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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/13177

DOI URL: <http://dx.doi.org/10.21474/IJAR01/13177>



RESEARCH ARTICLE

CHEMICAL AND PHARMACOLOGICAL EVOLUTION OF SOME SYNTHESIZED CHALCONES AND HETEROCYCLIC COMPOUNDS

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Manuscript Info

Manuscript History

Received: 19 May 2021

Final Accepted: 20 June 2021

Published: July 2021

Key words:-

Synthesis, Chalcone, Heterocyclic
Compound, Antioxidant

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-diarylprop-2-en-1-one, which can be functionalized 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 α,β -unsaturated carbonyl system (Dhar, 1981). Microorganisms are a heterogeneous group of several distinct classes of living beings. They were classified under third kingdom, the Protista. Based on differences in cellular organization and biochemistry, the kingdom protista 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 Aspergillosis. These agents prevent from fungal infection. Anti-oxidant drugs are among the most frequently prescribed preparations prevent Oxidation.

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Introduction:-

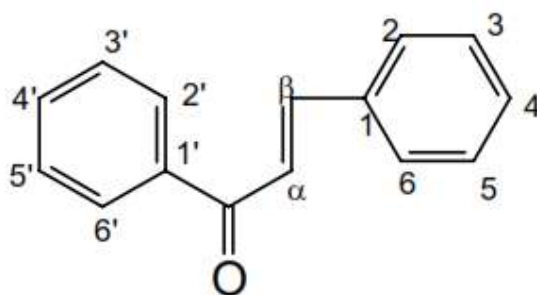
Pharmaceutical chemistry is focused on quality aspects of medicines and aims to assure fitness for the purpose of medicinal products. With centuries medicinal chemistry had emerged as a magnanimous field of science getting a facelift from the available natural compounds for synthesis of newer and complex 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).

Chalcones

Chalcones is a generic term given to compounds bearing the 1,3-diarylprop2-en-1-one, which can be functionized 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 α,β -unsaturated carbonyl system (Dhar, 1981). Pharmacological properties of chalcones are due to the presence of both α,β -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).

General structure of chalcone:



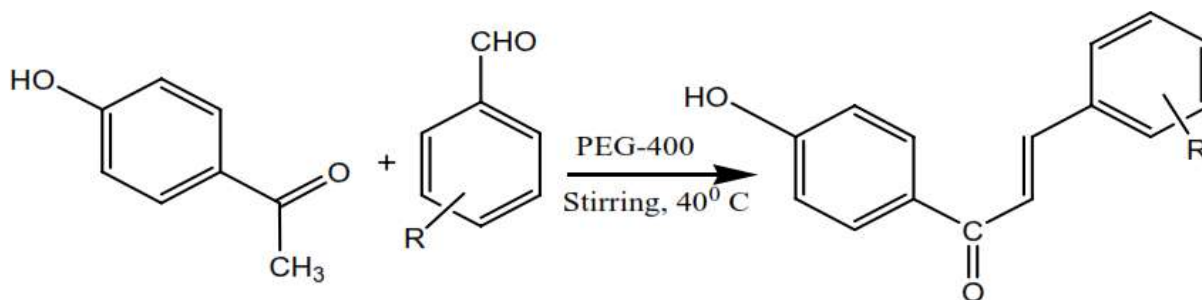
Chalcones are one of the major classes of natural products which occur widely in nature particularly in colored flowers and wide spread distribution in fruits, vegetables, spices and tea. Various natural or synthetic chalcones have been found to possess diverse biological activities (Di Carlo *et al.*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

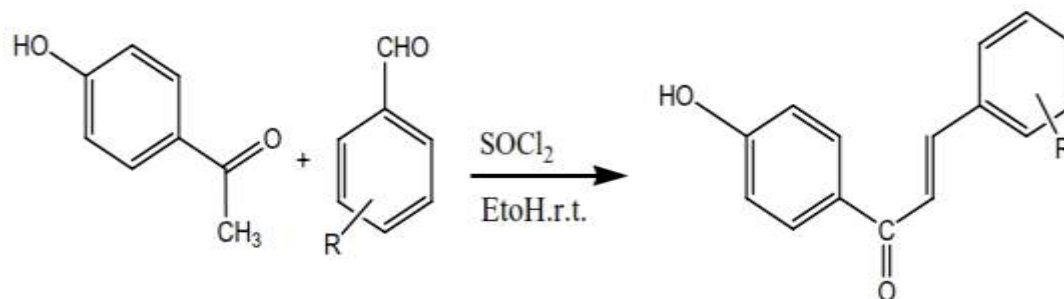
General methods of synthesis of chalcones

Chalcones are well known intermediates 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).

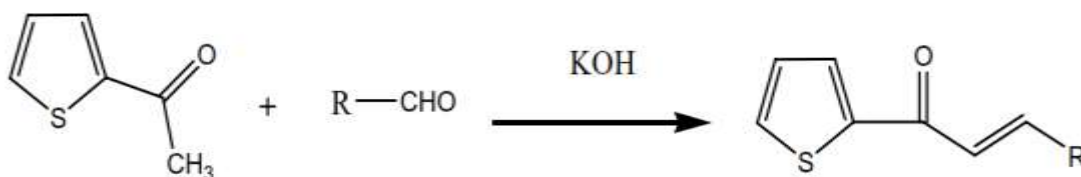
1) Claisen-Schmidt condensation between 4-hydroxy acetophenone and benzaldehyde was carried out in the presence of a base catalyst was stirred in PEG-400 as a recyclable solvent for 4'-hydroxy chalcones (Sreedhar *et al.* 2010).



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



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

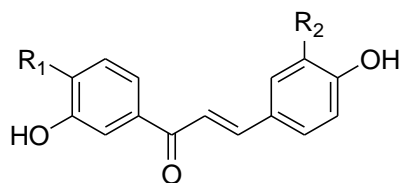


Literature Review:-

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).

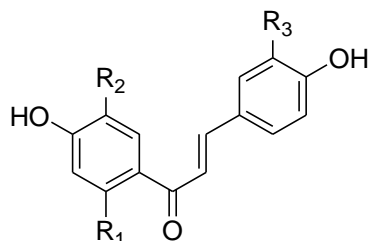
3, 4-Dihydroxy chalcones, such as butein (**10**) and okanin (**57**), are particularly effective antioxidants in the range of concentrations 0.025–0.1%, as judged by induction period measurements (Dziedzic and Hudson 1983). Some synthetic chalcones and some structurally related compounds were investigated 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 IC₅₀ 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 IC₅₀ 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).

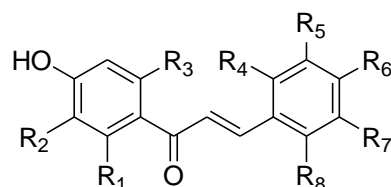
Comp.	R ₁	R ₂	R ₃	R ₄	R ₅
(62)	OH	H	OCH ₃	Cl	H
(63)	OCH ₃		OH	Br	H
(64)	OCH ₃		OH	Cl	H
(65)	OCH ₃		OH	H	Cl

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 IC₅₀ was 8.1 μ M, 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 IC₅₀ of 0.2 and 0.02 μ M, 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 K_i 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 tyrosinase 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).

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 possess 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 relevant 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:

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

Plan Of Work

The work was planned as follows;

Synthesis and physicochemical studies

1. Synthesis of chalcone derivatives
2. Synthesis of 2-pyrazoline derivatives
3. Synthesis of semicarbazide derivatives
4. Characterization of synthesized compounds by following physicochemical methods
 - A. Physical constant (colour, mp)
 - B. Thin layer chromatography (TLC)
 - C. Infrared spectroscopy (IR)
 - D. Nuclear magnetic resonance spectroscopy
 - E. Mass spectrometry (MS)
 - F. Elemental Analysis

Biological evaluation

1. Antioxidant activities of synthesized compounds
2. Antifungal activities of synthesized compounds

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

IR spectra were recorded 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 $^1\text{H-NMR}$ spectra of the synthesized compounds in $\text{CDCl}_3/\text{DMSO}$ were recorded at 400 MHz by Bruker Advance II 400 NMR spectrometer. Chemical shift values are given in δ scale using tetramethylsilane (TMS) as an internal standard. Significant $^1\text{H-NMR}$ 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) CHCl₃, 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).

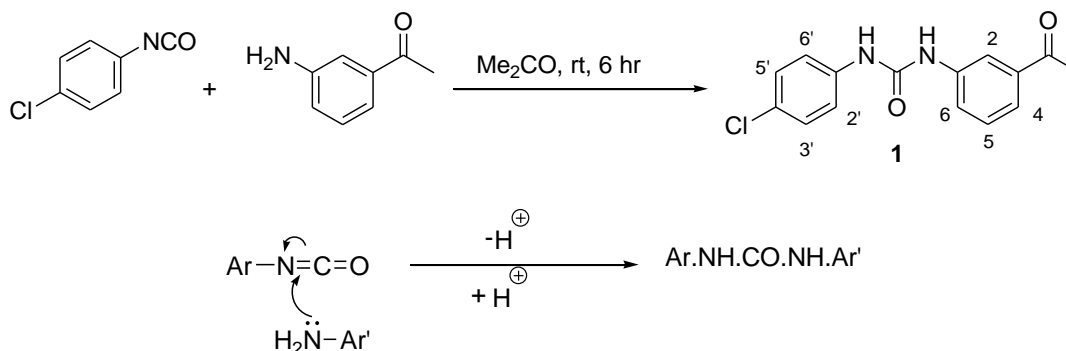


Figure :- Scheme for synthesis of 3-N-(N'-*p*-chlorophenylurenyl)acetophenone

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 (COCH₃), 1645 (C=O), 1614, 1534, 1461 (Ar C=C), 1515, 1290, 1185 (ArC-N), 1147 (Ar-Cl) 756, 687 (Ar); ¹H-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-COCH₃).

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).

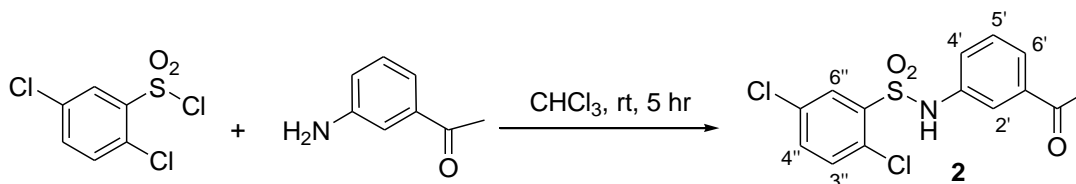


Figure :- Scheme for synthesis of 3'-N[(2'',5''-dichlorophenyl) sulfonyl-amide] acetophenone

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 (COCH₃), 1337, 1270 (SO₂), 1142 (Ar-Cl), 3060 (Ar-H), 2967 (C-H), 1584, 1461, 1357, 1297, 1273, 1166, 993, 852, 819, 795, 720 (Ar); ¹H-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, CH₃CO).

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 .

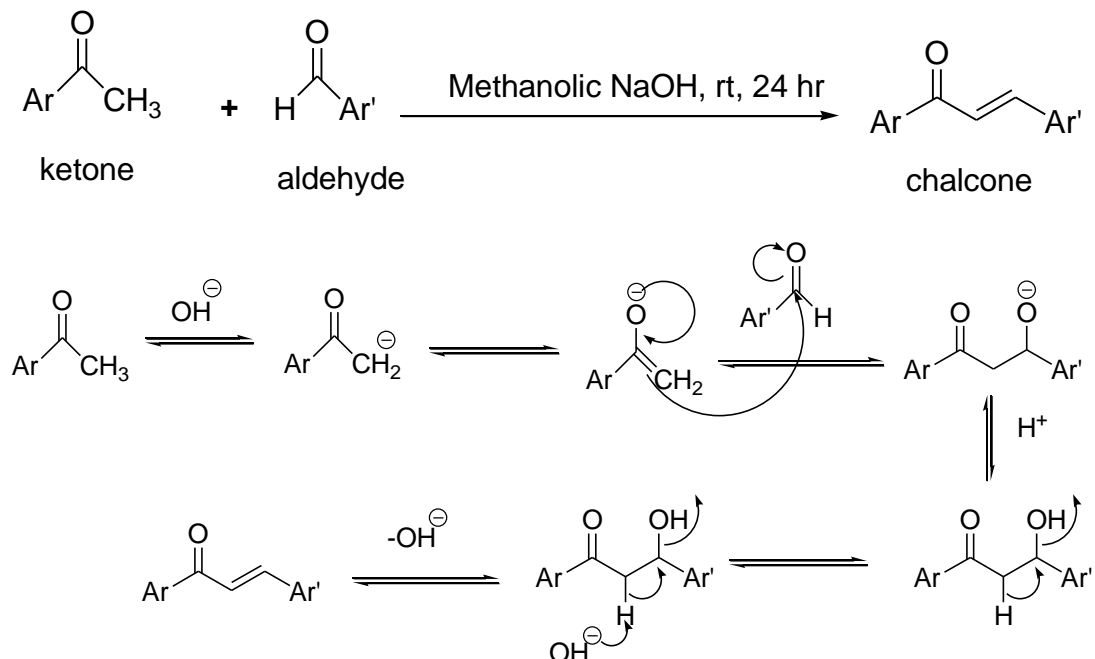


Figure :-Mechanism of reaction for synthesis of chalcone derivatives (1a-1p)

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.

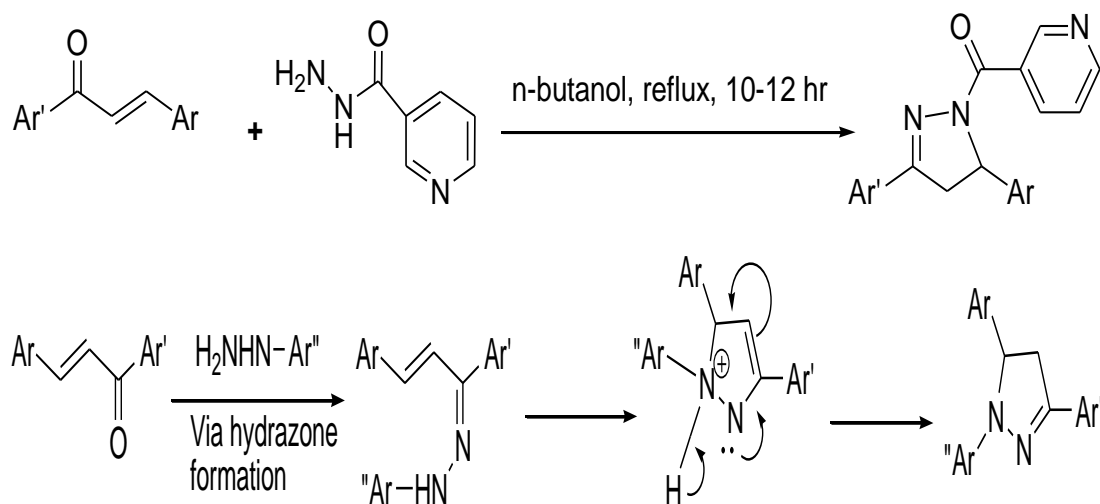


Figure :-Scheme and mechanism of reaction for synthesis of compounds (2a-2p)

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) $\nu_{\max}/\text{cm}^{-1}$ 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); $^1\text{H-NMR}$, 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 C₂₈H₂₂ClN₅O₃: 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) $\nu_{\max}/\text{cm}^{-1}$ 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); $^1\text{H-NMR}$, 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, OCH₃-3'), 3.10 (1H, dd, *J* 17.8 and 4.8, 4-H_x); FAB-MS *m/z*: 541.31 [M +H]⁺; Analysis Calcd. (%) for C₂₉H₂₄ClN₅O₄: 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.

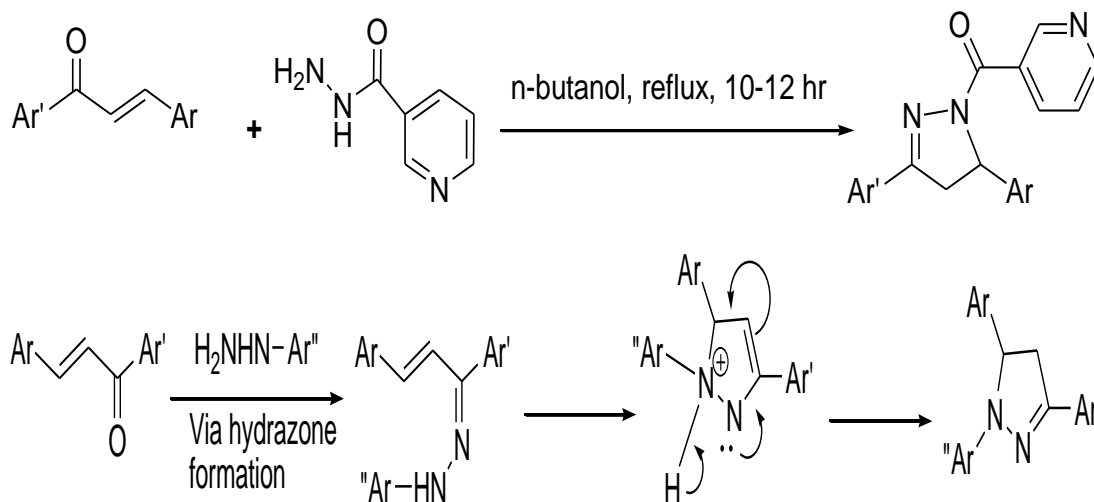


Figure :-Scheme and mechanism of reaction for synthesis of compounds (2a-2p)

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) $\nu_{\max}/\text{cm}^{-1}$ 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); $^1\text{H-NMR}$, 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_x), 3.18 (1H, dd, *J* 17.1 and 4.3, 4-H_x); FAB-MS *m/z*: 511.54 [M +H]⁺; Analysis Calcd. (%) for C₂₈H₂₂ClN₅O₃: 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) $\nu_{\max}/\text{cm}^{-1}$ 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); $^1\text{H-NMR}$, 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, OCH₃-3'), 3.10 (1H, dd, J 17.8 and 4.8, 4-H_x); FAB-MS m/z : 541.31 [M +H]⁺; Analysis Calcd. (%) for C₂₉H₂₄ClN₅O₄: 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) $\nu_{\max}/\text{cm}^{-1}$ 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); $^1\text{H-NMR}$, 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, OCH₃-2',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 C₃₀H₂₆ClN₅O₄: 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) $\nu_{\max}/\text{cm}^{-1}$ 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); $^1\text{H-NMR}$, 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, OCH₃-3', 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 C₃₀H₂₆ClN₅O₄: C, 64.80; H, 4.71; N, 12.60; Found: C, 64.72; H, 4.19; N, 12.23

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, $^1\text{HNMR}$ and Mass. The synthesized compounds were screened for , Antioxidant 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. $\mu\text{g/ml}$	Absorbance at 546 nm	% Antioxidant Activity	IC ₅₀ $\mu\text{g/ml}$
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-picryl hydrazyl) reduction method

Antioxidant activity of synthesized compounds by DPPH method

Sl.No	Compound	% Inhibition	IC ₅₀ \pm SEM DPPH Method
1	1g	19.97 – 85.95	47.47 \pm 2.473
2	1h	3.07-64.92	186.36 \pm 2.285
3	1j	7.4 - 48.75	>500
4	1k	10.47 - 68.37	57.27 \pm 1.375
5	1l	10.42 - 82.58	>500
6	1m	15.37 - 75.28	145.57 \pm 2.862
7	1o	4.1 - 76.37	87.19 \pm 1.845
8	1p	5.37 – 73.12	83.53 \pm 2.476
STD	Ascorbic acid	44.95 - 87.5	16.8 \pm 0.95

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.

p-chlorophenyl

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

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				

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, ¹H-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.

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. flavus*. The results of *in vitro* antibacterial as well as antifungal activities of synthesized compounds are summarized in Table.

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.

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.

References:-

1. Abdullah Sulaiman Al-Ayed, Synthesis, spectroscopy and electrochemistry of new 3-(5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-4-hydroxy-2H-chromene-2-one as a novel class of potential antibacterial and antioxidant derivatives, *Inter. J. Org. Chem.*, 1: 87-96, (2011).
2. Acharya B.N., Saraswat D., Tiwari M., Shrivastava A.K., Ghorpade R., Bapna S., Kaushik M.P., *Eur. J. Med. Chem.* 45 (2010) 430-438.
3. Acharya, B.N.; Saraswat, D.; Tiwari, M.; Shrivastava, A.K.; Ghorpade, R.; Bapana, S.; Kaushik, M.P. Synthesis and antimalarial evaluation of 1,3,5-trisubstituted pyrazolines. *Eur. J. Med. Chem.*, **2010**, 45, 430-438.
4. Agrawal M, Sonar PK, Saraf SK, Synthesis of 1,3,5-trisubstituted pyrazoline nucleus containing compounds and screening for antimicrobial activity, *Med. Chem. Res.*, 21: 3376–3381(2012).
5. Alberton, E.H.; Damazio, R.G.; Cazarolli, L.H.; Chiaradia, L.D.; Leal, P.C.; Nunes, R.J.; Yunes, R.A.; Silva, F.R.M.B. Influence of chalcone analogues on serum glucose levels in hyperglycemic rats. *Chemico-Biological Interactions*, **2008**, 171, 355–362.
6. Andrighetti-Froehner, C.R.; Oliveira, K.N.; Gaspar-Silva, D.; Pacheco, L.K.; Joussef, A.C.; Steindel, M.; Simoes, C.M.O.; Souza, A.M.T.; Magalhaes, U.O.; Afonso, I.F., Rodrigues, C.R.; Nunes, R.J.; Castro, H.C. Synthesis, biological evaluation and SAR of sulfonamide 4-methoxychalcone derivatives with potential antileishmanial activity. *European Journal of Medicinal Chemistry*, **2009**, 44, 755-763.
7. Anjani Solankee, Smruti Lad, Sejal Solankee & Ghanshyam Patel. Chalcones, pyrazolines and aminopyrimidines as antibacterial agents. *Indian J Chem* 2009;48(B):1442-1446.
8. Anto, R.J.; Sukumaran, K.; Kuttan, G.; Rao, M.N.A.; Subbaraju, V.; Kuttan, R. Anticancer and antioxidant activity of synthetic chalcones and related compounds. *Cancer Letters*, **1995**, 97, 33-37.
9. Aponte, J.C.; Vera'stegui, M.; Malaga, E.; Zimic, M.; Quiliano, M.; Vaisberg, A.J.; Gilman, R.H.; Hammond, G.B. Synthesis, Cytotoxicity, and Anti-Trypanosoma cruzi Activity of New Chalcones. *J. Med. Chem.*, **2008**, 51, 6230–6234.
10. Auwers, K. V. and Kreuder, A., *Ber. Dtsch. Chem. Ges.*, **58**, 1974 (1925).
11. Bandgar, B.P.; Gawande, S.S. Synthesis and biological screening of a combinatorial library of β -chlorovinyl chalcones as anticancer, anti-inflammatory and antimicrobial agents. *Bioorganic & Medicinal Chemistry*, **2010b**, 18, 2060–2065.
12. Bandgar, B.P.; Gawande, S.S.; Bodade, R.G.; Gawande, N.M.; Khobragade, C.N. Synthesis and biological evaluation of a novel series of pyrazole chalcones as anti-inflammatory, antioxidant and antimicrobial agents. *Bioorganic & Medicinal Chemistry*, **2009**, 17, 8168–8173.
13. Bandgar, B.P.; Gawande, S.S.; Bodade, R.G.; Totre, J.V.; Khobragade, C.N. Synthesis and biological evaluation of simple methoxylated chalcones as anticancer, anti-inflammatory and antioxidant agents. *Bioorganic & Medicinal Chemistry*, **2010a**, 18, 1364–1370.

14. Bandgar, B.P.; Patil, S.A.; Gacche, R.N.; Korbad, B.L.; Hote, B.S.; Kinkar, S.N.; Jalde, S.S. Synthesis and biological evaluation of nitrogen-containing chalcones as possible anti-inflammatory and antioxidant agents. *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, 730–733.
15. Bansal E., Srivastava V.K., Kumar, A. *Eur. J. Med. Chem.* 36 (2001) 81-92.
16. Bari SB, Mahajan Bm, Surana SJ. Resistance to Antibiotics: A Challenge in Chemotherapy. *Indian J Pharm Educ Res.* 2008; 42(1):3-11.
17. Barry, A.L. in Illus (Ed.). *The antimicrobial susceptibility test: principle and practice*, Lea and Febiger, Philadelphia, PA, USA. 180 (1976).
18. Batovska, D.I.; Todorova, I.T. Trends in utilization of the pharmacological potential of chalcones. *Curr. Clin. Pharmacol.*, **2010**, 5, 1-29.
19. Battu, G.R., Zeitlin, I. J. and Gray, A.I. *Br. J. Pharmacol.*, 133, 199 (2000).
20. Bekhit, A.A.; Hymete, A.; Asfaw, H.; Bekhit, A.E.D.A. Synthesis and biological evaluation of some pyrazole derivatives as anti-malarial agents. *Arch. Pharm. Chem. Life Sci.*, **2012**, 345, 147-154.
21. Beveridge, E. Chemotherapy of leishmaniasis, in: Schnitzer, R.J.; Hawking, F. (Eds.), *Experimental Chemotherapy*, vol. 1, Academic Press, New York, London, 1963, pp. 257–280.
22. Bharatham, K.; Bharatham, N.; Park, K.H.; Lee, K.L. Binding mode analyses and pharmacophore model development for sulfonamide chalcone derivatives, a new class of alpha-glucosidase inhibitors. *J. Mol. Graph. Model.*, **2008**, 26, 1202–1212.
23. Bhatnagar I and George M V, *Tetrahedron*, 1968, **24(3)**, 1293-1298.
24. Bhatnagar, S.; Guru, P.Y.; Katiyar, J.C.; Srivastava, R.; Mukherjee, A.; Akhtar, M. S.; Seth, M.; Bhaduri, A.P. *Indian J. Med. Res.* 1989, 89, 439–444.
25. Boeck, P.; Leal, P.C.; Yunes, R.A.; Fiiho, V.C.; Lopez, S.; Sortino, M.; Escalante, A.; Furlan, R.L.E.; Zacchino, S. Antifungal activity and studies on mode of action of novel xanthoxylone-derived chalcones. *Arch. Pharm. Chem. Life Sci.*, **2005**, 338, 87-95.
26. Bowden, K., Dal Pozzo, A. and Duah, C.K. *J. Chem. Res.*, (S), 377 (1990).
27. Braulio Insuasty, Alexis Tigreros, Fabian Orozco, Jairo Quiroga, Rodrigo Abonia, Manuel Noguerras, Adolfo Sanchez, and Justo Cobo. Synthesis of novel pyrazolic analogues of chalcones and their 3-aryl-4-(3-aryl-4,5-dihydro-1H-pyrazol-5-yl)-1-phenyl-1H-pyrazole derivatives as potential antitumor agents, *Bioorg. Med. Chem.*, 18(14): 4965–4974, (2010).
28. Braulio Insuasty, Leidy Chamizo, Jhon Munoz, Alexis Tigreros, Jairo Quiroga, Rodrigo Abonia, Manuel Noguerras, and Justo Cobo. Synthesis of 1-substituted 3-aryl-5-aryl(hetaryl)-2-pyrazolines and study of their antitumor activity, *Arch. Pharm. Chem. Life Sci.*, 345: 275–286, (2012).
29. Bremner, P.D.; Meyer, J.J.M. Pinoembriin chalcone: an antibacterial compound from *Helichrysum trilineatum*. *Planta Med.* **1998**, 64, 777.
30. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, Simmons DL. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci USA* 2002;99:13926-13931.
31. Chen, F.C.; Yang, C.H.; Hsu, K.K. Synthesis of Halogenoflavonoids I. Synthesis of 6-Chloro-flavanone and flavone. *J. Formosan Sci.*, **1953**, 7, 51-53.
32. Chen, M.; Christensen, S.B.; Zhai, L.; Rasmussen, M.H.; Theander, T.G.; Frokjaer, S.; Steffansen, S.; Davidsen, J.; Kharazmi, A. The novel oxygenated chalcone, 2,4-dimethoxy-4'-butoxychalcone, exhibits potent activity against human malaria parasite *Plasmodium yoelii* in vivo. *J. Infect. Dis.* **1997**, 176, 1327-1333.
33. Chen, M.; Theander, T.G.; Christensen, B.S.; Hviid, L.; Zhai, L.; Kharazmi, A. Licochalcone A, a new antimalarial agent, inhibits *in vitro* growth of the human malaria parasite *Plasmodium falciparum* and protects mice from *P. yoelii* infection. *Antimicrob. Agents Chemother.* **1994**, 38, 1470-1475.
34. Cheng, J.H.; Hung, C.F.; Yang, S.C.; Wang, J.P.; Wond, S.J.; Lin, C.N. Synthesis and cytotoxic, anti-inflammatory, and anti-oxidant activities of 2',5'-dialkoxychalcones as cancer chemopreventive agents. *Bioorganic & Medicinal Chemistry*, **2008**, 16, 7270–7276.
35. Cheng, Z.J.; Lin, C.N.; Hwang, T.L.; Teng, C.M. Brousochalcone A, a potent antioxidant and effective suppressor of inducible nitric oxide synthase in lipopolysaccharide-activated macrophages. *Biochemical Pharmacology*, **2001**, 61, 939–946.
36. Chiaradia, L.D.; Santos, R.; Vitor, C.E.; Vieira, A.A.; Leal, P.C.; Nunes, R.J.; Calixto, J.B.; Yunes, R.A. Synthesis and pharmacological activity of chalcones derived from 2,4,6-trimethoxyacetophenone in RAW 264.7 cells stimulated by LPS: Quantitative structure–activity relationships. *Bioorganic & Medicinal Chemistry*, **2008**, 16, 658–667.

37. Chin, Y.W.; Jung, H.A.; Liu, Y.; Su, B.N.; Castoro, J.A.; Keller, W.J.; Pereira, M.A.; KINGHORN, A.D. Antioxidant Constituents of the Roots and Stolons of Licorice (*Glycyrrhiza glabra*). *J. Agric. Food Chem.*, **2007**, *55*, 4691-4697.
38. Chovatia PT, Akabarij JD, Kachhadia PK, Zalavadia PD and Joshi HS, Synthesis and selective antitubercular and antimicrobial inhibitory activity of 1-acetyl- 3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives, *J. Serb. Chem. Soc.*, *71*(7): 713–720, (2007).
39. Cohen FL, Tartasky D. Microbial resistance to drug therapy: A review. *AmJInfectControl*. 1997; *25*(1):51-63.
40. Coleman, J.W. Nitric oxide in immunity and inflammation. *Int. Immunopharmacol*, **2001**, *1*, 1397–1406.
41. Cronstein BN. Cyclooxygenase-2-selective inhibitors: Translating pharmacology into clinical utility. *Clev Clin J Med* 2003;*69*:13-19.
42. Daikonya, A.; Katsuki, S.; Kitanaka, S. Antiallergic Agents from Natural Sources 9. Inhibition of Nitric Oxide Production by Novel Chalcone Derivatives from *Mallotus philippinensis* (Euphorbiaceae). *Chem. Pharm. Bull.*, **2004**, *52*, 1326-1329.
43. Damazio, R.G.; Zanatta, A.P.; Cazarolli, L.H.; Chiaradia, L.D.; Mascarello, A.; Nunes, R.J.; Yunes, R.A.; Silva, F.R.M.B. Antihyperglycemic activity of naphthylchalcones. *European Journal of Medicinal Chemistry*, **2010**, *45*, 1332–1337.
44. Damazio, R.G.; Zanatta, A.P.; Cazarolli, L.H.; Mascarello, A.; Chiaradia, L.D.; Nunes, R.J.; Yunes, R.A.; Silva, F.R.M.B. Nitrochalcones: Potential in vivo insulin secretagogues. *Biochimie*, **2009**, *91*, 1493–1498.
45. Detsi, A.; Majdalani, M.; Kontogiorgis, C.A.; Hadjipavlou-Litina, D.; Kefalas, P. Natural and synthetic 20-hydroxy-chalcones and auronones: Synthesis, characterization and evaluation of the antioxidant and soybean lipoxygenase inhibitory activity. *Bioorganic & Medicinal Chemistry*, **2009**, *17*, 8073–8085.
46. Dhar D N and Raghunathan R, *Indian J Chem.*, 1984, **23B**, 1187.
47. Dhar, D.N. *The Chemistry of Chalcones and Related Compounds*, John Wiley: New York, **1981**.
48. Di Carlo, G.; Mascolo, N.; Izzo, A.A.; Capasso, F. Flavonoids: Old and new aspects of a class of natural therapeutic drugs. *Life Sci.*, **1999**, *65*, 337-353.
49. Dimmock, J.R.; Elias, D.W.; Beazely, M.A.; Kandepu, N.M. Bioactivities of chalcones. *Curr. Med. Chem.*, **1999**, *6*, 1125-1149.
50. Dinkova-Kostova, A.T.; Abeygunawardana, C.; Talalay, P. *J. Med. Chem.*, **1998**, *41*, 5287.
51. Dominguez, J.N.; Leon, C.; Rodrigues, J.; Dominguez N.G.; Gut, J.; Rosenthal, P.J. Synthesis of chlorovinyl sulfones as structural analogs of chalcones and their antiplasmodial activities. *Eur. J. Med. Chem.*, **2009**, *44*(4), 1457-1462..
52. Dominguez, J.N.; Leon, C.; Rodrigues, J.; Dominguez, N.G.; Gut, J.; Rosenthal, P.J. Synthesis and evaluation of new antimalarial phenylurenyl chalcone derivatives. *J. Med. Chem.*, **2005**, *48*, 3654–3658.
53. Dominguez, J.N.; Leon, C.; Rodrigues, J.; Dominguez, N.G.; Gut, J.; Rosenthal, P.J. Synthesis and antimalarial activity of sulfonamide chalcone derivatives. *Il Farmaco*, **2005**, *60*, 307–311.
54. Dominquez, J.N.; Charris, J.E.; Caparelli, M.; Riggione, F. Synthesis and antimalarial activity of substituted pyrazole derivatives. *Drug Res.*, **2002**, *52*, 482-488.
55. Ducki, S.; Rennison, D.; Woo, M.; Kendall, A.; Chabert, J.F.D.; McGown, A.T.; Lawrence, N.J.; Combretastatin-like chalcones as inhibitors of microtubule polymerization. Part 1: Synthesis and biological evaluation of antivascular activity. *Bioorganic & Medicinal Chemistry*, **2009**, *17*, 7698–7710.
56. Duwiejua, M., Zeitlin, I.A., Waterman, P.G. and Gray, A.I. *J. Pharm. Pharmacol.*, *46*, 286 (1994).
57. Dzedzic S.Z.; Hudson, B.J.F. Polyhydroxy chalcones and flavanones as antioxidants for edible oils. *Food Chemistry*, **1983**, *12*(3), 205-212.
58. Eddarir, S.; Cotelte, N.; Bakkour, Y.; Rolando, C. An efficient synthesis of chalcones based on the Suzuki reaction. *Tetrahedron Lett.*, **2003**, *44*, 5359-5363.
59. Eddy, N.B. and Leimtach, D. *J. Pharmacol. Exp. Ther.*, *106*, 385 (1953).
60. ElSohly, H.N.; Joshi, A.S.; Nimrod, A.C.; Walker, L.A.; Clark, A.M. Antifungal Chalcones from *Maclura tinctoria*. *Planta Med.*, **2001**, *67*, 87-89.
61. Enoki, T.; Ohnogi, H.; Nagamine, K.; Kudo, Y.; Sugiyama, K.; Tanabe, M.; Kobayashi, E.; Sagawa, H.; Gato, I. Antidiabetic activities of chalcones isolated from a Japanese herb, *Angelica keiskei*. *J. Agric. Food Chem.*, **2007**, *55*, 6013–6017.
62. Finney, D.J.; *Probit Analysis*, third ed. Cambridge University Press, 1971.
63. Foroumadi A, Emani S, Hassanzadeh A, Rajaei M, Sokhanvar K, Moshafi M H. Synthesis and antibacterial activity of N-(5-benzylthio-1,3,4-thiadiazol-2-yl)piperazinylquinolone. *Bioorg Med Chem Lett* 2005;*15*:4488-4492.

64. Friis-Moller, A.; Chen, M.; Fursted, K.; Christensen, S.B.; Kharazmi, A. *In vitro* antimycobacterial and antilegionella activity of licochalcone A from Chinese licorice roots. *Planta Med.*, **2002**, 68, 416-419.
65. Fukai, T.; Marumo, A.; Kaitou, K.; Kanda, T.; Terada, S.; Nomura, T. Anti-Helicobacter pylori flavonoids from licorice extract. *Life Sci.*, **2002**, 71, 1449-1463.
66. Fukai, T.; Marumo, A.; Kaitou, K.; Kanda, T.; Terada, S.; Nomura, T. Antimicrobial activity of licorice flavonoids against methicillin-resistant *Staphylococcus aureus*. *Fitoterapia*, **2002**, 73, 536-539.
67. Furniss, B.S.; Hannaford, A.J.; Rogers, V.; Smith, P.W.G.; Tatchell, A.R. (1989). Vogel's Textbook of Practical Organic Chemistry, 5th ed.; Longman Group Limited: New York, p. 1034.
68. Ganesh A. Biological activities of some pyrazoline derivatives Int J Pharm Bio Sci 2013 4(2): (P) 727 - 733 .
69. Grosscurt, A.C., Vanher, R. and Wellinga, K., *J. Agri. Food Chem.*, **27**, 406 (1979).
70. Guantai, E.M.; Ncokezi, K.; Egan, T.J.; Gut, J.; Rosenthal, P.J.; Smith, P.J.; Chibale, K. Design, synthesis and in vitro antimalarial evaluation of triazole-linked chalcone and dienone hybrid compounds. *Bioorganic & Medicinal Chemistry*, **2010**, 18(23), 8243-8256
71. Guida, A.; Lhouty, M. H.; Tichit, D.; Figueras, F.; Geneste, P. Hydrotalcites as base catalysts. Kinetics of Claisen-Schmidt condensation, intramolecular condensation of acetylacetone and synthesis of chalcone. *Appl. Catal. A*, **1997**, 164, 251-264.
72. Gupta R, Gupta N, Jain A. Indian Journal of Chemistry, 2010, 49B, 351-355.
73. Gupta, A. S.; Sundar R. S.; Goyal, N. Antimicrob. Agents Chemother. 2005, 49, 3776-3783.
74. Gupta, S.; Tiwari, S.; Bhaduri A.P.; Jain, G.K. Acta Trop. 2002, 84, 165-173.
75. Habib, O.M.O., Khalil, A.M., Kandeel, E.M. and Abdalla, E.B., *Rev. Roum. Chim.*, **31**, 629 (1986).
76. Habibullah Khalilullah, Shamshir Khan, Mohamed Jawed Ahsan, Bahar Ahmed, Synthesis and antihepatotoxic activity of 5-(2,3-dihydro-1,4-benzodioxane-6-yl)-3-substituted-phenyl-4,5-dihydro-1H-pyrazole derivatives, *Bioorg. Med. Chem. Lett.*, 21(24): 7251-7254, (2011).
77. Han, Y.; Riwanto, M.; Go, M.L.; Rachel Ee, P.L. Modulation of breast cancer resistance protein (BCRP/ABCG2) by non-basic chalcone analogues. *European Journal of Pharmaceutical Sciences*, **2008**, 35, 30-41.
78. Haraguchi, H.; Tanimoto, K.; Yukiyoishi, T.; Mizutani, K.; Kinoshita, T. Mode of antibacterial action of retrochalcones from Glycyrrhiza inflata. *Phytochemistry*, **1998**, 48, 125-129.
79. Hatano, T.; Shintani, Y.; Aga, Y.; Shiota, S.; Tsuchiya, T.; Yoshida, T. Phenolic constituents of Licorice. VIII. Structures of Glicophenone and Glicoisoflavanone and effects of Licorice phenolics on methicillin-resistant *Staphylococcus aureus*. *Chem. Pharm. Bull.*, **2000**, 48, 1286-1292.
80. Helio Bonacorso G, Susiane Cavinatto, Patrick Campos T, Liliane Porte MF, Jussara Navarini, Gisele Paim R, Marcos Martins AP, Nilo Zanatta, Caroline Stuker Z, New trifluoromethyl-containing (E)-N'-arylidene-[3-alkyl(aryl/heteroaryl)-4,5-dihydro-1H-pyrazol-1-yl]carbohydrazides: Synthesis, crystal structure and antimicrobial/antioxidant activity, *J. Flu. Chem.*, 135: 303-314, (2012).
81. Herencia, F.; Ferrandiz, M.L.; Ubeda, A.; Dominguez, J.N.; Charris, J.E.; Lobo, G.M.; Alcaraz, M.J.; Synthesis and anti-inflammatory activity of chalcone derivatives. *Bioorg. Med. Chem. Lett.*, **1998**, 8, 1169-1174.
82. Hermoso, A.; Jimenez, I.A.; Mamani, Z.A.; Bazzocchi, I.L.; Pinero, J.E.; Ravelo, A.G.; Valladares, B. Antileishmanial activities of dihydrochalcones from piper elongatum and synthetic related compounds. Structural requirements for activity. *Bioorg. Med. Chem.*, **2003**, 11, 3975-3980.
83. Howell, W.C., Ktenas, M. and MacDonald, J.M., *Tetrahedron Lett.*, **26**, 1719 (1964).
84. Insuasty, B.; Montoya, A.; Becerra, D.; Quiroga, J.; Abonia, R.; Robledo, S.; Velez, I.D.; Upegui, Y.; Nogueras, M.; Cobo, J. Synthesis of novel analogs of 2-pyrazoline obtained from [(7-chloroquinolin-4-yl)amino]chalcones and hydrazine as potential antitumor and antimalarial agents. *Eur. J. Med. Chem.*, **2013**, 67, 252-262.
85. Jha A., Mukherjee, C.; Rolle, A.J.; Clercq, E.D.; Balzarini, J.; Stables, J.P. Cytostatic activity of novel 40-aminochalcone-based imides. *Bioorganic & Medicinal Chemistry Letters*, **2007**, 17, 4545-4550.
86. Joshi M G and Wadodkar K N, *Indian J Chem.*, 1981, **20B**, 1090.
87. Joshi, A.S.; Li, X.C.; Nimrod, A.C.; ElSohly, H.N.; Walker, L.A.; Clark, A.M. Dihydrochalcones from *Piper longicaudatum*. *Planta Med.*, **2001**, 67, 186-188.
88. Jun, N.; Hong G.; Jun, K. Synthesis and evaluation of 2', 4', 6'-trihydroxychalcones as a new class of tyrosinase inhibitors. *Bioorganic & Medicinal Chemistry*, **2007**, 15, 2396-2402.
89. Kamal, A.; Ramakrishna, G.; Raju, P.; Viswanath, A.; Ramaiah, M.J.; Balakishan, G.; Bhadra, M.P. Synthesis and anti-cancer activity of chalcone linked imidazolones. *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, 4865-4869.
90. Karad, S.C.; Purohit, V.B.; Raval, D.K. Design, synthesis and characterization of fluoro substituted novel pyrazolopyrazolines scaffold and their pharmacological screening. *Eur. J. Med. Chem.*, **2014**, 84, 51-58.

91. Karthikeyan, M.S., Bantwal, S.H. and Sucheta, N.K., *Eur. J. Med. Chem.*, **42**, 30 (2007).
92. Khatib, S.; Nerya, O.; Musa, R.; Shmuel, M.; Tamir, S.; Vaya, J. Chalcones as potent tyrosinase inhibitors: the importance of a 2,4-substituted resorcinol moiety. *Bioorganic & Medicinal Chemistry*, **2005**, 13, 433–441.
93. Khunt RC, Khedkar VM, Chawda RS, Chauhan NA, Parikh AR, Coutinho EC, Synthesis, antitubercular evaluation and 3D-QSAR study of N-phenyl-3-(4-fluorophenyl)-4-substituted pyrazole derivatives, *Bioorg. Med. Chem. Lett.*, 22(6): 666–678, (2012)
94. Kini, S.; Gandhi, A.M. (2008). Novel 2-pyrazoline derivatives as potential antibacterial and antifungal agents. *Indian J. Pharm. Sci.* 70, 105-108.
95. Kromann, H.; Larsen, M.; Boesen, T.; Schønning, K.; Nielsen, S.F. Synthesis of prenylated benzaldehydes and their use in the synthesis of analogues of licochalcone A. *Eur. J. Med. Chem.*, **2004**, 39, 993-1000.
96. Kumar, D.; Kumar, N.M.; Akamatsu, K.; Kusaka, E.; Harada, H.; Ito, T. Synthesis and biological evaluation of indolyl chalcones as antitumor agents. *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, 3916–3919.
97. Kumar, R.; Mohanakrishnan, D.; Sharma, A.; Kaushik, N.K.; Kalia, K.; Sinha, A.K.; Sahal, D. Reinvestigation of structure-activity relationship of methoxylated chalcones as antimalarials: Synthesis and evaluation of 2,4,5-trimethoxy substituted patterns as lead candidates derived from abundantly available natural α -asarone. *European Journal of Medicinal Chemistry*, **2010**, 45, 5292-5301.
98. Lavie, D. Evaluation of analgesic property of compounds. *Lewis Pharmacology*. 5 Edn, 461 (1999).
99. Lee, S.H.; Sohn, D.H.; Jin, X.Y.; Kim, S.W.; Choi, S.C.; Seo, G.S. 2',4',6'-Tris(methoxymethoxy) chalcone protects against trinitrobenzene sulfonic acid-induced colitis and blocks tumor necrosis factor- α -induced intestinal epithelial inflammation via heme oxygenase 1-dependent and independent pathways. *Biochemical pharmacology*, **2007**, 74, 870–880.
100. Lemke TL, Williams DA., Roche V F, Zito SW. Antibiotics and Antimicrobial agents. In: Foye's Principles of Medicinal Chemistry. 6th ed. Lippincott Williams and Wilkins; 2008. pp. 1028-1083.
101. Leon, C.; Rodrigues, J.; Dominguez, N.; Rosenthal, P.J.; Dominguez, J.N. (2007). Synthesis and evaluation of sulfonylurea derivatives as novel antimalarials. *Eur. J. Med. Chem.* 42, 735-742.
102. Li, R.; Kenyon, G.L.; Cohen, F.E.; Chen, X.; Gong, B.; Dominguez, J.N.; Davidson, E.; Kurzban, G.; Miller, R.E.; Nuzum, E.O.; Rosenthal, P.J.; McKerrow, J.H. *In vitro* Antimalarial Activity of Chalcones and Their Derivatives. *J. Med. Chem.* **1995**, 38, 5031-5037.
103. Lin, Y.M.; Zhou, Y.; Flavin, M.T.; Zhou, L.M.; Nie, W.; Chen, F.C. Chalcones and Flavonoids as Anti-Tuberculosis Agents. *Bioorg. Med. Chem.*, **2002**, 10, 2795-2802.
104. Litchfield, J.T. and Wilcoxon, F. *J. Pharmacol. Exp. Ther.*, 96, 99 (1949).
105. Liu X.; Go, M.L. Antiproliferative activity of chalcones with basic functionalities. *Bioorganic & Medicinal Chemistry*, **2007**, 15, 7021–7034.
106. Liu, M.; Wilairat P.; Go, M.L. Antimalarial Alkoxyated and Hydroxylated Chalcones: Structure-Activity Relationship Analysis. *J. Med. Chem.*, **2001**, 44, 4443-4452.
107. Lopez, A. In *Disease Control Priorities in Developing Countries*; Jamison, D. T., Mosely, W. H., Eds.; Oxford: New York, 1993; p35.
108. Lopez, S.; Castelli, M.V.; Zacchino, S.; Dominguez, J.N.; Lobo, G.; Charris-Charris, J.; Coetrs, J.C.C.; Ribas, J.C.; Devia, C.; Rodrigues, A.M.; Enriz, R.D. In Vitro Antifungal Evaluation and Structure-Activity Relationships of a New Series of Chalcone Derivatives and Synthetic Analogues, with Inhibitory Properties Against Polymers of the Fungal Cell Wall. *Bioorg. Med. Chem.*, **2001**, 9, 1999-2013.
109. Loudon, J.D., in: *Chemistry of Carbon Compounds, Elsevier Publishing Company*, New York (1957).
110. Machado, T.B.; Leal, I.C.R.; Kuster, R.M.; Amaral, A.C.F.; Kokis, V.; Silva, M.G.; Santos, K.R.N. Brazilian phytopharmaceuticals evaluation against hospital bacteria. *Phytother. Res.*, **2005**, 19, 519-525.
111. Madan, B.; Batra, S.; Ghosh, B. 2'-hydroxychalcone inhibits nuclear factor-kappaB and blocks tumor necrosis factor-alpha- and lipopolysaccharide-induced adhesion of neutrophils to human umbilical vein endothelial cells. *Mol. Pharmacol.*, **2000**, 58, 526-534.
112. Manikandan D, Krishnaraj K and Nanjan M J, *Int J Chem Res.*, 2012, **4**, 532-538.
113. Marella A *et al.* Pyrazolines: A biological review. *Mini-Reviews in Medicinal Chemistry*, 2013, 13(6), 921-931.
114. Mendes, V.; Monteiro, R.R.; Pestana, D.; Teixeira, D.; Calhau, C.A.O.; Azevedo, I. Xanthohumol Influences Preadipocyte Differentiation: Implication of Antiproliferative and Apoptotic Effects. *J. Agric. Food Chem.*, **2008**, 56, 11631–11637.
115. Meng, C.Q.; Ni, L.; Worsencroft, K.J.; Ye, Z.; Weingarten, M.D.; Simpson, J.E.; Skudlarek, J.W.; Marino, E.M.; Suen, K.L.; Kunsch, C.; Souder, A.; Howard, R.B.; Sundell, C.L.; Wasserman, M.A.; Sikorski, J.A.; Carboxylated, Heteroaryl-Substituted Chalcones as Inhibitors of Vascular Cell Adhesion Molecule-1 Expression for Use in Chronic Inflammatory Diseases. *J. Med. Chem.*, **2007**, 50, 1304-1315.

116. Mifflin RC, Powell DW. Cyclooxygenases. *The Regulatory Peptide Letter* 2001;8: 49-56.
117. Mishra, N.; Arora, P.; Kumar, B.; Mishra, L.C.; Bhattacharya, A.; Awasthi, S.K.; Bhasin, V.K. Synthesis of novel substituted 1,3-diaryl propenone derivatives and their antimalarial activity *in vitro*. *European Journal of Medicinal Chemistry*, **2008**, 43, 1530-1535.
118. Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N.E.; Huang, P.; Khana, S.R. Anticancer activities of novel chalcone and bis-chalcone derivatives. *Bioorganic & Medicinal Chemistry*. **2006**, 14, 3491-3495.
119. Mohamed Aboul-Enein N, AidaEl- Azzouny A, Mohamed Attial, Yousreya Maklad A, Kamilia Amin M, Mohamed Abdel-Rehim, and Mohammed El-Behairy F, Design and synthesis of novel stiripentol analogues as potential anticonvulsants, *Eur. J. Med. Chem.*, 47(1): 360-369, (2012).
120. Mohan, H. in *Textbook of Pathology, Inflammation and Healing*. Jaypee brothers medical publishers Ltd. 3rd ed, 1998, 133-190.
121. Morel, I.; Lescoat, G.; Cogrel, P.; Sergent, O.; Padeloup, N.; Brissot, P.; Cillard, P.; Cilliard, J. Antioxidant and iron-chelating activities of the flavonoids catechin, quercetin and diosmetin on iron-loaded rat hepatocyte cultures. *Biochem. Pharmacol.*, **1993**, 45, 13-19.
122. Mustafa, K.A.; Kjaergaard, H.G.; Perry, N.B.; Weavers, R.T. Hydrogen-bonded rotamers of 2',4',6'-trihydroxy-3'-formyldihydrochalcone, an intermediate in the synthesis of a dihydrochalcone from *Leptospermum recurvum*. *Tetrahedron*, **2003**, 59, 6113-6120.
123. Mustafa, K.A.; Kjaergaard, H.G.; Perry, N.B.; Weavers, R.T. Hydrogen-bonded rotamers of 2',4',6'-trihydroxy-3'-formyldihydrochalcone, an intermediate in the synthesis of a dihydrochalcone from *Leptospermum recurvum*. *Tetrahedron*, **2003**, 59, 6113-6120.
124. Nakamura, C.; Kawasaki, N.; Miyataka, H.; Jayachandran, E.; Kim, I.H.; Kirk, K.L.; Taguchi, T.; Takeuchi, Y.; Horie H.; Satoh, T. Synthesis and biological activities of fluorinated chalcone derivatives. *Bioorganic & Medicinal Chemistry*, **2002**, 10, 699-706.
125. Narender, T.; Khaliq, T.; Shweta, Goyal, N.N.; Gupta, S. Synthesis of chromenochalcones and evaluation of their *in vitro* antileishmanial activity. *Bioorganic & Medicinal Chemistry*, **2005**, 13, 6543-6550.
126. Navarini, A.L.F.; Chiaradia, L.D.; Mascarello, A.; Fritzen, M.; Jose´ Nunes, R.; Yunes, R.A.; Creczynski-Pasa, T.B. Hydroxychalcones induce apoptosis in B16-F10 melanoma cells via GSH and ATP depletion. *European Journal of Medicinal Chemistry*, **2009**, 44, 1630-1637.
127. Nazarian, Z.; Emami, S.; Heydari, S.; Ardestani, S.K.; Nakhjiri, M.; Poorrajab, F.; Shafiee, A.; Foroumadi, A. Novel antileishmanial chalconoids: Synthesis and biological activity of 1- or 3-(6-chloro-2H-chromen-3-yl)propen-1-ones. *European Journal of Medicinal Chemistry*, **2010**, 45, 1424-1429.
128. Nerya, O.; Vaya, J.; Musa, R.; Izrael, S.; Ben-Arie, R.; TAMIR, S. Glabrene and isoliquiritigenin as tyrosinase inhibitors from licorice roots. *J. Agric. Food Chem.*, **2003**, 51, 1201-1207.
129. Ni, L.; Meng, C.Q.; Sikorski, J.A. Recent advances in therapeutic chalcones. *Expert Opin. Ther. Pat.*, **2004**, 14, 1669-1691.
130. Nielsen, S.F.; Boesen, T.; Larsen, M.; Schønning K.; Kromann, H. Antibacterial chalcones—bioisosteric replacement of the 4'-hydroxy group. *Bioorganic & Medicinal Chemistry*, **2004**, 12, 3047-3054.
131. Nielsen, S.F.; Chen, M.; Theander, T.G.; Kharazmi, A.; Christensen, S.B. Synthesis of Antiparasitic Licorice Chalcones. *Bioorg. Med. Chem. Lett.*, **1995**, 5, 449-452.
132. Nielsen, S.F.; Larsen, M.; Boesen, T.; Schønning, K.; Kromann, H. Cationic Chalcone Antibiotics. Design, Synthesis, and Mechanism of Action. *J. Med. Chem.*, **2005**, 48, 2667-2677.
133. Nowakowska, Z. A review of anti-infective and anti-inflammatory chalcones. *European Journal of Medicinal Chemistry*, **2007**, 42, 125-137.
134. Okunade, A.L.; Hufford, D.C.; Clark, A.L.; Lentz, D. Antimicrobial Properties of the Constituents of *Piper aduncum*. *Phytother. Res.*, **1997**, 11, 142-144.
135. Omneya Khalil M, Synthesis and anti-inflammatory activity of 1-acetyl/propanoyl-5-aryl-3-(4-morpholinophenyl)-4,5-dihydro-1H-pyrazole derivatives, *Med. Chem. Res.*, 21: 3240-3245, (2012).
136. Ozdemir, A.; Turan-Zitouni, G.; Kaplancikli, Z.M. (2008). Novel analogues of 2-pyrazoline: Synthesis and antimycobacterial evaluation. *Turk. J. Chem.* 32, 529-538.
137. Pablo Machado, Fernanda Rosa A, Marcelo Rossatto, Gabriela da Sant'Anna S, Patricia Sauzem D, Rubia Siqueira da Silva M, Maribel Rubin A, Juliano Ferreira, Helio Bonacorso G, Nilo Zanatta, and Marcos Martins AP, Synthesis and structure of novel 4,5-dihydro-1H-pyrazoles: salicylic acid based analgesic agents, *Arkivoc*, 16: 281-297, (2007).
138. Palaska, E. and Biligin, A.A. *Pharmazie*, 49 (1), 67 (1994).
139. Palaska, E., Erol, D. and Demirdamar, R.B., *Eur. J. Med. Chem.*, **31**, 43 (1996).
140. Parmar, S.S., Pandey, B.R., Dwivedi, C. and Harbison, R.D. *J. Pharm. Sci.*, 63, 1152(1974).

141. Pasha TY, Udipi RH, Bhat AR. Synthesis and antimicrobial screening of some pyrimidine derivatives. *Indian J Heterocycl Chem* 2005;15:149-152.
142. Pechmann, H.V., *Ber. Dtsch. Chem. Ges.*, **27**, 1890 (1894).
143. Peng-Cheng Lv, Huan-Qiu Li, Juan Sun, Yang Zhou, and Hai-Liang Zhu, Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents, *Bioorg. Med. Chem.*, 18(13): 4606–4614, (2010)
144. Porsolt, R.D. and Bertin, A. *Arch. Int. Pharmacodyn.*, 229, 327 (1977).
145. Porsolt, R.D. In antidepressants: Neurochemical behavioural and clinical perspectives; Enna, S.J., Mallick, J.B., Richelson, E., Eds., Raven Press: New York, 121 (1981).
146. Porsolt, R.D., Anton, G., Blavet, N. and Jalfre, M. Behavioural despair in rats: A new model sensitive to antidepressive treatments. *Eur. J. Pharmacol.*, 47, 379 (1978).
147. Prasad, Y. R., Rao, L. A., Prasoona, L., Murali, K. and Ravi Kumar, P., *Bioorg Med. Chem. Lett.*, **15**, 5030 (2005).
148. Raiford, L. C. and Entrikin, J. B., *J. Am. Chem. Soc.*, **55**, 1125 (1933).
149. Ram, V.J.; Saxena, A.S.; Srivastava, S.; Chandra, S. Oxygenated chalcones and bischalcones as potential antimalarial agents. *Bioorg Med Chem Lett.*, **2000**, 10(19), 2159-61.
150. Rang HP, Dale MM, Ritter JM, Moore PK. "Pharmacology", Fifth edition, Churchill Livingstones pub., New York, 2003, 217-243.
151. Rao, Y.K.; Fang, S.H.; Tzeng, Y.M. Synthesis and biological evaluation of 3', 4',5'-trimethoxychalcone analogues as inhibitors of nitric oxide production and tumor cell proliferation. *Bioorganic & Medicinal Chemistry*, **2009**, 17, 7909–7914.
152. Reddy, M.V.B.; Su, C.R.; Chiou, W.F.; Liu, Y.N.; Chen, R.Y.H.; Bastow, K.F.; Lee, K.H.; Wu, T.S. Design, synthesis, and biological evaluation of Mannich bases of heterocyclic chalcone analogs as cytotoxic agents. *Bioorganic & Medicinal Chemistry*, **2008**, 16, 7358–7370.
153. Reddy, N.P.; Aparoy, P.; Reddy, T.C.M.; Achari, C.; Sridhar, P.R.; Reddanna, P. Design, synthesis, and biological evaluation of prenylated chalcones as 5-LOX inhibitors. *Bioorganic & Medicinal Chemistry*, **2010**, 18, 5807–5815.
154. Rojas, J.; Dominguez, J.N.; Charris, J.E.; Lobo, G.M.; Paya, M.; Ferrandiz, M.L. Synthesis and inhibitory activity of dimethylamino-chalcone derivatives on the induction of nitric oxide synthase. *Eur. J. Med. Chem.*, **2002**, 37, 699-705.
155. Rojas, J.; Paya, M.; Dominguez, J.N.; Ferrandiz, M.L. ttCH, a selective inhibitor of inducible nitric oxide synthase expression with antiarthritic properties. *Eur. J. Pharm.*, **2003**, 465, 183-189.
156. Romagnoli, R.; Baraldi, P.G.; Carrion, M.D.; Cruz-Lopez, O.; Cara, C.L.; Balzarini, J.; Hamel, E.; Canella, A.; Fabbri, E.; Gambari, R.; Basso, G.; Viola, G. Hybrid α -bromoacryloylamido chalcones. Design, synthesis and biological evaluation. *Bioorganic & Medicinal Chemistry Letters*, **2009**, 19, 2022–2028.
157. Sammour, A.E.A., *Tetrahedron*, **20**, 1067 (1967).
158. Sashidhara, K.V.; Kumara, A.; Kumar, M.; Sarkar, J.; Sinha, S. Synthesis and in vitro evaluation of novel coumarin–chalcone hybrids as potential anticancer agents. *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20, (24), 7205-7211.
159. Saydam, G.; Aydin, H.H.; Sahin, F.; Kucukoglu, O.; Erciyas, E.; Terzioglu, E.; Buyukkececi, F.; Omay, S.B. Cytotoxic and inhibitory effects of 4,4-dihydroxy chalcone (RVC-588) on proliferation of human leukemic HL-60 cells. *Leukemia Research*, **2003**, 27, 57–64.
160. Schobert, R.; Biersack, B.; Dietrich, A.; Knauer, S.; Zoldakova, M.; Fruehauf A.; Mueller, T. Pt(II) Complexes of a Combretastatin A-4 Analogous Chalcone: Effects of Conjugation on Cytotoxicity, Tumor Specificity, and Long-Term Tumor Growth Suppression. *J. Med. Chem.*, **2009**, 52, 241–246.
161. Seely, H.W. and Van Demark, P.J. *Microbes in Action: A Laboratory Manual c Microbiology*, D.B. Taraporewala Sons and Co., Bombay. 55 (1975).
162. Seham Hassan Y, Synthesis and biological activity of some new pyrazoline and pyrimidine derivatives, *J. Braz. Chem. Soc.*, 22(7): 1286-1298, (2011).
163. Seo, S.Y.; Sharma, V.K.; Sharma, N.; Mushroom tyrosinase: recent prospects. *J. Agric. Food Chem.*, **2003**, 51, 2837–2853.
164. Seo, W.D.; Ryu, Y.B.; Curtis-Long, M.J.; Lee, C.W.; Ryu, H.W.; Jang, K.C.; Park, K.H. Evaluation of anti-pigmentary effect of synthetic sulfonylamino chalcone. *European Journal of Medicinal Chemistry*, **2010**, 45, 2010–2017.
165. Sham M Sondhia, Monica Dinodiaa, Reshma Rania, Rakesh Shuklab, Ram Raghurib. Pyrimidine derivatives Synthesis, anti-inflammatory and analgesic activity evaluation of some. *Indian J Chem* 2009;49(B):273-281.

166. Sharma S., Kaur S., Bansal T., Gaba J. Chemical Science Transactions, 2014, 3(3), 861-875.
167. Sharma, A.; Chakravarti, B.; Gupt, M.P.; Siddiqui, J.A.; Konwar, R.; Tripathi, R.P. Synthesis and anti breast cancer activity of biphenyl based chalcones. *Bioorganic & Medicinal Chemistry*, **2010**, 18, 4711–4720.
168. Sievert, D.M.; Boulton, M.L.; Stoltman, G.; Johnson, D.; Stobierski, M.G.; Downes, F.P.; Somsel, P.A.; Rudrik, J.T.; Brown, W.; Hafeez, W.; Lundstrom, T.; Flanagan, E.; Johnson, R.; Mitchell, J.; Chang, S. *Staphylococcus aureus* resistant to vancomycin - United States *MMWR*, **2002**, 51, 565-567.
169. Simirgiotis, M.J.; Adachi, S.; To, S.; Yang, H.; Reynertson, K.A.; Basile, M.J.; Gil, R.R.; Weinstein, I.B.; Kennelly, E.J. Cytotoxic chalcones and antioxidants from the fruits of *Syzygium samarangense* (Wax Jambu). *Food Chemistry*, **2008**, 107, 813–819.
170. Singh Vinayaditya, Argal Ameeta, Mishra Vikash, Raghuvanshi Ramsneh, Agnihotri Savita, Synthesis, structural analysis & biological evaluation of anticonvulsant activity of pyrazole derivatives containing thiourea, *Inter. J. Res. Phar. Sci.*, 1(3): 125-146, (2011).
171. Sivakumar, P.M.; Seenivasan, S.P.; Kumar V.; Doble, M. Synthesis, antimycobacterial activity evaluation, and QSAR studies of chalcone derivatives. *Bioorganic & Medicinal Chemistry Letters*, **2007**, 17, 1695–1700.
172. Solankee, A.; Kapadia, K.; C' iric', A.; Sokovic', M.; Doytchinova, I.; Geronikaki, A. Synthesis of some new S-triazine based chalcones and their derivatives as potent antimicrobial agents. *European Journal of Medicinal Chemistry*, **2010**, 45, 510–518.
173. Soni, N., Pande, K., Kalsi, R., Gupta, T.K., Parmar, S.S. and Barthwal, J.P. *Res. Commun. Chem. Pathol. Pharm.*, 56, 129 (1987).
174. Sonmez, F.; Sevmezler, S.; Atahan, A.; Ceylan, M.; Demir, D.; Gencer, N.; Arslan, O.; Kucukislamoglu, M. (2011). Evaluation of new chalcone derivatives as polyphenol oxidase inhibitors. *Bioorg. Med. Chem. Lett.* 21, 7479-7482.
175. Sreedhar NY, MR Jayapal, K Seenivasa Prasad and P Reddy Prasad. *Res. J. Pharm Bio. Chemical Sci.* 2010; 1(4): 480-484.
176. Srinivasan, B.; Johnson, T.E.; Lad, R.; Xing, C. Structure-Activity Relationship Studies of Chalcone Leading to 3-Hydroxy-4,3',4',5'-tetramethoxychalcone and Its Analogues as Potent Nuclear Factor KB Inhibitors and Their Anticancer Activities. *J. Med. Chem.*, **2009**, 52, 7228–7235.
177. Sunal, R., Gumusel, B. and Kayaalp, S.O. *Pharmacol Biochem. Behav.*, 49, 891 (1994).
178. Svetaz, L.; Tapia, A.; Lopez, S.N.; Furlan, R.L.E.; Petenatti, E.; Pioli, R.; Schmeda-Hirschmann, G.; Zacchino, S.A. Antifungal chalcones and new caffeic acid esters from *Zuccagnia punctata* acting against soybean infecting fungi. *J. Agric. Food Chem.*, **2004**, 52, 3297-3300.
179. Thomas L, David A Willams, Victoria F Roche, Willams S Zito. Foyes Principle of Medicinal chemistry. 6th ed. Newyork: Lippincott publishers; 1998.
180. Tomar, V., Bhattacharjee, G.; Kamaluddin, Rajakumar, S.; Srivastava, K.; Puri, S.K. Synthesis of new chalcone derivatives containing acridinyl moiety with potential antimalarial activity. *European Journal of Medicinal Chemistry*, **2010**, 45, 745–751.
181. Tsukiyama, R.I.; Katsura, H.; Tokuriki, N.; Kobayashi, M. Antibacterial activity of licochalcone A against spore-forming bacteria. *Antimicrob. Agents Chemother.*, **2002**, 46, 1226-1230.
182. Tu, H.Y.; Huang, A.M.; Hour, T.C.; Yang, S.C.; Pu, Y.S.; Lin, C.N. Synthesis and biological evaluation of 2',5'-dimethoxychalcone derivatives as microtubule-targeted anticancer agents. *Bioorganic & Medicinal Chemistry*, **2010**, 18, 2089–2098.
183. Turner, R.A. Screening Methods in Pharmacology. Demic Press, New York, 152 (1965).
184. Umesha KB, Rai KML, Harish Nayaka MA, Antioxidant and antimicrobial activity of 5-methyl-2-(5-methyl-1,3-diphenyl-1Hpyrazole-4-carbonyl)-2,4-dihydro-pyrazol-3-one, *Int. J. Biomed. Sci.*, 5(4): 359-368, (2009).
185. Vane Jr. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat. New. Biol* 1971; 231:232–235.
186. Vergiya, V. D., Kothari, S. and Verma, B.L., *Ind. J. Het. Chem.*, **13**, 105 (2003).
187. Vogel, S.; Ohmayer, S.; Brunner, G.; Heilmann, Natural and non-natural prenylated chalcones: Synthesis, cytotoxicity and anti-oxidative activity. *J. Bioorganic & Medicinal Chemistry*, **2008**, 16, 4286–4293.
188. Wanare, G.; Aher, R.; Kawathekar, N.; Ranjan, R.; Kaushik, N.K.; Sahal, D. Synthesis of novel α -pyranochalcones and pyrazoline derivatives as *Plasmodium falciparum* growth inhibitors. *Bioorg. Med. Chem. Lett.*, **2010**, 20, 4675-4678.
189. Whitaker, J.R., Polyphenol oxidase. In: Wong, D.W.S. (Ed.), Food Enzymes, Structure and Mechanism. Chapman & Hall, New York, **1995**, 271–307.
190. Winter, C.A., Risley, E.A. and Nuss, G.W. *J. Pharmacol. Exp. Ther.*, 141, 369 (1963).
191. Winter, C.A., Risley, E.A. and Nuss, G.W. *Pro. Soc. Exp. Biol. Med.*, **III**, 544(1962).

192. Wright GD. Bacterial resistance to antibiotics: Enzymatic degradation and modification. *Ad Drug Delivery Reviews*. 2005; 57:1451-1470.
193. Wu, X.; Wilairat, P.; Go, M. Antimalarial Activity of Ferrocenyl Chalcone. *Bioorg. Med. Chem. Lett.*, **2002**, 12, 2299-2302.
194. Xia, Y.; Yang, Z.Y.; Xia, P.; Bastow, K.F.; Nakanishi Y.; Lee, K.H. Antitumor Agents. Part 202: Novel 20-Amino Chalcones: Design, Synthesis and Biological Evaluation. *Bioorganic & Medicinal Chemistry Letters*, **2000**, 10, 699-701.
195. Yadav, H.L.; Gupta, P.; Pawar, R.S.; Singour, P.K.; Patil, U.K. Synthesis and biological evaluation of anti-inflammatory activity of 1,3 diphenyl propenone derivatives. *Med. Chem. Res.*, **2010**, 20, 461-465.
196. Yenesew, A.; Duli, M.; Derese, S.; Midiwo, J.O.; Heydenreich, M.; Peter, M.G.; Akala, H.; Wangui, J.; Liyala, P.; Waters, N.C. *Phytochemistry*, **2004**, 65, 3029-3032.
197. Yuvaraj S, Sunith DK, Ahmed Riyaz TK, Soumya EN, Biji PK, Prajitha PP, Synthesis, analysis and antibacterial evaluation of pyrazole derivative, *Hygeia*, 1(1): 36-37, (2009)
198. Zeitlin, I.J., Al-Haboubi. and Hussain, A. *Eur. J. Pharmacol.*, 88, 169 (1983).
199. Zhai, L.; Chen, M.; Blom, J.; Theander, T.G.; Christensen, S.B.; Kharazmi, A. The antileishmanial activity of novel oxygenated chalcones and their mechanism of action. *Journal of Antimicrobial Chemotherapy*. *J. Antimicrob. Chemother.*, **1999**, 43, 793-803.
200. Zhang, L.R.; Chen, W.; Li, X. A novel anticancer effect of butein: Inhibition of invasion through the ERK1/2 and NF- κ B signaling pathways in bladder cancer cells. *FEBS Letters*, **2008**, 582, 1821-1828.
201. Zhao, F.; Nozawa, H.; Daikonnya, A.; Kondo, K.; Kitanaka, S. Inhibitors of nitric oxide production from hops (*Humulus lupulus* L.). *Biol. Pharm. Bull.*, **2003**, 26, 61-65.
202. Zhao, L.M.; Jin, H.S.; Sun, L.P.; Piao H.R.; Quan, Z.S. Synthesis and evaluation of antiplatelet activity of trihydroxychalcone derivative. *Bioorganic & Medicinal Chemistry Letters*, **2005**, 15, 5027-5029.