CHEMICAL AND PHARMACOLOGICAL EVOLUTION OF SOME SYNTHESIZED CHALCONES AND HETERO CYCLIC COMPOUNDS

Geeta N Lodhi and Amit Nayak

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 a generic term given to compounds bearing the 1,3-diyarylprop2-1-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 $a,b$-unsaturated carbonyl system (Dhar, 1981). Microorganisms are a heterogeneous group of several distinct classes of living beings. They were classified under third kingdom, the Prostata. Based on differences in cellular organization and biochemistry, the kingdom prostata 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.

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).

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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-diarylprop-2-en-1-one, which can be functionalyzed 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 ringings are joined by a three carbon 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 widespread 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 form 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).
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 antioxidant assay in which *isoliquiritigenin* (60), and *paratocarpin B* (61) were found to be the most potent anti-oxidant agents (Chin et al. 2007).

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).

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 monoxygenase), 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 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 tetrahydroxylchalcones 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 0.02µM, 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).

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).

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 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
   1. Physical constant (colour, mp)
   2. Thin layer chromatography (TLC)
   3. Infrared spectroscopy (IR)
   4. Nuclear magnetic resonance spectroscopy
   5. Mass spectrometry (MS)
   6. 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), $^1$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 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 $^1$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.

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**Fig. 1** - The synthesis of the designed compounds 1a-1h, 2a-2h, 3a-3h (i) Me$_2$CO, 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.

| S.No | Comp. No. | R₂ | R₃ | R₄ | R₅ |
|------|-----------|----|----|----|----|
| 1    | 2a        | 3a | -  | OCH₃| -  |
| 2    | 2b        | 3b | -  | OCH₃| OH |
| 3    | 2c        | 3c | OCH₃| -  | OCH₃|
| 4    | 2d        | 3d | -  | OCH₃| OCH₃|
| 5    | 2e        | 3e | OCH₃| -  | -  |
| 6    | 2f        | 3f | Cl  | -  | Cl |
| 7    | 2g        | 3g | OCH₃| OCH₃| OCH₃|
| 8    | 2h        | 3h |     |    |    |
| 9    | 2i        | 3i | -  | OCH₃| -  |
| 10   | 2j        | 3j | -  | OCH₃| OH |
| 11   | 2k        | 3k | OCH₃| -  | OCH₃|
| 12   | 2l        | 3l | -  | OCH₃| OCH₃|
| 13   | 2m        | 3m | OCH₃| -  | -  |
| 14   | 2n        | 3n | Cl  | -  | Cl |
| 15   | 2o        | 3o | OCH₃| OCH₃| OCH₃|
| 16   | 2p        | 3p |     |    |    |

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

![Diagram](https://example.com/diagram.png)

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

Yield 3.3 g, 58%. White solid; mp 272-274 °C;IR(KBr) \( \nu_{\text{max}} \text{cm}^{-1} \) 3372 (N-H), 3056 (Ar-C=H), 2962 2872 (C-H), 1711 (COCH3), 1645 (C=O), 1614, 1534, 1461 (Ar C=C), 1515, 1290, 1185 (ArC-O), 756, 687 (Ar); \( ^1\text{H-NMR (DMSO-d6, 400 MHz):} \delta_H \) 9.12 (br s, 1H, NH), 8.91 (br s, 1H, NH); 8.18 (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 ).

![Diagram](https://example.com/diagram.png)

Figure :Scheme for synthesis of 3’-N[2’”-dichlorophenyl] sulfonyl-amide] acetophenone

A mixture of 3-aminacetophenone (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); \( ^1\text{H-NMR:} \delta_H \) 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.
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.
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) $\nu_{\text{max}}$/cm$^{-1}$: 3414 (O-H), 1665 (N=C=O), 1596 (Ar C=C), 1260, 1092 (C=O), 1108 (C=Cl), 3045, 2956 (C-H), 1502, 1465, 922, 816, 798 (Ar); $^1$H-NMR, $\delta$ 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), 3.89 (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 $m/z$: 511.54 [M +H]$^+$; Analysis Calcd. (%) for C$_{28}$H$_{22}$ClN$_5$O$_3$: C, 65.69; H, 4.33; N, 13.68; Found: C, 65.38; H, 4.18; N, 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) $\nu_{\text{max}}$/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, $\delta$ 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$_x$), 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$_5$O$_4$: C, 64.27; H, 4.46; N, 12.92; Found: C, 64.36; H, 4.26; N, 12.71
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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”), 3.18 (1H, dd, J 17.1 and 4.3, H-3”); FAB-MS m/z: 511.54 [M +H]+; Analysis Calcd. (%) for C_{28}H_{22}ClN_{5}O_{3}: C, 65.69; H, 4.33; N, 13.68; Found: C, 65.38; H, 4.18; N, 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) \( \tilde{\nu} \)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, \( \delta \) 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”), 6.75-6.94 (3H, m, H-2”, 5”, 6”), 3.83 (3H, s, OCH\(_3\)–3”), 3.10 (1H, dd, J 17.8 and 4.8, 4-H’); FAB-MS m/z: 541.31 [M +H]+; Analysis Calcd. (%) for C_{29}H_{24}ClN_{5}O_{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) \( \tilde{\nu} \)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, \( \delta \) 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 and 6.2, H-5), 3.93 (1H, dd, J 17.5 and 11.6, 4-H”), 3.83 (3H, s, OCH\(_3\)-2”, 4”), 3.11 (1H, d, J 17.5 and 4.6, 4-H’); FAB-MS m/z: 556.31 [M +H]+; Analysis Calcd. (%) for C_{30}H_{26}ClN_{5}O_{4}: C, 64.27; H, 4.46; N, 12.71; Found: C, 64.39; H, 4.17; N, 12.25

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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) $\nu_{\text{max}}$/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, $\delta$ 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 12.0, H-12, 14), 7.80 (1H, d, J 6.7, 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 6.5, H-6"), 6.60 (2H, t, J 6.5, 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-Hy), 3.72 (6H, s, OCH$_3$-3",4"), 3.18 (1H, dd, J 17.5 and 4.6, 4-Hx); FAB-MS $m/z$: 556.16 [M +H]$^+$; Analysis Calcd. (%) for C$_{30}$H$_{26}$ClN$_5$O$_4$: 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, $^1$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.

| S.No. | Compound | Conc. µg/ml | Absorbance 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-picryl hydrazyl) reduction method Antioxidant activity of synthesized compounds by DPPH method

| Sl.No | Compound | % Inhibition | IC$_{50}$ DPPH Method ± SEM |
|-------|----------|--------------|-----------------------------|
| 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               |
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. flavus*. 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* |
| 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 |
| 2n        | 23 | 27 | 21 | 26 | 20 | 22 |
| 2o        | 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*.

### 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.

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

| S.No | Comp. No. | R<sub>2</sub> | R<sub>3</sub> | R<sub>4</sub> | R<sub>5</sub> |
|------|-----------|-------------|-------------|-------------|-------------|
| 1    | 2a        | 3a          | OCH<sub>3</sub> | -           | -           |
| 2    | 2b        | 3b          | OCH<sub>3</sub> | OH          | -           |
| 3    | 2c        | 3c          | OCH<sub>3</sub> | OCH<sub>3</sub> | -           |
| 4    | 2d        | 3d          | OCH<sub>3</sub> | OCH<sub>3</sub> | -           |
| 5    | 2e        | 3e          | OCH<sub>3</sub> | -           | Cl          |
| 6    | 2f        | 3f          | Cl           | -           | Cl          |
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.

1. Antifungal activity
2. 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 5.1 and 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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