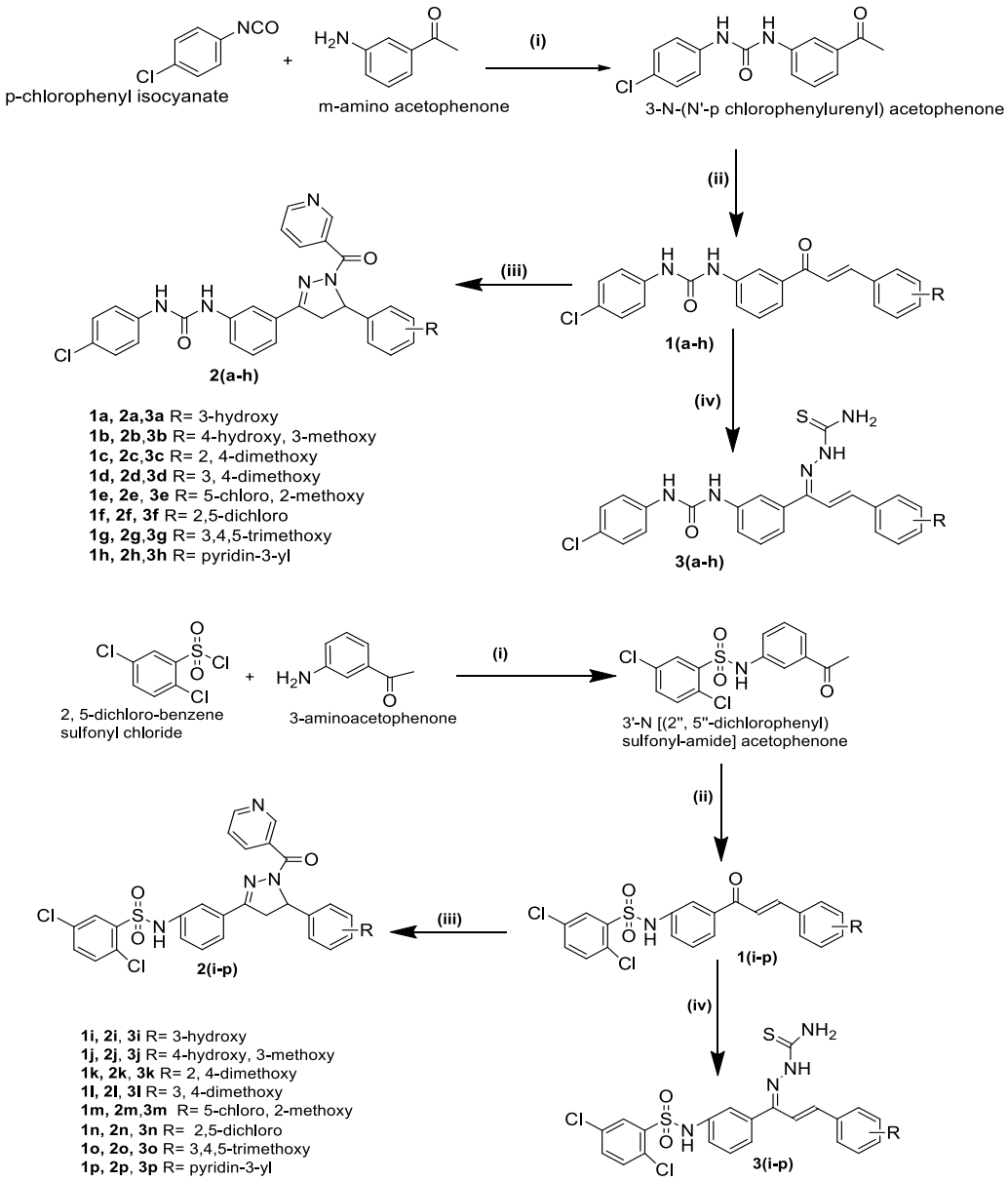
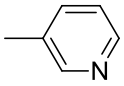
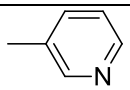


Fig. 6.1: The synthesis of the designed compounds 1a-1p, 2a-2p, 3a-3p

Table 6.1: Different substitutions on new synthesized substituted Chalcones and pyrazolines compounds (1a- 1p, 2a-2p, 3a-3p)

S.No	Comp. No.		R_2	R_3	R_4	R_5
1	**2a**	**3a**	-	OCH_3	-	-
2	**2b**	**3b**	-	OCH_3	OH	-
3	**2c**	**3c**	OCH_3	-	OCH_3	-
4	**2d**	**3d**	-	OCH_3	OCH_3	-
5	**2e**	**3e**	OCH_3	-	-	Cl
6	**2f**	**3f**	Cl	-	-	Cl
7	**2g**	**3g**	-	OCH_3	OCH_3	OCH_3
8	**2h**	**3h**				
9	**2i**	**3i**	-	OCH_3	-	-
10	**2j**	**3j**	-	OCH_3	OH	-
11	**2k**	**3k**	OCH_3	-	OCH_3	-
12	**2l**	**3l**	-	OCH_3	OCH_3	-
13	**2m**	**3m**	OCH_3	-	-	Cl
14	**2n**	**3n**	Cl	-	-	Cl
15	**2o**	**3o**	-	OCH_3	OCH_3	OCH_3
17	**2p**	**3p**				

In the first step, syntheses of chalcones **1a-1p** were carried out by Claisen-Schmidt reaction and products were purified by recrystallization from methanol (60–70% yield). In the second step, chalcones and nicotinic acid hydrazide or thiosemicarbazide were refluxed in n-butanol or hot ethanol respectively, in order to synthesize the desired products. Purity of the compounds was checked on TLC plates (silica gel G) which were visualized by exposing to iodine vapours.

Physico-chemical characterization, melting point, FT-IR, ^{1}H-NMR mass spectral and elemental analysis of the synthesized compounds were done. The results showed that the observed values are in full agreement with the expected values and confirm the anticipated structures of synthesized compounds.

The IR spectra of synthesized compounds showed absorption bands which are characteristic of the anticipated structure of the synthesized compounds. The NMR spectra of synthesized compounds showed signals for both aliphatic and aromatic protons, characteristic of the anticipated structure of the synthesized compounds. The fragmentation patterns obtained in the mass spectra also confirm the anticipated structures of the synthesized compounds.

All the synthesized compounds were found to be soluble in most of the organic solvents (chloroform, DMSO, ethyl acetate, acetone and dichloromethane) and insoluble in water.

After synthesis of the 32 designed compounds (**2a-2p, 3a-3p**) and subsequent confirmation of their structure, biological evaluation was carried out on the following line.

- Antifungal activity
- Anti-oxidant activity

All the synthesized compounds (**2a-2p, 3a-3p)** have been evaluated for their antibacterial activity against, *Bacillus pumilis, Bacillus subtilis* (gram-positive) and *Escherichia coli, Proteus vulgaris* (gram-negative). Compounds were also evaluated for their *in vitro* antifungal activity against *A .niger, R. oryzae* and *A. Jlavus.* The results of *in vitro* antibacterial as well as antifungal activities of synthesized compounds are summarized in Table **5.1 a**nd Table **5.2**.

It could be observed from the table 5.1 that all the compounds have a noticeable degree of inhibition, especially against *B. pumilis, B. subtilis* and *E. coli*. Compounds **2f, 2g, 2h, 2i, 2j, 2k, 2l, 2m, 2n, 2o, 2p, 3o and 3p** only showed mild inhibitory action on *P. vulgaris.* Compounds **2g, 2h, 2j, 2k, 2l, 2m, 2n, 2o, 2p, 3o** and **3p** have shown significant activity on *B. pumilis, B. subtilis, P. vulgaris* and *E. coli.*

It is also observed from the Table 5.2 that all the compounds exhibited considerable inhibitory action specially against *A. niger* and *R. oryzae.* However, their action has been found to be very weak against *A. flavus.* Compounds **2m, 2o, 2p, 3i** and **3p** have shown high potency specially against *A. niger, R. oryzae* and *A. flavus.*
The anti-inflammatory activity of the sixteen chalcones (**2a-2p**) has been evaluated by using carrageenan-induced rat paw oedema method (Table 5.3 and Fig 5.1). Compound **2o** has shown highest percent inhibition of 80.73 at 3rd hour. This has been followed by compounds **2p, 2g, 2k** and **2m** with highest percent inhibition of 78.35, 75.30, 69.83, and 65.59 respectively.

The analgesic activity of the sixteen chalcones (**2a-2p**) has been evaluated by using acetic acid induced writhing method using aspirin as the standard drug. The observed analgesic activity of chalcones and pyrazoline derivatives by writhing method is presented in Table 5.4 and Fig 5.2.

The synthesized compounds (**2a-2p**) showed analgesic activity (percent inhibition) ranging from 16.48 to 70.39%. It was noted that compounds **2a, 2b, 2h, 2o** and **2p** showed significant analgesic activity throughout the test period. The activity of compound **2o and 2p** are very much comparable to that of standard reference drug aspirin. It indicates that they are effective against acetic acid induced writhing model.

In conclusion, novel pyrazoline derivatives **(2a-2p, 3a-3p)** were synthesized and their antileishmanial activity against *Leishmania donovani* was evaluated. Compound **2p** and **3p** showed better activity in comparison to Pentamidine and Sodium Stibogluconate. As a consequence of the above results and considerations, these molecules can serve as promising prototypes for the development of potent antileishmanial agents.

These observations indicated that these chalcone and 2-pyrazoline derivatives constitute attractive chemical scaffold for the establishment of new chemical entities with antimicrobial, anti-inflammatory and analgesic activities.

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