Synthesis of allylated chalcones and their derivatives with enhanced solubility for antimalarial and pesticidal activity

Infectious diseases caused by bacteria, fungi, viruses and parasites such as malaria, tuberculosis etc are still a major threat to public health, despite tremendous progress in medicinal chemistry. The impact is more acute in developing countries due to non-availability of desired medicines and emergence of widespread drug resistance. The requirement is to synthesize/semi-synthesize novel molecules having good potential with high therapeutic index. Till date, nature has remained an ever evolving source for the discovery and development of new compounds of medicinal importance. Among the various natural products, chalcones (1,3-diarylprop-2-en-1-one; Figure 1) have attracted considerable interest as potential drug candidates due to their economical, facile, and rapid synthesis.

Chalcones occur mainly as petal pigments and have also been found in the heartwood, bark, leaf, fruit, and root of a variety of trees and plants. The appeal of working with chalcones stems from their synthetic accessibility, the various ways the core structure can be diversified depending on the substitution pattern on the two aromatic rings (Figure 1) and their ability to confer drug-like properties to compound libraries modeled on them [Nowakowska (2007)]. Moreover, in accordance with its privileged status, a wide range of pharmacological activities have been identified for chalcone derivatives [Edwards et al. (1990); Mukherjee et al. (2001); Bhat et al. (2005); Göker et al. (2005); Nielsen et al. (2005); Boeck et al. (2006); Wei et al. (2007)]. In our pursuit to develop novel molecules having good therapeutic potential, we aimed at the synthesis of natural chalcone analogues as antimalarial and pesticidal agents.
2.1. Synthesis of allylated chalcones and their derivatives with enhanced solubility for antimalarial activity

2.1.1. Introduction

Despite years of continual efforts for its eradication, malaria still remains globally prevalent parasitic disease; killing approximately three million people per annum mainly from developing countries like Central- and South-America, Asia, and Sub-Saharan Africa [Phillips (2001); Greenwood and Mutabingwa (2002); Tripathi et al. (2005)]. The British major, Ronald Ross, discovered the transmittance of human malarial parasites by female Anopheles mosquito more than 100 years ago. Malaria is caused by four species of parasite belonging to the genus Plasmodium: P. falciparum, P. vivax, P. ovale and P. malariae. Among these, P. falciparum is the parasite causing most of the deaths [Phillips (2001); Kaur et al. (2009); Kumar et al. (2009)].

2.1.2. Pathogenesis and the life cycle of malaria parasite

The life cycle, immunological defense mechanisms, and clinical development of malaria in humans is a complex process. Plasmodium parasites have a complex life cycle, which is shared between a vertebrate host (human) and an insect vector (female Anopheles mosquito) [Hoffman et al. (2002)]. The parasite enters the bloodstream in the form of sporozoites through the bite of an infected female Anopheles mosquito. In humans, the sporozoites invade the parenchymal cells of the liver. They remain in liver cells (safe from an immune response) for 9-16 days, undergoing multiple asexual fission and producing merozoites. During development in the liver the patient remains asymptomatic but after a variable period of time, 6-8 days for vivax, 9 days for ovale, 12-16 days for malariae, and 5-7 days for falciparum, merozoites are released from the liver [Christensen and Kharazmi (2001)]. The merozoites invade the erythrocytes, where they feed on the haemoglobin. After proliferation, the erythrocyte rupture and the liberated merozoites invade other erythrocytes. Some merozoites are converted into gametocytes [Casteel (1997)]. When a mosquito takes a blood meal from an infected person it swallows some gametocytes which undergo sexual reproduction in the digestive tract of the mosquito; ultimately producing many sporozoites which migrate to the salivary gland for injection into another host, beginning the cycle again (Figure 2) [Murder (2000); Christensen and Kharazmi (2001)].
Clinical malaria is characterized by periodic fever, which follows the lysis of infected erythrocytes and caused mainly by the induction of cytokines interleukin-1 and tumor necrosis factor. *P. falciparum* infection can have serious effects, for example, anemia, cerebral complications (from coma to convulsions), hypoglycemia and glomerulonephritis. The disease is most serious in the non-immune individuals, including children and pregnant women [Christensen and Kharazmi (2001)].

**Figure 2:** Simplified presentation of the life cycle of the malaria parasite [Adapted from: Ridley (2002)]

### 2.1.3. Approaches to control malaria

WHO has given malaria a high priority and a number of programmes have been initiated to control malaria [(WHO (2010))]. Three important attempts are: a) vector control [Greenwood (1997)], b) development of vaccine against malaria [Facer and Tanner (1997); Riley (1997); Kumar *et al.* (1999)], and c) chemotherapy [Tripathi *et al.* (2005)]. In addition, mapping of the genome of the parasite might reveal new possibilities for the control of malaria [Christensen and Kharazmi (2001)].
2.1.3.1. Vector Control

Vector control can be achieved either by making contact of human host and mosquito impossible or by killing the mosquitoes through insecticides [Mitchel (1996); Tripathi et al. (2005)]. Use of artificial barrier such as insecticidal nets, repellents, protective clothing’s by people at risk and destruction of breeding sites and resting areas of vector mosquito by spraying with insecticide- predominantly DDT- afforded a considerable decrease of malaria incidence in many parts of the tropical world [Jayaraman (1997); Day (1998)]. However, development of resistance to DDT amongst mosquitoes, together with the delirious effects of entry of insecticides in the human food chain [Mitchel (1996)], malaria has again become one of the three most fatal diseases in the world.

2.1.3.2. Development of vaccine against malaria

Vaccination in malaria represents one of the most important approaches that provide a cost-effective intervention in addition to currently available malaria control strategies [Mendis et al. (2001); Tripathi et al. (2005)]. Most of the vaccine trials have been directed against liver stages or sporozoites, and these vaccines include completely synthetic peptides, conjugates of synthetic peptides with proteins such as tetanus-toxoid to provide Helper T-cell, recombinant malarial proteins, recombinant viruses, and bacteria- & DNA-based vaccines [Offman (1996)].

2.1.3.3. Chemotherapy

The efficacy of antimalarial drugs depends primarily on their ability to kill malaria parasites by interrupting their essential life functions, leading to inhibition of multiplication and allowing the immune system to remove damaged parasites completely from the circulation [Luzzi and Peto (1993); White (1996); Meinnel (2000); Christensen and Kharazmi (2001)]. During its life cycle in human erythrocytes the Plasmodium parasite requires several metabolic adaptations and innovations which render it susceptible to chemotherapeutic attack [Ridley (2002)]. The parasite degrades haemoglobin in its acidic food vacuole producing free heme which react with molecular oxygen and generate reactive oxygen species as toxic by-products. A major pathway of detoxification of heme moieties is polymerization of heme to hemazoin. Majority of quinoline [Casteel (1997); Ridley (1997)] and peroxide [Posner et al. (1992); Robert and Meunier (1998)] antimalarial drugs act by disturbing the polymerization (and/or the detoxification by any other way) of heme; thus killing the parasite with its own metabolic waste. Some drugs are reported to block biosynthesis of pyrimidines- necessary for the growth
of the parasites- by inhibition of the respiratory chain of malaria mitochondria [Casteel (1997); Olliaro and Wirth (1997); Rathod (1997)] or prevent formation of dihydrofolate reductase [Casteel (1997)]. Tetracycline antimalarials act by inhibition of mitochondria protein synthesis [Casteel (1997)]. A number of iron (III) chelators have antimalarial activity in vitro, apparently through the mechanism of withholding iron from vital metabolic pathways of the intraerythrocytic parasite [Hider and Liu (1997); Mabeza et al. (1999)]. Other iron chelators appear to inhibit malaria parasites by forming toxic complexes with iron [Mabeza et al. (1999)].

2.1.4. Development of new antimalarial drugs

Discovery of lead compounds is still mainly based on screening of libraries of chemicals or plant extracts. An alternative approach, developed in the 1970s, is to examine the ability of the compound to inhibit the growth of parasites [Trager and Jensen, (1976); Khalid et al. (1986)] through in vitro and in vivo screening assays.

2.1.4.1. Bioassays used for antimalarial drug discovery

2.1.4.1.1. In vitro screening assays

The first step in the antimalarial drug discovery process is to evaluate the antimalarial activity of the test compounds or plant extracts in vitro systems using well characterized strains of P. falciparum. Usually, two strains of P. falciparum are used- a chloroquine sensitive such as 3D7 and a chloroquine resistant such as Dd2. Human peripheral blood erythrocytes are used for the in vitro screening studies. Although several in vitro methods exist, the [3H]-hypoxanthine assay [Desjardins et al. (1979)] is the standard test for screening potential drugs for antiplasmodial activity or monitoring parasite sensitivity to available antimalarial drugs. However, it is an expensive assay that requires radioactive materials which pose safety and disposal problems. Another method is the WHO micro-test developed by Rieckmann and co-workers and adopted by the WHO [Rieckmann et al. (1978)] with endpoint of assay evaluated microscopically. Although inexpensive, this method is highly labor-intensive and subjective due to variation in the expertise of the microscopists. There are other methods which are based on enzymatic reaction and antibodies that specifically detect the presence of histidine-rich protein II or parasite lactate dehydrogenase [Makler et al. (1993); Druilhe et al. (2001); Noedl et al. (2002)]. These assays involve multiple steps which make them not well-suited for high-throughput antimalarial drug screening. Non-radioactive DNA stains [SYBR Green I (SG), PICO green®
(PG)] have been reported for measurement of parasite growth in a short term assay using a 96-well format [Corbett et al. (2004); Smilkstein et al. (2004); Baniecki et al. (2007)]. This method appears to be safe, cost-effective, easily interpretable, and readily available. Its use eliminates the challenge of appropriate disposal of radioactive waste and thus facilitates antimalarial drug discovery process.

2.1.4.1.2. **In vivo screening assays**

A promising compound showing good *in vitro* activity (preferentially an IC$_{50}$ value below 1 μM) and ready solubility in pharmaceutically suitable solvents is subjected to *in vivo* screening. Different species of *Plasmodium* are used in these assays. The most common ones are *P. berghei* K173, *P. yoelii* YM, *P. chabaudi*, and *P. vinckei*. These strains are lethal to animal and kill the infected untreated animal within 7 to 12 days. In the most common assay the animals are inoculated intraperitoneally with 106 parasitised erythrocytes suspended in 0.2 mL saline. Control animals receive normal saline. Chloroquine, or another drug, ought to be used as a positive control. From day four of infection, thin blood smears are made from tail blood of the mice for determination of parasitemia. The mortality of the mice is determined up to 28 days following the last treatment [Peters (1980)]. In addition to mice, non-human primates, such as *Aotus lemurinus* and *Saimiri* spp. monkeys, Macaques etc. are also used as test models for *in vivo* antimalarial efficacy against infections with human parasites *P. falciparum* and *P. vivax*.

2.1.5. **Natural product based antimalarial agents**

The emergence and spread of strains of *P. falciparum* resistant to almost all available antimalarial drugs necessitate constant monitoring of parasite susceptibility to antimalarial drugs and concerted effort towards the search for new potent antimalarials [Bruno et al. (1997)]. Natural products have always remained in focus for the discovery of new drug leads [Buss and Waigh (1995); Senior (1996); Cragg et al. (1997); Pandey (1998); Shu (1998)], especially for the treatment of human diseases [Newman et al. (2003)]. Even today, the majority of drugs used against malaria has been developed from, or are, natural products and form a rich source of diverse structures for optimization to obtain improved therapeutics. The major groups of antimalarial phytochemicals can be divided into several categories that include alkaloids, terpenoids, flavanoids, lignans, coumarins, quinones, xanthones, peptides etc. Table 1 covers a spectrum of antimalarials from natural sources.
Table 1: Major groups along with representative examples of natural product based antimalarial agents [Christensen and Kharazmi (2001); Kaur et al. (2009)]

<table>
<thead>
<tr>
<th>Group</th>
<th>Definition</th>
<th>Representative examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkaloids</td>
<td>Heterogeneous group of naturally occurring nitrogen containing compounds derived from amino acid precursor.</td>
<td><img src="image1" alt="Quinine" />, <img src="image2" alt="Berberine" />, <img src="image3" alt="Girolline" />, <img src="image4" alt="Cryptoleine" /></td>
</tr>
<tr>
<td>Terpenoids</td>
<td>Heterogeneous group of natural products formed from mevalonic acid. They are characterised by the presence of the isoprene unit in the skeleton, though this unit might be changed by rearrangement in the molecule.</td>
<td><img src="image5" alt="Artemisinin" />, <img src="image6" alt="Helenalin" />, <img src="image7" alt="Eudesmane" />, <img src="image8" alt="Diisocyanoadociane" /></td>
</tr>
<tr>
<td>Flavanoids</td>
<td>Flavanoids are a complex group of natural products composed of a C_6C_3-moiety having shikimic acid as a precursor and a C_6 moiety of polyketide origin. Some examples are known in which the two moieties have been alkylated might contain seven carbons.</td>
<td><img src="image9" alt="Licochalcone" />, <img src="image10" alt="cis-3-Acetoxo-4',5,7-t rihydroxyflavanone" />, <img src="image11" alt="4-Hydroxy Lonchocarpin" />, <img src="image12" alt="5-Prenylbutein" /></td>
</tr>
</tbody>
</table>
### Group | Definition | Representative examples
--- | --- | ---
**Lignans** | The lignans are biogenetically built by dimerisation of two C₆C₃-moieties originating from shikimic acid. | ![Nyasole](Image), ![Termilignan](Image), ![Justicidan B](Image), ![Dehydroconiferyl dibenzaate](Image)

**Coumarins** | The coumarins contain the 2-oxobenzopyrane skeleton. | ![5,6,7-trimethoxycoumarin](Image), ![isofraxidin](Image)

**Quinones** | Quinones may either be formed *via* the acetate pathway or by a sequence involving shikimate and mevalonate. | ![Newbouldiaquinone A](Image), ![Xylariaquinone A](Image), ![Plumbagin](Image), ![Naphthoquinoid](Image)

**Xanthones** | Xanthones are organic compounds with the molecular formula C₁₃H₁₃O₂ and are known as "adaptagens" for their unique ability to adapt to the needs of the body. | ![Cowaxanthone](Image), ![Calothwaitesixanthone](Image), ![Mangostin](Image)

**Peptides** | Peptides are short polymers of amino acids linked by peptide bonds. | ![Apicidin](Image)
Among these existing antimalarial natural products, quinine has remained the drug of choice [Rogers and Randolph (2000)] for treating the chloroquine- and multidrug- resistant *falciparum* malaria; however its use is declining because of potential toxicity [Kapoor and Kumar (2005)]. At present, artemisinins-based drug is the most effective treatment for curing chloroquine-resistant *P. falciparum* infections [de Vries and Dien (1996); Price *et al.* (1997); Kapoor and Kumar (2005), Woodrow *et al.* (2005)]; however their indiscriminate use as monotherapy has raised the concern of emerging drug resistance [Luxemburger *et al.* (1998); Meshnick (2002); Alker *et al.* (2007); Enserink (2008); Dondorp *et al.* (2009)]. To slow down the resistance to this vital class of drugs; Artemisinin based combination therapies (ACT) are being advocated by WHO e.g. artemether-lumefantrine combination therapy [WHO (1998)]. This will also lessen the pressure on rising artemisinin demand- a natural product in short supply and with commercially unviable synthesis [Bhasin and Nair (2003)]. The situation demands developing new antimalarial agents or drug combinations that are effective and support treatment at affordable cost.

### 2.1.5.1. Chalcones as antimalarials

Chalcones or 1,3-diaryl-2-propen-1-ones, have drew the attention of chemists when licochalcone A (Figure 3, IC$_{50}$ 4.1 µM) isolated from Chinese liquorice (*Glycyrrhiza inflata*) roots was reported to exhibit potent *in vivo* and *in vitro* antimalarial activity against both chloroquine-susceptible and chloroquine-resistant *P. falciparum* strains [Chen *et al.* (1994)]. In another report, 5-prenylbutein (Figure 3) from *Erythrina abyssinica* [Yenesew *et al.* (1994)] and methyllinderatin (Figure 3) from *Piper hostmannianum* [Portet *et al.* (2007)] exhibiting antimalarial activity have been reported with IC$_{50}$ of 10.3 µM and 5.64 µM, respectively.

![Figure 3](image)

Since then, several natural chalcones such as xanthohumol and related chalcones, medicagenin, crotorixin, homobutein etc. (Figure 4) have been reported for *in vitro* antiplasmodial activity
against the *P. falciparum* strains with IC$_{50}$ values in the range of 10.3–16.1 µM [Stevens and Page (2004); Frölich et al. (2005); Narender et al. (2005)].

![Chemical structures](image)

**Figure 4**

Ngameni *et al*. (2007) isolated bartericin A, stipulin, 4-hydroxylonchocarpin from *Dorstenia barteri var. subtriangularis* (Figure 5) which were found to be active *in vitro* against *P. falciparum* (IC$_{50}$ = 2.15, 5.13 and 3.36 µM, respectively).

![Chemical structures](image)

**Figure 5**

Similarly, the bioassay-guided isolation of dichloromethane extract of the aerial parts of *Boronia bipinnata* led to the isolation of two isoprenylated chalcones, bipinnatones A and B
(Figure 6) which were found to inhibit the malarial parasite enzyme target hemoglobinase II - an enzyme essential for the survival of the parasite [Carroll et al. (2008)].

![Figure 6]

However, limitations associated with these chalcones such as their low percentage in natural resources, toxicity, low bioavailability, poor solubility and tedious total synthesis [Chen et al. (1997); Stevens and Page (2004)] have generally restrained their use in humans. Nevertheless, the compounds described above provide useful synthons for semisynthetic transformations of easily available precursors into newer and modified antimalarials against not only drug-sensitive, but also drug-resistant strains of *Plasmodium* [Li et al. (1995); Liu et al. (2001); Wu et al. (2002); Go et al. (2004); Dominguez et al. (2005); Tomar et al. (2010)].

In this context, an analog of licochalcone, 2,4-dimethoxy-4'-butoxychalcone (Figure 7) was found to exhibit potent activity against *P. falciparum* in vitro and the rodent parasites *P. berghei* and *P. yoelii* in vivo [Chen et al. (1997)].

![Figure 7]

Recently, a series of acetylenic chalcones were evaluated for antimalarial activity. The obtained data series suggested that introduction of a methoxy group ortho to acetylenic group contributed towards increasing the lipophilicity of the compounds; thus leading to growth inhibition of the W2 strain of *P. falciparum* (Scheme 1) [Hans et al. (2010)].
In a structure-activity relationship study conducted by Kumar et al. (2010) for exploring the basic chalcone moiety for antimalarial activity, it was revealed that the presence of methoxy substitution, particularly 2,4,5-trimethoxy substitution, on ring A of chalcone and electron withdrawing groups at ring B significantly favors the antimalarial activity as compared to other counterparts (Figure 8).

In the context of searching novel pharmaceutically promising analogs of natural chalcones and inspired by the Licochalcone template, we designed and synthesized a series of novel allylated chalcones including their heterocyclic and bis derivatives for antimalarial activity.
2.1.6. Results and discussion

A close scrutiny of natural antimalarial chalcones reveals that these generally possess substituted allylated aromatic rings (prenyl or geranyl group) as an important part of their structure [Kromann et al. (2004)]. The importance of allyl or prenyl group for enhancing the bioactivities of flavonoids, including chalcones, is also well documented in literature [Henderson et al. (2000); Maitrejean et al. (2000); Milligan et al. (2000); Miranda et al. (2000); Stevens and Page (2004)]. Furthermore, the use of allyl or prenyl moiety is known to contribute towards lipophilicity of the molecule- an important requirement for antimalarial activity [Mukherjee et al. (2001); Hans et al. (2010)] and could be replaced by groups with comparable lipophilic characters. Thus, the significant antiplasmodial activity of natural chalcones prompted us to synthesize a novel series of Licochalcone A congeners for in vitro antimalarial activity and to study their structure-activity relationship. Attention has been focused on the modification of the aldehyde moiety (ring A, Figure 1) of Licochalcone by substituting the 1,1-dimethyl allyl group with C- or O-allyl and prenyl groups to achieve a new antimalarial profile. The chalcones are divided into four main types according to the substitution of A ring (Figure 1): C-allylated, O-allylated, C- and O-allylated and O-diallylated. Further, to address the demands of green chemistry, vanillin-an easily available natural precursor, has been utilized for the synthesis of these chalcones.

2.1.6.1. Chemistry and synthesis of chalcones

As shown, 4-allyloxy-3-methoxy benzaldehyde (1b) was obtained by refluxing vanillin (1a) with allyl bromide in the presence of K$_2$CO$_3$ in dry acetone [Xu et al. (2006); Vogel and Heilmann (2008)] (Scheme 2). Compound 1b upon microwave irradiation at 200°C underwent Claisen reaction to yield 2b which was transformed into 3b using dimethyl sulfate as methylating agent [Aponte et al. (2008); Srinivasan et al. (2009)] and into 4b with allyl bromide [Aponte et al. (2008)] (Scheme 2). Claisen-Schmidt condensation of 1a, 1b-4b with the corresponding acetophenones in the presence of aqueous NaOH [Cabrera et al. (2007); Boumendjel et al. (2008)] gave chalcone products (1-19) which were purified by chromatography and crystallization (Scheme 2).
Scheme 2: Reagents and conditions: (a) allyl bromide, potassium carbonate, anhydrous acetone, reflux; (b) MW at T= 200°C for 10 min; (c) 10% aq. NaOH, methanol, substituted acetophenone, stir at rt; (d) dimethyl sulfate, NaOH, stir at rt; or allyl bromide, K₂CO₃ and anhydrous acetone, reflux.

Similarly, 4-allyloxyacetophenone (5b) was formed by reacting 4-hydroxy acetophenone (2a) with allyl bromide [Xu et al. (2006)], which was condensed with 1b in the presence of aqueous NaOH [Cabrera et al. (2007); Boumendjel et al. (2008)] to give corresponding chalcone 20 (Scheme 3). Likewise, corresponding allyloxy benzaldehydes (6b, 7b) were obtained by refluxing 2-hydroxy-3-methoxy benzaldehyde (3a) and 3-hydroxy-4-methoxy benzaldehyde (4a), respectively with allyl bromide in the presence of K₂CO₃ in dry acetone [Xu et al. (2006); Vogel and Heilmann (2008)]. Compounds 6b and 7b upon Claisen-Schmidt condensation with 4-chloro acetophenone in the presence of aqueous NaOH [Cabrera et al. (2007); Boumendjel et al. (2008)] gave chalcone products (21 and 22) which were purified by chromatography and crystallization (Scheme 3).
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Scheme 3: Reagents and conditions: (a) allyl bromide, potassium carbonate, anhydrous acetone, reflux; (b) 10% aq. NaOH, ethanol, 1b, stir at rt; (c) 10% aq. NaOH, methanol, 4-chloro acetophenone, stir at rt.

Chalcone 23 was obtained by condensation of 1a with chloro acetophenone in the presence of KOH (Scheme 4) [Cabrera et al. (2007); Boumendjel et al. (2008)]. 23 upon reaction with prenyl bromide, 1-butyl bromide and 4-bromobenzyl bromide yielded 24, 25 and 26, respectively (Scheme 4) [Vogel and Heilmann (2008)]. All chalcones (23-26) were purified by chromatography and crystallization.

Scheme 4: Reagents and conditions: (a) KOH, ethanol, 4-chloro acetophenone, stir at rt; (b) prenyl bromide or bromobutane or 4-bromo benzyl bromide, potassium carbonate, anhydrous acetone, reflux.

In the similar vein, syringaldehyde (5a), 4-hydroxy benzaldehyde (6a), 2-hydroxy benzaldehyde (7a), 3-ethoxy-4-hydroxy benzaldehyde (8a) and 3,4-dihydroxy benzaldehyde (9a) were reacted with allyl bromide in the presence of K$_2$CO$_3$ in dry acetone [Xu et al. (2006); Vogel and Heilmann (2008)] to provide corresponding O-allylated benzaldehydes (8b-12b) (Scheme 5). Compounds 8b-12b upon Claisen-Schmidt condensation with 4-chloro acetophenone in the presence of aq. NaOH [Cabrera et al. (2007); Boumendjel et al. (2008)] gave chalcone products (27-31) which were purified by chromatography and crystallization.
Similarly, 4-allyloxy-3-methoxyacetophenone (13b) was obtained by reaction of 4-hydroxy-3-methoxyacetophenone (10a) with allyl bromide in the presence of K₂CO₃ in dry acetone which on condensation with 4-chloro benzaldehyde provided chalcone 32 (Scheme 5). 14b was obtained by reaction of 2,4-dihydroxy acetophenone (11a) with allyl bromide in the presence of K₂CO₃ in dry acetone (Scheme 5) [Xu et al. (2006); Vogel and Heilmann (2008)].

![Chemical Structures](image)

**Scheme 5**: Reagents and conditions: (a) allyl bromide, potassium carbonate, anhydrous acetone, reflux; (b) 10% aq. NaOH, ethanol, 4-chloro acetophenone, stir at rt; (c) 10% aq. NaOH, ethanol, 4-chloro benzaldehyde, stir at rt.

Chalcones 33-38 were prepared by reacting 1b with various heteroaromatic acetophenones (Scheme 6). Compound 39 was synthesized by reaction of 18 with 4,7-dichloroquinoline in THF in the presence of K₂CO₃ [Mehta and Patel (2009)] which on further reaction with allyl bromide in presence of KOH and THF yielded 40 (Scheme 6). Similarly, compounds 41 and 42 were prepared by refluxing 9 with phenyl hydrazine [Lévai (2005)] and guanidine
hydrochloride [Rahaman et al. (2009)], respectively. Bis(dimeric)chalcones 43-45 by prepared by reacting 1,3-diacyl benzene with 3b, 1b and 12b, respectively in the presence of base [Khan et al. (2002)]. Compounds 46 and 47 were prepared by Claisen-Schmidt condensation of terephthaldehyde with 5b and 14b, respectively [Pinto et al. (2003)] (Scheme 6).

**Scheme 6:** Reagents and conditions: (a) aq. NaOH, ethanol, substituted heteroatomic acetophenone stir, rt; (b) 4,7-dichloro quinoline; THF, reflux; (c) allyl bromide, KOH, THF, CTAB, stir rt; (d) phenyl hydrazine, sodium acetate, aq. acetic acid, MW at P = 180 W for 30 min; (e) guanidine HCl, KOH, ethanol, reflux; (f) NaOH, aq. ethanol, substituted aldehyde (1b or 3b or 12b); (g) NaOH, aq. ethanol, substituted acetophenone (5b or 14b) stir, rt.
2.1.6.2. Evaluation of antimalarial activity

All the above compounds were tested for antimalarial activity against chloroquine sensitive *P. falciparum* 3D7 (*Pf*3D7) strain (Tables 2-6) by SYBR-Green-I assay [Smilkstein *et al*. (2004)]. This method is based on the fact that in the mature human red blood cells (which lack DNA), the quantitative estimation of SYBR green fluorescence acts as an index of the growth of the malaria parasite allowing precise estimation of IC\(_{50}\) value for each compound.

(a) C-allylated chalcones (Hydroxy vs methoxy derivatives): Initially 3-[4-hydroxy-3-methoxy-5-(prop-2-en-1-yl)phenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one (1, Table 2) was synthesized as an analogue of Licochalcone (Figure 3). However, the low activity of 1 (IC\(_{50}\): 38.5 \(\mu\)M) combined with the tedious synthesis due to the presence of hydroxy substituents on both rings A and B prompted us to explore variants leading to enhanced activity, solubility as well as ease of synthesis. Consequently, compound 2 was synthesized by replacing the hydroxy group on ring B with isosteric chloro group. The selection of chloro group was guided by its lipophilic nature [Mishra *et al*. (2008)] and several reports on antimalarial potency of chlorinated compounds [Fu and Xiao (1991); Kesten *et al*. (1992); Manohar *et al*. (2010)]. Even so, no significant improvement was observed in activity (IC\(_{50}\): 28 \(\mu\)M, Table 2) or solubility. Moreover, the presence of hydroxy group on ring A was still proving a holdup for facile synthesis of molecules. Thus, protection of this hydroxy group was needed to proceed with the synthesis. Consequently, methylation was carried out and thus obtained compound (3) was assessed for antimalarial potency (3, Table 2). To our delight, not only the solubility but also the activity increased almost nine folds (IC\(_{50}\): 3.9 \(\mu\)M). Thereafter, keeping the substituents on ring A constant, we next ventured to evaluate the effect of electron withdrawing and electron donating groups on ring B (4-7, Table 2). However, all the substitutions provided compounds with lower activity as compared to 3 indicating the importance of chloro group on ring B (4-7, Table 2).

(b) C- and O-allylated chalcones (Effect of allyloxy group): To make the initial template more lipophilic, allyloxy group was introduced (8) [Aponte *et al*. (2008)] in place of hydroxyl position of compound 2. It resulted in slight decrease of activity (IC\(_{50}\): 7.8 \(\mu\)M) when compared with 3 (IC\(_{50}\): 3.9 \(\mu\)M) though it was still considerably higher than 2 (IC\(_{50}\): 28 \(\mu\)M) (8 vs 3 vs 2, Table 2).
Table 2: Antimalarial activity, resistance and therapeutic indices of C- and both C- & O-allylated chalcones

![Diagram of chalcone structure](image)

1. R = H, R' = 4-OH
2. R = H, R' = 4-Cl
3. R = CH₃, R' = 4-Cl
4. R = CH₃, R' = 4-OCH₃
5. R = CH₃, R' = 3,4-OCH₂O-
6. R = CH₃, R' = 4-Br
7. R = CH₃, R' = 4-NO₂
8. R = allyl, R' = 4-Cl

<table>
<thead>
<tr>
<th>Compd. Mol. Wt No.</th>
<th>IC₅₀ (µM) P/3D7</th>
<th>IC₅₀ (µg/mL) P/3D7</th>
<th>Resistance Index</th>
<th>Therapeutic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC₅₀ Indo/IC₅₀ 3D7</td>
<td>IC₅₀ Dd2/IC₅₀ 3D7</td>
<td>IC₅₀ HeLa/IC₅₀ 3D7</td>
<td>IC₅₀ L29/IC₅₀ 3D7</td>
</tr>
<tr>
<td>1</td>
<td>310.3</td>
<td>38.5</td>
<td>11.9</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>328.7</td>
<td>28</td>
<td>9.21</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>342.8</td>
<td>3.9</td>
<td>1.34</td>
<td>3.6</td>
</tr>
<tr>
<td>4</td>
<td>338.4</td>
<td>4.3</td>
<td>1.45</td>
<td>3.5</td>
</tr>
<tr>
<td>5</td>
<td>352.3</td>
<td>4.7</td>
<td>1.65</td>
<td>2.0</td>
</tr>
<tr>
<td>6</td>
<td>387.2</td>
<td>5.3</td>
<td>2.05</td>
<td>2.9</td>
</tr>
<tr>
<td>7</td>
<td>353.3</td>
<td>12.5</td>
<td>4.41</td>
<td>&quot;</td>
</tr>
<tr>
<td>8</td>
<td>368.8</td>
<td>7.8</td>
<td>2.87</td>
<td>&gt;2.6</td>
</tr>
<tr>
<td>CQ</td>
<td>319.9</td>
<td>40 nM</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

(c) **O-allylated chalcones and structure-activity investigations:** To appraise the effect of removal of C-allyl group, compound 9 was prepared and evaluated against 3D7. Delightedly, the compound exhibited profound *in vitro* antimalarial activity (IC₅₀: 2.5 µM, Table 3) which was comparable to Licochalcone and far superior to its well-reported analogue, 4-dimethoxy-4'-butoxychalcone. Thereafter, the structure–activity studies were carried out by varying the substitutions on ring B (10-20, Table 3). It is clear that introduction of 3,4-dichloro (10), bromo (11), iodo (12), fluoro (13), 3-chloro (14), methoxy (15), methylenedioxy (16), nitro (17), amino (18) or allyl (20) group at ring B (Table 3) did not lead to enhancement of activity when compared to 9.
Table 3: Antimalarial activity, resistance and selectivity indices of O-allylated chalcones

<table>
<thead>
<tr>
<th>Compd. Mol. Wt</th>
<th>IC_{50} (µM)</th>
<th>IC_{50} (µg/mL)</th>
<th>Resistance Index</th>
<th>Therapeutic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pf3D7</td>
<td>Pf3D7</td>
<td>IC_{50} Indol/IC_{50} 3D7</td>
<td>IC_{50} Dd2/IC_{50} 3D7</td>
</tr>
<tr>
<td>9</td>
<td>328.8</td>
<td>2.5</td>
<td>0.82</td>
<td>6.6</td>
</tr>
<tr>
<td>10</td>
<td>363.2</td>
<td>10</td>
<td>3.63</td>
<td>&gt;2</td>
</tr>
<tr>
<td>11</td>
<td>373.2</td>
<td>8.1</td>
<td>3.02</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>12</td>
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<td>8.5</td>
<td>3.57</td>
<td>&gt;2.4</td>
</tr>
<tr>
<td>13</td>
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<td>23</td>
<td>7.78</td>
<td>0.7</td>
</tr>
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<td>5.3</td>
<td>1.74</td>
<td>2.6</td>
</tr>
<tr>
<td>15</td>
<td>324.4</td>
<td>22.5</td>
<td>7.29</td>
<td>0.6</td>
</tr>
<tr>
<td>16</td>
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<td>38.5</td>
<td>13.05</td>
<td>0.6</td>
</tr>
<tr>
<td>17</td>
<td>339.3</td>
<td>&gt;50</td>
<td>-</td>
<td>-</td>
</tr>
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<td>18</td>
<td>309.4</td>
<td>36</td>
<td>11.13</td>
<td>0.4</td>
</tr>
<tr>
<td>19</td>
<td>294.3</td>
<td>38</td>
<td>11.18</td>
<td>0.4</td>
</tr>
<tr>
<td>20</td>
<td>350.4</td>
<td>7.4</td>
<td>2.59</td>
<td>1.6</td>
</tr>
<tr>
<td>CQ</td>
<td>319.9</td>
<td>40 nM</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

We next ventured to evaluate the positional importance of allyl group (ortho vs meta vs para) on ring A (Table 4, 21, 22). The fact that activity was markedly affected by changing the position of allyl group at the phenyl ring (21 & 22 vs 9, Table 4) emphasized the importance of para-substitution of O-allyl group for activity. Subsequently, the effect of changing the nature of the O-substituent (H, prenyl, C4H9, and CH2C6H4Br) was evaluated and reduced activity was observed in each instance (23-26, Table 4). Likewise, any change in the position, nature and number of methoxy groups at ring A markedly affected the activity (27-31, Table 4) signifying the particular special contribution of 3-methoxy group (as revealed in compound 9) which may be due to its orientation and binding ability with the malarial parasite proteins.

In the backdrop of a study by Liu et al. (2003), where size parameter of ring B (large, alkoxylated) and electron deficient nature of ring A were found significant for antimalarial activity, compound 32 was synthesized by reversal of substituents between rings A and B of 9. However, the compound exhibited lesser antimalarial potential (IC_{50}: 8.6 µM, Table 4) as compared to 9 (Table 3), thus underlying the importance of enhanced electron density on ring A of chalcone for good activity [Kumar et al. (2010)].
Table 4: SAR investigation for antimalarial activity, resistance and selectivity indices of O-allylated chalcones

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Mol. Wt</th>
<th>IC_{50} (μM) Pf3D7</th>
<th>IC_{50} (μg/mL) Pf3D7</th>
<th>Resistance Index IC_{50} Indo/IC_{50} 3D7</th>
<th>IC_{50} Dd2/IC_{50} 3D7</th>
<th>Therapeutic Index IC_{50} HeLa/IC_{50} 3D7</th>
<th>IC_{50} L29/IC_{50} 3D7</th>
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</thead>
<tbody>
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<td>21</td>
<td>328.8</td>
<td>12.5</td>
<td>4.11</td>
<td>&gt;1.6</td>
<td>0.8</td>
<td>1.0</td>
<td>3.8</td>
</tr>
<tr>
<td>22</td>
<td>328.8</td>
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<td>5.92</td>
<td>1.05</td>
<td>0.94</td>
<td>2.3</td>
<td>4.2</td>
</tr>
<tr>
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<td>28</td>
<td>8.09</td>
<td>1.2</td>
<td>1.3</td>
<td>1.1</td>
<td>2.4</td>
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<tr>
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<td>356.8</td>
<td>5.0</td>
<td>1.78</td>
<td>4.6</td>
<td>0.9</td>
<td>5.2</td>
<td>5.4</td>
</tr>
<tr>
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<td>-</td>
</tr>
<tr>
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<td>3.66</td>
<td></td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
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<td>358.8</td>
<td>3.8</td>
<td>1.36</td>
<td>4.5</td>
<td>5.9</td>
<td>7.9</td>
<td>11.6</td>
</tr>
<tr>
<td>28</td>
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<td>43</td>
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<td>0.74</td>
<td>0.72</td>
<td>2.3</td>
<td>1.5</td>
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<td>9.0</td>
<td>2.69</td>
<td>2.2</td>
<td>1.0</td>
<td>&gt;11.1</td>
<td>5.6</td>
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<tr>
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<td>9.60</td>
<td>0.64</td>
<td>0.75</td>
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<td>1.21</td>
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<td>1.0</td>
<td>6.8</td>
<td>29.4</td>
</tr>
<tr>
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<td>328.8</td>
<td>8.6</td>
<td>2.83</td>
<td>&gt;2.3</td>
<td>1.3</td>
<td>4.1</td>
<td>6.0</td>
</tr>
<tr>
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<td>319.9</td>
<td>40 nM</td>
<td>-</td>
<td>-</td>
<td>4.2</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

(d) Effect of incorporation of heterocyclic moiety: Heteroaryl-substitution is an attractive strategy for the development of drugs with desirable activity and several inspiring reports on the antimalarial activity of heterocyclic chalcone derivatives [Trivedi et al. (2007)] provided us impetus to synthesize such analogues. To begin with, we designed chalcones by the condensation of 1b with different heterocyclic carbonyls like 2-acetyl furan (33), 3-acetyl coumarin (34), 3-acetyl-4-hydroxy coumarin (35) [Sandeep et al. (2009)], 2-acetyl pyrrole (36), meldrum acid (37) and barbituric acid (38). However, in each case the antimalarial potential was found significantly reduced (33-38, Table 5). Given that the quinoline, particularly with 7-chloro group, is considered an excellent lead prototype for the development of antimalarial drugs [Egan et al. (2000); Kaur et al. (2010)], compound 39 was synthesized which, however,
was found to be quite inactive against malarial parasites. Interestingly, \( N \)-allylation of 39 significantly improved the activity of resulting compound (40 vs 39, Table 5).

In the similar vein, cyclization of chalcones leading to the synthesis of heterocyclics, such as pyrazoles and pyrimidines, is of great interest in drug designing because of their broad spectrum of biological activities [Wiley (1967); Lévai (2005)]. Although, introduction of pyrazole ring at double bond (41) had no or little effect on activity, the pyrimidine derivative (42) displayed considerable loss of activity (Table 5).

Table 5: Antimalarial activity, resistance and selectivity indices of heterocyclic derivatives of \( O \)-allylated chalcones

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Mol. Wt</th>
<th>( IC_{50} ) ( \mu M )</th>
<th>( IC_{50} ) (( \mu g/mL ))</th>
<th>Resistance Index</th>
<th>Therapeutic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( P/3D7 )</td>
<td>( P/3D7 )</td>
<td>( IC_{50} ) Indo/IC ( 50 ) 3D7</td>
<td>IC ( 50 ) Dd2/IC ( 50 ) 3D7</td>
</tr>
<tr>
<td>33</td>
<td>284.3</td>
<td>95</td>
<td>26.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>34</td>
<td>362.4</td>
<td>100</td>
<td>36.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>35</td>
<td>378.3</td>
<td>&gt;100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>36</td>
<td>283.3</td>
<td>48</td>
<td>13.58</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td>37</td>
<td>318.3</td>
<td>&gt;100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>38</td>
<td>302.3</td>
<td>&gt;100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>39</td>
<td>470.9</td>
<td>75</td>
<td>35.33</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40</td>
<td>511.0</td>
<td>3.5</td>
<td>1.79</td>
<td>1.9</td>
<td>0.9</td>
</tr>
<tr>
<td>41</td>
<td>418.9</td>
<td>3.3</td>
<td>1.38</td>
<td>5.2</td>
<td>0.9</td>
</tr>
<tr>
<td>42</td>
<td>367.8</td>
<td>&gt;50</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CQ</td>
<td>319.9</td>
<td>40 nM</td>
<td>-</td>
<td>-</td>
<td>4.2</td>
</tr>
</tbody>
</table>

(e) Bis/dimeric chalcones: Among the five bischalcones (43-47) screened against chloroquine sensitive strain, only compounds 43 and 46 showed significant activity, the order being 43>46>45>44=47. The results revealed that the type of oxygenated substituents in the phenyl ring greatly influence the activity profile (Table 6).
Table 6: Antimalarial activity, resistance and selectivity indices of bis (dimeric) chalcones

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Mol. Wt</th>
<th>IC(_{50}) ((\mu)M) (Pf3D7)</th>
<th>IC(_{50}) ((\mu)g/mL) (Pf3D7)</th>
<th>Resistance Index (IC_{50}) (Indo3D7)/ (IC_{50}) (3D7)</th>
<th>Therapeutic Index (IC_{50}) HeLa/ (IC_{50}) (3D7)</th>
<th>(IC_{50}) L29/ (IC_{50}) (3D7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>538.6</td>
<td>2.5</td>
<td>1.35</td>
<td>&gt;8.0</td>
<td>1.4</td>
<td>11.2</td>
</tr>
<tr>
<td>44</td>
<td>510.6</td>
<td>&gt;50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>45</td>
<td>562.6</td>
<td>18</td>
<td>10.13</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>46</td>
<td>450.5</td>
<td>&gt;12.5</td>
<td>-</td>
<td>-</td>
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<td>47</td>
<td>482.5</td>
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<td>-</td>
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<tr>
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<td>319.9</td>
<td>40 nM</td>
<td>-</td>
<td>-</td>
<td>4.2</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

2.1.6.3. Evaluation of resistant index and therapeutic indices

The identified lead chalcones were also tested against chloroquine resistant Dd2 strain of \textit{P. falciparum} (Tables 2-6). Against a resistance Index (\(IC_{50}\) Dd2/\(IC_{50}\) 3D7) of 4.2 for chloroquine, the indices for the potent chalcones were found to be in the range of 0.5-5.9 (Tables 2-6). Finally, the active compounds were analyzed for their cytotoxic behavior against two mammalian cell lines viz. HeLa and fibroblast L29. The obtained therapeutic indices (\(IC_{50}\) HeLa cell line/\(IC_{50}\) \(Pf\) 3D7) (Tables 2-6) values indicated that the most active compounds (9, 40, 41, 43) were also relatively non-toxic.

2.1.6.4. Calculation of physical chemical properties

The molecular properties for absorption, distribution, metabolism and excretion (ADME) are crucial to enhance the probability of success through the drug development stage [Kassel (2004)]. Absorption is a primary focus in drug development and medicinal chemistry since the drug must be absorbed in the body before any medicinal effects can take place. This requirement makes lipophilicity and solubility the two major properties responsible for absorption and bioavailability of drugs [Alavijeh \textit{et al.} (2005); Bergström (2005)]. The 1-octanol-water partition coefficient, log P, is a well known parameter to estimate lipophilicity (or solubility in lipids) of chemical compounds [Tetko \textit{et al.} (2008)]. Aqueous solubility is usually measured as its logarithm of intrinsic or pH-dependent solubility, AlogS [Viswanadhan \textit{et al.} (2000)]. Similarly, topological polar surface area (TPSA) is a good indicator of drug
absorbance in the intestines, Caco-2 monolayers penetration, and blood-brain barrier crossing [Ertl et al. (2000)]. It has been well established that optimal lipophilicity range along with low molecular weight and low polar surface area is the major driving force that leads to good absorption of compounds in the intestine by passive diffusion [Mannhold, et al. (2009)]. A very high TPSA value contributes for a low bioavailability for the molecule [Rajasekaran et al. (2011)].

Accordingly, a computational study for prediction of ADME properties of all the molecules was performed (Molinspiration Cheminformatics) and is presented in Table 7. TPSA was used to calculate the percentage of absorption (%Abs) according to the equation: %Abs = 109 - 0.345 × TPSA, as reported by Zhao et al. (2002). In addition, number of rotatable bonds (n-ROTB) and other parameters of Lipinski’s rule of five [Lipinski et al. (1997)] were also calculated. From all the parameters, it was observed that all the active molecules exhibited a low TPSA value when compared to Licochalcone (LC) except 43 and hence greater %Abs ranging from 85.9 to 99.9%. Furthermore, all the active molecules violate one or none of Lipinski’s parameters, except 43; thus making them potentially promising agents for antimalarial therapy.

**Table 7:** Physical-chemical properties of compounds 1-47

<table>
<thead>
<tr>
<th>ID</th>
<th>Mol. wt</th>
<th>%Abs</th>
<th>TPSA</th>
<th>miLogP</th>
<th>ALogS</th>
<th>$n$ atoms</th>
<th>$n$ rotb</th>
<th>$n$ON acceptors</th>
<th>$n$OHNH donors</th>
<th>Lipinski's violations</th>
</tr>
</thead>
<tbody>
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<td>85.9</td>
<td>66.7</td>
<td>4.84</td>
<td>-4.66</td>
<td>25</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>310.3</td>
<td>85.9</td>
<td>66.7</td>
<td>3.65</td>
<td>-4.27</td>
<td>23</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>328.7</td>
<td>92.9</td>
<td>46.5</td>
<td>4.81</td>
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<td>23</td>
<td>6</td>
<td>3</td>
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<td>0</td>
</tr>
<tr>
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<td>5.08</td>
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<td>1</td>
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<td>44.8</td>
<td>4.46</td>
<td>-5.76</td>
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<td>----</td>
</tr>
</tbody>
</table>
|   | 373.2 | 96.7 | 35.5 | 4.91 | -5.97 | 23 | 7 | 3 | 0 | 0 | 420.2 | 96.7 | 35.5 | 5.18 | -6.22 | 23 | 7 | 3 | 0 | 1 | 312.3 | 96.7 | 35.5 | 4.26 | -5.64 | 23 | 7 | 3 | 0 | 0 | 328.8 | 96.7 | 35.5 | 4.75 | -5.83 | 23 | 7 | 3 | 0 | 0 | 324.4 | 93.5 | 44.7 | 4.15 | -5.35 | 24 | 8 | 4 | 0 | 0 | 338.4 | 90.3 | 54.0 | 3.99 | -5.26 | 25 | 7 | 5 | 0 | 0 | 339.3 | 80.9 | 81.3 | 4.06 | -5.62 | 25 | 8 | 6 | 0 | 0 | 309.4 | 87.7 | 61.5 | 3.17 | -4.82 | 23 | 7 | 4 | 2 | 0 | 294.3 | 96.7 | 35.5 | 4.10 | -5.18 | 22 | 7 | 3 | 0 | 0 | 350.4 | 93.5 | 44.7 | 4.80 | -5.82 | 26 | 10 | 4 | 0 | 0 | 328.8 | 96.7 | 35.5 | 4.77 | -5.80 | 23 | 7 | 3 | 0 | 0 | 328.8 | 96.7 | 35.5 | 4.78 | -5.84 | 23 | 7 | 3 | 0 | 0 | 288.7 | 92.9 | 46.5 | 3.82 | -4.71 | 20 | 4 | 3 | 1 | 0 | 356.8 | 96.7 | 35.5 | 5.81 | -5.95 | 25 | 7 | 3 | 0 | 1 | 344.8 | 96.7 | 35.5 | 5.57 | -6.18 | 24 | 8 | 3 | 0 | 1 | 457.7 | 96.7 | 35.5 | 6.54 | -7.18 | 28 | 7 | 3 | 0 | 1 | 358.8 | 93.5 | 44.7 | 4.76 | -5.81 | 25 | 8 | 4 | 0 | 0 | 298.8 | 99.9 | 26.3 | 5.19 | -5.89 | 21 | 6 | 2 | 0 | 1 | 298.8 | 99.9 | 26.3 | 4.96 | -5.86 | 21 | 6 | 2 | 0 | 0 | 342.8 | 96.7 | 35.5 | 5.15 | -6.05 | 24 | 8 | 3 | 0 | 1 | 354.8 | 96.7 | 35.5 | 5.42 | -6.17 | 25 | 9 | 3 | 0 | 1 | 328.8 | 96.7 | 35.5 | 4.78 | -5.82 | 23 | 7 | 3 | 0 | 0 | 284.3 | 92.2 | 48.6 | 3.36 | -4.26 | 21 | 7 | 4 | 0 | 0 | 362.4 | 86.3 | 65.7 | 4.10 | -5.66 | 27 | 7 | 5 | 0 | 0 | 378.3 | 79.3 | 85.9 | 3.81 | -4.99 | 28 | 7 | 6 | 1 | 0 | 283.3 | 91.3 | 51.3 | 3.25 | -3.89 | 21 | 7 | 4 | 1 | 0 | 318.3 | 84.5 | 71.0 | 3.25 | -4.34 | 23 | 5 | 6 | 0 | 0 | 302.3 | 74.1 | 101.2 | 0.58 | -3.86 | 22 | 5 | 7 | 2 | 0 | 470.9 | 88.2 | 60.4 | 6.98 | -6.56 | 34 | 9 | 5 | 1 | 1 | 510.0 | 91.2 | 51.6 | 7.43 | -7.01 | 37 | 11 | 5 | 0 | 2 | 418.9 | 97.2 | 34.1 | 6.22 | -6.70 | 30 | 7 | 4 | 0 | 1 | 367.8 | 84.8 | 70.2 | 4.34 | -6.74 | 26 | 6 | 5 | 2 | 0 | 538.6 | 84.5 | 71.0 | 6.85 | -7.45 | 40 | 14 | 6 | 0 | 2 | 510.6 | 84.5 | 71.0 | 6.24 | -6.99 | 38 | 14 | 6 | 0 | 2 | 562.6 | 84.5 | 71.0 | 7.53 | -6.94 | 42 | 18 | 6 | 0 | 2 | 450.5 | 90.8 | 52.6 | 7.08 | -7.04 | 34 | 12 | 4 | 0 | 1 | 482.5 | 76.9 | 93.1 | 6.92 | -5.53 | 36 | 12 | 6 | 2 | 1

%Abs = percentage of absorption; TPSA = topological polar surface area; miLogP = logarithm of compound partition coefficient between n-octanol and water; ALogS = logarithm of intrinsic or pH-dependent solubility; natoms = no. of atoms; nrotb = no. of rotatable bonds; nOHNH = no. of hydrogen bond donors; nON = no. of hydrogen bond acceptors
After testing the above chalcones for antimalarial activity, it was contemplated to screen these for their potential as pesticidal agents.

### 2.2. Pesticidal activity of allylated chalcones against diamondback moth 
*(Plutella xylostella)*

#### 2.2.1. Introduction

The diamondback moth (*Plutella xylostella*), also known as cabbage moth, is one of the most destructive pests of cruciferous crops in the world and usually feed on plants that produce glucosinolates such as broccoli, Brussels sprouts, cabbage, Chinese cabbage, cauliflower, kale, mustard, radish and turnip [Talekar and Shelton (1993); Capinera (2001)]. The larvae (Figure 9) damage the leaves, buds, flowers, and seed-buds of cultivated cruciferous plants and cause complete removal of foliar tissue except for the leaf veins. It is believed that absence of effective natural enemies, especially parasitoids is a major cause of the diamondback moth’s pest status in most parts of the world [Lim (1986)]. Another reason for the lack of effective biological control in an area may be destruction of natural enemies by the use of broad-spectrum insecticides. In 1953, the diamondback moth became the first crop pest in the world to develop resistance to DDT [Johnson (1953); Asakawa (1975)], and now in many countries the pest has become resistant to every basic insecticide classes, such as organochlorides, organophosphates, and carbamates [Talekar *et al.* (1985); Sun *et al.* (1986)]. Moreover, the non-restricted use of highly toxic insecticides for several decades has provoked negative effects to the humans, animals and environment [Eskenazi *et al.* (1999)]. Thus, there is a worldwide search for alternative chemical pesticides with greater selectivity and environmental profiles.

In the fervent research targeted for the synthesis of eco-friendly bio-pesticides, chalcones (1,3-diaryl-2-propen-1-ones) have gained importance due to their remarkably divergent array of bioactivities [Edwards *et al.* (1990); Mukherjee *et al.* (2001); Bhat *et al.* (2005); Göker *et al.* (2005); Nielsen *et al.* (2005); Boeck *et al.* (2006); Wei *et al.* (2007)] as well as easily degradable nature. Moreover, the molecule is viewed as a template for molecular modifications with a view to prepare new compound libraries.
In one report, 1,5-diphenyl-2-penten-1-one, extracted from *Stellera chamaejasme*, was shown to have strong contact activity and very good antifeedant activity against *Aphis gossypii* and *Schizaphis graminum* [Ping et al. (2001)]. Nalwar *et al.* also reported significant insect antifeedant activity of twelve chalcones against the mealy bug of cotton (*Phenacoccus solanopsis*) [Nalwar *et al.* (2009)]. Similarly, chalcone derivatives were evaluated for their antifilarial activity on *Setaria cervi* using glutathione-S-transferase (GST) as a drug target [Awasthi *et al.* (2009)]. In a recent report, insect antifeedant activity of substituted styryl 4'-fluorophenyl ketones was evaluated against 4<sup>th</sup> instar larvae of *Achoea janata* whereby halogen containing compounds were found to have better activity among all the tested compounds [Thirunarayanan and Vanangamudi (2011)]. In addition, larvicidal activities have also been reported for several chalcone derivatives [Das *et al.* (2005); Gautam and Chourasia (2010); Begum *et al.* (2011)]. Of late, a study by Kumar *et al.* (2011) regarding the pesticidal activity of chalcones against *Plutella xylostella* has appeared wherein, it has been revealed that electron-withdrawing substituents, in particular chloro substitution, on ring A of chalcone provided good pesticidal agents. Thus in view of above promising reports, it was contemplated to screen some of the allylated chalcones (Figure 10) for pesticidal activity against diamondback moth (*Plutella xylostella*) for their potential as pesticidal agents.

![Figure 10](image_url)

### 2.2.2. Results and discussion

Chalcones (1-11) were prepared by Claisen-Schmidt condensation [Cabrera *et al.* (2007); Boumendjel *et al.* (2008)] as described in section 2.1.6.1 and tested against second instar larvae of *P. xylostella* after 48 h of exposure time. The preliminary screening was carried out at 1000 µg/mL and results (expressed as mortality %) is presented in Table 8. In the initial screening, chalcone with *O*-allylation on ring A and 4-Cl substitution (1; electron withdrawing) and 4-*O*-allylation (2; electron releasing) at ring B were subjected for pesticidal activity. Among these, 1 showed moderate pesticidal activity which was in corroboration to earlier report on well-known pesticidal potency of chlorinated compounds [Kumar *et al.* (2011)]. However, replacement of...
Cl on ring B with more electron-withdrawing substituents i.e. 3,4-dichloro (3) exhibited lesser activity (Table 8; entry 3 vs 1). Furthermore, the positional importance of allyl group at different positions in terms of O-allylation (1) vs C-allylation (5), both C- and O-allylation (6), di-O-allylation (7) and absence of allyl group (8) on ring A was evaluated with a view to enhance the activity where compounds 5 and 7 exhibited more than 90% larval mortality in the order 5 > 7. From the structure–activity perspective, compound 5 with mortality of 96.7% was selected as a lead to study the effect of various substitutions on ring B. It was observed that replacement of Cl on ring B with 3,4-dioxymethylene (9) or methoxy (10) or Br (11) substituents showed significant reduction in activity when compared to 5. Even the reversal of substituents of 1 did not resulted in any enhancement of pesticidal activity (4, Table 8). Thus, the data generated (Table 8; entries 1-11) revealed that besides electronic consideration, lipophilic and hydrophilic characteristics of various substituents are responsible for influencing the pesticidal activity. Overall pesticidal activity of the screened chalcones was found to obey the order: 5 > 7 > 9 > 6 > 1 > 4 > 8 > 10 > 11 > 3 > 2 (Table 8).

Table 8: Preliminary screening of chalcone derivatives against second instar larvae of *P. xylostella* after 48 h

<table>
<thead>
<tr>
<th>S.No</th>
<th>Structure</th>
<th>Conc. (µg/mL)</th>
<th>Mortality [%]a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1000</td>
<td>43.0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1000</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1000</td>
<td>20.0</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1000</td>
<td>40.0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1000</td>
<td>96.7</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1000</td>
<td>75.0</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1000</td>
<td>93.3</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>1000</td>
<td>36.6</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1000</td>
<td>86.6</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>1000</td>
<td>26.6</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>1000</td>
<td>23.0</td>
</tr>
</tbody>
</table>

aData represent the mean values of the three replicates and present corrected mortality using Abbott’s formula
2.3. Conclusion
A series of novel allylated Licochalcone congeners were synthesized by Claisen-Schmidt condensation of an abundantly available precursor i.e. vanillin with various substituted acetophenones and thus obtained compounds were evaluated for \textit{in vitro} antimalarial activity against \textit{P. falciparum} 3D7 where several compounds have shown good antimalarial potential. Compounds 9 and 43 were found to be most potent antimalarials with IC\textsubscript{50} of 2.5 \textmu M each. These series of compounds showed not only promising drug-like properties but are also easy and economical to prepare and thus might prove useful leads towards future antimalarial drug discovery. In addition, some of the above chalcones were screened for pesticidal activity against diamondback moth, \textit{Plutella xylostella} where compound 5 was found to be most potent among all. Though preliminary in nature, the study may prove a pivotal point in designing compounds with comparable potency to commercial pesticides.

2.4. Experimental
2.4.1. Chemical and reagents
All the reagents were obtained from commercial sources (Merck or Acros). The solvents used for isolation/purification of compounds were obtained from commercial sources (Merck) and used without further purification. \textsuperscript{1}H (300 MHz) and \textsuperscript{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. TMS was used as internal reference for \textsuperscript{1}H NMR. HRMS-ESI spectra were determined using micromass Q-TOF ultima spectrometer.

2.4.2. Procedure for the synthesis of C-allylated chalcones via 1b and 2b (1-2; Table 2)
\textbf{(a) Synthesis of 4-allyloxy-3-methoxybenzdehyde (1b)}
To a 250-mL round bottom flask containing vanillin (1a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol), and anhydrous K\textsubscript{2}CO\textsubscript{3} (3.8 mmol) were added. The mixture was refluxed for 6 h. After consumption of aldehyde (monitored by TLC), the mixture was filtered to remove K\textsubscript{2}CO\textsubscript{3}. The filtrate was vacuum evaporated and washed with hexane to remove excess of allyl bromide. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (9:1) to provide the desired compound which was characterized by \textsuperscript{1}H & \textsuperscript{13}C NMR and HRMS data.
4-allyloxy-3-methoxybenzaldehyde (1b)

White solid (Yield 88%) m.p. 30-35°C, $^1$H NMR (CDCl$_3$, 300 MHz):

\[ \delta 9.82 (1H, s), 7.42 (2H, s), 6.97 (1H, d, J = 7.75 Hz), 6.11-6.00 (1H, m), 5.45 (1H, d, J = 17.25 Hz), 5.34 (1H, d, J = 10.47 Hz), 4.68 (2H, s), 3.91 (3H, s); ^13$C NMR (CDCl$_3$, 75.4 MHz):

\[ \delta 191.3, 153.8, 150.2, 132.6, 130.5, 127.0, 119.2, 109.5, 70.1 \text{ and } 56.4. \]  

HRMS-ESI: m/z [M+H]$^+$ for C$_{11}$H$_{12}$O$_3$, calculated 193.0996; observed 193.1011.

(b) **Synthesis of 5-allyl-4-hydroxy-3-methoxybenzaldehyde (2b)**

The product obtained from step (a) was taken in round bottom flask and subjected to microwave at 150 W for 15 min at 195-205°C to undergo Claisen rearrangement. The progress of reaction was monitor with the help of TLC. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (9:1) to provide the desired compound which was characterized by $^1$H & $^{13}$C NMR and HRMS data.

5-allyl-4-hydroxy-3-methoxybenzaldehyde (2b)

White solid (Yield 55%) m.p. 75-79°C, $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$

\[ 10.81 (1H, s), 9.72 (2H, s), 6.82 (2H, s), 5.87-5.75 (1H, m), 4.97-4.95 (1H, s), 3.76 (3H, s), 3.23 (2H, d, J = 6.63 Hz); ^13$C-NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.2, 149.6, 146.9, 135.1, 128.8, 127.8, 126.1, 116.7, 107.2, 56.1 and 33.1. HRMS-ESI: m/z [M+H]$^+$ for C$_{11}$H$_{12}$O$_3$, calculated 193.0996; observed 193.0998.

(c) **Synthesis of C-allylated chalcones (1 and 2)**

To a solution of 2b (3 mmol) and 4-hydroxy acetophenone or 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The reaction mixture was stirred till completion of starting material (monitored by TLC). The reaction mixture was vacuum evaporated to remove the organic solvent and poured in cold water. The obtained precipitates were washed with dilute HCl, excess of water, methanol, dried in air and finally recrystallized with methanol to obtain pure chalcones (1 or 2) whose structure were confirmed by NMR and mass spectroscopy.
**Synthesis of allylated chalcones... Chapter 2**

(2E)-3-[4-Hydroxy-3-methoxy-5-(prop-2-en-1-yl)phenyl]-1-(4-hydroxyphenyl)prop-2-en-1-one (compound 1, Table 2) (obtained by condensation of 2b with 4-hydroxy acetophenone)

Yellow viscous liquid (Yield 40%), \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 8.00\) (2H, d, \(J = 8.64\) Hz), \(7.80\) (1H, d, \(J = 15.54\) Hz), \(7.45\) (1H, d, \(J = 15.54\) Hz), \(7.20\) (2H, m), \(7.01\) (2H, d, \(J = 8.64\) Hz), \(6.87\) (2H, d, \(J = 7.1\) Hz), \(6.12-6.01\) (1H, m), \(5.45\) (2H, dd, \(J = 17.23, 10.50\) Hz), \(4.66\) (2H, d, \(J = 5.39\) Hz), \(3.93\) (3H, s); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta 190.4, 161.8, 150.8, 149.9, 145.3, 133.6, 133.0, 131.7, 130.8, 128.5, 123.5, 120.2, 118.9, 116.2, 113.4, 70.2\) and \(56.4\). HRMS-ESI: m/z [M+H]\(^+\) for C\(_{19}\)H\(_{18}\)O\(_4\), calculated 311.1458; observed 311.1442.

(2E)-1-(4-Chlorophenyl)-3-[4-hydroxy-3-methoxy-5-(prop-2-en-1-yl)phenyl]prop-2-en-1-one (compound 2, Table 2) (obtained by condensation of 2b with 4-chloro acetophenone)

Yellow viscous liquid (Yield 58%), \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 7.92\) (2H, d, \(J = 8.50\) Hz), \(7.89\) (1H, d, \(J = 15.30\) Hz), \(7.67\) (1H, d, \(J = 15.30\) Hz), \(7.39-7.26\) (3H, m), \(7.06\) (2H, d, \(J = 8.50\) Hz), \(6.01-5.92\) (1H, m), \(5.10\) (2H, dd, \(J = 17.22, 10.30\) Hz), \(4.07\) (3H, s), \(3.41\) (2H, d, \(J = 6.76\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta 191.6, 149.9, 147.4, 146.5, 135.9, 130.2, 129.4, 128.3, 126.8, 124.7, 119.4, 116.7, 116.4, 108.7, 107.6, 56.6\) and \(34.1\). HRMS-ESI: m/z [M+H]\(^+\) for C\(_{19}\)H\(_{17}\)ClO\(_3\), calculated 329.5913; observed 329.5927.

**2.4.3. Procedure for the synthesis of C-allylated chalcones via 3b (3-7; Table 2)**

(a) **Synthesis of 5-allyl-3,4-dimethoxy benzaldehyde (3b)**

To the 2b (6.6 mmol; section 2.4.2) taken in round bottom flask was added sodium hydroxide (6.6 mmol) dissolved in 2 mL of water (to increase solubility benzytrimethylammonium chloride (PTC) was added in a catalytic amount). The reaction mixture was stirred for 5-10 min. Thereafter, dimethyl sulfate (12.2 mmol) was added drop-wise to the above reaction mixture at 0°C and then stirred at room temperature for 5-6 h. After the completion of reaction (monitored by TLC), reaction mixture was acidified with dilute HCl (pH 6) and partitioned between ethyl acetate (70 mL) and water (15 mL). The ethyl acetate layer was washed with
water till neutral, dried over sodium sulfate and evaporated. The obtained residue was purified by column chromatography (silica gel, hexane: ethyl acetate (7:3; v/v)) to afford the desired compound whose structure was confirmed through NMR and mass spectrometry.

**5-allyl-3,4-dimethoxy benzaldehyde (3b)**

![Chemical structure of 5-allyl-3,4-dimethoxy benzaldehyde (3b)](attachment:image)

Pale yellow viscous liquid (Yield 80%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.88 (1H, s), 7.34 (2H, d, $J = 4.24$ Hz), 6.03-5.93 (1H, m), 5.12-5.06 (2H, m), 3.93 (6H, s), 3.46 (2H, d, $J = 5.43$ Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.4, 153.4, 152.8, 136.5, 134.5, 132.4, 126.6, 116.4, 109.3, 60.9, 56.6 and 34.1. HRMS-ESI: m/z [M+H]$^+$ for C$_{12}$H$_{14}$O$_3$, calculated 207.1152; observed 207.1164.

**(b) Synthesis of C-allylated chalcones (3-7)**

To a solution of 3b (3 mmol) and appropriate acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compounds obtained after recrystallization were characterized by $^1$H & $^{13}$C NMR and HRMS data.

**(2E)-1-(4-Chlorophenyl)-3-[3,4-dimethoxy-5-(prop-2-en-1-yl)phenyl]prop-2-en-1-one**

(compound 3, Table 2) (obtained by condensation of 3b with 4-chloro acetophenone)

Yellow solid (Yield 72%) m.p. 65-69°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.97 (2H, d, $J = 7.70$ Hz), 7.77 (1H, d, $J = 15.57$ Hz), 7.48 (2H, d, $J = 7.70$ Hz), 7.33 (1H, d, $J = 15.57$ Hz), 7.10 (1H, s), 7.06 (1H, s), 6.03-5.94 (1H, m), 5.12 (2H, d, $J = 11.77$ Hz), 3.92 (3H, s), 3.87 (3H, s), 3.45 (2H, d, $J = 6.39$ Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.6, 153.4, 150.1, 145.8, 139.4, 137.1, 134.8, 130.8, 130.3, 130.1, 129.3, 123.7, 121.0, 116.5, 110.7, 61.2, 56.3 and 34.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{20}$H$_{19}$ClO$_3$, calculated 343.6069; observed 343.6072.
**Synthesis of allylated chalcones...**  

(2E)-3-[3,4-Dimethoxy-5-(prop-2-en-1-yl)phenyl]-1-(4-methoxyphenyl)prop-2-en-1-one (compound 4, Table 2) (obtained by condensation of 3b with 4-methoxy acetophenone)

**Yellow solid (Yield 70%)** m.p. 64-66°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.88 (2H, d, $J = 6.19$ Hz), 7.57 (1H, d, $J = 15.56$ Hz), 7.27 (1H, d, $J = 15.56$ Hz), 6.93 (1H, s), 6.88 (1H, s), 6.82 (2H, d, $J = 6.27$ Hz), 5.84-5.78 (1H, m), 4.94 (2H, d, $J = 12.67$ Hz), 3.75 (3H, s), 3.64 (6H, s), 3.27 (2H, d, $J = 6.27$ Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.4, 163.9, 153.5, 149.9, 144.6, 137.4, 134.9, 131.8, 131.3, 123.8, 123.6, 121.6, 116.6, 114.4, 110.8, 61.3, 56.4, 56.0 and 34.6. HRMS-ESI: m/z [M+H]$^+$ for C$_{21}$H$_{22}$O$_4$, calculated 339.1770; observed 339.1738.

(2E)-1-(1,3-Benzodioxol-5-yl)-3-[3,4-dimethoxy-5-(prop-2-en-1-yl)phenyl]prop-2-en-1-one (compound 5, Table 2) (obtained by condensation of 3b with 3,4-dioxymethylene acetophenone)

**Pale yellow solid (Yield 71%)** m.p. 88-92°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.88 (2H, d, $J = 6.19$ Hz), 7.54 (1H, d, $J = 15.56$ Hz), 7.45 (1H, d, $J = 15.56$ Hz), 7.11 (2H, d, $J = 6.20$ Hz), 6.90 (1H, s) 6.08 (2H, s), 6.06-5.94 (1H, m), 5.13 (2H, d, $J = 14.64$ Hz), 3.93 (3H, s), 3.45 (3H, s), 3.46 (2H, d, $J = 5.72$ Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 188.7, 153.4, 151.9, 149.7, 148.7, 144.7, 137.2, 134.7, 133.5, 131.1, 125.0, 123.4, 121.2, 116.4, 110.6, 108.9, 108.3, 102.2, 61.2, 56.3 and 34.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{21}$H$_{20}$O$_5$, calculated 353.1608; observed 353.1631.

(2E)-1-(4-Bromophenyl)-3-[3,4-dimethoxy-5-(prop-2-en-1-yl)phenyl]prop-2-en-1-one (compound 6, Table 2) (obtained by condensation of 3b with 4-bromo acetophenone)

**Yellow solid (Yield 70%)** m.p. 58-60°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.90 (2H, d, $J = 8.29$ Hz), 7.77 (1H, d, $J = 15.61$ Hz), 7.67 (2H, d, $J = 8.29$ Hz), 7.38
(1H, d, J = 15.61 Hz), 7.11 (1H, s), 7.06 (1H, s), 6.04-5.95 (1H, m), 5.13 (2H, d, J = 11.40 Hz), 3.94 (3H, s), 3.93 (3H, s), 3.46 (2H, d, J = 6.38 Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.9, 153.5, 150.1, 146.0, 136.8, 136.7, 134.9, 132.4, 130.8, 130.5, 128.7, 123.8, 120.9, 116.6, 110.6, 61.3, 56.3 and 34.3. HRMS-ESI: m/z [M+H]$^+$ for C$_{20}$H$_{19}$BrO$_3$, calculated 388.0582; observed 388.0597.

$^{(2E)}$-3-[3,4-Dimethoxy-5-(prop-2-en-1-yl)phenyl]-1-(4-nitrophenyl)prop-2-en-1-one (compound 7, Table 2) (obtained by condensation of 1b with 4-nitro acetophenone)  

Bright yellow solid (Yield 68%) m.p. 93-96°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.38 (2H, d, J = 8.20 Hz), 8.16 (2H, d, J = 8.20 Hz), 7.80 (1H, d, J = 15.62 Hz), 7.39 (1H, d, J = 15.62 Hz), 7.13 (1H, s), 7.08 (1H, s), 6.03-5.92 (1H, m), 5.13 (2H, d, J = 11.69 Hz), 3.94 (3H, s), 3.89 (3H, s), 3.46 (2H, d, J = 6.13 Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.6, 153.5, 150.4, 150.3, 147.4, 143.7, 136.9, 134.9, 130.3, 130.2, 129.8, 124.2, 124.0, 120.8, 116.7, 61.3, 56.3 and 34.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{20}$H$_{19}$NO$_5$, calculated 354.1561; observed 354.1579.

2.4.4. Procedure for the synthesis of C-allylated chalcone via 4b (8; Table 2)  

(a) Synthesis of 5-allyl-4-allyloxy-3-methoxy benzaldehyde (4b)  

To a 250-mL round bottom flask containing 2b (1.9 mmol; section 2.4.2) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

5-allyl-4-allyloxy-3-methoxy benzaldehyde (4b)  

Pale yellow viscous liquid (Yield 84%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.81 (1H, s), 7.27 (2H, s), 6.02-5.90 (2H, m), 5.31 (1H, d, J = 17.16 Hz), 5.18 (1H, d, J = 10.35 Hz), 5.05-5.00 (2H, m), 4.54 (2H, s), 3.86 (3H, s), 3.41 (2H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.6, 153.6, 151.7, 136.7, 134.9, 134.2, 133.1, 126.8, 118.2, 116.7, 109.4, 74.2, 56.2 and 34.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{14}$H$_{16}$O$_3$, calculated 233.1308; observed 233.1321.
(b) **Synthesis of C-allylated chalcones** (8)

To a solution of 4b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by \(^1\)H & \(^{13}\)C NMR and HRMS data.

\((2E)\)-1-(4-Chlorophenyl)-3-[3-methoxy-5-(prop-2-en-1-yl)-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 8, Table 2)

![Chemical structure of compound 8](image)

Yellow solid (Yield 74%) m.p. 69-71°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 8.02 (2\text{H}, \text{d}, J = 8.30 \text{ Hz}), 7.71 (1\text{H}, \text{s}), 7.54-7.33 (3\text{H}, \text{m}), 7.15 (2\text{H}, \text{d}, J = 8.30 \text{ Hz}), 6.11-5.99 (2\text{H}, \text{m}), 5.42-5.09 (4\text{H}, \text{m}), 4.59 (2\text{H}, \text{d}, J = 5.44 \text{ Hz}), 3.93 (3\text{H}, \text{s}), 3.47 (2\text{H}, \text{d}, J = 6.50 \text{ Hz}); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta 189.7, 153.4, 148.8, 145.8, 139.4, 137.1, 137.0, 135.0, 134.5, 130.8, 130.3, 129.3, 123.7, 121.0, 118.0, 116.8, 110.6, 74.3, 56.3 \text{ and } 34.6. \)

HRMS-ESI: \(m/z\) [M+H]\(^+\) for C\(_{22}\)H\(_{21}\)ClO\(_3\), calculated 369.6225; observed 369.6257.

2.4.5. **Procedure for the synthesis of O-allylated chalcones** (9-19; Table 3)

To a solution of 1b (3 mmol) and appropriate acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compounds obtained after recrystallization was characterized by \(^1\)H & \(^{13}\)C NMR and HRMS data.

\((2E)\)-1-(4-Chlorophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 9, Table 3) (obtained by condensation of 1b with 4-chloro acetophenone)

![Chemical structure of compound 9](image)

Pale yellow solid (Yield 85%) m.p. 90-93°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 7.97 (2\text{H}, \text{d}, J = 8.45 \text{ Hz}), 7.79 (1\text{H}, \text{d}, J = 15.56 \text{ Hz}), 7.48 (2\text{H}, \text{d}, J = 8.45 \text{ Hz}), 7.37 (1\text{H}, \text{d}, J = 15.56 \text{ Hz}), 7.22-7.17 (2\text{H}, \text{m}), 6.92 (1\text{H}, \text{d}, J = 8.43 \text{ Hz}), 6.15-6.03 (1\text{H}, \text{m}), 5.47 (2\text{H}, \text{dd}, J = 17.25, 10.45 \text{ Hz}), 4.68 (2\text{H}, \text{d}, J = 5.27 \text{ Hz}), 3.95 (3\text{H}, \text{s}); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta 189.6, 151.1, 150.1, 145.9, 139.3, 137.2, 133.1, 130.2, 129.3, 128.3, 123.5,
119.9, 118.9, 113.4, 111.1, 70.2 and 56.5. HRMS-ESI: m/z [M+H]^+ for C_{19}H_{17}ClO_3, calculated 329.5913 observed 329.5945.

(2E)-1-(3,4-Dichlorophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 10, Table 3) (obtained by condensation of 1b with 3,4-dichloro acetophenone)

Light yellow solid (Yield 80%) m.p. 80-82°C, ^1H NMR (CDCl_3, 300 MHz): δ 8.10 (1H, s), 7.86-7.77 (2H, m), 7.60 (1H, d, J = 8.00 Hz), 7.33-7.17 (3H, m), 6.93 (1H, d, J = 8.08 Hz), 6.15-6.04 (1H, m), 5.48 (2H, dd, J = 17.27, 10.46 Hz), 4.70 (2H, d, J = 4.17 Hz), 3.97 (3H, s); ^13C NMR (CDCl_3, 75.4 MHz): δ 188.4, 151.2, 150.0, 146.7, 138.5, 137.4, 133.6, 133.0, 131.1, 130.8, 128.0, 127.9, 123.8, 119.2, 118.9, 113.3 110.9, 70.2 and 56.5. HRMS-ESI: m/z [M+H]^+ for C_{19}H_{16}ClO_3, calculated 364.0962; observed 364.0928.

(2E)-1-(4-Bromophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 11, Table 3) (obtained by condensation of 1b with 4-bromo acetophenone)

Yellow solid (Yield 80%) m.p. 100-103°C, ^1H NMR (CDCl_3, 300 MHz): δ 7.90 (2H, d, J = 10.83 Hz), 7.79 (1H, d, J = 15.59 Hz), 7.66 (2H, d, J = 10.83 Hz), 7.36 (1H, d, J = 15.59 Hz), 7.23-7.16 (2H, m), 6.92 (1H, d, J = 8.30 Hz), 6.15-6.04 (1H, m), 5.47 (2H, dd, J = 17.26, 10.48 Hz), 4.69 (2H, d, J = 5.30 Hz), 3.96 (3H, s); ^13C NMR (CDCl_3, 75.4 MHz): δ 189.8, 151.0, 150.0, 145.9, 137.6, 133.0, 132.3, 130.4, 128.3, 128.0, 123.5, 119.8, 118.9, 113.3, 111.0, 70.2 and 56.5. HRMS-ESI: m/z [M+H]^+ for C_{19}H_{16}BrO_3, calculated 374.0426; observed 374.0453.

(2E)-1-(4-Iodophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 12, Table 3) (obtained by condensation of 1b with 4-iodo acetophenone)

Pale orange solid (Yield 78%) m.p. 95-97°C, ^1H NMR (CDCl_3, 300 MHz): δ 7.88-7.85 (2H, m), 7.79-7.70 (3H, m), 7.35 (1H, d, J = 15.59 Hz), 7.23-
7.16 (2H, m), 6.92 (1H, d, \( J = 8.30 \) Hz), 6.17-6.04 (1H, m), 5.48 (2H, dd, \( J = 17.26, 10.47 \) Hz), 4.69 (2H, d, \( J = 5.31 \) Hz), \( \delta \) 3.96 (3H, s); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \( \delta \) 190.1, 151.0, 150.0, 145.9, 138.3, 138.2, 133.1, 128.3, 123.5, 119.9, 118.9, 113.3, 111.0, 100.7, 70.2 and 56.5. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{19}\)H\(_{17}\)O\(_2\), calculated 421.0431; observed 421.0418.

\((2E)\)-1-(4-Fluorophenyl)-3-[3-methoxy-4-(prop-2-en-1-yl oxy)phenyl]prop-2-en-1-one (compound 13, Table 3) (obtained by condensation of 1\( b\) with 4-fluoro acetophenone)

![Diagram of allylated chalcone structure]

Bright yellow solid (Yield 82%) m.p. 96-99°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 8.08 (2H, d, \( J = 8.40 \) Hz), 7.79 (1H, d, \( J = 15.56 \) Hz), 7.40 (1H, d, \( J = 15.56 \) Hz), 7.22-7.15 (4H, m), 6.92 (1H, d, \( J = 8.41 \) Hz), 6.15-6.04 (1H, m), 5.47 (2H, dd, \( J = 17.24, 10.49 \) Hz), 4.69 (2H, d, \( J = 5.28 \) Hz), 3.96 (3H, s); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \( \delta \) 189.3, 150.9, 150.0, 145.6, 135.2, 133.1, 131.3, 128.4, 123.4, 119.9, 118.8, 116.2, 115.9, 113.4, 111.0, 70.2 and 56.4. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{19}\)H\(_{17}\)FO\(_3\), calculated 313.1370 observed 313.1343.

\((2E)\)-1-(3-Chlorophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 14, Table 3) (obtained by condensation of 1\( b\) with 3-chloro acetophenone)

![Diagram of allylated chalcone structure]

Yellow solid (Yield 83%) m.p. 80-84°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \( \delta \) 6.76 (1H, s), 6.66 (1H, d, \( J = 6.48 \) Hz), 6.58 (1H, dd, \( J = 5.44, 15.58 \) Hz), 6.31 (1H, d, \( J = 4.74 \) Hz), 6.23 (1H, d, \( J = 5.96 \) Hz), 6.13 (1H, dd, \( J = 5.44, 15.58 \) Hz), 6.00-5.93 (2H, m), 5.70 (1H, t, \( J = 5.34 \) Hz), 4.92-4.79 (1H, m), 4.27-4.08 (2H, m), 3.45 (2H, s), 2.73 (3H, s); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \( \delta \) 188.3, 149.9, 148.8, 145.0, 139.3, 134.0, 131.8, 131.6, 129.1, 127.7, 126.9, 125.7, 122.4, 118.6, 117.7, 112.1, 109.7, 68.9 and 55.2. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{19}\)H\(_{17}\)ClO\(_3\), calculated 329.5913; observed 329.5938.
(2E)-1-(4-Methoxyphenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 15, Table 3) (obtained by condensation of 1b with 4-methoxy acetophenone)

Light orange solid (Yield 77%) m.p. 62-64°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.06 (2H, d, $J = 8.68$ Hz), 7.79 (1H, d, $J = 15.55$ Hz), 7.44 (1H, d, $J = 15.55$ Hz), 7.22-7.18 (2H, m), 7.00 (2H, d, $J = 8.68$ Hz), 6.89 (1H, d, $J = 4.93$ Hz), 6.16-6.03 (1H, m), 5.47 (2H, dd, $J = 17.26$, 10.47 Hz), 4.68 (2H, d, $J = 5.24$ Hz), 3.95 (3H, s), 3.89 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.2, 163.7, 150.7, 149.9, 144.5, 133.2, 131.7, 131.1, 128.7, 123.1, 120.3, 118.8, 114.2, 113.4, 111.0, 70.1, 56.4 and 55.9. HRMS-ESI: m/z [M+H]$^+$ for C$_{20}$H$_{20}$O$_4$, calculated 325.1614; observed 325.1647.

(2E)-1-(1,3-benzodioxol-5-yl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 16, Table 3) (obtained by condensation of 1b with 3,4-dioxymethylene acetophenone)

Creamish solid (Yield 79%) m.p. 86-89°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.76 (1H, d, $J = 15.52$ Hz), 7.66 (1H, d, $J = 8.26$ Hz), 7.52 (1H, s), 7.37 (1H, d, $J = 15.52$ Hz), 7.20-7.15 (2H, m), 6.90 (2H, d, $J = 8.26$ Hz), 6.13-6.02 (3H, m), 5.46 (2H, dd, $J = 15.20$, 10.47 Hz), 4.67-4.65 (2H, m), 3.94 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 188.7, 151.9, 150.7, 149.9, 148.6, 144.8, 133.6, 133.2, 128.6, 124.9, 123.2, 120.1, 118.8, 113.3, 110.9 108.8, 108.3, 102.2, 70.1 and 56.4. HRMS-ESI: m/z [M+H]$^+$ for C$_{20}$H$_{18}$O$_5$, calculated 339.1452; observed 339.1418.

(2E)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]-1-(4-nitrophenyl)prop-2-en-1-one (compound 17, Table 3) (obtained by condensation of 1b with 4-nitro acetophenone)

Orange solid (Yield 72%) m.p. 107-112°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.37 (2H, d, $J = 8.60$ Hz), 8.16 (2H, d, $J = 8.60$ Hz), 7.83 (1H, d, $J =$
15.56 Hz), 7.37 (1H, d, J = 15.56 Hz), 7.28-7.18 (2H, m), 6.94 (1H, d, J = 8.29 Hz), 6.15-6.04 (1H, m), 5.48 (2H, dd, J = 17.24, 10.45 Hz), 4.70 (2H, d, J = 5.25 Hz), 3.96 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.4, 151.5, 150.3, 150.1, 147.4, 143.8, 132.9, 129.7, 127.9, 124.2, 123.9, 119.7, 118.9, 113.3, 111.1, 70.2 and 56.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{19}$H$_{17}$NO$_5$, calculated 340.1416; observed 340.1451.

(2E)-1-(4-aminophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 18, Table 3) (obtained by condensation of 1b with 4-amino acetophenone)

![Chemical structure]

Bright yellow solid (Yield 70%) m.p. 103-107°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.38 (1H, d, J = 8.25 Hz), 8.11 (2H, d, J = 8.25 Hz), 7.82 (1H, d, J = 15.20 Hz), 7.62 (1H, s), 7.48 (1H, d, J = 15.20 Hz), 7.34-7.21 (3H, m), 6.98-6.72 (2H, m), 6.12-6.09 (1H, m), 5.48 (2H, dd, J = 17.20, 10.25 Hz), 4.70 (2H, d, J = 5.30 Hz), 3.96 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 188.6, 151.7, 150.5, 149.9, 143.6, 133.2, 131.4, 128.9, 122.9, 120.5, 118.7, 114.3, 114.1, 113.5, 111.1, 70.2 and 56.4. HRMS-ESI: m/z [M+H]$^+$ for C$_{19}$H$_{19}$NO$_3$, calculated 310.1573; observed 310.1544.

(2E)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]-1-phenylprop-2-en-1-one (compound 19, Table 3) (obtained by condensation of 1b with acetophenone)

![Chemical structure]

Yellow solid (Yield 88%) m.p. 78-81°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.04 (2H, d, J = 8.15 Hz), 7.80 (1H, d, J = 15.63 Hz), 7.59-7.49 (3H, m), 7.43 (1H, d, J = 15.63 Hz), 7.22-7.81 (2H, m), 6.93 (1H, d, J = 8.15 Hz), 6.15-6.04 (1H, m), 5.48 (2H, dd, J = 17.26, 7.17 Hz), 4.69-4.66 (2H, m), 3.96 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.0, 150.9, 150.1, 145.4, 138.9, 133.2, 132.9, 128.9, 128.8, 128.5, 123.3, 120.6, 118.8, 113.4, 111.1, 70.2 and 56.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{19}$H$_{18}$O$_3$, calculated 295.1464; observed 295.1438.
2.4.6. **Procedure for the synthesis of O-allylated chalcone via 5b (20; Table 3)**

(a) **Synthesis of 4-allyloxyacetophenone (5b)**

To a 250-mL round bottom flask containing 4-hydroxy acetophenone (2a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol), and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**4-allyloxyacetophenone (5b)**

![Structure of 4-allyloxyacetophenone (5b)]

Colorless viscous liquid (Yield 85%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.86 (2H, d, $J = 8.66$ Hz), 6.88 (2H, d, $J = 8.66$ Hz), 6.02-5.91 (1H, m), 5.39 (2H, dd, $J = 17.26$, 10.84 Hz), 4.52 (2H, d, $J = 4.87$ Hz), 2.46 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 197.0, 162.8, 132.9, 130.9, 130.7, 118.4, 117.7, 69.2 and 26.7. HRMS-ESI: m/z [M+H]$^+$ for C$_{11}$H$_{12}$O$_2$, calculated 177.0996; observed 177.0984.

(a) **Synthesis of O-allylated chalcone (20)**

To a solution of 5b (3 mmol) 10% aqueous NaOH (4 mmol) was added. Thereafter, 1b (3 mmol) dissolved in 20 mL of methanol was added drop wise. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**2E)-3-[3-Methoxy-4-(prop-2-en-1-yloxy)phenyl]-1-[4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 20, Table 3)**

![Structure of 2E)-3-[3-Methoxy-4-(prop-2-en-1-yloxy)phenyl]-1-[4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 20, Table 3)]

Light yellow solid (Yield 87%) m.p. 73-76°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.06 (2H, d, $J = 8.85$ Hz), 7.79 (1H, d, $J = 15.56$ Hz), 7.44 (1H, d, $J = 15.56$ Hz ), 7.22-7.17 (2H, m), 7.02 (2H, d, $J = 8.85$ Hz), 6.92 (1H, d, $J = 8.22$ Hz), 6.15-6.04 (2H, m), 5.48 (4H, dd, $J = 16.20$, 10.26 Hz), 4.68 (4H, d, $J = 5.45$ Hz), 3.96 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.1, 162.7, 150.7, 149.9, 144.5, 133.2, 132.9, 131.8, 131.1, 128.7, 123.1, 120.3, 118.8, 118.6, 114.9, 113.4, 110.9, 70.2, 69.3 and 56.4. HRMS-ESI: m/z [M+H]$^+$ for C$_{22}$H$_{22}$O$_4$, calculated 351.1770; observed 351.1739.
2.4.7. Procedure for the synthesis of chalcones (21-32; Table 4)

2.4.7.1. Procedure for the synthesis of chalcone 21 via 6b

(a) **Synthesis of 2-allyloxy-3-methoxy benzaldehyde (6b)**

To a 250-mL round bottom flask containing 2-hydroxy-3-methoxy benzaldehyde (3a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

![Chemical structure of 2-allyloxy-3-methoxy benzaldehyde (6b)](attachment:chemical_structure.png)

Bright yellow viscous liquid (Yield 80%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 10.38 (1H, s), 7.33 (1H, d, $J = 6.87$ Hz ), 7.10 (2H, dd, $J = 7.68$, 7.92 Hz), 6.06-5.95 (1H, m), 5.32 (1H, d, $J = 17.13$ Hz), 5.21 (1H, d, $J = 10.24$ Hz), 4.60 (2H, d, $J = 5.85$ Hz), 3.83 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 190.3, 152.9, 151.1, 133.1, 129.9, 123.9, 118.8, 118.3, 77.4, 75.0 and 55.9. HRMS-ESI: m/z [M+H]$^+$ for C$_{11}$H$_{12}$O$_3$, calculated 193.0996; observed 193.0998.

(b) **Synthesis of chalcone (21)**

To a solution of 6b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

![Chemical structure of (2E)-1-(4-chlorophenyl)-3-[3-methoxy-2-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 21, Table 4)](attachment:chemical_structure.png)

Light yellow solid (Yield 77%) m.p. 70-75°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.14 (1H, d, $J = 15.89$ Hz), 7.98 (2H, d, $J = 8.54$ Hz), 7.60 (1H, d, $J = 15.89$ Hz), 7.50 (2H, d, $J = 6.70$ Hz), 7.29 (1H, d, $J = 7.80$ Hz), 7.14 (1H, t, $J = 8.03$ Hz), 7.01 (1H, d, $J = 8.10$ Hz), 6.16-6.05 (1H, m), 5.41 (2H, dd, $J = 17.15$, 10.31 Hz), 4.59 (2H, d, $J = 5.90$ Hz), 3.90
2.4.7.2. Procedure for the synthesis of chalcone 22 via 7b (Table 4)

(a) *Synthesis of 3-allyloxy-4-methoxy benzaldehyde (7b)*

To a 250-mL round bottom flask containing 3-hydroxy-4-methoxy benzaldehyde (4a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**3-allyloxy-4-methoxy benzaldehyde (7b)**

![Structure of 3-allyloxy-4-methoxy benzaldehyde (7b)](image)

Colorless viscous liquid (Yield 78%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.81 (1H, s), 7.45-7.38 (2H, m), 6.98 (1H, d, $J = 8.19$ Hz), 6.11-6.00 (1H, m), 5.45 (2H, dd, $J = 17.20$, 10.40 Hz), 4.65 (2H, d, $J = 5.36$ Hz), 3.93 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.2, 155.2, 148.9, 132.9, 130.4, 127.1, 118.9, 111.3, 111.1, 70.1 and 56.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{11}$H$_{12}$O$_2$, calculated 193.0996; observed 193.0989.

(b) *Synthesis of chalcone (22)*

To a solution of 7b (3 mmol) and chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**(2E)-1-(4-chlorophenyl)-3-[4-methoxy-3-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one**

**(compound 22, Table 4)**

![Structure of (2E)-1-(4-chlorophenyl)-3-[4-methoxy-3-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one](image)

Light yellow solid (Yield 84%) m.p. 80-83°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.99 (2H, d, $J = 8.31$ Hz), 7.73 (1H, d, $J = 15.31$ Hz), 7.51 (2H, d, $J = 8.31$ Hz),
7.35-7.19 (3H, m), 6.94 (1H, d, J = 15.31 Hz), 6.13-6.04 (1H, m), 5.48-5.29 (2H, m), 4.72 (2H, d, J = 10.29 Hz), 3.94 (3H, s); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta\) 189.6, 152.5, 148.7, 145.4, 139.4, 137.2, 133.4, 130.2, 129.3, 128.0, 123.9, 119.8, 118.8, 113.0, 112.0, 70.4 and 56.4. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{19}\)H\(_{17}\)ClO\(_3\), calculated 329.5913; observed 329.5941.

2.4.7.3. Procedure for the synthesis of chalcone 23 (Table 4)

To the solution of vanillin (3 mmol) and chloroacetophenone (3 mmol) in ethanol (20 mL), KOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by \(^1\)H & \(^{13}\)C NMR and HRMS data.

\(2E\)-1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (compound 23, Table 4)

\[
\begin{array}{c}
\text{Bright yellow solid (Yield 60%) m.p. 110-115°C, } \text{H NMR}\\
\text{(CDCl}_3\text{, 300 MHz): } \delta 7.98 (2H, d, J = 8.50 Hz), 7.79 (1H, d, J = 15.57 Hz), 7.49 (2H, d, J = 8.50 Hz), 7.36 (1H, d, J = 15.57 Hz), 7.24 (1H, dd, J = 1.30, 1.27 Hz), 7.13 (1H, s), 6.99 (1H, d, J = 8.20 Hz), 6.11 (1H, s), 3.97 (3H, s); \text{C NMR (CDCl}_3\text{, 75.4 MHz): } \delta 189.7, 148.9, 147.3, 146.2, 139.4, 137.2, 130.2, 129.3, 127.7, 123.9, 119.6, 115.4, 110.5 and 56.4. \text{HRMS-ESI: m/z } [M+H]^+ \text{ for C}_{16}H_{13}ClO_3, \text{calculated 289.5601; observed 289.5627.}
\end{array}
\]

2.4.7.4. Procedure for the synthesis of chalcone 24 (Table 4)

To a 250 mL round bottom flask containing 1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (23) (1.9 mmol) in dry acetone (20 mL), prenyl bromide (2.0 mmol) and anhydrous K\(_2\)CO\(_3\) (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by \(^1\)H & \(^{13}\)C NMR and HRMS data.
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(2E)-1-(4-chlorophenyl)-3-{3-methoxy-4-[3-methylbut-2-en-1-yl]oxy[phenyl]prop-2-en-1-one (compound 24, Table 4)

\[ \begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{OC}_3 \text{H}_3
\end{array} \]

Yellow solid (Yield 62%) m.p. 71-74°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\ 7.79-7.95\) (2H, m), \(7.82\) (1H, dd, \(J = 7.79, 15.52\) Hz), \(7.50-7.46\) (2H, m), \(7.39\) (1H, dd, \(J = 7.80, 15.55\) Hz), \(7.29-7.16\) (2H, m), \(6.93\) (1H, s), \(5.52\) (1H, s), \(4.66\) (2H, s), \(3.96\) (3H, d, \(J = 4.85\) Hz), \(1.78\) (6H, s); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta\ 189.7, 151.4, 150.0, 146.1, 139.3, 137.2, 130.7, 130.3, 129.3, 127.9, 123.6, 119.7, 113.0, 112.0, 110.7, 66.2, 56.4, 26.3 and 18.7. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{21}\)H\(_{21}\)ClO\(_3\), calculated 357.6212; observed 357.6235.

2.4.7.5. Procedure for the synthesis of chalcone 25 (Table 4)

To a 250 mL round bottom flask containing 1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (23) (1.9 mmol) in dry acetone (20 mL), 1-bromo butane (2.0 mmol) and anhydrous K\(_2\)CO\(_3\) (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by \(^1\)H & \(^{13}\)C NMR and HRMS data.

(2E)-3-(4-butoxy-3-methoxyphenyl)-1-(4-chlorophenyl)prop-2-en-1-one (compound 25, Table 4)

\[ \begin{array}{c}
\text{O} \\
\text{Cl} \\
\text{OCH}_3 \\
\end{array} \]

Yellow solid (Yield 81%) m.p. 47-50°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\ 7.99\) (2H, d, \(J = 8.44\) Hz), \(7.81\) (1H, d, \(J = 15.60\) Hz), \(7.50\) (2H, d, \(J = 8.43\) Hz), \(7.37\) (1H, d, \(J = 15.55\) Hz), \(7.26-7.18\) (2H, m), \(6.93\) (1H, d, \(J = 8.30\) Hz), \(4.11\) (2H, t), \(3.95\) (3H, s), \(1.89-1.83\) (2H, m), \(1.57-1.49\) (2H, m), \(1.01\) (3H, t); \(^{13}\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta\ 189.7, 151.8, 149.9, 146.1, 139.3, 137.2, 130.2, 129.3, 127.9, 123.8, 119.7, 112.8, 111.1, 69.1, 56.5, 31.5, 19.6 and 14.2. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{20}\)H\(_{21}\)ClO\(_3\), calculated 345.6225; observed 345.6203.

2.4.7.6. Procedure for the synthesis of chalcone 26 (Table 4)

To a 250 mL round bottom flask containing 1-(4-chlorophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one (23) (1.9 mmol) in dry acetone (20 mL), 4-
bromobenzylbromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**(2E)-3-{{4-[(4-bromobenzyl)oxy]-3-methoxyphenyl}-1-(4-chlorophenyl)prop-2-en-1-one (compound 26, Table 4)**

![Chemical Structure of (2E)-3-{{4-[(4-bromobenzyl)oxy]-3-methoxyphenyl}-1-(4-chlorophenyl)prop-2-en-1-one (compound 26, Table 4)](image)

Creamish solid (Yield 75%) m.p. 115-120°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.98 (2H, d, $J$ = 8.47 Hz), 7.78 (1H, d, $J$ = 15.57 Hz), 7.53-7.46 (4H, m), 7.37-7.28 (3H, m), 7.18 (2H, d, $J$ = 5.46 Hz), 6.89 (1H, d, $J$ = 8.77 Hz), 5.15 (2H, s), 3.96 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.6, 150.8, 150.2, 145.7, 139.4, 137.1, 135.9, 132.2, 130.3, 129.3, 128.7, 123.3, 122.4, 120.1, 113.9, 111.3, 70.6 and 56.4. HRMS-ESI: m/z [M+H]$^+$ for C$_{23}$H$_{18}$ClBrO$_3$, calculated 458.5031; observed 458.5054.

**2.4.7.7. Procedure for the synthesis of chalcone 27 via 8b (Table 4)**

**a) Synthesis of 4-allyloxy-3,5-dimethoxy benzaldehyde (8b)**

To a 250 mL round bottom flask containing syringaldehyde (5a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**4-allyloxy-3,5-dimethoxy benzaldehyde (8b)**

![Chemical Structure of 4-allyloxy-3,5-dimethoxy benzaldehyde (8b)](image)

White solid (Yield 70%) m.p. 45-47°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.87 (1H, s), 7.31 (2H, s), 6.10-6.04 (1H, m), 5.36 (2H, dd, $J$ = 17.15, 10.24 Hz), 4.64(2H, d, $J$ = 6.07 Hz), 3.93 (6H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.5, 154.3, 142.7, 134.3, 132.2, 118.7, 107.1, 74.6 and 56.6. HRMS-ESI: m/z [M+H]$^+$ for C$_{12}$H$_{14}$O$_4$, calculated 223.1146; observed 223.1147.
(b) **Synthesis of chalcone (27)**

To a solution of 8b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**(2E)-1-(4-chlorophenyl)-3-[3,5-dimethoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one** (compound 27, Table 4)

![Chemical Structure]

Yellow solid (Yield 76%) m.p. 120-123°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.99 (2H, d, $J = 8.53$ Hz), 7.52 (1H, d, $J = 15.60$ Hz), 7.50 (2H, d, $J = 8.53$ Hz), 7.38 (1H, d, $J = 15.60$ Hz), 6.86 (2H, s), 6.16-6.06 (1H, m), 5.37-5.20 (2H, m), 4.61 (2H, d, $J = 5.20$ Hz), 3.91 (6H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 189.6, 154.1, 145.9, 139.7, 139.5, 136.9, 134.5, 130.6, 130.3, 129.3, 121.2, 118.5, 106.2, 74.7 and 56.6. HRMS-ESI: m/z [M+H]$^+$ for C$_{20}$H$_{19}$ClO$_4$, calculated 359.6063; observed 359.6042.

**2.4.7.8. Procedure for the synthesis of chalcone 28 via 9b (Table 4)**

(a) **Synthesis of 4-allyloxy benzaldehyde (9b)**

To a 250 mL round bottom flask containing 4-hydroxy benzaldehyde (6a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**4-allyloxy benzaldehyde (9b)**

![Chemical Structure]

Pale yellow viscous liquid (Yield 80%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.89 (1H, s), 7.86 (2H, d, $J = 8.32$ Hz), 7.07 (2H, d, $J = 8.32$ Hz), 6.11-6.02 (1H, m), 5.48 (2H, dd, $J = 17.32$, 10.35 Hz), 4.65 (2H, d, $J = 5.21$ Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 191.2, 164.0, 132.7, 132.4, 130.5, 118.7, 115.4 and 69.6. HRMS-ESI: m/z [M+H]$^+$ for C$_{10}$H$_{10}$O$_2$, calculated 163.0846; observed 163.0853.
b) **Synthesis of chalcone (28)**

To a solution of 9b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**$(2E)$-1-(4-chlorophenyl)-3-[4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 28, Table 4)**

\[
\begin{align*}
\text{Cl} & \quad \text{Light yellow solid (Yield 90\%) m.p. 101\text{-}104^\circ\text{C},} \\
^1\text{H NMR} \quad \text{(CDCl}_3, \ 300 \text{ MHz): } & \delta 7.99 \ (2\text{H}, \ d, \ J = 8.73 \text{ Hz}), \ 7.82 \ (1\text{H}, \ d, \ J = 15.60 \text{ Hz}), \ 7.62 \ (2\text{H}, \ d, \ J = 8.73 \text{ Hz}), \ 7.50 \ (2\text{H}, \ d, \ J = 8.73 \text{ Hz}), \ 7.40 \ (1\text{H}, \ d, \ J = 15.60 \text{ Hz}), \ 6.99 \ (2\text{H}, \ d, \ J = 8.73 \text{ Hz}), \ 6.14-6.01 \ (1\text{H}, \ m), \ 5.47 \ (2\text{H}, \ dd, \ J = 18.78, \ 10.5 \text{ Hz}), \ 4.61-4.59 \ (2\text{H}, \ m); \ ^{13}\text{C NMR} \quad \text{(CDCl}_3, \ 75.4 \text{ MHz): } & \delta 189.6, \ 161.3, \ 145.6, \ 139.3, \ 137.2, \ 133.1, \ 130.7, \ 130.2, \ 129.3, \ 127.9, \ 119.7, \ 118.3, \ 115.6 \text{ and 51.2.} \\
\text{HRMS-ESI: } & \text{m/z [M+H]}^+ \text{ for C}_{18}\text{H}_{15}\text{ClO}_2, \text{ calculated 299.5763; observed 299.5738.}
\end{align*}
\]

**2.4.7.9. Procedure for the synthesis of chalcone 29 via 10b (Table 4)**

(a) **Synthesis of 2-allyloxy benzaldehyde (10b)**

To a 250 mL round bottom flask containing 2-hydroxy benzaldehyde (7a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

**2-allyloxy benzaldehyde (10b)**

\[
\begin{align*}
\text{Yellow viscous liquid (Yield 72\%),} \\
^1\text{H NMR} \quad \text{(CDCl}_3, \ 300 \text{ MHz): } & \delta 10.73 \ (1\text{H}, \ s), \ 8.04 \ (1\text{H}, \ s), \ 7.73 \ (1\text{H}, \ d, \ J = 7.72 \text{ Hz}), \ 7.19 \ (2\text{H}, \ d, \ J = 8.4 \text{ Hz}), \ 6.32-6.21 \ (1\text{H}, \ m), \ 5.65 \ (1\text{H}, \ dd, \ J = 8.32, \ 8.30 \text{ Hz}), \ 5.54 \ (1\text{H}, \ m), \ 4.85 \ (2\text{H}, \ s); \ ^{13}\text{C NMR} \quad \text{(CDCl}_3, \ 75.4 \text{ MHz): } & \delta 189.8, \ 161.1, \ 135.9, \ 132.5, \ 128.4, \ 125.2, \ 120.9, \ 118.1, \ 113.0 \text{ and 69.3.} \\
\text{HRMS-ESI: m/z [M+H]}^+ \text{ for C}_{10}\text{H}_{10}\text{O}_2, \text{ calculated 163.0846; observed 163.0858.}
\end{align*}
\]

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(b) **Synthesis of chalcone (29)**

To a solution of 10b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

(2E)-1-(4-chlorophenyl)-3-[2-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 29, Table 4)

![Chemical structure of compound 29](image)

Creamish solid (Yield 78%) m.p. 91-93°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.19 (1H, d, $J = 15.39$ Hz), 7.99 (2H, d, $J = 6.80$ Hz), 7.68 (2H, d, $J = 6.87$ Hz), 7.50 (2H, d, $J = 6.87$ Hz), 7.41 (1H, d, $J = 15.39$ Hz), 7.05-6.95 (2H, m), 6.18-6.08 (1H, m), 5.51 (2H, dd, $J = 17.23$, 10.45 Hz), 4.66 (2H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 190.5, 158.6, 141.7, 139.7, 137.6, 133.5, 132.6, 130.7, 130.4, 129.6, 124.7, 123.2, 121.7, 118.8 113.3 and 69.9. HRMS-ESI: m/z [M+H]$^+$ for C$_{18}$H$_{15}$ClO$_2$, calculated 299.5685; observed 299.5746.

2.4.7.10. **Procedure for the synthesis of chalcone 30 via 11b (Table 4)**

(a) **Synthesis of 3-ethoxy-4-allyloxy benzaldehyde (11b)**

To a 250 mL round bottom flask containing 3-ethoxy-4-hydroxy benzaldehyde (8a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K$_2$CO$_3$ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by $^1$H & $^{13}$C NMR and HRMS data.

3-ethoxy-4-allyloxy benzaldehyde (11b)

![Chemical structure of compound 11b](image)

Pale yellow viscous liquid (Yield 80%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 9.82 (1H, s), 7.42 (2H, d, $J = 7.48$ Hz), 6.98 (1H, d, $J = 8.66$ Hz), 6.12-6.02 (1H, m), 5.47 (2H, dd, $J = 17.26$, 10.54 Hz), 4.70 (2H, d, $J = 5.21$ Hz), 4.19 (2H, q, $J = 7.00$ Hz), 1.50 (3H, t, $J = 7.0$ Hz); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$191.3, 154.2, 149.6, 132.8, 130.6, 126.7, 118.6, 112.7,
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111.2, 70.1, 64.9 and 15.0. HRMS-ESI: m/z [M+H]+ for C_{14}H_{16}O_{3}, calculated 207.1152; observed 207.1158.

(b) Synthesis of chalcone (30)

To a solution of 11b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by ¹H & ¹³C NMR and HRMS data.

(2E)-1-(4-chlorophenyl)-3-[3-ethoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 30, Table 4)

Light yellow solid (Yield 88%) m.p. 85-89°C, ¹H NMR (CDCl₃, 300 MHz): δ 7.89 (2H, d, J = 8.23 Hz), 7.78 (1H, d, J = 15.52 Hz), 7.36 (2H, d, J = 8.23 Hz), 7.31 (1H, d, J = 15.52 Hz), 7.21 (2H, d, J = 7.67 Hz), 6.92 (1H, s), 6.11-6.05 (1H, m), 5.47-5.31 (2H, m), 5.31 (2H, s), 4.18 (2H, d, J = 6.82 Hz), 1.53 (3H, t); ¹³C NMR (CDCl₃, 75.4 MHz): δ 189.6, 151.5, 149.4, 145.9, 139.3, 137.2, 133.3, 130.2, 129.3, 128.3, 123.5, 119.8, 118.4, 113.9, 113.0 70.2, 65.2 and 15.2. HRMS-ESI: m/z [M+H]+ for C_{20}H_{19}ClO_{3}, calculated 343.5991; observed 343.6034.

2.4.7.11. Procedure for the synthesis of chalcone 31 via 12b (Table 4)

(a) Synthesis of 3,4-diallyloxy benzaldehyde (12b)

To a 250 mL round bottom flask containing 3,4-dihydroxy benzaldehyde (9a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (4 mmol) and anhydrous K₂CO₃ (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by ¹H & ¹³C NMR and HRMS data.

3,4-diallyloxy benzaldehyde (12b)

Pale yellow viscous liquid (Yield 80%), ¹H NMR (CDCl₃, 300 MHz): δ 9.82 (1H, s), 7.42 (2H, d, J = 8.28 Hz ), 6.97 (1H, d, J = 7.93 Hz), 6.11-6.02 (2H, m), 5.44 (2H,
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d, J = 17.25 Hz), 5.32 (2H, dd, J = 6.18, 7.19 Hz), 4.67 (4H, m); 13C NMR (CDCl3, 75.4 MHz): δ 191.3, 154.2, 149.2, 133.0, 132.7, 130.4, 127.0, 118.7, 118.5, 112.6, 111.7, 77.7 and 70.1. HRMS-ESI: m/z [M+H]+ for C13H14O3, calculated 219.1152; observed 219.1167.

(b) Synthesis of chalcone (31)

To a solution of 12b (3 mmol) and 4-chloro acetophenone (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by 1H & 13C NMR and HRMS data.

(2E)-3-[3,4-bis(prop-2-en-1-yloxy)phenyl]-1-(4-chlorophenyl)prop-2-en-1-one (compound 31, Table 4)

Light yellow solid (Yield 90%) m.p. 72-75°C, 1H NMR (CDCl3, 300 MHz): δ 7.99 (2H, d, J = 7.83 Hz), 7.79 (1H, d, J = 15.54 Hz), 7.51 (2H, d, J = 6.16 Hz), 7.37 (1H, d, J = 15.54 Hz), 7.20 (2H, d, J = 7.83 Hz), 6.94 (1H, s), 6.13-6.09 (2H, m), 5.50-5.33 (4H, m), 4.69 (4H, s); 13C NMR (CDCl3, 75.4 MHz): δ 189.6, 151.6, 149.0, 145.8, 139.6, 137.2, 133.5, 133.2, 130.2, 129.3, 128.3, 123.8, 119.9, 118.5 118.4, 113.9, 113.7, 70.5 and 70.1. HRMS-ESI: m/z [M+H]+ for C21H19ClO3, calculated 355.5991; observed 355.6069.

2.4.7.12. Procedure for the synthesis of chalcone 32 (Table 4)

(a) Synthesis of 4-allyloxy-3-methoxyacetophenone (13b)

To a 250 mL round bottom flask containing 4-hydroxy-3-methoxy acetophenone (10a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (2.0 mmol) and anhydrous K2CO3 (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by 1H & 13C NMR and HRMS data.

White solid (Yield 80%) m.p. 39-41°C, 1H NMR (CDCl3, 300 MHz): δ 7.49 (2H, d, J = 4.57 Hz), 6.86 (1H, s), 6.10-5.97 (1H, m), 5.42-5.26 (2H, m), 4.64 (2H, s), 3.89 (3H, s), 2.52 (3H, s); 13C NMR (CDCl3, 75.4 MHz): δ 197.1, 152.7, 149.6, 132.9, 130.9, 123.4,
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118.9, 111.9, 110.8, 70.0, 56.3 and 26.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{12}$H$_{14}$O$_3$, calculated 207.1152; observed 207.1171.

(b) Synthesis of chalcone (31)

To a solution of 13b (3 mmol), 10% aqueous NaOH (4 mmol) was added. Thereafter, 4-chlorobenzaldehyde (3 mmol) dissolved in 20 mL of methanol was added drop wise. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

$(2E)$-3-(4-chlorophenyl)-1-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 32, Table 4)

![Image](OClOCH3)

Light yellow solid (Yield 80%) m.p. 120-123°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.79 (1H, d, $J$ = 15.63 Hz), 7.67-7.64 (2H, m), 7.59-7.55 (3H, m), 7.40 (2H, $d$, $J$ = 8.18 Hz ), 6.95 (1H, d, $J$ = 8.18 Hz), 5.49-5.18 (1H, m), 5.49 (2H, dd, $J$ = 17.25, 10.47 Hz), 4.73-4.70 (2H, m), 3.98 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 188.6, 152.8, 150.0, 142.8, 136.6, 133.9, 132.9, 131.7, 129.9, 129.6, 123.3, 122.5, 119.0, 112.0, 111.5, 70.2 and 56.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{19}$H$_{17}$ClO$_3$, calculated 329.5913; observed 329.5929.

2.4.8. General procedure for the synthesis of heterocyclic chalcone derivatives (33-38; Table 5)

To a solution of 1b (3 mmol) and appropriate aceto derivatives (3 mmol) in methanol (20 mL), 10% aqueous NaOH (4 mmol) was added. The remaining procedure was similar to that described in step (c) of section 2.4.2. The desired compounds obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

$(2E)$-1-(furan-2-yl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (compound 33, Table 5)

![Image](OCH3)

Light yellow solid (Yield 70%) m.p. 132-135°C, $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.82 (1H, d, $J$ = 15.81 Hz), 7.29-7.11 (5H, m), 6.91 (1H, d, $J$ = 8.36 Hz ), 6.38 (1H, d, $J$ = 5.80 Hz), 6.13-6.02 (1H, m), 5.46 (2H, dd, $J$ = 17.26, 10.47 Hz), 4.67 (2H, d, $J$ = 5.20 Hz), 3.95 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 179.5, 150.6, 150.0, 142.7, 133.7,
133.3, 128.7, 126.0, 122.9, 120.6, 118.7, 116.7, 113.5, 111.3, 111.2, 70.2 and 56.5. HRMS-ESI: m/z [M+H]⁺ for C₁₇H₁₆O₄, calculated 285.1302; observed 285.1345.

3-{(2E)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-enoyl}-2H-chromen-2-one (compound 34, Table 5)

Yellow solid (Yield 70%) m.p. 148-151°C, ¹H NMR (CDCl₃, 300 MHz): δ 8.58 (1H, s), 7.82 (2H, s), 7.69 (2H, d, J = 7.44 Hz), 7.41-7.33 (2H, m), 7.27 (2H, d, J = 8.58 Hz), 6.91 (1H, d, J = 7.44 Hz), 6.14-6.07 (1H, m), 5.47 (2H, dd, J = 17.22, 10.26 Hz), 4.68 (2H, s), 3.95 (3H, s); ¹³C NMR (CDCl₃, 75.4 MHz): δ 186.6, 159.8, 155.6, 151.2, 149.9, 148.2, 145.7, 134.5, 133.1, 130.2, 128.5, 126.0, 125.3, 124.1, 122.3, 119.0, 118.9, 117.0, 113.2, 111.1, 70.1 and 56.4. HRMS-ESI: m/z [M+H]⁺ for C₂₂H₁₈O₅, calculated 363.1452; observed 363.1433.

4-hydroxy-3-{(2E)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-enoyl}-2H-chromen-2-one (compound 35, Table 5)

Orange solid (Yield 68%) m.p. 150-153°C, ¹H NMR (CDCl₃, 300 MHz): δ 8.30 (1H, d, J = 15.34 Hz), 8.10 (1H, d, J = 7.62 Hz), 8.00 (1H, d, J = 15.34 Hz), 7.68-7.63 (1H, m), 7.42-7.23 (4H, m), 6.91 (1H, d, J = 8.15 Hz), 6.14-6.07 (1H, m), 5.47 (2H, dd, J = 17.20, 10.25 Hz), 4.72 (2H, d, J = 5.20 Hz), 3.96 (3H, s), 3.09 (1H, s); ¹³C NMR (CDCl₃, 75.4 MHz): δ 181.7, 161.6, 154.9, 151.6, 150.1, 147.2, 145.5, 135.8, 133.0, 128.5, 126.2, 124.7, 124.6, 121.5, 118.9, 117.8, 117.3, 113.2, 111.4, 101.3, 70.2 and 56.4. HRMS-ESI: m/z [M+H]⁺ for C₂₂H₁₈O₆, calculated 379.1446; observed 379.1426.
(2E)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]-1-(1H-pyrrol-2-yl)prop-2-en-1-one
(compound 36, Table 5)

Light yellow solid (Yield 63%) m.p. 132-135°C, 1H NMR (CDCl₃, 300 MHz): δ 9.81 (1H, s), 7.84 (1H, d, J = 15.85 Hz), 7.29-7.12 (5H, m), 6.91 (1H, d, J = 8.40 Hz), 6.36-6.33 (1H, m), 6.15-6.03 (1H, m), 5.46 (2H, dd, J = 17.26, 10.47 Hz), 4.67 (2H, d, J = 5.31 Hz), 3.95 (3H, s); 13C NMR (CDCl₃, 75.4 MHz): δ 179.5, 150.6, 150.0, 142.7, 133.7, 133.2, 128.7, 125.9, 125.9, 120.5, 118.7, 116.7, 113.5, 111.2, 70.2 and 56.5. HRMS-ESI: m/z [M+H]+ for C₁₇H₁₇NO₃, calculated 284.1417; observed 284.1442.

5-[3-methoxy-4-(prop-2-en-1-yloxy)benzylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione
(compound 37, Table 5)

Fluorescent yellow solid (Yield 91%) m.p. 128-133°C, 1H NMR (CDCl₃, 300 MHz): δ 8.34 (1H, s), 8.29 (1H, s), 7.63 (1H, d, J = 8.52 Hz), 6.95 (1H, d, J = 8.52 Hz), 6.08-6.03 (1H, m), 5.46-5.33 (2H, m), 4.74 (2H, d, J = 5.37 Hz), 3.95 (3H, s), 1.79 (6H, s); 13C NMR (CDCl₃, 75.4 MHz): δ 164.6, 161.0, 158.6, 154.2, 149.4, 132.7, 132.4, 125.5, 119.4, 116.5, 112.4, 111.0, 104.6, 70.2, 56.4 and 27.8. HRMS-ESI: m/z [M+H]+ for C₁₇H₁₈O₆, calculated 319.1446; observed 319.1479.

5-[3-methoxy-4-(prop-2-en-1-yloxy)benzylidene]pyrimidine-2,4,6(1H,3H,5H)-trione
(compound 38, Table 5)

Bright yellow solid (Yield 90%) m.p. 250-256°C, 1H NMR (DMSO-d₆, 300 MHz): δ 9.99 (1H, s), 9.87 (1H, s), 7.06 (1H, s), 6.91 (1H, s), 6.49 (1H, d, J = 8.32 Hz), 5.78 (1H, d, J = 8.36 Hz), 4.12-3.97 (1H, m), 4.12-3.97 (2H, m), 3.37 (2H, d, J = 3.39 Hz), 2.31 (3H, s); 13C NMR (DMSO-d₆, 75.4 MHz): δ 164.2, 162.4, 155.9, 152.7, 150.4,
148.0, 132.9, 131.7, 125.4, 118.6, 116.9, 115.2, 112.3, 69.1 and 55.6. HRMS-ESI: m/z [M+H]^+ for C_{15}H_{14}N_{2}O_{5}, calculated 303.1172; observed 303.1149.

2.4.9. General procedure for the synthesis of heterocyclic chalcone derivative (39; Table 5)

To a solution of 4,7-dichloro quinoline (2.5 mmol) in tetrahydrofuran (20 mL), compound 18 (2.75 mmol; section 2.4.5.) was added and the mixture was refluxed for 8 h. Thereafter the reaction mixture was cooled and thus formed precipitates were filtered, washed with water, diethyl ether and recrystallized from alcohol. The desired compound obtained after recrystallization was characterized by $^1$H & $^{13}$C NMR and HRMS data.

(E)-3-(4-(allyloxy)-3-methoxyphenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)prop-2-en-1-one (compound 39, Table 5)

Yellow solid (Yield 76%) m.p. 168-171°C, $^1$H NMR (CDCl$_3$ + DMSO-$d_6$, 300 MHz): δ 7.35 (2H, d, J = 8.41 Hz), 6.93 (2H, d, J = 7.83 Hz), 6.78 (1H, s), 6.60 (1H, s), 6.50-6.29 (4H, m), 6.08 (1H, s), 6.02 (1H, d, J = 7.8 Hz), 5.92 (1H, d, J = 4.82 Hz), 5.71 (1H, d, J = 8.42 Hz ), 4.84-4.76 (1H, m), 4.20 (2H, dd, J = 15.34, 10.52 Hz), 3.39 (2H, d, J = 5.10 Hz), 2.68 (3H, s); $^{13}$C NMR (CDCl$_3$ + DMSO-$d_6$, 75.4 MHz): δ 188.8, 151.5, 150.9, 150.1, 149.6, 147.9, 145.1, 144.9, 143.9, 137.9, 135.1, 133.4, 130.8, 128.5, 127.5, 125.7, 124.1, 123.9, 122.7, 120.2, 118.6, 113.7, 111.5, 103.4, 69.9 and 56.6. HRMS-ESI: m/z [M+H]^+ for C$_{28}$H$_{32}$ClN$_{2}$O$_{3}$, calculated 471.6449; observed 471.6421.

2.4.10. General procedure for the synthesis of heterocyclic chalcone derivative (40; Table 5)

To the solution of compound 39 (2.7 mmol; section 2.4.9) in dry tetrahydrofuran (15 mL), potassium hydroxide (13.5 mmol), allyl bromide (5.5 mmol) and cetyltrimethylammonium bromide (CTAB) (0.7 mmol) was added. The contents were stirred at room temperature for 12-14 h till the starting disappeared (monitored by TLC). After the completion of reaction, the reaction mixture was partitioned between ethyl acetate (70 mL) and water (15 mL). The ethyl acetate layer was washed with water till neutral, dried over sodium sulfate and evaporated. The
obtained residue was purified by column chromatography (silica gel, hexane: ethyl acetate (7:3 v/v) to afford the desired compound whose structure was confirmed through NMR and mass spectrometry.

(E)-1-(4-(allyl(7-chloroquinolin-4-yl)amino)phenyl)-3-(4-(allyloxy)-3-methoxyphenyl) prop-2-en-1-one (compound 40, Table 5)

Orange-yellow viscous liquid (Yield 61%), $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.40 (2H, d, $J$ = 8.30 Hz), 6.92 (2H, d, $J$ = 7.80 Hz), 6.73 (1H, s), 6.56 (1H, s), 6.49-6.30 (4H, m), 6.06 (1H, s), 6.05 (1H, d, $J$ = 7.80 Hz), 5.90 (1H, d, $J$ = 4.85 Hz), 5.70 (1H, d, $J$ = 8.40 Hz), 4.80-4.75 (2H, m), 4.19-4.02 (4H, m), 3.40 (2H, d, $J$ = 5.10 Hz), 3.30 (2H, d, $J$ = 5.11 Hz), 2.60 (3H, s); $^{13}$C NMR (CDCl$_3$, 75.4 MHz): $\delta$ 188.9, 151.4, 151.0, 150.0, 149.5, 147.7, 145.0, 144.7, 143.7, 137.6, 136.0, 135.0, 133.6, 130.7, 128.6, 127.7, 125.1, 124.0, 123.7, 122.7, 120.2, 118.4, 116.2, 113.7, 111.5, 103.4, 70.0, 56.3 and 44.5. HRMS-ESI: m/z [M+H]$^+$ for C$_{31}$H$_{27}$ClN$_2$O$_3$, calculated 511.6759; observed 511.6782.

2.4.11. General procedure for the synthesis of heterocyclic chalcone derivative (41; Table 5)

In a 100 mL round bottom flask, mixture of 9 (1.5 mmol), phenylhydrazine hydrochloride (4.5 mmol) and sodium acetate (0.25 mmol) was taken. To this mixture, added 15 mL of aq. acetic acid (HAc/H$_2$O; 2:1) and refluxed the contents for 8-10 hrs till the starting was consumed (monitored by TLC). Thereafter the reaction mixture was cooled and poured in ice cold water. The obtained precipitates were filtered, washed with water till neutral pH and recrystallized from alcohol to afford the desired compound whose structure was confirmed through NMR and mass spectrometry.
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5-(4-(allyloxy)-3-methoxyphenyl)-3-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (compound 41, Table 5)

\[ \text{Creamish solid (Yield 60%) m.p. 116-121°C, } ^1\text{H NMR (CDCl}_3, 300 \text{ MHz): } \delta 7.68 \text{ (2H, dd, } J = 1.69, 1.70 \text{ Hz)}, 7.38 \text{ (2H, dd, } J = 1.71, 1.67 \text{ Hz)}, 7.24-7.18 \text{ (2H, m), 7.11 (2H, d, } J = 8.22 \text{ Hz)}, 6.86 \text{ (4H, d, } J = 6.03 \text{ Hz)}, 6.17-6.06 \text{ (1H, m), 5.44-5.28 (2H, m), 4.62 (2H, d, } J = 4.46 \text{ Hz)}, 3.83 (3H, s), 3.17 (1H, t, } J = 1.50 \text{ Hz), 1.60 (2H, s); } ^{13}\text{C NMR (CDCl}_3, 75.4 \text{ MHz): } \delta 150.5, 147.9, 146.1, 145.3, 135.7, 134.7, 133.7, 131.7, 129.3, 129.2, 127.3, 119.9, 118.4, 114.0, 109.5, 70.3, 65.2, 56.4 \text{ and 43.9. HRMS-ESI: m/z [M+H]}^+ \text{ for } C_{25}H_{23}ClN_2O_2, \text{ calculated 419.6449; observed 419.6456.}

2.4.12. General procedure for the synthesis of heterocyclic chalcone derivative (42; Table 5)

In a 100 mL round bottom flask, mixture of 9 (1.5 mmol), guanidine hydrochloride (1.5 mmol) and potassium hydroxide (5 mmol) was taken in ethanol (25 mL). The contents were refluxed for 6 h till the starting was consumed (monitored by TLC). Thereafter, the organic layer was evaporated in vacuo and the product was recrystallized from hexane-alcohol system whose structure was confirmed through NMR and mass spectrometry.

4-(4-(allyloxy)-3-methoxyphenyl)-6-(4-chlorophenyl)pyrimidin-2-amine (compound 42, Table 5)

\[ \text{Creamish solid (Yield 82%) m.p. 184-186°C, } ^1\text{H NMR (CDCl}_3, 300 \text{ MHz): } \delta 8.02 \text{ (2H, d, } J = 7.73 \text{ Hz)}, 7.72 \text{ (1H, s), 7.61 (1H, d, } J = 8.43 \text{ Hz), 7.49 (2H, d, } J = 7.73 \text{ Hz)}, 7.38 \text{ (1H, d, } J = 8.31 \text{ Hz)}, 6.17-6.06 \text{ (1H, m), 5.48-5.29 (4H, m), 4.71 (2H, d, } J = 4.46 \text{ Hz)}, 4.01 (3H, s); } ^{13}\text{C NMR (CDCl}_3, 75.4 \text{ MHz): } \delta 166.3, 165.1, 163.9, 150.7, 150.0, 136.9, 136.7, 133.3, 130.9, 129.4, 128.8, 120.4, 118.8, 113.2, 110.7, 103.7, 70.2} \]
2.4.13. **General procedure for the synthesis of bis(dimeric) chalcones (43-45; Table 6)**

To a solution of diacetyl benzene (1.5 mmol) in ethanol, sodium hydroxide (2 mmol) was added and the contents were stirred for 3-5 min. Thereafter, substituted aldehyde (1b or 3b or 12b; 3 mmol) in ethanol (10 mL) was added drop wise. The reaction mixture was stirred at 40°C for 6-8 h till completion of starting material (monitored by TLC). The reaction mixture was vacuum evaporated to remove the organic solvent and poured in cold water. The obtained precipitates were washed with dilute HCl, excess of water, methanol, dried in air and finally recrystallized with methanol to obtain pure chalcones whose structures were confirmed by NMR and mass spectroscopy.

**(2E,2'E)-1,1'-(1,3-phenylene)bis(3-(3-allyl-4,5-dimethoxyphenyl)prop-2-en-1-one**

(compound 43, Table 6)

Yellow viscous liquid (Yield 68%), ¹H NMR (CDCl₃, 300 MHz): δ 8.63 (1H, s), 8.24 (2H, d, J = 7.73 Hz), 7.83 (2H, d, J = 15.69 Hz), 7.68 (1H, t, J = 7.73 Hz), 7.49 (2H, d, J = 15.69 Hz), 7.13 (4H, d, J = 7.70 Hz), 6.04-5.95 (2H, m), 5.12-5.07 (4H, m), 3.94 (6H, s), 3.88 (6H, s), 3.45 (4H, d, J = 6.50 Hz); ¹³C NMR (CDCl₃, 75.4 MHz): δ 190.3, 153.4, 150.1, 146.2, 139.2, 137.1, 134.8, 132.7, 130.7, 129.4, 128.6, 124.0, 121.0, 116.5, 110.6, 61.2, 56.3 and 34.5. HRMS-ESI: m/z [M+H]+ for C₃₄H₃₄O₆, calculated 539.2694; observed 539.2683.

**(2E,2'E)-1,1'-(1,3-phenylene)bis(3-(4-(allyloxy)-3-methoxyphenyl)prop-2-en-1-one**

(compound 44, Table 6)

Bright yellow solid (Yield 71%), m.p. 63-65°C, ¹H NMR (CDCl₃, 300 MHz): δ 8.64 (1H, s), 8.25 (2H, s), 7.86 (2H, dd, J = 5.68, 5.70 Hz), 7.66 (1H, t, J = 7.71 Hz), 7.49 (2H, dd, J = 5.70, 5.73 Hz), 7.29-7.20 (4H, m), 6.95 (2H, t,
\[ J = 7.68 \text{ Hz} \), 6.17-6.05 (2H, m), 5.49-5.33 (4H, m), 4.70 (4H, s), 3.99 (6H, s); \]
\[^{13}\text{C NMR (CDCl}_3, 75.4 \text{ MHz):} \delta 190.3, 151.1, 150.1, 146.3, 139.3, 133.1, 132.6, 129.4, 128.6, 128.3, 123.7, 120.0, 118.9, 113.4, 111.1, 70.2 \text{ and 56.5.} \]
HRMS-ESI: m/z [M+H]^+ for C\(_{32}\)H\(_{30}\)O\(_6\), calculated 511.2382; observed 511.2347.

\((2E,2'E)-1,1'-(1,3-\text{phenylene})\text{bis}(3-(3,4-bis(allyloxy)phenyl)prop-2-en-1-one} \quad \text{(compound 45, Table 6)}

\begin{align*}
\text{Yellow solid (Yield 75\%) m.p. 189-190^\circ\text{C}, } \text{^1H NMR (CDCl}_3, 300 \text{ MHz):} \delta & 8.62 (1H, s), 8.22 (2H, d, J = 7.66 \text{ Hz}), 7.83 (2H, d, J = 15.56 \text{ Hz}), 7.68 (1H, t), 7.45 (2H, d, J = 15.56 \text{ Hz}), 7.28-7.23 (4H, m), 6.94 (2H, d, J = 8.11 \text{ Hz}), 6.82-6.04 (4H, m), 5.50 (4H, dd, J = 6.86, 6.87 \text{ Hz}), 5.35 (4H, d, J = 10.46 \text{ Hz}), 4.68 (8H, s); \text{^{13}C NMR (CDCl}_3, 75.4 \text{ MHz):} \delta 190.2, 151.6, 149.1, 146.2, 139.3, 133.5, 133.2, 132.6, 129.4, 128.6, 128.2, 123.9, 120.0, 118.5, 118.4, 113.8, 113.7, 70.5 \text{ and 70.1.} \]
HRMS-ESI: m/z [M+H]^+ for C\(_{36}\)H\(_{34}\)O\(_6\), calculated 563.2694; observed 563.2651.

2.4.14. **General procedure for the synthesis of bis(dimeric) chalcone (46; Table 6)**

To a solution of terephthaldehyde (1.5 mmol) in ethanol, sodium hydroxide (2 mmol) was added and the contents were stirred for 3-5 min. Thereafter, substituted acetophenone (8b; 3 mmol) in ethanol (10 mL) was added drop wise. The reaction mixture was stirred at 40°C till for 6-8 h completion of starting material (monitored by TLC). The reaction mixture was vacuum evaporated to remove the organic solvent and poured in cold water. The obtained precipitates were washed with dilute HCl, excess of water, methanol, dried in air and finally recrystallized with methanol to obtain pure chalcone whose structure was confirmed by NMR and mass spectroscopy.
(2E,2′E)-3,3′-(1,4-phenylene)bis(1-(4-(allyloxy)phenyl)prop-2-en-1-one (compound 46, Table 6)

Yellow solid (Yield 68%) m.p. 208-210°C,

\[^{1}\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz): } \delta 8.09 (2\text{H, d, } J = 8.89 \text{ Hz}), 8.07 (2\text{H, d, } J = 8.90 \text{ Hz}), 7.96 (2\text{H, d, } J = 8.87 \text{ Hz}), 7.83 (1\text{H, d, } J = 15.67 \text{ Hz}), 7.69 (2\text{H, d, } J = 5.58 \text{ Hz}), 7.58-7.49 (3\text{H, m}), 7.04 (2\text{H, d, } J = 8.87 \text{ Hz}), 6.97 (2\text{H, d, } J = 8.89 \text{ Hz}), 6.11-6.01 (2\text{H, m}), 5.36-5.32 (4\text{H, m}), 4.65 (4\text{H, d, } J = 4.46 \text{ Hz}); \]

\[^{13}\text{C} \text{NMR (CDCl}_3, 75.4 \text{ MHz): } \delta 189.1, 163.5, 145.9, 133.5, 132.7, 130.9, 128.9, 126.7, 122.2, 118.7, 114.9 \text{ and 69.3. HRMS-ESI: m/z [M+H]}^+ \text{ for C}_{30}\text{H}_{26}\text{O}_4, \text{ calculated 451.2082; observed 451.2058.}

2.4.15. General procedure for the synthesis of bis(dimeric) chalcone via 14b (47; Table 6)

a) Synthesis of 4-allyloxy-2-hydroxyacetophenone (14b)

To a 250 mL round bottom flask containing 2,4-dihydroxy acetophenone (11a) (1.9 mmol) in dry acetone (20 mL), allyl bromide (1.9 mmol) and anhydrous K\textsubscript{2}CO\textsubscript{3} (3.8 mmol) were added. The remaining procedure was similar to that described in step (a) of section 2.4.2. The desired compound obtained after column chromatography over silica gel with hexane-ethyl acetate (9:1) was characterized by \[^{1}\text{H} \& \ ^{13}\text{C} \text{NMR and HRMS data.}

4-allyloxy-2-hydroxyacetophenone (14b)

Pale yellow viscous liquid (Yield 65%), \[^{1}\text{H} \text{NMR (CDCl}_3, 300 \text{ MHz): } \delta 12.73 (1\text{H, s}), 7.65 (1\text{H, d, } J = 8.85 \text{ Hz}), 6.48-6.42 (2\text{H, m}), 6.08-5.99 (1\text{H, m}), 5.46-5.30 (2\text{H, m}), 4.58-4.56 (2\text{H, m}), 2.56 (3\text{H, s}); \]

\[^{13}\text{C} \text{NMR (CDCl}_3, 75.4 \text{ MHz): } \delta 202.9, 165.6, 165.4, 132.7, 132.6, 118.7, 114.4, 108.4, 102.1, 69.3 \text{ and 26.6. HRMS-ESI: m/z [M+H]}^+ \text{ for C}_{11}\text{H}_{12}\text{O}_3, \text{ calculated 193.0996; observed 193.0984.}

(b) Synthesis of chalcone (47)

To a solution of terephthaldehyde (1.5 mmol) in ethanol, sodium hydroxide (2 mmol) was added and the contents were stirred for 3-5 min. Thereafter, substituted acetophenone (14b; 3
mmol) in ethanol (10 mL) was added drop wise. The reaction mixture was stirred at 40°C till for 6-8 h completion of starting material (monitored by TLC). The reaction mixture was vacuum evaporated to remove the organic solvent and poured in cold water. The obtained precipitates were washed with dilute HCl, excess of water, methanol, dried in air and finally recrystallized with methanol to obtain pure chalcone whose structure was confirmed by NMR and mass spectroscopy.

\((2E,2'E)-3,3'-(1,4-phenylene)bis(1-(4-(allyloxy)-2-hydroxyphenyl)prop-2-en-1-one)\) (compound 47, Table 6)

![Chemical structure](image)

Bright yellow solid (Yield 70%)

m.p. 192-194°C, \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta\) 13.38 (2H, s), 7.93-7.85 (4H, m), 7.72-7.62 (6H, m), 6.57-6.51 (4H, m), 6.14-6.00 (2H, m), 5.44 (4H, dd, \(J = 17.26, 10.49\) Hz), 4.63 (4H, d, \(J = 5.31\) Hz); \(^1^3\)C NMR (CDCl\(_3\), 75.4 MHz): \(\delta\) 191.9, 167.1, 165.8, 143.5, 137.3, 132.5, 131.6, 129.5, 121.9, 118.9, 114.6, 108.7, 102.4 and 69.5. HRMS-ESI: m/z [M+H]\(^+\) for C\(_{30}\)H\(_{26}\)O\(_6\), calculated 483.2070; observed 483.2049.

2.5. References


Synthesis of allylated chalcones...

Chapter 2


Synthesis of allylated chalcones


NMR spectra of some compounds

$^1$H NMR (in CDCl$_3$) spectrum of (2E)-1-(4-Chlorophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (9, Table 3)

$^{13}$C NMR (in CDCl$_3$) spectrum of (2E)-1-(4-Chlorophenyl)-3-[3-methoxy-4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (9, Table 3)
Synthesis of allylated chalcones...

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$\text{H NMR (in CDCl}_3\text{) spectrum of 5-[3-methoxy-4-(prop-2-en-1-ylxy)benzylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (37, Table 5)}$

$\text{C NMR (in CDCl}_3\text{) spectrum of 5-[3-methoxy-4-(prop-2-en-1-ylxy)benzylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (37, Table 5)}$
Synthesis of allylated chalcones...

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\[
\begin{align*}
\text{1H NMR (in CDCl}_3 + \text{DMSO-}d_6 \text{ spectrum of } E-3-(4-(allyloxy)-3-methoxyphenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)prop-2-en-1-one (39, Table 5)}
\end{align*}
\]

\[
\begin{align*}
\text{13C NMR (in CDCl}_3 + \text{DMSO-}d_6 \text{ spectrum of } E-3-(4-(allyloxy)-3-methoxyphenyl)-1-(4-((7-chloroquinolin-4-yl)amino)phenyl)prop-2-en-1-one (39, Table 5)}
\end{align*}
\]
Synthesis of allylated chalcones

\[ \begin{align*}
\text{\( ^1\text{H} \text{NMR (in CDCl}_3\text{)} \text{ spectrum of 5-(4-(allyloxy)-3-methoxyphenyl)-3-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (41, Table 5)\)}}
\end{align*} \]

\[ \begin{align*}
\text{\( ^{13}\text{C} \text{NMR (in CDCl}_3\text{)} \text{ spectrum of 5-(4-(allyloxy)-3-methoxyphenyl)-3-(4-chlorophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (41, Table 5)\)}}
\end{align*} \]
Synthesis of allylated chalcones...

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\[
\text{N} \quad \text{Cl}
\]

\[
\text{N} \quad \text{Cl}
\]

\[
\text{H NMR (in CDCl}_3\text{)} \text{ spectrum of 4-(4-(allyloxy)-3-methoxyphenyl)-6-(4-chlorophenyl)pyrimidin-2-amine (42, Table 5)}
\]

\[
\text{C NMR (in CDCl}_3\text{)} \text{ spectrum of 4-(4-(allyloxy)-3-methoxyphenyl)-6-(4-chlorophenyl)pyrimidin-2-amine (42, Table 5)}
\]
Synthesis of allylated chalcones...

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\[ \text{H NMR (in CDCl}_3\text{) spectrum of (2E,2'E)-1,1'-(1,3-phenylene)bis(3-(3-allyl-4,5-dimethoxyphenyl)prop-2-en-1-one (43, Table 6)} \]

\[ \text{H NMR (in CDCl}_3\text{) spectrum of (2E,2'E)-1,1'-(1,3-phenylene)bis(3-(3-allyl-4,5-dimethoxyphenyl)prop-2-en-1-one (43, Table 6)} \]