SYNTHESIS, CHARACTERIZATION AND EFFICIENT CYCLIZATION METHOD OF 2'-HYDROXYCHALCONE WITH L-PROLINE

A DISSERTATION

Submitted in partial fulfillment of the requirements for the award of the degree of

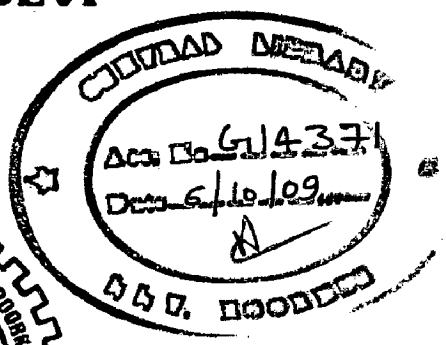
MASTER OF TECHNOLOGY

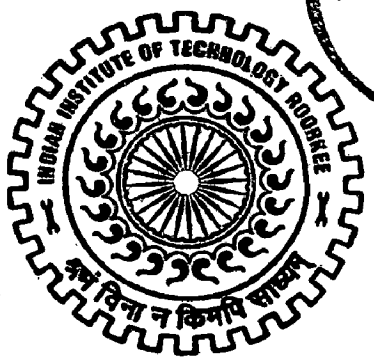
in

ADVANCED CHEMICAL ANALYSIS

By

KM. SEEMA DEVI





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JUNE, 2009

DECLARATION

I hereby declare that the work which is being presented in this thesis entitled **"Synthesis, Characterization and Efficient Cyclization method of 2'-Hydroxychalcone with L-proline"**, in partial fulfillment of the requirement for award of the degree of **Master of Technology in Advanced Chemical Analysis**, submitted in Chemistry Department, Indian Institute of Technology, Roorkee, is an authentic record of my own work, carried out during the period from July 2008 to June 2009 under the guidance and supervision of **Dr. Naseem Ahmed**, Assistant Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

I have not submitted the matter embodied in the dissertation for the award of any other degree or diploma.

Place : Roorkee

Date : 30-6-09

Seema

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This is to certify that the above statement made by the candidate is correct to the best of my knowledge

30.6.2009

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Supervisor

ABSTRACT

Chalcones are one of the important classes of natural products with widespread distribution in fruits, vegetables, spices, tea and soya based foodstuff. It is a generic term given to compounds during the course of flavonoids biosynthesis in plants. Chalcones considered as the precurses of flavone, flavanones, isoflavonoids, aurones, catechins, anthocyanidines, and are abundant in edible plants. Chemically chalcones are open chain flavonoids in which two aromatic ring are by a three carbon α,β unsaturated carbonyl system.

α,β unsaturated carbonyl moiety is a key constituent of many biologically important natural compound (flavanone). Among the derivatives of chalcones, 2'-hydroxychalcone are important building blocks for the synthesis of several natural products. Consequently, cyclization of 2'-hydroxychalcone has attracted tremendous attention for simplification or improvement of the exiting methods. Synthesis of flavanones from the cyclization of different 2'-hydroxychalcone derivatives with L-proline as a novel catalyst is described. This method proved to be an efficient with respect of several other methods reported under different reaction condition to affored the same products. All the products are characterized based on ^{1}HNMR, ^{13}CNMR, IR and GC MS spectral analysis.

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CHAPTER 1

INTRODUCTION

1.1 INTRODUCTION

There is no exaggeration in the statement that plants have sustained and are sustaining human life on this planet. The plant chemistry (also known natural products chemistry) is a wide and distinct field, which concerned with the enormous variety of organic substances accumulated by plants, for example, alkaloids, amino acids, flavonoids, terpenes, fatty acids, steroids, etc.[1] The flavonoids is one of the most fascinating areas of the plant chemistry. They are a complex group of natural products found in plants as the largest single group conferring oxygen ring compounds. There are numerous physiological and pharmaceutical activities have been attributed to flavonoids.[2]

Flavonoids (also known Bioflavonoids) are secondary metabolites in almost all vascular plants and are widely distributed in leaves, stems, roots, fruits, and seeds. More than 5000 chemically unique flavonoids have been identified in different plant species, which are responsible for the vibrant colors of leaves, flowers and fruits.[3] These polyphenolic organic compounds have no direct involvement with the growth or development of plants. However, they play an important role in protecting the plants from microbe and insect attacks.[4]

Among the natural compounds with high antioxidant activity, flavonoids, widely distributed class of phytochemicals have a central role (Figure 1.1a). Flavonoids alone provide minimal antioxidant benefit to the human body and biologically trigger the production of natural enzymes that reduce the risk of certain cancers, heart disease, and age-related degenerative diseases like Alzheimer's, Perkinson, etc.[5] Foods containing high amounts of flavonoids includes blueberries, red beans, cranberries, blackberries, red

& yellow fruits, vegetables, some nuts, red wine and certain teas have numerous health benefits.[5b] It is observed that high intake of red wine mainly

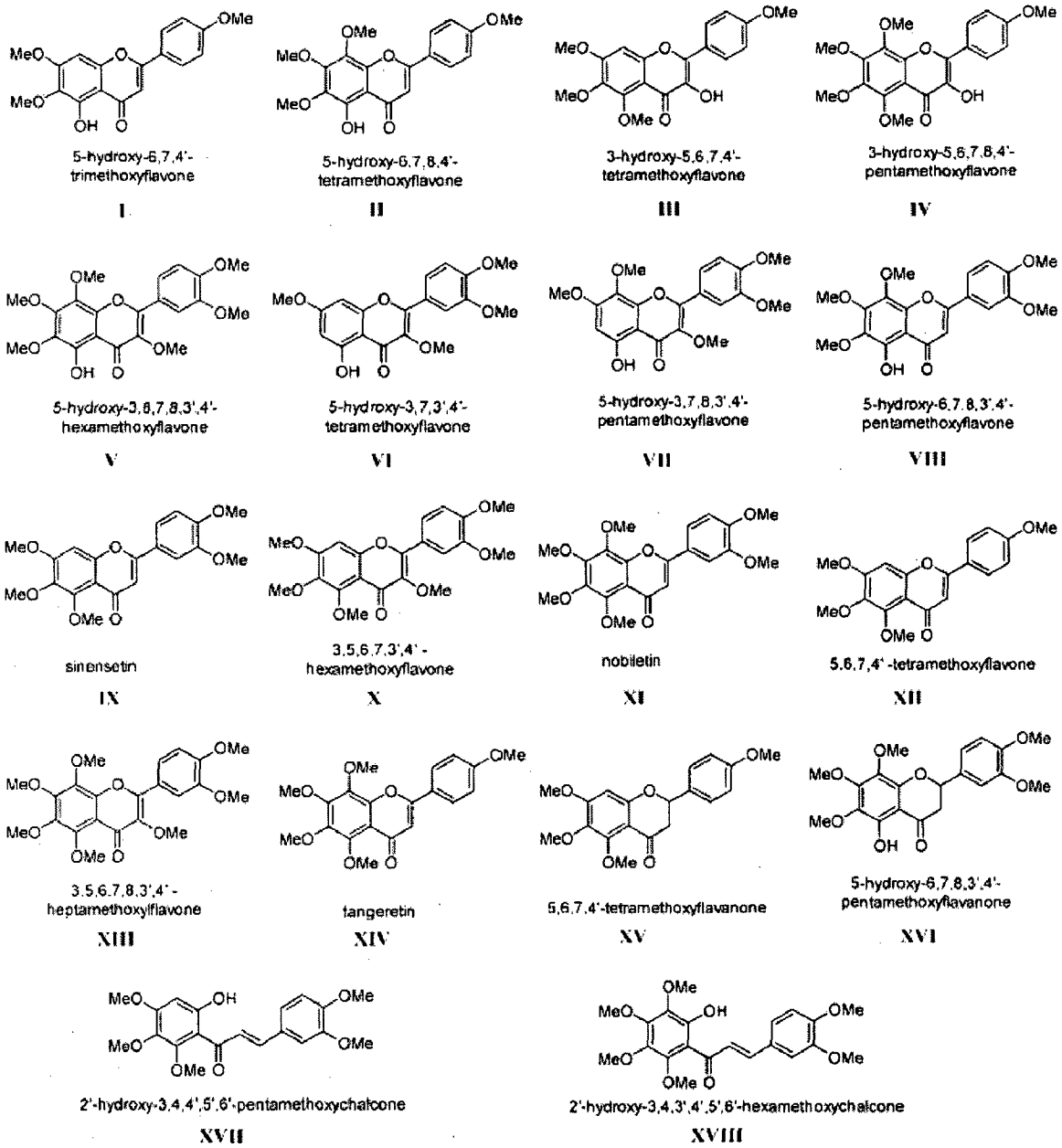


Figure 1.1a Polymethoxyflavones (PMFs) and polyhydroxyflavones (PHFs) molecules.

(quercetin and rutin flavonoids) by the French people might explain why they suffer less from coronary heart disease than other Europeans, although their consumption of cholesterol rich foods is higher called "French paradox".[6] Tea flavonoids have many health benefits in reducing the oxidation of low-density lipoprotein, lowers the blood levels of cholesterol and triglycerides.[7] Similarly, soy flavonoids (mainly isoflavones)

can reduce blood cholesterol and can help to prevent osteoporosis and ease menopausal symptoms.[8]

Some new flavonoid glucuronides, luteolin and chrysoeriol 7-*O*-β-D-glucopyranosiduronic acid-(1→2)-β-D-glucopyranoside (**1**,**2**), and chromone derivative, 2-(2-hydroxypentyl)-5-carboxy-7-methoxychromone (**5**), chrysoeriol 7-*O*-β-(6-*O*-malonyl) glucopyranoside (**3**) have been isolated from water plants. Additionally, secondary metabolites luteolin 7-*O*-β-(6-*O*-malonyl) lucopyranoside (**4**), and the chlorophyll derivative phaeophorbide *a* were also isolated and identified by NMR and MS data (Figure 1.1b). Compounds (**1**,**2**) screened against bacteria *Escherichia coli* BW25113, *Pseudomonas pudida* KT2440, and *Enterobacter cloacae* subsp. *dissolVens* and the cytotoxic activities of **1** toward human Patu 8902 carcinoma cells as well as human SH-SY5Y neuroblastoma cells were reported as biologically active.[9] Recently, the beneficial effects of natural polyphenolic antioxidants have been reviewed.[10]

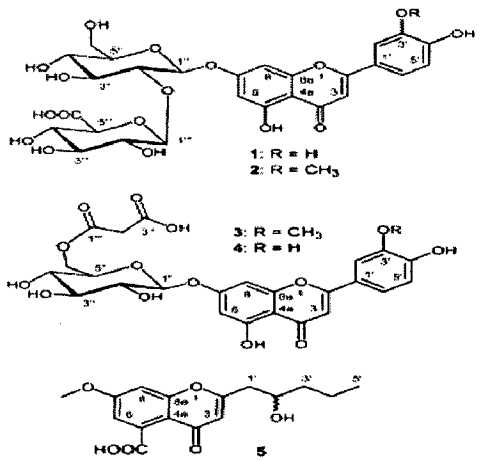


Figure 1.1b: Flavonoid glucuronides.

The key stage in biosynthesis of all flavonoids is reached via the formation of chalcones, which is distributed in different plant tissues. Along with aurones, the chalcones are best known yellow to orange colored flower pigment. Structurally, chalcone is deriving from three acetates and cinnamic acid as shown in [Fig.1.1c], are one of the most diverse groups of flavonoids present in dimers, oligomers, Diels-Alder

adducts and conjugates of various kinds. Chemically, chalcone is a generic term given to compound bearing 1,3-diphenylprop-2-en-1-one framework[11] 2'-hydroxychalcone derivatives are very important precursor for the isomerization to give different products, flavone, flavanone, flavanol, etc.

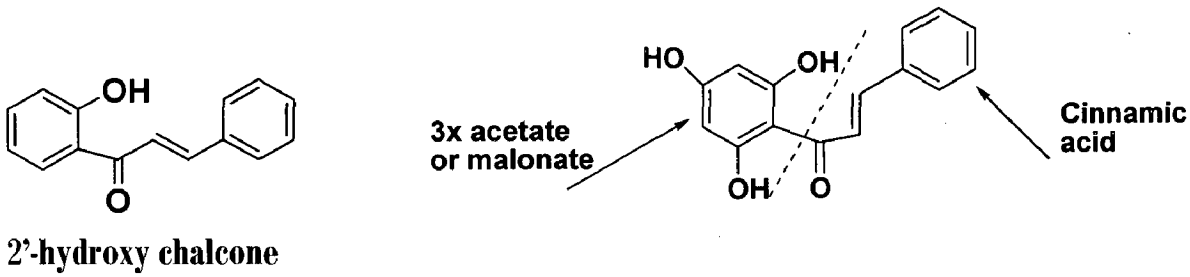


Figure 1.1c Structure of 2'-hydroxy chalcone

Chalcones have shown potent pharmacological profile and are associated with the plethora of biological activities,[12] more importantly, the structure features of chalcone, the presence of reactive enone moiety and its relatives flexibility compared to other related natural products to interactions with diverse receptors and enzymes. The C_6-C_3-C_6 moiety is recognized as a "privileged structure" in drug design.[13] The chalcones are synthesized further enrich the structural diversity of the template through the introduction features normally associated with lingand receptor interaction, namely hydrophobic groups hydrogen bond donor and receptor features.[14]

1.2 STRUCTURE AND CLASSIFICATION OF FLAVONOIDS

Chalcones are isolable intermediate during flavonoid biosynthesis in plants but do not necessarily accumulate to any appreciable extent unless the enzyme chalcone isomerase, which catalyses the cyclization of chalcone to flavanone.[15] The flavonoids are polyphenolic compounds possessing 15-carbon atoms; two benzene rings joined by a linear three carbon chain.[16]

Flavonoids occur as aglycones (i.e., flavonoids without attached sugar), glycosides and methylated derivatives. In plants, flavonoids aglycones occur in a variety of structural

forms, containing 15-carbon atoms in their basic nucleus. Two aromatic rings linked with a three carbon unit, which may or may not a part of third ring.[17,18] For convenience, the rings are labeled A, B and C [fig. 1.2] and the individual carbon atoms are based on a numbering system which uses ordinary numerals for the A and C and "primed" numerals for B-ring (**1**). Primed modified numbering system is not used for chalcones (**2**) and the isoflaviones derivatives (**6**) in pterocarpans and rotenoids.[19] The most important natural pigments are carotenoids which are tetrapyrrol derivatives of naturally occurring phenol compounds. The different way to close this ring associated with the different oxidation degrees of ring A provide the various classes of flavonoids.[20] The six- membered ring condensed with the benzene ring is either a γ-pyrone flavanones (**4**) and flavan-3 *ols* (**5**)*)*.The position of the benzenoid substituent divides the flavonoides into two classes: flavonoids (**1**) (2-position) and isoflavonoids (**6**) (3-position).[21,22]

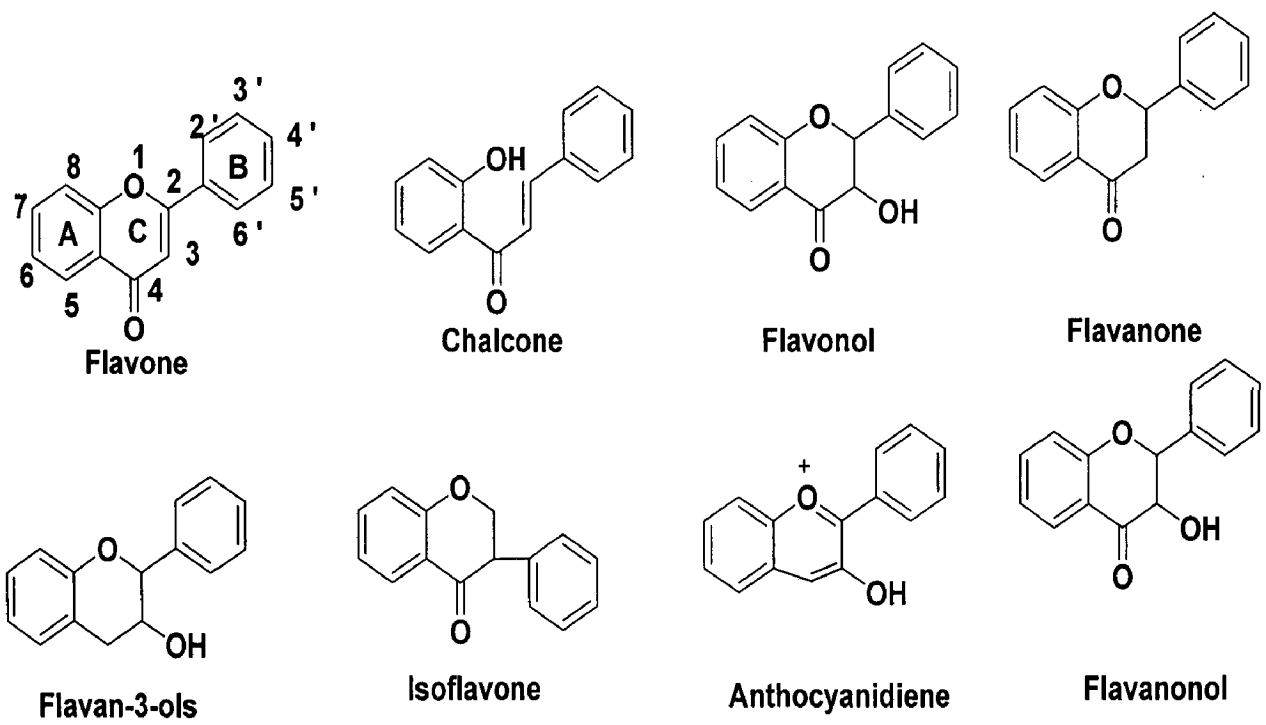
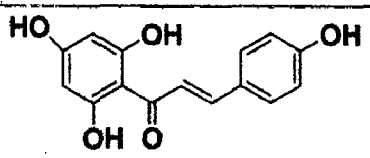
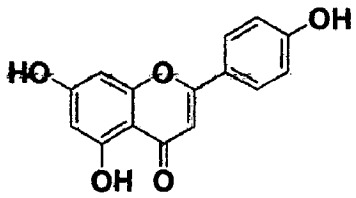
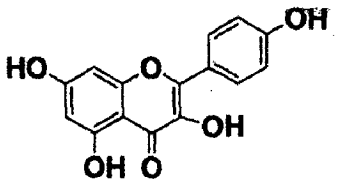
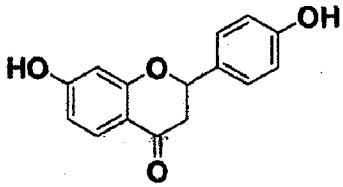
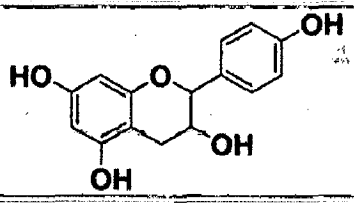
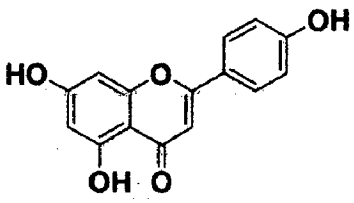


Fig. 1.2 Chemical structure of some representative flavanoids

1.3 FLAVANOIDS AND SIX MAJOR SUB-GROUP

The relationship between flavonoids intake and heart health, to determine recommended daily intake and to determine future research properties (Table 1). Flavonoids are phytochemical belonging to the group of phenolics. Other phenolics are tannins. couarins and phenolic acid.[23] More than 5000 flavonoids have been identified. Flavonoids are further divided into five groups: flavonols, flavones, flavanones, flavan-3-ols and anthocyanins. Most flavonoids occur in plants as glycosides, meaning that they are bound to sugar molecules. Some well known flavonols are quercetin and kaempferol. Flavanones are mainly found in citrus fruits. The bioavailability and metabolism of flavonoids are important factor in determining their efficacy. It is very difficult to estimate the total consumption of flavonoids because their content in foods shows large variations.[24] The USDA has on its website comprehensive tables of flavonoids (flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins), proanthocyanidins and isoflavones of many food. Flavonoids are well for their health benefits but they may also have adverse effects, such as antinutritional effects, thyroid toxicity, carcinogenic, development effects and drug interaction.[25] Very high intakes of flavonoids have been associated with antinutritional effects,[26] such as reduced intake of glucose or minerals. However, the slower absorption of glucose may protect against diabetes mellitus. Some flavonoids have an effect on the thyroid function: they inhibit thyroid peroxidase and interfere with the production of the thyroid hormone. .Flavonoids are the anti-oxidant phytochemicals.[27] Many studies have already demonstrated that high consumption of fruits and vegetables reduced cancer risk. The mean intake of flavonoids was 17 mg and the mean intake of isoflavones 47 mg. The following phytochemicals were determined in the food: genistein, daidzein, myrcetin, fisetin, quercetin, kaempferol and luteolin. Quercetin was the most important flavonoids, followed by kaempferol.[28,29]

Table 1 Subgroups of flavonoids

S.No.	Flavnoid subgroups	Structure
1	Chalcones	
2	Flavone (generally in herbaceous families, e.g. Labiatae, Umbelliferae, Compositae) Apigenin, Luteolin	
3	Flavonol (generally in wood angiosperms), Quercitol, Kaempferol, Myricetin	
4	Flavanone	
5	Anthocynin	
6	Isoflavanone	

1.4.1 Antioxidant

The flavones and catechins seem to be the most powerful flavonoids for protecting the body against reactive oxygen species (ROS).[30] Body cell and tissues are continuously threatened by the damage caused by free radicals and ROS which are produced during normal oxygen metabolism or are induced by exogeneous damage [32,33]

Quercetin, kaempferol, morin, myricetin and rutin, by acting as antioxidant, exhibited beneficial effect such as anti-inflammatory, antiallergic, antiviral, anticancer activity as well as play a protective role in liver diseases, cataracts, and cardiovascular diseases.Quercetin and silybin,acting as free radical scavengers, to exert a protective effect in liver reperfusion ischemic tissue damage. [34,35] The scavengering activity of flavonoids reported to be in the order: Myrcetin >quercetin > rhamnetin > morin > diosmetin > naringenin > apigenin > catechin >5,7-dihydroxy-3',4',5',- trimethoxy-flavone > robinin > kaempferol > flavones.[36]

1.4. Antimicrobial, Antibacterial and antifungal activity

Flavonoids and esters of phenolic acids have also been investigated for theirs antimicrobial, antifungal and antiviral activities.[37] Quercetin has been reported to completely inhibit the growth of *staphylococcus* aureus. Most of the flavonones having no sugar moiety showed antimicrobial activities.[38]

A number of flavonoids isolated for fungistatic activity. Chlorflavonin was the first chlorine- containing flavonoid which used antifungal antibiotic.Now synthetic modifications of natural compounds to improve antiviral activity. Quercetin, morin, rutin, taxifolin, apigenin, catechin, and have been reported to possess antiviral activity againt some of the 11 types of viruses. [39] Recently, world wide spread of HIV since the 1980s, the antiviral activity of flavonoids has mainly focused.[40] A natural plant flavonoid polymer of molecular weight 2,100 daltons was found to have antiviral activity against two strain of ***type 1, type 2*** *Herpes simplex viruses.*[41,41]

1.4.3 Antiulcer and anti-inflammatory activity

Hesperidin, a citrus flavonoid, possesses sinnificant anti-inflammatory and analgesic effects.[43] Recentaly apigenin, luteolin and quercetin have been reported to exhibit anti-inflammatory activity. Some recent studies have indicated that flavonoid

glycosides of *Ocimum basilicum* decreased ulcer index. Flavone/flavonol glycosides as well as flavonoid/flavonols kaempferol, quercetin, myricetin, fisetin were reported to possess LO and COX inhibatiory activities.[44, 45] (fig1.4.3)

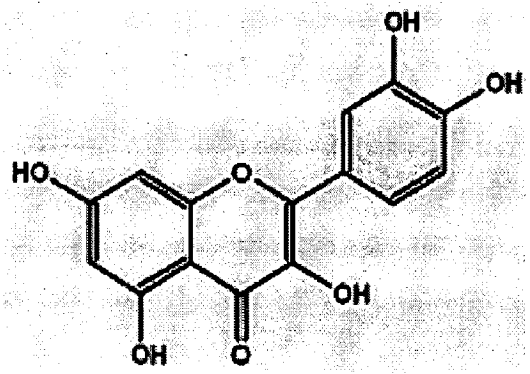


Fig. 1.4.3 Structure of Quercetin flavanoil

1.4.4 Antidiabetic and antineoplastic activity

Flavonoid, especially quercetin, has been reported to possess antidiabetic activity. Vessal et al reported that quercetin regenerated islets and proprably increase insulin release and enhanced Ca^{+2} uptake from isolation islets cell which suggest a place for flavonoids in non insulin-dependent diabetes.[46,47] A sufficient number of flavonoids have exhibited antineoplastic activity. The flavonoids, kaempferol, catechin, toxifolin and fisetin, also used cell growth. Genistein, an isoflavone founded to have strong effect [48, 49]

1.4.5 Antithrombogenic and cadioprotective effects

Platelet aggregation plays a pivotal role in the physiology of thrombotic diseases. Activated platelets adhering to vascular endothelium generate peroxides and oxygen free radicals which inhibit the endothelial formation of prostacyclin and nitrous

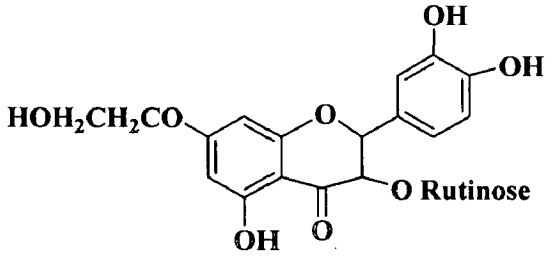


Figure 1.4.5 Structure of doxorubicin (7-monohydroxyethylrutoside)

Summary

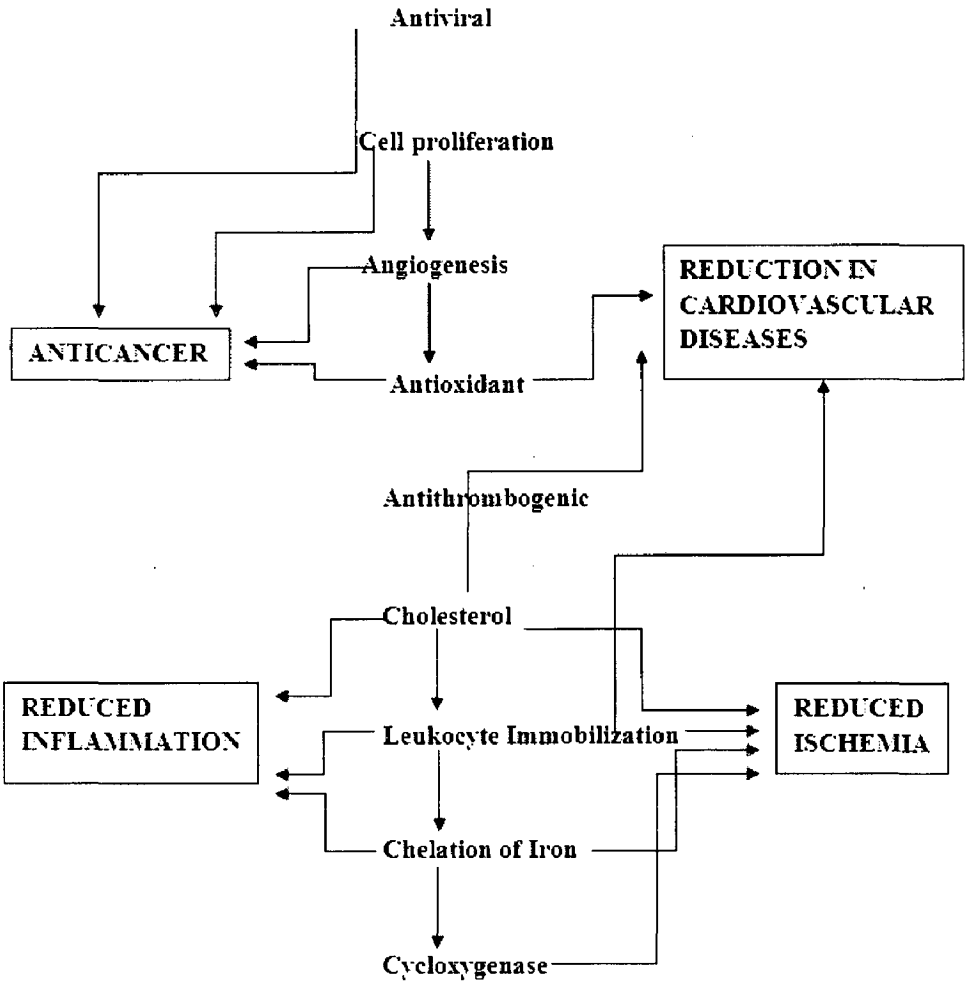
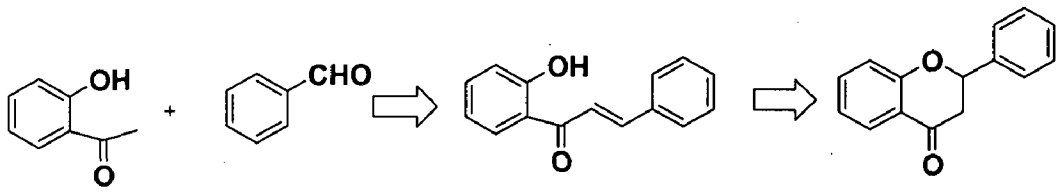


Fig. 1.4 .6 Links indicating effects of flavonoids on different diseases

oxide.Flavonoids are powerful antithrombotic agent in vitro and in vivo because of their inhibition of the activity of cyclooxygenase and lipoxigenase pathways.[50] Flavonoids are polyphenolic compound have higher propensity to transfer electrons,to chelate ferrous ions, due to this properties, flavonoids have been considered as potential protectors against chronic cardiotoxicity caused by the cytostatic drug doxorubicin.[56]

1.5 LITERATURE SURVEY

The simple and direct method for synthesis of 2'-hydroxyacetophenone with different substituted benzaldehyde involve the condensation in the presence of acid and base (Scheme 1).

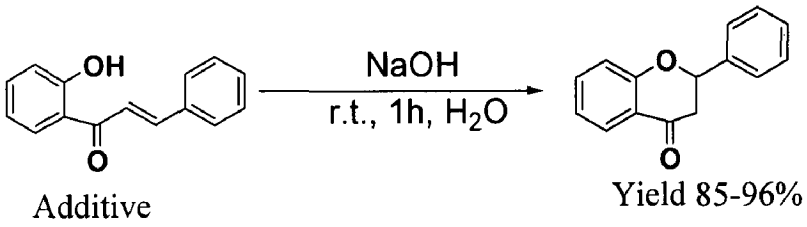


Cyclization of 2'-hydroxychalcone under condition of Clasien- Schmidt condensation

Scheme 1

The synthesis of the flavonoids has been carried out through a variety of procedures, but the most common one is performed via the Claisen–Schmidt condensation and subsequent intramolecular Michael addition between substituted benzaldehydes and substituted 2'-hydroxyacetopheones in basic or acidic media under homogeneous conditions.[57] It is widely accepted that there is a need to develop clean and economical processes, where the use of noxious substances and the generation of wastes can be avoided. Thus, the synthesis of flavanones has been carried out by intramolecular cyclization of 2'-hydroxychalcone under various conditions using acids[58] base[59] thermolysis, electrolysis, and photolysis.[60] However the yields of these reactions are often moderate (20-90%). A very efficient cyclization reaction of 2'-hydroxychalcone to 2,3-dihydroflavanols by using NaOH-H_2O_2 in a water suspension medium and the products isolated simply by filtration and waste minimization, simple operation, and easier product work-up can be achieved. The intermolecular cyclization in MeOH using NaOH as a base give flavanone only 20% yield at room temperature for 2-3 days. When the reaction carried out in water suspension medium using surfactant flavanone give a quantitative yield. A mixture of powdered 2'-hydroxychalcone (1.0 g, 4.5mmol), NaOH (8 M, 0.1 ml)

and sodium 1-dodecane sulfonic acid (0.01 g) in water (10 ml). Similarly, tetrabutylammoniumiodide, tetrabutylphosphonium bromide, hexadecyltrimethylammonium bromide, glycine, L-proline, L-alanine and L-leucine, pyridine were also used for effective conversion yield (Scheme 2).

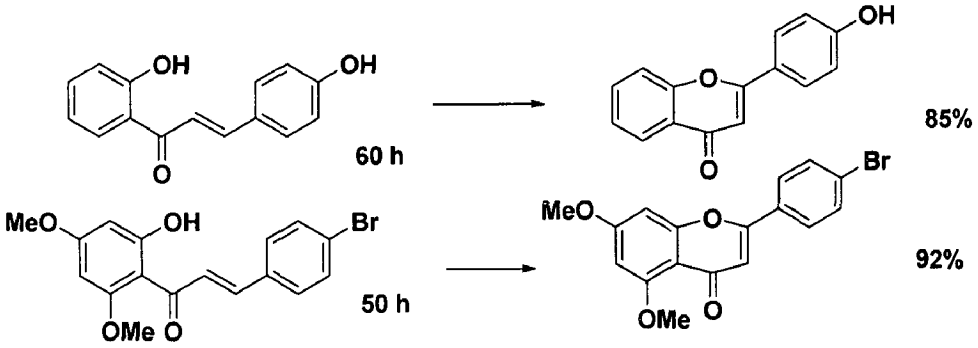


None
$Bu^n_4N^+I^-$
$Bu^n_4P^+Br^-$
Glycine
$C_{16}H_{33}N^+Me_3Br^-$(CTAB)
$C_{12}H_{25}SO_3^-Na^+$ (SDS)
L-Alanine
L-Proline
L-Leucine

Scheme 2:

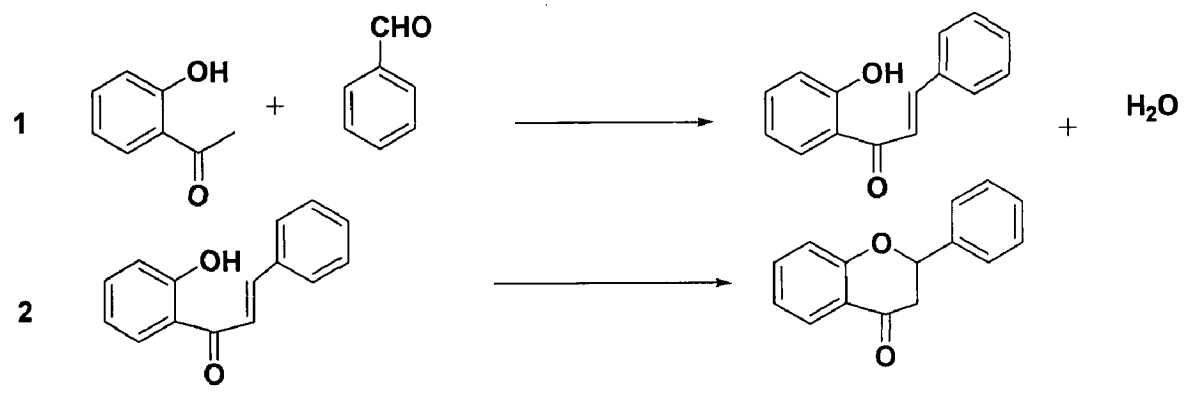
Silica gel supported $InBr_3$ or $InCl_3$ (15-20 mol %) were explored as a new solid-support catalysts for the facile and efficient oxidation, under solvent free conditions, of 2'-hydroxychalcone and flavanone to yield the corresponding flavones in >80% yield.[61] The 2'-hydroxychalcone or flavanones (1.0 mmol, dissolved in minimum amount of ethyl acetate) are added to silica gel supported $InBr_3$ (2.0g, 15-20 mol%) and solvent is removed (Scheme 3). The dry mixture is heated with stirring at 130-140 ^{0}C in an inert container for different periods of time.[62]

Scheme 3:



Liquid phase Claisen- Schmidt condensation between 2'-hydroxyacetophenone and benzaldehyde to from 2'-hydroxychalcone followed by intermolecular cyclization to from flavanone was carred out Zinc oxide supported metal oxide catalysts under solvent free condition.[70] The reaction was carried out over ZnO supported MgO, BaO , K_2O and Na_2O catalysts with 0.2 g of each catalyst at 140 ^{0}C for 3 h. Magnesium oxide impregnated zinc oxide impregnated with various other supports as HZSM -5, Al_2O_3 and

SiO_2 were also used for the reaction to assess the suitability of the support. The order of reactivity of the support is ZnO > SiO_2 > Al_2O_3 > HZSM.[71] Various weight percentage of MgO was loaded on ZnO to optimize maximum efficiency of the catalyst system. The impregnation of MgO (wt%) in ZnO was optimized for better conversion of 2'-hydroxyacetophenone (Scheme 4).

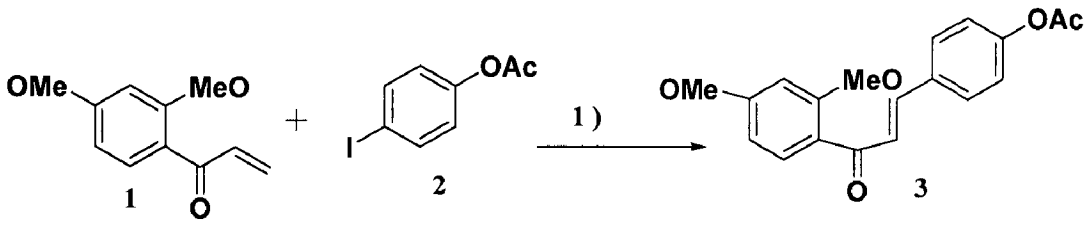


Scheme 4:

The yield of flavanone is less at 100 ^{0}C which may be attributed to less adsorption on the active sites, giving high yield of flavanone.But further increase of temperature the yield of flavanone is reduced, as adsorption is prevented at temperature above 160^{0}C.[72] Thus the optimum temperature for high yield of flavanone is 140^{0}C.[73]

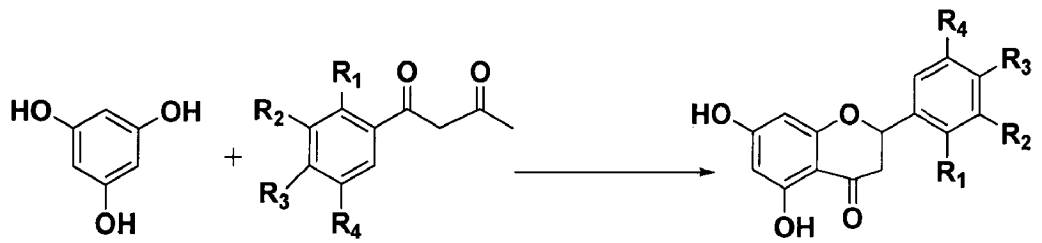
Flavanones have been prepared via several method including condensation of phenylpropiolic acid with phenols[74, 75] and heating 2-iodophenols with acrylacetyllenes in the presence of $PdCl_2$[bis(diphenylphosphino)ferrocene] $(dppf)_2$ give flavones.[76] The

palladium-catalysed carbonylative coupling of 2'–hydroxyaryliodides and ethynylarenes has been carried out using $Pd(OAC)_2$ $(dppf)_2$ as a catalyst affording mixture of flavones and aurones in varying yields, depending on the substituent on both reactants.[77] On same reaction condition by using the Heck coupling reaction for the synthesis of the intermediate chalcone in between an α,β–unsaturated ketone and aryl iodine. This procedure is very simple and suggest the possibility of preparing the flavanoid skeleton with a wide Varity of substitution pattern without side products.[78] The reported reaction proceeds in a very short time(about 4h) affording the flavanoid moiety in very satisfactory yield (94%) (Scheme 5).



Scheme 5: Reagent and condition: (1) Pd $(OAC)_2$, Ph_3P, CH_3CN, Et_3N.

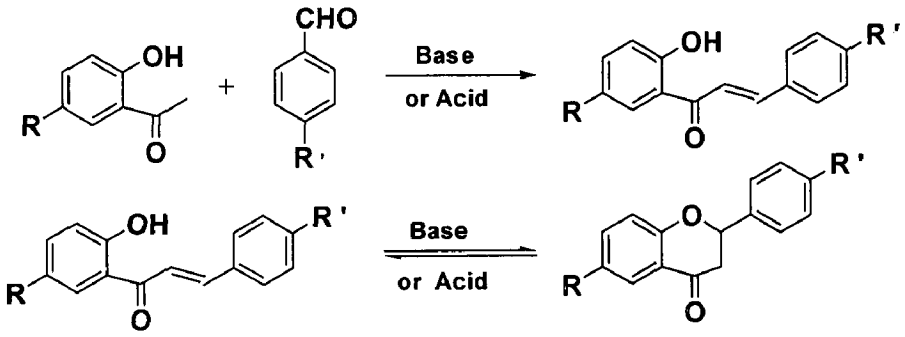
Eco-friendly direct solvent free synthesis of flavanones is achieved by microwave irradiation of phloroglucinol and β-ketoesters. Heating with microwave versus under classical conditions was shown to be higher yielding, cleaner, and faster (Scheme 6). The reaction goes through a cycloaddition of a α-oxo ketene intermediate followed by an uncatalyzed thermal Fries rearrangement .[79]



R_1 ,R_2 ,R_3 ,R_4 ,= H , OH ,OMe , Cl ,NO_2

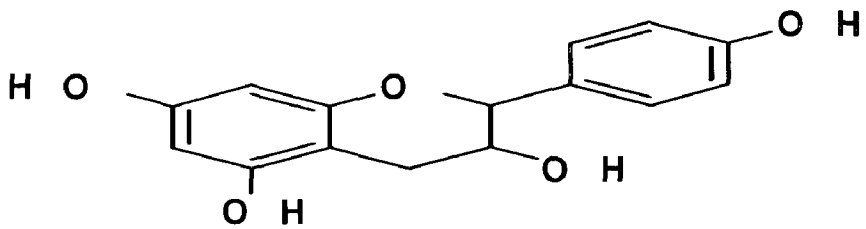
Scheme 6:

The synthesis of the flavanoids has been carried out through a variety of procedures, but the most common one is performed via the Clasien-Schmidt condensation and subsequent intermolecular Michal addition between substituted benzaldehydes and substituted 2'-hydroxyacetophenone in basic or acidic media under homogenous conditions.[80] It is widely accepted to develop clean and economical processes, where the use of noxious substances and the generation of waste can be avoided. A survey of literature shown that aminopropyl-functionalized SBA-15 of ordered hexagonally arranged mesoporous structure was an efficient base catalyst for the synthesis of flavanones between 4-substituted benzaldehyde and 2'-hydroxyacetophenones and the subsequent isomerization of the 2'-hydroxychalcone intermediate in the absence of solvents markedly decreased both the catalytic activity and the selectivity to flavanone.[81]The ordered pore size and large pore volume of the amino–functionalized SBA-15 facilitate the diffusion of the reactant and product molecules in the pore channels.[82] The catalytic activity decrease with higher amino loading on SBA-15 probably due to the decrease in surface area and pore volume. The substituents in the aromatic ring of the benzaldehyde have great effect on the catalytic performance in the Clasien-Schmidt condensation under solvent-free condition. The presence of the electron withdrawing groups at the para-position of benzaldehyde decreased the conversion but increased the flavanone selectivity, while electron-donating groups on benzaldehyde favored the conversion but decreased the selectivity to flavanones.[83] (Scheme 7).



Scheme 7:

The traditional method for the synthesis of flavanones consists of an intramolecular conjugated addition of o-hydroxychalcones, to the corresponding cyclic carbonylic system. This reaction can be performed using acids, silicagel, bases, light, heat, or electrons.[84] The acid catalyzed cyclization can be carried out by refluxing the chalcone in acetic acid, or also in ethanol or other suitable solvent, in the presence of an acid catalyst such as H_2SO_4 or H_3PO_4.[85] Basic conditions are seldom used due to decomposition or retro aldol reaction.[86] Since the first reports on chemical application of microwave- induced or conventional thermal cyclization,[87] this methodology has now become a useful technique for organic synthesis and functional group interconversions.[88](Scheme 8)

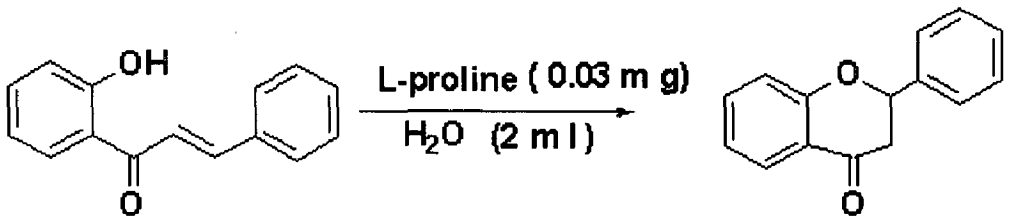


Scheme 8:

This has very shorter reaction times, ease of manipulation, higher yields, and lower costs. It was concluded that the best method is irradiation of chalcone with 30% TFA over silica gel for 3 periods of 3 min. Due to increase the acceleration rate of reaction in order of 500-fold.

1.6 AIM AND SCOPE OF THE PRESENT WORK

chalcone is a very special α, β unsaturated carbonyl system. Many natural product and biological active compounds are found to contain 2'-substituted chalcones as their basic structure making these molecules pharmaceutically useful and important. All, cyclization reaction of 2'-hydroxychalcone to different substituted aromatic aldehyde constitutes a key reaction in the total synthesis of complex natural products. Typically, such reactions are performed under the influence of strong base such as alkali metal alkoxides or hydroxides. The strong basic conditions often lead to a number of undesirable side reactions such as aldol cyclization, base induced rearrangements such as retro-Michael reactions and polymerization reactions. Subsequently, Lewis base have been found to catalyze Clasien-Schmidt reaction in different temperature conditions. Previously also many Lewis base have been used for the cyclization reactions oh 2'-hydroxychalcone. The aim of this work is to synthesis flavanone using L-proline as a mild and cheap catalyst. The cyclization of 2'-hydroychalcone has been studied which is presented by Scheme 9. To the best our knowledge, cyclization of 2'-hydroxychalcone in the presence of L-proline in subsequently has not been reported in literature.



REFERENCES

1. Beecher, G. R. In Antioxidant Food Supplements in Human Health; Packer, L.; Hiramatsu, M.; Yoshikawa, T., Ed.; Academic Press: New York, 1999; (b) Harborne, J. B.; Williams, C. A. Phytochem. 2000, 55, 481.

2. Harborne, J. B.; "The Flavonoids- Advances in Research since 1986," Chapman & Hall, London, 1994.

3. (a) McCord, J. M. Am. J. Med. 2000, 108, 652; (b) Enes, R. F; Farinha, A. S. F; Cavaleiro, J. A. S.; Amorati , R.; Petrucci , S.; Pedulli, G. F. Tetrahedron 2009, 65, 253; (c) Hileman, E. O.; Liu, J.; Albitar, M.; Keating, M. J.; Huang, P. Cancer Chemother. Pharmacol. 2004, 53, 209; (d) Gomes, A.; Fernandes, E.; Silva, A. M. S.; Santos, C. M. M.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Lima, J. L. F. C. Bioorg. Med. Chem. 2007, 15, 6027.

4. (a) Calabrese, V.; Scapagnini, G.; Colombrita, C.; Ravagna, A.; Pennisi, G.; Stella, A. M. G.; Galli, F.; Butterfield, D. A. Amino Acids 2003, 25, 437; (b) Schramm, D. D.; Karim, M.; Schrader, H. R.; Holt, R. R.; Cardetti, M.; Keen, C. L. J. Agric. Food Chem. 2003, 51, 1732; (c) Conforti, F.; Sosa, S.; Marrelli, M.; Menichini, F.; Statti, G. A.; Uzunov, D.; Tubaro, A.; Menichini, F.; Loggia, R. D. J. Ethnopharmacol. 2008, 116, 144.

5. (a) Erdman Jr., J. W. D.; Arab, B. L.; Beecher, G.; Dwyer, J. T.; Folts, J.; Harnly, J.; Hollman, P.; Keen, C. L.; Mazza, G.; Messina, M.; Scalbert, A.; Vita, J.; Williamson, G.; Burrowes, J. Journal of Nutrition, 2007; 137, 718S; (b) Dinand, E.; Zloh, M.; Brocchini, S. Aust. J. Chem. 2002, 55, 467; (c) Pawlowska, A. M.; de Leo, M.; Braca, A. J. Agric. Food Chem. 2006, 54, 10234; (d) Li, Z.; Ngojeh, G.; DeWitt, P.; Zheng, Z.; Chen, M.; Lainhart, B.; Li, V.; Felpo, P. Tetrahedron Letts. 2008, 49, 7243.

6. (a) Stevenson, D. E.; Hurst, R. D. Cell. Mol. Life Sci. 2007, 64, 2900; (b) Boudet, A.-M. Phytochemistry 2007, 68, 2722; (c) Espin, J. C.; García-Conesa, M. T.; Tomas-Barberan, F. A. Phytochemistry 2007, 68, 2986.

7. (a) Maiti, A.; Cuendet, M.; Croy, V. L.; Endringer, D. C.; Pezzuto, J. M.; Cushman, M. J. Med. Chem. 2007, 50, 2799; (b) Lee, D.; Bhat, K. P.; Fong, H. H. S.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. J. Nat. Prod. 2001, 64, 1286; (c) Nielsen, S. F.; Larsen, M. T.; Schønning, B. K.; Kromann, H. J. Med. Chem. 2005, 48, 2667; (d) Boeck, P.; Falcão, C. A. B.; Leal, P. C.; Yunes, R. A.; Filho, V. C.; Terres-Santos, E. C.; Rossi-Bergman, B. Bioorg. Med. Chem. 2006, 14, 1538; (e) Menichincheri, M.; Ballinari, D.; Bargiotti, A.; Bonomini, L.;

Ceccarelli, W.; D'Alessio, R.; Fretta, A.; Moll, J.; Polucci, P.; Soncini, C.; Tibolla, M.; Trosset, J.-Y.; Vanotti, E. J. Med. Chem. 2004, 47, 6466; (f) Qin, C. X.; Chen, X.; Hughes, R. A.; Williams, S. J.; Woodman, O. L. J. Med. Chem. 2008, 51, 1874; (g) Gates, M. A.; Tworoger, S. S.; Hecht, J. L.; De Vivo, I.; Rosner, B.; Hankinson, S. E. Int. J. Cancer 2007, 121, 2225; (h) Hogan, F. S.; Krishnegowda, N. K.; Mikhailova, M.; Kahlenberg, M. S. J. Surg. Res. 2007, 143, 58.

8. (a) Kirk, C. J.; Harris, R. M.; Wood, D. W.; Waring, R. H.; Hughes, P. J. Biochem. Soc. Trans. 2001, 29, 209; (b) Ohno, S.; Matsumoto, N.; Watanabe, M.; Nakajin, S. J. Steroid Biochem. Mol. Biol. 2004, 88, 175; (c) Schweizer, R. A.; Atanasov, A. G.; Frey, B. M.; Odermatt, A. Mol. Cell. Endocrinol. 2003, 212, 41; (d) Carcache-Blanco, E. J.; Cuendet, M.; Park, E. J.; Su, B.-N.; Rivero-Cruz, J. F.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. Nat. Prod. Res. 2006, 20, 327; (e) Cuendet, M.; Oteham, C. P.; Moon, R. C.; Pezzuto, J. M. J. Nat. Prod. 2006, 69, 460; (f) Kinghorn, A. D.; Su, B.-N.; Lee, D.; Gu, J.-Q.; Pezzuto, J. M. Curr. Org. Chem. 2003, 7, 213; (g) Maiti. A.; Cuendet, M.; Kondratyuk, T.; Croy, V. L.; Pezzuto, J. M.; Cushman, M. J. Med. Chem. 2007, 50, 350.

9. (a) Karakaya, S.; Nel, S. S. Food Chem 1999, 66, 289; (b) Middleton Jr, E.; Kandaswami, C.; Theoharides, T. C. Pharmacol Rev. 2000, 52, 673.

10. (a) Ellem, S. J.; Risbridger, G. P. Minerva Endocrinol. 2006, 31, 1; (b) Narashimamurthy, J.; Rao, A. R.; Sastry, G. N. Curr. Med. Chem. Anticancer Agents 2004, 4, 523.

11. Jones, S. B.; DePrimo, S. E.; Whitfield, M. L.; Brooks, J. D. Cancer Epidemiol. Biomarkers Prev., 2005, 14, 596.Bohm, B. A., "Introduction to flavonoids." Harwood Academic Publishers: Amsterdam. (1998).

12. Dhar, D.N., "The Chemistry of Chalcones and related compound" Wiley : New York, (1981).

13. Oyvind. M. A. and Kenneth R. M., "flavonoids chemistry, biochemistry and applications," CRC press: Boca raton, p 1003 (2006).

14. J. Med. Chem. 41, 4819 (1998).

15. J. Med. Chem. 38, 3031 (1995).

16. De Groot H, Raven U. Fundam Clin Pharma Col 1998; 12:249-255.

17. Robak J, Gryglewski RJ. Bioactivity of flavonoids. Pol J Pharmacol 1996; 48: 555-556.

18. Ranaud S, de Lorgeril M. Wine, alcohol, platelets, and the French paradox for coronary heart disease. Lancet 1992; 339 (8808): 1523-1526.

19. Harbone JB. The flavonoids- Advances in Research Since 1980. ed 1. London: Chapman and Hall; 1988.

20. Middleton E. The flavanoids. Trends Pharmacol Sci 1984; 5:335-338.

21. Havesteen B. Biochem Pharmacol 1983; 32 (7): 1141-1148.

22. Harbone JB. Nature, In: Cody V, Middleton Elliott Jr, Harbone JB (eds). New York, USA: Alan R Liss, Inc; 1986. 15-24.

23. Griebel G, Perrault G, Tan S, Schoemarker H, Sanger DJ. Neuropharmacology 1999; 38: 965-77.

24. Lackeman GM, Claeys M, Rwangabo PC, Herman AG, J Planta Med 1986; 52: 433-9.

25. Harbone JB, Baxter, H. Vol. 1-2. New York: John Wily and Son; 1999.

26. DeFelice S. L. Nutraceuticals: Scrip Mag 1992; 9.

27. Dillard, C. J.' German. J. B. Phytochemicals: J Sci Food Agric 2000; 80: 1744-1756.

28. De Groot H. Hepatogastroenterology 1994; 41: 328-332.

29. Grace PA. Br J Surg 1994; 81: 637-647.

30. Wegener T, Fintelmann V. Flavonoids and bioactivity. Wein Med Wochem Schr 1999; 149: 241-247.

31. Ares JJ, Outt PE. Curr Pharm Des 1998; 4: 7-36.

32. Hillwell B. Free radicals, cause or constipation Lancet 1994; 344: 721-724.

33. Bors W, Heller W, Michel C, and Saran M. Flavonoids as antioxidant: Methods Ezymol 1990; 186: 343-355.

34. Havsteen B. Flavonoids Biochem Pharmacol 1983; 32 (7): 1141-1148.

35. Selway JWT. Antiviral activity New York: Alan R Liss, Inc: 1986, 521-536.

36. Thomas PRS, Nash GB, Dormandly JA. Br.Med J 1988; 296: 1673-1695

37. Loewenstein WR. Biochem Biophys Acta 1976; 560: 1-65.

38. Ng TB, Huang B, Fong WP, Yeung HW.Life Sci 1997; 61:933-954.

39. Lee SJ, Son KH, Chang HW et al. Arch Pharm Res 1993; 16 (1) : 25-28.

40. Hang T, Jin JB, Cho S, Cyang JC. Planta Med 2002; 68 (2) ; 268-271.

41. Shahid F, Yang Z, Saleemi ZO J Food Lipids 1998; 1: 69-75.

42. Farmica JV, Regelson W. Fd Chem Toxic 1995; 33 (12): 1061-1080.

43. Kim HP, Mani I, Iversen L, Ziboh VA. 1998; 58: 17-28.

44. Jachak SM. Natural product: CRIPS 2001; 2 (1): 12-15.

45. Vessal M, Hemmati M. Comp Biochem Physiol C 2003; 135: 357-365.

46. Hif CS, Howell SL. J Endocrinol 1985; 107: 1-8.

47. Bernatova I, Pechanova O, BALAL Pet al. Am J Physiol Heart Cir Physiol 2002; 282: 942-948.

48. Jayakody TL, Senaratne MPJ, Thompson ABR CT. J Physiol Pharmacol 1985; 63: 1206-1209.

49. Gryglewski RJ, Korbut R, Robak J, Swips J. Biochem Pharmacol 1987; 36: 317-322.

50. Muarakami S, Muramatsu M, Otomo S. J Pharm Pharamacol. 1992; 44: 926-928.

51. Gill B, Sanz MJ, Terencio MC, Life Sci 1994; 54: 333-339.

52. Hirano T, Gotoh M, Oak K. Life Sci 1994; 55; 1061-1069.

53. Griebel G, Perrault G, Tan S, H, Sanger. Neuropharmacol 1999; 38: 965-977.

54. M.Shimokoriyama, in The Chemistry of Flavonoid Compounds, ed. T. A. Geissman, Pergamon, New York , 1962.p 286.

55. S. V. Kostanecki and W. Szabranski. Can. J. Chem., 1990, 68, 1780.

56. K. Freudenberg and L. Orthner, Ber., J. Chem. Soc.1997, 12 .645.

57. Naseem Ahmed, Hasrat Ali and Johan E. van Lier., T.L. 46 (2005) 253-256.

58. Chu, H.-W, Wu, H.-T. Lee, Y. –J. Tetrahedron 2004, 60, 2647-2655.

59. Naseem Ahmed and Johan E. van Lier Tetrahedron letters 47 (2006) 2725-2729.

60. Shibata I, Nose, K, Sakamoto, K Yasuda, M Baba., J. Org. Chem.69 (2004) 2185.

61. Chandrasekhar, S. Ramachandar, T. Shyamsunder Indian J. Chem. 2004, 43B, 813.

62. Ahmed, N. v an.San Lieer, J. E. Tetrahedron Lett. 47(2006) 2725-2729.

63. Naseem Ahmed and Johan E. van Lie., Tetrahedron Letters 48(2007) 13-15.

64. Cave, G. W.V. Raston, C.L. Scott. Chem. Commun.2001, 2159.(b) Toda, F. Tanaka, K Chem. Rev.100 (2000) 1025.

65. Welton T. Chem. Rev. 99 (1999) 2071.

66. S. Saravanamurugan, M. Palanichamy, B A Catalysis Commonications 6(2005) 399-403.

67. T.W. Bastock, J.H. Clark , Green Chem. 4 (2002) 615.

68. J.L. Scott, C. L. Raston, Green Chem. 2 (2000) 245.

69. A. Mitsutani, Catal. Today 73 (2002) 57.

70. Armandodoriano Bianco. Claudia Cavarischia.Tetrahedron Letters 44(2003) 9107-9109.

71. Lebedev, M. V. Nensjdenko, V. G. Balenkov, E. S. synthesis 89 (1998).

72. Cragg, J.M.Boyed, M.R. Biorg. Med. Chem. Lett. 3 (1993) 581.

73. Whitting, D.A. Nat. Prod. Rep. 18 (2001) 583-606.

74. Rao, Y.K. Gunasekar, D.J. Nat. Prod. 64 (2001) 368-369.

75. Seijas, J.A. Vazquez-Tato, J. Green Chem. 4 (2002) 390-391.

76. Xueguang Wang, Soofin Cheng.Catalytic Communication 7(2006) 689-695.

77. M.D. Ankhiwala, J. Indian Chem. Soc.67 (1990) 913.

78. R.T. Blickenstaff, W.R. Hanson, S Reddy, Bioorg. Med. Chem. 3 (1995) 917.

79. M.J. Climent, A. Corma, S. I. borra, J. Catal. 221 (2004) 474.

80. Gabriel J. Sagrera and Gustavo A. Seoane Chem. Soc. Vol. 16, No. 4 (2005) 851-856.

81. Seoane, G. Pandolfi, E. Gamenara, Chem, Soc. 7 (1996) 307.

82. Lopez, G. Pandolfi, E. Seoane, Synthesis, 10 (2000) 1403.

83. Varma, R. S. Dahiya, R. J. Org. Chem. 63 (1998) 8038.

84. Perreux, L. Loupy. A. J. Tetrahedron 57 (2001) 9199.

85. Hitoshi Kagawa, Yoshihiro Harigaya.Chem. Pharm. Bull. 53 (5) 547-554 (2005).

86. Beecher G. R. J. Nutr.133 (2003).

87. Paganga G, rice-Evans C.A. FEBS Lett. 401(1997) 78-82.

88. Ikovits J. A. Ruscetti F.W. Wang J.M. Biochem. Biophys. Res. Commun. 276 (2000) 534-538.

89. B. S. Xie Q. Dial S. L. Chem. Res. Toxicol, 14 (2001) 280-294.

CHAPTER -2

SYNTHESIS OF 2'-HYDROXYCHALCONES FROM 2'-HYDROXY-ACETOPHENONE AND AROMATIC ALDEHYDES

2.1 GENERAL EXPERIMENTAL PROCEDURES:

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded in a Nexus Thermo Nicolet FT-IR spectrometer using KBr pellets. ^{1}H-NMR & ^{13}C-NMR in $CDCl_3$ were recorded on a Brucker Ultra Shield TM 500 MHz and 125.758 MHz spectrometers respectively using TMS as an internal standard. The chemical shifts were quoted with reference to the residual solvent signal. The electron spray ionization mass spectra were recorded in dichloromethane by Perkin Elamer GC-MS spectrometer. The elemental analysis was carried out by Vario EL CHNS analyzer. The purity of the compounds was checked by TLC-silica gel-G (Merck) with UV-light and different developing reagents and purified on silica gel column chromatography (Merck, 60-120 mesh).

2.2 GENERAL PROCEDURE FOR THE SYNTHESIS OF 2'-HYDROXY-CHALCONES:

An equimolar aqueous solution of sodium hydroxide was added to a stirred solution of 2'-hydroxyacetophenone and aromatic aldehydes in ethanol. The reaction mixture was kept with stirring at room temperature for different time. TLC showed the complete conversion. The reaction mixture was poured into crushed ice and acidified with dilute hydrochloric acid (10%). The products (2'hydroxychalcones) precipitated out as solid at

room temperature or after cooling for sometime. The crude products were filtered, washed with water and dried under vacuo, followed by crystallized in ethanol or mixture of solvents. In some cases, crude products were purified on silica gel column chromatography in a mixture of hexane–dichloromethane (1:1 v/v) as eluent.

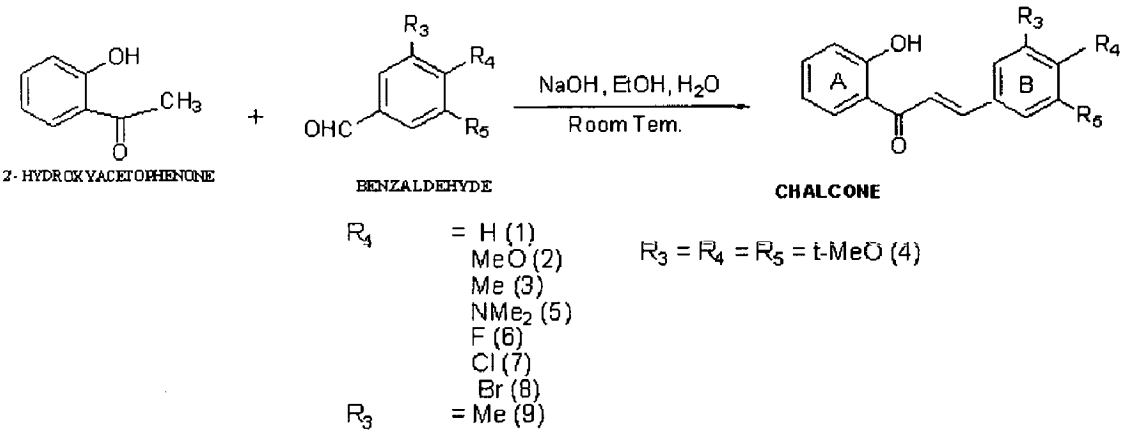


Figure 2.1 General Synthesis route of Chalcone

2.2.1 Synthesis of 1- (2'-Hydroxyphenyl)-3-phenyl-2-propen-1-one [1]

2'-hydroxyacetophenone (1.76 ml, 1.47 mmol) and benzaldehyde (1.48 ml, 1.4 mmol) were dissolved in ethanol (10 ml) with stirring. Aqueous NaOH (0.58 mg, 1.4 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 24 hours, during which 2'-hydroxychalcone precipitated as the sodium salt. The solution/suspension was poured into cold 1N HCl (10 ml), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (2 x 20 mL), and recrystallized from solvent (EtOH or $MeOH/CH_2Cl_2$) to give the product or silica gel column chromatography is used in a mixture of hexane and dichloromethane (1:1) as eluent to purify the products. Yield 85%; m.p. 158-160^{0}C (lit. 160^{0}C).[1] Elemental Anal. Calcd. For $C_{15}H_{11}O_2$: C-75.00, H-5.00, O-16.94%. Found: C-75.1, H-5.09, O-15.92%. IR (ν_{max} KBr, cm^{-1}): 3415(OH), 3100, 1680(CO), 1660, 1572, 1480,

1266, 973, 756. ^{1}H-NMR ($CDCl_3$, 500MH_Z) δ ppm: 12.82 (s, C-2'-O*H*, 1H), 7.93 (d, J=16Hz, =C*H*-Ar, 1H,), 7.87 (dd, J_1=7.8 Hz, J_2=1.7 Hz 1H), 7.43-7.66 (m, Ar-*H*, 6H), 7.20-7.26 (m, 2H), 6.94 (d, J=16Hz, -CO-C*H*-, 1H), ^{13}C-NMR ($CDCl_3$,125 MH_Z) δ ppm: 192.06, 161.09, 138.7, 136.2, 128.0, 127.0, 120.9, 79.6, 44.7. GC-MS (m/z): 224 [M^+, $C_{15}H_{11}O_2$], 223 (14), 221 (28), 207 (22), 147 (41), 73 (100).

2.2.2 Synthesis of 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one [2]

2'-hydroxyacetophenone (2.65 ml, 1.9 mmol) and 4-methoxybenzaldehyde (2.69 ml, 1.9 mmol) were dissolved in ethanol (15 ml) with stirring. Aqueous NaOH (0.88 mg, 2.2 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 26 hours, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. The solution/suspension was poured into cold 1N HCl (15 mL), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (2 x 20 mL) and recrystallized from solvent (EtOH or $MeOH/CH_2Cl_2$) to give the product or purified by silica gel column chromatography in a mixture of hexane and dichloromethane (1:1) as eluent. Yield: 80%; m.p.160-162 ^{0}C (lit. 165 ^{0}C). Elemental Anal. Calcd. for $C_{16}H_{14}O_3$: C-68.18; H-5.42; O-17.80%. Found: C-68.20; H-5.29; O-16.87%. IR (ν_{max} KBr, cm^{-1}): 3440(OH), 2725, 1638(CO), 1511, 1491, 1259, 1160, 827. ^{1}H-NMR ($CDCl_3$, 500MH_Z) δ ppm: 12.94 (s, C-2'-O*H*, 1H), 7.93 (d, J=16Hz, =C*H*-Ar, 1H), 7.88 (dd, J_1=8.0Hz, J_2=1.6Hz 1H), 7.63-7.65 (m, 1H), 7.52-7.58 (m, 4H), 7.02-7.09 (m, 2H), 6.97 (d, J=16Hz, -CO-C*H*-1H), 3.88 (s, OCH_3, 3H). ^{13}C-NMR ($CDCl_3$, 125 MH_Z) δ ppm: 195.6, 190.7, 163.5, 162.0, 145.3, 136.3, 133.3, 130.5, 129.9, 118.7, 114.5, 77.5. GC-MS (m/z): 255 [M^+, $C_{16}H_{14}O_3$], 254 (19), 147 (11), 134 (84), 121 (49), 71 (69), 57 (100).

2.2.2 Synthesis of 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one [3]

2'-hydroxyacetophenone (1.76 ml, 1.4 mmol) and 4-methylbenzaldehyde (1.48 ml, 1.4 mmol) were dissolved in ethanol (10 ml) with stirring. Aqueous NaOH (0.58 mg, 1.4 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 4 hour, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. The solution/suspension was poured into cold 1N HCl (15 mL), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (2 x 20 mL), and recrystallized from solvent (EtOH or $MeOH/CH_2Cl_2$) to give the product or purified by silica gel column chromatography in a mixture of hexane and dichloromethane (1:1) as eluent. Yield 90%; m.p. 156-158^{0}C (lit.160^{0}C).[2] Elemental Anal. Calcd. for $C_{16}H_{14}O_2$: C-69.94; H-4.25; O-12.38%. Found: C-69.98; H-4.29; O-12.42%. IR (ν_{max} KBr, cm^{-1}): 3440(OH), 3410, 1647(CO), 1610, 1266, 820, 829; ^{1}H-NMR ($CDCl_3$, 500MH_Z) δ ppm: 12.91 (s, C-2'-O*H*, 1H), 7.96 (d, J=16Hz, =C*H*-Ar, 1H), 7.90 (dd, J_1=8.2, J_2=1.6Hz, 1H), 7.50-7.54 (m, 1H), 7.59-7.67 (m, 4H), 7.20 (m, 2H), 6.96 (d, J =16Hz, –CO-C*H* -,1H), 2.87 (s, CH_3, 3H). ^{13}C-NMR ($CDCl_3$, 125 MH_Z) δ ppm: 146.4, 126.9, 129.6, 128.7, 115.6, 71.3, 77.0, 76.0, 31.6. GC-MS (m/z): 238 [M^+, $C_{16}H_{14}O_2$], 237 (32), 224 (46), 147 (54), 115 (46), 118 (100), 117 (48), 65 (59).

2.2.4 Synthesis of 1-(2'-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one [4]

2'-hydroxyacetophenone (1.76 ml, 1.4 mmol) and 4-chlorobenzaldehyde (1.48 ml, 1.4 mmol) were dissolved in ethanol (10 ml) with stirring. Aqueous NaOH (0.58 mg, 1.4 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 6 hour, during which 2'-hydroxychalcone derivative precipitated as the sodium salt.

Following the above work up procedure, a rose red color compound was obtained. Yield 85 %; m.p.154-156 ^{0}C (lit. 158 ^{0}C).[3] Elemental Anal. Calcd. for $C_{15}H_{11}O_2Cl$: C-69.94; H- 4.25; O-12.38%. Found: C-69.98; H-4.29; O-12.40%. IR (ν_{max} KBr, cm^{-1}): 3435(OH), 3100, 1647(CO), 1610, 1582, 1438, 1230, 820, 720. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ ppm: 12.80 (s, C-2'-O*H*, 1H). 7.93 (d, J =16Hz, =C*H*-Ar, 1H), 7.87 (dd, J_1=7.8, J_2=1.6 Hz, 1H), 7.52-7.56 (m, 1H), 7.45-7.65 (m, 4H), 6.9-7.0 (m, 2H), 6.94 (d, J =16Hz, –CO-C*H*-, 1H). ^{13}C-NMR ($CDCl_3$, 125MHz) δ ppm: 193.4, 163.6, 143.9, 136.9, 126.5, 123.3, 119.9, 118.9, 77.2, 77.0, 76.7, 29.7, GC-MS (m/z) : 258 [M$^+$, $C_{15}H_{11}O_2Cl$] 257 (37), 165 (16), 147 (62), 120 (100), 92 (37), 65 (24).

2.2.5 Synthesis of 1-(2'-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one [5]

2'-hydroxyacetophenone (1.76 ml, 1.4 mmol) and 4-bromobenzaldehyde (1.48 ml, 1.4 mmol) were dissolved in ethanol (10 ml) with stirring. Aqueous NaOH (0.58 mg, 1.4 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 6 hours, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. Following the above work up procedure, a rose red color compound was obtained. Yield 84%; m.p.160-162^{0}C. Elemental Anal. Calcd. For $C_{15}H_{11}O_2Br$: C- 68.12; H-4.20; O-12.38%. Found: C-68.38; H-4.23; O-12.42%. IR (ν_{max} KBr, cm^{-1}): 3443(OH), 3100, 1638(CO), 1620, 1538, 1420, 1574, 1230, 980,760; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ ppm: 12.90 (s, C-2'-O*H*, 1H). 7.95 (d, J =16Hz, =C*H*-Ar, 1H), 7.92 (dd, J_1=7.7, J_2=1.4 Hz, 1H), 7.50-7.56 (m, 1H), 7.40-7.49 (m, 4H) 7.0-7.09 (m, 2H), 6.98 (d, J =16Hz, –CO-C*H*-, 1H), ^{13}C-NMR ($CDCl_3$,125 MHz) δ ppm: 193.4, 165.6, 146.1, 136.6, 132.5, 129, 119.9, 116.9,

99.1, 91.2, 77.0, 76.7. GC-MS (m/z): 303 [M^+, $C_{15}H_{11}O_2Br$], 285 (0.99), 287 (1.29), 147 (34.6), 120 (57.6), 57 (100).

2.2.6 Synthesis of 1-(2'-Hydroxyphenyl)-3-(3-methylphenyl)-2-propen-1-one [6]

2'-hydroxyacetophenone (2.65 ml, 1.9 mmol) and 3-methylbenzaldehyde (2.69 ml, 1.9 mmol) were dissolved in ethanol (15 ml) with stirring. Aqueous NaOH (0.88 mg, 2.2 mmol) was added in portions. Resulting solution was stirred for 8 hours, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. The solution/suspension was poured into cold 1N HCl (15 mL), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (2 x 20 mL), and recrystallized from corresponding solvent (EtOH or $MeOH/CH_2Cl_2$) to give the product or purified by silica gel column chromatography in a mixture of hexane and dichloromethane (1:1) as eluent. Yield 60%; m.p. 160-165^{0}C (lit. 170^{0}C).[4] Elemental Anal. Calcd. for $C_{16}H_{14}O_2$: C-68.24; H- 5.25; O-14.38%. Found: C-69.58; H-6.29; O-14.62%. IR (ν_{max} KBr, cm^{-1}); 3440(OH), 3410, 1648(CO), 1610, 1266, 820, 829; ^{1}H-NMR ($CDCl_3$, 500MHz) δ ppm: 12.90 (s, C-2'-O*H*, 1H), 7.75 (d, J =16Hz, =C*H*-Ar, 1H), 7.15-7.60 (m, Ar-*H*, 8H), 6,57 (d, J =16Hz ,–CO-C*H* -, 1H), 3.80 (s, CH_3, 3H) .^{13}C-NMR ($CDCl_3$,125 MHz) δ ppm:146.5, 129.9, 128.1, 128., 120.1, 115.6, 77.4, 77.1, 76.5, 31.0. GC-MS (m/z): 238 [M^+, $C_{16}H_{14}O_2$], 237 (32), 224 (46), 147 (54), 115 (46), 117 (48), 65 (59).

2.2.7 Synthesis of 1-(2'-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one [7]

2'-hydroxyacetophenone (1.76 ml, 1.4 mmol) and 3, 4, 5-trimethoxybenzaldehyde (1.48 ml, 1.4 mmol) were dissolved in ethanol (10 ml) with stirring. Aqueous NaOH (0.58 mg, 1.4 mmol) was added in portions to give a blood-red solution. Resulting solution was

stirred for 36 hours, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. The solution/suspension was poured into cold 1N HCl (15 mL), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (2 x 20 mL), and recrystallized from solvent (MeOH or $MeOH/CH_2Cl_2$) to give the product or purified by silica gel column chromatography in a mixture of hexane and dichloromethane (1:1) as eluent. Yield 75%; m.p. 180-182 ^{0}C. Elemental Anal. Calcd. for $C_{18}H_{18}O_5$: C-68.78; H-5.73; O-25.47%. Found: C-68.72; H-5.65; O-25.39%. IR (ν_{max} KBr, cm^{-1}): 3433 (OH), 3410, 1636(CO), 1610, 1570, 1474, 1127, 850, 726. ^{1}H-NMR ($CDCl_3$, 500 MH_Z) δ ppm: 12.85 (s, C-2'-O*H*, 1H), 7.96 (d, J =16Hz, =C*H*-Ar, 1H), 7.86 (dd, J_1=8.5, J_2=8.6Hz, 1H), 7.55-7.58 (m, 1H), 7.07 (m, 2H), 6.99 (d, J =16Hz, –CO-C*H* -,1H), 6.91 (s, 3H), 3.96 (s, 3xOCH_3, 9H). ^{13}C-NMR ($CDCl_3$,125MH_Z) δ ppm: 195.5, 194.0, 160, 149.0, 136.9, 135.6, 132.3, 132.0, 124.2, 119.1, 115.2, 67.0, 40.4, 39.7, 38.5. GC-MS (m/z): 316 [M^+, $C_{18}H_{18}O_5$], 315 (42), 194 (60), 181 (97), 179 (100), 151 (25), 121 (30), 119 (20).

2.2.8. Synthesis of 1-(2'-Hydroxyphenyl)-3-(4-N, N-dimethylaminephenyl)-2-propen-1-one [8]

2'-hydroxyacetophenone (1.76 ml, 1.4 mmol) and 4-N,N-dimethylbenzaldehyde (1.48 ml, 1.4 mmol) were dissolved in ethanol (10 ml) with stirring. Aqueous NaOH (0.58 mg, 1.4 mmol) was added in portions to give a blood-red solution. Resulting solution was stirred for 28 hour, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. Following the above work up procedure, a rose red color compound was obtained. Yield 80 %; m.p 175-176 ^{0}C (lit. 180^{0}C).[5] Elemental Anal. Calcd. for $C_{15}H_{20}O_2N$: C-68.78; H-4.73; O-12.40; N-4.89%. Found: C-68.80; H-4.76; O-12.45; N-4.10%. IR (ν_{max} KBr, cm^{-1}): 3434(OH), 3100, 2998, 2825, 1640(CO), 1542, 1400, 1232, 1174, 985, 881. ^{1}H-NMR

($CDCl_3$, 500MH_Z) δ ppm: 12.90 (s, C-2'-O*H*, 1H), 7.97 (d, J =16Hz, =C*H*-Ar, 1H), 7.92 (dd, J1=8.2, J2=8.0 Hz 1H), 7.52-7.68 (1H, m), 7.47-7.61 (4H, m), 6.92-6.98 (m, 2H), 6.72 (1H, d, J =16Hz, –CO-C*H*-), 3.29 (s, 2xCH_3, 6H). ^{13}C-NMR ($CDCl_3$,125 MH_Z) δ ppm: 193.4, 163.6, 145.6, 144.0, 136.6, 132.5, 132.5, 129.9, 129.6, 119.9, 116.7, 99.9, 77.0, 76.7, 21.7. GC-MS (m/z): 267 [M^+, $C_{17}H_{18}O_2N$], 266 (32), 207 (9), 191 (6), 147 (16), 57 (100).

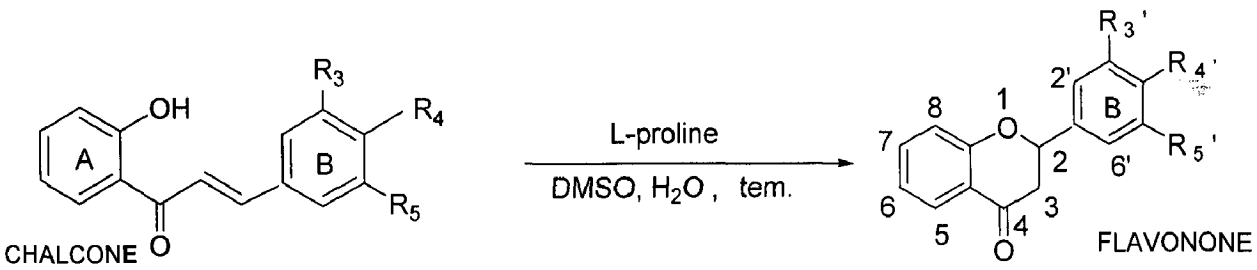
2.2.9 Synthesis of 1-(2'-Hydroxyphenyl)-3-(4-flourophenyl)-2-propen-1-one [9]

2'-hydroxyacetophenone (2.65 ml, 1.9 mmol) and 4-fluorobenzaldehyde (2.69 ml, 1.9 mmol) were dissolved in ethanol (15 ml) with stirring. Aqueous NaOH (0.88 mg, 2.2 mmol) was added in portions. Resulting solution was stirred for 10 hours, during which 2'-hydroxychalcone derivative precipitated as the sodium salt. The solution/suspension was poured into cold 1N HCl (15 mL), and further concentrated HCl was added until the solution was acidic. The resulting yellow solid was filtered, washed with water (2 x 20 mL), and recrystallized from corresponding solvent (EtOH or $MeOH/CH_2Cl_2$) to give the product or purified by silica gel column chromatography in a mixture of hexane and dichloromethane (2:1) as eluent. Yield 70 %; m.p. 189-190^{0}C. Elemental Anal. Calcd. for $C_{15}H_{11}O_2F$: C-74.38; H-4.54; O-13.22%. Found: C-74.40; H-4.52; O-13.28%. IR (ν_{max} KBr, cm^{-1}); 3432(OH), 3200, 1687, 1720, 1638(CO), 1534, 1468, 1230, 830. ^{1}H-NMR ($CDCl_3$, 500 MH_Z) δ ppm : 12.77 (s, C-2'-O*H*, 1H). 7.92 (d, J =16Hz, =C*H*-Ar, 1H), 7.85 (dd, J_1=7.8, J_2=1.6 Hz, 1H), 7.50-7.56 (m, 1H), 7.40-7.60 (m, 4H), 6.94-7.0 (m, 2H), 6.90 (d, J = 16Hz, –CO-C*H*, 1H). ^{13}C-NMR ($CDCl_3$, 125 MH_Z) δ ppm : 193.1, 164.2, 142.2, 136.5, 133, 128.1, 124, 120, 118.1, 77.5, 77. GC-MS (m/z): 239 [M^+, $C_{15}H_{11}O_2F$], 238 (38), 162 (29), 147 (58), 120 (100), 93 (20).

(i) SYNTHESIS OF FLAVONONES FROM DIFFERENT 2'-HYDROXYCHALCONE

2.3 general procedures for synthesis of various flavonones:

To a stirred solution of 2'-hydroxychalcones (30-60 mg) in water (2 ml) and minimum amount of DMSO (0.2-0.5 ml, to solubilize) at 90-140°C was added L-proline (0.5-2 mg) with continued stirring at the same temperature for the indicated time (Table 2) After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. If necessary the product was purified by column chromatography on silica gel in hexane-dichloromethane (1:1 to 2:1 v/v). All products were characterized by comparison of their spectral and physical properties with those of authentic samples.



R_4 = H (10)
MeO (11)
Me (12)
Cl (13)
Br (14)

R_3 = Me (15)

Figure 2.2 Synthesis route of Flavonone.

2.3.1 Synthesis of 2-phenyl-chroman-4-one [10]

To a stirred solution of 1-(2'-Hydroxyphenyl)-3-phenyl-2-propen-1-one (30 mg, 0.144 mmol) in water (2 ml) and minimum amount of DMSO (0.2 ml, to solubilize) at 90-95°C was added L-proline (0.5 mg, ..mmol) with continued stirring at the same temperature for 36 hours. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. The residue was separated on silica gel column chromatography using dichloromethane and hexane (2:1) to obtain flavonone and remaining chalcone (3:1) ratio. The product was recrystaline by using *n*-hexane to obtain the white solid. Yield 90%; m.p. 74-75 °C (lit. 77-79 °C).[6] IR (ν_{max} KBr, cm^{-1}): 3035, 2962, 1688(CO), 1606, 1462, 1304, 1228, 1065, 760, 696. ^{1}H-NMR ($CDCl_3$, 500 MH_Z) δ ppm: 7.94 (dd, J_1=8.1 Hz, J_2=1.7 Hz, 1*H*), 7.28-7.53 (m, 6*H*), 7.08-7.11 (m, 2*H*), 5.55 (dd,J_1=13.2 Hz, J_2=3.0 Hz, 1*H*), 3.12 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*), 2.95 (dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*); ^{13}C-NMR ($CDCl_3$,125 MH_Z) δ ppm: 192.4, 162.0, 139.1, 136.6, 129.3 129.2, 127.5, 126.6, 122.0, 121.3, 118.5, 80.0, 45.1. GC-MS (m/z): 224 [M^+, $C_{15}H_{11}O_2$], 147 (36.5), 120 (100), 104 (42.3), 77 (7.42).

2.3.2 Synthesis of 2-(4'-methoxyphenyl)-chroman-4-one [11]

To a stirred solution of 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (60 mg, 0.236 mmol) in water (3 ml) and minimum amount of DMSO (0.2 ml) at 120-125°C was added L-proline (2 mg, 0.012 mmol) with continued stirring at the same temperature for 48 hours. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with

ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. The crude yellow solid was dissolved in dichloromethane. TLC showed the presence of two minor products (R_f =0.64, and 0.44 respectively in dichloromethane-hexane (1:1). The major product (R_f =0.80) was purified on silica gel column chromatography using dichloromethane - hexane (2:1) to obtain flavonone. The product was recrystaline by using *n*-hexane to obtain the white solid. Yield 60%; m.p. 96-97 °C (lit. 98-100°C).[7] IR (ν_{max} KBr, cm^{-1}): 3010, 2960, 1680 (CO), 1616, 1461, 1226, 1034,769, 696. ^{1}H-NMR ($CDCl_3$, 500MHz) δ ppm: 7.94 (dd, J_1=8.3 Hz, J_2=1.7 Hz, 1*H*), 7.55-7.60 (m, 1*H*), 7.40-7.48 (m, 4H), 7.04-7.15 (m, 2H), 5.44 (dd, J_1=13.3 Hz, J_2= 3.0 Hz, 1*H*)), 3.07 (dd, J_1=17.0 Hz, J_2=13.5 Hz, 1*H*), 2.88 (dd, J_1=17.0 Hz, J_2=3.0 Hz, 1*H*), 3.88 (s,OCH_3). ^{13}C-NMR ($CDCl_3$, 125 MHz) δ ppm: 192.5, 156.7, 154.6, 139.2, 129.2, 129.1, 126.5, 125.8, 121.2, 119.8, 107.7, 80.1, 56.2, and 45.0. GC-MS (m/z): 255 [M^+, $C_{16}H_{14}O_3$], 254 (19), 147 (15), 134 (82), 121 (52), 71 (69), 57 (100).

2.3.3 Synthesis of 2-(4'-methylphenyl)-chroman-4-one [12]

To a stirred solution of 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one (35 mg, 0.147 mmol) in water (2 ml) and minimum amount of DMSO (0.2 ml) at 120°C was added L-proline (2 mg, 0 .012 mmol) with continued stirring at the same temperature for 36 hours. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. The residue was separated on silica gel column chromatography using dichloromethane - hexane (2:1) to obtain flavonone. The product was recrystaline by using *n*-hexane to obtain the white solid. Yield 85%; m.p. 82-85

°C (lit. 87 °C).[8] IR (ν_{max} KBr, cm^{-1}): 3000, 2964, 1675 (C=O), 1615, 1478, 1150, 835, 762; ^{1}H-NMR ($CDCl_3$, 500 MH_Z) δ ppm: 7.96 (dd, J_1=8.5 Hz, J_2=1.8 Hz, 1*H*), 7.53 -7.58 (m, 1*H*), 7.26 -7.4 (m, 4*H*), 7.06-7.10 (m, 2*H*), 5.5 (dd,J_1=13.0 Hz, J_2=3.2 Hz, 1H), 3.10 (dd, J_1=17.8 Hz, J_2=13.6 Hz, 1H), 2.92 (dd, J_1=17.8 Hz, J_2= 3.2 Hz, 1H), 2.48 (s, CH_3, 3H); ^{13}C-NMR ($CDCl_3$, 125 MH_Z) δ ppm: 192.1, 161.1, 159.2, 136.6, 136.1, 129, 124, 121, 118, 114, 76.7, 31.4, 30.2, 29.9. GC-MS (m/z): 238 [M^+, $C_{16}H_{14}O_2$], 118 (100), 120 (25) 147 (56).

2.3.4 Synthesis of 2- (4'-chlorophenyl)-chroman-4-one [13]

To a stirred solution of 1-(2'-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one (35 mg, 0.134 mmol) in water (2 ml) and minimum amount of DMSO (0.2 ml) at 140°C was added L-proline (2 mg, 0.012 mmol) with continued stirring at the same temperature for 18 hours. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. The residue was separated on silica gel column chromatography using dichloromethane - hexane (2:1) to obtain flavonone. The product was recrystaline by using n-hexane to obtain the white solid. Yield 85%; m.p. 84-85oC (lit.85oC).[9] IR (vmax KBr, cm-1): 3036, 2977, 1697 (CO), 1602, 1471, 1152, 821. 1H-NMR (CDCl3, 500MHZ) δ ppm: 7.93 (dd, J1=7.8 Hz, J2=1.6 Hz, 1H), 7.49 -7.55 (m, 1H), 7.39 -7.45 (m, 4H), 7.03-7.10 (m, 2H), 5.47 (dd,J1=13.0 Hz, J2=3.2 Hz, 1H), 3.04 (dd, J1=16.8 Hz, J2=13.0 Hz, 1H), 2.88 (dd, J1=16.8 Hz, J2= 3.2 Hz, 1H); 13C-NMR (CDCl3,125MHZ) δ ppm: 191.5, 161.3, 137.3, 136.3 134.6, 129.1, 127.5, 127.1, 121.8, 120.9, 118.1, 78.8, 44.6; GC-MS (m/z): 257 [M +, C15H12O2Cl], 256 (16), 237 (22), 147 (49), 120(90), 97 (48), 85 (69), 57 (100).

2.3.5 Synthesis of 2-(4'-bromophenyl)-chroman-4-one [14]

'To a stirred solution of 1-(2'-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one (40 mg, 0.133 mmol) in water (2 ml) and minimum amount of DMSO (0.2 ml) at 140°C was added L-proline (2 mg, 0.012 mmol) with continued stirring at the same temperature for 18 hours. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. The residue was separated on silica gel column chromatography using dichloromethane - hexane (2:1) to obtain flavonone. The product was recrystaline by using *n*-hexane to obtain the white solid. Yield 87%; m.p. 86-87°C (lit. 85 °C).[11] IR (ν_{max} KBr, cm^{-1}): 3040, 2978, 1687 (CO), 1602, 1476, 1151, 825. ^{1}H-NMR ($CDCl_3$, 500MH_Z) δ ppm: 7.97 (dd, J_1=7.6 Hz, J_2=1.4 Hz, 1*H*), 7.55 -7.6 (*m*, 1*H*), 7.40 -7.53 (m 4H,),7.04-7.12 (m, 2H), 5.50 (dd, J_1=13.0 Hz, J_2=3.2 Hz, 1*H*), 3.09 (dd, J_1=16.8 Hz, J_2=13.0 Hz, 1*H*), 2.93 (dd, J_1=16.8 Hz, J_2= 3.2 Hz, 1*H*); ^{13}C-NMR ($CDCl_3$,125MH_Z) δ ppm: 191.4, 161.3, 136.2, 127.8, 127.0, 121.0, 120.9, 120.0, 78.6, 77.2, 77.0, 76.7, 44.5, 31.9, 30.2, 29.7. GC-MS (m/z): 303 [M^+, $C_{15}H_{11}O_2Br$], 301 (13), 184 (28), 120 (92), 103 (24), 92 (44), 77 (31), 57 (100).

2.3.6 Synthesis of 2-(3'-methylphenyl)-chroman-4-one [15]

To a stirred solution of 1-(2'-Hydroxyphenyl)-3-(3-methylphenyl)-2-propen-1-one (35 mg, 0.147 mmol) in water (2 ml) and minimum amount of DMSO (0.2 ml) at 120°C was added L-proline (2 mg, 0.012 mmol) with continued stirring at the same temperature for 36

hours. After completion of the reaction (TLC monitoring), the mixture was cooled to room temperature and poured into water (5 ml) and the aqueous phase was extracted with ethyl acetate (3x5 ml). The organic phase was washed with HCl (5 ml, 10%) solution, dried over anhyd. Na_2SO_4 and concentrated under vacuo. The residue was separated on silica gel column chromatography using dichloromethane - hexane (2:1) to obtain flavonone. The product was recrystaline by using *n*-hexane to obtain the white solid. Yield 56%; m.p. 80-82 ^{o}C. IR (ν_{max} KBr, cm^{-1}): 3015, 2970, 1676 (CO), 1620, 1480, 1160, 825, 760; ^{1}H-NMR ($CDCl_3$, 500 MH_Z) δ ppm: 7.95 (dd, J_1=8.3 Hz, J_2=1.6 Hz, 1*H*), 7.50 -7.52 (m, 1*H*), 7.55 - 7.78 (m, 4H), 7.10-7.16 (m, 2*H*), 5.66 (dd, J_1=13.0 Hz, J_2=3.2 Hz, 1*H*), 3.08 (dd, J_1=17.8 Hz, J_2=13.6 Hz, 1*H*), 2.98 (dd, J_1=17.8 Hz, J_2= 3.2 Hz, 1*H*), 2.53 (s, 3*H*). ^{13}C-NMR ($CDCl_3$, δ ppm): 192.2, 161.6, 139.2, 136.6, 129.5, 126.2, 121.5, 120.9, 79.5, 77.3. GC-MS (m/z): 238 [M^+, $C_{16}H_{14}O_2$], 237 (32), 224 (46), 147 (54), 115 (46), 18 (100), 117 (48), 65 (59).

REFERENCES

1. Merk Index, 11th Edition, 2028.

2. Zhao, L. M.; Jin, H. S.; Sun, L. P.; Piao, H. R.; Quan, Z. S. Bioorg. Med. Chem. Lett. 2005, 15, 5027.

3. Mukarami, S.; Muramatsu, M.; Aihara, H.; Otomo, S.; Biochem.Pharmacol. 1991, 42, 1447.

4. Macqarrie, D. J.; Nazih, K.; Sebti, S. Green Chem. 2002, 4 l, 56.

5. Robinson, R. J. Chem. Soc. 1938, 56, 4154.

6. Henaff, N., Whiting, A. Tetrahedron 2000, 56, 5193.

7. Lee, J. I.; Jung, M. G. Bull.Korean Chem. Soc.2005, 26, 2044

8. Bhat, B.A.; Dhar, K.L.; Puri, S.C.; Saxena, A.K.; Shanmugavel, M.; Quzi, G.N. Bioorg. Med. Chem.

Lett. 2005, 15, 3177.

9. Wei, X.; Fang, J.; Hu, Y.; Hu, H. Synthesis 1992, 1205.

10. Palleros, D.R.; Green Chem. 2004, 81, 1345.

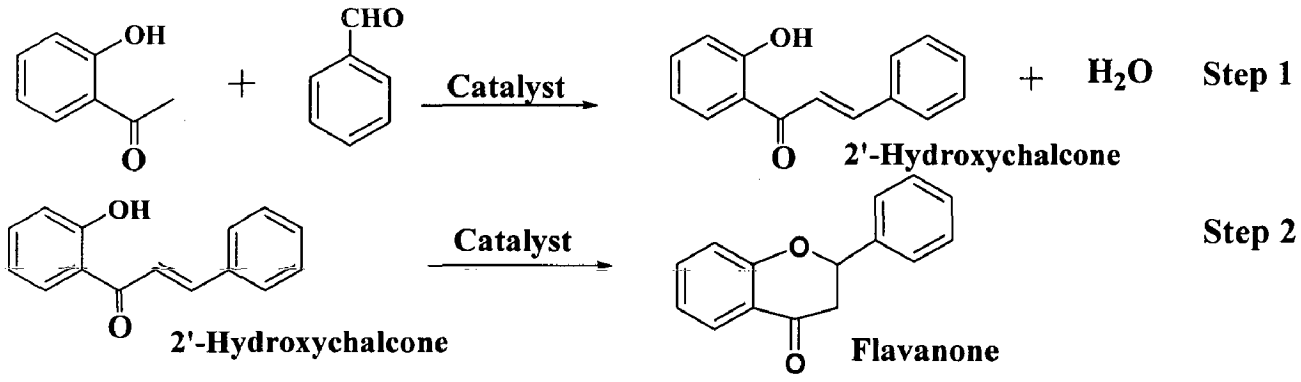
11. Makrandi, J.K.; Bala, S.Synth.Comm.2000, 30, 3555

CHAPTER 3

RESULT AND DISCUSSIONS

Solvent free reactions under heterogeneous system play a significant role in the greening of fine and specialty chemical production and offer clean route to a wide range of organic products. Most of the base catalyzed reaction are homogeneous and use NaOH/KOH or alkali alcoholate under the condition of solvent Claisen–Schmidt condation between 2'-hydroxyacetophenone and benzaldehyde to give α, β unsaturated ketone (2'-hydroxychalcone).The condensation was optimized on the reaction of 2'-hydroxyacetophenone (2 mM) with benzaldehyde (2 mM). This reaction was carried out with different catalyst under different condition. Normally in case our work the reaction carried out using 10-60% wt of alkaline hydroxide as a catalyst over a period 24 hrs at room temperature. The product obtained was in 80% yield by using simple benzaldehyde (Scheme 11). The amount of yield decrease and increase depend on the electron withdrawal or electron donating group attached on the different meta- and para- position. In first step the synthesis 2'-hydroxyachalcone followed by intermolecular cyclization to gives flavanone under the solvent free condition. This reaction was carried out with different catalysts before L-proline was taken as the organocatalyst of choice. Because of Inexpensive compared to Metal-Based catalysts, Environmentally Benign, Non-toxic-Pharmaceutical and Agrochemical Industry, Relatively Mild Conditions, and Biomimetic-Induce cascade reactions. It has been extensively used in the synthesis of various heterocycles.[1] as well as in aldol, Mannich, Hantzsch reaction and Michael reactions.[2] As the mechanism of multi-component such as Knoevenagel condensation and Michael addition, the use of *L*-proline for the same reaction will be a useful and attractive modification for the same. Here in, we have taken water as a green solvent at different

temperature with *L*-proline as an organo-catalyst for the efficient cyclization reaction of 2'-hydroxychalcones under benign reaction conditions. Minimal quantity of DMSO is used for solubility purpose. Our results demonstrate that *L*-proline is a very effective, environmentally friendly catalyst for this reaction to form flavanones in excellent yields (Scheme 11).

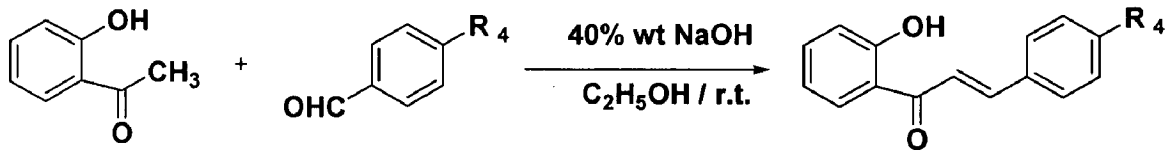


Scheme 11

3.1 CHARACTERIZATION OF CHALCONES (1).

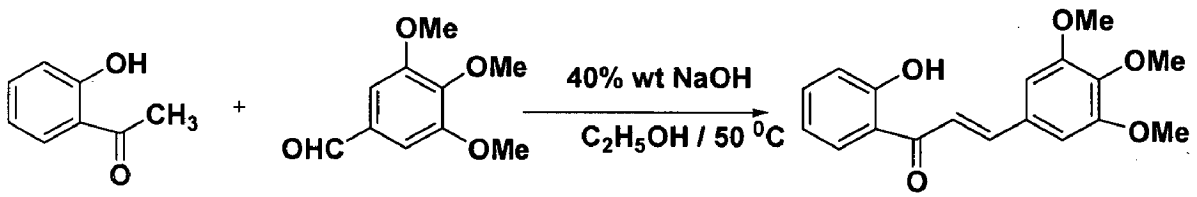
The structure of 2'-hydroxychalcone and flavanone were assigned on the basis of their IR, ^{1}H NMR (500 MH_Z), ^{13}C NMR (125 MH_Z) and GC-MS spectral analysis. The products 2'-hydroxychalcone (1) give a singlet. The procedure worked well with various substituted aldehyde and 2'- hydroxyaldehyde (Scheme 12, 13) peak at 12.97 confirming the presence of O-H proton. Same apply for all examples. Inspection of ^{1}H NMR spectral data clearly indicated(table 4) that the compounds were both geometrically pure and were configured *trans* ($J_{Ha - Hb}$ = 15 -16 H_Z). ^{13}C NMR spectra also show peak at 198, 145 which are characteristic of carbon attached to electronegative atoms and here for carbonyl carbon and carbon attached to unsaturation. Other peaks are aromatic carbons and two alkyl carbons. IR spectra of all examples showed one characteristic vibration frequency for the carbonyl group at 1650-1660 cm^{-1} , which was assigned to the *s-cis conformation.* And one common characteristic peak of O-H bond (3400-3000 cm^{-1}), and 1500-1400

peak at aromatic bonds only. Due to different substituent on 2'-hydroxychalcones and benzyl rings, IR spectra of all molecules shows absorption bands in the range of 800-600 cm^{-1}(Scheme 12, 13).Table 6 shown different GC-MS fragement of chalcones.



Where R_4 = H , OMe , Me , F , Cl , Br ,

Scheme 12: Synthetic route of 1 series, yield 80 – 90%



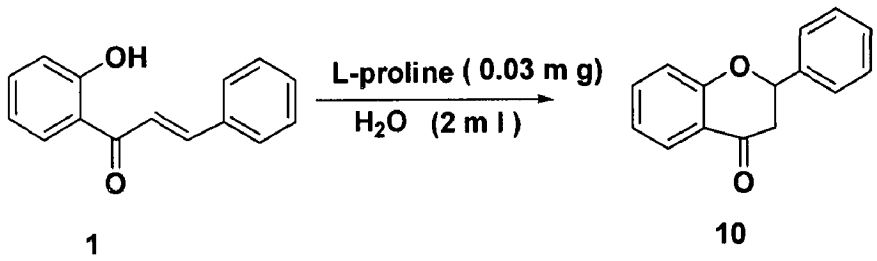
Where R_4 = N $(Me_2)_3$, R_3 = Me

Scheme 13: Synthetic route of 1.1 series, yield 75-85 %

3.2 CHARACTERIZATION OF FLAVANONE (10).

Following the synthesis procedure reported in experimental section, compound 10 was afforded a single product in excellent yield. The product (10) was characterized for the molecular formula $C_{15}H_{11}O_2$ melting point 74-75 ^{0}C. It gave negative alcoholic $FeCl_3$-test and pink color with Mg-conc. HCl.The IR-spectrum displayed diagnostic bands at 1688 cm-^{1} (CO str.), 1606, 1462, 1320, 1300, 1225, 760, 696.cm-^{1}(flavanone skeleton) and other absorption frequencies. The ^{1}H-NMR-spectrum gave a three type of double doublet (a) 5.55 (dd, J_1=13.2 Hz, J_2=3.0 Hz, 1*H*). Due to axial – axial interaction of H_c and H_b (b) 3.12 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*). Due to axial – equatorial interaction of H_c and H_a. (c) 2.95(dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*).Due to axial – equatorial interaction

of H_a and H_b confirming the presence of one pyrone ring, other aromatic characteristic peaks are shown in table 5, ^{13}C NMR spectra assigned for 192.4, 162.0, 139.1, 122, 121.3, 80.0. Which are characteristic of carbon attached to electronegative atoms and here for carbonyl carbon carbon attached to oxygen atom in pyron ring. GC-MS for EIMS fragmentations followed the established pattern, which further confirmed the the product 10(Scheme 14). The molecular ion peak ($M^{+\cdot}$) at m/z 224, 147(15), 120(100), 104(42.3), 77(7.42). etc. shown in the table 7. On the basis of these spectral data, product 10 was characterized as name 2-phenyl-chroman-4-one.



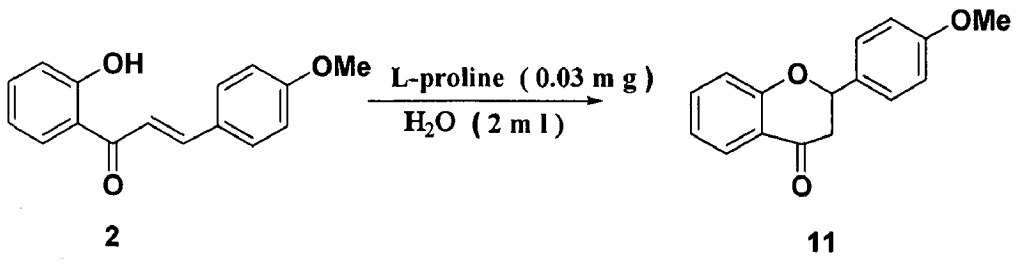
1 10

Scheme14: synthetic route of 10, yield 93%

3.3 CHARACTERIZATION OF FLAVANONE (11).

Following the synthesis procedure reported in experimental section, compound 11 was afforded a single product in excellent yield. The product (11) was characterized for the molecular formula, $C_{16}H_{14}O_3$ melting point 96-97 ^0C. It gave negative alcoholic $FeCl_3$-test and pink color with Mg-conc. HCl.The IR-spectrum displayed diagnostic bands at 1680 cm^{-1} (CO,str.), 1616, 1320, 1226, 769, 696 cm^{-1}(flavanone skeleton) and other absorption frequencies The ^1H-NMR-spectrum gave the three type of double doublet (a) 5.54 (dd, J_1=13.2 Hz, J_2=3.0 Hz, 1*H*). Due to axial – axial interaction of H_c and H_b (b) 3.07 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*). Due to axial – equatorial interaction of H_c and H_a. (c) 2.88(dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*).Due to axial – equatorial interaction of H_a and H_b confirming the presence of one pyrone ring, other aromatic characteristic

peaks are shown in table 5, ^{13}C NMR spectra assigned for 196.2.5, 156.7, 139.2, 125.8, 121.2, 80.1. Which are characteristic of carbon attached to electronegative atoms and here for carbonyl carbon carbon attached to oxygen atom in pyron ring. GC-MS for EIMS fragmentations followed the established pattern, which further confirmed the product 11(Scheme 15). The molecular ion peak ($M^{+\cdot}$) at m/z 259, (19), 147(15), 134(82), 121(52), 71(69), 57(100).etc. shown in the table 7. On the basis of these spectral data, product 11 was characterized as name 2-(4'-methoxyphenyl)-chroman-4-one.



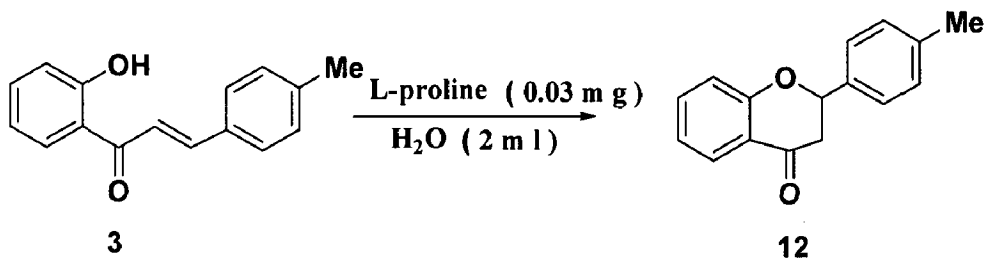
2 11

Scheme 15: Synthetic route of 11, yield 60%

3.4 CHARACTERIZATION OF FLAVANONE (12).

Following the synthesis procedure reported in experimental section, compound 12 was afforded a single product in excellent yield. The product (12) was characterized for the molecular formula, $C_{16}H_{14}O_2$ melting point 84-85 ^0C. It gave negative alcoholic $FeCl_3$-test and pink color with Mg-conc. HCl.The IR-spectrum displayed diagnostic bands at 1675 cm^{-1} (CO str.),1478, 1300, 1150, 895, 762 cm^{-1}(flavanone skeleton) and other absorption frequencies. The 1H-NMR-spectrum gave a three type of double doublet (a) 5.50 (dd, J_1=13.2 Hz, J_2=3.0 Hz, 1*H*). Due to axial – axial interaction of H_c and H_b (b) 3.10 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*). Due to axial – equatorial interaction of H_c and H_a. (c) 2.92(dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*).Due to axial – equatorial interaction of H_a and H_b confirming the presence of one pyrone ring, other aromatic characteristic peaks are shown in table 5, ^{13}C NMR spectra assigned for 192.1, 161.1, 136.6, 124, 121 76.7. which are characteristic of carbon attached to electronegative atoms and here for carbonyl

carbon carbon attached to oxygen atom in pyron ring. GC-MS for EIMS fragmentations followed the established pattern, which further confirmed the the product 12(Scheme 16). The molecular ion peak ($M^{+\cdot}$) at m/z 238, 118(100), 120(25), 147(56).etc. shown in the table 7. On the basis of these spectral data, product 12 was characterized as name 2-(4'-methylphenyl)-chroman-4-one.



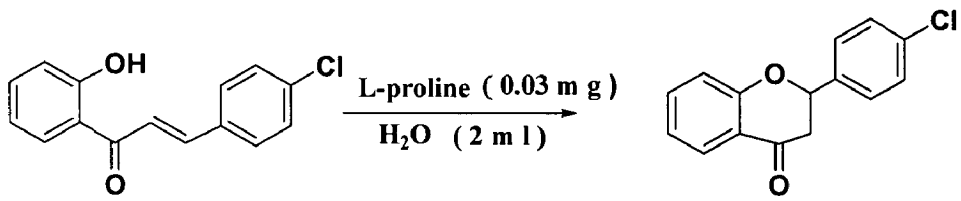
3 12

Scheme 16: Synthetic route of 12, yield 85%

3.5 CHARACTERIZATION OF FLAVANONE (13).

Following the synthesis procedure reported in experimental section, compound 13 was afforded a single product in excellent yield. The product (13) was characterized for the molecular formula, $C_{15}H_{11}O_2Cl$ melting point 86-87 ^{0}C .It gave negative alcoholic $FeCl_3$-test and pink color with Mg-conc. HCl.The IR-spectrum displayed diagnostic bands at 1687 cm-^{1} (C=O str.), 1602, 1476, 1320, , 1225, 964, 786 cm^{-1}(flavanone skeleton) and other absorption frequencies. The ^{1}H-NMR-spectrum gave a three type of double doublet (a) 5.47 (dd, J_1=13.2 Hz, J_2=3.0 Hz, 1*H*). Due to axial – axial interaction of H_c and H_b (b) 3.04 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*). Due to axial – equatorial interaction of H_c and H_a. (c) 2.88(dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*).Due to axial – equatorial interaction of H_a and H_b confirming the presence of one pyrone ring, other aromatic characteristic peaks are shown in table 5, ^{13}C NMR spectra assigned for 196.18, 161 which are characteristic of carbon attached to electronegative atoms and here for carbonyl carbon carbon attached to oxygen atom in pyron ring. GC-MS for EIMS fragmentations followed the established pattern, which further confirmed the the product

13(Scheme 17). The molecular ion peak ($M^{+\cdot}$) at m/z 256(16), 237(22), 147(490, 120(900, 97(48), 85(69), 57(100). etc. These compoundcomtain two molecular ion peaks (M and M+2) in 1:3 intensity ratio, which is characteristic of the presence of chlorine atom in molecule. shown in the table 7. On the basis of these spectral data, product 13 was characterized as name 2-(4'-chlorophenyl)-chroman-4-one.



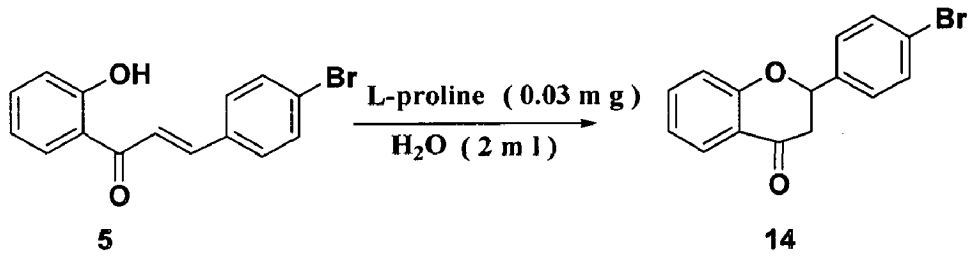
4 13

Scheme 17: Synthetic route of 13, yield 87%

3.6 CHARACTERIZATION OF FLAVANONE (14).

Following the synthesis procedure reported in experimental section, compound 14 was afforded a single product in excellent yield. The product (14) was characterized for the molecular formulas C15H11O2Br melting point 86-87 ^{0}C. It gave negative alcoholic $FeCl_3$-test and pink color with Mg-conc. HCl. The IR-spectrum displayed diagnostic bands at 1687 cm-^{1} (CO str.), 1476, 1320, 1300, 1225, 964, 825 cm-1(flavanone skeleton) and other absorption frequencies. The 1H-NMR-spectrum gave a three type of double doublet (a) 5.50 (dd, J_1=13.2 Hz, J_2=3.0 Hz, 1*H*). Due to axial – axial interaction of H_c and H_b (b) 3.09 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*). Due to axial – equatorial interaction of H_c and H_a. (c) 2.93(dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*).Due to axial – equatorial interaction of H_a and H_b confirming the presence of one pyrone ring, other aromatic characteristic peaks are shown in table 5, ^{13}C NMR spectra assigned for 191.4, 161.3, 127.8, 120, 78.6. which are characteristic of carbon attached to electronegative atoms and here for carbonyl carbon carbon attached to oxygen atom in pyron ring. GC-

MS for EIMS fragmentations followed the established pattern, which further confirmed the the product 14(Scheme 18). The molecular ion peak ($M^{+\cdot}$) at m/z. 303, 301(13), 184(28), 120(920, 103(224), 92(44), 77(31), 57(100).etc. This compound contains two molecular ion peaks (M and M+2) in almost equal intensity indicating the presence of bromine atom shown in the table 7. On the basis of these spectral data, product 14 was characterized as name 2-(4'-bromophenyl)-chroman-4-one.



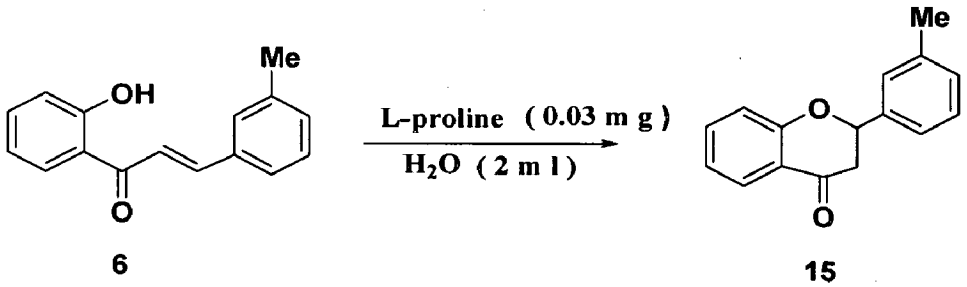
5 14

Scheme 18: Synthetic route of 14, yield 86-87%

3.7 CHARACTERIZATION OF FLAVANONE (15).

Following the synthesis procedure reported in experimental section, compound 15 was afforded a single product in excellent yield. The product (15) was characterized for the molecular formula $C_{16}H_{14}O_2$ melting point 80-82 ^{0}C. It gave negative alcoholic $FeCl_3$-test and pink color with Mg-conc. HClThe IR-spectrum displayed diagnostic bands at 1670 cm-^{1} (C=O str.), 1320, 1300, 1225, 964, 951 cm-1(flavanone skeleton) and other absorption frequencies. The ^{1}H-NMR-spectrum gave give a three type of double doublet (a) 5.53 (dd,J_1=13.2 Hz, J_2=3.0 Hz, 1*H*). Due to axial – axial interaction of H_c and H_b (b) 3.12 (dd, J_1=16.9 Hz, J_2=13.2 Hz, 1*H*). Due to axial – equatorial interaction of H_c and H_a. (c) 2.98(dd, J_1=16.9 Hz, J_2= 3.0 Hz, 1*H*).Due to axial – equatorial interaction of H_a and H_b confirming the presence of one pyrone ring, other aromatic characteristic peaks are shown in table 5, ^{13}C NMR spectra assigned for 192.2, 16.16, 129.2, 126.2, 121.5. Which

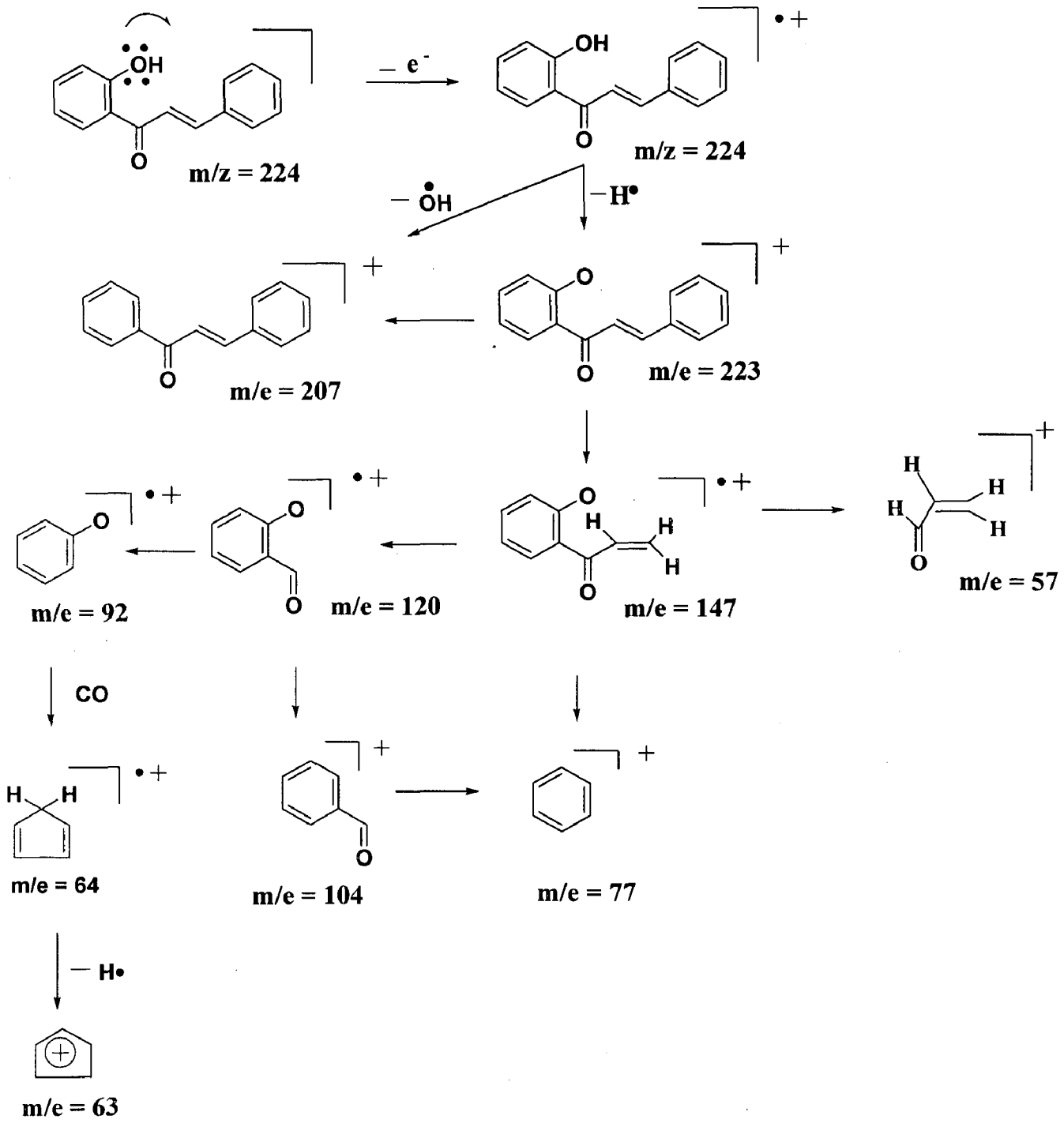
are characteristic of carbon attached to electronegative atoms and here for carbonyl carbon carbon attached to oxygen atom in pyron ring. GC-MS for EIMS fragmentations followed the established pattern, which further confirmed the the product 15(Scheme 19). The molecular ion peak ($M^{+\cdot}$) at m/z 238, 237(32), 224(46), 147(54), 115(46), 118(100), 65(590.etc. shown in the table 7. On the basis of these spectral data, product 15 was characterized as name 2-(3'-methylphenyl)-chroman-4-one.



6 15

Scheme 19: Synthetic route of 15, yield 56%

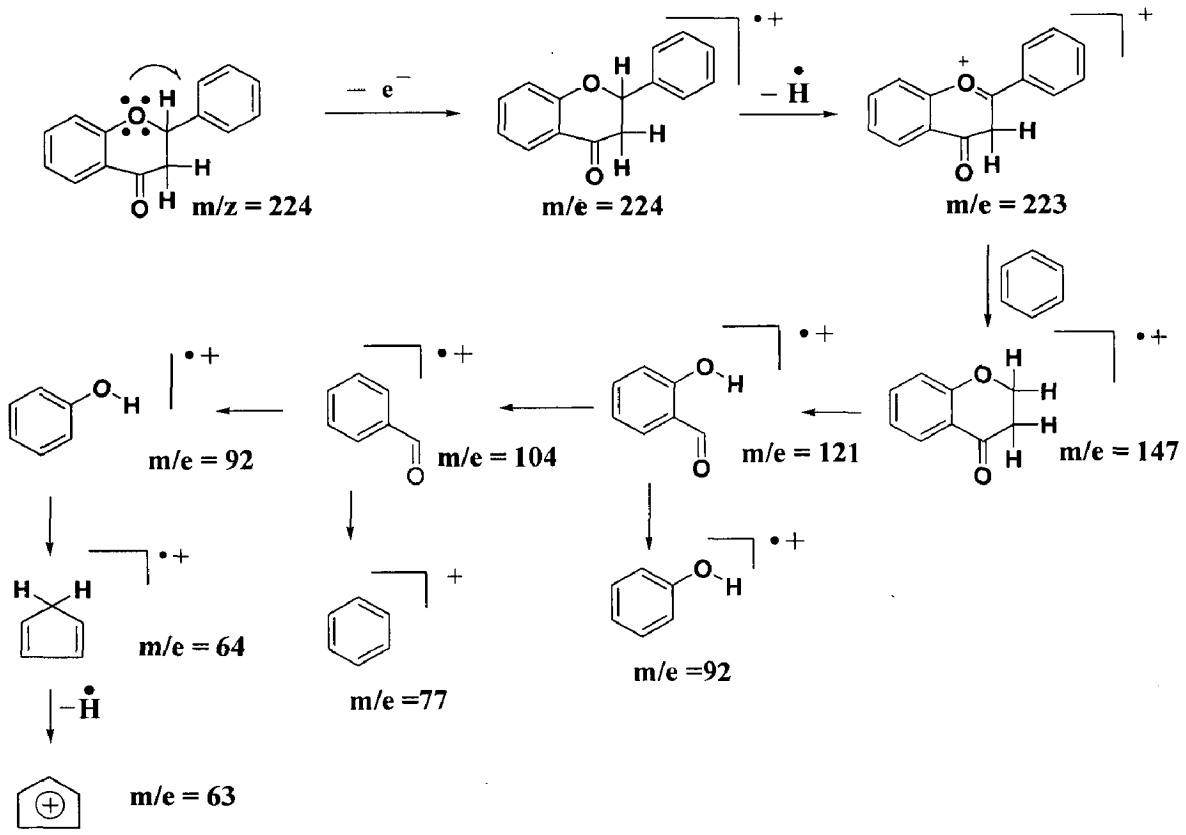
3.8 PROPOSED GC-MS FRAGMENTATION OF CHALCONES PRODUCT 1 TO 9:



Scheme 20

3.9 PROPOSED GC-MS FRAGEMENTATION OF FLAVANONE 10 TO 15

Scheme 20 show the fragmentation of product 1to 9 and(table 6) Scheme 21 shows that of 10, to 15, common fragmentation pattern which have m/z values according to the substituent present. Their different fragments are shown in table 7:

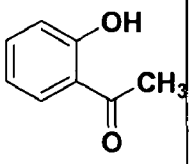
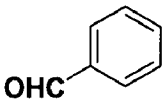
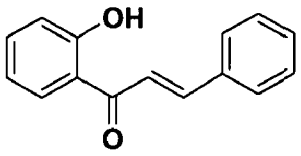
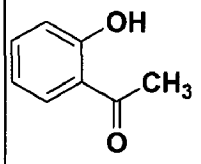
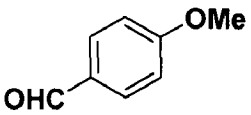
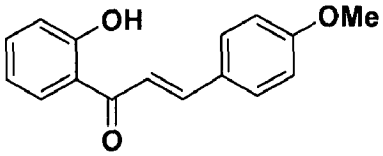
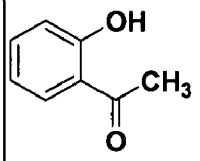
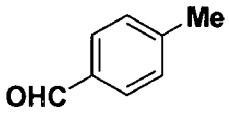
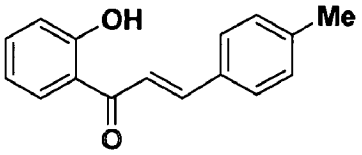
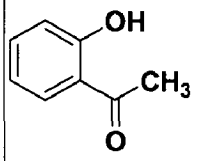
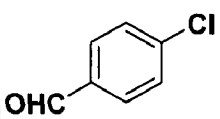
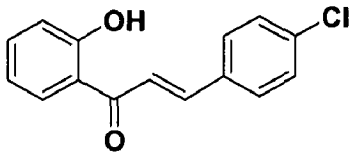
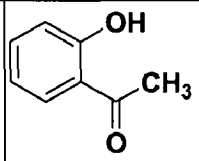
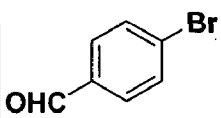
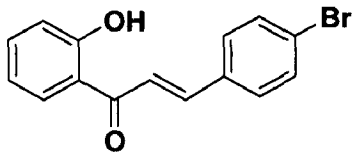
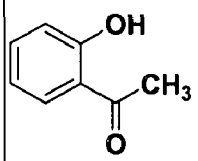
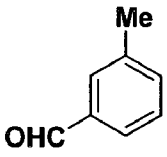
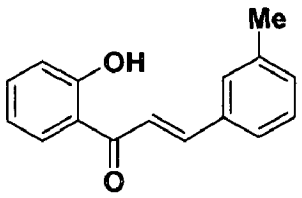


Scheme 21

References

1. Nielsen S F, Chem M, Thender T G, Kharazmi. Bioorg. Med. Chem, 1995, 5,449
2. Miranda C L. Aponso G L M.Stevens M L Bucker Bioorg. Med. Chem, 2001, 2 460

Table2: Condensation of 2'-hydroxyacetophenone with different aldehydes

S. NO	2'-hydroxy acetophenone	Aldehyde	Reaction time (hrs)	Product	Yield (%)
1.			24		85
2.			26		80
3.			4		90
4.			6		85
5.			6		84
6.			8		60

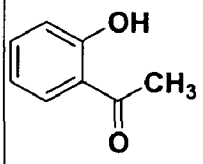
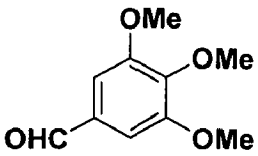
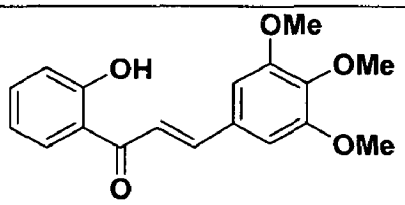
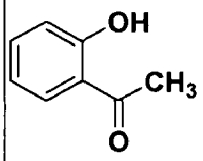
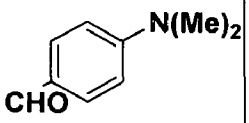
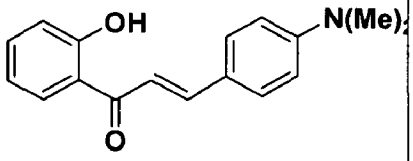
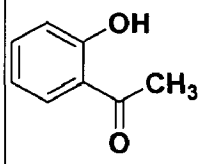
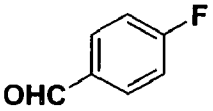
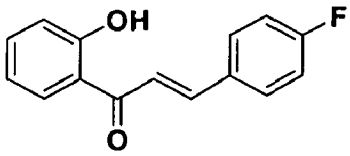
7.			36		75
8.			18		80
9.			10		70

Table3: Cyclization of 2'- hydroxychalcone into Flavanones

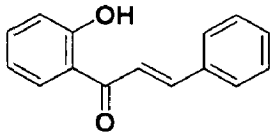
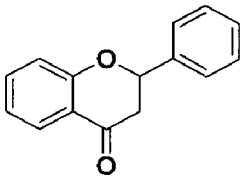
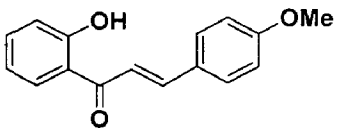
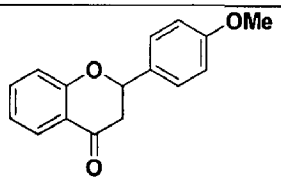
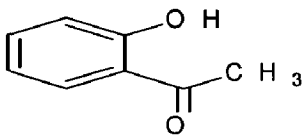
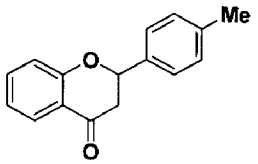
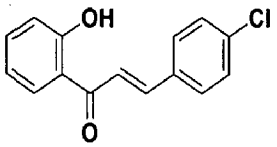
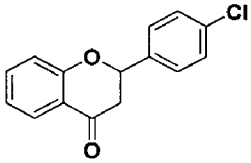
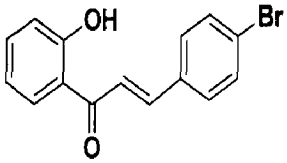
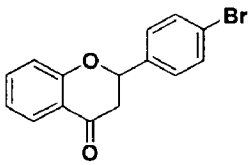
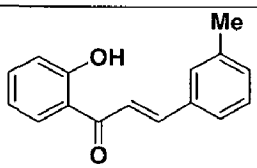
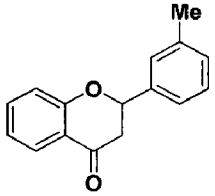
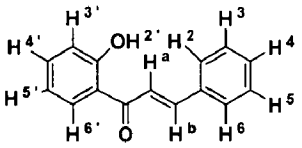
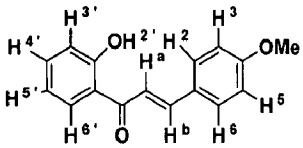
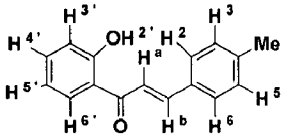
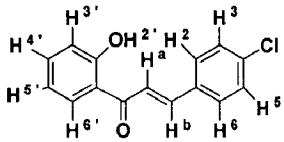
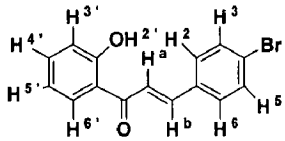
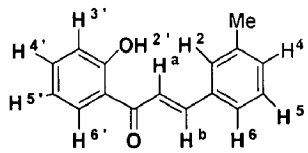
S.No	2'-hydroxy Chalcone	Temperature (°C)	Reaction time(hrs)	Product	Yield (%)
11.		90 - 95	36		93
12.		120-125	48		60
13.		120	36		85
14.		140	18		87
15.		140	18		87
16.		120	36		56

Table4: Selected chemical shift (in ppm) from 1H NMR (500MHZ) spectra of product 1-9

S.No	Compound	$H^{2'}$	$H^{3'}$	$H^{4'}$, $H^{5'}$,	$H^{6'}$	H^{a}	H^{b}	Me, OMe, N-Me
1		12.82	7.87	7.20-7.26	_	6.94	7.93	_
2		12.94	7.88	7.63-7.65	7.02-7.09	6.97	7.93	3.88
3		12.91	7.90	7.50-7.54	7.20	6.96	7.96	2.43
4		12.80	7.87	7,50-7.56	6.9-7.3	6.94	7.93	
5		12.90	7.92	7.50-7.56	7.00-7.09	6.98	7.95	-
6		12.90	7.75	7.15	6.57			3.80

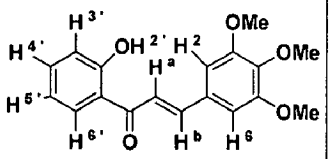
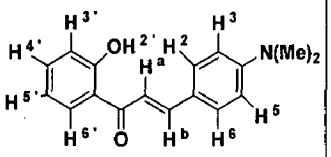
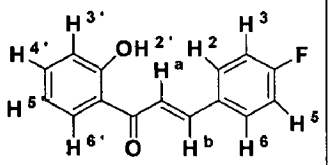
7		12.85	7.84	7.55-7.58	7.07	6.99	7.96	3.96
8		12.90	7.92	6.92-6.98	7.52-7.68	6.92	7.97	3.29
9		12.77	7.87	7.5-7.56	6.94-7.0	6.90	7.92	

Table5: Selected chemical shifts (in ppm) from 1H NMR (500MHZ) spectra of products 10-15

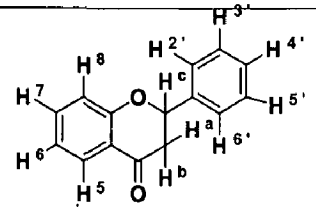
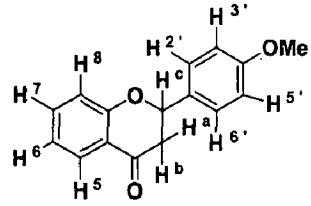
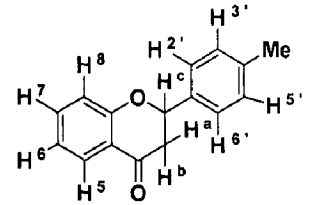
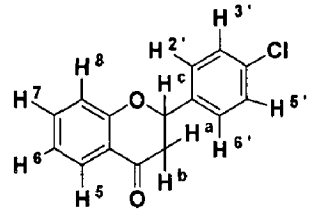
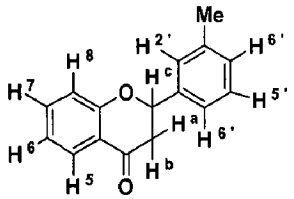
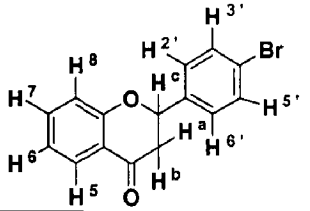
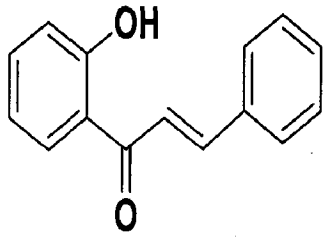
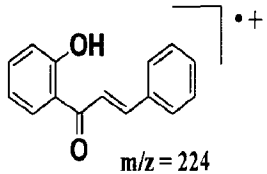
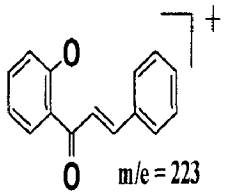
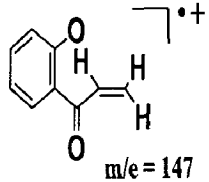
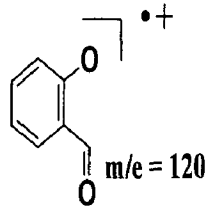
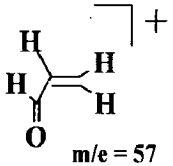
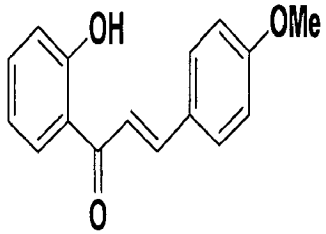
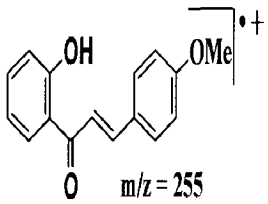
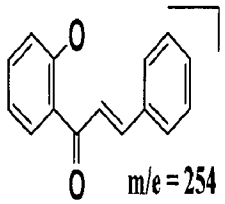
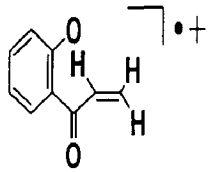
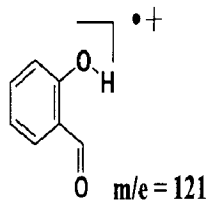
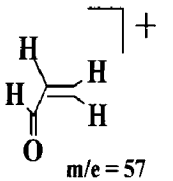
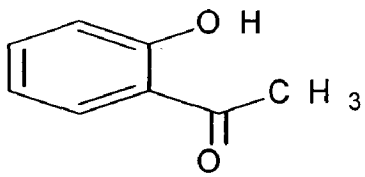
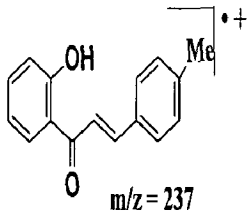
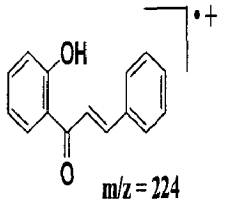
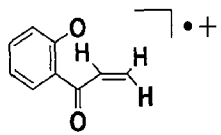
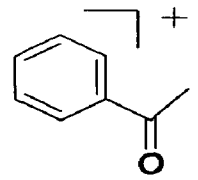
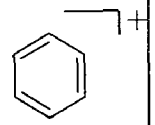
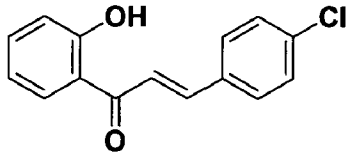
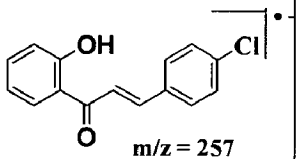
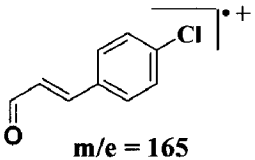
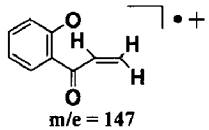
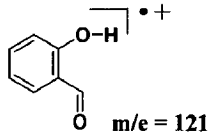
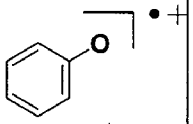
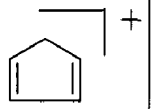
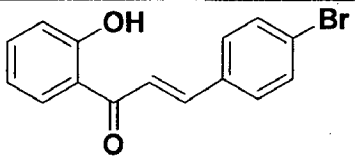
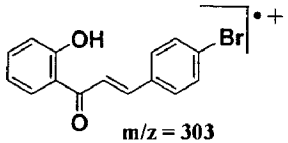
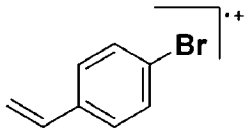
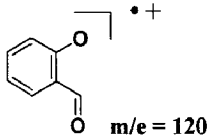
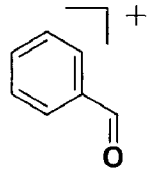
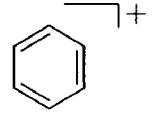
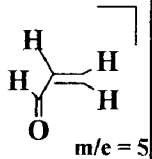
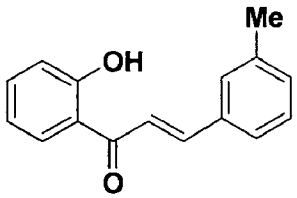
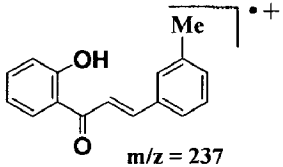
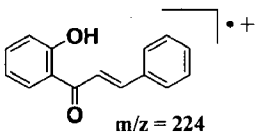
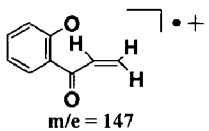
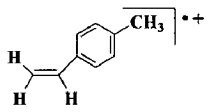
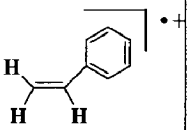
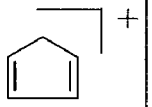
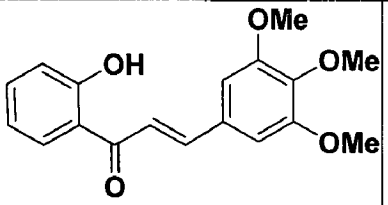
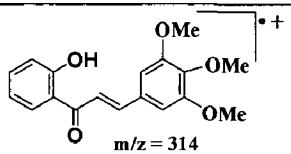
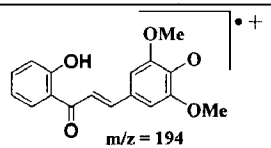
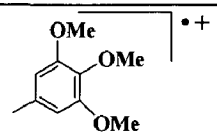
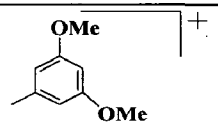
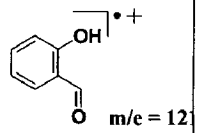
S.No	Compound	H^c	H^a	H^b	H^5	H^6, H^7	H^8	Me, OMe, N-Me
10		3.12	2.95	5.55	–	7.08-7.11	7.94	–
11		3.07	2.88	5.44	7.55-7.60	7.04-7.15	7.94	3.88
12		3.10	2.92	5.50	7.53-7.58	7.06-7.10	7.96	2.41
13		3.04	2.88	5.47	7.49-7.55	7.03-7.10	7.93	
14		3.09	2.93	5.50	7.55-7.60	7.04-7.12	7.97	
15		3.08	2.98	5.53	7.50-7.52	7.10-7.16	7.95	2.53

Table6: Selected fragments from GC-MS spectra of compounds 1-9

S. No	Product	A	B	C	D	E	G
1.		 m/z = 224	 m/e = 223	 m/e = 147	 m/e = 120	 m/e = 57	-
2.	 zzz	 m/z = 255	 m/e = 254	 m/e = 147	 m/e = 121	 m/e = 57	 m/e = 65
3.		 m/z = 237	 m/z = 224	 m/e = 147	 m/e = 115	-	 m/e = 77

4.		 m/z = 257	 m/e = 165	 m/e = 147	 m/e = 121	 m/e = 92	 m/e = 65
5.		 m/z = 303	 m/e = 184	 m/e = 120	 m/e = 103	 m/e = 77	 m/e = 5
6.		 m/z = 237	 m/z = 224	 m/e = 147	 m/e = 118	 m/e = 103	 m/e = 65
7.		 m/z = 314	 m/z = 194	 m/z = 181	 m/z = 151	 m/e = 121	

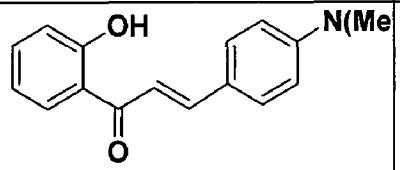
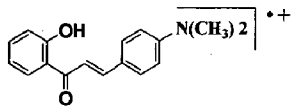
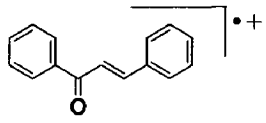
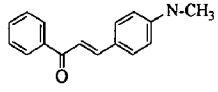
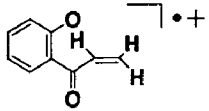
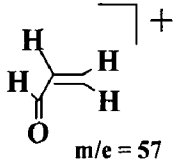
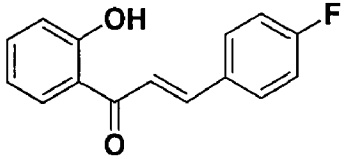
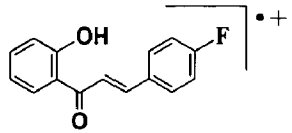
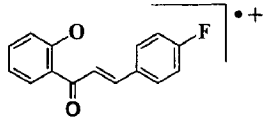
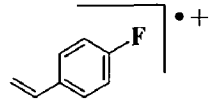
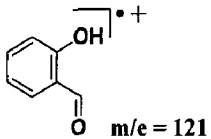
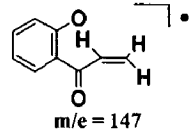
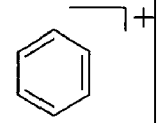
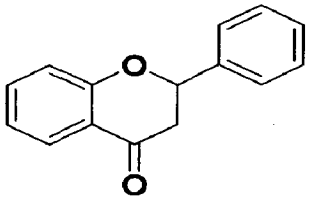
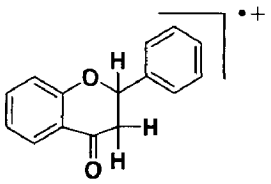
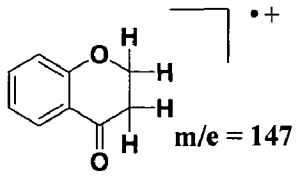
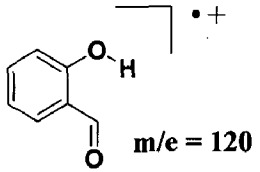
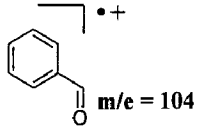
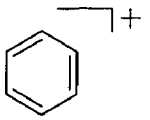
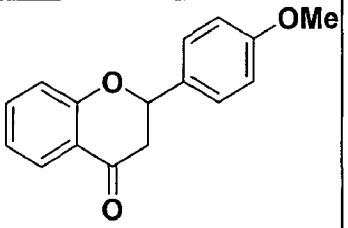
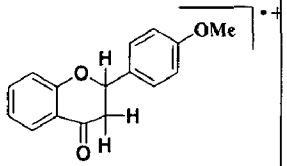
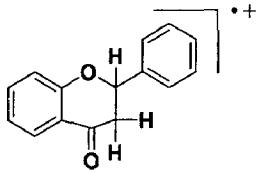
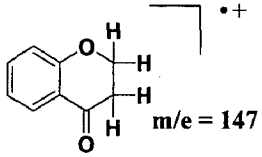
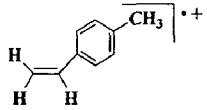
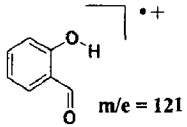
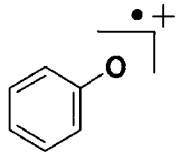
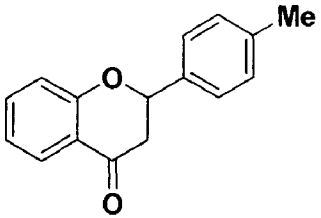
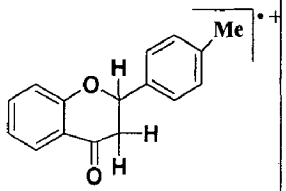
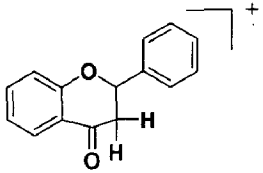
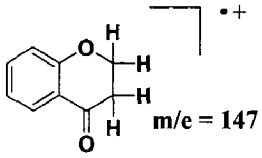
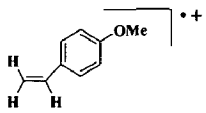
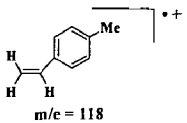
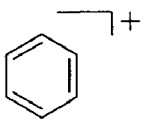
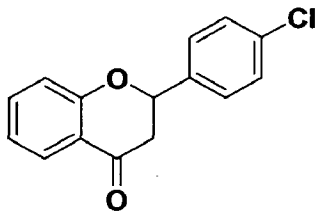
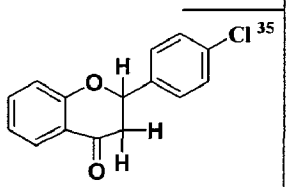
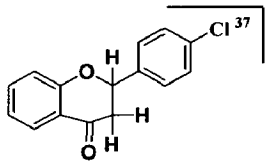
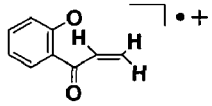
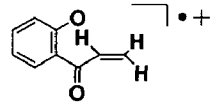
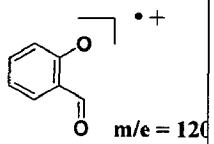
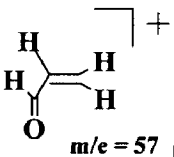
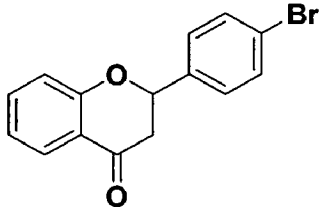
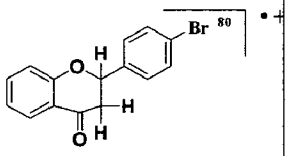
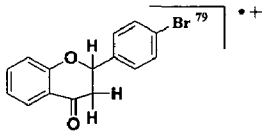
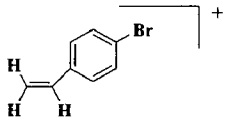
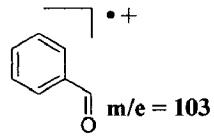
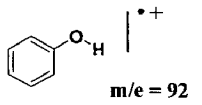
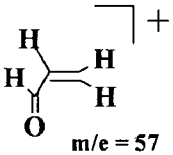
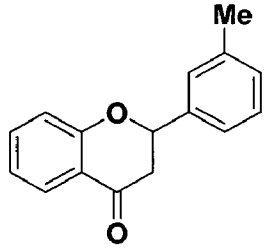
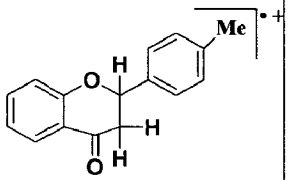
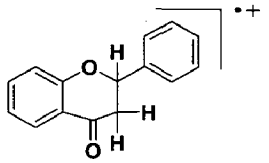
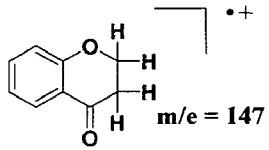
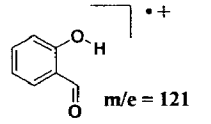
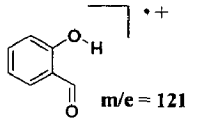
	Product	A	B	C	D	E	G
8.		 m/z = 267	 m/z = 207	 m/z = 191	 m/e = 147	 m/e = 57	-
9.		 m/z = 244	 m/e = 243	 m/e = 122	 m/e = 121	 m/e = 147	 m/e = 77

Table7: Selected fragments from GC-MS spectra of compounds 10-15

10.		 **m/e = 224**	 **m/e = 147**	 **m/e = 120**	 **m/e = 104**	-	 **m/e = 77**
11.		 **m/e = 255**	 **m/e = 224**	 **m/e = 147**	 **m/e = 118**	 **m/e = 121**	 **m/e = 92**
12.		 **m/e = 239**	 **m/e = 223**	 **m/e = 147**	 **m/e = 134**	 **m/e = 118**	 **m/e = 77**

13.		 m/e = 256	 m/e = 258	 m/e = 147	 m/e = 147	 m/e = 120	 m/e = 57
14.		 m/e = 303	 m/e = 301	 m/e = 184	 m/e = 103	 m/e = 92	 m/e = 57
15.		 m/e = 239	 m/e = 224	 m/e = 147	 m/e = 121	 m/e = 121	

Chapter 4

CONCLUSSION

We have demonstrated L-proline as a novel organocatalyst for Clasien-Schmidt type condensation of 2'-hydroxychalcone and its derivatives in water at different temperature to obtain flavanones (2-phenyl-chroman-4-one) that are potential building blocks for synthesis of natural products. The catalyst used is cheap, easily available and environmentally benign for the reaction to furnish the products in moderate to higher yields. All the compounds were fully characterized by analytical tool and by comparison of the known data for the available compounds.

SUPPORTING INFORMATION

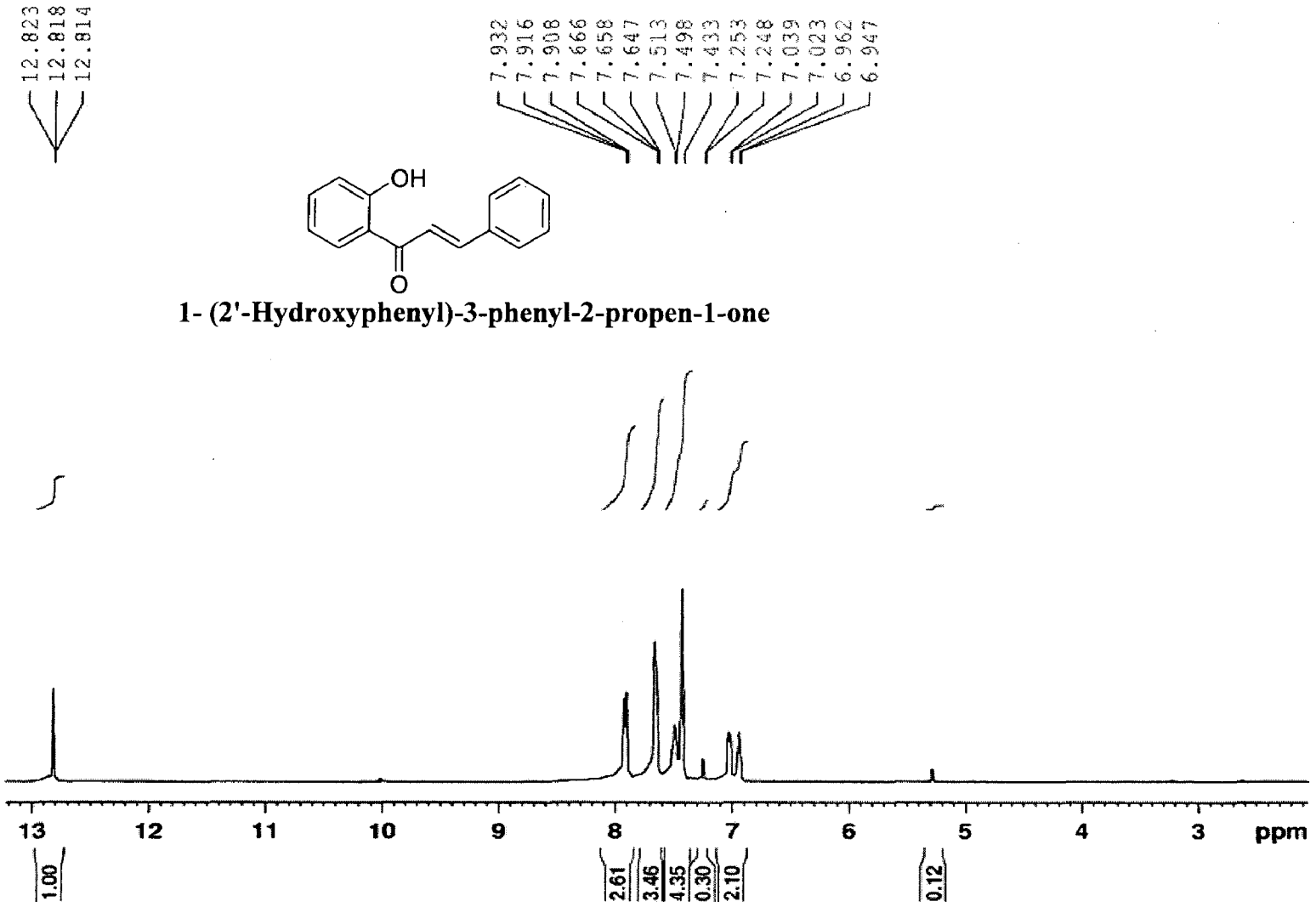
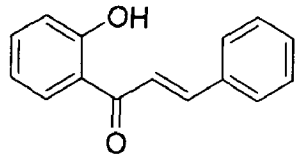


Figure S1. ^{1}H NMR spectra of 1-(2'-Hydroxyphenyl)-3-phenyl -2-propen-1-one



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

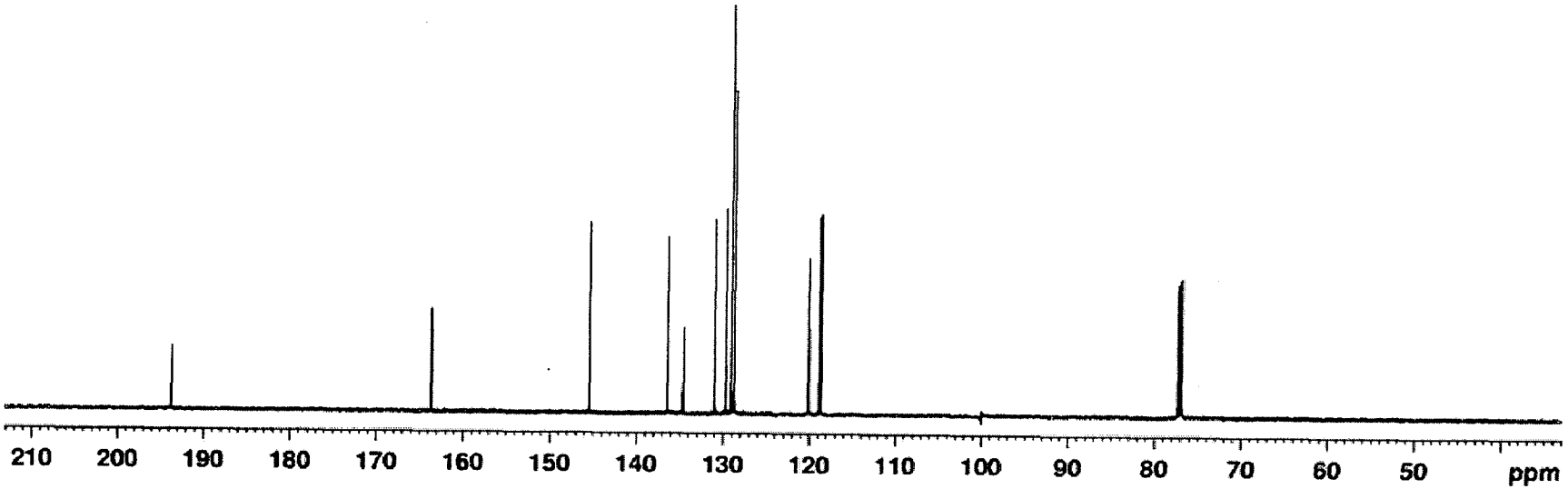


Figure S2. ^{13}C NMR spectra of 1-(2'-Hydroxyphenyl)-3-phenyl -2-propen-1-one

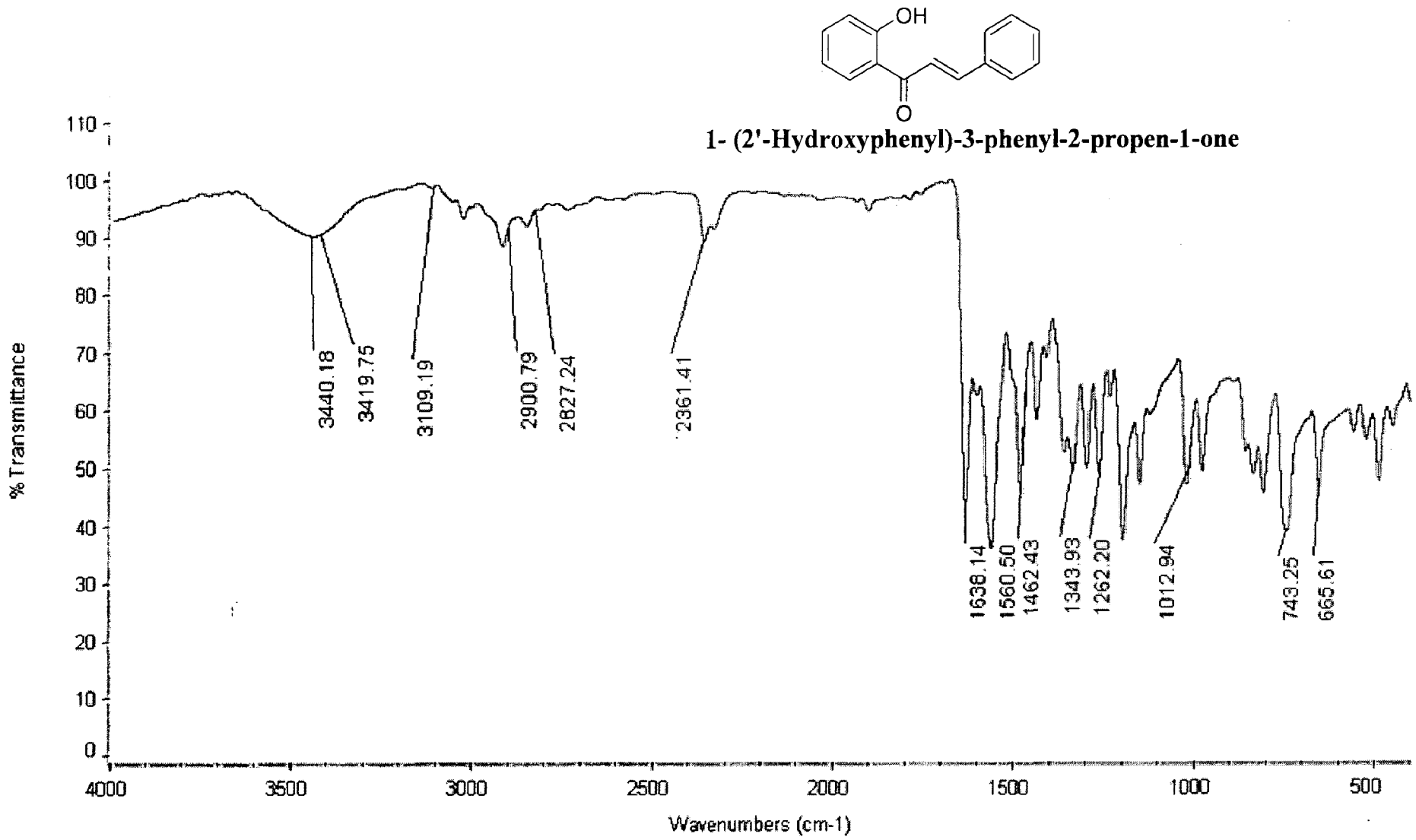


Figure S3.. Infrared spectra of 1-(2'-Hydroxyphenyl)-3-phenyl -2-propen-1-one

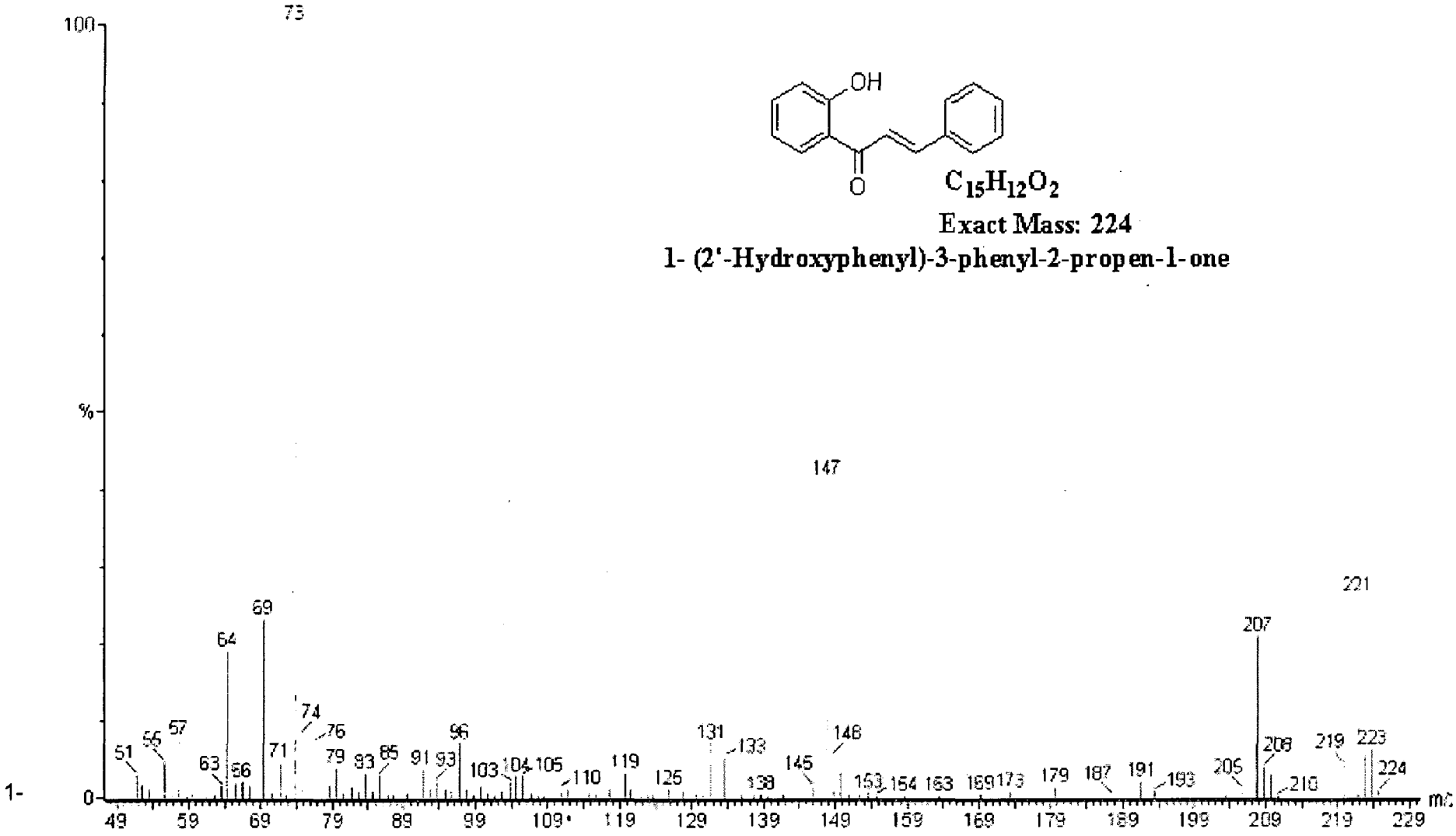
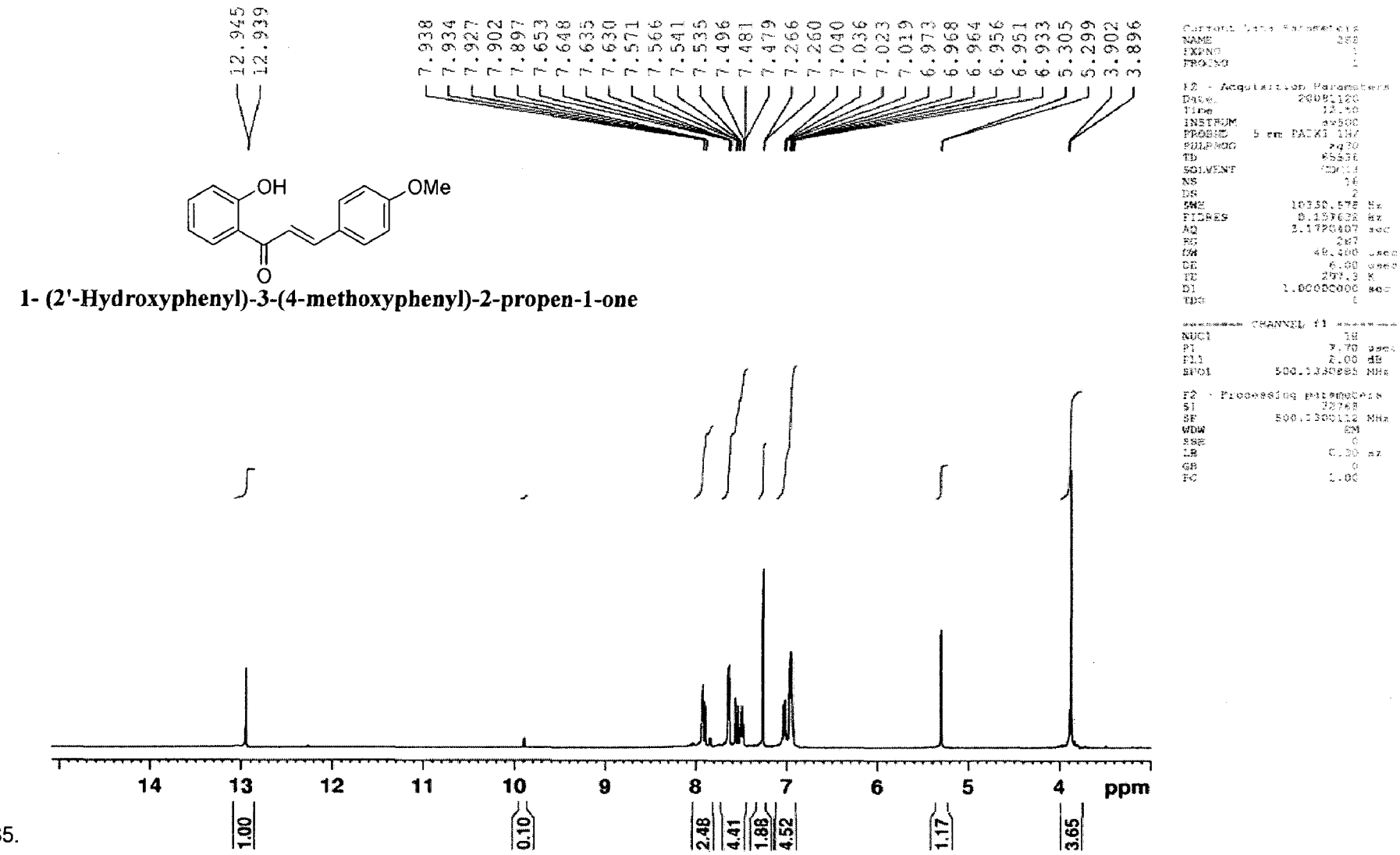


Figure S4. GCMS spectra of (2'-Hydroxyphenyl)-3-phenyl -2-propen-1-one



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

Figure S5. ^{1}H NMR 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one

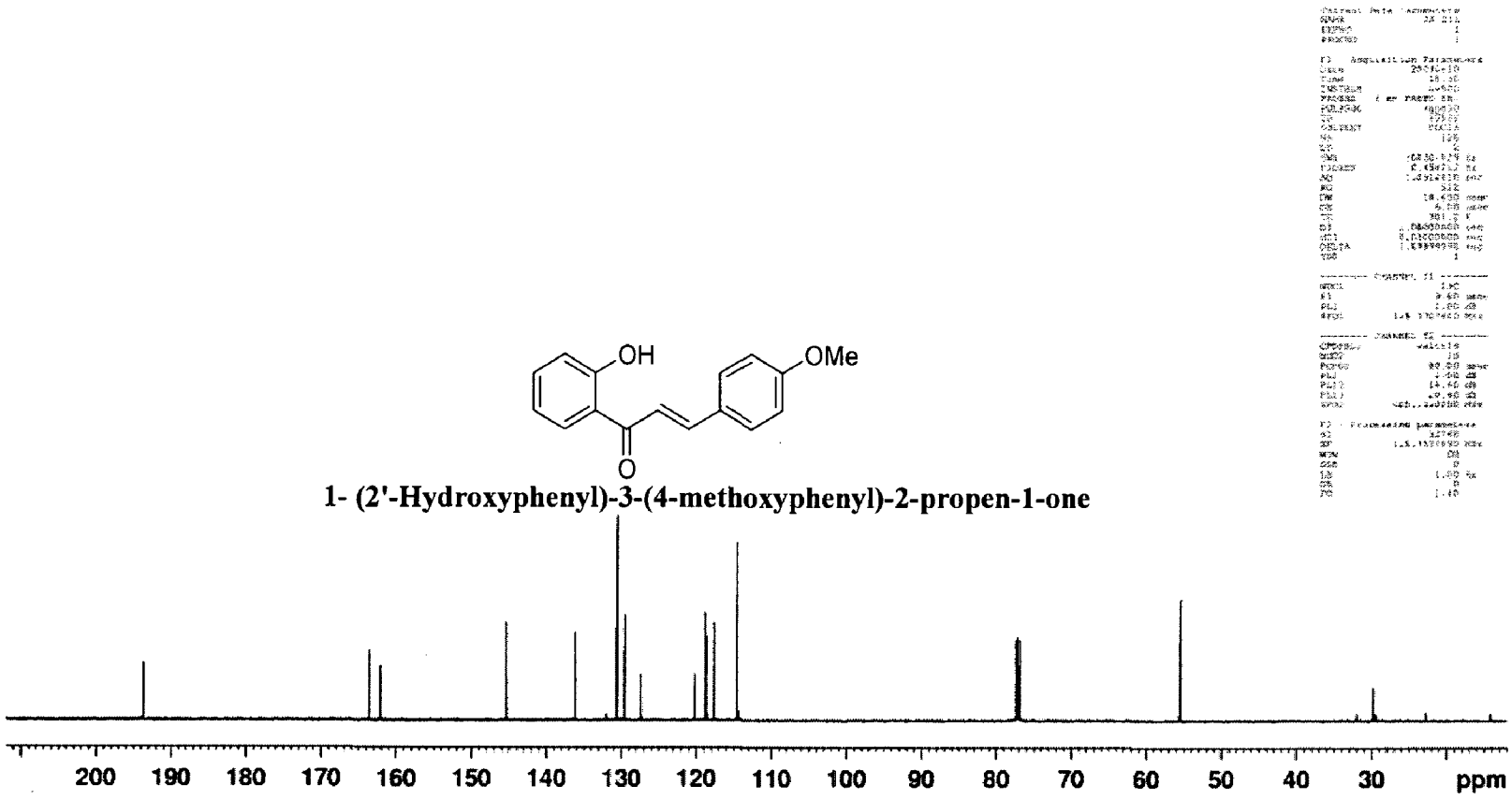


Figure S6. ^{13}C NMR 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one

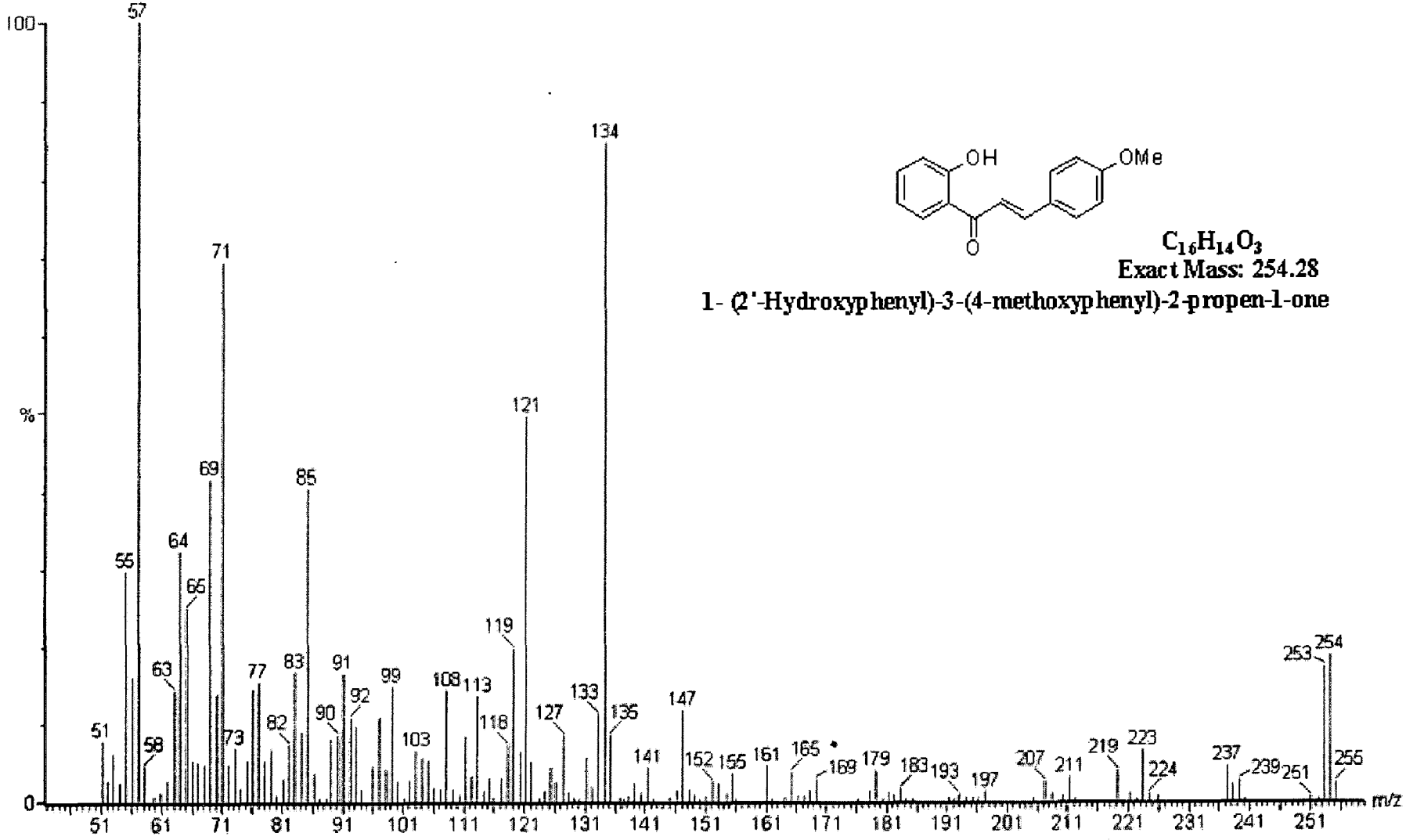


Figure S7. GC-MS spectra of 1-(2'-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one

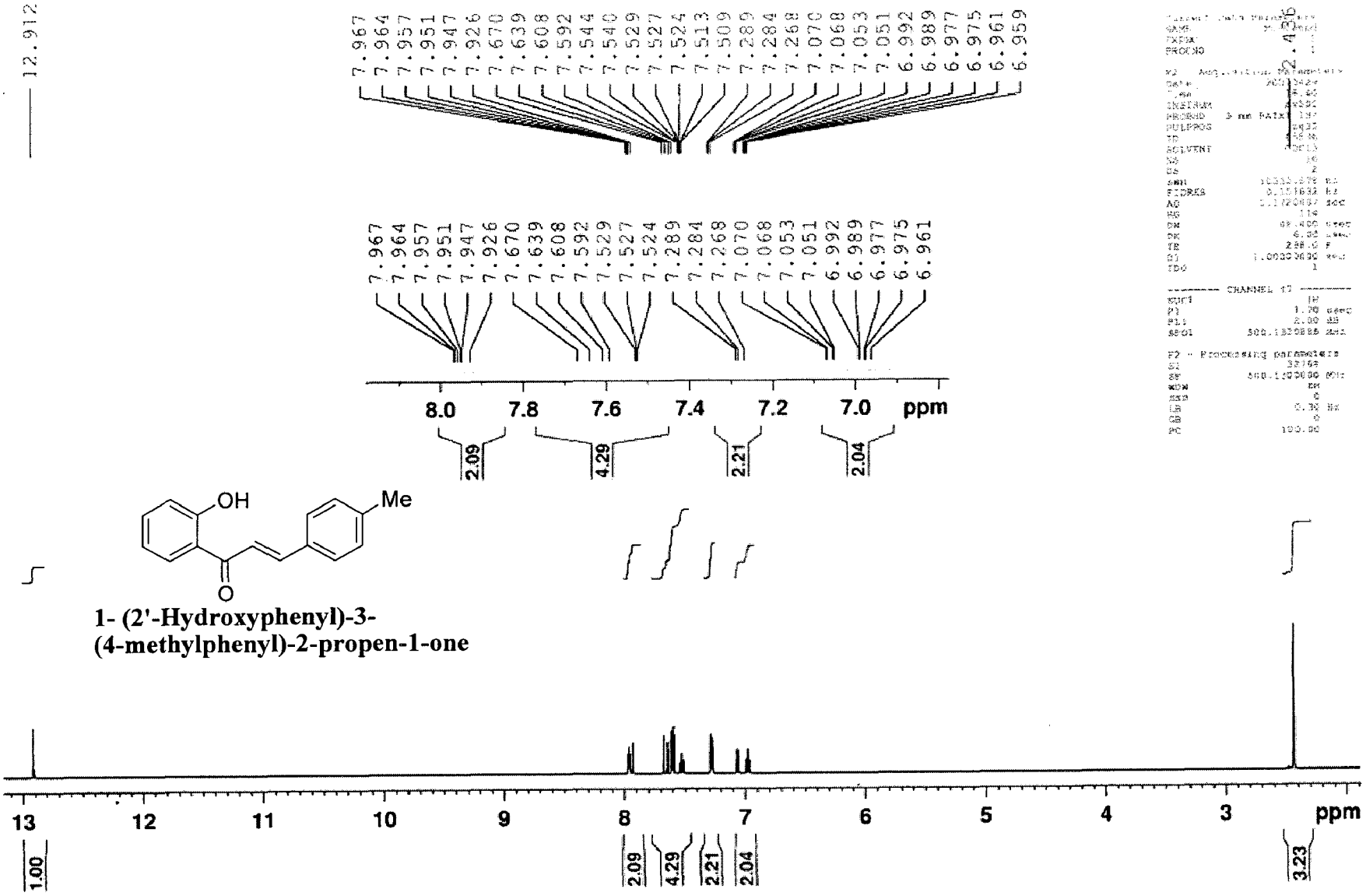


Figure S8. ^{1}H NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one

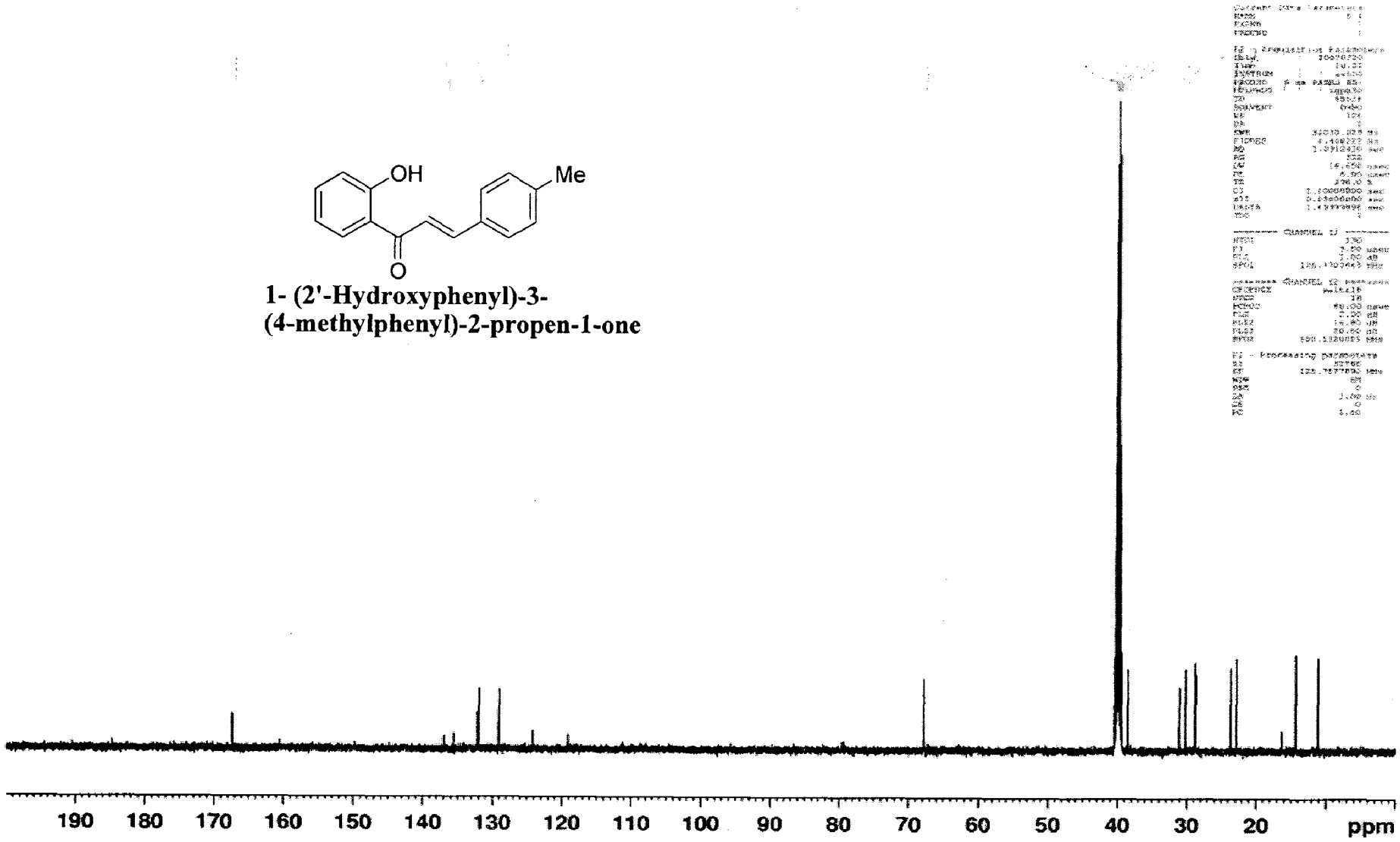


Figure S9. ^{13}C NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one

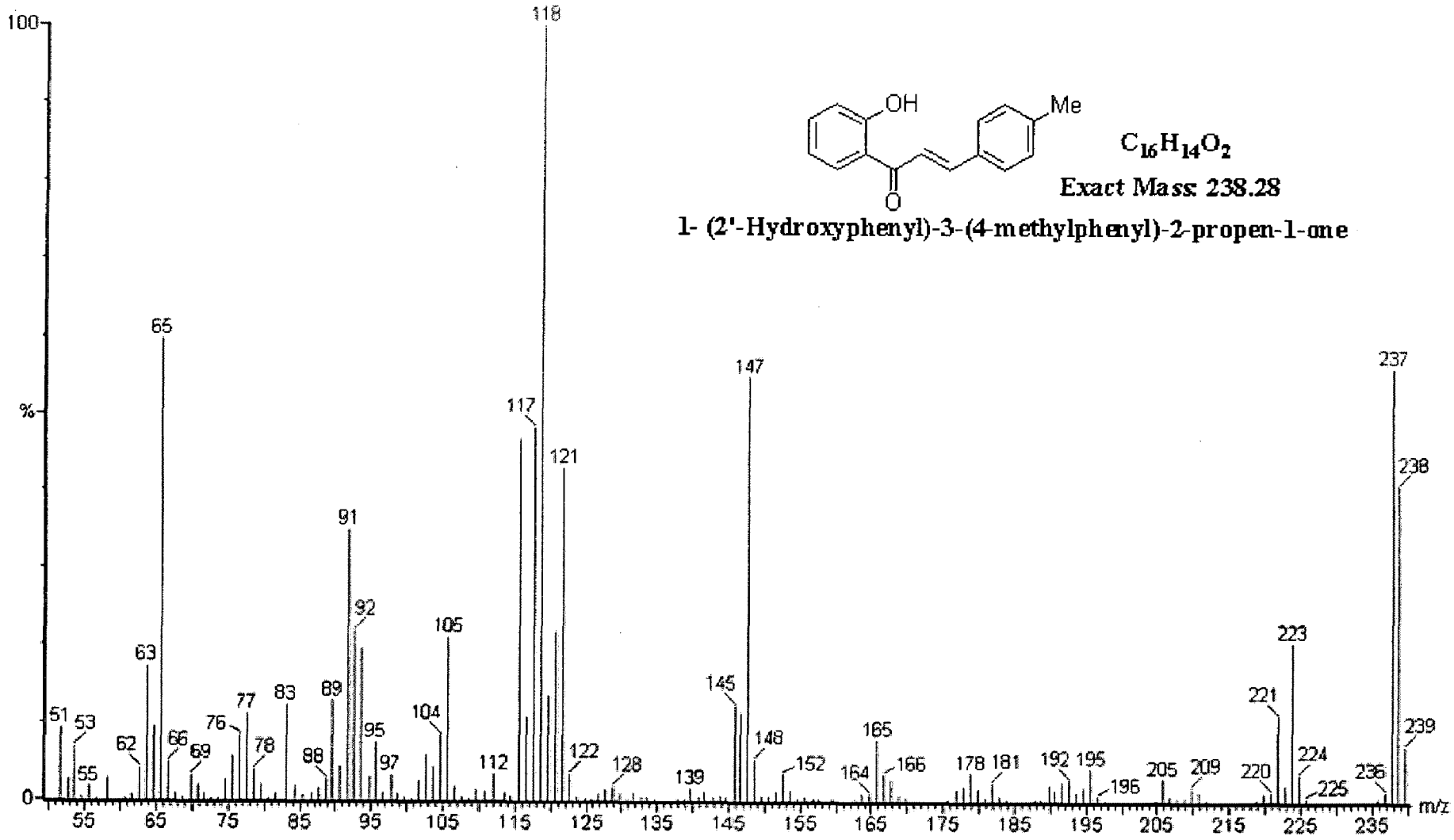


Figure S10. GC-MS spectra of 1-(2'-Hydroxyphenyl)-3-(4-methylphenyl)-2-propen-1-one

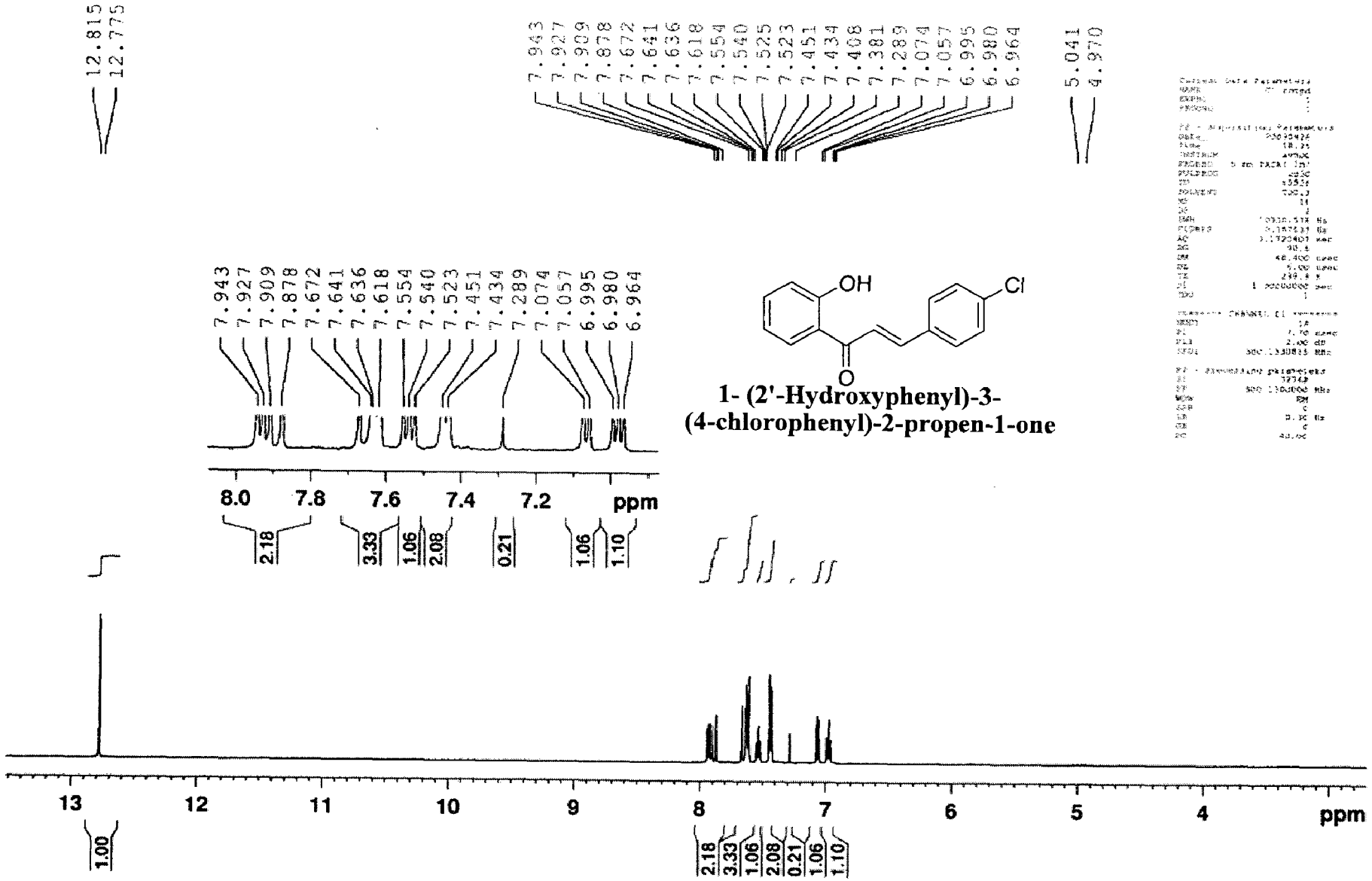


Figure S11. 1H NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one

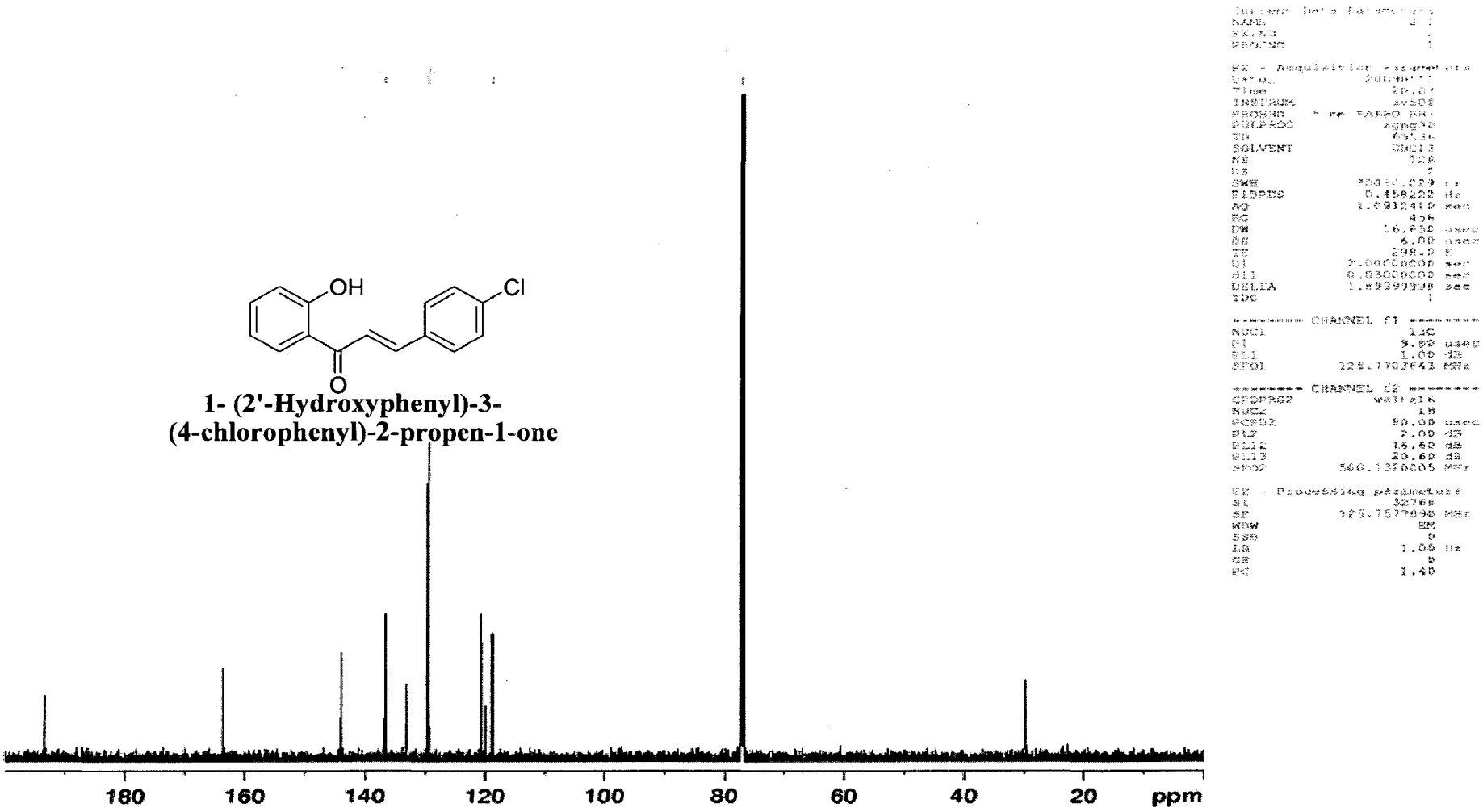


Figure S12. ^{13}C NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one

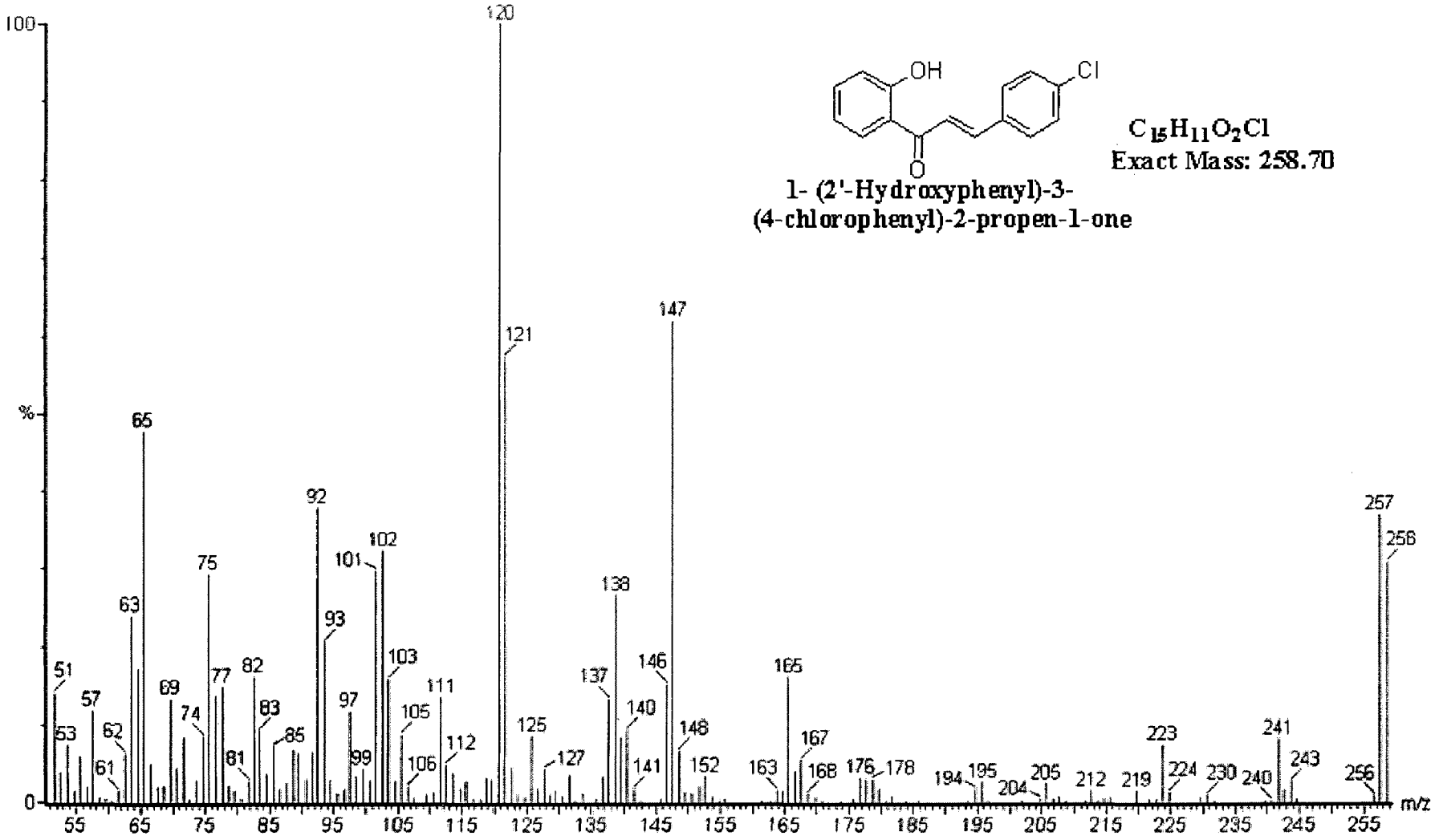


Figure S13. GCMS spectra of 1-(2'Hydroxyphenyl)-3-(4-chlorophenyl)-2-propen-1-one

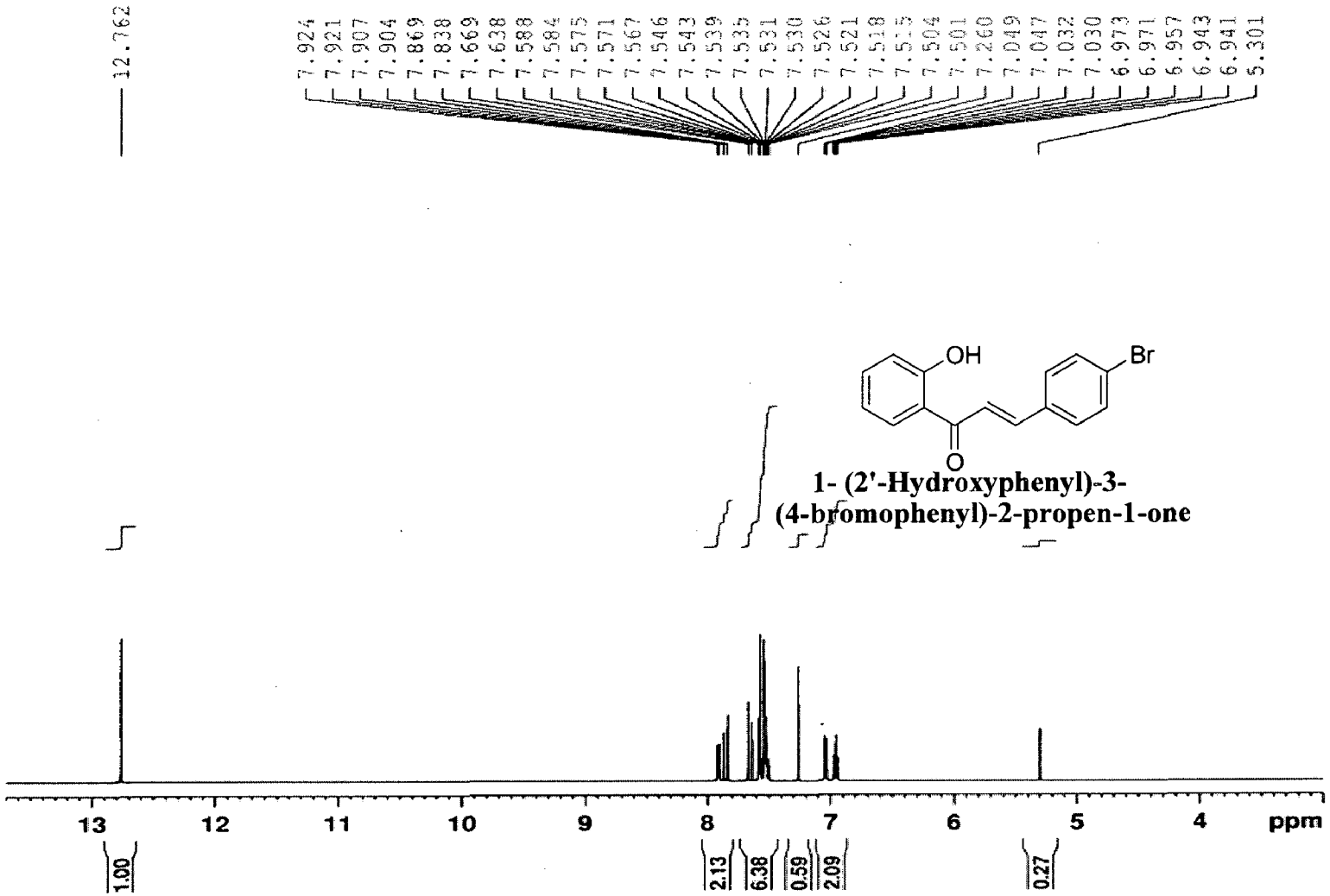


Figure S14. ^{1}H NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one

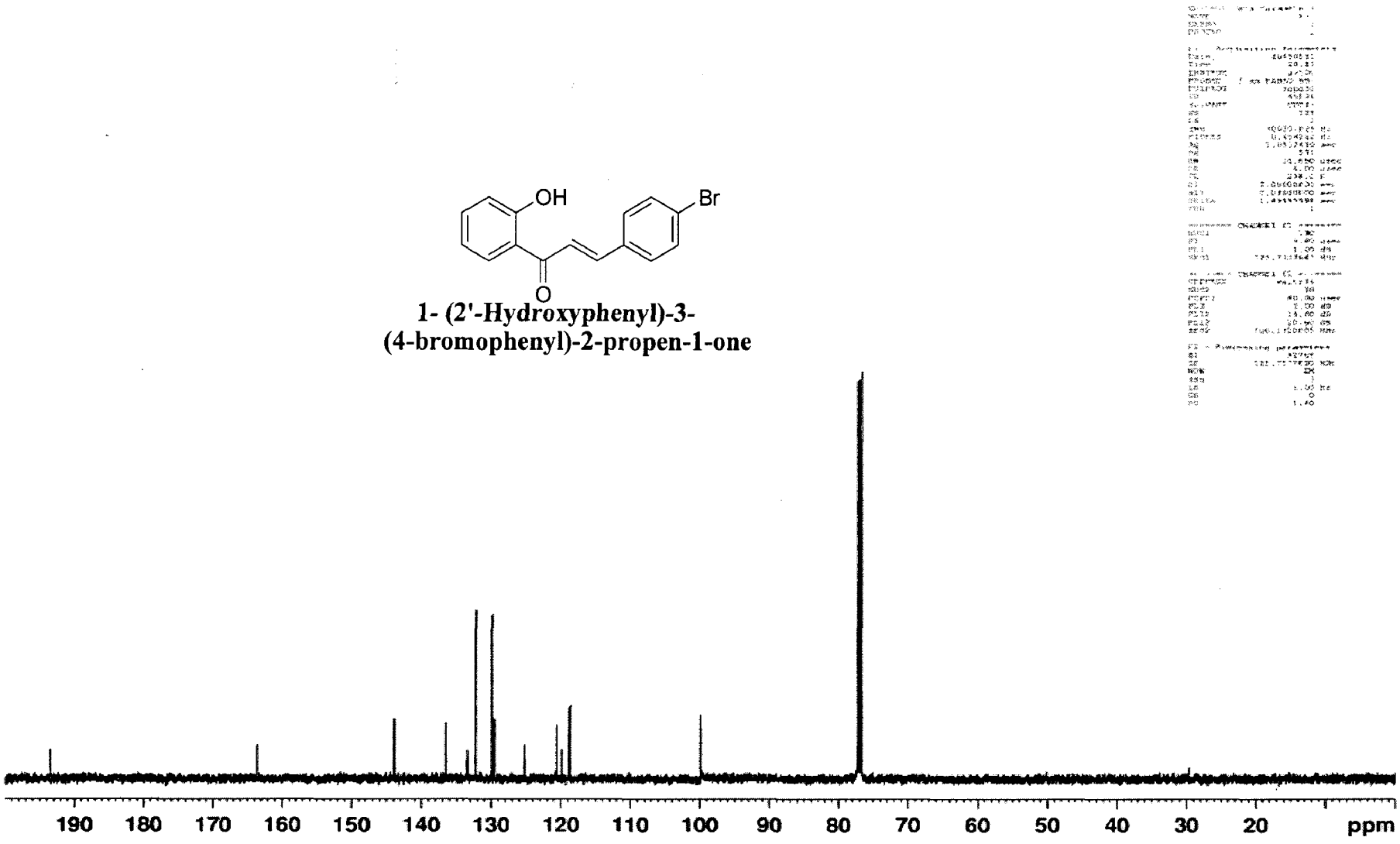


Figure S15. ^{13}C NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one

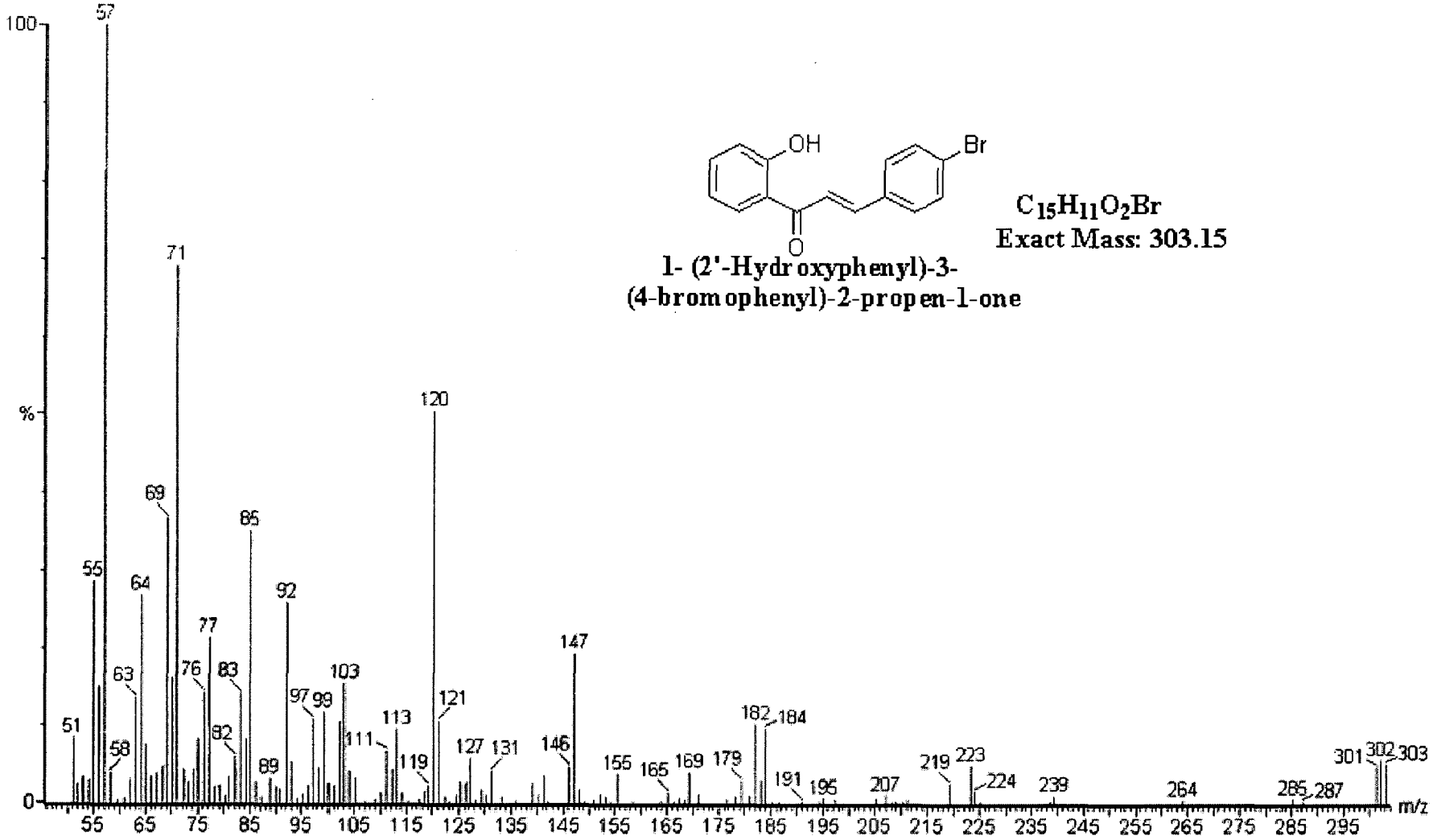


Figure S16. GCMS spectra of 1-(2'-Hydroxyphenyl)-3-(4-bromophenyl)-2-propen-1-one

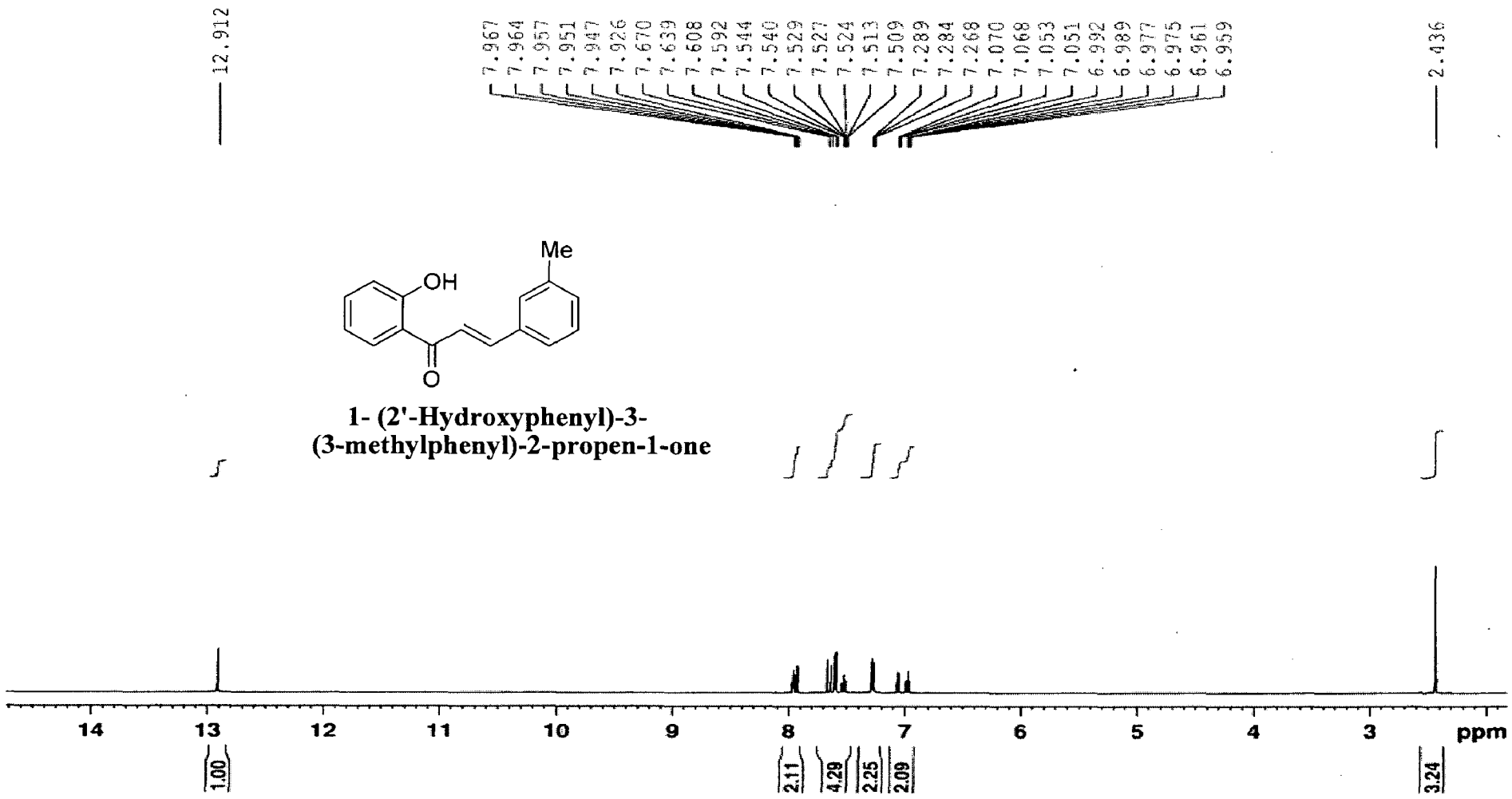
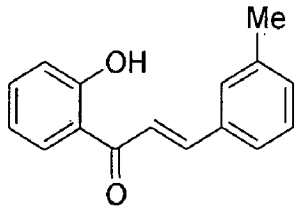


Figure S17. ^{1}H NMR spectra of 1-(2'-Hydroxyphenyl)-3-(3-methylphenyl)-2-propen-1-one



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

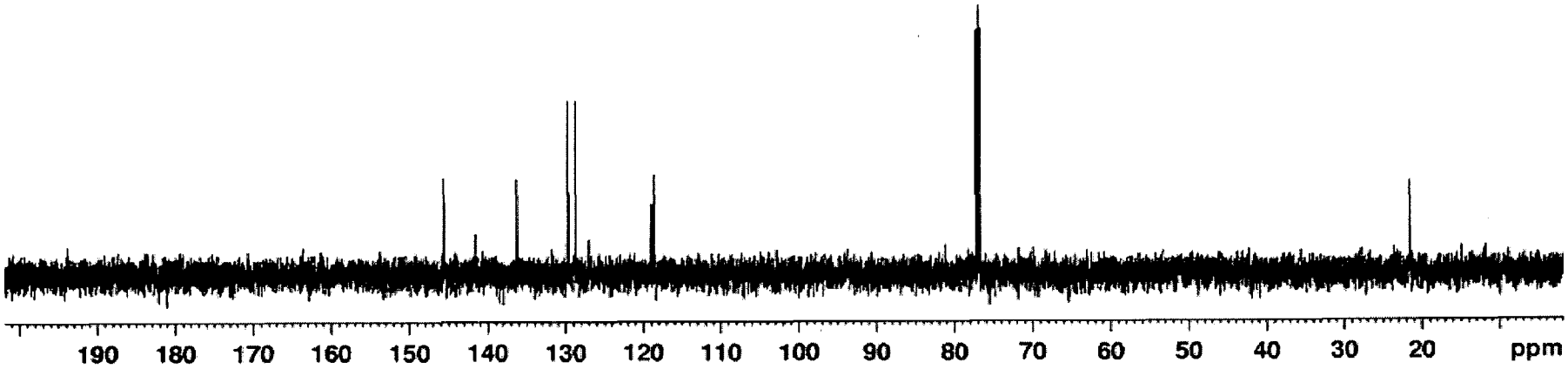


Figure S18. ^{13}C NMR spectra of 1-(2'-Hydroxyphenyl)-3-(3-methylphenyl)-2-propen-1-one

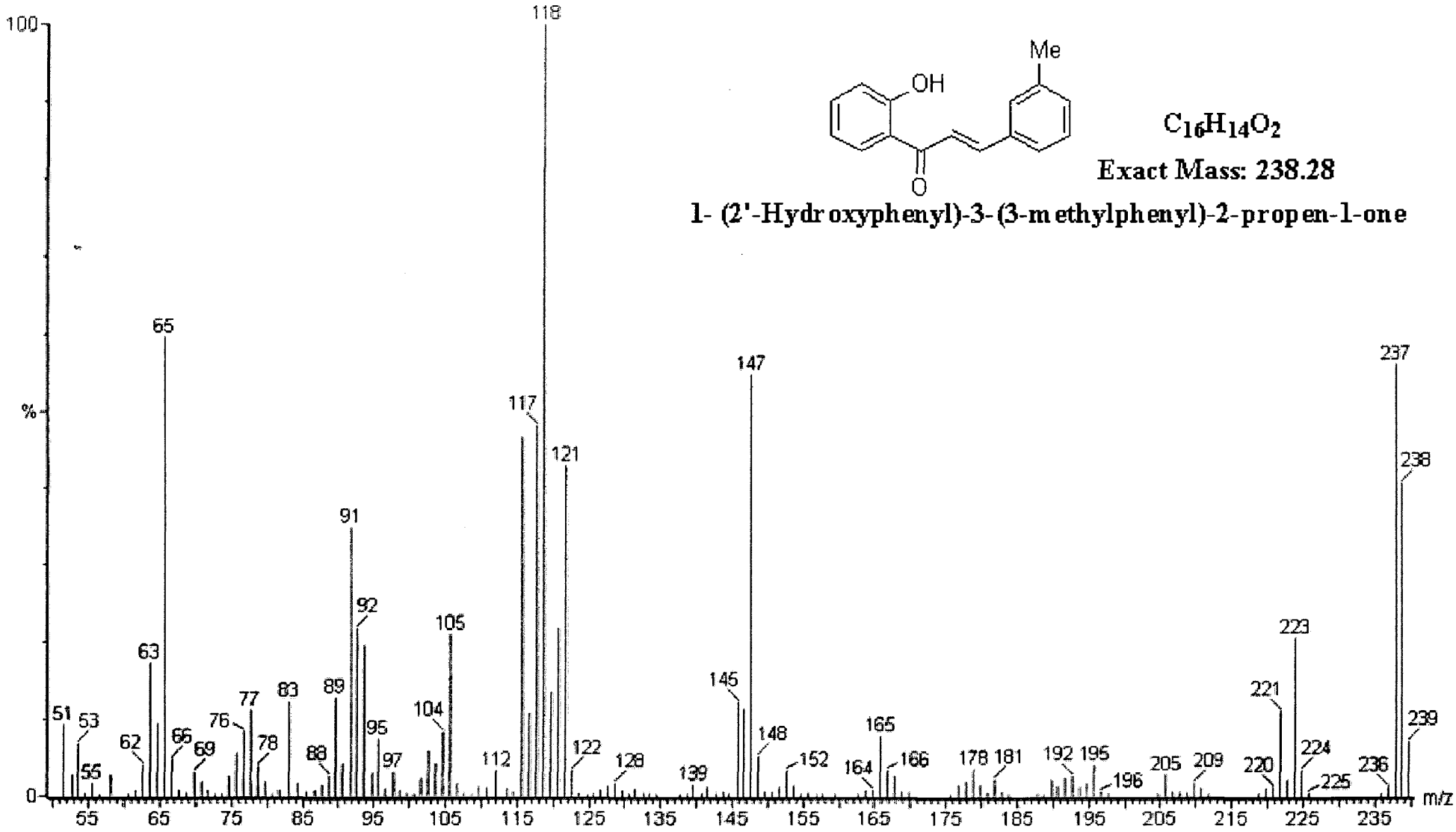


Figure S19. GC-MS spectra of 1-(2'-Hydroxyphenyl)-3-(3-methylphenyl)-2-propen-1-one

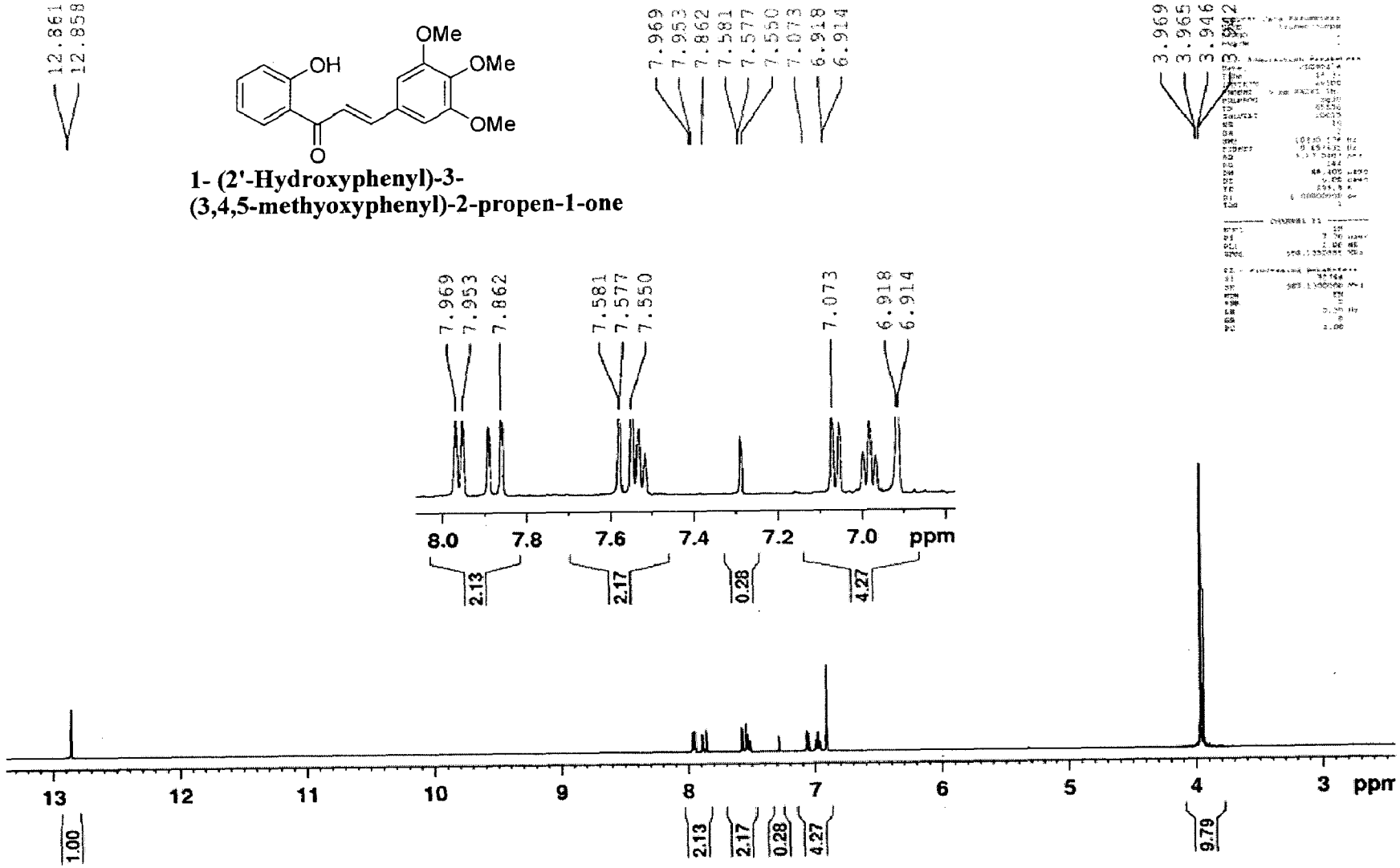


Figure S20. ^{1}H NMR spectra of 1-(2'-Hydroxyphenyl)-3-(3, 4, 5,-tri-methoxyphenyl)-propen-1-one

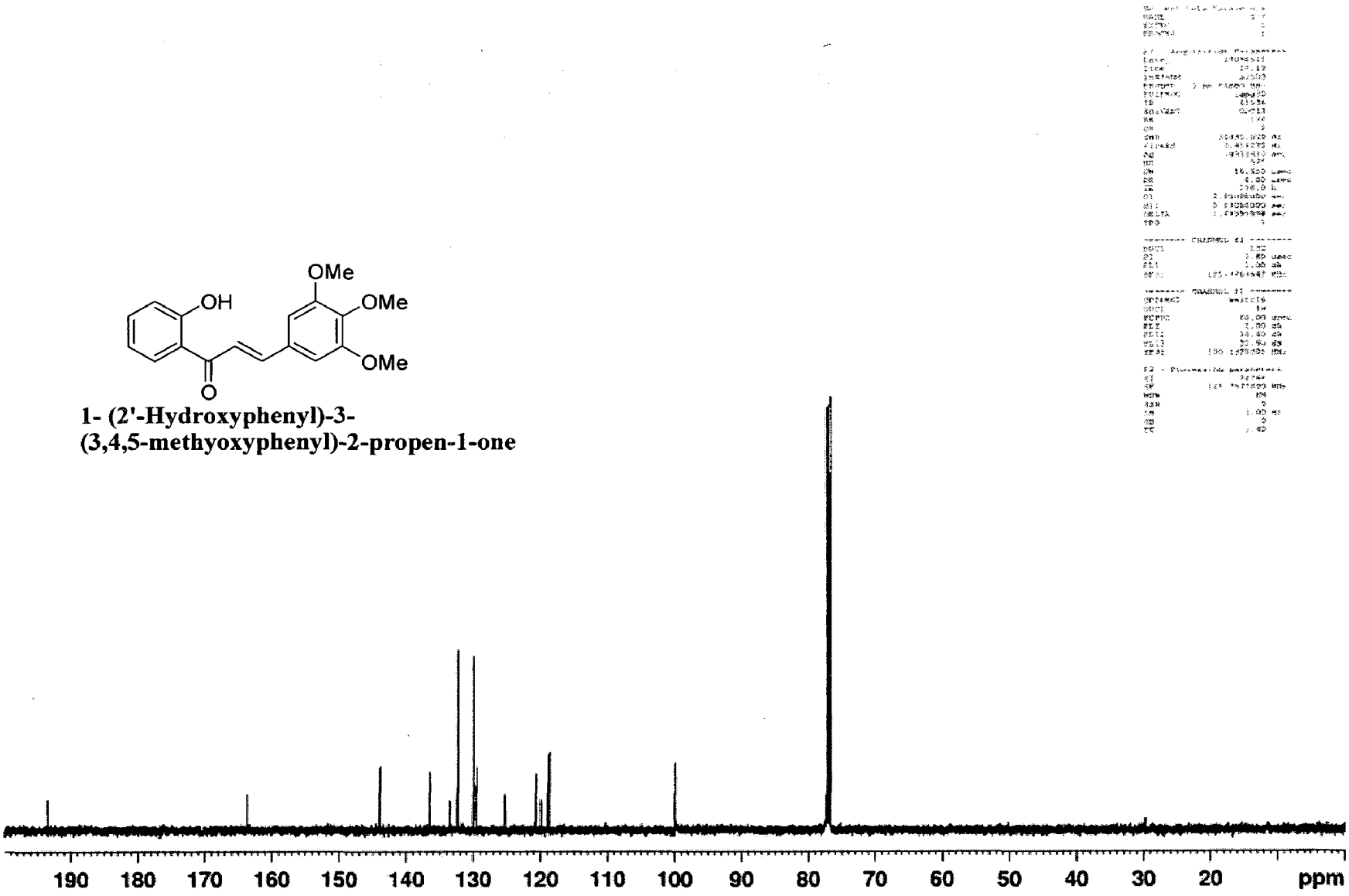


Figure S21.[13]C NMR spectra of 1-(2'-Hydroxyphenyl)-3-(3, 4, 5,-tri-methoxyphenyl)-propen-1-one

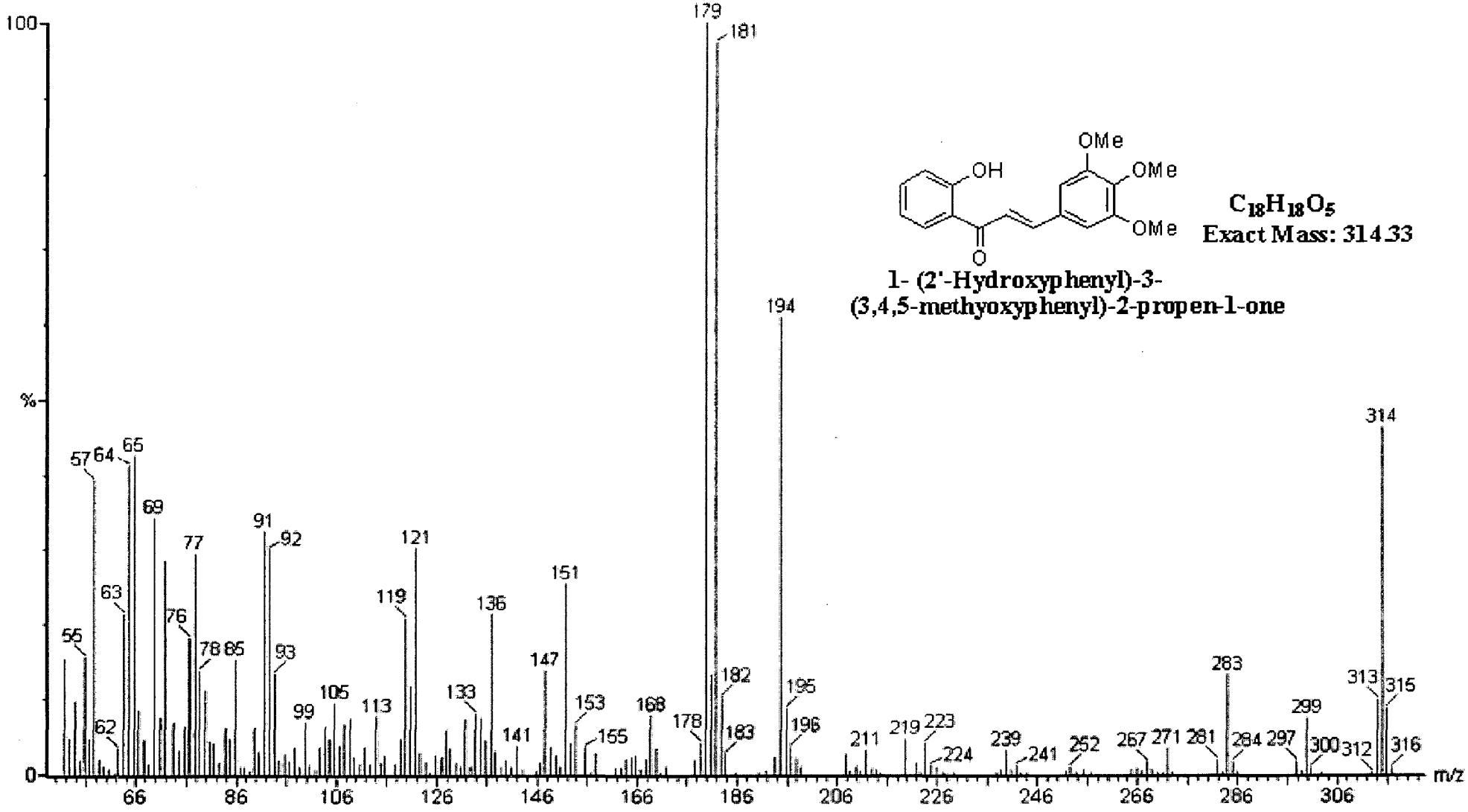
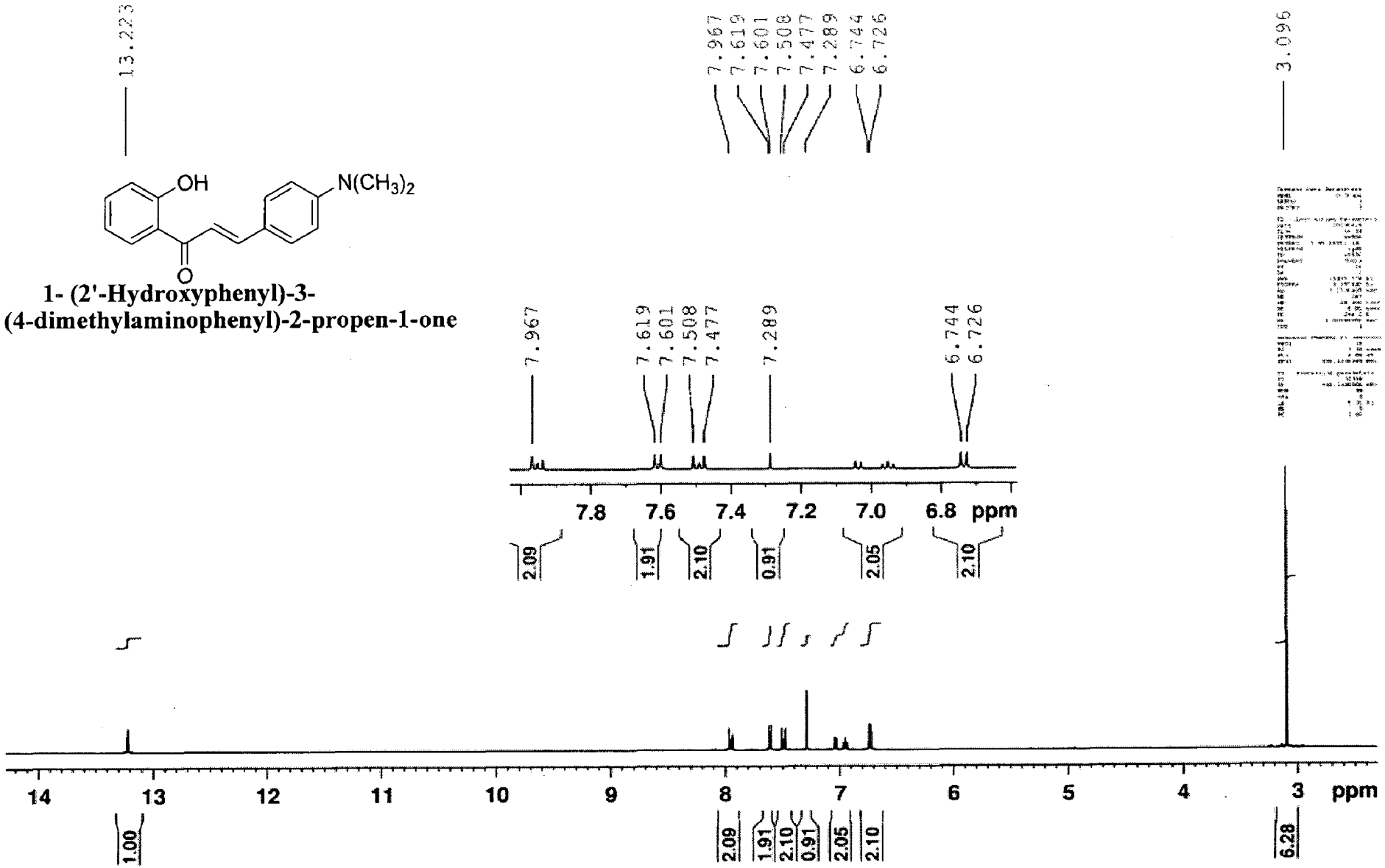
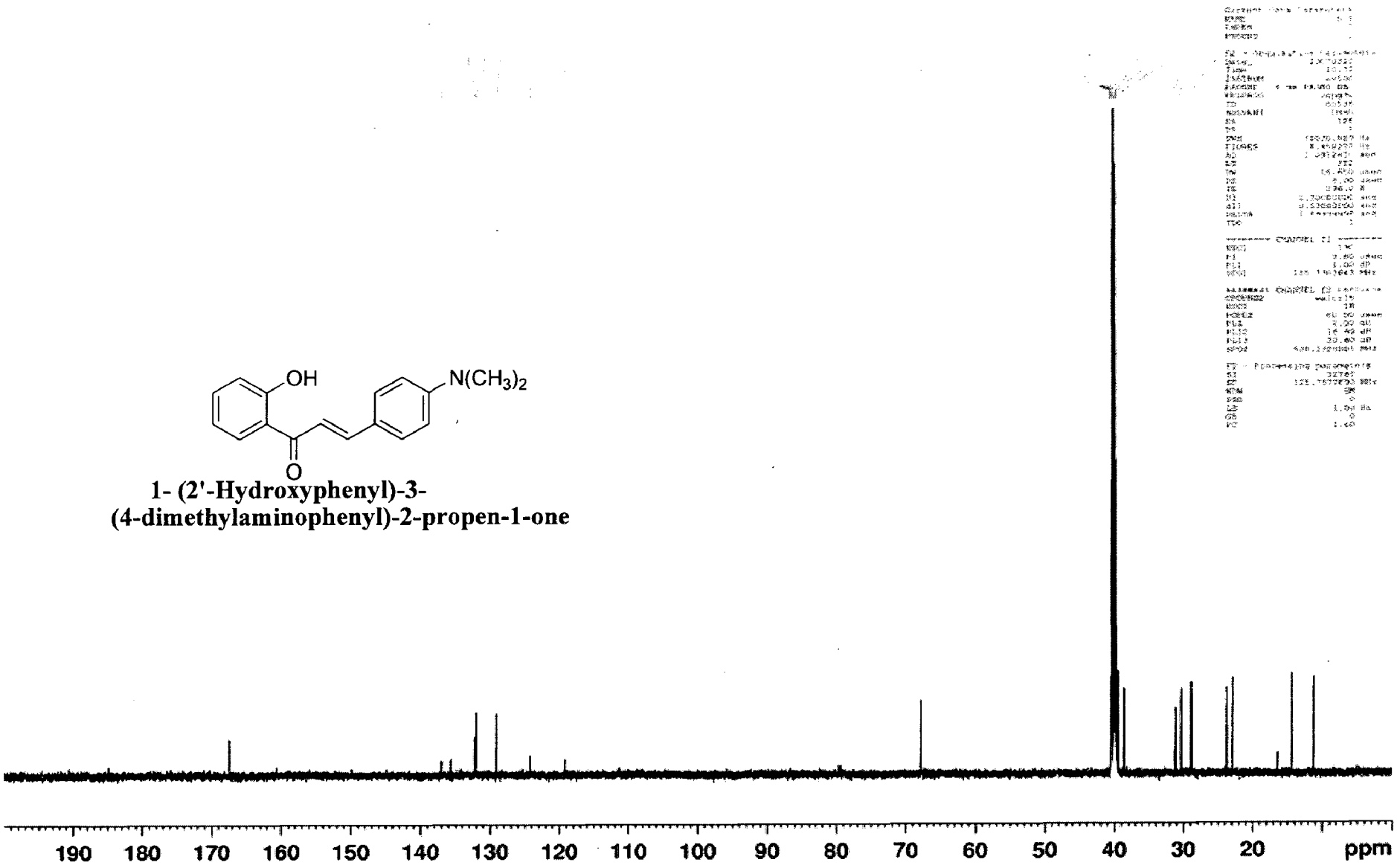


Figure S22 : GCMS spectra of spectra of1-(2'-Hydroxyphenyl)-3-(3, 4, 5,-tri-methoxyphenyl)-propen-1-one



FigureS23 ^{1}HNMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-dimethylaminephenyl)-2-propen-1-one



FigureS24 ^{13}CNMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-dimethylaminephenyl)-2-propen-1-one

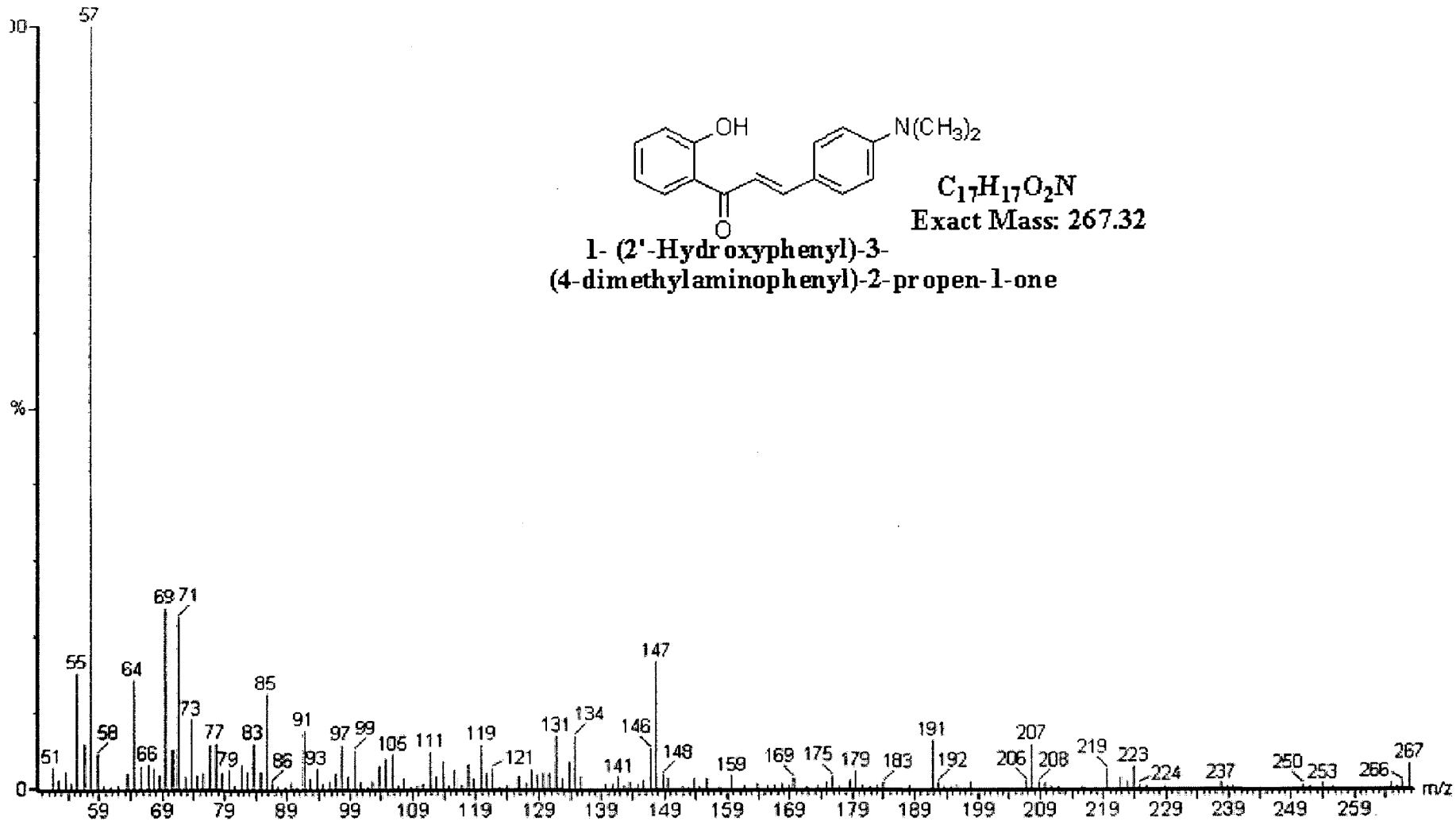


Figure S25. GC-MS spectra of 1-(2'-Hydroxyphenyl)-3-(4-dimethylaminephenyl)-2-propen-1-one

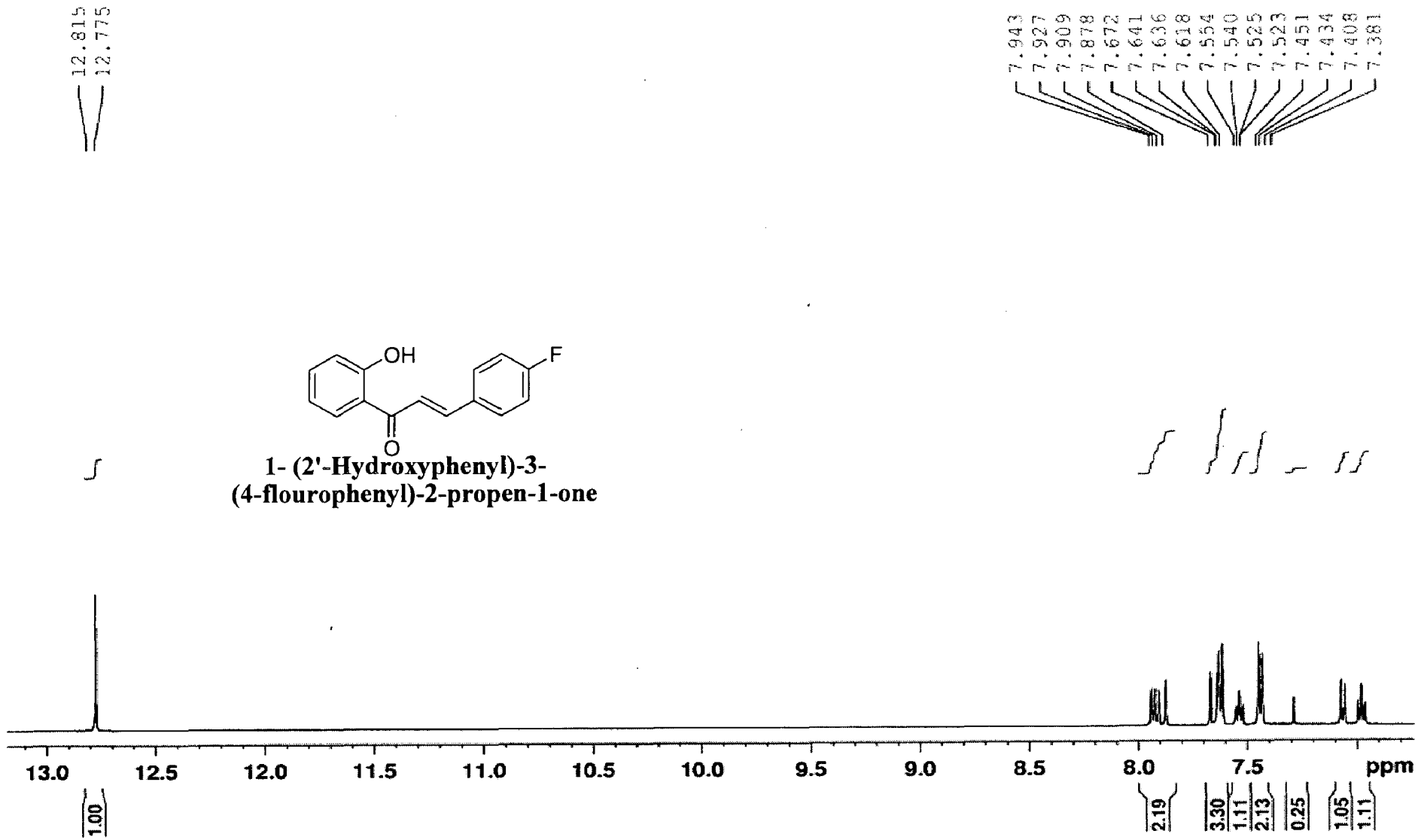


Figure S26. ^{1}H NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-flurophenyl)-2-propen-1-one

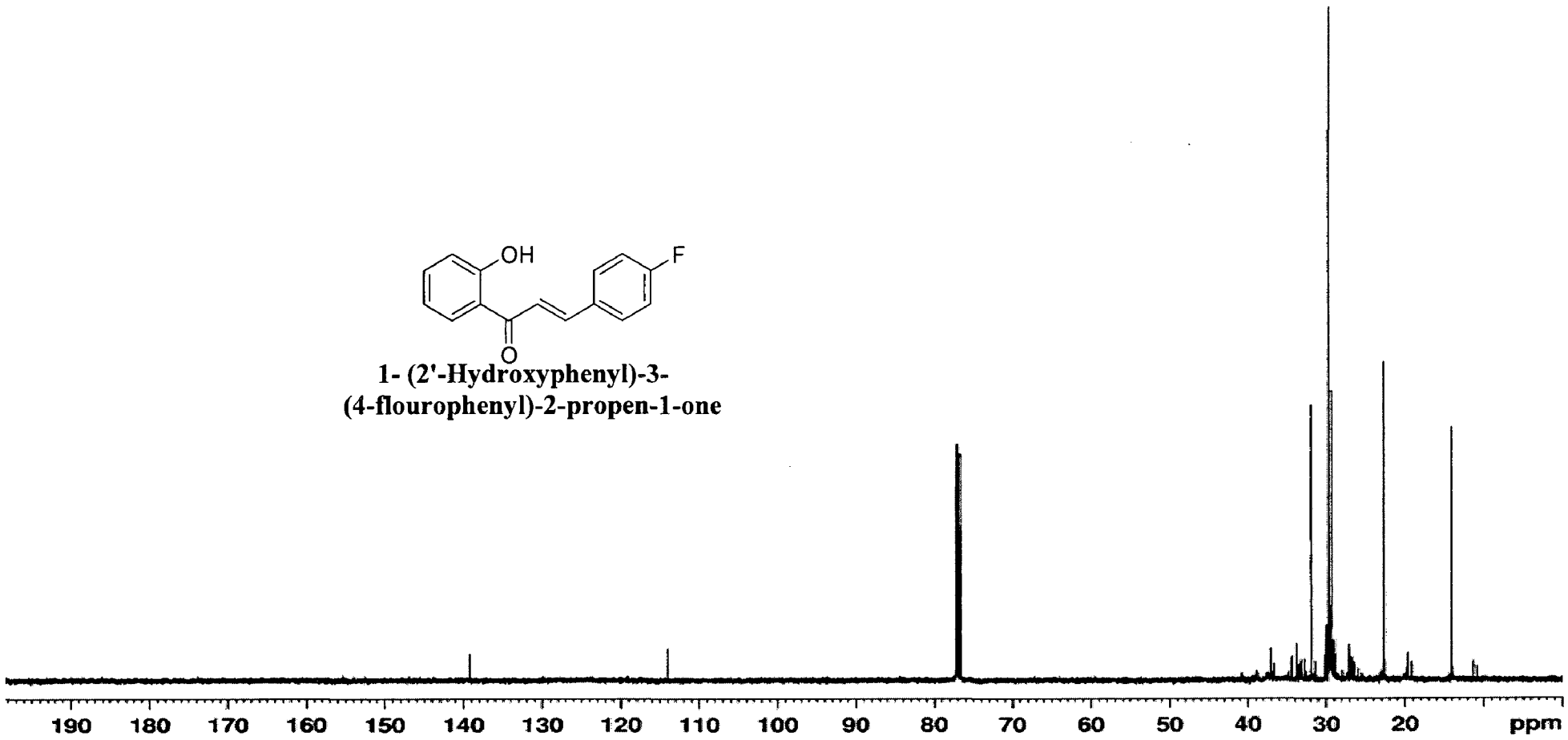


Figure S27. ^{13}C NMR spectra of 1-(2'-Hydroxyphenyl)-3-(4-flurophenyl)-2-propen-1-one

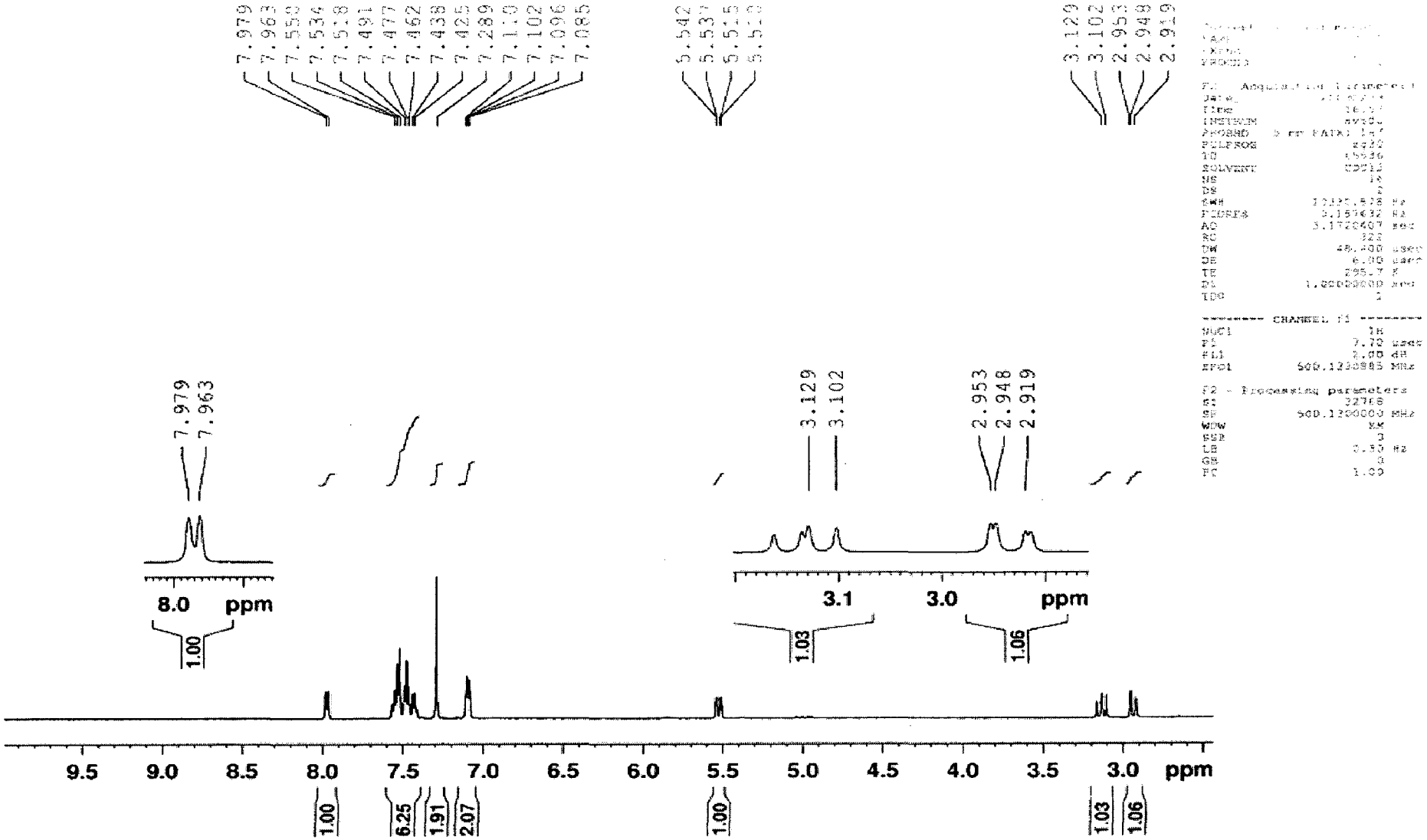


Figure S28. ^{1}H NMR spectra of 2-phenyl-chroman-4-one

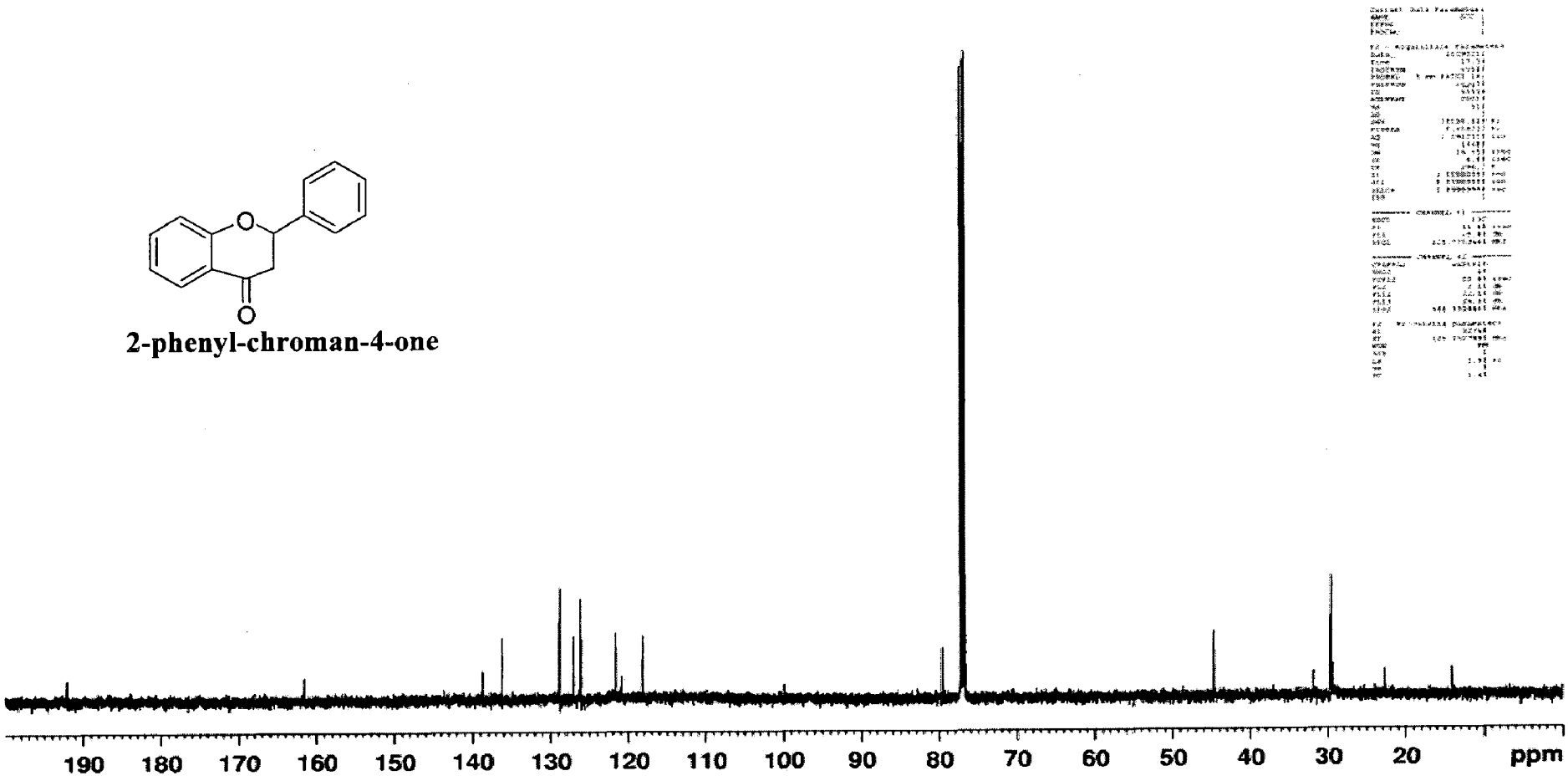


Figure S29. ^{13}C NMR spectra of 2-phenyl-chroman-4-one

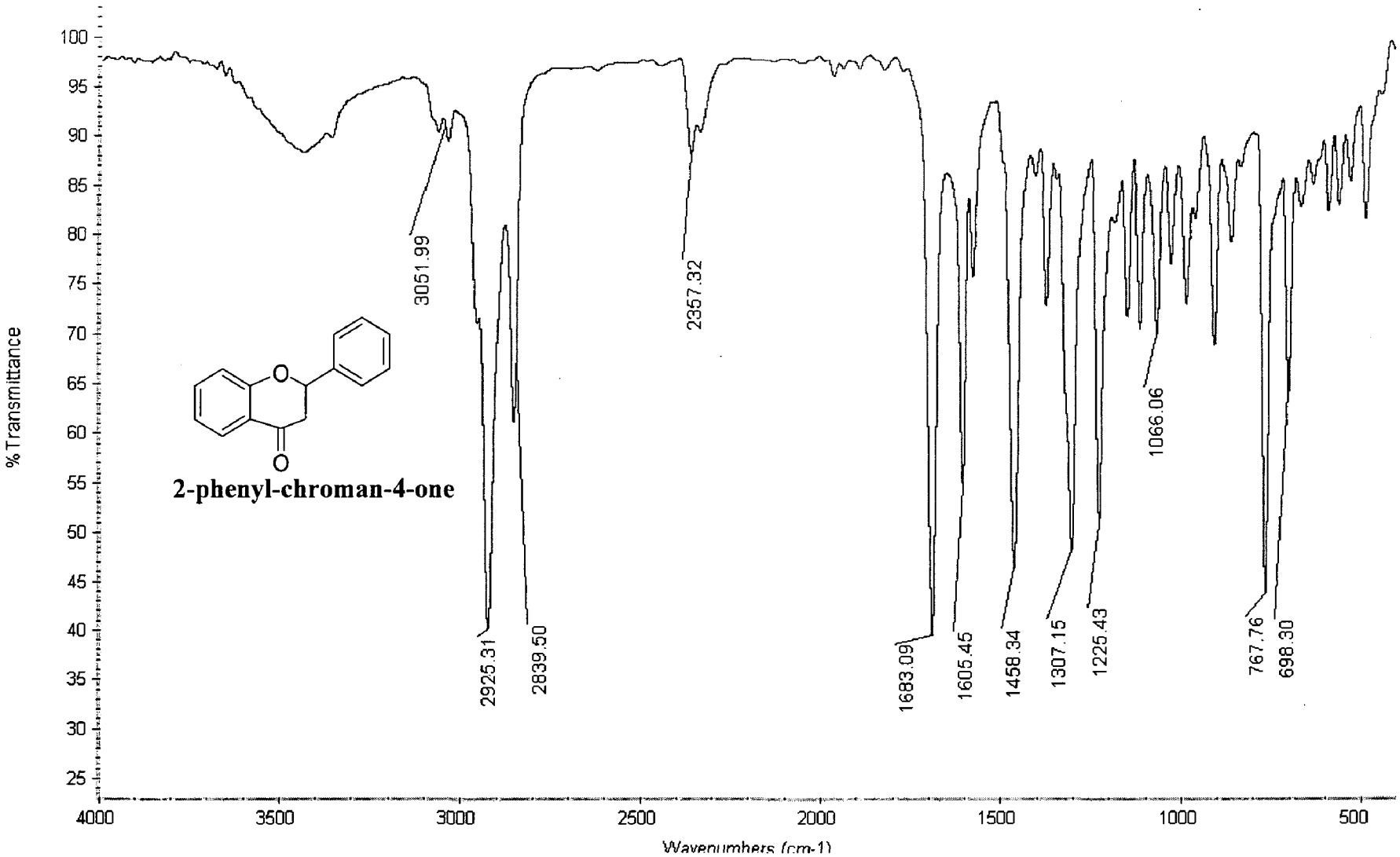


Figure S30. Infrared spectra of 2-phenyl-chroman-4-one

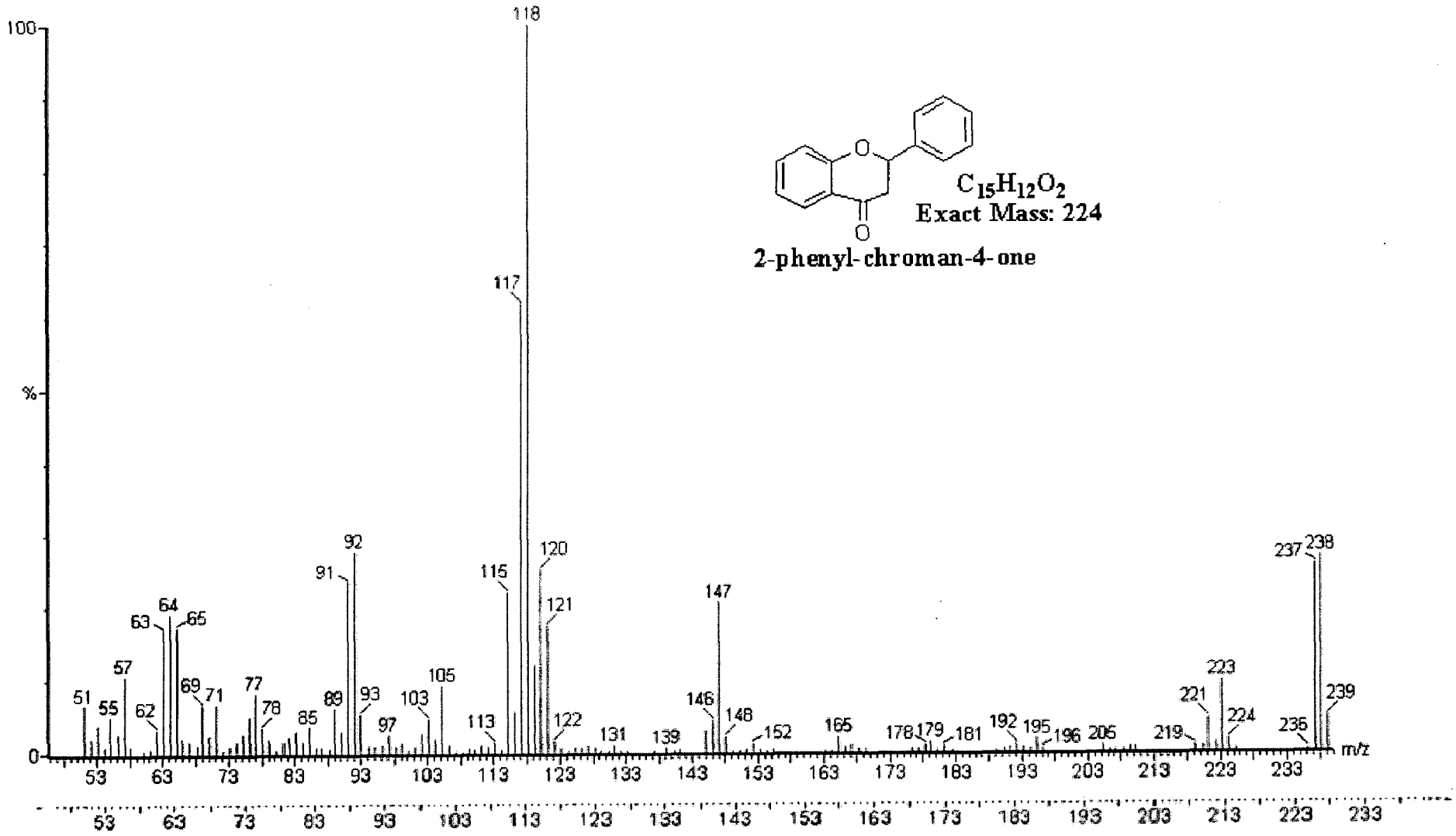
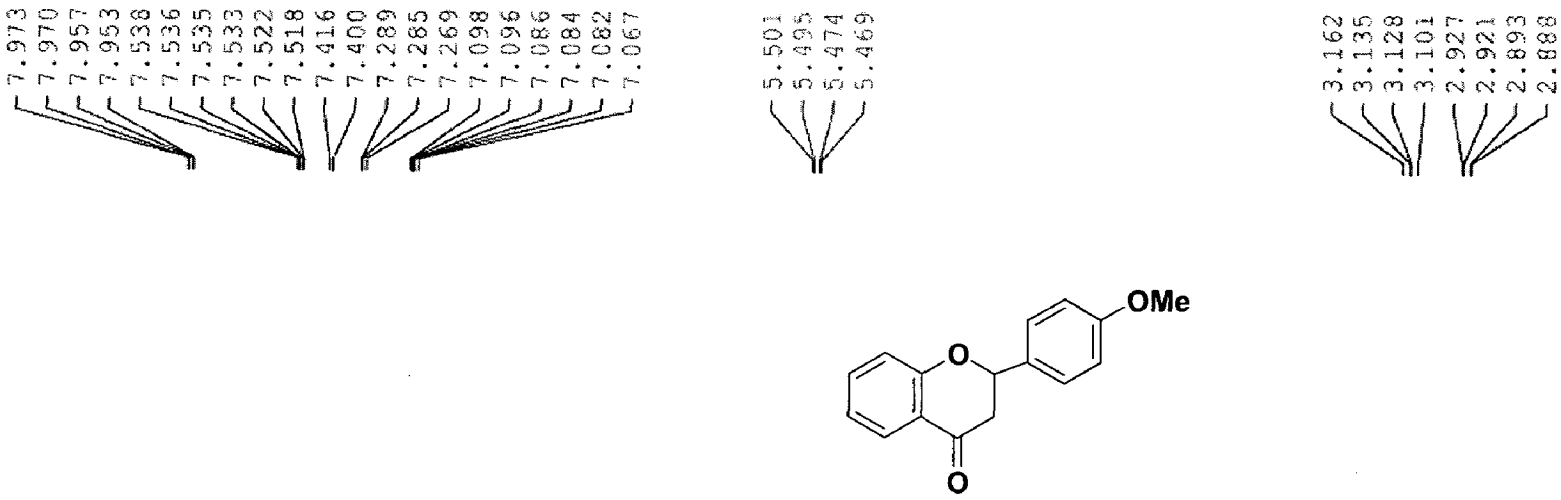


Figure S31. GC-MS spectra of 2-phenyl-chroman-4-one



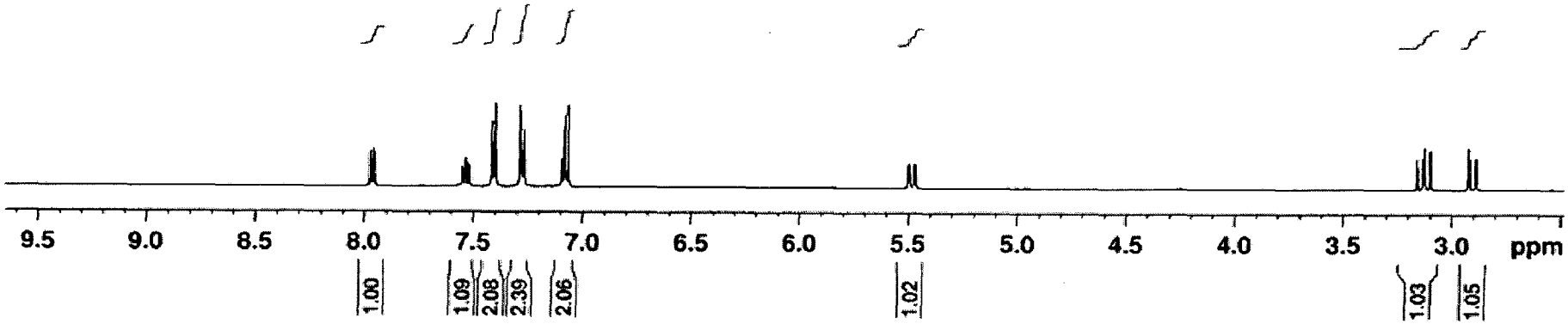


Figure S32. ^{1}HNMR spectra of 2-(4'-chlorophenyl)-chroman-4-one

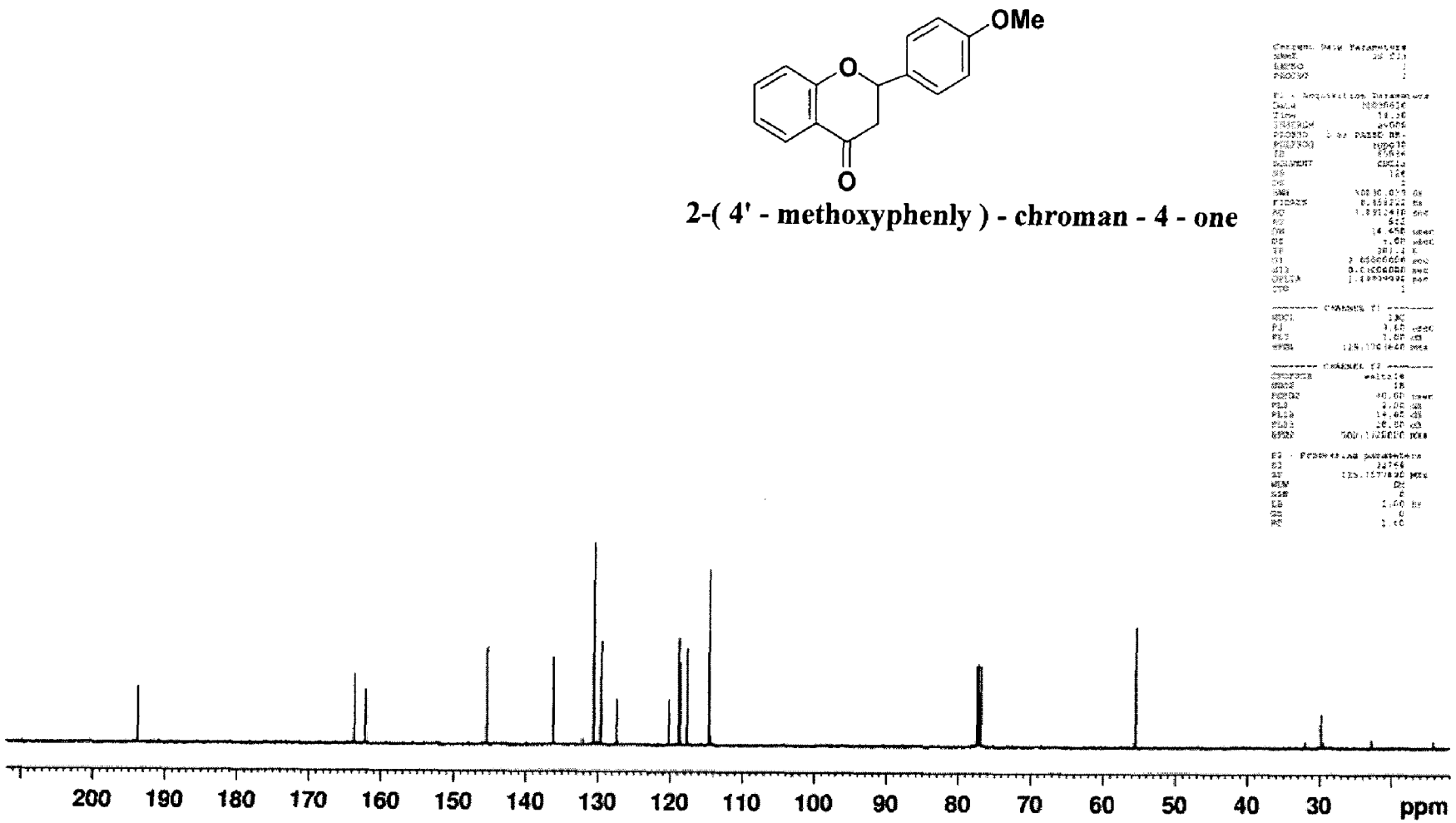


Figure S33. ^{1}HNMR spectra of 2-(4'-chlorophenyl)-chroman-4-one

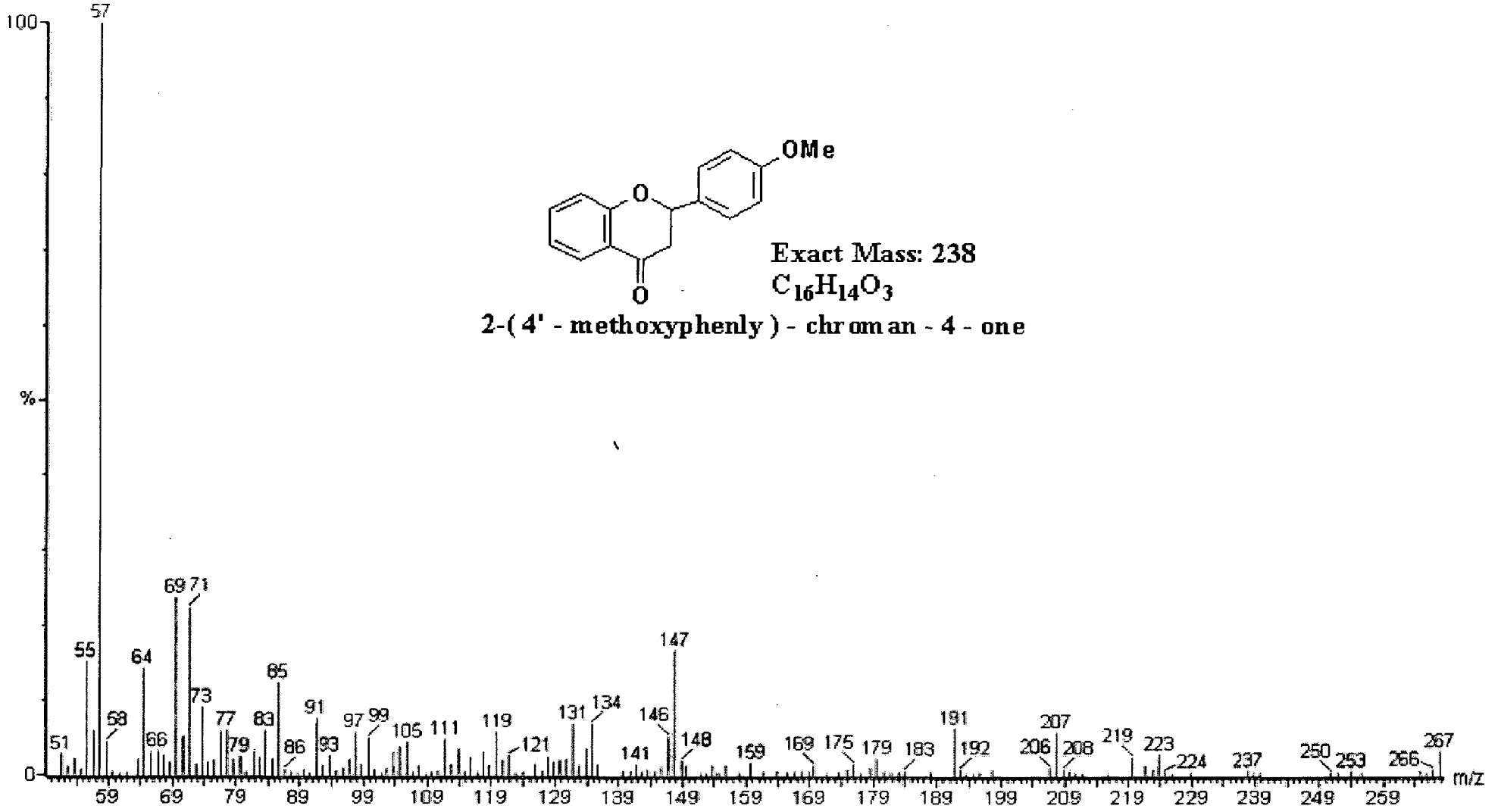


Figure S34.GC-MS spectra of 1-(2'-Hydroxyphenyl)-3-(3-methylphenyl)-2-propen-1-one

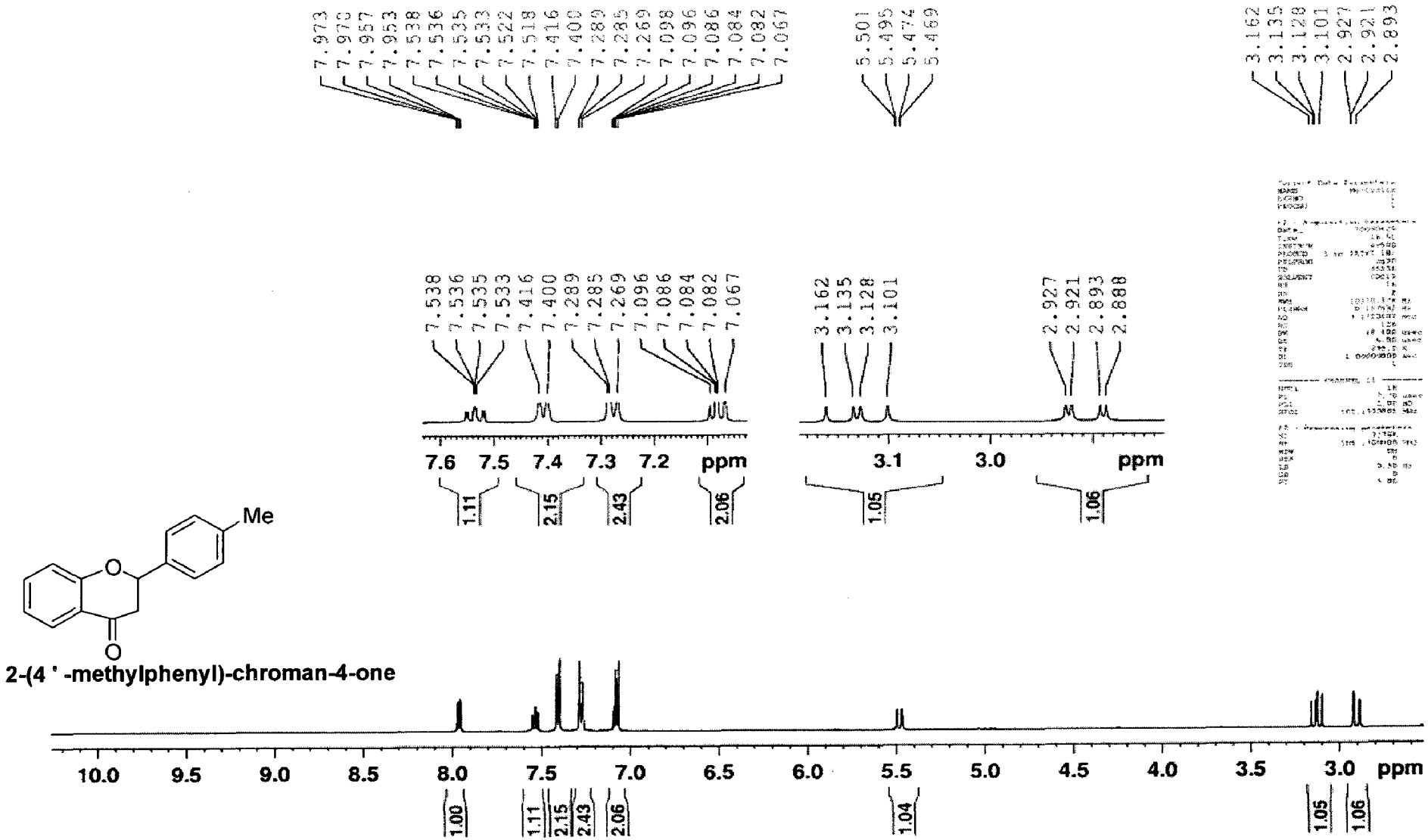


Figure S35. ^{1}HNMR spectra of 2-(4'-methylphenyl)-chroman-4-one

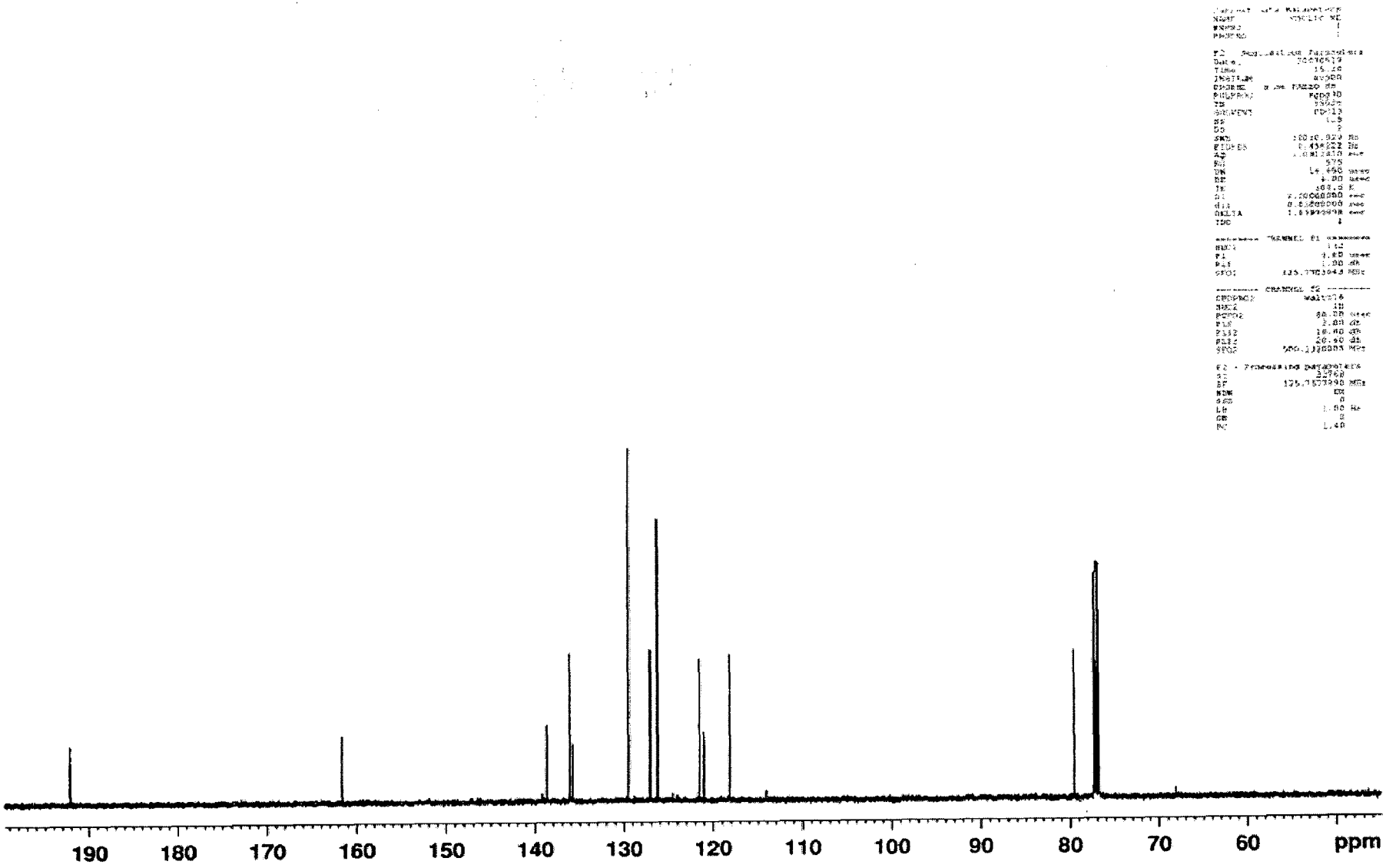


Figure S36. ^{13}N NMR spectra of 2-(4'-methylphenyl)-chroman-4-one

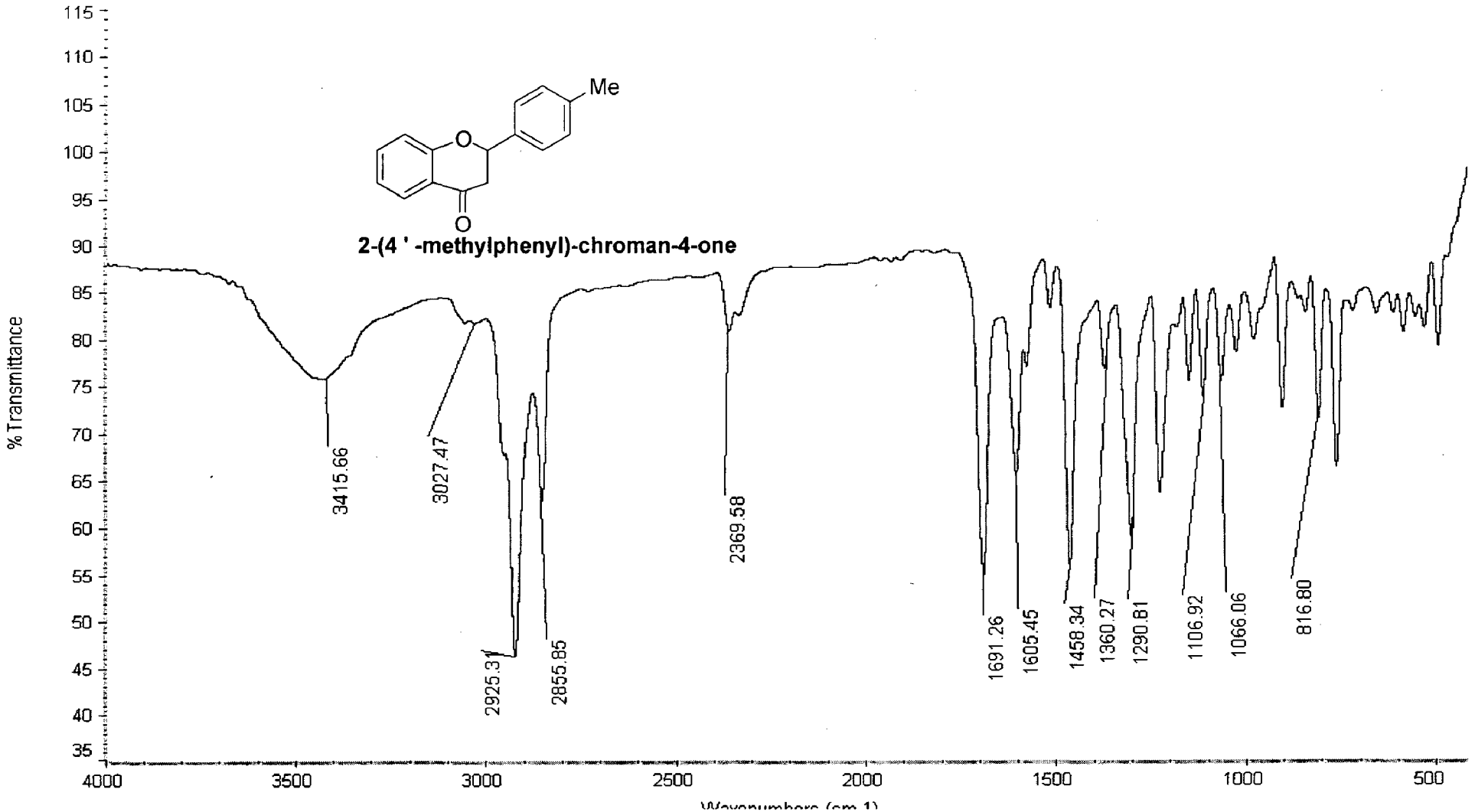


Figure S37. ^{1}H NMR spectra of 2-(4'-methylphenyl)-chroman-4-one

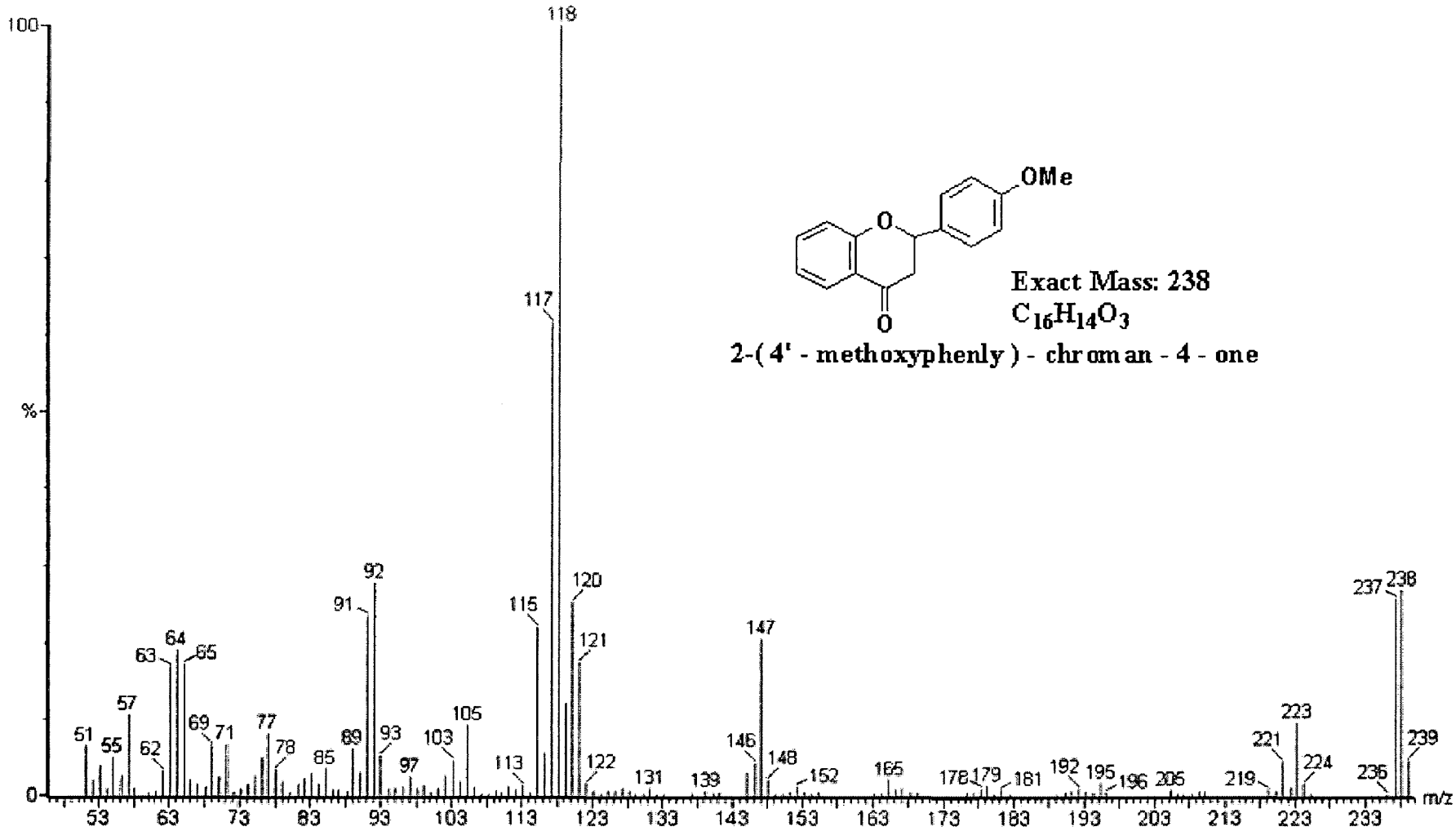


Figure S38. GC-MS spectra of 2-(4'-methylphenyl)-chroman-4-one

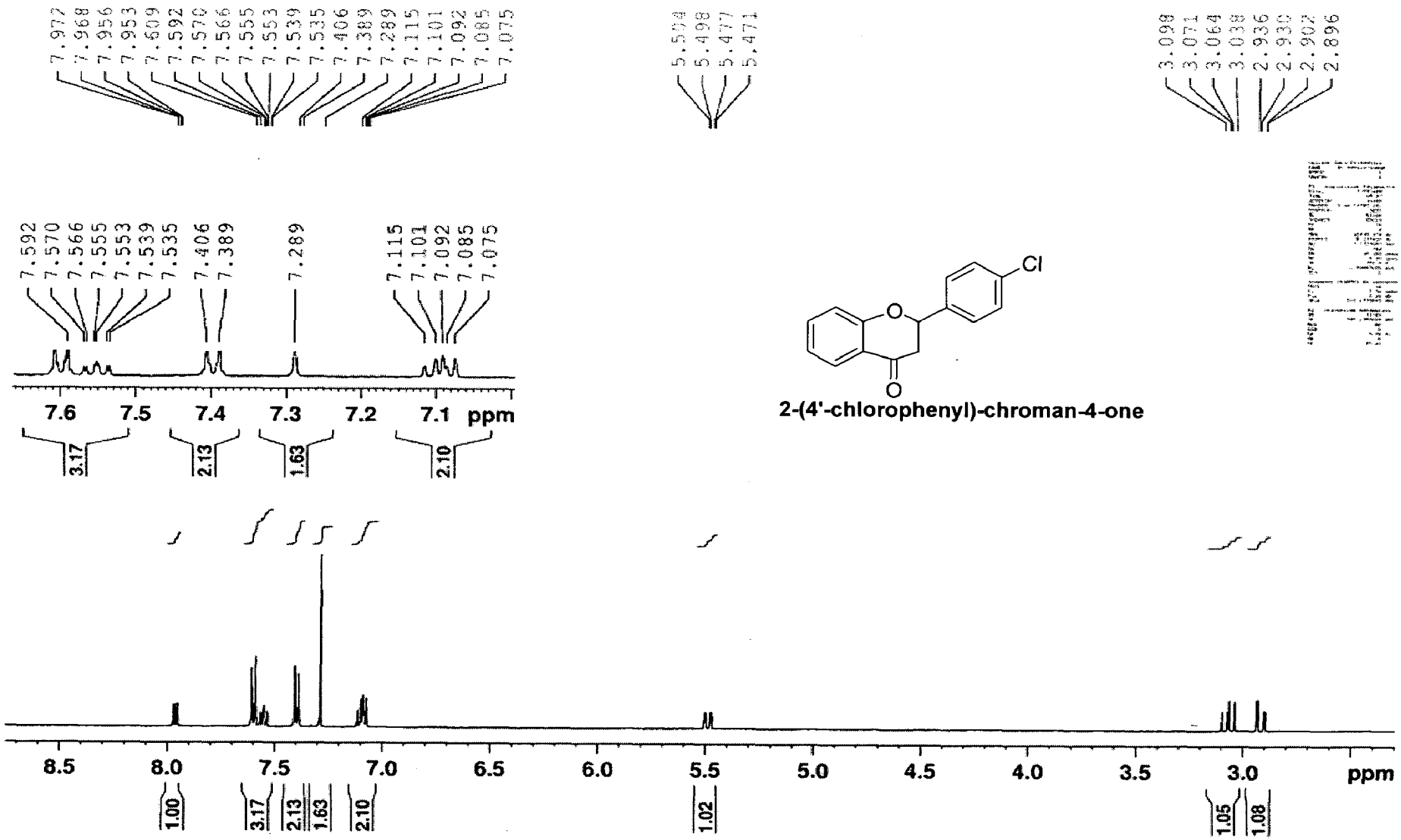
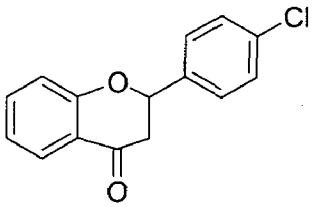


Figure S39. 1HNMR spectra of 2-(4'-chlorophenyl)-chroman-4-one



2-(4'-chlorophenyl)-chroman-4-one

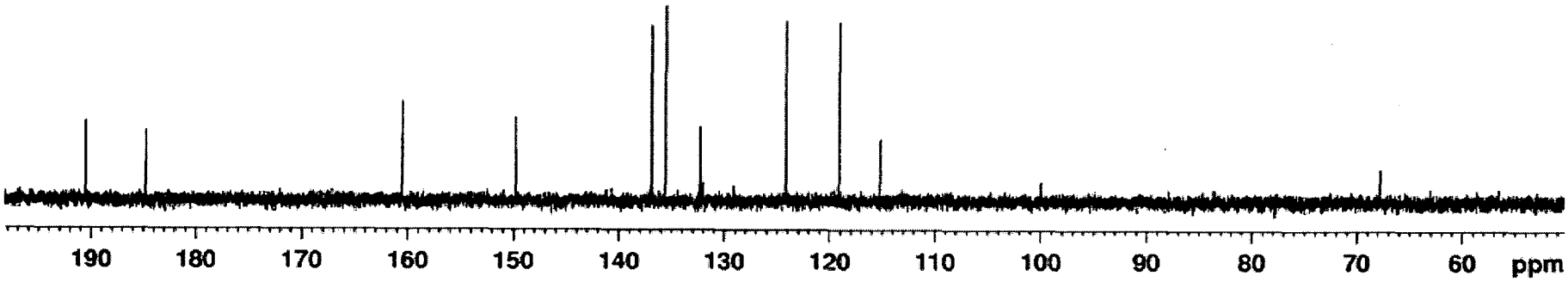


Figure S40. ^{13}C NMR spectra of 2-(4'-chlorophenyl)-chroman-4-one

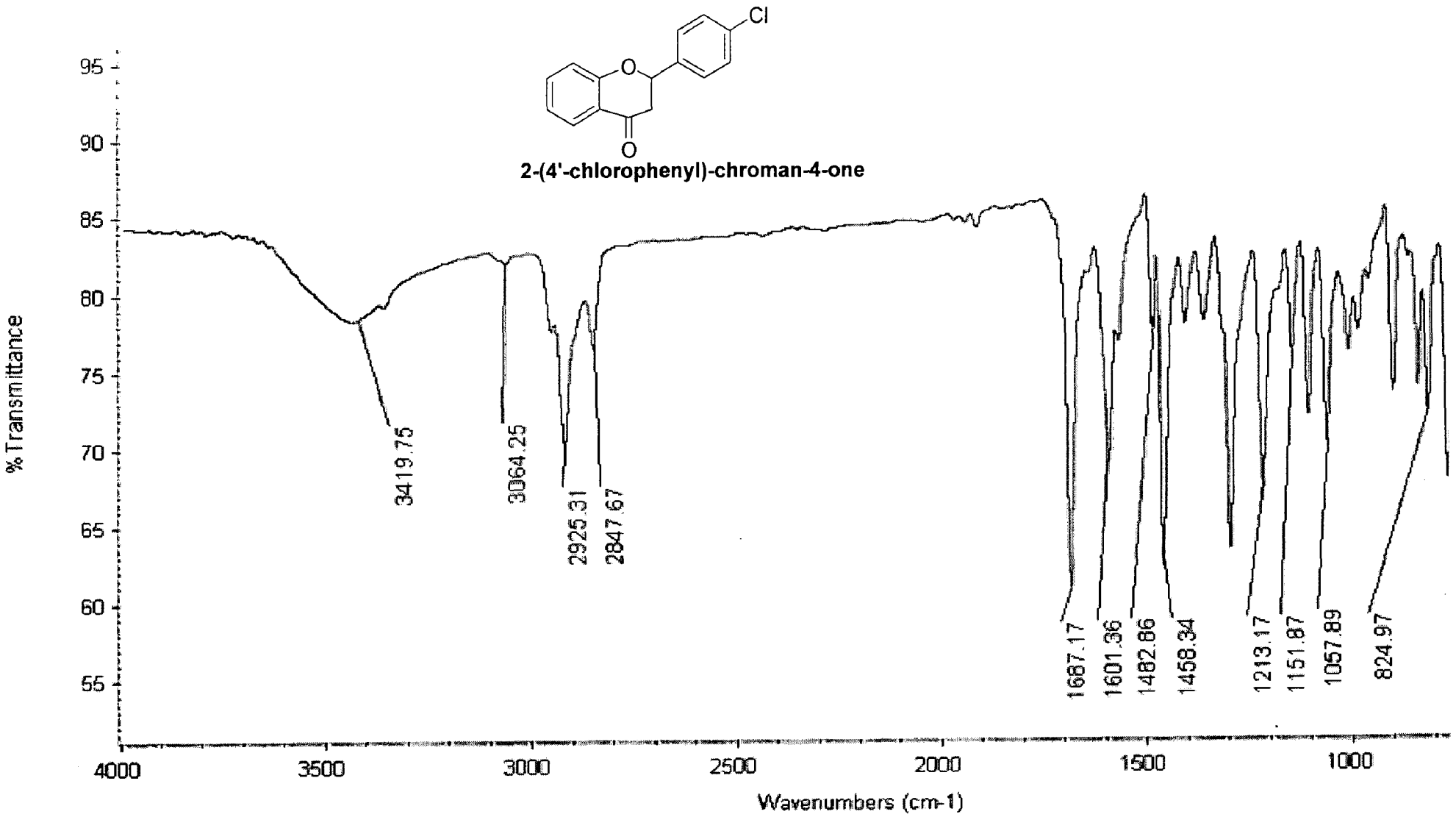


Figure S41. IR spectra of 2-(4'-chlorophenyl)-chroman-4-one

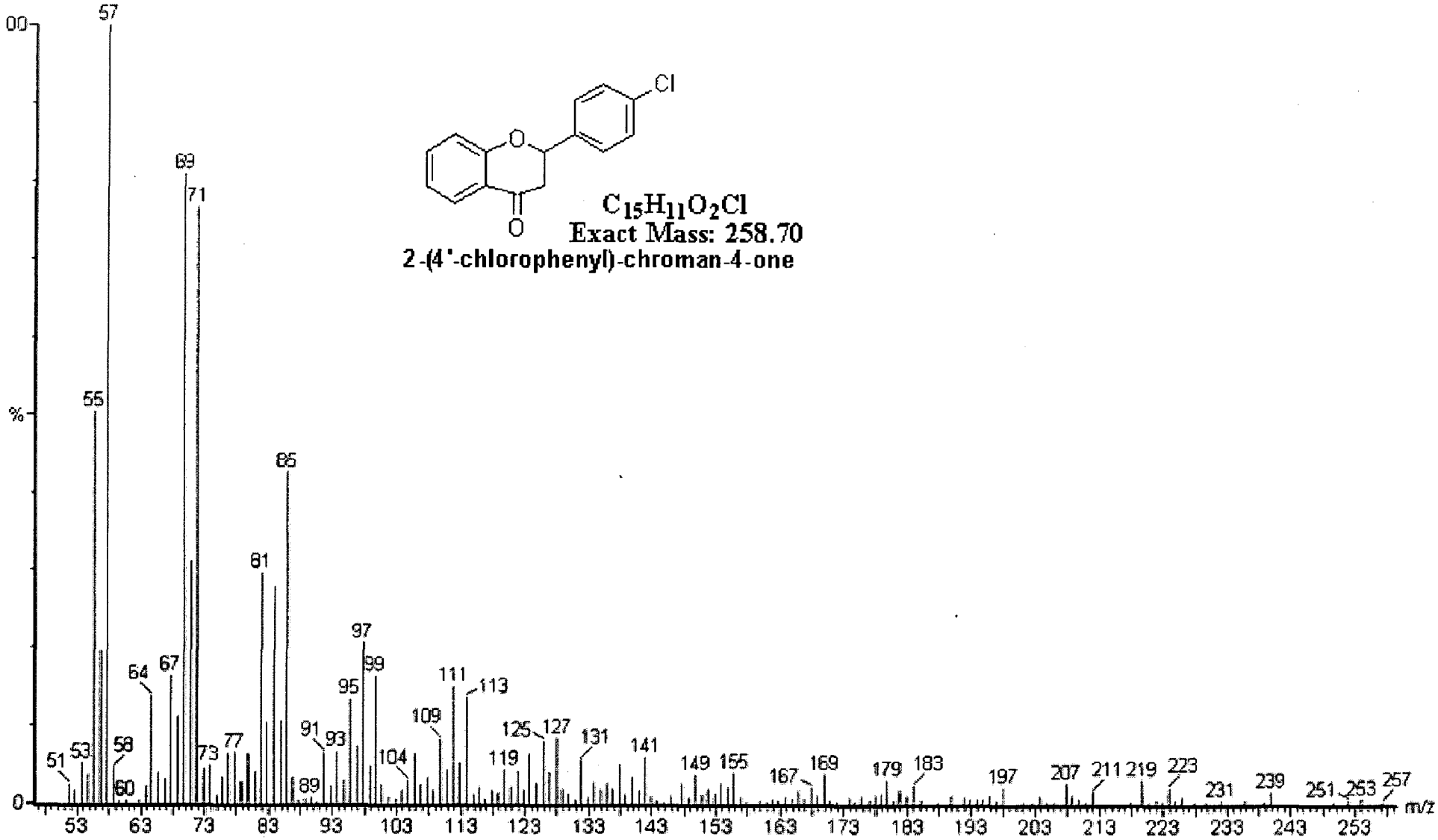


Figure S42. GCMS spectra of 2-(4'-chlorophenyl)-chroman-4-one

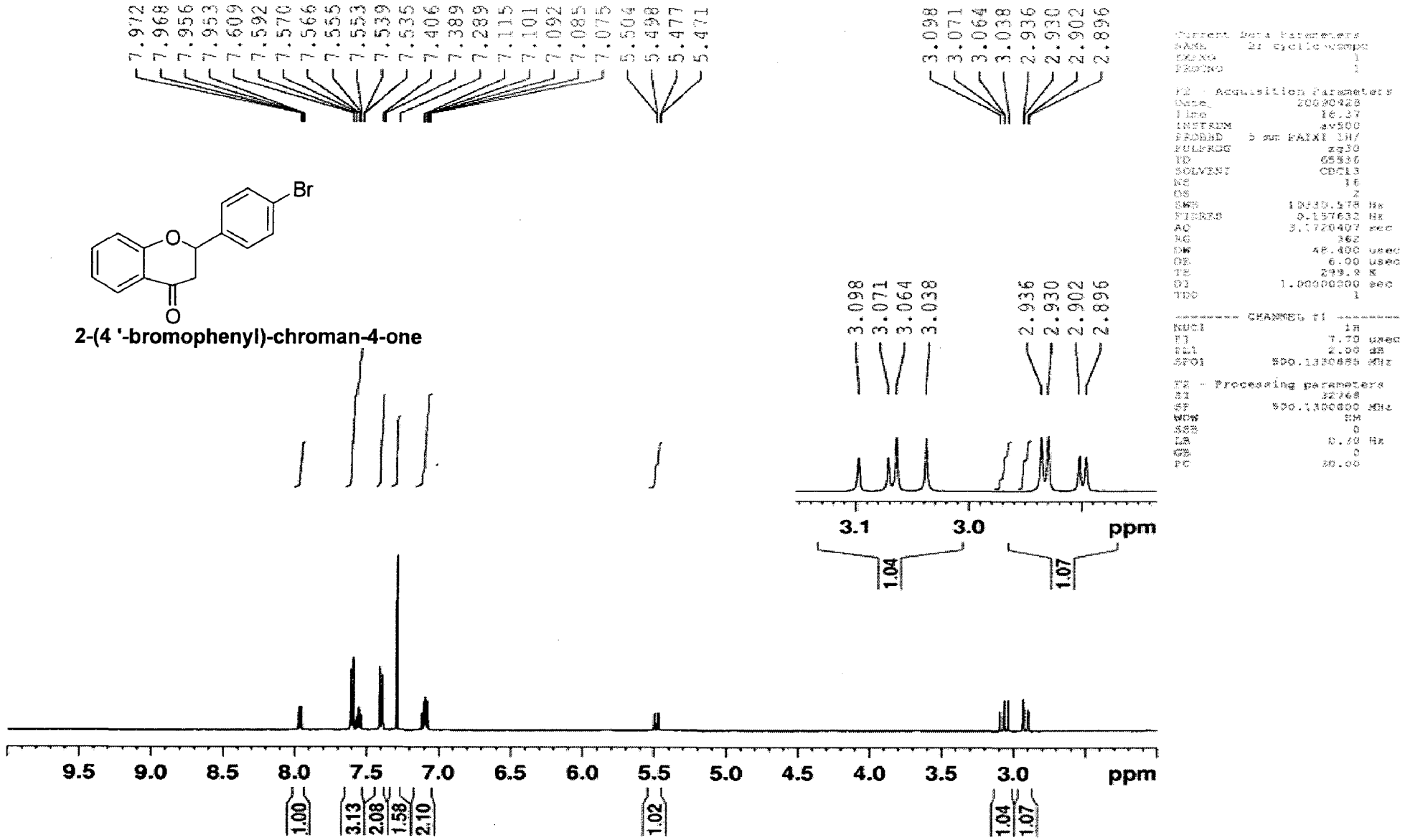
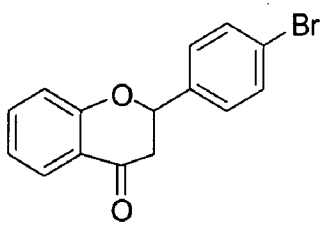


Figure S43. ^{1}H NMR spectra of 2-(4'-bromophenyl)-chroman-4-one



2-(4 '-bromophenyl)-chroman-4-one

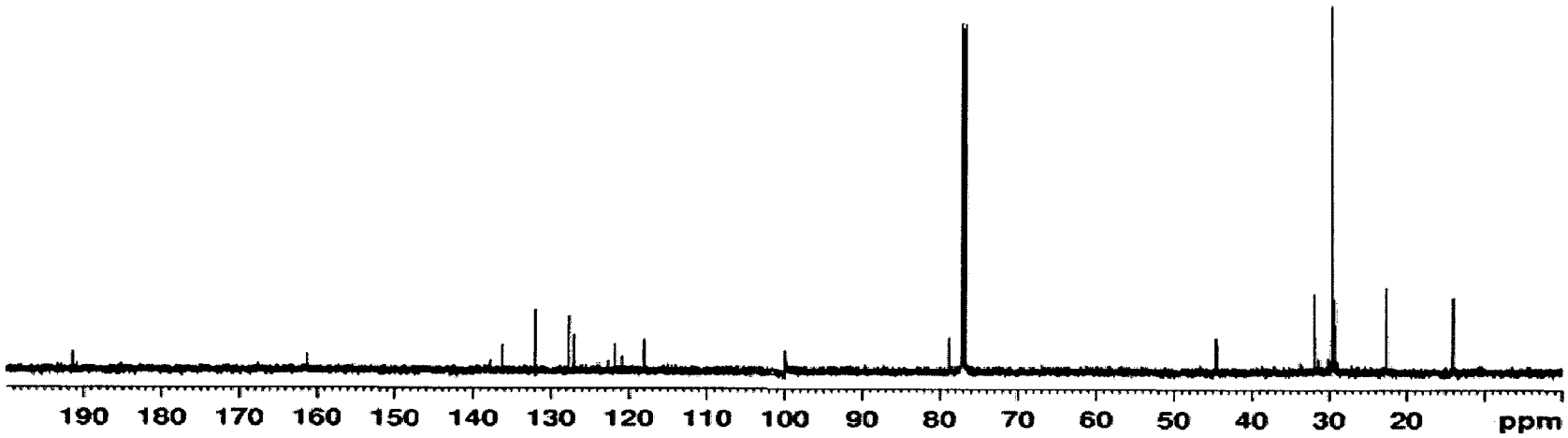


Figure S44. ^{13}C NMR spectra of 2-(4'-bromophenyl)-chroman-4-one

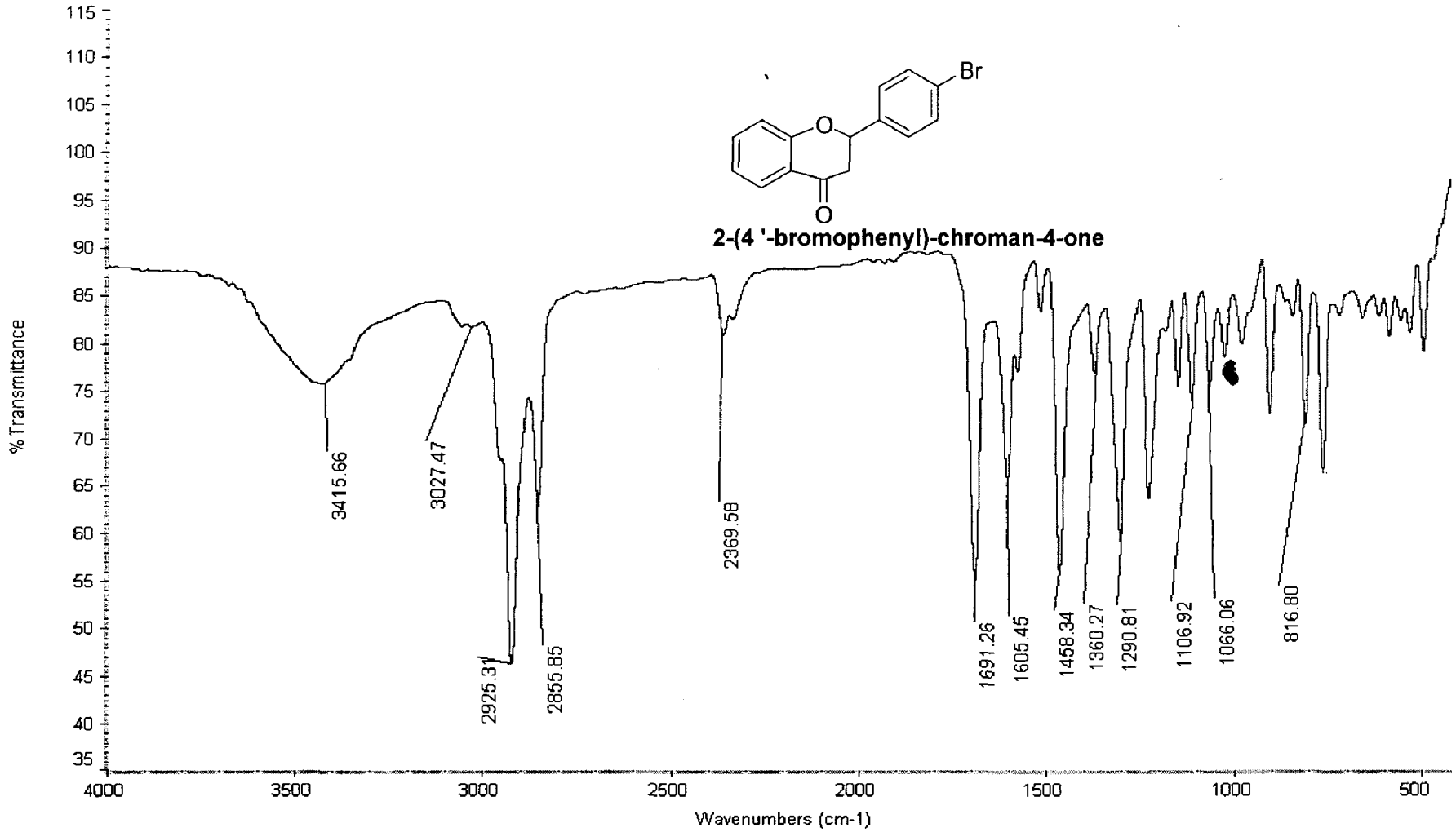


Figure S45. IR spectra of 2-(4'-bromophenyl)-chroman-4-one

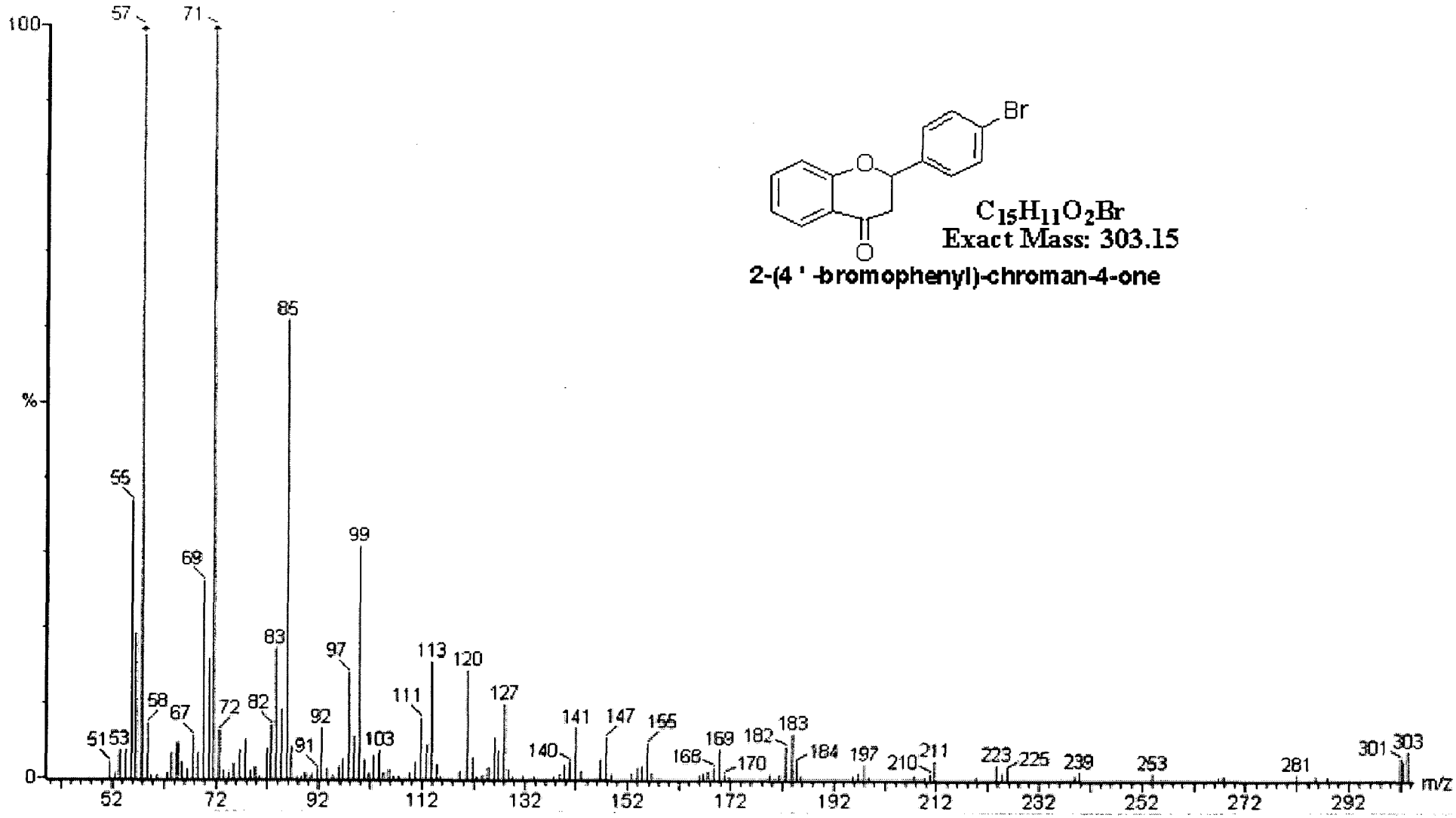
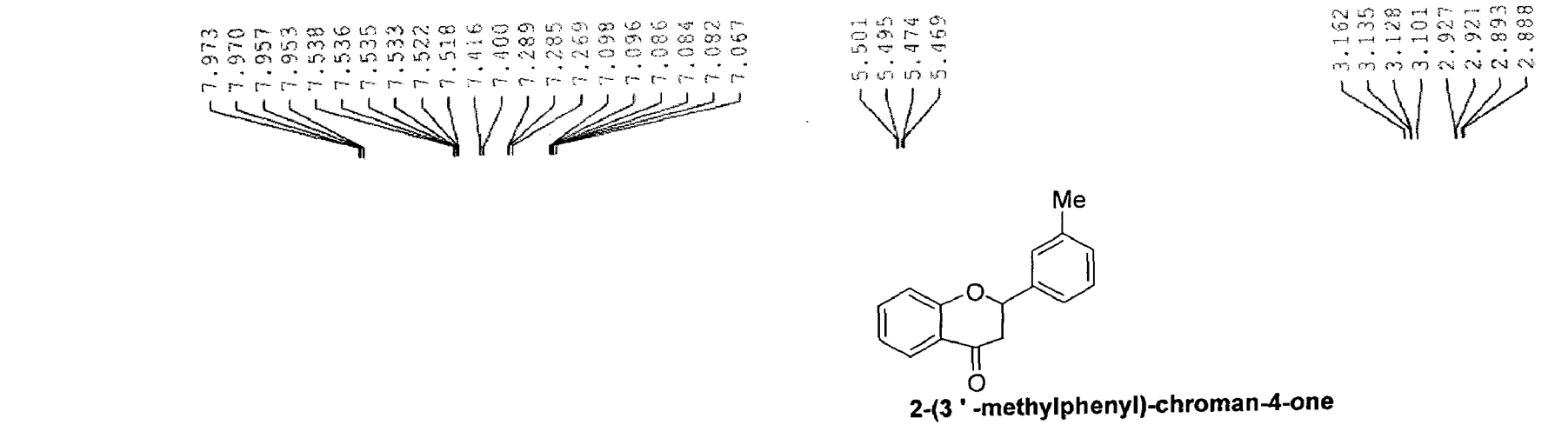


Figure S46. GC-MS spectra of 2-(4'-bromophenyl)-chroman-4-on



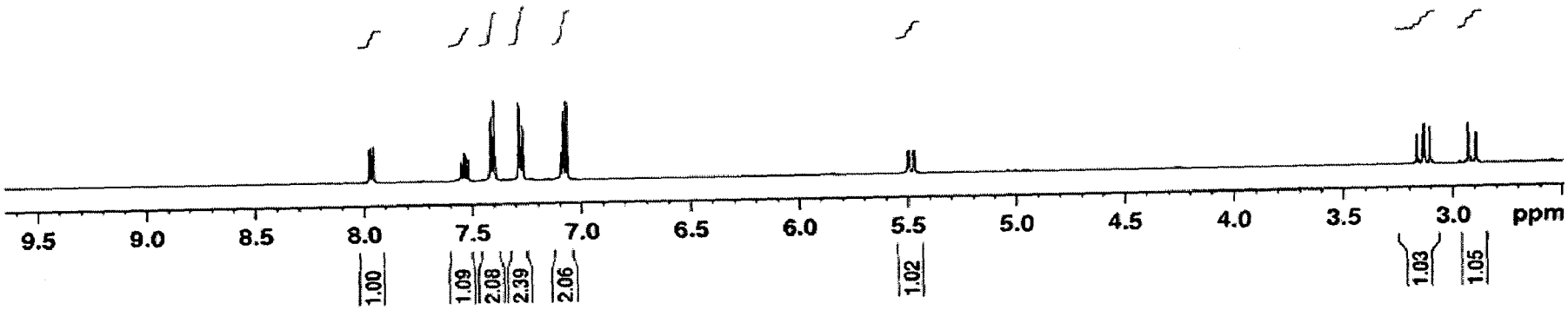


Figure S47. ^{1}H NMR spectra of 2-(4'-methylphenyl)-chroman-4-one

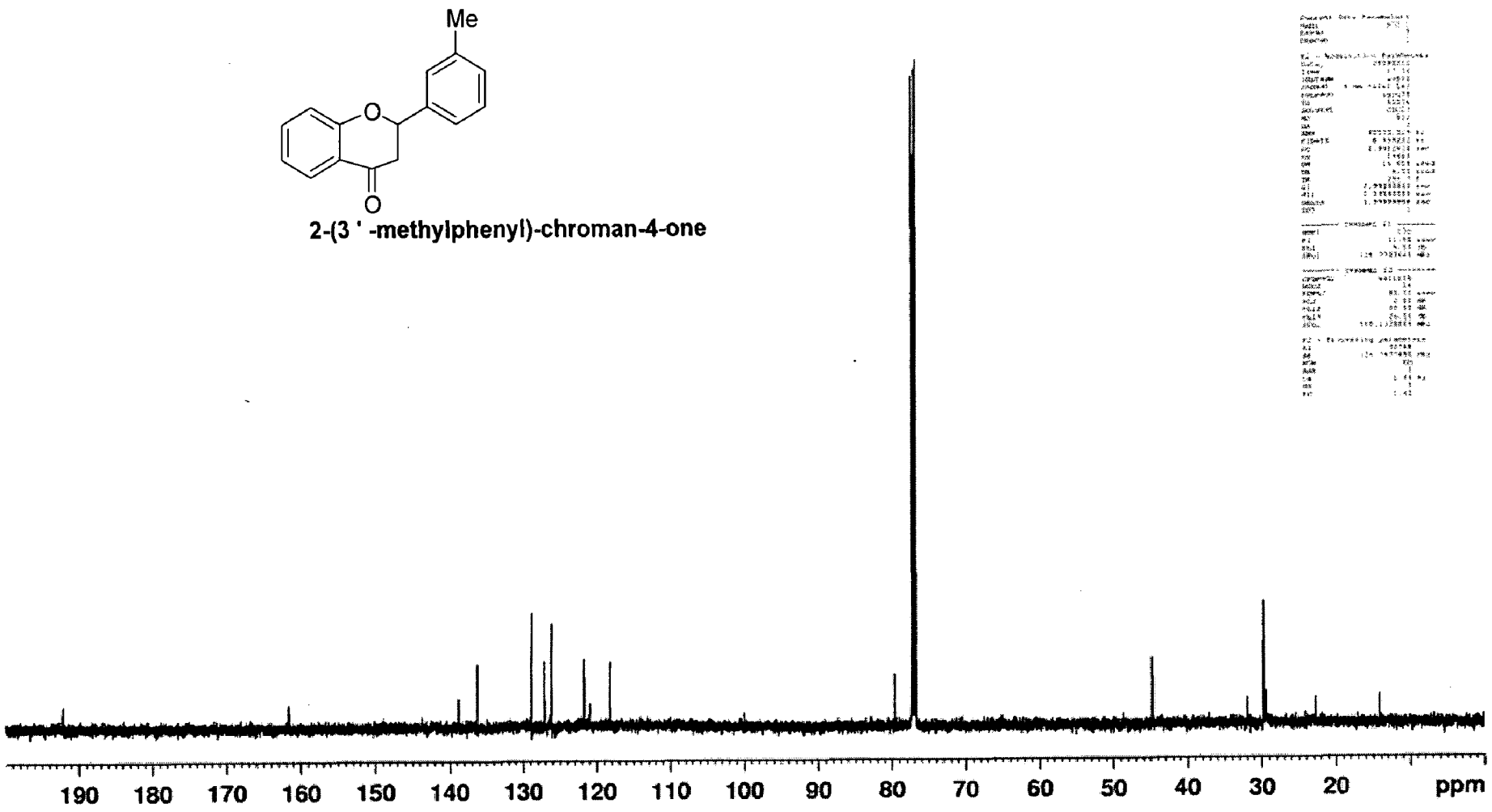


Figure S48. ^{1}H NMR spectra of 2-(4'-methylphenyl)-chroman-4-one

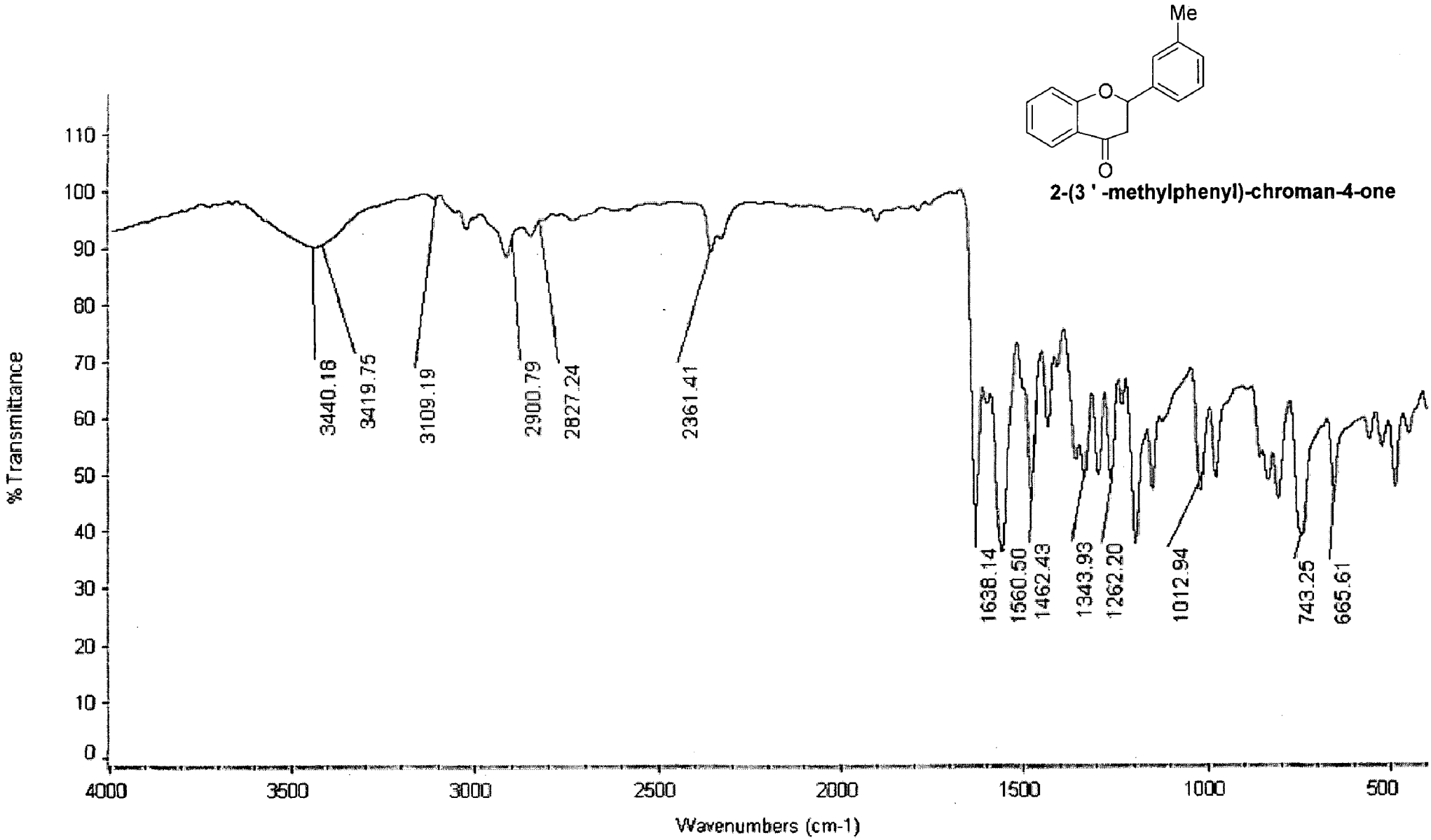


Figure S49. ^{1}H NMR spectra of 2-(4'-methylphenyl)-chroman-4-one

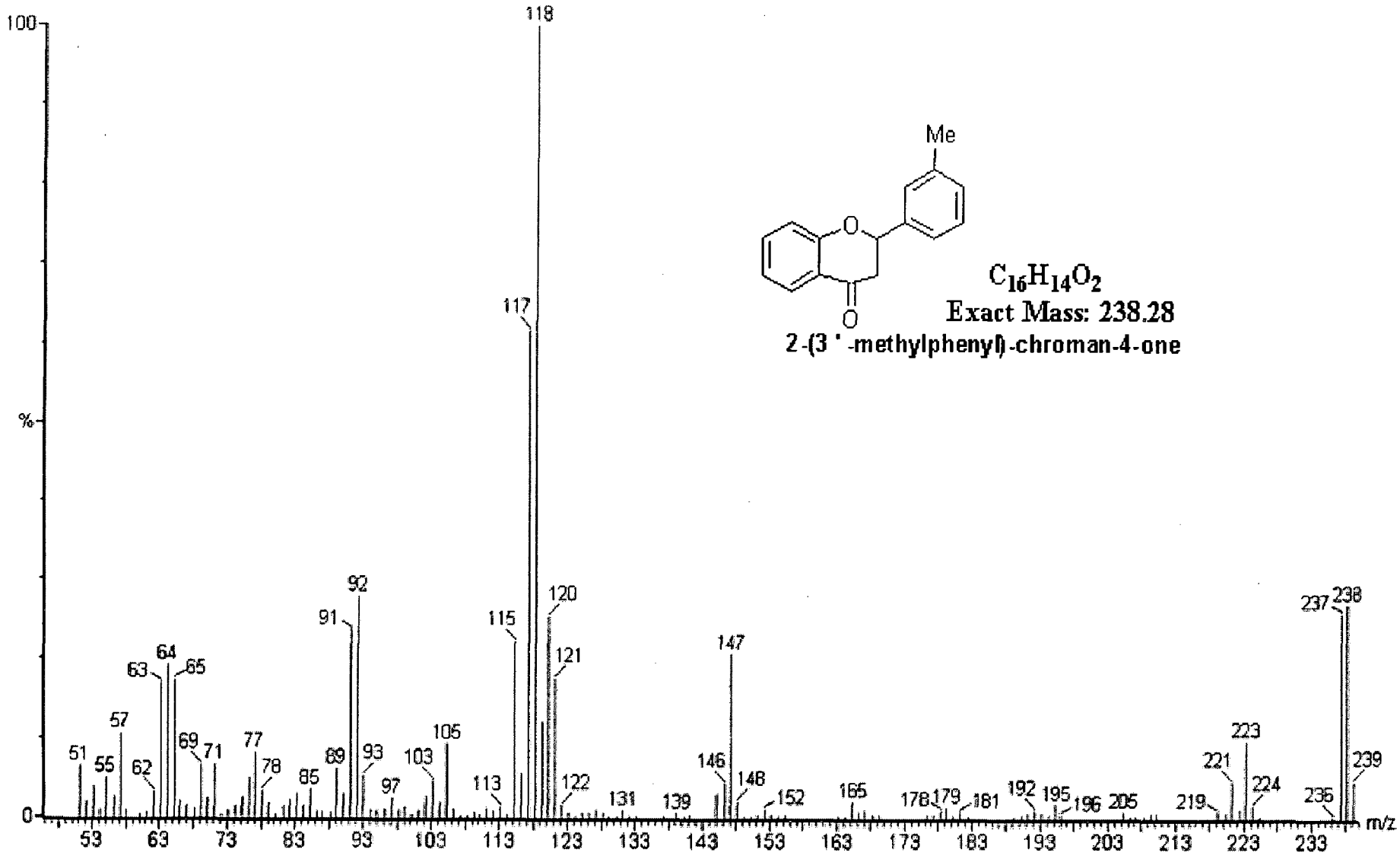


Figure S50. ^{1}H NMR spectra of 2-(4'-methylphenyl)-chroman-4-one