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Review article

Promising anti-inflammatory effects of chalcones via inhibition of cyclooxygenase, prostaglandin E_2, inducible NO synthase and nuclear factor κb activities

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ABSTRACT

Chalcones (1, 3-Diphenyl-2-propen-1-one) consist of a three carbon α, β-unsaturated carbonyl system and act as precursors for the biosynthesis of flavonoids in plants. However, laboratory synthesis of various chalcones has also been reported. Both natural and synthetic chalcones are known to exhibit a variety of pharmacological activities such as anti-inflammatory, antitumor, antibacterial, antifungal, antimalarial and antituberculosis. These promising activities, ease of synthesis and simple chemical structure have awarded chalcones considerable attraction. This review focuses on the anti-inflammatory effects of chalcones, caused by their inhibitory action primarily against the activities and expressions of four key inflammatory mediators viz., cyclooxygenase, prostaglandin E_2, inducible NO synthase, and nuclear factor κB. Various methodologies for the synthesis of chalcones have been discussed. The potency of recently synthesized chalcones is given in terms of their IC_{50} values. Structure-Activity Relationships (SARs) of a variety of chalcone derivatives have been discussed. Computational methods were applied to calculate the ideal orientation of a typical chalcone scaffold against three enzymes, namely, cyclooxygenase-1, cyclooxygenase-2 and inducible NO synthase for the formation of stable complexes. The global market of anti-inflammatory drugs and its expected growth (from 2018 to 2026) have been discussed. SAR analysis, docking studies, and future prospects all together provide useful clues for the synthesis of novel chalcones of improved anti-inflammatory activities.

1. Introduction

Leukocytes or white blood cells are involved in counteracting foreign substances, microorganisms, and infectious diseases and therefore, constitute a key component of the host immune system. However, they can also generate cellular impairment in host tissues in inflammatory disorders via degranulation and production of reactive species [1–3]. Inflammation is a defensive strategy in higher organisms in which the immune system identifies impaired cells, irritants, pathogens, and other harmful stimuli, and initiates the curing process [4]. Inflammation constitutes part of the body's immune feedback. An inflammatory response is responsible for healing infections, injuries, and any impairment to the tissues. A number of physical responses initiated by the immune system as a reaction to a physical injury or an infection cause inflammation [5]. Acute inflammation initiates quickly and becomes intense in a short period. Symptoms last for several days but may continue for a few weeks in some conditions. Acute inflammation is characterized by pain, redness, immobility, swelling, and heat. Acute bronchitis, infected ingrown toenail, a sore throat from a cold or flu, a scratch or cut on the skin, high-intensity exercise, acute appendicitis, dermatitis, tonsillitis, infective meningitis, sinusitis, and physical trauma are the conditions and diseases which can cause acute

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Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; NOS, nitric oxide synthase; CAM, cell adhesion molecules; LOX, lipooxygenase; PGs, prostaglandins; PGE_2, prostaglandin E_2; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; LOX, lysyl oxidase; mPGES-1, microsomal prostaglandin E synthase-1; LPS, Lipopolysaccharide; TNF-α, tumor necrosis factor-α; NO, nitric oxide; nNOS, neural NO Synthase; eNOS, endothelium NO synthase; ERK, extracellular signal-regulated kinase; IFN-g, interferon-g; IκBα, the inhibitor of kappa B; IL-1, interleukin-1; EMSA, electrophoretic mobility shift assay; IKK, inhibitor κB kinase; IκB, inhibitor κB; RANKL, receptor activator of NF-κB ligand; TRAP, tartrate-resistant acid phosphatase

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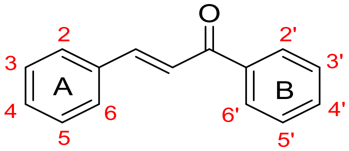


Fig. 1. Chemical structure of chalcone.

inflammation [6,7]. Chronic inflammations refer to a long-standing inflammation and can last for a few months and even years. Symptoms of chronic inflammation include fatigue, mouth sores, chest pain, abdominal pain, fever, rash, and joint pain. Asthma, hepatitis, ulcerative colitis, crohn's disease, periodontitis, rheumatoid arthritis, tuberculosis, and chronic peptic ulcer are the commonly known diseases caused by chronic inflammations [8]. Some common medications such as Non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and herbal supplements are used to reduce the pain caused by various inflammations [9]. However, numerous chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease etc. still present a challenge to the researchers since no safe medicines are available to cure these ailments [10]. Currently, NSAIDs, e.g. aspirin and ibuprofen are extensively used to reduce inflammatory pain. The underlying mechanism indicates that NSAIDs exert their effect by inhibiting cyclooxygenase (COX). COX is a crucial enzyme responsible for the synthesis of prostanoids, biologically active substances involved in numerous physiological processes and pathological disorders, such as inflammation. Research indicates that pharmacological suppression of COX can provide relief from inflammatory pain [11,12]. Side effects, particularly gastric corrosion, ulcer, and kidney toxicity have been associated with the use of NSAIDs. Consequently, modern research has been focused on the design and development of new anti-inflammatory drugs with minimum or no side effects as an alternative to NSAIDs [13]. Natural products carrying anti-inflammatory properties have long been practiced as a traditional medicine for inflammatory ailments such as fevers, pain, migraine, and arthritis. As the inflammatory mechanism of diseases becomes obvious, anti-inflammatory foods attract more attention [14]. According to British nutrition foundation, foods consisting of flavonoids, terpenoids, allied phenolic and polyphenolic and sulfur-containing compounds have been reported to be useful as anti-inflammatory diet [15]. Chalcone (Fig. 1) is a simple chemical structure which forms the backbone of many natural products and is widely distributed in vegetables, fruits, teas, and other plants. Chalcones are 1,3-diphenyl-2-propene-1-one, containing two aromatic rings (A and B) connected by an electrophilic three carbon α, β-unsaturated carbonyl structure [16–19]. Kostanecki and Tambor, for the first time, reported the synthesis of natural products consisting of α, β unsaturated carbonyl link and named them as "chalcones" [20]. The presence of reactive keto ethylenic group (−CO−CH═CH−) and α, β- unsaturated carbonyl system in chalcones derivatives enable them to exhibit a wide range of biological activities (Fig. 2) including antimicrobial, analgesic, anti-inflammatory, anti-ulcerative, antiplatelet, antiviral, antimalarial, anticancer, antileishmanial, antihyperglycemic, antioxidant and antitubercular [16,21,22]. Though chalcones possess numerous medicinal applications, their broad bioactivity spectrum shows a casual target

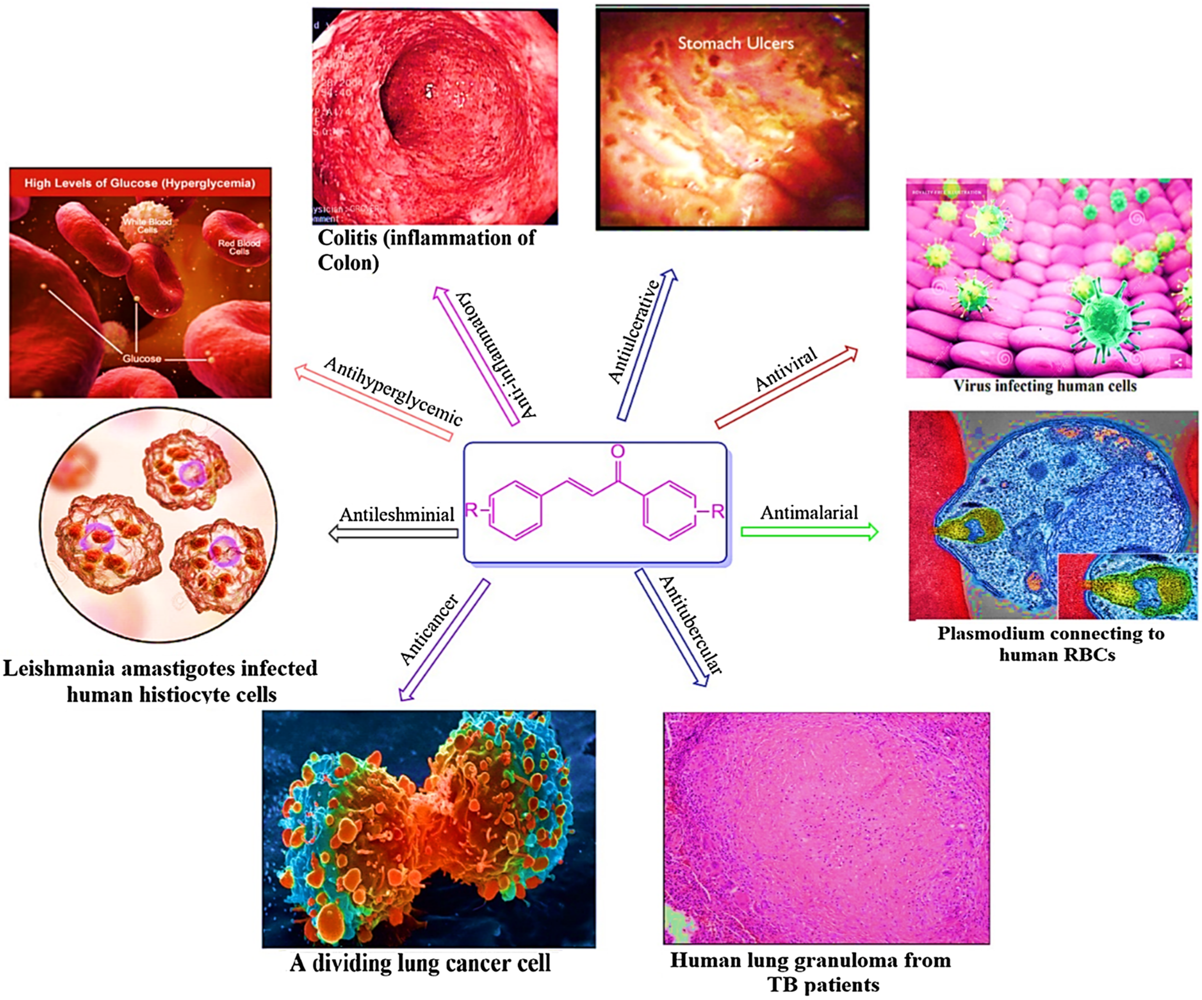
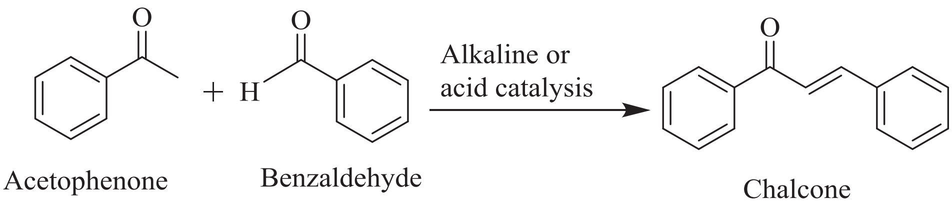
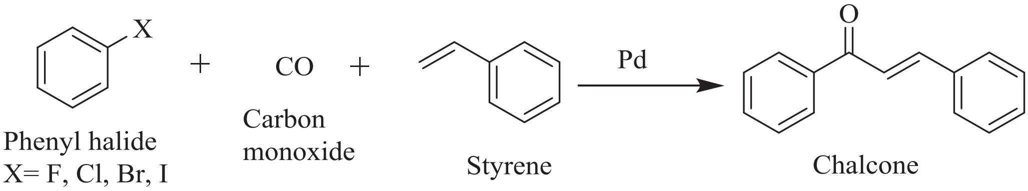


Fig. 2. Biological activities of chalcones.



Scheme 1. The Claisen-Schmidt condensation.



Scheme 2. Carbonylative Heck coupling reaction.

profile, which offers a challenging task for their clinical application. Due to the electrophilic nature of α, β-unsaturated carbonyl moiety, it has the potential to form irreversible bonds with biological macromolecules, causing a number of harmful effects, for example, allergenic reactions, mutagenicity, and carcinogenicity [23,24]. On the contrary, the decoration of the aromatic system and α-X-substitution of the double bond in the enone group can both effectively affect the reactivity of chalcones. Consequently, the design and synthesis of novel analogues are specifically vital for developing chalcone derivatives with better clinical applications in the future [25].

This review is focused on the synthesis, anti-inflammatory activities, structure-activity relationship (SAR) analysis and computational studies of chalcone and its derivatives.

2. Chalcones synthesis

Chalcones possess simple chemistry which allows a variety of substitutions with facile synthesis. Presently, several methodologies are applied for the synthesis of chalcone derivatives. In each of these synthetic methodologies, the most significant part is the condensation of two aromatic moieties (with nucleophilic and electrophilic groups) to produce the chalcone system. Regardless of the array of substitutions allowed, we outline the reaction scheme below by means of the typical scaffold of chalcones (1,3-diphenyl-2-propen-1-one).

2.1. Claisen-Schmidt condensation

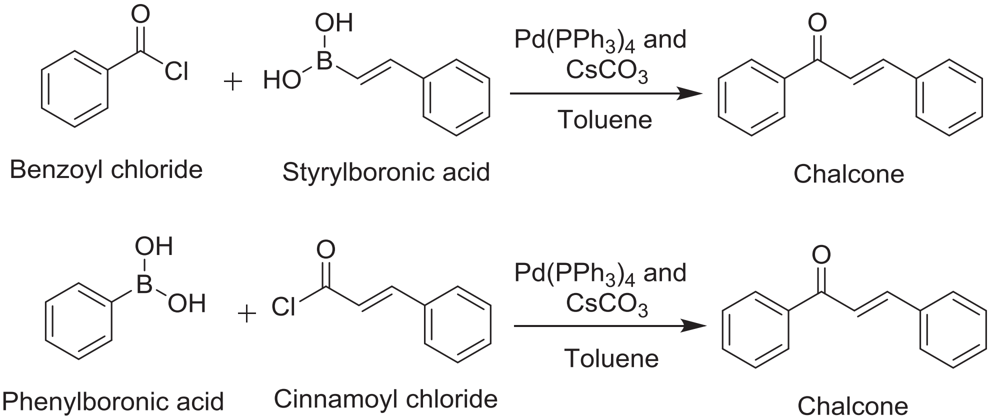
Claisen-Schmidt condensation (Scheme 1) is one of the most widely used methodologies for the synthesis of chalcone derivatives. The reaction is named after two inventive researchers, R. L. Claisen and J. G. Schmidt, and it illustrates a method in which a benzaldehyde and acetophenone are condensed together after their treatment with each other in the presence of strong basic or acidic catalysts in a liquid solvent at 50–100 °C for several hours. In base-catalyzed reactions, the chalcone is produced from the aldol product through dehydration in an enolate mechanism, whereas in the acid-catalyzed reaction, it is produced by an enol mechanism. A key limitation of this reaction is the mild reaction rate, the reaction usually requires a longer time for completion. The reaction could also produce a complex mixture having the desired products, byproducts, and occasionally the reactants. Consequently, the yield could fluctuate drastically (from 10% to near 100% conversion), depending on the type of reactants and catalysts. Still, this reaction has been applied in most of the publications due to its experimental easiness and extremely productive formation of the carbon-carbon double bond with slight limitations to the complexity of the molecules. The presence of electron-donating and electron-withdrawing substituents in aldehydes prefer condensation by acids and base respectively [17,21].

2.2. Carbonylative Heck coupling reaction

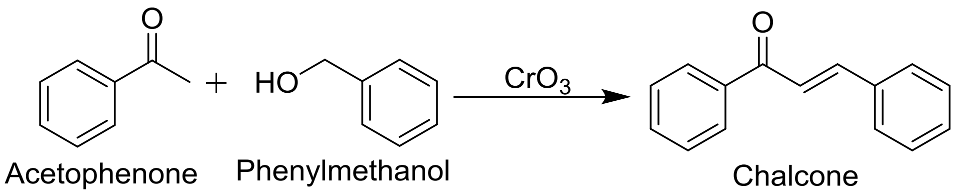
Carbonylative Heck coupling reaction (Scheme 2) involves the carbonylative vinylation of phenyl halide with styrene in the presence of carbon monoxide while applying palladium (Pd) as a catalyst to yield chalcones [26].

2.3. Suzuki–Miyaura coupling reaction

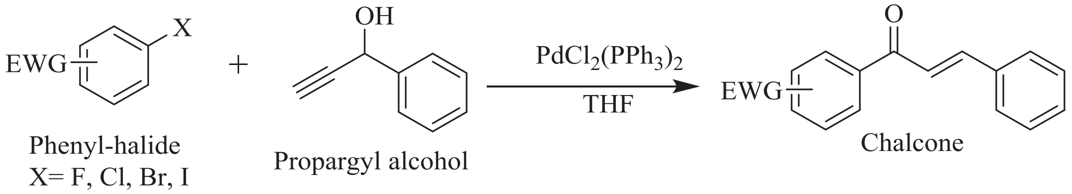
In Suzuki–Miyaura coupling reaction (Scheme 3), benzoyl chloride is coupled with styryl boronic acid in the presence of Pd(PPh_3)$_4$, $CsCO_3$



Scheme 3. Suzuki–Miyaura coupling reaction.



Scheme 4. One-pot synthesis of chalcones.



Scheme 5. Sonogashira coupling–isomerization reaction for chalcone synthesis. EWG represents the electron-withdrawing group.

and dry toluene to yield chalcones. Alternatively, phenylboronic acid can be coupled with cinnamoyl chloride using $Pd(PPh_3)_4$, $CsCO_3$, and dry toluene to produce chalcones [27].

2.4. One-pot synthesis

One pot synthesis provides an easy, effective and green technique for chalcone synthesis in just one container. This synthetic methodology has advantages of better reaction productivity and avoidance of the extensive purification procedure of the intermediates, and hence is time-saving and cost-effective. The reaction involves the treatment of phenylmethanol and acetophenone with each other in the presence of oxidizing agent CrO_3. Benzaldehyde is produced by the action of CrO_3 on phenylmethanol. Acetophenone then reacts with benzaldehyde to yield chalcones (Scheme 4) [28].

2.5. Sonogashira coupling–isomerization reaction

In Sonogashira coupling–isomerization reaction, chalcones are synthesized by treatment of equimolar amounts of electron-deficient (hetero)aryl halides and (hetero)aryl or alkenyl 1-propargyl alcohols in THF, catalyzed by $PdCl_2(PPh_3)_2$ under microwave radiation (Scheme 5) [29].

2.6. Heterogeneous solid acid catalyst facilitated synthesis

Chalcone synthesis has also been reported in the presence of a heterogeneous solid acid catalyst. Equimolar amounts of benzaldehyde and phenylacetylene were treated in 1,2-dichloroethane as solvent under microwave irradiation and ion-exchange molecules resin amberlyst-15 as heterogeneous solid acid catalyst (Scheme 6) [30].

2.7. Coupling reaction

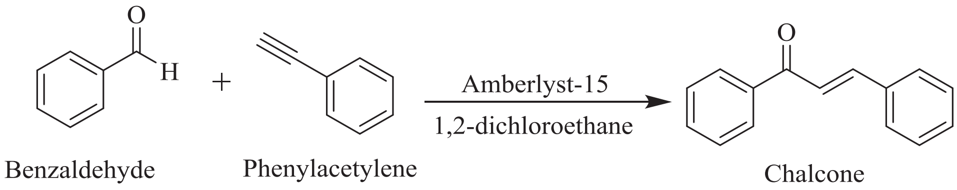
Coupling reaction between benzaldehyde and phenylacetylene in the presence of TsOH or HBr (as a catalyst) and ionic liquids, such as 1-butyl-3-methyl-1H-imidazolium 4-methyl benzenesulfonate (BmimOTs) or its 1-ethyl analogue (EmimOTs) for 12 h at 100 °C can yield chalcones (Scheme 7) [31].

2.8. Julia-Kocienski olefination

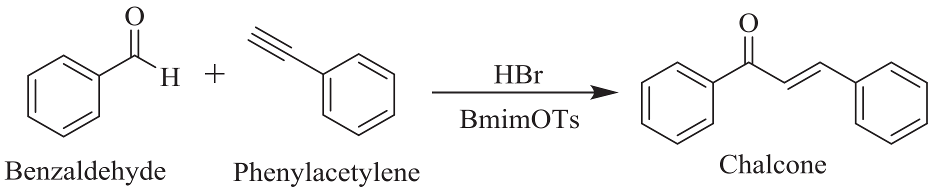
In a modified Julia-Kocienski olefination, 2-(Benzo[*d*]thiazol-2-yl-sulfonyl)-1 phenylethanones is treated with benzaldehyde at −78 °C in the presence of a base to afford *(E)*-chalcone as a major diastereomeric product in good to excellent yields (Scheme 8). Nonpolar solvents were found to be superior compared to polar solvents, and the study indicated a remarkable correlation between solvent polarity and yield. A substantial decrease in yield was observed at −78 °C. However, generation of the anion (which might then be stabilized by a carbonyl group at α-position in addition to the comparatively large stability of the sulfonyl anion at a lower temperature) restricts the reactivity of this reaction [32].

3. Anti-inflammatory activities of chalcone derivatives

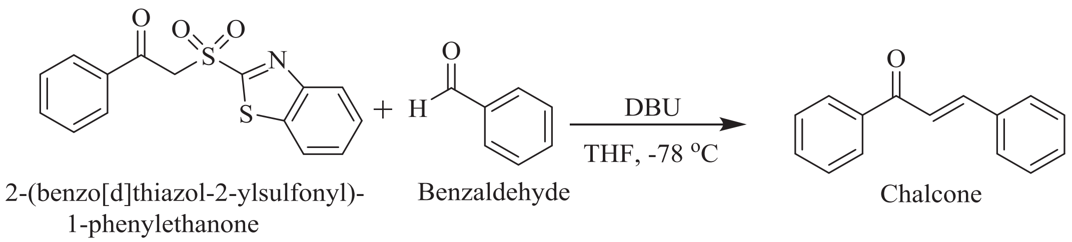
Several research groups reported the anti-inflammatory activities of natural as well as synthetic chalcones against several therapeutic targets such as COX, interleukins, nitric oxide synthase (NOS), expression of cell adhesion molecules (CAM), lipooxygenase (LOX) and



Scheme 6. Chalcones synthesis facilitated by a heterogeneous solid acid catalyst.



Scheme 7. Coupling reaction between benzaldehyde and phenylacetylene for chalcone synthesis.



Scheme 8. Chalcone synthesis via modified Julia-Kocienski Olefination.

prostaglandins (PGs) etc. However, we will restrict this review to the inhibitory effects of chalcone derivatives against four important inflammatory mediators i.e. COX, prostaglandin E_2 (PGE_2), inducible NO synthase (iNOS) and nuclear factor kappa B (NF-κB) (Fig. 3).

3.1. Cyclooxygenase inhibition

The suppression of COX activity can relieve inflammatory symptoms and pain; therefore, several attempts have been made to develop novel and more efficient anti-inflammatory drugs by inhibiting COX activity.

Bano et al. synthesized new chalcone derivatives (Fig. 4) and evaluated their anti-inflammatory activity via carrageenan-induced hind paw oedema model at a dosage of 20 mg/kg body weight. The anti-inflammatory activity (26–91% after 3 h) of the target derivatives was observed to be similar to the reference drug (indomethacin) with a minor ulcer. SAR analysis indicated that the introduction of nitro, methoxy or chloro moieties at *ortho* or *para* positions considerably decreased the activity, while methoxy group at *meta* position enhanced the activity profiles. The most potent derivative, *5′-Chloro-2′-hydroxy-4′6′-dimethyl-3, 4, 5-trimethoxychalcone* (**1**) showed maximum anti-inflammatory activity (90% inhibition of Oedema). Derivative **1** was also tested for its ability to suppress ovine COX-1 and COX-2 enzymes by means of COX inhibitory screening assay kits. Half maximal inhibitory concentration of **1** (IC_{50} values) for COX-1 and COX-2 were calculated to be 87.5 μM and 87.0 μM, respectively (Table 1) [33].

A series of novel indole-based chalcones (Fig. 5) was synthesized from *5-substituted-1H-indole-3-carboxaldehydes* or *1-methylindole-3-carboxaldehyde* and appropriate acetophenone derivatives. The synthesized

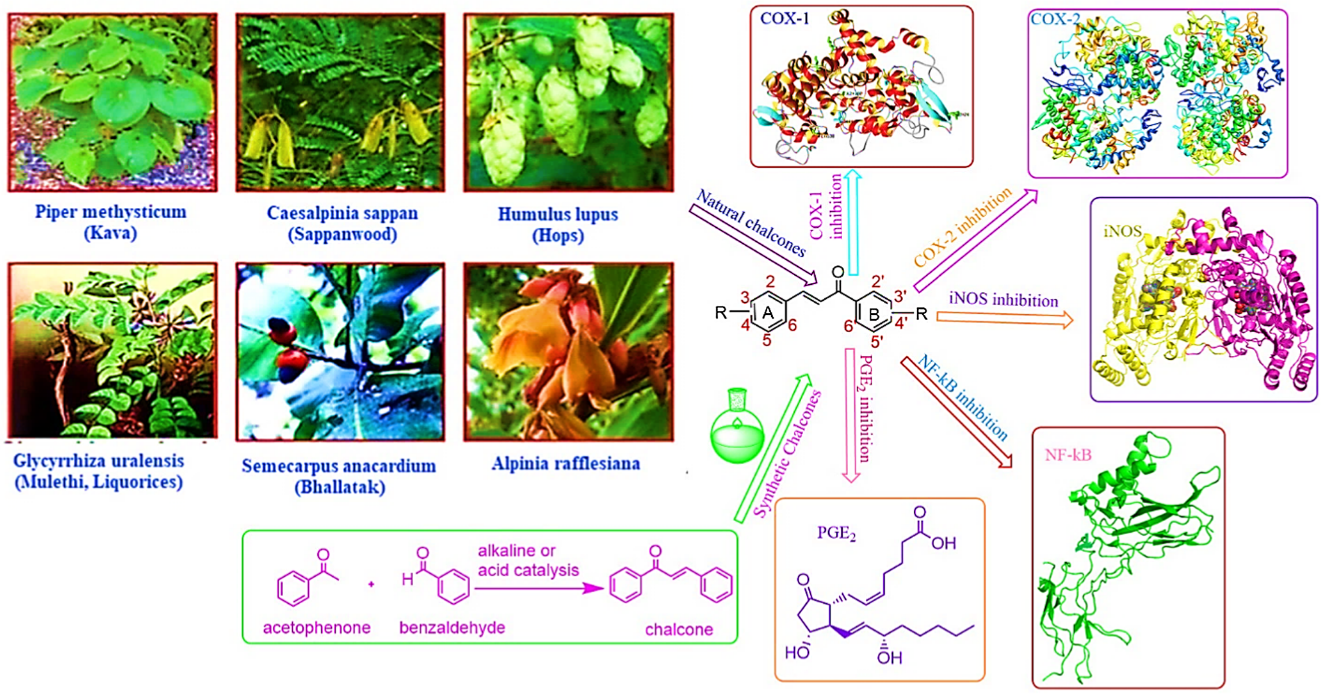


Fig. 3. Synthesis, natural sources and inhibitory effects of chalcone against COX, PGE_2, iNOS, and NF-κB.

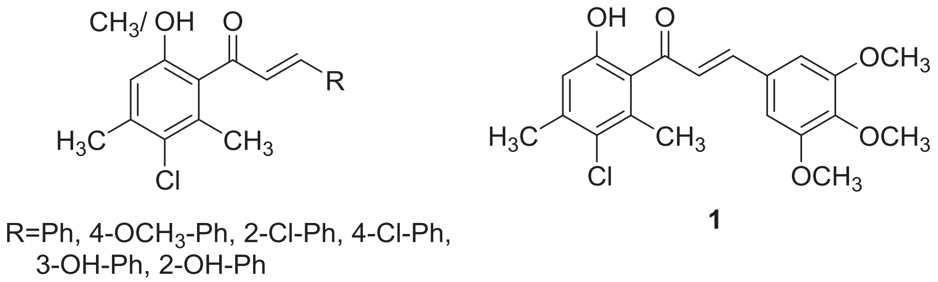
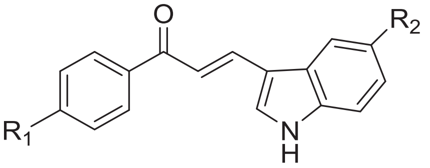


Fig. 4. Anti-inflammatory chalcones and the most potent derivative (**1**).

Table 1
List of selected chalcone derivatives as cyclooxygenase inhibitors in terms of their IC_{50} values.

Compound No.	Chalcone derivatives	Source	COX-1 inhibition (IC_{50}/μM)	COX-2 inhibition (IC_{50}/μM)	Type of inhibition	Reference
1	*5′-Chloro-2′-hydroxy-4′6′-dimethyl-3, 4, 5-trimethoxy-chalcone*	Synthetic	87.5	87.0	–	[33]
2a	*3-(5-bromo-1H-indol-3-yl)-1-(4-cyanophenyl)prop-2-en-1-one*	Synthetic	23.1 ± 0.6	27.1 ± 2.3	–	[34]
2b	*3-(5-methoxy-1H-indol-3-yl)-1-(4-(methylsulfonyl) phenyl)prop-2-en-1-one*	Synthetic	24.2 ± 0.3	–	–	[34]
5	*2-Hydroxy-3,4,6-trimethoxychalcone*	*Toussaintia orientalis*	95.5		–	[37]
7	Licochalcone A	*Glycyrrhiza inflata*	0.94	1.93	Competitive	[40]
9	*(E)-3-(4-((ethylamino)methyl)-phenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one*	Synthetic	25.86	10.09	Competitive	[42]
11a	*1-ferrocenyl-3-(4-methylsulfonylphenyl) propen-1-one*	Synthetic		0.05	–	[45]
12	*(E)-4-methyl-N-((4-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenyl)-carbamoyl)benzenesulfonamide* (Me-UCH 5)	Synthetic	–	0.06	–	[47]



2a R_1=Br, R_2=CN;
2b R_1=OCH_3; R_2=SO_2CH_3

Fig. 5. Chemical structures (**2a and 2b**) of Indole-based chalcone derivatives.

derivatives were subsequently screened for *in vivo* inhibitory activity against COX-1 and COX-2. Experimental data indicated that *3-(5-bromo-1H-indol-3-yl)-1-(4-cyanophenyl)prop-2-en-1-one* **(2a)** had the maximum non-selective COX suppression with IC_{50} values of 23.1 ± 0.6 μM and 27.1 ± 2.3 μM (Table 1) for COX-1 and COX-2, respectively. Moreover, *3-(5-methoxy-1H-indol-3-yl)-1-(4-(methylsulfonyl) phenyl)prop-2-en-1-one* (**2b**) also exhibited substantial inhibition of COX-1 with its IC_{50} value reported to be 24.2 ± 0.3 μM (Table 1). Overall, **2a** and **2b** were confirmed to be potential anti-inflammatory agents [34].

Synthesis of numerous nitrogen-containing chalcone derivatives (Fig. 6) has been reported by the mannich reaction. The synthesized compounds were screened for anti-inflammatory activity by investigating their potential to inhibit pro-inflammatory enzymes, COX-2, trypsin, and β-glucuronidase. The results indicated that the tested compounds effectively inhibited COX-2, trypsin, and β-glucuronidase. SAR analysis revealed that these derivative carrying fluoro substituent at 3-position could inhibit trypsin (19.50%). Moreover, substitution of *N*-methyl-piperidine, pyrrolidine methyl, and morpholine methyl moieties at 3-position of the ring-A was key for β-glucuronidase inhibition. Likewise, chalcones with piperidine methyl substitution were stronger inhibitors of COX-2 than COX-1. *(E)-3-(2-chlorophenyl)-1-(2-hydroxy-4,6-dimethoxy-3-(piperidin-1-ylmethyl)phenyl)prop-2-en-1-one* **(3)** exhibited maximum anti-inflammatory activity with (%) inhibition of 91.45 (Table 2) against COX-2 [35].

Jadhav et al. reported the synthesis of numerous fluoro-hydroxy substituted pyrazole chalcones by using polyethylene glycol as an alternative reaction medium (Scheme 9). Using colorimetric COX (human ovine) inhibitor screening assay kit, the synthesized compounds were screened for *in vitro* anti-inflammatory activities by an assessment of their ability to inhibit the expression of COX-1 and COX-2. Indomethacin was applied as a reference drug. The results revealed that majority of the synthesized derivatives possessed selective inhibition against COX-2 enzyme. The derivatives demonstrated substantial inhibitory effect against COX-2 (22–53%). With reference to the activity of indomethacin (28.24%), compounds **4b** (43.69%), **4c** (44.72%), **4d** (46.58%), **4f** (53.83%) (shown in Table 2) and **4 g** (34.94%) were more active than **4a** (22.34%) and **4e** (24.38%). It was concluded that majority of the synthesized derivatives (except compounds **4a** and **4e**) had the most potent anti-inflammatory activities since they suppressed the expression of COX-2 enzyme more selectively than COX-1 [36].

Nyandoro et al. isolated *2-Hydroxy-3,4,6-trimethoxychalcone* (**5**) (Fig. 7) from the root and stem bark extracts of *Toussaintia orientalis*. At a dose of 30 μg/mL, the isolated chalcone derivative showed 50% (Table 2) inhibition of COX-1 with IC_{50} value of 95.5 μM (Table 1). Moreover, **5** also caused substantial inhibition (88%) (Table 2) of COX-2 at 30 μg/mL. The overall inhibition caused by **5** was relatively greater than the inhibition caused by indomethacin [37].

Yadav and coworkers synthesized five chalcone analogues (**6a-e**) (Fig. 8) by Claisen–Schmidt condensation of acetophenone with properly substituted benzaldehyde in the presence of a base. The synthesized compounds were screened for anti-inflammatory activities using the carrageenan-induced rat hind paw edema model in mice. Results from the inhibitory action of synthesized chalcones against chemical

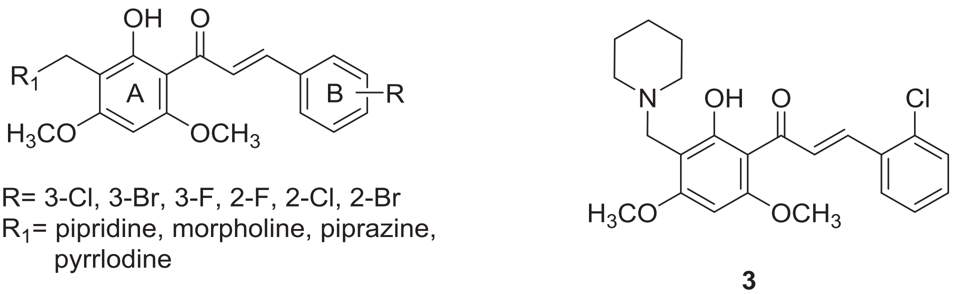


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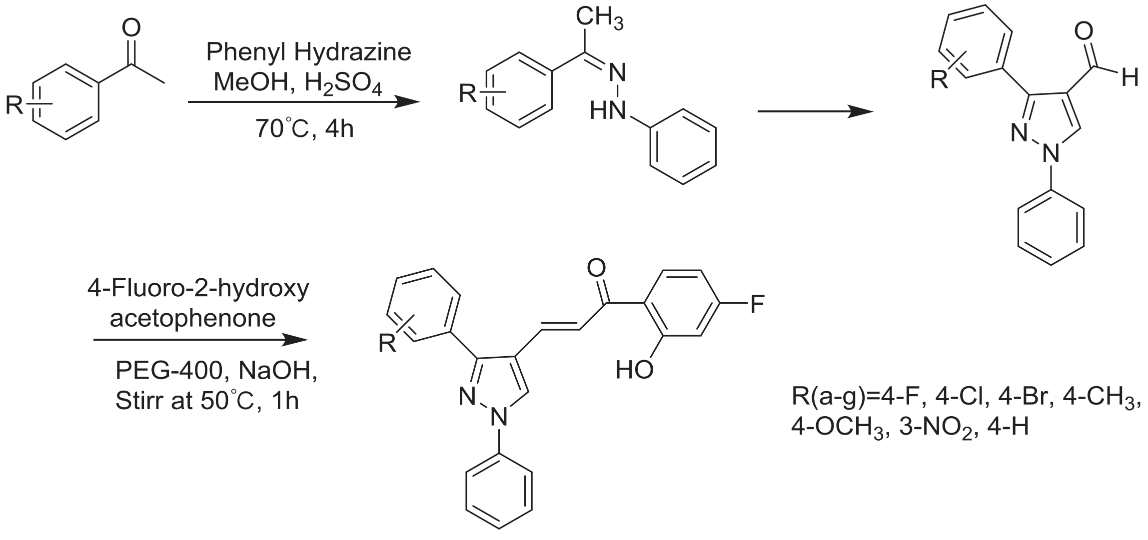
Fig. 6. Chemical structures of chalcone-mannich adducts and a representative compound (**3**).

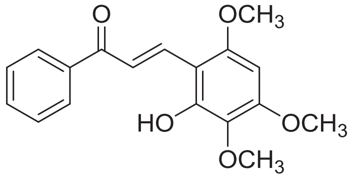
Table 2
List of selected chalcone derivatives as cyclooxygenase inhibitors in terms of their (%) inhibition values.

Compound No.	Chalcone derivatives	Source	COX-1 inhibition (%)	COX-2 inhibition (%)	Reference
3	*(E)-3-(2-chlorophenyl)-1-(2-hydroxy-4,6-dimethoxy-3-(piperidin-1-ylmethyl) phenyl)prop-2-en-1-one*	Synthetic	–	91.45	[35]
4f	*(E)-1-(4-fluoro-2-hydroxyphenyl)-3-(3-(3-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl) prop-2-en-1-one*	Synthetic	–	53.83	[36]
5	*2-Hydroxy-3,4,6-trimethoxychalcone*	*Toussaintia orientalis*	50	88	[37]
7	*Licochalcone A*	*Glycyrrhiza inflata*		59.4	[39]
10a	*3-(2′-Nitrophenyl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one*	Synthetic	23.1	69.7	[43]
10b	*3-(4′-Methoxyphenyl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one*	Synthetic	19.0	73.3	[43]
13a	*(E)-1-(3-bromo-2-hydroxyl-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one*	Synthetic	79.95	84.45	[48]



4a-g

Scheme 9. Synthesis of fluoro-hydroxy pyrazole chalcones (**4a-g**).



5

Fig. 7. Chemical structure of compound (**5**).

mediators liberated from neutrophils, mast cells, macrophages as well as microbial cells indicated that all derivatives (at 25 mg/kg dose) suppressed carrageenan-induced inflammation. 4-methoxy chalcone (**6a)** and 4-fluoro chalcone (**6c)** exhibited strong inhibitory action on the liberation of chemical mediators from inflammatory cells. The anti-inflammatory effect of these compounds is associated with the inhibition of COX and reduced prostaglandin formation. The (%) inhibition of five chalcone derivatives (**6a-e**) was reported to be 75.38, 49.23, 67.69, 57.53, 30.46, respectively as compared to the (%) inhibition of the standard drug, Indomethacin (65.23). SAR studies indicated that electron-withdrawing groups on ring-B of chalcone skeleton contributed to the enhanced anti-inflammatory activity [38].

Licochalcone A (**7**) (Fig. 9) extracted from the roots of *Glycyrrhiza inflata* was investigated for its anti-inflammatory activity in xylene-induced mice ear edema and carrageenan-induced paw edema tests. The results revealed that licochalcone A (at 5 mg/ ear) exhibited significant activities against xylene-induced acute inflammation. Moreover, licochalcone A (at 2.5, 5, 10 mg/kg doses) also substantially reduced carrageenan-induced paw edema as compared to the control at the fourth hour. Licochalcone A caused considerable inhibition of both COX-2 activity and expression at all tested concentrations. Licochalcone A (at 0.1, 0.5 and 1 µg/mL doses) caused 31.0%, 44.8% and 59.4% (shown in Table 2) inhibition, respectively to the COX-2 activity as compared to 13% inhibition caused by the standard drug, Indomethacin (at 0.5 µg/mL). Consequently, licochalcone A could be a useful chalcone derivative for the development of new anti-inflammatory agents [39]. Direct interaction of licochalcone A with COX has also been investigated. COX-1 or COX-2 was pre-incubated in the presence of licochalcone A (0.5–100 µM) and inhibition assays were performed. Results indicated that licochalcone A directly suppressed the activities of COX-1 and COX-2 *in vitro* with its IC_{50} values of 0.94 µM and 1.93 µM, respectively (Table 1). Moreover, licochalcone A decreased PGE_2 generation dose-dependently [40].

Karim et al. performed molecular docking investigations of quinolyl-thienyl chalcone derivatives and determined the necessary structural features for the suppression of COX-2. A strong interaction between *quinolyl-thienylchalcone* **(8)** **(**Fig. 10) and COX-2 was confirmed via hydrogen bonding between oxygen of the carbonyl functional group and Tyr356 (at a distance of 2.9 Å). Computational calculations further confirmed hydrophobic interactions between other groups of the molecule and numerous binding sites like Leu385, Ser531, Met523, Val524, Val117, Gly527, Trp388, and Ala528. The results indicated that the **8** has the potential to act as an anti-inflammatory agent [41].

Anti-inflammatory activities of numerous 4-methlyamino ethanol substituted and methoxylated chalcone derivatives (Fig. 11) were evaluated by Jantan and coworkers. The results indicated that the synthesized derivatives substantially suppressed the activities of inflammatory mediators COX and LOX (Lysyl oxidase). *(E)-3-(4-((ethylamino)methyl)phenyl)-1-(5-methylfuran-2-yl)prop-2-en-1-one* (**9**) was the most potent inhibitor against COX-1 and COX-2 with its IC_{50} values of 25.86 µM and 10.09 µM (Table 1), respectively [42].

Synthesis of chalcone derivatives of *ethyl 2-(4-carboxyphenylazo) acetoacetate* and corresponding aldehydes (Fig. 12) and their anti-inflammatory activities against COX-1 and COX-2 were reported by Bukhari et al. Experimental data revealed that *3-(2′-Nitrophenyl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one* (**10a**) containing nitro substituent exhibited inhibitory activity against COX-1 and COX-2 with its (%) inhibition values of 23.1 and 69.7, respectively (Table 2). While methoxylated derivative *3-(4′-Methoxyphenyl)-1-[(4)-carboxyphenylazomethyl]-2-propene-1-one* (**10b**) showed an inhibitory effect against COX-1 and COX-2 with its (%) inhibition values of 19.0 and 73.3, respectively (Table 2). The inhibitory effects of the two derivatives against COX were much better than shown by widely used drug aspirin. SAR study indicated that the substitution pattern influences the inhibitory potential of the synthesized derivatives. Methoxy-containing analogue were stronger inhibitors of COX-2 as compared nitro-containing analogue. Moreover, the substitution of nitro-group on position 2 produced chalcone derivative with better activity compared to its substitution at position 3 [43].

The appearance of microsomal prostaglandin E synthase-1 (mPGES-1) as a novel predictable medicinal target for inflammation and pain provided new prospect to develop an anti-inflammatory drug with negligible side effects. Thus, selective suppression of COX-2 and mPGES-1 is likely to deliver anti-inflammatory effects without adverse effects. Using structure-based drug design, Md Idris and coworkers performed a study to recognize chalcone analogues which can decrease the generation of the inducible PGE_2 by aiming at COX-2 and mPGES-1. For screening chalcone analogues from ASINEX catalog, a hybrid pharmacophore model of COX-2 termed as “phore 1” was developed and utilized. Forty-two compounds were positively mapped on “phore 1”, among which fifteen compounds were chosen. The selected compounds were exposed to pharmacophore investigation, followed by docking for mPGES-1. Three main compounds (BAS00384673, BAS00643043, and BAS02557914) were found to be selective towards COX-2 and had good binding interaction with mPGES-1 [44]. Farzaneh et al. reported a novel group of ferrocene compounds (Fig. 13) by incorporating the ferrocenyl moiety into suitable chalcone based scaffold. Chalcones were prepared through Clasien-Schmidt condensation of methylsulfonyl aldehyde and acetyl ferrocene. The synthesized compounds were screened for their COX-2 inhibitory activity using chemiluminescent enzyme assays. *In vitro* COX-1/COX-2 inhibition results proved that all compounds selectively suppressed the activity of COX-2 with their IC_{50} values in the highly potent range (0.05–0.12 µM). COX-2 selectivity indexes (SI) of three compounds were reported to be in 148.3–313.7 range. *1-ferrocenyl-3-(4-methylsulfonylphenyl) propen-1-one* (**11a**) was identified as a potent inhibitor of COX-2 with its IC_{50} value of 0.05 µM. (Table 1) Experimental data further revealed that the nature and size of the substituents on the C-3 position of propane-1-one influenced either efficacy or selectivity of COX-2 inhibitory activity. Overall, the results suggested that ferrocene-based chalcones can efficiently suppress the activity of COX-2 [45].

Synthesis of a murrayanine-chalcone i.e. *(E)-3-(benzo[d]*[1,3]*dioxol-5-yl)-1-(1-methoxy-9H-carbazol-3-yl)prop-2-en-1-one*, was reported by coupling of murrayanine with *3′,4′-(methylenedioxy)acetophenone*. The effect of 3′,4′-methylenedioxy group (present in ring-B of the murrayanine-chalcone scaffold) was examined against COX-2. The optimization of this vital structure and its effect on substantial activity was observed. The study further indicated the fabrication of 3′,4′-methylenedioxy moiety bearing murrayanine based chalcone via a semi-synthetic methodology. Target compound (through its 3′,4′-methylenedioxy moiety) displayed anti-inflammatory potential by inhibiting COX-2 and lipoxygenase (LOX) after 3 h [46]. Araico and coworkers tested the biological activities of substituted phenylsulphonylurenyl chalcones via examining their inhibitory effect against the human leukocyte activity, lysosomal enzyme secretion, and eicosanoids production. Direct suppression of 5-LOX activity was caused by few potential derivatives with their IC_{50} values reported being 0.5–0.8 µM. *(E)-4-methyl-N-((4-(3-(3,4,5-trimethoxyphenyl)acryloyl)phenyl)-carbamoyl)benzenesulfonamide* (Me-UCH 5) **12** **(**Fig. 14) was the most potent inhibitor of COX-2 activity in human monocytes with its IC_{50} value of 0.06 µM (Table 1) [47].

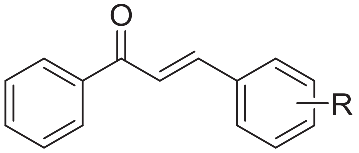
Bandgar and coworkers synthesized novel chalcone derivatives and evaluated them for their possible inhibitory effects against COX, Lipopolysaccharide (LPS)-stimulated TNF-α and pro-inflammatory enzymes such as trypsin and β-glucuronidase. Among the tested chalcones, compounds **13a-13d** (Fig. 15) were detected to suppress the COX activity. The (%) inhibition of chalcones (**13a-13d**) against COX-1 and COX-2 were recorded to be 79.95–68.47 and 84.45–74.77, respectively. *(E)-1-(3-bromo-2-hydroxyl-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl) prop-2-en-1-one* (**13a**) exhibited most potent anti-inflammatory effect against COX-1 and COX-2 with its (%) inhibition of 79.95 and 84.45, respectively (Table 2) [48].

Selected chalcone derivatives (as COX inhibitors), their sources and IC_{50} values are given in Table 1.

Selected chalcone derivatives (as COX inhibitors), their sources and (%) inhibition are given in Table 2.

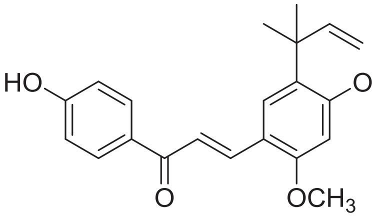
3.2. Inhibition of PGE_2 and NO

The suppression of PGE_2 and NO liberation has been suggested as a possible remedy for various inflammatory diseases. Arachidonic acid initiates PGE2 production via the enzymatic cascade (caused by COX enzymes). PGE_2 is an important inflammatory mediator and is extensively distributed in the human body. It is the most abundant metabolic product which plays a vital part in hyperalgesia, pyresis and vascular permeability. Therefore, its activity may be a target for the development of different COX inhibitors to reduce a variety of inflammatory diseases. NO is another key inflammatory mediator and occurs in three forms viz.; neural NO Synthase (nNOS), Endothelium NO Synthase (eNOS), and iNOS in numerous mammalian cells. Tissue damage is caused by the generation of a large amount of NO. In



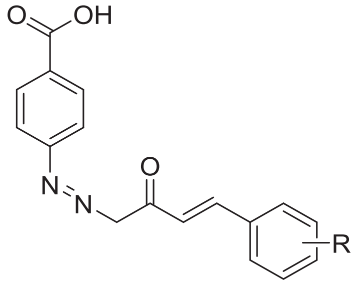
6a R=4-OCH_3
6b R=4-OH
6c R=4-F
6d R=4-Cl
6e R=2-OH

Fig. 8. Chemical structures of compounds (**6a-e**).



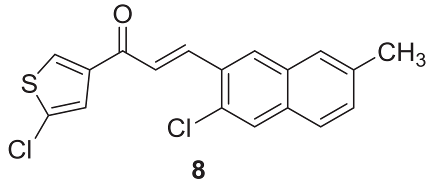
Licochalcone A
7

Fig. 9. Chemical structure (**7**) of Licochalcone A.



10a R=2-NO_2;
10b R=4-OCH_3

Fig. 12. Chemical structures of compounds (**10a** and **10b**).



8

Fig. 10. Chemical structure (**8**) of quinolyl-thienyl chalcone derivative.

inflammatory disorders like rheumatoid arthritis, large NO liberation by activated macrophages has been detected. Consequently, it would be exciting to design strong and selective NO inhibitors for possible therapeutic application [49–53]. Inhibitory action of dimethylamino-chalcones (Fig. 16) on the generation of NO and PGE_2 mediators (induced by LPS-stimulated RAW 264.7 macrophage cells) was investigated *in vitro*. The production of NO was suppressed by chalcone derivatives *(E)-1-(2,6-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one* **(14a)** and *(E)-1-(2,5-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl) prop-2-en-1-one* **(14b)** dose-dependently with their IC_{50} values of 0.6 and 0.7 µM (Table 3), respectively. The active chalcone derivatives exhibited their inhibitory activity against NO and PGE_2 generation by suppressing the expression of iNOS and COX-2. Furthermore, the formation of oedema in the carrageenan-induced model of inflammation in mice was considerably suppressed by **14b** (25 mg/kg) administered orally. SAR study indicated that monomethylation, 2′,4′-dimethoxylation, trimethoxylation, and dichlorination resulted in the formation of less active/ inactive chalcone derivatives [54].

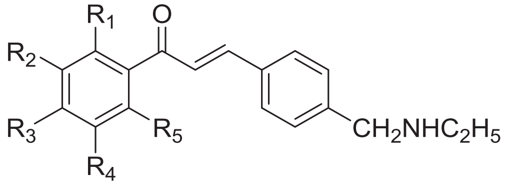
Rajos et al. also investigated the inhibitory effect of trimethoxychalcone derivatives (having several patterns of fluorination) on NO production. Their results indicated that the generation of NO and PGE_2 in LPS-activated RAW 264.7 macrophage cells was suppressed dose-dependently by *2,4,6-trimethoxy-20-trifluoromethylchalcone* **(15)** (Fig. 17). Without producing significant cytotoxic effects, chalcone derivative **15** (at 10 µM dose) caused 76.3% inhibition of NO production, which was attributed to the inhibition of iNOS expression, whereas a PGE_2 decrease was not through an inhibitory action against COX-2 activity or expression. Moreover, **15** also caused *in vivo* inhibition of nitrite and PGE_2 levels [55].

The inhibitory effect of *3,4,5-trimethoxy-4′-fluorochalcone* (**16**) (Fig. 18) against NO production *in vivo* indicated that **16** suppressed NO production in LPS-induced RAW 264.7 macrophages in a dose-dependent fashion with IC_{50} value of 0.033 µM (Table 3). Moreover, **16** (at 10 µM dose) also caused a reduction in PGE_2 generation by 58% and it did not directly inhibit iNOS and COX-2 activities. Inhibition of iNOS expression caused a decrease in NO production. *In vivo* results further revealed that **16** also inhibited nuclear factor-kappa B (NF-kappa B) pathway of cellular activation in macrophages [56].

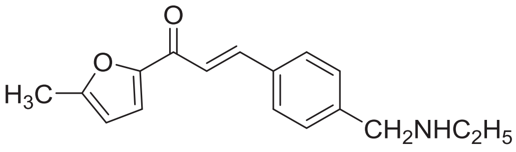
Some naturally occurring chalcones have also been reported to be potent inhibitors against NO production. Novel chalcone derivatives termed as mallotophilippens, **17a-c** (Fig. 19) were isolated from the fruits of *Mallotus philippinensis* and were identified as *1-[6-(3,7-dimethyl-octa-2,6-dienyl)-5,7-dihydroxy-2,2-dimethyl-2H-chromen-8-yl]-3-(4-hydroxy-phenyl)-propenone* **(17a)** *3-(3,4-dihydroxy-phenyl)-1-[6-(3,7-dimethyl-octa-2,6-dienyl)-5,7-dihydroxy-2,2-dimethyl-2H-chromen-8-yl]-propenone* **(17b)** and *1-[5,7-dihydroxy-2-methyl-6-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-2H-chromen-8-yl]-3-(3,4-dihydroxy-phenyl)-propenone* **(17c)** through spectral analysis. All three chalcone analogues suppressed NO production and iNOS gene expression in a murine macrophage-like cell line (RAW 264.7), induced by LPS and recombinant mouse interferon-g (IFN-g). The IC_{50} values of mallotophilippens (**17a**-**17c**) for NO production were 7.6, 9.5 and 38.6 µM (Table 3), respectively [57].

Similarly, xanthohumol B (**18a**), D (**18b**) and dihydroxanthohumol (**18c**) (Fig. 20), isolated from hops (*Humulus lupulus* L.) considerably blocked NO production and the expression of iNOS induced by LPS and INF-γ in a murine macrophage-like cell line, RAW 264.7 [58].

Cheng and coworkers reported that broussochalcone A (**19**)

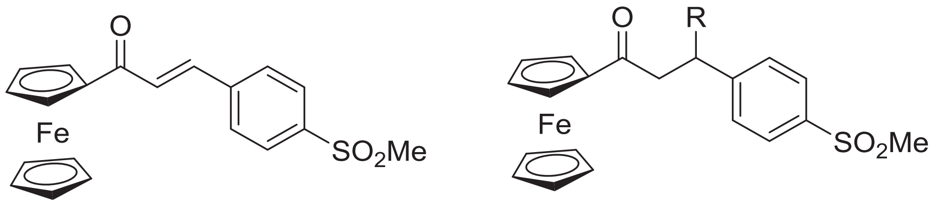


R_1=R_3=R_5=H, R_2=R_4=OCH_3
R_1=R_3=R_5=OCH_3, R_2=R_4=H



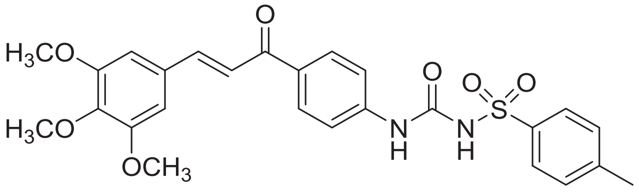
9

Fig. 11. Chemical structures of 4-methlyamino ethanol substituted and methoxylated chalcones and a representative compound (**9**).



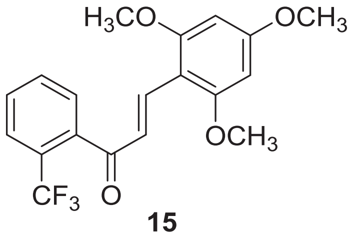
11a **11b**

Fig. 13. Chemical structures (**11a and 11b**) of Ferrocene-based chalcones.



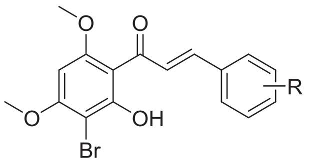
12

Fig. 14. Chemical structure (**12**) of substituted phenylsulphonylurenyl chalcone.



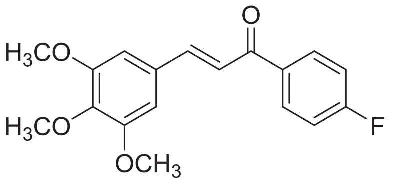
15

Fig. 17. Chemical structure of compound (**15**).



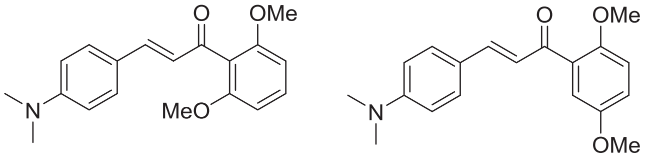
13a R=4-OCH$_3$ **13b** R=2-Br
13c R=2-F **13d** R=2-NO$_2$

Fig. 15. Chemical structures of compounds **(13a-13d)**.



16

Fig. 18. Chemical structure compound **(16)**.



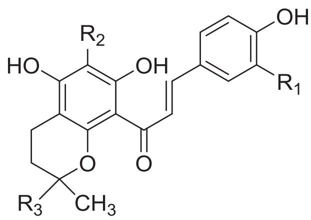
14a **14b**

Fig. 16. Chemical structures (**14a, 14b**) of dimethylamino-chalcones.

(Fig. 21) suppressed NO production in LPS-stimulated macrophages dose-dependently with its IC$_{50}$ value of 11.3 µM (Table 3). Experimental data revealed that **19** strongly inhibited NO production mediated by its suppression of IκBα (the inhibitor of kappa B) phosphorylation, IκBα degradation, NF-κB stimulation and iNOS expression instead of direct inhibition against the enzymatic activity of iNOS. Based on the results, it was concluded that **19** has the potential to act as

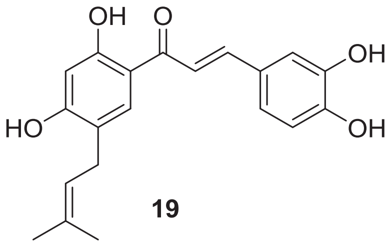
Table 3
List of selected chalcones (as NO inhibitors), their sources and IC$_{50}$ values.

Compound No.	Chalcone derivatives	Source	IC$_{50}$ value (µM)	Reference
14a	*(E)-1-(2,6-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one*	Synthetic	0.6	[54]
14b	*(E)-1-(2,5-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one*	Synthetic	0.7	[54]
16	*3,4,5-trimethoxy-4′-fluorochalcone*	Synthetic	0.033	[56]
17a	*1-[6-(3,7-dimethyl-octa-2,6-dienyl)-5,7-dihydroxy-2,2-dimethyl-2H-chromen-8-yl]-3-(4-hydroxy-phenyl)-propenone*	*Mallotus philippinensis*	7.6	[57]
17b	*3-(3,4-dihydroxy-phenyl)-1-[6-(3,7-dime-thyl-octa-2,6-dienyl)-5,7-dihydroxy-2,2-dimethyl-2H-chromen-8-yl]-propenone*	*Mallotus philippinensis*	9.5	[57]
17c	*1-[5,7-dihydroxy-2-methyl-6-(3-methyl-but-2-enyl)-2-(4-methyl-pent-3-enyl)-2H-chromen-8-yl]-3-(3,4-dihydroxy-phenyl)-propenone*	*Mallotus philippinensis*	38.6	[57]
19	Broussochalcone A	*Broussonetia papyrifera* (L.)	11.3	[59]
22a	Isobavachalcone	*Cullen corylifolium*	1.6 ± 0.11	[63]
22b	Bavachromene	*Cullen corylifolium*	2.4 ± 0.18	[63]
22c	Kanzonol B	*Cullen corylifolium*	2.2 ± 0.21	[63]
23	*(3-(2-Hydroxyphenyl)-1-(thiophene-3-yl)prop-2-en-1-one) (TI-I-174)*	Synthetic	5.75	[64]
24	*2-(3-(3,4-dimethoxyphenyl)propyl)-5-methoxyphenol*	Synthetic	6.5	[65]
25a	*(E)-1-(4-hydroxy-3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one*	Synthetic	4.19	[66]
25b	*(E)-1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one*	Synthetic	2.88	[66]
30a	*2′-methoxy-3,4-dichlorochalcone*	Synthetic	7.1	[71]
30b	*2′-hydroxy-6′-methoxychalcone*	Synthetic	9.6	[71]
30c	*2′-hydroxy-3-bromo-6′-methoxychalcone*	Synthetic	7.8	[71]
30d	*2′-hydroxy-4′,6′-dimethoxychalcone*	Synthetic	9.6	[71]
31	*2′, 5′, -dihydroxy-4-chloro-dihydrochalcone*	Synthetic	4.0 ± 1.6	[72]
32	*4-hydroxylonchocarpin*	*Psoralea corylifolia*	10.2	[74]



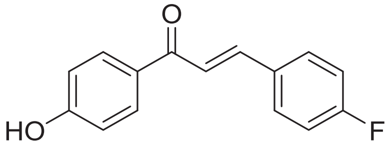
17a R_1=H R_2=$CH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$ R_3=CH_3
17b R_1=OH R_2=$CH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$ R_3=CH_3
17c R_1=OH R_2=$CH_2CH=C(CH_3)_2$ R_3=$CH_2CH_2CH=C(CH_3)_2$

Fig. 19. Chemical structures (**17a**-**17c**) of mallotophilippens.



19

Fig. 21. Chemical Structure (**19**) of broussochalcone A.



20

Fig. 22. Chemical structure of compound (**20**).

an anti-inflammatory agent [59].

Fluorinated chalcone derivatives have been reported to display anti-inflammatory activity owing to their inhibitory effect on NO generation. The valuable variations in anti-inflammatory activity often result from the introduction of fluorine in the chalcone scaffold [60]. Hasan et al. reported the synthesis of a novel fluorinated chalcone derivative, *(E)-3-(4-fluorophenyl)-1-(4-hydroxyphenyl) prop-2-en-1-one* (**20**) (Fig. 22) via Claisen-Schmidt condensation, using $SOCl_2$/EtOH as a catalyst. The synthesized chalcone derivative was screened for anti-inflammatory activity using cotton pellet-induced granuloma in rats as a model. Compound **20** showed a good inhibitory effect (36.8%) against NO production, similar to that displayed by dexamethasone using ANOVA (Analysis of variance) [61].

Herencia and coworkers evaluated the inhibitory effects of three chalcone derivatives (**21a-c**) (Fig. 23) against NO and prostanoid generation in LPS-induced-mouse peritoneal macrophages. Their results revealed that all three compounds caused a dose-dependent inhibition of NO generation with their IC_{50} values in μM range [62].

Recently, three prenylated chalcone derivatives (Fig. 24) namely isobavachalcone (**22a**), bavachromene (**22b**), and kanzonol B (**22c**) were isolated from *Cullen corylifolium*, which displayed dose-dependent inhibitory activities against NO and PGE_2 production in LPS-induced microglia with respective IC_{50} values of 1.6 ± 0.11 μM, 2.4 ± 0.18 μM and 2.2 ± 0.21 μM (Table 3). The results further indicated that prenylated chalcones caused a reduction in the expression of protein and mRNA of iNOS and COX-2 in LPS-induced microglia, and hence can be used to cure neuro-inflammatory disorders [63].

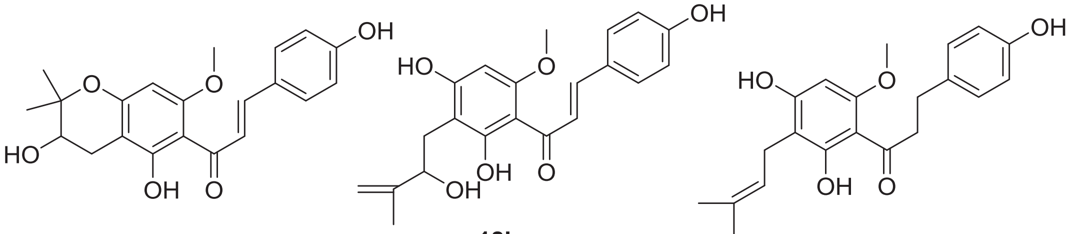
TI-I-174, *(3-(2-Hydroxyphenyl)-1-(thiophene-3-yl)prop-2-en-1-one)* (**23**) (Fig. 25), a synthetic chalcone derivative has been reported to strongly suppress LPS-induced NO production in RAW 264.7 macrophages. Pretreatment with **23** showed stronger inhibitory action with an IC_{50} value of 5.75 μM (Table 3). Moreover, iNOS expression was also inhibited via **23** treatment in a dose-dependent fashion, which suggested that NO production was inhibited via suppression of iNOS expression after LPS activation, making **23** a promising agent to cure inflammatory disorders [64].

Synthesis of dihydrochalcone and *1,3-diphenylpropane* derivatives has been reported by aldol condensation followed by reduction of the corresponding products. The derivatives were screened for inhibitory effects against NO production in LPS-induced mouse peritoneal macrophages. Experimental data revealed that NO production significantly decreased in a dose-dependent way with IC_{50} values in a range of 2.0–9.8 μg/mL. Among the tested compounds, *2-(3-(3,4-dimethoxyphenyl)propyl)-5-methoxyphenol* (**24**) (Fig. 26) showed the most potent inhibitory action with its IC_{50} of 6.5 μM (Table 3) against LPS induced iNOS-dependent NO production in RAW 264.7 cells. These results concluded that **24** is capable of blocking iNOS expression in LPS-activated RAW264.7 cells via weakening of NF-κB signaling by ERK (extracellular-signal-regulated kinase), p38, and JNK (c-Jun *N*-terminal kinase) [65].

Hidabeni chalcones represent a class of chalcone glycosides isolated from *Brassica rapa* L. Hara et al. reported the synthesis of ten novel Hidabeni chalcone derivatives. The synthesized compounds were screened for their potential to inhibit LPS-induced NO production in rat microglia Highly Aggressively Proliferating Immortalized (HAPI) cells. Compounds *(E)-1-(4-hydroxy-3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one* (**25a**) and *(E)-1-(3-methoxyphenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one* (**25b**) (Fig. 27) were reported to be the most potent inhibitors of iNOS expression with their IC_{50} values of 4.19 and 2.88 μM (Table 3), respectively [66].

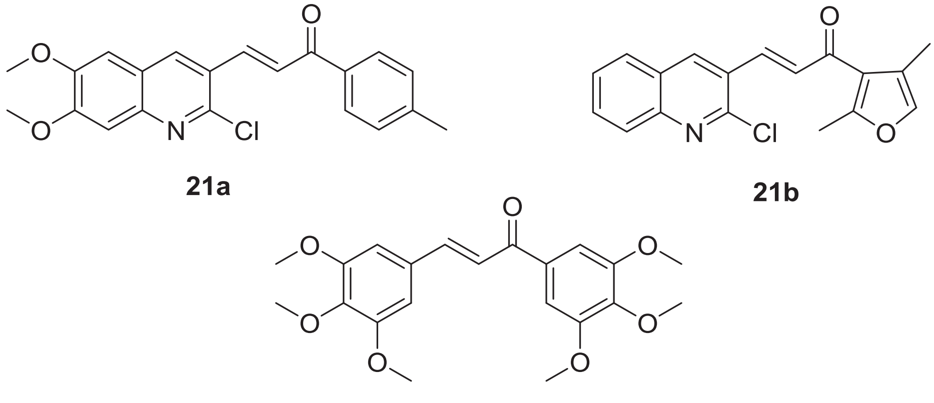
2′-carboxymethoxy-4,4′-bis(3-methyl-2-butenyloxy)chalcone also known as sofalcone (**26**) (Fig. 28) was evaluated for its inhibitory effects against NO production. Results indicated that sofalcone potently inhibited NO production in the culture medium comprising RAW 264.7 macrophages and LPS stimulated 3 T3-F442A adipocytes. Moreover, sofalcone enhanced the levels of HO-1 in cells and suppressed the differentiation of 3T3-F442A pre-adipocytes into adipocytes [67].

Rücker et al. synthesized fourteen α-halogen-substituted *2′,3,4,4′-tetramethoxychalcones* (Fig. 29). The anti-inflammatory effects of the synthesized compounds were measured by testing their ability to inhibit iNOS activity. Results revealed that the more potent electrophiles like (CF_3, Br and Cl) caused significant suppression of iNOS, thus confirming a correlation between the anti-inflammatory activity and thiol



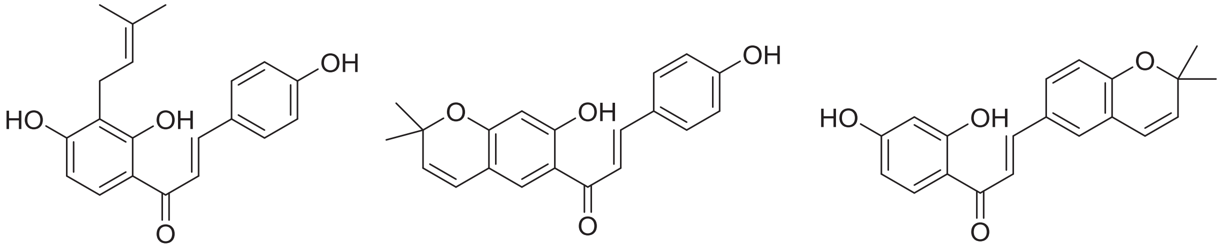
18a **18b** **18c**

Fig. 20. Chemical structure of xanthohumol B **(18a)**, D **(18b)** and dihydro xanthohumol **(18c)**.



21a **21b** **21c**

Fig. 23. Chemical structures of compounds (**21a-c**).



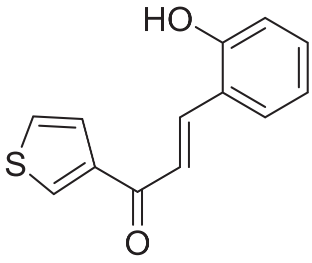
22a **22b** **22c**

Fig. 24. Chemical structures **(22a-22c)** of prenylated chalcone.

alkylating activity. Interestingly, tetramethoxychalcones bearing the most potent electrophiles (CN and NO_2) did not exhibit any anti-inflammatory activity [68].

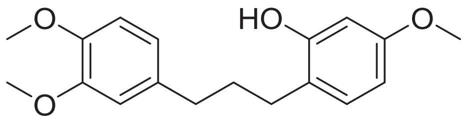
A series of methoxymethoxychalcone (MMC) derivatives (Fig. 30) have been reported to inhibit iNOS expression as well as NO production in LPS-induced RAW 264.7 murine macrophages. The underlying mechanism indicated that four MCC derivatives, viz., *2′,4′,6′-tris(methoxymethoxy)chalcone* (**TMMC**), (**28a**) *2-methoxy-4′6′-bis(methoxymethoxy) chalcone* (**MBMC**) (**28b**), *(E)-1-(2-methoxy-4,6-bis(methoxymethoxy) pheny1)-3-phenylprop-2-en-1-ol* (**MBMP**), (**28c**) and *(E)-3-pheny1-1-(2,4,6 tris(methoxymethoxy)pheny1) prop-2-en-1-ol* (**PTMP**) (**28d**) behave as anti-inflammatory agents by suppressing p38/JNK and LPS-induced activation of NF-κB. Among four derivatives, **MBMC** was found to be the most potent inhibitor. SAR analysis indicated that methoxylation at C-2′ position is vital for suppressing NO production and iNOS expression [69].

Jin and coworkers synthesized fifteen **TMMC** derivatives bearing substituents in ring-B (Fig. 31). The chalcones were then coupled with Glutahione (GSH-H) via Michael addition to produce GSH adducts. The inhibitory effects of resultant adducts against LPS-induced NO generation in RAW 264.7 cells were measured. SAR study confirmed that *(E)-1-(2-methoxy-4,6-bis(methoxymethoxy)phenyl)-3-(3-nitrophenyl) prop-2-en-1-one* **(29a)** (3-NO_2), *(E)-1-(2-methoxy-4,6-bis(methoxymethoxy)phenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one* **(29b)** (4-SCH_3), and *(E)-3-(3,5-difluorophenyl)-1-(2-methoxy-4,6-bis(methoxymethoxy)phenyl)prop-2-en-1-one* **(29c)** (3,5-difluoro) were the most potent inhibitors of NO production (by more than 75%) at 1.0 μM. Interestingly, ring-B of the most potent derivatives contains both an electron donating group (4-SMe) and electron-withdrawing groups (4-NO_2, 3,5-difluoro). However, a methylthio (-SMe) group is not an effective electron donating group since the bigger p orbital in the sulfur atom inhibits it from efficiently contributing the electron pair to the



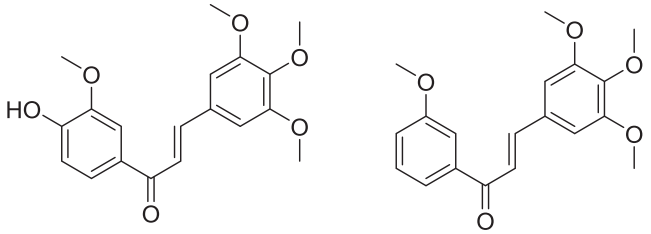
23

Fig. 25. Chemical structure of compound (**23**).



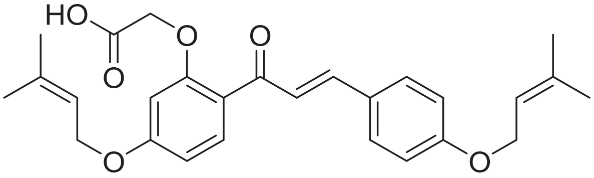
24

Fig. 26. Chemical structure of compound (**24**).



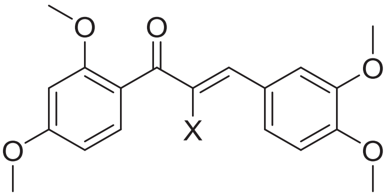
25a **25b**

Fig. 27. Chemical structures (**25a** and **25b**) of Hidabeni' chalcone derivatives.



26

Fig. 28. Chemical structure (**26**) of sofalcone.



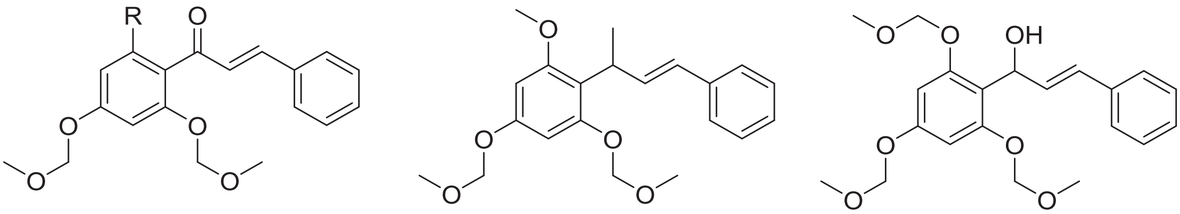
27a X=CF_3
27b X=Br
27c X=Cl

Fig. 29. Chemical structures of compounds (**27a-c**).

carbonyl group. *(E)-3-(4-(dimethylamino)phenyl)-1-(2-methoxy-4,6-bis(methoxymethoxy)phenyl) prop-2-en-1-one* **(29d)** (4-N$(Me)_2$) was detected to be the least potent among all chalcone derivatives. Its weak nature was credited to the presence of an electron pair on the dimethylamino group which was donated through the benzene ring, causing C—S bond weakening in GSH adduct [70].

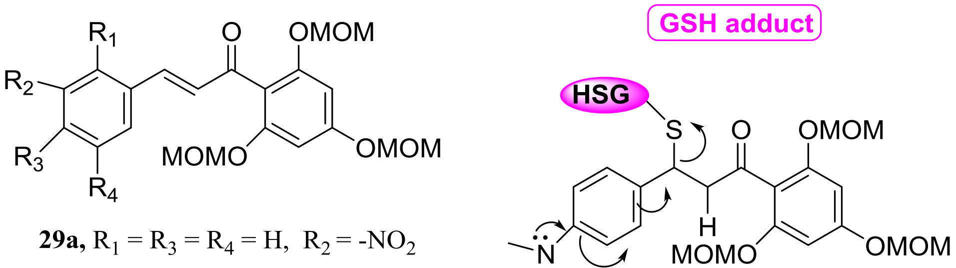
Synthesis of 41 chalcones with a different substituent(s) on rings-A and -B was reported by Kim and coworkers. The synthesized derivatives were screened for their effect over LPS-induced and iNOS-catalyzed NO production in RAW 264.7 cells. Among the tested compounds, *2′-methoxy-3,4-dichlorochalcone* (**30a**), *2′-hydroxy-6′-methoxychalcone* (**30b**), *2′-hydroxy-3-bromo-6′-methoxychalcone* (**30c**) and *2′-hydroxy-4′,6′-dimethoxychalcone (**30d**)* (Fig. 32) were detected to be the most potent inhibitors of NO production with their IC_{50} values of 7.1, 9.6, 7.8 and 9.6 μM, respectively (Table 3). Methoxyl substitution in ring-A at a neighboring position (2′ or 6′) to carbonyl functional group with/without 2′-(or 6′-)hydroxyl moiety and 3-halogen substitution in ring-B were the most promising structures. Results further revealed that **30a** and **30c** clearly reduced iNOS expression. It was concluded that these chalcones derivatives can be used as promising compounds for synthesizing new anti-inflammatory agents [71].

Huang et al. investigated the influence of *2´, 5´, -dihydroxy-4-chloro-dihydrochalcone* (**31**) (Fig. 33) on LPS-activated responses in murine macrophage cell line RAW 264.7. The results indicated that exposure of LPS-induced cells to **31** suppressed the nitrite deposition in a culture medium dose-dependently with an IC_{50} value of 4.0 ± 1.6 μM (Table 3). Moreover, compound **31** also suppressed the LPS-stimulated enhancement of iNOS expression. However, it had a negligible influence on the iNOS enzyme activity, proposing that the inhibitory activity of **31** is primarily due to the suppression of iNOS expression instead of iNOS activity. Furthermore, LPS-induced break up of IkB-α and NF-κB were considerably inhibited after treatment with **31**. Overall, results suggested that **31** showed inhibitory action on NO production via the suppression of IkB-α degradation and NF-κB stimulation, and therefore



28a R=$OCOCH_3$; **28b** R=OCH_3 **28c** **28d**

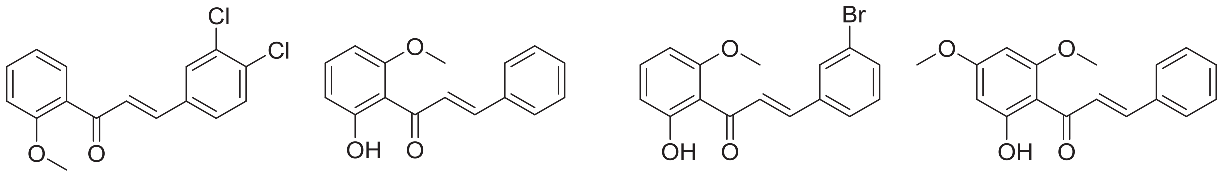
Fig. 30. Chemical structures of TMMC **(28a)**, MBMC **(28b)**, MBMP **(28c)**, and PTMP **(28d)**.



29a, $R_1 = R_3 = R_4 = H$, $R_2 = \text{-}NO_2$
29b, $R_1 = R_2 = R_4 = H$, $R_3 = \text{-}SCH_3$
29c, $R_2 = R_4 = F$, $R_1 = R_3 = H$
29d, $R1 = R2 = R4 = H$, $R_3 = \text{-}NCH_3$

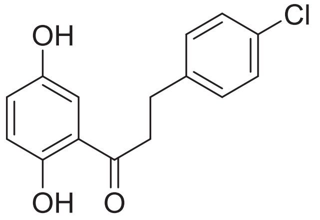
(29d-GSH adduct)
GSH-SH =Glutathione

Fig. 31. Chemical structures (**29a-d**) of **TMMC** derivatives.



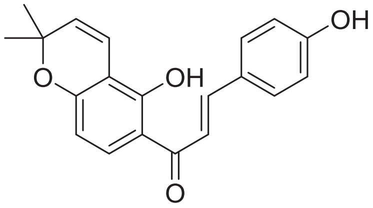
30a **30b** **30c** **30d**

Fig. 32. Chemical structures of compounds (**30a-30d**).



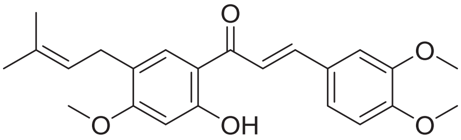
31

Fig. 33. Chemical structure compound (**31**).



32

Fig. 34. Chemical structure of compound (**32**).



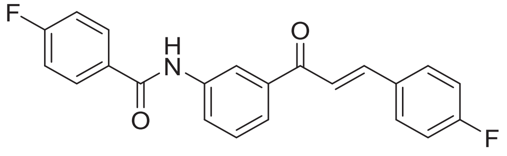
33

Fig. 35. Chemical structure compound (**33**).

the inhibition of iNOS expression [72].

3′,4′,5′,3,4,5-hexamethoxy-chalcone (**21c**) **(**Fig. 23) was screened as an anti-inflammatory agent through the evaluation of its potential to reduce nitric oxide (NO) production and suppression of iNOS synthesis. It was found that **21c** (at 10–30 μM dose) reduced NO production and iNOS synthesis in LPS-induced RAW 264.7 macrophages due to the suppression of NF-κB activation [73]. A chalcone derivative viz. *4-hydroxylonchocarpin* (**32)** (Fig. 34) was isolated for the first time from the methanol extracts of *Psoralea corylifolia*. The isolated chalcone derivative was screened for its inhibitory effect against NO production in LPS-activated microglia. It was deduced that **32** suppressed the NO production in a dose-dependent way with its IC_{50} value of 10.2 μM (Table 3). Moreover, western blot analysis and RT-PCR experiment confirmed that **32** inhibited the expression of protein and mRNA of iNOS in LPS-induced microglial cells at 10 μM [74].

Sensitization of afferent nerve ending is blocked by inhibition of PGE_2 which in turn prevents the spreading of inflammation. The inhibitory effect of licochalcone A (**7**) (Fig. 9) against chemical mediator PGE_2 was investigated by Furuhashi and coworkers. The results indicated that licochalcone A (**7**) selectively inhibited the COX-2-dependent PGE_2 production (IC_{50} = 15.0 nM), thus decreasing inflammation [75]. A vital approach for the inhibition of PGE_2 activity is to couple chalcone derivatives with a prenylated moiety. Synthesis of chalcone derivatives coupled to a prenylated moiety was reported and their inhibitory ability was assessed using LPS-induced mouse macrophage cell line. Compound (**33**) (Fig. 35) was found to be the most potent PGE_2 inhibitor with 90% inhibitory activity at 50.0 μM [76].



35

Fig. 37. Chemical structure (**35**) of carboxamide linked chalcone derivative.

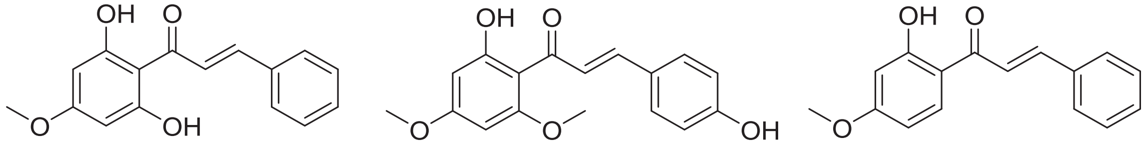
2′-hydroxychalcone analogues (Fig. 36) were reported to show inhibition against PGE_2 production in 12-O-tetradecanoylphorbol 13-acetate (TPA) induced murine macrophages. PGE_2 production was potently inhibited by *2′,4-dihydroxy-4′-methoxychalcone* (**34a**), *2′,4- dihydroxy-6′-methoxychalcone* (**34b**) and *2′-hydroxy-4′-methoxychalcone* (**34c**) with IC_{50} values of about 3.0 μM. Results concluded that 4′-OCH_3 and 6′-OCH_3 moieties are essential for the suppression of PGE_2 production. Moreover, the activity of COX-1 was selectively blocked by compound (**34c**) [77].

Selected chalcone derivatives (as NO inhibitors), their sources and IC_{50} values are given in **table**

3.3. NF-κB inhibition

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that modulates transcription of DNA, cytokine generation and cell existence. NF-κB pathway has long been known as an ideal pro-inflammatory signaling path, mainly based on the role of NF-κB in the expression of pro-inflammatory genes comprising cytokines, chemokines, and adhesion molecules. NF-κB is a favorable target for designing novel anti-inflammatory medicines and has been associated with interleukin-1 (IL-1, acting as a pro-inflammatory cytokine) and Tumor Necrosis Factor-α (TNF-α, a cell signaling protein involved in systematic inflammation) signaling pathways. They behave as pro-inflammatory cytokines and their inhibitors are used in the treatment of chronic inflammatory diseases [78,79]. Chu et al. reported the synthesis of novel chalcone derivatives via Claisen-Schmidt condensation, and evaluated them against the activity of LPS-induced NF-κB. The results indicated that all synthetic compounds efficiently suppressed the activity of LPS-induced NF-κB. However, *(E)-4-Fluoro-N-(3-(3-(4-fluorophenyl)acryloyl)phenyl)-benzamide* (**35) (**Fig. 37) showed the most potent inhibition of NF-κB with its IC_{50} value of 1.12 ± 0.53 μM (Table 4). Moreover, **35** also suppressed miscellaneous inflammatory mediators such as TNF-α, IL-1β, IL-6, and PGE_2 [80].

Chalcone derivatives namely, Isoliquiritigenin **36a**, butein **36b** and homobutein **36c** (Fig. 38) have been reported to suppress TNF-α activated NF- κB activity in addition to the inhibition of histone deacetylase activity. SAR analysis indicated that hydroxy groups at 2′-, 4′-, 3- and 4-positions were key for the double activity of the three compounds [23,81]. Derivative **36a** was also evaluated for its anti-inflammatory activity by Watanabe et al. and was found to minimize the inflammation of adipose tissues via both inflammasome-dependent and



34a **34b** **34c**

Fig. 36. Chemical structures (**34a-c**) of 2′-hydroxychalcone analogues.

Table 4
Selected chalcone derivatives (as NF-κB inhibitors), their sources and IC_{50} values.

Compound No.	Chalcone derivatives	Source	IC_{50} values (μM)	Reference
35	*(E)-4-Fluoro-N-(3-(3-(4-fluorophenyl)acryloyl)phenyl) benzamide*	Synthetic	1.12 ± 0.53	[80]
41	*(E)-1-(6-Amino-3/,4/-dimethoxy-[1,1/-biphenyl]-3-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one*	Synthetic	1.70	[90]
42	*4′-hydroxychalcone*	Synthetic	30	[91]
43a	*(E)-1-(2-(decyloxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one*	Synthetic	2.7	[92]
43b	*(E)-1-(2-hydroxy-6-(tetradecyloxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one*	Synthetic	4.2	[92]
45a	*Kuwanon J 2,4,10″-trimethyl ether*	*Morus alba* root barks	4.65	[94]
45b	*Kuwanon R*	*Morus alba* root barks	7.38	[94]
37	Cardamomin	*Alpinia conchigera*	1.2	[96]
48	*(E)-3-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one*	Synthetic	5.1 ± 1.9	[101]

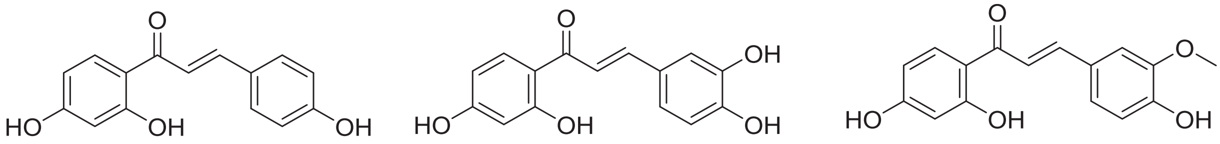

36a **36b** **36c**

Fig. 38. Chemical structures of Isoliquiritigenin (**36a**), butein (**36b**), and homobutein (**36c**).

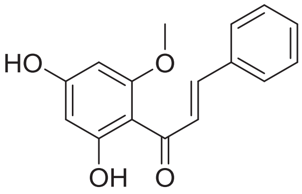

37

Fig. 39. Chemical structure (**37**) of Cardamonin.

independent pathways producing inhibition of IκBα phosphorylation in sequence, hence resulting in the suppression of NF-κB activation. Palmitic acid-induced macrophage activation was also reduced by **36a**, thus causing additional anti-inflammatory activity [82]. Kumar et al investigated the effect of **36a** on NF-κB activation in human primary endothelial cells via electrophoretic mobility shift assay, and found that **36a** prevents the translocation and stimulation of NF-κB (TNF-α induced) by hindering the phosphorylation and subsequent decomposition of IkBα. Overall, the results suggested that **36a** and its derivatives can be useful precursors for the development of efficient anti-inflammatory agents [83]. Pandey and coworkers reported that **36b** blocked NF-κB activation induced by TNF and numerous other inflammatory agents in a dose- and time-dependent manner. Human myeloid leukemia KBM-5 cells were nurtured with 50 μM **36b** for 4 h, exposed to 0.1 nM TNF for a specified duration of time, and then examined for NF-κB activation by EMSA (electrophoretic mobility shift assay). EMSA results revealed that **36b** alone did not exert an inhibitory effect on NF-κB activation, rather it suppressed TNF-facilitated NF-κB activation dose- and time-dependently. Experimental data further indicated that **36b** also suppressed the NF-κB reporter activity stimulated by TNFR1, TRADD, TRAF2, NIK, TAK1/TAB1, and IKK-β. Furthermore, **36b** inhibited the phosphorylation and degradation of IκBα by preventing activation of IκBα kinase [84].

Cardamonin (*2′,4′-dihydroxy-6′-methoxychalcone*) **37** (Fig. 39), is a chalcone principally isolated from the seeds of *Alpinia Katsumadai Hayata*. Ren and coworkers administered **37** in dextran sulfate sodium-induced mouse and noted considerable improvement in physio-pathological conditions. This study opened a new window to cure experimental inflammatory bowel disorders. Derivative **37** caused inhibition of nuclear translocation of NF-κB p65, suppression of κBα, NF-κB-luciferase, κB kinase-α/β activity, and decreased NF-κB target genes [85]. Compound **37** has also been reported to exhibit an anti-inflammatory effect in cellular models of inflammation. In order to know the molecular target of **37**, its potential to suppress NO and PGE_2 synthesis, COX-2, and iNOS expression and enzymatic activity, and crucial molecules in the NF-κB pathway were evaluated [86].

Chalcone derivative, *E-α-(p-methoxyphenyl)-2′,3,4,4′-tetramethoxychalcone* (E-α-p-OMe-C_6H_4-TMC) **38** (Fig. 40) has been reported to be an extremely effective and safe anti-inflammatory compound. Experimental data revealed that **38** blocked the activity of NF-κB expression dose-dependently in LPS-exposed RAW264.7 macrophages and suppressed pro-inflammatory factors like interleukins in Jurkat and HK-2 cells [87].

Two novel dihydrotriazine-chalcones, *(E)-1-(3-(3-((7,9-diamino-6,8,10-triazaspiro[4.5]deca-7,9-dien-6-yl)oxy)propoxy)phenyl)-3-phenylprop-2-en-1-one,hydrogen chloride* (**39a)** and *(E)-1-(3-(4-((7,9-diamino-6,8,10-triazaspiro[4.5]deca-7,9-dien-6-yl)oxy)butoxy)phenyl)-3-phenylprop-2-en-1-one, hydrogen chloride* (**39b)** (Fig. 41) were assessed for their anti-inflammatory potential. It was observed that both compounds (at non-toxic doses) suppressed iNOS and COX-2 in LPS-stimulated murine macrophage-like RAW 264.7 cells as well as TNF-α in LPS-stimulated human monocytes isolated from healthy donors. The underlying mechanism revealed that both chalcone-derivatives caused suppression of NF-κB signaling pathway which in turn inhibited inflammation. The anti-inflammatory effects of dihydrotriazine-chalcones were credited to the chalcone pharmacophore as the triazine-only compound exhibited a slight suppression against inflammatory mediators [88].

2′,4-dihydroxy-3′,4′,6′-trimethoxychalcone **40** (Fig. 42) is a chalcone derivative isolated from *Chromolaena odorata (L.)*. Its anti-inflammatory mechanism against LPS-induced inflammation in RAW 264.7 macrophages has been investigated. The results revealed that **40** considerably decreased the production of NO and pro-inflammatory cytokines, TNF-α, interleukin-1β, and IL-6 dose-dependently. Additionally, **40** blocked NF-κB activation by inhibiting stimulation of

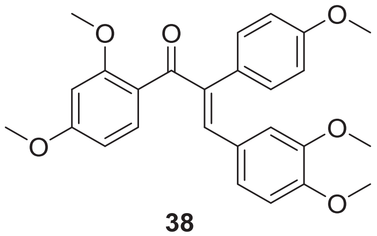

38

Fig. 40. Chemical structure (**38**) of E-α-p-OMe-C_6H_4-TMC.

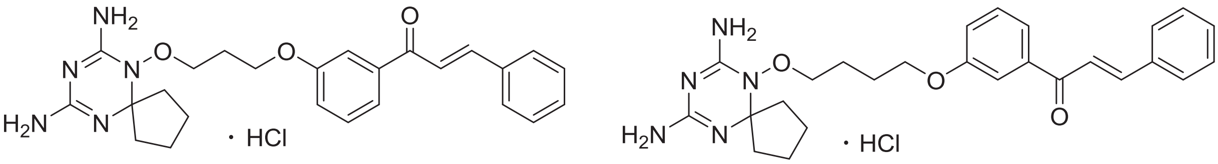

39a **39b**

Fig. 41. Chemical structures (**39a** and **39b**) of dihydrotriazine-chalcones.

inhibitor κB kinase (IKK) α/β, degradation of inhibitor κB (IκB) α, and translocation of p65 NF-κB into the nucleus. The half-maximal cytotoxic concentration (CC_{50}) value of **40** was 108.78 ± 1.76 μM, showing its low cytotoxic effects, while its IC_{50} value for the inhibition of NO-production was 7.80 ± 0.36 μM. It was further deduced that pre-treatment with **40** (4–16 μM) reduced the high levels of TNF-a, IL-1b, and IL-6 dose-dependently. The IC_{50} values of **40** for TNF-a, IL-1b, and IL-6 were reported to be 6.46 ± 0.81, 6.06 ± 1.09, and 5.23 ± 0.92 μM, respectively. Overall, the study suggests a new role of this chalcone derivative and it may be considered as a possible drug for relieving inflammation [89].

A series of new biaryl-based chalcones were synthesized and examined for NF-κB suppression. NF-κB activation inhibition assay was carried out on A549 based model. The results indicated that majority of the synthesized chalcones exhibited potent to average inhibitory activities (IC_{50} = 1.70 μM-35.28 μM) against TNFα induced NF-κB activation while few of them showed no evident effects (IC_{50} > 50 μM). Among all the synthesized chalcones, *(E)-1-(6-Amino-3′,4′-dimethoxy-[1,1′-biphenyl]-3-yl)-3-(2,4-dimethoxyphenyl)prop-2-en-1-one* (**41**) (Fig. 43) was the strongest inhibitor of TNFα induced NF-κB activation having IC_{50} value of 1.70 μM (Table 4). The biaryl-based chalcone derivatives also exhibited anticancer activities to a panel of cancer cell lines. Since research has confirmed the correlation between inflammation and cancer therefore, it was proposed that the NF-κB inhibition might be one of the potential mechanisms responsible for the anticancer activities of chalcone derivatives [90].

Orlikova and coworkers investigated the anti-inflammatory activity of *4′-hydroxychalcone* (**42**) (Fig. 44) against TNFα-induced NF-κB pathway. They found that **42** suppressed the TNFα-induced NF-κB pathway activation dose-dependently with an IC_{50} value of 30 μM (Table 4). Moreover, compound **42** did not show toxicity against healthy cells. SAR study showed that hydroxyl groups contributed to the enhanced inhibitory effect of **42** against TNFα-induced NF-κB pathway activation [91].

A series of 2,4-dihydroxy-6-isopentyloxychalcones were synthesized by Venkateswararao et al. The synthesized derivatives were screened for their *in vitro* inhibitory effects against LPS induced NF-κB activation in RAW 264.7 cells. Experimental data indicated that *(E)-1-(2-(decyloxy)-6-hydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one* (**43a**) and *(E)-1-(2-hydroxy-6-(tetrade-cyloxy)phenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one* (**43b**) (Fig. 45) exhibited the strongest inhibitory activities with IC_{50} values of 2.7 μM and 4.2 μM, respectively (Table 4). Moreover, SAR analysis indicated that the length (C8–C14) and C-6 position of a linear alkyl chain of ring-A are the key factors for the enhanced inhibitory activity. Moreover, α, β-unsaturated ketone moiety and the presence of the hydroxyl group at 4-position on ring-B are vital for the inhibitory activity of 2,4-dihydroxy-6-isopentyloxychalcone derivatives against LPS induced NF-κB activation [92].

The effect of Xanthohumol (**44**) (Fig. 46) on NF-κB levels and phosphorylation of IκBα has been studied. Experimental data revealed that **44** shows anti-inflammatory effect via the inhibition of NF-κB. Splenic T lymphocytes were pre-exposed to **44** (2.5–20 μM) for 18 h before activation with Con A (1 μg/mL) for 1.5 h. Overall, the results confirmed that the suppression of T cell responses (caused by **44**) is partly attributed to the inhibition of NF-κB via suppression of IκBα phosphorylation and its breakup [93].

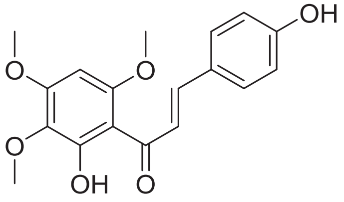

40

Fig. 42. Chemical structure compound (**40**).

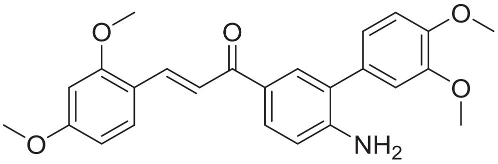

41

Fig. 43. Chemical structure of compound (**41**).

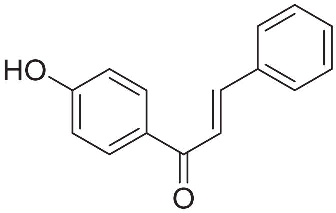

42

Fig. 44. Chemical structure compound (**42**).

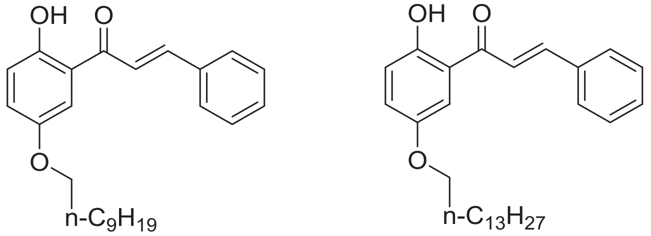
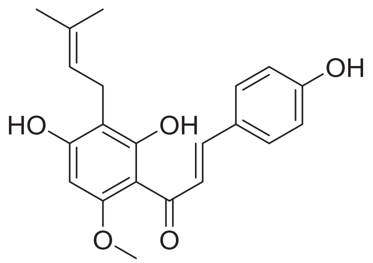

43a **43b**

Fig. 45. Chemical structures **(43a and 43b)** of dihydroxychalcone derivatives.

Two chalcone-derived Diels-Alder adducts (**45a** and **45b**) (Fig. 47) were isolated from the methanol extract of *Morus alba* root barks and were subsequently screened for inhibitory effects against NF-κB activity. It was observed that *kuwanon J 2,4,10″-trimethyl ether* (**45a**) and *kuwanon R* (**45b**) strongly inhibited the activity of NF-κB in human cervical cancer HeLa cells activated through TNF-α with their IC_{50} values of 4.65 and 7.38 μM, respectively (Table 4) [94].

Four chalcone derivatives, i.e. xanthoangelol, xanthoangelol **46a**, **46b** and **46c** (Fig. 48) isolated from the root of *Angelica keiskei KOIDZUMI* (Umbelliferae) were investigated for their inhibitory effects against NF-κB activation and ET-1 gene expression in cultured porcine aortic endothelial cells (PAECs). The results indicated that only **46a**



44

Fig. 46. Chemical structure (**44**) of Xanthohumol.

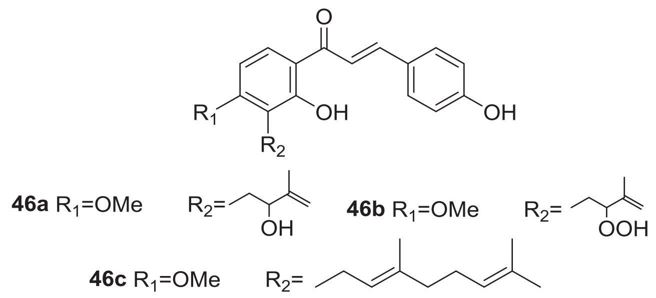
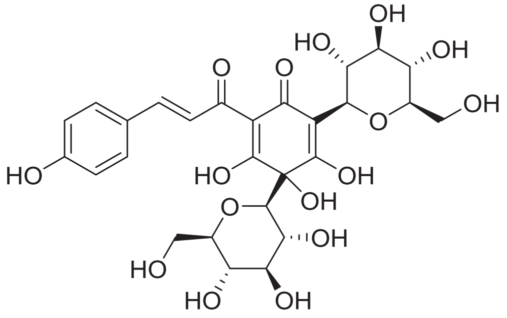


Fig. 48. Chemical structures (**46a**, **46b**, and **46c)** of xanthoangelol.



47

Fig. 49. Chemical structure (**47**) of Hydroxysafflor yellow A.

exposure significantly inhibited both basal and TNF-α-induced NF-κB stimulation in PAECs, whereas the remaining three derivatives were inactive. The underlying mechanism revealed that **46a** selectively inhibited the phosphorylation of IκBα instead of the decomposition of phosphorylated IκBα. Moreover, **46a** considerably decreased basal and TNF-α-activated prepro ET-1 mRNA expression in PAECs [95].

Cardamonin (**37**) (Fig. 39) has also been identified as an inhibitor of NF-κB activation. An NF-κB reporter gene assay was performed to examine the effect of cardamomin on the induced NF-κB activation through numerous stimuli. Experimental data revealed that cardamomin suppressed the LPS-induced expression of NF-κB reporter gene construct dose-dependently with an IC$_{50}$ value of 1.2 μM (Table 4). Moreover, TNFα-activated expression of NF-κB reporter gene construct was also suppressed by cardamonin in a similar way [96]. Shen and coworkers reported that chalcone (1,3-diphenyl-2-propenone) suppressed the translocation and activation of NF-κB in human bladder cancer cells. Western blot analysis indicated that chalcone caused a substantial improvement in the expression of IκBα in T24 and HT-1376 cells after 3, 6 and 12 h in the cytoplasm. On the other hand, chalcone treatment caused a decrease in the protein expression of NF-κB in the nuclei of both cell lines after 3, 6 and 12 h, whereas NF-κB was deposited in the cytoplasm [97]. Hydroxysafflor yellow A (47) (Fig. 49) is one of the principal bioactive and water-soluble chalcones isolated from *Carthamus tinctorius* L [98]. The suppressive effects of 47 on the inflammatory signal transduction pathway related factors (activated by stable cerebral ischemia) in rats were studied. The result revealed that administration of 47 (10 mg × kg(−1)) in rats caused considerable inhibition of the phosphorylation of IκBα (after cerebral occlusion). Moreover, compound 47 suppressed the transcriptional level of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, and stimulated mRNA expression of anti-inflammatory cytokine IL-10. Overall, the results suggested that the anti-inflammatory effect of 47 is due to its potential to inhibit NF-**κ**B activity and the mRNA expression of cytokines in the inflammatory transduction pathway [99].

Licochalcone (**7**) (Fig. 9) has the ability to suppress the formation of osteoclasts through preventing activation of the ERK (extracellular signal-regulated kinase) and NF-kB signaling pathways which could subsequently influence the stimulation of AP-1 components such as Fra-2. Moreover, licochalcone A also suppressed the translocation of NF-κB into the nucleus and mRNA expression of Fra-2 [100]. Synthesis of three sets of chalcones was reported by Srinivasan et al. The synthesized compounds were investigated for their inhibitory effects against kinases upstream of NF-κB. Results indicated that majority of the chalcones had a broad range inhibitory activities against NF-κB with few of them showing IC$_{50}$ values less than 10 μM. SAR study showed that the structural complexity of chalcones had no correlation with the inhibition of NF-κB activity. Moreover, alteration in the electron cloud on chalcone scaffold had no effect on NF-κB inhibition and simple chalcones with only hydroxyl and methoxy substituents possessed significant potency against NF-κB activity. Additionally, the inhibitory effect was totally lost after reduction of the alkene moiety in chalcone, supporting the concept that the mechanism of suppression is probably via covalent Michael addition of nucleophiles (such as SH from cysteine) of protein candidate(s) to chalcones. Among all chalcones, *(E)-3-(3-hydroxy-4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one* (**48**) (Fig. 50) exhibited the most potent inhibitory effect against NF-κB activity with its IC$_{50}$ of 5.1 ± 1.9 μM (Table 4). Chalcone derivative **48** directly blocks the kinase activities of I kappa B kinase 2 (IKKβ) and interleukin-1 receptor-associated kinase 4 (IRAK4), possibly

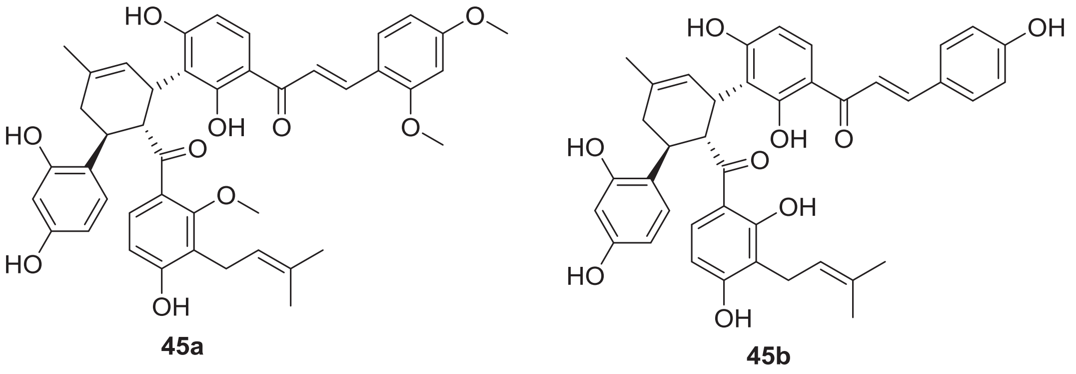
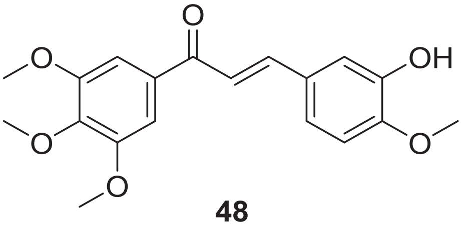


Fig. 47. Chemical structures of *kuwanon J 2,4,10″-trimethyl ether* (**45a**) and *kuwanon R* (**45b**).



48

Fig. 50. Chemical structure of compound (**48**).

causing its NF-κB inhibitory effects [101].

Selected chalcone derivatives (as NF-κB inhibitors), their sources and IC_{50} values are given in Table 4

3.4. Inhibition of miscellaneous inflammatory mediators

Synthesis and evaluation of the anti-inflammatory activity of 2-choroquinolinyl chalcones (Fig. 51) through human cell systems and the mouse air pouch model have been reported by Herencia et al. The results indicated that most of the synthesized compounds had anti-inflammatory activities *in vitro*. Chalcone derivatives, **49a, 49b, 49f, 49g,** and **49i** suppressed degranulation and 5-1ipoxygenase (5-LO) in human neutrophils. The 5-LO inhibitor ZM230, 487 exhibited IC_{50} values and 95% confidence limits of 0.06 (0.03–0.1) and 0.09 (0.06–0.1) μM on intact cells and cytosolic portions, respectively. *(E)-1-(3,4-dimethoxyphenyl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one* **(49 h)** acted as a scavenger of superoxide anion produced by activated human neutrophils or by the hypoxanthine/xanthine oxidase system with IC_{50} values of 0.1 (0.1–0.2) and 0.3 (0.1–0.9) μM, respectively. Moreover, **49 h** also suppressed the iNOS expression via a superoxide-dependent mechanism in activated mouse peritoneal macrophages and safeguarded cells against oxidant stress. COX-2 activity was suppressed by four chalcone derivative (**49b-e**) with their percentage inhibitions of 36.3 ± 4.5, 35.6 ± 5.3, 41.8 ± 5.5 and 46.6 ± 4.4, respectively [102].

Synthesis of a new series of chalcones-curcumin conjugates (Fig. 52) has been reported. The target conjugates were screened for their anti-inflammatory activity via mouse RAW 264.7 macrophages. Most of the synthesized compounds efficiently suppressed (50–95% at 10 μmol concentration) the expression of TNF-α and IL-6 promoted by LPS, preferably IL-6, comparable to or stronger than the curcumin at equal concentration. *(1E,4E)-1-(3-allyl-4-methoxyphenyl)-5-(2,5-dibromophenyl)penta-1,4-dien-3-one* **(50)** exhibited the strongest inhibitory effects on LPS-promoted TNF-α and IL-6 generation with inhibition rates of 67.5% and 91.1%, respectively. Additionally, SAR analysis revealed that the asymmetric derivatives had greater anti-inflammatory activity than their symmetric analogues, whereas the electro-negativity and molecular polarizability were considered as key parameters for the suppression of LPS-promoted IL-6 expression [103].

Nassar et al. reported the synthesis of a series of chalcone-based diaryl pyrazole containing a phenyl sulphone or carbonitrile scaffolds (Fig. 53). The synthesized compounds were investigated for anti-inflammatory activity using carrageenin-induced rat hind paw oedema model. The results indicated that some target compounds caused a substantial decrease in inflammation after 3 h of dose administration. Among the tested diarylpyrazole-based chalcones, *(E)-1-(1,5-diphenyl-4-(phenylsulfonyl)-1H-pyrazol-3-yl)-3-(p-tolyl)prop-2-en-1-one* (**51**) had the highest anti-inflammatory activity (83.77%) with small gastrointestinal toxicity. SAR analysis suggested that majority of the phenylsulfonylpyrazoles possessed greater anti-inflammatory activity than

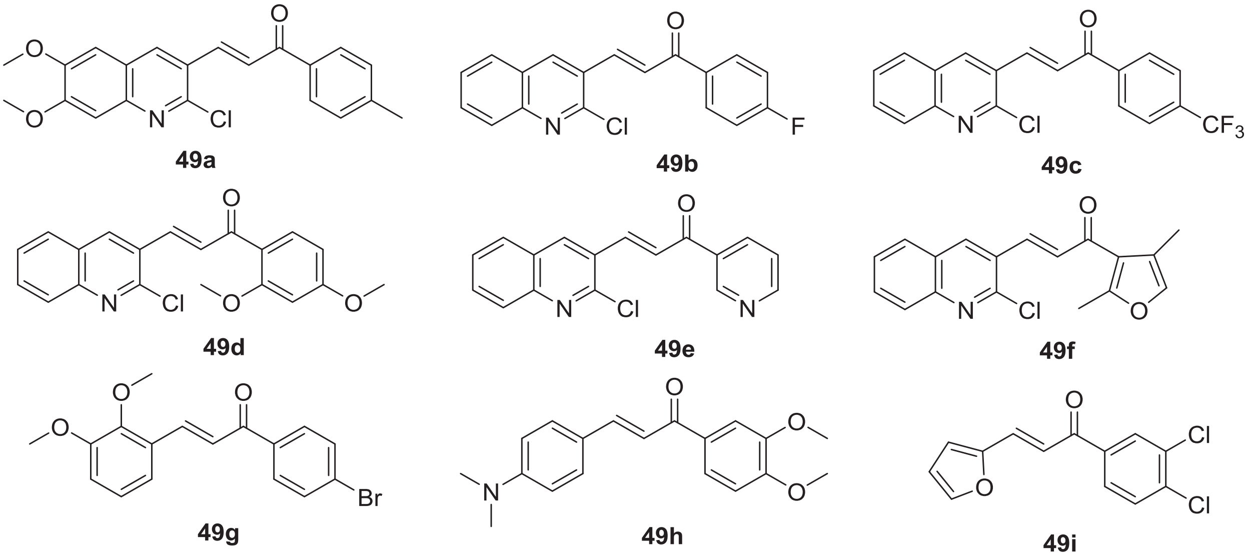


Fig. 51. Chemical structures of compounds (**49a-i**).

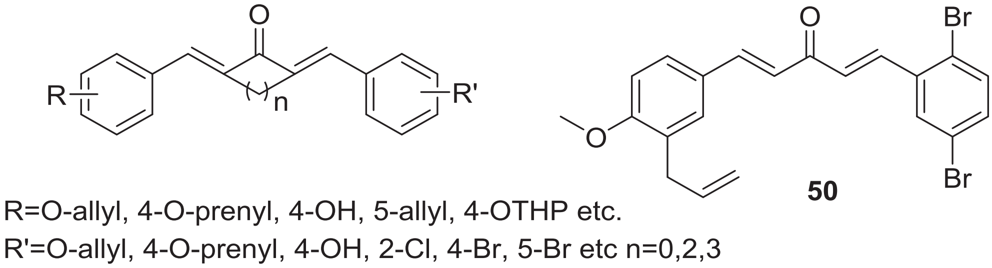


Fig. 52. Chemical structures of chalcone-curcumin conjugates and a representative derivative (**50**).

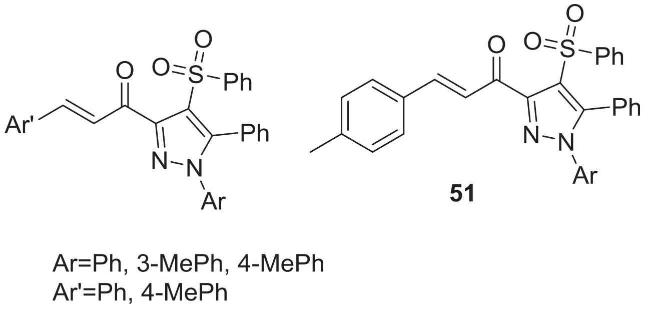


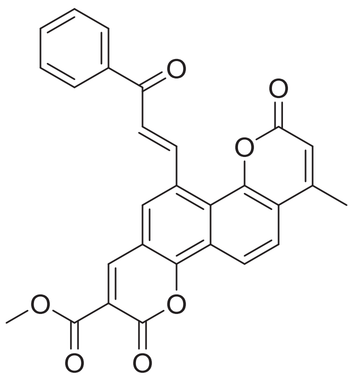
Fig. 53. Chemical structures of diarylpyrazole-based chalcones and a representative derivative (**51**).

carbonitrilepyrazoles. Moreover, the phenyl sulphone moiety and carbonyl group connected to the pyrazole structure is an important pharmacophore to control the anti-inflammatory activity [104].

Sashidhara and coworkers reported the synthesis and anti-inflammatory screening of bis-coumarin-chalcone hybrids via the carrageenin-induced paw oedema in albino rats. Among the synthesized derivatives, *(E)-methyl 7-methyl-3,9-dioxo-11-(3-oxo-3-phenylprop-1-enyl)-3,9-dihydrochromeno[8,7-h]chromene-2-carboxylate* (**52**) (Fig. 54) was the most potent anti-inflammatory agent (33% anti-inflammatory activity) at 100 mg/kg concentration along with 4% and 21% TNF-∝ inhibition at doses of 200 and 400 µg/mL, respectively. The results suggested that the anti-inflammatory activity of **52** might partially be owing to its radical scavenging action [105].

Synthesis and anti-inflammatory activities of six chalcone derivatives (Scheme 10), namely *1-(4-nitrophenyl)-3-(2,4,6-trimethoxyphenyl) propen-1-one* (**53a**), *1-(4-nitrophenyl)-3-(3-bromo-phenyl)propen-1-one* (**53b**), *1-(4-methoxyphenyl)-3-(3-bromophenyl)propen-1-one* (**53c**), *1-(4-methoxyphenyl)-3-(2,4,6-trimethoxyphenyl)-propen-1-one* (**53d**), *1-(2,4-dihydroxyphenyl)-3-(phenyl)propen-1-one* (**53e**), *1-(4-nitrophenyl)-3-(4-chlorophenyl)propen-1-one* (**53f**) were reported. The synthesized compounds were evaluated for anti-inflammatory activities at doses of 20, 40 and 80 mg/kg. It was found that all compounds effectively suppressed carrageenan-induced rat paw edema in Wistar rats in a dose-dependent way. The inhibitory action increased with an increase in concentration from 20 to 80 mg/kg and between the third and fourth hour. SAR analysis indicated that methoxy moieties are required for a quicker initiation of activity. Additionally, a bromine atom at position 3 of ring-B appeared to be essential for stronger suppression of inflammation, while chlorine atom at position 4 of ring-B caused comparatively lower activity [106].

Synthesis of chlorinated chalcone derivatives, *(E)-3-(2-chlorophenyl)-1-phenylprop-2-en-1-one* (**54a**) and *(E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one* (**54b**) (Fig. 55) has also been reported by the condensation of acetophenone with chlorinated benzaldehyde in the presence of sodium hydroxide. Cotton pellets induced granuloma method was used to assess the anti-inflammatory activity of the synthesized compounds. The results indicated that chlorinated chalcone derivatives had better anti-inflammatory activity compared to diclofenac sodium, but exhibited weaker activity than dexamethasone. The total inhibition rates (%) of 2-chlorochalcone and 4-chlorochalcone were 0.28 and 0.22, respectively, compared to those of standard drugs diclofenac sodium (0.10) and dexamethasone (0.35). It was deduced that the anti-inflammatory activity of chlorinated chalcone derivatives was related to the inhibition of inflammatory facilitators, TNF-α, NO, COX-2, and interleukins [107].



52

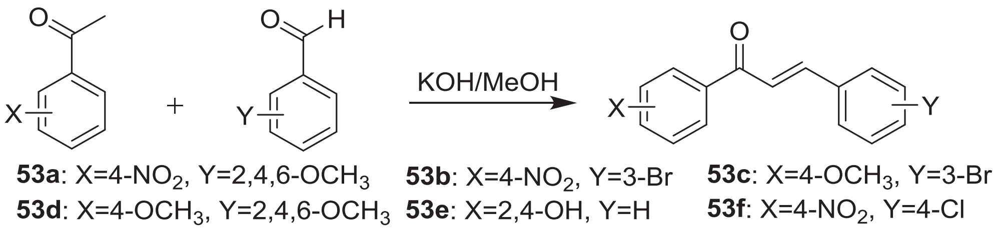
Fig. 54. Chemical Structure (**52**) of a biscoumarin-chalcone hybrid.

Kotra et al. synthesized a new series of quinolinyl chalcone derivatives (Fig. 56) and evaluated their anti-inflammatory activities via carrageenin-induced acute paw oedema model in rats using indomethacin as a control. Some derivatives showed a substantial reduction in paw oedema. Compound carrying furyl ring and chloro substituent i.e. *1-(7-Chloro-3-methyl-1-phenyl-2-napthyl)-3-(2-furyl)-2-propen-1-one* (**55**) showed substantial anti-inflammatory activity with an 81.78% decrease in paw oedema. Furthermore, most potent derivatives were safe (up to 2000 mg/kg) in acute oral toxicity studies [108].

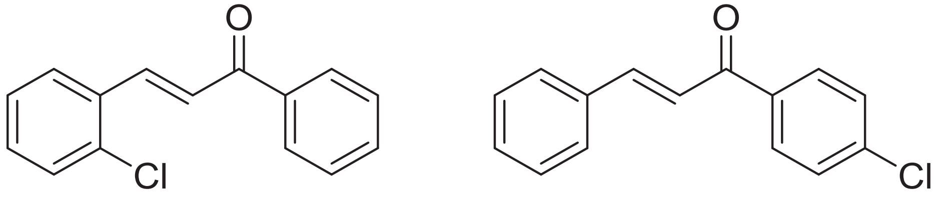
Prasad and coworkers reported the synthesis of new 4′-amino chalcone derivatives by Claisen-Schmidt condensation of 4-amino acetophenone with numerous substituted aromatic and heteroaromatic aldehydes. Their anti-inflammatory activities were measured using spraygue-Dawley rats. The results revealed that majority of the tested compounds possessed moderate anti-inflammatory activities. *(E)-1-(4-aminophenyl)-3-(4-nitrophenyl)prop-2-en-1-one* (**56**) (Fig. 57) exhibited the highest anti-inflammatory activity (97.35 ± 2.98) compared to that of reference standard aceclofenac (99.98 ± 2.00) after 4 h. SAR analysis revealed that the enhanced activity of **56** is due to the presence of nitro group at 4-position on the aromatic ring-B of chalcone. Furthermore, it was also noted that the compounds carrying 4-pyridinyl and 2-quinolinyl as ring-B of chalcone exhibited higher anti-inflammatory activity [109].

A series of compounds was synthesized by carrying out substitution on 2′,4′-dihydroxychalcones or *4′-hydroxychalcones* (Scheme 11). The synthesized compounds were screened for anti-inflammatory activity by measuring their potential to inhibit xylene-induced ear edema in mice. Numerous tested compounds showed substantial anti-inflammatory activities. However, the highest anti-inflammatory activity was exhibited by *[(E)-1-(2,4-dihydroxyphenyl)-3-(4-dimethylamino)-phenyl)prop-2-en-1-one]* (**57 f**) and *[(E)-3-(4-chlorophenyl)-1-(2,4-dihydroxy-phenyl)prop-2-en-1-one]* (**57 h**) with their inhibition rates recorded to be 62% and 68%, respectively at a dose of 200 mg/kg administered orally 2 h prior to the inflammatory agent xylene. The inhibitory effects of the two compounds are stronger than that of ibuprofen (53%) under similar experimental conditions. SAR study revealed that an increase in the number of hydroxyl groups on the chalcone ring-A might affect the inhibitory effect related to anti-inflammatory activity, nevertheless the efficiency depended on the variation in the substituent of ring-B. The position of the substituent on the phenyl ring significantly affected the anti-inflammatory effect, with an activity order of -3,4-(OH)$_2$ < 4-OH < –3,4-OCH$_2$O– < –3–OCH$_3$-4-OH < –4-OCH$_3$ < –4-N(CH$_3$)$_2$. Moreover, the position of Cl atom on the phenyl ring might have affected the anti-inflammatory activity, with the potency order of the two Cl-substituted derivatives being -2,4-Cl$_2$ < 4-Cl, in which **57 h** demonstrated the strongest anti-inflammatory activity [110].

Gómez-Rivera et al. synthesized three nitro-substituted chalcone derivatives (compounds **58a-c**) (Fig. 58) via aldol condensation and evaluated their anti-inflammatory activity in carrageenan-induced edema in rats. The compounds (at a dose of 200 mg/kg) exhibited anti-inflammatory protective activity by both oral and intraperitoneal administration in a time-dependent way. After intraperitoneal administration, the Maximum Anti-inflammatory Protective Effect (MAPE) for

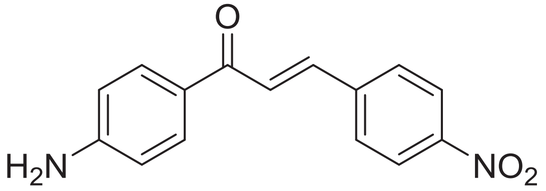


Scheme 10. Synthesis of chalcone derivatives (**53a-f**).



54a **54b**

Fig. 55. Chemical structures **(54a and 54b)** of chlorinated chalcone derivatives.



56

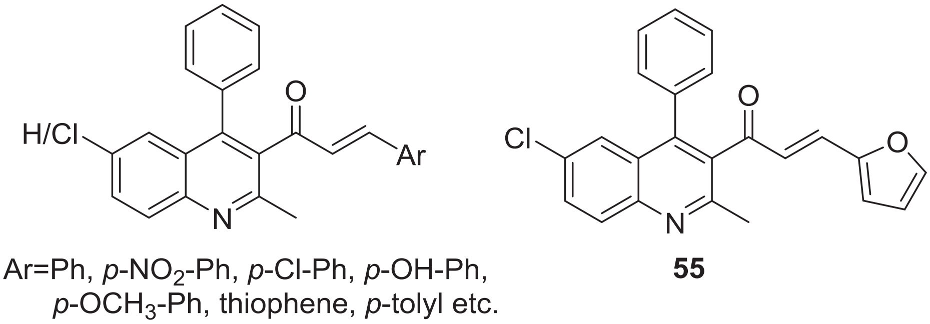
Fig. 57. Chemical structure of compound (**56**).

(E)-1-(2′-nitrophenyl)-3-phenylprop-2-en-1-one **(58a)** (58.2 ± 3.2%) was achieved 1 h after the administration. For *(E)-1-(3′-nitrophenyl)-3-phenylprop-2-en-1-one* **(58b)**, highest MAPE (68.0 ± 3.8%) was also recorded 1 h after administration, whereas *(E)-1-(4′-nitrophenyl)-3-phenylprop-2-en-1-one* **(58c)** attained its highest MAPE (43.2 ± 3.3%) 2 h after the administration. The highest MAPE (59.3 ± 3.8%) for the reference drug, meloxicam was attained 2 h after its administration. SAR study indicated that chalcone with the nitro group at *ortho* position was most effective, statistically with no substantial change compared to a reference drug [111].

Li and coworkers reported the synthesis of 35 new chalcone derivatives carrying aryl-piperazine or aryl-sulfonyl-piperazine moiety. The *in vivo* and *in vitro* anti-inflammatory activities were measured using classical *para*-xylene-induced mice ear-swelling model and ELISA assays. Results indicated that *(E)-3-phenyl-1-(4-(4-((2,4,6-triisopropylphenyl)sulfonyl)-piperazin-1-yl)phenyl)prop-2-en-1-one* **(59)** (Fig. 59) has the strongest anti-inflammatory activity *in vivo* (with an inhibition rate of 75.46% at a dose of 40 mg/kg) compared to aspirin (with an inhibition rate of 64.91% at 100 mg/kg) and celecoxib (with an inhibition rate of 77.03% at a dose of 5 mg/kg). Moreover, **59** considerably suppressed the liberation of LPS-induced IL-6 and TNF- α in RAW264.7 macrophages dose-dependently *in vitro*. Primary SAR study showed that substitution of the electron-withdrawing group at 4-position of arylpiperazine or arylsulfonyl-piperazine contributed more to the improvement of anti-inflammatory activity compared to the substitution of the electron-donating group. Moreover, substitution at 4′ position of the benzene ring did not improve the anti-inflammatory activity of the target compound [112].

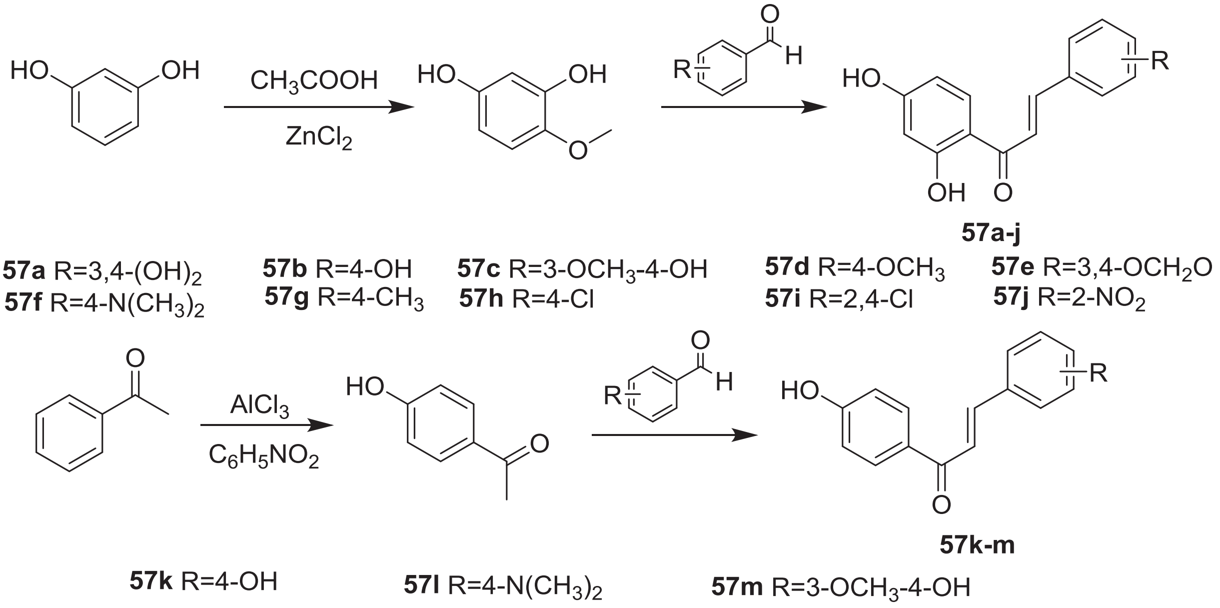
Talukdar et al. reported the synthesis of a new series of chalcone derivatives by Claisen-Schmidt condensation of suitable acetophenones with numerous aldehydes in ethanolic KOH solution. Bovine serum albumin assay (*in vitro*) and carrageenan-induced rat paw oedema method (*in vivo*) were used to evaluate the anti-inflammatory activities of the synthesized compounds. Among the tested compounds, *4-chloro-N-(4 – [3- (2, 4-dimethoxy-phenyl)-acryloyl]-phenyl)-benzamide* **(60a)** and *4-Chloro-N-(4-[3-(4-ethoxy-phenyl)-acryloyl]-phenyl)-benzamide* **60b** (Fig. 60) showed substantial anti-inflammatory activities, whereas introduction of methoxy and ethoxy moieties in target compounds caused activity enhancement [113].

Srinath and coworkers reported the synthesis of a series of some novel chalcone derivatives by Claisen-Schmidt condensation of 3′-methyl-4′-hydroxyacetophenone with numerous substituted aromatic/heteroaromatic aldehydes in the presence of a base. Their anti-inflammatory activity was measured using carrageenan-induced rat paw oedema method. Results indicated that some of them possessed substantial activity compared to the standard drug, aceclofenac. At a dose level of 10 mg/kg, (%) inhibition of *1-(3′–Methyl -4′-hydroxyphenyl)-3-(2″-pyrrolyl)-2-propen-1-one* (**61a**) and *1-(3′–Methyl -4′-hydroxyphenyl)-3-(2″-indolyl)-2-propen-1-one* (**61b**) (Fig. 61) was reported to be the highest (97 ± 1% and 98 ± 1% respectively) compared to that of the

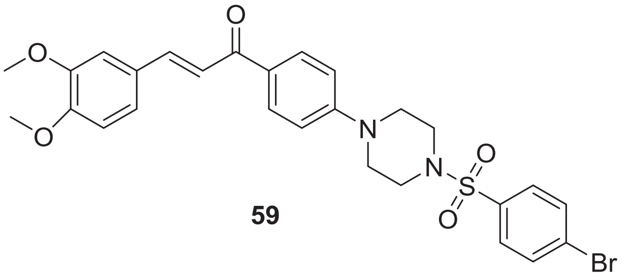


55

Fig. 56. Chemical structures of quinoline-substituted chalcones and the most potent derivative (**55**).



Scheme 11. Synthetic route for compounds (**57a-m**).



59

Fig. 59. Chemical Structure of compound (**59**).

aceclofenac (99 ± 1%) after 6 h. Moreover, chalcone derivatives containing electron-donating groups on the aromatic ring exhibited significantly higher anti-inflammatory activities. SAR analysis suggested that chalcone derivatives containing heterocyclic nuclei (indole and pyrrole) and substituents with electron-donating groups (alkoxy and alkyl) exhibit enhanced anti-inflammatory activities [114].

Synthesis of a novel series of pyrazole chalcones via Claisen–Schmidt condensation of *1-(2,4-dimethoxy-phenyl)-ethanone* and substituted *1,3-diphenyl-1H-pyrazole-4-carbaldehydes* was reported by Bandgar and coworkers. None of the synthesized compounds showed a significant inhibitory effect against TNF-α. However, compounds *1-(2,4-Dimethoxy-phenyl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)-propenone* (**62a**), *1-(2,4-Dimethoxy-phenyl)-3-[3-(4-methoxy-phenyl)-1-(1-methyl-buta-1,3-dienyl)-1H-pyrazol-4-yl]-pro-penone* (**62b),** and *3-[3-(3-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]-1-(2,4-dimethoxy-phenyl)-propenone* (**62c**) (Fig. 62) exhibited promising inhibitory activity against IL-6 with their % inhibition to be 64.72, 38.16 and 67.48, respectively at 10 µM dose without any noticeable toxicity [115].

Shih et al. synthesized a series of halo-substituted azachalcones (Fig. 63) via Claisen–Schmidt condensation and compared their anti-inflammatory activities. Mouse BALB/c macrophage RAW 264.7 cell lines were pre-exposed to 10 µg/mL of each compound for 1 h prior to stimulation of inflammation by LPS (1 µg/mL) for 6 h. The results indicated that some halo-chalcones and –azachalcones inhibited the expression of pro-inflammatory factors, comprising toll-like receptor 4 (TLR4), IκB-α, the transcription factor p65, interleukine 1β (IL-1β), IL-6, TNF-α, and COX-2. Moreover, synthetic halo-azachalcones (**64a–i**) showed more potent inhibition than halo-chalcones (**63a-i**). Amongst the azachalcones, *(E)-3-(4-fluorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one* (**64a),** *(E)-3-(3-bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one* **(64f),** *(E)-3-(2-chlorophenyl)-1-(pyridin-2-yl)prop-2-en-1-one* **(64h),** and *(E)-3-(2-bromophenyl)-1-(pyridin-2-yl)prop-2-en-1-one* **(64i)** exhibited greater anti-inflammatory activity, attributed to the presence of a nitrogen atom in azachalcones compared to the C-2 hydroxyl group in halo-chalcones [116].

Two chalcone analogues, *3-(4-Hydroxyphenyl)-1-(2-hydroxyphenyl) propenone* (**65a)** and *1-(2,6-Dihydroxy-4-methoxyphenyl)-3-phenylpropenone* **(34a) (**Scheme 12) were synthesized and their anti-inflammatory activities *in vivo* were examined. Chalcone and its two analogues were investigated using a caudal fin-wounded transgenic zebrafish line "Tg (*mpx:gfp*)" to predict the effect of neutrophil recruitment effectively. The results indicated that exposure to **34a** not only affected wound-induced neutrophil recruitment but also exerted an influence on Mpx enzymatic activity. Furthermore, compound **34a** also controlled the protein expression levels of pro-inflammatory factors (Mpx, NFκB, and TNFα). Overall, the results provided strong evidence about the anti-inflammatory effects of synthesized chalcone derivatives on wound-induced inflammation [117].

Hsieh et al. synthesized a new series of 2′-hydroxy- and 2′,5′-dihydroxychalcone derivatives by the reaction of suitable acetophenones with appropriate aromatic aldehydes using Claisen-Schmidt

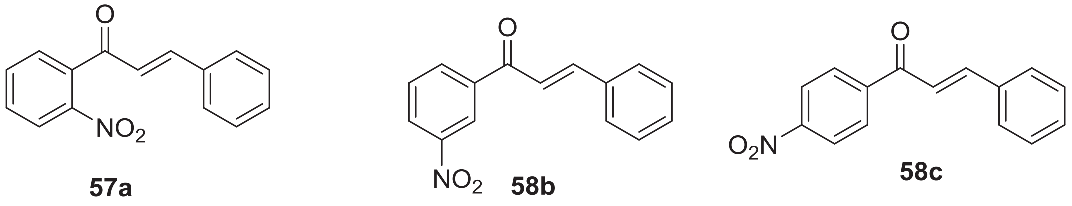
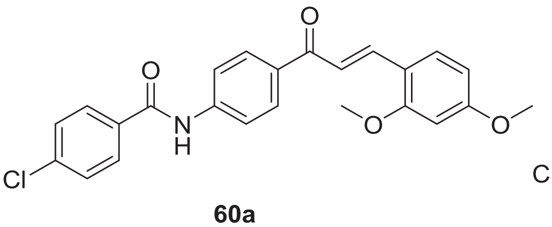
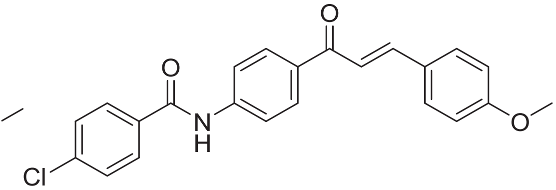


Fig. 58. Chemical structures (**58a-c)** of nitro-substituted chalcone derivatives.

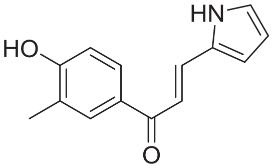


60a

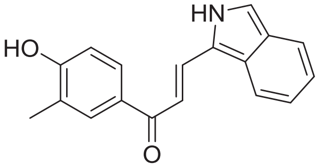


60b

Fig. 60. Chemical structures of compounds (**60a** and **60b**).



61a



61b

Fig. 61. Chemical structures of chalcone derivatives bearing pyrrole (**61a**) and indole (**61b**) moieties.

condensation. The inhibitory action of the synthesized derivatives on the stimulation of mast cells, neutrophils, microglial cells, and macrophages was evaluated *in vitro*. Majority of the synthesized hydroxychalcones were reported to have strong inhibitory effects on the liberation of *β*-glucuronidase and lysozyme from rat neutrophils activated with formyl-Met-Leu-Phe/cytochalasin B (fMLP/CB). *2′,2-Dihydroxychalcone* (**66a**) (Fig. 64) was the strongest inhibitor of the liberation of *β*-glucuronidase and lysozyme with its IC_{50} values of 1.6 ± 0.2 μM and 1.4 ± 0.2 μM, respectively. Moreover, most of the 2′,5′-dialkoxychalcones showed strong inhibitory action on NO production from N9 murine microglial cell lines activated with LPS. Among the 2′,5′-dialkoxychalcone derivatives, *2′,5′-Dipropoxy-4-chlorochalcone* (**66b**) (Fig. 64) displayed the maximum inhibitory effect with its IC_{50} value to be 0.7 ± 0.06 μM [118].

Wu et al. synthesized 54 chalcone derivatives and screened them for anti-inflammatory activity against TNF-α and IL-6 production in LPS-stimulated macrophages. RAW264.7 macrophages were pre-exposed to the most promising chalcone derivatives **67a-67e** (Fig. 65) at various concentrations (2.5, 5.0, and 10 μM) for 2 h followed by incubation of macrophages with LPS (0.5 μg/mL) for 22 h. The ELISA assay technique was used to determine the release of TNF-α and IL-6. The results indicated that compounds **67a-67e** suppressed TNF-α and IL-6 release dose-dependently and reduced LPS-stimulated TNF-α, IL-1β, IL-6, IL-12, and COX-2 mRNA production. The IC_{50} values of these derivatives were under 10 μM except that of *(E)-3-(4-hydroxy-3-methoxyphenyl)-1-(4-methoxyphenyl)prop-2-en-1-one* (**67a**) against IL-6 liberation. Compounds **67a** and *(E)-3-(2,4-dimethoxyphenyl)-1-(3,4-dimethoxyphenyl) prop-2-en-1-one* (**67e**) showed the lowest IC_{50} values (2.76 μM and 2.70 μM) against the expression of TNF-α and IL-6, respectively. Quantitative structure-activity relationship (QSAR) models indicated that the existence of electron-withdrawing groups (F, Cl, $-NO_2$, −CN, CF_3, $-CCl_3$ etc.) in ring-B and electron-donating groups ($-OCH_3$, $-NH_2$, −OH etc.) in ring-A of chalcone derivatives was vital for suppression of LPS-stimulated IL-6 expression. The anti-inflammatory potential of the synthetic chalcone derivatives was confirmed by their ability to inhibit TNF-α and IL-6 release dose-dependently [119].

A series of eight chalcone derivatives (**68a-h**) (Fig. 66) through Claisen–Schmidt condensation of appropriate acetophenones with suitable aromatic aldehyde was reported by Ku and coworkers. The inhibitory action against the activation of mast cells, neutrophils, macrophages, and microglial cells indicated that majority of the 2′,5′-dihydroxychaclone analogues showed strong inhibition on the liberation of β-glucuronidase and lysozyme from rat neutrophils activated

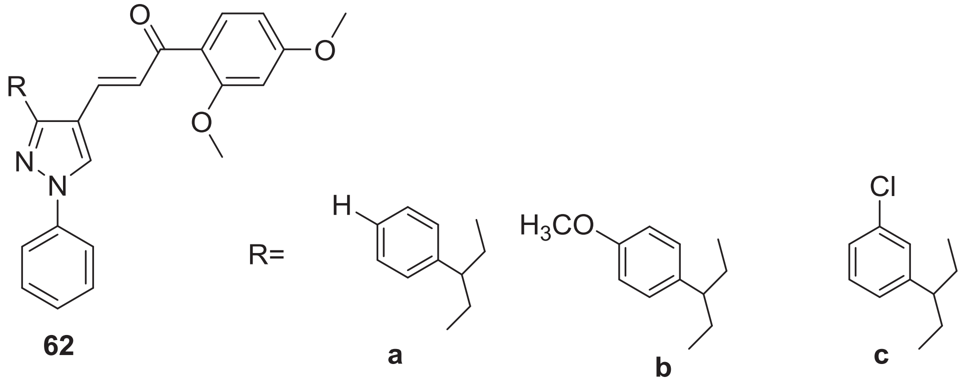
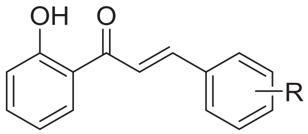
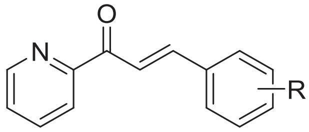


Fig. 62. Chemical structures of compounds (**62a-62c**).

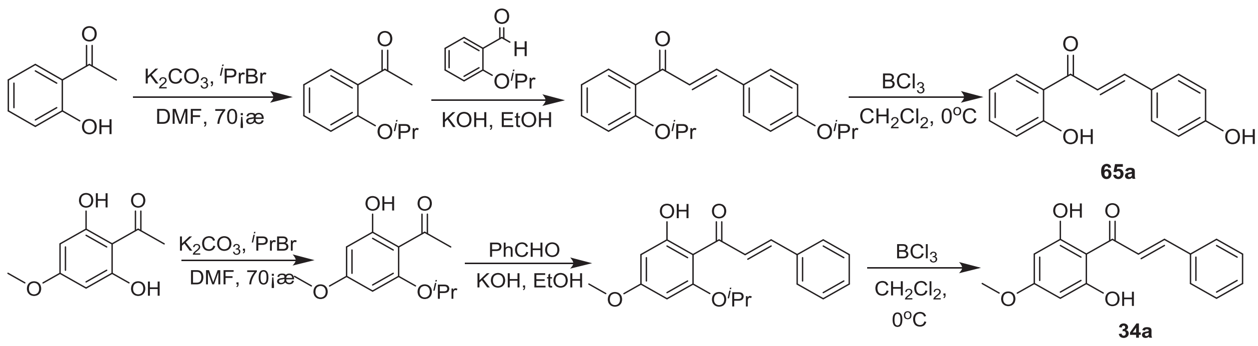


63a R=4-F; **63b** R=4-Cl; **63c** R=4-Br; **63d** R=3-F; **63e** R=3-Cl; **63f** R=3-Br; **63g** R=2-F; **63h** R=2-Cl; **63i** R=2-Br;



64a R=4-F; **64b** R=4-Cl; **64c** R=4-Br; **64d** R=3-F; **64e** R=3-Cl; **64f** R=3-Br; **64g** R=2-F; **64h** R=2-Cl; **64i** R=2-Br

Fig. 63. Chemical structures of synthetic chalcones (**63a-i**) and azachalcones (**64a-i**).



Scheme 12. Synthesis of chalcone analogues (**65a** and **34a**).

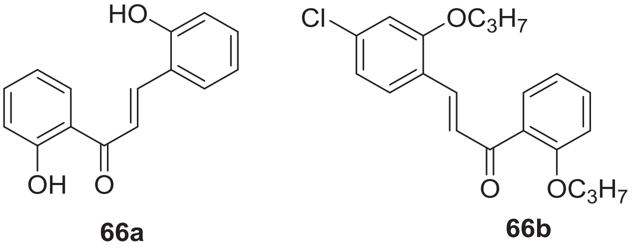


Fig. 64. Chemical structures (**66a** and **66b)** of hydroxychalcones.

with formyl-Met-Leu-Phe (fMLP)/cytochalasin B (CB). Moreover, some derivatives exerted a strong inhibitory influence on superoxide anion production in rat neutrophils as feedback to fMLP/CB. NO generation in macrophages and microglial cells was strongly inhibited by *2′,5′-Dimethoxy-4-hydroxychalcone* (**68a)** and *3,4-Dichloro-2′,5′-diethoxychalcone* (**68e)**. NO generation and iNOS protein expression in RAW 264.7 cells were inhibited by **68a**. A set of independent or related mechanisms is likely responsible for the inhibitory effects of chalcone derivatives on the COX-2 activity and NO production in RAW 264.7 macrophages. Potent inhibitory action of 2′,5′-dihydroxy-dihydrochaclones on NO generation in LPS-induced macrophage (via the inhibition of iNOS protein expression) was favorable for the relief of septic shock [120].

Hsieh et al. also synthesized a series of 2′- and 3′-hydroxychalcones, 2′,5′-dihydroxychalcones (Fig. 67) along with flavanones through Claisen-Schmidt condensation of appropriate acetophenones with a suitable aromatic aldehyde, and their inhibitory actions on the stimulation of mast cells, neutrophils were measured. The results indicated that chalcone derivatives *2′,3-Dihydroxychalcone* **(69a), 2′***-Hydroxy-3,4-dimethoxychalcone* **(69d),** *3′-Hydroxy-3,4-dimethoxychalcone* **(69e),** and *2′,5′-Dihydroxy-3,4-dimethoxychalcone* **(69f)** potently inhibited mast cell degranulation activated by compound 46/80 (10 μg/mL). Nearly all chalcone derivatives caused a strong inhibition of the liberation of β-glucuronidase and lysozyme from rat neutrophils stimulated with formyl-Met-Leu-Phe (fMLP). Moreover, compounds **69a,** *2′,5′-Dihydroxy-2-napthylchalcone* **(69b),** and **69e** caused a strong inhibition of superoxide formation of rat neutrophils stimulated with fMLP/cytochalasin B (CB). Whereas, *2′,5′-Dihydroxy-2-furfurylchalcone* **(69c)** showed strong inhibitory action against superoxide anion formation from rat neutrophils. Compounds **69a, 69b,** and **69c** caused significant inhibition of hind-paw edema stimulated by polymyxin B in normal as well as in adrenalectomized mice. Overall, the results confirmed that the suppression of chemical mediators liberated from mast cells and neutrophils partially facilitated the anti-inflammatory action of chalcone derivatives reported in this study [121].

Won et al. also synthesized hydroxyl- and dihydroxychalcones (Fig. 68) via Claisen–Schmidt condensation. Their inhibitory effects against the activation of mast cells, neutrophils, macrophages, and microglial cells were studied, which showed that 2′-Hydroxychalcones (**70a-c**), and *2′,5′-dihydroxychalcone* (**70d**) caused a strong inhibition of the liberation of β-glucuronidase or lysozyme from rat neutrophils activated with formyl-Met-Leu-Phe (fMLP)/cytochalasin B (CB). The IC_{50} values of *2′-Hydroxy-2-thienylchalcone* **(70b),** *2′-Hydroxy-3-thienylchalcone* **(70c),** and *2′,5′-Dihydroxy-indol-3-yl-chalcone* **(70d)** for the release of β-glucuronidase were recorded to be 23.5 ± 1.4, 8.7 ± 0.7 and 17.1 ± 4.2 μM, respectively, while those of compounds (**70a-c**) for the release of lysozyme from rat neutrophils were reported to be 7.5 ± 0.3, 27.4 ± 0.7 and 13.4 ± 2.5 μM, respectively. Compounds **70a** (*2′,4-Dihydroxychalcone)* and **70b** strongly suppressed superoxide anion generation in rat neutrophils as feedback to fMLP/CB with their IC_{50} values calculated to be 6.4 ± 0.3 and 8.2 ± 0.3 μM, respectively [122].

Synthesis of some novel chalcones i.e. *1-[3-methoxy-4-(5-nitro-furan-2-ylmethoxy)-phenyl]-3-(substituted phenyl)-propenone* derivatives (**71a-k)** (Fig. 69) via Claisen-Schmidt condensation of *1-(4-((5-nitrofuran-2-yl)methoxy)-3-methoxyphenyl)ethanone* with aromatic aldehydes under solvent-free conditions in the presence of solid NaOH as a catalyst at

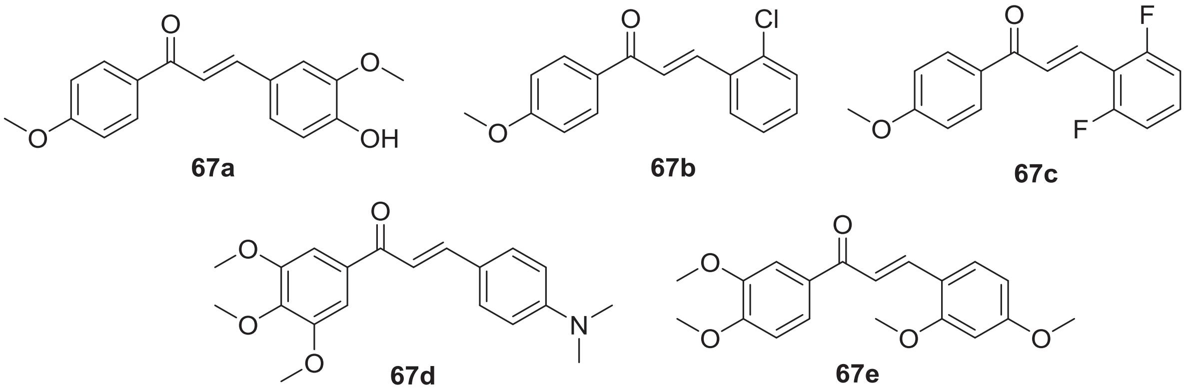


Fig. 65. Chemical structures of compounds (**67a-67e**).

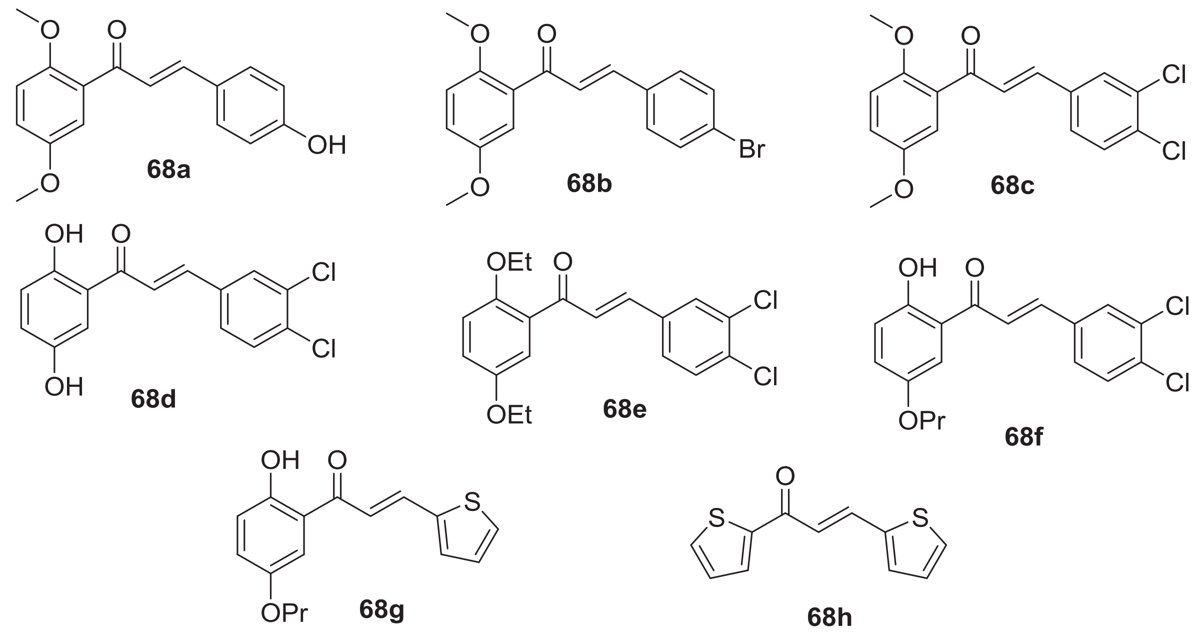

68a 68b 68c 68d 68e 68f 68g 68h

Fig. 66. Chemical structures of compounds **(68a-h)**.

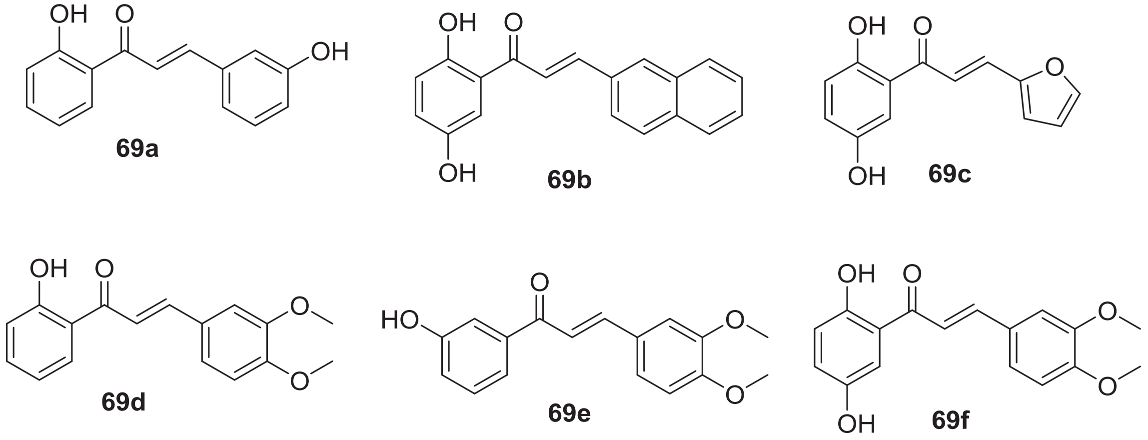

69a 69b 69c 69d 69e 69f

Fig. 67. Chemical structures of 2′- and 3′-hydroxychalcones **(69d and 69e)**, and 2′,5′-dihydroxychalcones **(69a, 69b, 69c and 69f)**.

room temperature has been reported. The synthesized chalcone derivatives were subsequently screened for anti-inflammatory activities via the carrageenan-induced inflammatory rat model. The standard drug, diclofenac sodium (at a dose of 10 mg/kg) and test compounds **(71a-k)** (at10 mg/kg doses) were administered through intraperitoneal injection. The extent of paw thickness (in millimeters) of all the groups was measured. Compounds, *1-[3-Methoxy-4-(5-nitro-furan-2-ylmethoxy) phenyl]-3-(4-trifluoromethoxyphenyl)propenone* **(71d),** *3-(4-Fluorophenyl)-1-[3-methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]propenone* **(71c),** *3-(4-Methanesulfonyl-phenyl)-1-[3-methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]propenone* **(71f),** *3-(3,4,5-Triimethoxy-phenyl)-1-[3-methoxy-4-(5-nitrofuran-2-ylmethoxy)phenyl]propenone* **(71 k)** and *1-[3-Methoxy-4-(5-nitro-furan-2-ylmethoxy)phenyl]-3-(4-nitrophenyl)propenone* **(71e)** showed substantial anti-inflammatory activities with their paw thickness measurement values of 1.08 ± 0.22, 0.98 ± 0.28, 0.88 ± 0.22, 0.85 ± 0.82 and 0.78 ± 0.86 mm, respectively [123].

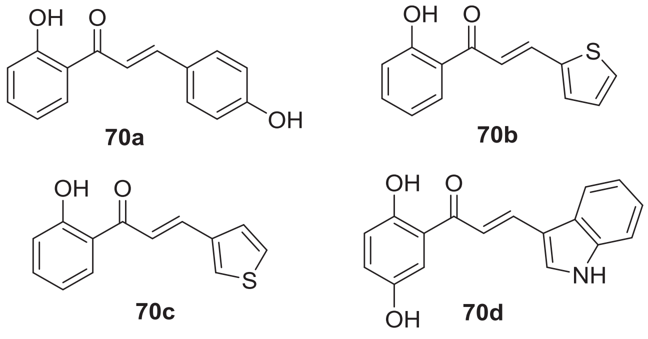
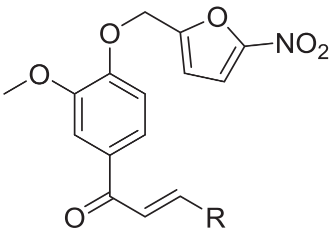

70a 70b 70c 70d

Fig. 68. Chemical structures of compounds **(70a-70d)**.

4. Overall SAR analysis of chalcones

Overall SAR analysis of chalcone and its derivatives is given in Fig. 70. The SAR of synthetic chalcone derivatives as anti-inflammatory agents can be summarized in the following elucidations [43,69,77,79,91,92,103,106,109,111,113,119].

(a) The structural significance of α, β-unsaturated carbonyl moiety is a vital characteristic of chalcone based anti-inflammatory agents.
(b) Introduction of a long alkyl chain at *para*-position of the ring-A reduces the anti-inflammatory activity of chalcones.
(c) Presence of −OH group at *para*-position in ring-B increases the anti-inflammatory activity of chalcones.



71a R=4-Br-phenyl **71b** R=4-Cl-phenyl **71c** R=4-F-phenyl
71d R=4-OCF_3-phenyl **71e** R=4-NO_2-phenyl **71f** R=4-SO_2Me-phenyl
71g R=4-OMe-phenyl **71h** R=2,4-OMe-phenyl **71i** R=2,5-OMe-phenyl
71j R=2,6-OMe-phenyl **71k** R=3,4,5-OMe-phenyl

Fig. 69. Chemical structures of compounds (**71a-k**).

(d) Substitution of polar groups, for example −OH and $-OCH_3$ on both the rings brings an increase in the anti-inflammatory activity via the suppression of NO production.
(e) −OH substitution in ring-A of chalcone scaffold exhibits favorable NF- κB inhibitory activity.
(f) Substitution of −OH and/or $-OCH_3$ in ring-A and quinoline moiety in ring-B promote the inhibition of PGE_2 activity.
(g) COX inhibition can be increased by introducing heterocyclic rings (such as thiophene/furan/ indole), phenylsulphonyl urea, methylsulfone, and piperidine in ring-A of chalcone scaffold [79,92].
(h) $-OCH_3$-containing derivatives cause more potent inhibition of COX-2 than nitro-containing analogues. Moreover, substitution of $-NO_2$ group on position 2 of ring-B yields chalcone derivative with better anti-inflammatory activity than $-NO_2$ substitution at position 3 of the same ring [43].
(i) Fluorinated chalcones efficiently suppress NO production and therefore, exhibit improved anti-inflammatory activities [60].
(j) Introduction of prenyl group, e.g. 3-methylbut-2-en-1-yl (prenylation) on ring-A substantially suppresses NO production [63].
(k) Methoxylation at C-2′ position of ring-A is vital for inhibiting NO production and iNOS expression [69].
(l) Introduction of $-OCH_3$ at -4′ and -6′ positions are essential for the suppression of PGE_2 production [77].
(m) Presence of −OH and $-OCH_3$ groups in chalcones results in their enhanced inhibitory effect against TNFα-induced NF-κB pathway. Moreover, electronic density on chalcone scaffold has no effect on NF-κB inhibition [91,101].
(n) The asymmetric chalcones have higher anti-inflammatory activity

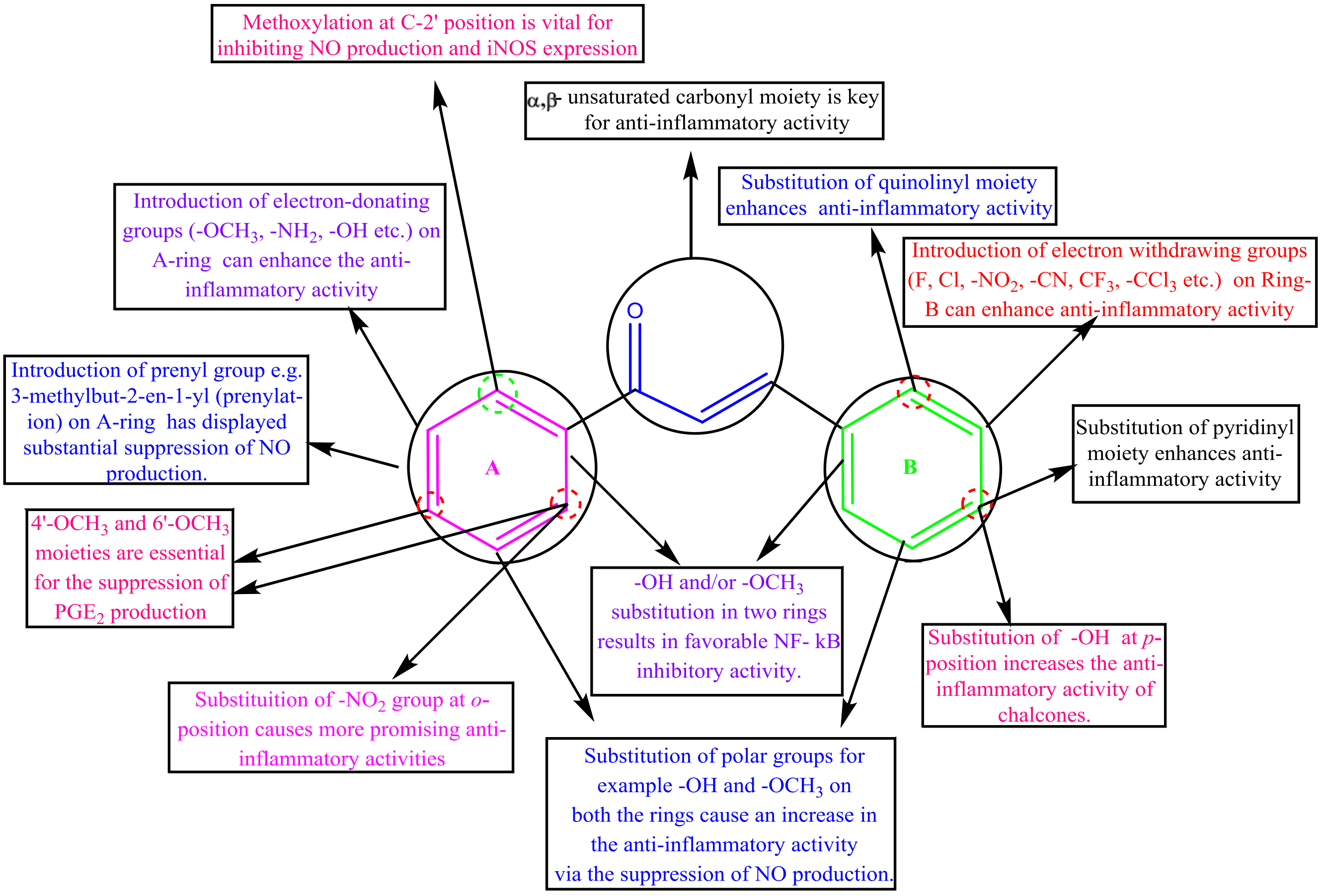


Fig. 70. Overall SAR analysis of chalcones.

Table 5
SAR analysis of chalcones to improve their anti-inflammatory properties.

S.NO.	Biological activity	Functional groups enhancing anti-inflammatory activity	Target inflammatory mediator	Ref.
1	Anti-inflammatory activity	$-OCH_3$-containing chalcone derivatives	COX-2 inhibition	[43]
		Fluorinated chalcones	inhibition of NO production	[60]
		Prenylation on ring-A	inhibition of NO production	[63]
		Methoxylation at C-2′ position	inhibition of NO production and iNOS expression	[69]
		Substitution of $-OCH_3$ and at −4′ and −6′ positions	inhibition of PGE_2 production	[77]
		Introduction of polar groups e.g. −OH and $-OCH_3$ on both the rings of chalcone scaffold	inhibition of NO production	[79]
		Substitution of heterocyclic rings, phenylsulphonyl urea, methylsulfone, and piperidine in ring-A of a chalcone scaffold	COX inhibition	[79]
		−OH substitution in ring-A of a chalcone scaffold	NF- κB inhibition	[79]
		quinoline substitution in ring-B	Inhibition of PGE_2 activity	[79]
		−OH groups in chalcone scaffold	inhibition of TNFα-induced NF-κB pathway	[91]
		−OH and $-OCH_3$ substitution in chalcone scaffold	NF-κB inhibition	[101]

than their symmetric analogues [103].

(o) Presence of $-OCH_3$ moieties causes a faster beginning of activity while presence bromine atom at position 3 of ring-B causes more potent inhibition of inflammation [106].

(p) Chalcones carrying $-NO_2$ group at 4-position of ring-B and those carrying 4-pyridinyl and 2-quinolinyl in ring-B exhibit significant anti-inflammatory activities [109].

(q) Chalcone derivatives carrying $-NO_2$ group at the *ortho* position of ring-A show more promising anti-inflammatory activities [111].

(r) Introduction of electron-withdrawing groups (F, Cl, $-NO_2$, −CN, CF_3, $-CCl_3$ etc.) in ring-B and electron-donating groups ($-OCH_3$, $-NH_2$, −OH etc.) in ring-A of chalcone derivatives can contribute to the overall anti-inflammatory activities [119].

Based on SAR analysis, selected functional groups in chalcone scaffold and their target pro-inflammatory mediators are given in Table 5.

5. Docking studies on the interaction of parent chalcone with COX-2, COX-1, and iNOS

Docking studies of a typical parent chalcone scaffold (1,3-diphenyl-2-propen-1-one) with COX-2, COX-1, and iNOS enzymes were carried out through MOE (Molecular Operating Environment) software. In case of COX-1 (PDB.ID. 5WBE) enzyme [124], its two residues His43 and Arg83 interacted with parent chalcone via hydrogen bonding and arene-cation interaction, respectively, whereas the docking score was calculated to be −15.4532 kcal/mol. Parent chalcone molecule also expressed two interactions with COX-2 (PDB.ID. 3LN1) enzyme residues [125]. Lys68 and Lys64 residues of COX-2 interacted through hydrogen bonding and arene-cation interaction respectively, whereas the docking score was calculated to be −14.6787 kcal/mol. Chalcone scaffold established two arene-cation interactions with two residues, Lys339, and Arg292 of iNOS (PDB.ID. 2NOS) enzyme [126], whereas the docking score was calculated to be −12.3597 kcal/mol. Overall, 2D and 3 D images of docking interactions of parent chalcone scaffold with COX-2, COX-1, and iNOS are given in Figs. 71a-71c.

6. The market of anti-inflammatory drugs and expected growth

The discovery of new anti-inflammatory targets continues to drive the expansion of small molecule therapeutics to cure inflammatory disorders. The story of curing fever, pain, and inflammation continues to progress. Small molecule NSAIDs have controlled the market for decades. Regardless of the recent growth in a market stake of biological therapeutics to cure inflammatory disorders, small molecule therapeutics continues to govern the pharmaceutical industry [127]. Based on the drug kinds, the global anti-inflammatory pharmaceutical market is divided into biologics, corticosteroids, immune selective anti-inflammatory derivatives (ImSAIDs), and NSAIDs. The anti-inflammatory biologics segment occupied 3/5th of the overall market in 2014. Additionally, the global anti-inflammatory therapeutics market is expected to touch US$ 130.6 billion by 2026, growing at a compound annual growth rate (CAGR) of 8.5% from 2018 to 2026. The study of global anti-inflammatory drug market (from 2018 to 2026) is based on the extensive investigation with insights from industry stakeholders.

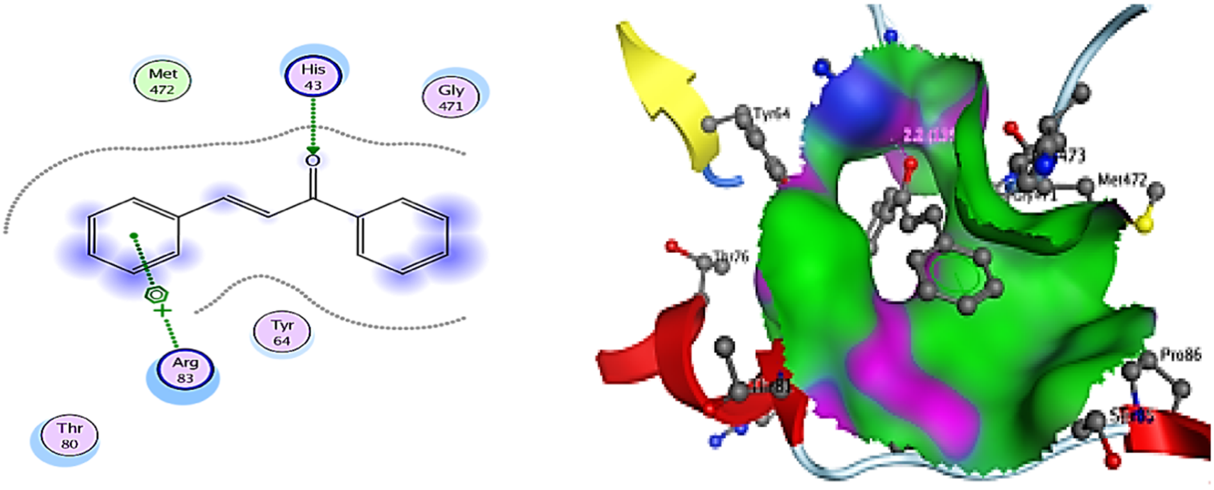


Fig. 71a. 2D and 3D docking images of COX-1 enzyme with chalcone.

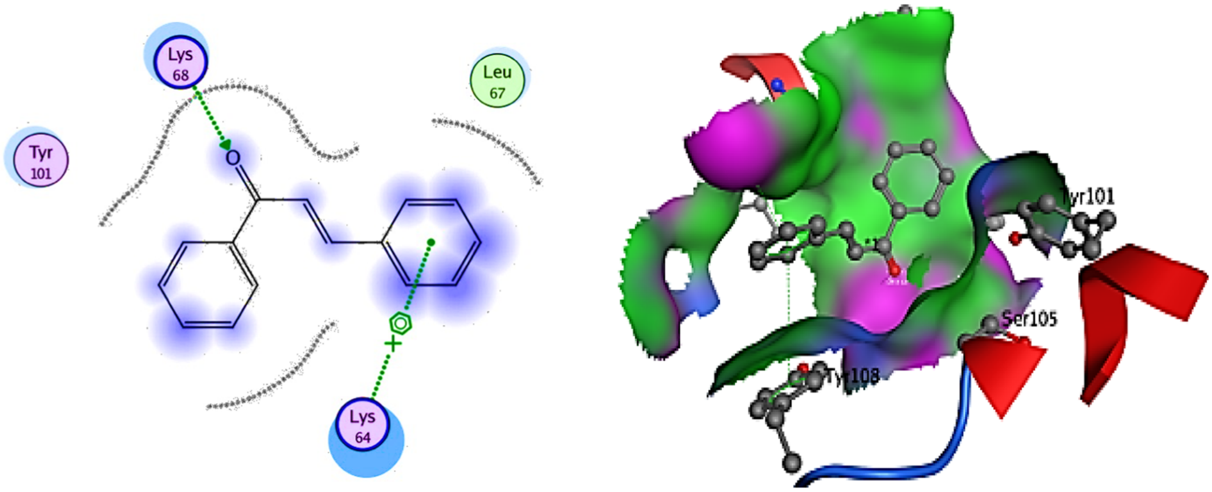


Fig. 71b. 2D and 3D docking images of COX-2 enzyme with chalcone.

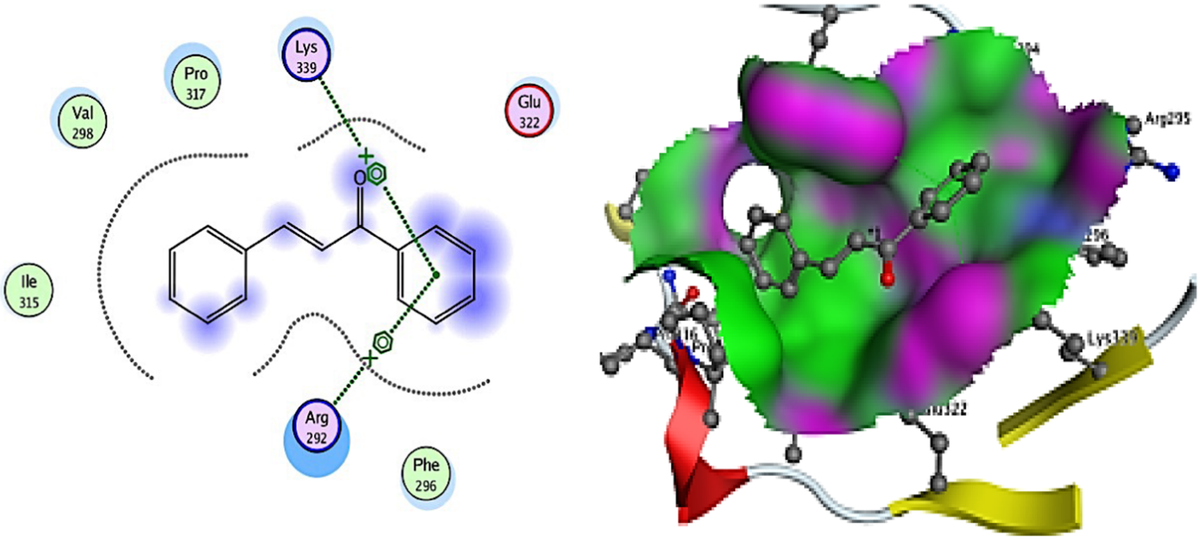


Fig. 71c. 2D and 3D docking images of iNOS enzyme with chalcone.

The comprehensive study integrates the market landscape and its growth developments for the anticipating period from 2018 to 2026 [128]. Geographically, total anti-inflammatory therapeutics market is expected for North America, the Middle East, and Africa, Latin America, Asia Pacific, and Europe. Regarding the profit share, North America led the global market in 2017 and it is expected that the situation will continue to be stable within the forecast period. However, Asia Pacific countries are expected to challenge the North American dominance. Investors have huge chances to penetrate into anti-inflammatory therapeutics market of countries like China, India, and Mexico [129]. Bayer Health Care Pharmaceuticals LLC, Novartis International AG, AstraZeneca plc, Reckitt Benckiser Group plc, Pfizer Inc. Johnson & Johnson, and Daiichi Sankyo Company, Limited are the key global suppliers of non-steroidal anti-inflammatory drugs [130].

7. Conclusions

Inflammation is an immune system response to detrimental stimuli, such as microorganisms, injured cells, or irritations. Besides protecting itself against viruses and bacteria, inflammation also activates the immune system to cure and mend damaged tissue [4,5]. However, chronic inflammations can lead to serious diseases such as asthma, hepatitis, rheumatoid arthritis, tuberculosis, and chronic peptic ulcer etc. [8]. A variety of non-steroidal anti-inflammatory drugs are used to treat inflammation [9]. Chalcone (1,3-diphenyl-2-propene-1-one) belongs to the flavonoids family of natural products and its derivatives have extensively been studied as anti-inflammatory agents [16]. Claisen-Schmidt condensation is one of the most widely used methodologies for the preparation of chalcones in the laboratory [17,21]. Chalcone-based anti-inflammatory agents work by inhibiting the activity and expression of inflammatory mediators. The inhibitory effects of chalcones against four inflammatory mediators COX, PGE_2, iNOS, and NF-κB are discussed. α, β- unsaturated carbonyl moiety of chalcones is key to anti-inflammatory activities. Detailed SAR analysis indicated that $-OCH_3$-containing chalcones are more potent COX-2 inhibitors [43]. Moreover, substitution of heterocyclic rings, phenylsulphonyl urea, methylsulfone, and piperidine in ring-A of chalcones causes COX inhibition [79]. −OH and $-OCH_3$ containing chalcones are stronger inhibitors of both PGE_2 and NF-κB. 4′-OCH_3 and 6′-OCH_3 groups are mandatory to suppress PGE_2 production [77,101]. Introduction of polar groups in chalcone scaffold enhances the inhibitory potential of the resultant derivatives against NO production [79]. Introduction of the methoxy group on C-2′ position can also increase the inhibition capability of the synthesized chalcones against NO production [69]. Moreover, prenylated chalcones are also potent inhibitors of NO production [63]. Introduction of −OH groups into chalcones lead to a substantial inhibition of TNFα-induced NF-κB pathway [91].

8. Future directions

It is vital to understand the mechanism of action and direct molecular targets for the development of clinically beneficial chalcone-based anti-inflammatory drugs in future. More investigation from molecular to cellular level will provide us better knowledge about the mechanisms. Future research should be focused on molecular mechanisms for useful applications of natural chalcones in various inflammatory disorders. Moreover, the design and synthesis of novel chalcone analogues are also significant for the development of clinically useful anti-inflammatory drugs in future. Like natural chalcones, green tea polyphenols, curcumin, resveratrol, boswellic acid, colchicine, capsaicin, epigallocatechin-3-gallate (EGCG), quercetin and cucurbitacins are other natural products possessing anti-inflammatory activities [131,132]. A useful methodology to synthesize novel chalcone-based anti-inflammatory agents of better activities might be the coupling of natural chalcones to the aforementioned natural products. The synergistic effect is expected to enhance the anti-inflammatory activities of the synthesized conjugates. Moreover, such conjugates are expected to be of lower toxicity, as compared to NSAIDs.

Another useful approach to synergistically increase the anti-inflammatory activity might be through the synthesis of chalcones-NSAIDs hybrids [133]. Such hybrids can be obtained through coupling of various chalcones with a variety of NSAIDs (such as aspirin, diclofenac, ibuprofen, indomethacin, and oxaprozin etc.). The resultant hybrids are expected to exhibit enhanced anti-inflammatory activities due to drug synergism. However, the safety of such hybrids must be tested by *in vitro* and *in vivo* investigations.

High absorption and enhanced bioavailability can improve the efficacy of a drug. Many plant-extracted compounds such as genistein, quercetin, naringin, piperine, sinomenine, glycyrrhizin, and nitrile glycoside have shown the potential to increase the bioavailability of various drugs. Therefore, these compounds can also be used as potential bioavailability enhancers in the future to improve the bioavailability of novel chalcone-based anti-inflammatory agents [134].

Development or discovery of a novel drug is a complex, ambiguous, expensive and time-consuming task. A computational methodology is one of the new approaches which can increase the efficiency of conventional drug discovery and design process. Mathematical procedures and computer simulation are used for chemical events, structural analysis and chemical properties of the molecules. Large catalogues are used to integrate chemical concept and modeling with experimental elucidations. This key technique has also played a pivotal role in designing new anti-inflammatory drugs. Therefore, computational approaches should also be fully exploited in order to discover and design novel chalcone-based anti-inflammatory drugs. Various computational approaches will compute and predict events such as drugs binding to pro-inflammatory factors as their targets, and the chemical properties for designing novel chalcone-based anti-inflammatory drugs. This approach will prove to be time-saving and cost-effective. Likewise, mathematical models should be applied in order to elucidate the decomposition mechanism of chalcone-based anti-inflammatory drugs and compute the results of formulation and process alterations and scale-up. To gain genuine advantage from novel chalcone-based anti-inflammatory drugs in the future, clinical investigations should be focused on the considerable benefits for patients. These drugs should be more effective than existing anti-inflammatory drugs or any other available cure. New delivery procedures, like nanotechnology, should be used in order to enhance the efficacy of the novel chalcones-based anti-inflammatory drugs when introduced to the patients. If there is no enhancement in terms of efficacy, they should nevertheless be less toxic, easier to use, more tolerable, or less expensive as compared to the active standard anti-inflammatory drugs. Side effects of future chalcone-based anti-inflammatory agents can be reduced by synthesizing their analogues as more potent inhibitors of pro-inflammatory mediators since a lesser dose of such drugs would be needed to treat inflammation. The safety of anti-inflammatory drugs can also be improved by decreasing their cytotoxicity [135]. Overall, the synthesis and discovery of novel chalcones are important, credited to their promising potential to act as lead compounds against inflammatory disorders.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.03.033.

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