Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2016, 8(1):458-477

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Recent advances and potential pharmacological activities of chalcones and their heterocyclic derivatives-a valuable insight

Srinivasa Rao D.[1], Pavan Kumar G.[1]*, Harika G.[2], Pooja B.[2], Sadasiva Rao[3] and Anil Kumar Y.[3]

[1]*KC Reddy Institute of Pharmaceutical Sciences, Jangamguntapalem, Medikonduru(Md), Guntur (Dt), A.P, India*
[2]*Sims College of Pharmacy, Mangaldas Nagar, Guntur (Dt), A.P, India*
[3]*Hindu College of Pharmacy, Amaravathi Road, Guntur(Dt), A.P, India*

ABSTRACT

Chalcones, precursors of open chain flavonoids and isoflavonoids present in edible plants, and their derivatives have attracted increasing attention due to numerous potential pharmacological applications. They have displayed a broad spectrum of pharmacological activities. Changes in their structure have offered a high degree of diversity that has proven useful for the development of new medicinal agents having improved potency and lesser toxicity. The present review highlights the recently synthesized chalcones and their derivatives possessing important pharmacological activities.

Keywords: Chalcone; *trans*-1,3-diaryl-2-propen-1-one; potential pharmacological activity.

INTRODUCTION

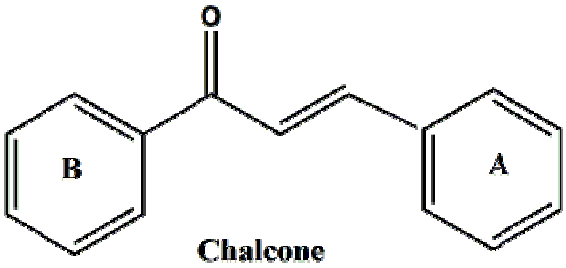
Chalcones (*trans*-1,3-diaryl-2-propen-1-ones) **(1)**, a biosynthetic product of the shikimate pathway, belonging to flavanoid family are precursors of open chain flavonoids and isoflavonoids, which are abundant in edible plants. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines,1,4-diketones, and flavones. Thus the synthesis of chalcones has generated vast interest to organic as well as for medicinal chemists. The traditional methods for the synthesis of 1,3-diaryl-2-propenones involves the use of strong bases such as NaOH, KOH, Ba(OH)2, hydrotalcites, LiHMDS, calcined NaNO3/natural phosphate. There are also some reports of acid-catalyzed aldol condensations, e.g. AlCl3, BF3, dry HCl, ZrH2/NiCl2 and RuCl3 (for cyclic and acyclic ketones).

Chalcones and its derivatives have attracted increasing attention due to numerous pharmacological applications. They have displayed a broad spectrum of pharmacological activities,among which antimalarial[1-4],anticancer[5-9],antiprotozoal(antileishmanial and antitrypanosomal) [10], anti-inflammatory[11, 12],antibacterial[13, 14],antifilarial[15],antifungal[16,17],antimicrobial[18],larvicidal[19],anticonvulsant [20],antioxidant [21-23] activities have been reported.They have also shown inhibition of the enzymes,especially mammalian alpha-amylase [24],cyclo-oxygenase (COX) [25] and monoamine oxidase (MAO) [26].

Chalcones are α,β-unsaturated ketones consisting of two aromatic rings (ring A and B) having diverse array of substituents. Rings are interconnected by a highly electrophilic three carbon α,β-unsaturated carbonyl system that assumes linear or nearly planar structure [2,4].They contain the ketoethylenic group –CO–CH=CH-[9].Chalcones

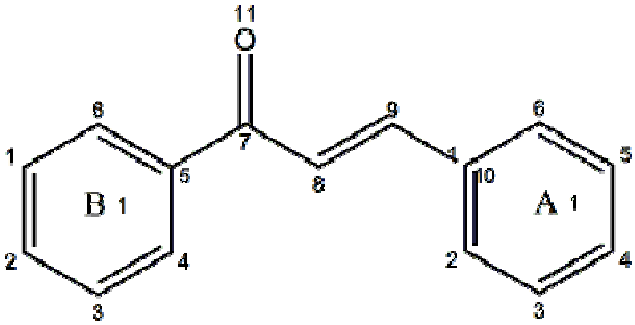
possess conjugated double bonds and a completely delocalized π-electron system on both benzene rings.The energy minimized 3D structure of chalcone has been shown in the figure **(2)**.

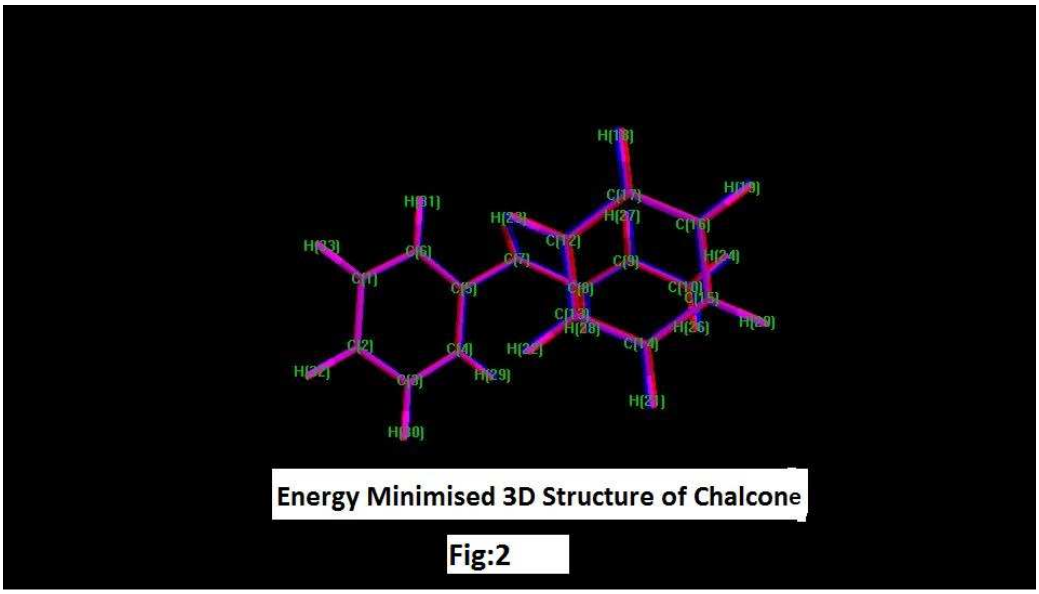
Chalcones have crystal structure. The dihedral angle between the two phenyl rings is 13.0(1)°, and the dihedral angle from the plane of C7/C8/C9 to the phenyl rings (C1 to C6 and C10 to C15) are 13.8(1)° and 2.6(1)°, respectively, indicating that the central C7-C8-C9 fragment lies nearly in the phenyl ring plane of C10 to C15, but rather more displaced out of the other benzene ring of C1 to C6. The molecule forms a zigzag chain by C-H··π (arene) hydrogen bonds along the *c* axis. There also exist intermolecular hydrogen bonding interactions involving C11 acting as H-bond donor, via H11, to O in the adjacent molecules at -*x*,1-*y*,1-*z*, resulting in a three-dimensional network [27]. They can be readily synthesized in laboratory by the Claisen-Schmidt reaction which is very easy and simple to conduct as well as inexpensive [28]. The structure of chalcone with plane, centroid and exclusion sphere have been shown in the figure **(3)**.

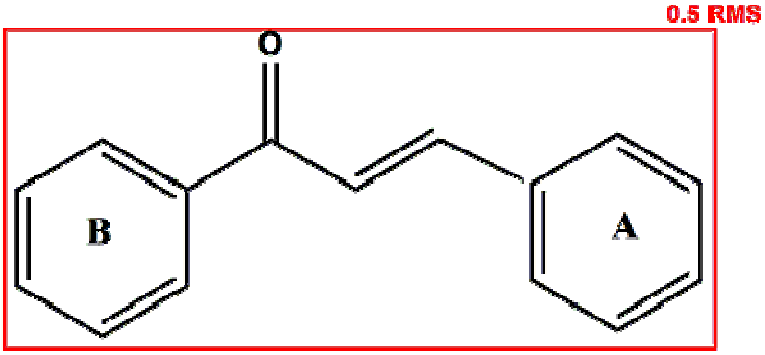


Chalcone

Fig:1

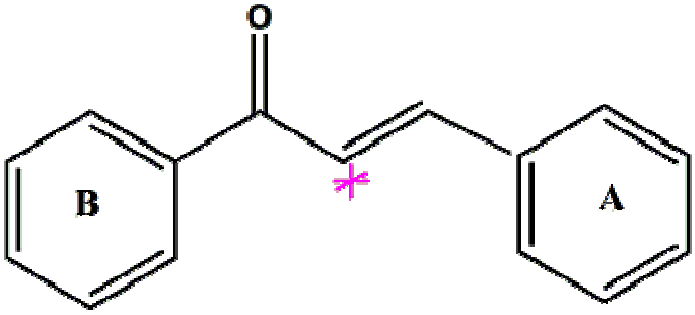






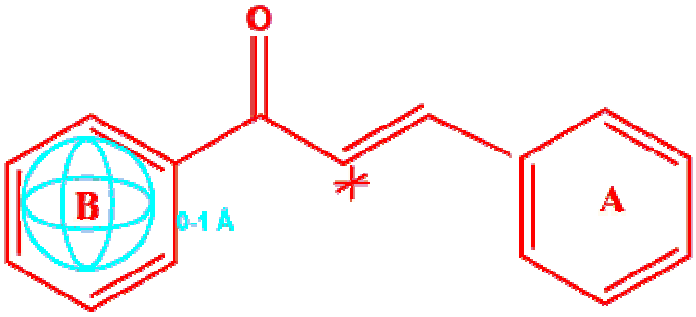
structure of Chalcone showing plane of symmetry

Fig:3a



structure of Chalcone showing centroid

Fig:3b



structure of Chalcone showing Exclusion Sphere

Fig:3c

2. Pharmacological Activities

2.1. Antimalarial Activity

Malaria is globally recognized as a serious problem of public health, mainly in the tropical and subtropical regions of the world. The increase of resistant malarial parasite strains represents the largest obstacle to antimalarial chemotherapy. Motta *et al* [1] studied chalcone derivatives. He performed quantitative structure-activity relationships of a series of chalcone derivatives (1,3-Diphenyl-2-propen-1-one) as anti-*Plasmodium falciparum* agents (antimalarial agents). The study investigated the factors that may be important in the inhibitory activity of

chalcone derivatives on *P. falciparum* cysteine protease. The obtained models presented good capacity to explain the observed values of biological activity, high adjustment level, statistical significance and good predictive capacity. Hydrophobic and steric properties seemed to play an important role in the explanation of the activity of the dataset. The results indicated that the activity on W2 and D6 strains was favored if ring A had a width-limited chemical substituent on it. The limited molecular width of these derivatives can be related with the activity against the D6 strain. The molecular weight, which is related to molecular volume, appeared to influence only the activity of D6 strain. The results also indicated that molar refractivity and molecular length have positive contributions to the activity against chloroquine-resistant(W2) *Plasmodium falciparum* strains, while molecular weight against mefloquine-resistant (D6) strains. The main conclusions of this work were: (*i*) The C2–C3 double bond is essential for high inhibitory activity. It is not only a conjugated linker between A and B aromatic substituents, but it keeps extended the molecular conformation. In this way, the drug molecule seems to bind much better to the active site, which resembles a cleft on the surface of falcipain; (*ii*) Substitutions on the bridge portion of the chalcone series caused a pronounced decrease in the inhibitory activity, probably due to steric interactions; (*iii*) Chloro or fluoro substitution on the ring B and electron-donating substitution on the ring A increased the antimalarial activity; (*iv*) Quinolinyl group in the ring B resulted in increased activity.

Awasthi *et al* [2] synthesized several new chalcone analogues and evaluated as inhibitors of malaria parasite. Inhibitory activity was determined *in vitro* against a chloroquine-sensitive*P.falciparum* strain of parasites.The chalcone '3-(4-methoxyphenyl)-1-(4-pyrrol-1-yl-phenyl)prop-2-en-1-one' **(4)** was found to be the most active with 50% inhibition concentration (IC50) of 1.61 µg/ml. This inhibitory concentration was comparable to a prototype phytochemical chalcone, licochalcone, with an IC50 of 1.43 µg/ml. The study suggested that small lipophilic nitrogen heterocyclic at ring B together with small hydrophobic functionality at ring A can enhance antimalarial activity. These results suggested that chalcones are a class of compounds that provides an option of developing inexpensive, synthetic therapeutic antimalarial agents in the future.

In order to accelerate the development of relatively inexpensive antimalarials that are effective against chloroquine-resistant strains of *P. falciparum*, Cheng *et al* [3] had developed a methodology for the solid phase synthesis of chalcone analogues in reasonably high yields. On the basis of their structure activity relationship (SAR) and computer modeling data, they expected that the chalcone derivatives with hydroxyl functionality on one of the aromatic rings and with some other appropriate substitutions on the other ring will be even more potent as antimalarials.They found that the chalcone'1-(2-chloroquinolin-3-yl)-3-(3-hydroxyphenyl)prop-2-en-1-one'**(5)**was synthesized in the highest percentage yield, 97%.

As a part of the search for novel antimalarial agents from plants or via chemical synthesis, Lim *et al* [4] prepared twenty derivatives of flavonoids and chalcones, four derivatives for each of flavones, flavanones, chalcones, dihydrochalcones, and 3'-chlorochalcones, and evaluated for *in vitro* antimalarial activity against *P. falciparum* strain FCR-3 and cytotoxicity against FM3A cells (a mouse mammary tumor cell). The aim was to derive predictive structure activity relationships to guide lead compound design. Among the chalcones tested, the most active compound was 3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4-methoxy-phenyl)propan-1-one **(6)** showing 100% inhibition against *P. falciparum* at the final concentration of 5.4 µg/ml (EC50 = 1.0 µg/ml). The compound also showed strong cytotoxicity against FM3A cells, a model of the host, with relatively low EC50 values (>3.3 µg/ml) and low selectivity index (>3.3) indicating that the compound have non-selective antimalarial activity.

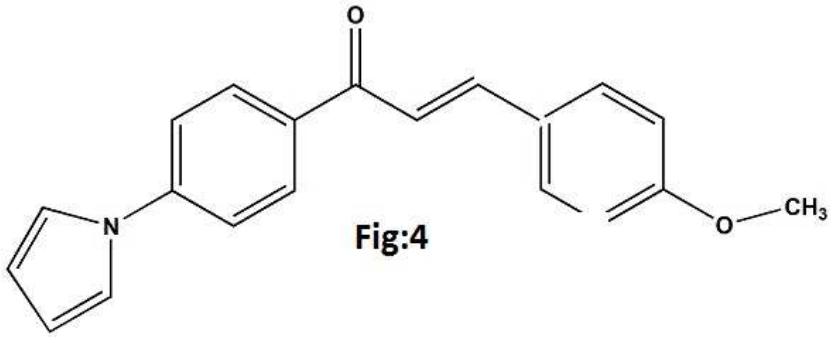


Fig:4

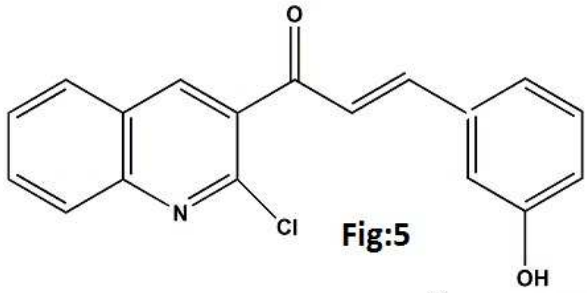


Fig:5

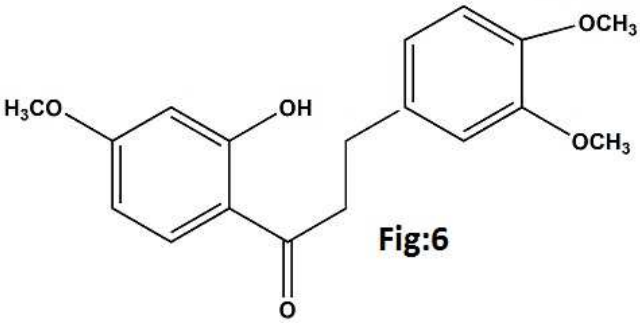


Fig:6

2.2. Anticancerous Activity

Achanta *et al* [5] evaluated a series of boronic chalcones for their anticancer activity and mechanisms of action. Among the eight chalcone derivatives tested, the chalcone '3,5-bis-(4-boronic acid-benzylidene)-1-methylpiperidin-4-one'**(7)**exhibited most potent growth inhibitory activity with IC50 values of 1.5 and 0.6 μM in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and colony formation assay respectively.

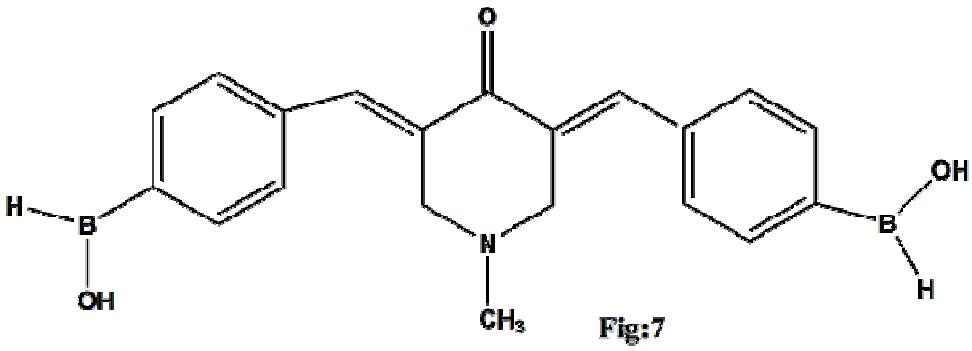


Fig:7

The cytotoxic activity of AM114 was shown to be associated with the accumulation of p53 and p21 proteins and induction of apoptosis. Mechanistic studies showed that AM114 treatment inhibited the chymotrypsin like activity of the 20S proteasome *in vitro*, leading to a significant accumulation of ubiquitinated p53 and other cellular proteins in whole cells. *In vitro* studies showed that AM114 did not significantly disrupt the interaction of p53 and murine double minute 2 protein. It was noteworthy that AM114 as a single agent was preferentially toxic to cells with wild type p53 expression, whereas combination of this compound with ionizing radiation significantly enhanced the cell killing activity of ionizing radiation in both wild type p53 and p53 null cells. Together, these results indicated that the boronic chalcone derivative AM114 induced significant cytotoxic effect in cancer cells through the inhibition of the cellular proteasome and provided a rationale for the further development of this class of compounds as novel cancer chemotherapeutic agents.

A series of chalcone-like agents, in which the double bond of the enone system is embedded within a thiophene ring, were synthesized and evaluated by Romagnoli *et al* [6] for antiproliferative activity and inhibition of tubulin assembly and colchicine binding to tubulin. The replacement of the double bond with a thiophene maintained antiproliferative activity and therefore must not significantly alter the relative conformation of the two aryl rings. The synthesized compounds were found to inhibit the growth of several cancer cell lines at nanomolar to low micromolar concentrations. In general, all compounds having significant antiproliferative activity inhibited tubulin

polymerization with an IC50 < 2 μM. Several of these compounds caused K562 cells to arrest in the G2/M phase of the cell cycle. Turning to the effects of an electron-releasing group (ERG) on the phenyl moiety, they found that a *p*-methyl group caused only minor changes in antiproliferative activity. Reduced activity occurred when the methyl substituent was moved from the *para* to *ortho* position. The more active compounds were evaluated for their *in vitro* inhibition of tubulin polymerization and for their inhibitory effects on the binding of [3H]colchicine to tubulin (in the latter assay, the compounds and tubulin were examined at a concentration of 1 μM with the colchicine at 5 μM). For comparison, the antitubulin agent CA-4 was examined in contemporaneous experiments as a reference compound. Compounds '3,4,5-trimethoxyphenyl-(5-(thiophen-2-yl)thiophen-2-yl)methanone' **(8)** and '3,4,5-trimethoxyphenyl-(5-*p*-tolylthiophen-2-yl)-methanone' **(9)** were the most active (IC50, 0.8 μM), having twice the potency of CA-4 (IC50, 1.4 μM).

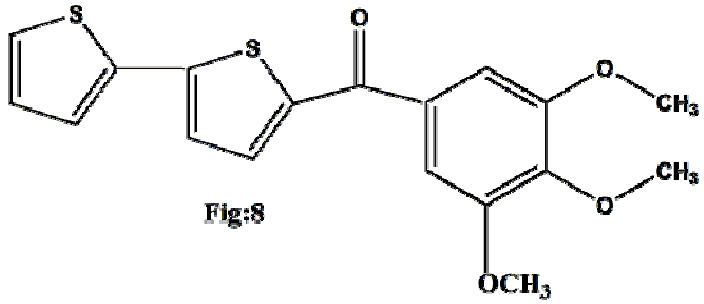


Fig:8

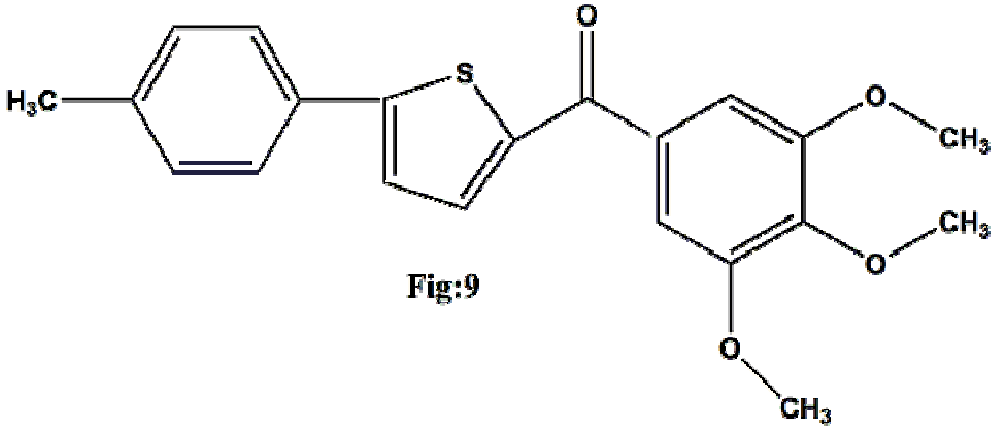


Fig:9

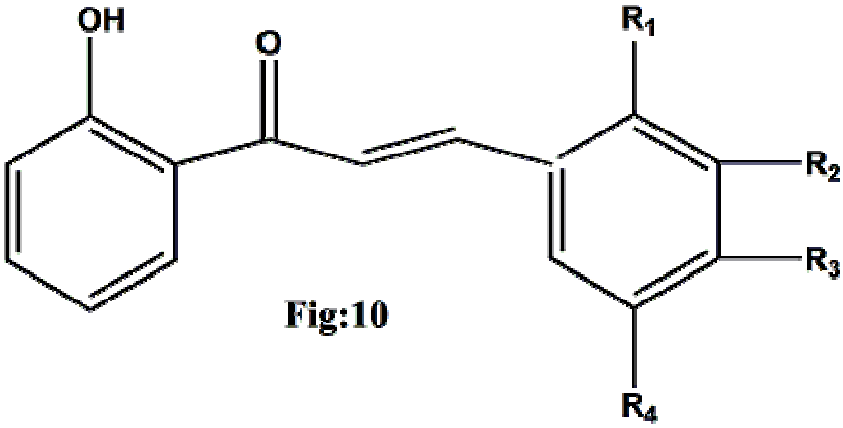
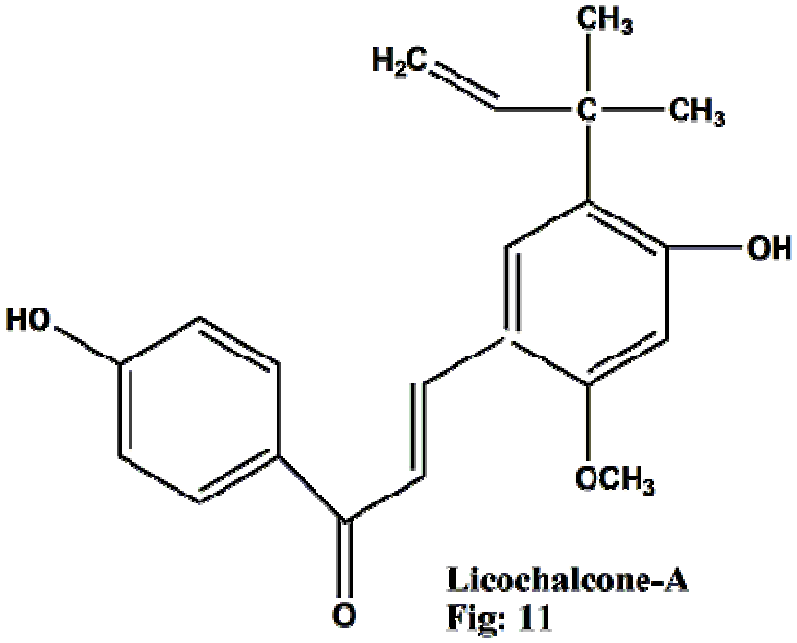


Fig:10

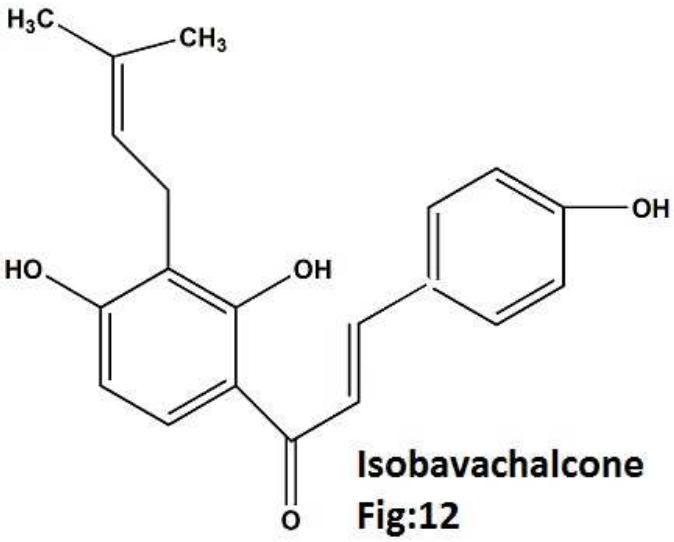
Echeverria *et al* [7] studied relationships between the structural characteristic of synthetic chalcones and their antitumoral activity. Treatment of HepG2 hepatocellular carcinoma cells for 24h with synthetic 2'-hydroxychalcones resulted in apoptosis induction and dose-dependent inhibition of cell proliferation. The calculated reactivity indexes and the adiabatic electron affinities using the DFT method including solvent effects, suggested a structure-activity relationship between the chalcone structure and the apoptosis in HepG2 cells. The absence of methoxy substituents in the ring A of synthetic 2'-hydroxychalcones, showed the major structureactivity pattern

along the series and because of this, the chalcone '1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one' **(10)** was found to be the most active.

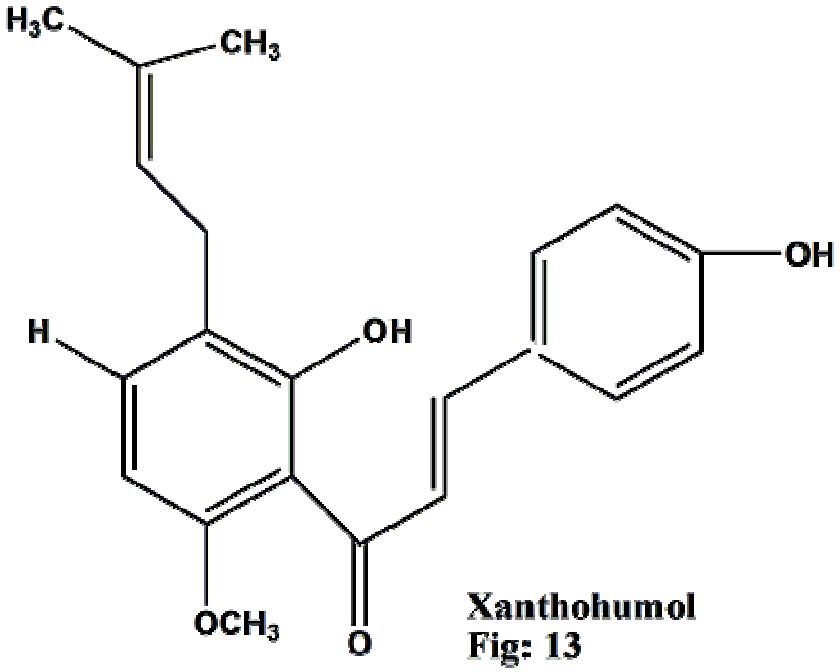
Chalcones exhibit chemopreventive and antitumor effects. Tumor necrosis factor-related apoptosis-inducing ligand(TRAIL) is a naturally occurring anticancer agent that induces apoptosis in cancer cells and is non-toxic to normal cells. Szliszka *et al* [8] examined the cytotoxic and apoptotic effect of five chalcones in combination with TRAIL on prostate cancer cells and evaluated the cytotoxicity by the MTT and Lactate Dehydrogenase (LDH) assays. The apoptosis was determined using flow cytometry with annexin V-FITC. Their study showed that all the five tested chalcones: chalcone **(1)**, licochalcone-A **(11)**, isobavachalcone **(12)**, xanthohumol **(13)**, butein **(14)** markedly augmented TRAIL-mediated apoptosis and cytotoxicity in prostate cancer cells and confirmed the significant role of chalcones in chemoprevention of prostate cancer. They showed for the first time that chalcones sensitize prostate cancer cells to TRAIL-induced apoptosis. The obtained results suggested that chalcones help anticancer immune defense in which endogenous TRAIL takes part. The TRAIL-mediated cytotoxic and apoptotic pathways may be a target to the chemopreventive agents in prostate cancer cells and the overcoming TRAIL resistance by chalcones may be one of the mechanisms responsible for their cancer-preventive effects.



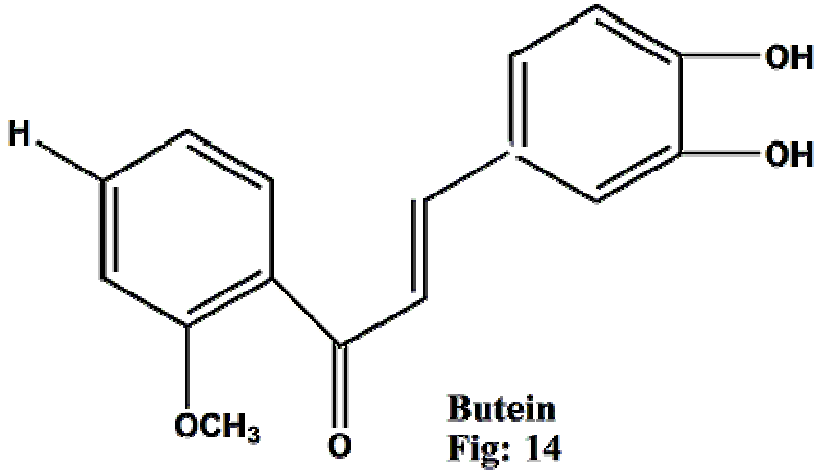
Licochalcone-A
Fig: 11



Isobavachalcone
Fig:12



Xanthohumol
Fig: 13



Butein
Fig: 14

Lango *et al* [9] synthesized a series of chalcones and evaluated them for their *in vitro* cytotoxic activity by microculture Tetrazolium Test Assay method using two breast cancer cell lines MCF-7 and T47D. The IC50 value was calculated at the 0.1-100 µM concentration range. The assay was dependent on the activity of mitochondrial dehydrogenase enzymes that reduce yellow MTT to a blue formazan product and the activity of enzyme that is directly proportional to cell viability. The result showed significant cytotoxicity against both of the cell lines and value lied between 52-89 µM. All the compounds showed good cytotoxic activity and the compound '*N*-(4-hydroxy-3-(3-(2/3/4-nitrophenyl)acryloyl)phenyl)acetamide'**(15)**showed better activity than other compounds,this may be due to presence of nitro group in the compound.

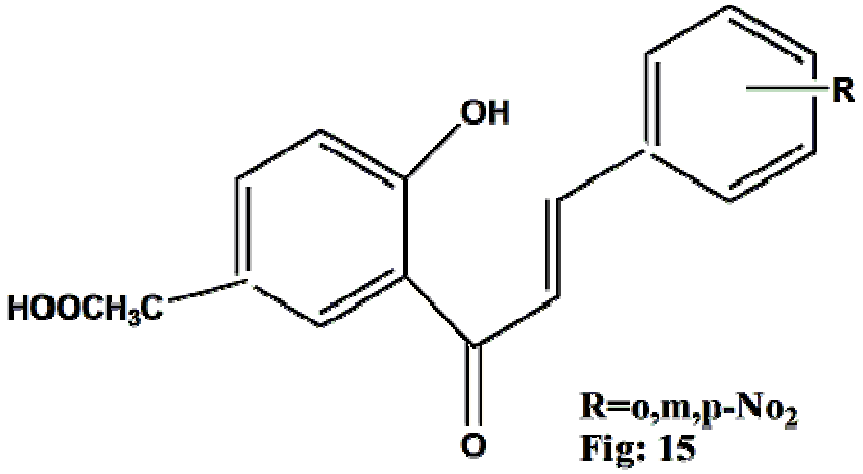
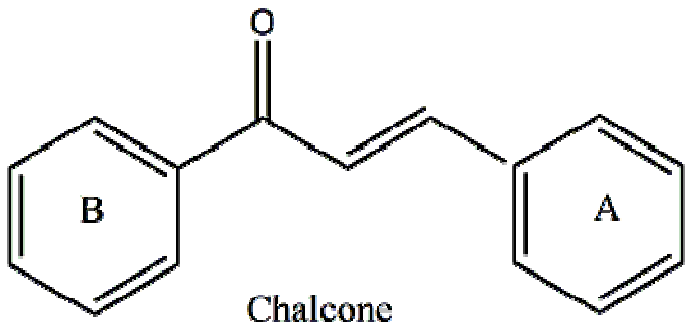


Fig: 15

2.3. Antiprotozoal Activity

Ten chalcones were synthesized and tested as leishmanicidal and trypanocidal agents by Lunardi *et al* [10] against *in vitro* growth of *Leishmania braziliensis* and *Trypanosoma cruzi*.The results showed that the positions of the substituents seem to be critical for their antiprotozoal activities. The results also showed that some synthesized substitution-containing chalcones exhibited promising concentration-dependent (i.e.,at high concentration) leishmanicidal and trypanocidal activities with no evidence of a cytotoxic effect on mouse macrophages. The chalcone **(1)**, which has no substituent groups, revealed both pronounced leishmanicidal and trypanocidal activities even at low concentration with no evidence of a cytotoxic effect on mouse macrophages.



2.4. Anti-inflammatory Activity

Chalcone derivatives contain α,β-unsaturated carbonyl moiety which is responsible for anti-inflammatory activity.Yadav *et al* [11] synthesized a series of five chalcone derivatives and were subjected to anti-inflammatory screening using the carrageenan-induced rat hind paw edema model. Chalcone derivatives at dose 25 mg/kg by oral route inhibited significantly the formation of edema. The *P* value was found to be <0.05 showing significant anti-inflammatory activity. The compound '4-fluoro/4-chloro chalcone' **(16)** showed more activity comparable to standard drug indomethacin due to -F/-Cl groups present in the compound. Hence, the anti-inflammatory activity of chalcone derivatives was increased when electron withdrawing groups (EWG) were present on the chalcone moiety.

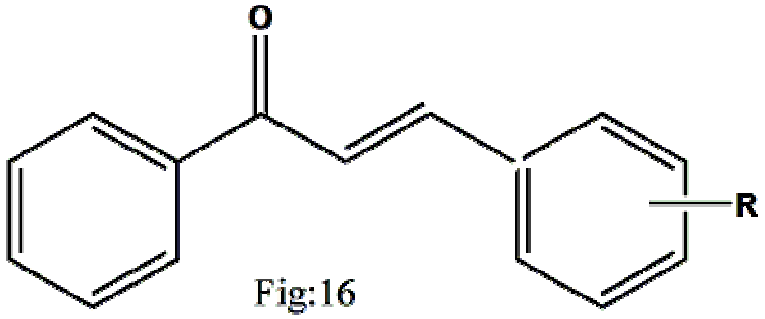


Fig:16

In an effort to develop potent anti-inflammatory agents, a series of substituted chalcone derivatives was synthesized and evaluated for anti-inflammatory activity by Zhang *et al* [12] through *in vivo* inhibition assay monitoring of their ability to inhibit xylene-induced ear edema in mice.Some of the tested compounds exhibited Significant activity, and the compound '3-(4-chlorophenyl)-1-(2,4 dihydroxyphenyl)prop-2-en-1-one' **(17)** showed the highest anti-inflammatory activity (68% inhibition) comparable with or even slightly more potent than the reference drug ibuprofen (53%).Furthermore, the structure-activity relationship of these substituted chalcone derivatives demonstrated that the substituted 2',4'-dihydroxychalcone derivatives was stronger than that of 4'-hydroxychalcone. The position of the substituted group on the phenyl ring greatly influenced the anti-inflammatory activity, with an activity order of-4-N(CH3)2>-4-OCH3>-3-OCH3-4-OH>-3,4-OCH2O->-4-OH>-3,4-(OH)2.The potency order of the two Cl-substituted derivatives being 4-Cl>2,4-Cl2. the potency order of the two NO2-substituted derivatives being 3-NO2>2-NO2. These results indicated that the character of the substitution on the ring A had a significant influence on the anti-inflammatory activity.

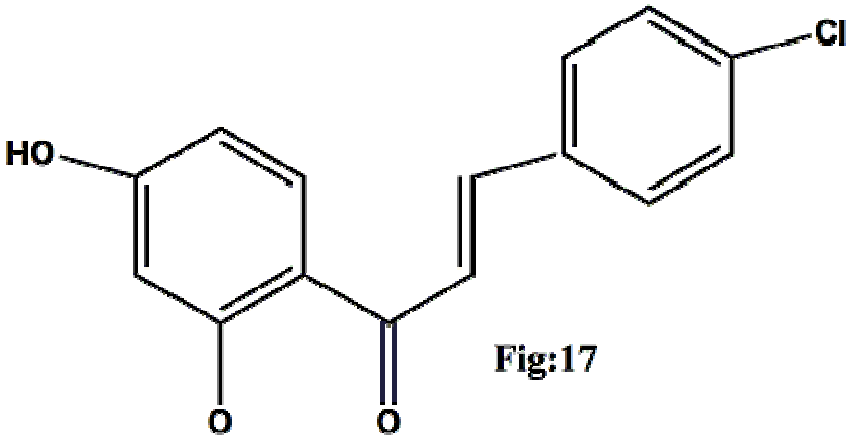


Fig:17

2.5. Antibacterial Activity

Hamdi *et al* [13] synthesized a series of new coumarin derivatives containing a chalcone moiety and evaluated for possible anti-oxidant and antibacterial activities. The coumarinic chalcone '4-hydroxy-3-(3-*p*-tolylacryloyl)-2*H*chromen-2-one' **(18)** had been found to be the most active (IC50 = 2.07 μM). The derivatives were screened *in vitro* for their antibacterial activity against Gram +ve bacteria, *Staphylococcus aureus* using the paper disc diffusion method for the antibiotic sensitivity technique. It showed that the activity against bacteria is moderate, but in addition, it was clearly demonstrated that this kind of compound could be an antibacterial agent; its activity depends on its chemical composition. The moderate active antibacterial effects observed showed that this kind of compound could be an antibacterial agent. series of chalcone derivatives were synthesized and evaluated for antibacterial activity by Bhatia *et al* [14].All the compounds were screened for their antibacterial activities against four different bacterial strains *S. aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* by the cup plate agar diffusion method. Dimethyl formamide was used as a solvent, and ciprofloxacin as the standard drug. QSAR equation revealed that selected electronic, steric and lipophilic parameters had good correlation with antibacterial activity. The findings suggested that the chalcone framework is an attractive template for structure optimization to achieve higher potency, lower toxicity, and a wider spectrum of antibacterial activity. Although more hydrophobic surface areas tend to favor antibacterial activity and Gram -ve and Gram +ve selectivity, the increase in the size of

molecules may lead to a decrease in the antibacterial activity. The hydrophobic surface area should be increased without increasing the molecule size. An increase in the dipole and quadrupole moments leads to charge separation which increases biological activity.

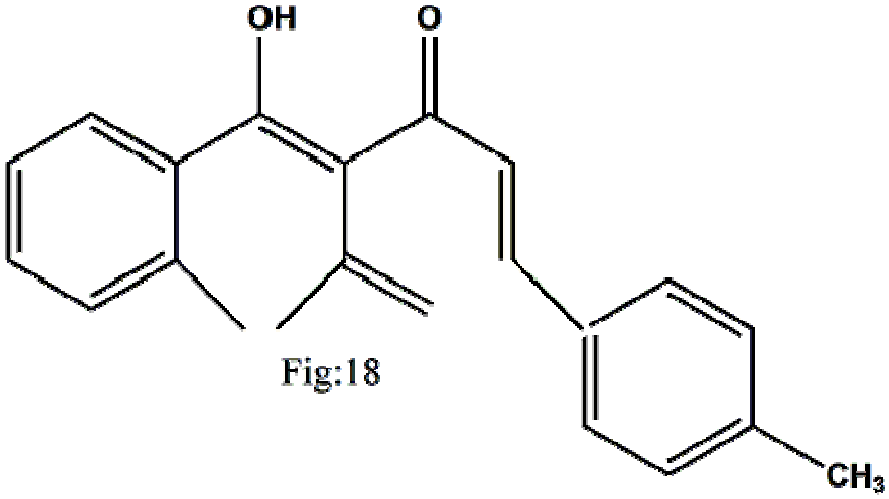


Fig:18

2.6. Antifilarial Activity

Chalcone derivatives were evaluated by Awasthi *et al* [15] for their antifilarial activity on *Setaria cervi* using glutathione-*S* -transferase (GST) enzyme as a drug target. The compounds '1-(4-benzotriazol-1-yl-phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one' **(19)** and '3-(4-methoxyphenyl)-1-(4-pyrrolidin-1-yl-phenyl)prop-2-en-1-one' **(20)**showed a significant suppression ($P < 0.01$) in GST activity of adult female parasite extract at 3 μM concentration *invitro*. However, GST activity was detected along with depletion in GSH level. More or less, all compounds showed a paralyzing effect on the motility and viability of parasites, ranging from 25% to 97% inhibition.

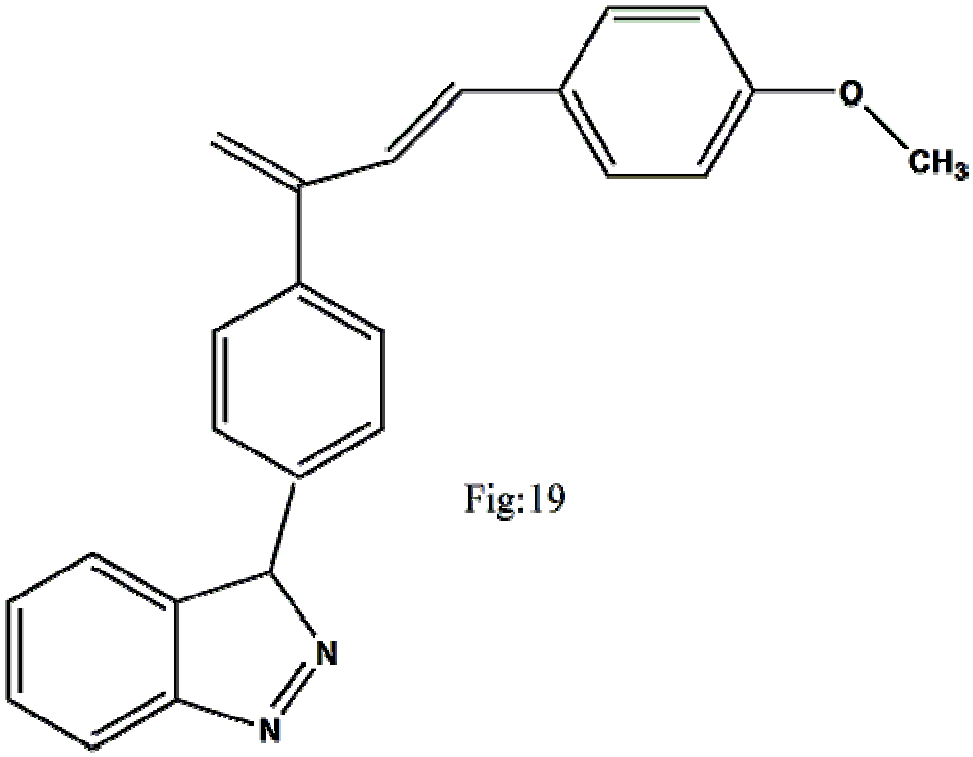


Fig:19

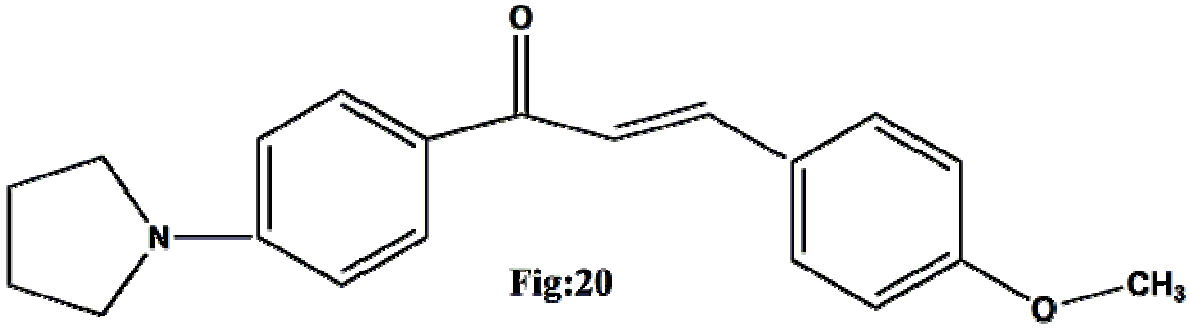


Fig:20

The compounds '1-(4-benzotriazol-1-yl-phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one' and '3-(4-methoxyphenyl)-1-(4-pyrrolidin-1-ylphenyl)prop-2-en-1-one' exhibited major irreversible effects on viability and resulted in parasite death and also inhibited the GST activity by 84-100% *in vitro*. They reported for the first time the antifilarial activity of chalcones on GST of adult parasites. This study also strengthened their previous findings where GST was reported as a potential drug target for antifilarials. However, this was a preliminary *in vivo* and *in vitro* study in which living worms were incubated with chalcones. The results of 4-chloro and 4-methoxy-substituted chalcones strongly supported that small- and medium-sized highly lipophilic or hydrophobic groups containing single or multiple nitrogen or oxygen in an acetophenone ring of chalcone have potent inhibitory effects on motility, viability, and GST activity of the parasite, supporting the antifilarial efficacy of chalcone. The most significant effect on parasites was exerted by methoxy-substituted chalcones, suggesting that these substituents can be used for further studies against filariasis.

2.7. Antifungal Activity

With the aim of developing potential antifungals, Bag *et al* [16]synthesized a series of chalcones incorporating sulfur either as part of a hetero-aromatic ring(thiophene) or as a side chain (thiomethyl group) and tested for their *invitro* activity.Some of the compounds showed appreciable activity against a fluconazole-sensitive and fluconazole-resistant strain with the chalcone'3-(4-(methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one'**(21)** exhibiting the highest activity. Maximum activity was obtained with *p*-fluoro substitution on ring A.Activity was decreased with increasing halogen size. Presence of *p*-methoxy or hydroxy groups at the *o-, m- or, p-* position also resulted in good activity while the *p*-nitro group as well as the bulky *p*-phenyl substitution decreased activity as compared with the unsubstituted compound.The *m-* and *p*-disubstitution with methoxy led to increased activity while again the *p*-phenyl-substituted compounds exhibited considerably decreased activity.

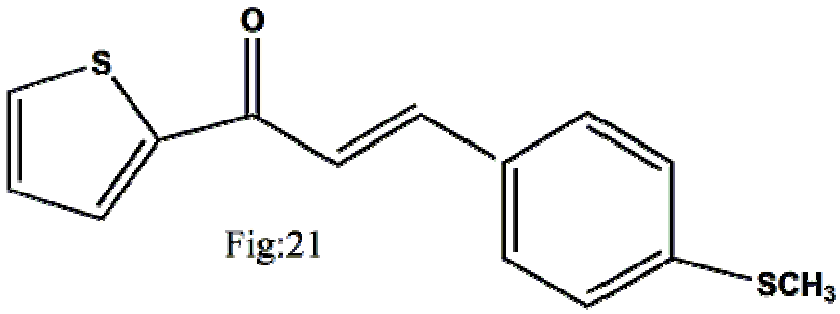


Fig:21

All compounds with the bromo thiophene ring in place of ring B exhibited less activity compared with those with the unsubstituted thiophene ring. Bromine substitution on the thiophene ring B decreased antifungal activity. Compounds with unsubstituted thiophene ring B and thiomethyl substitution at the *p-* position of ring A, exhibited good antifungal activity. Highest activity was found when both thiophene ring B and thiomethyl substitution at ring A were present together in the chalcone '3-(4 (methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one'.

Lahtchev *et al* [17] reported the synthesis, antifungal evaluation and study on substituent effects of several chalcones.A lot of genetically defined strains belonging to different yeast genera and species, namely *Saccharomyces cerevisiae, Hansenula polymorpha* and *Kluyveromyces lactis*, were used as test organisms.

Concerning the mode of the antifungal action of chalcones it was shown that DNA was probably not the main target for the chalcones. It was revealed that the yeast's intracellular glutathione and cysteine molecules play significant role as defence barrier against the chalcone action. It was also shown that chalcones may react with some proteins involved in cell separation. The antifungal effects of the substituted chalcones were compared with those of the parent chalcone. The following correlations were observed:

(i) Introduction of EW substituents (Cl, CN and NO2 groups) in *p*-position in ring A yielded less active chalcones than the parent chalcone. (ii) Introduction of ED substituents (OH, CH3 and OCH3 groups) in *p*-position in ring Aproduced inactive chalcones. (iii) Presence of a single hydroxyl group was effective at *m*-position in ring A. Introduction of a single methoxy group at *m*-position in ring A led to inactive compound. (iv)The combination of *m*-hydroxyl and *p*-methoxy groups in ring A was effective. Loss of activity was observed with the interchange of the positions of the hydroxyl and methoxy groups and when the hydroxyl group was placed in *o*-position and the methoxy group was in *m*-position. (v) Introduction of *p'*-chloro atom in ring B was beneficial only for the chalcones with a single hydroxyl group at *m*- and *p*-positions. The *m*-position was more favourable than the *p*-position.Presence of *m*- and *p*-hydroxyl groups together led to the inactive chalcone.(vi) Elongation of the conjugated system by introduction of one additional double bond between the ketovinyl moiety and the ring A did not produce an active compound. Based on these observations, it was concluded that the electronic effects of the *p*substituents in ring A of chalcones are not crucial for displaying antifungal activity towards the tested fungi. This is contradictory to the antifungal effects, which chalcones with EW and ED substituents in ring A have shown against several *dermatophytes* and the yeast *C. albicans*. Besides, in this study the position of the hydroxyl group in ring A was found important for the chalcone activity as opposed to some other antifungal studies. Interestingly, the favored location for the hydroxyl group was the *m*-position in ring A.

2.8. Antimicrobial Activity

Yayli *et al* [18] synthesized *N*-alkyl derivatives and photochemical dimers of 3 *o*-, *m*-, and *p*-nitro substituted 4-azachalcones. The monomeric compounds showed good antimicrobial activity against test micro-organisms *E.coli*, *K.pneumoniae*, *Yersinia pseudo tuberculosis*, *P.aeruginosa*, *Enterococcus faecalis*, *S.aureus*, *Bacillus cereus*, and *Candida tropicalis*. The most sensitive micro-organisms were Gram +ve bacteria. The compounds '1-decyl-4-(3-(3-nitrophenyl)-3-oxoprop-1 enyl)pyridinium bromide' **(22)** and '1-decyl-4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' **(23)** exhibited broad-spectrum antimicrobial activity. The MIC values (MBC) for the test micro-organisms were between <0.35 and 25 µg/ml. The synthesized compounds were also tested for their antioxidant activity based on their ability to scavenge the stable radical DPPH (2,2-diphenyl-1-picrylhydrazine).Themonomers showed high anti-oxidant activity, while the dimerization products were less active.The monomeric compounds exhibited higher radical scavenging potential in general, with low IC50 values. The compound '1-decyl-4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' was found to have similar or even higher activity when compared to the standard anti-oxidants Trolox and vitamin C, respectively.

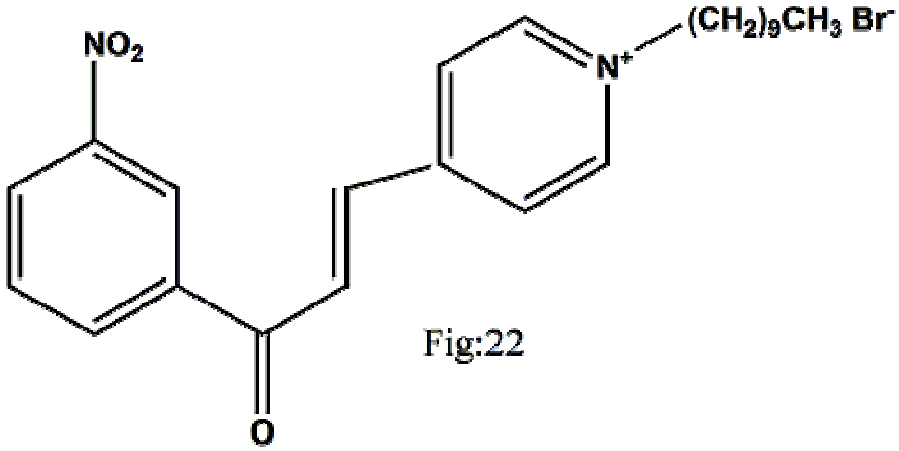


Fig:22

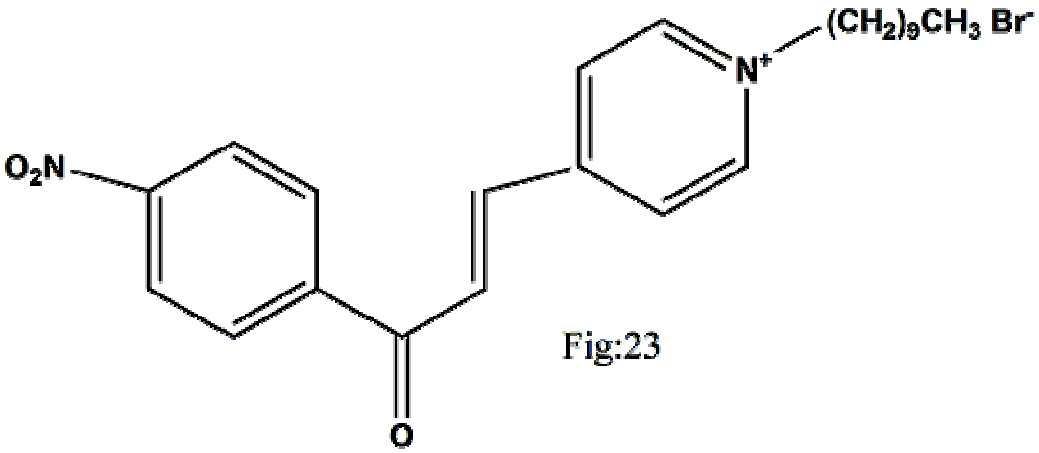


Fig:23

2.9. Mosquito Larvicidal Activity

A series of chalcone analogues and some of their derivatives were synthesized and subjected to the mosquito larvicidal study (larvae of *Culex quinquefasciatus*), SAR and QSAR by Begum *et al* [19]. The chalcones showed % mortality ranging from a very low value (10%) to a very high value (90%). Chalcones having EDG(s) on either ring A or ring B showed high toxicity to larva of the mosquito. EWG(s), especially at ring A, reduced the activity of chalcones. The activity was abruptly decreased due to replacement of ring B by CH3,extension of conjugation or blocking of α,β-unsaturated ketone part of chalcones by derivation.QSAR studies of these compounds were performed using various spatial,electronic and physicochemical parameters. Genetic function approximation with linear and spline options was used as the chemometric tool for developing the QSAR models. The investigation had clearly shown that certain chalcone analogues had potent mosquito larvicidal activity. Most of the hydroxyl chalcones showed toxicity against the third instar larvae of *C.quinque fasciatus*. The favorable chemical structures were found to be a hydroxyl substituent in ring B at 2'-position which may be hydrogen bonded with the electron pair on α,β-unsaturated ketone moiety, thereby decreasing the electrophilicity of this part of the molecule.Presence of hydroxyl group at 2'-position of ring B and replacement of ring A (phenyl) by a furan ring also increased the larvicidal activity. Besides that 3-chlorine substitution in ring A was also another feature of favorable activity. Presence of methylenedioxy group at 3,4 positions of ring A also enhanced the larvicidal activity of chalcone-type compound. However, extension of conjugation and blocking of α,β-unsaturated ketone part of chalcones had bad effects toward the activity of these compounds.

The chalcone '3-(furan-2-yl)-1-(2- hydroxyphenyl) prop-2-en-1-one' **(24)** had shown 100% mortality and LC50 was very low with a value of 19µmole/dm3. QSAR analysis also suggested that charge distribution on molecular surface and surface area are important determinants of the larvicidal activity. The derived models suggested that for the good larvicidal activity positively charged surface areas of the compounds should be limited. Moreover, there should be a balanced distribution of +ve and -ve charges on the molecular surfaces of the compounds.

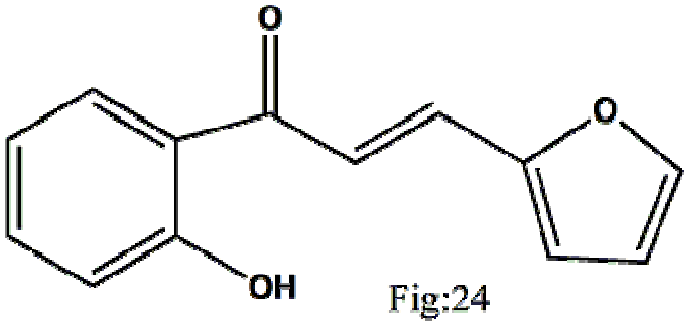


Fig:24

2.10. Anticonvulsant Activity

Some new phenoxy chalcones were prepared and screened for their anticonvulsant activity using Maximal Electroshock Method (MES) by Kaushik *et al* [20].Neurotoxicity study was performed using rotarod method. It was

found that substitution of 4-methoxy and 3,4-dimethoxy group in the substituted ring A of phenoxy chalcone showed significant anticonvulsant activity without neurotoxicity while hydrogen and chloro substitution does not showed the significant anticonvulsant activity.It was also found that the compounds'3-(4-methoxyphenyl)-1-(4 phenoxyphenyl) prop-2-en-1-one' **(25)** and '3-(3,4-dimethoxyphenyl)-1-(4 phenoxyphenyl)prop-2-en-1-one' **(26)** showed the most potent anticonvulsant activity without neurotoxicity.

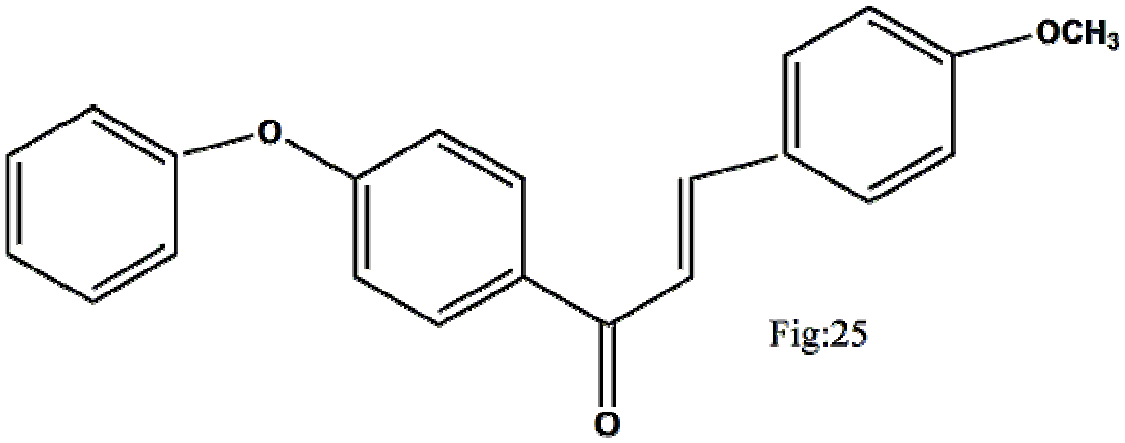


Fig:25

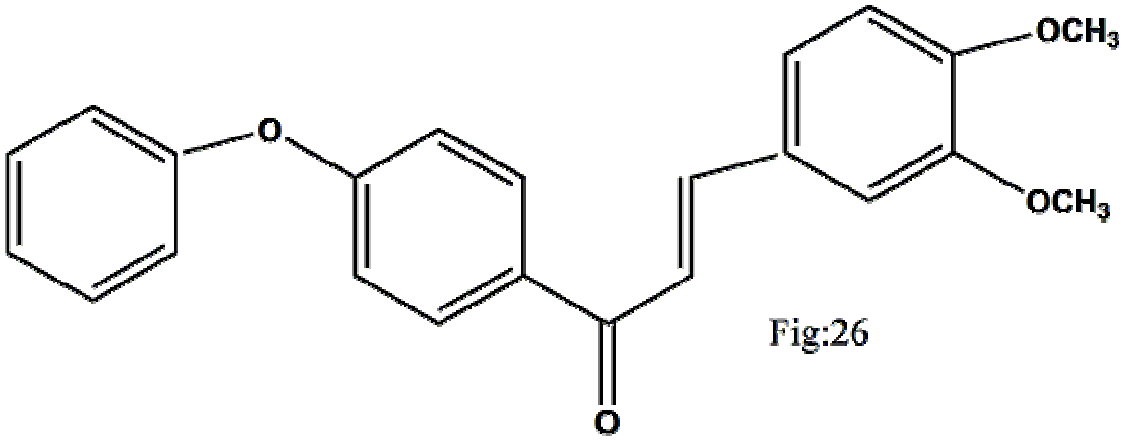


Fig:26

2.11. Antioxidant Activity

Vasil'ev *et al* [21] studied six anti-oxidants from the class of chalcones (ArOH), compounds from which flavonoids are obtained in nature. The antiradical activity of chalcones and a number of related compounds was determined by a chemiluminescence method using the scavenging of peroxide radicals ROO• + ArOH → ROOH + OAr• (with the rate constant *k*7) in a model reaction of diphenylmethane (RH) oxidation. The structures and energies of the reagents and intermediates were determined by semi-empirical quantum chemical (PM3, PM6) calculations. 3-(3,4-Dihydroxyphenyl)-1-phenylprop-2-en-1-one **(27)** and caffeic acid, which have a catechol structure, that is, two neighboring OH groups in phenyl ring A, exhibited high antioxidant activity ($k7 \approx 107$ l/mol/s); this is consistent with the lowest bond strengths *D*(ArO–H) of 79.2 and 76.6 kcal/mol, respectively. The abstraction of a hydrogen atom by the ROO• radical is the main reaction path of these compounds; however, the low stoichiometric co-efficients of inhibition ($f = 0.3$-0.7) suggested a contribution of secondary and/or side reactions of ArOH and OAr•. In the other chalcones, the ArO–H bond was stronger (*D*(ArO–H) = 83-88 kcal/mol) and the antioxidant activity was lower($k7 = 104$-105 l/mol/s).

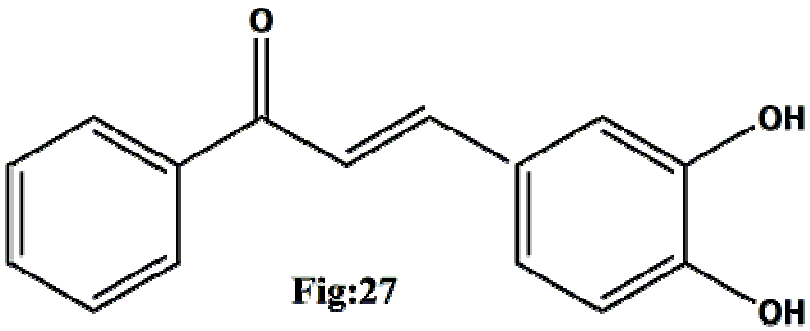


Fig:27

Sivakumar *et al* [22] synthesized 25 of chalcone derivatives and evaluated their antioxidant activity, and (QSAR). Antioxidant activity was evaluated through four different methods namely,superoxide radical-scavenging, hydrogen peroxide scavenging, reducing power, and DPPH radical-scavenging assays at 50 µg/ml *in vitro*. The antioxidant potential of the compound was related to its *(i)*hydrogen or electron donation capacity, *(ii)* its ability to stabilize and delocalize the unpaired electron, and*(iii)* potential to chelate transition metal ions. These actions were achieved either by the hydrogen atom or single electron transfer. In the case of ferric reducing anti-oxidant power (FRAP), it was due to the single electron transfer and in the cases of superoxide radical-scavenging, hydrogen peroxide scavenging, and DPPH radical-scavenging activities, it was due to the transfer of hydrogen atom. The antioxidant activity of the flavonoids was due to the inhibition of the enzyme responsible for the superoxide radical production, chelation of the metal ions and scavenging of ROS. Generally, compounds with –SCH3 and OCH3 in the *para* position of the ring A and –OH in the ring B were most active than others. The chalcone '1-(4-hydroxyphenyl)-3-(4-(methylthio)phenyl)prop-2-en-1-one' **(28)** was showing the highest superoxide radical-scavenging activity (>50%), reducing power activity (>46%), DPPH scavenging activity (>20%). In few cases, some of the compounds were more active than ascorbic acid or butylated hydroxyl toluene. QSAR was developed correlating the antioxidant activity with the structural features of the compounds and the predictive capability of the models was estimated using internal and external validation methods. All the predictions were within the 99% confidence level. Spatial, structural, and lipophilic properties of the compounds determined their antioxidant properties.

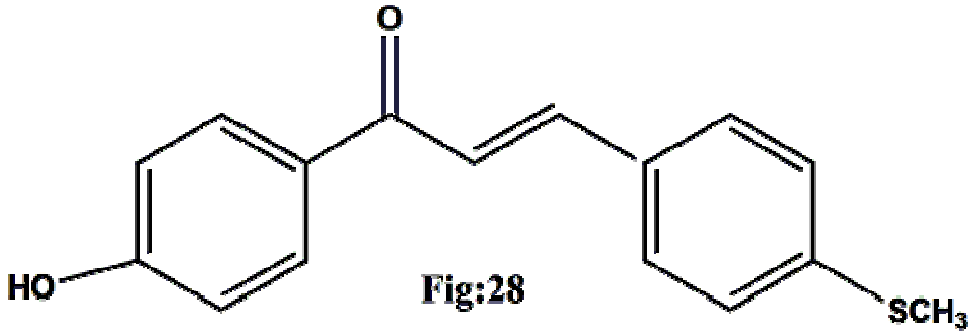


Fig:28

Vogel *et al* [23] established a general strategy for the synthesis of 3'-prenylated chalcones and synthesized a series of prenylated hydroxychalcones, including the hop *(Humulus lupulusL.)* secondary metabolites xanthohumol, desmethyl xanthohumol, xanthogalenol, and 4 methyl xanthohumol. They investigated the influence of the ring A hydroxylation pattern on the cytotoxic activity of the prenylated chalcones in a HeLa cell line and revealed that non-natural prenylated chalcones, like 2',3,4',5-tetrahydroxy-6'-methoxy-3'-prenylchalcone **(29)** (IC50 3.2 ± 0.4µM) as well as the phase I metabolite of xanthohumol, 3-hydroxy xanthohumol'1-(2,4-dihydroxy-6-methoxy-3-(3-methylbut-2enyl)phenyl)-3-(3,4-dihydroxyphenyl)prop-2-en-1-one'**(30)** (IC50 2.5 ± 0.5 µM), were more active in comparison to xanthohumol (IC50 9.4 ± 1.4 µM). A comparison of the cytotoxic activity of xanthohumol and 3-hydroxyxanthohumol with the non-prenylated analogs helichrysetin (IC50 5.2 ± 0.8) and 3-hydroxy helichrysetin(IC50 14.8 ± 2.1) showed that the prenyl side chain at C-3' has an influence on the cytotoxicity against HeLa cells only for the dihydroxylated derivative. This offers interesting synthetic possibilities for the development of more potent compounds. The ORAC (Oxygen Radical Absorbance Capacity) fluorescein activity of the synthesized compounds was also investigated for their antioxidant activity evaluation and revealed the highest

activity for the compounds helichrysetin'1-(2,4-dihydroxy-6-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one'**(31)**,4'methylxanthohumol,and desmethy lxanthohumol, with 4.4 ± 0.6, 3.8 ± 0.4, and 3.8 ± 0.5 Trolox equivalents,respectively.

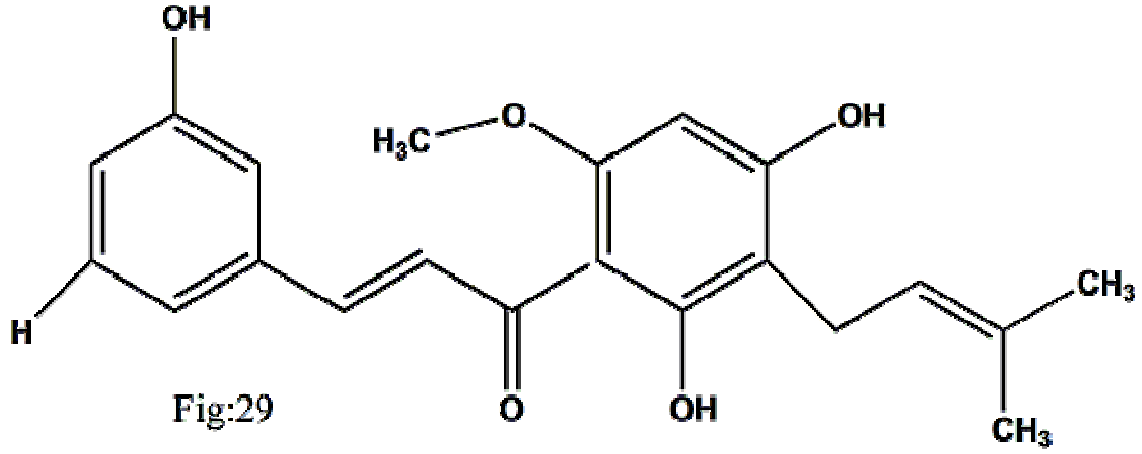


Fig:29

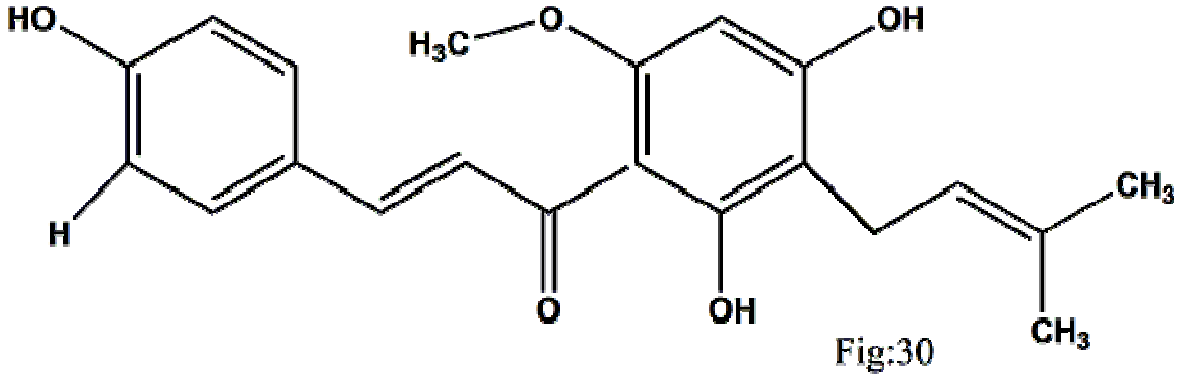


Fig:30

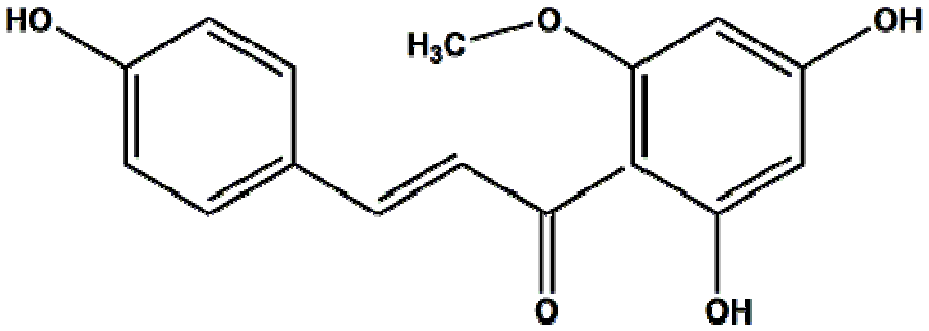


Fig:31

2.12. Cyclooxygenase (COX) Inhibitory Activity

Zarghi *et al*[25] synthesized chalones possessing a methanesulfonamido (MeSO2NH) or an azido (N3)pharmacophore at the *para*-position of the C-1 phenyl ring and evaluated their biological activity as cyclooxygenase-1/-2 inhibitors. *In vitro* COX-1/COX-2 structure-activity relationships were determined by varying the substituents on the C-3 phenyl ring (4-H, 4-Me, 4-F, and 4-OMe). Among the chalones possessing a C-1*para*-MeSO2NH COX-2 pharmacophore'1-(4-methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2-en-1-one'**(32)**was identified as a selective COX-2 inhibitor (COX-2 IC50 = 1.0 μM; selectivity index >100) that was less potent than the reference drug rofecoxib (COX-2 IC50 = 0.50 μM; SI > 200).The corresponding chalcone analogue possessing a C-1 *para*-N3 COX-2 pharmacophore'1-(4-azidophenyl)-3-(4-methylphenyl)prop-2-en-1-one' **(33)**, exhibited potent and selective COX-2 inhibition (COX-1 IC50 = 22.2 μM; COX-2 IC50 = 0.3 μM; SI = 60). A molecular modeling study where these two chalcones were docked in the binding site of COX-2 showed that the *p*-MeSO2NH and N3

substituents on the C-1 phenyl ring are oriented in the vicinity of the COX-2 secondary pocket (His90, Arg513, Phe518, and Val523).The structure-activity data acquired indicated that the propenone moiety constitutes a suitable scaffold to design new acyclic 1,3-diphenylprop-2-en-1-ones with selective COX-1 or COX-2 inhibitory activity.

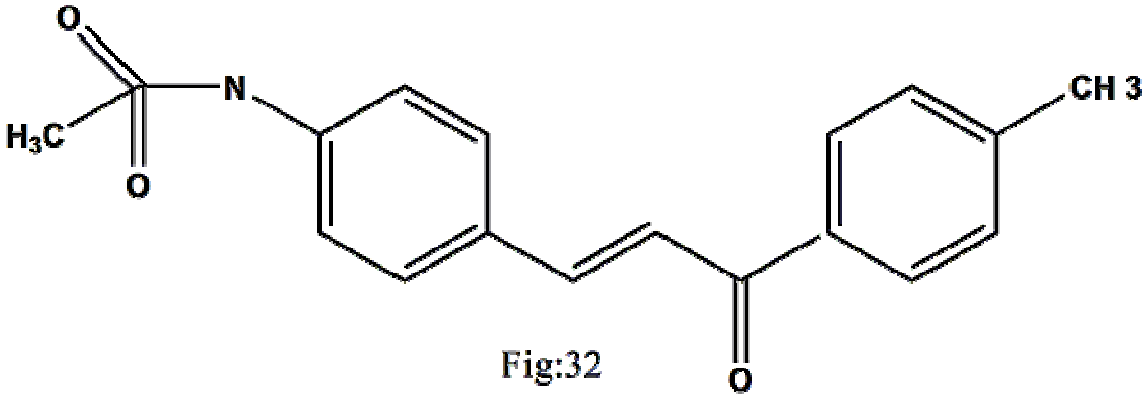


Fig:32

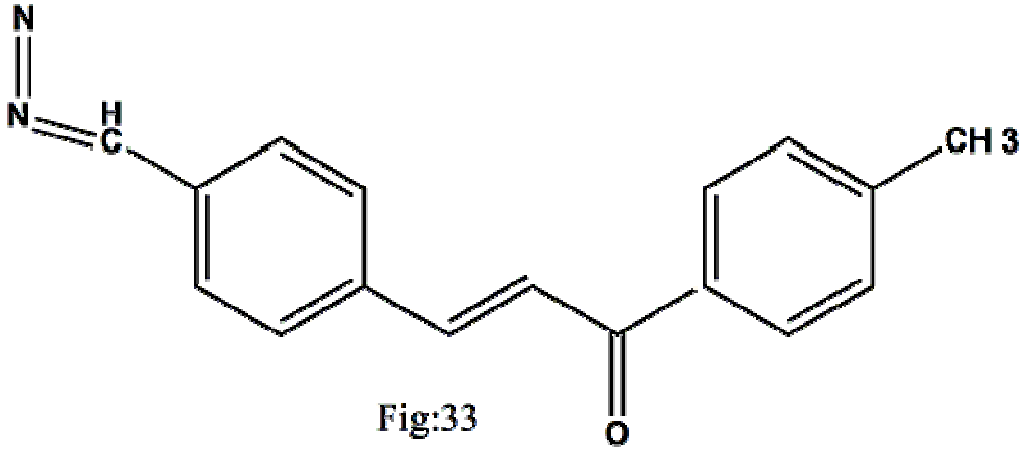


Fig:33

2.14. Monoamine Oxidases (MAOs) Inhibitory Activity

Chimenti *et al* [26] synthesized a large series of substituted chalcones tested *in vitro* for their ability to inhibit human monoamine oxidases A and B (hMAO-A and hMAO-B). The potential effects of the test drugs on hMAO activity were investigated by measuring their effects on the production of hydrogen peroxide (H2O2) from *p*tyramine using the Amplex Red MAO assay kit and microsomal MAO isoforms prepared from insect cells infected with recombinant baculovirus containing cDNA inserts for hMAO-A or hMAO-B. While all the compounds showed hMAO-B selective activity in the micro- and nano-molar ranges, the best results were obtained in the presence of chlorine and hydroxyl or methoxyl substituents.The most active compounds,'3-(4-chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one'**(34)**and'3-(4-chlorophenyl)-1-(2,4dihydroxy phenyl) prop-2-en-1-one'**(35)** (IC50=0.0044+0.00027 µM and 0.0051+0.00019 µM, respectively), are disubstituted in the 2- and 4-position of the B aromatic moiety with two hydroxyls or hydroxyl and methoxy groups and in 4'-position of the A aromatic moiety with a chlorine atom.

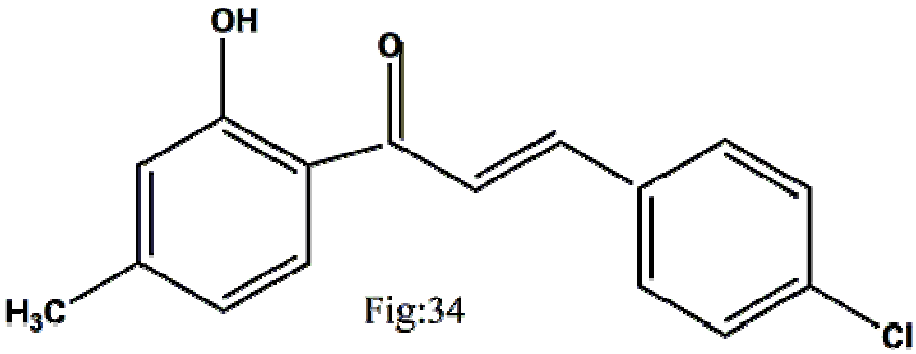


Fig:34

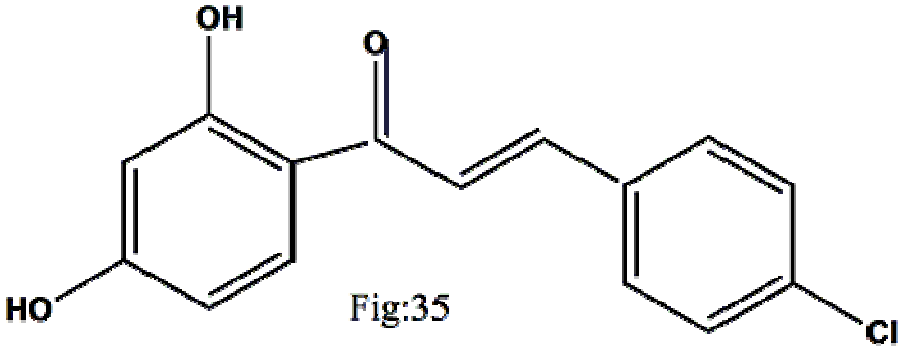


Fig:35

To better understand the enzyme-inhibitor interaction and to explain the selectivity of the most active compounds toward hMAO-B, molecular modeling studies were carried out on new, high resolution, hMAO-B crystallographic structures. For the only compound that also showed activity against hMAO-A as well as low selectivity, the molecular modeling study was also performed on the hMAO-A crystallographic structure. The docking technique provided new insight on the inhibition mechanism and the rational drug design of more potent/selective hMAO inhibitors based on the chalcone scaffold. In the reversibility and irreversibility tests, hMAO-B inhibition was found to be irreversible in presence of the compounds‘3-(4-chlorophenyl)-1-(2-hydroxy-4-methoxyphenyl) prop-2-en-1-one’and‘3-(4-chlorophenyl)-1-(2,4dihydroxy phenyl) prop-2-en-1-one’ (chosen for docking experiments).

CONCLUSION

From the above review, it can be said that chalcones and their derivatives display a wide range of pharmacological activities, such as antimalarial, anticancer, antiprotozoal(antileishmanial and antitrypanosomal), antiinflammatory, antibacterial, antifilarial, antifungal, antimicrobial, larvicidal, anticonvulsant and antioxidant activities. They also show inhibition of the enzymes, especially mammalian alpha-amylase, cyclooxygenase (COX) and monoamine oxidase (MAO) and antimitotic activity too. Because of this, chalcones and their derivatives have attracted increasing attention of the scientists for the search of new potent pharmacological activity in it.

Acknowledgement
The author is thankful to KC Reddy Institute of Pharmaceutical Sciences, Jangamguntapalem, Medikonduru,Guntur District for availing the facilities of Computer Laboratory, text- and e-journal access in their library sections.

REFERENCES

[1] Motta LF, Gaudio AC, Takahata Y, **2006**. *Internet Electronic Journal of Molecular Design*, 5:555-569.
[2] Awasthi SK, Mishra N, Kumar B, Sharma M, Bhattacharya A, Mishra LC, Bhasin VK, **2009**. *Medicinal Chemistry Research*, 18:407-420.
[3] Cheng MS, Shili R, Kenyon G, **2000**. *Chinese Chemical Letters*, 11:851-854.
[4] Lim SS, Kim HS, Lee DU, **2007**. *Bulletin of the Korean Chemical Society*, 28:2495-2497.
[5] Achanta G, Modzelewska A, Feng L, Khan SR, Huang P, **2006**. *Molecular Pharmacology*, 70:426-433.

[6] Romagnoli R, Baraldi PG, Carrion MD, Cara CL, Cruz-Lopez O, Preti D, **2008**. *Bioorganic and Medicinal Chemistry*, 16:5367-5376.
[7] Echeverria C, Santibanez JF, Donoso-Tauda O, Escobar CA, Tagle RR, **2009**. *International Journal of Molecular Sciences*, 10:221-231.
[8] Szliszka E, Czuba ZP, Mazur B, Sedek L, Paradysz A, Krol W, **2010**. *International Journal of Molecular Sciences***,** 11:1-13.
[9] Ilango K, Valentina P, Saluja G, **2010**. *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 1:354-359.
[10] Lunardi F, Guzela M, Rodrigues AT, Corre R, Eger-Mangrich I, Steindel M, Grisard EC, Assreuy J, Calixto JB, Santos ARS, **2003**. *Antimicrobial Agents and Chemotherapy*, 47:1449-1451.
[11] Yadav HL, Gupta P, Pawar PS, Singour PK, Patil UK, **2010**. *Medicinal Chemistry Research*, 19:1-8.
[12] Zhang XW, Zhao DH, Quan YC, Sun LP, Yin XM, Guan LP, **2010**. *Medicinal Chemistry Research*, 19:403-412.
[13] Hamdi N, Fischmeister C, Puerta MC, Valerga P, **2010**. *Medicinal Chemistry Research*, 19:1-16.
[14] Bhatia NM, Mahadik KR, Bhatia MS, **2009**. *Chemical Papers*, 63:456-463.
[15] Awasthi SK, Mishra N, Dixit SK, Singh A, Yadav M, Yadav SS, Rathaur S, **2009**. *American Journal of Tropical Medicine and Hygiene*, 80:764-768.
[16] Bag S, Ramar S, Degani MS, **2009**. *Medicinal Chemistry Research*, 18:309-316.
[17] Lahtchev KL, Batovska DI, Parushev SP, Ubiyvovk VM, Sibirny AA, **2008**. Eur*opean Journal of Medicinal Chemistry*, 43:2220-2228.
[18] Yayli N, Ucuncu O, Yasar A, Kucuk M, Akyuz E, Karaoglu SA, **2006**. *Turkish Journal of Chemistry*, 30:505-514.
[19] Begum NA, Roy N, Laskar RA, Roy K, **2010**. *Medicinal Chemistry Research*, 19:1-14.
[20] Kaushik S, Kumar N, Drabu S, **2010**. *The Pharma Research*, 3:257-262.
[21] Vasil'ev RF, Kancheva VD, Fedorova GF, Batovska DI, Trofimov AV, **2010**. *Kinetics and Catalysis*, 51:507-515.
[22] Sivakumar PM, Prabhakar PK, Doble M, **2010**. *Medicinal Chemistry Research*, 19:1-17.
[23] Vogel S, Ohmayer S, Brunner G, Heilmann J, **2008**. *Bioorganic & Medicinal Chemistry*. 16:4286-4293.
[24] Najafian M, Ebrahim-Habibi A, Hezareh N, Yaghmaei P, Parivar K, Larijani B, **2010**. *Molecular Biology Reports*, 10:271-274.
[25] Zarghi A, Zebardast T, Hakimion F, Shirazi FH, Rao PNP, Knaus EE, **2006**. *Bioorganic and Medicinal Chemistry*, 14:7044-7050.
[26] Chimenti F, Fioravanti R, Bolasco A, Chimenti P, Secci D, Rossi F, Yanez M, Francisco OF, Ortuso F, Alcaro S,**2009**. *Journal of Medicinal Chemistry*, 10:1-8.
[27] Wu MH, Yang XH, Zou WD, Liu WJ, Li C, **2006**. *Zeitschrift fur Kristallographie*, 221:323-324.
[28] Siddiqui AA, Rahman MA, Shaharyar M, Mishra R, **2010**. *Chemical Sciences Journal*, 2010: CSJ-8.