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DMAP AS A CATALYST FOR CARBON ACYLATION.
ELUCIDATION OF MECHANISTIC PATHWAY, INCLUDING SPECTRAL

CHARACTERIZATION OF THE PUTATIVE REACTIVE INTERMEDIATE
(TITLE)

BY

JAGADISH K.BOPPISETTI

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

Master of Science in Chemistry

IN THE GRADUATE SCHOOL, EASTERN ILLINOIS UNIVERSITY
CHARLESTON, ILLINOIS

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DEDICATION

I would like to dedicate this graduate research work to my parents, Venkateshwar Rao and Pushpanjani, who have nourished me with their endless love and warmth, taught me great things about life, and also encouraged me throughout my career.

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ABSTRACT

DMAP AS A CATALYST FOR CARBON ACYLATION. ELUCIDATION OF MECHANISTIC PATHWAY, INCLUDING SPECTRAL CHARACTERIZATION OF THE PUTATIVE REACTIVE INTERMEDIATE

3-Phenylbenzofuranone, when deprotonated with sodium hydride, forms an extended enolate system which, when treated with excess alkyl chloroformates, affords only oxygen-acylated products, as opposed to the usually desired carbon-functionalized derivatives. It was discovered that such molecules, when treated with a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP), rearrange quantitatively to the carbon acylated isomers.

These migrations, which are accompanied by a deep blue color, are proposed to involve a reactive intermediate. This intermediate, which is postulated as an ion pair charge transfer (IPCT) complex, has been closely studied in order to gain a better understanding of the rearrangement mechanism. The spectral data was obtained while the rearrangement was going on, and the lifetime of the reactive intermediate was found to be less than 15 seconds.

The rearrangement times and colors of this intriguing reaction were observed by substituting various substituents on the 3-Phenylbenzofuranone ring system. The λ_{max} values of the reaction color, with various substituents on 3-

Phenylbenzofuranone ring system, were correlated with the Hammett substituent constants.

ACKNOWLEDGEMENT

It is a great pleasure to express my heartfelt gratitude to my wonderful research advisor Dr.Howard Black for his diligent, knowledgeable, valuable and professional guidance throughout my graduate research project.

I would like to gratefully acknowledge my sisters and brother-in-laws from the bottom of my heart for their cherished love and affection. I would like to thank my true friend Prashanth Padakanti for the best of his contributions in supporting me and helping me out in my hard times. I also wish to thank my good friend Fatema Siamwala for her great encouragement throughout my stay at Eastern Illinois University.

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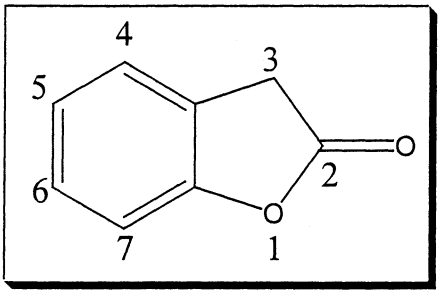
INTRODUCTION

Benzofuranone (**Figure 1**) and its derivatives comprise a large class of natural products and are well known for their wide spectrum of biological activity, including the free radical scavenging action of polymers,[1] curing ability for hormone-dependent disorders,[2] having anti-inflammatory nature,[3] showing cytotoxic property,[4] remedying oxidative stress in terms of ageing,[5] performing anti-hyperlipidemic function,[6] expressing anti-microbial activity.[7] They are also used as blood platelet-activating factor antagonists.[8] Several syntheses of benzofuranones and various analogs, along with their 3-aryl derivatives, have been featured in frequently appearing articles, providing ample evidence of the special interest among various research groups.[9]

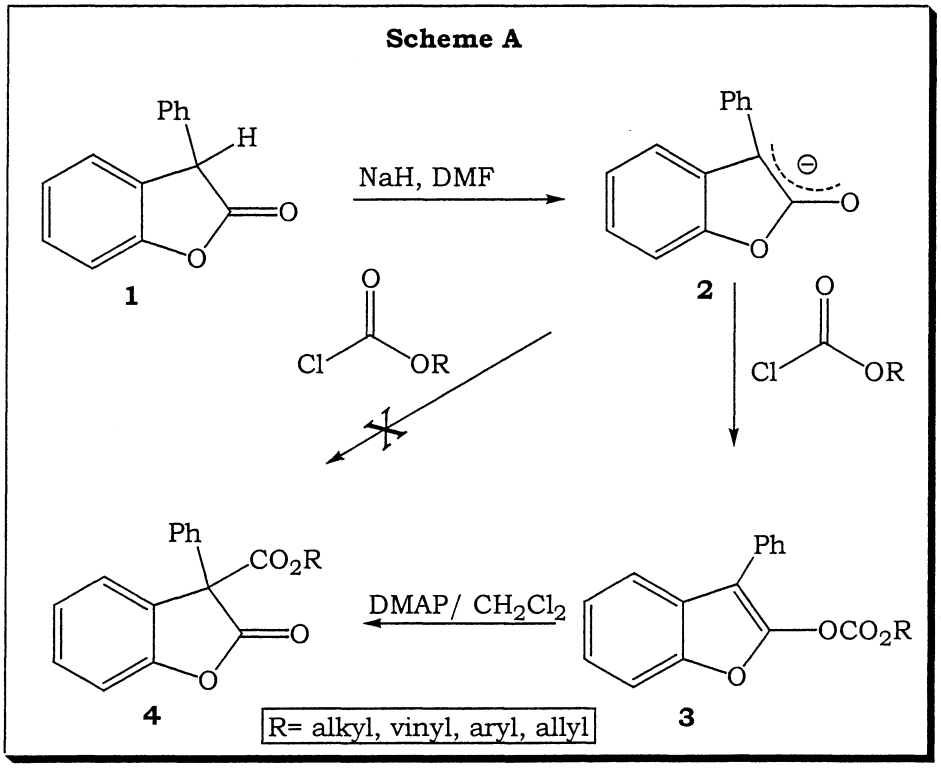
Figure 1



Regioselective acylation of enolate systems has been a difficult task in the field of synthetic organic chemistry for a long time, particularly when carbon derivitization is required.[10] Prof. Howard Black and his research group,

working on a project pertaining to benzofuranones under a contract with the National Cancer Institute, developed a reaction where the ester **A4** was a compound to be synthesized for testing in the context of its potential activity as an antineoplastic agent.

3-Phenylbenzofuranone **A1** was deprotonated with sodium hydride resulting in the delocalized enolate anion **A2**, which, when treated with chloroformates, gave oxygen acylated adducts **A3** as the only products, rather than the desired carbon acylated isomers **A4**. The colorless enol



carbonates **A3** were then treated with a catalytic amount of *N,N*-dimethylaminopyridine (DMAP) in dichloromethane (CH_2Cl_2), which resulted in an immediate deep blue

coloration of the solution, which persisted for *ca.* 45 seconds and faded over a period of 15 seconds, resulting in the desired ester **A4** via a nearly quantitative transfer of the acyl group from oxygen to the adjacent carbon.[11] It was then subsequently discovered that the inclusion of DMAP in the reaction mixture which typically afforded enol carbonates resulted in the desired C-acylated isomer in even higher yields.

Numerous efforts have been made by various research groups to effect regioselective acylation of enolate anions preferentially either at carbon or oxygen.[12] Exclusive carbon acylation in lithium or sodium enolates vs. potassium enolates of ketones,[13] and preferential carbon acylation of aromatic aldehydes and ketones promoted by Mg metal were observed.[14] Selective O-acylation in reaction of enolates with ketenes was also observed.[15] The acylation of carbon vs. oxygen depends on the conditions employed, such as the temperature, stoichiometry of the reactants, polarity of the medium, and other factors etc.,[13] Moreover the regioselective acylation of enolate anions is extremely sensitive to the type of substrate being examined. The delocalized enolate anions of malonates and diaryl acetic acid esters were found to give exclusive oxygen acylated

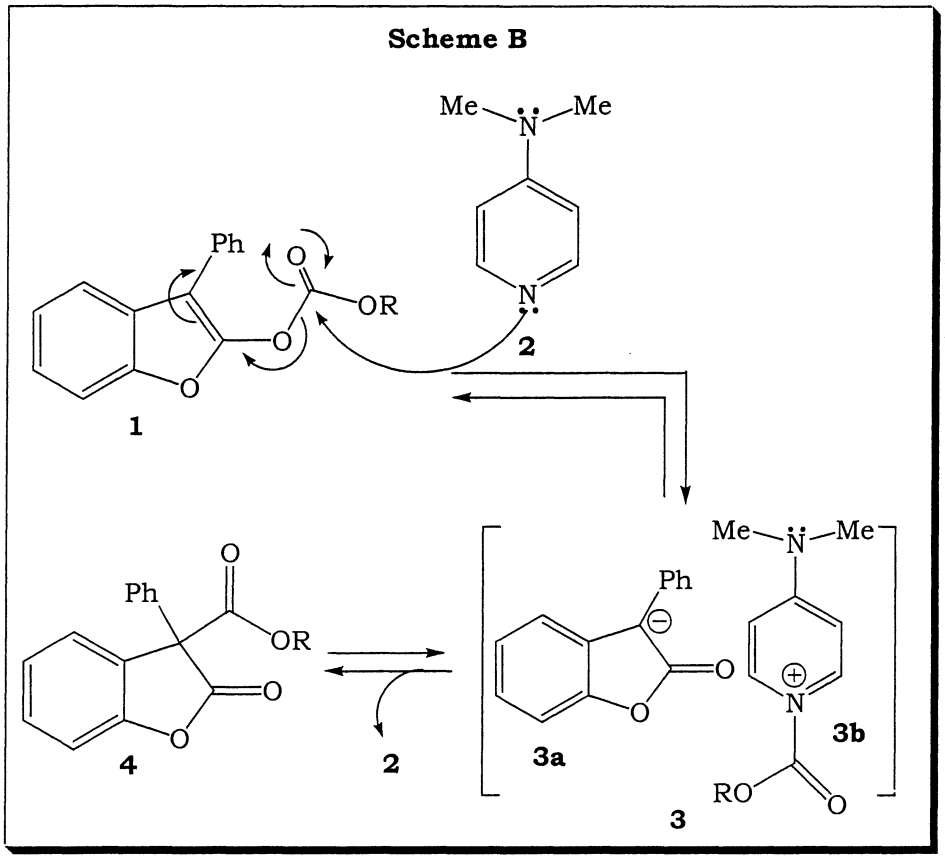
products due to the huge electron density on the oxygen atom,[16] and thus is kinetically favored.

3-Phenylbenzofuranone exhibits a tendency towards O-acylation which is analogous to diaryl acetic acid esters, since both exhibit extended π-conjugation, and these are highly resonance stabilized due to the extensive delocalization.

The kinetic acylation of oxygen can be understood in both electronic and steric terms.[10] The electron density on the oxygen atom is much greater than that on the adjacent carbon, due to its greater electronegativity; also, the oxygen is relatively unencumbered, while tertiary C (3) carbon is sterically surrounded. Therefore, nucleophilic attack by oxygen is more favored than by carbon in 3-phenylbenzofuranones.

For about a century, pyridine and its derivatives have played a major role as nucleophilic catalysts, and dialkylamino pyridines have been proven to be hypernucleophilic.[17] As already mentioned, 4-(*N,N*-dimethylamino) pyridine (DMAP) has been used to facilitate carbon acylation in benzofuranones.[11] As shown in **Scheme B**, the putative mechanism of the reaction involves the attack of DMAP (**B2**) on the carbonyl of the enol carbonate (**B1**), delocalizing the electrons onto the oxygen resulting in the

reactive intermediate (**B3**) in which the anionic counterpart (**B3a**) is extensively conjugated. Finally, attack by C-3 on the acylated pyridinium species (**B3b**) results in the carbon acylated isomer **B4** in quantitative yield. The same reaction, when carried out in non-polar solvents like diethyl ether or hexanes, did not facilitate the carbon acylation; instead, a deep purple precipitate fell out of



the solution, and addition of this precipitate to CH_2Cl_2 resulted in the C-acylated isomer **B4** following the formation of the characteristic blue color.

Obviously, a rearrangement was taking place, delivering the ester group from the oxygen atom in enol

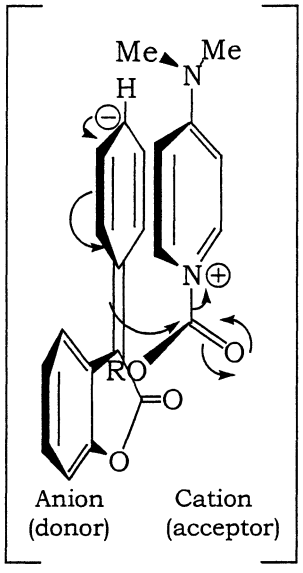
carbonate (**B1**) to the carbon atom in C-acylated isomer (**B4**) and thus classifying DMAP as a transacylation catalyst. The migration of the acyl group to the carbon in very high yield could be accounted for the stronger C-C bond than that of C-O bond and is favored thermodynamically.

The intense blue color of the reaction, when its reactants and products are colorless, implies the intermediacy of a highly-colored reactive intermediate. It also suggested that this migration might have taken place via an ion-paired charge transfer (donor-acceptor) complex (IPCTC) (**B3**), because most charge-transfer complexes are colored.

In this IPCTC, an acylated pyridinium species (**B3b**), suggested by the earlier research work on oxazolidines,[17] functions as the cationic moiety, with the benzofuranone enolate (**B3a**) serving as the anionic counterpart. In such complexes (**Figure 2**), on irradiation by light, an electron transfer of a characteristic wavelength initiates from the electron rich enolate anion (**B3a**) (donor) to the electron deficient acylated pyridinium cation (**B3b**) (acceptor). This process is analogous to the ultraviolet radiation promotion of an electron from HOMO to the LUMO of a molecule, except that, in IPCTCs, the HOMO and LUMO are in different species. The proximity and planarity of these two ions

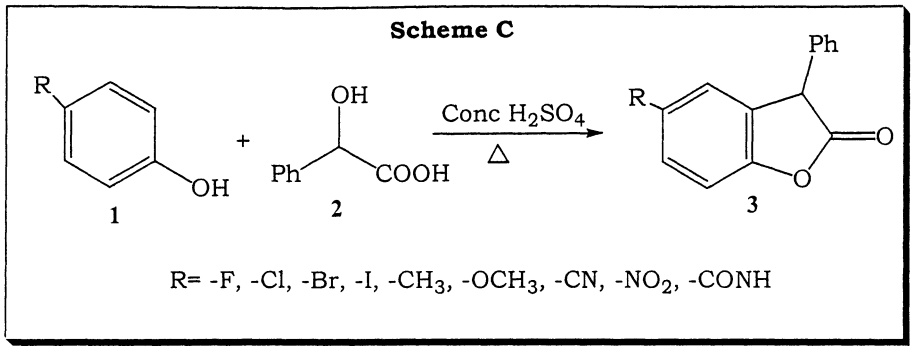
facilitate this electron transfer from the HOMO of the donor to the LUMO of the acceptor, as deduced from the research work on inorganic IPCT complexes.[18]

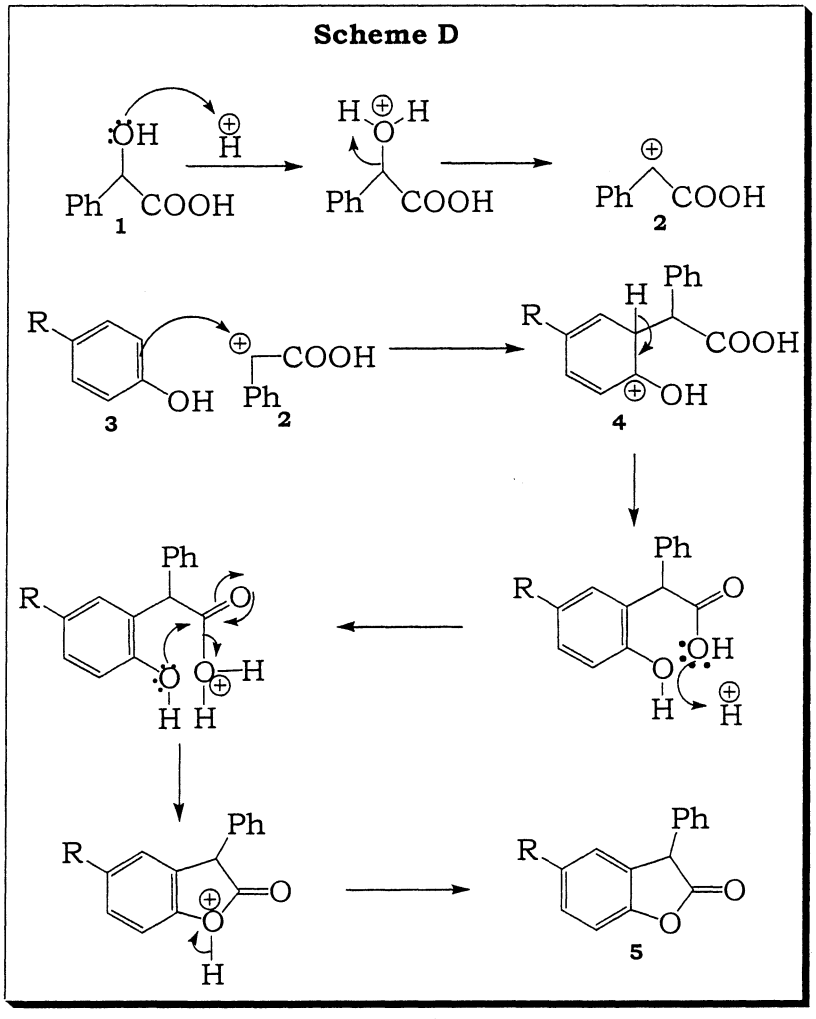
Figure 2



Exploration of the proposed mechanism (**Scheme B**) involves the extensive study of these transacylation reactions, examining the effect of certain reaction variables, such as of variously substituted benzofuranones bearing both electron withdrawing and electron releasing substituents.

Substituted phenols (**C1**) and mandelic acid (**C2**) and similar acids, as the reactants, undergo acid-catalyzed condensation in the presence of 70% sulfuric acid, shown in **Scheme C** result in benzofuranone (**C3**);[19] the mechanism is portrayed in **Scheme D**.

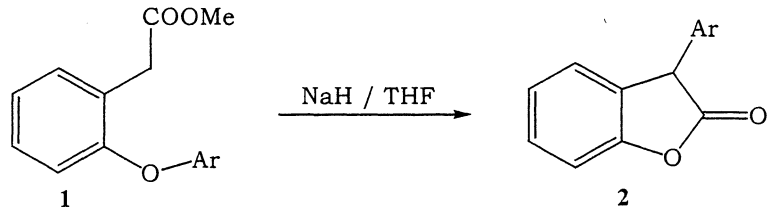




Another method for preparing 3-aryl benzofuranones has also been recently reported,[20] shown in **Scheme E,** that takes place via a Truce-Smiles rearrangement of various methyl esters of 2-(2-aryloxy) phenylacetic acid (**E1**); the

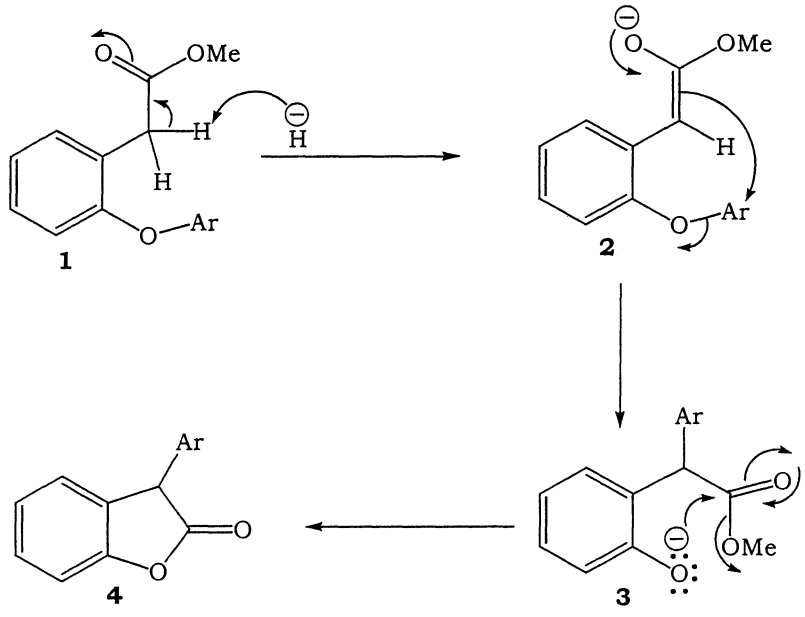
mechanism is depicted in **Scheme F**, and will be discussed later.

Scheme E



Ar = 2-pyridyl , 2-pyrimidinyl , 4-nitrophenyl

Scheme F

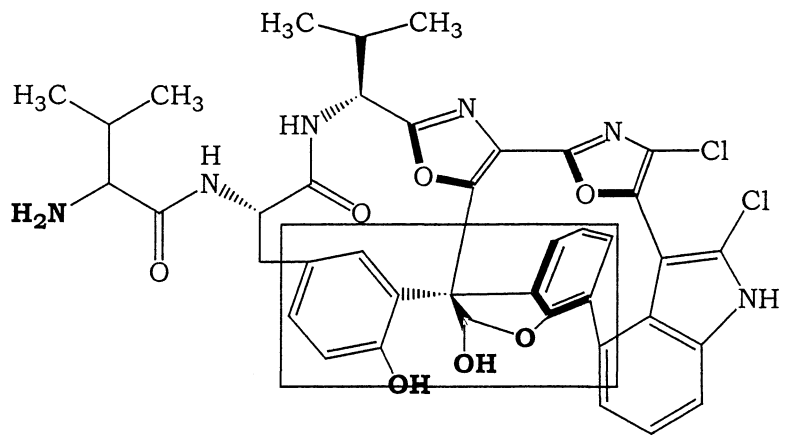


This method involves only two steps (esterification of the corresponding carboxylic acids followed by the Truce-Smiles rearrangement), and is used when the aryl substituents present on C-3 are electron withdrawing such as *p*-nitrophenyl, pyridyl, and pyrimidinyl moieties, which

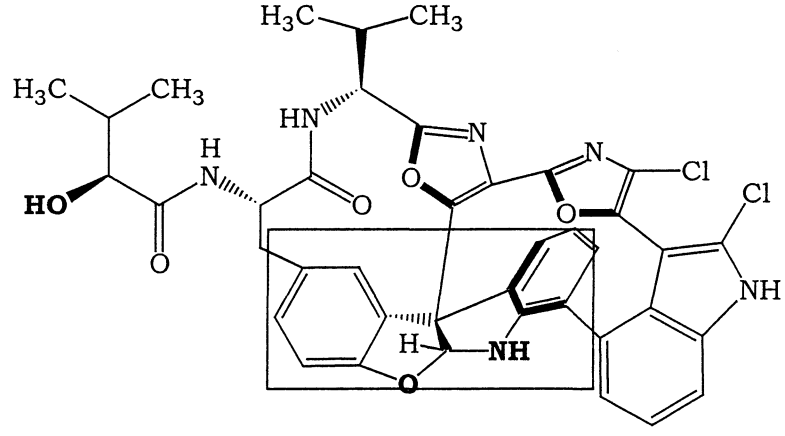
facilitate the formation of the ether (**E1**). Thus, depending on the type of benzofuranone needed, either with the electron-rich aryl substituents (**C3**) or with the electron-deficient aryl substituents (**E2**), the benzofuranone derivatives can be prepared by employing the appropriate synthetic method.

Several research groups have used the above discussed transacylation reaction, using DMAP as the catalyst.[21] Several natural products and synthetic intermediates have the benzofuranone core. One very important cytotoxic natural product is diazonamide A (**Figure 3**), which was isolated from the marine colonial ascidian *diazona angulata;* its structure was first reported in 1991 by Fenical and co-workers.[22] This paper triggered great interest among synthetic chemists throughout the world, who were attracted to the molecule as a synthetic target due both to its structural complexity and its unprecedented biological activity.[23] The first total synthesis of this compound was reported in 2001, and it was identical to the reported structure in 1991 with the highlighted PBF center (**1**, **Figure 3**).[24] However, it was quickly found that the structure of diazonamide A had been incorrectly reported; this was then revised and corrected (**2**, **Figure 3**).[24 b]

Figure 3



1. Original structure (before revision)



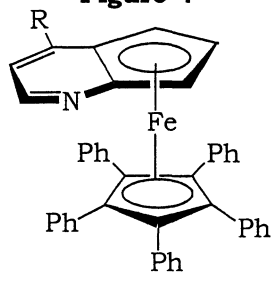
2. Revised and corrected structure

The structures of the various natural products and therapeutic agents featuring benzofuranone and its derivatives are highly asymmetric. The preparation of acylated isomers of 3-phenyl benzofuranones in high enantiomeric excess would thus be extremely useful; thus, in order to achieve high *ee*'s, the transacylation reaction must be highly asymmetric. Obviously, the transacylation reaction of PBF results in racemic products; the use of a

chiral catalyst with a highly asymmetric environment is the fastest and most economical method for producing enantioenriched products.

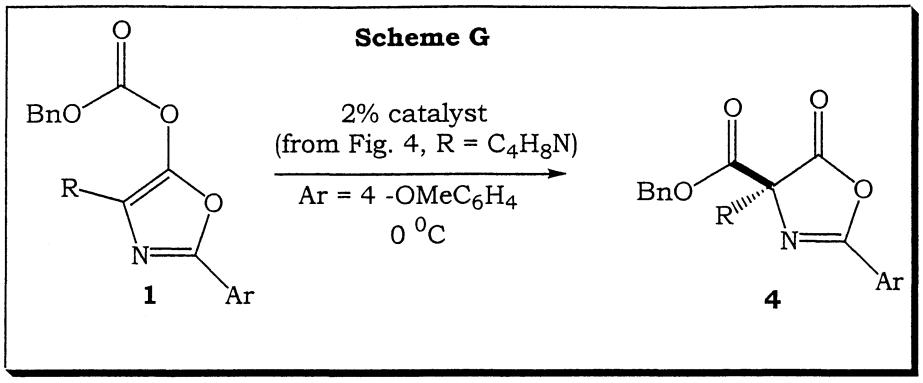
Prof. Gregory Fu at MIT has developed several chiral DMAP derivatives (**Figure 4**) with a ferrocene core.[25] The applicability of his catalyst can be seen in the enantioselective rearrangement of O-acylated azlactones (**G1**) to acyl oxazolines (**G2**), as shown in **Scheme G**. Using this catalyst, high ee's of around 88-91% were obtained, depending on the type of R group present on the substrate. The Fu group also studied the efficacy of this catalyst in benzofuranone substrates, observing ee's of around 70-80%.[26]

Figure 4



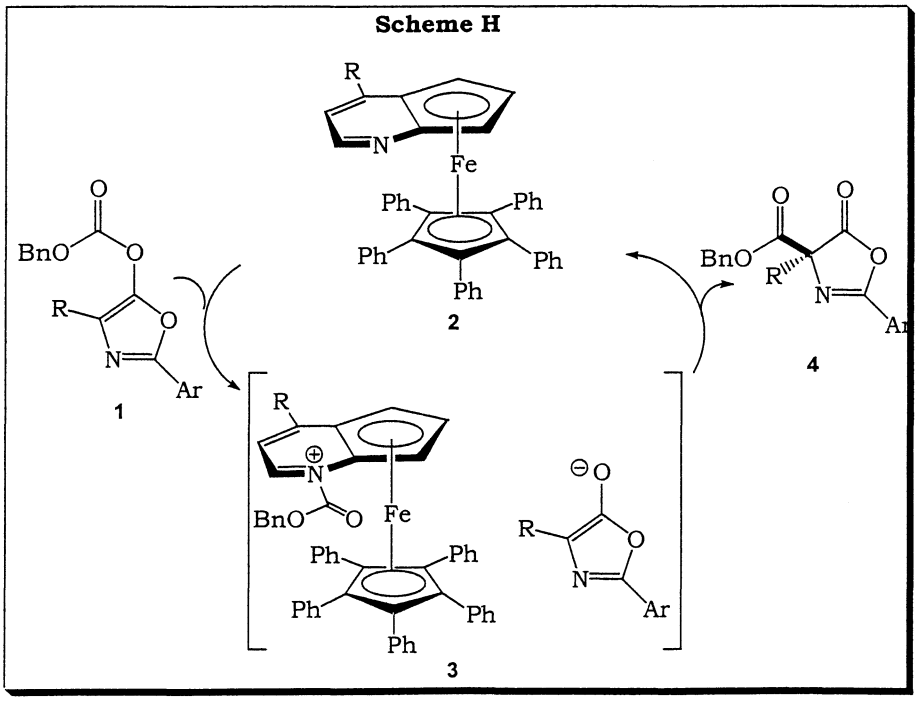
R= Me_2N, C_4H_8N

The potency of this catalyst must be studied extensively in benzofuranones with different substituents in order to know the substituent effects on ee's of these reactions. With this catalyst, as portrayed in **Scheme H**, the pentaphenyl cyclopentadienyl ring, blocks one face of



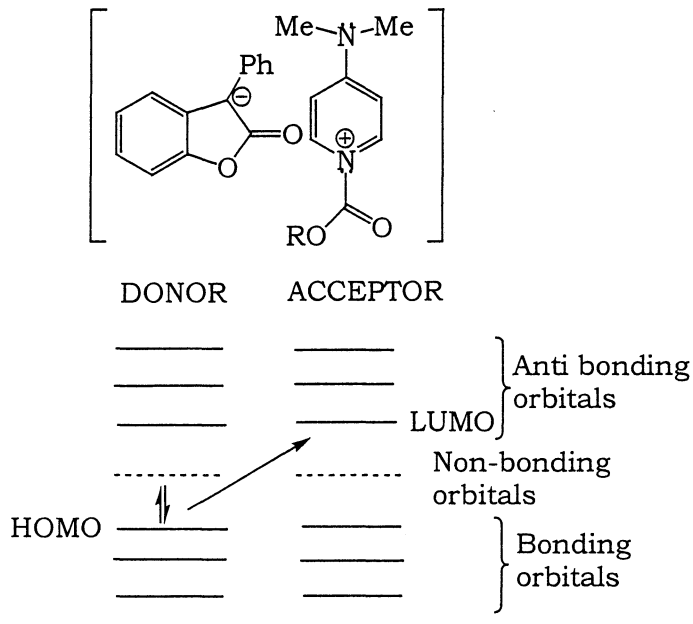
the carbonyl in the acylated pyridinium moiety from enolate attack. An x-ray crystal structure of the reactive intermediate[26] was also acquired.

Prof. Fu's catalysts were proven to be highly efficient in carrying out enantioselective acylation reactions, but a major disadvantage is the expensive chiral HPLC separations needed at two different points during their syntheses.



The hypothetical reactive intermediate (IPCTC), having a lifetime of a few seconds to few minutes, lends itself to an in-depth spectral investigation; one valuable method entails a series of UV-vis experiments. If the proposed mechanism is indeed operative, the reaction color is due to an electron transfer from the HOMO of the donor to the LUMO of the acceptor, as depicted in **Figure 5.** The increase or decrease of the energy levels in these two moieties depends on the nature of any substituents present. This situation

Figure 5



Energy level diagram depicting the electron transfer from HOMO of donor to the LUMO of acceptor

is analogous to the classic particle-in-a-box problem, where the energy of the electronic transition and the

corresponding wavelength can be calculated by substituting the values of the energy levels (x and y) between which the transition is taking place, and the length of conjugation (L) into **Eq 1.**[27]

$$E_x - E_y = \frac{h^2}{8\ m\ L^2}\ (x^2 - y^2) \qquad \textbf{Eq. 1}$$

E_x , E_y = X th and Y th energy levels of electronic transition
h = Planck's constant (6.626×10^{-34} J.s)
m = mass of the electron (9.109×10^{-31} kg)
L = length of conjugation in meters

Collecting the λ_{max} values of the transacylation reaction colors of various substituted benzofuranones should lead us to deduce the effect of the substituents on the wavelength of the absorption. The λ_{max} is defined as the wavelength at which maximum absorption occurs, and it can be affected by a number of variables, such as the electron withdrawing or electron releasing nature of any substituents, and the solvent, which also affects the λ_{max} of the reaction.[28] The presence of the electron withdrawing substituents will cause the intensity of absorption shift to shorter wavelength (high frequency) known as a hypsochromic, or blue shift. The presence of electron releasing substituents will shift to longer wavelength (low

frequency) known as bathochromic shift or red shift; the reasons will be discussed in detail shortly. The effect of the solvent on the λ_{max} of the reaction is termed solvatochromism; negative solvatochromism corresponds to a hypsochromic shift which results due to the increase in polarity of the solvent and vice versa, due to the dipole-dipole interactions and hydrogen bonding of the molecule with the solvent.

These wavelength maxima obtained for different substituents can be correlated with the values of Hammett substituent constants and thus the validity of the experimental results can be authenticated.

Hammett derived a relationship showing the effect of substituents on the rate constants of a given reaction, and formulated an equation (**Eq 2**).[29] He experimentally obtained many values for the effect of *m*- and *p*- substituents on the aromatic rings during his research work on benzoates; these values came to be known as Hammett substituent constants designated as σ; electron withdrawing substituents bear a positive sign ($\sigma+$) and electron releasing substituents bear a negative sign ($\sigma-$). These values are specific for different substituents and are obtained by dividing the values of the rate constants, for the reaction bearing the

substituent (log K) by the reaction bearing no substituent (log K_0), taking the reaction constant ρ as unity.

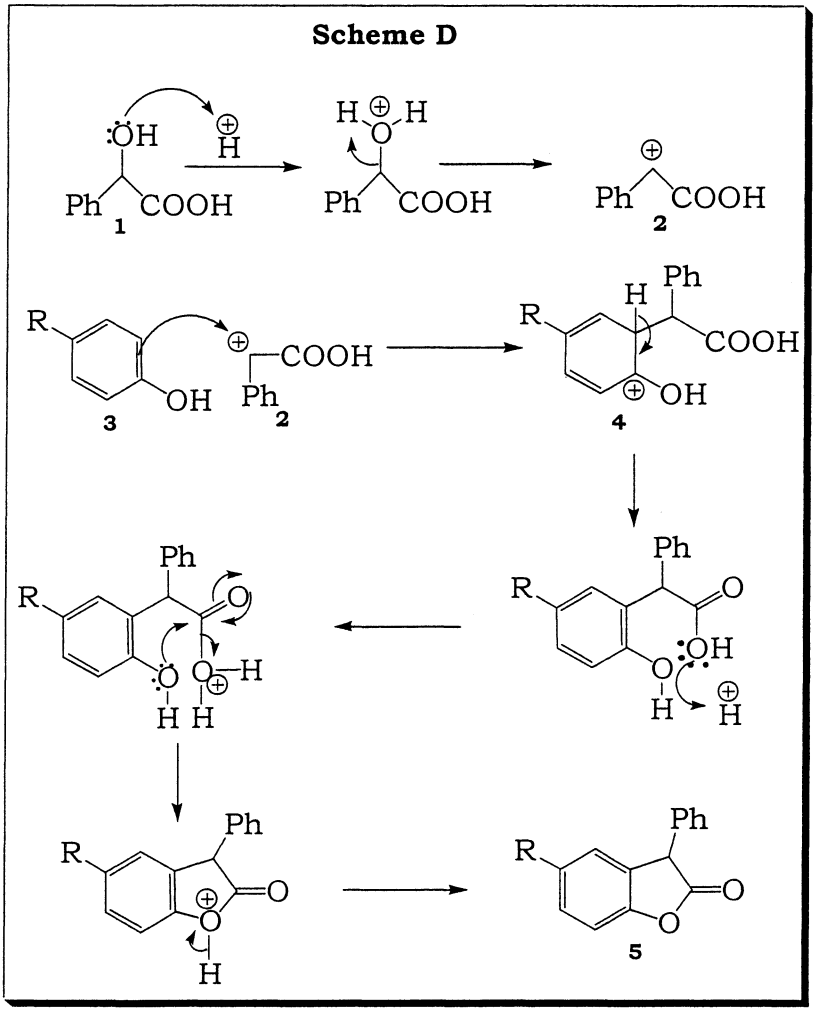
$$\frac{\log K}{\log K_o} = \rho\sigma \qquad \textbf{Eq. 2}$$

This experimentation would be quite helpful to strongly support the results with that of theory in terms of deriving a relation between the Hammett constants and the λ_{max}.

Thus, the spectral and kinetic studies carried out on the transacylation reactions (**Scheme B**) would be of much help in characterizing the first fully organic reactive intermediate (IPCTC) involving no metals (this has yet to be accomplished), while, more importantly, paving the way toward the development of a new chiral DMAP catalyst which is neither difficult to synthesize nor expensive.

RESULTS AND DISCUSSION

3-Phenylbenzofuranone (**C3**) was prepared by following the procedure shown in **Scheme C**,[19] wherein the phenol undergoes electrophilic attack by mandelic acid in the presence of 70% sulfuric acid. As shown mechanistically in **Scheme D**, protonation of the alcoholic hydroxyl group of



mandelic acid (**D1**) and elimination of water leaves a carbocation (**D2**), which is attacked by phenol (**D3**) to afford the hydroxy acid (**D4**). The intramolecular attack of

the phenolic oxygen on the carbonyl group of the carboxylic acid, followed by elimination of water, led to the ring closure (**D5**). After workup and recrystallization from 95% ethanol, the products were obtained in yields ranging from 25-45% depending on the type of the benzofuranone substrate. Various 5-substituted benzofuranones were synthesized by utilizing the respective *p*-substituted phenols; specifically, *p*-bromo-, fluoro- and cyanophenols were employed.

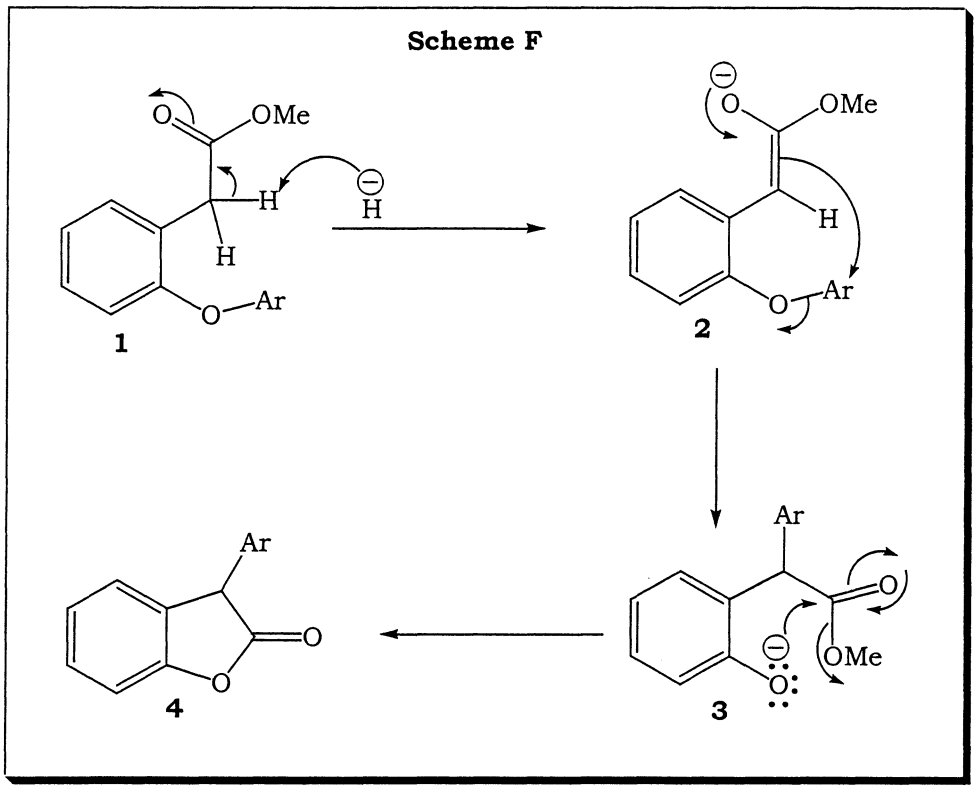
Problems were encountered in the recrystallization of 5-cyano-3-phenylbenzofuranone, in that, for every solvent tried, (95% ethanol, methanol, isopropyl alcohol, water, mixed solvents like ethanol and water, methanol and water isopropyl alcohol and water) the pure product did not precipitate.

For the preparation of the remaining substituted benzofuranones, which were obtained as thick gels when method A was employed, where the reaction mixture was heated at 115 ^{0}C for 45 minutes, method B, a slightly modified procedure from method A, was found successful. By this method, substituted benzofuranones were synthesized (**Scheme C**), by employing *p*-chlorophenol, *p*-iodophenol, *p*-acetamidophenol, *p*-cresol and *p*-methoxyphenol as reactants. The reaction conditions were maintained as in method A

except for the reaction time and reaction temperature, which involved heating for three hours at 100 ^{0}C. Standard workup and recrystallization from 95% ethanol, except for 5-methoxybenzofuranone, which was recrystallized from methanol, provided the products in yields ranging from 35-55%. Due to similar problems mentioned in method A with recrystallization, the substituted benzofuranones with -iodo, and -acetamido groups could not be purified. Further time was not invested in purifying these products by other methods such as HPLC, or standard column chromatography because the aim was to focus on the mechanistic aspects of the rearrangement reaction, performed with the pure substrates which were already on hand, rather to concentrate on the synthetic part.

The benzofuranones with various aryl substituents at C-3 position were synthesized by following a literature procedure,[20] of which the final step is shown in **Scheme E**. The methyl ester **E1** was obtained in two steps, wherein the first involves the deprotonation and reaction of 2-hydroxyphenylacetic acid with the appropriate aryl halide such as 2-chloropyridine, 2-chloropyrimidine and 4-fluoronitrobenzene. Second, the carboxylic acid is converted to the methyl ester via deprotonation of carboxylic acid proton and followed by nucleophilic attack

of the ester anion on the iodomethane resulting in the methyl ester **E1** that then undergoes Truce-Smiles rearrangement; the mechanism is shown in **Scheme F**. The methyl ester **E1**, which is **F1** here, undergoes intramolecular



nucleophilic aromatic substitution results in the migration of the aromatic ring from one atom to the other to give desired 3-arylbenzofuranone **F4**. The purification of these compounds might have involved HPLC and column chromatography that were not done for the above stated reasons.

The spectral characterization of the various 5-substituted 3-phenylbenzofuranones was done to confirm the identity of the products, and to establish bonding

parameters for comparison with values to be obtained during the mechanistic studies. The IR data for benzofuranones with electron withdrawing and electron releasing substituents are collected in **Table 1.0,** and show that the carbonyl group absorption for the unsubstituted benzofuranone at 1796 cm^{-1}.

R	**C=O** cm^{-1}	**C=C** cm^{-1}	**C-O-C** cm^{-1}	**C-R** cm^{-1}
H	1796	1614	1222	
F	1798	1606	1211	743
Cl	1815	1606	1228	828
Br	1813	1606	1226	756
Me	1802	1612	1228	
OMe	1804	1603	1221	

Table 1.0. IR absorptions of unsubstituted and substituted benzofuranones.

The substituted benzofuranones follow the trend of electronegativity of the substitutents present on the aromatic ring. From a theoretical point of view, the inductive effect of the substituents shortens the length of the C=O bond leading to higher force constant and increased frequency of absorption. Hence, if the carbonyl absorptions for all the substituted benzofuranones are closely observed, they are seen to depend on the type of the substituent present; i.e the more electron withdrawing the substituent is, the higher is the frequency of carbonyl absorption and vice versa.

The experimental results are in concurrence with the theory except for the C=O in 5-fluoro-3-phenylbenzofuranone which unusually absorbs at lower frequency when compared to 5-chloro- or 5-bromo-3-phenylbenzofuranones. The reason for this unusual behavior of fluorine is not known. The expected aromatic ring C=C stretch at 1603-1612 cm^{-1} and a C-O-C stretch at 1211-1282 cm^{-1} were also observed, as were characteristic absorptions at 828cm^{-1} for chloro-, 756cm^{-1} for bromo-, and 743cm^{-1} for fluoro-substituted benzofuranones.

Proton NMR spectral characterization (**Table 2.0**) was also carried out on these compounds. Actually, certain peaks in spectra obtained were not first order; hence,

R	NMR (ppm)	UV(nm)	R	NMR (ppm)	UV(nm)
H	δ 4.8 (s, 1 H), 7.3 (m, Ar 9 H)	261.61	**Br**	δ 4.8 (s, 1 H), 7.3 (m, Ar 8 H)	268.72
F	δ 4.8 (s, 1 H), 7.2 (m, Ar 8 H)	264.60	**Me**	δ 2.3 (s, - 3 H, - CH_3) 4.8 (s, 1 H), 7.2 (m, Ar 8 H)	267.60
Cl	δ 4.8 (s, 1 H), 7.2 (m, Ar 8 H)	266.47	**OMe**	δ 3.8 (s, 3 H, - OCH_3) 4.8 (s, 1 H), 7.1 (m, Ar 8 H)	274.32

Table 2.0. NMR and UV data of the unsubstituted and substituted benzofuranones.

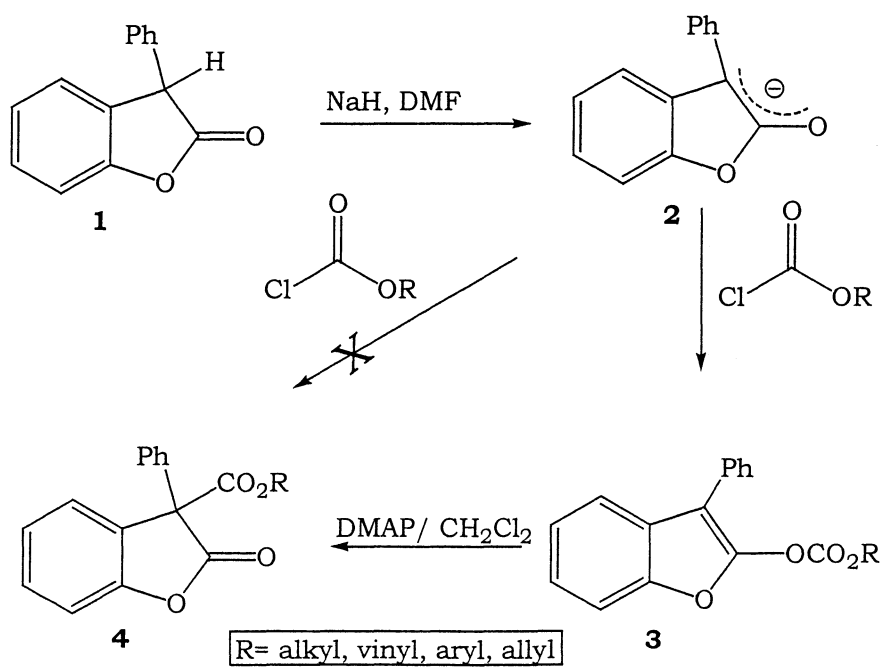
there was no clear separation in chemical shifts and all the aromatic peaks corresponding to the unsubstituted and substituted benzofuranones appeared as multiplets. The main peak of interest in all these benzofuranones, was a singlet seen at ~4.8 ppm corresponding to the non-aromatic proton at C-3 which validates the product (**C3**) with two aromatic rings, one carbonyl and one hydrogen attached to that carbon. A multiplet is observed at ~7.2 ppm corresponding to the aromatic protons clustered together, and this is where the typical aromatic protons absorb. Additionally, a singlet is observed at 2.3 ppm for 5-methyl-3-phenylbenzofuranone corresponding to the methyl protons, indicating that the three methyl protons are isolated and equivalent, with no adjacent protons for coupling. A singlet at 3.8 ppm corresponding to isolated methoxy protons in 5-methoxy-3-phenylbenzofuranone is standard for the presence of methoxy group.

UV data were also collected and the λ_{max} were measured for all the benzofuranone substrates; the trend of wavelengths shown in **Table 2.0** is due to the dipole-dipole interactions in substituted benzofuranones. These interactions tend to lower the energy of the excited state as well as the ground state for π-π^* transitions and thus decrease the wavelength of absorption. The more electron

withdrawing the substituent is, the smaller is the λ_{max} of absorption of that compound. As can be seen, the benzofuranones with the electron withdrawing substituents absorbed at shorter wavelength or higher energy and the benzofuranones with electron releasing substituents absorbed at longer wavelength or lower energy.

The synthesis of enol carbonates (**A3**) involves the deprotonation of the C-3 proton in 3-phenylbenzofuranone (**A1**) with sodium hydride in dimethylformamide (DMF), resulting in a highly extended enolate (**A2**). This, on treatment with ethyl chloroformate and overnight stirring at room temperature undergoes O-acylation kinetically,

Scheme A



owing to the nucleophilic oxygen with greater electron density on it. Moreover, the oxygen is more sterically available for functionalization due to its unencumbered environment; the planarity of the enolate anion is particularly noteworthy. Various enol carbonates were prepared from the corresponding substituted benzofuranones and were obtained in yields ranging from 69%-98%. All the enol carbonates prepared were spectrally characterized by IR (**Table 3.0**) and NMR (**Table 4.0**). In IR spectra, the carbonyl absorption of the enol carbonates of unsubstituted and substituted benzofuranones do not show any distinct comparison to one another. This is due to the fact that carbonyl is not under the direct influence of either electron withdrawing

R	**C=O** cm^{-1}	**C=C** cm^{-1}	**C-O-C** cm^{-1}	**C-R** cm^{-1}
H	1784	1644	1234	
F	1785	1642	1241	801
Cl	1785	1640	1232	804
Br	1785	1643	1231	756
Me	1784	1640	1228	
OMe	1783	1640	1245	

Table 3.0. IR data of the enol carbonates of unsubstituted and substituted benzofuranone.

or releasing groups but instead, it is influenced by the inductive effect of the adjacent oxygens. These oxygens in the enol carbonate (**A3**) increase the length of the C=O bond and thus by lowering the frequency of absorption in

comparison with the unsubstituted benzofuranone. The absorption at 1640-1644 cm^{-1} corresponding to aromatic ring C=C stretch, at 2978-2982 cm^{-1} corresponding to C-H stretch of ethyl group and also for the methyl and methoxy substituents, and absorption at 1231-1245 cm^{-1} corresponding to C-O-C stretch were also observed for enol carbonates of various substituted benzofuranones. The absorptions at 804cm^{-1} for chloro, 756cm^{-1} for bromo and 801cm^{-1} for fluoro-substituted benzofuranones were also observed.

In NMR, the singlet at 4.8 ppm corresponding to benzofuranones **A1** is now absent due to the deprotonation of the C-3 proton to result in enol carbonate **A3.** Hence in addition to the multiplets discussed for the aromatic protons appearing at ~7.2, in context of benzofuranones **C3**

	R					
	H	**F**	**Cl**	**Br**	**Me**	**OMe**
NMR (ppm)	δ 1.4 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.4 (m, Ar 9 H)	δ 1.3 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.3 (m, Ar 8 H)	δ 1.3 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.4 (m, Ar 8 H)	δ 1.3 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.4 (m, Ar 8 H)	δ 1.3 (t, 3 H, -CH_3), 2.3 (s, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.4 (m, Ar 8 H)	δ 1.2 (t, 3 H, -CH_3), 3.8 (s, 3 H, -OCH_3) 4.3 (q, 2 H, -CH_2), 7.2 (m, Ar 8 H)
UV (nm)	265.7	265.73	266.47	267.60	266.47	276.56

Table 4.0. NMR and UV data of the enolcarbonates of the unsubstituted and substituted benzofuranone.

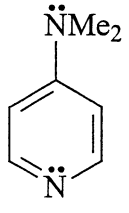
which is also **A1** in this case, the chemical shifts corresponding to $-CH_2$ and $-CH_3$ of ethyl group of enol carbonate **A3** are of interest. Since all the enol carbonates were prepared from ethyl chloroformate, $-CH_2$ and $-CH_3$ show up as a quartet and triplet respectively because they are coupled with each other. A triplet was observed at 1.2-1.4 ppm for $-CH_3$ group due to the coupling with the $-CH_2$ protons and a quartet was observed at 4.3 ppm for $-CH_2$ group due to the coupling with the adjacent $-CH_3$ protons. These chemical shift values obtained at about the same frequency are true for all the enol carbonates of substituted benzofuranones.

UV experiments were also performed on these enol carbonates of substituted benzofuranones (**Table 4.0**). The λ_{max} values obtained follow the trend for the reasons discussed in the earlier part of this section in context of substituted 3-phenylbenzofuranones.

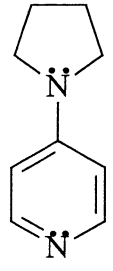
The third step is the most interesting part of the whole step sequence portrayed in **Scheme A**. The enol carbonate **A3** is dissolved in dichloromethane (CH_2Cl_2), and a catalytic amount (~40 mg) of dimethylaminopyridine (DMAP) is added; an immediate deep blue coloration is observed

R		DMAP[1](cat)	DMAP(1:1)	4-PP[2](cat)	4-PP(1:1)
H	Rxn color	Deep blue	Deep blue	Deep blue	Deep blue
	Rxn time	45sec	35 sec	60 sec	50 sec
	IR(cm^{-1})	1816, 1737	1816, 1737	1822	1816, 1736
F	Rxn color	Deep purple	Deep purple	Deep purple	Deep purple
	Rxn time	4 min	5 min 45 sec	7 min	7 min
	IR(cm^{-1})	1819,1739	1820,1739	1819,1738	1818,1736
Cl	Rxn color	Deep purple	Deep purple	Deep purple	Deep purple
	Rxn time	10min45sec	120sec	8min	3min35sec
	IR(cm^{-1})	1821, 1739	1821, 1739	1821, 1739	1821, 1739
Br	Rxn color	Deep purple	Deep purple	Deep purple	Deep purple
	Rxn time	4min	2min30sec	8min	4min
	IR(cm^{-1})	1820,1739	1820,1739	1820,1739	1820,1739
CH_3	Rxn color	Deep blue	Deep blue	Deep blue	Deep blue
	Rxn time	75sec	30sec	50sec	25sec
	IR(cm^{-1})	1813, 1742	1813,1739	1820,1739	1813,1742
OCH_3	Rxn color	Deep blue	Deep blue	Deep blue	Deep blue
	Rxn time	3min20sec	50sec	1min45sec	1min10sec
	IR(cm^{-1})	1813,1739	1813,1739	1813,1739	1813,1740

Table 5.0. The reaction color and reaction time of migration of acyl group from oxygen to adjacent carbon via DMAP and 4-PP catalysis along with IR absorption of carbonyl group on 3-phenylbenzofuranone ring system.



1) 4-(dimethylamino)pyridine
(DMAP)



2) 4-pyrrolidinopyridine
(4-PP)

which persists for about 45 seconds and fades over 15 seconds. Washing with dilute acid as part of the standard aqueous workup resulted in the C-acylated isomer of benzofuranone ester **A4**. The deep blue coloration is an indication of a migration of a group from oxygen to the adjacent carbon in an equilibrium process. The quantitative yields characteristic of this reaction are probably a consequence of the greater strength of the bonds newly formed in C-acylated isomer **A4** than that of the bonds broken in O-acylated isomer **A3**.

The substituent effects on the rearrangement colors and times were observed for all the substituted benzofuranones and are tabulated in **Table 5.0**. Conceptually, it should take more time for the rearrangement involving the electron withdrawing substituents, and less time for the reaction involving electron releasing substituents. This is because the electron withdrawing substituents exert a stabilizing influence on the enolate anion, rendering it less nucleophilic and thus is slower in attacking the acylated pyridinium cation. Similarly, the electron releasing substituents exert destabilizing influence on the enolate anion, rendering it more nucleophilic and thus are faster in attacking the acylated pyridinium cation. These

rearrangement times and colors were also observed by employing 4-pyrrolidinopyridine (4-pp) as a catalyst. It was noticed that the data were inconsistent for the catalysts, when used in catalytic amount. These catalysts when used in stoichiometric ratio, showed that, the rearrangement was slower in case of 4-PP than DMAP with an exception of $-CH_3$ substituent.

The products were characterized by IR (**Table 6.0**) and NMR (**Table 7.0**). The IR spectra showed two carbonyl

R	**C=O** cm^{-1}	**C=C** cm^{-1}	**C-O-C** cm^{-1}	**C-R** cm^{-1}
H	1817, 1739	1601	1226	
F	1819, 1739	1608	1234	816
Cl	1821, 1739	1614	1232	819
Br	1820, 1739	1614	1233	737
Me	1813, 1742	1617	1234	
OMe	1813, 1739	1605	1228	

Table 6.0. IR data of the C-acylated isomers of the unsubstituted and substituted benzofuranones.

absorptions, one resulting from the ethyl ester at C-3 where the carbonyls in regular ester functionalities absorb, and one from the C-2 carbonyl at 1739 and 1817 cm^{-1} respectively for the unsubstituted benzofuranone. The trend of carbonyl absorptions for the substituted benzofuranones as tabulated is due to the same reasons discussed earlier. Other absorptions include symmetric C=C stretching of aromatic ring at 1605-1617 cm^{-1}, C-O stretch of ester at 1226-1234 cm^{-1}, and C-X stretch at 737,816 and

819 cm^{-1} corresponding to the -bromo, -fluoro and -chloro substituents, respectively.

In proton NMR spectral characterizations, the chemical shifts observed were similar to those showed up in the enol carbonate. The reasons for the chemical shift values were discussed earlier.

	R					
	H	**F**	**Cl**	**Br**	**Me**	**OMe**
NMR (ppm)	δ 1.2 (t, 3 H, -CH_3), 4.2 (q, 2 H, -CH_2), 7.3 (m, Ar 9 H)	δ 1.2 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.3 (m, Ar 8 H)	δ 1.2 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.3 (m, Ar 8 H)	δ 1.2 (t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.3 (m, Ar 8 H)	δ 1.2 (t, 3 H, -CH_3), 2.3 (s, 3 H, -CH_3) 4.3 (q, 2 H, -CH_2), 7.3 (m, Ar 8 H)	δ 1.2 (t, 3 H, -CH_3), 3.8 (s, 3 H, -OCH_3) 4.2 (q, 2 H, -CH_2), 7.2 (m, Ar 8 H)
UV (nm)	263.83	267.60	268.72	270.59	268.72	279.17

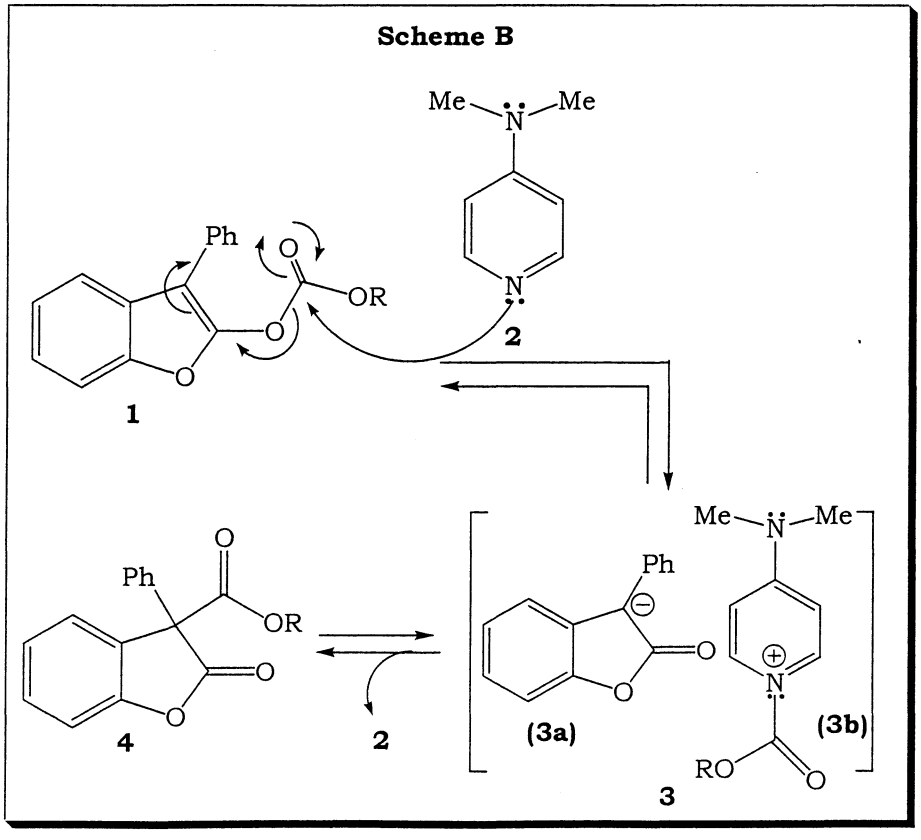
Table 7.0. NMR and UV data of the C-acylated isomers of the unsubstituted and substituted benzofuranone.

UV data were obtained for the C-acylated isomer of unsubstituted benzofuranone (**Table 7.0**), and the λ_{max} values of the C-acylated isomers of substituted benzofuranones follow the similar trend discussed earlier.

The earlier paper[11] indicated that the rearrangement reaction, which when carried out in non-polar solvents like hexanes and diethyl ether resulted in a deep purple

precipitate immediately after the addition of DMAP. This precipitate was assumed to be the reactive intermediate, the so-called ion-pair charge transfer complex (IPCTC) **B3** which, when dissolved in dichloromethane, rearranged to the C-acylated isomer **B4.** It was deemed important to isolate this reactive intermediate and fully characterize, so as to know its nature and stability.

This precipitate was isolated and spectrally characterized ~15 seconds after the addition of DMAP, and the IR spectrum indicated the carbonyl absorptions corresponding to the C-acylated isomer **B4** at 1817 and 1732 cm^{-1} respectively. The IR spectrum of this compound (**B3**),



which was stored under nitrogen atmosphere in the refrigerator for two days, indicated the carbonyl absorptions at 1822 and 1744 cm^{-1}. These spectra when compared to the IR spectrum of the C-acylated isomer obtained by the regular rearrangement reaction indicated the completion of rearrangement. Hence it appears that the rearrangement reaction is complete in less than ~15 seconds, and also the lifetime of the reactive intermediate (IPCTC) is less than ~15 seconds; the possible reasons will be discussed shortly.

Since the characterization of the reactive intermediate was not feasible, it was believed that FT-IR experiments would help in studying the course of rearrangement reaction. In regard to this, the anionic (**B3a**) and cationic partners (**B3b**) of the IPCTC **B3** were isolated separately and characterized by IR spectra. The acylated pyridinium cation (**B3b**) was prepared by adding ethyl chloroformate to DMAP in tetrahydrofuran, then adding silver hexafluoroantimonate, and finally evaporating the solvent after fifteen minutes.

The enolate anion (**B3a**) was prepared by deprotonating the C-3 proton in 3-phenylbenzofuranone with sodium hydride, in hexane solvent, and then evaporating the solvent under reduced pressure. The carbonyl absorptions

of these two species, which were quite stable at room temperature in air, were of special interest. IR spectra indicated carbonyl absorption at 1797 cm^{-1} for the enolate anion and 1785 cm^{-1} for the acylated DMAP cation, as compared to the carbonyls of the benzofuranone and ethyl chloroformate at 1796 and 1780 cm^{-1} respectively. Taking these results into consideration, FT-IR experiments were performed; the main intention was to collect the IR spectra while the rearrangement was occurring and to observe the carbonyl absorptions of the ester functional group. If the rearrangement occured as it was described in the mechanism of the reaction, the IR spectra should show the carbonyl absorptions of enol carbonate, enolate anion, acylated pyridinium cation and finally the C-acylated isomer in a sequential manner starting right after the addition of DMAP.

The carbonyl absorption should change gradually from 1785 cm^{-1} in enol carbonate to 1817 and 1739 cm^{-1} in C-acylated isomer via 1797 cm^{-1} of enolate anion (**B3a**) and 1785 cm^{-1} of acylated DMAP cation (**B3b**), during the course of rearrangement. The IR data were collected every 16 seconds, starting from the addition of DMAP to the enol carbonate solution. The spectra collected showed the carbonyl absorptions at 1813 and 1738 cm^{-1} after only 16

seconds, indicating that the reaction was complete after between 1-16 seconds; this conclusion is also evident from the IR data obtained for the isolated purple precipitate discussed above.

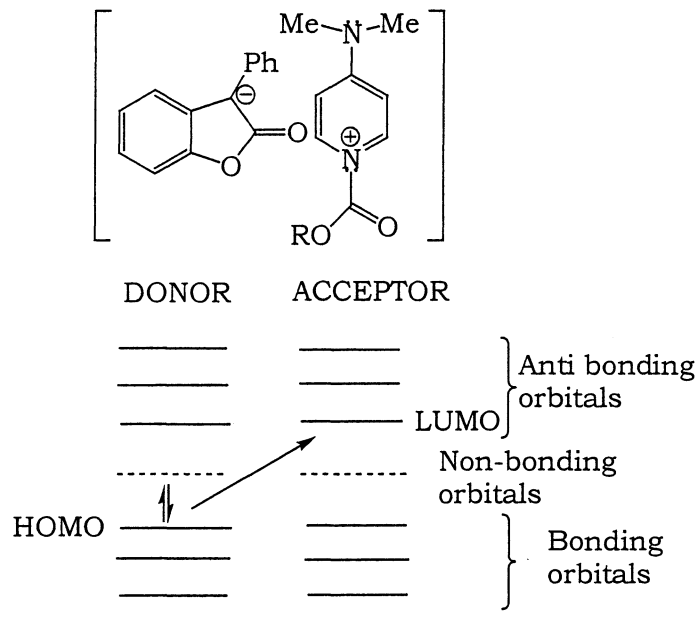
The persistence of the color for ~45 seconds and fading over ~15 seconds apparently disguised the early completion of the reaction but this can be explained in terms of the IPCTC extinction coefficient, which is usually very high for charge-transfer complexes and even a tiny amount of the reactants can cause the color formation. So, even though the rearrangement was completed in less than 16 seconds, the presence of minute quantities of reactants was causing the color to still exist.

In the context of examining the substituent effects on the color of transformation, UV-vis experiments were performed to obtain the λ_{max} values for the rearrangement reaction color. The idea was to correlate these λ_{max} values with the Hammett constant values, which are unique for each electron withdrawing substituent as well as electron releasing substituent, discovered by Hammett during his research work on benzoates.[29]

The hypothesis is that the benzofuranone substrates with the electron withdrawing substituents should absorb at shorter wavelength or higher energy, and the ones with the

electron releasing substituents should absorb at longer wavelength or lower energy. This is because, as discussed earlier (**Figure 5**), the electron withdrawing substituents

Figure 5



Energy level diagram depicting the electron transfer from HOMO of donor to the LUMO of acceptor

tend to stabilize the negative charge on the enolate anion (**B3a**) by lowering the energy of its HOMO, and thus it requires more energy for the electronic excitation from the HOMO to the higher energy (LUMO) of the acylated DMAP cation in (**B3b**). The converse is true in case of electron releasing substituents, which, by increasing its electron density, effect the destabilization of the enolate by increasing the HOMO energy.

Stock solutions of each reactant for the series of experiments were prepared in dichloromethane. The substituted enol carbonate solutions were 0.04M, while the DMAP concentration was 0.05M and UV-vis experiments were carried out on a diode-array spectrometer.

The λ_{max} values collected (**Table 8.0**) were in concurrence with the hypothesis with a couple of exceptions for the fluoro and methyl substituents. The reason for the unusual absorption with the fluoro and methyl substituents is not known.

R	**R_1**	**Rxn Color**	**λ_{max}**	**HammettConstant (σ)**
F	C_2H_5	Deep purple	562.25	0.06
Cl	C_2H_5	Deep purple	542.56	0.23
Br	C_2H_5	Deep purple	558.65	0.23
H	C_2H_5	Deep blue	583.43	0.00
CH_3	C_2H_5	Deep blue	593.14	-0.17
OCH_3	C_2H_5	Deep blue	580.18	-0.27

Table 8.0. λ_{max} and Hammett constant values for different substituents along with the reaction color

CONCLUSION

The effect of various substituents on the colors and times of the transacylation reaction have been carefully studied. The λ_{max} values obtained for the color of the transformation are in accordance with the substituents effects on the molecule's/ion's environment.

Although the experimental efforts for the characterization of the reactive intermediate (IPCTC) involved in this reaction did not meet expectations, an important inference was made regarding the lifetime of the reactive intermediate and the time for reaction completion. Before, it was assumed that the lifetime of the reactive intermediate is more due to the persistence of the color, but the experimental results show that the color may be due more to the mere effect of a very high IPCTC extinction coefficient, and the actual lifetime is less than 16 seconds.

Future investigations might entail an in-depth study of this reactive intermediate by isolating and attaining the x-ray crystal structure employing different methods such as different solvent systems at different temperatures. Successful characterization of this reactive intermediate will be helpful in setting a stage for further extensions of this reaction in organic synthetic chemistry.

This will also provide a strong support to the proposed mechanism (**Scheme B**), which will stand as a guide to develop an inexpensive chiral DMAP analog for enantioselective synthesis of C-acylated isomer (**B4**) with high *ee*'s. Therefore, this enatiomerically pure C-acylated isomer, which is a part of various classes of drugs, can be synthesized by a relatively cheap and efficient method, which will be extremely useful, having paramount values both in terms of medicinal as well as synthetic chemistry.

Experimental

All pure chemicals were purchased from Fisher Scientific or Aldrich Chemical Company. All the reactions were carried out under a nitrogen atmosphere unless otherwise specified, and glassware was oven-dried at 120 ^{0}C for at least four hours. Thin-layer chromatography (TLC) was performed on Analtech silica gel GF chromatography plates (250 μ) using dichloromethane as eluant unless otherwise specified, and plates were visualized with an ultraviolet lamp. Proton (^{1}H) NMR spectra were acquired on samples dissolved in deuterochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard, using a 60MHz Varian EM360L NMR spectrometer. Chemical shift values are reported in parts per million (ppm) relative to TMS, and the peak multiplicities were denoted as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Infrared spectra were recorded on an Avatar 360 FT-IR Nicolet E.S.P spectrophotometer or a BareBones Bio-Rad/Digilab FT-IR Excalibur spectrophotometer; absorbencies are recorded in wavenumbers (cm^{-1}). UV-Vis experiments were carried out on a Shimadzu UV-3100 spectrophotometer or an OceanOptics USB 2000 diode-array spectrophotometer. All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Anhydrous solvents were

purified by simple distillation at atmospheric pressure. Dimethyl sulfoxide (DMSO) was distilled from calicium hydride (CaH_2) at 189 ^{0}C. *N,N*-Dimethyl formamide (DMF) was distilled from magnesium sulfate ($MgSO_4$) at 153 ^{0}C. Tetrahydrofuran (THF) was pre-dried over sodium metal and distilled from sodium-benzophenone ketyl.

General Procedure for the Preparation of Starting Material

Method A

3-Phenylbenzofuran-2-one (**C3**):

A 160 mL quantity of 70% sulfuric acid was added to a ground mixture of 53g of phenol and 61g of mandelic acid taken in a round-bottomed flask in an ice-bath, and no change in color was observed at this time. This reaction mixture was stirred until complete dissolution was obtained, heated at 115 ^{0}C for 45 min and allowed to cool to room temperature, diluted with 500 g of crushed ice water slurry and extracted with six 100 mL portions of dichloromethane. The organic layer was washed with three 100 mL portions of aqueous saturated sodium bicarbonate solution, dried over magnesium sulfate and filtered. The solvents were removed from the filtrate under reduced pressure to give the crude product as off-white powder and recrystallization from 95% ethanol gave 3-

phenylbenzofuranone as white crystals in 25% yield with the following analytical data: mp 110-112 ^{0}C. (Lit[19] m.p. 113-114^0). IR (Nujol®) 1796, 1601, 1222, 1162 1055, 756 cm^{-1}; NMR δ 4.8 (s, 1 H), 7.3 (m, Ar 9 H); TLC R_f 0.73.

Procedure for Preparation of Substituted Benzofuranones

Method B

5-Chloro-3-phenylbenzofuran-2-one (**C3A**):

A 10mL quantity of 70% sulfuric acid was added to the ground mixture of 3.31 g of 4-chlorophenol and 3.81 g of mandelic acid taken in a round-bottomed flask in an ice-bath, stirred until complete dissolution was obtained and heated at reflux for three hours at 100 ^{0}C .The solution was then allowed to cool to room temperature and diluted with 200 g of crushed ice, and extracted with three 50 mL portions of dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate solution, dried over magnesium sulfate and filtered. The solvents were evaporated from filtrate under reduced pressure to give the crude product, which, upon recrystallization from 95% ethanol, afforded pure product as white crystals in 45 % yield which gave the following analytical data: mp 118-121 ^{0}C; IR (Nujol®) 1815, 1606, 1046, 855, 828 cm^{-1}; NMR δ 4.8

(S, 1 H), 7.2 (m, Ar 8 H); TLC R_f 0.77; Comb.anal. calcd. for $C_{14}H_9ClO_2$: C, 68.72%; H, 3.71%. Found:

5-Bromo-3-phenylbenzofuran-2-one (**C3B**):

This compound was synthesized by employing method A; the product was collected as a white crystalline solid after recrystallization from 95% ethanol, and provided the following analytical data: mp 115-117 ^{0}C; IR (KBr) 1813, 1606, 1226, 1134, 1062, 756 cm^{-1}; NMR δ 4.8 (S, 1 H), 7.3 (m, Ar 8 H); TLC R_f 0.76; Comb.anal. calcd. for $C_{14}H_9BrO_2$: C, 58.16%; H, 3.13%. Found:

5-Methyl-3-phenylbenzofuran-2-one (**C3C**):

This compound was prepared by following method B and the product was collected as shining white crystals in 44 % yield after recrystallization from 95% ethanol, which gave the following analytical data: mp 79-82 ^{0}C; IR (KBr) 1802, 1612, 1228, 1140, 1062 cm^{-1}; NMR δ2.3 (s, - 3 H, $-CH_3$) 4.8 (S, 1 H), 7.2 (m, Ar 8 H); TLC R_f 0.74; Comb.anal. calcd. for $C_{15}H_{12}O_2$: C, 80.32%; H, 5.39%. Found:

5-flouro-3-phenylbenzofuran-2-one (**C3D**):

This compound was prepared by following method A and the product was collected as a white crystalline solid in 46% yield after recrystallization from 95% ethanol, which gave the following analytical data: mp 64-67 ^{0}C; IR (Nujol®)

1798, 1606, 1211,1064, 743 cm^{-1}; NMR δ 4.8 (S, 1 H), 7.2 (m, Ar 8 H); TLC R_f 0.74; Comb.anal. calcd. for $C_{14}H_9FO_2$: C, 73.68%; H, 3.97%. Found:

5-Methoxy-3-phenylbenzofuran-2-one (**C3E**):

This was synthesized by method B and the product was collected as white crystals in 26% yield after recrystallization from methanol, which gave the following analytical data: mp 130-132 ^0C; IR (Nujol®) 1804, 1603, 1282, 1137, 1064 cm^{-1}; NMR δ3.8 (s, 3 H, $-OCH_3$) 4.8 (S, 1 H), 7.1 (m, Ar 8 H); TLC R_f 0.79; Comb. anal. calcd. for $C_{15}H_{12}O_3$: C, 74.97%; H, 5.03%. Found:

Procedure for Preparation of O-Acylated Isomer of 3-phenyl benzofuranone

Carbonic acid, ethyl 3-phenylbenzofur-2-yl ester (**A3**):

A 0.4g (16 mmol) quantity of sodium hydride (60 % dispersion in oil) was added to an oven dried three-necked round-bottomed flask and was washed with three 5-mL portions of hexanes. A 6.5 mL quantity of dimethylformamide (DMF) was added while stirring and cooling in an ice bath. A 2 g quantity of 3-phenylbenzofuranone in small quantities was added to this stirring solution at room temperature as effervescence was observed. This dark green solution was

allowed to stir for 90 minutes; ethyl chloroformate (1mL, 10 mmol) was added over several minutes. This reaction mixture was stirred overnight at room temperature and diluted with 200 mL water, extracted with three 50 mL portions of ether. The extract was washed with water and brine, dried over anhydrous magnesium sulfate, filtered. The solvents were removed under reduced pressure and the product was obtained in 98% yield as thick colorless oil, which afforded the following analytical data: IR (neat) 2981, 1784, 1644, 1453, 1234, 1058 cm^{-1}; NMR δ1.4(t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.4 (m, Ar 9 H); TLC R_f 0.92.

Carbonic acid, ethyl 5-chloro-3-phenylbenzofur-2-yl ester (**A3A**):

The product was obtained as viscous yellow oil in 69 % yield, which gave the following analytical data: IR (neat) 2982, 1785, 1640, 1448, 1232, 1182, 804 cm^{-1}; NMR δ1.3(t, 3 H, -CH_3), 4.3 (q, 2 H, -CH_2), 7.4 (m, Ar 8 H); TLC R_f 0.93; Comb. anal. calcd. for $C_{16}H_{13}ClO_2$: C, 70.46%; H, 4.80%. Found:

Carbonic acid, ethyl 5-bromo-3-phenylbenzofur-2-yl ester (**A3B**):

The product was obtained as a thick colorless oil in 89% yield, which afforded the following analytical data: IR

(neat) 2979, 1785, 1643, 1447, 1231, 1054 cm^{-1}; NMR δ1.3(t, 3 H, $-CH_3$), 4.3 (q, 2 H, $-CH_2$), 7.4 (m, Ar 8 H); TLC R_f 0.93; Comb. anal. calcd. for $C_{16}H_{13}BrO_2$: C, 60.59%; H, 4.12%. Found:

Carbonic acid, ethyl 5-methyl-3-phenylbenzofur-2-yl ester (**A3C**):

The product was obtained as thick pale yellow oil in 85% yield, which afforded the following analytical data: IR (neat) 2981, 1784, 1640, 1473, 1365 cm^{-1}; NMR δ1.3(t, 3 H, $-CH_3$), 2.3 (s, 3 H, $-CH_3$), 4.3 (q, 2 H, $-CH_2$), 7.4 (m, Ar 8 H); TLC R_f 0.91; Comb.anal. calcd. for $C_{17}H_{16}O_2$: C, 80.93%; H, 6.38%. Found:

Carbonic acid, ethyl 5-flouro-3-phenylbenzofur-2-yl ester (**A3D**):

The product was obtained as thick colorless oil in 78% yield, which afforded the following analytical data: IR (neat) 2984, 1785, 1642, 1469, 1241, 1169, 801 cm^{-1}; NMR δ1.3(t, 3 H, $-CH_3$), 4.3 (q, 2 H, $-CH_2$), 7.3 (m, Ar 8 H); TLC R_f 0.84; Comb.anal. calcd. for $C_{16}H_{13}FO_2$: C, 74.99%; H, 5.10%. Found:

Carbonic acid, ethyl 5-methoxy-3-phenylbenzofur-2-yl ester (**A3E**):

The product was obtained as thick colorless oil in 82% yield, which afforded the following analytical data: IR (neat) 2978, 1783, 1640, 1475, 1365, 1245 cm^{-1}; NMR δ1.2(t, 3 H, $-CH_3$), 3.8 (s, 3 H, $-OCH_3$) 4.3 (q, 2 H, $-CH_2$), 7.2 (m, Ar 8 H); TLC R_f 0.90; Comb.anal. calcd. for $C_{17}H_{16}O_3$: C, 76.10%; H, 6.00%. Found:

Procedure for the Rearrangement of Enol Carbonates to C-Acylated Isomers via DMAP Catalysis.

2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylicacid, ethyl ester (**A4**):

A 1g quantity of enol carbonate was dissolved in 20 mL dichloromethane in a 125 mL separatory funnel. To this solution was added a 40 mg of *N,N*-dimethylaminopyridine (DMAP), an immediate deep blue color was observed, persisted for about 45 seconds and faded over the course of 15 seconds. The reaction solution was washed with three 20 mL of 5 % hydrochloric acid, and with 100 mL of water, and then was dried over anhydrous magnesium sulfate, where upon solvent evaporation under reduced pressure afforded the product as light yellow oil in 80 % yield, which provided the following analytical data: IR (neat) 1817,1739, 1226,

1183, 1055 cm^{-1}. R_f (CH_2Cl_2): 0.78; NMR δ1.2(t, 3 H, $-CH_3$), 4.2(q, 2 H, $-CH_2$), 7.3 (m, Ar 9 H); TLC R_f 0.71.

2,3-Dihydro-5-chloro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester (**A4A**):

A deep purple coloration of the reaction solution was observed which persisted for 10 minutes and 45 seconds; upon workup a thick yellow oil was isolated in 90 % yield, which provided the following analytical data: IR (neat) 1821, 1739, 1614, 1470, 1232, 1134, 1076, 819 cm^{-1}; NMR δ1.2(t, 3 H, $-CH_3$), 4.3(q, 2 H, $-CH_2$), 7.3 (m, Ar 8 H); TLC R_f 0.76.

2,3-Dihydro-5-bromo-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester (**A4B**):

A deep purple coloration of solution was observed which persisted for four minutes; upon workup a thick colorless liquid was isolated in 98 % yield, which provided the following analytical data: IR (neat) 2982, 1820, 1739, 1614, 1468, 1233, 1135, 1068, 737 cm^{-1}; NMR δ1.2(t, 3 H, $-CH_3$), 4.3(q, 2 H, $-CH_2$), 7.3 (m, Ar 8 H); TLC R_f 0.83.

2,3-Dihydro-5-methyl-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester (**A4C**):

A deep blue coloration of solution was observed which persisted for 75 seconds; upon workup a thick yellow oil

was obtained in 86 % yield, which provided the following analytical data: IR (neat) 2982, 1813, 1742, 1617, 1486, 1234, 1069 cm^{-1}; NMR δ1.2(t, 3 H, $-CH_3$), 2.3 (s, 3 H, $-CH_3$) 4.3(q, 2 H, $-CH_2$), 7.3 (m, Ar 8 H); TLC R_f 0.68.

2,3-Dihydro-5-flouro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester (**A4D**):

A deep purple coloration of solution was observed which persisted for 4 minutes; upon workup a colorless viscous oil was isolated in 77 % yield, which provided the following analytical data: IR (neat) 1819, 1739, 1608, 1480, 1234, 1120, 1067, 816 cm^{-1}; NMR δ1.2(t, 3 H, $-CH_3$), 4.3(q, 2 H, $-CH_2$), 7.3 (m, Ar 8 H); TLC R_f 0.73.

2,3-Dihydro-5-methoxy-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester (**A4E**):

A deep blue coloration of solution was observed which persisted for 3 minutes and 20 seconds; upon workup a thick yellow oil was collected in 90 % yield, which provided the following analytical data: IR (neat) 2981, 1813, 1739, 1605, 1536, 1228, 1027 cm^{-1}; NMR δ1.2(t, 3 H, $-CH_3$), 3.8 (s, 3 H, $-OCH_3$) 4.2(q, 2 H, $-CH_2$), 7.2 (m, Ar 8 H); TLC R_f 0.64.

Preparation of Solutions and Collection of UV-Vis Spectral Data

Solutions of the enol carbonate of unsubstituted and substituted benzofuranones in dichloromethane were prepared at 0.04M concentration, and a solution of DMAP was prepared at 0.05M concentration in dichloromethane.

These solutions were taken in Erlenmeyer flask to the diode-array spectrophotometer; the reference spectrum of dichloromethane was collected and the spectrum mode was switched to absorbance. A 2.5 mL quantity of enol carbonate solution was taken a quartz cuvette and placed in a cuvette holder, and then an equal amount of DMAP was taken in a syringe and transferred to the cuvette and an immediate coloration was observed along with a broad signal, which decayed with time, which is specific for a specific substituent; the times of reaction were shown in **Table 5.0**.

The λ_{max} of the reaction color for benzofuranone and its substituted derivatives is tabulated in **Table 9.0**:

R	Rxn Color	λ_{max}
F	Deep purple	562.25
Cl	Deep purple	542.56
Br	Deep purple	558.65
H	Deep blue	583.43
CH_3	Deep blue	593.14
OCH_3	Deep blue	580.18

Table 9.0. λ_{max} values of the reaction color for unsubstituted and substituted benzofuranones.

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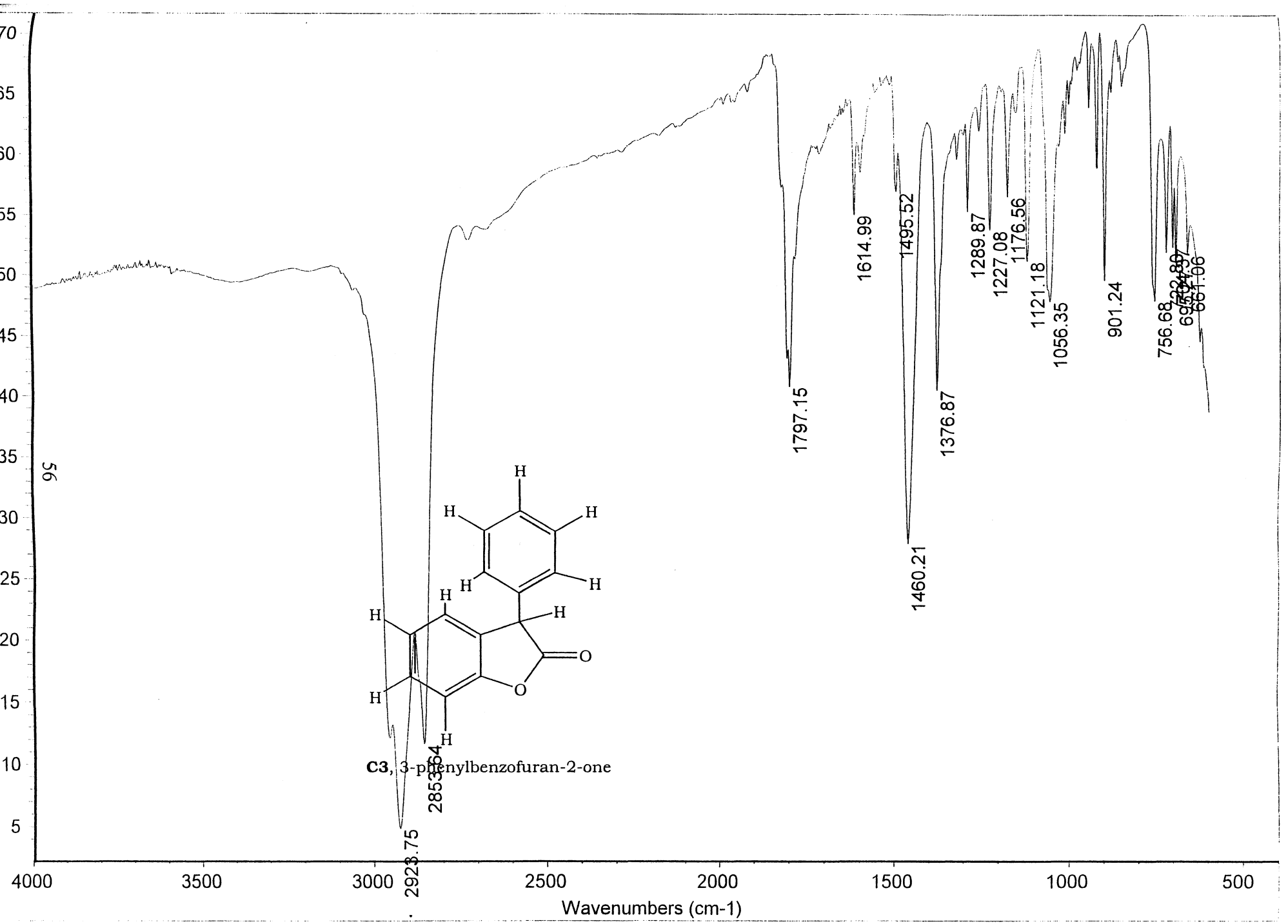

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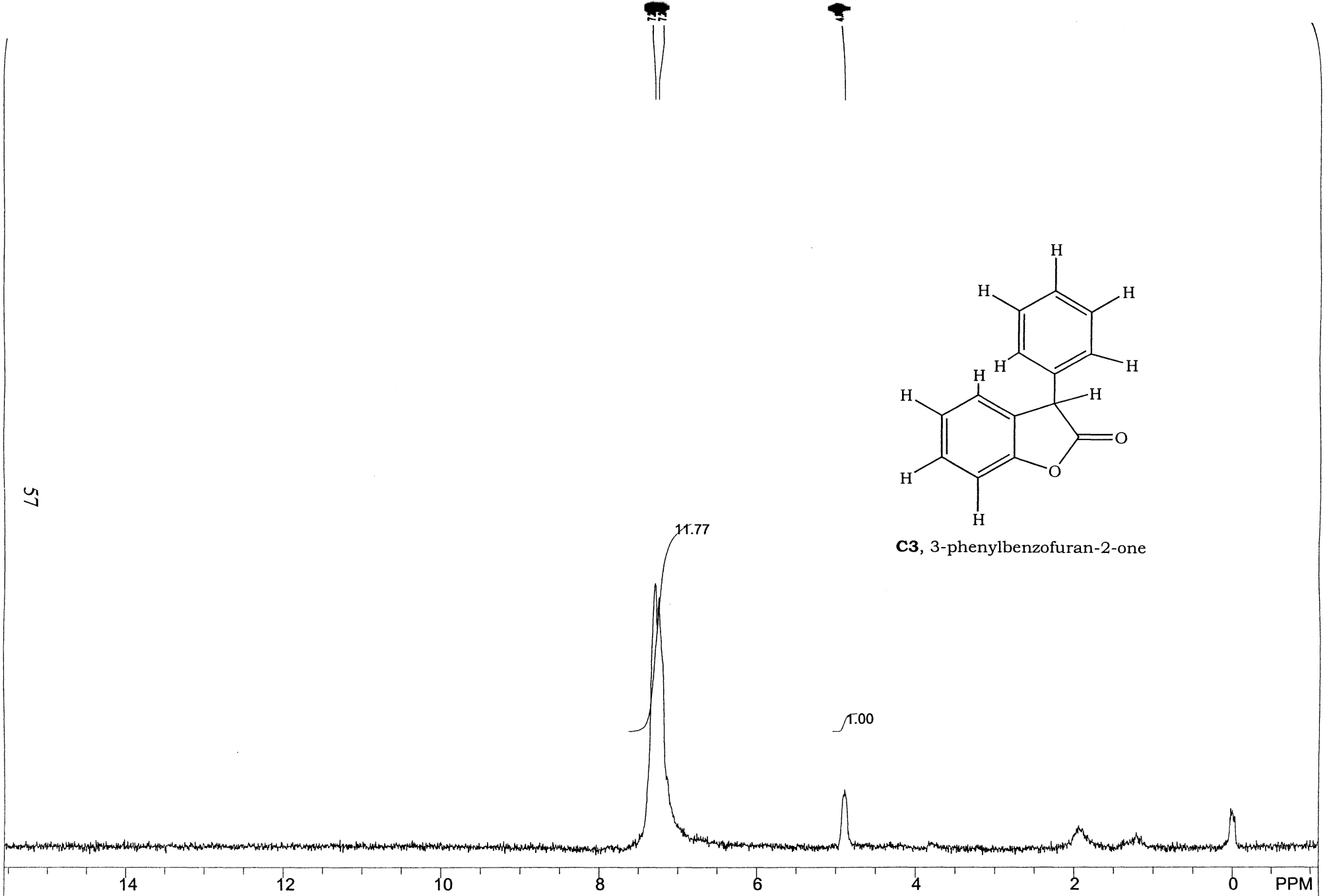

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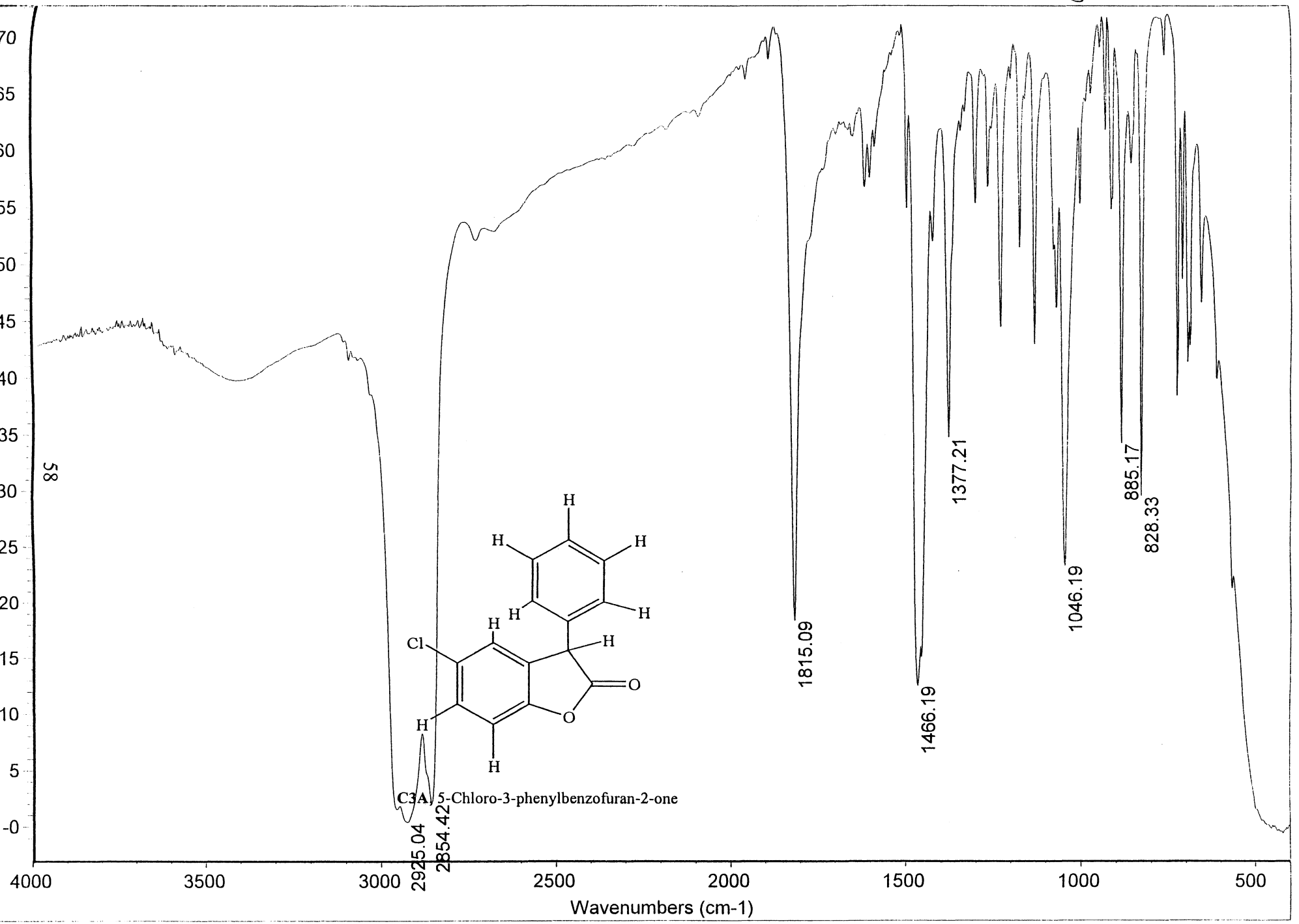
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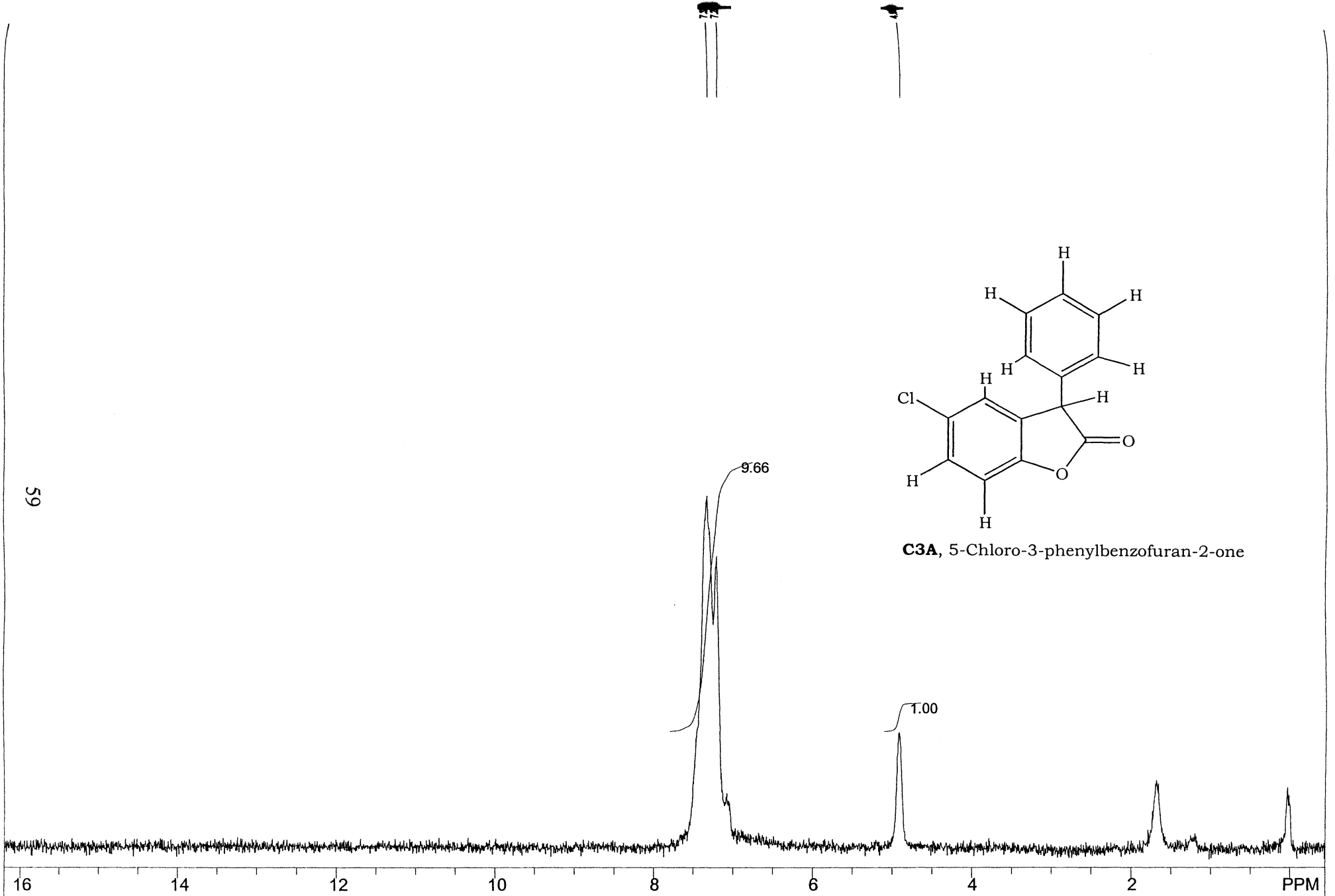

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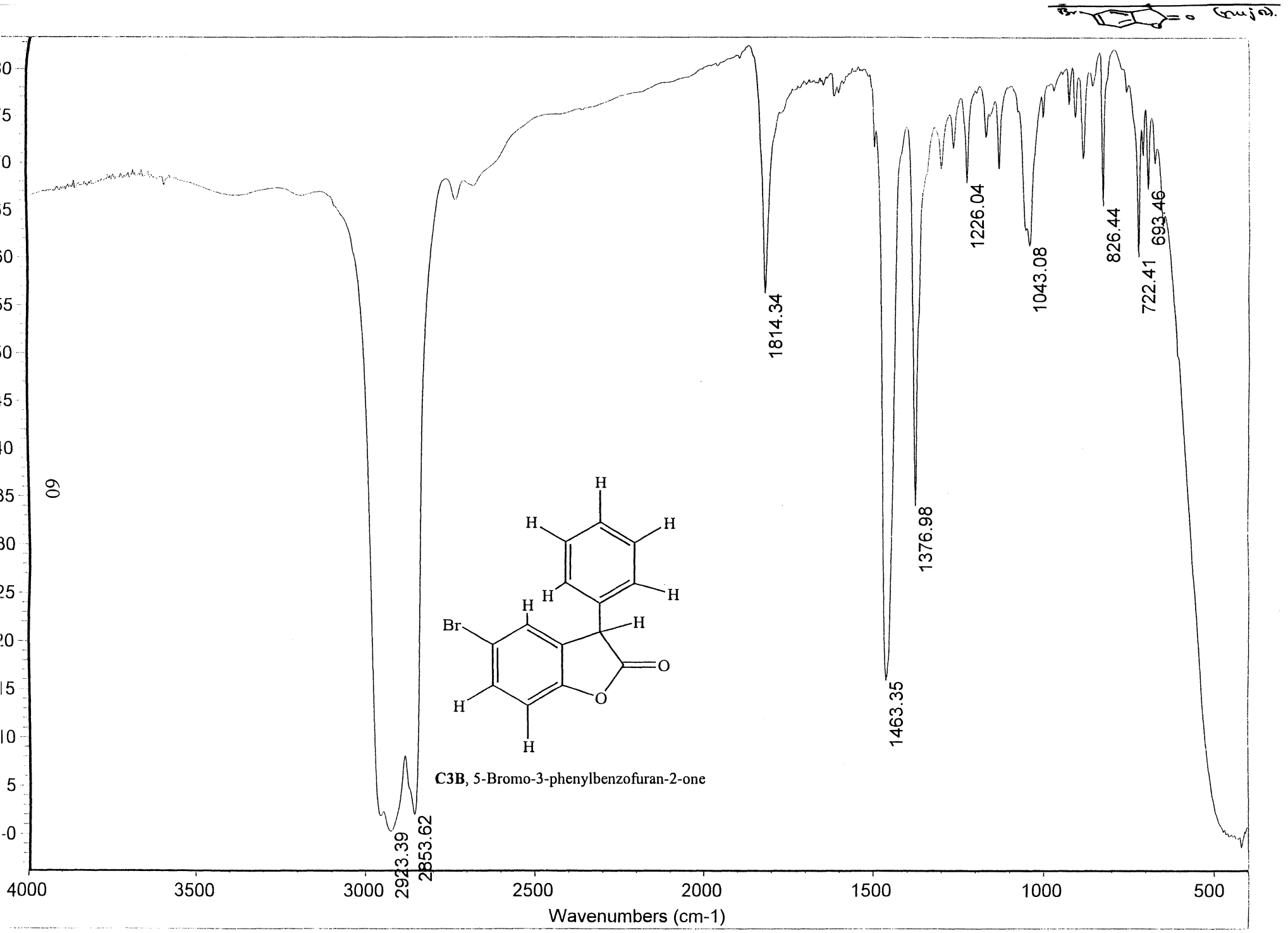

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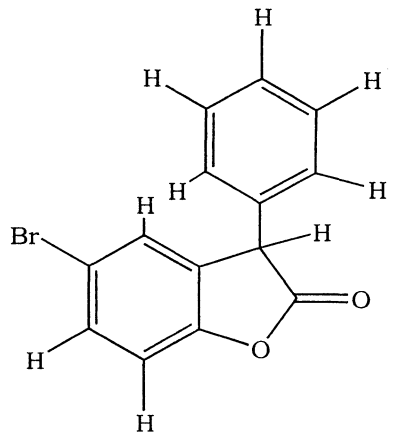

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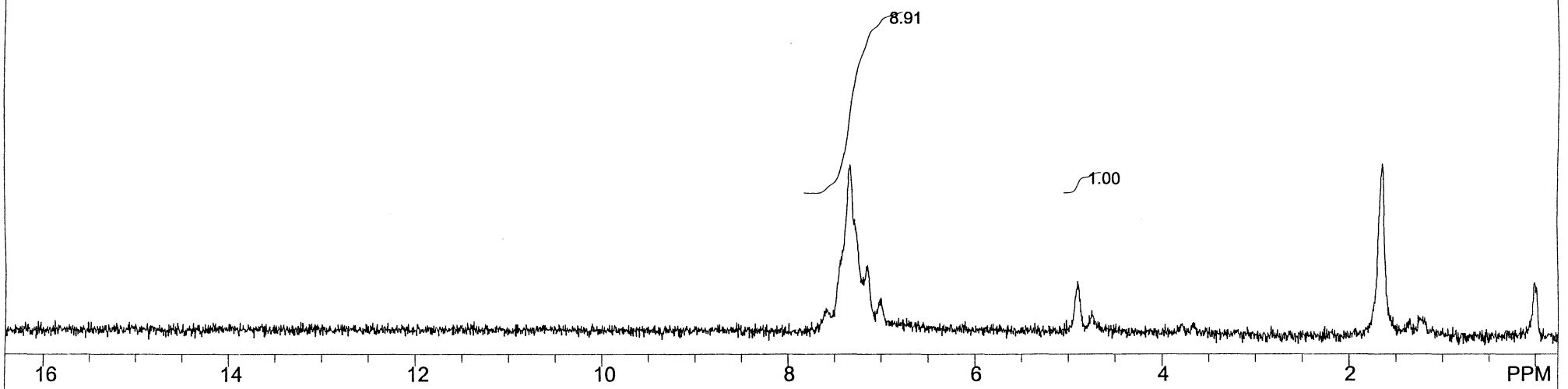

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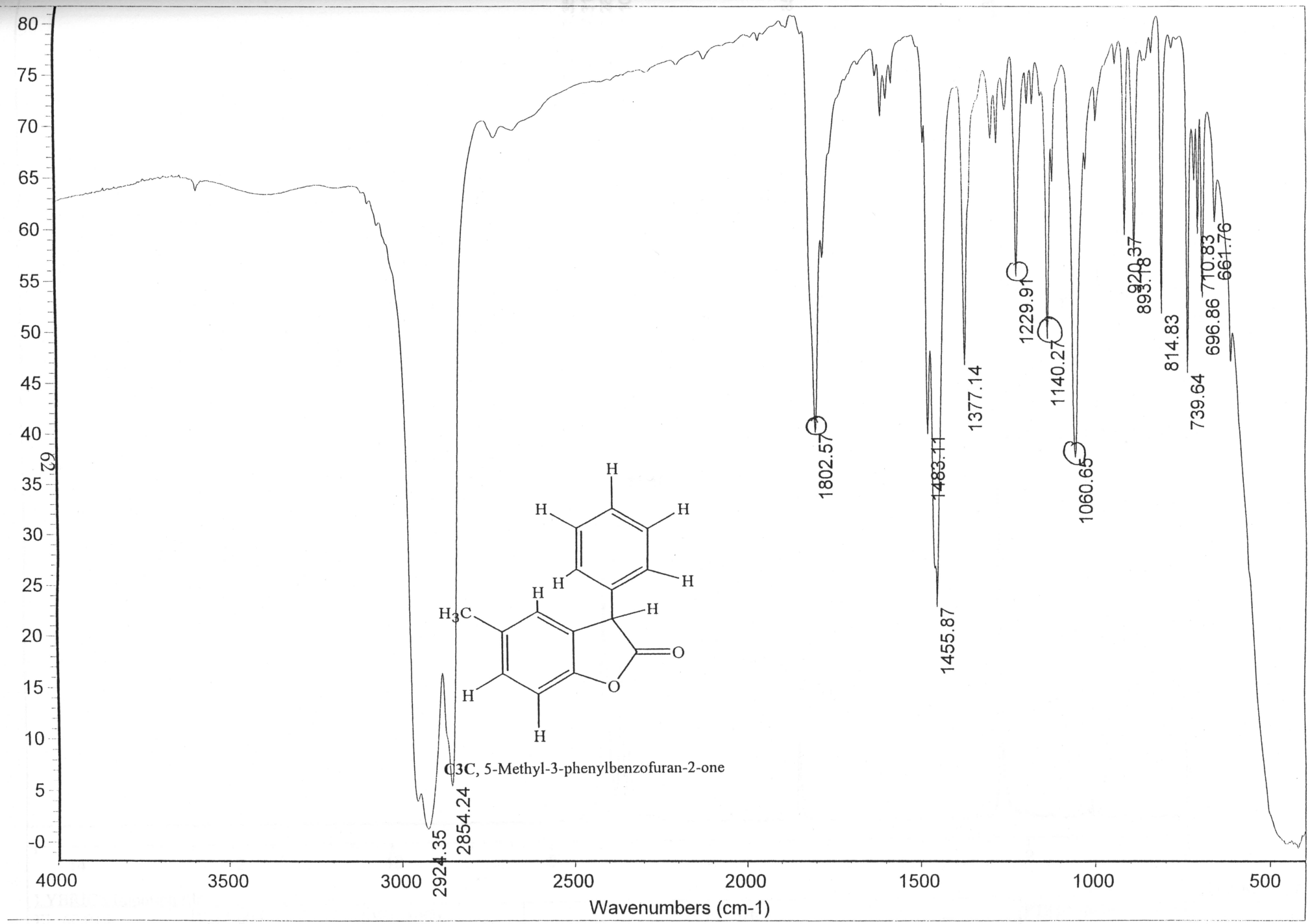
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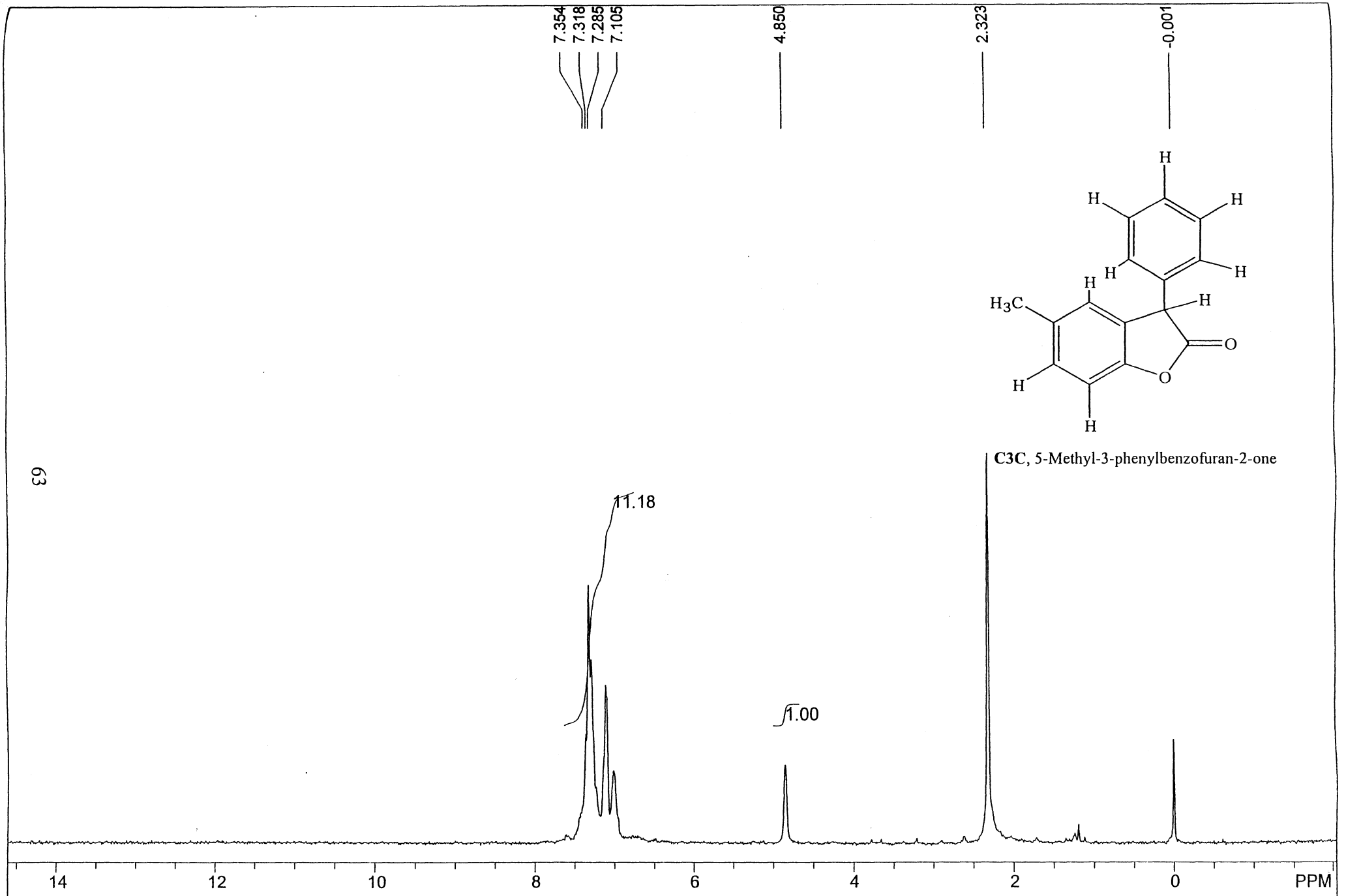
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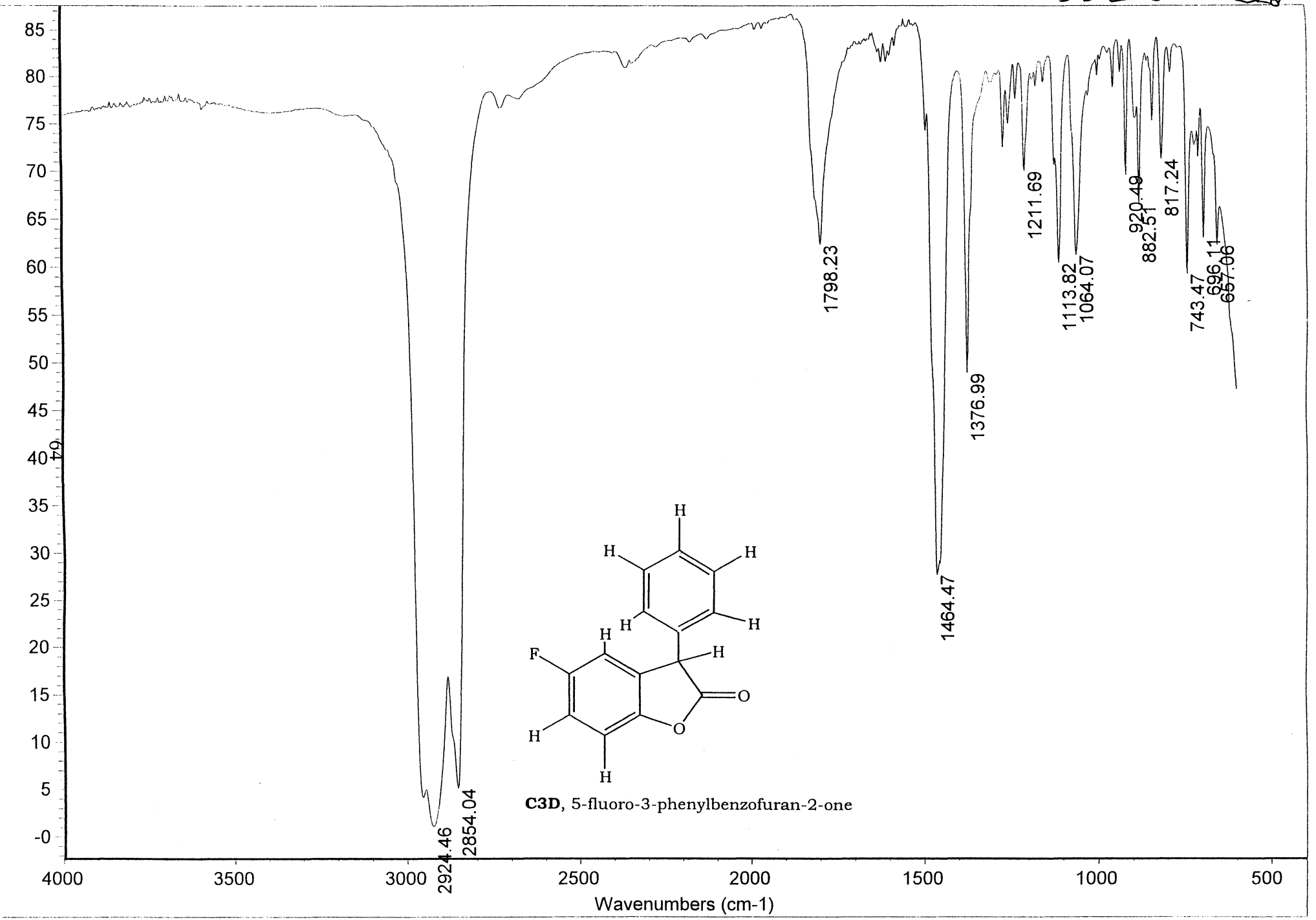
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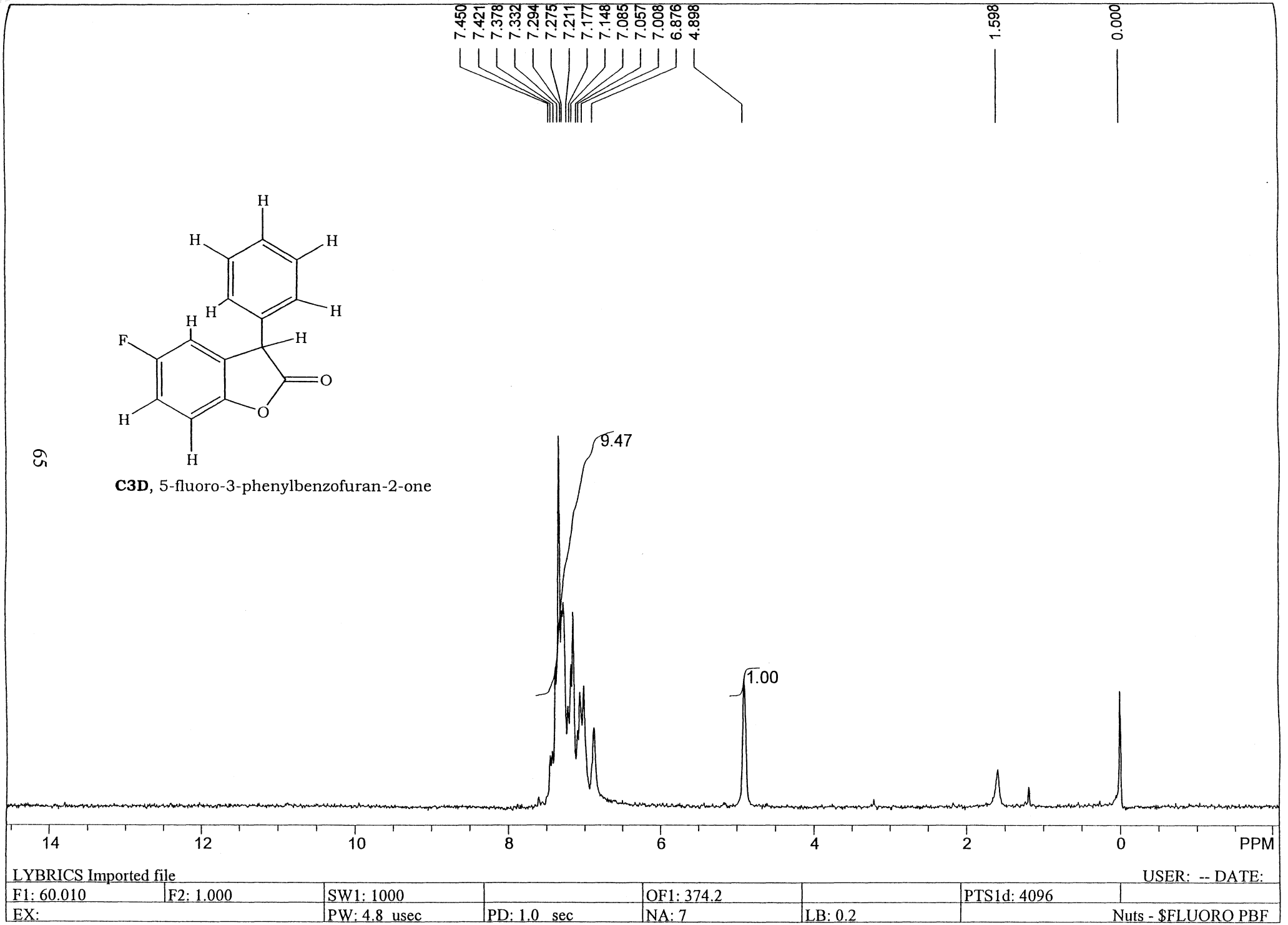
70
65
60
55
50
45
40
35
30
25
20
15
10
5
-0
64
C3D, 5-fluoro-3-phenylbenzofuran-2-one



C3D, 5-fluoro-3-phenylbenzofuran-2-one

LYBRICS Imported file USER: -- DATE:

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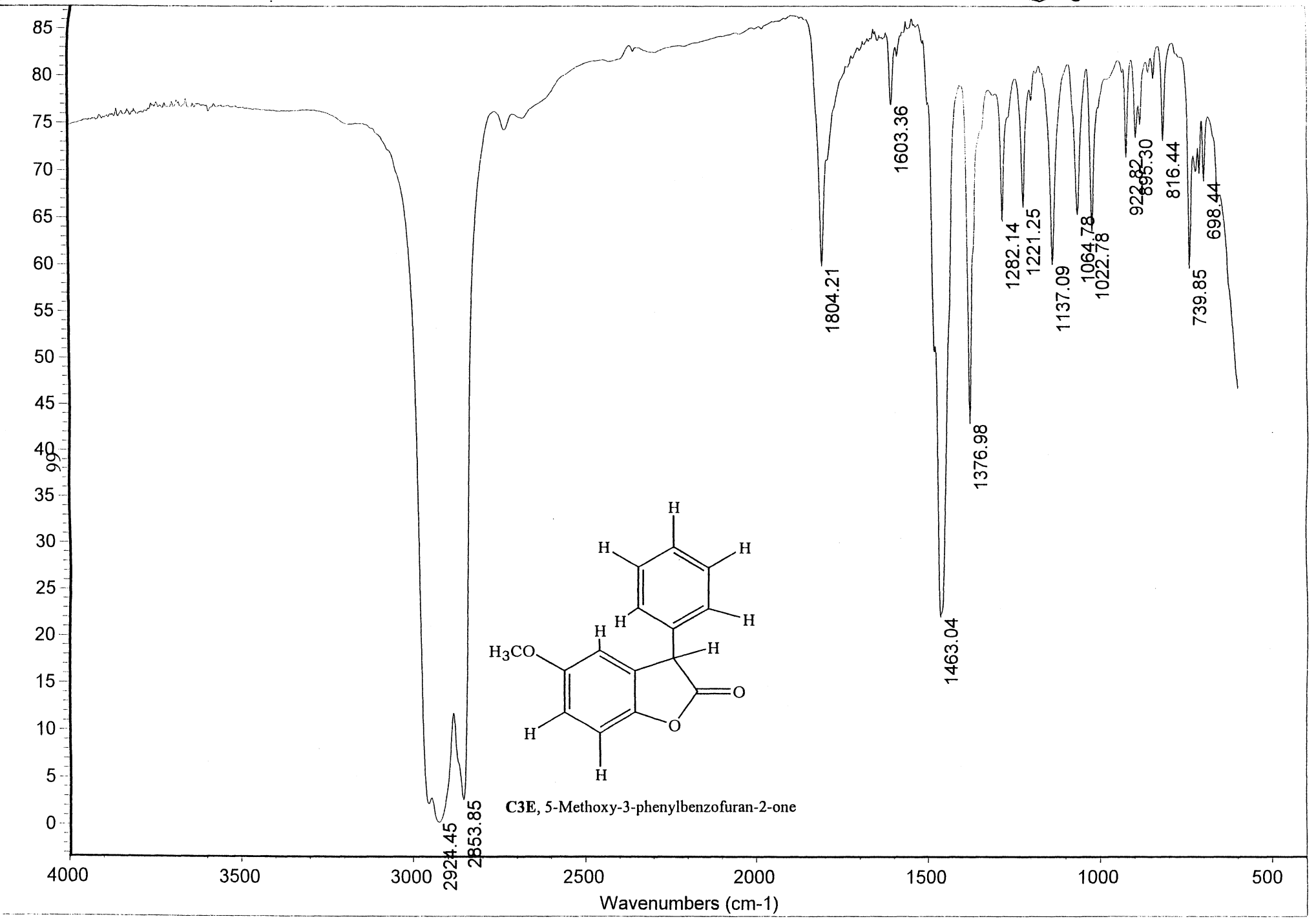
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 7	LB: 0.2	Nuts - $FLUORO PBF

JB.I.58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1603.36
1463.04
1376.98
1282.14
1221.25
1137.09
1064.78
1022.78
922.82
895.30
816.44
739.85
698.44
2924.45
2853.85
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
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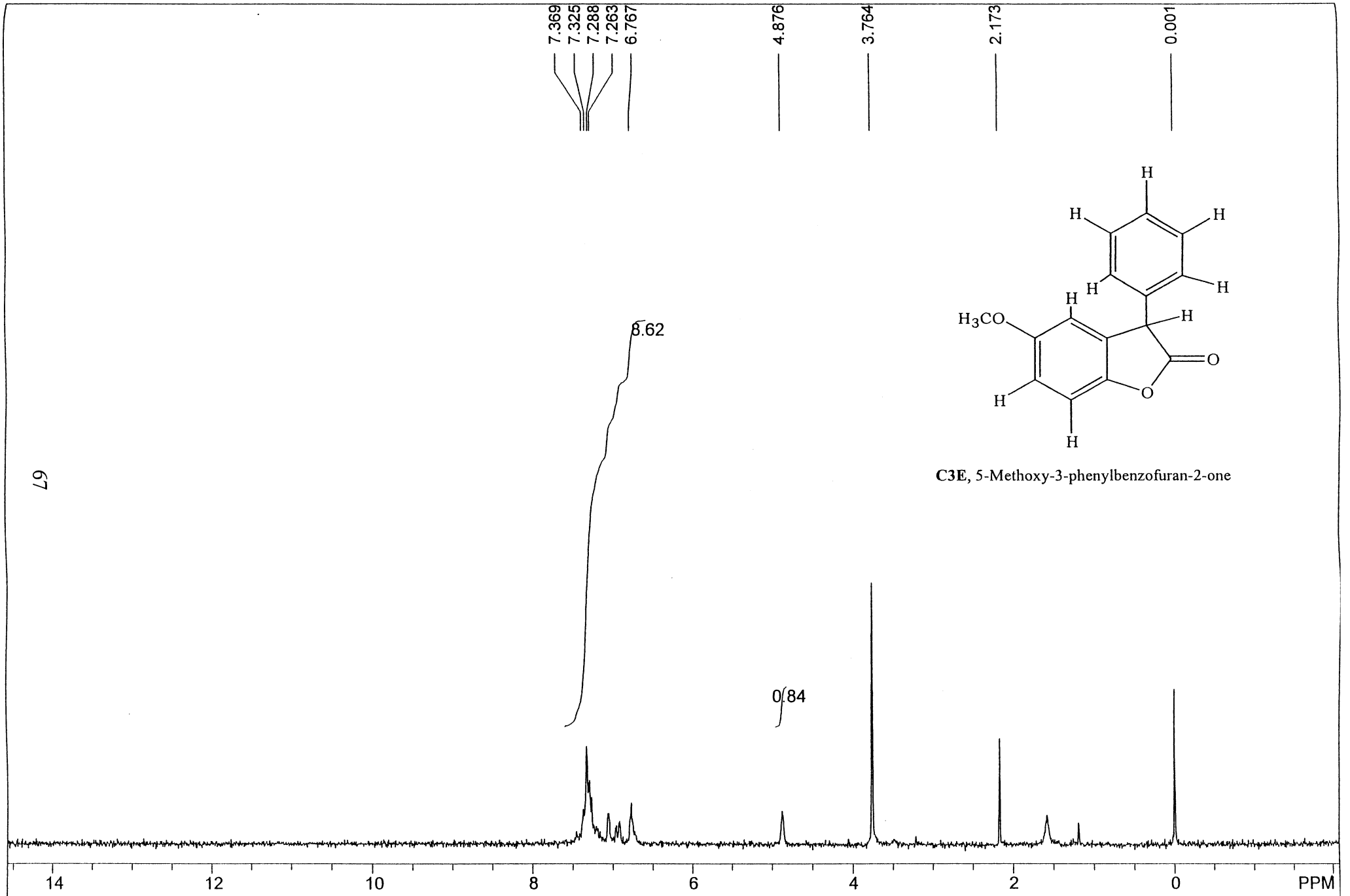
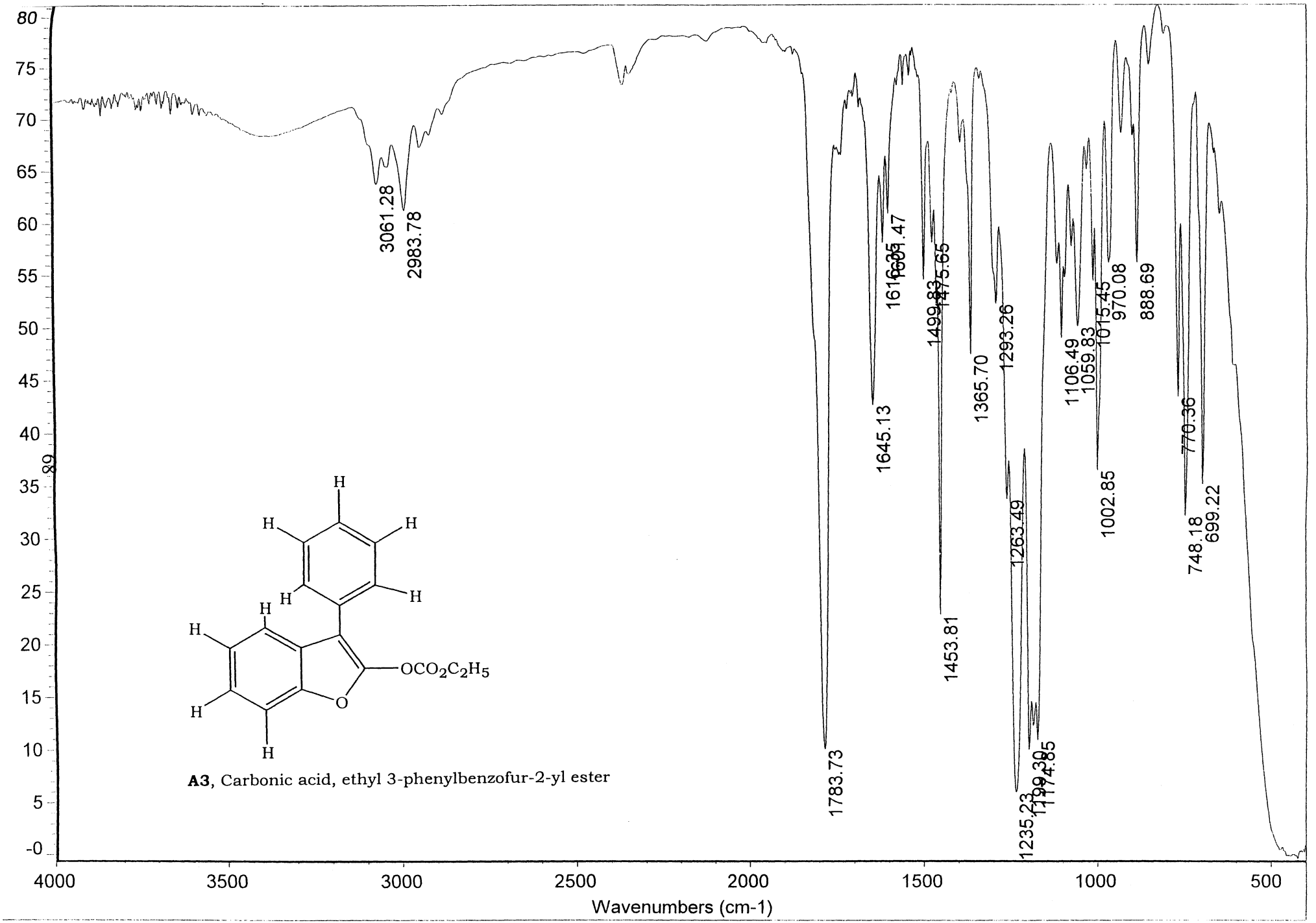
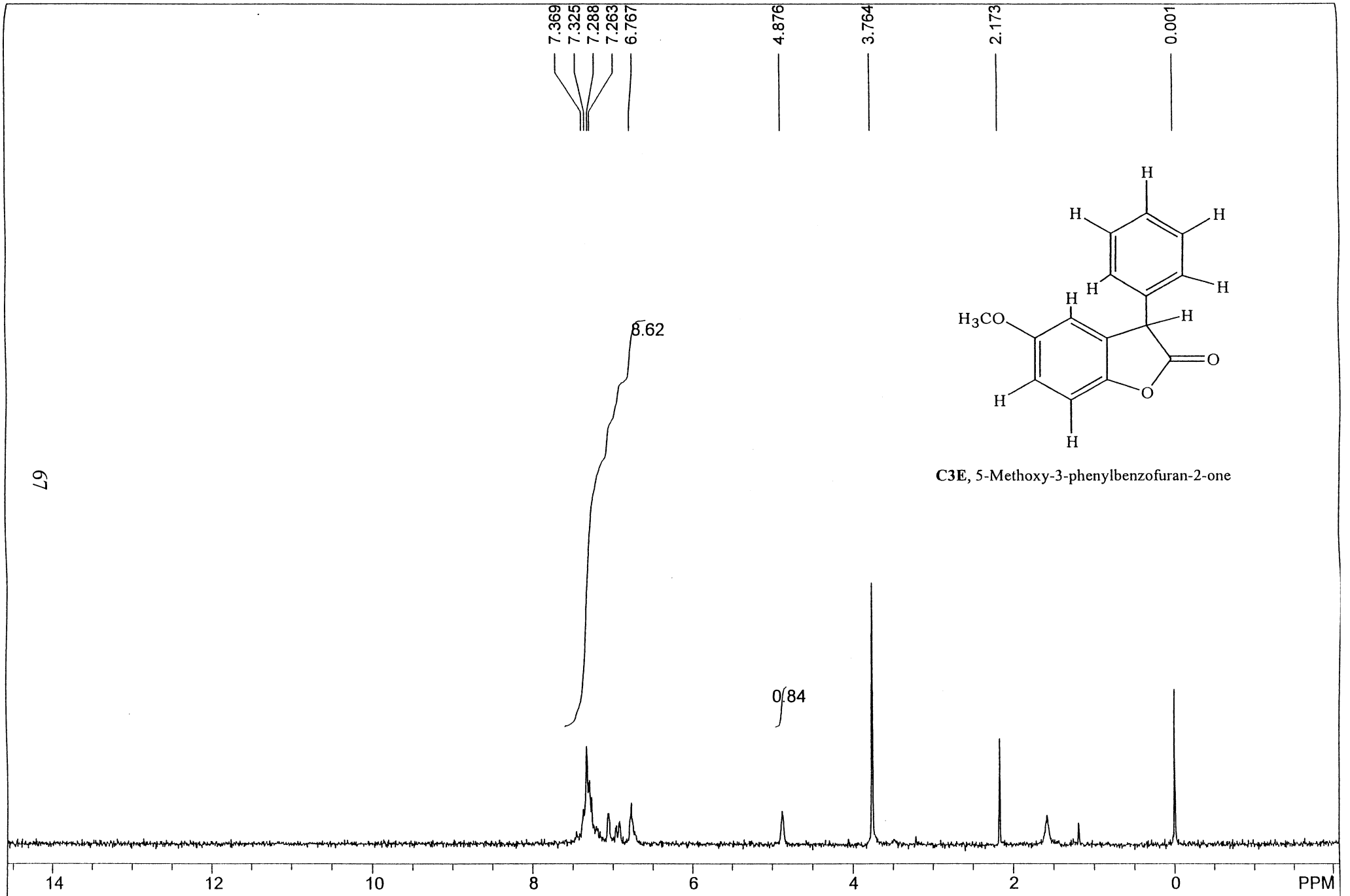
99
H
H
H


7.369
7.325
7.288
7.263
6.767
4.876
3.764
2.173
0.001
8.62
0.84
14
12
10
8
6
4
2
0
PPM

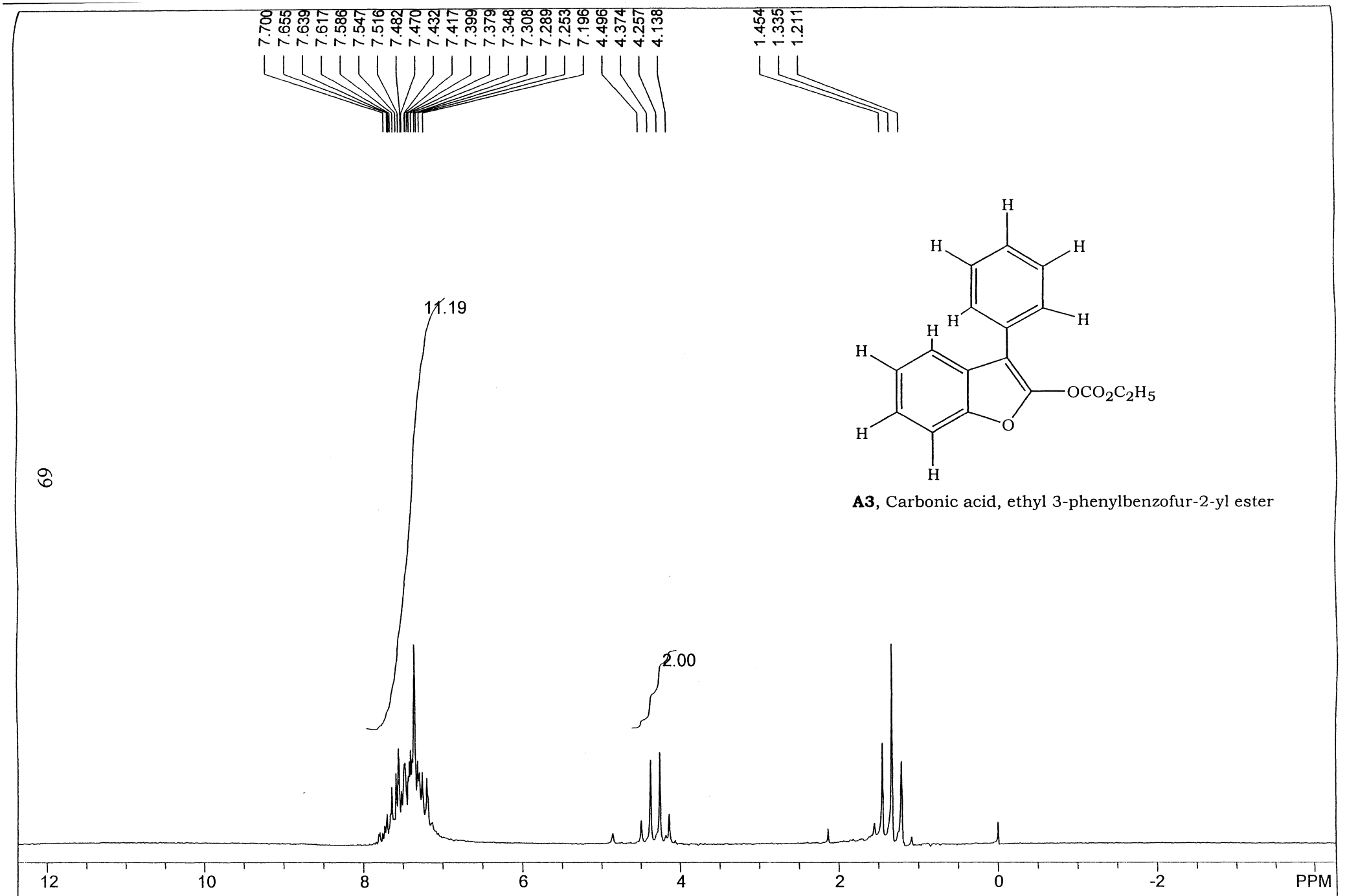
H
H
H



A3, Carbonic acid, ethyl 3-phenylbenzofur-2-yl ester


7.369
7.325
7.288
7.263
6.767
4.876
3.764
2.173
0.001
8.62
0.84
14
12
10
8
6
4
2
0
PPM

H
H
H



A3, Carbonic acid, ethyl 3-phenylbenzofur-2-yl ester

LYBRICS Imported file

USER: -- DATE:

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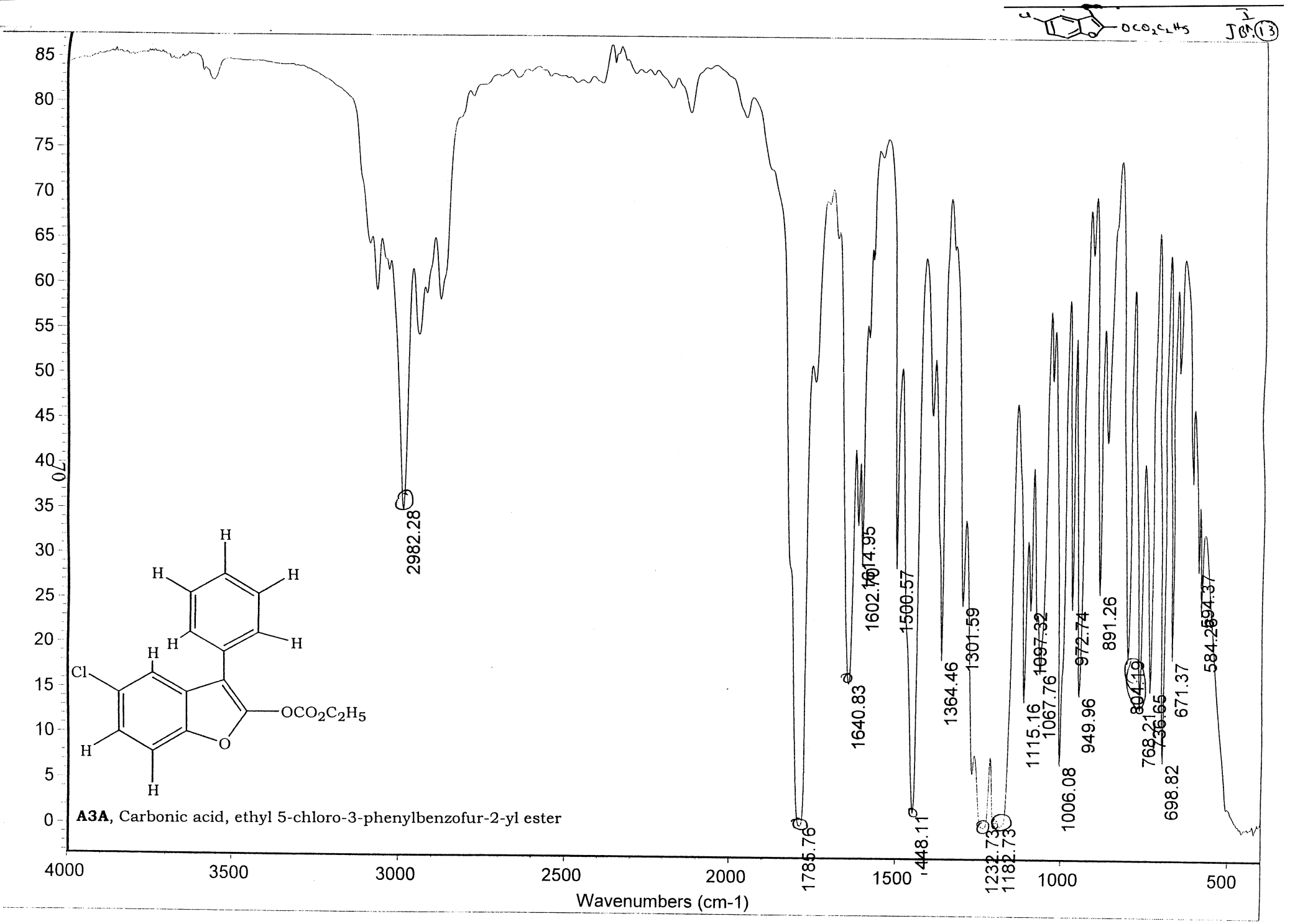
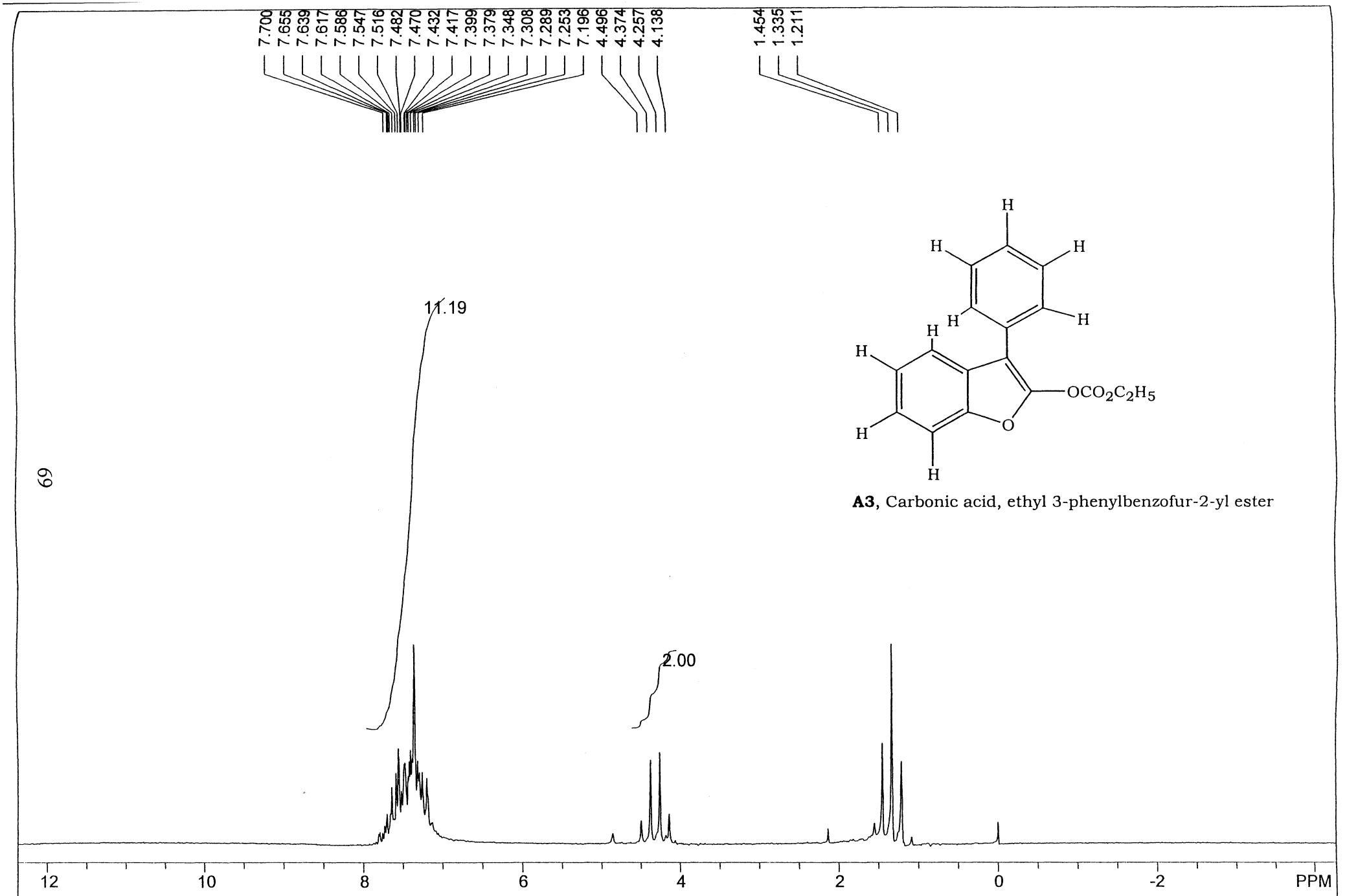
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 2	LB: 0.2	Nuts - $PBF EC


85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
2982.28
1785.76
1640.83
1614.95
1602.70
1500.57
1448.11
1364.46
1301.59
1232.73
1182.73
1115.16
1097.32
1067.76
1006.08
972.74
949.96
891.26
804.19
768.21
736.65
698.82
671.37
594.37
584.28
OCO2C2H5
Cl
O
H
A3A, Carbonic acid, ethyl 5-chloro-3-phenylbenzofur-2-yl ester

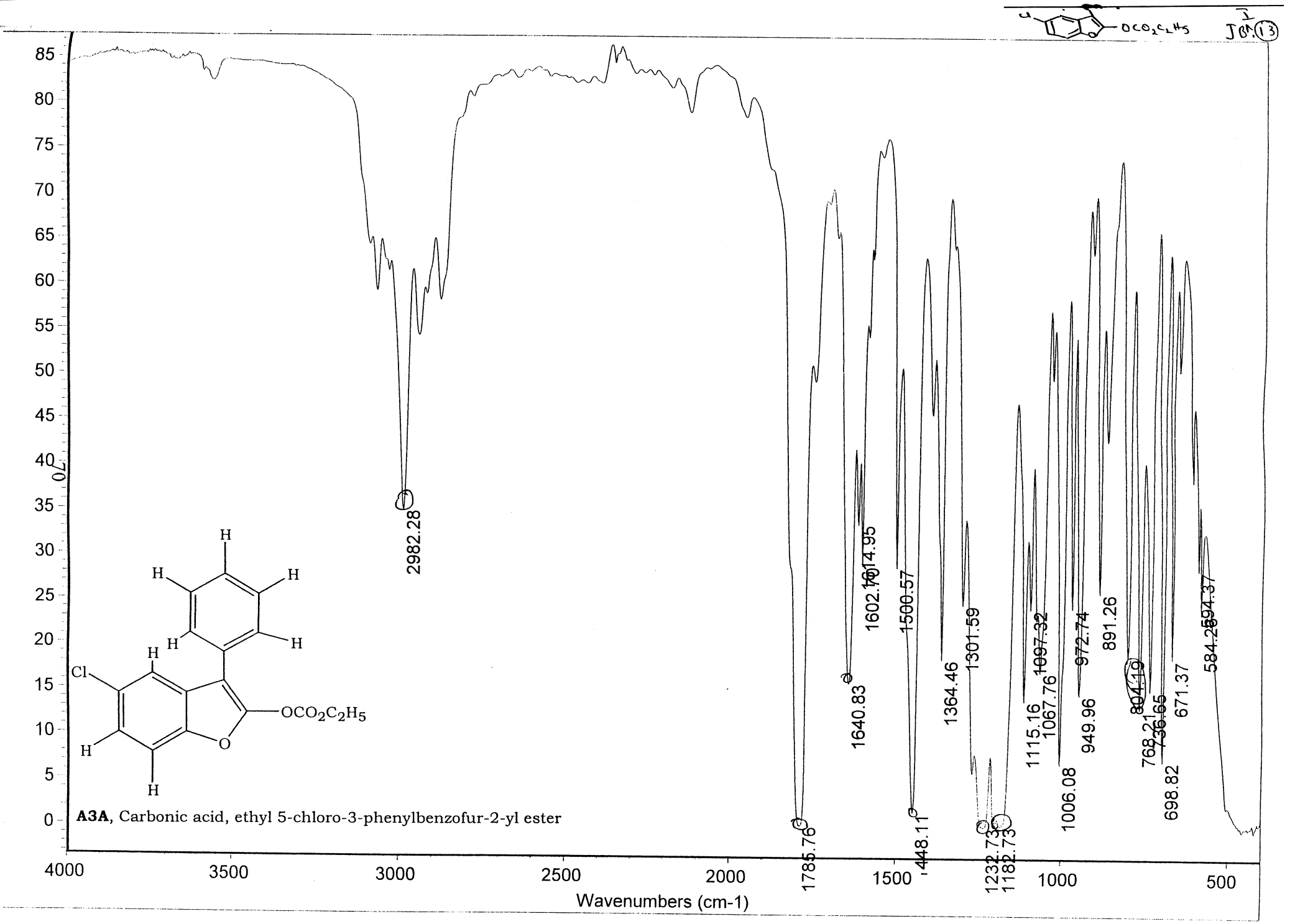


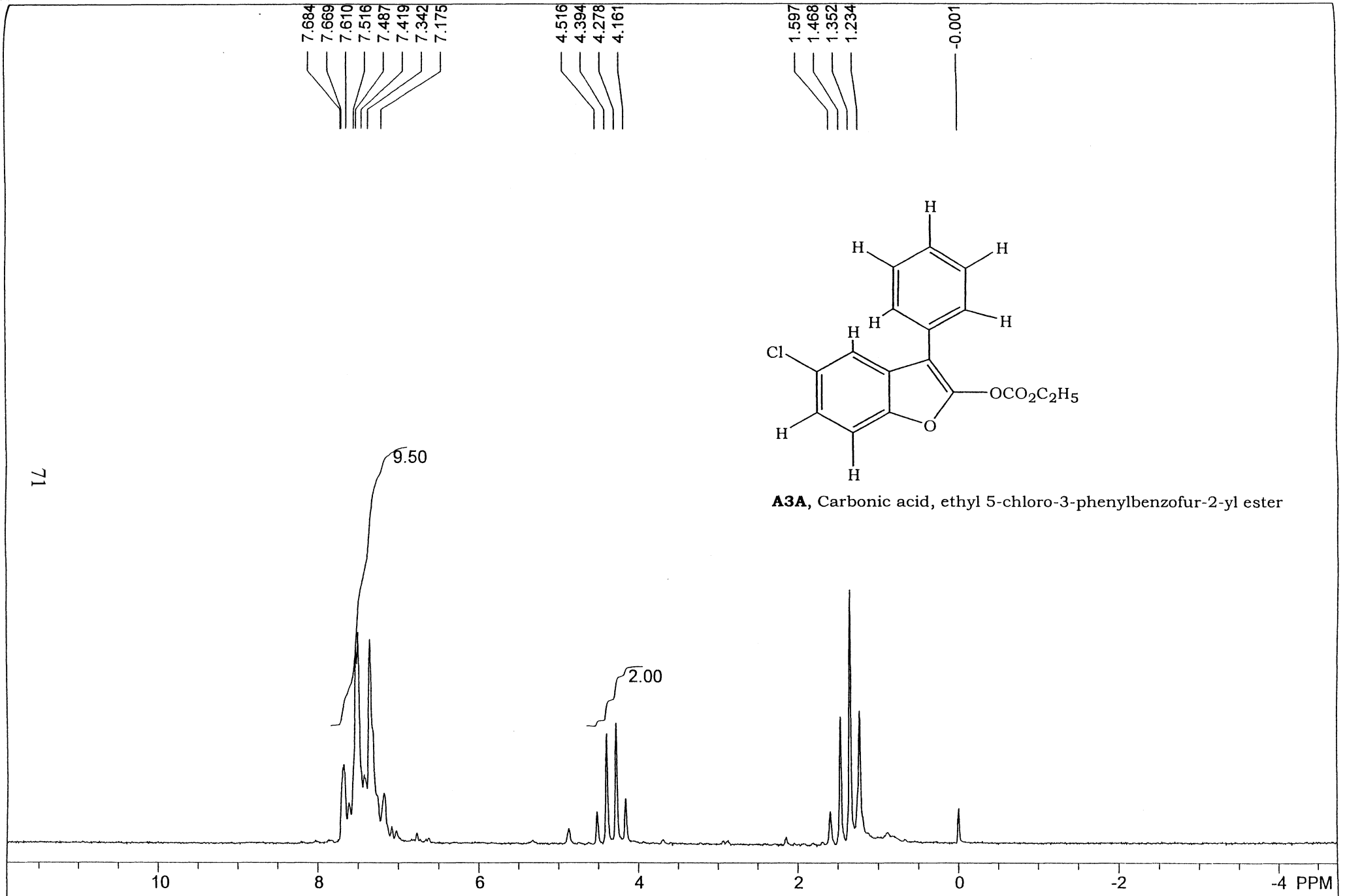
A3, Carbonic acid, ethyl 3-phenylbenzofur-2-yl ester

LYBRICS Imported file

USER: -- DATE:

F1: 60.010	F2: 1.000	SW1: 1000		OF1: 242.5		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 2	LB: 0.2	Nuts - $PBF EC


85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
2982.28
1785.76
1640.83
1614.95
1602.70
1500.57
1448.11
1364.46
1301.59
1232.73
1182.73
1115.16
1097.32
1067.76
1006.08
972.74
949.96
891.26
804.19
768.21
736.65
698.82
671.37
594.37
584.28
OCO2C2H5
Cl
O
H
A3A, Carbonic acid, ethyl 5-chloro-3-phenylbenzofur-2-yl ester



A3A, Carbonic acid, ethyl 5-chloro-3-phenylbenzofur-2-yl ester

ñ□ï□□						USER: ‡.d‹ -- DATE: LYBRICS Imported file
F1: 60.010		SW1: 1000		OF1: 214.6		PTS1d: 4096
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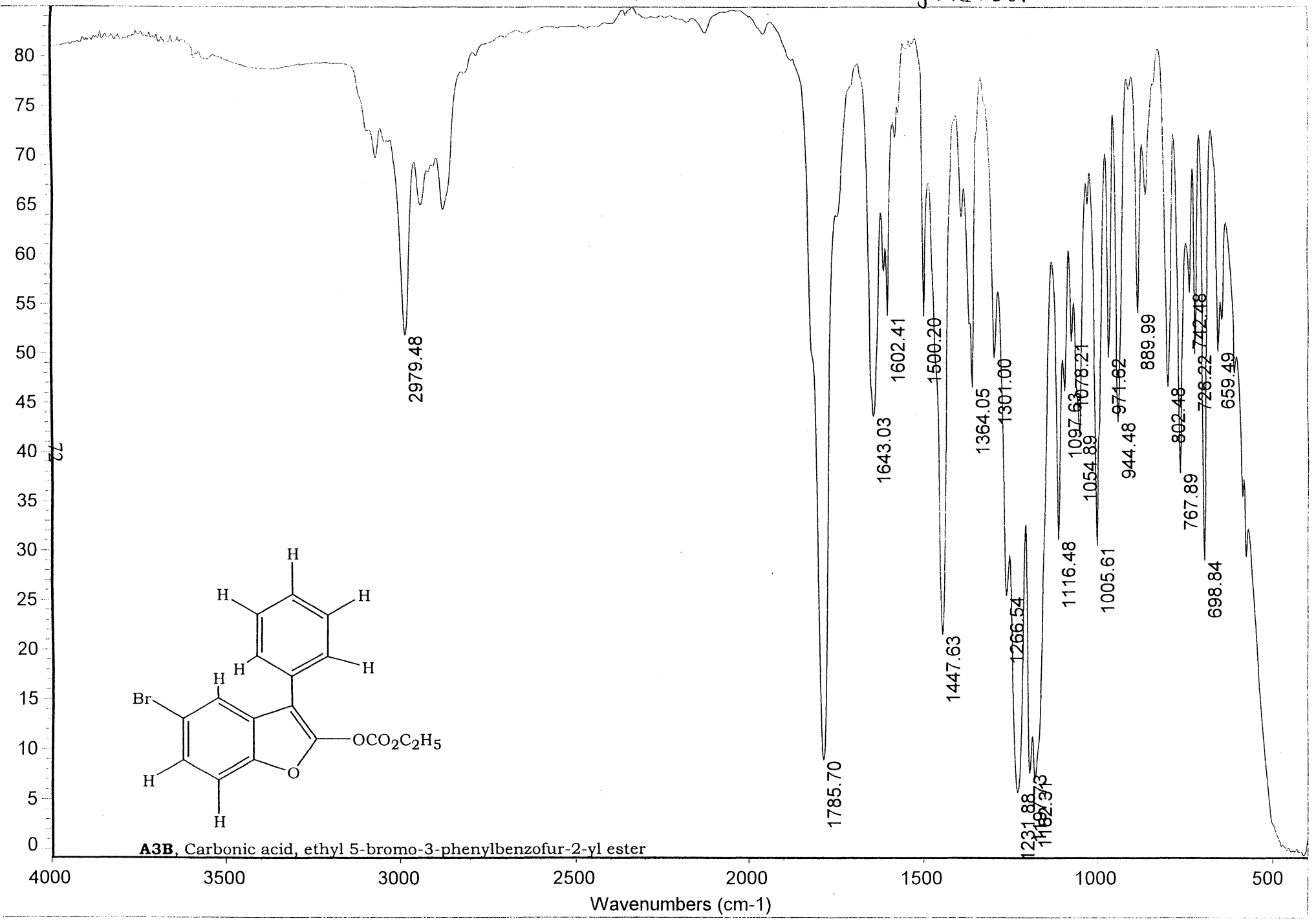
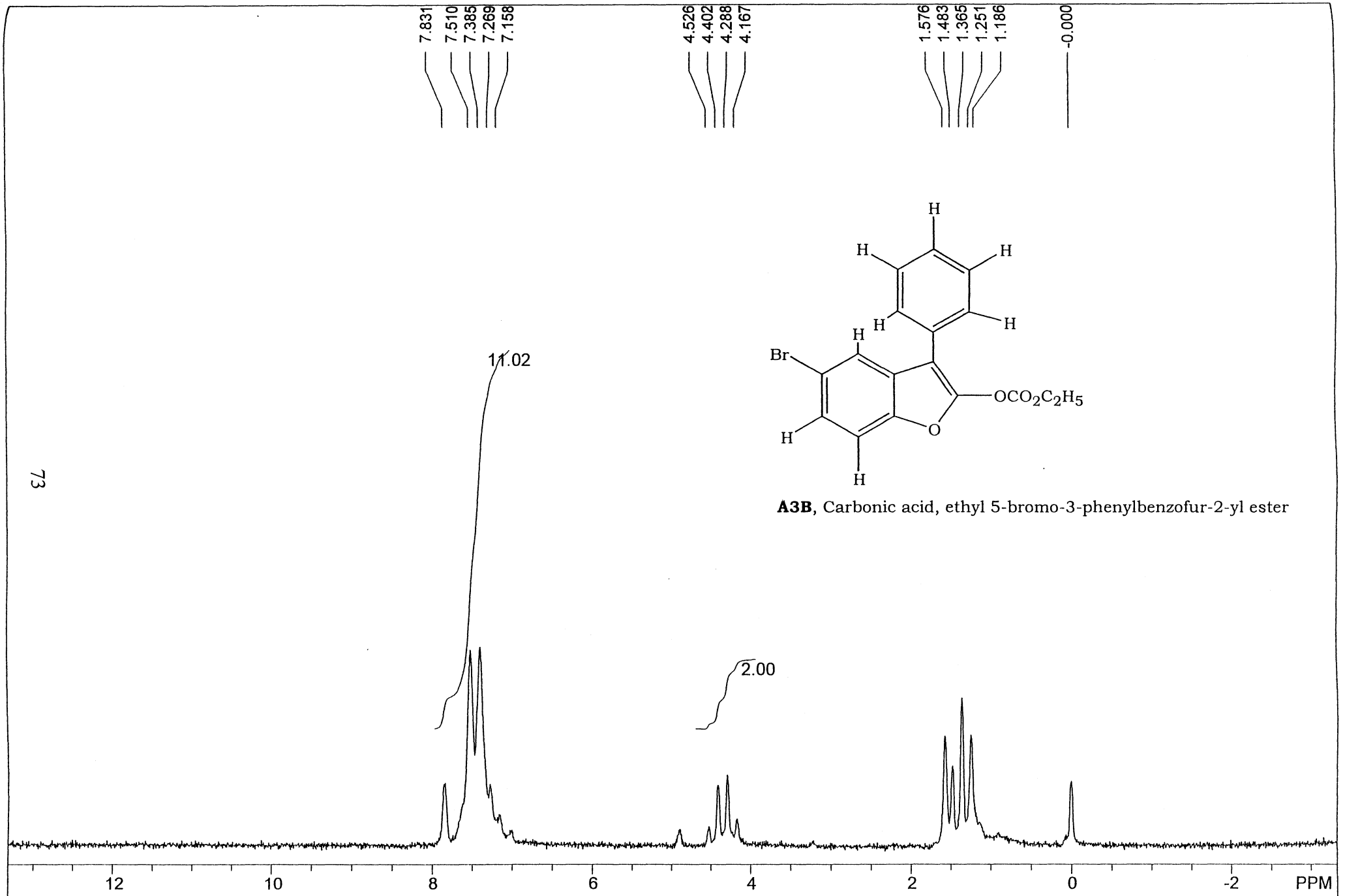
JB.I.36.



A3B, Carbonic acid, ethyl 5-bromo-3-phenylbenzofur-2-yl ester

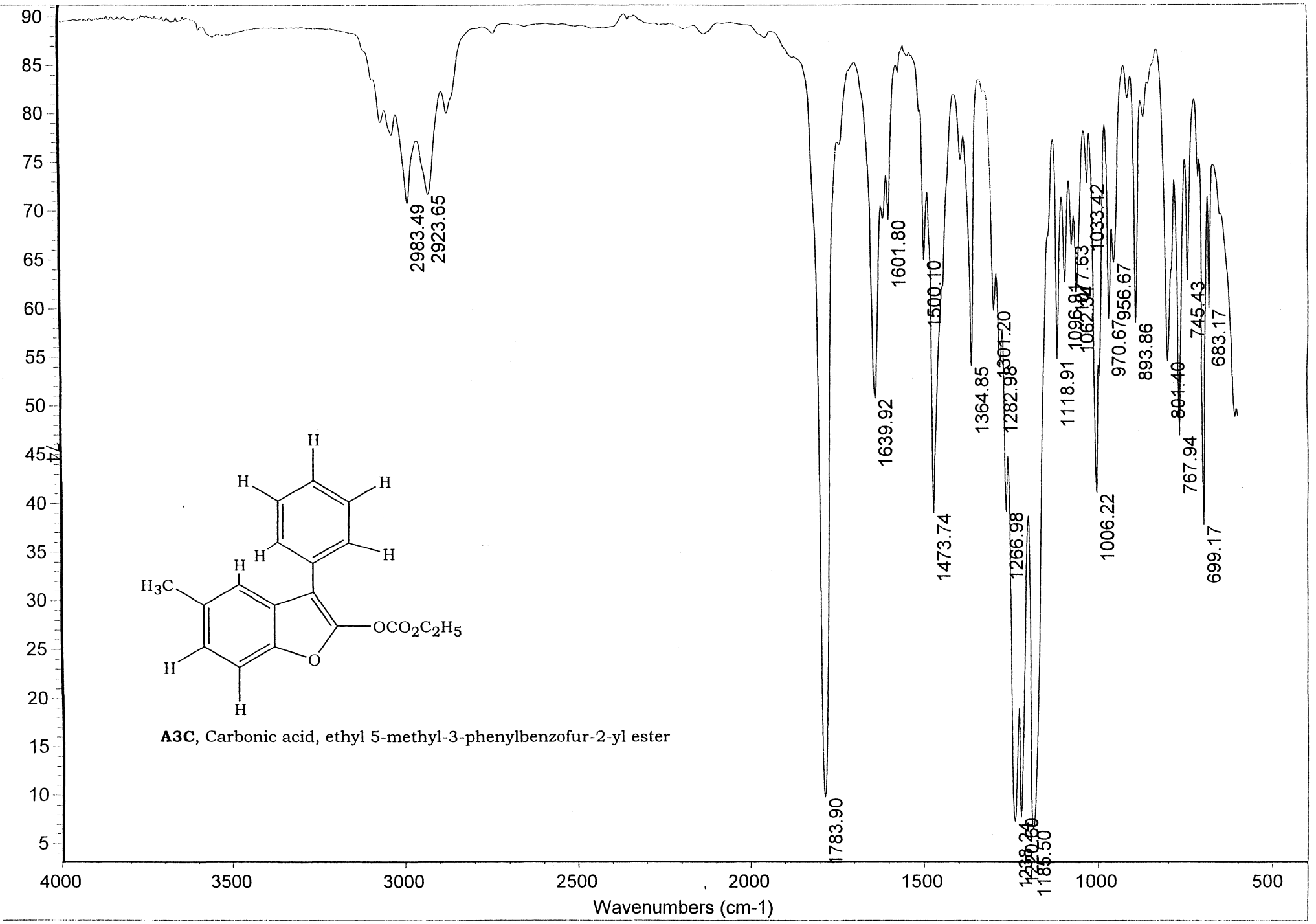


A3B, Carbonic acid, ethyl 5-bromo-3-phenylbenzofur-2-yl ester

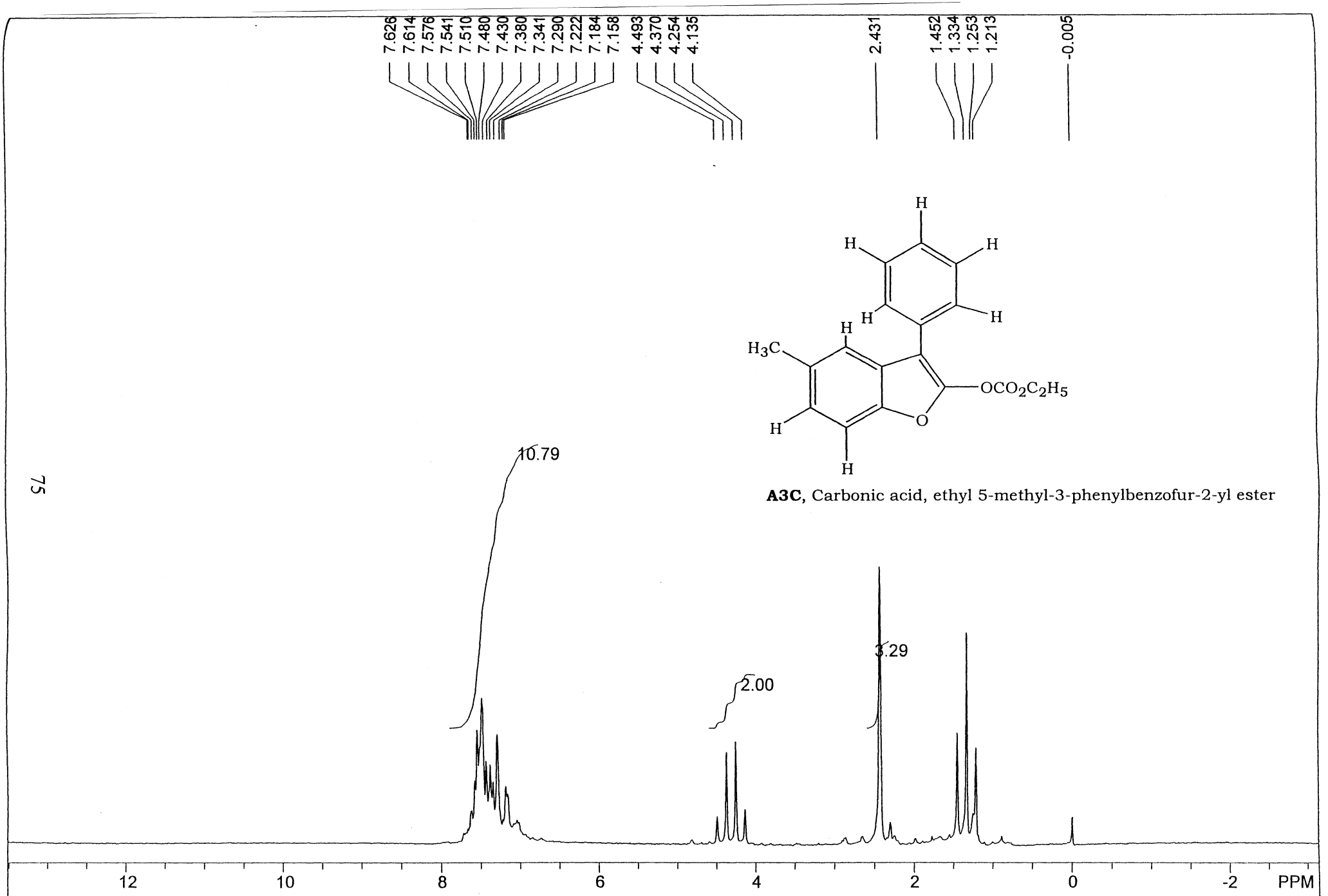
ñ□ï□□ USER: ç/d‹ -- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 299.4		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 20	LB: 0.0	Nuts - BR.EC

JB.I.91



A3C, Carbonic acid, ethyl 5-methyl-3-phenylbenzofur-2-yl ester



A3C, Carbonic acid, ethyl 5-methyl-3-phenylbenzofur-2-yl ester

LYBRICS Imported file USER: -- DATE:

F1: 60.010	F2: 1.000	SW1: 1000		OF1: 310.9		PTS1d: 4096
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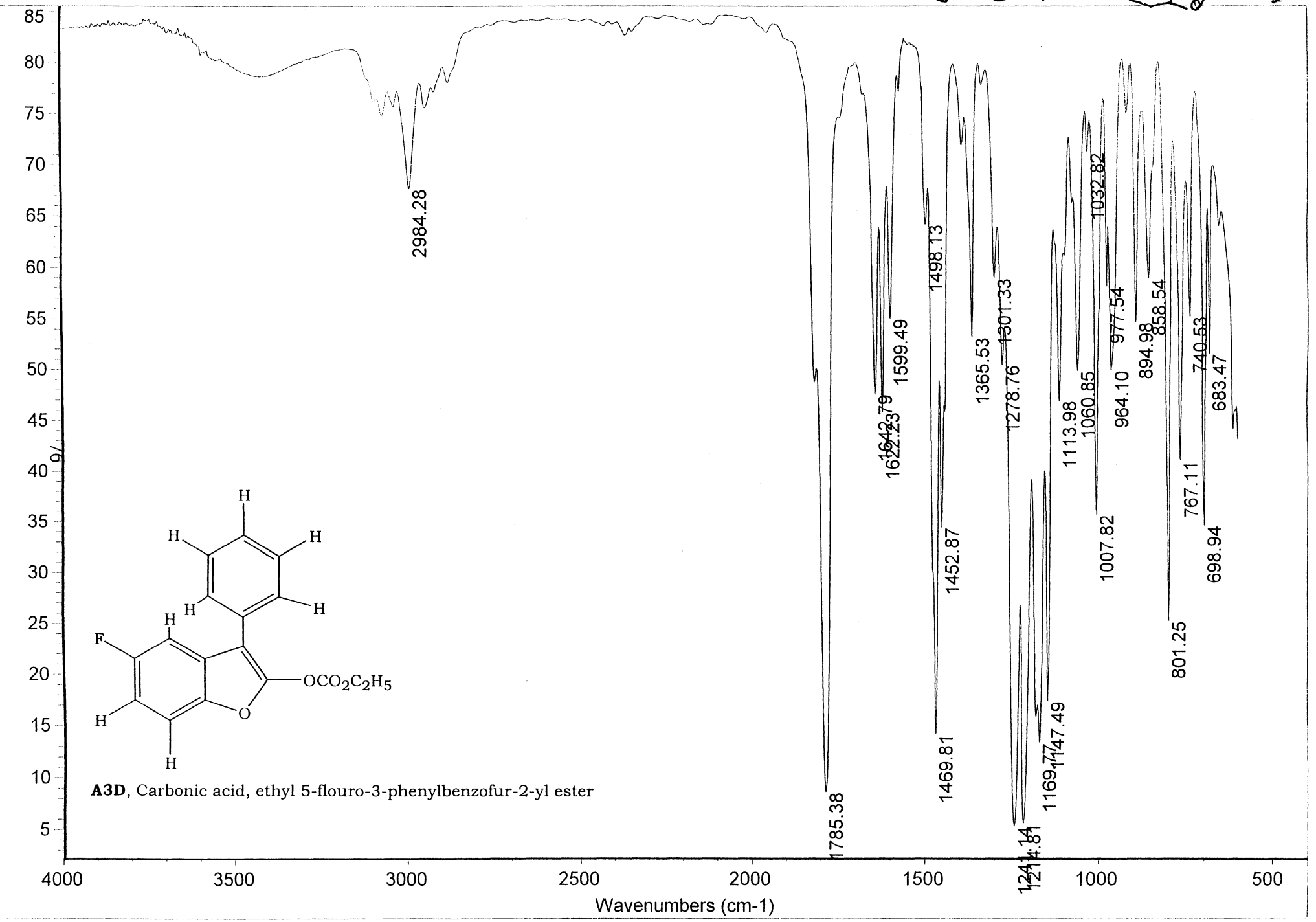
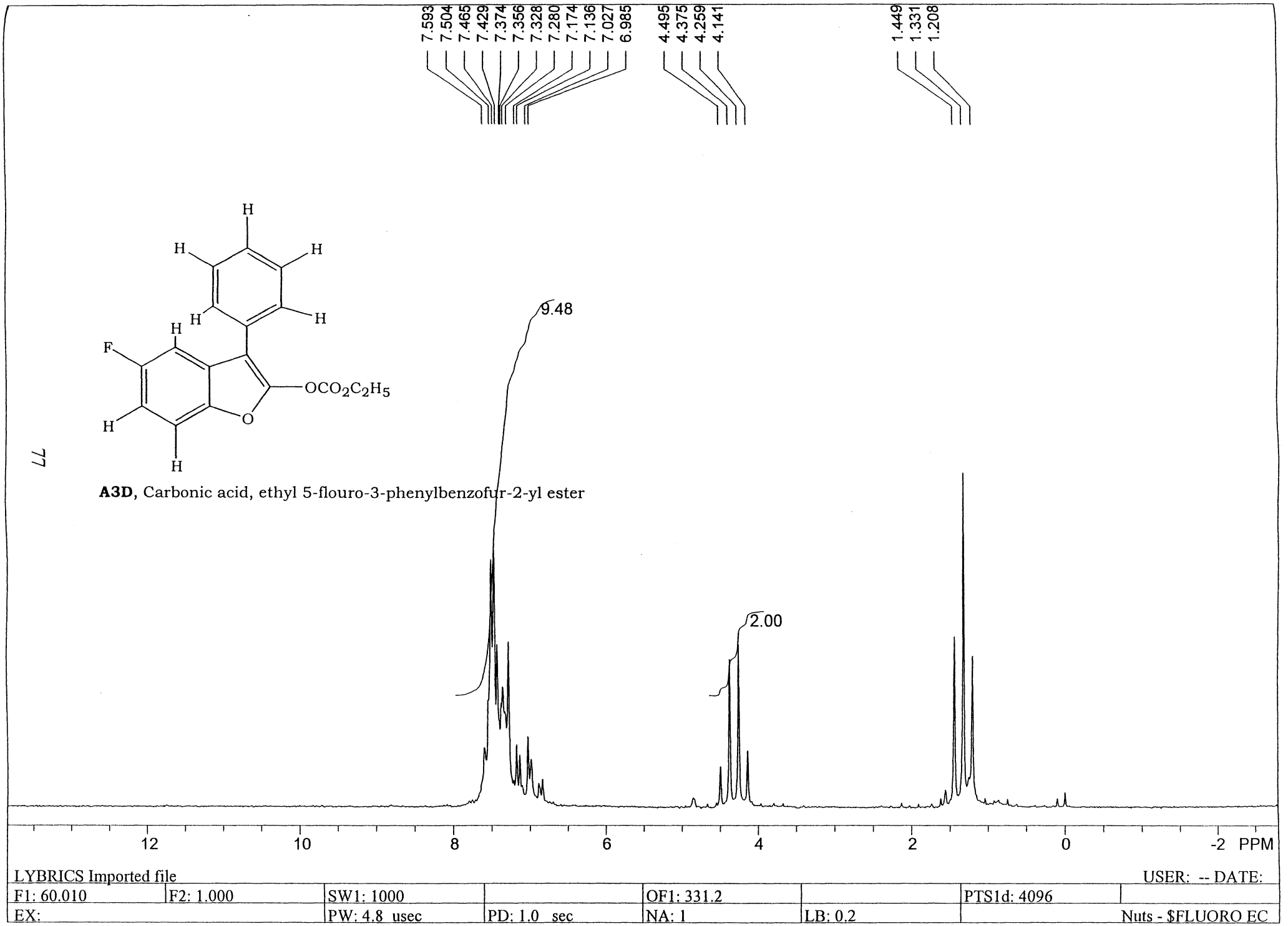
JB.I.70


2984.28
1785.38
1642.79
1622.23
1599.49
1498.13
1469.81
1452.87
1365.53
1301.33
1278.76
1241.14
1214.81
1169.77
1147.49
1113.98
1060.85
1032.82
1007.82
977.54
964.10
894.98
858.54
801.25
767.11
740.53
698.94
683.47
F
H
O
$OCO_2C_2H_5$
A3D, Carbonic acid, ethyl 5-flouro-3-phenylbenzofur-2-yl ester
%
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5

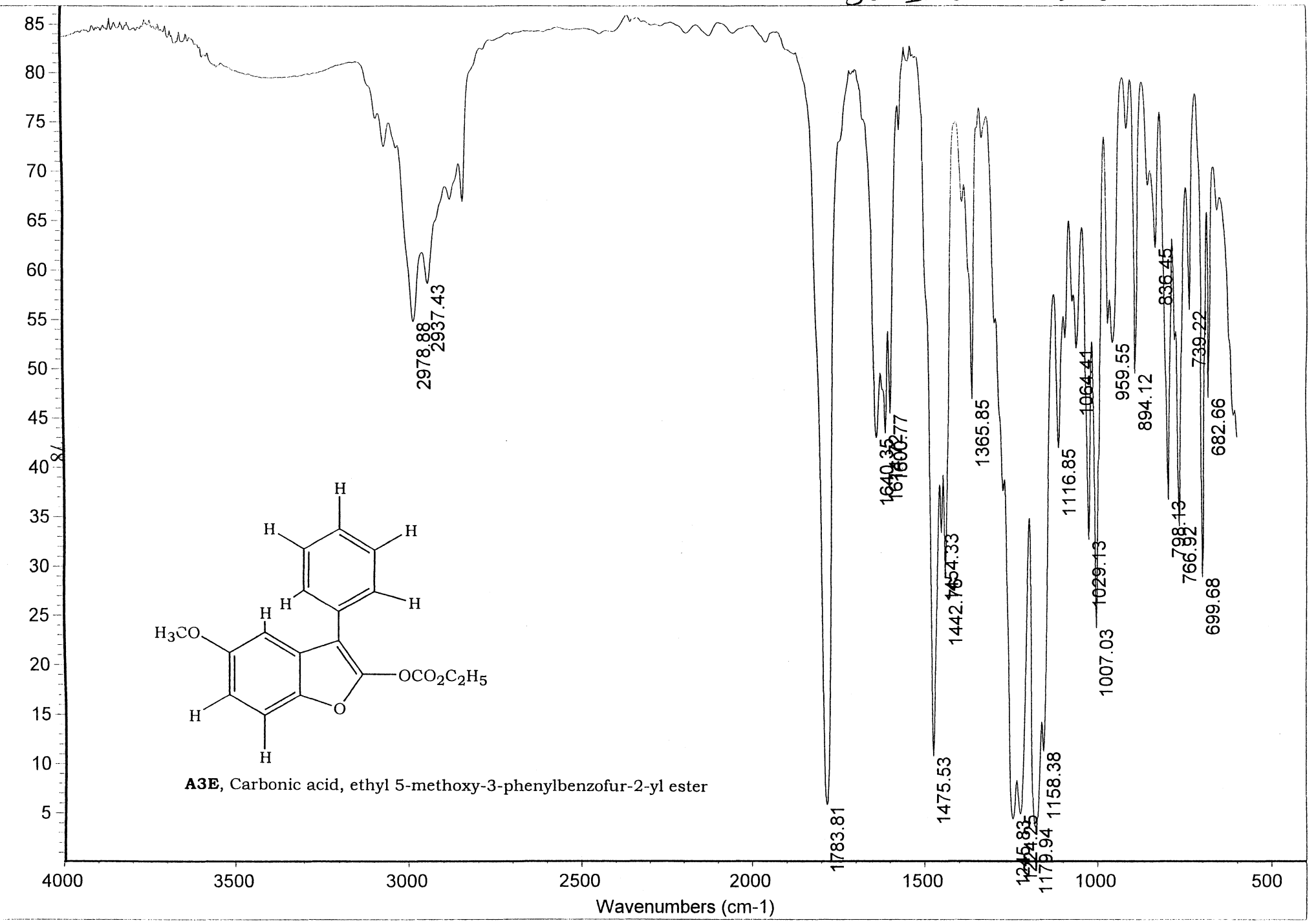


A3D, Carbonic acid, ethyl 5-flouro-3-phenylbenzofur-2-yl ester

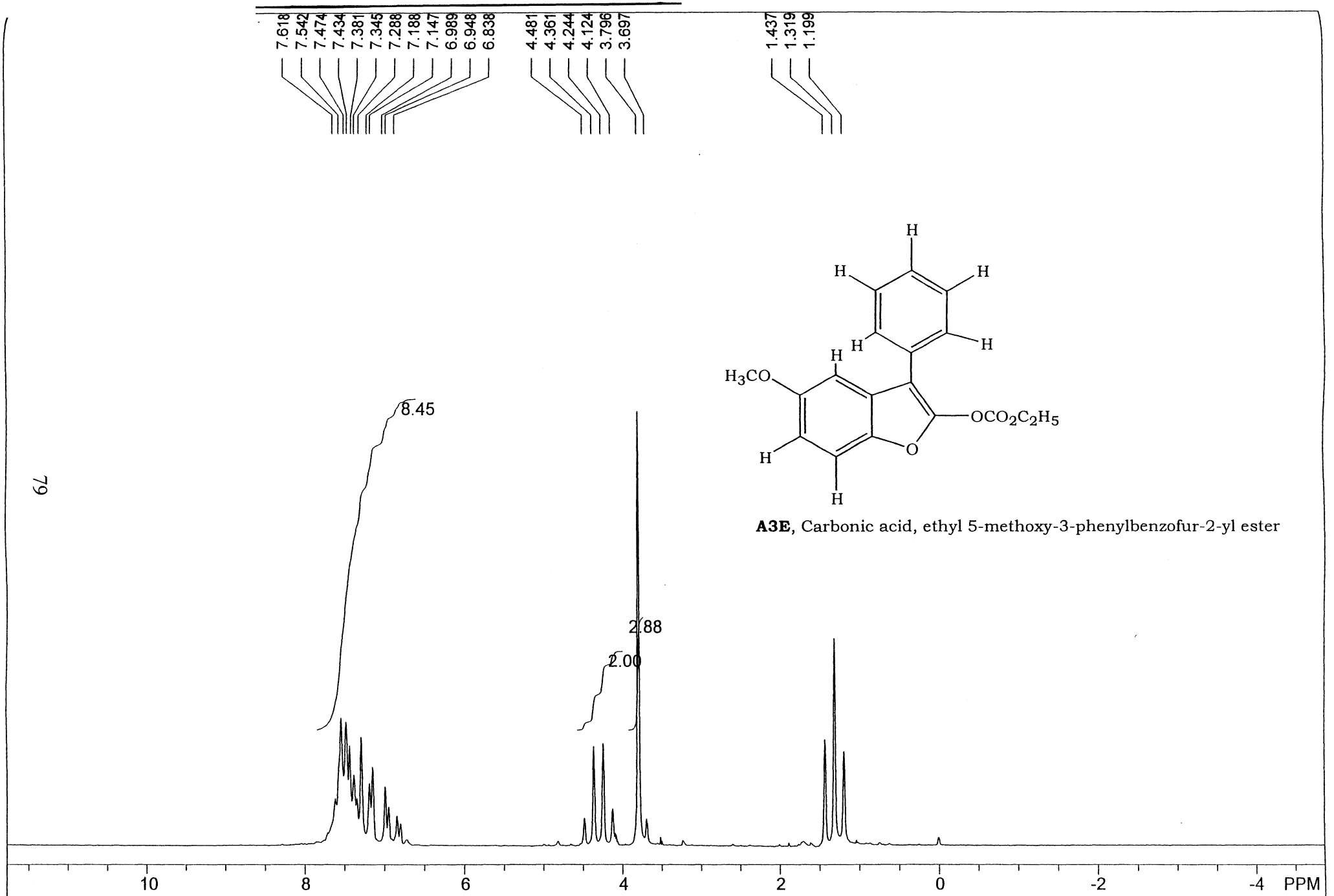
LYBRICS Imported file USER: -- DATE:

F1: 60.010	F2: 1.000	SW1: 1000		OF1: 331.2		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 1	LB: 0.2	Nuts - $FLUORO EC

JB. I. 63



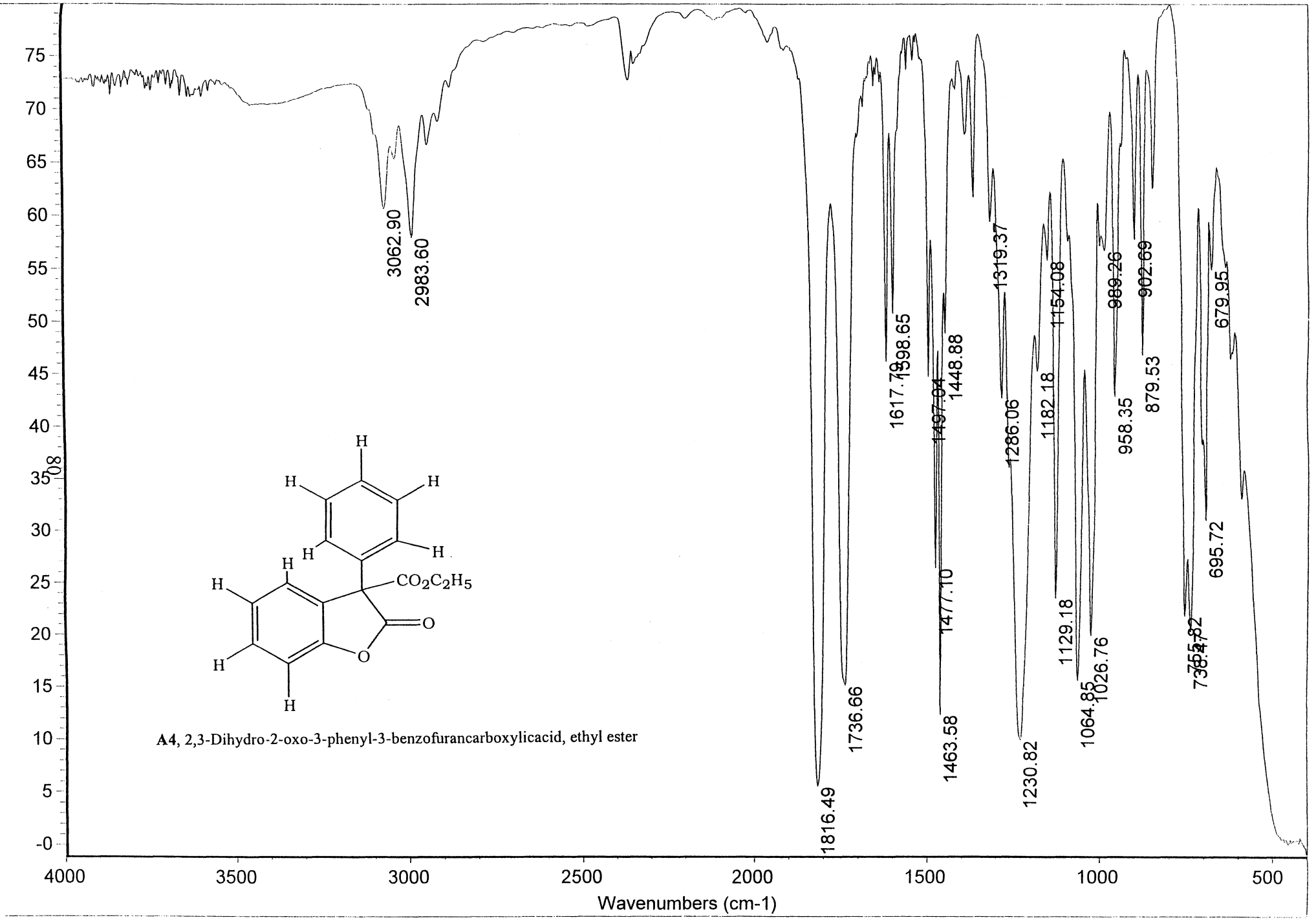
A3E, Carbonic acid, ethyl 5-methoxy-3-phenylbenzofur-2-yl ester



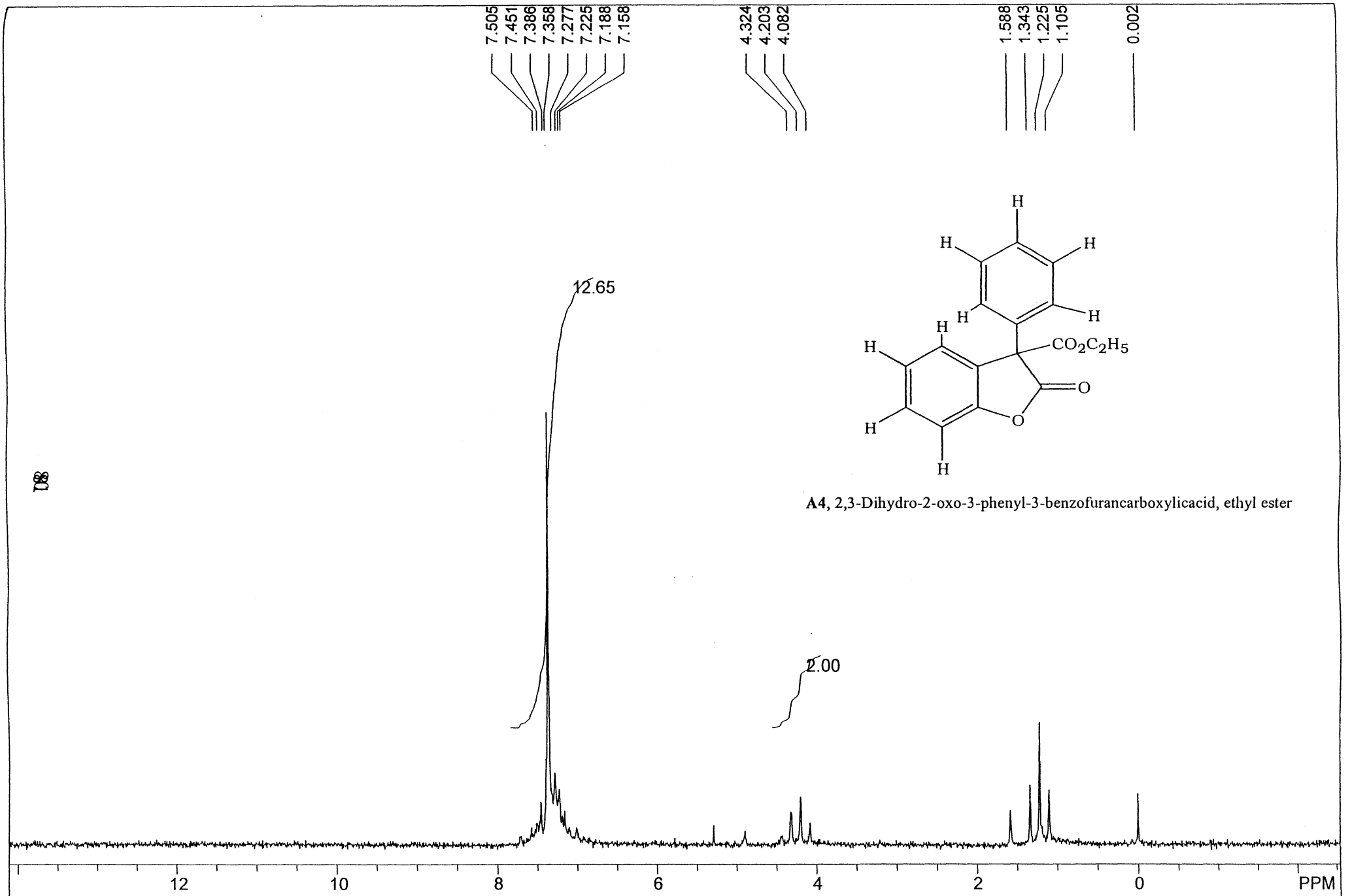
A3E, Carbonic acid, ethyl 5-methoxy-3-phenylbenzofur-2-yl ester

ñ□ï□□ USER: □□d‹ -- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 207.1		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 10	LB: 0.0	Nuts - OME.EC



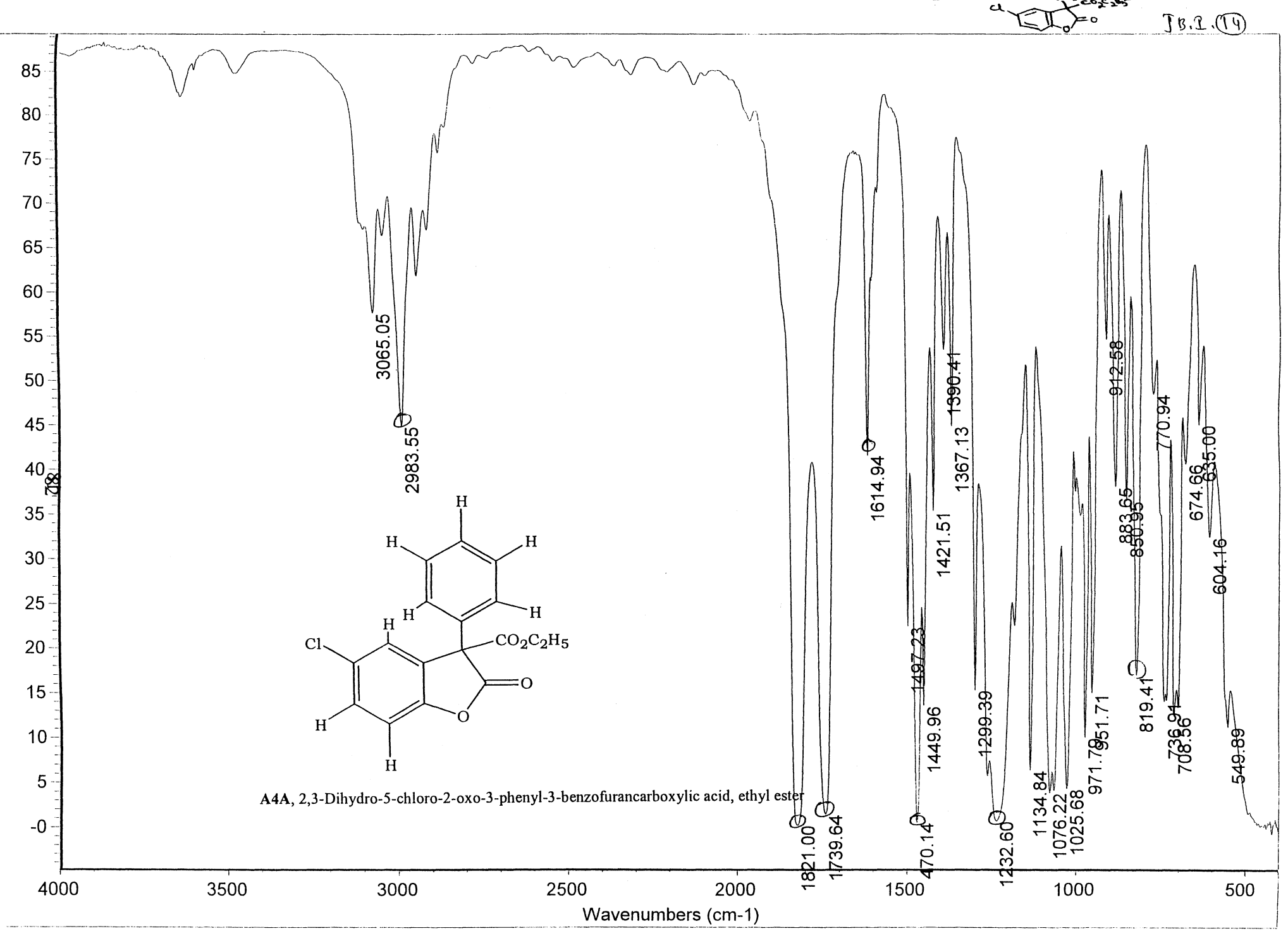
A4, 2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylicacid, ethyl ester



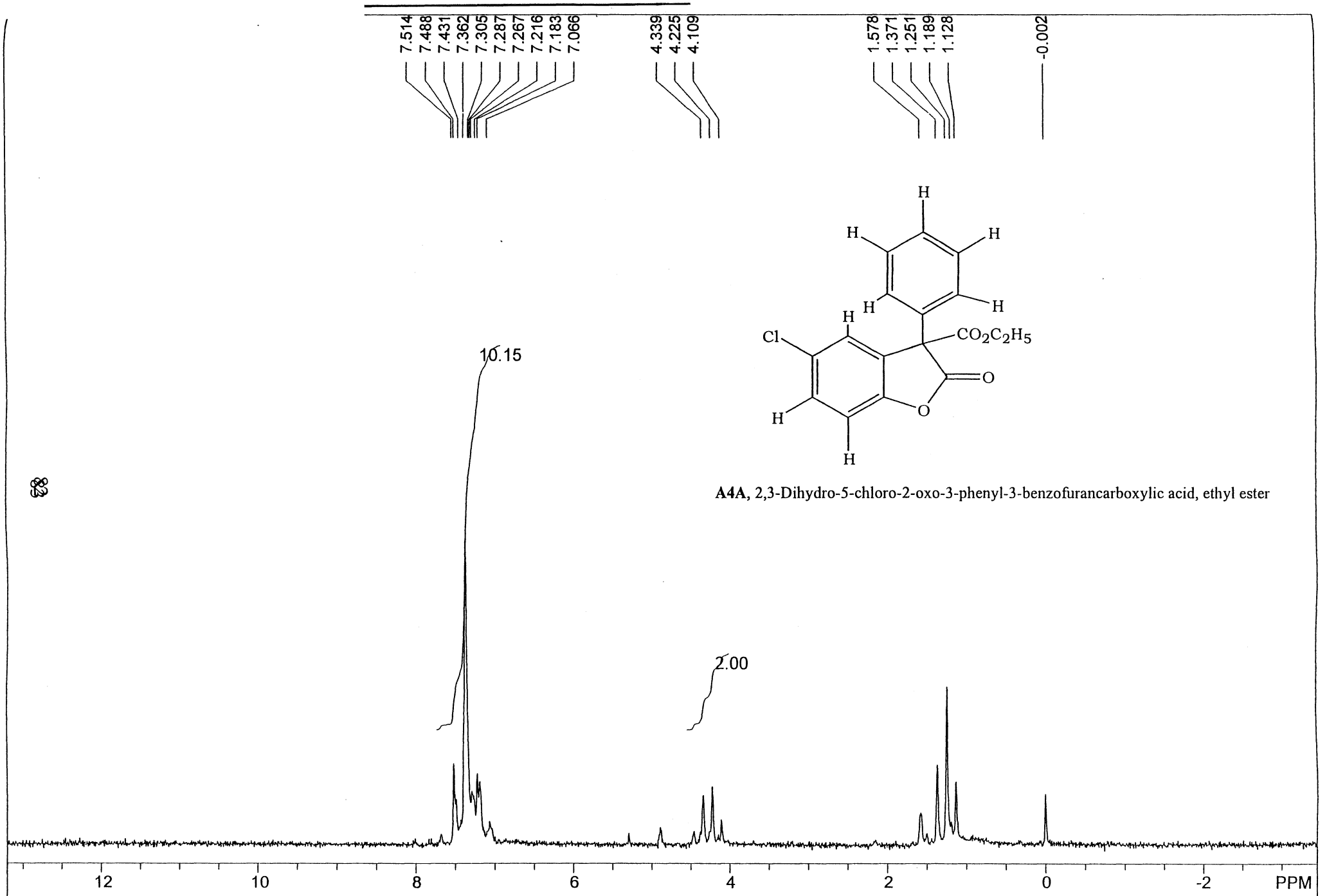
A4, 2,3-Dihydro-2-oxo-3-phenyl-3-benzofurancarboxylicacid, ethyl ester

USER: Ïd‹ -- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 347.1		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 1	LB: 0.0	Nuts - pbf.prod



A4A, 2,3-Dihydro-5-chloro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

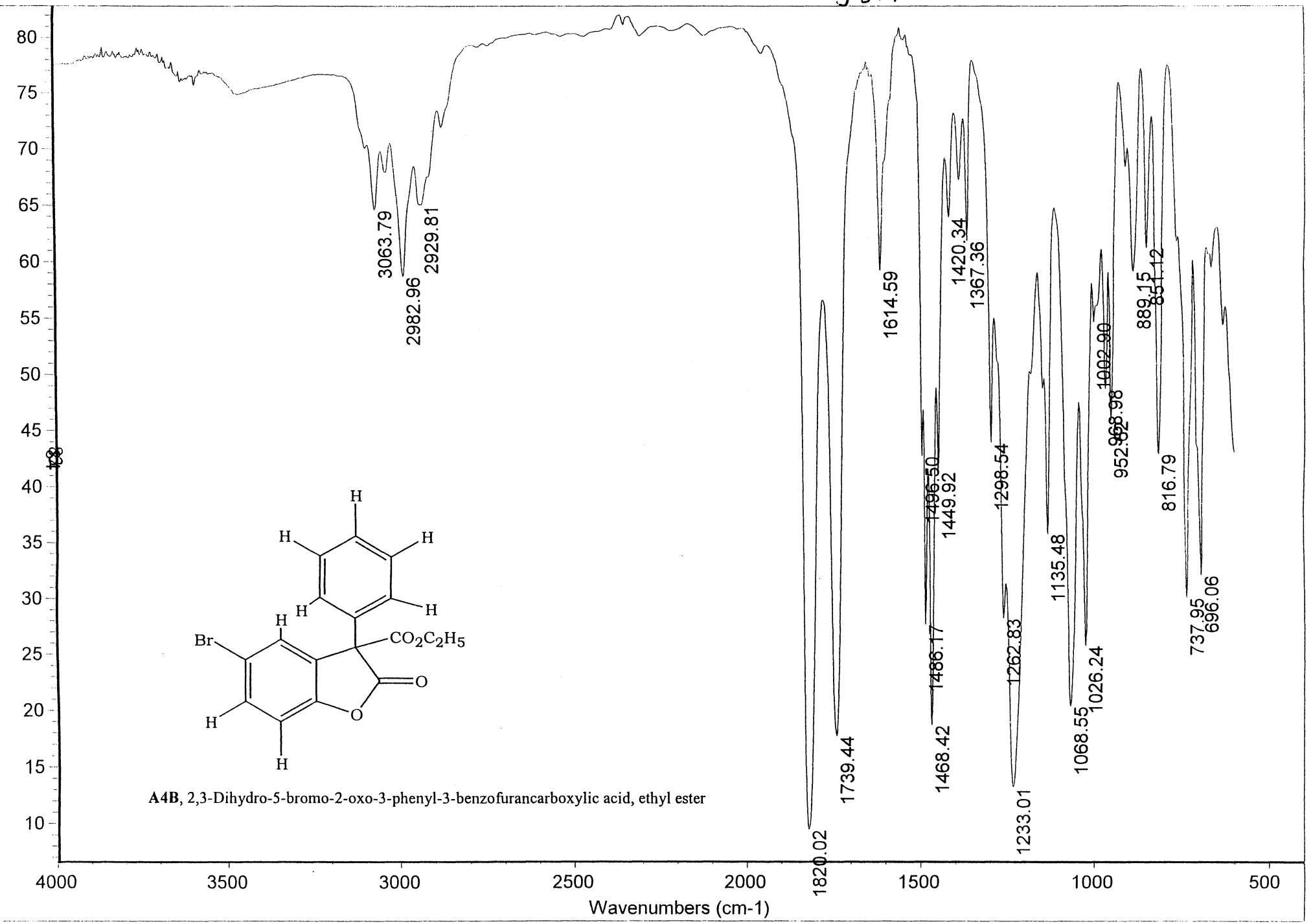


A4A, 2,3-Dihydro-5-chloro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

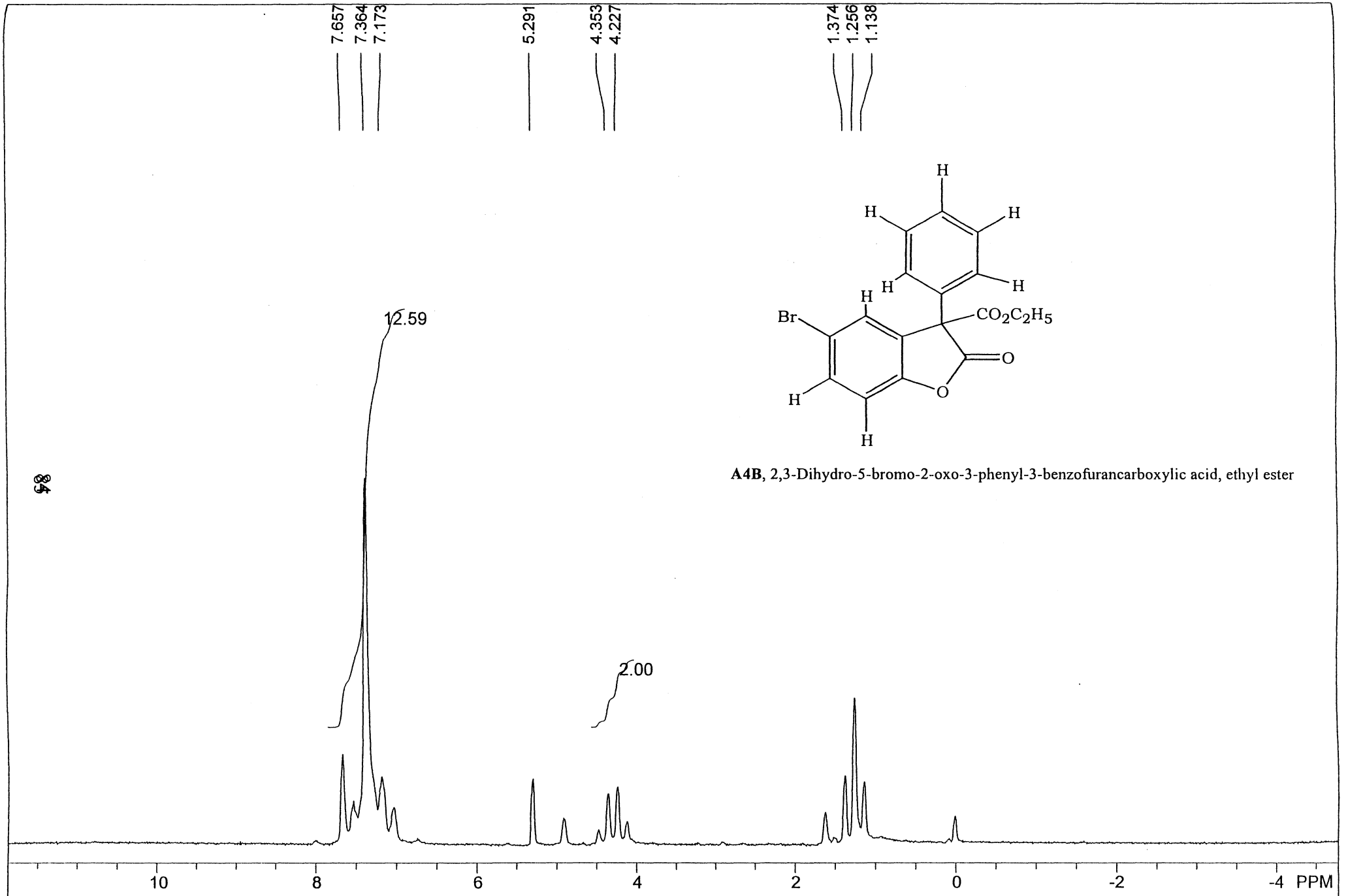
USER: G5d< -- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 292.4		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 3	LB: 0.0	Nuts - cl.prod

JB. 2. 55



A4B, 2,3-Dihydro-5-bromo-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

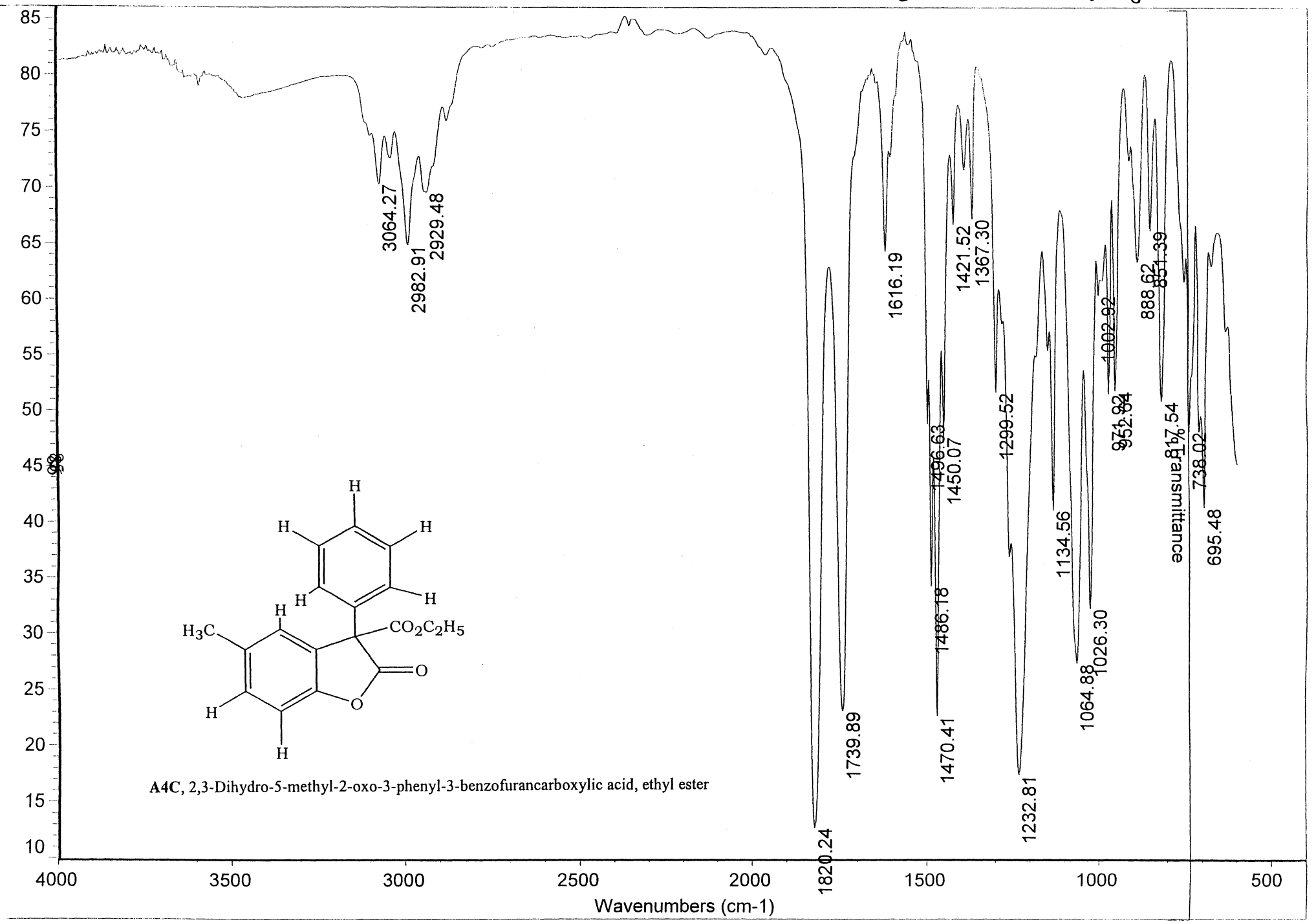


A4B, 2,3-Dihydro-5-bromo-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

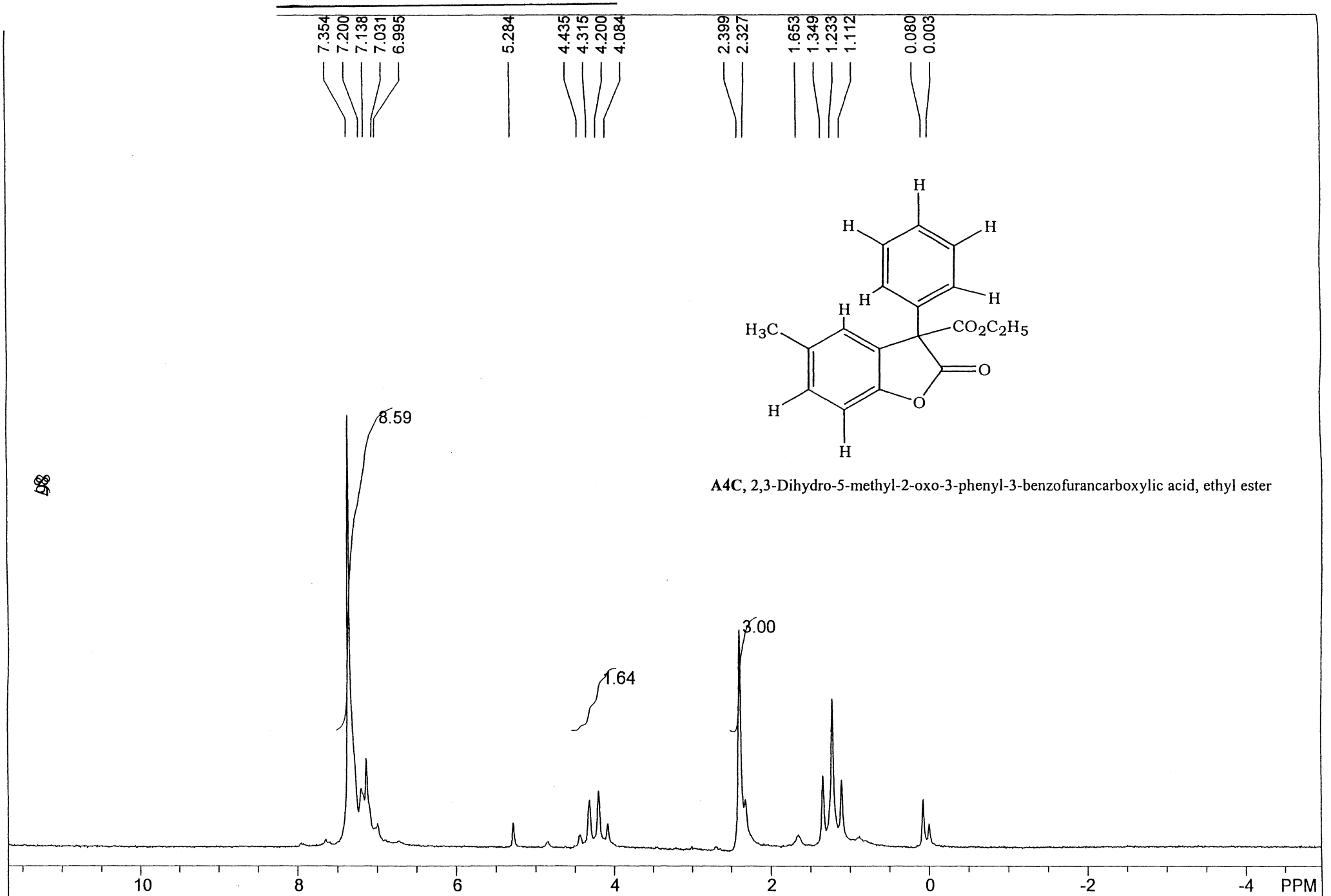
ñ□ï□□ USER: □□d‹ -- DATE: LYBRICS Imported file

F1: 60.010	SW1: 1000		OF1: 212.7		PTS1d: 4096
EX:	PW: 4.8 usec	PD: 1.0 sec	NA: 20	LB: 0.0	Nuts - BR.PROD night

JB.I.54



A4C, 2,3-Dihydro-5-methyl-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

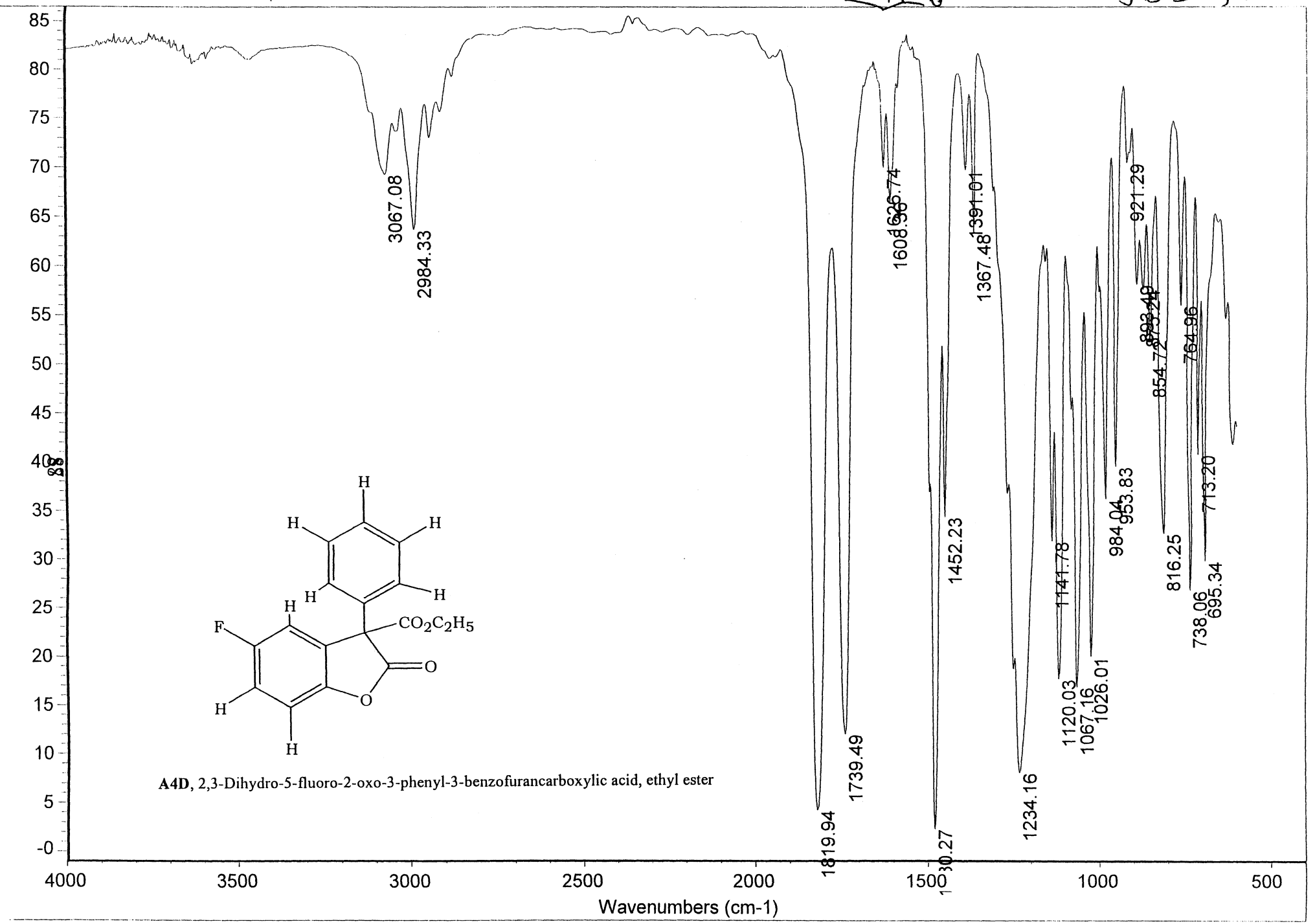


A4C, 2,3-Dihydro-5-methyl-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

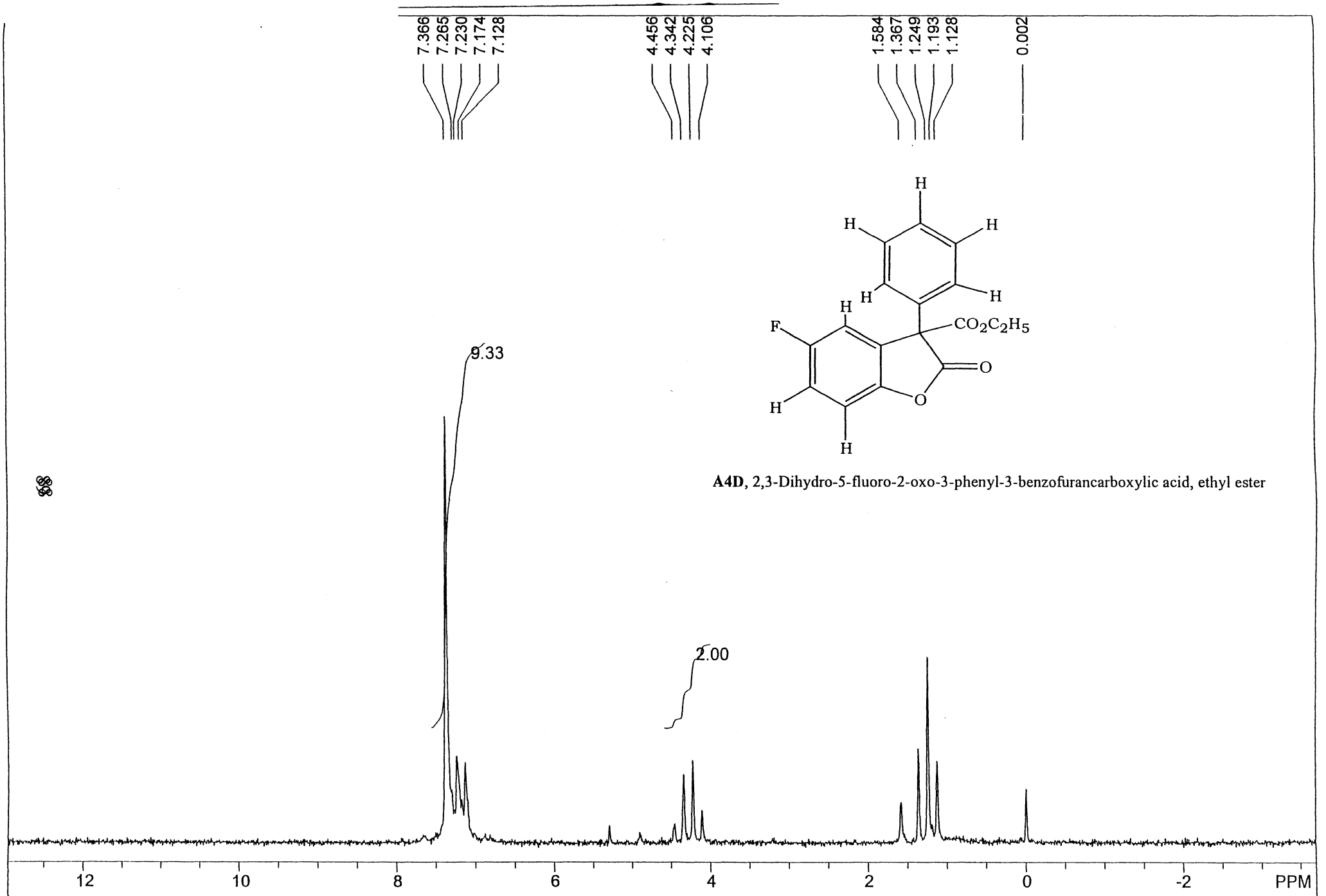
ñ□ï□□ USER: ?(d(-- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 201.3		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 10	LB: 0.0	Nuts - ME.PROD

JB.I.71



A4D, 2,3-Dihydro-5-fluoro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester



A4D, 2,3-Dihydro-5-fluoro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

USER: ¯3d‹ -- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 277.7		PTS1d: 4096
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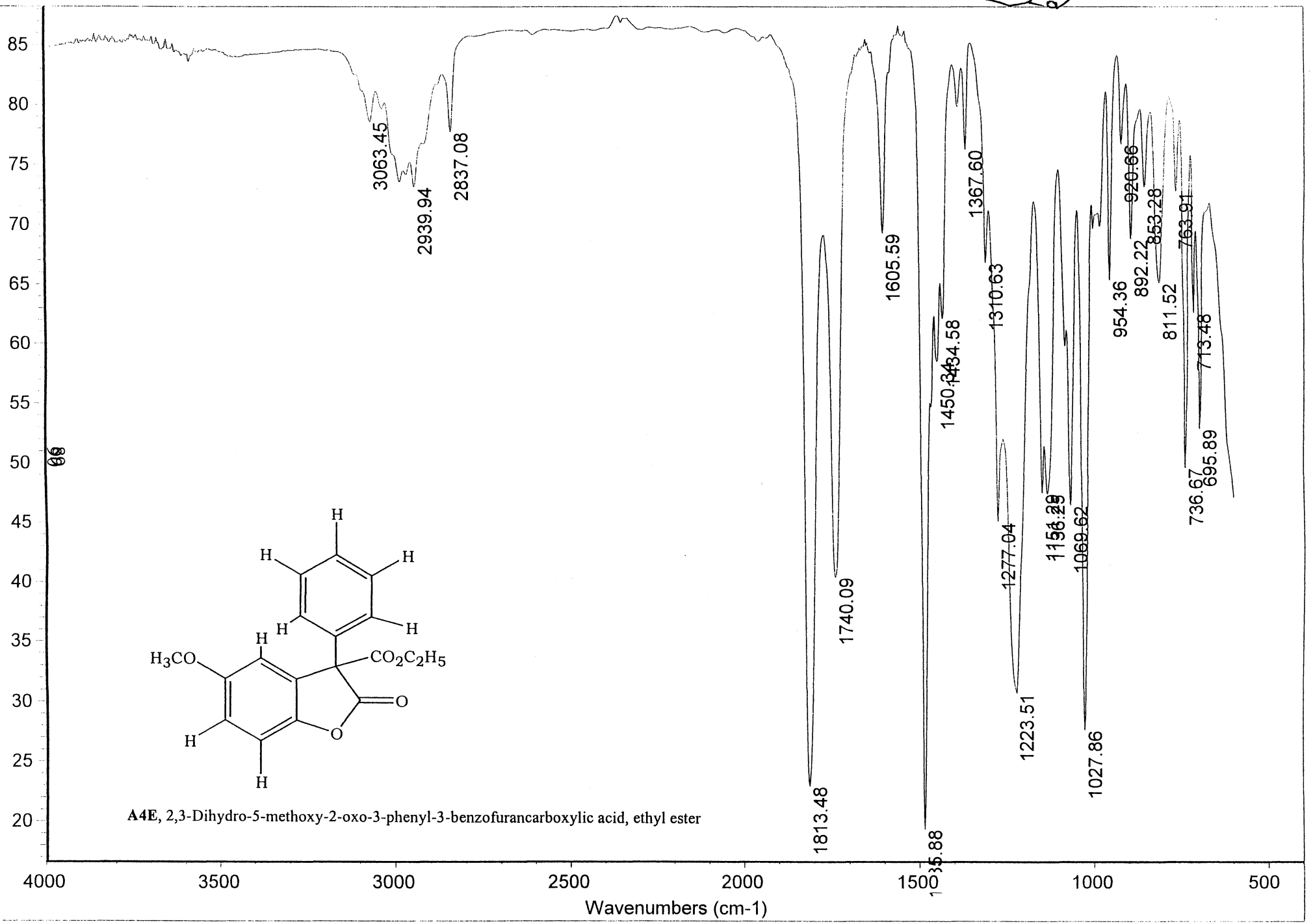
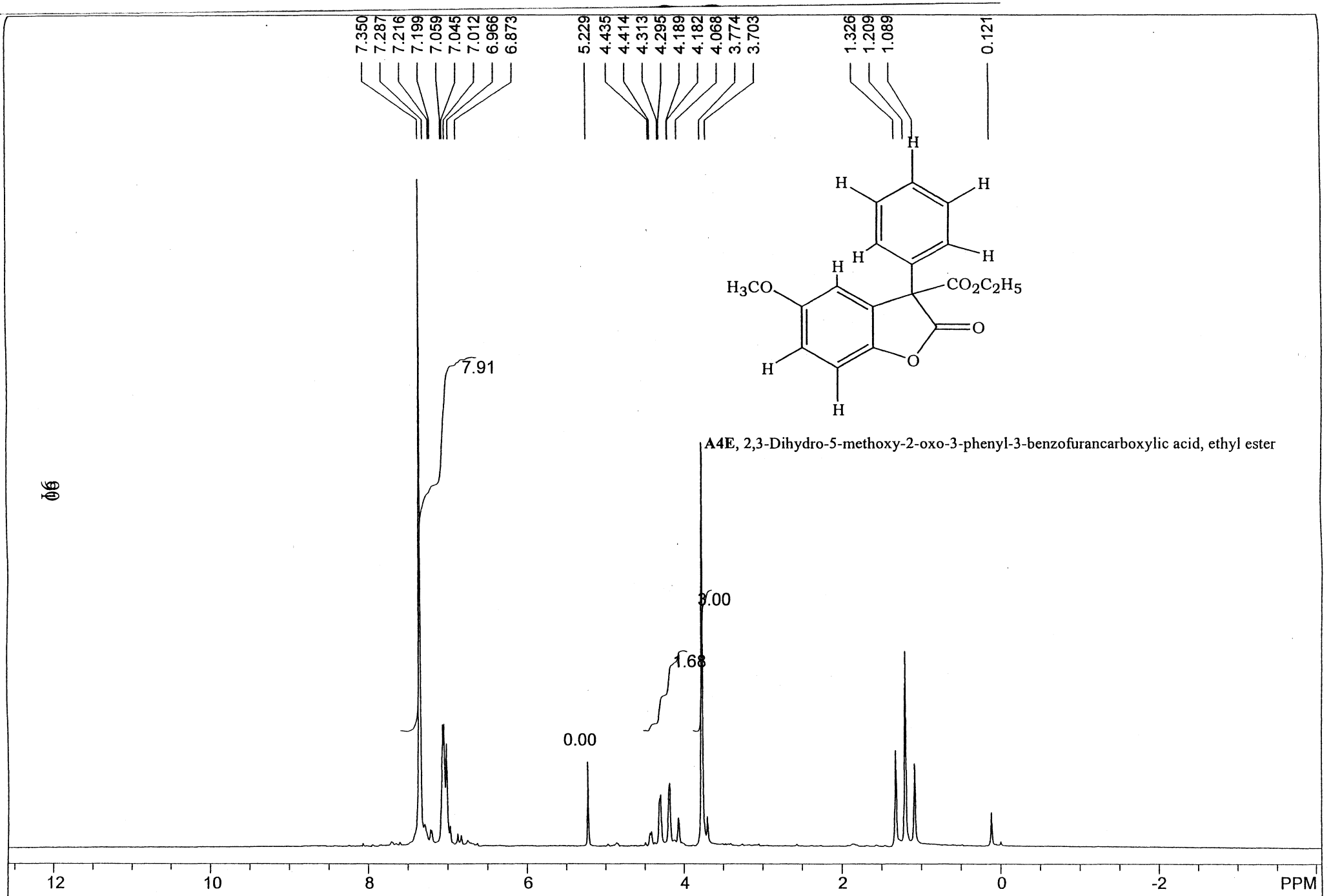
JB I. 67



A4E, 2,3-Dihydro-5-methoxy-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester



A4E, 2,3-Dihydro-5-methoxy-2-oxo-3-phenyl-3-benzofurancarboxylic acid, ethyl ester

ñ□ï□□ USER: ?(d‹ -- DATE: LYBRICS Imported file

F1: 60.010		SW1: 1000		OF1: 255.4		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 5	LB: 0.0	Nuts - OME.PROD