Synthetic Studies & Characterization of Some 1,3-diphenyl-2-propen-1-one (Chalcones) Having Electron Donating and Electron Withdrawing Substituents

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BY

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DECLARATION

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CHAIRMAN

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(Ishtiaq Ahmed)

CONTENTS

ABSTRACT

Chalcones are members of a class of secondary metabolites called flavonoids. They can also be considered as open chain flavonoids in which two aromatic rings are joined by a three carbon unsaturated carbonyl system. They are widely distributed in plant kingdom. However these compounds can be synthesized in the laboratory using well established methods. In the present work Claisen-Schmidt condensation method was employed and as a result 40 compounds were synthesized which were classified under four series as mentioned below;

A Series Chalcones: B-ring substituted Chalcones

A_1 =1-Phenyl-3-(4-methoxyphenyl)-2-propen-1-one
A_2 =1-Phenyl-3-(3-methoxyphenyl)-2-propen-1-one
A_3 =1-Phenyl-3-(2-methoxyphenyl)-2-propen-1-one
A_4 =1-Phenyl-3-(3,4-dimethoxyphenyl)-2-propen-1-one
A_5 =1-Phenyl-3-(2-hydroxyphenyl)-2-propen-1-one
A_6 =1-Phenyl-3-(3-hydroxyphenyl)-2-propen-1-one
A_7 =1-Phenyl-3-(4-hydroxyphenyl)-2-propen-1-one
A_8 =1-Phenyl-3-(2-chlorophenyl)-2-propen-1-one
A_9 =1-Phenyl-3-(4-chlorophenyl)-2-propen-1-one
A_{10} =1Pphenyl-3-(4-dimethylaminophenyl)-2-propen-1-one
A_{11}=1-Phenyl-3-(4-diethylaminophenyl)-2-propen-1-one
A_{12} =1-Phenyl-3-(3-methylphenyl)-2-propen-1-one
A_{13} =1-Phenyl-3-(4-methylphenyl)-2-propen-1-one
A_{14} =1-Phenyl-3-(4-nitrophenyl)-2-propen-1-one

B Series Chalcones: 2'-Methyl-B-ring substituted Chalcones

B_1= 1-(2'-Methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one
B_2= 1-(2'-Methylphenyl)-3-(4-dimethoxyphenyl)-2-propen-1-one
B_3= 1-(2'-Methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-one
B_4= 1-(2'-Methylphenyl)-3-(4-methylphenyl)-2-propen-1-one

C Series Chalcones: 2'-Hydroxy-B-ring substituted Chalcones

C_1= 1-(2'-Hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one
C_2= 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one
C_3= 1-(2'-Hydroxyphenyl)-3-(3-methoxyphenyl)-2-propen-1-one
C_4= 1-(2'-Hydroxyphenyl)-3-phenyl-2-propen-1-one

C_5= 1-(2'-Hydroxyphenyl)-3-(2-chlorophenyl)-2-propen-1-one
C_6= 1-(2'-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one
C_7= 1-(2'-Hydroxyphenyl)-3-(4-fluorophenyl)-2-propen-1-one
C_8= 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one
C_9= 1-(2'-Hydroxyphenyl)-3-(3- methylphenyl)-2-propen-1-one
C_{10}= 1-(2'-Hydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one
C_{11}= 1-(2'-Hydroxyphenyl)-3-(4-diethylaminophenyl)-2-propen-1-one
C_{12}= 1-(2'-Hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one

D Series Chalcones: 5'-Chloro-2'-hydroxy-B-ring substituted Chalcones

D_1= 1-(5'-Chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one
D_2= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(3-methoxylphenyl)-2-propen-1-one
D_3= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-methoxylphenyl)-2-propen-1-one
D_4= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(3,4-dimethoxylphenyl)-2-propen-1-one
D_5= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-chlorophenyl)-2-propen-1-one
D_6= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-bromophenyl)-2-propen-1-one
D_7= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-fluorophenyl)-2-propen-1-one
D_8= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one
D_9= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-methylphenyl)-2-propen-1-one
D_{10}= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(3-methylphenyl)-2-propen-1-one

The physical data (%age Yield, m. p., R_f value, Solubility) were recorded and purity of each compound was checked by HPLC. Structures of these compounds were elucidated by spectroscopic techniques such as I.R, UV, ^{1}H NMR & EIMS.

CHAPTER 1

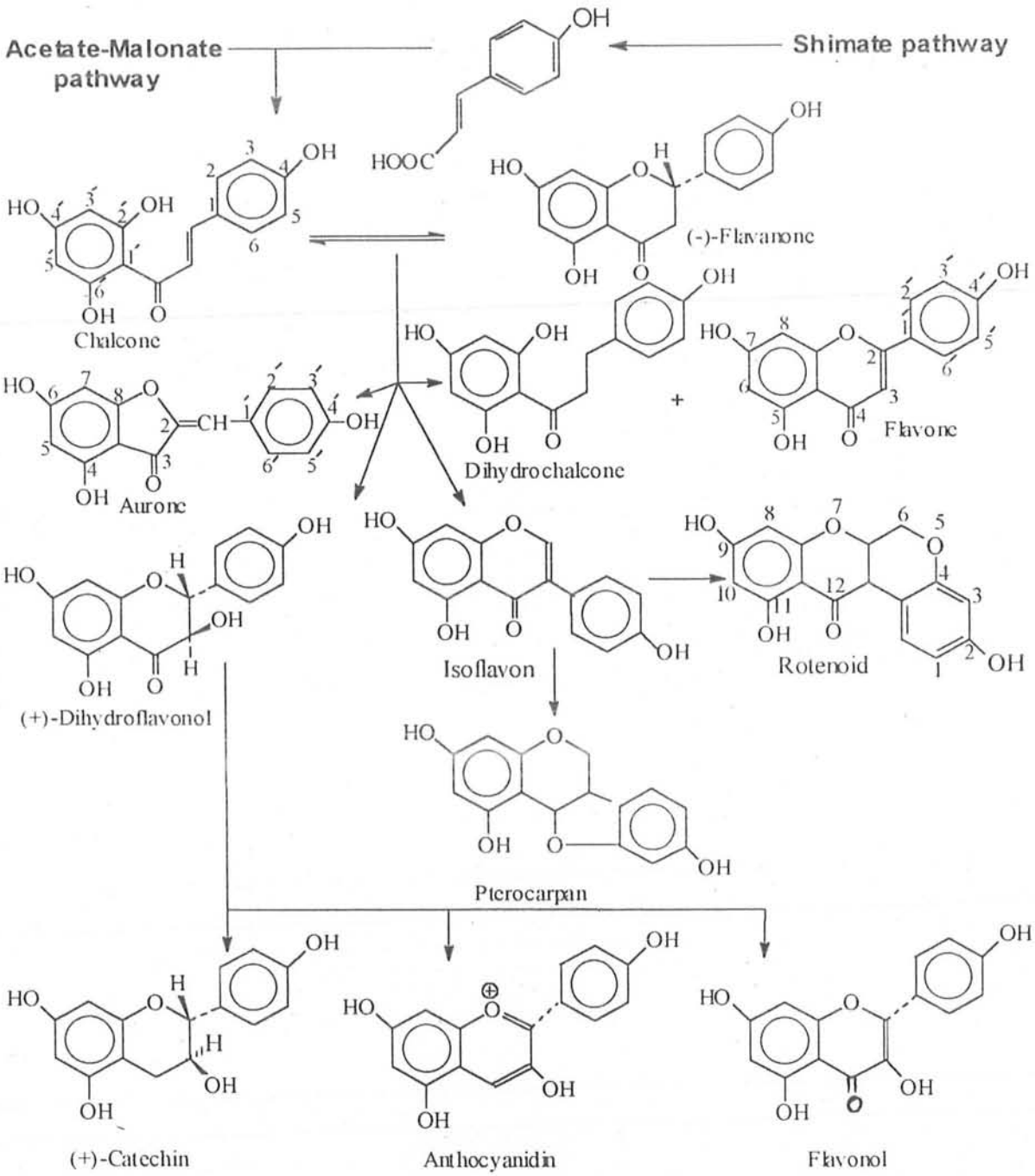
Introduction

1.1 Introduction

Anabolism and catabolism constitute an important process of living organisms, called metabolism. The process of building up of protoplasm is called anabolism and breaking down of it, is called catabolism. Energy is consumed and released; physical and chemical changes take place in the life cycle of living organisms during metabolism. The substances, which are produced and degraded during these complex processes, are collectively known as metabolites.

Plant physiologists differentiate metabolites into two types i.e. primary metabolites and secondary metabolites. On one hand, the substances which could be detected in practically all plants and which seem to be functional constituents of living organisms are called primary metabolites (e.g.; lipids, proteins and chlorophyll etc.). On the other hand secondary metabolites are not the functional constituents of living organisms and could be obtained only from particular plant species such as camphor or tannins We can also define secondary metabolites either as having a restricted taxonomic distribution or the products, which are not formed under all circumstances. Regardless of their utility to the plants, they are valuable to man as dyes, drugs and poisons etc.

Chalcones are members of a class of secondary metabolites called flavonoids which are widely distributed in higher plants. The flavonoid variants are all related by a common biosynthetic pathway, which incorporates precursors from both the ''Shikimate'' and ''Acetate-Malonate'' pathways. Initially chalcone is formed, and all other forms are derived from this by a variety of routs **(Scheme 1)**. Majority of chalcones have been isolated from various species of genera, *Flemingia, Derris, Alpinia, Piper, Lindera, Pityrogramma, Pinus, Didymocarpus, Acacia, Citrus, Cyclolobium, Dalbergia, Macherium, Platymiscium, Pterocarpus, Robina* and *Cryptocaryone*etc. Chalcones are open chain flavonoids in which the two aromatic rings are joined by a three carbon, unsaturated carbonyl system (1). Naturally occurring chalcones are all hydroxylated to a greater or lesser extent; the parent compound chalcone itself is not known as a natural product.

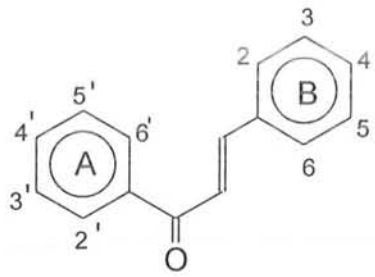


Scheme 1. Biosynthesis of Flavonoids

Besides their biosynthetic importance as the first isolable C_{15} precursors in flavonoid biosynthesis, the chalcones play an ecological role in nature, in relation to plant colour. These brightly yellow coloured compounds are found in many plant organs, but most conspicuously in flowers. Most yellow flower colour is due to the presence of carotenoids but in the presence of certain members of the *Compositae, Oxalidaceae, Scrophulariaceae, Gesneriaceae, Acanthaceae* and *Liliaceae,* chalcones contribute significantly to the corolla pigmentation.

1.2 Nomenclature

Fundamentally chalcones can be considered to be derivatives of phenyl styryl ketone. Benzylideneacetophenone(1) is the parent member of the chalcone series. The numbering of the positions of substitution in the chalcone nucleus is reversed from that in most other flavonoids, i.e. the A-ring is numbered 2'-6' and the B-ring 2-6 thus the following pattern of numbering the 15-C is adopted by **IUPAC**.



(1)

The alternative names given to chalcone are phenyl styryl ketone, benzalacetophenone, β- phenylacrylophenone, γ-oxo-α,γ–diphenyl-α-propylene, 1,3-diphenyl-2-propen-1-one and α-phenyl-β-benzoylethylene[1].

As in case of other classes of natural products (alkaloids, steroids, terpenoids etc.) some of naturally occurring chalcones have been assigned trivial names, which are derived from the generic name of the source plant. Examples of such names derived from the parent genera are derricidin (*Derris*), flemichapparin (*Flemingia*), cryptocaryone (*Cryptocarya*), linderone (*Lindera*), rottelerin (*Rottlera*), sophoradochromene (*Sophora*) , olivin (*Olea*) etc.

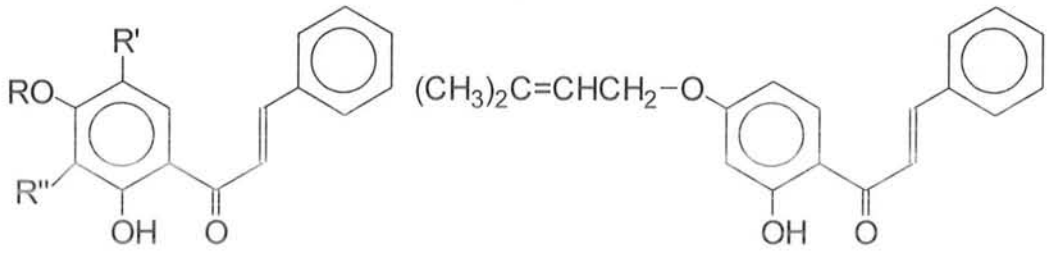
1.3 Structures of naturally occurring chalcones

With only a few exceptions, the chalcone aglycones can be classified according to the nature of the B-ring substitution pattern[2].

1.3.1 Chalcones lacking B-ring hydroxyls

Chalcone itself has not been encountered as a naturally occurring compound but its 4'-methoxy derivative has been reported[3] to be a constituent of the oil cells of *Citrus limon.*

Several chalcones are known which are based upon the resorcinol or 2',4'–dihydroxychalcone (2) itself, which has been isolated from *Flemingia chappar*[4,5]. Accompanying it in this plant is the related 2',4'-dihydroxy-5'–methoxychalcone[6] (3).

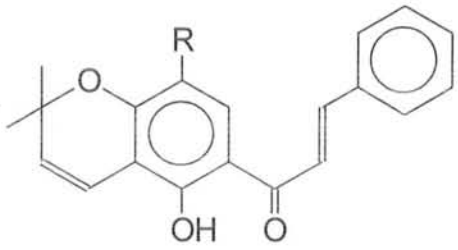


(2, R=R'=R''= H) (5)

(3, R=R''= H, R'=MeO)

(4, R= Me, R'= H R''= γ,γ–dimethylallyl)

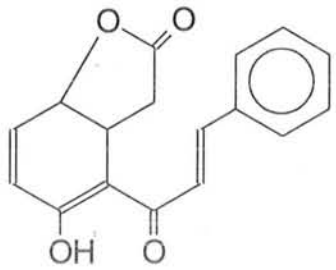
Cardillo[7] et al. also isolated compound (3) from this plant, together with a new chromenochalcone (7). A series of 2',4'–dihydroxychalcones (and related flavanones) bearing a, dimethylally1 grouping has been isolated from another member of the *Leguminosae*, from *Derris sericea*[8]. The chalcones isolated were derricin (4), derricidin (5) and lonchocarpin (6).



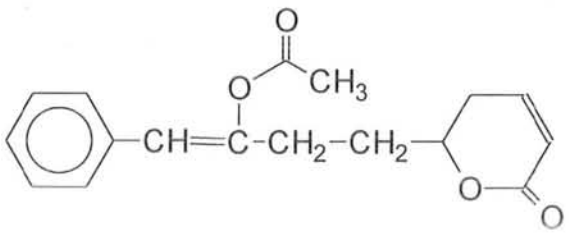
(6, R=H)

(7, R=OH)

Cryptocaryone (8), a unique chalcone from *Cryptocarya bourdilloni*[9], is the only known flavonoid, which has a partially reduced A-ring. It is possibly related biosynthetically to cryptocaryolactone (9), which occurs in the same species[10].

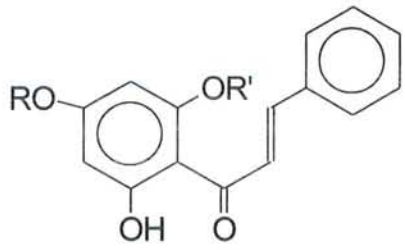


(8)



(9)

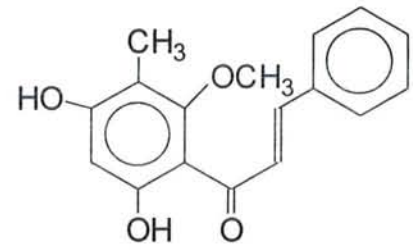
The next group of chalcones are those with the 2',4',6'–trihydroxy A-ring substitution pattern (phloroglucinol pattern) and are all partially methylated. The 4'-*O*-methyl ether (10) occurs in *Lindera umbellate*[11,12], *Pityrogramma chrysophylla*[13] and a new *Piper*[14] species from New Guinea, The 6'–O-methyl ether (11) occurs in *Piper*, in *Alpinia katsumadai*[15] and was found in an extract of "dragon's blood[16]" by Cardillo and co-workers. 2'–Hydroxy-4',6'–dimethoxychalcone (12) was isolated from *Piper*[17,18] and *Pinus excelsa*[19]. The final variant in this group is 2',4'–dihydroxy-5'–*C*-methyl-6'–methoxychalcone (13) found in "dragon's blood" extracted by Cardillo and co-workers.



(10, R=Me, R'=H)

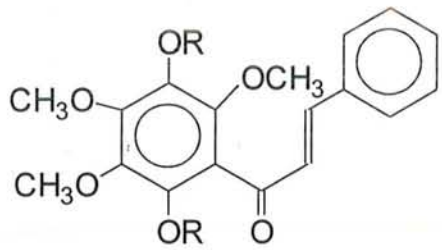
(11, R=H, R'=Me)

(12, R,R'=Me)



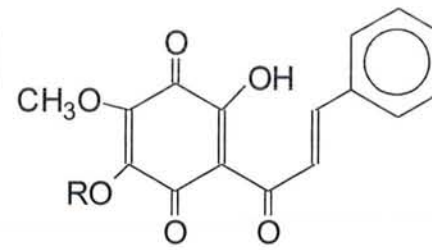
(13)

Four chalcones are known which have fully oxygenated A-rings, all from *Didymocarpus pedicellatus*[20,21]. These are pedicin (14), pedicellin (15), pedicinin (16) and methylpedicinin (17). The first two are normal flavonoids in that they possess only hydroxyl and/or methoxyl groups but pedicinin and methylpedicin are unusual in having a p-benzoquinone system in the A-ring. They occur in the free form as a dust on the undersides of the leaves.



(14, R=H)

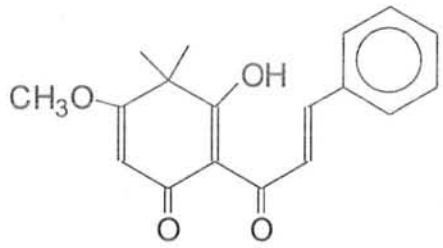
(15, R=Me)



(16, R=H)

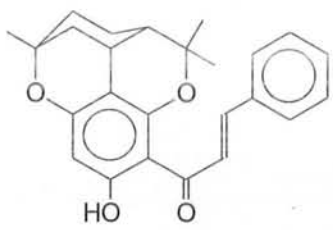
(17, R=Me)

The remaining chalcones are distinguished by structural variations in the A-ring or by the presence of complex or numerous substituent groups. The first one is ceroptin (18) isolated from *Pityrogramma triangularis*[22] and its structure was elucidated by Nilson[23]. The distinguishing feature of this molecule is the gem-dimethyl substitution which prevents aromatization of the A-ring. This compound has not been reported in other *Pityrogramma species* but the occurrence of other flavonoids with several *O*-methyl groups attests to the high capacity for alkylation among members of the genus.

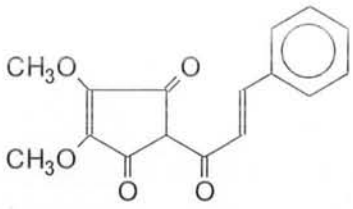


(18)

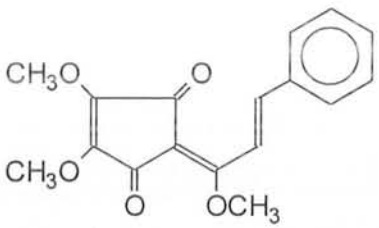
Another chalcone is rubranine (19), isolated from *Aniba rosaeodora*[24]. A C_{10} monoterpenoid substituent in the A-ring appears to have undergone cyclization and etherification with the two phenolic groups to yield the remarkable pentacyclic structure (19). Two other Lauraceaous pigments are linderone (20) and methyllinderone (21), which were isolated from *Lindera pipericarpa*[25]. Instead of the usual benzenoid A-ring, both molecules have a dimethoxycyclopentenedione moiety.



(19)

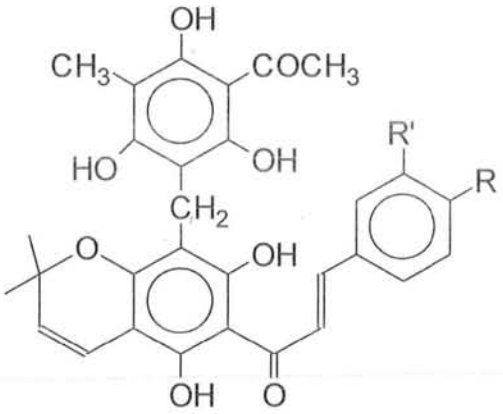


(20)



(21)

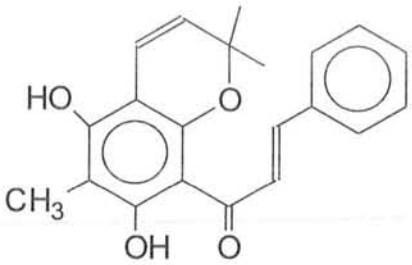
The most highly alkylated group of chalcones are the rottlerins (22), obtained from the dye, *Kamala*, present in the capsules of *Rottlera tinctoria* (*syn. Mallotus philippinensis*)[26-28]. More recently, Merlini reported the presence of 4-hydroxyrottlerin (23) and 3,4-dihydroxyrottlerin (24) in the same plant. A simpler, but obviously related, chalcone (25) has also been isolated from this plant[29]. In this case the highly substituted benzylic function prominent in the rottlerins is replaced by the methyl group. In the compounds (22-24), the chromene ring is closed upon the 4'–hydroxyl group of the A-ring, wherease the simpler compound (25) has the chromene ring closed upon the 2'(or 6')-hydroxyl position. Merlini[30] has indicated that the rottlerins have the same 2'–linkage.



(22, R=R'=H)

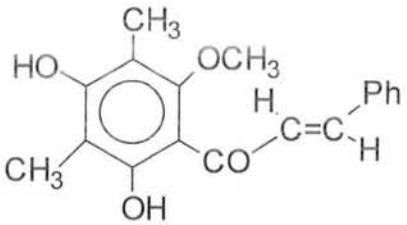
(23, R=OH, R'=H)

(24, R=R'=OH)



(25)

Gonzales[31] isolated the new 4',6'-dihydroxy-3',5'-dimethyl-2'-methoxychalcone (26) from the petroleum ether extract of *Dalea caerullacea.*

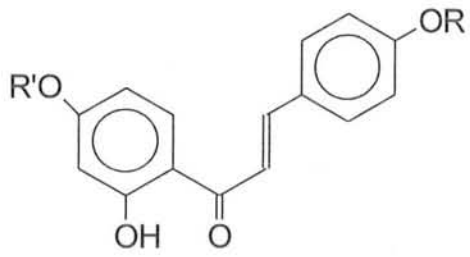


(26)

1.3.2 Chalcones having one B-ring hydroxyl

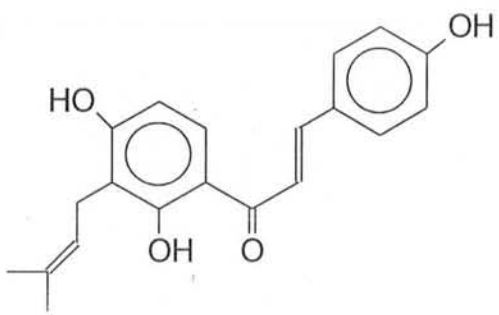
The simplest representative of this group is 2',4',4-trihydroxychalcone (27), or isoliquiritigenin, which occurs free in bark and/or wood of several leguminous trees. A wide variety of glycosylated forms have been found, the first to be described was the 4-*O*-glucoside (28) from *Glycyrrhiza glabra*[32]. Litvinenko[33] reported the 4'-*O*-glucoside (29) and Litvinenko and Obolentzova[34] a 4-*O*-apiosylglucoside (30) in *G. glabra* while Van Hulle[35] and co-workers found a 4-*O*-rhamnosylglucoside (31) in *G. glabra* var. *typica*. The 4-*O*-apiosylglucoside has also been found in *G. uralensis*[36]. The 4'-O-glucoside has been

reported in *Cicer arietinum* and in *Glycine max*[37]. Harborne[38] isolated a complex mixture of isoliquiritigenin glucosides from *Ulex europaeus*; the 4'-*O*-glucoside, 4'-*O*-glucoside-4-*O*-glucoside (32), 4'-*O*-diglucoside (33) and 4'-*O*-diglucoside–4-*O*-glucoside (34). Wong and Frahncis[39-41] found the 4-*O*-glucoside in *Trifolium subterraneum*. Such glycosylation systems are not the sole property of the Leguminosae, since the 4'-*O*-glucoside and 4'-*O*-diglucoside have been found in *Dhlia varieties*[42,43] (Compositae).

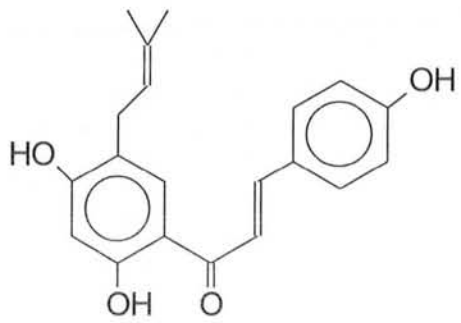


(27, R=R'=H)
(28, R=Glc, R'=H)
(29, R'=Glc, R=H)
(30, R=Glc-Api, R'=H)
(31, R=Glc-*O*-Rha, R'=H)
(32, R=Glc, R'=Glc)
(33, R=H, R'=Glc-*O*-Glc)
(34, R=Glc, R'=Glc-*O*-Glc)
(35, R=H,R'=Me)

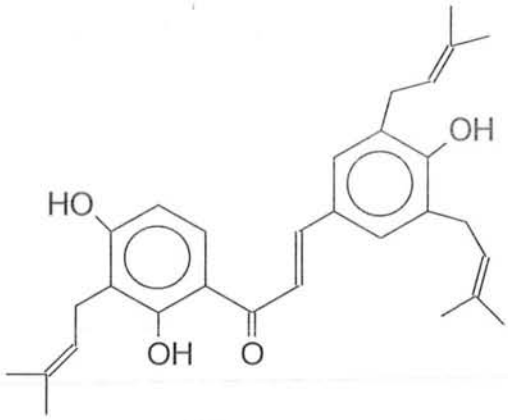
The only simple methyl ether of isoliquiritigenin is 2',4-dihydroxy-4'-methoxychalcone (35), isolated from the resin of *Xanthorrhoea australis*[44] one of the striking 'grass trees' of the Australian bush. However, an interesting series of C-alkylated chalcones based on the resorcinol A-ring system are known. Isobavachalcone (36) and bavachalcone (37), plus the related flavanones, were isolated from whole seeds of *Psoralea corylifolia*[45]. *Sophorodin* (38) and sophoradochromene (39) were isolated from *Sophora subprostrata*[46-48]. In (38), there are three dimethylallyl functions, at positions 3', 3 and 5, while in (39), one of the B-ring substituents has undergone cyclization with the phenolic group to produce a dimethylchromeno grouping.



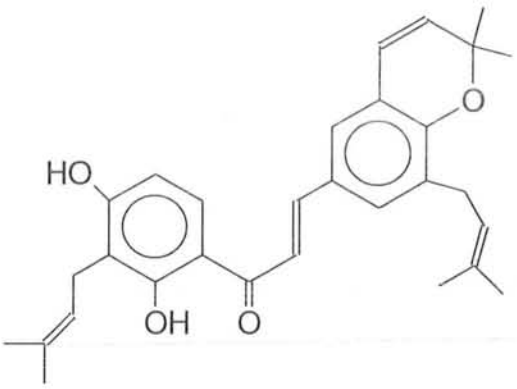
(36)



(37)

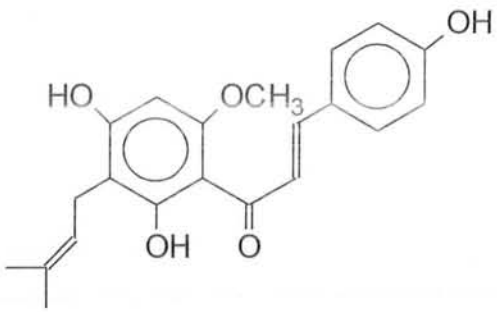


(38)



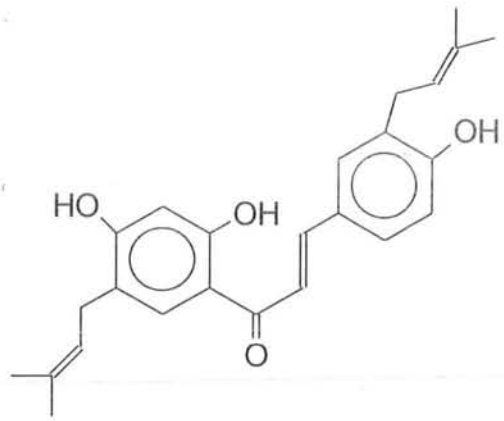
(39)

Xanthoumol (40), although it has a phloroglucionl-based A-ring was isolated first from hop resin[49,50] (*Humulus lupulus*). Komatsu and his colleagues have described its isolation from *Sophora angustifolia*. In this latter plant it occurs with the isomeric flavanone, isoxanthohumol.



(40)

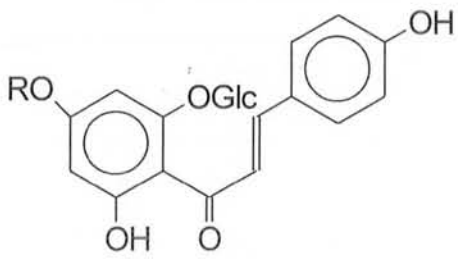
Xanthohumol possesses *O*-methyl and a *C*-isoprenyl functions. Parthasarathy and Seshadri[51] argued for the 6'-*O*-methyl structure on theoretical grounds. Proof of 6'-*O*-methyl structure came from synthetic studies[52-55]. A new diprenyalted chalcone stipulin (41) has been isolated and characterized from the roots of *Dalbergia stipulacea*[56].



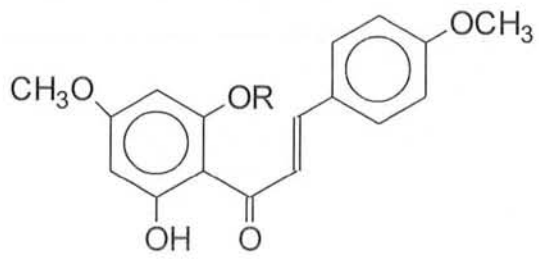
(41)

The simplest phloroglucinol-based A-ring chalcone is isosalipuposide (42), also known as chalcononaringenin 2'-glucoside, a name which relates it to its isomeric flavanone isolated from the cambial tissue of *Salix purpurea*[57,58]. The work of Jarrett and Williams[59] suggests that the chalcone glucoside is not a metabolic end product. Using *Salix pupurea* cultivar 'Helix', they showed that young bark contained the chalcone glucoside is not a metabolic end product.

Neosakuranin (43) or chalconosakuranetin, the 4'-O-methyl ether of (42), has been found in *Purnus puddum*[60,61] and *P. cerasoides*[62]. Two *O*-methylated derivatives of chalcononaringenin are also known 2',6'-dihydroxy-4',4-dimethoxychalcone (44) from *Pityrogramma chrysophylla* and *P. calomelanos*[63] and 2'–hydroxy–4,4',6'–trimethoxychalcone (45) from the resin of *Xanthorrhoea preissii*[64] and in *Piper methysticum*.

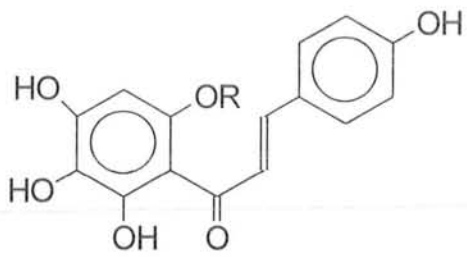


(42, R=H)
(43, R=Me)



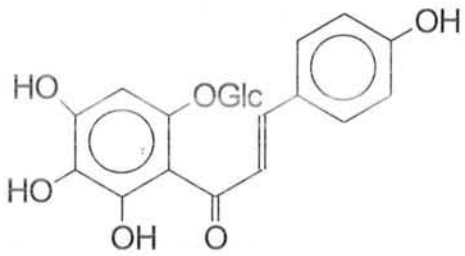
(44, R=H)
(45, R=Me)

A study of Australian *Acacia*[65] disclosed a large number of polyphenols, including 2',3',4,4'–tetrahydroxychalcone (46).

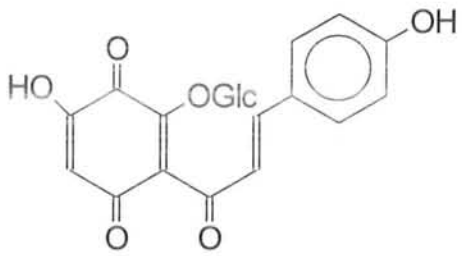


(46)

Finally two compounds isolated from saf-flower, *Carthamus tinctoria* must be mentioned. The first is carthamin (47) which has a phloroglucinol based A-ring with an additional hydroxyl function. The related red pigment, carthamone (48) is one of the very few known flavonoids which possess a quinonoid A-ring.

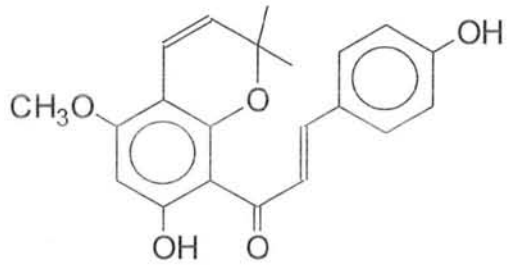


(47)



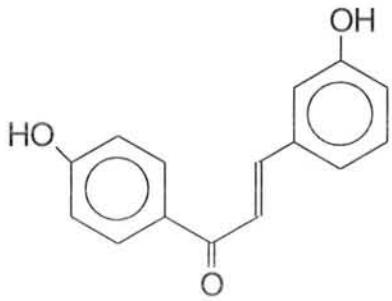
(48)

A new chalcone citrunobin (49) together with citflavaone were isolated from the root bark of *Citrus. Sinensis*[66]. It was also isolated from the corresponding bark of *C. nobilis* var. *sunki*. The structure of citrunobin was elucidated on the basis of spectroscopic and chemical evidence.

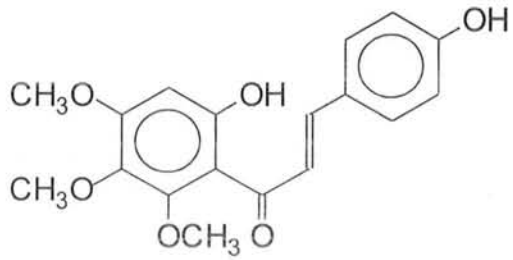


(49)

Two dihydroxy chalcones (50) & (51) have been isolated from the *Primula macrophylla*[67] and from *Eupatorium odoratum* respectively. Their structures were elucidated by the spectroscopic methods.

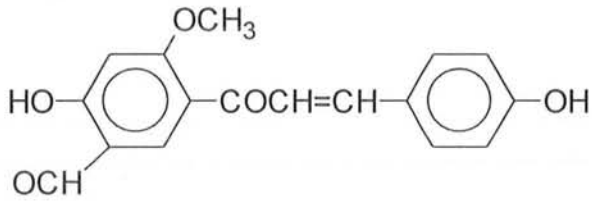


(50)



(51)

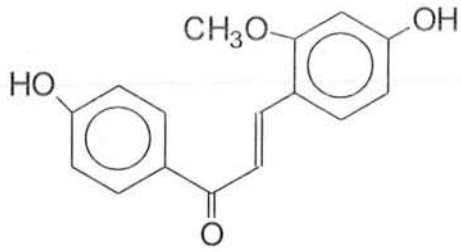
A *C*-formylated chalcone (52), isoneobavachalcone has been isolated from the seed of *Psoralea corylifolia*[68].



(52)

1.3.3 Chalcones having two B-ring hydroxyls

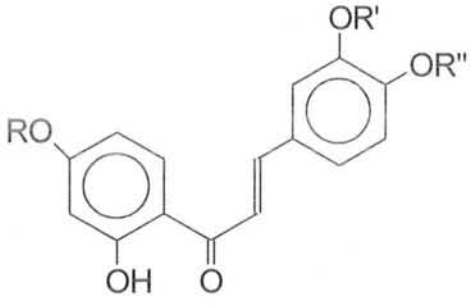
The novel chalcone echinatin (53), which was isolated from tissue cultures of *Glycyrrhiza chinata*[69], is interesting because of its unusual substitution pattern. Ring-A has only a 4'–hydroxyl group, while ring-B has 2,4-dihydroxylation.



(53)

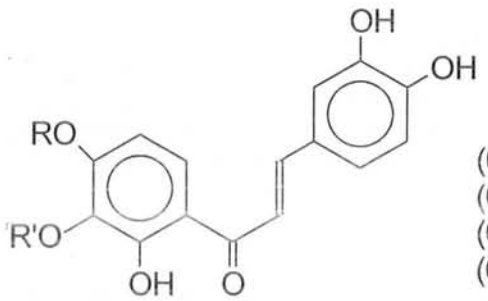
One of the most common chalcones is butein, 2',4',3,4-tetrahydroxychalcone(54). Butein occurs free in the wood or bark of several trees, e.g. *Acacia, Adenanthera, Macherium* and *Rhus*. This compound was also reported[70] in the pigments of *Butea frondosa* (*syn. B. monosperma*). Several glycosides of butein occur naturally. The 4'-O-glucoside (55), coreopsin, is known from *Butea monosperma*[71] where it occurs with the 3-*O*-glucoside (56), monospermoside, and the 3,4'–di-O-glucoside (57), isobutrin[72]. Coreopsin has been isolated from at least six genera in the Compositae. Homobutein 2',4',4-trihydroxy-3-methoxychalcone (58), has been isolated from *Acacia* species[73] where it occurs free in the heartwood The 4-*O*-glucoside (59) was identified as a constituent of *Trifolium subterraneum* by Wong and Francis.

Okanin (60) is another chalcone which is known both free and bound. The free phenol occurs in the heartwood of *Acacia* species, *Albizzia* and *Cylicodiscus*. In the latter plant, it occurs in both the cis- and trans-forms[74]. Okanin has also been found, presumably free, in the sedge, *Kyllinga*[75].



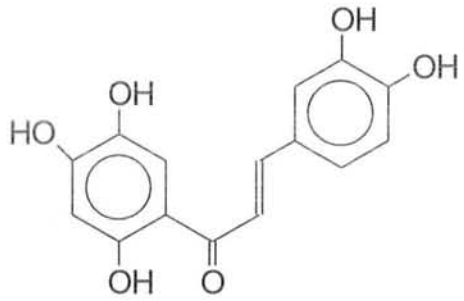
(54, R=R'=R"=H)
(55, R=Glc, R'=R"=H)
(56, R'=Glc, R=R"=H)
(57, R=R'=Glc, R"=H)
(58, R=R"=H, R'=Me)
(59, R"=Glc, R'=Me, R=H))

The 4-*O*-glucoside of okanin (61), known as marein, occurs in *Coreopsis maritima* and several other composites. A sigle okanin *O*-methyl derivative[76] is isolated 2',4',3,4-tetrahydroxy-3'–methoxychalcone (62) as its 4'–glucoside (63), lanceolin, from the ray florets of *Coreopsis lanceolata*, and *C. saxicola*.



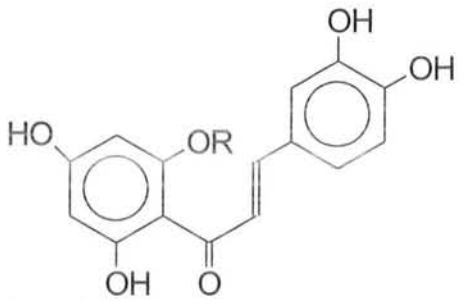
(60, R=R'=H)
(61, R=Glc, R'=H)
(62, R=H, R'=Me)
(63, R=Glu, R'=Me)

A hexoside of 2',4',5',3,4-pentahydroxychalcone (64) was isolated from *Coreopsis stillmani*[77]. Although the authors stated that the position of the glycosyl was uncertain, they assumed that it was probably the 4'-*O* glucoside. A few years later, King and co-workers[78] isolated a chalcone from the heartwood of *Plathymenia reticulata* and showed that it had the same structure as the aglycone obtained from *Coreopsis stillmani*. The compound, called neoplathymenin, occurred free in the heartwood. This compound was called stillopsidin by Seikel and Geissman.



(64)

Five compounds to be mentioned are based upon 2',4',6',3,4-pentahydroxychalcone (65). In the study of *Petunia hybrid* Asen and Plimmer[79] have described the isolation of this compound from *Limonium cv.* 'Gold Coast'. Acid treatment yielded no sugar but did bring about its conversion to eriodictyol, the related flavanone. The 2'-O-glucoside (66) has been identified in *Helichrysum bracteatum*[80,81].



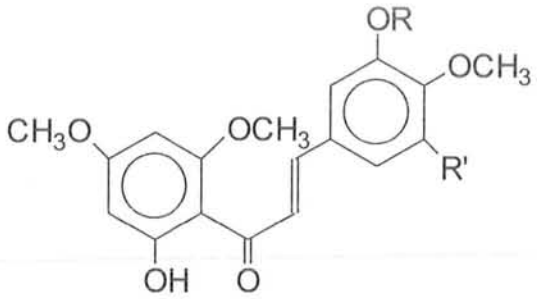
(65, R=H)

(66, R=Glc)

The existence in nature of chalcones having free 2',6'–hydroxyl groups has been doubted in the past because of the ease of their isomerization to the corresponding flavanones. It is not clear, of course, in these cases whether the chalcones are formed from pre-existing flavanones during the isolation process or whether they do genuinely occur in vivo in the chalcone form.

Fraser and Lewis[82] in studying the chemistry of *Merrillia caloxylon* fruit, found 2',3-dihydroxy–4',6',4-trimethoxychalcone (67), 2'-hydroxy-4',6',3,4-tetramethoxychalcone (68)

and 2'-hydroxy-4',6',3,4,5-pentamethoxychalcone (69). This last compound is one of the very few chalcones, which have 3,4,5-trihydroxylation in the B-ring.

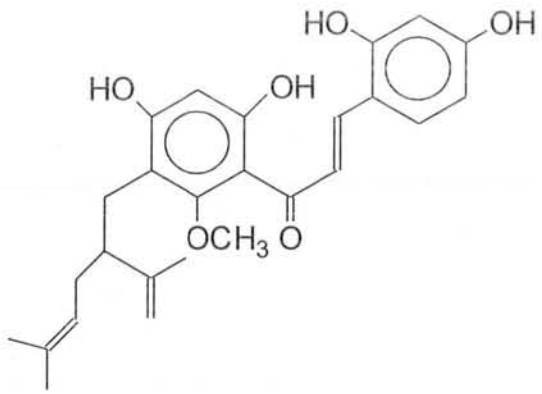


(67, R=R'=H)

(68, R=Me, R'=H)

(69, R=Me, R'=OMe)

While studying the polyphenols of *Sophora*, Komatsu and his students have encountered a fascinating array of C-alkylated chalcones. Kuraridin (70) was identified as a constituent of the roots of *S. angustifolia*[83].

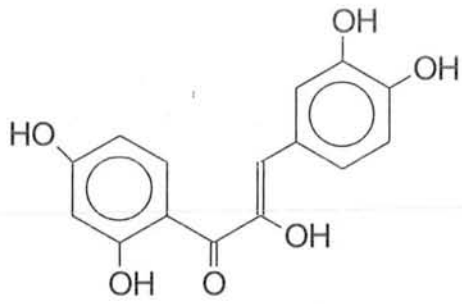


(70)

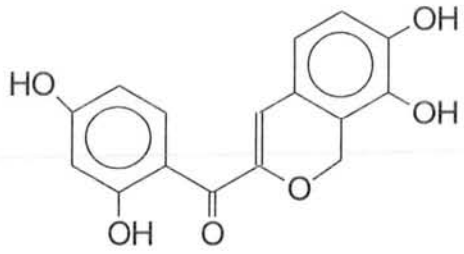
This compound has two striking features: one is the rare 2,4-dihydroxylation B-ring patterns and the second is the branched C_{10}, 5-methyl-2-isopropenylhex-4-enyl side chain.

Four chalcones are known which have a substituent located on a bridge carbon at the position alpha to the carbonyl. Hydroxybutein (71) was found in *Trachylobium*

verrucosum[84]. The corresponding peltogynoid chalcone (72), though not found in *Trachylobium*, was isolated from *Goniorrhachis marginata*[85].



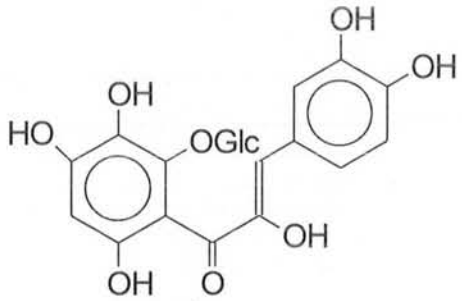
(71)



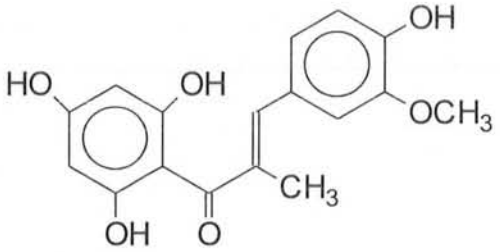
(72)

The most highly hydroxylated naturally occurring chalcone is 2',3',4',6',3,4,α-heptahydroxychalcone 2'–O-glucoside (73) isolated from *Gossypium barbadense* flowers[86].

Bockova[87] and co-workers presented evidence for the existence of the methylchalcone olivine (74) and its glucoside in leaves of *Olea europea*, the olive.

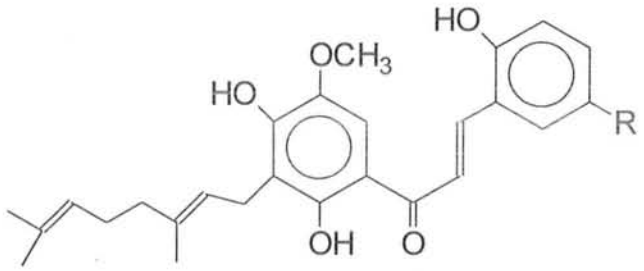


(73)



(74)

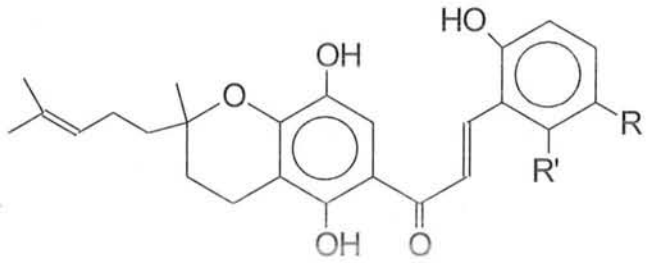
The simplest members of *Fleminga rhodocarpa*[88-90] are 5-deoxyhomoflemingin (75) properly named 2',4',2-trihydroxy-5'–methoxy-3'–(3,7–dimethyloct-3,7-dienyl)chalcone and homoflemingin (76).



(75, R=H)

(76, R=OH)

Cyclization of the hydroxyl group at position-4 with the proximal double bond of the geranyl side chain yields the chromano ring system typical of flemingin-A (77), flemingin-B(78) and flemingin-C (79).

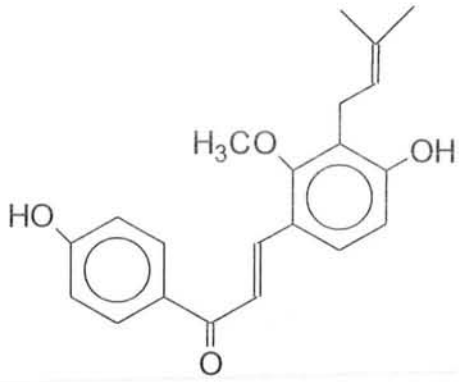


(77, R=R'=H)

(78, R=H, R'=OH)

(79, R=OH, R'=OH)

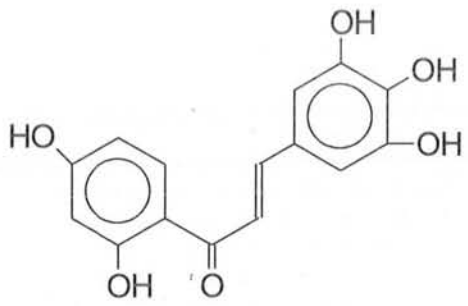
A new prenylated chalcone (80) has been isolated[91] from the root of *Glycyrrhiza inflanta*.



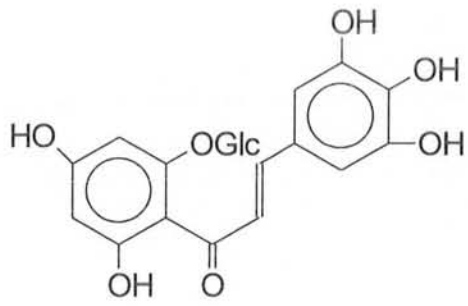
(80)

1.3.4 Chalcones having three B-ring hydroxyls

This is the smallest group of chalcones. One member, 2'-hydroxy-4',6',3,4,5-pentamethoxychalcone (69) was mentioned above. Two other members of the group are robtein, 2'4',3,4,5-pentahydroxychalcone (81) isolated[92,93] from the heartwood of *Acacia* and *Robinia* and 2',4',6',3,4,5-hexahydroxychalcone 2'-O-glucoside (82), found in *Helichrysum*.



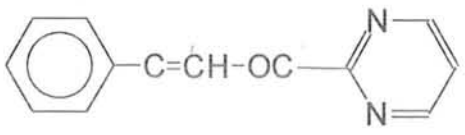
(81)



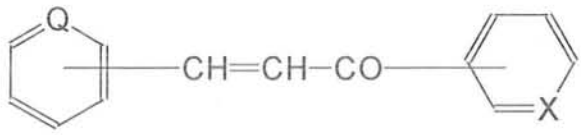
(82)

Beside these naturally occurring chalcones, analogues of chalcones containing heterocycilc rings with different substituents have been reported. The method for the formation of these heterocyclic analogues are also related to those for simple chalcones.

Metzner[94] *et al* and Liptaj[95] *et al*. prepared the six membered heterocyclic analogue of chalcones (83 & 84), while Ates[96] *et al* synthesized antipyrine derivative (85) of chalcone.

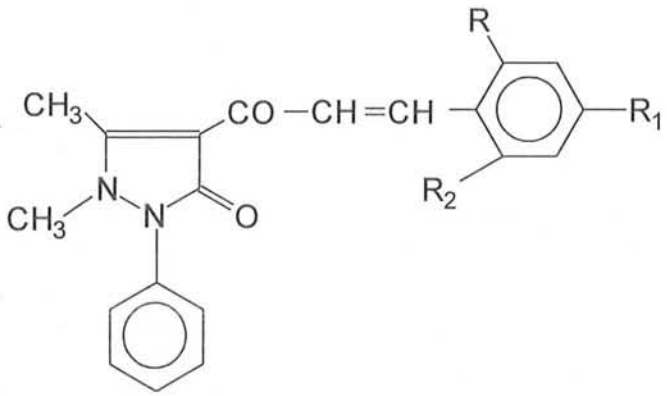


(83)



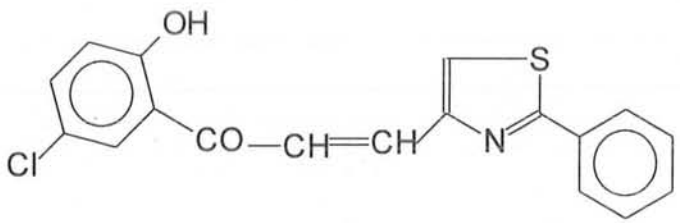
(84)

X, Q= CH, N

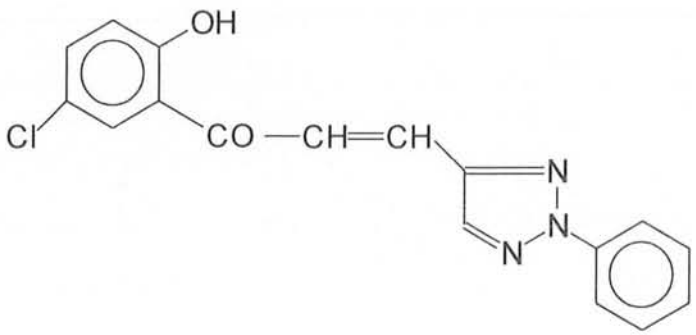


(85)

Litkei[97] and *et al* prepared the thiazol (86) and triazol (87) derivatives by the alkaline condensation of 2-phenyl-4-formylthiazol or 2-phenyl-4-formyltriazol with acetophenone.

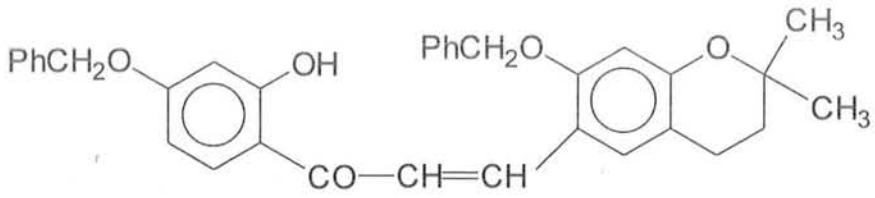


(86)

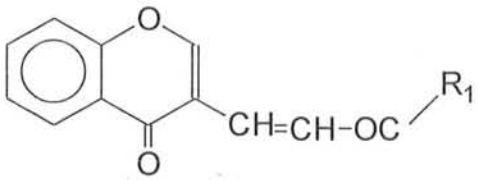


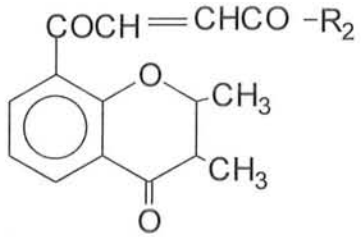
(87)

Dihydropyranochalcone (88), chromonylchalcone (89a,b) and pyronochalcone (90) were synthesized by Jain[98] *et al*, Shankker[99] *et al* and Tsukayama[100] *et al* respectively.



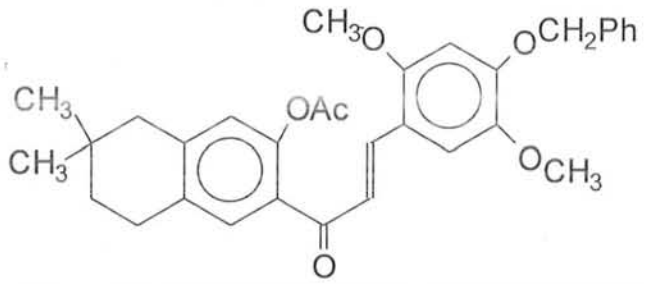
(88)





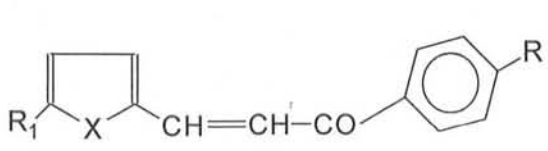
(89a) R_1=Ph, Cl-Ph, tolyl, anisyl

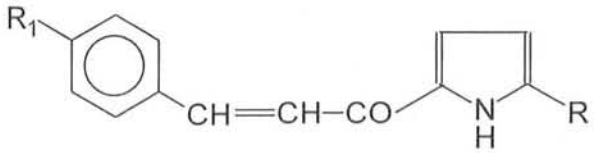
(89b) R_1=Ph, Cl-Ph, tolyl, anisyl, $(MeO)_2$Ph



(90)

Five memberd hetrocyclic chalcone analogs (91), (92) & (93) were prepared by Arcoria[101] *et al,*, Reinhardt[102] *et al* and Ballistreri[103] repectively.





(91)

R=H,NO_2

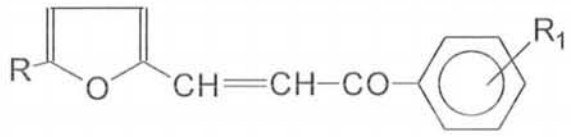
R_1=MeO, Me,Br,NO_2

X=O,S

(92)

R=H,NO_2

R_1=MeO, Me,Br,NO_2



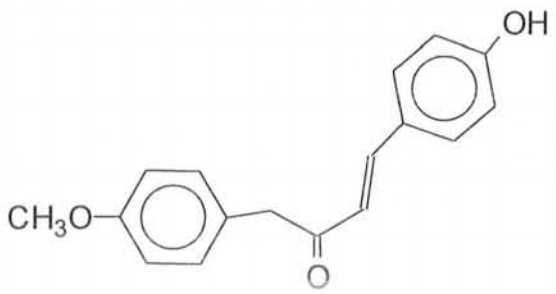
(93)

R=H, Me and R_1=H, MeO, F, Cl, CN, NO_2

1.4 Biological Activity

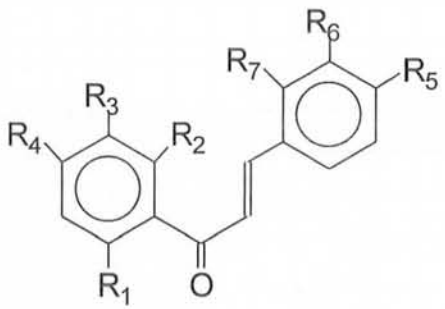
Chalcones are very active compounds; some of them are useful as antitumor, antiulcer, antifungal, antimalerial, antidandruff etc.

For example compound (94) showed 65.8% inhibition of peptic ulcer at 30mg/kg orally in rats[104].



(94)

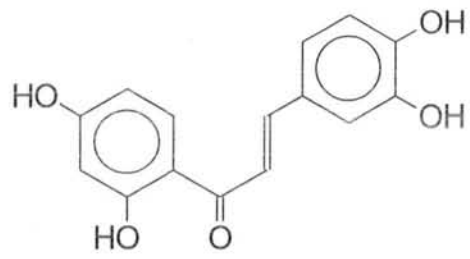
Compound (95) inhibites the 99.4 % 5 α-reductase and showed good antidandruff[105] and hair growth stimulating properties in mice and human.



(95)

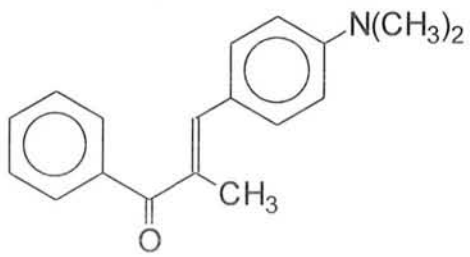
$R_1 = R_3 = R_6 = H$, $R_2 = OH$, $R_4 = Me$, R_5= OE t, $R_7 = OMe$.

Pharmaceutically acceptable salt of compound (96) is used for the treatment of renal diseases, allergy, ulcer and inflammation[106].



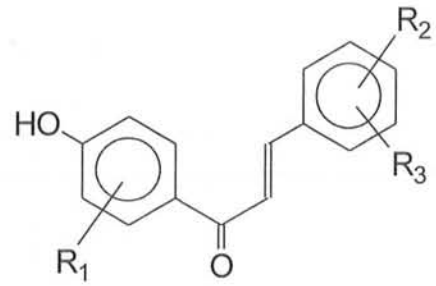
(96)

The trans chalcone (97) is effective as antimitoic agent[107] at 4n M in vitro HeLa cell test system. When evaluated in experimental. Tumo model in *vivo*. It exhibited antitumor activity agaist L 1210 Leukemia and B_{16} melanpma.



(97)

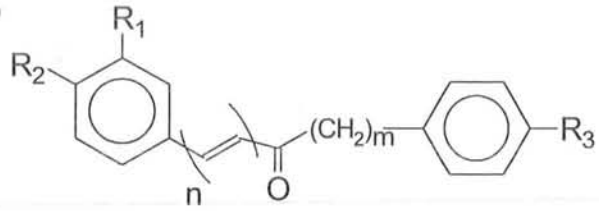
Copmound (98) showed > 90% inhibition of preoxidation and useful as sun screening cosmetic products[108].



(98)

R_1 = H; OH R_2, R_3 = H, alky, alkoxy, halo,

Compound (99) is interleukin-1 formation inhibitors[109] and useful as antirheumatics, inflammation inhibitor, psoriasis inhibitors and anti terosclerotic agents

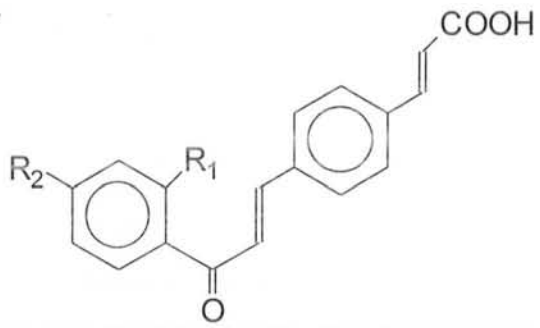


(99)

$R_1 - R_3$ = H, OH, lower alkoxy

M = 0-2, n = 1,2.

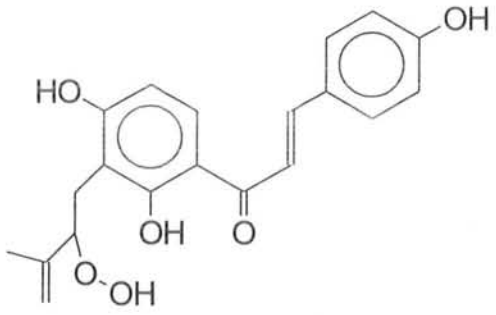
4-Carboxyvinylene chalcone (100) showed antifungal activity[110]



(100)

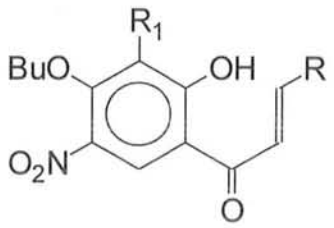
R_1=H; R_2=Br

Xanthoangelol-E (101) was extracted from the roots of *Angelica keiskei*[111] showed antiulcer activity



(101)

Compound (102) showed antimicrobial activity[112]

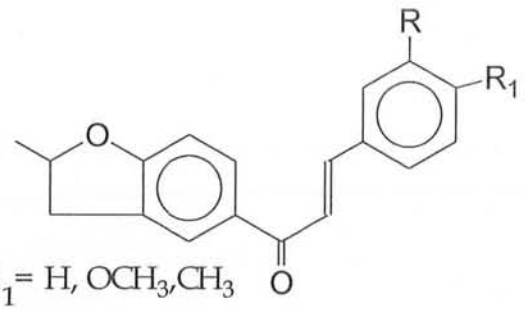


(102)

R = ph, and p-Cl-Ph

R_1 = H, Br

Furanyl chalcone (103) showed bactericidal and herbicidal activity[113]

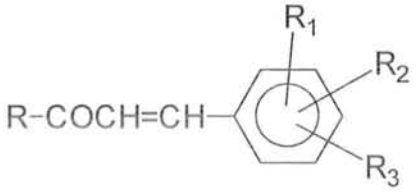


R=H, R_1= H, OCH_3,CH_3

R=R_1= OCH_3

(103)

Chalcone (104) showed bactericidal activity[114] against S. aureus and E. coli

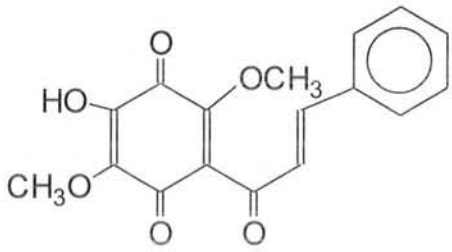


(104)

R =biphenylyl, phenthryl

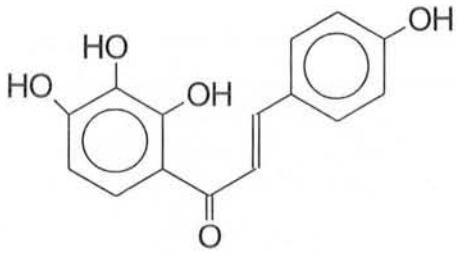
R_1,R_2,R_3 = H, halo, OH, NH2, OAC. Alkoxy

Chalcone (105) isolated from *Didymocarpus pedicellate*[115] inhibited the spore germination of fungi by inhibiting the phytopathogenic bacterium.

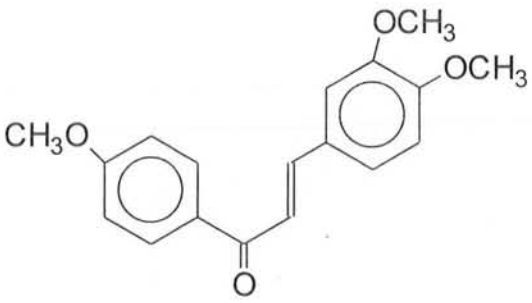


(105)

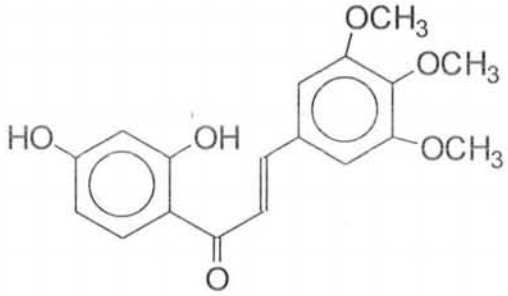
These four chalcones (106), (107), (108) & (109) showed inhibitory action against the tomato ringspot neporvirus (To RSV) [116].



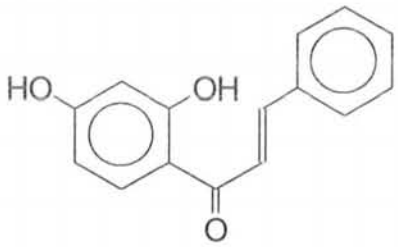
(106)



(107)

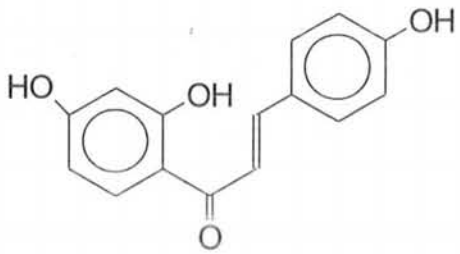


(108)

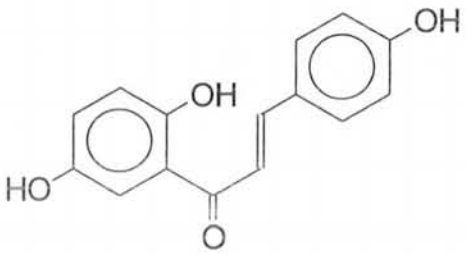


(109)

Platymiscium yucatanum (a tropical wood) highly resistant to the fungi *Lenzites trabea* and *Coriolus versicolor* due to the inhibitory (antifugal) effects[117] of the two chalcones (110) and (111) present in this plant.

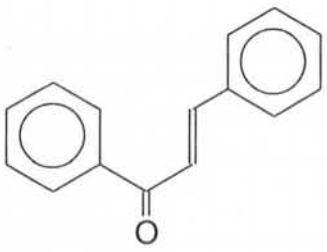


(110)



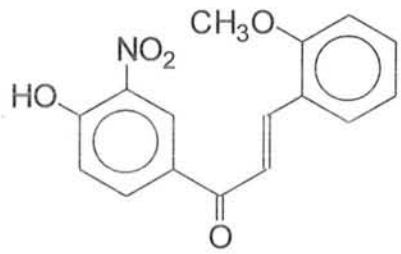
(111)

trans–1,3–Diphenyl propenone (112) was found highly toxic for the phytoparasitic nematodes. It is also acting as a potent inhibitor of nematode hatch[118].



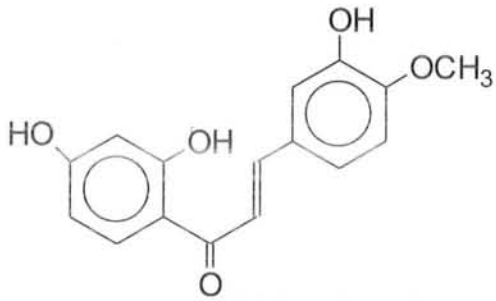
(112)

3'-Niro-4'-hydroxy-2-methoxychalcone (113) has a storng antibacterial action on S-albus *in vitro*[119]

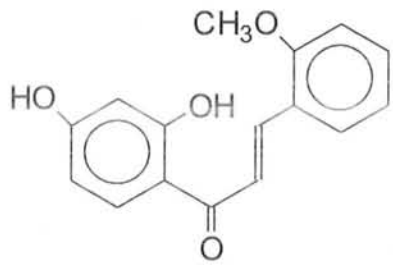


(113)

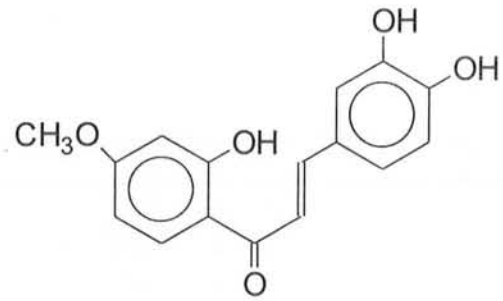
3,2',4'–Trihydroxy–4–methoxychalcone (114) has a strong inhibitory effect on the growth of plant *triticale*. 1-(2',4'-Dihydroxyphenyl)-3-(2-methoxyphenyl)-2-propen-1-one (115) had activity of inhibiting aldose reductase (ALR_2) enzymes and 3,4,2'-trihydroxy-4'-methoxychalcone (116) (trivially known as calthropsin) isolated from the bark of *Faramea salicifolia*[120] showed antitumor activity.



(114)



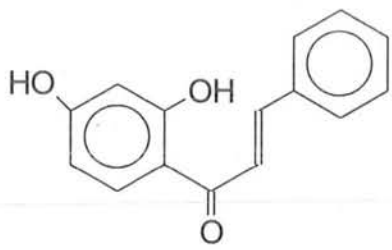
(115)



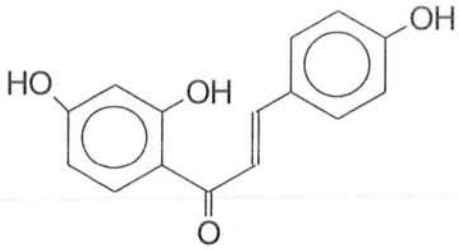
(116)

2-Hydorxyderricn (117), 2',4'-dihdroxy cahlcone (118) and 4,2',4'-trihydroxychalcone (119) have a marked affinity to the estrogen receptors of type II and an

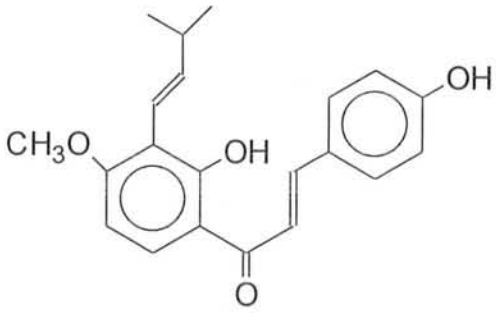
antiproliferative activity on uterus, ovary and breast tumor cell lines. These molecules proved to be useful both in therapy and in the prevention of such tumors[121].



(117)



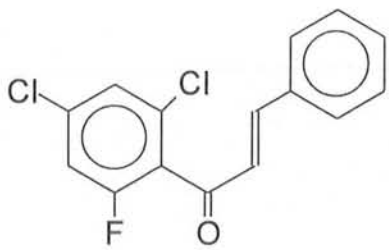
(118)



(119)

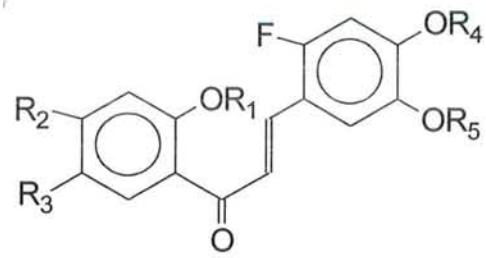
2'-Hydroxy-3'-bromo-5'-ethylchalcones (120) showed medium antibacterial activity while 2',4'-dichloro5'-fluorochalcone (121) showed strong antibacterial activity against *Staphylococcus* aureus[122].

(120)



(121)

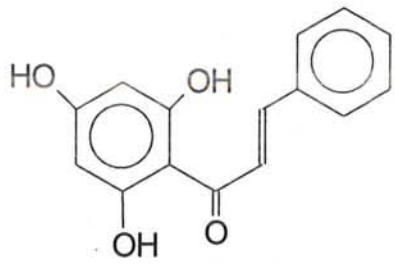
2-Fluoro-4,5-dihydroxy-2',4'-dimethoxychalcone (122) inhibited the proliferation of various tumor cells at low concentration[123].



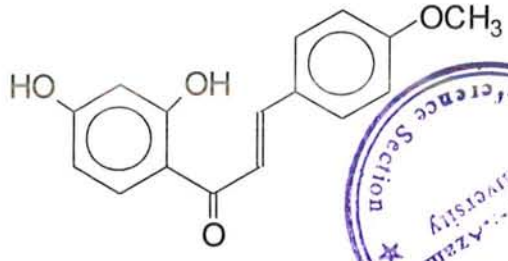
(122)

R_1, R_4, R_5=H, alkyl ; R_2, R_3=H, OH,
alkoxy and their salts are useful as anticancer agents.

Chalcones (123), (124) were isolated form leaf extract of the New Zealand native plant, *Ozothamnus leptophullus* possess autifungal and antiviral activity[124].

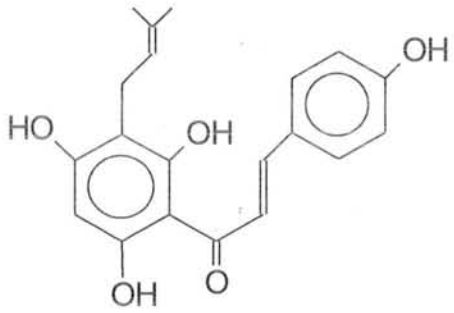


(123)

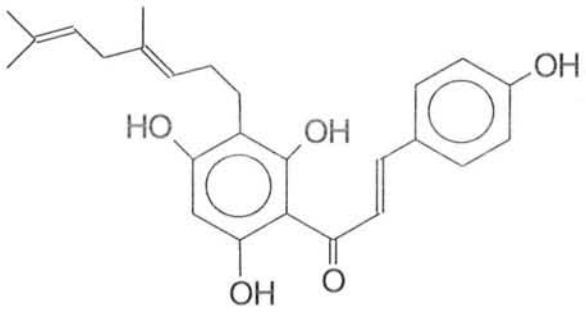


(124)

Compounds (125) (126) were isolated from the plant hops *(Humulus lupulus)* acting as antiproliferative agents and chemoprevented activity in human breast cancer[125].

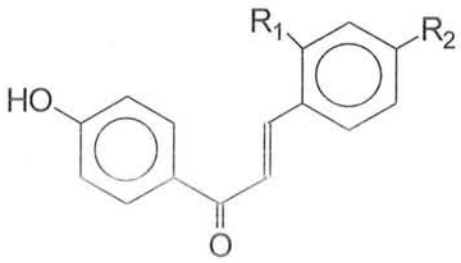


(125)



(126)

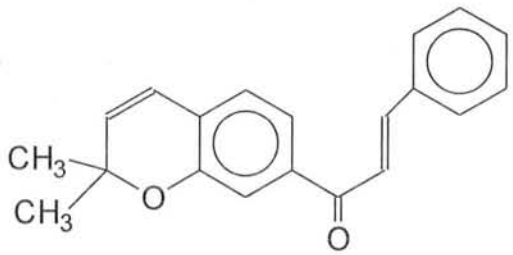
Chalcone (127) have 4'-hydroxyl and halogenic substituents (in 2 and 4 positions) possess marked antibacterial activity against *S.Albus* and *S.aureus*[126]. The chalcone (127) with fluoro substituent have better antibacterial activity compared to bromo or chlorochalcones.



(127)

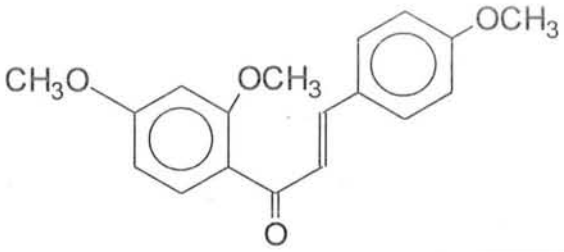
R_1= F, Cl, Br R_2=H R_1=H R_2= F , Cl, Br

Pyranoanalog of chalcone (128) possessed fungistatic and fungicidal activity against *Helminthosporium oryzae*[127].

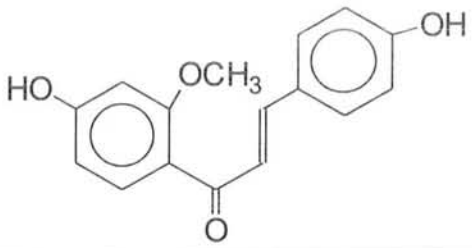


(128)

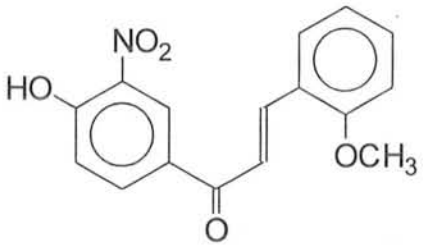
Chalcones (129), (130), (131), (132) and (133) possessed chloretic activity *in vivo* in rats[128].



(129)



(130)



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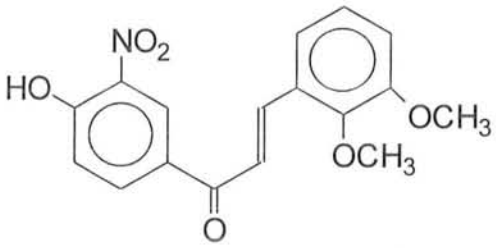

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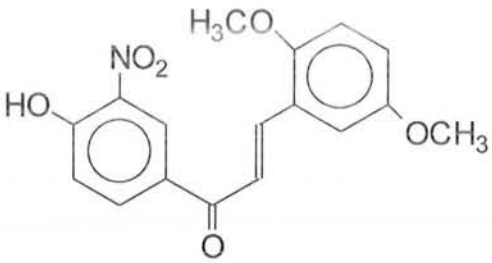
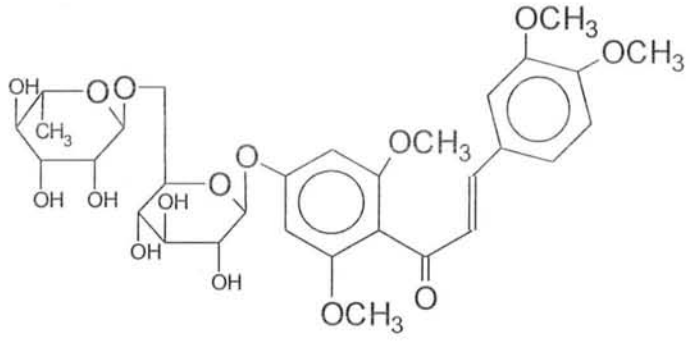


(133)

Chalcone diglycoside (134) decreases capillary fragility and also effects the venous circulation[129].



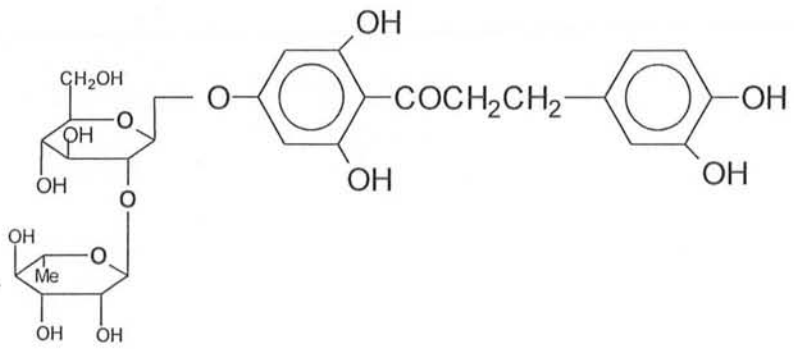
(134)

1.5 Applications

Many patents have appeared in the literature describing the usefulness of chalcones and their derivatives. These find application as artificial sweeteners, stabilizer against heat, visible light, ultraviolet light, aging, color photography, scintillators, polymerization catalysts, fluorecent whitening agents, and organic brightening additives.

1.5.1 Sweetners

The chalcone derivatives dihydrochalcones[130] and their corresponding glycosides have been employed as food-sweetening agents. Dihydrochalcone xylosides[131] and galactoside[132,133], for example, are claimed to be 1.5-2 times sweeter than saccharin. 3, 2', 4', 6'-Tetrahydroxy-4-propoxydihydrochalcone-4'β-neohesperdoside(135) has been used as a synthetic sweetener[134] and is 2200 times sweeter than glucose.



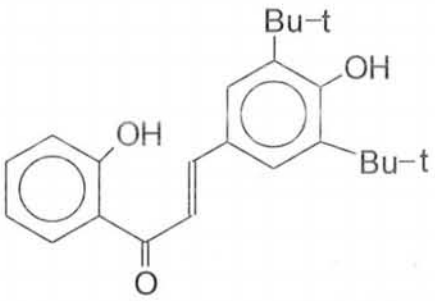
(135)

1.5.2 Stabilizers

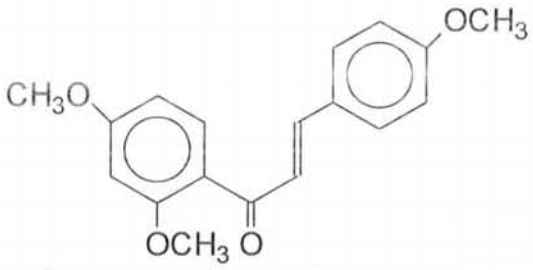
2`, 4-Dihydroxy-3,5-di-tert-butylchalcone (136) has been employed as an oxidation inhibitor[135] and stabilizer[136] to polypropylene polymer.

Chalcone is a natural constituent of beer and plays, in combination with other polyphenols, an important role in its sability[137] Chalcone forms the constituent of corrosion-inhibiting lubricants suited for internal combustion engines containing silver and similar metal components[138]. According to one patent the efficiency of lubricant additive is retained by incorporation of chalcone, otherwise it is diminished by reaction of the additive with olefinic components of base oils or grease[139].

The incorporation of 2', 4,4'-trimethoxychalcone (137a) into pulp sheets (on which pesticide was absorbed) helped in retarding the air degradation[140].

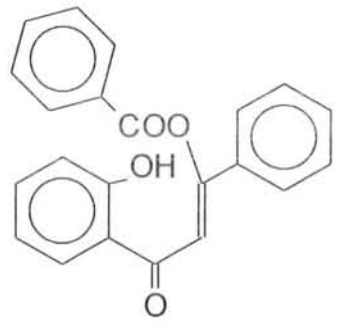


(136)



(137a)

Chalcone[141] and β- (benzoyloxy)-2'-hydroxychalcone[142] (137b) have proved to be good light absorbers and heat stabilizers for polymeric materials, for example, polymethyl methacrylate film and PVC resin sheet.

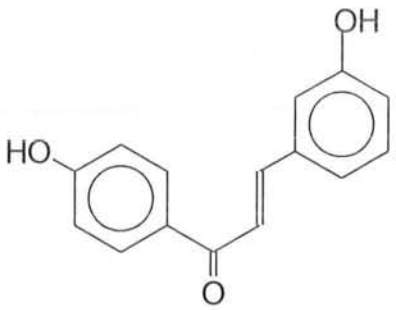


(137 b)

1.5.3 Photosensitive Material

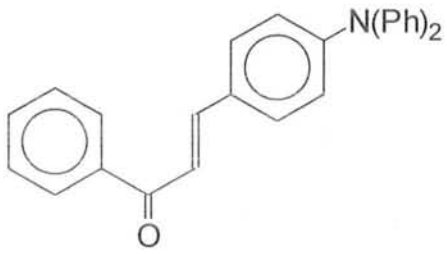
A number of chalcone derivatives from the principal ingredients in the preparation of photosensitive polymeric material, some of which possess good film-forming properties[143-149].

The light-sensitive resin has been reported[150], which possesses good adhesion, toughness, alkali resistance, and stability toward oxidation. The resin has been obtained by heating 3,4'-dihydroxychalcone(138) with an epoxy resin in a suitable solvent, in the presence of alkali.

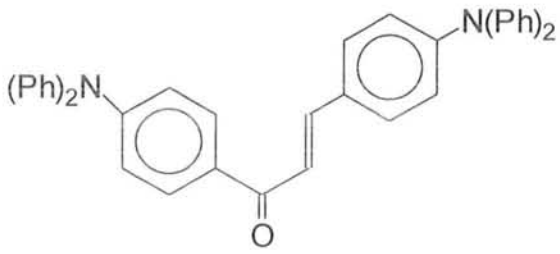


(138)

4-Diphenylaminochalcone (139) and 4,4`-bis (diphenylamino)chalcone(140) have been used as constituents of a photoconducting composition for use in electrophotographic products[151-153].



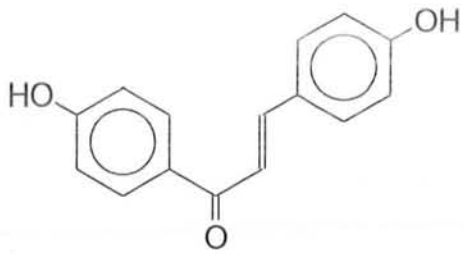
(139)



(140)

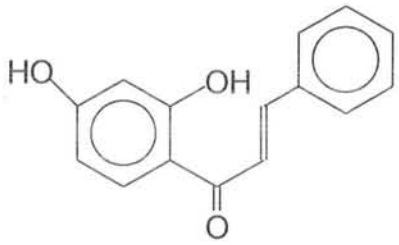
1.5.4 Polymers

Dihydroxychalcone[154-156] has been used for the preparation of uncured epoxy resins. 4,4'-Dihydroxychalcone (141) forms the component of a duroplastic mixture, which possesses good mechanical properties and a high thermal stability.



(141)

Chalcones react with a number of metal ions and are reported to be more reactive than the aldehyde or ketone from which they have been prepared[157]. This reaction has been exploited for the detection of Fe^{3+} (limit of identification: 0.33γ/0.05ml) by 2',4'-dihydroxychalcone (142), provided the concentration of interfering ions is kept at a minimum.



(142)

Chalcone sulfonic acid serves as intermediates in the preparation of fluorescent whitening agents[158]. Chalcones have also been employed as organic brightening additives[159-160].

In view of the immense importance of natural and synthetic chalcones in the pharmaceutical, food and cosmetic industries, the present work was undertaken to synthesize chalcone having electron donating and electron withdrawing substituents and to study the structure-activity relationship.

CHAPTER 2

Synthetic Methods & Reactions of Chalcones

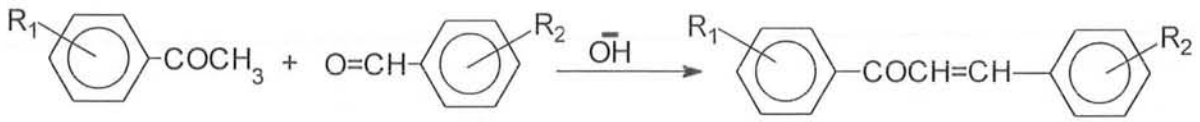
CHAPTER 2

2.1 Synthetic Methods

A wide spectrum of synthetic methods have been used towards the synthesis of chalcones and derivatives. A number of new methods are being developed and reported each year some of the most important, high yield methods applicable to the synthesis of chalcones are being mentioned below.

2.1.1 Claisen-Schmidt reaction

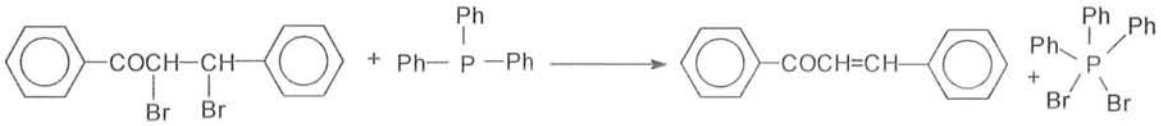
The most convenient method for the synthesis of chalcones (145) is one that involves the Claisen-Schmidt condensation of equimolar quantities of substituted acetophenone (143) with a substituted benzaldehyde (144) in the presence of aquous alcoholic alkali. In the claisen- Schmidt reaction the concentration of alkali used usually ranges between 10 and 60%[161-165]. The reaction is carried out at about 0-30°C for 12-15 hours or at room temperture for one week. Under these conditions the Cannizzaro reaction also takes place and thereby decreases the yield of the desired product. To avoid the disprportionation of aldehyde in the above reaction the use of benzylidene diacetate in place of aldehyde has been recommended.



(143) (144) (145)

2.1.2 Chalcone α,β-dibromides

Debromination of chalcone α,β-dibromide (146) with 1 mole equivalent of trialkylphosphine[166,167] produces chalcone in an excellent yield (92%). Tripheny1phosphine[168] likewise brings about debromination of the vicinal dibromochalcone as below



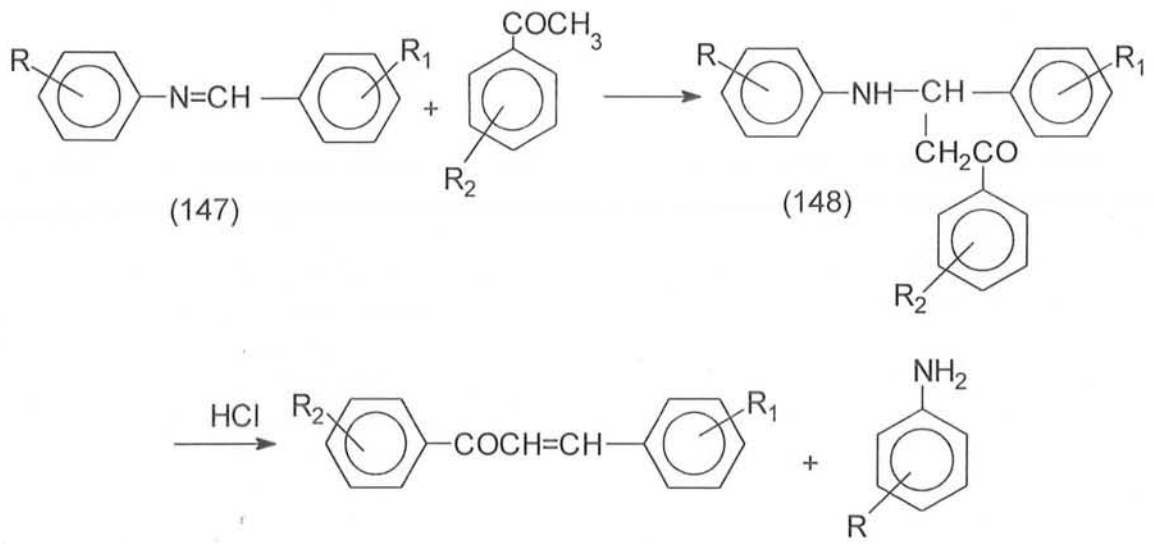
(146)

Chalcone has also been secured by the debromination of chalcone α,β-dibromide, either in the presence of chromous chloride or by the action of potassium hydroxid in an acetone medium.

2.1.3 Schiff's base

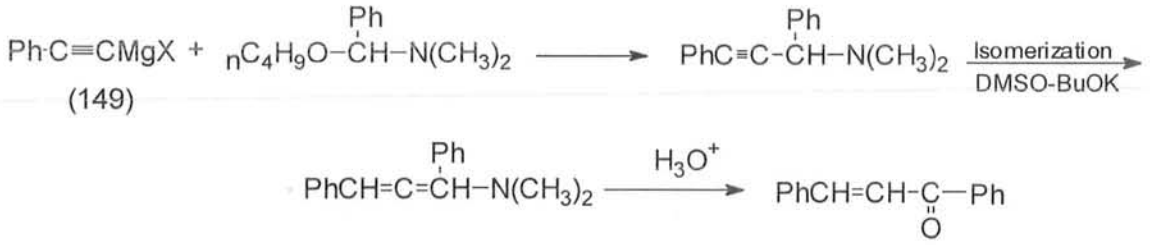
Schiff's bases (147) are reported to react with acetophenone and its derivative in the presence of a catalytic amount of amine hydrochloride to yield β-arylaminoketone[169a,b,170] (148).

On heating with concentrated hydrochloric acid these ketones undergo the hydramine cleavage to yield primary aromatic amine and chalcone. Hydramine cleavage is favored by the presence of electron-withdrawing substituents in β-arylaminoketones.



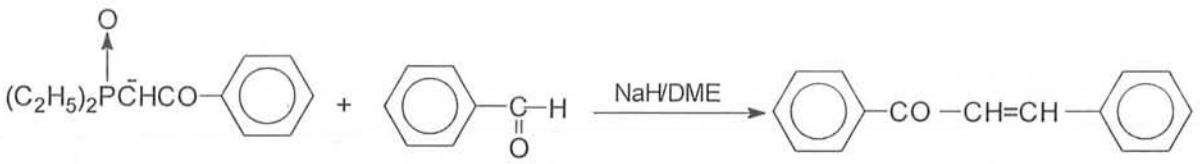
2.1.4 Organometallic compounds

Chalcone in 20% yield has been secured from acetylenic Grignard reagent (149) by carrying it through the following series of transformations[171,172]



2.1.5 Wittig Reaction

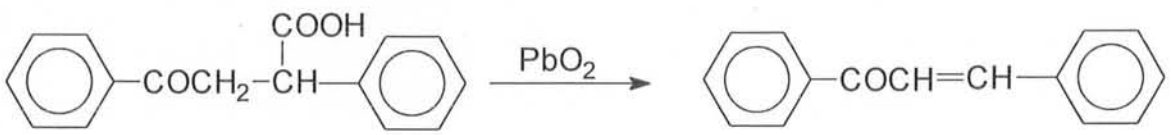
Chalcone (60%) has also been obtained by the reaction of benzaldehyde with phosphonate carbanion[173] (150) derived from diethylphenyl phosphonate with sodium hydride:



(150)

2.1.6 Oxidative decarboxylation of γ-oxo acids

Lead dioxide is reported to bring about the oxidative decarboxylation of 3-benzoy1-2-phenylpropionic acid (151) to yied chalcone[174].



(151)

2.1.7 Photo-Fries reaction

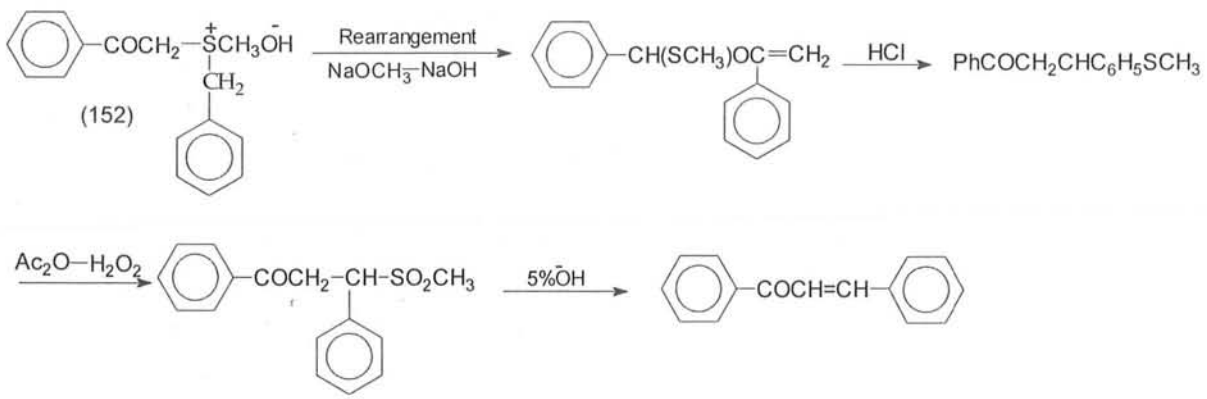
Photo-Fries rearrangement of phenyl cinnamates has been exploited for the synthesis of 2'-hydroxychalcone (20-50%). The same reaction has been extended to the synthesis of 2',3',2',4'- and 2',5'-dihydroxychalcones from the corresponding hydroxypheny1 cinnamates[175]. The synthesis of 2',3',5''-trihydroxychalcone has been achieved by the photolysis of 2,4-dihydroxycinnamate (the hydroxy1 groups protected by methoxymethylation) followed by treatment with methanolic hydrochloric acid[176].

2.1.8 Benzal chloride and acetophenone

Chalcone, in 75% yield, is reported to be formed by heating a mixture of benzal chloride and acetophenone at 120-130^0 in the presence of copper powder[177].

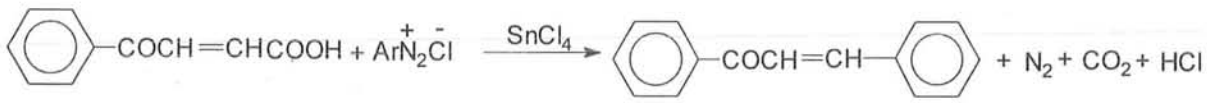
2.1.9 Methylbenzylphenacylsulfonium hydroxide

The synthesis of chalcone from methylbenzylphenacylsulfoniumhydroxide[178] (152) involves a number of synthetic steps, thus



2.1.10 β-Benzoylacrylic acid

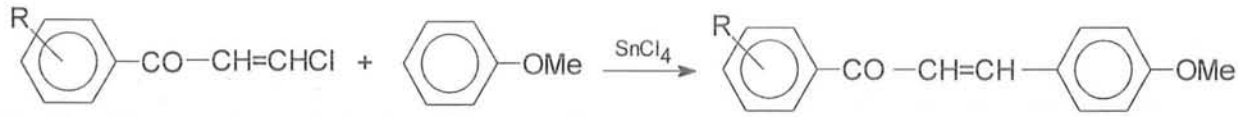
Aryldiazonium chloride (carrying an electon-withdrowing substituent) reacts with trans-β-benzoylacrylic acid[179,180] (153) to give chalcones. The aryl group attacks the carbon atom α-of the carboxylic group, and this initial coupling is followed by decarboxylation.



(153)

2.1.11 β-Chlorovinyl ketone

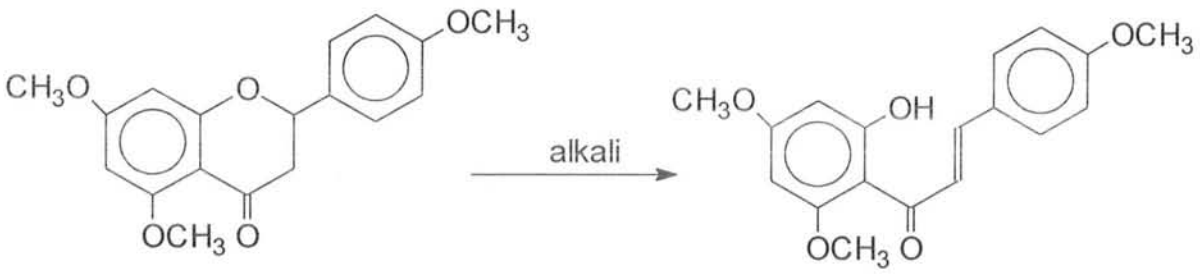
Substituted β-chlorovinyl ketone (154) has been condensed with phenolic ethers[181-183] in the presence of stannic chloride to give chalcones in fairly good yield (47-65%).



(154)

2.1.12 Treatment of flavanone with alkali

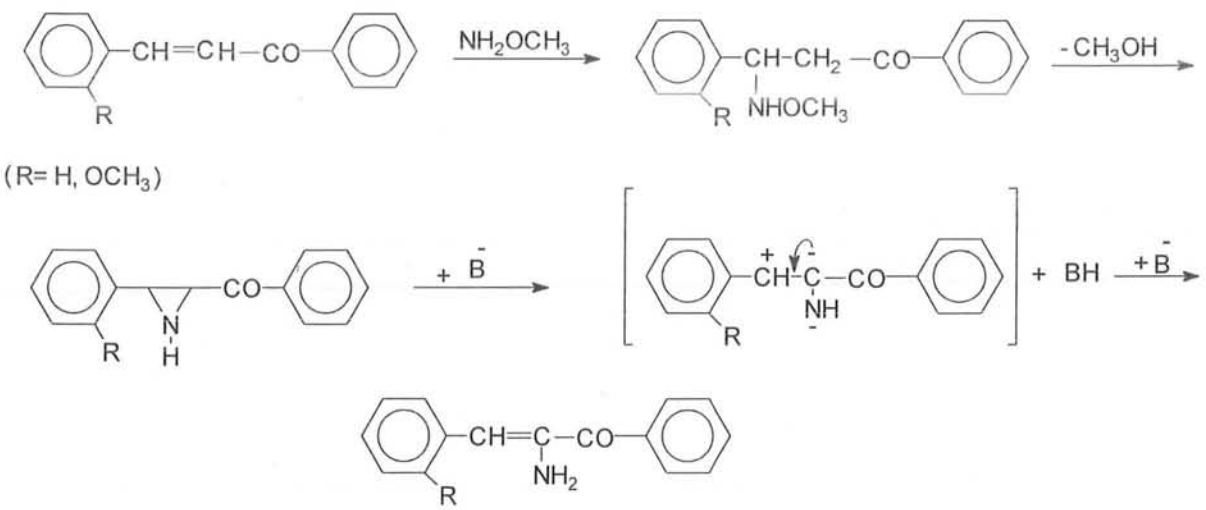
Treatment of flavanones with alkali results in the opening of γ-pyrone ring and formation of 2'-hydroxychalcone[184-187]. Thus satisfactory yield of 2'-hydroxy-4,4',6'-trimethoxychalcone has (II) been obtained from 4',5,7-trimethoxyflavanone (I) in this manner.



(I) (II)

2.1.13 α-Aminochalcones

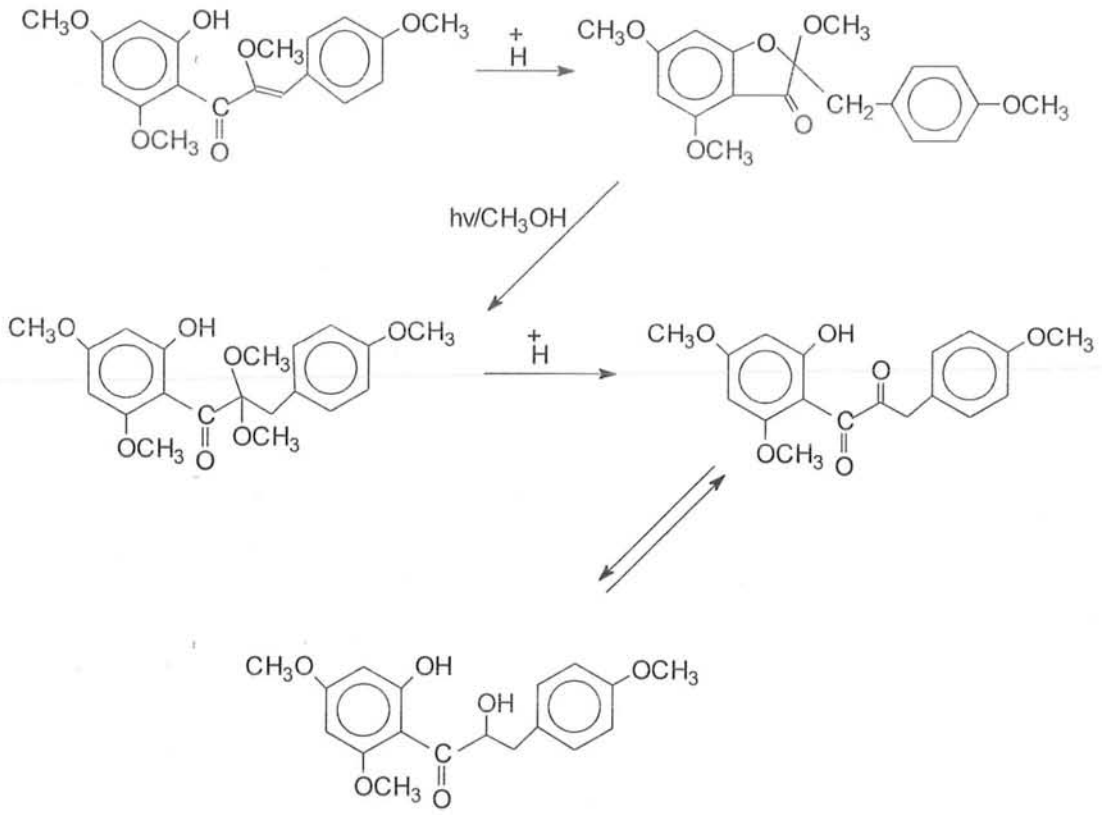
The synthesis of α-amino chalcone[188] (155) has been achieved by the following series of reactions



(155)

2.1.14 α-Hydroxychalacones

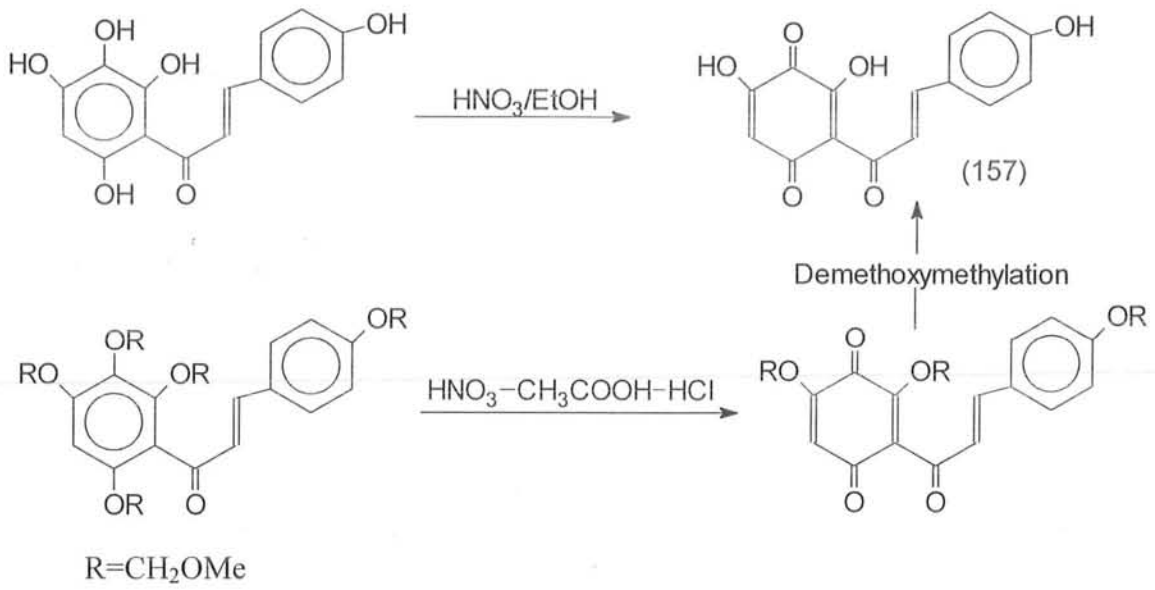
A multistep synthesis of α-hydroxychalcone (156) has been described and involves the following sequence of reaction steps[189]



(156)

2.1.15 Quinochalcones

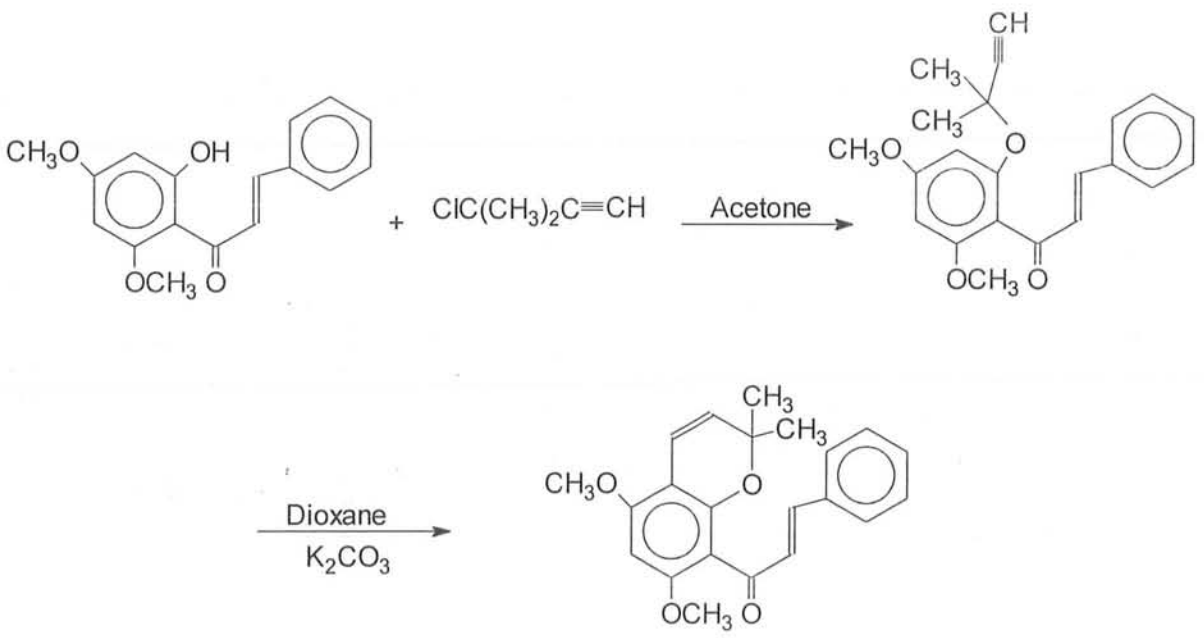
The synthesis of some quinochalcone (157) has been achieved by the oxidation of appropriately substituted hydroxychalcones[190]. The preparation of 2', 4, 4'-trihydroxy-3', 6'-quinochalcone serves as an illustrative example



R=CH_2OMe

2.1.16 Chromenochalcones

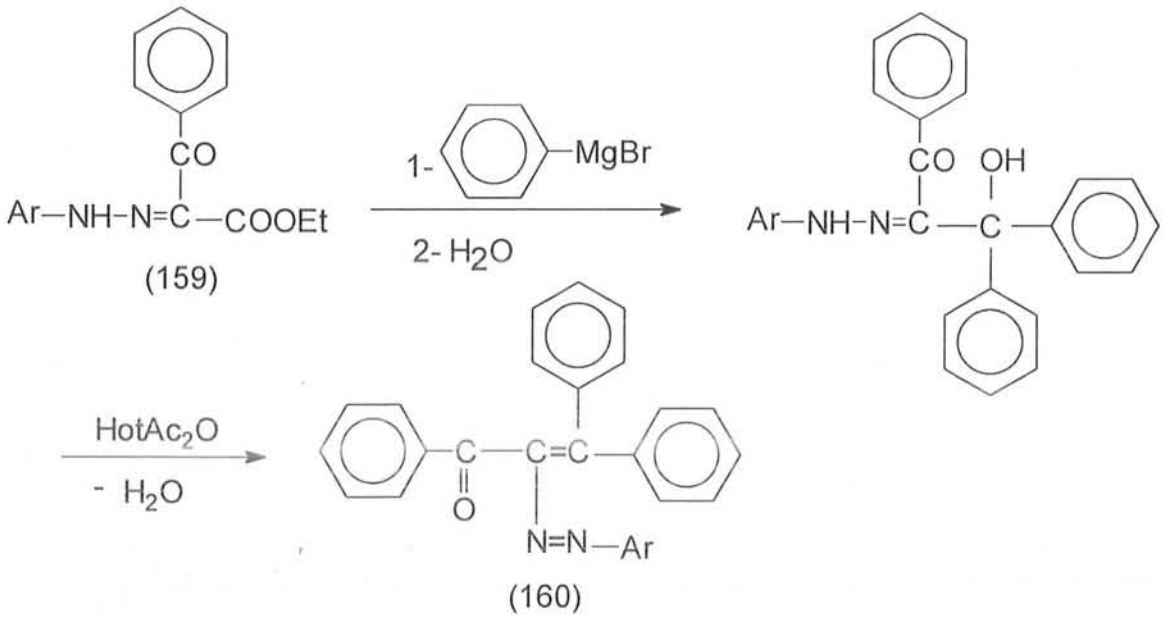
A method for the preparation of chromenochalcone (158) is described and involves the following steps[191]



(158)

2.1.17 α-Arylazo-β-arylchalcones

Starting from α,β-diketoester (159), α-arylazo-β-arylchalcone (160) have been synthesized[192]. Thus



2.2 Reactions of Chalcones

2.2.1 Reduction of olefine group

Chalcone on catalytic hydrogention with Raney nickel in ethanol yields benzylacetophenone[193-197]. The latter compound has been secured in high (yield (96%) by employing dichloroethane in place of ethanol as a solvent.

2.2.2 Reduction of carbonyl group

p'-Methylchalcone is reduced by hydrogen to the corresponding unsaturated secondry alcohol[198] by using platinum black and a large excess of ferric chloride. Selective reduction of the carbonyl group in chalcone has likewise been achieved by using an optimum amount of palladium catalyst (promoters: ferrous sulfate-zinc acetate) at ordinary atmospheric pressure and room temperature[199]. Hydrogenation of chalcone at atmospheric pressure, with colloidal palladium or with palladium precipitated on animal charcoal, is reported to reduce the carbonyl group smoothly[200].

2.2.3 Reduction of olefinic and carbonyl groups

1,3-Diphenylpropanol has been secured by the catalytic hydrogenation of ehanolic solution of chalcone with Raney nickel. According to a report the same transformation has been accomplished in 45 minutes by incorporating traces of alkali in the reaction medium.

2.2.4 Saturation of olefine bond and reduction of carbonyl to methylene group

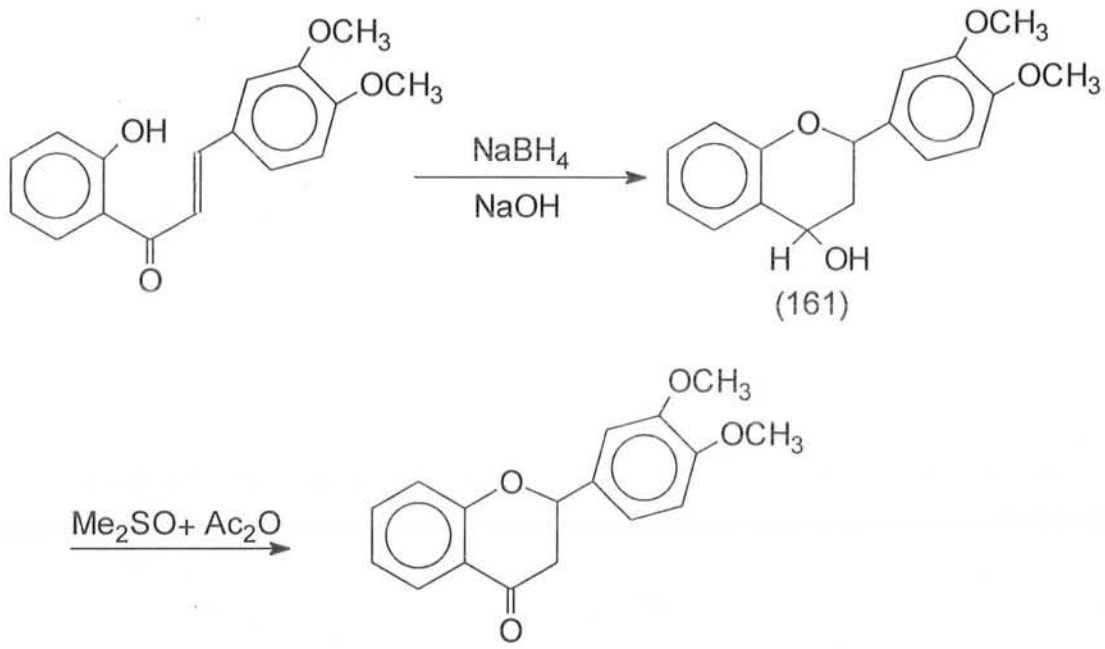
Cathalytic reduction of chalcone by hydrogen in the presence of nickel (reduced at 250^0, and partial deactiviated at 200^0C yields 1, 3-diphenylpropane. A quantitative yield of this compound is obtained by the catalytic hydrogenation of chalcone with platinum catalyst[201] in ethanol in the presence of concentrated hydrochloric acid.

2.2.5 Reduction of aromatic rings and enone function

Chalcone undergoes hydrogenation in the presence of activated nickel catalyst at elevated temperature to give dicylohexylpropane[202]. Formation of a similar perhydro compound is reported in the case of *p*'-methylchalcone, using platinum black as a catalyst.

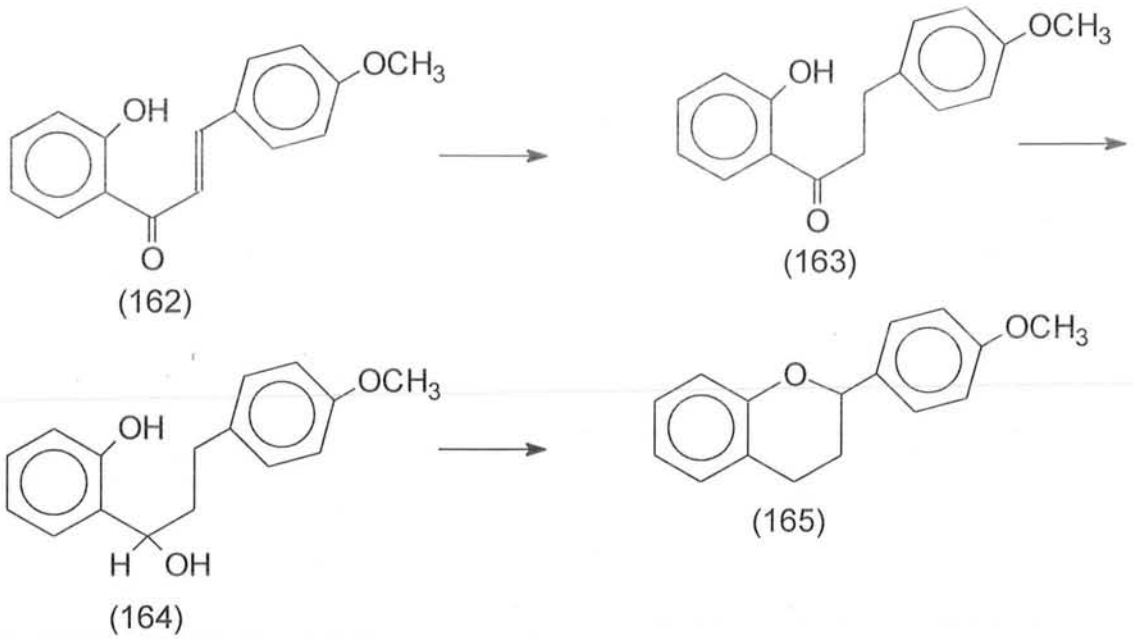
2.2.6 Alkali metal borohydrides

The synthesis of flavan-4-ol (161) and its corresponding flavnone has been achieved by reacting chalcone with $NaBH_4$ in NaOH[203]



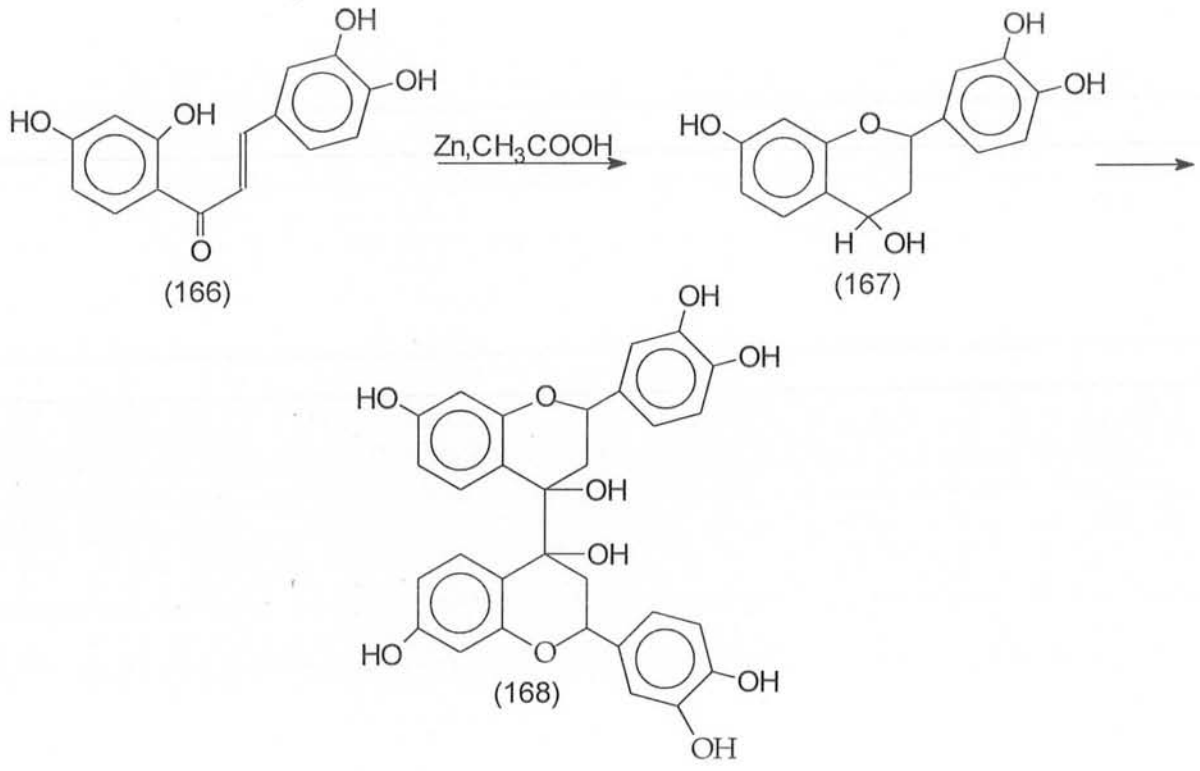
2.2.7 Hydrogenolysis

In the hydrogenolysis of some chalcones two isomeric disubstituted propenes have been obtained[204,205]. In one instance the formation of an additional compound, 1- (*o*-hydroxyphenyl)-3-phenyl-1-propanone, has been reported. It is interesting to note that 2'-hydroxy-4-methoxychalcone (162) on hydrogenolysis yield three products: a saturated ketone (163), a secondary alcohol (164) and 4'-methoxyflavan[206] (165).



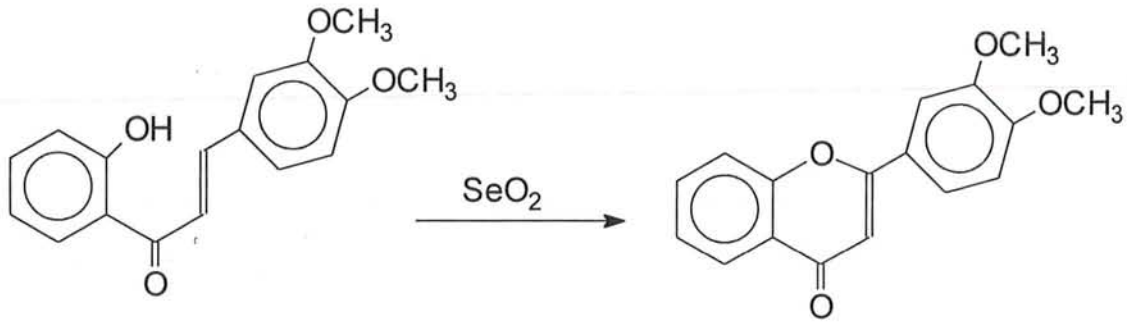
2.2.8 Reduction by metals

Butein (166) on reduction with zinc in ethyl alcohol-acetic acid yields the corresponding flavan (167) or the pinacol[207] (168):



2.2.9 Reaction with selenium dioxide

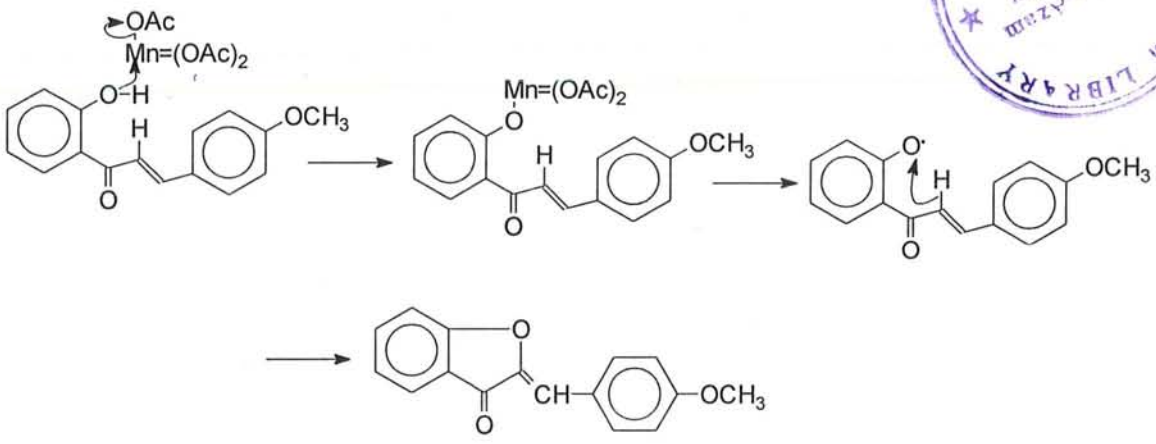
Chalcones are oxidized smoothly with selenium dioxide to the flavones (169). The following serves as an example for such a transformation[208-210]



(169)

2.2.10 Reaction with manganic acetate

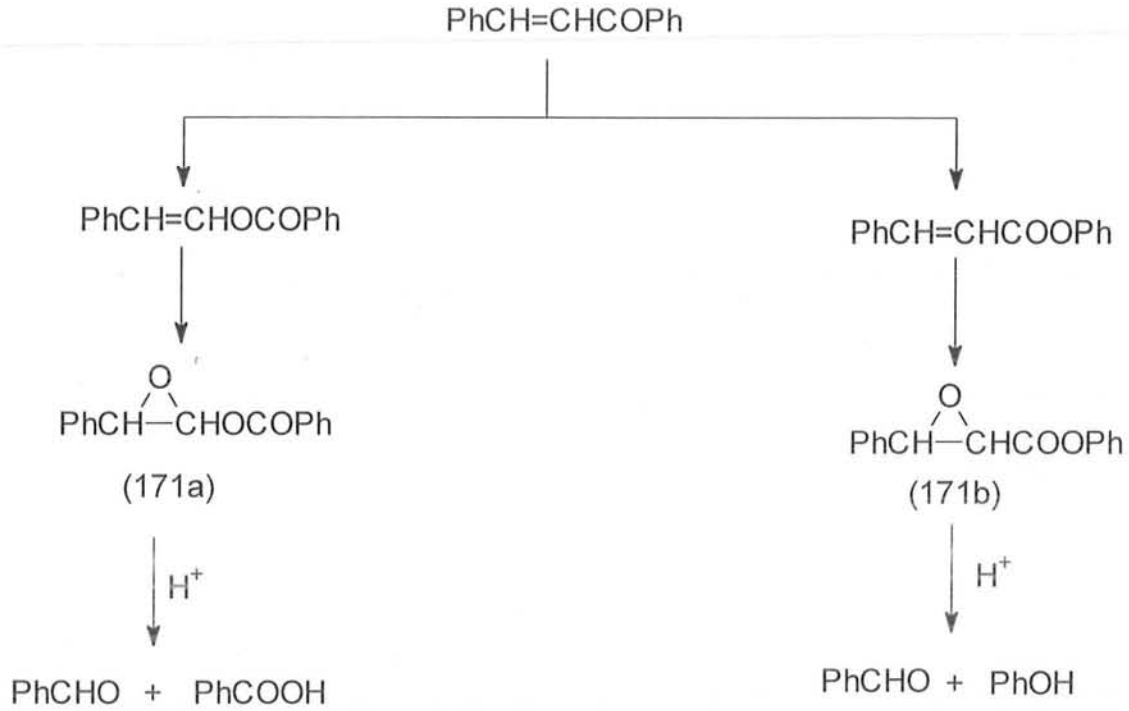
Fairly good yields of aurone[211] (170) is obtainable from 2'-hydroxychalcones by oxidation with manganic acetate in acid. The mechanism of the reaction is outlined as follows



(170)

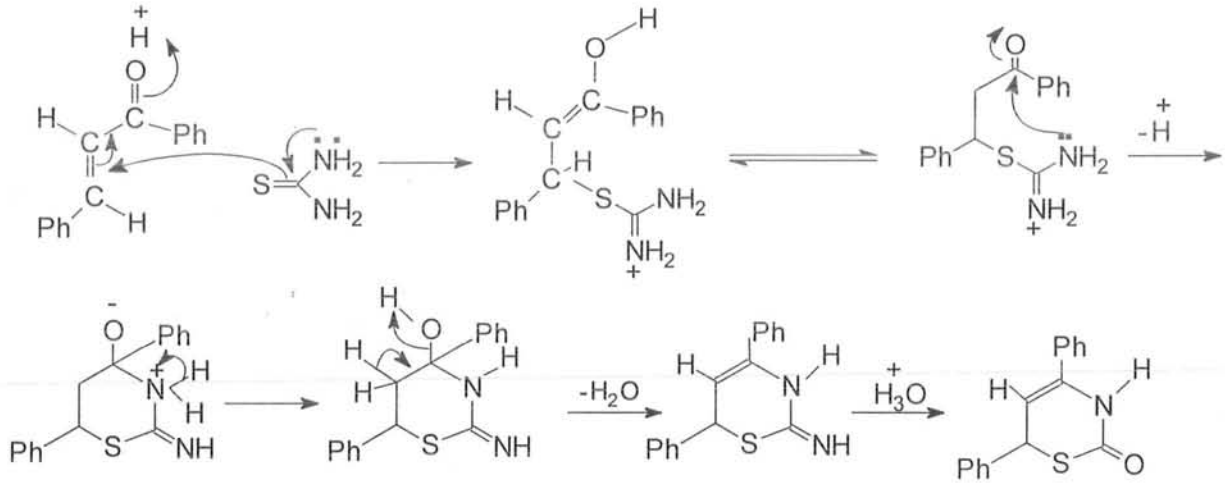
2.2.11 Reaction with perbenzoic acid

The reaction of perbenzoic acid with chalcone has been studied[212]. The oxidation of chalcone is considered to proceed through the intermediate formation of epoxy esters[213] (171a), (171b), as follows



2.2.12 Reaction with thiourea

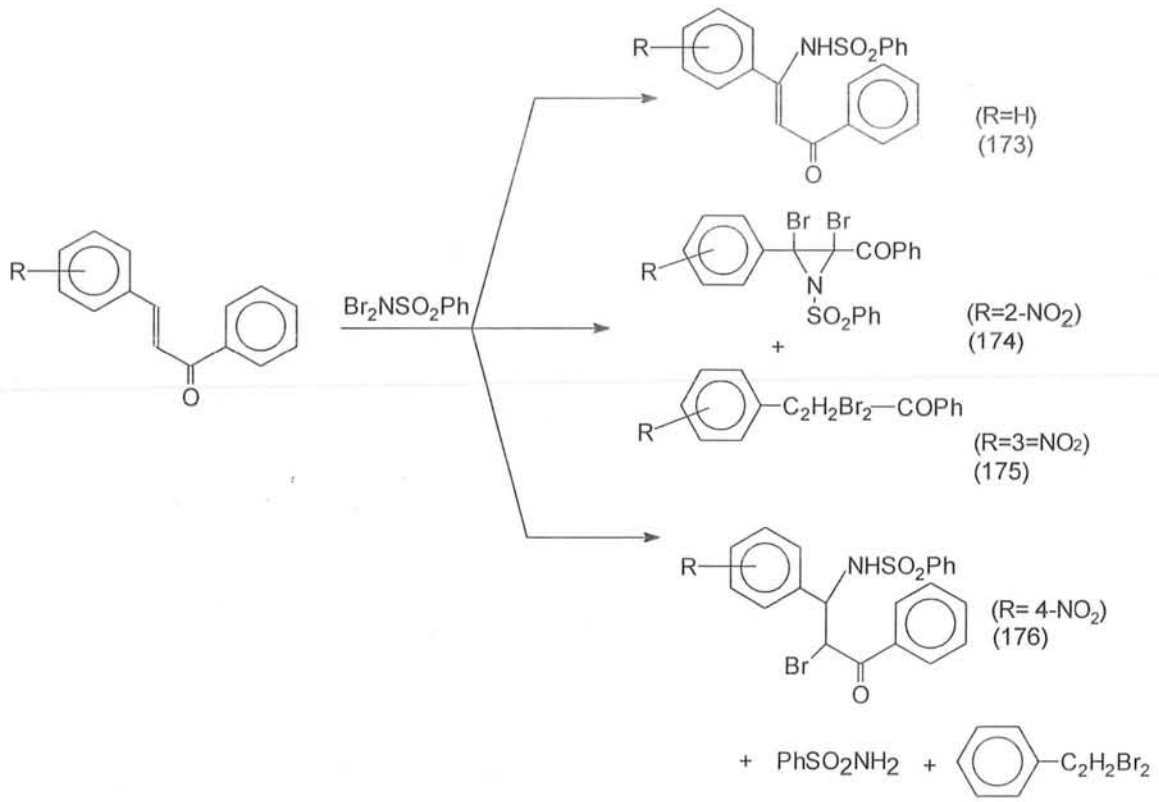
2-Oxo-4, 6,-diphenyl-3, 6-dihydro-1,3-thiazine (172) is obtainted by the reaction of chalcone with thiourea in the preaence of dilute sulfuric acid[214]. The formation of (172) has been rationalized as follows



(172)

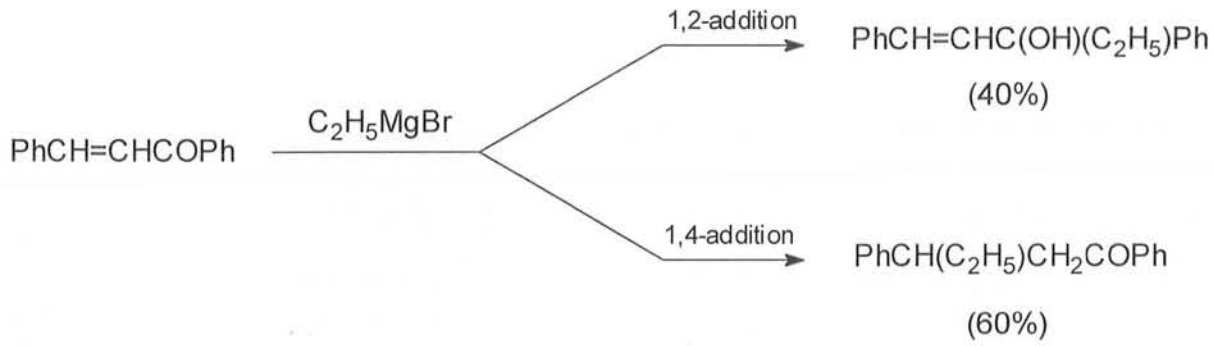
2.2.13 Recation with *N,N*-Dibromobenzenesulfonamide

The reaction of *N, N*-dibromobezenesulfonamide with chalcones presents an interesting example. Thus different products (173), (174), (175), (176) are formed[215] with variously substituted chlcones



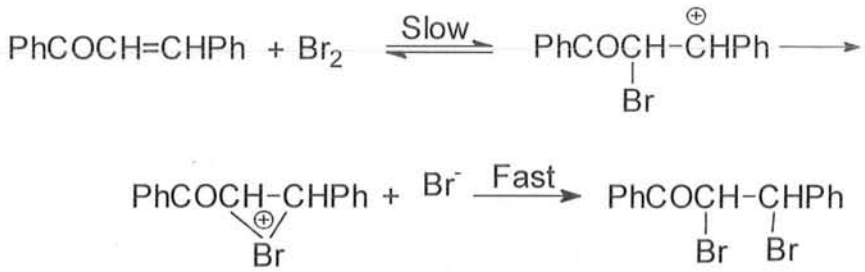
2.2.14 Recation with Grignard reagent

The products formed in the reaction of chalcone with ethylmagnesium bromide correspond to 1,2-and 1,4-addition[216].



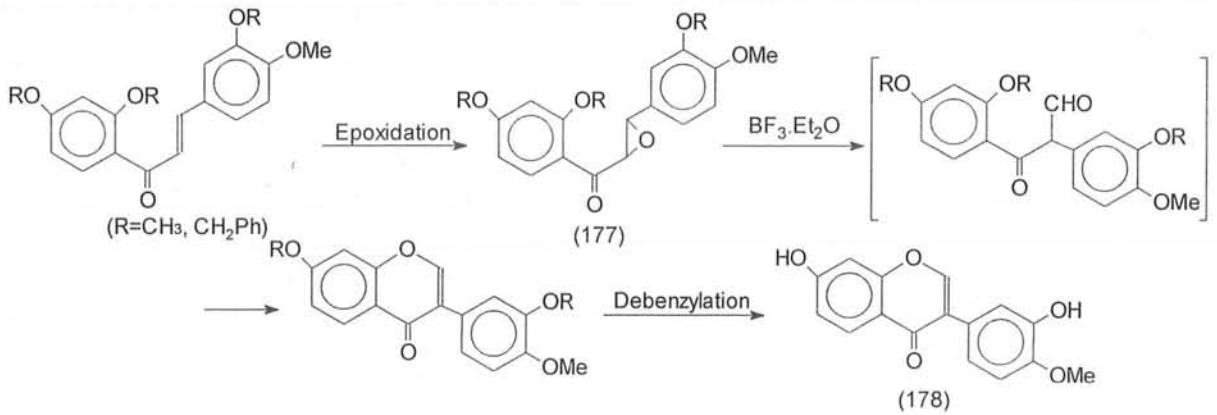
2.2.15 Reaction with bromine

A large number of chalcone α,β-dibromides have been prepared[217-227]. The kinetics of bromine addition to chalcone and its derivatives has been investigated[228, 229], and a two-step mechanism of this reaction has been proposed.



2.2.16 Formation of isoflavones

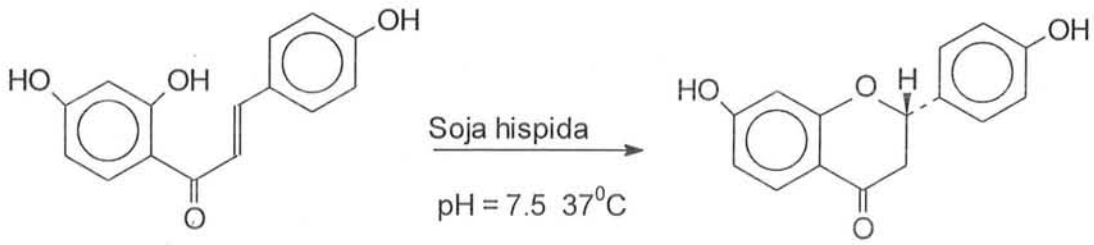
The methods are available for the synthesis of isoflavones from chalcones[230-232]. The method indolves the preparation of an epoxide (177), followed by BF_3-catalyzed rearrangement and cyclization. The preparation of 3',7-dihydroxy-4'-methoxyisoflavone (178) is illustrated as



2.2.17 Formation of flavanones

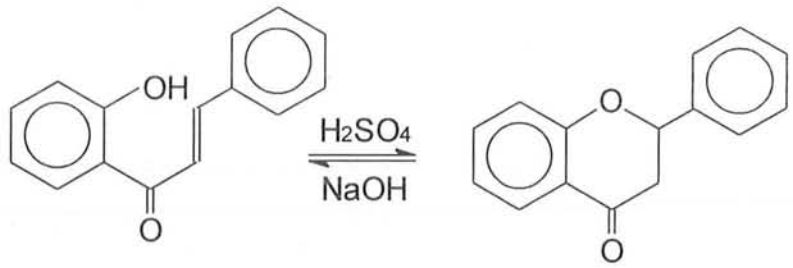
The interconversion of chalcone and flavanone with a phloroglucinol type of substitution has been accomplished at pH 7 by the aid of an enzyme isolated from the peel of *citrus aurantium*[233]. Other sources of the enzyme are the peels of *C. natsudaidai, C. Junos, C. nobilis, C. Pseudoparadisi,* and *poncirus trifoliate.*

2', 4', 4-trihydroxychalcone (179a) has been successfully isomerized[234] to the optically active 4',7-dihydroxyflavanone (179b) by the mediation of the isomerase isolated from soyabean seedling



(179a) (179b)

2'-Hydroxychalcone (III) can also be converted to flavanone (IV) by refluxing in sulfuric acid. There is equilibrium exists between chalcone and flavanone[235].

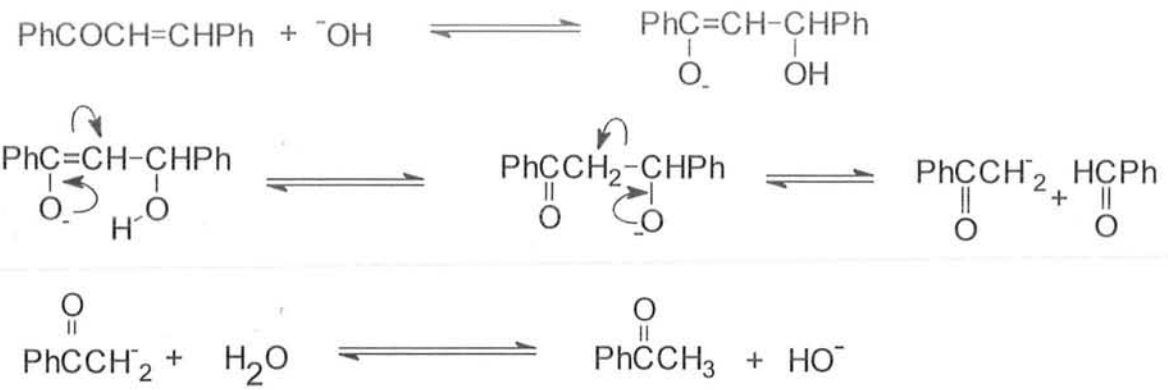


(III) (IV)

2.2.18 Reaction with caustic alkali

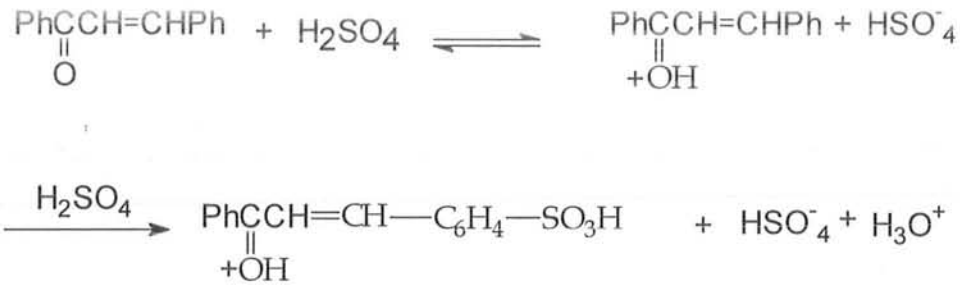
The olefinic bond in the chalcone molecule undergoes cleavage when refluxed with concentrated alkali (i.e., 0.3 *M*)[236] giving rise to acetophenone and benzaldehyde. A kinetic

study of the above reaction has been carried out, and a mechanism[237] has been put forward to explain the formation of these products



2.2.19 Recation with sulfuirc acid

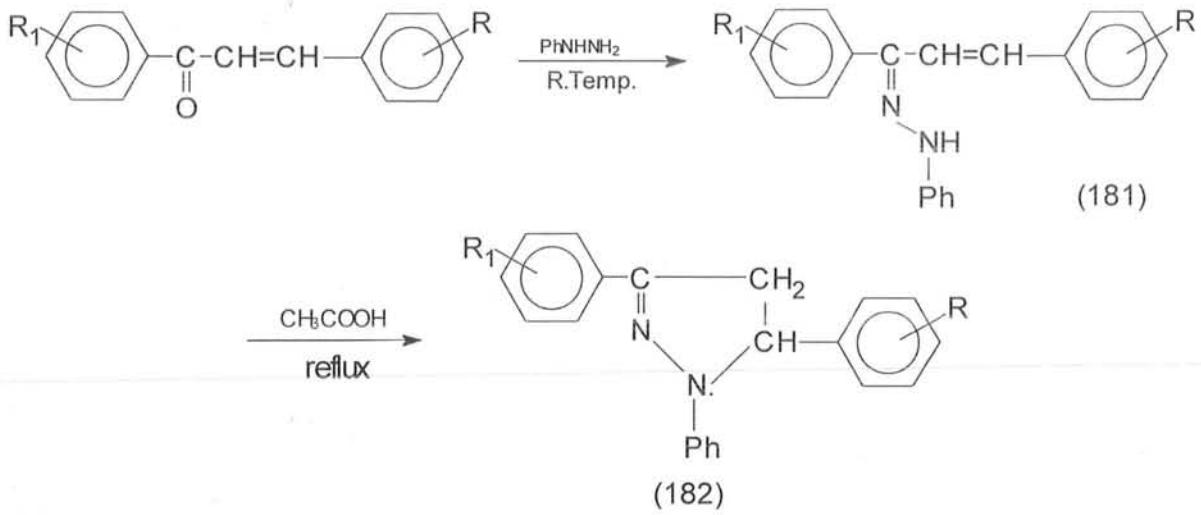
Chalcone is converted to their sulfonic acid derivative (180) when wetted with concentrated sulfuric acid[238, 239].



(180)

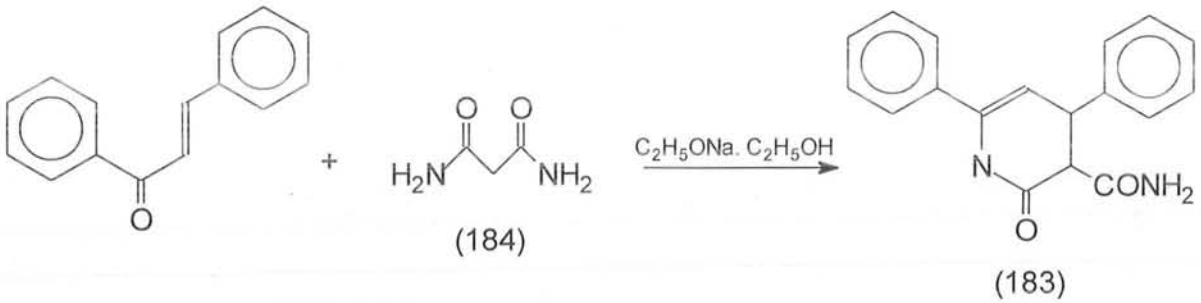
2.2.20 Reaction with phenylhydrazine

Chalcones react with phenylhydrazine in acetic acid medium to yield the corresponding phenylhydrazones[240-243] (181). The phenylhydrazones can be transformed into 1,3,5-triphenylpyrazolines[244] (182) by refluxing these with acetic acid.



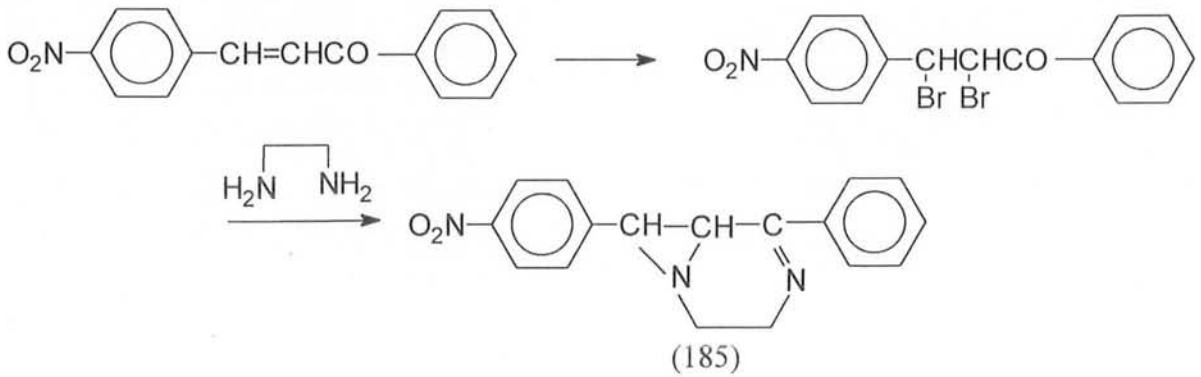
2.2.21 Recation with malonamide

Chalcone gave high yield of 2-pyridone[245] (183) by the direct condensation with malonamide (184) in the presence of EtONa.EtOH.



2.2.22 Formation of aziridinyl anil

Chalcone is converted to α,β–dibromide which when reacted with diamines[246] to give aziridinyl anil (185).



CHAPTER 3

Experimental, Results & Discussion

CHAPTER 3

3.1Plan of Work

This chapter describes the type of methods, experimental procedures and instrumentation used for the synthesis of following series of compounds.

A) B-ring substituted chalcones

B) 2'-Methy B-ring substituted chalcones

C) 2'-Hydroxy B-ring substituted chalcones

D) 5'-Chloro-2'-hydroxy B-ring substituted chalcones

Experimental procedures, physical constants and spectral data of first member of each series are discussed in detail where as physical constants and spectral data of other members of the series are presented collectively in tabulated form.

3.2 Experimental

Substrate and Reagents:

The following substrates and reagents were used.

Acetyl chloride, acetophenone, phenol, p-chlorophenol, aniline, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, 2-chlorobenzaldehyde, 4-chlorobenzaldehyde, 3-methylbenzaldehyde, 4-methylbenzaldehyde, 4-bromobenzaldehyde and 4-fluorobenzaldehyde which were obtained from Fluka. The liquid reagents were distilled at their boiling points and the solid reagents were characterized by recording their melting points. No further purification was required. Sulphuric acid and hydrochloric acid (37%) were obtained from Stedec Ltd.

Solvents:

The following solvents were purchased from BDH (England), purified and dried using standard procedures[247] which are described below.

Chloroform

Chloroform was treated with excess amount of water then dried over by using 200gms. / L of $CaCl_2$ and then distilled at 61 ^{0}C.

Dichloromethane

Dichloromethane was treated with successively small portions of conc. H_2SO_4 until the two layers became colorless. The organic layer was then treated with a concentrated

aqueous solution of sodium carbonate followed by distilled water. Organic layer was separated and dried with 150gms/L of $CaCl_2$ after which it was distilled at 40-41^{0}C. Distilled dichloromethane was stored in brown bottle over 4 Å molecular sieves.

Ethyl acetate

In one liter of ethyl acetate 50ml of acetic anhydride and 10~15 drops of conc. H_2SO_4 was added and refluxed for 5 hours. It was fractionated and treated with 25gms of anhydrous potassium carbonate. This mixture was filtered and distilled over 40gms of CaH_2 at 77 ^{0}C.

Pet-ether

Pet-ether was obtained by fractional distillation of petroleum in the range of 40-60^{0}C.

Acetone

200 grams of $CaCl_2$ (anhydrous) was introduced into a round bottom flask containing one liter of acetone and it was left for 4~5 hours. Pure acetone was distilled at 56 ^{0}C.

Absolute methanol

250 grams of CaO dried in an oven at 120 ^{0}C was introduced into a round bottom flask containing one liter of methanol. It was refluxed for 6 hours and then distilled at 68 ^{0}C.

Absolute ethanol

Procedure for absolute ethanol is the same as described for absolute methanol however it was distilled at 77-78 ^{0}C.

3.3 Instrumentation

R_f values were calculated by using precoated Silica gel aluminum plates HF-254 Merck (Germany), in Ethylacetate: pet-ether (1:9). Melting points of the compounds were determined in open capillaries using Gallenkemp melting point apparatus. UV spectra were recorded on 1601-Schimadzu (Japan) in MeOH. IR spectra were recorded on 460-Schimadzu spectrophotometer using KBr discs or neat liquid. ^{1}H NMR (400 MHz) spectra were recorded on Bruker AM-250 in CD_3OD solution using TMS internal standard. EIMS was recorded on MAT-311-A machine. Purity of compounds was monitored by Shimadzu HPLC LC-6A.

3.4 Methods Used for the Synthesis of Chalcones

Synthesis of chalcone has been accomplished using two different approaches

3.4.1) Claisen-Schmidt condensation

3.4.2) Schiff Base Reaction:

3.4.1 Claisen-Schmidt Condensation

The simplest approach for the synthesis of chalcones involves the Claisen-Schmidt condensation. This condensation reaction involves reacting equimolar quantities of acetophenone with benzaldehyde in the presence of aqueous alcoholic alkali (e.g. potassium hydroxide) or sodium ethoxide, resulting in the formation of an α,β-unsaturated ketone **(Fig 1).**

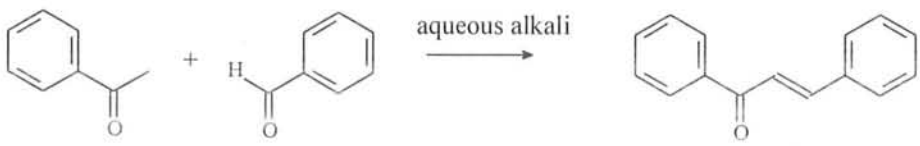


Figure 1. Chalcone formation by the Claisen-Schmidt condensation

From kinetic studies on the base catalysed formation of chalcone and its derivatives, two alternative mechanisms[248-250] have been proposed for the reaction of benzaldehyde with acetophenone in the presence of a basic catalyst. In the first mechanism **(Figure 2),** the base abstracts a proton from the methyl group of acetophenone, creating a nucleophile which then attacks the electrophilic carbon atom of benzaldehyde to form the intermediate (i), which then accepts a proton from water to form the intermediate (ii). The intermediate (ii) then undergoes a dehydration step to form the chalcone.

In the second mechanism, the ethoxide anion acts as a nucleophile and attacks the electrophilic carbon atom of benzaldehyde forming intermediate (i) **(Figure 3).** The nucleophilic acetophenone then attacks the electrophilic centre of intermediate (i), with the

negative oxygen ion simultaneously accepting a proton from the solution to form intermediate (ii), which then undergoes a dehydration step to form the chalcone.

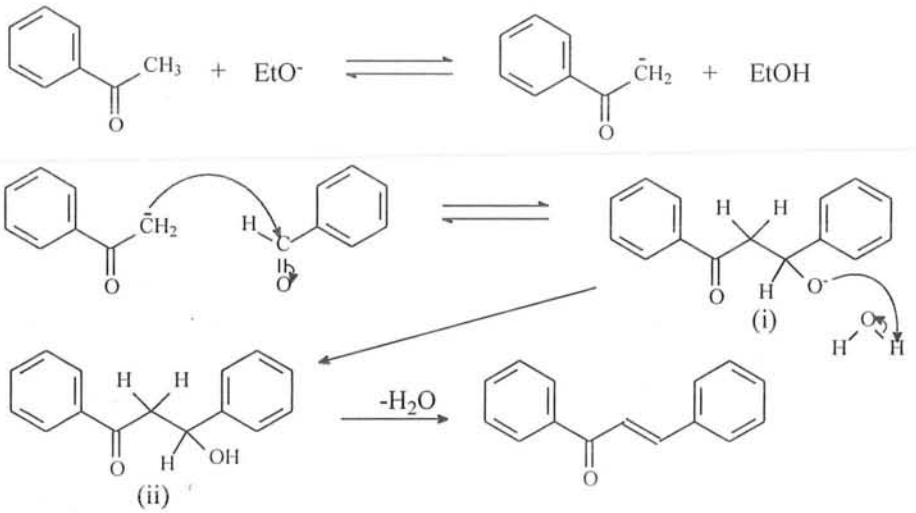


Figure 2. Mechanism of chalcone formation by carbanion.

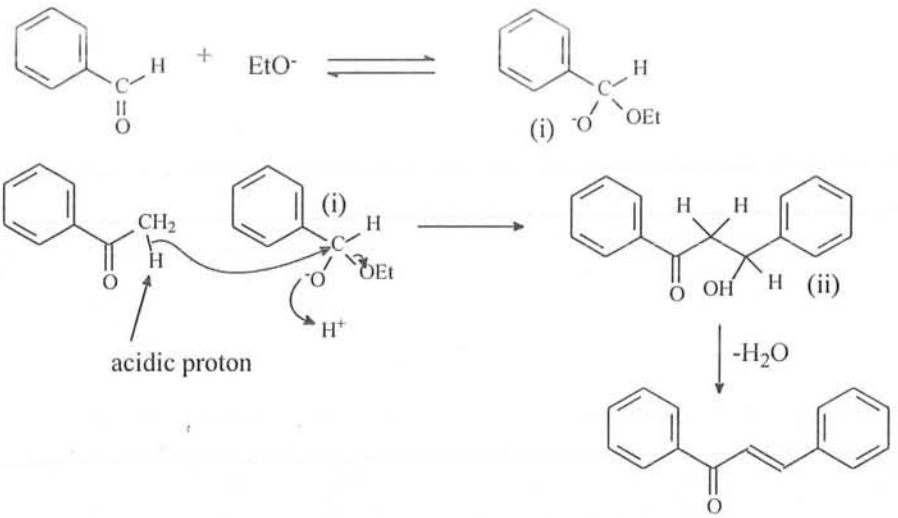


Figure 3. Mechanism of chalcone formation by ethoxide.

In the Claisen-Schmidt reaction, the concentration of alkali usually ranges between 10 and 60%[251-269].

Schiff's bases are reported to react with acetophenone and its derivative in the presence of a catalytic amount of amine hydrochloride to yield β-arylaminoketone (I).

On heating with concentrated hydrochloric acid these ketones undergo the hydramine cleavage to yield primary aromatic amine and chalcone. Hydramine cleavage is favored by the presence of electron-withdrawing substituents in β-arylamineketones (Fig 4).

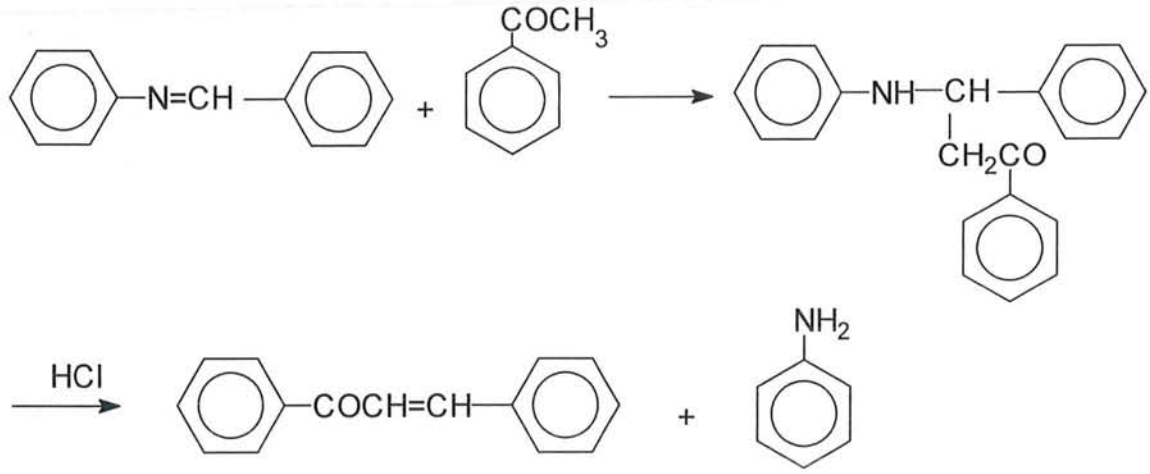


Figure 4. Chalcone Formation by Schiff Base Method

The mechanism of the reaction is as follow (Fig 5)

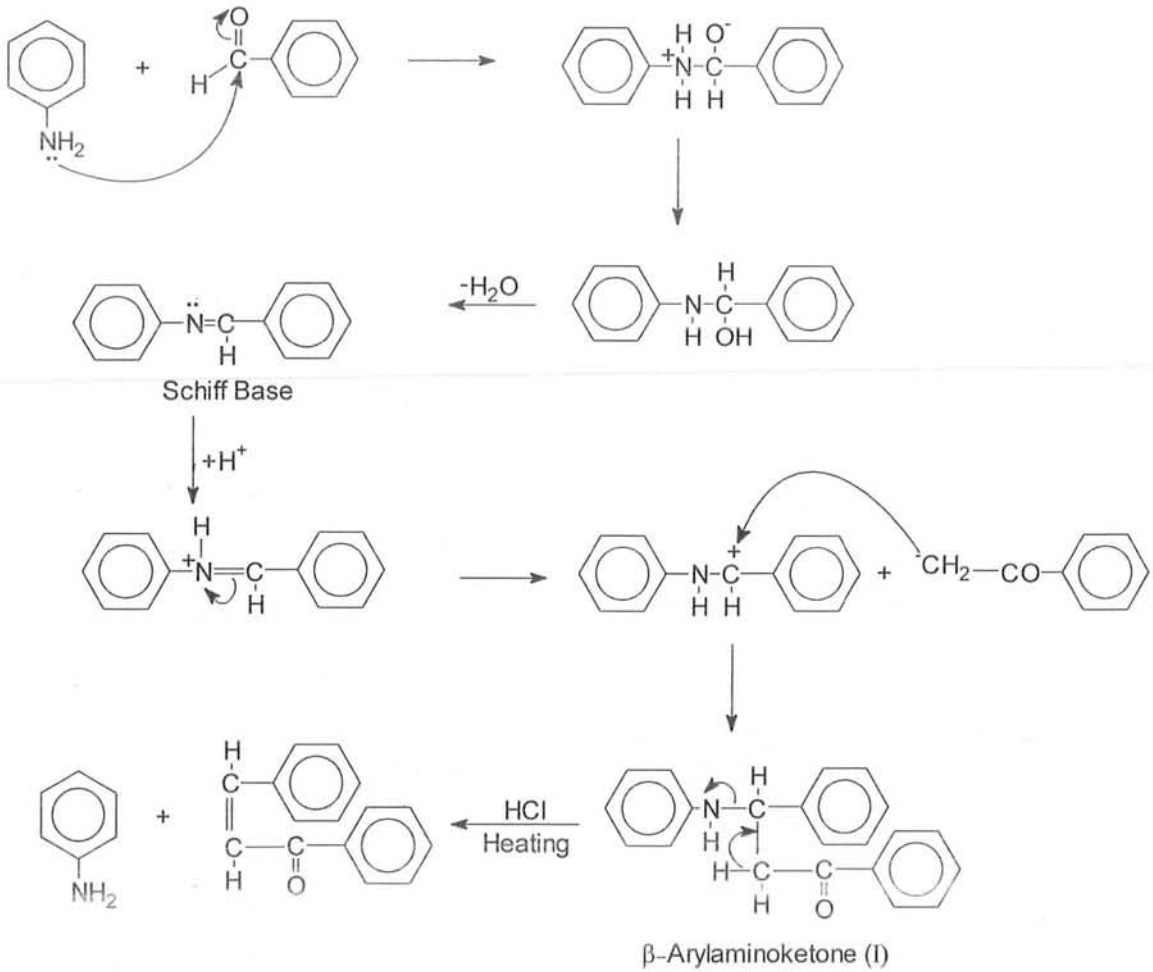
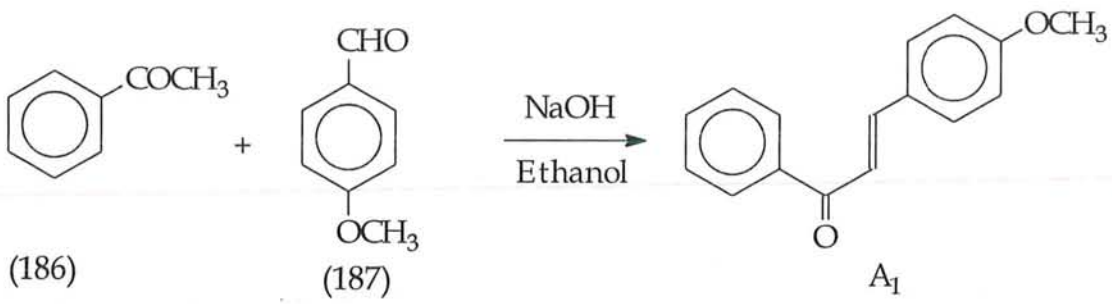


Figure 5. Mechanism of Chalcone Formation by Schiff Base Method

We have adopted Claisen Schmidt method for the synthesis of target chalcones due to the following reasons,

i) High yield
ii) Easy to handle
iii) Manipulation of common glassware etc.

3.5 Synthesis of B-Ring Substituted Chalcones (A-series Chalcones)



(186) (187) A_1

Scheme 2

3.5.1 Synthesis of 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one (A_1)

3.5.1.a Synthesis of Anisaldehyde (187)

30g(30ml, 0.28mol) of anisole was placed in 500ml three necked flask with a reflux condenser, an efficient sealed stirrer and a wide inlet tube. 75ml of sodium dried benzene was added along with 52g (0.44mol) of powdered zinc cyanide. The mixture was cooled in a bath of cold water. The stirring was continued with a rapid steam of hydrogen chloride for 1 hour. The gas inlet tube was removed without stopping the stirrer. 45g of powdered anhydrous aluminum chloride were added slowly. The reaction mixture was allowed to cool and dilute HCl was added. The imine hydrochloride separated as a heavy precipitate. The mixture was refluxed for half an hour in order to decompose the imine hydrochloride and steam distilled the organic layer was separated and benzene is distilled off. The anisaldehyde was distilled at 246-248^{0}C. The yield was 30g (78%). The **IR** showed carbonyl stretching at 1675 and aldehydic C-H stretching at 2610 cm^{-1}.

3.5.1.b Claisen-Schmidt Condensation

80ml of 4.0 M solution of sodium hydroxide was dissolved in 60ml of rectified spirit in a conical flask. The solution was cooled in an ice bath to 0^{0}C. 1.86ml (0.016moles) of

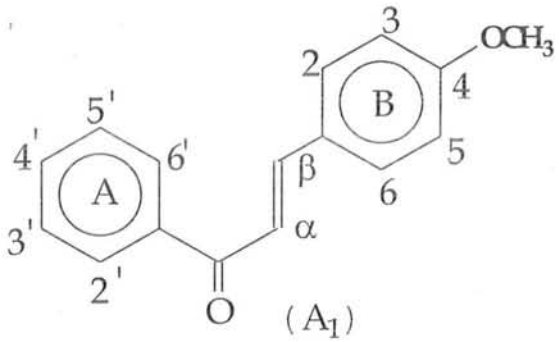
freshly distilled acetophenone **(186)** were added to it. The mixture was stirred by a magnetic stirrer for half an hour in an ice bath keeping the temperature at 0-5^{0}C. Then 1.94ml (0.016moles) of 4-methoxybenzaldehyde **(187)** were added and mixture was stirred vigorously for 2-3 hours. The reaction mixture was kept at 0-5^{0}C for overnight. The thick oil obtained was diluted with chilled water and aqueous hydrochloric acid was added to neutralize it. The product was obtained as yellow precipitates. The precipitate was filtered and recrystallized from aqueous ethanol to afford 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)**. Further purification of chalcone was carried out on preparative TLC plates [silica gel HF-60 in pet-ether : ethylacetate (9:1)]. The purity was also checked by HPLC using solvent system Acetonitrile: Water (80:20). **(Chromatogram 1)**. Yield of 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)** was 3.2g (0.013mol, 81%). m.p.65^{0}C. **UV** (λ_{max}^{MeOH}) 341 nm & 264 nm, **IR** (υ_{max}, KBr): 1635, 1596cm^{-1}; **^{1}H-NMR** (CD_3OD, δ-values in PPM); 6.99 (2H, dd, J=1.9, 7.02 Hz), 6.97 (2H, dd, J=1.9, 7.03 Hz), 7.59 (1H, d, J=15.47 Hz), 7.75 (1H, d, J=15.49 Hz), 8.05 (2H, ddd, J=1.9, 1.4, 7.3), 7.50-7.54 (2H, m), 7.68 (1H, m), 3.84 (3H, s); **EIMS** (70 eV): m/z (%)= **238 (100% M^+),** 237 (62.46), 223 (27.02), 210 (6.2), 208 (4.21), 161 (49.15), 131 (15), 121 (9.3), 105 (60.93), 77 (62.46), 51 (24.17).

3.6 Results and Discussion

4-Methoxybenzaldehyde **(187)** and freshly distilled acetophenone **(186)** were reacted in ethanol for 2-3 hours at 0-5^{o}C under basic conditions to yield 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)**. Compound **A_1** was found to have a molecular formula of $C_{16}H_{14}O_2$ and molecular weight 238. Compound **A_1** gave UV absorption maxima at λ_{max}^{MeOH} 341 nm **(Band-I)** and 264 nm **(Band-II),** which is characteristic of chalcones **(Spectrum 1)**. Band-**I** results from the conjugation of the whole molecule and Band-**II** is considered due to the *cis* or the *trans* isomers. The IR spectrum showed stretching frequencies at 1635 cm^{-1} and 1596 cm^{-1} which are characteristic of C=O and aromatic C=C respectively.

The mass spectrum **(Spectrum 2)** of 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)** showed a molecular ion peak (which is also the base peak) at m/z 238 and is in agreement with its molecular weight. The peak at m/z 237 results from the simultaneous loss of hydrogen atom of the B-ring and its cyclization with the oxygen of the carbonyl group. The characteristic peaks in the mass spectrum were at m/z 223 and 210, which are due to the loss of a methyl radical and carbon monoxide respectively. Other peaks in the mass spectrum were at m/z 161, 133, 121, 105, 77 and 51 resulting from the fragmentation on both sides of the carbonyl group, a common fragmentation process in chalcones. The fragmentation pattern of 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)** is given in **(Scheme 3)**.

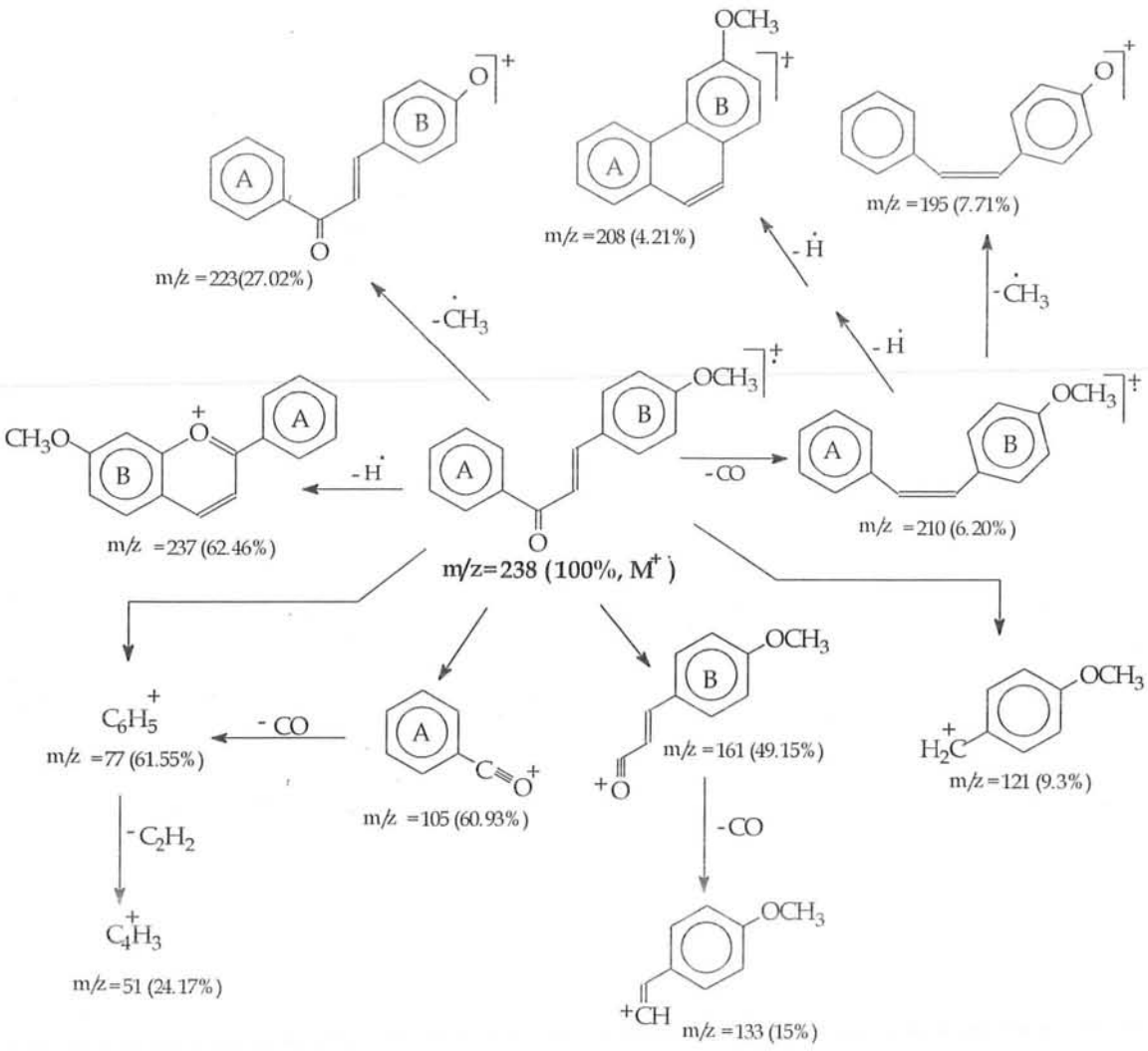
The **^{1}H NMR** spectrum **(Spectrum 3)** of compound 1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)** showed a pair of doublets at 7.59 ppm and 7.75 ppm with a large coupling constant of 15.47 and 15.49 Hz which are characteristic of *trans* olefinic protons. Thus the chalcone A_1 is *trans*-1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one. The three protons for OCH_3 group gave a singlet at δ_H 3.84 ppm. δ values, multiplicity and J values of all protons of *trans*-1-phenyl-3-(4-methoxyphenyl)-2-propen-1-one **(A_1)** are tabulated in (Table 1).



(A_1)

Table 1: ^{1}H NMR Spectral Data of Compound A_1 (CD_3OD, 400 MHz)

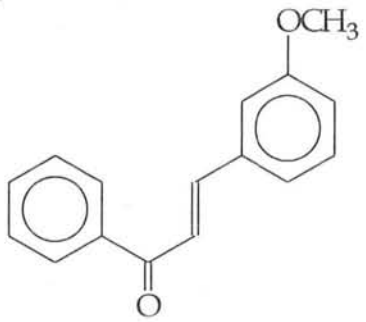
Carbon	*^{1}H-δ (ppm),*	*Multiplicity*	*J (Hz)*
2,6	6.99	2H, dd	1.9, 7.02
3,5	6.97	2H, dd	1.9, 7.03
α	7.59	1H, d	15.47
β	7.75	1H, d	15.49
2', 6'	8.04	2H, ddd	1.9, 1.4, 7.3
3', 5'	7.50-7.54	2H, m	----
4'	7.65-7.68	1H, m	----
OCH_3	3.84	3H, s	----



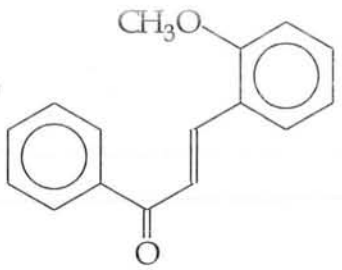
Scheme 3: Mass fragmentation pattern of A_1

Using the same synthetic procedure, other members of the A-series chalcones (A_2-A_{14}) were synthesized. Molar quantities, physical constants **UV, IR, ^{1}H NMR** and **Mass** spectral data for these 13 chalcones are presented in **(Table 2-7).** Structures of these chalcones are:

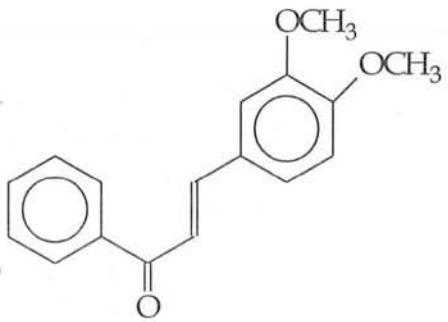
A_2 =1-Phenyl-3-(3-methoxyphenyl)-2-propen-1-one



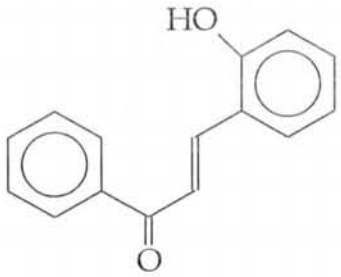
A_3 =1-Phenyl-3-(2-methoxyphenyl)-2-propen-1-one



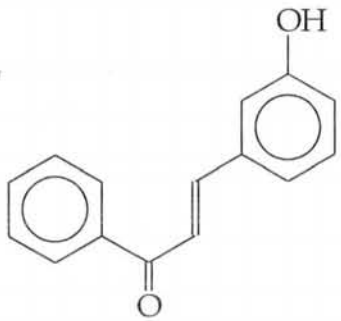
A_4 =1-Phenyl-3-(3,4-dimethoxyphenyl)-2-propen-1-one



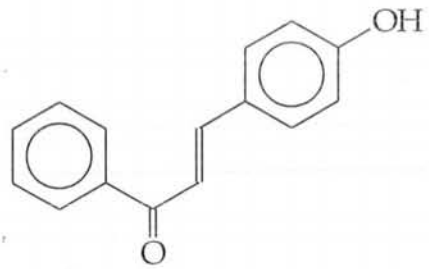
A_5=1-Phenyl-3-(2-hydroxyphenyl)-2-propen-1-one



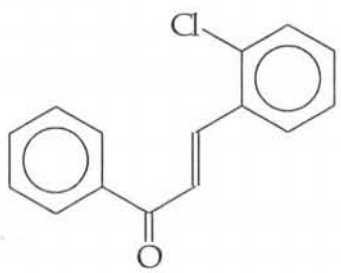
A_6=1-Phenyl-3-(3-hydroxyphenyl)-2-propen-1-one



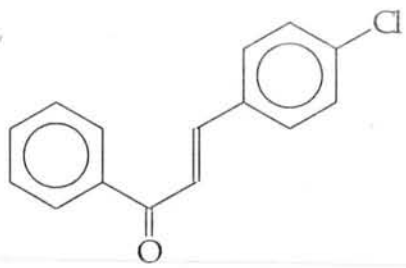
A_7=1-Phenyl-3-(4-hydroxyphenyl)-2-propen-1-one



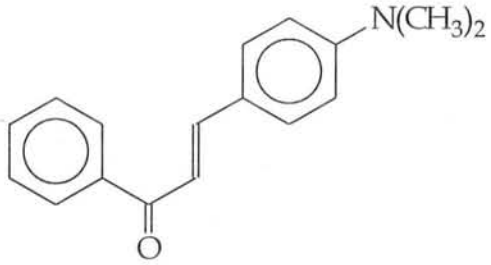
A_8=1-Phenyl-3-(2-chlorophenyl)-2-propen-1-one



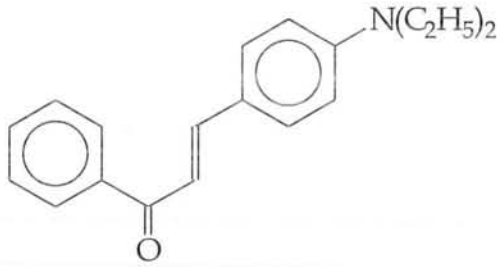
A_9 =1-Phenyl-3-(4-chlorophenyl)-2-propen-1-one



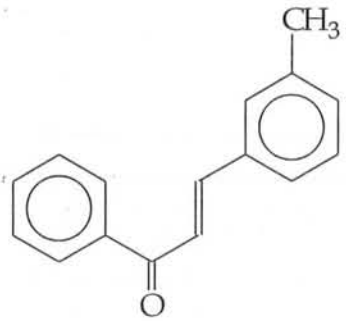
A_{10} =1-Phenyl-3-(4-dimethylaminophenyl)-2-propen-1-one



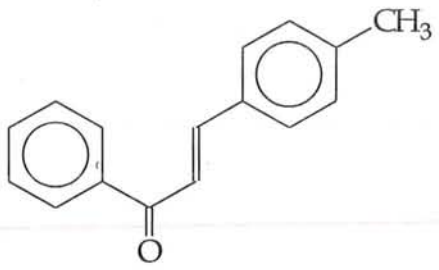
A_{11}=1-Phenyl-3-(4-diethylaminophenyl)-2-propen-1-one



A_{12} =1-Phenyl-3-(3-methylphenyl)-2-propen-1-one



$\mathbf{A_{13}}$ =1-Phenyl-3-(4-methylphenyl)-2-propen-1-one



$\mathbf{A_{14}}$ =1-Phenyl-3-(4-nitrophenyl)-2-propen-1-one

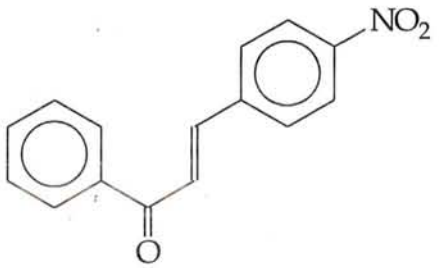


Table 2: Molar Ratios of Compounds A_2-A_{14}

Compounds	*Acetophenone*	*Substituted Benzaldehydes*	**Yield**	*Solvent for Recrystallization*
A_2	1.86ml (0.016moles)	1.94ml (0.016moles)	3.0g (0.012mol, 75%)	Ethanol
A_3	1.86ml (0.016moles)	1.94ml (0.016moles)	3.2g (0.013mol, 81%)	Ethanol
A_4	1.86ml (0.016moles)	2.65g (0.016moles)	3.4g (0.012mol, 75%)	Ethanol
A_5	1.86ml (0.016moles)	1.70ml (0.016moles)	2.9g (0.013mol, 81%)	Ethanol
A_6	1.86ml (0.016moles)	1.95g (0.016moles)	2.5g (0.011mol, 68%)	Ethanol
A_7	1.86ml (0.016moles)	1.95g (0.016moles)	2.7g (0.012mol, 75%)	Ethanol
A_8	1.86ml (0.016moles)	1.80ml (0.016moles)	2.8g (0.012mol, 75%)	Ethanol
A_9	1.86ml (0.016moles)	2.24g (0.016moles)	3.1g (0.013mol, 81%)	Ethanol
A_{10}	1.86ml (0.016moles)	2.38g (0.016moles)	3.4g (0.013mol, 81%)	Ethanol
A_{11}	1.86ml (0.016moles)	2.83g (0.016moles)	2.9g (0.010mol, 62%)	Ethanol
A_{12}	1.86ml (0.016moles)	1.88ml (0.016moles)	2.5g (0.011mol, 68%)	Ethanol
A_{13}	1.86ml (0.016moles)	1.88ml (0.016moles)	2.8g (0.012mol, 75%)	Ethanol
A_{14}	1.86ml (0.016moles)	2.41ml (0.016moles)	3.0g (0.012mol, 75%)	Ethanol

Table 3: Physical Data of Compounds A_2-A_{14}

Compound	*Molecular Formula*	*Molecular wt.*	*m.p ^0C*	*Rf value × 100*	*Solubility*
A_2	$C_{16}H_{14}O_2$	238	75	72	Methanol, Ethyl acetate
A_3	$C_{16}H_{14}O_2$	238	86	68	"
A_4	$C_{17}H_{16}O_3$	268	61	76	"
A_5	$C_{15}H_{12}O_2$	224	130	47	"
A_6	$C_{15}H_{12}O_2$	224	151	34	"
A_7	$C_{15}H_{12}O_2$	224	101	38	"
A_8	$C_{15}H_{11}ClO$	242.5	45	73	"
A_9	$C_{15}H_{11}ClO$	242.5	114	85	"
A_{10}	$C_{17}H_{17}NO$	251	103	66	"
A_{11}	$C_{19}H_{21}NO$	279	Oil	75	"
A_{12}	$C_{16}H_{14}O$	222	54	86	"
A_{13}	$C_{16}H_{14}O$	222	95	71	"
A_{14}	$C_{15}H_{11}NO_3$	253	88	53	"

Table 4: UV Spectral Data of Compounds A_2-A_{14}

Compound	λ_{max}^{MeOH}	
	Band-I	**Band-II**
A_2	305	259
A_3	323	253
A_4	358	264
A_5	354	269
A_6	307	260
A_7	308	270
A_8	315	251
A_9	313	256
A_{10}	422	260
A_{11}	349	267
A_{12}	312	264
A_{13}	322	268
A_{14}	314	222

Table 5: IR Spectral Data of Compounds A_2- A_{14}

Compound	*-C=C- Str.* (cm^{-1})	*-C=O Str.* (cm^{-1})	*-OH Str.* (cm^{-1})	*-C-Cl Str.* (cm^{-1})	*-NO_2 Str.* (cm^{-1})
A_2	1571	1656	—	—	—
A_3	1578	1643	—	—	—
A_4	1594	1645	—	—	—
A_5	1596	1635	3205	—	—
A_6	1591	1648	3195	—	—
A_7	1599	1663	3305	—	—
A_8	1587	1642	—	717	—
A_9	1595	1651	—	723	—
A_{10}	1578	1644	—	—	—
A_{11}	1582	1647	—	—	—
A_{12}	1571	1656	—	—	—
A_{13}	1577	1664	—	—	—
A_{14}	1551	1657	—	—	1338

Table 6: ^{1}H NMR Spectral Data of Compounds A_2-A_{14}

(CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_2)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_3)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_4)*
2	7.24, 1H, dd, (1.4,1.5)		7.36, 1H, d, (1.8)
3	----	6.72, 1H, dd, (8.01, 1.7)	----
4	6.98,1H,ddd,(1.5, 1.62, 8.1)	7.03,1H,ddd,(7.6,7.65,1.4)	----
5	7.29-7.34, 2H, m	6.76-6.78, 1H, m	6.98, 1H d, (9.01)
6		7.10, 1H, dd, (8.3, 1.6)	7.29, 1H, dd, (9.3, 1.7)
A	7.66, 1H, d, (15.66)	7.56, 1H, d, (15.35)	7.61, 1H, d, (15.58)
B	7.74, 1H, d, (15.75)	7.98, 1H, d, (15.51)	7.73, 1H, d, (15.53)
2', 6'	8.05,2H, ddd, (1.4,1.4,7.08)	7.85,2H,ddd,(1.5,1.62,7.3)	7.81,2H,ddd,(1.4,1.6,7.8)
3', 5'	7.52,2H,ddd,(1.4, 7.79, 7.3)	7.56,2H,ddd,(1.6,7.9,7.83)	7.81,2H,ddd,(7.7,7.3,1.5)
4'	7.61-7.63, 1H, m	7.63-7.64, 1H, m	7.57-7.59, 1H, m
OCH_3	3.83, 3H, s	3.83, 3H, s	3.86, 3H, s 3.89, 3H, s

Table 6 Continued: ^{1}H NMR Spectral Data of Compounds A_2-A_{14}

CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_5)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_6)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_7)*
2	----	6.80, 1H, dd, (1.40, 1.48)	7.49-7.53, 2H, m
6	7.63, 1H, dd, (1.3. 7.22)	6.85, 1H, m	
4	7.51, 1H, m	6.78, 1H, m	----
5	7.23, 1H,ddd, (1.4, 8.2,7.19)	7.01, 1H, dd, (8.01, 7.95)	6.83, 2H, dd, (1.9,6.97)
3	6.87, 1H dd, (8.3, 1.4)	----	
A	7.77, 1H, d, (15.7)	7.61, 1H, d, (14.83)	7.54, 1H, d, (14.22)
B	8.09, 1H, d, (15.8)	7.75, 1H, d, (14.92)	7.73, 1H, d, (15.44)
2', 6'	8.0-8.02, 2H, m	7.98-8.0. 2H, m	8.0-8.02, 2H, m
3', 5'	7.55-7.57, 2H, m	7.63-7.67, 3H, m	7.56-7.61, 2H, m
4'	7.58-7.60, 1H, m		7.73-7.76, 1H, m
OH	9.30, 1H, s, exchangeable with D_2O	9.23, 1H, s, exchangeable with D_2O	9.13, 1H, s, exchangeable with D_2O

Table 6 Continued: ^{1}H NMR Spectral Data of Compounds A_2-A_{14}

(CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_8)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_9)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_{10})*
2	----	7.28, 2H, dd, (7.85,1.6)	6.97, 2H, dd, (7.8, 1.6)
6	7.24, 1H, dd, (7.53, 1.7)		
4	7.08,1H,ddd, (7.44,7.52,1.5)	----	----
5	7.10-7.12, 1H, m	7.22, 2H, dd, (1.7,8.01)	6.75, 2H, dd, (1.7, 7.3)
3	7.22, 1H, dd, (7.39, 1.4)		
A	7.39, 1H, d, (14.83)	7.60, 1H, d, (15.31)	7.46, 1H, d, (15.5)
B	8.17, 1H, d, (14.98)	7.71, 1H, d, (15.35)	7.74, 1H, d, (15.4)
2', 6'	7.36-7.53, 5H, m	7.81, 2H, dd, (8.03,1.6)	7.55-7.56, 2H, m
3', 5'		7.45,2H,ddd,(1.4,7.5,7.83)	7.52,2H,dd,(1.4,8.4,7.8)
4'		7.52-7.54, 1H, m	8.01-8.02, 1H, m
$N(CH_3)_2$			3.03, 6H, s

Table 6 Continued: ^{1}H NMR Spectral Data of Compounds A_2-A_{14}

(CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_{11})*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_{12})*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (A_{13})*
2	7.03, 2H,dd, (1.71,7.83)	7.19, 1H, dd,(1.5,1.7)	7.18, 2H,dd,(7.71,1.52)
6		7.11-7.13, 1H, m	
4	----	6.98,1H,ddd,(7.9,1.6,1.73)	----
5	6.75, 2H, dd, (1.7, 7.2)	7.15, 1H, dd, (7.91, 7.83)	7.01, 2H, dd, (7.9, 1.6)
3		----	
A	7.31, 1H, d, (15.12,)	7.68, 1H, d, (15.3)	7.67, 1H, d, (15.6)
B	7.37, 1H, d, (15.23)	7.87, 1H, d, (15.4)	7.81, 1H, d, (15.7)
2', 6'	7.79-7.81, 2 H, m	7.62-7.77, 5H, m	8.05, 2H, dd, (7.14, 1.3)
3', 5'	7.53-7.59, 3H, m		7.6, 2H, dd, (1.3, 7.8)
4'			7.60-7.62, 1H, m
N-CH_2	3.39, 4H, q, (7.8)	----	----
CH_3	1.13, 6H, t, (7.5)	2.39, 3H, s	2.35, 3H, s

Table 6 Continued: ^{1}H NMR Spectral Data of Compounds A_2-A_{14} (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), A_{14}*	*Multiplicity*	*J(Hz)*
2,6	7.56	2H, dd	7.2, 1.6
3,5	8.14	2H, dd	1.4, 7.9
A	7.56	1H, d	15.32
B	7.90	1H, d	15.35
2', 6'	8.03	2H, dd	7.3, 1.4
3', 4', 5'	7.60-7.64	3H, m	----

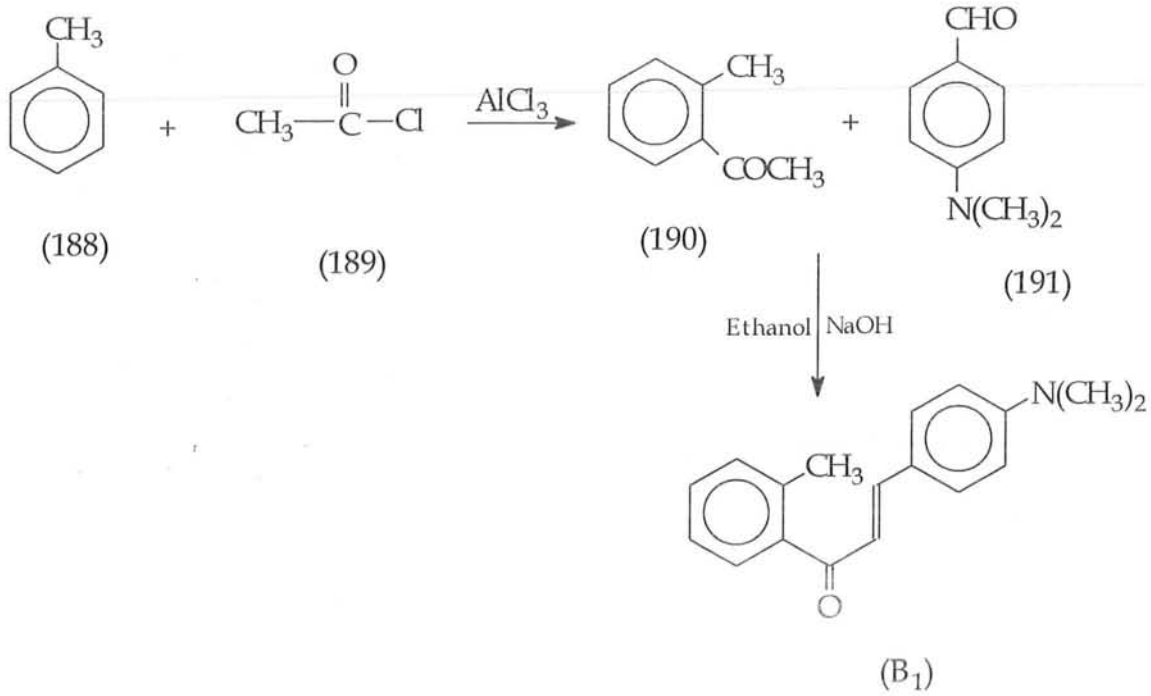
Table 7: Mass Spectral Data of Compounds A_2-A_{14}

Peaks	*Compounds*					
	A_2	A_3	A_4	A_5	A_6	A_7
$M^{+\cdot}$ m/z (%)	238 (100)	238 (72.10)	268 (87.24)	224 (29.51)	224 (21.30)	224 (5.60)
$[M-H]^+$	237 (2.61)	237 (3.02)	267 (54.31)	223 (8.10)	223 (9.70)	223 (2.71)
$[M-CO]^+$	210 (28.94)	210 (21.31)	240 (15.08)	196 (1.94)	196 (1.21)	196 (2.31)
$[M-30]^{+\cdot}$	208 (1.91)	208 (1.97)	238 (35.04)	--	194 (3.2)	194 (2.1)
A_2^+	105 (78.10)	105 (72.10)	105 (3.23)	105 (73.81)	105 (91.05)	105 (2.88)
$[A_2-CO]^+$	77 (93.96)	77 (98.01)	77 (100)	77 (100)	77 (28.21)	77 (7.05)
$[\{A_2-CO\}-C_2H_2]^+$	51 (79.75)	51 (31.0)	51 (98.06)	51 (68.86)	51 (48.3)	51 (18.77)
B_5^+	161 (67.30)	161 (100)	191 (70.05)	147 (54.70)	147 (100)	147 (4.63)
$[B_5-CO]^+$	133 (44.27)	133 (27.31)	163 (20.33)	119 (33.02)	119 (30.91)	119 (2.07)
$[M-CH_3]^+$	223 (38.63)	223 (27.21)	253 (55.48)	--	--	--
$[M-OH]^+$	--	--	--	207 (42.68)	207 (48.1)	207 (3.1)
$[M-117]^+$	121 (1.86)	--	151 (18.04)	--	107 (13.1)	--
$[M-103]^+$	--	--	--	--	--	121 (100)

Table 7 Continued: Mass Spectral Data of Compounds A_2-A_{14}

Peaks	*Compounds*						
	A_8	*A_9*	*A_{10}*	*A_{11}*	*A_{12}*	*A_{13}*	*A_{14}*
$M^{+\cdot}$ m/z (%)	242 (29.51, ^{35}Cl) 244 (2.3, ^{37}Cl)	242 (21.1, ^{35}Cl) 244 (2.1, ^{37}Cl)	251 (100)	279 (100)	222 (71)	222 (44.65)	253 (23)
$[M-H]^+$	241 (4.0, ^{35}Cl) 243 (1.1, ^{37}Cl)	241 (8.0, ^{35}Cl) 243 (1.3, ^{37}Cl)	250 (38.36)	278 (3.1)	221 (27)	221 (49.07)	252 (25.1)
$[M-CO]^+$	214 (21.0, ^{35}Cl) 216 (3.0, ^{37}Cl)	214 (5.0, ^{35}Cl) 216 (1.0, ^{37}Cl)	223 (5.05)	251 (7.1)	194 (3)	194 (1.3)	225 (23)
$[M-30]^{+\cdot}$	212 (5.0, ^{35}Cl) 214 (1.1, ^{37}Cl)	212 (10.0, ^{35}Cl) 214 (1.3, ^{37}Cl)	--	249 (2.1)	192 (1.2)	192 (2.1)	223 (2.1)
A_2^+	105 (91.01)	105 (100)	105 (14.38)	105 (80.3)	105 (80)	105 (65)	105 (71.83)
$[A_2-CO]^+$	77 (100)	77 (3.1)	77 (78)	77 (67)	77 (100)	77 (35.17)	77 (100)
$[\{A_2-CO\}-C_2H_2]^+$	51 (43.10)	51 (55.0)	51 (13.62)	51 (81)	51 (78.1)	51 (26.60)	51 (48.10)
B_5^+	165 (71.1, ^{35}Cl) 167 (1.3, ^{37}Cl)	165 (7.7, ^{35}Cl) 167(1.8, ^{37}Cl)	174 (56.06)	202 (65.1)	145 (56.12)	145 (45.16)	176 (36.10)
$[B_5-CO]^+$	137 (8.71, ^{35}Cl) 139 (1.8, ^{37}Cl)	137 (35.3, ^{35}Cl) 139 (3.1, ^{37}Cl)	146 (24.87)	174 (31)	117 (28.0)	117 (22.09)	148 (24.10)
$[M-CH_3]^+$	--	--	--	-- ()	-- ()	207 (100)	-- ()
$[M-117]^+$	125 (21.0, ^{35}Cl) 127 (2.0, ^{37}Cl)	125 (3.0, ^{35}Cl) 127 (1.0, ^{37}Cl)	134 (13)	162 (27)	105 (78.1)	105 (35.17)	136 (3.7)

3.7 Synthesis of 2'-Methyl-B ring Substituted Chalcones (B-series Chalcones)



Scheme 4

3.7.1 Synthesis of 1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one (B_1)

3.7.1.a Synthesis of 2-methylacetophenone (190)

30 g (0.22 mol) of anhydrous finely powdered aluminum chloride was added in a three necked flask and 100g (0.87 mol) of toluene was added in it. The stirring started and 40 g (0.50 mol) of acetyl chloride was added slowly during about half an hour. After the complete addition of acetyl chloride the flask was heated on water bath for two hours. The reaction mixture was cooled and poured into 250 ml of water and a little crushed ice. After

the addition of HCl the oil was obtained washed with water and anhydrous magnesium sulphate was added, the excess of toluene was distilled off to afford 12 g (17 %) 2-methylacetophenone. The **IR** spectrum showed carbonyl and methyl absorptions at 1675 cm^{-1} and 2933 cm^{-1} respectively.

3.7.1.b Synthesis of 4-(dimethylamino)benzaldehyde (191)

44ml (0.56mol) of dimethylformamide was taken in 1 liter three necked round bottom flask equipped with sealed stirrer, dropping funnel and a reflux condenser topped by a $CaCl_2$ tube. 21.2ml (0.22mol) of phosphorous oxichloride was added drop wise, the exothermic reaction occurred with the addition of $POCl_3$. The flask was cooled carefully in an ice bath when all the $POCl_3$ was added and heat of the reaction subsided. 28.5ml (0.22mol) of dimethylaniline was added drop wise with stirring, when yellow green ppt. began to form. The reaction mixture was heated with water steam for 2 hours. The mixture was cooled and poured over 210 g of crushed ice in a beaker. The solution was neutralized to pH 6-8 by the drop wise addition of aq. sod. Acetate. p-Dimethylaminobenzaldehyde began to form, the neutral mixture was stored in the refrigerator. The ppt was filtered by suction and the green color was removed by washing with water to afford 20 g (61%) of dimethylaminobenzaldehyde, m.p 73^{0}C. The **IR** showed carbonyl stretching at 1661 and aldehydic C-H stretching at 2599 cm^{-1}.

3.7.1.c Claisen-Schmidt Condensation

80ml of 4.0 M solution of sodium hydroxide was dissolved in 60ml of rectified spirit in a conical flask. The solution was cooled in an ice bath to 0^{0}C. 1.96ml (0.015moles) of freshly distilled 2-methylacetophenone **(190)** were added to it. The mixture was stirred by a magnetic stirrer for half an hour in an ice bath keeping the temperature at 0-5^{0}C. Then 2.23g (0.015moles) of 4-dimethylaminobenzaldehyde **(191)** was added and mixture was stirred vigorously for 2-3 hours. The reaction mixture was kept at 0-5^{0}C for overnight. The thick oil obtained was diluted with chilled water and aqueous hydrochloric acid was added to neutralize it. The product was obtained as yellow precipitates. The precipitate was filtered

and recrystallized from aqueous ethanol to afford 1-(2'-methylphenyl)-3-(4-Dimethylaminophenyl)-2-propen-1-one $\mathbf{B_1}$. Further purification of chalcone was carried out on preparative TLC plates [silica gel HF-60 in pet-ether: ethylacetate (9:1)]. The purity was also checked by HPLC using solvent system acetonitrile:water (80:20) **(Chromatogram 2).** Yield of 1-(2'-methylphenyl)-3-(4''-Dimethylaminophenyl)-2-propen-1-one $\mathbf{B_1}$ was 2.9g (0.011mol, 73%). m.p.75^{0}C. **UV** (λ_{max}^{MeOH}) 378 nm & 260 nm, **IR** (υ_{max}, KBr): 1644, 1578cm^{-1}; **^{1}H-NMR** (CD_3OD, δ-values in PPM); 6.72 (2H, dd, J=1.8, 7.06 Hz), 7.01 (2H, dd, J=1.5, 7.86 Hz), 6.91 (1H, d, J=15.88 Hz), 7.33 (1H, d, J=15.83 Hz), 7.38 (1H, dd, J=1.3, 7.6), 7.25-7.29 (2H, m), 7.45 (1H, m), 2.34 (3H, s), 3.2 (6H, s); **EIMS** (70 eV): m/z (%)= 265 (78.77% M^+), 264 (19.01), 250 (6.59), 237 (2), 235 (1.95), 174 (24.38), 146 (31.79), **134 (100)**, 120 (9.69) 119 (10.80), 91 (30.77), 65 (14.77).

3.8 Results and Discussion:

4-Dimethylaminobenzaldehyde **(191)** and freshly distilled 2-methylacetophenone **(190)** were reacted in ethanol for 2-3 hours at 0-5 ^{0}C under basic conditions to yield 1-(2'-methylphenyl)-3-(4-Dimethylaminophenyl)-2-propen-1-one **($\mathbf{B_1}$)**. Compound $\mathbf{B_1}$ was found to have a molecular formula of $C_{18}H_{19}NO$ and molecular weight 265. Compound $\mathbf{B_1}$ gave UV absorption maxima at λ_{max}^{MeOH} 378 nm **(Band I)** and 260 nm **(Band II),** which is characteristic of chalcones **(Spectrum 4)**. Band-**I** results from the conjugation of the whole molecule and Band-**II** is considered due to the *cis* or the *trans* isomers. The IR spectrum showed stretching frequencies at 1644cm^{-1}, 1578cm^{-1} and 2952 cm^{-1} which are characteristic of C=O, aromatic C=C and CH_3 groups respectively.

The mass spectrum **(Spectrum 5)** of 1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one **($\mathbf{B_1}$)** showed a molecular ion peak at m/z 265, and is in agreement with its molecular weight. The peak at m/z 264 results from the simultaneous loss of hydrogen atom of the B-ring and its cyclization with the oxygen of the carbonyl group. The base peak in mass spectrum of 1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one **($\mathbf{B_1}$)** appeared at m/z 134, which is formed by the Mc-Lafferty rearrangement. The characteristic peak in the mass spectrum is at m/z 237 due to the loss of carbon monoxide. Other peaks in the mass spectrum were at m/z 174, 119 and 91 resulting

from the fragmentation on both sides of the carbonyl group, which is a common fragmentation process in chalcones. The fragmentation pattern of 1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one **(B_1)** is given in **(Scheme 5)**.

The **^{1}H NMR** spectrum **(Spectrum 6)** of 1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one **(B_1)** showed a pair of doublets at 6.91 ppm and 7.33 ppm with a large coupling constants of 15.88 and 15.83 Hz which are characteristic for trans olefinic protons. Thus the chalcone **B_1** is *trans*-1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one **(B_1)**. The six protons for $N(CH_3)_2$ group gave a singlet at 3.02 ppm. δ values, multiplicity and J values of all protons of 1-(2'-methylphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one **(B_1)** are tabulated in **(Table 8)**

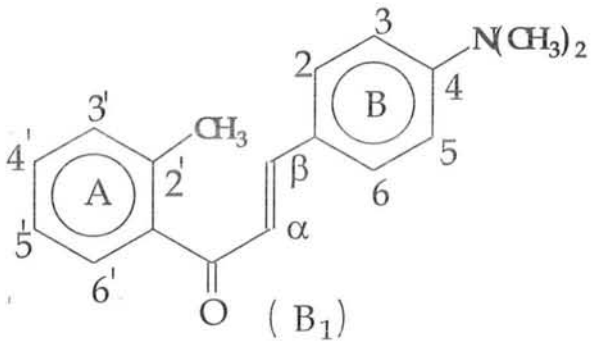
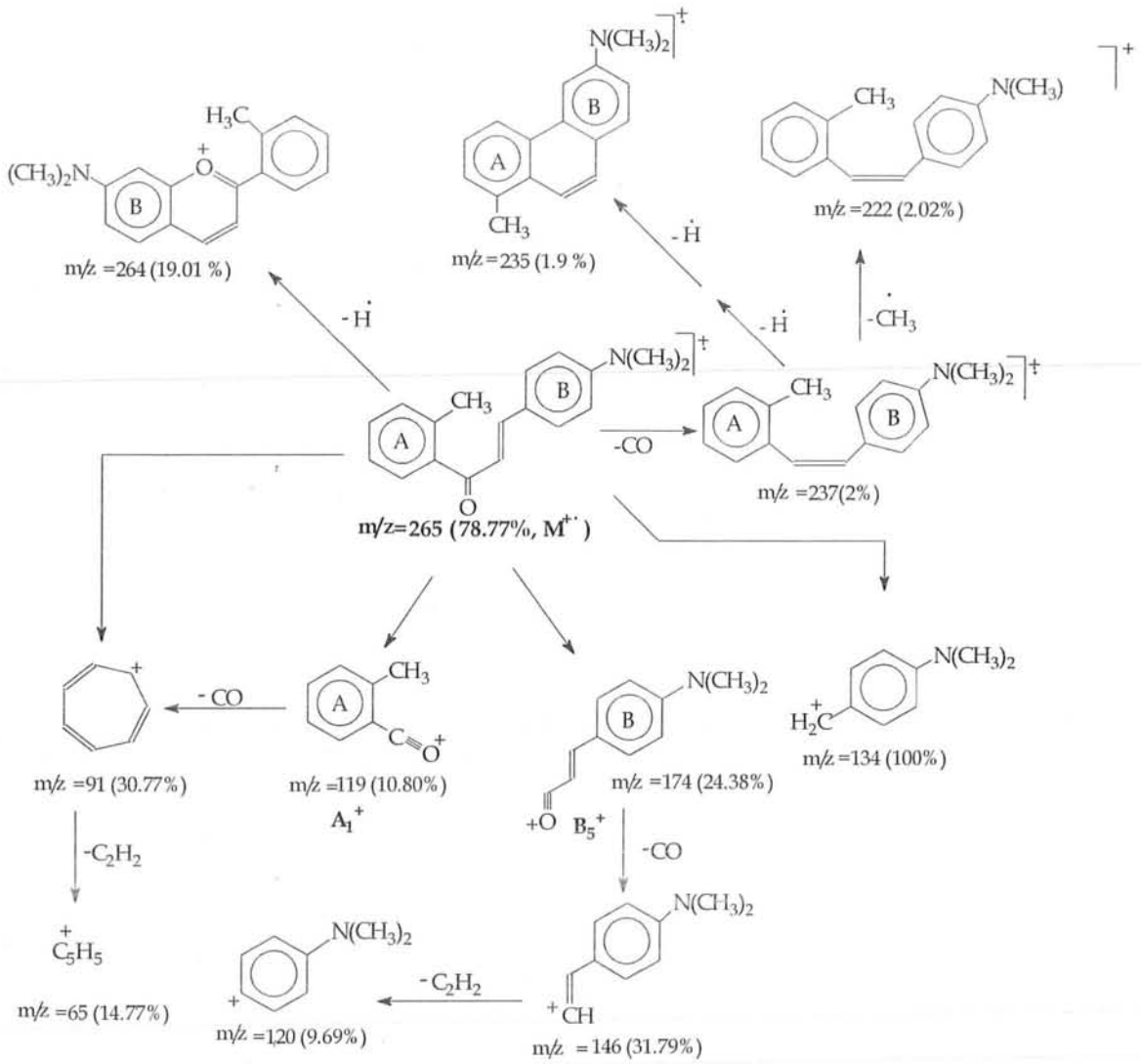


Table 8: ^{1}H NMR Spectral Data of Compound B_1 (CD_3OD, 400 MHz)

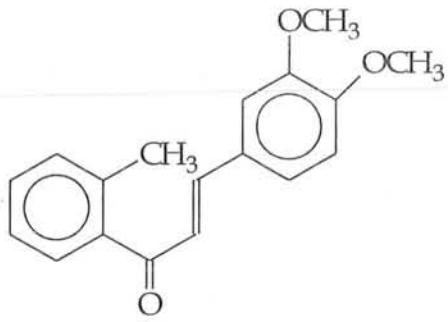
Carbon	*^{1}H-δ (ppm)*	*Multiplicity*	*J(Hz)*
2, 6	7.01	2H, dd	1.5, 7.86
3, 5	6.72	2H, dd	1.8, 7.06
α	6.91	1H, d	15.88
β	7.33	1H, d	15.83
6'	7.38	1H, dd	1.3, 7.6
3', 5'	7.25-7.29	2H, m	----
4'	7.44-7.46	1H, m	----
CH_3	2.34	3H, s	----
$N(CH_3)_2$	3.02	6H, s	----



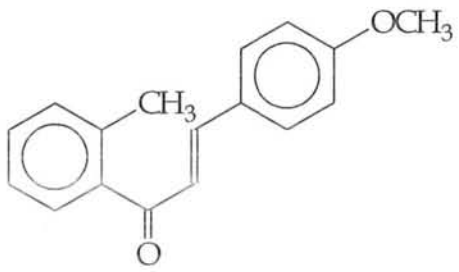
Scheme 5: Mass Fragmentation Pattern of B_1

Using the same synthetic procedure, other members of the B-series chalcones **(B_2-B_4)** were synthesized. Molar quantities, physical constants **UV, IR, ^{1}H NMR** and **Mass** spectral data for these 3 chalcones are presented in **(Table 9-14).** Structures of these chalcones are:

B_2= 1-(2'-Methylphenyl)-3-(4-dimethoxyphenyl)-2-propen-1-one



B_3= 1-(2'-Methylphenyl)-3-(4-methoxyphenyl)-2-propen-1-one



B_4= 1-(2'-Methylphenyl)-3-(4-methylphenyl)-2-propen-1-one

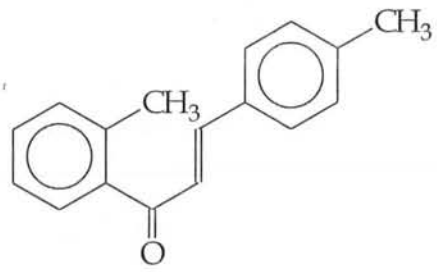


Table 9: Molar Ratios of Compounds B_2-B_4

Compounds	*2-Methyl acetophenone*	*Substituted Benzaldehyde*	*Yield*	*Solvent for Recrystallization*
B_2	1.96ml (0.015moles)	2.49g (0.015moles)	3.1g (0.011mol, 73%)	Ethanol
B_3	1.96ml (0.015moles)	1.81ml (0.015moles)	2.8g (0.011mol, 73%)	Ethanol
B_4	1.96ml (0.015moles)	1.76ml (0.015moles)	2.9g (0.012mol, 80%)	Ethanol

Table 10: Physical Data of Compounds B_2-B_4

Compound	*Molecular Formula*	*Molecular wt.*	*m.p °C*	*Rf value × 100*	*Solubility*
B_2	$C_{18}H_{18}O_3$	282	78	52	Methanol, Ethyl acetate
B_3	$C_{17}H_{16}O_2$	252	Oil	74	"
B_4	$C_{17}H_{16}O$	236	Oil	72	"

Table 11: UV Spectral Data of Compounds B_2-B_4

Compound	λ_{max}^{MeOH}	
	Band-I	**Band-II**
B_2	346	262
B_3	332	257
B_4	338	269

Table 12: IR Spectral Data of Compounds B_2- B_4

Compound	*-C=C- Str. (cm^{-1})*	*-C=O Str. (cm^{-1})*
B_2	1585	1639
B_3	1569	1647
B_4	1588	1637

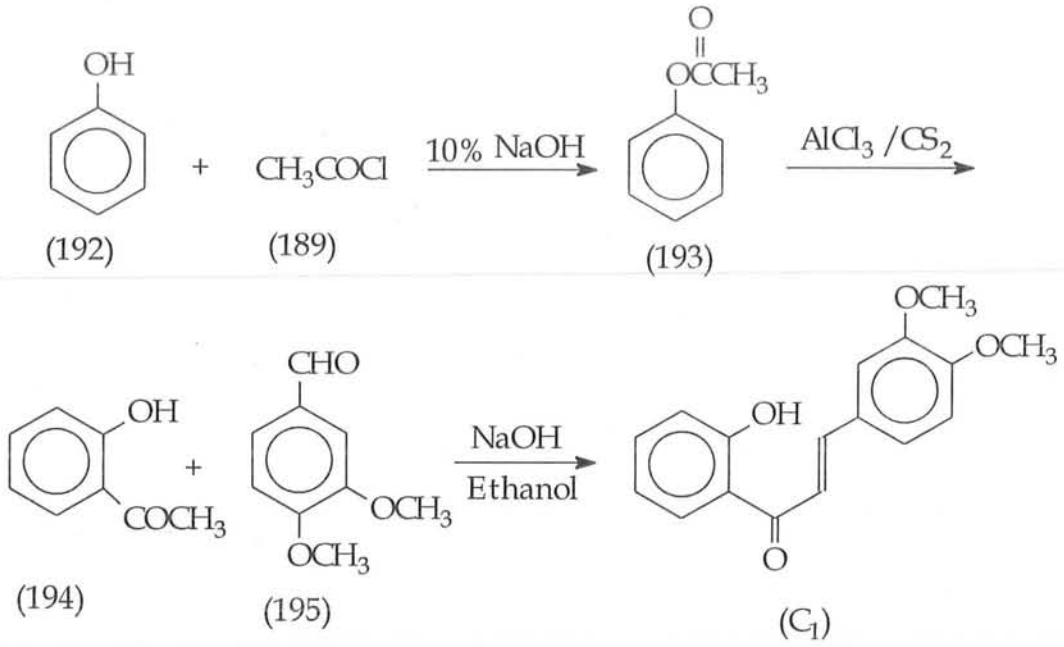
Table 13: ^{1}H NMR Spectral Data of Compound B_1 (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (B_2)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (B_3)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (B_4)*
2	7.23, 1H, d, (1.9)	7.48, 2H, dd, (8.4, 1.4)	7.53, 2H, dd, (8.31, 1.5)
6	7.17, 1H, dd, (1.9, 8.2)		
5	6.96, 1H, d, (8.3)	7.03, 2H, dd, (6.9, 1.4)	7.59, 2H, dd, (1.47, 8.37)
3			
α	7.08, 1H, d, (15.77)	7.70, 1H, d, (15.31)	7.11, 1H, d, (14.70)
β	7.28, 1H, d, (14.76)	7.90, 1H, d, (15.33)	7.28, 1H, d, (14.74)
6'	7.47, 1H, dd, (1.2, 8.7)	7.47, 1H, dd, (7.8, 1.31)	7.47, 1H, dd, (7.81, 1.6)
3', 5'	7.30-7.35, 2H, m	7.31-7.34, 2H, m	7.30-7.35, 2H, m
4'	7.39, 1H,ddd,(1.2, 7.2,7.3)	7.37,1H,ddd,(1.3,7.9,7.7)	7.37-7.39, 1H, m
OCH_3	3.85, 6H, s	3.81, 3H, s	----
CH_3	2.36, 3H, s	2.35, 3H, s	----

Table 14: Mass Spectral Data of Compounds B_2-B_4

Peaks	*Compounds*		
	B_2	***B_3***	***B_4***
$M^{+\cdot}$ m/z (%)	282 (28.82)	252 (24.26)	236 (21.01)
$[M-H]^+$	281 (15.27)	251 (8.41)	235 (14.30)
$[M-CO]^+$	254 (1.53)	224 (2.31)	208 (3.02)
$[M-30]^{+\cdot}$	252 (2.78)	222 (1.92)	206 (1.19)
A_2^+	119 (19.66)	119 (14.05)	119 (23.21)
$[A_2-CO]^+$	91 (49.12)	91 (38.29)	91 (100)
$[\{A_2-CO\}-C_2H_2]^+$	65 (25.48)	65 (23.01)	65 (34.1)
B_5^+	191 (12.69)	161 (16.37)	145 (60.1)
$[B_5-CO]^+$	163 (5.42)	133 (12.80)	117 (33.01)
$[M-CH_3]^+$	267 (4.53)	237 (1.1)	--
$[M-131]^+$	151 (100)	121 (100)	105 (70.12)

3.9 Synthesis of 2'-Hydroxy-B ring Substituted Chalcones (C-series Chalcone)



Scheme 6

3.9.1 Synthesis of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one (C_1)

3.9.1.1 Synthesis of 2-hydroxy acetophenone (194)

3.9.1.1.a Synthesis of Phenyl acetate (193)

50g (0.53 moles) of phenol **(192)** was taken in conical flask containing 100ml of 10% NaOH solution. The mixture was stirred for 15 minutes so that the phenol becomes dissolved in it. The flask was cooled in ice bath and 65ml (0.53 moles) of acetyl chloride **(189)** was added drop wise in the reaction mixture. The flask was shaken vigorously for 10 minutes and the emulsion formed was extracted with 50ml of carbon tetrachloride. The organic layer was washed carefully with dilute Na_2CO_3 solution until effervescence ceased. Distillation of carbon tetrachloride affords the 54g (76%) of phenyl acetate **(193).** The **IR** showed stretching frequency at 1725cm^{-1} for ester linkage.

3.9.1.1.b Fries rearrangement

56g (0.42 mole) of anhydrous aluminum chloride were taken in round bottom and 40ml of dried CS_2 was added drop wise to the round bottom flask. After 10 minutes 46 ml (0.37 moles) of phenyl acetate **(193)** was added. The reaction mixture was kept for overnight. The solidified oil was diluted with toluene and $MgSO_4$ was added to dry the solution. Distillation of toluene at atmospheric pressure afforded residue oil, which was distilled under reduced pressure (15-20 mm of Hg) until the *p*-isomer begins to collect in the condenser. Finally 16ml (41%) of 2'-hydroxy acetophenone **(194)** was collected at 105-106° at 20mm Hg. The **IR** showed stretching frequency at 1625 cm^{-1} which is characterstic of C=O group.

3.9.1.1.c Synthesis of 3,4-dimethoxybenzaldehyde (195)

25g (0.16mol) of commercial vanillin was added in a 1litre three necked flask equipped with a reflux condenser, a mechanical stirrer and two separating funnels. One of which is supported over the top of the reflux condenser. The vanillin was melted on water bath and stirred vigorously. One separatory funnel was charged with 14g of pure potassium hydroxide in 20ml of water and other funnel with 25g in 20ml (0.21 mol) of pure dimethylsulphate. Potassium hydroxide solution was run at the rate of two drops a second. After 20 second dimethylsulphate solution was run at the same rate. The external heating stopped after a few minutes and let the solution be refluxed from the heat of reaction. The coluor of the reaction became pale reddish-brown, which is indication of alkaline solution. When half to three quarters of the reagent have been added. The reaction mixture become turbid and separated into two layers. As soon as all the regents have consumed, the solution became yellow and poured into a large porcelain basin and allowed to cool with out disturbance. The hard crystalline mass of veratraldehyde was filtered, grinded in a glass with 100ml of ice-cooled water, again filtered and dried in a vacuum dedicator. The yield of varatraldehyde was 22g(0.13mol, 81%) m.p. 46°C. The **IR** showed carbonyl stretching at 1670 and aldehydic C-H stretching at 2601 cm^{-1}.

3.9.1.1.d Claisen Schmidt Condensation

80ml of 4.0 M solution of sodium hydroxide was dissolved in 60ml of rectified spirit in a conical flask. The solution was cooled in an ice bath to 0^0C. 1.80ml (0.015moles) of freshly distilled 2-hydroxyacetophenone **(194)** were added to it. The mixture was stirred by a magnetic stirrer for half an hour in an ice bath keeping the temperature at 0-5^0C. Then 2.49g (0.015moles) of 3,4-dimethoxybenzaldehyde **(195)** was added and mixture was stirred vigorously for 2-3 hours. The reaction mixture was kept at 0-5^0C for overnight. The thick oil obtained was diluted with chilled water and aqueous hydrochloric acid was added to neutralize it. The product was obtained as yellow precipitates. The precipitate was filtered and recrystallized from aqueous ethanol to afford 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)**. Further purification of chalcone was carried out on preparative TLC plates [silica gel HF-60 in pet-ether : ethylacetate (9:1)]. The purity was also checked by HPLC using solvent system acetonitrile: water (80:20) **(Chromatogram 3)**. Yield of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** was 3.2g (0.011mol, 73%). m.p.108^{0}C. **UV** (λ_{max}^{MeOH}) 360 nm & 261 nm, **IR** (υ_{max}, KBr): 1648, 1603 cm^{-1}, **^{1}H-NMR** (CD_3OD, δ-values in PPM); 7.02 (1H, d, J=1.96 Hz), 6.96 (1H, d, J=7.60 Hz), 7.42 (1H, t, J=8.34 Hz), 7.68 (1H, d, J=15.40 Hz), 7.87 (1H, d, J=15.36), 7.34 (1H, dd, J=1.75, 8.3), 7.50 (1H, ddd, J=8.4, 7.9, 1.3), 7.22 (1H, ddd, J=8.3, 8.1, 1.5), 8.17 (1H, dd, J=1.18, 7.90), 3.88 (3H, s), 3.92 (3H, s); **EIMS** (70 eV): m/z (%)= 284 (69.01% M^+)283 (28.87), 269 (9.43), 267 (7.84), 191 (8.61), **164 (100)**, 163 (6.85), 147 (29.20), 137 (1.2), 121 (45.60), 120 (3.3), 93 (17.96), 92 (6.64).

3.10 Results and Discussion:

3,4-Dimethoxybenzaldehyde **(195)** and freshly distilled 2-hydroxyacetophenone **(194)** were reacted in ethanol for 2-3 hours at 0-5 ^{0}C under basic conditions to yield 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)**. Compound **(C_1)** was found to have a molecular formula of $C_{17}H_{16}O_4$ and molecular weight 284. 1-(2'-Hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** gave UV absorption maxima at λ_{max}^{MeOH} 360

nm **(Band I)** and 261 nm **(Band II)** which are characteristics of chalcones **(Spectrum 7)**. Band-**I** results from the conjugation of the whole molecule and Band-**II** is considered due to the *cis* or the *trans* isomers. The addition of $AlCl_3$ in the methanolic solution of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** shifted the bands at 378 nm **(Band I)** and 260 nm **(Band II)**, which show free hydroxyl group at 2'- position of the A-ring **(Spectrum 8)**. The IR spectrum showed stretching frequencies at 1648cm^{-1}, 1603cm^{-1}and 3335cm^{-1} which are characteristic of C=O, aromatic C=C and OH groups respectively.

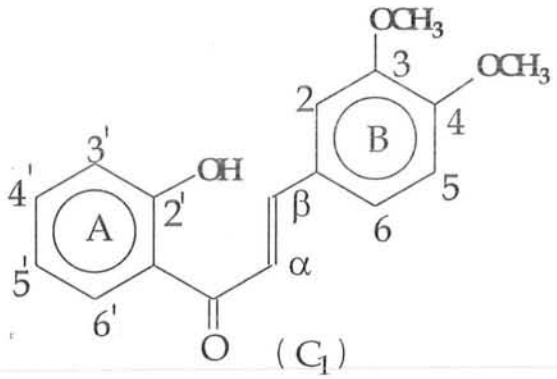
The mass spectrum **(Spectrum 9)** of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** showed a chalcone and flavanone type of molecular ion peak at m/z 284, and is in agreement with its molecular weight. The peak at m/z 283 results from the simultaneous loss of hydrogen atom of the B-ring and its cyclization with the oxygen of the carbonyl group. The characteristic peaks in the mass spectrum are at m/z 269, 267 and 254 appeared due to the loss of a methyl radical, hydroxyl group and carbon monoxide respectively. Other peaks in the mass spectrum are at m/z 191, 163, 121, 93, resulting from the fragmentation on both sides of the carbonyl group, a common fragmentation process in chalcones.

As the chalcone **C_1** possess 2'-hydroxy group in A-ring, there is an intramolecular equilibrium exist between chalcone **C_1** and respective flavanone, so the mass spectrum also showed the flavanone type fragment ions. The base peak in mass spectrum of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** appeared at m/z 164, which is formed by the retro-Diels Alder ring fission of flavanone type of molecular ion. The peak at m/z 147 is due to the loss of B-ring from the flavanone.

The fragmentation pattern of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** is given in **(Scheme 7)**.

The **^{1}H NMR** spectrum **(Spectrum 10)** of a 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)** showed a pair of doublets at $\delta_{H\alpha}$ 7.68 and $\delta_{H\beta}$ 7.87 ppm with a large coupling constant of 15.14 and 15.36 Hz which are characteristic for *trans* olefinic protons. Thus the chalcone is *trans*-1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one **(C_1)**. The six protons of two OCH_3 groups gave a singlet at δ_H 3.88 ppm. δ

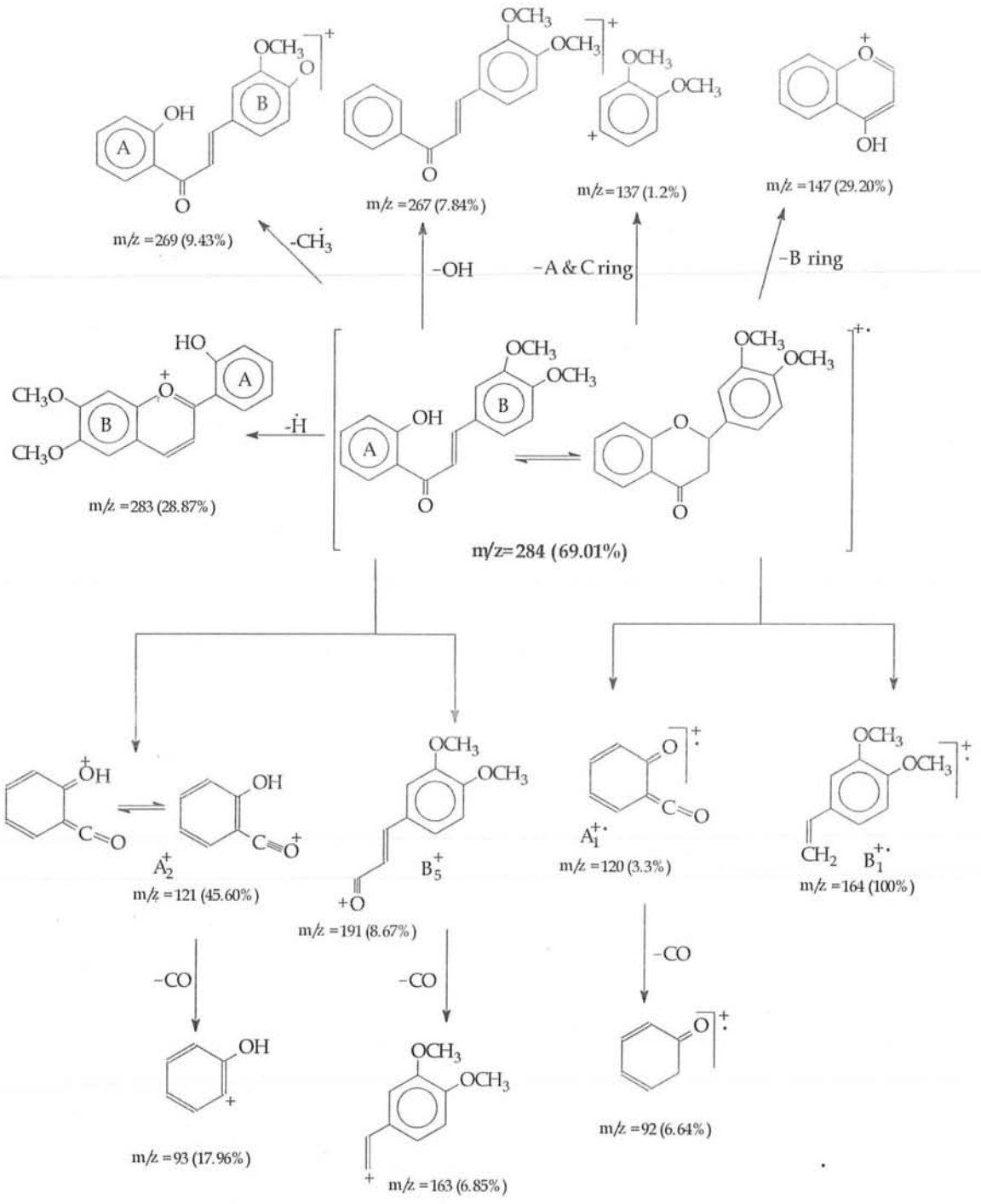
values, multiplicity and J values of all protons of 1-(2'-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one (C_1) are tabulated in **(Table 15).**



(C_1)

Table 15: ^{1}H NMR Spectral Data of Compound C_1 (CD_3OD, 400 MHz)

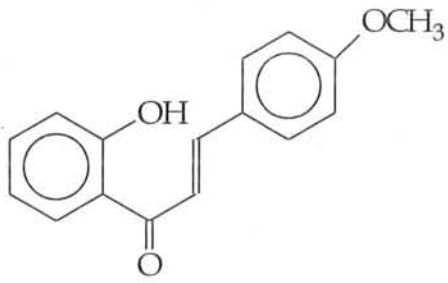
Carbon	*^{1}H-δ (ppm)*	*Multiplicity*	*J(Hz)*
2	7.02	1H, d	1.96
5	6.96	1H, d	7.6
6	7.42	1H, dd	8.34
α	7.68	1H, d	15.4
β	7.87	1H, d	15.36
3'	7.34	1H, dd	1.75, 8.3
4'	7.50	1H, ddd	8.4, 7.9, 1.3
5'	7.22	1H, ddd	8.3, 8.1, 1.5
6'	8.17	1H, dd	1.18, 7.9
OCH_3	3.88 3.92	3H, s 3H, s	---- ----
OH	9.51	1H, s, exchangeable with D_2O	----



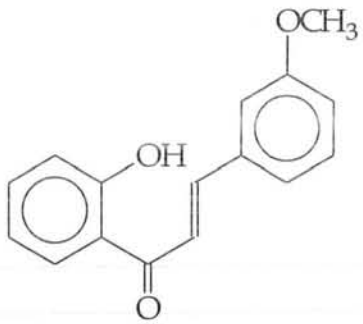
Scheme 7: Mass Fragmentation Pattern of C_1

Using the same synthetic procedure, other members of the C-series chalcones (C_2-C_{12}) were synthesized. Molar quantities, physical constants **UV, IR, ^{1}H NMR** and **Mass** spectral data for these 11 chalcones are presented in **(Table 16-21).** Structures of these chalcones are:

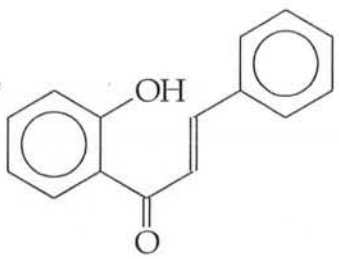
C_2= 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one



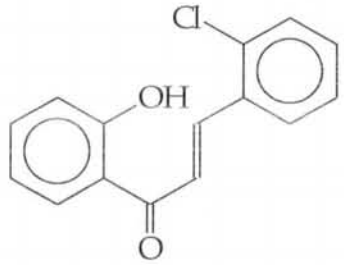
C_3= 1-(2'-Hydroxyphenyl)-3-(3-methoxyphenyl)-2-propen-1-one



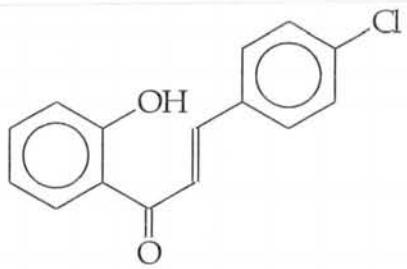
C_4= 1-(2'-Hydroxyphenyl)-3-phenyl-2-propen-1-one



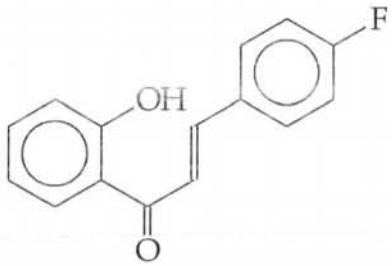
C_5= 1-(2'-Hydroxyphenyl)-3-(2-chlorophenyl)-2-propen-1-one



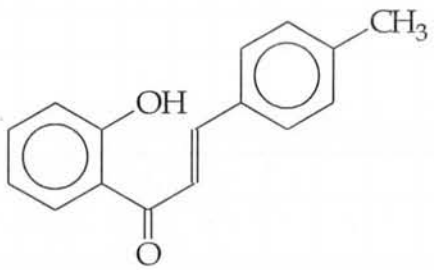
C_6= 1-(2'-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one



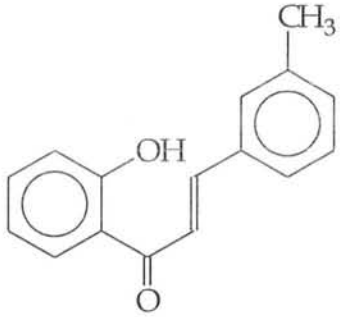
C_7= 1-(2'-Hydroxyphenyl)-3-(4-fluorophenyl)-2-propen-1-one



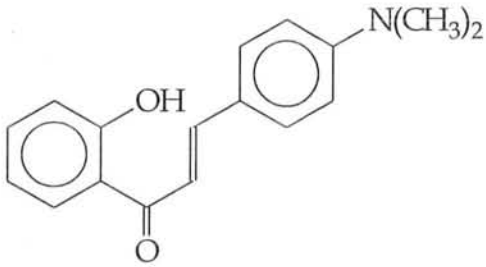
C_8= 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one



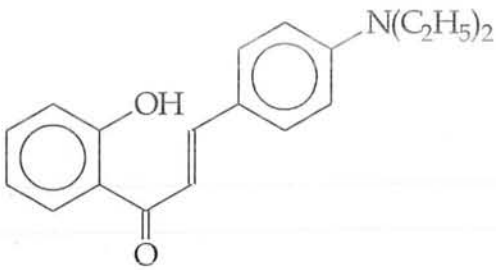
C_9= 1-(2'-Hydroxyphenyl)-3-(3- methylphenyl)-2-propen-1-one



C_{10}= 1-(2'-Hydroxyphenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one



C_{11}= 1-(2'-Hydroxyphenyl)-3-(4-diethylaminophenyl)-2-propen-1-one



C_{12}= 1-(2'-Hydroxyphenyl)-3-(4-nitrophenyl)-2-propen-1-one

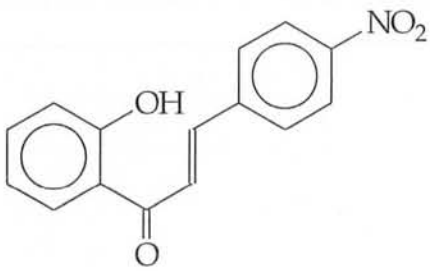


Table 16: Molar Ratios of Compounds C_2-C_{12}

Compounds	*2-Hydroxy acetophenone*	*Substituted Benzaldehydes*	*Yield*	*Solvent for Recrystallization*
C_2	1.80ml (0.015moles)	1.82ml (0.015moles)	3.0g (0.012mol, 80%)	Ethanol
C_3	1.80ml (0.015moles)	1.82ml (0.015moles)	2.9g (0.011mol, 77%)	Ethanol
C_4	1.80ml (0.015moles)	1.52ml (0.015moles)	2.7g (0.012mol, 80%)	Ethanol
C_5	1.80ml (0.015moles)	1.68ml (0.015moles)	2.7g (0.012mol, 80%)	Ethanol
C_6	1.80ml (0.015moles)	2.10g (0.015moles)	2.8g (0.011mol, 73%)	Ethanol
C_7	1.80ml (0.015moles)	1.63ml (0.015moles)	2.7g (0.011mol, 73%)	Ethanol
C_8	1.80ml (0.015moles)	1.76ml (0.015moles)	2.5g (0.010mol, 66%)	Ethanol
C_9	1.80ml (0.015moles)	1.76ml (0.015moles)	2.4g (0.010mol, 66%)	Ethanol
C_{10}	1.80ml (0.015moles)	2.23g (0.015moles)	2.6g (0.009mol, 60%)	Ethanol
C_{11}	1.80ml (0.015moles)	2.65g (0.015moles)	2.9g (0.010mol, 66%)	Ethanol
C_{12}	1.80ml (0.015moles)	2.26g (0.015moles)	2.9g (0.011mol, 73%)	Ethanol

Table 17: Physical Data of Compounds C_2-C_{12}

Compound	*Molecular Formula*	*Molecular wt.*	*m.p °C*	*Rf value × 100*	*Solubility*
C_2	$C_{16}H_{14}O_3$	254	110	47	Methanol, Ethyl acetate
C_3	$C_{16}H_{14}O_3$	254	72	39	"
C_4	$C_{15}H_{12}O_2$	224	88	52	"
C_5	$C_{15}H_{12}ClO_2$	258	42	64	"
C_6	$C_{15}H_{12}ClO_2$	258	142	50	"
C_7	$C_{15}H_{12}FO_2$	242	130	51	"
C_8	$C_{16}H_{14}O_2$	238	132	70	"
C_9	$C_{16}H_{14}O_2$	238	Oil	44	"
C_{10}	$C_{17}H_{17}NO_2$	267	58	73	"
C_{11}	$C_{19}H_{21}NO_2$	295	Oil	73	"
C_{12}	$C_{15}H_{11}NO_4$	269	135	80	"

Table 18: UV Spectral Data of Compounds C_2-C_{12}

Compound	λ_{max}^{MeOH}		$\lambda_{max}^{MeOH+AlCl_3}$	
	Band-I	**Band-II**	**Band-I**	**Band-II**
C_2	351	261	377	275
C3	311	258	339	268
C_4	313	256	331	261
C_5	319	259	333	260
C_6	308	260	349	279
C_7	319	257	342	261
C_8	330	260	356	263
C_9	323	260	356	261
C_{10}	350	251	376	258
C_{11}	339	264	357	266
C_{12}	322	268	359	274

Table 19: IR Spectral Data of Compounds C_2-C_{12}

Compound	*-C=C- Str.* (cm^{-1})	*-C=O Str.* (cm^{-1})	*-OH Str.* (cm^{-1})	*-C-X Str.* (cm^{-1})	*-NO_2 Str.* (cm^{-1})
C_2	1587	1637	3315	—	—
C_3	1590	1635	3340	—	—
C_4	1567	1640	3295	—	—
C_5	1573	1655	3266	756 (C-Cl)	—
C_6	1581	1663	3299	715 (C-Cl)	—
C_7	1599	1643	3270	1135 (C-F)	—
C_8	1594	1659	3375	—	—
C_9	1568	1643	3297	—	—
C_{10}	1589	1665	3413	—	—
C_{11}	1597	1660	3257	—	—
C_{12}	1588	1651	3375	—	1345

Table 20: ^{1}H NMR Spectral Data of Compounds C_2-C_{12} (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_2)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_3)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_4)*
2	6.90, 2H, dd, (1.9, 7.3)	7.20, 1H, dd, (1.4, 1.6)	7.21-7.30, 5H, m
6		7.16-7.18, 1H, m	
4		7.13-7.15, 1H, m	
5	7.01, 2H, dd(1.3, 7.1)	7.27, 1H, dd, (7.81, 7.85)	
3		----	
α	7.65, 1H, d, (15.21)	7.56, 1H, d, (15.4)	7.85, 1H, d, (13.9)
β	7.90, 1H, d, (15.29)	7.91, 1H, d, (15.7)	8.04, 1H, d, (14.2)
6'	8.05, 1H, dd, (1.3, 7.6)	7.95, 1H, dd, (1.6, 7.9)	7.64, 1H, dd, (8.1, 1.7)
3'	7.33, 1H, dd, (1.34, 8.1)	7.33, 1H. dd, (1.6, 8.1)	6.92, 1H, dd, (8.3, 1.5)
4'	7.47, 1H,ddd, (8.4,7.8,1.4)	7.51-7.53, 1H, m	7.38-7.39, 1H, m
5'	7.24,1H,ddd, (7.6, 7.9,1.3)	7.20-7.21, 1H, m	6.99-7.01, 1H, m
OH	9.12, 1H, s, exchangeable with D_2O	9.23, 1H, s, exchangeable with D_2O	9.60, 1H, s, exchangeable with D_2O
OCH_3	3.87, 3H, s	3.86, 3H, s	

Table 20 Continued: ^{1}H NMR Spectral Data of Compound C_2-C_{12} (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_5)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_6)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_7)*
2	----	7.29, 2H, dd,(1.5,8.79)	6.97, 2H, dd, (8.8,1.93)
6	7.26, 1H, dd, (7.63, 1.6)		
4	7.09,1H,ddd,(7.67,1.49, 7.8)	----	----
5	7.9-7.11, 1H, m	7.40, 2H, dd,(1.7,8.73)	7.40, 2H, dd, (8.6,1.98)
3	7.21, 1H, dd, (7.59, 1.6)		
α	7.73, 1H, d, (15.3)	7.39, 1H, d, (14.65)	7.73, 1H, d, (15.4)
β	7.97, 1H, d, (15.6)	7.98, 1H, d, (14.80)	8.01, 1H, d, (15.5)
6'	7.9, 1H, dd, (1.6, 8.3)	7.69, 1H, dd, (1.5, 8.4)	7.93, 1H, dd, (1.6,7.98)
3'	7.01, 1H, dd, (8.5, 1.4)	7.21, 1H, dd, (8.3, 1.3)	7.30, 1H, dd, (8.3,1.3)
4'	7.15-7.17, 1H, m	7.51-7.53, 1H, m	7.71-7.73, 1H, m
5'	7.11-7.12, 1H, m	7.9-7.11, 1H, m	7.25,1H,ddd,(8.3,8.5,1.5)
OH	9.5, 1H, s, exchangeable with D_2O	9.8, 1H, s, exchangeable with D_2O	9.3, 1H, s, exchangeable with D_2O

Table 20 Continued: ^{1}H NMR Spectral Data of Compound C_2-C_{12} (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_8)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_9)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_{10})*
2	7.31, 2H, dd, (7.91, 1.32)	7.20,1H, dd, (1.4, 1.6)	6.56, 2H, dd, (8.7,1.63)
6		7.11-7.13, 1H, m	
4	----	6.97-6.98, 1H, m	----
5	7.21, 2H, dd, (1.4, 8.03)	7.15, 1H, dd, (8.01, 7.5)	7.30, 2H, dd, (8.6,1.56)
3		----	
α	7.63, 1H, d, (14.8)	7.71, 1H, d, (14.9)	7.56, 1H, d, (13.97)
β	8.01, 1H, d, (14.9)	7.98, 1H, d, (15.01)	8.3, 1H, d, (14.20,)
3'	7.34, 1H, dd, (8.6, 1.6)	7.27-7.35, 4H, m	7.31, 1H, dd, (1.70,8.5)
4'	7.51, 1H, ddd, (8.5, 8.1, 1.5)		7.51-7.53, 1H, m
5'	7.24-7.25, 1H, m		7.15-7.18, 1H, m
6'	8.20, 1H, dd, (1.49, 7.9)		7.90, 1Hdd, (8.3, 1.6)
CH_3	2.38, 3H, s	2.36, 3H, s	----
$N(CH_3)_2$	----	----	2.85, 6H, s
OH	9.3, 1H, s, exchangeable with D_2O	9.4, 1H, s, exchangeable with D_2O	9.13, 1H, s, exchangeable with D_2O

Table 20 Continued: ^{1}H NMR Spectral Data of Compounds C_2-C_{12} (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_{11})*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (C_{12})*
2	6.54, 2H, dd, (8.7, 1.8)	7.53, 2H, dd, (7.5, 1.7)
6		
5	7.12, 2H, dd, (1.7, 8.8)	8.17, 2H, dd, (7.9, 1.5)
3		
α	7.69, 1H, d, (15.3)	7.85, 1H, d, (15.32)
β	7.90, 1H, d, (15.45)	8.05, 1H, d, (15.40)
3'	6.92, 1H, dd, (8.6, 1.7)	6.92, 1H, dd, (8.7, 1.8)
4'	7.37, 1H, ddd, (1.6, 7.5, 8.7)	7.37, 1H. ddd, (1.65, 8.1, 8.3)
5'	6.99-7.01, 1H, m	7.80-7.81, 1H, m
6'	7.64, 1H, dd, (8.5, 1.6)	7.64, 1H, dd, (1.5, 8.7)
CH_3	1.13, 6H, t, (7.8)	----
CH_2	3.39, 4H, q, (7.7)	----
OH	9.53, 1H, s, exchangeable with D_2O	9.45, 1H, s, exchangeable with D_2O

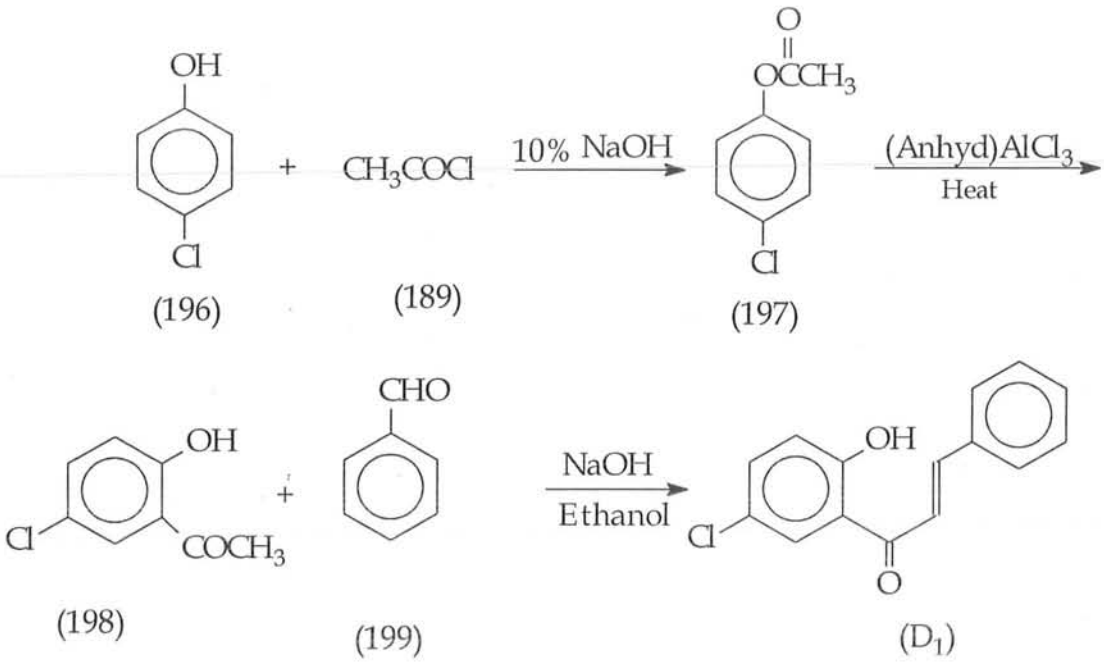
Table 21: Mass Spectral Data of Compounds C_2-C_{12}

Peaks	*Compounds*				
	C_2	C_3	C_4	C_5	C_6
$M^{+\cdot}$ m/z (%)	254 (96.1)	254 (67.37)	224 (41.97)	258 (28.01)	258 (21.23)
$[M-H]^+$	253 (2.31)	253 (3.20)	223 (34.13)	257 (7.83)	257 (8.32)
A_2^+	121 (76.10)	121 (39.10)	121 (21.31)	121 (27.3)	121 (79.3)
$[A_2\text{-}CO]^+$	93 (21.31)	93 (100)	93 (33.51)	93 (13.39)	93 (41.31)
B_5^+	161 (61.11)	161 (42.56)	131 (100)	165 (37.81)	165 (100)
$[B_5\text{-}CO]^+$	133 (23.12)	133 (33.12)	103 (33.96)	137 (29.31)	137 (31.21)
$A_1^{+\cdot}$	120 (31.35)	120 (21.56)	120 (23.3)	120 (29.52)	120 (30.20)
$[A_1\text{-}CO]^{+\cdot}$	92 (3.43)	92 (5.70)	92 (12.92)	92 (7.23)	92 (11.21)
$B_1^{+\cdot}$	134 (100)	134 (87.81)	104 (89.39)	138 (29.31)	138 (60.21)
[M -B ring]$^+$	147 (86.01)	147 (76.87)	147 (71.36)	147 (100)	147 (67.81)
[M - A&C ring]$^+$	107 (35.1)	107 (39.31)	77 (100)	111 (51.31)	111 (37.31)
$[M\text{-}CH_3]^+$	239 (51.50)	239 (21.23)	--	--	--
$[M\text{-}OH]^+$	237 (35.31)	237 (13.24)	207 (18.39)	241 (13.31)	241 (21.23)

Table 21 Continued: Mass Spectral Data of Compounds C_2-C_{12}

Peaks	*Compounds*					
	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}
$M^{+\cdot}$ m/z (%)	242 (24.01)	238 (100)	238 (71.36)	267 (100)	295 (5.31)	269 (31.31)
$[M-H]^+$	241 (2.31)	237 (33.31)	237 (13.25)	266 (22.31)	294 (14.21)	268 (2.31)
A_2^+	121 (100)	121 (76.10)	121 (65.31)	121 (71.31)	121 (63.50)	121 (19.30)
$[A_2\text{-}CO]^+$	93 (31.37)	93 (23.25)	93 (33.51)	93 (45.35)	93 (51.31)	93 (57.31)
B_5^+	149 (49.39)	145 (35.35)	145 (100)	174 (91.25)	202 (51.31)	176 (22.36)
$[B_5\text{-}CO]^+$	121 (29.30)	117 (22.10)	117 (27.10)	146 (34.31)	174 (52.51)	148 (100)
$A_1^{+\cdot}$	120 (67.31)	120 (81.13)	120 (31.8)	120 (81.35)	120 (63.11)	120 (72.31)
$[A_1\text{-}CO]^{+\cdot}$	92 (5.39)	92 (31.21)	92 (20.13)	92 (43.35)	92 (3.51)	92 (4.31)
$B_1^{+\cdot}$	122 (53.1)	118 (43.12)	118 (3.31)	147 (76.81)	175 (100)	149 (34.4)
[M -B ring]$^+$	147 (14.31)	147 (11.35)	147 (8.31)	147 (15.31)	147 (43.21)	147 (64.31)
[M - A&C ring]$^+$	95 (13.11)	91 (81.31)	91 (65.31)	120 (56.13)	164 (61.31)	122 (22.32)
$[M\text{-}OH]^+$	225 (41.31)	221 (33.51)	221 (27.31)	250 (61.35)	278 (44.31)	252 (39.37)

3.11 Synthesis of 5'- Chloro-2'-hydroxy-B ring Substituted Chalcones (D-series Chalcones)



Scheme 8:

3.11.1 Synthesis of 1-(5'-chloro-2'-hydroxyphenyl)-3-phenyl-2-propen-1-one (D_1):

3.11.1.1 Synthesis of 5-chloro-2-hydroxyacetophenone (198)

3.11.1.1.a Synthesis p-chlorophenylacetate (197)

70g (0.54 moles) of p-chlorophenol **(196)** was added in 200 ml of 10% NaOH solution and was stirred. After 10 minutes the solution became clear and all the *p*-chlorophenol was completely dissolved in the solution. The reaction mixture was kept in an ice bath to maintain the temperature at 0-5^{0}C with constant stirring and 66 ml (0.84 moles) of acetyl chloride **(189)** was added drop wise. The temperature was kept low for an hour. The oil formed was extracted with dichloromethane (2 × 30 ml), which afforded 39g (82%) of *p*-

chlorophenyl acetate **(197).** The **IR** showed stretching frequency at 1745 cm^{-1} which is characterstic of ester group.

3.11.1.1.b Fries rearrangement

45g (0.33 moles) of anhydrous aluminum chloride were taken in a dry 2-necked round bottom flask and 30g (0.175 moles) of dried *p*-chlorophenylacetate **(197)** was added to it. The drying tube and gas trapping apparatus was used. The mixture was heated on an oil bath at 120^0C for 75 minutes. The reaction mixture was allowed to cool at room temperature and 100g of crushed ice was added followed by 200 ml of chilled water. Then 100 ml of toluene was added and the solution was kept on stirring for an hour. Extraction was made and toluene was distilled off to obtain residue oil. The Vacuum distillation (20mm/Hg, 25^0C) of oil afforded 20g of 5-chloro-2-hydroxyacetophenone **(198)** m.p. 55^0C. The **IR** showed carbonyl stretching at 1645 cm^{-1}.

3.11.1.1.c Claisen-Schmidt Condensation

80ml of 4.0 M solution of sodium hydroxide was dissolved in 60ml of rectified spirit in a conical flask. The solution was cooled in an ice bath to 0^0C. 2g (0.012moles) of freshly distilled 5-chloro-2-hydroxyacetophenone **(198)** were added to it. The mixture was stirred by a magnetic stirrer for half an hour in an ice bath keeping the temperature at 0-5^0C. Then 1.18ml (0.012moles) of benzaldehyde **(199)** were added and mixture was stirred vigorously for 2-3 hours. The reaction mixture was kept at 0-5^0C for overnight. The thick oil obtained was diluted with chilled water and aqueous hydrochloric acid was added to neutralize it. The product was obtained as yellow precipitates. The precipitate was filtered and recrystallized from aqueous ethanol to afford 1-(5'-chloro-2'-hydroxyphenyl)-3-phenyl-2-propen-1-one **(D_1)**. Further purification of chalcone was carried out on preparative TLC plates [silica gel HF-60 in pet-ether: ethylacetate (9:1)]. The purity was also checked by HPLC using solvent system acetonoitrile:water (80:20) **(Chromatogram 4)**. Yield of 1-(5'-chloro-2'-hydroxyphenyl)-3-phenyl-2-propen-1-one **(D_1)** was 1.9g (0.007mol, 58%). m.p.98^0C. **UV**

(λ_{max}^{MeOH}) 345 nm & 257 nm, **IR** (υ_{max}, KBr): 1642, 1587 cm^{-1}, **^{1}H-NMR** (CDC_3OD, δ-values in PPM); 7.36-7.53 (5H, m), 7.84 (1H, d, J=15.42 Hz), 7.93 (1H, d, J=15.43 Hz), 6.97 (1H, d, J=8.90 Hz), 7.79 (1H, dd, J=6.94, 1.08), 8.12 (1H, d, J=1.20), 9.42 (1H, s, exchangeable with D_2O); **EIMS** (70 eV): m/z (%)= 258 (73.39 %, M^+, ^{35}Cl), 260 (24.42 %, M^+, ^{37}Cl), 257 (51.97), 241 (7.27), 181 (57.74), 155 (24.69), **154 (100)**, 131 (15.15), 126 (20.64), 104 (57.4), 103 (42.03), 77 (41.07), 51 (26.09.

3.12 Results and Discussion

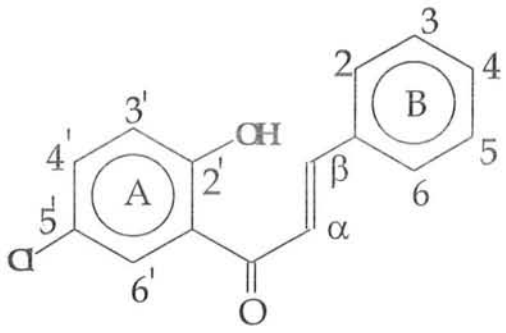
Benzaldehyde **(199)** and 5'-chloro-2'-hydroxyacetophenone **(198)** were reacted in ethanol for 2-3 hours at 0-5 °C under basic conditions to yield 1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1)**. Compound **(D_1)** was found to have a molecular formula of $C_{15}H_{11}ClO_2$ and molecular weight 258. 1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1)** gave UV absorption maxima at λ_{max}^{MeOH} 345 nm **(Band I)** and 257 nm **(Band II)**, which were characteristics of chalcones **(Spectrum 11)**. Band-**I** results from the conjugation of the whole molecule and Band-**II** is considered due to the *cis* or the *trans* isomers. The addition of $AlCl_3$ in the methanolic solution of 1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1)** shifted the bands at 378 nm **(Band I)** and 260 nm **(Band II)**, which show free hydroxyl group at 2'- position of the A-ring **(Spectrum 12)**. The **IR** spectrum showed stretching frequencies at 1642cm^{-1}, 1587$cm^{-1}$and 3335cm^{-1} which are characteristic of C=O, aromatic C=C and OH groups respectively.

The mass spectrum **(Spectrum 13)** of 1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1)** showed a chalcone and flavanone type of molecular ion peaks at m/z 258(M^+, Cl^{35}) and 260 (M^++2, Cl^{37}), which are in agreement with molecular weight. The peaks at m/z 257(Cl^{35}) and 259(Cl^{37}) are the fragment ions resulting from the simultaneous loss of hydrogen atom of the B-ring and its cyclization with the oxygen of the carbonyl group. The characteristic peaks in the mass spectrum was at m/z 241(Cl^{35}) and 243(Cl^{37}) appeared due to the loss of hydroxyl group. Other peaks in the mass spectrum are at m/z 157(Cl^{37}), 155(Cl^{35}) and 131, resulting from the fragmentation on both sides of the carbonyl group, a common fragmentation process in chalcones.

As the chalcone **D_1** possess 2'-hydroxy group in A-ring, there is an intramolecular equilibrium exist between chalcone **D_1** and respective flavanone, so the mass spectrum also showed the flavanone type fragment ions. The base peak at m/z 154 along with another peak at m/z 104 is formed by retro Diels-Alder ring fission of flavanone type of molecular ion. The peak at m/z 181 appeared due to the loss of B-ring from the flavanone.

The fragmentation pattern of 1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1)** is given in scheme **(Scheme 9).**

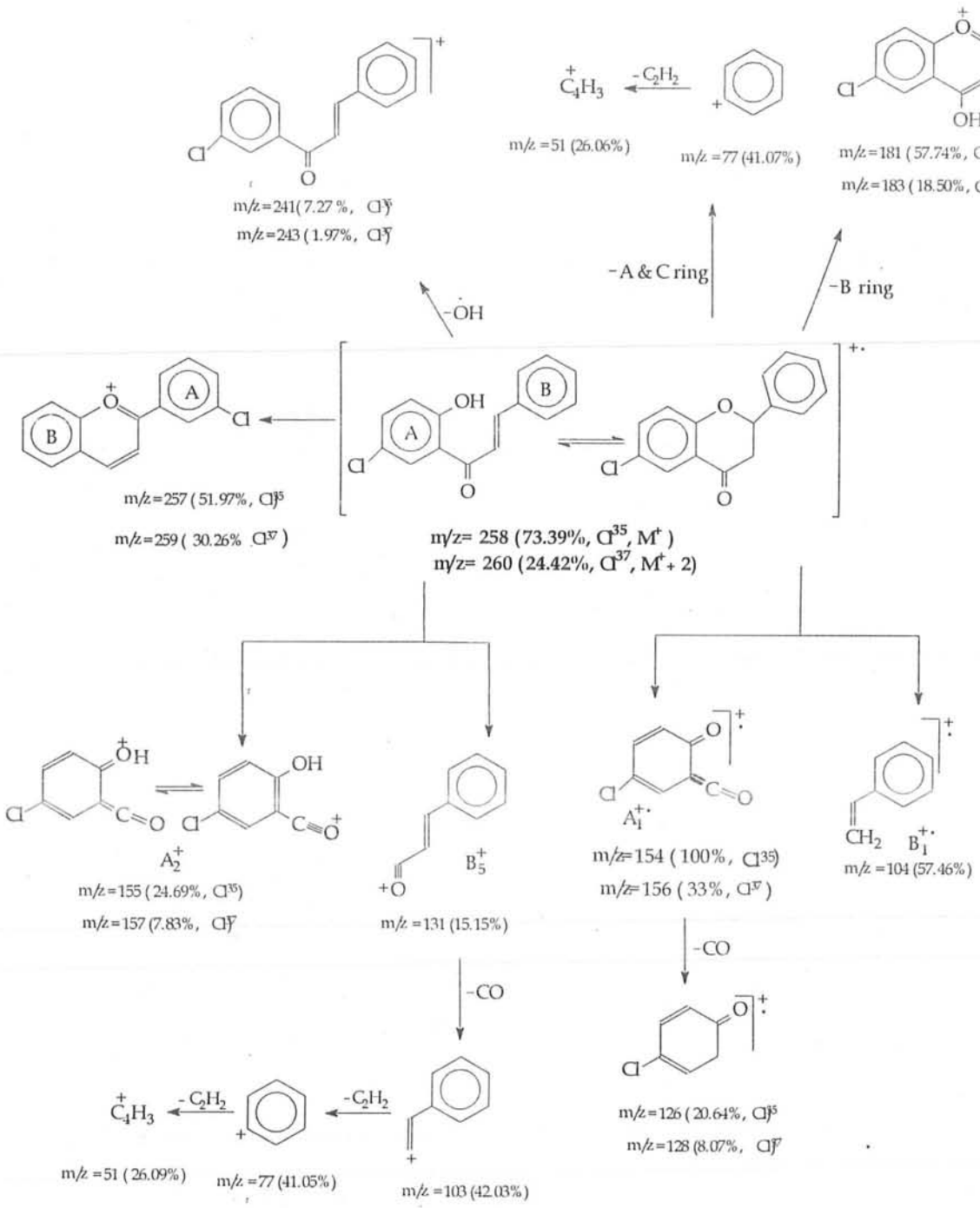
The **^{1}H NMR** spectrum **(Spectrum 14)** of a 1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1)** showed a pair of doublets at 7.84 ppm and 7.93 ppm with a large coupling constant of 15.42 and 15.43 Hz, which is characteristic of *trans* olefinic protons. Thus the chalcone **D_1** is *trans*-1-(5'-chloro-2'-hydroxy phenyl)-3-phenyl-2-propen-1-one **(D_1).** The hydroxyl proton gave a singlet at 9.15. δ values, multiplicity and J values of all protons of chalcone **D_1** are tabulated in **(Table 22).**



(D_1)

Table 22: ^{1}H NMR Spectral Data of Compounds D_1 (CD_3OD: 400 MHz)

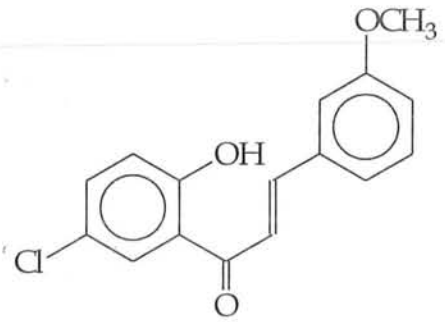
Carbon	*^{1}H-δ (ppm)*	*Multiplicity*	*J(Hz)*
2-6	7.36-7.53	5H, m	----
α	7.84	1H, d	15.42
β	7.93	1H, d	15.43
3'	6.97	1H, d	8.9
4'	7.79	1H, dd	6.94, 1.08
6'	8.12	1H, d	1.2
OH	9.53	1H, s	exchangeable with D_2O



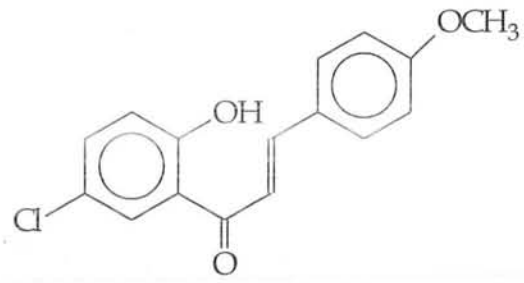
Scheme 9: Mass Fragmentation Pattern of D_1

Using the same synthetic procedure, other members of the A-series chalcones **(D_2-D_{10})** were synthesized. Molar quantities, physical constants **UV, IR, ^{1}H NMR** and **Mass** spectral data for these 9 chalcones are presented in **(Table 23-28).** Structures of these chalcones are:

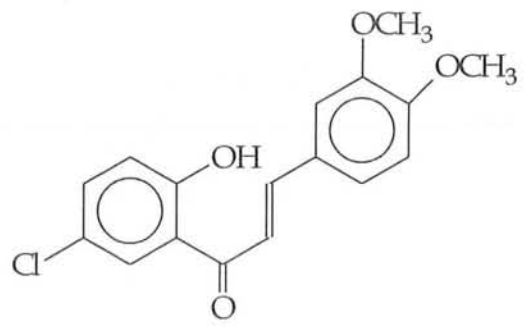
D_2= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(3-methoxylphenyl)-2-propen-1-one



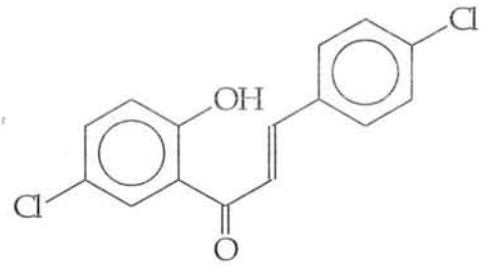
D_3= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-methoxylphenyl)-2-propen-1-one



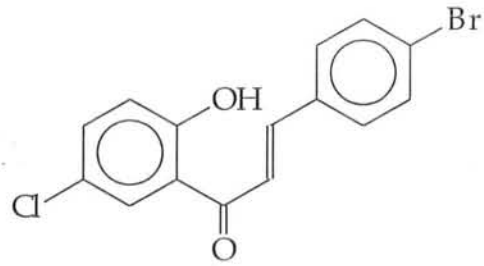
D_4= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(3,4-dimethoxylphenyl)-2-propen-1-one



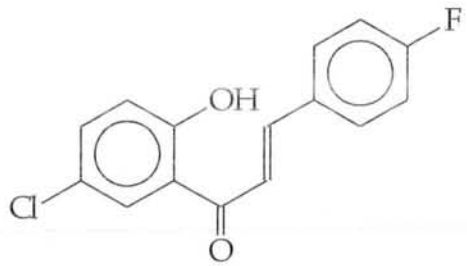
D_5= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-chlorophenyl)-2-propen-1-one



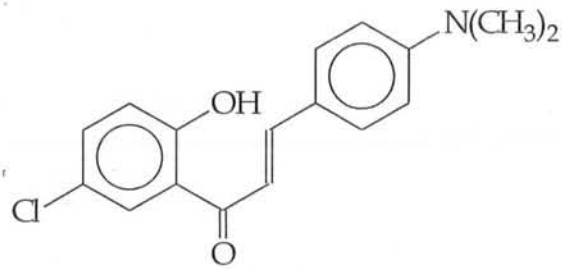
D_6= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-bromophenyl)-2-propen-1-one



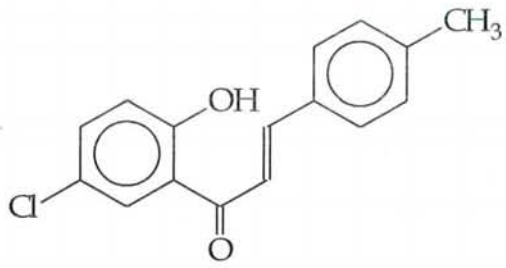
D_7= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-fluorophenyl)-2-propen-1-one



D_8= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-dimethylaminophenyl)-2-propen-1-one



D_9= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(4-methylphenyl)-2-propen-1-one



D_{10}= 1-(5'-Chloro-2'-hydroxy phenyl)-3-(3-methylphenyl)-2-propen-1-one

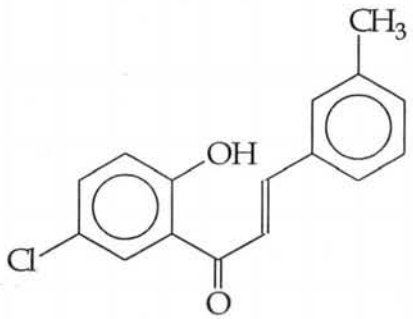


Table 23: Molar Ratios of Compounds D_2-D_{10}

Compd.	*5-Chloro-2-hydroxy acetophenone*	*Substituted Benzaldehydes*	*Yield*	*Solvent for Recrystallization*
D_2	2.0g (0.012moles)	1.42ml (0.012moles)	2.4g (0.008mol, 66%)	Ethanol
D_3	2.0g (0.012moles)	1.42ml (0.012moles)	2.4g (0.009mol, 75%)	Ethanol
D_4	2.0g (0.012moles)	1.94g (0.012moles)	2.9g (0.009mol, 75%)	Ethanol
D_5	2.0g (0.012moles)	1.64g (0.012moles)	2.7g (0.009mol, 75%)	Ethanol
D_6	2.0g (0.012moles)	2.16g (0.012moles)	2.8g (0.008mol, 66%)	Ethanol
D_7	2.0g (0.012moles)	1.92g (0.012moles)	2.5g (0.009mol, 75%)	Ethanol
D_8	2.0g (0.012moles)	1.74g (0.012moles)	2.4g (0.008mol, 66%)	Ethanol
D_9	2.0g (0.012moles)	1.37ml (0.012moles)	2.1g (0.008mol, 66%)	Ethanol
D_{10}	2.0g (0.012moles)	1.37ml (0.012moles)	2.5g (0.009mol, 75%)	Ethanol

Table 24: Physical Data of Compounds D_2-D_{10}

Compound	*Molecular Formula*	*Molecular wt.*	*m.p °C*	*Rf value × 100*	*Solubility*
D_2	$C_{16}H_{13}ClO_3$	288	Oil	69	Methanol, Ethyl acetate
D_3	$C_{16}H_{13}ClO_3$	288	103	48	"
D_4	$C_{17}H_{15}ClO_4$	318	170	78	"
D_5	$C_{15}H_{10}Cl_2O_2$	292	93	81	"
D_6	$C_{15}H_{10}BrClO_2$	337	80	80	"
D_7	$C_{15}H_{10}ClFO_2$	276	65	81	"
D_8	$C_{17}H_{16}ClNO_2$	301	40	78	"
D_9	$C_{16}H_{13}ClO_2$	272	121	79	"
D_{10}	$C_{16}H_{13}ClO_2$	272	112	75	"

Table 25: UV Spectral Data of Compounds D_2-D_{10}

Compound	λ_{max}^{MeOH}		$\lambda_{max}^{MeOH+AlCl_3}$	
	Band-I	**Band-II**	**Band-I**	**Band-II**
D_2	329	289	387	294
D_3	340	261	370	268
D_4	347	268	382	272
D_5	335	259	347	261
D_6	304	258	346	271
D_7	332	260	345	261
D_8	340	264	393	269
D_9	323	257	363	264
D_{10}	335	257	349	268

Table 26: IR Spectral Data of Compounds D_2- D_{10}

Compound	*-C=C- Str. (cm^{-1})*	*-C=O Str. (cm^{-1})*	*-OH Str. (cm^{-1})*	*-C-X Str. (cm^{-1})*
D_2	1597	1649	3395	665 (C-Cl)
D_3	1563	1634	3475	723 (C-Cl)
D_4	1594	1645	3267	695 (C-Cl)
D_5	1587	1642	3317	630 (C-Cl)
D_6	1578	1638	3435	655 (C-Cl) 543 (C-Br)
D_7	1599	1633	3275	701 (C-Cl) 1383 (C-F)
D_8	1583	1648	3305	673 (C-Cl)
D_9	1584	1641	3415	637 (C-Cl)
D_{10}	1573	1650	3312	688 (C-Cl)

Table 27: ^{1}H NMR Spectral Data of Compounds D_2-D_{10}

(CD_3OD, 400 MHz)

Carbon	***^{1}H-δ (ppm), Multiplicity, J(Hz) (D_2)***	***^{1}H-δ (ppm), Multiplicity, J(Hz) (D_3)***	***^{1}H-δ (ppm), Multiplicity, J(Hz) (D_4)***
2	6.88, 1H, dd, (1.4, 1.3)	6.72, 2H, dd, (8.9, 1.34)	7.02, 1H, d, (1.8)
6	6.96, 1H, dd, (8.01, 1.4)		7.5, 1H, dd, (7.83, 1.9)
3	----	7.19, 2H, dd, (1.4, 8.3)	----
5	7.11, 1H, dd, (7.98,7.91)		6.96, 1H, d, (7.9)
4	6.65,1H,ddd,(7.95,1.5,1.45)	----	----
α	7.83, 1H, d, (14.73)	7.70, 1H, d, (15.3)	7.56, 1H, d, (14.14)
β	7.97, 1H, d, (14.70)	7.90, 1H, d, (15.3)	7.90, 1H, d, (14.15)
3'	6.86, 1H, d, (8.3)	6.95, d, (8.8)	7.01, 1H, d, (7.9)
4'	7.38, 1H, dd, (8.21, 1.4)	7.77, 1H, dd, (6.97, 1.8)	7.24, 1H, dd, (7.2, 1.7)
6'	7.65, 1H, d (1.3)	8.1, 1H, d, (1.3)	7.48, 1H, d, (1.5)
OH	9.43, 1H, s, exchangeable with D_2O	9.57, 1H, s, exchangeable with D_2O	9.33, 1H, s, exchangeable with D_2O
OCH_3	3.73, 3H, s	3.81, 3H, s	3.73, 3H, s 3.75, 3H, s

Table 27 Continued: ^{1}H NMR Spectral Data of Compounds D_2-D_{10}

(CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (D_5)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (D_6)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (D_7)*
2,6	7.28, 2H, dd, (7.8, 1.7)	7.38, 2H, dd, (8.3, 1.6)	6.92, 2H, dd, (7.4, 1.4)
3,5	7.22, 2H, dd, (1.65,8.1)	7.19, 2H, dd, (8.1, 1.4)	7.28, 2H, dd, (1.6, 7.4)
α	7.56, 1H, d, (14.35)	7.9, 1H, d, (15.29)	7.61, 1H, d, (14.2)
β	7.9, 1H, d, (14.37)	8.1, 1H, d, (15.3)	7.80,1H, d, (14.2)
3'	7.08, 1H, d, (8.03)	6.97, 1H, d, (7.8)	7.01. 1H, d, (7.3)
4'	7.36, 1H, dd, (7.9,1.45)	7.39, 1H, dd, (7.9,1.45)	7.48, 1H, dd, (7.5, 1.3)
6'	7.60, 1H, d, (1.45)	7.65, 1H, d, (1.4)	7.75, 1H, d, (1.4)
OH	8.93, 1H, s, exchangeable with D_2O	9.43, 1H, s, exchangeable with D_2O	9.55, 1H, s, exchangeable with D_2O

Table 27 Continued: ^{1}H NMR Spectral Data of Compounds D_2-D_{10} (CD_3OD, 400 MHz)

Carbon	*^{1}H-δ (ppm), Multiplicity, J(Hz) (D_8)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (D_9)*	*^{1}H-δ (ppm), Multiplicity, J(Hz) (D_{10})*
2	6.93, 2H, dd, (8.3,1.53)	7.01, 2H, dd, (8.05, 1.7)	7.15, 1H,d d, (1.4, 1.3)
6			7.12, 1H, dd, (8.2, 1.3)
3	7.17, 2H, dd, (8.21, 1.51)	7.18, 2H, dd, (1.10, 1.73)	----
5			7.05, 1H, dd, (7.4, 8.1)
4	----	----	6.93-6.94, 1H, m
α	7.7, 1H, d, (15.01)	7.53, 1H, d, (14.87)	6.93, 1H, d, (13.98)
β	8.01, 1H, d, (15.02)	8.07, 1H, d, (14.9)	7.5, 1H, d, (14.0)
3'	6.86, 1H, d, (7.5)	6.93, 1H, d, (8.21)	6.89, 1H, d, (7.4)
4'	7.38, 1H, dd, (7.5, 1.9)	7.20, 1H, dd, (8.1, 1.8)	7.31, 1H, dd, (7.56, 1.39)
6'	7.70, 1H, d, (1.7)	7.65, 1H, d, (1.9)	7.53, 1H, d, (1.33)
OH	9.56, 1H, s, exchangeable with D_2O	9.32, 1H, s, exchangeable with D_2O	9.81, 1H, s, exchangeable with D_2O
$N(CH_3)_2$	3.81, 6H, s	----	----
CH_3	----	2.36, 3H, s	2.35, 3H, s

Table 28: Mass Spectral Data of Compounds D_2-D_{10}

Peaks	*Compounds*				
	D2	***D3***	***D4***	***D5***	***D6***
$M^{+\cdot}$ m/z (%)	288 (100)	288 (32.25)	318 (76.31)	292 (47.27)	338 (41.59)
$[M-H]^+$	287 (16.21)	287 (14.01)	317 (17.35)	291 (12.38)	337 (21.21)
A_2^+	155 (8.76)	155 (5.71)	155 (8.15)	155 (8.38)	155 (9.91)
$[A_2\text{-}CO]^+$	127 (8.25)	127 (8.21)	127 (6.35)	127 (43.13)	127 (31.29)
B_5^+	161 (8.98)	161 (6.96)	191 (76.10)	165 (81.31)	2101 (67.21)
$[B_5\text{-}CO]^+$	133 (9.96)	133 (18.95)	163 (33.51)	137 (32.39)	183 (5.29)
$A_1^{+\cdot}$	154 (2.51)	154 (2.51)	154 (31.31)	154 (100)	154 (100)
$[A_1^{+\cdot}\text{-}CO]^{+\cdot}$	126 (2.31)	126 (12.34)	126 (3.5)	126 (41.37)	126 (33.23)
$B_1^{+\cdot}$	134 (76.10)	134 (100)	164 (100)	138 (47.21)	184 (51.39)
[M –B ring]$^+$	181 (7.95)	181 (6.91)	181 (31.21)	181 (91.30)	181 (85.21)
[M –A&C ring]$^+$	107 (1.31)	107 (2.31)	137 (41.35)	111 (7.31)	157 (21.07)
$[M\text{-}CH_3]^+$	273 (4.48)	273 (2.46)	303 (9.31)	--	--
$[M\text{-}OH]^+$	271 (2.39)	271 (2.2)	301 (6.97)	275 (23)	320 (24.23)

Table 28 Continued: Mass Spectral Data of Compounds D_7-D_{10}

Peaks	*Compounds*			
	D7	***D8***	***D9***	***D10***
$M^{+\cdot}$ m/z (%)	276 (27.31)	301 (23.31)	272 (100)	272 (71.31)
$[M-H]^+$	275 (3.2)	300 (17.32)	271 (31.47)	271 (6.11)
A_2^+	155 (47.31)	155 (48.91)	155 (41.97)	155 (100)
$[A_2\text{-CO}]^+$	127 (31.37)	127 (14.31)	127 (23.81)	127 (32.37)
B_5^+	149 (18.31)	174 (35.31)	145 (33.51)	145 (43.10)
$[B_5\text{-CO}]^+$	121 (36.76)	146 (43.37)	117 (39.67)	117 (46.03)
$A_1^{+\cdot}$	154 (100)	154 (31.38)	154 (16.27)	154 (13.60)
$[A_1^{+\cdot}\text{-CO}]^{+\cdot}$	126 (21.39)	126 (19.39)	126 (19.31)	126 (26.73)
$B_1^{+\cdot}$	122 (31.37)	147 (100)	118 (29.37)	118 (43.78)
[M –B ring]$^+$	181 (51.52)	181 (17.39)	181 (39.41)	181 (67.35)
[M – A&C ring]$^+$	95 (13.13)	120 (74.31)	91 (13.19)	91 (71.31)
[M-OH]$^+$	259 (19.33)	283 (12.32)	255 (14.87)	255 (63.38)

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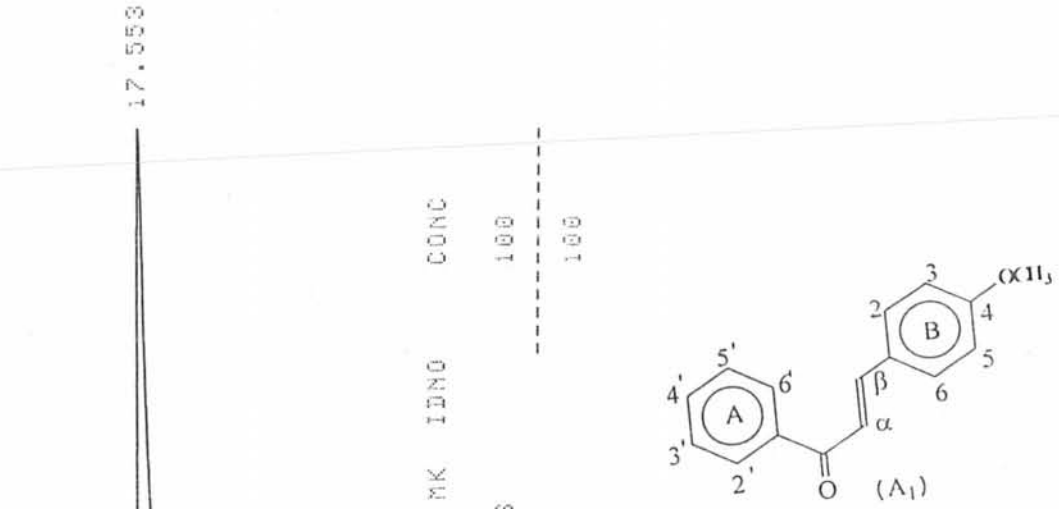
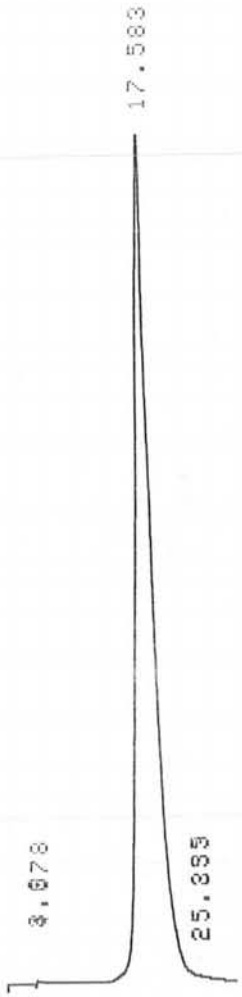
Annex

HPLC Chromatograms of A_1, B_1, C_1 & D_1



Chromatogram 1. HPLC of A_1



CHROMATOPAC C-R3A
SAMPLE NO 0
REPORT NO 541

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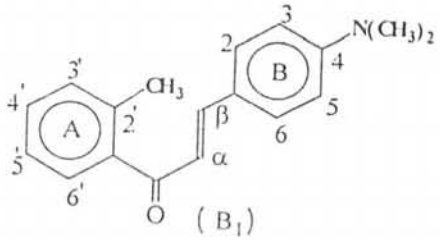
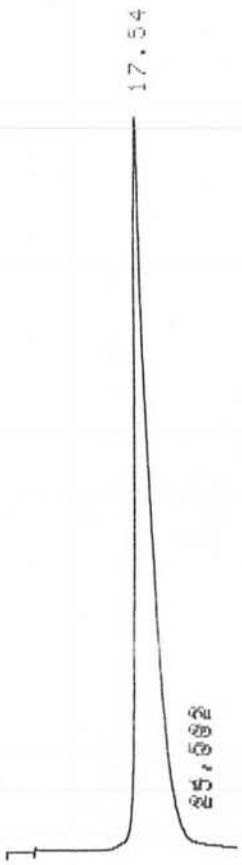
TOTAL		7947193			100



Chromatogram 2. HPLC of B_1



CHROMATOPAC C-R3A

SAMPLE NO 0

REPORT NO 539

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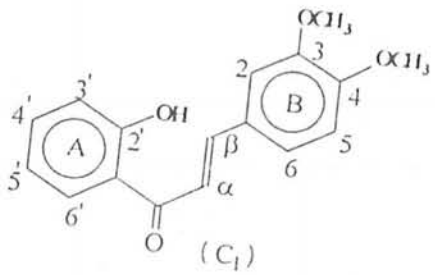
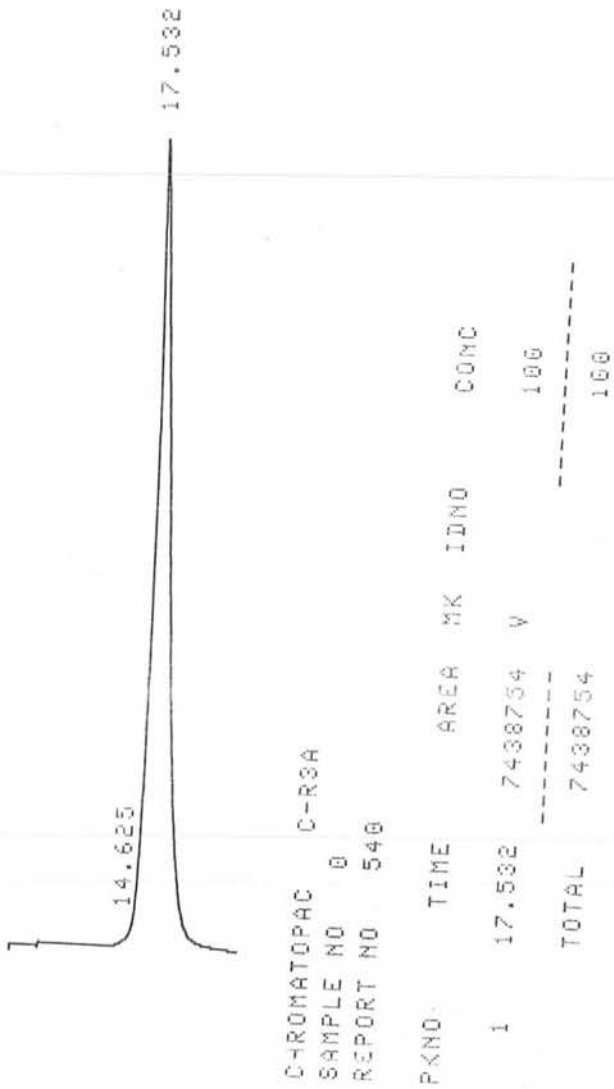
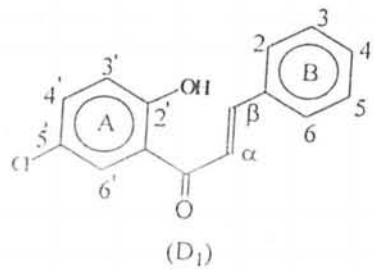
TOTAL		65942153			100



Chromatogram 3. HPLC of C_1

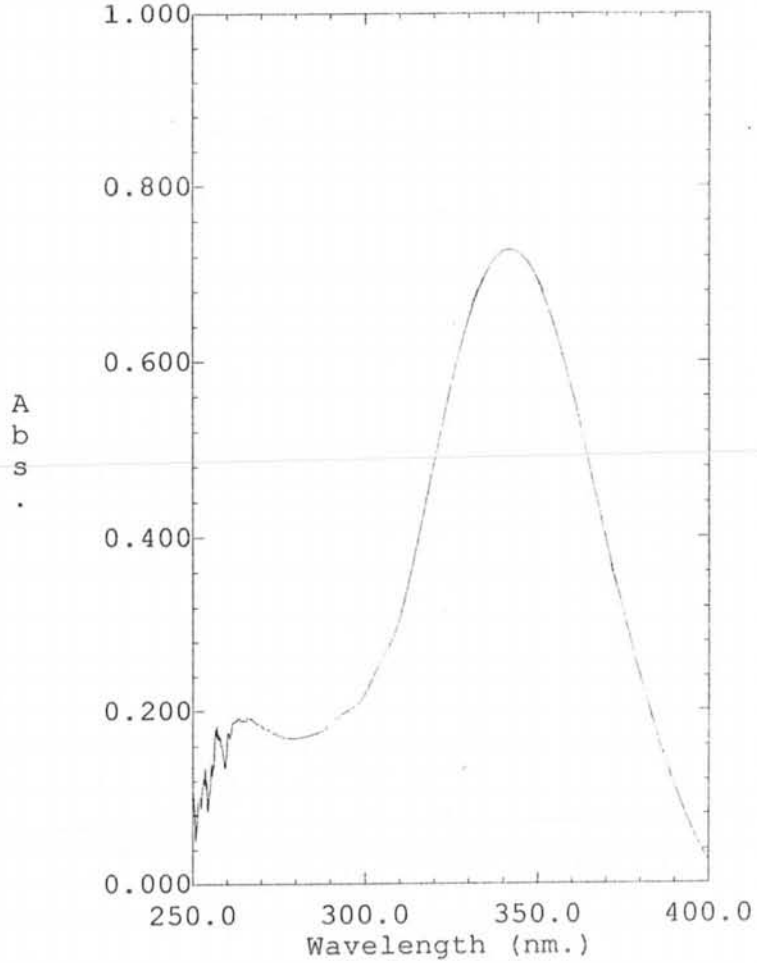




(D_1)

Chromatogram 4. HPLC of D_1

UV, ^1H NMR & EIMS of D_1



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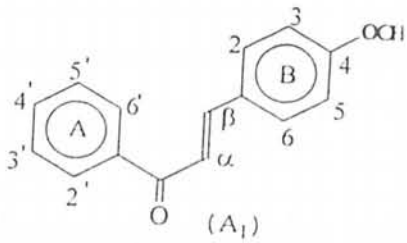

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Spectrum 1. UV Spectrum of compound A_1 in MeOH

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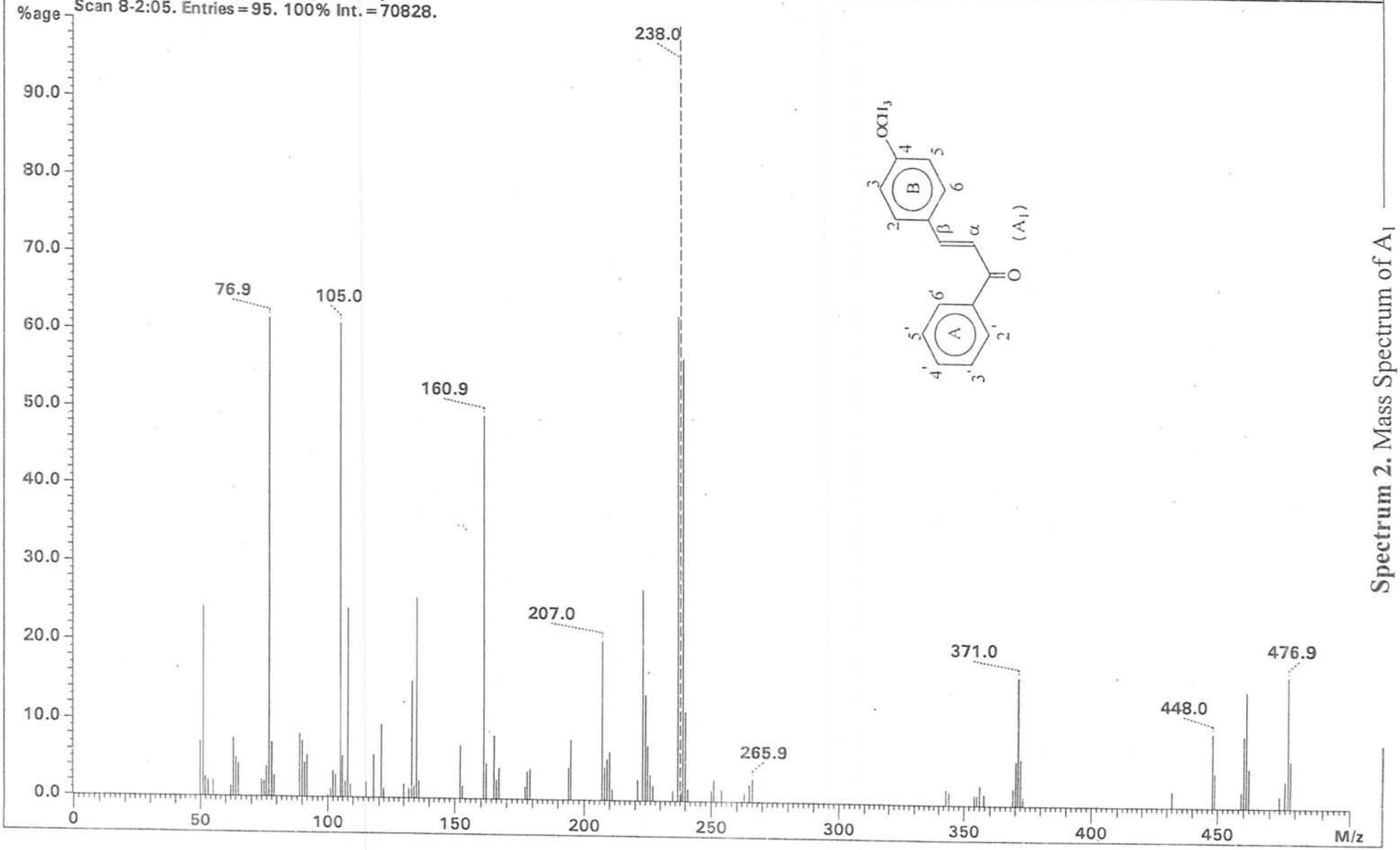
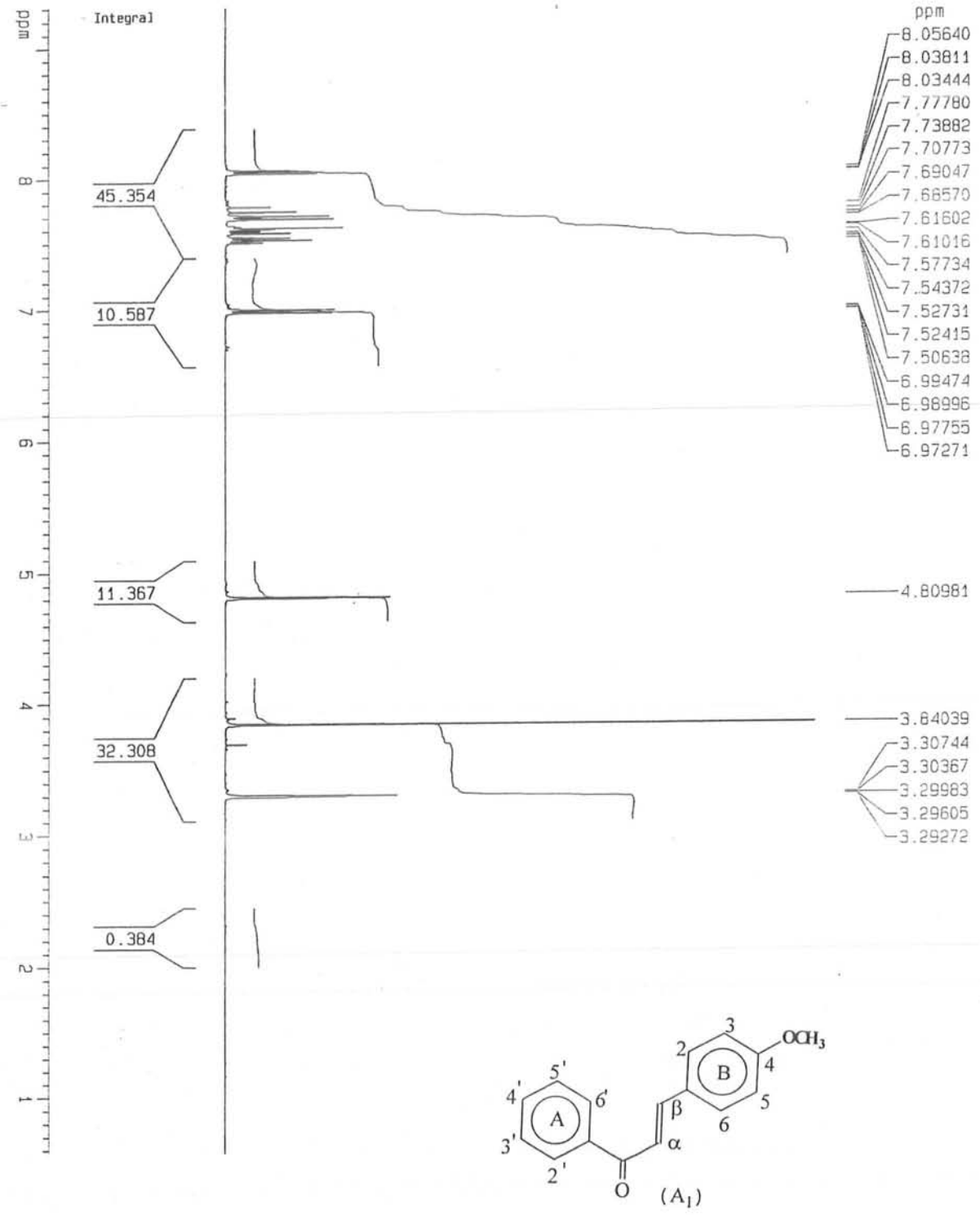
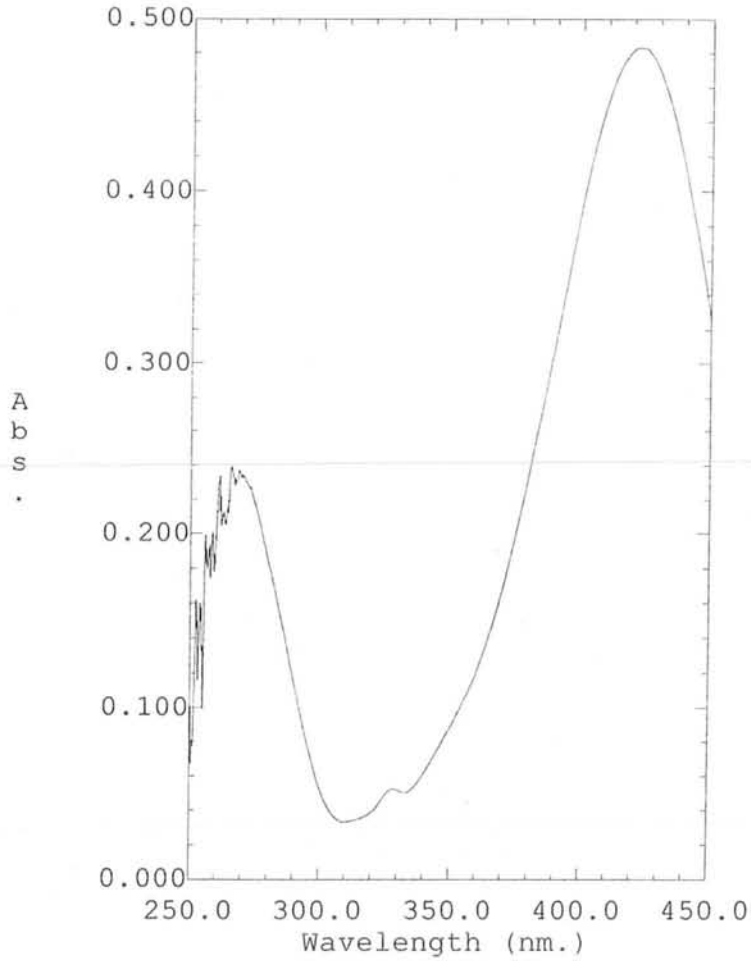


Spectrum 2. Mass Spectrum of A_1



Spectrum 3. ^{1}HNMR Spectrum of A_1

UV, ^1H NMR & EIMS of B_1



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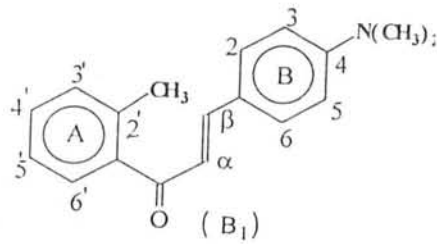

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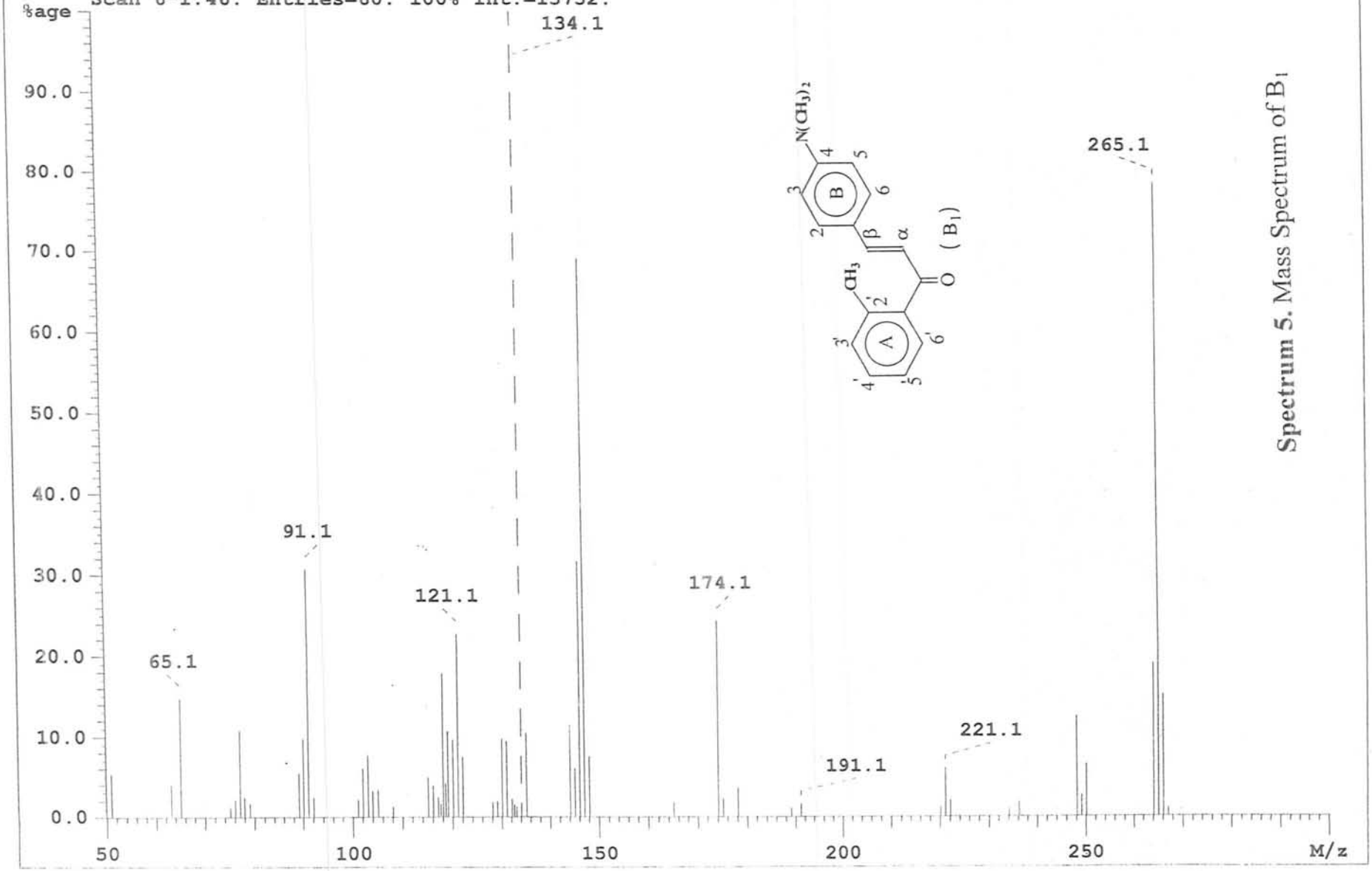
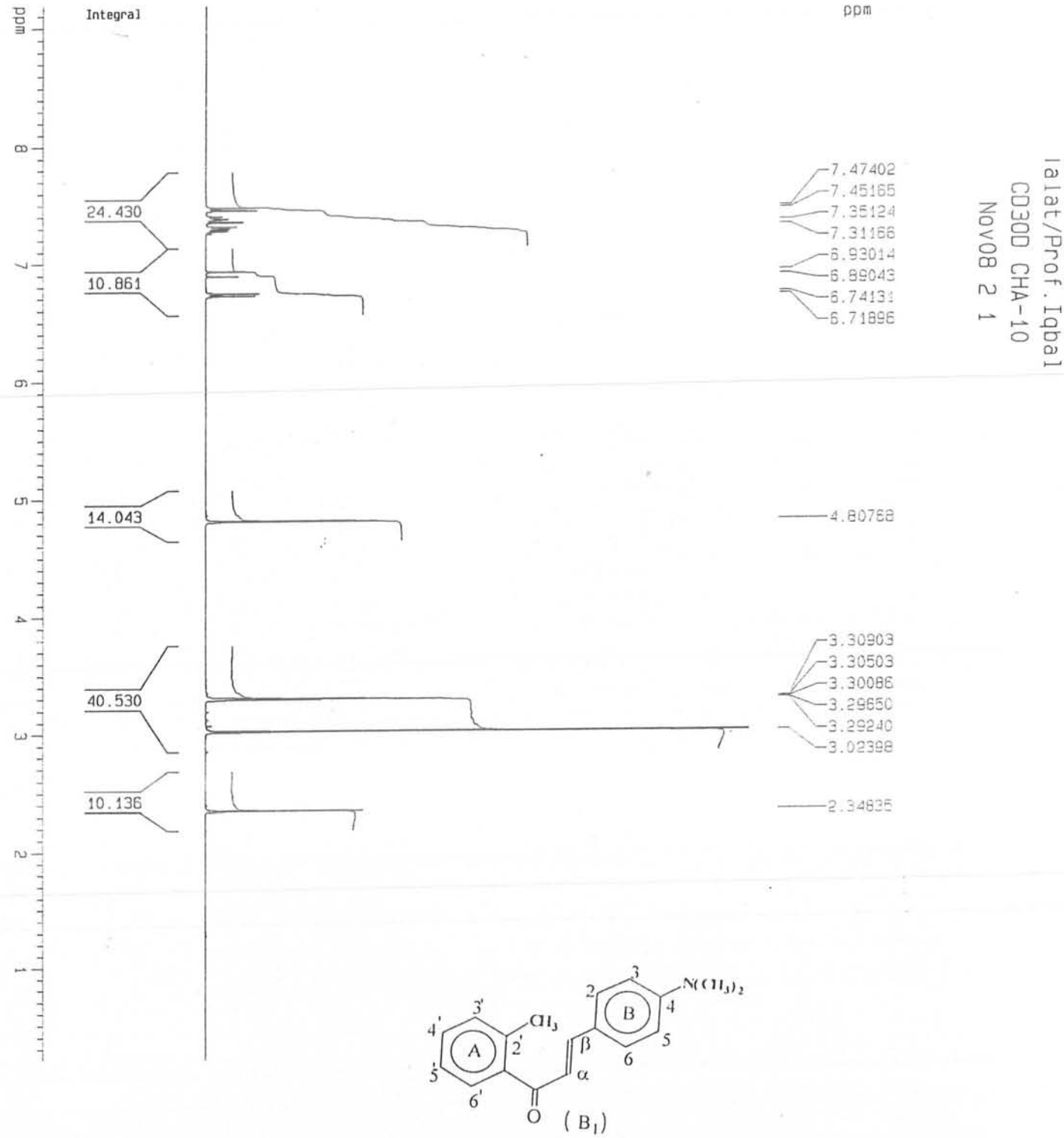


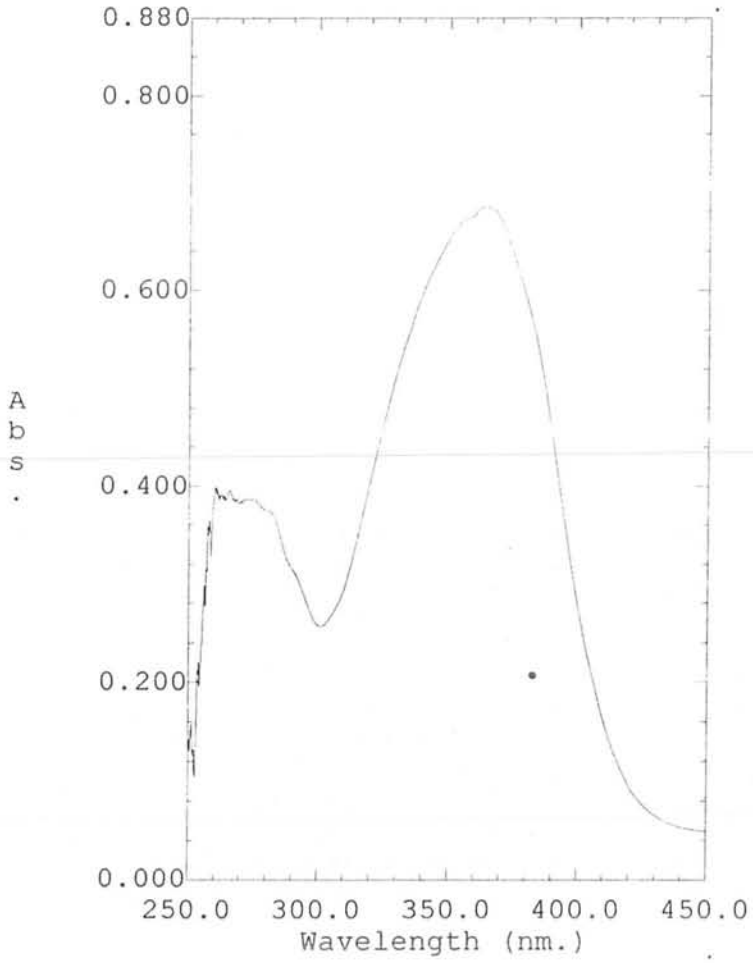
Spectrum 5. Mass Spectrum of B_1



(B_1)

Spectrum 6. ^{1}HNMR Spectrum of B_1

UV, ^{1}H NMR & EIMS of C_1



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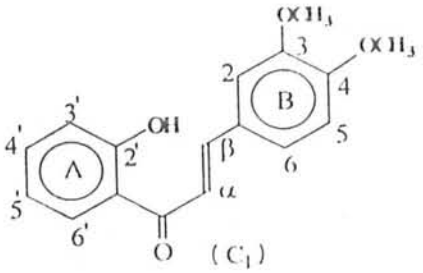

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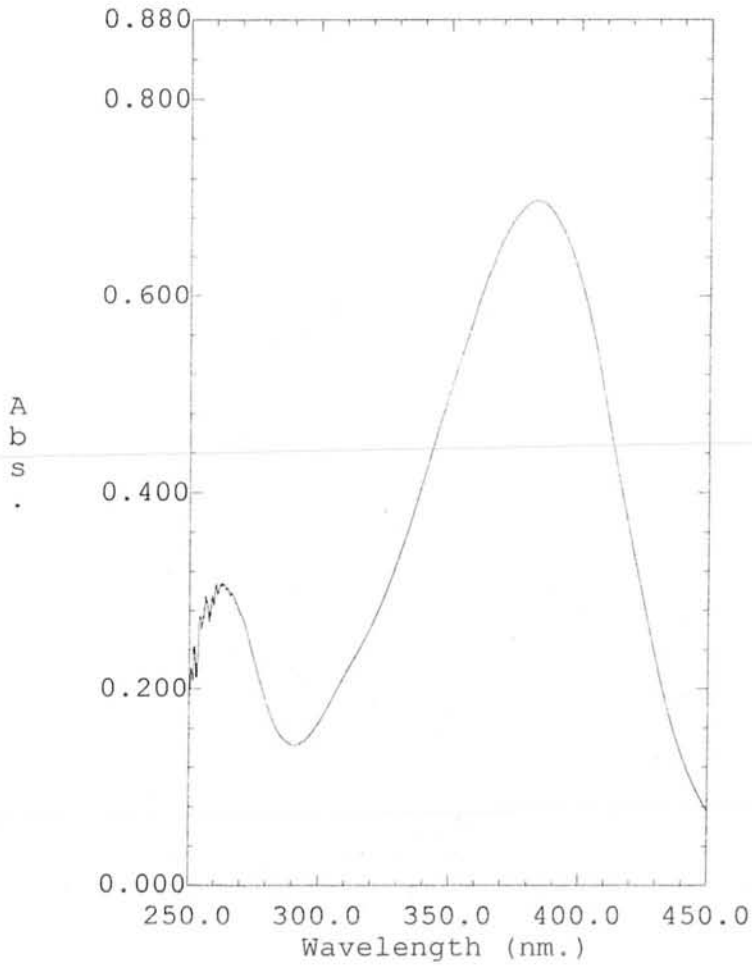
Spectrum 7. UV Spectrum of compound C_1 in MeOH



Point Pick

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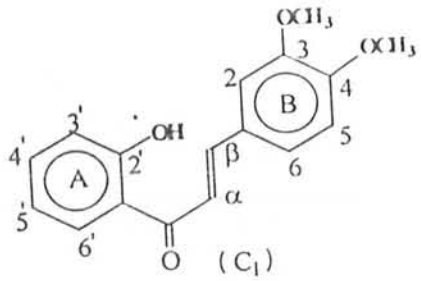

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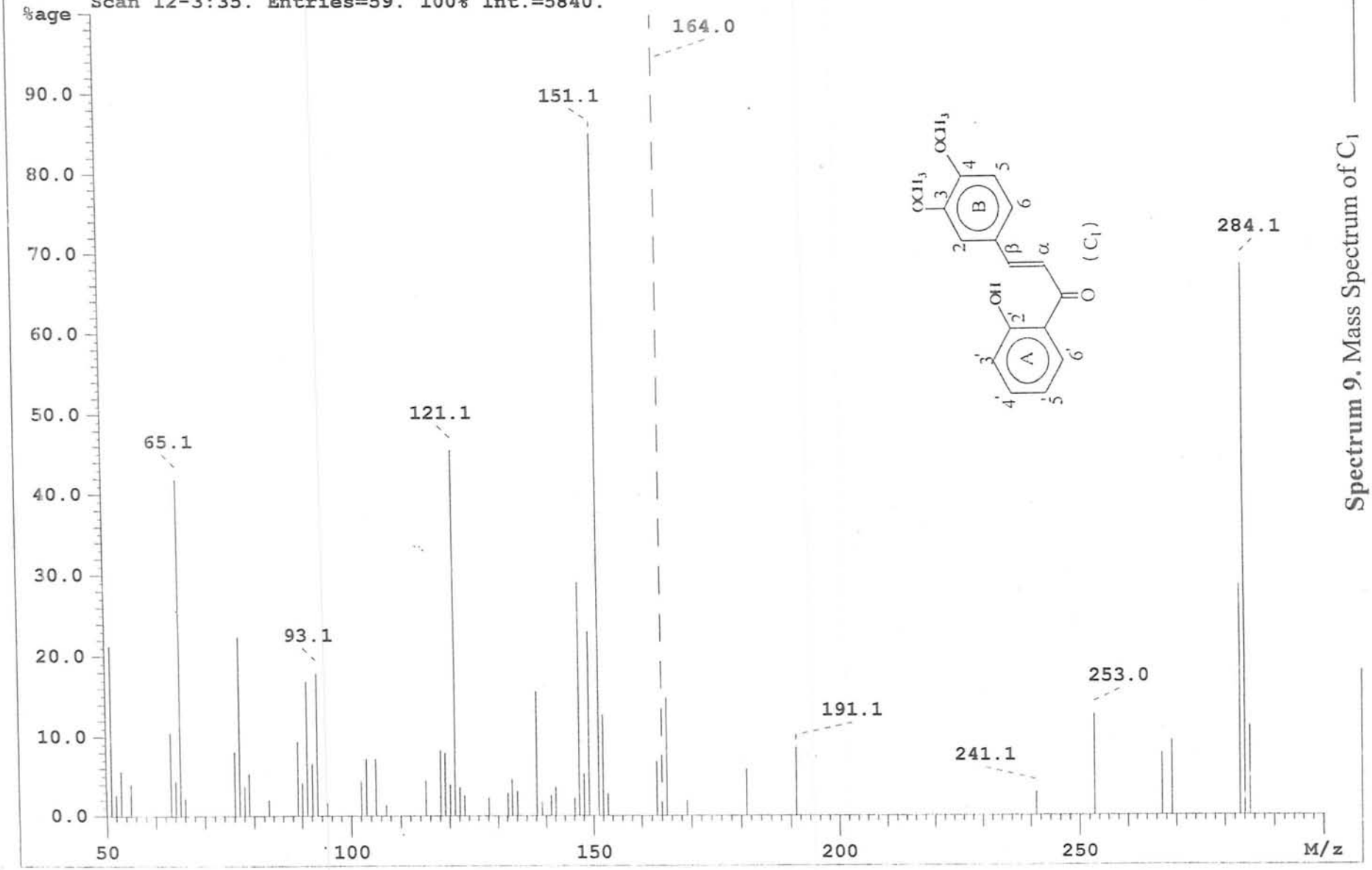
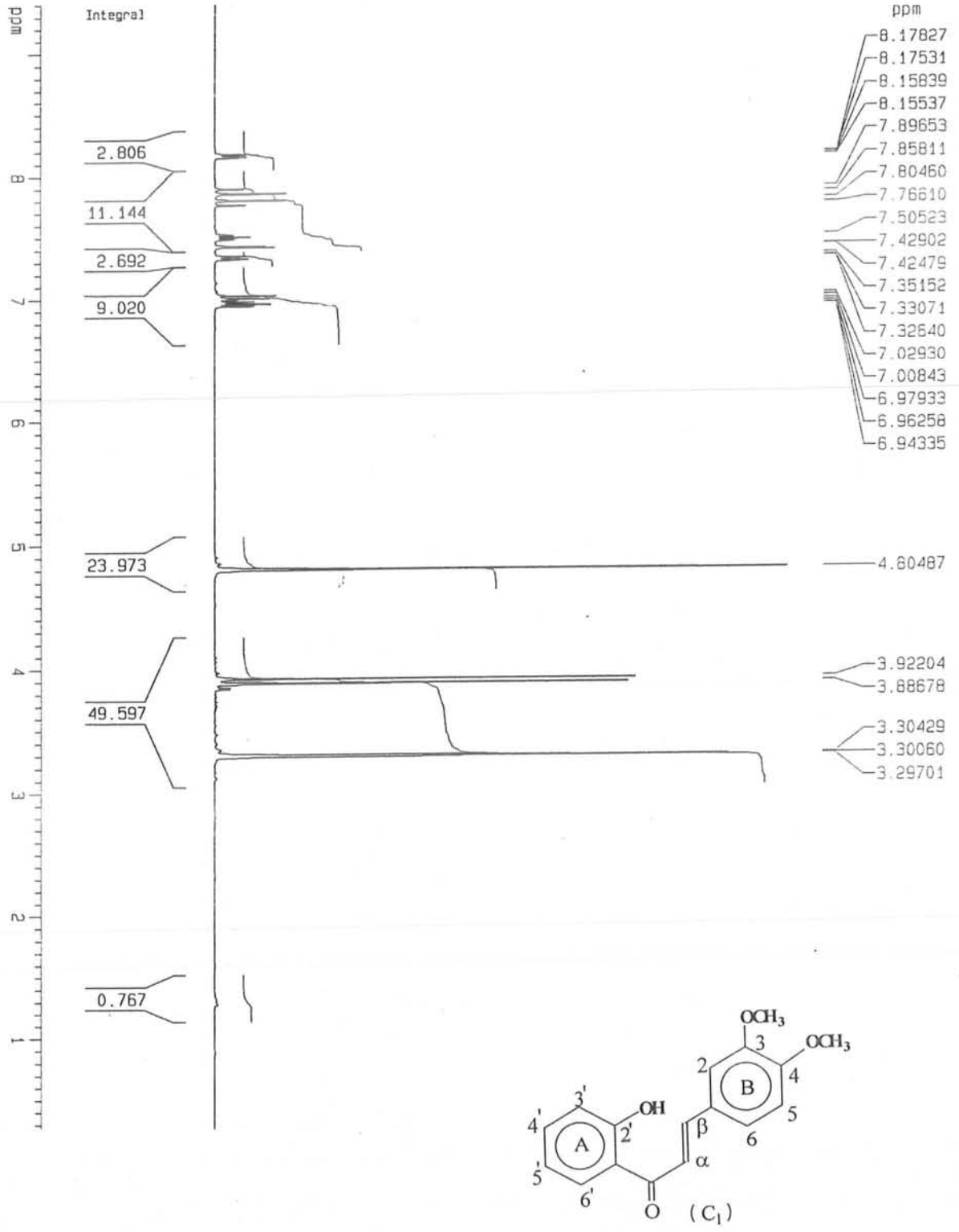
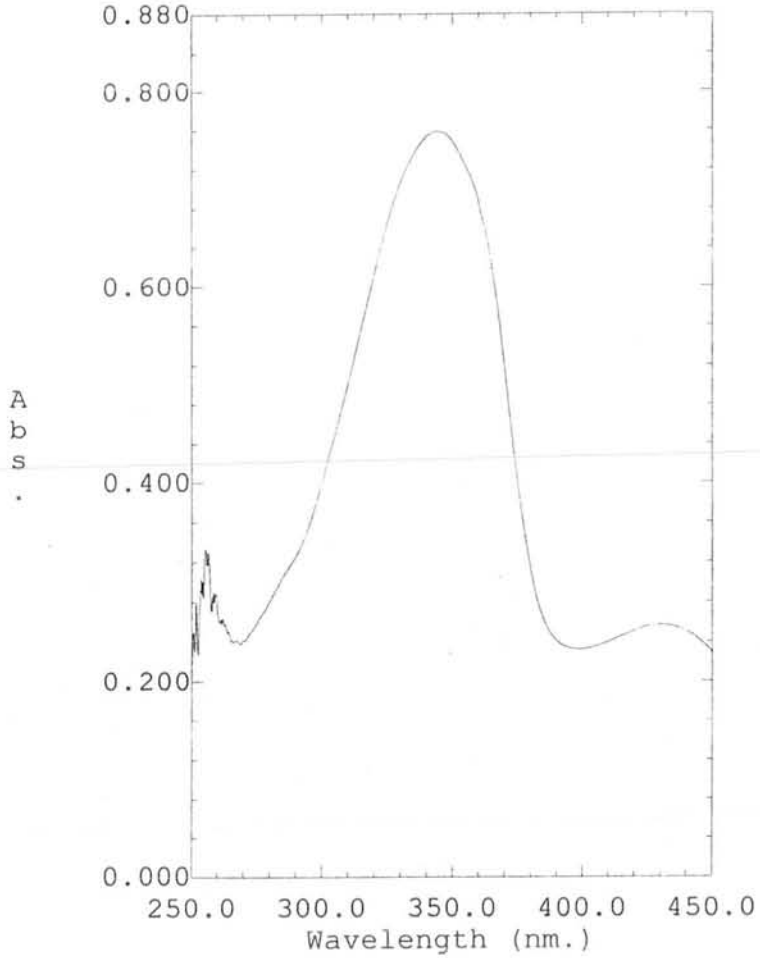


Spectrum 9. Mass Spectrum of C_1



Spectrum 10. ^{1}HNMR Spectrum of C_1

UV, ^{1}H NMR & EIMS of D_1



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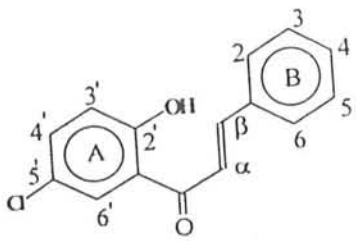

(D_1)

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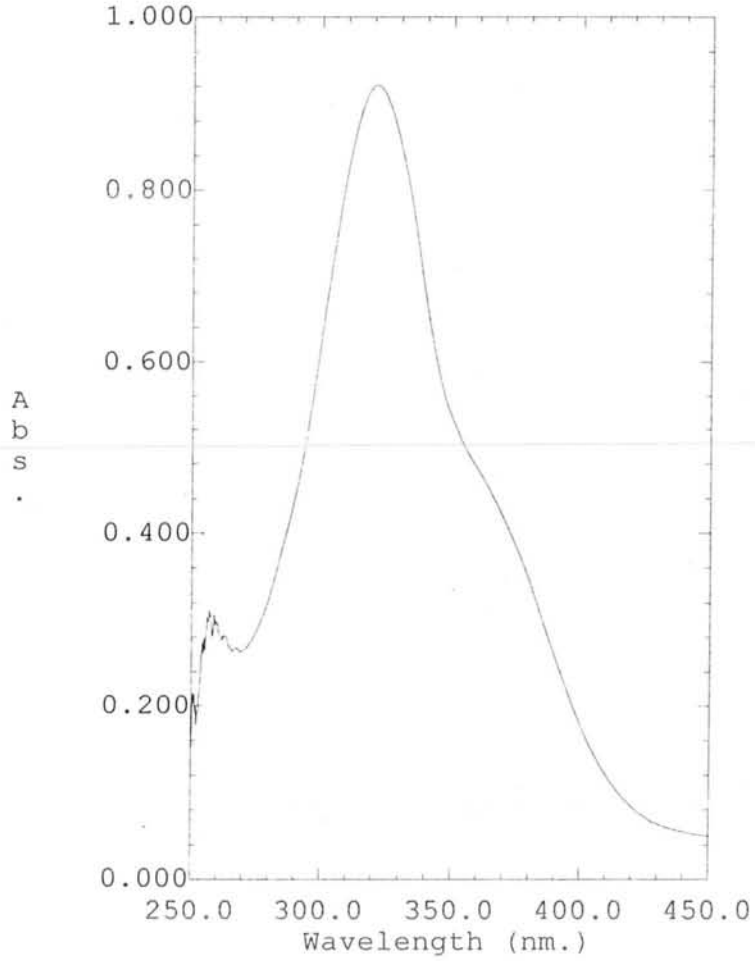
Spectrum 11. UV Spectrum of compound D_1 in MeOH



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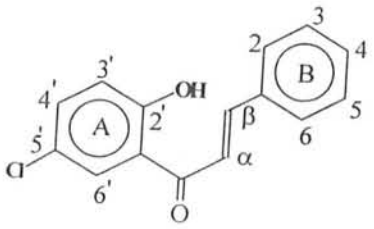

(D_1)

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Spectrum 12. UV Spectrum of compound D_1 in MeOH + $AlCl_3$

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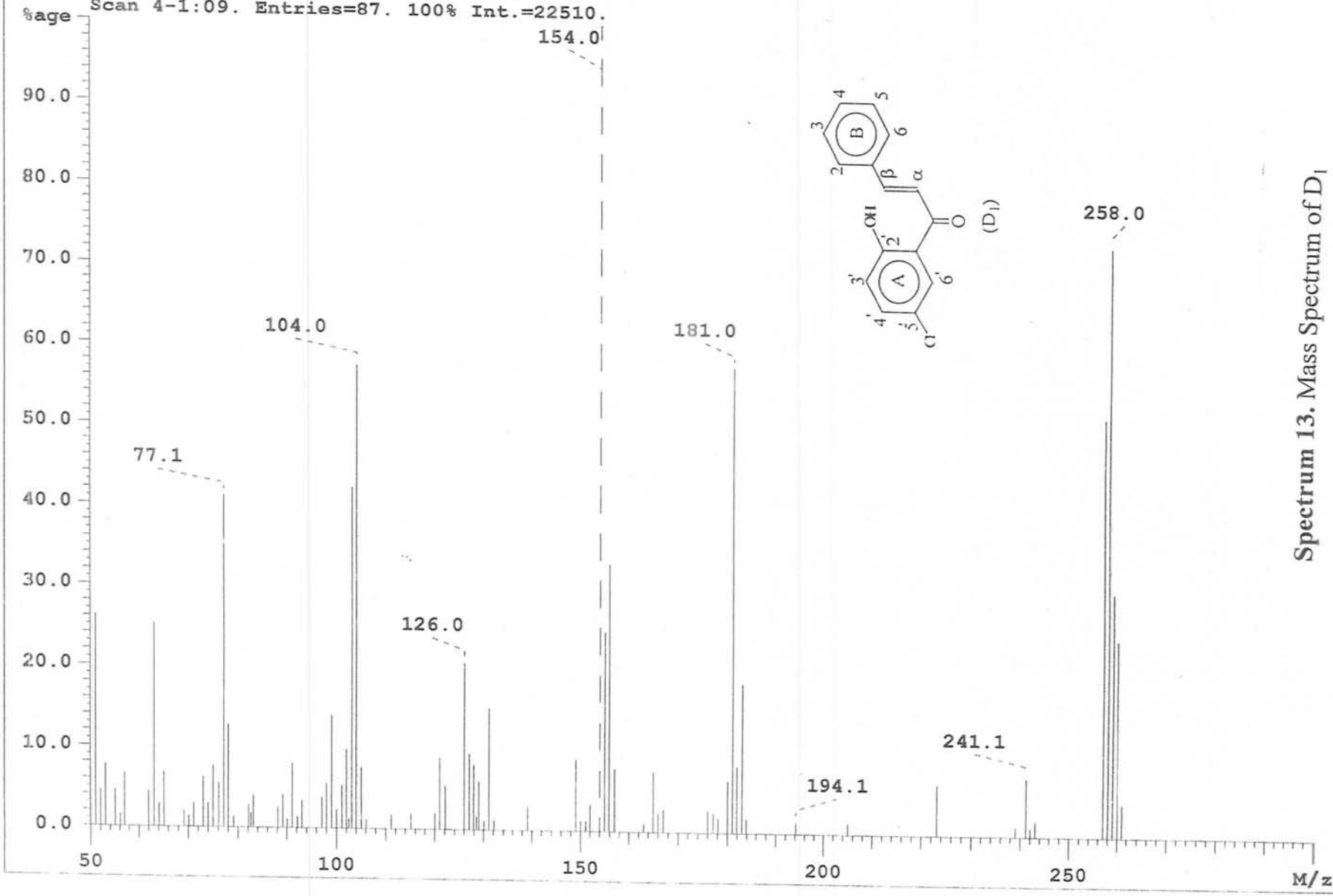
SCAN GRAPH. Flagging=M/z. Filter=[Int:1%.].
Scan 4-1:09. Entries=87. 100% Int.=22510.



(D$_1$)

Spectrum 13. Mass Spectrum of D$_1$