CHAPTER 5

SYNTHESIS AND ANTI-INFLAMMATORY EVALUATION OF INDOLE DERIVATIVES

Section A: Microwave-Assisted Solvent-Free Synthesis of Indolylchalcones and pyrazolines

*(Green Chemistry Letters and Reviews 4, 2011, 63-68)*

5.1. REVIEW AND LITERATURE

In recent years, green chemistry has been focus of considerable attention and is becoming an increasingly popular technology.\(^1\) The aim of green chemistry is to reduce chemical-related impacts on human health and virtually eliminate contamination of the environment through dedicated sustainable prevention program. Therefore, several newer strategies such as solvent-free (dry media), solid-supported with and without microwave (MW) irradiation,\(^2\)-\(^6\) mechanochemical mixing (grinding),\(^7\)-\(^9\) use of room temperature ionic liquids,\(^10,11\) supercritical carbon dioxide,\(^12\) and water\(^13\) as reaction media and many more techniques include approaches for the creation of ‘‘benign-by-design’’ are now accepted worldwide by different researchers for the synthesis of a variety of organic compounds. The processes which are designed by green routes help in the promotion of resource and energy utilization efficiently. It involves low level of waste, and is inherently safe making the processes economically and environmentally beneficial.

In recent years, Microwave-assisted organic reaction enhancement (MORE) is well-established technique for rapid and efficient synthesis of variety of heterocycles particularly from the viewpoint of green chemistry. It provides a safe, clean and convenient way to heat reactions to elevated temperatures, accelerates many syntheses
providing selective activation and allows fast optimization of chemical reactions compared to conventional heating. Generally, most of the organic synthesis are carried out by conductive heating with an external heat source such as Bunsen burner, hot plate mantle, water bath, oil bath etc. This technique is comparatively slow and inefficient for transferring energy into the system. It depends on the thermal conductivity of the various materials that must be penetrated and results in the temperature of the vessel being higher than that of the reaction mixture leading to formation of side product or decomposition of product, substrate and reagent. In microwave heating, microwave irradiation passes through the walls of the reaction vessel and produces efficient internal heating by direct coupling of microwave energy with molecules (solvent, reagents, catalysts) that are present in the reaction mixture by avoiding the local overheating at the reaction walls, which can lead to high product yield with less side product. Molecules with a permanent dipole that are subjected to the high frequency oscillating electromagnetic field associated with microwaves will try to align themselves with this field. As the field oscillates, these molecules are continuously aligning and realigning with this field. The rapid motion and resulting intermolecular friction cause intense internal heat that can increase up to 10 °C per second. Due to this rapid increase in temperature the heating profile is different from conventional thermal heating and this is the main contributing factor to accelerate the rate of reactions under microwaves irradiation. Another phenomenon encountered when performing microwave heating is the specific microwave effect. This can be expected when the polarity is increased during the reaction from the ground state to the transition state. When stabilization by dipole-dipole electrostatic interactions of the transition state is more effective than that of the ground state, this results in an enhancement of reactivity by
lowering the activation energy. It also provides an opportunity to work with open vessels, thus, avoiding the risk of high pressure and hazards of inflammable solvents.\textsuperscript{15} Microwave technologies have also found especially extensive application in medicinal chemistry in the field of drug discovery processes.\textsuperscript{16}

Chalcone or 1,3-diaryl-2-propene-1-ones, are essential group of natural as well as synthetic products with widespread distribution in fruits, vegetables, spices, tea and soy based foodstuff and has been subject of great interest for possessing interesting pharmacological activities.\textsuperscript{17} Chemically, chalcones consist of open-chain flavanoids in which two aromatic or heteroaromatic rings are joined by three carbons, \(\alpha,\beta\)-unsaturated carbonyl system. The presence of a reactive \(\alpha,\beta\)-unsaturated keto function in chalcones is found to be responsible for their biological activities such as antimicrobial,\textsuperscript{18} anti-inflammatory,\textsuperscript{19} anticancer,\textsuperscript{20} cytotoxic,\textsuperscript{21} chemo preventive,\textsuperscript{22} antilieshmanial,\textsuperscript{23} antinociceptive,\textsuperscript{24} antiproliferative,\textsuperscript{25} antimalarial,\textsuperscript{26} antiviral\textsuperscript{27} anti–HIV,\textsuperscript{28} antioxidant\textsuperscript{29} etc. Due to this diversity of bioactivity, chalcone could be considered a ‘privileged structure’, as described by Evans and coworkers.\textsuperscript{30} Chalcones also belong to the class of the anthochlor pigments which usually give yellow to orange colours to the tissues in which they are located. Although chalcones are not responsible for pigmentation in the most yellow-coloured flowers, but they are still attractive to insects and in such a way they contribute to the flowers’ pollination\textsuperscript{31}. Some of the synthesized chalcones with important biological activities are highlighted below.
5.1.1. Antilieshmanial Chalcones

Mei-Lin Go and his co-workers synthesized different substituted chalcones and studied their antilieshmanial activity.\(^\text{32}\)

\[
\text{\includegraphics[width=0.8\textwidth]{chalcones.png}}
\]

\[ \text{R} = 4-\text{CH}_3, 4-\text{Cl}, 3-\text{Cl}, 2,4- \text{F}, 4-\text{NO}_2, 4-\text{OCH}_3, 3-\text{Quinoliny}, 4-\text{Quinoliny} \]

5.1.2. Antimicrobial activity

A. Geronikaki et al\(^\text{33}\) synthesized novel thiazole based chalcone and evaluated their antimicrobial activities.

\[
\text{\includegraphics[width=0.4\textwidth]{thiazole_chalcone.png}}
\]

\[ \text{R} = \text{H}, 4-\text{NO}_2, 4-\text{OMe}, 3-\text{Cl}, 3-\text{OMe} \]

Baviskar et al\(^\text{34}\) have synthesized novel chalcones and studied their antimicrobial activities.

\[
\text{\includegraphics[width=0.8\textwidth]{baviskar_chalcone.png}}
\]

\[ \text{R} = \text{C}_\text{6H}_4, 3-\text{NO}_2\text{C}_\text{6H}_4, 4-\text{N}(\text{CH}_3)_2, \text{C}_\text{6H}_4, 4-\text{OCH}_3\text{C}_\text{6H}_4, 3,4,5-(\text{OCH}_3)_2, \text{C}_\text{6H}_4, 4-\text{OHC}_\text{6H}_4, 3-\text{BrC}_\text{6H}_4, 3-\text{FC}_\text{6H}_4 \]
Batovska and his co-workers\textsuperscript{35} have prepared chalcones and studied their antifungal activities.

\[ \text{Images of chalcones with structures} \]

\subsection*{5.1.3. Antioxidant chalcones}

Rayees Ahmad et al\textsuperscript{36} synthesized novel chalcones and evaluated for antioxidant activity.

\[ \text{Images of antioxidant chalcones with structures} \]

\subsection*{5.1.4. Anti-inflammatory chalcones}

Kumar and et al\textsuperscript{37} have synthesized heterocyclic indole derivatives and reported anti-inflammatory activity\textsuperscript{[72]}.

\[ \text{Images of anti-inflammatory chalcones with structures} \]

Okunrobo and co-workers\textsuperscript{38} have prepared novel chalcone and studied their anti-inflammatory and gastroprotective activities.
Ramaa et al.\textsuperscript{39} have prepared fluorinated chalcones and studied their anti-inflammatory activities.

\[ \text{Ramaa et al.}\textsuperscript{39} \]

5.1.5. Anticancer chalcones

Khan et al.\textsuperscript{40} synthesized novel boronic and bis chalcones and evaluated their anticancer activity.

\[ \text{Khan et al.}\textsuperscript{40} \]

5.1.6. Antimalarial chalcone

Liu et al.\textsuperscript{41} studied invitro antimalarial activity of some novel cahlcone.

\[ \text{Liu et al.}\textsuperscript{41} \]

Chalcones are good accessible starting materials for the synhesis of various biologically important heterocyclic compounds such as benzothiazepine,\textsuperscript{42} pyrazolines,\textsuperscript{43} 1,4-diketones,\textsuperscript{44} flavones,\textsuperscript{45} pyrazoles,\textsuperscript{46} dihydropyrimidines,\textsuperscript{46} isoxazolines\textsuperscript{46} etc. Additionally,
these are also important intermediates in many addition reactions of nucleophiles due to inductive polarization of carbonyl group present at the β-position. Thus, the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. Therefore, several strategies for the synthesis of these systems have been reported in the literature. The most common method involves the Claisen-Schmidt condensation of equimolar quantities of substituted acetophenone with substituted benzaldehyde in the presence of an aqueous alcoholic alkali. A number of acid-catalyzed methods are also reported in the literature which includes the use of AlCl₃, dry HCl, Zn(bpy)(OAc)₂, TiCl₄, Cp₂ZrH₂/NiCl₂ and RuCl₃. Recently various modified methods for the synthesis of chalcones has been also reported in the literature, such as using SOCl₂, lithium nitrate, amino grafted zeolites, zinc oxide, water, Na₂CO₃, PEG- 400, silica-sulfuric acid, ionic liquid and microwave irradiation. Unfortunately, many of these methods have drawbacks such as use of organic solvents either during condensation reactions or during isolation of the products by way of extraction, use of expensive stoichiometric amount of reactants, use of hazardous and environmentally polluting solvents, low yields, extended time, tedious procedure etc. Although, several modifications have also been made to counter these problems, yet, the development of selective and better strategies for the synthesis of α, β-unsaturated carbonyl compounds is still in high demand.
5.2. Some recent examples for the synthesis of Chalcones under green environment

(a) *Solvent-free synthesis of chalcone under Ultrasound irradiation catalyzed by alkaline doped carbons*

Ultrasound irradiation has been increasingly used in organic synthesis in last three decades. Comparing with traditional methods, this method is more conveniently and easily controlled. Recently, Aranda et.al\(^{65}\) presented a green protocol for the Claisen–Schmidt condensation between benzaldehyde and acetophenone catalyzed by alkaline-doped carbons (solid phase) under ultrasonic activation in the absence of any solvent to yield the chalcone in excellent yields.

\[
\begin{align*}
\text{CHO} & \quad + \quad \text{O} \\
\text{Activated carbons} & \quad \text{Ultrasound activation} \\
\text{O} & \quad + \quad \text{O}
\end{align*}
\]

(b) *I2-Al2O3 mediated synthesis of chalcone under microwave irradiation*

A simple and convenient method for the synthesis of chalcones using I2-Al2O3 under microwave irradiation has been reported.\(^{66}\) Reaction completed in short time period (80sec) with excellent yields (79-95%) of the products.

\[
\begin{align*}
\text{R} & \quad + \quad \text{O} \\
\text{I2-Al2O3, MW} & \quad \text{80 Sec} \\
\text{R} & \quad + \quad \text{O}
\end{align*}
\]

R = H, 4-OH, 4-Cl, 4-NO2, 4-OMe, 3,4-OH, 3-OMe, 2NO2, 3,4-OCH3O
R' = H, 2-OH, 4-OH, 4-OMe, 2,4-OMe

(c) *Bronsted acidic Ionic liquid mediated synthesis of chalcones*\(^{55}\)

According to Liu et.al\(^{67}\) the –SO3H- functionalized acidic ionic liquids was found to be an efficient dual catalyst and solvent for Claisen–Schmidt condensation of benzaldehyde and acetophenone by providing an easy synthesis of chalcones under mild reaction conditions.
(d) Bismuth (III) chloride mediated synthesis of chalcones under solvent-free condition

Sandhu et al\textsuperscript{68} reported an environmentally benign protocol for the synthesis of chalcones by the Claisen Schmidt condensation of aldehydes with ketones using eco-friendly, non-toxic bismuth(III)chloride catalyst under solvent-free condition. In this protocol, the reaction time is very short, yields are high and there are no other pollutants formed.

(e) Synthesis of chalcones using C-200 as solid support under grinding conditions

Kumar et al\textsuperscript{69} reported an easy, safe and effective method for the synthesis of pyrazolyl chalcones by grinding pyrazole aldehydes and acetophenones in the presence of activated barium hydroxide (C-200) in high yield within short span of time.
Among the various derivatives of chalcones, the pyrazoline nucleus is a ubiquitous feature of various compounds possessing many pharmacological and physiological activities and are present in a number of pharmacologically active molecules such as phenazone/amidopyrene/methampyrone (analgesic and antipyretic), azolid/tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric). The pyrazoline function is quite stable and has inspired chemists to utilize this stable fragment in bioactive moieties to synthesize new compounds such as cyclopropane and pyrazole. The discovery of this class of drugs provides an outstanding case history of modern drug development and points out the unpredictability of biological activity from structural modification of a prototype drug molecule. Literature survey reveals that numerous pyrazoline derivatives have found their clinical applications as non-steroidal anti-inflammatory drugs (NSAIDs) such as felcobuzone, famprofazole, and ramifenazone. Certain compounds containing the pyrazoline moiety have been demonstrated to have an important therapeutic potential, such as anti-inflammatory, antibacterial, antipyretic, anticonvulsant, antidepressant, antihypertensive, antioxidant, antitumor, anticancer and antidiabetic agents etc. Some recently explored pyrazoline derivatives with important biological activity are listed below.

5.2.1. Antimicrobial activity

Bharmal et al synthesized some pyrazoline derivatives as biologically active agents. All the compounds showed antimicrobial activity against S. typhosa and A. niger.
Basawaraj et al\textsuperscript{85} synthesized some \textit{1\textsubscript{H}}-pyrazolines bearing benzofuran as biologically active agents. They exhibited high antimicrobial activity against \textit{S. aureus} and moderate activity against \textit{E. coli}.

5.2.2. \textit{Antinociceptive pyrazolines}

Kaplancikli et al\textsuperscript{86} synthesized \textit{1-}[(\textit{Benzoxazole/Benzimidazole-2-yl}) thioacetyl] pyrazoline derivatives and evaluated for antinociceptive activity.

5.2.3. \textit{Antidepressant pyrazolines}

Palaska et al\textsuperscript{87} synthesized ten new 3, 5-diphenyl-2- pyrazoline derivatives and evaluated their antidepressant activities by the ‘Porsolt Behavioural Despair Test’ on Swiss-Webster mice.
5.2.4. Antimycobacterial pyrazolines

Ozdemir et al$^{88}$ synthesized new 1-[(N, N-disubstituted thiocarbamoylthio) acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives and evaluated for in vitro antimycobacterial activity against *M. tuberculosis* H37Rv.

![Antimycobacterial pyrazoline structure](image)

Mamolo et al$^{89}$ synthesized 5-aryl-1-isonicotinoyl-3- (pyridin-2-yl)-4, 5-dihydro-1*H*-pyrazole derivatives and tested for their in vitro antimycobacterial activity. The compounds showed an interesting activity against a strain of *M. tuberculosis* and a human strain of *M. tuberculosis* H4.

![Pyrazole derivative structure](image)

5.2.5. Analgesic and Anti inflammatory pyrazoline

Khode S et al.$^{90}$ synthesized a novel series of 5-(substituted)aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines and evaluated significant anti-inflammatory activity in acute inflammation such as carrageenan induced paw edema in rat model.

![Pyrazoline structure](image)

\[X = \text{C}_6\text{H}_5, 4-\text{OMe-C}_6\text{H}_4, -\text{CH}=\text{CH}-\text{C}_6\text{H}_4, 4-\text{Cl-C}_6\text{H}_4, 4-\text{OH}\]
Panneer Selvam et al\cite{91} synthesized a series of 1-(4-substitutedphenyl)-3-phenyl-1H-pyrazole-4-carboxaldehyde and tested for their anti-inflammatory and analgesic activities.

\[
\begin{align*}
\text{R} & = \text{H, Br, Cl, F, NHCOCH}_3 \\
\end{align*}
\]

5.2.6. Antimalarial pyrazolines

B.N. Acharya et al\cite{92} synthesized a series of 1,3,5-trisubstituted pyrazolines and evaluated for in vitro antimalarial efficacy against chloroquine sensitive (MRC-02) as well as chloroquine resistant (RKL9) strains of *Plasmodium falciparum*.

Pyrazoline, derivatives as typical ICT (Intramolecular Charge Transfer) compounds are known as fluorescent brightening agent, which exhibit excellent fluorescent property\cite{93}. It can absorb light of 300-400 nm and emit blue fluorescence. Pyrazoline contains two nitrogen atoms, one of which forms an electron-donating p-π conjugated system. Therefore, it is able to function as hole-transporting material\cite{5} used in Organic electroluminescent devices (OELD).\cite{94} A variety of methods have been reported for the preparation of this privileged class of compounds but one of the most convenient method for the synthesis of 2-pyrazolines was described by Fischer and Knoevenagel in the late nineteenth century by the reaction of α, β-unsaturated ketones (acrolein) with phenyl
hydrazine in acetic acid under refluxing condition." However depending on the reactivity of molecules and need of the chemist they have synthesized the pyrazolines under different solvent media & acidic or basic conditions. Later, Auwers et al. corroborated that the product of this reaction was 1-phenyl 2-pyrazoline. During the last century, after these pioneering studies, numerous 2-pyrazolines were synthesized by the reaction of α, β-enones with hydrazines. This simple and convenient procedure has remained one of the most popular method for the preparation of 2-pyrazolines.

5.3. Some recent examples for the synthesis of pyrazolines under green environment

(a) Synthesis of 1,3,5-triaryl-2-pyrazolines under ultrasound irradiation

Ji-Tai Li et al. reported an efficient and practical procedure for the synthesis of 1,3,5-triaryl-2-pyrazolines by the reaction of chalcones and phenylhydrazine hydrochloride in sodium acetate-acetic acid aqueous solution under ultrasound irradiation in 83–96% yield in 1.5–2 h.

(b) Synthesis of 3,5-arylated 2-pyrazolines under microwave irradiation

Azarifar et al. demonstrates a rapid, efficient and environmentally friendly method for the synthesis of 3,5-arylated 2-pyrazolines under microwave heating, at 80 °C in excellent yields and the results obtained confirmed the superiority of the microwave irradiation method over the classical heating.
(c) Basic alumina mediated synthesis of pyrazolines under microwave irradiation

A new and efficient synthesis of pyrazoline derivatives was described by Desai et al.\textsuperscript{99} using basic alumina under microwave irradiation. With this environmentally benign approach, the reaction time brought down from hours to minutes along with a yield enhancement.

\[
\text{R} = \text{H, 2-NO}_2, 3-\text{NO}_2, 2-\text{Cl, 4-Cl, 4-\text{N(Me)}_2, 4-\text{OCH}_3, 3-\text{OC}_6\text{H}_5, 4-\text{OCH}_3, 3-\text{OH, 3,4,5(OCH}_3}_3
\]

(d) Synthesis of pyrazolines using Poly(ethylene glycol) (PEG-400) as green solvent

Dawane et al.\textsuperscript{100} prepared a series of 2-pyrazolines by the base catalyzed treatment of appropriate chalcones with 4-(4’-chlorophenyl)-2-hydrazino-thiazole using poly (ethylene glycol) (PEG-400) as a green reaction medium.
5.4. PRESENT WORK

The indole nucleus is an important structure in various natural or synthetic alkaloids and in medicinal chemistry. Indole derivatives have been reported to possess several biological activities including anticancer, antioxidant, antirheumatoidal, anti-HIV, anti-inflammatory, antimicrobial, antiviral and also play a vital role in the immune system. The substituted indoles have been referred to as privileged structures since they are capable of binding to many receptors with high affinity.

Prompted by the above-mentioned biological properties of indoles, chalcones, pyrazolines as well as the utility of microwave irradiation in organic synthesis, it was worthwhile to prepare novel series of indolyl chalcones and their substituted pyrazoline derivatives via microwave irradiation method. The present study also compares the efficacy of reaction techniques under the conventional and the microwave irradiation methods.
5.5. RESULTS AND DISCUSSION

During the present study, the synthesis of indolyl chalcone (192a-c) was carried out by Claisen-Schmidt condensation employing indole-3-carboxaldehyde (137) and heteroaryl active methyl compounds (191a-c) under conventional heating method in the presence of piperidine as a basic catalyst and methanol as solvent. The reaction took longer time period (9-12 h) for completion of reaction with moderate yield (65-70 %) of the products. Keeping in mind the key principles of ‘green chemistry’ and to obtain chalcones in a short span of time with improved yield, the reaction was carried out using microwave irradiation technique under solvent-free condition (Scheme 71). As visualized, the reaction proceeded smoothly under solvent-free condition and the chalcones (192a-c) were obtained with substantial increase in yield (82-92 %) within few minutes (6-13 min) (Table 21). The assigned molecular structures of all indolyl chalcones (192a-c) were based on spectroscopic analysis (IR, 1H NMR and MS) and elemental analysis data. The IR spectrum (Fig. 32) of (192a) showed characteristic absorption band at 3251 cm\(^{-1}\) and 3384 cm\(^{-1}\) due to the presence NH and OH groups of indole and coumarin moiety respectively. The coumarin carbonyl absorption band was present at 1689 cm\(^{-1}\). The 1H NMR spectrum (Fig. 33) showed trans olefinic protons Ha and Hb of α,β-unsaturated carbonyl system as ortho coupled doublets at δ 8.43 (J =16 Hz) and 8.58 (J =16 Hz). The value of spin-spin coupling constant \(J_{ab}\) in the range 15-16 Hz is indicative of the \(E\)-configuration of chalcone for the olefinic bond of the CO-CH=CH group. Four aromatic protons of coumarin and five protons of indole moieties including \(H_A\) proton were discernible in the form of multiplet at δ 7.29-8.21. Further support for the formation of (192a) was provided by mass
spectrum (Fig. 34) which showed molecular ion peak at \( m/z \ 331(M^+) \). The spectral data of other compounds followed similar pattern and are explained in experimental section.

Table 21 Synthesis of indolyl chalcones (192a-c) under conventional heating and Microwave irradiation method.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Conventional heating</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>192a</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>192b</td>
<td>12</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>192c</td>
<td>9</td>
<td>69</td>
</tr>
</tbody>
</table>

Scheme 71. Synthesis of indolyl chalcones (192a-c)

Efforts were made for the synthesis of novel pyrazolines (193a-f) by the reaction of indolyl chalcones with hydrazines both under conventional heating method and microwave irradiation. Under conventional method pyrazolines synthesized by refluxing of indolyl chalcones (192a-c) with hydrazine hydrate (177a) and phenyl hydrazine (177b) in methanol in the presence of catalytic amount of piperidine (Scheme 72). The reaction took longer time (7-15 h) for completion with lower yield (57-68 %) of the products. When the
same reaction was carried out under microwave-irradiation reaction in solvent- and catalyst-free environment, the reaction proceeded efficiently and the reaction time brought down from hours to minutes (5-13 min) with excellent yield of products (76-89%) (Table 22).

Formation of pyrazolines (193a-f) was confirmed on the basis of IR, 1H NMR, and mass spectral analysis. The IR spectrum (Fig. 35) of (193a) showed two broad absorption bands at 3189 cm⁻¹ and 3270 cm⁻¹ due to the presence of NH groups of pyrazoline and indole moieties. The absorption band for the coumarin carbonyl group was discernible at 1680 cm⁻¹. The 1H NMR spectrum (Fig. 36) showed a broad singlet (D₂O exchangeable) at δ 10.35 due to the presence of NH proton of indole moiety. The aromatic region of the spectrum exhibited nine protons in the range δ 7.09-8.11 due to four protons of coumarin and five protons of indole moieties including HA proton. The presence of pyrazoline unit was established by the presence of two doublet of doublets at δ 4.01 (He), 4.16 (Hf) and a triplet at δ 5.41 (Hd). Further evidence for the formation of pyrazoline (193a) was provided by recording the mass spectrum (Fig. 37) which showed molecular ion peak at m/z 345.15 (M⁺).
Table 22 Synthesis of indolyl pyrazolines 193a-f under conventional heating and Microwave irradiation method.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Conventional heating</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>193a</td>
<td>7</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>193b</td>
<td>10</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>193c</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>193d</td>
<td>15</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>193e</td>
<td>11</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>193f</td>
<td>9</td>
<td>68</td>
</tr>
</tbody>
</table>

Scheme 72. Synthesis of pyrazoline derivatives from indolyl chalcones (193a-f)
5.6. CONCLUSION

In search of potentially active molecules containing indole moiety we have developed an efficient, facile, and practically convenient green methodology for the synthesis of indolyl chalcones and corresponding pyrazolines employing microwave irradiation protocol. The notable features such as simplicity in operation, excellent yields of the products, faster reaction rates, and cleaner reaction profiles make the current protocol feasible and attractive.

5.7. EXPERIMENTAL

Melting points of all synthesized compounds were taken in Riechert Thermover instrument and are uncorrected. The IR spectra were recorded on Perkin Elmer RXI spectrometer in KBr. $^1$H NMR spectra were recorded on a Bruker DRX-300 and Bruker Avance II 400 spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-$d_6$/CDCl$_3$ as solvent. FAB mass spectra were obtained on Jeol-SX-102 spectrometer and DART-MS was recorded on a JEOL-Accu TOF JMS-T100LC mass spectrometer having a DART source. Elemental analyses (C, H and N) were conducted using the Elemental vario EL III elemental analyzer and their results were found to be in agreement with the calculated values. 5-Acetyl-1-3-dimethyl barbituric acid and 3-acetyl-4-hydroxycoumarin were synthesized by reported procedures$^{114, 115}$ Other chemicals were of commercial grade and used without further purification. The homogeneity of the compounds was checked by thin layer chromatography(TLC) on glass plates coated with silica gel G254(E. Merck) using chloroform-methanol (3:1) mixture as mobile phase and visualized by iodine vapors. All experiments under microwave irradiation were carried out using an unmodified domestic
microwave oven (National, Model NN-S557WF, 1.3 KW, 2450, multimode equipment, full power).

5.7.1. *Synthesis of indolyl chalcones (192a-c) under conventional heating method*

To a solution of 3-acetyl-4-hydroxy coumarin (1 mmol)/ 5-acetyl-1, 3-dimethyl barbituric acid (1 mmol)/ dehydroacetic acid (191a-c) (1 mmol) in methanol (10 mL) containing 0.2 mL of piperidine was added indole-3-carboxaldehyde (137) (1 mmol). The reaction mixture was heated under reflux on a water bath for 9-12 h. After completion of the reaction (monitored by TLC), the reaction mixture was cooled at room temperature. The solid, thus, obtained was filtered, washed with water, alcohol and dried to afford the (192a-c).

5.7.2. *Synthesis of indolyl chalcones (192a-c) under microwave irradiation method*

A mixture of indole-3-carboxaldehyde (137) (1 mmol), 3-acetyl-4-hydroxy coumarin (1 mmol)/5-acetyl-1,3-dimethylbarbituric acid (1 mmol)/dehydroacetic acid (191a-c) (1 mmol) and piperidine (0.2 mL) was placed in an open pyrex beaker and subjected to microwave irradiation using domestic microwave oven and irradiated for appropriate time till the reaction was completed. The progress of the reaction was monitored by TLC. On completion of the reaction, reaction mixture was slurred in cold water (50 mL) and the yellow solid obtained was filtered, dried and recrystallised from CHCl3-MeOH (2:3) mixture to give (192a-c) in excellent yields.
5.7.3. Spectral data of compounds

2E-1- (4-Hydroxy-1-benzopyran-2-one-3-yl)-3-(1H- indol-3-yl)-2-propene-1-one (192a)

Purified by recrystallization from chloroform-methanol (2:3 v/v) mixture.

Orange crystals

M.p. : >300 °C.

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1689 (C=O), 3251(NH), 3384 (OH).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 7.29-8.21 (m, 9H, Ar-H+H$_A$), 8.43 ($d$,1H, $J$=16 Hz, Ha), 8.58 (d, 1H, $J$=16 Hz, Hb), 8.68 (s, 1H, NH), 19.27(s, 1H, OH).

ESI-MS : m/z 331.13 (M$^+$).

Elemental analysis for

C$_{20}$H$_{13}$NO$_4$ : Calculated C, 72.57; H, 3.98; N 4.23

       Found  C, 72.84; H, 4.02; N, 4.21 %.

2E-1-(1,3-Dimethyl-2,4,6-pyrimidinetrione-5-yl)-3-(1H-indol-3-yl)-2-propen-1-one

(192b)

Purified by recrystallization from chloroform-methanol (2:3 v/v) mixture.

Yellow crystals

M.p. : >300 °C.

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1654 (C=O), 3276 (OH).

$^1$H NMR (400 MHz, DMSO- d$_6$) : $\delta$ (ppm) 3.35 (s, 6H, 2 N-CH$_3$), 7.25- 7.50 (m, 5H, Ar-H+H$_A$), 7.82 (d, 1H, $J$=16.1 Hz, Ha), 8.31 (d,1H, $J$=15.9 Hz, Hb), 11.05(s, 1H, NH).
ESI-MS : \( m/z \ 325.15 \ (M^+) \).

Elemental analysis for \( \text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_4 \) : Calculated C, 62.80; H, 4.65; N, 12.92; Found C, 62.97; H, 4.81; N, 12.90 %.

\((2E)-1-(4\text{-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl})-3-(1\text{-indolyl-3-yl})-2\text{-propene-1-one} \ (192c)\)

Purified by recrystallization from chloroform-methanol (2:3 v/v) mixture.

Light Orange crystals

M.p : 295-298 °C.

IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \) : 1699 (C=O), 3048 (NH), 3170 (OH).

\(^1\text{H} \text{NMR} \ (400 \text{ MHz, DMSO-} \text{d}_6) \) : \( \delta \) (ppm) 2.28 (s, 3H, CH\(_3\)), 5.96 (s, 1H, H\(^5\)), 7.25-7.58 (m, 5H, Ar-H+H\(_A\)), 7.78 (d, 1H, \( J=15.5 \text{ Hz, Ha} \)), 8.13 (d, 1H, \( J=15.4 \text{ Hz, Hb} \)), 11.6 (s, 1H, NH) 18.74 (1H, s, OH).

ESI-MS : \( m/z \ 295.12 \ (M^+) \).

Elemental analysis for \( \text{C}_{17}\text{H}_{13}\text{NO}_4 \) : Calculated C, 69.21; H, 4.43; N, 4.74 Found C, 69.29; H, 4.46; N, 4.70.

5.7.4 Preparation of indolyl pyrazolines (193a-f) under conventional heating method

A mixture of indolylchalcones (192a-c) (2.5 mmol), hydrazine hydrate (177a) (2.5 mmol)/phenyl hydrazine (177b) (2.5 mmol) and 0.1 mL of piperidine was refluxed in methanol on water bath for appropriate time. After completion of reaction (checked by TLC), reaction mixture was cooled at room temperature until yellow color crystals (193a-
f) were obtained. It was filtered, washed with MeOH, dried and recrystallised from CHCl₃-MeOH (2:3 V/V) mixture.

5.7.5. Preparation of indolyl pyrazolines (193a-f) under microwave irradiation method

A mixture of indolyl chalcones (192a-c) (2.5 mmol) and substituted hydrazine (2.5 mmol) (177a-b) were taken in an open Pyrex vessel and irradiated in a microwave oven for the appropriate time until the completion of reaction (monitored by TLC). After completion, the reaction mixture was cooled at room temperature and was poured into cold water (50 mL). The solid as obtained was filtered, dried and recrystallised from CHCl₃-MeOH.

5.7.6. Spectral data

3-(4-Hydroxy-1-benzopyran-2-one-3-yl) - 5-(1H indol-3-yl) pyrazoline (193a)

Purified by recrystallization from chloroform-methanol (2:3 V/V) mixture.

<table>
<thead>
<tr>
<th>Nature of compound</th>
<th>: Pale yellow crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.p.</td>
<td>: 250-253 °C.</td>
</tr>
<tr>
<td>IR (KBr) νmax/cm⁻¹</td>
<td>: 1680 (C=O), 3189 (NH), 3270 (OH).</td>
</tr>
<tr>
<td>¹H NMR (400 MHz, CDCl₃)</td>
<td>: δ (ppm) 4.01 ((1H, dd, J=18.8 Hz, 7.8 Hz, He), 4.16 (1H, dd, J=18.9 Hz, 9.72 Hz, Hf), 5.41 (1H, t, J= 17.9 Hz, Hd), 7.09-8.11 (m, 9H, Ar-H+Hₐ), 10.35 (s, 1H, NH).</td>
</tr>
<tr>
<td>ESI-MS</td>
<td>: m/z 345.15 (M⁺).</td>
</tr>
<tr>
<td>Elemental analysis for</td>
<td>: Calculated C, 69.62; H, 4.38; N, 12.17;</td>
</tr>
<tr>
<td>C₂₀H₁₅N₃O₃</td>
<td>: Found C, 69.59; H, 4.36; N, 12.13 %</td>
</tr>
</tbody>
</table>
1-Phenyl-3-(4-hydroxy-1-benzopyran-2-one-3-yl)-5-(1H indol-3-yl) pyrazoline (193b)

Purified by recrystallization from chloroform-methanol (2:3 V/V) mixture.

Yellow crystals

M.p. : 287-290 °C.

IR (KBr) $\nu_{max}/\text{cm}^{-1}$ : 1695 (C=O), 3058 (NH), 3344 (OH).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 3.80 (1H, dd, J=18.9 Hz, 8.1 Hz, He), 4.32 (1H, dd, J=18.9 Hz, 12.0 Hz, Hf), 5.53 (1H, t, J= 12.0 Hz, Hd), 6.83-8.06 (m, 14H, Ar-H+H$_A$), 8.24 (s, 1H, NH), 14.2 (1H, s, OH).

FAB-MS : $m/z$ 421 (M$^+$).

Elemental analysis for C$_{26}$H$_{19}$N$_3$O$_3$ : Calculated C, 74.17; H, 4.54; N, 9.98;

Found C, 74.29; H, 4.66; N, 9.94 %.

3-(1,3-Dimethyl-2, 4, 6-pyrimidinetrione-5-yl)-3-(1H indol-3-yl) pyrazoline (193c)

Purified by recrystallization from chloroform-methanol (2:3 V/V) mixture.

Yellow crystals

M.p. : 253-255 °C.

IR (KBr) $\nu_{max}/\text{cm}^{-1}$ : 1716 (C=O), 3224 (NH), 3344 (NH).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 3.35 (6H, s, 2N-CH$_3$), 3.95 (1H, dd, J=18.7 Hz, 8.1 Hz, He), 4.16 (1H, dd, J=18.7 Hz, 8.8 Hz, Hf), 5.22 (1H, t, J= 17.1 Hz, Hd), 6.99-7.63 (m, 5H, Ar-H+H$_A$), 10.41 (s, 1H, NH).
ESI-MS : \( m/z \) 339.18 (M⁺).

Elemental analysis for : Calculated C, 60.23; H, 5.05; N, 20.65;

\( \text{C}_{17}\text{H}_{17}\text{N}_{5}\text{O}_{3} \) : Found C, 60.33; H, 5.39; N, 20.63 %.

1-Phenyl-3-(1,3-dimethyl-2,6-pyrimidinetrione-5-yl)-3-(1H-indol-3-yl)-pyrazoline

(193d)

Purified by recrystallization from chloroform-methanol (2:3 V/V) mixture.

Yellow crystals

M.p. : 287-290 °C.

IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \) : 1694 (C=O), 3384 (NH).

\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) : \( \delta \) (ppm) 3.35 (6H, s, 2N-CH\textsubscript{3}), 3.97 (1H, dd, J=18.3 Hz, 8.1 Hz, He), 4.21 (1H, dd, J=18.3 Hz, 8.7 Hz, Hf), 5.17 (1H, t, J= 11.7 Hz, Hd), 7.14-7.66 (m, 11H, Ar-H+H\textsubscript{A}), 8.17 (s, 1H, NH).

ESI-MS : \( m/z \) 415.15 (M⁺)

Elemental analysis for : Calculated C, 66.56; H, 5.10; N, 1.68;

\( \text{C}_{23}\text{H}_{21}\text{N}_{5}\text{O}_{3} \) : Found C, 66.65; H, 5.14, N, 1.65%. 
3-(4-Hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-3-(1H-indolyl-3-yl)-pyrazoline (193e)

Purified by recrystallization from chloroform-methanol (2:3 V/V) mixture.

Yellow crystals

M.p. : 234-237 °C.

IR (KBr) $\tilde{\nu}_{\text{max}}$/cm$^{-1}$ : 1690 (C=O), 3085 (NH), 3199 NH), 3426 (OH).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 2.28 (3H, s, CH$_3$), 3.66 (1H, dd, $J$=19.0 Hz, 6.0 Hz, He), 4.01 (1H, dd, $J$=19.0 Hz, 9.8 Hz, He), 4.87(1H, dd, $J$= 9.7 Hz, 6.0 Hz, Hd), 7.42-8.20 (m, 5H, Ar-H+H$_A$), 12.1 (1H, s, NH).

ESI-MS : $m/z$ 310.17 (M$^+$).

Elemental analysis for C$_{17}$H$_{15}$N$_3$O$_3$ : Calculated C, 66.07; H, 4.89; N, 1.35;
Found C, 66.10; H, 4.96, N, 1.30%.

1-Phenyl-3-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)-3-(1H-indolyl-3-yl)-pyrazoline (193f)

Purified by recrystallization from chloroform-methanol (2:3 V/V) mixture.

Red crystals

M.p. : 238-240 °C.

IR (KBr) $\tilde{\nu}_{\text{max}}$/cm$^{-1}$ : 1695 (C=O), 3078 (NH), 3351 (OH).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 2.28 (3H, s, CH$_3$), 3.68 (1H, dd, $J$=18.8 Hz, 8.0 Hz, He), 4.21(1H, dd, $J$= 18.8 Hz,
12.0 Hz, Hf), 5.47(1H, dd, J = 12.0 Hz, 8.0 Hz, Hd), 6.05(1H, s, Hf), 6.80-7.61 (10H, m, Ar-H+H_A), 8.05 (1H, s, NH), 13.52 (1H, s, OH).

ESI-MS : m/z 386.22 (M+).

Elemental analysis for C_{23}H_{19}N_{3}O_{3} : Calculated C, 71.75; H, 4.97; N, 1.09;

Found C, 71.72; H, 4.99, N, 1.06. %.
Fig. 32. IR spectrum of 192a

Fig. 33. $^1$H NMR spectrum of 192a
Fig. 34. Mass spectrum of 192a

Fig. 35. IR spectrum of 193a
Fig. 36. $^1$H NMR spectrum of 193a

Fig. 37. Mass spectrum of 193a
5.8. REFERENCE


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   (b) Auwers K. V.; Kreuder, A. Ber. 1925, 58, 1974.


Section B: Anti-inflammatory activities

5.9. REVIEW & LITERATURE

Inflammation is a defensive response of body, which induces physiological adaptations to minimize tissue damage and to remove the pathogenic infections. Such mechanisms involve a complex series of cellular and modular events including dilation of arterioles, venules and capillaries with increased vascular permeability and exudation of fluids containing plasma proteins as well as migration of leukocytes into the inflammatory area. A chronic inflammation is however an important contributory factor in morbidity and mortality. At macroscopic level such inflammatory disorders include rheumatoid arthritis, osteoarthritis, inflammatory bowel diseases, retinitis, multiple sclerosis, psoriasis and atherosclerosis.¹

In recent years, there is considerable therapeutic interest in novel anti-inflammatory drugs with mode of action different from that of the classical non-steroidal anti-inflammatory drugs (NSAIDs), mainly for use in patients with arthritis of varying degree of severity. The most prevalent side effects of NSAIDs is the occurrence of gastrointestinal damage such as gastritis, gastric ulcer, and renal toxicity.²⁻⁵ Therefore, the discovery of new and safer anti-inflammatory drugs represents challenging goal for such a research area.⁶ A number of heterocyclic bioactive compounds are used in various traditional systems of medicine to relieve inflammation.⁷ The indole nucleus is present in an astonishing variety of natural products endowed with potent and multiform biological activities. Indole nucleus is the active principle in a number of natural drugs, such as reserpine, strychnine, ergotamine and other alkaloids. Indole and their derivatives have been reported to possess wide spectrum of activities of pharmacological importance.⁸
These pharmacological activities have been the major interest behind the syntheses of the indole and their derivatives. Indole ring also constitutes an important template for drug design such as the classical NSAIDs indomethacin, tanidap and indoxole.\(^9\)

![Chemical structures of Indomethacin, Indoxole, and Tanidap]

In addition, the importance of lead molecules for the discovery of new synthetic drugs, several chemical structures are used as a starting point for chemical modifications in order to improve potency, selectivity or pharmacokinetic parameters. Furthermore, a systematic variation of substituents around the indole ring at 3-position has led to the exploration of a large number of potent biologically active compounds.\(^10\) A literature survey reveals that the compounds with the backbone of chalcone and pyrazolines attached to an indole nucleus may show an improved anti-inflammatory activity in carrageenan induced inflammation model.\(^11\)

Edema formation, leukocyte infiltration and granuloma formation represents such components of inflammation.\(^12\) Edema formation in the paw is the result of a synergism between various inflammatory mediators that increase vascular permeability or the mediators that increase blood flow.\(^13\)

The carrageenan-induced edema in the rat hind paw most widely used for the screening of new anti-inflammatory agents.\(^14\) Carrageenan is the phlogistic agent of choice for testing anti-inflammatory drugs as it is not known to be antigenic and is devoid of apparent
systemic effects. It has been used to evaluate the effect of anti-inflammatory agents like NSAIDs, which primarily inhibits the cyclooxygenase involved in prostaglandin synthesis. Thus, keeping this in view, the present study has been undertaken to investigate the anti-inflammatory activity of the synthetic heterocyclic compounds (indolyl chalcones and pyrazolines) by carrageenan induced paw edema method. The evaluation of anti-inflammatory activity was carried out in the Department of Pharmacology, JNMC, Aligarh Muslim University, Aligarh.

5.9.1. Screening of anti-inflammatory activity of indolyl chalcone and pyrazoline compounds in rats

The anti-inflammatory activity of all the synthesised compounds was evaluated using carrageenan induced paw edema assay model of inflammation on Wistar rats, by adopting the method of Winter et al.\textsuperscript{15} using aspirin as standard drug. Structure for the compounds evaluated for anti-inflammatory activity listed in Scheme 73 and 74.

5.9.1a. Animals

Wistar rats (150-200 g) of either sex were used for anti-inflammatory studies. They were housed at the temperature 24 ± 2 °C with 12 h light/dark cycles in polypropylene cages in groups of six animals each. The animals were fasted overnight before the experiment and given water \textit{ad libitum}. The study confirmed to the guiding principles of Institutional Animal Ethics Committee (IAEC), J. N. Medical College, Aligarh, India.
5.9.1b. *Experimental Design and drug treatment*

The animals are weighed and divided into three groups of six animals each.

**Group I**- Received 2.5% DMSO in the dose of 2 mL/kg, p.o. 1 h prior to carrageenan and served as control.

**Group II**- Received aspirin in dose of 100 mg/kg, p.o. 1 h before injection of carrageenan.

**Group III to XI** – Received test compounds (192a-c and 193a-f) in the dose of 200 mg/kg, po. 1 h before injection of carrageenan.

5.9.1c. *Carrageenan - induced paw oedema in rats*

The animals were handled gently to avoid too much of stress on them which could result in an increased adrenal output. A mark was made at the lateral maleous of the left hind paw so that the dipping was done to the same level while measuring the paw volume. After 1 h of administration of a standard and the test compounds, the animals were injected subcutaneously with 0.1 mL of freshly prepared suspension of carrageenan (1% w/V) into the subplantar region of right hind paw of each rats. Immediately thereafter, the paw was immersed in water exactly to the mark. The measurement of the hind paw volume was carried out using digital Plethysmometer for animals in all the groups before treatment and after 1, 2, and 3 h of carrageenan injection. The initial volume of a paw was measured within thirty seconds of the injection of carrageenan. The anti-inflammatory activity was expressed as percent inhibition of the inflammation in the drug treated group in comparison with the control group.
The percent inhibition of edema was calculated by using the following formula:

\[
\text{% Inhibition} = \left\{\left(\frac{X - Y}{X}\right)\times 100\right\}
\]

\(X\) = mean increase in paw volume of rats in the control group,

\(Y\) = mean increase in paw volume of rats in the treated group

5.9.2. Indolyl chalcones screened for anti-inflammatory activities

The general synthetic strategy employed to prepare indolyl chalcone and indolyl pyrazolines analogues were based on Claisen-Schmidt condensation, which has been previously explained in section A.

![Scheme 73](image-url)
5.9.3. Indolyl pyrazolines screened for in vivo anti-inflammatory activity

![Chemical structures of indolyl pyrazolines](image)

**Scheme 74**

5.9.3a. *Statistical analysis*

All the values were expressed as Mean ± SEM. Statistical significance was calculated by one way ANOVA followed by post hoc Dunnett’s multiple comparison test. Rats in each group were six ($n=6$) and $P < 0.05$ was considered to be statistically significant. The software SPSS-20 was used to carry out all the statistical tests.
5.10. RESULTS

Carrageenan induced paw edema is one of the most commonly employed method for the screening of acute inflammation. The anti-inflammatory activity was evaluated by recording mean hind paw volumes at 0, 1, 2 and 3 hours following carrageenan injection in control and test groups.

The results of the anti-inflammatory effect of the indolyl chalcone (192a-c) and pyrazolines (193a-f) are presented in Table 24, 25 & 26, 27. As shown in Tables, the entire investigated compounds (192a-c and 193a-f) exhibited moderate to good anti-inflammatory activity with the percentage inhibition of edema formation ranged from 41.9 to 93.5 % at the end of 3 h, whereas, at the same time, the standard drug aspirin (100 mg/kg) showed 85.4% inhibition of inflammation in comparison with control.

As indicated in Table 24 & 25, the indolyl chalcones 192a, 192b and 192c decreased the paw edema at the end of 1, 2 and 3 h but test compound 192a showed the significant decrease in paw edema at 1 h ($P < 0.05$) whereas at the end of three hours all the compounds exhibited significant anti-inflammatory activity ($P < 0.01$) with the percentage inhibition of edema formation ranged from 41.9 to 69.3 % as compared to control group.
**Table 24** Effect of indolyl chalcones compounds on carrageenan induced paw oedema

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 h</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (DMSO) (2ml/kg)</td>
<td>0.74 ± 0.005</td>
<td>1.04 ± 0.01</td>
<td>1.15 ± 0.01</td>
<td>1.36 ± 0.005</td>
</tr>
<tr>
<td>Aspirin (100 mg/kg)</td>
<td>0.78 ± 0.005</td>
<td>0.94 ± 0.01*</td>
<td>0.97 ± 0.01**</td>
<td>0.87 ± 0.005**</td>
</tr>
<tr>
<td>TC 192a (200 mg/kg)</td>
<td>0.75 ± 0.02</td>
<td>0.93 ± 0.02*</td>
<td>0.97 ± 0.02**</td>
<td>0.94 ± 0.04**</td>
</tr>
<tr>
<td>TC 192b (200 mg/kg)</td>
<td>0.79 ± 0.01</td>
<td>0.97 ± 0.02</td>
<td>0.97 ± 0.03*</td>
<td>1.15 ± 0.02**</td>
</tr>
<tr>
<td>TC 192c (200 mg/kg)</td>
<td>0.81 ± 0.04</td>
<td>0.97 ± 0.03</td>
<td>1.01 ± 0.04**</td>
<td>1.01 ± 0.03**</td>
</tr>
</tbody>
</table>

TC = Test compound

* $P < 0.05$  ** $P < 0.01$

Each average value represents the mean ± SEM ($n=6$).

The difference in results were considered significant when $*P<0.05$, and $**P<0.01$ as compared with the control group.
Table 25 Percentage Inhibition of paw edema by indolyl chalcones compounds in carrageenan induced paw

<table>
<thead>
<tr>
<th>Groups</th>
<th>Time intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 h</td>
</tr>
<tr>
<td>Control (DMSO) (2 ml/kg)</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin (100 mg/kg)</td>
<td>46.6</td>
</tr>
<tr>
<td>TC 192a (200 mg/kg)</td>
<td>40.0</td>
</tr>
<tr>
<td>TC 192b (200 mg/kg)</td>
<td>36.64</td>
</tr>
<tr>
<td>TC 192c (200 mg/kg)</td>
<td>46.6</td>
</tr>
</tbody>
</table>

TC = Test compound

Cyclization of these indolyl chalcone into their corresponding pyrazolines also decrease the paw edema at the end of 1, 2, and 3 h but significant decrease in paw edema was seen in compound 193a, 193b, 193f (P < 0.01) and 193d (P < 0.05) at the end of 1 h, whereas at the end of three hours all the compounds exhibited significant decrease in paw edema (P < 0.01) with the percentage inhibition of edema formation ranged from 60.9 to 93.5 % as compared to control group. The percentage inhibition of edema of indolylpyrazolines (193a-f) was found to be greater as compared to their parent compounds (192a-c) Table 26 & 27.
Table 26 Effect of indolyl pyrazolines compounds on carrageenan induced paw oedema

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mean paw volume ± SEM (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 h</td>
</tr>
<tr>
<td>Control (DMSO) (2 ml/kg)</td>
<td>0.74 ± 0.005</td>
</tr>
<tr>
<td>Aspirin (100 mg/kg)</td>
<td>0.78 ± 0.005</td>
</tr>
<tr>
<td>TC 193a (200 mg/kg)</td>
<td>0.77 ± 0.04</td>
</tr>
<tr>
<td>TC 193b (200 mg/kg)</td>
<td>0.66 ± 0.02</td>
</tr>
<tr>
<td>TC 193c (200 mg/kg)</td>
<td>0.85 ± 0.03</td>
</tr>
<tr>
<td>TC 193d (200 mg/kg)</td>
<td>0.70 ± 0.02</td>
</tr>
<tr>
<td>TC 193e (200 mg/kg)</td>
<td>0.83 ± 0.03</td>
</tr>
<tr>
<td>TC 193f (200 mg/kg)</td>
<td>0.78 ± 0.04</td>
</tr>
</tbody>
</table>

TC = Test compounds
*P<0.05  ** P <0.01
Each average value represents the mean ± SEM (n=6).

The difference in results was considered significant when *P<0.05, and **P<0.01 as compared with the control group.
**Table 27** Percentage Inhibition of paw edema by indolyl pyrazolines compounds in carrageenan induced paw

<table>
<thead>
<tr>
<th>Groups</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (DMSO) (2 ml/kg)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aspirin (100 mg/kg)</td>
<td>46.6</td>
<td>70.7</td>
<td>85.4</td>
</tr>
<tr>
<td>TC 193a (200 mg/kg)</td>
<td>63.3</td>
<td>48.7</td>
<td>72.5</td>
</tr>
<tr>
<td>TC 193b (200 mg/kg)</td>
<td>76.6</td>
<td>78.0</td>
<td>93.5</td>
</tr>
<tr>
<td>TC 193c (200 mg/kg)</td>
<td>33.3</td>
<td>39.0</td>
<td>60.9</td>
</tr>
<tr>
<td>TC 193d (200 mg/kg)</td>
<td>43.3</td>
<td>53.6</td>
<td>64.5</td>
</tr>
<tr>
<td>TC 193e (200 mg/kg)</td>
<td>40.0</td>
<td>43.9</td>
<td>70.9</td>
</tr>
<tr>
<td>TC 193f (200 mg/kg)</td>
<td>46.6</td>
<td>68.2</td>
<td>85.4</td>
</tr>
</tbody>
</table>

TC = Test compounds
5.11. DISCUSSION

The carrageenan induced paw edema model was used to screen the anti-inflammatory activity of the test compounds in acute phase of inflammation. Edema induced by carrageenan is believed to be biphasic: the first phase (1 h) involves the release of serotonin and histamine and the second phase (over 3 h) is mediated by prostaglandins, cyclooxygenase products. Continuity between the two phases is provided by kinins.\textsuperscript{16}

An insight to the anti-inflammatory activity with respect to the chemical structure of synthesized compounds revealed that compounds having chalcone and pyrazoline moiety at 3 position of indole nucleus exhibited significant ($P < 0.01$) anti-inflammatory activity when compared with control group.

Among the indolyl chalcone, compounds (192a) and (192c) with hydroxyl group on the 4 position of coumarin and pyran moiety showed good anti-inflammatory activity ($P < 0.01$) at the end of third hours after carrageenan injection with 69.3 and 67.7 % reduction in the paw edema respectively. Compound (192b) also shows significant anti-inflammatory activity ($P < 0.01$) with 41.9 % edema inhibition indicating that the presence of groups forming hydrogen bonds in compounds (192a) and (192c) may be helpful in more efficient binding with the receptors. Whereas the presence of bulky substitution dimethyl group in compound 192b reduced the activity which may be due to the improper attachment with the receptor.

Among the indolyl pyrazolines 193b, 193d and 193f (addition of phenyl hydrazine to compound 192a, 192b and 192c respectively), compound (193b) was found to be highly active and exhibited significant anti-inflammatory activity ($P <0.01$) at first, second and third hours with 76.6, 78.0 and 93.5 % reduction of paw volume respectively compared to
control group and inflammatory activity was better than standard drug aspirin which decreased paw volume by 85.4 % at the end of third hour. Compound (193f) and (193d) exhibited significant anti-inflammatory activity ($P < 0.05$) at the end of 1 h with 46.6 % and 43.3 % inhibition of paw edema which increases ($P <0.01$) at the end of second (68.2 and 53.6 %) and third hrs (85.4 % and 64.5 %) respectively.

On the other hand compounds 193a, 193c and 193e in the pyrazoline series where phenyl group was replaced by hydrogen (addition of hydrazine hydrate to 192a, 192b and 192c respectively) also exhibited significant anti-inflammatory activity ($P < 0.01$) at the end of three hrs but to a lesser extent than 193b, 193d and 193f (addition of phenyl hydrazine to 192a, 192b and 192c respectively) indicating that addition of phenyl hydrazine markedly improved the anti-inflammatory activity. Compound (193a) of the coumarin moiety shows the significant decrease in paw edema at the end of 1 ($P < 0.05$) and third hrs ($P < 0.001$) which reduced paw edema by the value of 63.3 and 72.5 % respectively, whereas compound (193e) and (193c) exhibited significant anti-inflammatory activity ($P < 0.01$) at the end of three hrs with 70.9 and 60.9 % of edema inhibition.

From the results it is evident that all the chalcones and pyrazolines having indole substituent showed significant anti-inflammatory activity from first hour onwards and reached the maximum at the third hour and is comparable to that of the standard drug (aspirin). This type of anti-inflammatory activity for this chalcone is understandable since indole derivatives are known to possess significant anti-inflammatory activity and a number of drugs belonging to this class are also being used as a NSAIDs.
5.12. CONCLUSION

It is concluded that all the chalcones and pyrazolines (192a-c and 193a-f) having indole moiety showed significant anti-inflammatory activity from first hour onwards and reached the maximum at the third hour and is comparable to that of the standard drug (aspirin).

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Silica supported sodium hydrogen sulfate (NaHSO₄–SiO₂): A novel, green catalyst for synthesis of pyrazole and pyranyl pyridine derivatives under solvent-free condition via heterocyclic β-enaminones

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ABSTRACT
NaHSO₄·SiO₂ is used as an efficient, mild and reusable catalyst for the synthesis of novel heterocyclic pyrazole (5a–h) and pyranyl pyridine derivatives (7a–h) via heterocyclic β-enaminones (3a–d) under thermal solvent-free conditions. The remarkable features of this green, new methodology are high conversions, cleaner reaction profiles, simple experimental and work-up procedures. Structures of the newly synthesized compounds have been elucidated on the basis of elemental analysis and spectral data (1H NMR, 13C NMR and mass spectrometry). The catalyst is characterised for the first time by using scanning electron microscopy–energy dispersive X-ray (SEM–EDX) and powder XRD. The catalyst can be reused several times without significant loss of its catalytic activity.

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1. Introduction

Development of new solid phase (solvent-free) reactions and transferring solution phase reactions to solid phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of drug candidates [1]. Hence, the challenges facing chemists this century is to develop new transformations that are not only efficient, selective and high yielding but also environmentally benign. A solvent-free organic reaction is an important synthetic strategy from the viewpoint of green and sustainable chemistry. Researchers have demonstrated that the solvent free organic syntheses are generally faster, selective, higher yielding with cleaner products, environmentally benign and involve simple operational procedure as compared to the classical reaction [2].

Heterogeneous catalysts have gained much importance in recent years due to economic and environmental considerations. These catalysts are advantageous over homogeneous catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation, thereby making the process economically viable. A tremendous interest has sparked in various chemical transformations promoted by catalysts under heterogeneous conditions [3,4]. Silica supported sodium bisulfate (NaHSO₄–SiO₂) has been found to be an efficient, inexpensive, non-toxic, recyclable and eco-friendly heterogeneous catalyst in various useful chemical transformations such as protection and deprotection [5], Knoevenagel condensation [6], and Biginelli reaction [7]. It is also used in the synthesis of dihydropyridines [8], xanthenes [9], homocyclic amines [10], pyrazolines [11], amides [12], quinazolones [13] and imidazoles [14].

Pyrazole ring is an important structural motif present in numerous pharmacological and agrochemically important compounds, including inhibitors of HIV-1 reverse transcriptase [15] and celecoxib derivatives as anti-inflammatory agent [16]. Pyrazoles can be synthesized by 1,3-dipolar cycloadditions of diazo compounds [17], reaction of chlorones and hydrazines [18], a four-component coupling of terminal alkynes, hydrazine, carbon monoxide and aryl isocyanides [19] and the direct condensation of 1,3-diketones and hydrazines in fluorooctanol [20]. A variety of other catalysts such as H₂SO₄ [21], polystyrene supported sulfonic acid [22], zirconium sulfophenyl phosphate [23], Sc (OTf)₃ [24], Y-zeolite [25], Mg (CO₃)₂ [26] have been also employed to affect this transformation. On the other hand, pyridine is one of the most prevalent heterocycle being the core fragment of different natural products and pharmaceutical active agents [27]. In addition to classical pyridine syntheses such as the Knoevenagel reaction, many new approaches have been also reported in the literature including condensation of amines and carbon yl compounds, cycloaddition reactions, multicomponent reaction [28–31] etc. Despite the wide range of conceptually different syntheses of pyrazole and pyridine
Zn(Proline)$_2$: a novel catalyst for the synthesis of dicoumarols

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A novel, greener approach was adopted for the synthesis of dicoumarols (3a-j) using Zn(Proline)$_2$, as a mild, non-toxic, Lewis acid catalyst in water employing 4-hydroxy coumarin (1) and aromatic/heteroaromatic aldehydes (2a-j). The catalytic activity results suggest that the methodology adopted offers several advantages such as mild reaction conditions, low loading of catalyst, quantitative yields, short reaction time and operational simplicity.

Introduction

Dicoumarol (6a) (Scheme 1) is a naturally occurring anticoagulant drug that functions as a vitamin K antagonist. Chemically, it is designated as 3,3'-dimethyl-[4-hydroxy-coumarin] and obtained from metabolism of coumarin in the sweet clover (Medicago sativa and Medicago officinalis) by bacteria Pseudomonas aeruginosa and Pseudomonas jauregiae. Dicoumarol and its synthetic derivative warfarin sodium (Coumadin) have shown to decrease metastases in animal models. Moreover, warfarin sodium therapeutically as an anticoagulant has emerged as one of the most substantial classes of drugs for the treatment of a variety of cancers and has shown to improve tumor response rates. In clinical trials, such compounds have also demonstrated to have some activity against prostate cancer, malignant melanoma, and metastatic renal cell carcinoma. A recent study has revealed that the inhibition of NAD (P) H quinone oxidoreductase (NQO2) with dicoumarol induces cell killing and oxidative stress in pancreatic cancer cells. Further, lanthanum(III) complexes of dicoumarol have been reported to show potent cytotoxic activity. Compounds with this ring system also possess various other pharmacological activities such as insecticidal, anthelmintic, hypnotic, antifungal, phytoalexin, HIV protease inhibition, antimicrobial and antitoxin. During the last decades, several methods have been adopted for the synthesis of this important class of compounds and include use of DBU (1,8-diazabicyclo [5.4.0] dec-7-ene), refluxing ethanol or acetic acid, molecular iodine; POC$_3$ H$_3$ in dry DMF.

Scheme 1 Structure of dicoumarol.

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A practical one pot synthesis of novel 2-hydroxy-4-chromanone derivatives from 3-formylchromone

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Abstract. A one pot synthesis of 4-chromanone derivatives (5a–j) is described using Zn[(L)proline]_2 as catalyst in aqueous media. The compounds have been characterized on the basis of elemental and spectral data (IR, H NMR and mass). The advantages of this protocol include high yields, mild reaction conditions, environmentally benign and simple operational procedure. The use of water as solvent and Zn[(L)proline]_2 as recyclable, non-toxic catalyst make such synthesis a truly green process.

Keywords. 3-Formylchromone; Zn[(L)proline]_2; 4-chromanone; water; green synthesis.

1. Introduction

Chromone moiety forms an important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin. Chromone and their derivatives are found in nature as pigments in plant leaves and flowers. They are important for the synthesis of various oxygen heterocycles including xanthones and transition metal chelates. They are widely present in nature and exhibit low toxicity along with a wide variety of useful properties. They are reported to exhibit significant biological activities including anti-inflamatory, antiallergic, antibacterial, neuroprotective, antifungal, etc. They also display spasmolytic, cardiotoxic, antiarrhythmic and antiepileptic properties. 3-Formylchromone (4-carboxy-4H-1-benzopyran-3-carboxaldehyde) has been frequently used for the synthesis of various heterocyclic derivatives ever since its convenient synthesis was reported by Nohara et al. Derivatives of 3-formyl chromone are useful synthetic building blocks in both organic and medicinal chemistry. 3-Formylchromone has been chosen for the present study due to the reason that it carries three electron deficient centres viz. α,β-unsaturated keto function, a carbonyl group in the form of formyl group at position 3 and a very reactive electrophilic centre at C-2. In the present paper, the products (chromanones) of reaction of 3-formylchromone with primary aromatic/heteroaromatic amines under green reaction conditions have been investigated. It is pertinent to mention that chromanones represent an important group of compounds which display a remarkable domain of biochemical and pharmacological actions. They have been examined for antioxidant, antibacterial, antimalarial, antineoplastic, antifungal, etc. They also display spasmolytic, cardiotoxic, antiarrhythmic and antiepileptic properties. Some chromanone derivatives have been evaluated for in vitro antiviral activities against human immunodeficiency virus (HIV) and Simian immunodeficiency virus (SIV). They have also been claimed to be active in photosynthesis and have hereditary bleaching effect (similar to antibiotics) on the plastid system of Euglena gracilis. Other 4-chromanone derivatives have also been found useful in the treatment of bronchial asthma.

As a result, for the synthesis of 4-chromanone derivatives different methods have been developed. These methods have certain drawbacks such as prolonged reaction time, use of toxic and volatile organic solvents and varied yields. The replacement of these hazardous solvents with the environmentally benign solvent is one of the key areas of green chemistry. Among various green solvents, water is the most popular as it is inexpensive, thermally stable, recoverable, biologically compatible, and non-toxic. In recent years, water-mediated organic synthesis has become one of the most important aspects in organic chemistry in order to meet the environmental demands. This strategy becomes one of the most powerful green chemical technologies if such reactions could be carried out using homogeneous or
Synthesis, characterization and antimicrobial evaluation of novel halopyrazole derivatives

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KEYWORDS
5-Chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde; Pyrazoles; Antibacterial activity; Antifungal activity

Abstract Two novel halopyrazole derivatives (3, 5) were synthesized from 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (1) using appropriate synthetic routes. Newly synthesized compounds were characterized using elemental analysis, spectral data (IR, 1H NMR, 13C NMR and mass spectrometry) and were evaluated for their in vitro antimicrobial activity. The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were determined for the test compounds as well as for reference standards. The investigation of antimicrobial screening revealed that compounds (3, 5) showed good antibacterial and antifungal activities, respectively.

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1. Introduction

In recent years, the number of life-threatening infectious diseases caused by multi-drug resistant Gram-positive and Gram-negative pathogen bacteria has reached an alarming level in many countries around the world (Berber et al., 2003; Mitscher et al., 1999). Morbidity and mortality because of enteric bacterial infection are the major health problems in some areas like the Indian subcontinent, portions of South America and tropical fraction of Africa (Quadri et al., 2005; Devania et al., 2006). Every year millions of people are being killed by some or the other Gram-positive and Gram-negative strains of bacteria. These bacteria mostly lead to food poisoning, rheumatic, salmonellosis and diarrhea (Khan et al., 2008). Thus, antibiotics provide the main basis for the therapy of microbial (bacterial and fungal) infections. However, overuse of antibiotics has become the major factor for the emergence and dissemination of multi-drug resistant strains of several groups of microorganisms (Harbottle et al., 2006). Furthermore, the pharmacological drugs available are either too expensive or have undesirable side effects or contraindications (Berger, 1985). Thus, in light of the evidence of rapid global spread of resistant clinical isolates, the need to find new antimicrobial agents is of paramount importance.
A highly efficient, simple, and ecofriendly microwave-induced synthesis of indolyl chalcones and pyrazolines

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One-pot synthesis of indolyl chalcones (3a–e) employing indole-3-carboxaldehyde (1) and heterocyclic activated methyl compounds (2a–e) under microwave irradiation is described. The indolyl chalcones (3a–e) are transformed into structurally important pyrazolines (5a–f) using different hydrazines. Application of microwave irradiation leads to many remarkable advantages, such as solvent- and catalyst-free reaction conditions, simple work up procedure, shorter reaction time, in addition to ecofriendly ‘green chemistry’ economical and environmental impacts.

Keywords: green chemistry; microwave irradiation; indole-3-carboxaldehyde; chalcones; pyrazolines

Introduction

In recent years, green chemistry has been focus of considerable attention and is becoming an increasingly popular technology (1). The aim of green chemistry is to reduce chemical-related impacts on human health and virtually eliminate contamination of the environment through dedicated sustainable prevention program. For organic reactions there is an urgent need for reducing toxic, volatile solvents in use. Many green synthesis methods have been studied by different researchers for the synthesis of a variety of organic molecules (2). Microwave irradiation is a newly established, convenient synthetic method and continues to affect synthetic chemistry significantly by enabling rapid, reproducible, and scaleable chemistry development (3,4). This technique has been applied to a variety of reactions resulting in reduction of reaction time, higher yield, greater selectivity, dearer reaction products, and easier manipulations (5). It also provides an opportunity to work with open vessels, thus avoiding the risk of high pressure and hazards of inflammable solvents (6).

Indole nucleus annulated to carbocyclic and heterocyclic ring(s) is one of the most ubiquitous scaffolds found in an astonishing variety of pharmaceuticals (7), functional materials (8–10), agrochemicals (11), and alkaloids (12) endowed with potent and multifacet biological activities. They are also reported to possess anti-inflammatory (13), antimicrobial (14), antifungal (15), antioxidant (16), etc. activities. Indole derivatives display a diverse variety of pharmacological activities that are useful in the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome (17–19). Besides being biologically active, they are also used extensively as synths in organic synthesis that possess potentially reactive sites for a variety of chemical reactions. Indole-3-carboxaldehyde is a naturally occurring component of Brassica vegetables (cabbage, broccoli). It induces a G-1 cell cycle arrest of human breast cancer (20). The diversity of the indole nucleus has motivated research aimed at the development of new economical efficient and selective synthetic strategies. As a part of our ongoing research work in the identification of new chemical entities (21) with variety of pharmacological activities, we herein report microwave-assisted access to a series of indolyl chalcones and their conversion to other heterocycles like pyrazolines from indole-3-carboxaldehyde and demonstrate its superiority over classical heating methods. It is worth mentioning that chalcones are the precursor of flavonoids, isoflavonoids, and have displayed an impressive array of biological activities (22–25). Particularly, indolyl chalcones have been reported as anti-inflammatory (26), antiproteolytic (27), anthelmintic (28), anticancer (29), and antiproliferative (30). They are also reported as antimicrobial, immunosuppressant, cardio-protective, and therapeutic agents for autoimmune diseases (31), whereas pyrazolines are pharmacologically active compounds and have been reported to possess antiandrogenic (32), antibacterial (33), antifungal