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Review Article

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Chalcone and their Heterocyclic Analogue: A Review Article

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ABSTRACT

Chalcones are natural product belongs to Flavonoid family. Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system. They contain keto ethylenic group (-CO-CH=CH) and exist in cis and trans form due to the presence of double bond in which trans form is thermodynamically more stable. Various structural modifications of the heterocyclic analogs chalcone synthesized have been made to explore its promising biological potential in recent years. The various pharmacological activity is antihypertensive, antifungal, anticancer, anti-filarial, anti-protozoal, anti-HIV, antimalarial, antioxidant, antiviral, antifungal, anticonvulsant, antibacterial.

Keywords: Chalcones; Flavonoid; Antibacterial; Antifungal; Anticancer

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INTRODUCTION

The term "Chalcones" was coined by Kostanecki and Tambor. Chalcones are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three carbon α, β-unsaturated carbonyl system. These compounds are also known as benzalacetophenone or benzylidene acetophenone. Chalcone are aromatic ketone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones. Chalcone are class of natural product. These are considered as precursor of flavones in the biosynthesis of flavonoids and isoflavonoids and generally obtained from edible plants. Chalcones are widely spread in nature (fruits, vegetables, spices, tea and soy-based food stuff) and their 2'-hydroxy derivatives play an important role in the flavonoid synthesis and biosynthesis as both precursors and products. They show various pharmacological action such as antibacterial, antifungal, antitumor and anti-inflammatory properties. Chalcones are also intermediates in the Auwers synthesis of flavones. Chalcones can be prepared by an aldol condensation between a benzaldehyde and an acetophenone in the presence of sodium hydroxide as a catalyst. This reaction has been found to work in without any solvent at all - a solid-state reaction [1]

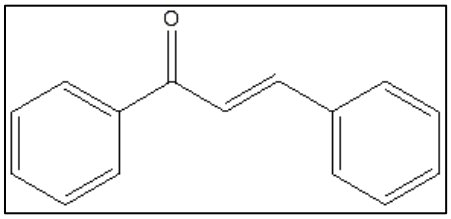


Figure 1: Chalcones

Chalcones possess conjugated double bonds and a completely delocalized Π-electron system on both benzene rings. Molecules possessing such system have relatively low redox potentials and have a greater probability of undergoing electron transfer reactions. Chalcones, also known as a-b-unsaturated ketones (Figure 1), are not only important precursors for synthetic manipulations but also form a major component of the natural products. Chalcones as well as their synthetic analogues (Figure 1) display enormous number of biological activities [2]. Chalcones are -unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. The presence of double bond in conjugation with carbonyl functionality is believed to be responsible for the biological activities of chalcones, as removal of this functionality make them inactive. They have the tendency to exist both in cis- and trans- forms and can easily be cyclized to form flavanones via Michael addition. A number of synthetic routes have been reported for synthesis of chalcones while their general synthesis involves Claisen-Schmidt condensation under homogeneous conditions in the presence of acid or base [3-5]. Traditionally, strong alkaline media including natural phosphates, $Ba(OH)_2$, KOH, NaOH, LiHMDS etc. have been employed for their synthesis [6-11]. The use of several lewis acids (p-toluene sulfonic acid, B_2O_3, $RuCl_3$, $AlCl_3$, BF_3 and dry HCl) in has also been demonstrated [12-17]. The conjugated double bond produces the delocalization of π electrons which reduces its electrophilic character and makes it an intermediate for the synthesis of various biologically important heterocycles such as pyrazoline, oxazoline, thiazine, oxazine, pyrimidine etc. Thus, synthesis of chalcones has generated vast interest to organic as well as medicinal chemists [18]. Formation of these nuclei involves cyclization of α-β unsaturated system of chalcones.

Physical Properties of Chalcone

The physical properties of chalcone are as follows (Table 1):

Table 1: Physical properties of chalcone

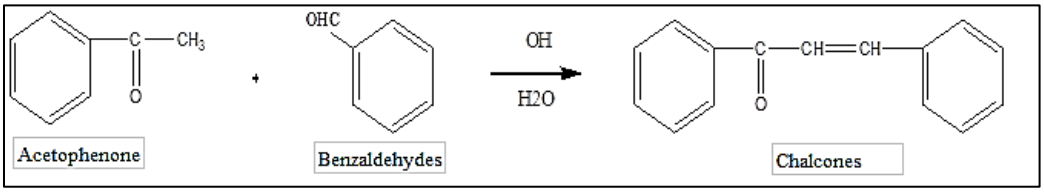
Molecular formula:	$C_{15}H_{12}O$
Molar mass:	208.26 g mol^{-1}
Exact mass	208.088815
Density	1.071
Melting point	55–57°C
Boiling point	345-348°C

Synthetic Methods for Chalcones

There are mainly two modes for the synthesis of Chalcones:
By the condensation of acetophenones with benzaldehydes (Claisen-schmidt condensation)
By the condensation of phenols with cinnamoyl chloride by Friede1-Crafts reaction.

Condensation of acetophenones with benzaldehydes (Claisen-schmidt condensation):

Claisen-Schmidt condensation is most convenient method for the synthesis of chalcones. The equimolar quantities of acetophenone and benzaldehydes are condensed in the presence of aqueous alcoholic alkali [19-26]. In the Claisen-Schmidt reaction, the concentration of alkali used, usually ranges between 10 and 60%. The reaction is carried out at about 50°C for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizzaro reaction also takes place and thereby decreases the yield of the desired product. To avoid the disproportionation of aldehyde in the above reaction, the use of benzylidene-diacetate in place of aldehyde has been recommended.



Various condensing agents used in synthesis of chalcones:

Alkali

Alkali has been the most used condensing agents for synthesis of chalcones. It is used as an aqueous solution of suitable concentration viz. 30%, 40%, 50% and 70%.

Hydrochloric Acid

Dry hydrochloric gas in a suitable solvent like ethyl acetate at 0°C was used as a condensing agent in a few syntheses of chalcones from aromatic ketones. Methanolic solution of dry hydrochloric acid gas at 0^{o}C was also used by Lyle, Paradis and Marathey.

Other Condensing Agents

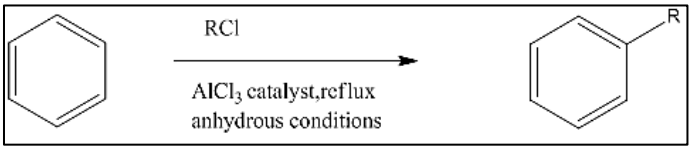
Raval and Shah used phosphorous oxychloride as a condensing agent to synthesize of chalcones. Szell and Sipos condensed 2-hydroxy-5-nitroacetophenone with benzaldehyde using anhydrous AlCl3. Kuroda, Matsukuma and Nakasmura obtained chalcone by condensing acetophenone derived from anisole and other polymethoxy benzenes with some methoxyaldehydes in presence of anhydrous aluminium chloride.

Besides the above, other condensing agents used in synthesis of
chalcones have been,

(1) Amino acid
(2) Aqueous solution of borax
(3) Perchloric acid
(4) Piperidine
(5) Boron trifloride
(6) Alkali metal alkoxide
(7) Magnesium tert-butoxide
(8) Organocadmium compound

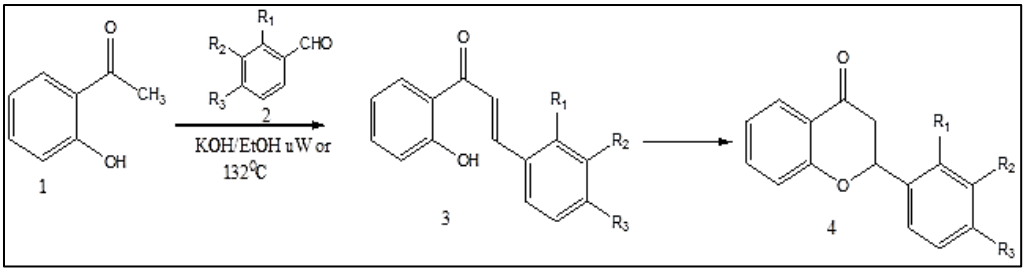
By the condensation of phenols with cinnamoyl chloride by Friedel-Crafts reaction:

Besides the Claisen-Schmidt reaction, chalcones can also be synthesized by direct Friedel-Crafts acylation of a phenol [27]. In this approach the phenol becomes the A-ring while the acylating agent provides both the B-ring carbons and the three-carbon bridge to form C6-C3-C6 unit. Friedel-Crafts acylation of 2,4-dimethyl-1,3,5-triolbenzene with 3- phenyl propionyl chloride gave 2',4',6'-trihydroxy-3',5'-dimethylchalcone. The Friedel– Crafts reactions are a set of reactions developed by Charles Friedel and James Crafts in 1877 to attach substituents to an aromatic ring. There are two main types of Friedel–Crafts reactions: alkylation reactions and acylation reactions. Both proceed by electrophilic aromatic substitution. The general reaction is shown below.



Microwave assisted synthesis: [28]

The Claisen–Schmidt condensation stays the most common method in homogeneous phase or in interfacial solid-liquid conditions using barium hydroxide catalyst (C-200). Unfortunately, 2'-hydroxychalcones always cyclized to flavanones. One synthetic pathway to avoid this undesirable reaction is using protective group or the Friedel–Crafts reaction of phenols with acyl halides. This method requests long reaction time and anhydrous conditions which limits the scope of its application. Convenient reaction procedure for the synthesis of 2'-hydroxychalcones with very good yields without formation of by-products. By applying successful microwave irradiation for the preparation of target molecules. The reaction took place in well closed pressure tube for 2 min with high yields. It is noteworthy to mention that to carry out the reaction in an open vessel failed. A mixture of two products (3 and 4) and starting compounds was obtained in this case. Obviously, the well closed tube affords to reach temperatures much higher than boiling point of ethanol. The measured temperature in the reaction tube immediately after the irradiation was 132°C.



Chemical Modifications of Chalcones

Flavonoids: [29]

Flavonoids or bioflavonoids are a ubiquitous group of polyphenolic substances which are present in most plants. Flavonoids have been shown to have antibacterial, anti-inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, anti-thrombotic and vasodilatory activity. The potent antioxidant activity of flavonoids their ability to scavenge hydroxyl radicals, superoxide anions and lipid peroxy radicals may be the most important function of flavonoids. The structural components common to these molecules include two benzene rings on either side of a 3-carbonring. Multiple combinations of hydroxyl groups, sugars, oxygen, and methyl groups attached to these structures create the various classes of flavonoids; flavanols, flavanones, flavones, flavan-3-ols (catechins), anthocyanins and isoflavones.

General Procedure for the Synthesis of Flavanone [30]

Reflux a solution of the 2'- hydroxychalcone (1 equiv) in AcOH glacial (25.0 ml/mmol of 2'-hydroxychalcone) for 72 hr. Pour the mixture into water. Extract with EtOAC (3x25.0ml). Wash the organic layer with brine until neutrality and dry with MgSO4 anhydrous. Evaporate the solvent in vacuum. Purify the residue by chromatographic column (SiO2, petroleum ether methylene dichloride (0-30%).

Synthesis of 3, 5-diphenyl-4, 5- dihydro-1, 2-oxazole: [31]

Dissolve anhydrous sodium acetate (0.02mole) in hot acetic acid. Add hydroxylamine hydrochloride (0.01 mol) in absolute alcohol (10ml) to the solution of chalcone in ethanol. Transfer the solution of sodium acetate in acetic acid to this reaction mixture and reflux for 10 hr. Pour the reaction mixture into ice cold water, Filter the product and recrystallize with ethanol.

Synthesis of 1, 3, 5-triphenyl-4, 5- dihydro-1H-pyrazole: [31]

To a mixture of chalcone and phenyl hydrazine (0.01 mol) in absolute alcohol, add catalytic amount of pyridine and reflux reaction mixture for 5-8 hr. Cool the reaction mixture, Pour slowly into crushed ice with stirring. Filter the solid product. Dry and recrystallize with ethanol.

Importance of Chalcones:

(1) They have close relationship with flavones, aurones, tetralones and aziridines.

(2) Chalcones and their derivatives find application as artificial sweeteners [32-36], scintillator [37], polymerization catalyst [38], fluorescent whitening agent, organic brightening agent, stabilizer against heat, visible light, ultraviolet light and aging.

(3) 3,2',4',6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside has been used as synthetic sweetener and is 2200 times sweeter than glucose.

(4) They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g. (a) phenyl hydrazine,

(b) 2-amino thiophenol etc.

(5) The chalcones have been found useful in elucidating structure of natural products like hemlock tannin, cyanomaclurin' phloretin, eriodyctiol and homo eriodyctiol, naringenin.

Ashitaba as A Natural Chalcone:

Ashitaba is a lush green plant found on the Island of Hachijo where the warm tropical currents pass by on their way North to meet the cold Arctic waters of the Pacific Ashitaba's scientific name, Angelica keiskei Koidzumi, comes from the Latin name for angel," most likely due to its "heavenly", well known health benefits that have given it such

notoriety. The inhabitants of Hachijo Island are well known for their longevity, having some of the longest life spans on earth (i.e. many commonly live well into their 90's in good health). Ashitaba has been an integral part of their diet for hundreds of years. Scientists discovered ashitaba is only plant that contain chalcone moiety a potent flavonoid this is main reason for long term resident of Island of Hachijo the chalcones in ashitaba include xanthoangeol, xanthoangelol E and 4-hydroxyderricin. Clinical trials performed on chalcones confirm that they are potent antioxidants which help to protect the organs from destructive free radical damage and slow the aging process on a cellular level Extensive research has shown chalcones are also anti-infective to prevent pathogens from entering into cells. Chalcone generally work on mucus membrane of stomach & suppresses excessive secretion of gastric juice. It inhibits general inflammation process in the body which is said as true of all flavonoids present naturally or synthetics chalcone.

Spectral Features of Chalcones

UV spectra of chalcones:

The major absorption band in chalcones (Band I) usually occurs in the range 340-390 nm, although chalcones lacking B-ring oxygenation may have their Band I absorption at considerably shorter wavelengths and Band II is usually a minor peak in the 220-270 nm region. In the spectra of chalcones containing a free 4"-hydroxyl group, the addition of NaOMe causes a 60-100 nm bathochromic shift of Band I with an increase in peak intensity. Chalcones without a 4"-hydroxyl group but with either a free 2" or 4'- hydroxyl group also give, in the presence of NaOMe, a 60-100 nm bathochromic shift of Band I but without an increase in peak intensity [16,17]. UV spectroscopy proved useful to distinguish between substituted chalcones and flavanones, which is not possible by EI mass spectrometry due to thermal isomerization of 2'-hydroxychalcones in the ion source [39-40].

IR spectra of Chalcones

The α, β-unsaturated carbonyl group, characteristic of a chalcone usually appear as a prominent band in between 1625-1650 cm-1 in its IR spectrum [41-42]. The region at which other absorption bands appear depends on the type of aromatic/ heteroaromatic rings as well as the substituents present on these rings.

NMR spectra of Chalcones

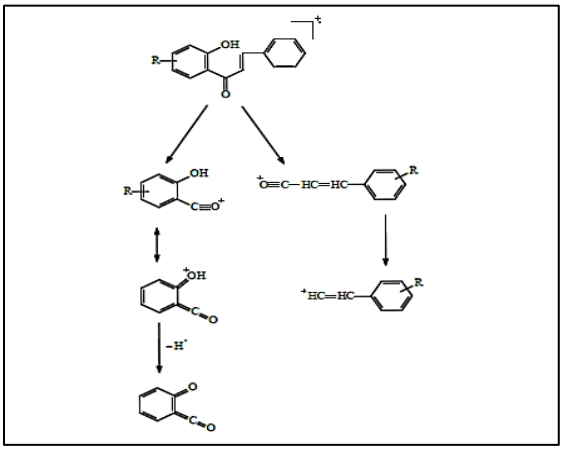
The H-α and H-β protons of chalcones occur as two doublets (J= 17 Hz) in the ranges 6.7 - 7.4 ppm (H- α) and 7.3 - 7.7 ppm (H- β) in the 1H NMR spectra [43]. The other aromatic protons usually appear in between δ 6.9-8.0, depending on the type of aromatic / heteroaromatic ring and also based on the electronic effects of the substituents present on these rings. The large J value (17 Hz) clearly reveals the *trans* geometry at the double bond. The carbonyl carbon of the chalcones usually appears between δ 188.6 and 194.6 in its 13C NMR spectrum [44]. The α and β-carbon atoms with respect to the carbonyl group give rise to characteristic signals in between δ 116.1-128.1 and δ 136.9-145.4 respectively, which can also be readily identified by their characteristic appearance as a six-line multiplet in the half resonance decoupled spectrum [45]. The presence of 2'-hydroxy group shifts the carbonyl carbon shift downfield by 3 ppm relative to corresponding acetoxy and methoxy compounds, presumably owing to hydrogen bonding. The β-hydroxychalcones are a relatively small group of chalcones that occur naturally sometimes as the enol-tautomers of dibenzoylmethane derivatives. The extent of keto-enol tautomerism is largely solvent dependent, and nuclear magnetic resonance spectroscopy (NMR) provides one of the best methods to determine the ratio of the tautomers present. In the 1H NMR spectra recorded in CDCl3, the exchangeable proton of the β-OH of the enol tautomer appears as a 1H singlet at δ 16.0, whereas the α-CH2 protons of the keto tautomer appear as a 2H singlet at δ 4.50. Another diagnostic resonance is the 1H methine singlet of the enol tautomer (α-CH), which is found at δ 6.5, with its corresponding C- α resonance at δ 90 to 92 in the 13C NMR spectra [46-47].

Mass spectra of Chalcones

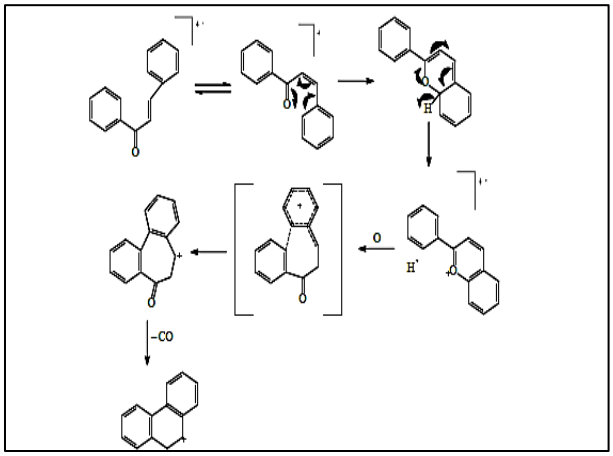
Cleavage of the heterocyclic C-ring via a Retro Diels-Alder (RDA) mechanism represents an important fragmentation pathway in chalcones. RDA fission leads to two characteristic fragments, which provides useful information as to the number of hydroxyl, methoxyl and other substituents on each ring [48] (Scheme 1). The same information was also obtained by a HPLC-tandem mass spectrometer system equipped with a heated nebulizer-atmospheric pressure chemical ionization (APCI) interface [49]. The EIMS of chalcones also give rise to the unusual fragment ion $(M-H)^+$ involving a type of intramolecular aromatic substitution reaction by the elimination of an *ortho* substitutent from an aromatic ring with further cyclization. This results in the formation of a highly stabilized benzopyrylium cation [50] (Scheme 2) and this type of fragmentation is sometimes known as proximity effect. The

cation so formed undergoes structural rearrangements, which permits fragmentation pathways that may eventually lead to loss of CO [51-53].

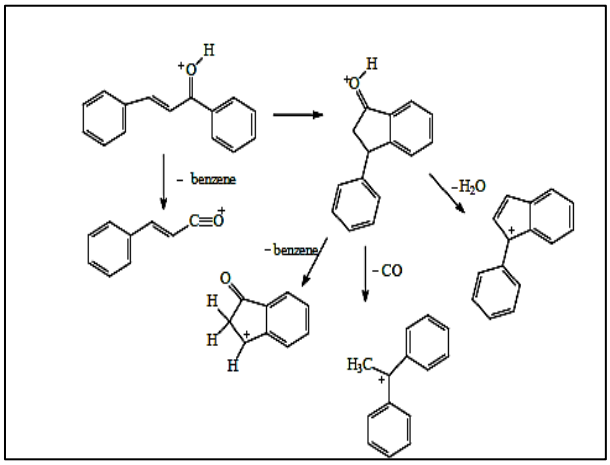
Protonated chalcones generated by electrospray ionization during MS/MS experiments were found to form three important fragment ions due to loss of H2O, CO and benzene Scheme 3.



Scheme 1: hydroxyl, methoxyl and other substituents



Scheme 2: Stabilized benzopyrylium cation



Scheme 3: Electrospray ionization

Heterocyclic Chalcones and Their Role in Biological Activity

Heterocyclic chalcones were prepared and obtained that these scaffolds have various biological activity such as antibacterial, anticancer, anti-HIV, anthelmintic, antimalarial, anti-fungal, anti-inflammatory, MAO inhibition, anti-angiogenic and anti-leishmanial activities. In the current scenario, a brief coverage of such activities is outlined below

Thiophene analogue:

Vasconcelos et al. [54] synthesized a series of thiophene based chalcones (Figure 2) from 2-acetyl thiophene and substituted aromatic aldehyde. All synthesized derivatives were assayed for cytotoxicity parameter on human colon adenocarcinoma cells. Firstly, the cytotoxic activity was tested on HT-29 cells of chalcones. Among tested compounds, 3-(4-bromophenyl)-1-(thiophen-2-yl) prop-2-en-1-one and 3-(2-nitrophenyl)-1-(thiophen-2-yl) prop-2-en-1-one showed greater cytotoxicity in the MTT assay (is a colorimetric assay for assessing cell metabolic activity), having the minimum IC_{50} values in all exposure times. Further apoptotic and non-apoptotic mechanism was studied to obtain the cell death caused by compound. The scientist concluded that the cytotoxic activity of chalcones on colorectal carcinoma cells occurs by apoptosis.

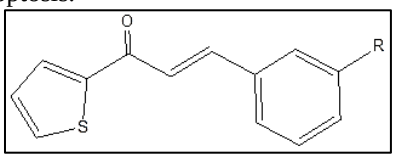


Figure 2: R= 2-nitro, 3-nitro, 4-nitro, 4-methoxy, 4-bromo

Furan analogue:

Robinson et al. [55] synthesized some selected furan based chalcones (Figure 3) and tested their MAO-A and MAO-B inhibitory activity. The results observed that these furans substituted phenyl propanone's are moderate to good inhibitory activities towards MAO-B but shows weak or no inhibition of the MAO-A enzyme. The most potent compound, 2E-3-(5-chlorofuran-2-yl)-1-(3-chlorophenyl) prop-2-en-1-one exhibit an IC_{50}value of 0.174 M for the inhibition of MAO-B and 28.6 M for the inhibition of MAO-A. The scientist concluded that furan chalcone which consist of a phenyl ring substituted with electron-withdrawing substituents, and a substituted furan ring are potent and selective MAO-B inhibitors.

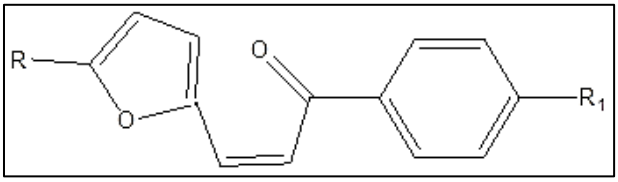


Figure 3: R= 5-bromo, 5-methyl, 5-chloro; R1= phenyl, 3-cholorophenyl, 3-methoxyphenyl

Thiazole analogue:

Rizvi et al. [56] synthesized a series of piperidyl-thienyl chalcones (Figure 4) and were screened for cytotoxic and anti-HIV-1activities. The synthetic process involved the reaction between 4-piperidin-1-ylbenzaldehyde nucleus and various substituted 2-acetyl thiophene derivatives. According to the results obtained, it is evident that the unsubstituted thienyl derivatives of chal-cones demonstrated no anti-HIV-1 activity, while the activity was considerably enhanced by the substitution of methyl and halo groups at position 3 of the thienyl ring. In these thiophene based chalcones,1-(3-methylthiophen-2-yl)-3-(4-(piperidin-1-yl) phenyl) prop-2-en-1-one demonstrated the most potent anti-HIV-1 activity (EC_{50}= 2.5M). It has been also noted that none of the compounds were more potent than the positive control 3-Azido-3-deoxythymidine (AZT).

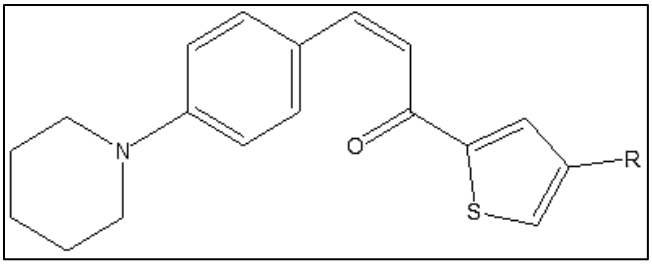


Figure 4: R=H, 3-methyl, 4-methyl, 5-methyl, 3,5-dimethyl, 3-chloro, 5-choloro, 3-bromo, 5-bromo, 5-iodo

Thiophene and furan analogue:

Solomon and Lee [57], a new series of thiophene chalcone compounds (Figure 5) were designed, synthesized, and examined for their antiproliferative effects on two breast cancer cell lines and one matching non-cancer breast cell line. It exhibited generally better antiproliferative activity than those derived from bioisoteric replacement of furan chalcones on MDA-MB231 breast cancer cells. They also a new series of furan compound designed (Figure 5) the compounds derived from furan chalcones showed generally better antiproliferative activity on MDA-MB468breast cancer cells. In these series 1-(4-chlorophenyl)-3-(5-(4-methoxyphenyl) furan-2-yl) prop-2-en-1-one was considered to be most desirable among this series, since its antiproliferative activity was 3 to 7-fold higher on cancer than non-cancer cells. They concluded that if this property shown in cell culture stands in vivo test, compound could be an effective and safe anticancer drug.

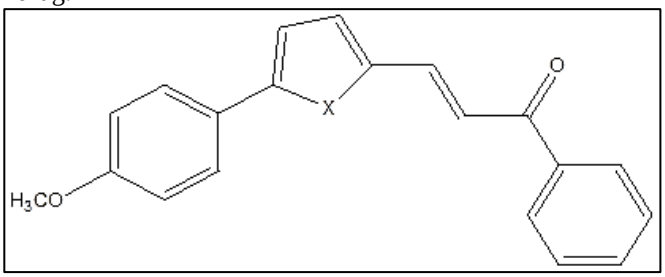


Figure 5: X= S, O

Lee et al. [58] screened the heteroaryl chalcones such as 3-phenyl-1-thiophen-2-yl-propenone (Figure 6) and 1-furan-2-yl-3-phenyl-propenone (Figure 7) for their inhibitory effect on VEGF-induced angiogenesis in vitro using HUVECs and in vivo using chick chorioallantoic membrane (CAM). In this study they compared the anti-angiogenic activities of phenyl propanone derivatives and they obtained that 1,2-diphenyl-2-propenone chalcone was most potent anti-angiogenic compound among the tested compound. They indicate the importance of the phenyl at 1-position of the phenyl propanone moiety for anti-angiogenic activity.

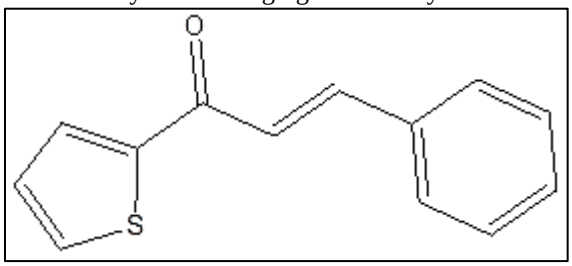


Figure 6: 3-phenyl-1-thiophen-2-yl-propenone

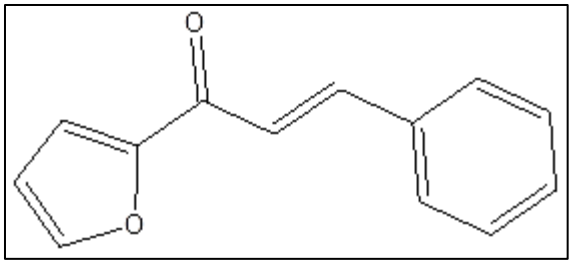


Figure 7: 1-furan-2-yl-3-phenyl-propenone

Indole analogue:

Zahran et al. [59] synthesized a series of novel Indole based chalcones (Figure 8) by the Claisen-Schmidt condensation with N-substituted indole-3-carbaldehyde and1-biphenyl-4-yl-ethanoneand evaluated their antitumor activity. All the newly synthesized indole chalcones were screened for in vitro antitumor activity by trypan blue exclusion method. Kumar et al [60], a series of indolyl chalcones (Figure 9) were synthesized and evaluated in vitro for their anticancer activity against three human cancer cell lines. All the indolyl chalcones were assayed for their in vitro cytotoxicity against three human cancer cell lines: epithelial (A-549), pancreatic carcinoma (PaCa-2) and androgen-independent human prostatic adenocarcinoma (PC-3). In their research the indolyl chalcone with the para methoxy phenyl group exhibited good activity. Introduction of a second methoxy group improved its activity ratio. They also concluded that N-methylation of indole ring nitrogen does not improve the activity. Cui et al. [61], a series of chalcone derivatives containing an indole moiety (Figure 10) were evaluated in competitive binding assays with $A\beta_{1-42}$ aggregates versus [^{125}I] IMPY. The affinity of these compounds ranged from 4.46 to > 1008 nM, depending on the substitution on the phenyl ring.

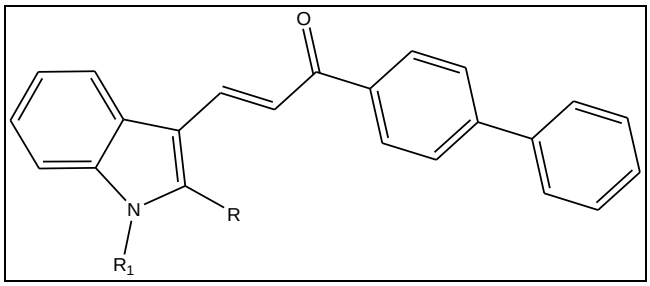


Figure 8: R= H, Phenyl,4-methylphenyl,4-chorophenyl,4-fluorophenyl allyl, benzyl, ethyl

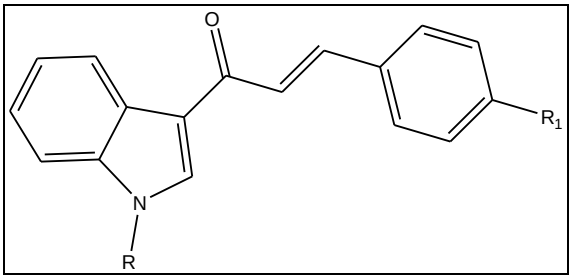


Figure 9: R= H, CH_3; R1= p-OH, p-OCH_3, p-F,3,5-OCH_3

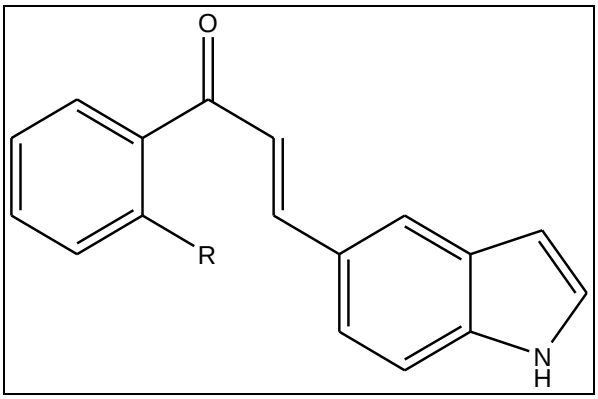


Figure 10: R= 4-fluro, 4-chloro, 4-bromo, 4-iodo, 4-methoxy, 4-hydroxy, 4-amino, 4-methyl, 4-dimethyl amino

Benzimidazole analogue:

Nofal et al. [62] synthesized series of 1-(1H-benzimidazol-2-yl)-3-(substituted)-2-propen-1-ones and cyclized with different reagents such as ethyl cyanoacetate, thiourea, hydroxylamine hydrochloride, guanidinium sulfate, methylhydrazine, phenyl-hydrazine and hydrogen peroxide in different reactions to produce pyridines, pyrimidinethione, isoxazole, amino pyrimidine, pyrazoline, epoxy derivatives and evaluated their anticancer derivatives. In this series (2E)-1-(1H-benzimidazol-2-yl)-3-(3,4, 5-trimethoxyphenyl) prop-2-en-1-one (Figure 11) was the most active compound in PC12 cell line showing (IC_{50}= 0.103 mM). Ouattara et al. [63] synthesized benzimidazole chalcone derivatives (Figure 12), evaluate their anthelmintic activity. Their results suggested that unsubstituted benzimidazole chalcone exhibit potent nematicidal action of about (LC100= 0.002 µg/ml). Mathew et al. [64] synthesized benzimidazole chalcone derivatives via microwave assisted and correlated their antimicrobial activity with C logP. SAR of the final candidates revealed a correlation between C logP and antimicrobial studies. It has been concluded that higher logP value favours the activity ratio.

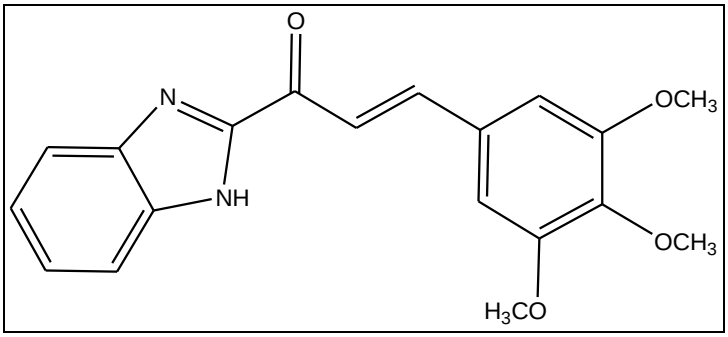


Figure 11: (2E)-1-(1H-benzimidazol-2-yl)-3-(3,4, 5-trimethoxyphenyl) prop-2-en-1-one

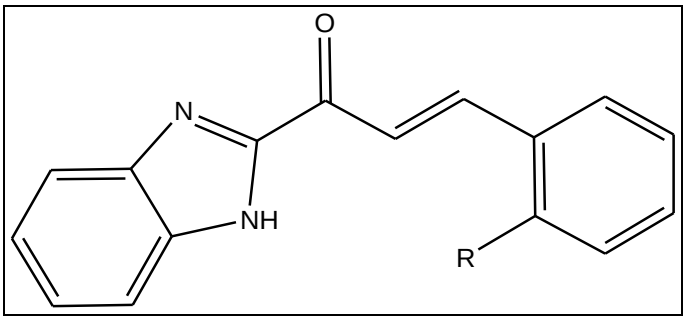


Figure 12: R= H, 2-CH_3, 3-CH_3, 4-CH_3, 2-OH, 3-OH, 4-OH, 2-OCH_3, 3-OCH_3, 4-OCH_3, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2, 2-Br, 4-$N(CH_3)_2$

Quinoline analogue:

Domynguez et al. [65] synthesized quinolinyl chalcones (Figure 13) and evaluated for their inhibition of the Plasmodium falciparum cystein protease falcipain and their activity against cultured P. falciparum parasites. They

were also tested for in vivo efficacy in a rodent P. berghei model. Their activity against falcipain and as antimalarials was moderate, but antimalarial activity was probably not due to the inhibition of falcipain and may follow a different mechanism. In their findings, it was highlighted that the substituted group in the benzoyl ring plays a significant role in determining the antimalarial activity of the tested quinolinyl chalcones. Among the series of quinoline based chalcones 1-(2, 4-Dichlorophenyl)-3- (3-(2-chloro-6, 7-dimethoxiquinolinyl))-2-propen-1-one was the most promising compound reported (IC_{50}19.0 µM). Chikhalia et al. [66] synthesized some new substituted quinolinyl chalcones (Figure 14) and evaluated for their in vitro antimicrobial activity against Gram-positive and Gram-negative strains usinga microdilution procedure. Kotra et al. [67] synthesized a series of new quinolinyl chalcones (Figure 15) and evaluated their anti-inflammatory and anticancer activities. All the compounds showed moderate to good activity profile. In these series, the 4-cholorophenyl substituted quinolinyl chalcone exhibited tremendous anti-cancer activity. Hayat et al. [68] synthesized a series of chloroquinoline based chalcones (Figure 16) and evaluated for in vitro antiamoebic and antimalarial activities. All quinolinyl chalcones were screened in vitro against HM1: IMSS strain of E. histolytica by microdilution method. In vitro antimalarial activity was carried out on the chloroquine-sensitive (3D7) strain of P. falciparum by use of the (3H)-hypoxanthine-incorporation assay. In the antiamoebic study, SAR showed that compounds which contained chloro and bromo groups as substituent's at C-3 and C-4 position of the phenyl ring with a methyl group as a substituent at C-6 and C-7 position of the chloroquinoline ring showed IC_{50}value in the range of 0.05-7.53 µM. Antimalarial activity was not as promising, none of the chloroquinoline based chalcones were capable of inhibiting parasite growth as effectively as the reference drugs chloroquine and quinine. Abonia et al. [69] synthesized novel quinoline-2-onebased chalcones (Figure 17) and evaluated their antitumor activity. Tseng et al. [70] synthesized some 3-phenylquinolinylchalconederivatives (Figure 18) evaluated for their antiproliferative activities. They concluded that the antiproliferative activity against H1299.

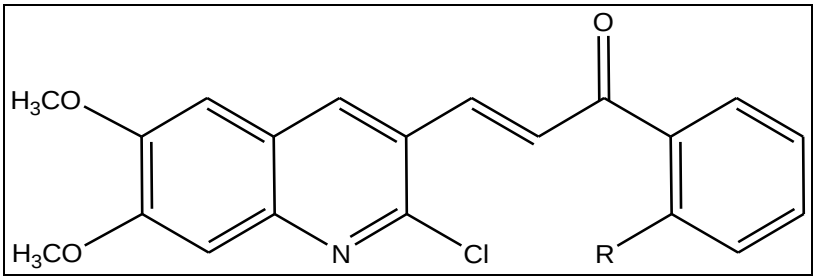


Figure 13: R= H, 4-CH_3, 4-Br, 4-Cl, 2,5-OCH_3, 2,6-OCH_3, 2,4-OCH_3, 3,4,5-OCH_3, 2,4-Cl, 3,4-Cl

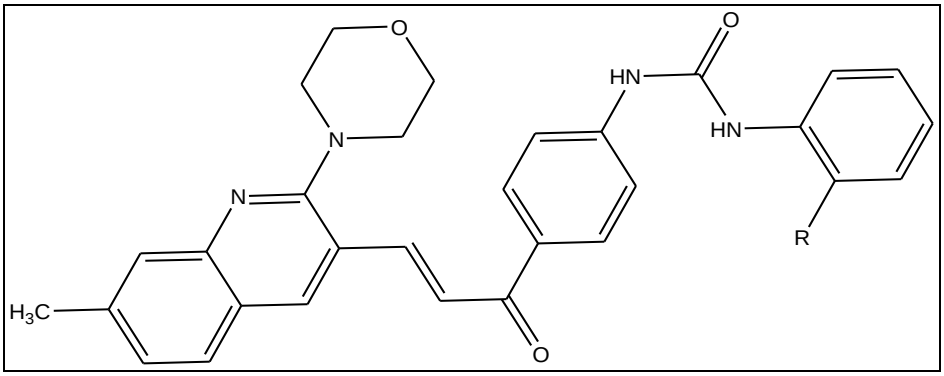


Figure 14: R= H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 3-Cl, 4-Cl, 3-NO_2, 4-NO_2, 2,4-$(NO_2)_2$

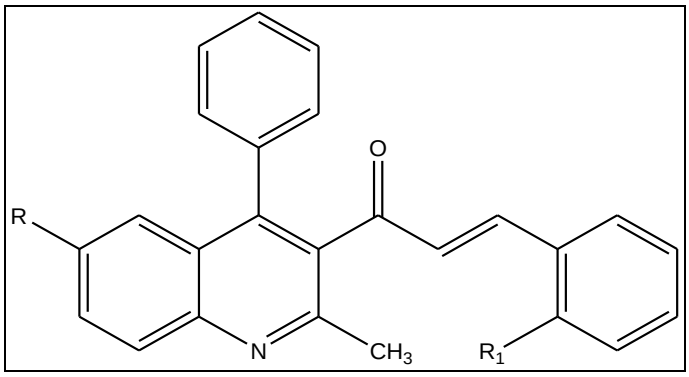


Figure 15: R = H, Cl; R_1 = p-NO_2, p-Cl, p-OH, p-CH_3, p-$N(CH_3)_2$, p-$N(C_2H_5)_2$

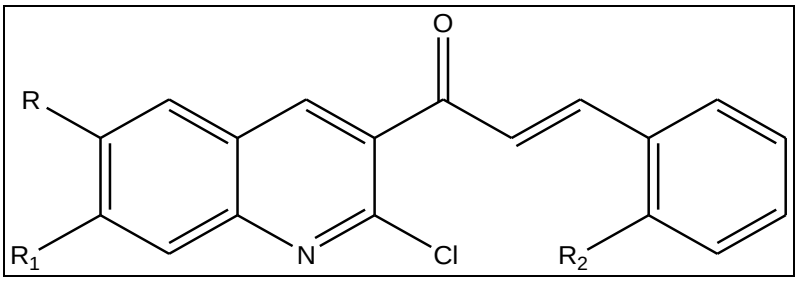


Figure 16: R=H, CH_3; R_1 =H, CH_3; R_2 = 3-Br, 4-Br, 3-Cl,4-Cl

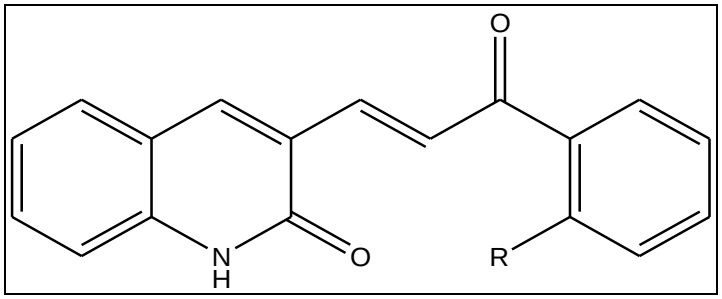


Figure 17: R=4-Br, 4-NO_2

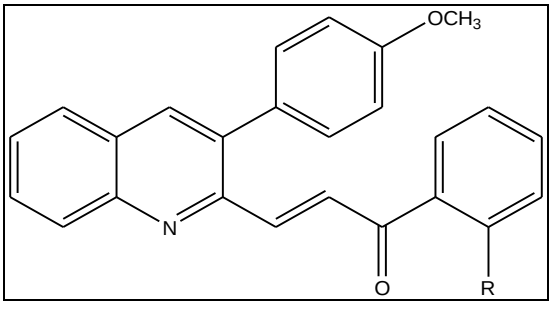


Figure 18: R=H,4-F,4-OH,4-OCH_3,2,4-OCH_3,2,6-OCH_3,3,4-OCH_3,3,5-OCH_3,4-NH_2

CONCLUSION

Chalcones are not only excellent scaffolds for synthetic manipulations but also possess multiple biological and medicinal properties. This review article is complementary to the previous reviews and has been focused on the latest pharmacological activities displayed by different chalcone. Analogues on the basis of heterocyclic moiety. The

introduction of a heterocyclic system unsaturated system displayed a broad spectrum of pharmacological activities. Chalcones have diverse biological potential, such as antibacterial, anticancer, anti-HIV, anthelmintic, antimalarial, antifungal, anti-inflammatory, MAO inhibition, anti-angiogenic and anti-leishmanial activities. The therapeutic potential about heteroaryl chalcones provided in the current review can be useful for the future investigation of this scaffold in order to evaluate their biological potential in a better way and for the discovery of further lead moiety for the treatment of various diseases.

REFERENCES

[1] GD Carlo; N Mascolo; AA Izzo; F Capasso. *Life Sci*. **1999**, 65, 337.
[2] A Guida; MH Lhouty; D Tichit; F Figueras; P Geneste. *Appl Catal A*. **1997**, 164, 251.
[3] G Romanelli; G Pasquale; A Sathicq; H Thomas; J Autino; PV Azquez. *J Mol Catal A Chem*. **2011**, 340, 24.
[4] S Eddarir; N Cotelle; Y Bakkour; C Rolando. *Tetrahedron Lett*. **2003**, 44, 5359.
[5] DN Dhar. Chemistry of Chalcones and Related Compounds, Wiley, New York, **1981**.
[6] MJ Climent; A Corma; S Iborra; A Velty. *J Catal*. **2004**, 221, 474.
[7] S Sebti; A Solhy; A Smahi; A Kossir; H Oumimoun. *Catal Commun*. **2002**, 335.
[8] F Micheli; F Degiorgis; A Feriani; A Paio; A Pozzan; P Zarantonello; PJ Seneci. *Comb Chem*. **2001**, 3, 224.
[9] X Bu; L Zhao; Y Li. *Synthesis*. **1997**, 1246.
[10] AR Alcantara; JM Marinas; JV Sinisterra. *Tetrahedron Lett*. **1987**, 28, 1515.
[11] JB Daskiewicz; G Comte; D Barron; AD Pietro; F Thomasson. *Tetrahedron Lett*. **1999**, 40, 7095.
[12] N Iranpoor; F Kazemi. *Tetrahedron*. **1998**, 54, 9475.
[13] NO Calloway; LD Green. *J Am Chem Soc*. **1937**, 59, 809.
[14] T Szell; I Sohalr. *Can J Chem*. **1969**, 47, 1254.
[15] K Irie; K Watanabe. *Bull Chem Soc Jpn*. **1980**, 53, 1366.
[16] L Mazza; A Guaram. *Synthesis*. **1980**, 41.
[17] T Nakano; S Irifune; S Umano; A Inada; Y Ishii; MJ Ogawa. *Org Chem*. **1987**, 52, 2239.
[18] Koo. *Ibid* J Fharm Sci. **1961**, 26, 4185.
[19] Devitt; Timoney; Vickars. *J Org Chem*. **1961**, 26, 4941.
[20] Tirouflet; Corvaisier. *Compt Rend*. **1960**, 250. 1276.
[21] Corvaisier. *Bull Soc Chim Franca*. **1962**, 528.
[22] Buu-Hoi; S Xuong. *Ibid*. **1956**, 1646.
[23] Buu-Hoi; Xuong; Trei. *Ibid*. **1961**, 584.
[24] Ariyan; Suschitzky. *J Chem Soc*. **1961**, 2242.
[25] Deutsch; U Garacia. Chem Ibstr. **1957**, H, 4437.
[26] Marvel; Sziraky. *J Org Chem*. **1956**, 1314.
[27] Krasnee; Durinda; Szucs. *Chem Zvesti*. 1961, 11, 558.
[28] V Edmont; A Stoyanov; Y Champavier. *Bioorganic Med Chem Lett*. **2002**, 12, 2685-2687.
[29] LM Alan. *Alternative Med Review*. **1996**, 1(2), 103-111.
[30] M Cabrera; M Simoens; G Falchi; ML Lavaggi; OE Piro; EE Castellano; A Vidal; A Azqueta; A Monge; AL de Cerain; G Sagrera; G Seoane; H Cerecetto; M Gonzalez. *Bioorganic Med Chem*. **2007**, 15, 3356-3367.
[31] A Bapna; S Ojha; GL Talesara. *Indian J Chem*. **2008**, 47B, 1096-1107.
[32] AB Linke; DE Eveleigh; *Naturorsch*. **1975**, 30B, 740.
[33] RM Horowitz; B Gentili. *Chem Abstr*. **1975**, 890, 298.
[34] JH Adams. *Chem Abstr*. **1971**, 16, 46956p.
[35] GP Rizzi; JS Neely. Chem Abstr. **1972**, 11, 86777h.
[36] J Fukomoto; S Okada. Chem Abstr. **1972**, 11, 152515z.
[37] M Delcarmen; G Barrio; JR Barrio; G Walker; A Noveli; NJ Leonard. *J Am Chem Soc*. **1973**, 95, 4891.
[38] Mitsubishi Petrochemical Co. Ltd., British Patent 1, 128, 090; Chem Abstr, 69, 97342y.
[39] M Takayama; T Fukai; Y Hano; T Nomura. *Heterocycles*. **1992**, 33, 405.
[40] TJ Mabry; KR Markham; MB Thomas. *Springer-Verlag*. **1970**, 227.
[41] HL Hegert; EF Kurth. *J Am Chem Soc*. **1953**, 1622.
[42] DN Dhar; VN Gupta. *Ind J Chem*. **1971**, 9, 818.
[43] TJ Mabry; KR Markham; MB Thomas. *Springer-Verlag*. **1970**, 267.
[44] A Pelter; RS Ward; TI Greg. *J Chem Soc*. **1976**, 2475.

[45] JB Sthothers. 13C NMR spectroscopy, Academic press, **1972**.
[46] JA Lopez. *Planta Med*. **1998**, 64, 76.
[47] T Tanaka. *Phytochem*. **1992**, 31, 993.
[48] TJ Mabry, KR Markham. The flavonoids, Academic press, London, **1975**, 78.
[49] TR Covey; ED Lee; AP Bruins; JD Henion. *Analytical Chem*. **1986**, 58, 1451.
[50] C Van de Sande; JW Serum; M Vandervalle. *Org Mass Spectrometry*. **1972**, 6, 1333.
[51] CE Ardanaz; J Kavka; FH Guidugli; D Favretto; P Traldi. *Rapid Commun Mass Spectrom*. **1998**, 12, 139.
[52] J Ronayne; D Willims; JH Bowie. *J Am Chem Soc*. **1966**, 88, 4980.
[53] CE Ardana; P Trali; U Vettori; J Kavka; FH Guidugli. *Rapid Commun Mass Spectrom*. **1991**, 5, 5.
[54] A De Vasconcelos; VF Campos; F Nedel; FK Seixas; OA Dellagostin; KR Smith KR. *Cell Biochem Funct*. **2013**, 31, 289-297.
[55] SJ Robinson; JP Petzer; A Petzer; JJ Bergh; ACU Lourens. *Bioorg Med Chem Lett*. **2013**, 23, 4985-4989.
[56] SUF Rizvi; HL Siddiqui; M Johns; M Detorio; RF Schinazi. *Med Chem Res*. **2012**, 21, 3741-3749.
[57] VR Solomon; H Lee. *Biomed Pharmacother*. **2012**, 66, 213-220.
[58] JS Lee; Y Kang; JT Kim; D Thapa; ES Lee; JE Kim. *Eur J Pharmacol*. **2012**, 67, 22-30.
[59] MAH Zahran; AM Ibrahim. *J Chem Sci*. **2009**, 121, 455-462.
[60] D Kumar; NM Kumar; K Akamatsu; E Kusaka; H Harada; T Ito. *Bio Org Med Chem Lett*. **2010**, 20, 3916-3919.
[61] M Cui; M Ono; H Kimura; BL Liu; H Saji. *Bioorg Med Chem Lett*. **2011**, 21, 980-982.
[62] ZM Nofal; EA Soliman; SSA Karim; S Sethumadavan; TJ Maher. *Act Polon Pharma Drug Res*. **2011**, 68, 519-534.
[63] M Ouattara; D Sissouma; MW Koné; HE Menan; SA Touré; L Ouattara. *Trop J Pharm Res*. **2011**, 10, 767-775.
[64] B Mathew; G Unnikrishnan; VP Shafeer; MC Muhamed; P Femina. *Der Pharma Chemica*. **2011**, 3, 627-631.
[65] JN Dom´yngueza; JE Charris; G Loboa; NG de Dom´ynguezb; MM Moreno; F Riggione. *Eur J Med Chem*. **2001**, 36, 555-560.
[66] KH Chikhalia; MJ Patel; DB Vashi. *ARKIVOC*. **2008**, 13, 189-197.
[67] V Kotra; S Ganapathy; SR Adapa. *Indian J Chem*. **2010**, 49B, 1109-1116.
[68] F Hayat; E Moseley; A Salahuddin; RLV Zyl; A Azam. *Eur J Med Chem*. **2011**, 46, 1897-1905.
[69] R Abonia; D Insuasty; J Castillo; B Insuasty; J Quiroga; M Nogueras. *Eur J Med Chem*. **2012**, 57, 29-40.
[70] CH Tseng; LC Chen; CY Hsu; TC Chen; CM Cheng; HC Tso. *Eur J Med Chem*. **2013**, 59, 274-382.