SPECTRAL AND ELECTROCHEMICAL ANALYSIS OF CHALCONE DERIVATIVES

A DISSERTATION

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

MASTER OF TECHNOLOGY

in

ADVANCED CHEMICAL ANALYSIS

By

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CERTIFICATE

It is certified that the Dissertation report entitled "**SPECTRAL AND ELECTROCHEMICAL ANALYSIS OF CHALCONE DERIVATIVES**" is the result of work carried out during the period of July, 2011 to June, 2012, by Ashutosh Shukla, Department of Chemistry, Indian Institute of Technology Roorkee, under my supervision. His work neither in part nor in whole has been submitted for any other degree.

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CANDIDATE'S DECLARATION

I hereby declare that the work which is being presented in the project entitled "**SPECTRAL AND ELECTROCHEMICAL ANALYSIS OF CHALCONE DERIVATIVES**" in partial fulfillment of the requirements for the award of the degree of Masters of Technology submitted in the Department of Chemistry, IIT Roorkee is an authentic record of my own work carried out during the period from July, 2011 to June, 2012 under the supervision and guidance of Dr. K. R. Justin Thomas.

The matter embodied in this project work has not been submitted for the award of any other degree.

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Abstract

A series of novel chalcone based dipolar compounds having different arylamines (*N, N*-dimethylaniline/triphenylamine/*N*-ethylcarbazole) or polyaromatic hydrocarbons (pyrene /anthracene) as donor, cyanovinyl unit as linker and/or acceptor and phenyl moiety at another end were synthesized and characterized in an attempt to unravel the effect of different donor unit as well as cyano substitution on optical, electrochemical and thermal properties. A model compound without cayno substitution was also synthesized for comparative analysis. They exhibited absorption peak around 359-447 nm attributed to transitions originated from delocalized π-π^* transitions and charge transfer transitions. Although the absorption spectra of the dyes were not significantly influenced by the nature of the solvents whereas, the fluorescence of chalcones was red-shifted to the range of 471-575 nm and was most intense in chloroform. The strong electron-attracting cyano group quenched the fluorescence in polar solvents. All the compounds were characterized by a quasi-reversible oxidation wave originated from the donor segment which underwent shift corresponding to electron-donating strength of donor moiety. The thermogravimetric analysis results indicate that cyano substitution is helpful in increasing the thermal stability.

Chapter 1

Aim and scope

Fluorescent dyes that absorb and emit in the visible (vis) and/or near-infrared (NIR) are of major interest in many fields of dye chemistry such as, e.g., development of luminescent pigments for plastics and fibers or fluorophore design for (bio) chemical or environmental analysis.[1-3] Whereas, the utilization of organic color-conversion material appears to be attractive with respect to low cost, easy fabrication and color tuning. Among those chalcones are well-known precursors of many naturally occurring pigments as flavones, and are used in many fields of applications such as UV-absorption filters in polymers,[4] in different kinds of optical materials,[5] in food industry,[6] and holographic recording technologies as well as in medical therapy.[7]

The photophysical properties of substituted chalcones have been studied by many researchers involving mostly asymmetrical donor–acceptor (D/A) chalcones and to a minor extent symmetrical donor–acceptor–donor chalcones.[8-18] In these systems, the acceptor part is the carbonyl group while a 4-donorsubstituted phenyl group serves as the donor part. In such D/A-molecules, very large changes in charge distribution can be induced in the excited state upon absorption of light photons. The sudden creation of a giant dipole (due to photoinduced intramolecular charge transfer, ICT) can result in a strong interaction with the surrounding

medium to cause not only solvent reorganization but also sometimes to structural rearrangement in the solute itself. These changes lead, in several molecules, to distinguishable spectroscopic properties such as a large Stokes-shifted fluorescence maximum.[19]

It was clearly demonstrated that the luminescence properties of several chalcones with strong electron-donating and accepting substituent strongly depend on the character of the substituent, the polarity of the solvent and the temperature. From the correlation of fluorescence quantum yield with solvent polarity, a clear maximum was observed indicating the presence of a negative solvatokinetic effect with moderately increasing solvent polarity and a positive solvatokinetic effect with highly polar solvents.[20] The spectral properties of enone (chalcone) derivatives also depend on the character of the bridge. The rigid structure of the enone bridge favors radiative decay even in polar solvents. In contrast, enone compounds with a free double bond have very low fluorescent quantum yields. The chalcones with a strong donating (D) and a strong accepting (A) substituent with a π-conjugated spacer are under investigation as potential materials for non-linear optics (NLO), because they are nonsymmetrical and exhibit high polarizability and hyperpolarizability.

In order to realize those advantages mentioned above, we designed and synthesized novel chalcone derivatives having conjugation of different donor unit (arylamine/polyaromatic hydrocarbon) with phenyl unit through cyanovinyl spacer. Since triphenylamine being an electron rich unit it can cause charge transfer transition upon excitation and further π-conjugation can help in increasing the transition probability for the transitions.[21] So that target molecule can show excellent photophysical properties. Pyrene is considered as potential component for advanced material. It contains extensive π-conjugated

system, high thermal stability and good performance in solution.[22] Carbazole is introduced as an important moiety in to the molecules for the following reasons: the thermal stability of molecule can be enahanced by the introduction of carbazole unit, also the moderately high oxidative potential of carbazole containing compounds can make them promising as hole transporting materials.[23] Anthracene's high oxidation potential, small π-surface, and high fluorescence quantum yield usually relegate materials based on this aromatic core to applications in light-emitting systems.[24] More often, the anthracene chromophore is used for its fluorescence characteristics, where any significant electronic interaction in the solid leads to an undesired broadening of the emission spectrum and a decrease in fluorescence yield.

We believe that having different donor unit these molecules can show valuable spectroscopic properties with as intense absorption in the visible region and strongly red-shifted red emission in solvents. Moreover, the emission properties of these chalcones can be tuned by changing the donor moiety. Aggregation may affect the absorption of light and also promote intermolecular quenching processes detrimental for the generation of electrons. We planned to evaluate the role of trigonal amine units, planar pyrene and twisted anthracene segments in such interactions. It is also known that the nature of the electron donating group significantly affects the position of absorption band and oxidation potential in donor-acceptor derivatives. A strong electron donating group can shift the absorption band towards the longer wavelength region and may shift the oxidation potential more cathodically and reversal may be observed in case of weak electron donating group. Therefore, we placed different donor moieties and studied the effect on the position of absorption band and oxidation potential.

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Chapter 2

Chalcones: A Review

2.1. Introduction

The emerging science of photonics, which includes the generation, emission, transmission, modulation, signal processing, switching, amplification, detection and sensing of light, is being explored today as the basis for the new technology that exploits the capability of a photon to carry information and energy.[1] To achieve this goal, new materials containing specific chromophores having properties such as fast response, large nonlinear susceptibility, easy preparation and handling are required be developed to achieve the parameters necessary for the further development of the photonic material itself and the technology using it as basis. Accordingly, considerable attention in the literature have been attaracted by the compounds having both donor (D) and acceptor (A) components that exhibit interesting optical and spectral properties due to the intramolecular charge transfer (ICT) phenomenon.[2] The electron-donating and electron-accepting substituents in these molecules are connected through a π-conjugated system of single and double bonds.[3]

The dipolar materials having wide applications like in organic light emitting diode (OLED), dye sensitized solar cells (DSSC), thin film transistors (TFTs), sensors, bukl

heterojunction solar cells, non linear optical devices (NLO devices) etc. there are various moieties acting as donor (D) and acceptor (A).

New n-type conjugated oligomers with p-type endgroups, '2,2'-bis(triphenylamine)-4,4'-diphenyl-(6,6')-biquinoline' (1) and '2,2'-bis(triphenylamine)-3,3'-diphenyl-(6,6')biquinoxaline' (2) were synthesized, characterized, and found to be efficient ambipolar blue-green and pure green emitters in organic light-emitting diodes (OLEDs). In toluene solution, oligoquinoline emitted bluegreen fluorescence with a quantum yield of 62% and a lifetime of 1.3 ns, whereas the oligoquinoxaline emitted green fluorescence with a 34% quantum yield and a lifetime of 5.3 ns.[4]

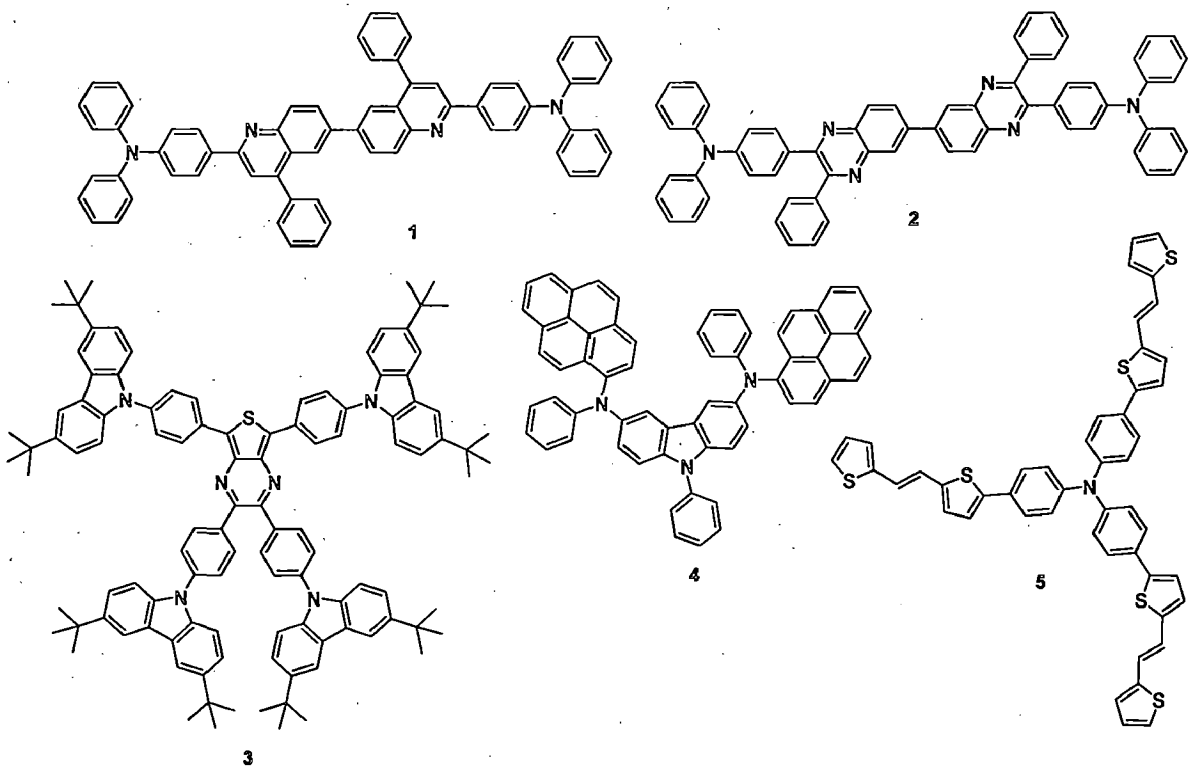


Fig.2.1. Structures of various dipolar molecules used in OLED.

A series of novel red-emitting thieno-(3,4-*b*)-pyrazine-cored molecules containing oligo-carbazole dendrons (3) are synthesized. The peripheral carbazolyl units facilitate the hole transporting ability and inhibit the intermolecular interactions. As a result, efficient

OLEDs with saturated red emission are fabricated by spin coating technique using these dendritic materials as nondoped emitting layer.[5-6] Thomas, K. R. J. et al reported pyrene based dipolar compounds (4). These were used in the fabrication of green emitting OLEDs.[7] Jean Roncali et al reported triphenylamine-thienylenevinylene hybrid systems (5) with internal charge transfer as donor materials for heterojunction solar cells.[8]

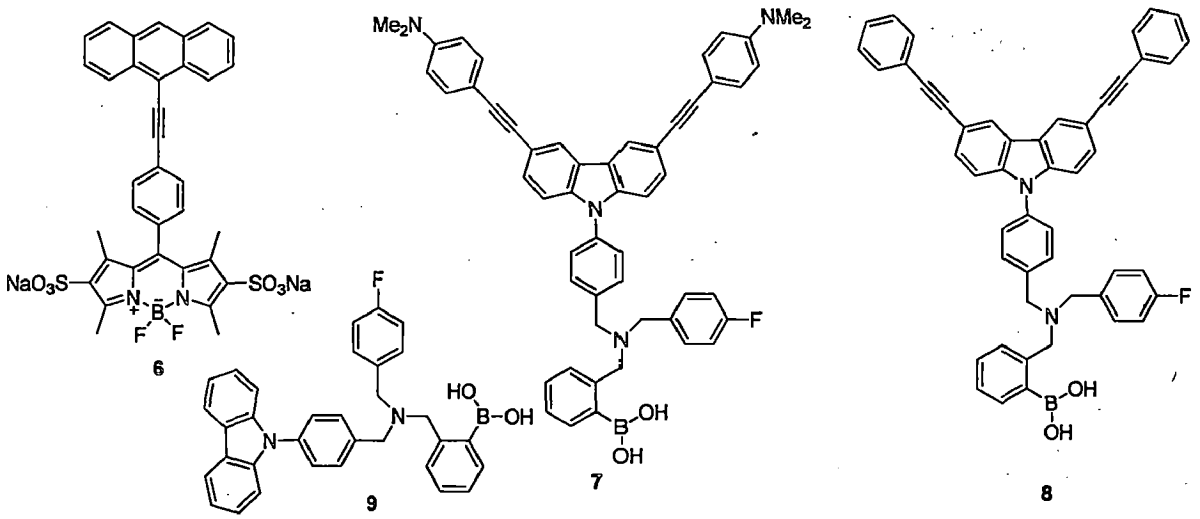


Fig.2.2. Structures of various dipolar molecules used as sensors.

Alexander Nierth et al reported anthracene-bodipy (6) dyads as fluorescent sensors for biocatalytic diels-alder reactions.[9] Jianzhang Zhao et al synthesized new carbazole-based fluorescent boronic acid (7, 8) sensors to investigate the fluorescence transduction efficiency of the novel d-PET effect, in which the fluorophore acts as the electron donor and the protonated amine/boronic acid group as the electron acceptor of the photoinduced electron transfer process (PET).[10]

K. R. J. Thomas et al developed new blue to yellow emitting material by incorporating fluorene-based chromophore on pyrene core with acetylene linkage and using multifold palladium-catalyzed cross-coupling reaction (10). The tetrasubstituted derivative displayed red-shifted emission.[11] Jian-Hua Su et al reported multifunctional diarylamine-

substituted benzo(*k*)fluoranthene derivatives (**11**, **12**) as green electroluminescent emitters and nonlinear optical materials.[12]

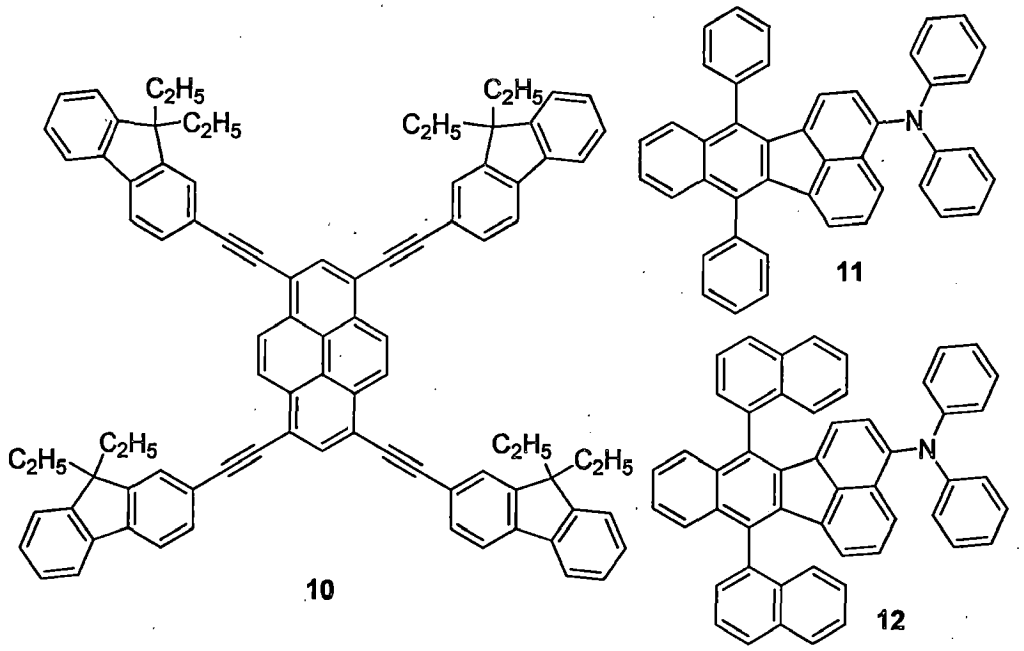


Fig.2.3. Structures of various dipolar molecules containing polyaromatic hydrocarbons.

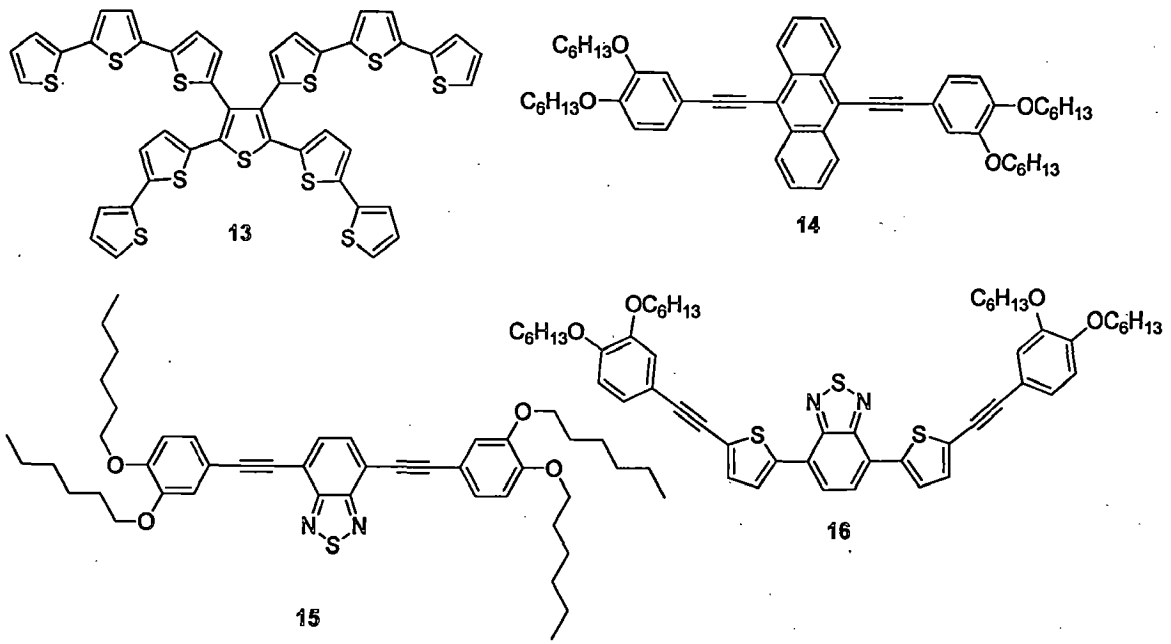


Fig.2.4. Structures of the compounds used for bulkheterojunction solar cells.

T. -Q. Nguyen, et al developed oligothiophene molecule used as donor in bulk heterojunction solar cells.[13] Anthracene based dyes for bulk heterojunction solar cells.[14] Benzothiadiazole based dyes for bulk heterojunction solar cells.[15]

The chemistry of chalcones has generated intensive scientific studies throughout the world. Especially interest has been focused on the synthesis and biodynamic activities of chalcones. The name "Chalcones" was given by Kostanecki and Tambor.[16] These compounds are also known as benzalacetophenone or benzylidene acetophenone. In chalcones, two aromatic rings are linked by an aliphatic three carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profile can be designed.

Chalcones are αβ-unsaturated ketone containing the reactive keto-ethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. Chalcones have crystal structure. They can be readily synthesized in laboratory by the Claisen-Schmidt reaction which is very easy and simple to conduct as well as inexpensive.[17]

Different methods are available for the preparation of chalcones.[18-20] The most convenient method is the Claisen-Schimdt condensation of equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic alkali.[21] Chalcones are used to synthesize several derivatives like cyanopyridines, pyrazolines, isoxazoles and pyrimidines having different heterocyclic ringsystems.[22-25]

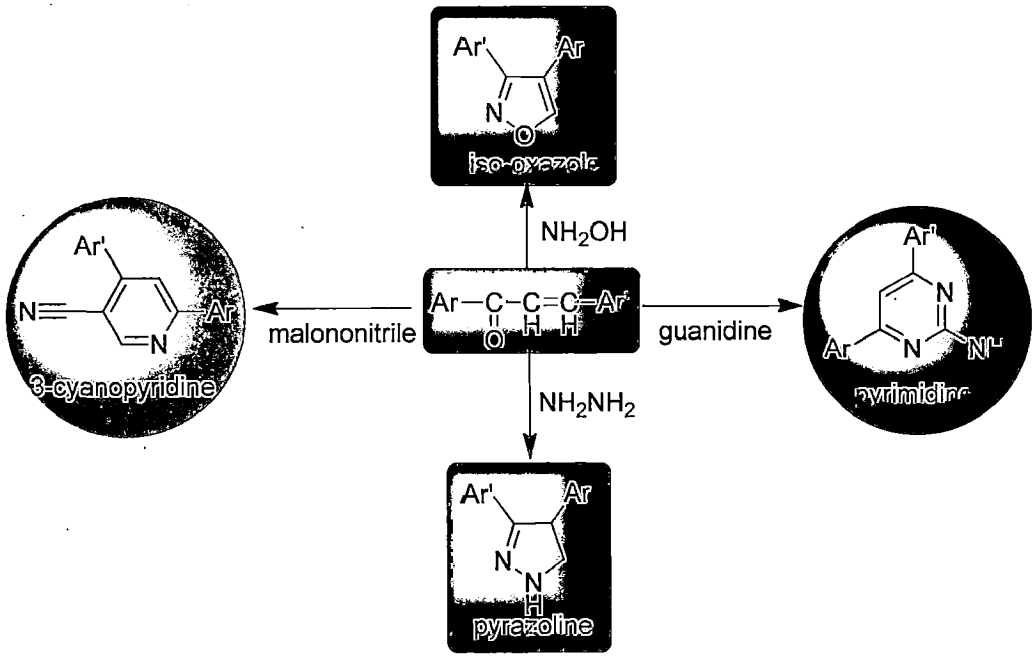
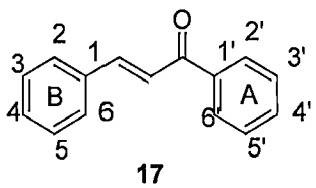


Fig.2.5. Different heterocyclic derivatives prepared from chalcones.

Nomenclatrure

Different methods of nomenclatures for chalcone were suggested at different times. The following pattern has been adopted by "Chemical Abstracts" published by American chemical society.



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The British Chemical Abstract and Journal of Chemical Society have followed the following system.

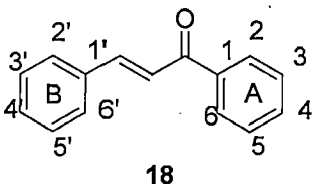

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Fig.2.6. Nomenclature systems used for chalcones.

2.2. Importance of chalcones

(1) A novel chalcone-analogue acts as an optical sensor based on ground and excited states intramolecular charge transfer. e.g. Steady-state absorption and emission spectroscopic techniques as well as semiempirical quantum calculations at the AM1 and ZINDO/S levels have been used to investigate the intramolecular charge transfer (ICT) behaviour of a novel chalcone namely; 1-(2-pyridyl)-5-(4-dimethylaminophenyl)-penta-2,4-diene-1-one, DMAC (**19**). The ground state DMAC has a significant ICT character and a great sensitivity to the hydrogen bond donating ability of the medium as reflected from the change of the absorption spectra in pure and mixed organic solvents. On the other hand, its excited singlet state exhibits high ICT characters as manifested by the drastic solvatochromic effects. These results are consistent with the data of charge density calculations in both the ground and excited state, which indicates enhancement of the charge transfer from the dimethyl amino group to the carbonyl oxygen upon excitation. Also, the dipole moment calculations indicate a highly dipolar excited singlet state (D_{leg} = 15.5 D). The solvent dependence of the fluorescence quantum yield of DMAC was interpreted on the basis of positive and negative solvatokinetic as well as the hydrogen bonding effects. Incorporation of the 2-pyridyl group in the chemical structure of the present DMAC led to design of a potential optical sensor for probing acidity of the medium and metal cations such as Zn^{2+}, Cd^{2+} and Hg^{2+}.[26]

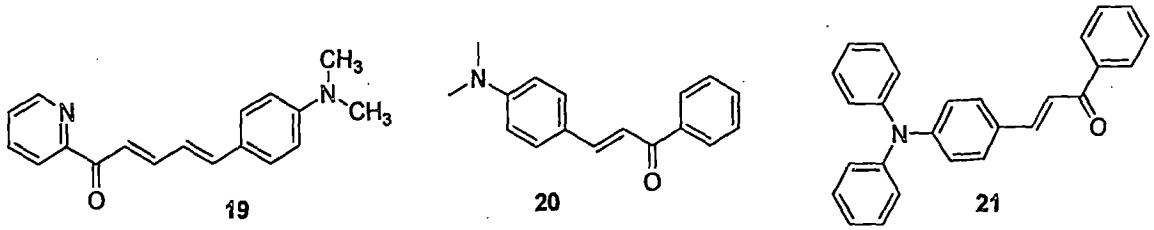


Fig.2.7. Chalcone derivatives used as optical sensors.

(2) Chalcones can be used as fluorescent probes to study the environmental properties of organic montmorillonite. Dimethylamino-chalcone (DMAC) (**20**) used as a fluorescence probe possesses quite strong solvatochromic properties. The polarity of the inner cavity of modified montmorillonite was characterized using fluorescence spectra of DMAC and the $E_T(30)$ value.[27]

(3) Chalcones can also be used as an efficient organic light color-conversion material for white LEDs, e.g. A novel efficient organic yellow-emitting dye, 3-(4 (diphenylamino)phenyl)-1-phenylprop-2-en-1-one (DPPO), (**21**) was synthesized. The compound was characterized by means of ^{1}H NMR and differential scanning calorimetry (DSC) and analyzed by quantum chemistry method. It was found that DPPO could be effectively excited by the InGaN-based blue LED. Photo-durability data of DPPO were studied. Bright white light of Commission International del' Eclairage (CIE) x ¼ 0.30, y ¼ 0.33 was obtained by using DPPO as a light color-conversion material (CCM).[28]

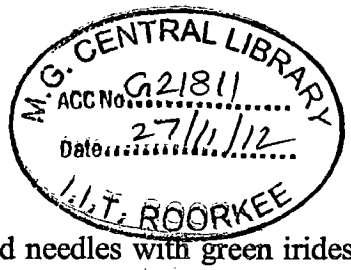
(4) They have close relationship with flavones, aurones, tetralones and aziridines.

(5) Chalcones and their derivatives find application as artificial sweeteners[29-33], stabilizer against heat, visible light, ultraviolet light and aging.[34-38] 3,2',4',6'-tetrahydroxy-4-propoxy-dihydrochalcone-4-β'-neohesperdoside[39] has been used as synthetic sweetener and is 2200 times sweeter than glucose.

(6) They contain a keto-ethylenic group and are therefore reactive towards several reagents e.g. (a) phenyl hydrazine, (b) 2-amino thiophenol etc.

(7) The chalcones have been found useful in elucidating structure of natural products like hemlock tannin[40], cyanomaclurin[41], ploretin[42], eriodictyol and homo eriodictyol[43], naringenin[44] etc.

(8) Chalcones having very vast pharmaceutical applications.



2.3. Methods of synthesis

Carthamin (22), a red pigment was first obtained as red needles with green iridescence using pyridine solvent from the flowers of cartharmus tinctoria (safflower) by Kmetaka and Perkin[45] and this was the first known example of chalcone in nature.It isomerizes to a yellow compound isocarthamin (23) on treatment with dil. HCl as reported by Kuroda.[46]

A variety of methods are available for the synthesis of chalcones. The most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of substituted acetophenone with substituted aldehydes in presence of aqueous alcoholic alkali.[47-82] Venkatraman and Nagrajan[83] prepared bis-chalcone (24, 25) from dihydroxy-diacetylbenzene and anisaldehydes using alkali. Several hydroxy-nitrochalcones were prepared using dry hydrogen chloride gas.[84-86] Onoda and Sasaki[87] used hydrochloric acid to synthesize hydroxy-nitrochalcone (26) from 2-hydroxy-5-nitroacetophenone and panisaldehyde.

The other condensing agents which have been employed are alkali metal alkoxide[88-89], magnesium-t-butoxide[90], borax[91], piperidine[92], aluminium chloride[93], boron trifluoride[94], amino acids[95] and perchloric acid.[96] Chalcones (28) were prepared by reaction of benzaldehyde with phosphonate carbanion (27) derived from diethyl phenacyl phosphonate.[97-100]

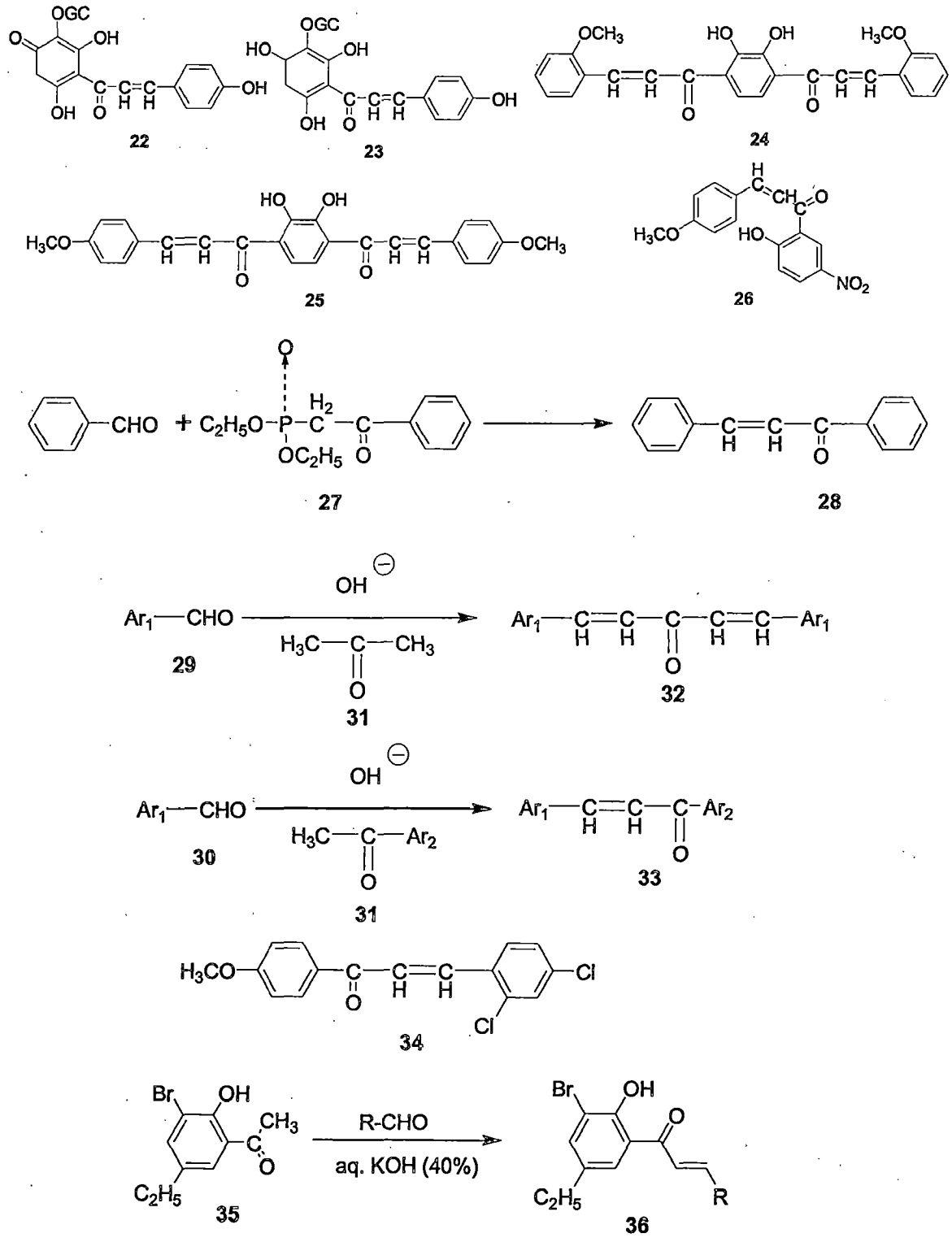


Fig.2.8. Synthetic protocols used for chalcone.

Several workers[101-103] prepared chalcones (**31, 32, 34**) from ketones (**29, 30**) and aromatic aldehyde in ethanol as energy transfer medium. Naik and Naik[104] synthesized chalcone derivative (**36**) from 2-hydroxy-3- bromo-5-ethyl acetophenone (**35**).

The chalcones are associated with different biological activities like insecticidal[105], anticancer[106], anti-inflammatory[107], bactericidal[108], fungicidal[109], antiviral[110], antitumor[111], antimalarial[112] and antiulcer.[113] Literature shows that lieochalcone and oxygenated chalcone has strong antileishmanial activity.[114-115] It is reported that chalcones exhibited potent activity against human malarial parasite.[116] Many workers have reported the different pharmaceutical activities of chalcones and its derivatives.[117-120] The antibacterial activities of some substituted chalcones have been studied by Modi et al.[121] De vincenzo et al[122] reported anti-inflammatory activity of some chalcone derivatives. Aldose reductase inhibitor activity of chalcone derivatives has also been reported by Okuyama et al[123], Toru et al[124] reported anticancer activities of chalcones and Ceo et al[125] reports the chalcones as a-glucosidase inhibitors. Antiplasmodial activity of ferrocenyl chalcones was reported by Xiang et al.[126] Bhatt and coworkers reported cytotoxic properties of chalcones and their pyrazoles derivatives.[127]

2.4. Biological importance

Antimalarial activity

Malaria is globally recognized as a serious problem of public health, mainly in the tropical and subtropical regions of the world. The increase of resistant malarial parasite strains represents the largest obstacle to antimalarial chemotherapy. Motta et al[128] studied

chalcone derivatives. He performed quantitative structure-activity relationships of a series of chalcone derivatives (1,3-Diphenyl-2-propen-1-one) as anti-*Plasmodium falciparum* agents

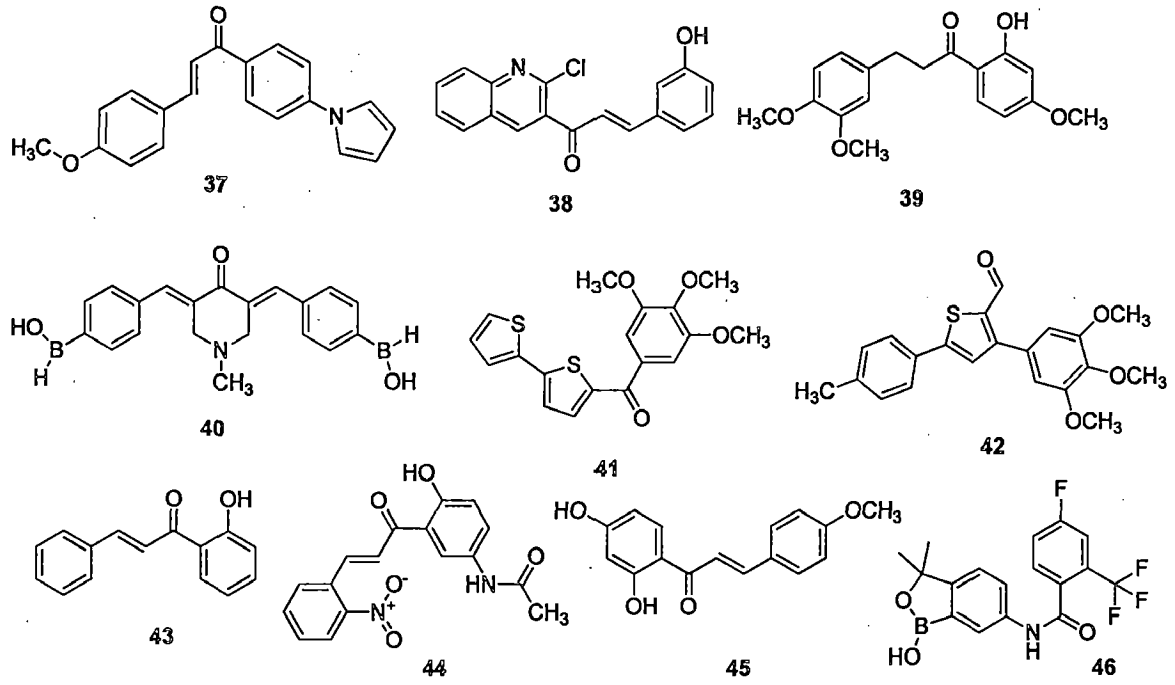


Fig.2.9. Chacone derivatives used for antimalarial, anticancerous, antiprotozoal activities.

(antimalarial agents). The study investigated the factors that may be important in the inhibitory activity of chalcone derivatives on *P. falciparum* cysteine protease. The obtained models presented good capacity to explain the observed values of biological activity, high adjustment level, statistical significance and good predictive capacity. Hydrophobic and steric properties seemed to play an important role in the explanation of the activity of the dataset. The results indicated that the activity on W2 and D6 strains was favored if ring A had a width-limited chemical substituent on it. The limited molecular width of these derivatives can be related with the activity against the D6 strain. The molecular weight, which is related to molecular volume, appeared to influence only the activity of D6 strain. The results also indicated that molar refractivity and molecular length have positive contributions to the activity against chloroquine-resistant (W2) *Plasmodium falciparum*

strains, while molecular weight against mefloquine-resistant (D6) strains. The main conclusions of this work were: (*i*) The C2–C3 double bond is essential for high inhibitory activity. It is not only a conjugated linker between A and B aromatic substituents, but it keeps extended the molecular conformation. In this way, the drug molecule seems to bind much better to the active site, which resembles a cleft on the surface of falcipain; (*ii*) Substitutions on the bridge portion of the chalcone series caused a pronounced decrease in the inhibitory activity, probably due to steric interactions; (*iii*) Chloro or fluoro substitution on the ring B and electron-donating substitution on the ring A increased the antimalarial activity; (*iv*) Quinolinyl group in the ring B resulted in increased activity. Awasthi et al[129] synthesized several new chalcone analogues and evaluated as inhibitors of malaria parasite. Inhibitory activity was determined *in vitro* against a chloroquine-sensitive *P. falciparum* strain of parasites. The chalcone '3-(4-methoxyphenyl)-1-(4-pyrrol-1-yl-phenyl)prop-2-en-1-one' **(37)** was found to be the most active with 50% inhibition concentration (IC_{50}) of 1.61 μg/ml. This inhibitory concentration was comparable to a prototype phytochemical chalcone, licochalcone, with an IC_{50} of 1.43 μg/ml. The study suggested that small lipophilic nitrogen heterocyclic at ring B together with small hydrophobic functionality at ring A can enhance antimalarial activity. These results suggested that chalcones are a class of compounds that provides an option of developing inexpensive, synthetic therapeutic antimalarial agents in the future.

In order to accelerate the development of relatively inexpensive antimalarials that are effective against chloroquine-resistant strains of *P. falciparum*, Cheng et al[130] had developed a methodology for the solid phase synthesis of chalcone analogues in reasonably high yields. On the basis of their structure activity relationship (SAR) and computer modeling data, they

expected that the chalcone derivatives with hydroxyl functionality on one of the aromatic rings and with some other appropriate substitutions on the other ring will be even more potent as antimalarials. They found that the chalcone '1-(2-chloroquinolin-3-yl)-3-(3 hydroxyphenyl)prop-2-en-1-one' **(38)** was synthesized in the highest percentage yield, 97%. As a part of the search for novel antimalarial agents from plants or via chemical synthesis, Lim et al[131] prepared twenty derivatives of flavonoids and chalcones, four derivatives for each of flavones, flavanones, chalcones, dihydrochalcones, and 3'-chlorochalcones, and evaluated for *in vitro* antimalarial activity against *P. falciparum* strain FCR-3 and cytotoxicity against FM3A cells (a mouse mammary tumor cell). The aim was to derive predictive structure activity relationships to guide lead compound design. Among the chalcones tested, the most active compound was 3-(3,4-dimethoxyphenyl)-1-(2-hydroxy-4-methoxy-phenyl)propan-1-one **(39)** showing 100% inhibition against *P. falciparum* at the final concentration of 5.4 μg/ml (EC_{50} = 1.0 μg/ml). The compound also showed strong cytotoxicity against FM3A cells, a model of the host, with relatively low EC_{50} values (>3.3 μg/ml) and low selectivity index (>3.3) indicating that the compound have non-selective antimalarial activity.

Anticancerous activity

Achanta et al[132] evaluated a series of boronic chalcones for their anticancer activity and mechanisms of action. Among the eight chalcone derivatives tested, the chalcone '3,5-bis-(4-boronic acid-benzylidene)-1 methylpiperidin- 4-one' **(40)** exhibited most potent growth inhibitory activity with IC_{50} values of 1.5 and 0.6 μM in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and colony formation assay respectively. The cytotoxic activity of AM114 was shown to be associated with the accumulation of p53

and p21 proteins and induction of apoptosis. Mechanistic studies showed that AM114 treatment inhibited the chymotrypsin like activity of the 20S proteasome *in vitro*, leading to a significant accumulation of ubiquitinated p53 and other cellular proteins in whole cells. *In vitro* studies showed that AM114 did not significantly disrupt the interaction of p53 and murine double minute 2 protein. It was noteworthy that AM114 as a single agent was preferentially toxic to cells with wild type p53 expression, whereas combination of this compound with ionizing radiation significantly enhanced the cell killing activity of ionizing radiation in both wild type p53 and p53 null cells. Together, these results indicated that the boronic chalcone derivative AM114 induced significant cytotoxic effect in cancer cells through the inhibition of the cellular proteasome and provided a rationale for the further development of this class of compounds as novel cancer chemotherapeutic agents. A series of chalcone-like agents, in which the double bond of the enone system is embedded within a thiophene ring, were synthesized and evaluated by Romagnoli et al[133] for antiproliferative activity and inhibition of tubulin assembly and colchicine binding to tubulin. The replacement of the double bond with a thiophene maintained antiproliferative activity and therefore must not significantly alter the relative conformation of the two aryl rings. The synthesized compounds were found to inhibit the growth of several cancer cell lines at nanomolar to low micromolar concentrations. In general, all compounds having significant antiproliferative activity inhibited tubulin polymerization with an $IC_{50} < 2$ μM. Several of these compounds caused K562 cells to arrest in the G2/M phase of the cell cycle. Turning to the effects of an electron-releasing group (ERG) on the phenyl moiety, they found that a *p*-methyl group caused only minor changes in antiproliferative activity. Reduced activity occurred when the methyl substituent was moved from the *para* to *ortho* position. The more

active compounds were evaluated for their *in vitro* inhibition of tubulin polymerization and for their inhibitory effects on the binding of (3H)colchicine to tubulin (in the latter assay, the compounds and tubulin were examined at a concentration of 1 μM with the colchicine at 5 μM). For comparison, the antitubulin agent CA-4 was examined in contemporaneous experiments as a reference compound. Compounds '3,4,5-trimethoxyphenyl-(5-(thiophen-2-yl)thiophen-2-yl)methanone' **(41)** and '3,4,5- trimethoxyphenyl-(5-*p*-tolylthiophen-2-yl) methanone' **(42)** were the most active (IC_{50}, 0.8 μM), having twice the potency of CA-4 (IC_{50}, 1.4 μM).

Echeverria et al[134] studied relationships between the structural characteristic of synthetic chalcones and their antitumoral activity. Treatment of HepG2 hepatocellular carcinoma cells for 24 h with synthetic 2'- hydroxychalcones resulted in apoptosis induction and dose-dependent inhibition of cell proliferation. The calculated reactivity indexes and the adiabatic electron affinities using the DFT method including solvent effects, suggested a structure-activity relationship between the chalcone structure and the apoptosis in HepG2 cells. The absence of methoxy substituents in the ring A of synthetic 2'-hydroxychalcones, showed the major structureactivity pattern along the series and because of this, the chalcone '1-(2-hydroxyphenyl)-3-phenylprop-2-en-1-one' **(43)** was found to be the most active. Chalcones exhibit chemopreventive and antitumor effects. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a naturally occurring anticancer agent that induces apoptosis in cancer cells and is non-toxic to normal cells. Szliszka et al[135] examined the cytotoxic and apoptotic effect of five chalcones in combination with TRAIL on prostate cancer cells and evaluated the cytotoxicity by the MTT and Lactate Dehydrogenase (LDH) assays. The apoptosis was determined using flow cytometry with annexin V-FITC. Their study showed

that all the five tested chalcones: chalcone, licochalcone-A, isobavachalcone, xanthohumol, butein markedly augmented TRAIL-mediated apoptosis and cytotoxicity in prostate cancer cells and confirmed the significant role of chalcones in chemoprevention of prostate cancer. They showed for the first time that chalcones sensitize prostate cancer cells to TRAIL-induced apoptosis. The obtained results suggested that chalcones help anticancer immune defense in which endogenous TRAIL takes part. The TRAIL-mediated cytotoxic and apoptotic pathways may be a target to the chemopreventive agents in prostate cancer cells and the overcoming TRAIL resistance by chalcones may be one of the mechanisms responsible for their cancer-preventive effects. Llango et al[136] synthesized a series of chalcones and evaluated them for their *in vitro* cytotoxic activity by microculture Tetrazolium Test Assay method using two breast cancer cell lines MCF-7 and T47D. The IC_{50} value was calculated at the 0.1-100 μM concentration range. The assay was dependent on the activity of mitochondrial dehydrogenase enzymes that reduce yellow MTT to a blue formazan product and the activity of enzyme that is directly proportional to cell viability. The result showed significant cytotoxicity against both of the cell lines and value lied between 52-89 μM. All the compounds showed good cytotoxic activity and the compound '*N*-(4-hydroxy-3-(3-(2/3/4-nitrophenyl)acryloyl)phenyl)acetamide' **(44)** showed better activity than other compounds, this may be due to presence of nitro group in the compound.

Antiprotozoal activity

Ten chalcones were synthesized and tested as leishmanicidal and trypanocidal agents by Lunardi et al[137] against *in vitro* growth of *Leishmania braziliensis* and *Trypanosoma cruzi*. The results showed that the positions of the substituents seem to be critical for their antiprotozoal activities. The results also showed that some synthesized substitution-

containing chalcones exhibited promising concentration-dependent (i.e., at high concentration) leishmanicidal and trypanocidal activities with no evidence of a cytotoxic effect on mouse macrophages. The example of chalcones having leishmanicidal and trypanocidal activities are '(*E*)-1-(2,4-dihydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one' (**45**) and '4-fluoro-*N*-(1-hydroxy-3,3-dimethyl-1,3-dihydrobenzo(*c*)(1,2)oxaborol-6-yl)-2-(trifluoromethyl)benzamide' (**46**).

Anti-inflammatory activity

Chalcone derivatives contain α,β-unsaturated carbonyl moiety which is responsible for anti-inflammatory activity. QSAR study revealed that the presence of electron-withdrawing groups in B-ring and electron-donating groups in A-ring of chalcones was important for inhibition of LPS-induced IL-6 expression. So, mRNA production.[138]

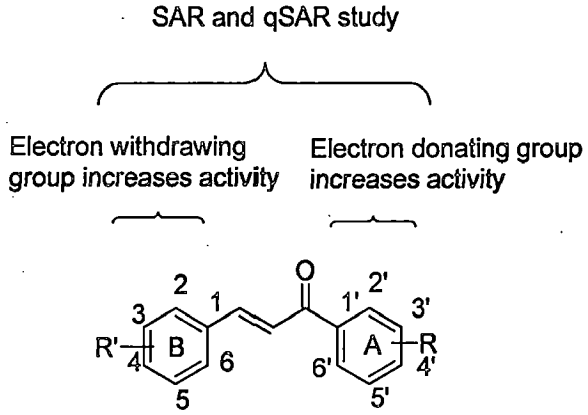


Fig.2.10. Stuctural skeleton of chalcone derivative used for anti-inflammatory studies.

Yadav et al[139] synthesized a series of five chalcone derivatives and were subjected to anti-inflammatory screening using the carrageenan-induced rat hind paw edema model. Chalcone derivatives at dose 25 mg/kg by oral route inhibited significantly the formation of edema. The *P* value was found to be <0.05 showing significant anti-inflammatory activity. The compound '4 fluoro/4 chloro chalcone' (**47, 48**) showed more activity comparable to

standard drug indomethacin due to -F/-Cl groups present in the compound. Hence, the anti-inflammatory activity of chalcone derivatives was increased when electron withdrawing groups (EWG) were present on the chalcone moiety.

In an effort to develop potent anti-inflammatory agents, a series of substituted chalcone derivatives was synthesized and evaluated for anti-inflammatory activity by Zhang et al[140] through *in vivo* inhibition assay monitoring of their ability to inhibit xylene-induced ear edema in mice. Some of the tested compounds exhibited significant activity, and the compound '3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one' **(49)** showed the highest anti-inflammatory activity (68% inhibition) comparable with or even slightly more potent than the reference drug ibuprofen (53%). Furthermore, the structure-activity relationship of these substituted chalcone derivatives demonstrated that the substituted 2',4'-dihydroxychalcone derivatives was stronger than that of 4'- hydroxychalcone. The position of the substituted group on the phenyl ring greatly influenced the anti-inflammatory activity, with an activity order of -4-$N(CH_3)_2$>-4-OCH_3>-3-OCH_3-4-OH>-3,4-OCH_2O->-4-OH>-3,4 $(OH)_2$. The potency order of the two Cl-substituted derivatives being 4-Cl>2,4-Cl_2. the potency order of the two NO_2- substituted derivatives being 3-NO_2>2-NO_2. These results indicated that the character of the substitution on the ring A had a significant influence on the anti-inflammatory activity.

Antibacterial activity

Hamdi et al[141] synthesized a series of new coumarin derivatives containing a chalcone moiety and evaluated for possible anti-oxidant and antibacterial activities. The coumarinic chalcone '4-hydroxy-3-(3-*p* tolylacryloyl)-2*H*chromen- 2-one' **(50)** had been found to be the most active (IC_{50} = 2.07 μM). The derivatives were screened *in vitro* for their antibacterial

activity against Gram +ve bacteria, *Staphylococcus aureus* using the paper disc diffusion method for the antibiotic sensitivity technique. It showed that the activity against bacteria is moderate, but in addition, it was clearly demonstrated that this kind of compound could be an antibacterial agent; its activity depends on its chemical composition. The moderate active antibacterial effects observed showed that this kind of compound could be an antibacterial agent.

A series of chalcone derivatives were synthesized and evaluated for antibacterial activity by Bhatia et al.[142] All the compounds were screened for their antibacterial activities against four different bacterial strains *S. aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa* by the cup plate agar diffusion method. Dimethyl formamide was used as a solvent, and ciprofloxacin as the standard drug. QSAR equation revealed that selected electronic, steric and lipophilic parameters had good correlation with antibacterial activity. The findings suggested that the chalcone framework is an attractive template for structure optimization to achieve higher potency, lower toxicity, and a wider spectrum of antibacterial activity. Although more hydrophobic surface areas tend to favor antibacterial activity and Gram -ve and Gram +ve selectivity, the increase in the size of molecules may lead to a decrease in the antibacterial activity. The hydrophobic surface area should be increased without increasing the molecule size. An increase in the dipole and quadrupole moments leads to charge separation which increases biological activity.

Antifilarial activity

Chalcone derivatives were evaluated by Awasthi et al[143] for their antifilarial activity on *Setaria cervi* using glutathione-*S* -transferase (GST) enzyme as a drug target. The compounds '1-(4-benzotriazol-1-yl-phenyl)-3 (4-methoxyphenyl)prop-2-en-1-one' **(51)** and

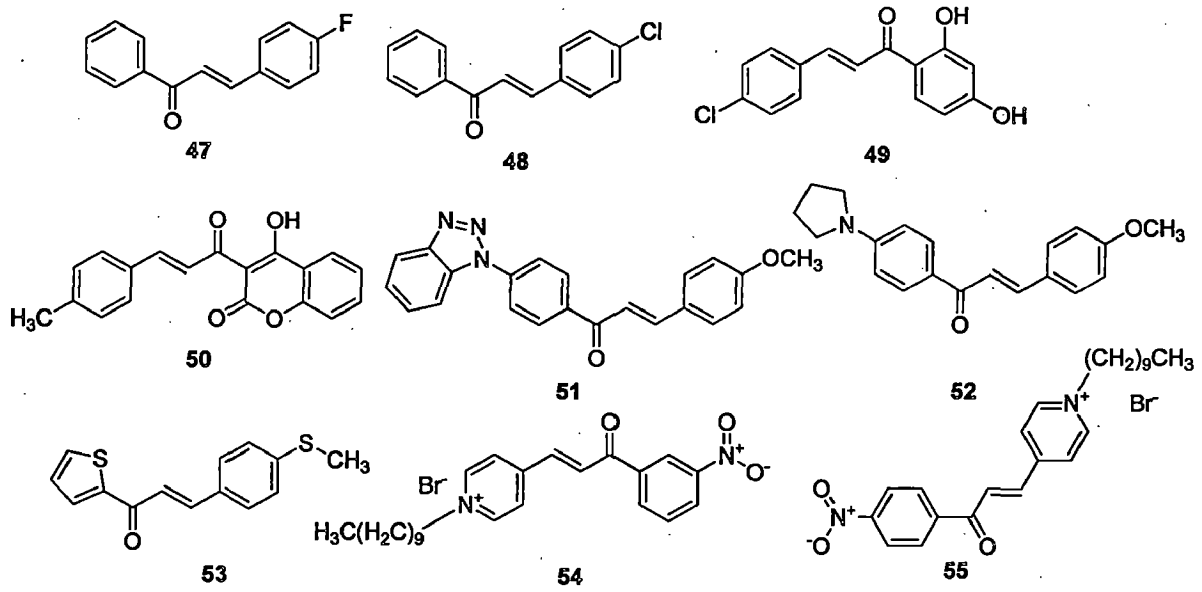


Fig.2.11. Chalcone derivatives used for anti-inflammatory, antibacterial, antifilarial, antifungal and antimicrobial activity.

'(*E*)-3-(4-methoxyphenyl)-1-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one' **(52)** showed a significant suppression ($P < 0.01$) in GST activity of adult female parasite extract at 3 μM concentration *in vitro*. However, GST activity was detected along with depletion in GSH level. More or less, all compounds showed a paralyzing effect on the motility and viability of parasites, ranging from 25% to 97% inhibition. The compounds '1-(4-benzotriazol-1-yl-phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one' and '3-(4-methoxyphenyl)-1-(4-pyrrolidin-1-ylphenyl)prop-2-en-1-one' exhibited major irreversible effects on viability and resulted in parasite death and also inhibited the GST activity by 84-100% *in vitro*. They reported for the first time the antifilarial activity of chalcones on GST of adult parasites. This study also strengthened their previous findings where GST was reported as a potential drug target for antifilarials. However, this was a preliminary *in vivo* and *in vitro* study in which living worms were incubated with chalcones. The results of 4-chloro and 4-methoxy-substituted

chalcones strongly supported that small- and medium-sized highly lipophilic or hydrophobic groups containing single or multiple nitrogen or oxygen in an acetophenone ring of chalcone have potent inhibitory effects on motility, viability, and GST activity of the parasite, supporting the antifilarial efficacy of chalcone. The most significant effect on parasites was exerted by methoxy-substituted chalcones, suggesting that these substituents can be used for further studies against filariasis.

Antifungal activity

With the aim of developing potential antifungals, Bag et al[144] synthesized a series of chalcones incorporating sulfur either as part of a hetero-aromatic ring (thiophene) or as a side chain (thiomethyl group) and tested for their *in vitro* activity. Some of the compounds showed appreciable activity against a fluconazole-sensitive and fluconazole-resistant strain with the chalcone '3-(4-(methylthio)phenyl)-1 (thiophen-2-yl)prop-2-en-1-one' (53) exhibiting the highest activity. Maximum activity was obtained with *p* fluoro substitution on ring A. Activity was decreased with increasing halogen size. Presence of *p*-methoxy or hydroxy groups at the *o-, m- or, p-* position also resulted in good activity while the *p*-nitro group as well as the bulky *p*-phenyl substitution decreased activity as compared with the unsubstituted compound. The *m-* and *p-* disubstitution with methoxy led to increased activity while again the *p*-phenyl-substituted compounds exhibited considerably decreased activity. All compounds with the bromo thiophene ring in place of ring B exhibited less activity compared with those with the unsubstituted thiophene ring. Bromine substitution on the thiophene ring B decreased antifungal activity. Compounds with unsubstituted thiophene ring B and thiomethyl substitution at the *p-* position of ring A, exhibited good antifungal activity. Highest activity was found when both thiophene ring B and thiomethyl substitution at ring A

were present together in the chalcone '3-(4-(methylthio)phenyl)-1-(thiophen-2-yl)prop-2-en-1-one'.

Lahtchev et al[145] reported the synthesis, antifungal evaluation and study on substituent effects of several chalcones. A lot of genetically defined strains belonging to different yeast genera and species, namely *Saccharomyces cerevisiae, Hansenula polymorpha* and *Kluyveromyces lactis*, were used as test organisms. Concerning the mode of the antifungal action of chalcones it was shown that DNA was probably not the main target for the chalcones. It was revealed that the yeast's intracellular glutathione and cysteine molecules play significant role as defence barrier against the chalcone action. It was also shown that chalcones may react with some proteins involved in cell separation. The antifungal effects of the substituted chalcones were compared with those of the parent chalcone. The following correlations were observed:

(i) Introduction of EW substituents (Cl, CN and NO_2 groups) in *p*-position in ring A yielded less active chalcones than the parent chalcone.

(ii) Introduction of ED substituents (OH, CH_3 and OCH_3 groups) in *p*-position in ring A produced inactive chalcones.

(iii) Presence of a single hydroxyl group was effective at *m*-position in ring A. Introduction of a single methoxy group at *m*-position in ring A led to inactive compound.

(iv) The combination of *m*-hydroxyl and *p*-methoxy groups in ring A was effective. Loss of activity was observed with the interchange of the positions of the hydroxyl and methoxy groups and when the hydroxyl group was placed in *o*-position and the methoxy group was in *m*-position.

(v) Introduction of *p'*-chloro atom in ring B was beneficial only for the chalcones with a single hydroxyl group at *m*- and *p*-positions. The *m*-position was more favourable than the *p*-position. Presence of *m*- and *p*-hydroxyl groups together led to the inactive chalcone.

(vi) Elongation of the conjugated system by introduction of one additional double bond between the ketovinyl moiety and the ring A did not produce an active compound.

Based on these observations, it was concluded that the electronic effects of the *p*substituents in ring A of chalcones are not crucial for displaying antifungal activity towards the tested fungi. This is contradictory to the antifungal effects, which chalcones with EW and ED substituents in ring A have shown against several *dermatophytes* and the yeast *C. albicans*. Besides, in this study the position of the hydroxyl group in ring A was found important for the chalcone activity as opposed to some other antifungal studies. Interestingly, the favored location for the hydroxyl group was the *m*-position in ring A.

Antimicrobial activity

Yayli et al[146] synthesized *N*-alkyl derivatives and photochemical dimers of 3 *o*-, *m*-, and *p*-nitro substituted 4- azachalcones. The monomeric compounds showed good antimicrobial activity against test micro-organisms *E. coli*, *K. pneumoniae*, *Yersinia pseudotuberculosis*, *P. aeruginosa*, *Enterococcus faecalis*, *S. aureus*, *Bacillus cereus*, and *Candida tropicalis*. The most sensitive micro-organisms were Gram +ve bacteria. The compounds '1-decyl-4-(3-(3- nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' **(54)** and '1-decyl-4-(3 (4-nitrophenyl)-3-oxoprop-1- enyl)pyridinium bromide' **(55)** exhibited broad-spectrum antimicrobial activity. The MIC values (MBC) for the test micro-organisms were between <0.35 and 25 μg/ml. The synthesized compounds were also tested for their

antioxidant activity based on their ability to scavenge the stable radical DPPH (2,2-diphenyl-1-picrylhydrazine). The monomers showed high anti-oxidant activity, while the dimerization products were less active. The monomeric compounds exhibited higher radical scavenging potential in general, with low IC_{50} values. The compound '1-decyl- 4-(3-(4-nitrophenyl)-3-oxoprop-1-enyl)pyridinium bromide' was found to have similar or even higher activity when compared to the standard anti-oxidants Trolox and vitamin C, respectively.

Mosquito Larvicidal activity

A series of chalcone analogues and some of their derivatives were synthesized and subjected to the mosquito larvicidal study (larvae of *Culex quinquefasciatus*), SAR and QSAR by Begum et al.[147] The chalcones showed % mortality ranging from a very low value (10%) to a very high value (90%). Chalcones having EDG(s) on either ring A or ring B showed high toxicity to larva of the mosquito. EWG(s), especially at ring A, reduced the activity of chalcones. The activity was abruptly decreased due to replacement of ring B by CH_3, extension of conjugation or blocking of α,β-unsaturated ketone part of chalcones by derivation. QSAR studies of these compounds were performed using various spatial, electronic and physicochemical parameters. Genetic function approximation with linear and spline options was used as the chemometric tool for developing the QSAR models. The investigation had clearly shown that certain chalcone analogues had potent mosquito larvicidal activity. Most of the hydroxyl chalcones showed toxicity against the third instar larvae of *C. quinquefasciatus*. The favorable chemical structures were found to be a hydroxyl substituent in ring B at 2'-position which may be hydrogen bonded with the electron pair on α,β-unsaturated ketone moiety, thereby decreasing the electrophilicity of this part of the molecule. Presence of hydroxyl group at 2'-position of ring B and replacement of ring A

(phenyl) by a furan ring also increased the larvicidal activity. Besides that 3-chlorine substitution in ring A was also another feature of favorable activity. Presence of methylenedioxy group at 3,4 positions of ring A also enhanced the larvicidal activity of chalcone-type compound. However, extension of conjugation and blocking of α,β-unsaturated ketone part of chalcones had bad effects toward the activity of these compounds. The chalcone '3-(furan-2-yl)-1-(2- hydroxyphenyl)prop-2-en-1-one' **(56)** had shown 100% mortality and LC_{50} was very low with a value of 19 μmole/dm3. QSAR analysis also suggested that charge distribution on molecular surface and surface area are important determinants of the larvicidal activity. The derived models suggested that for the good larvicidal activity positively charged surface areas of the compounds should be limited. Moreover, there should be a balanced distribution of +ve and -ve charges on the molecular surfaces of the compounds.

Anticonvulsant activity

Some new phenoxy chalcones were prepared and screened for their anticonvulsant activity using Maximal Electroshock Method (MES) by Kaushik et al.[148] Neurotoxicity study was performed using rotarod method. It was found that substitution of 4-methoxy and 3,4-dimethoxy group in the substituted ring A of phenoxy chalcone showed significant anticonvulsant activity without neurotoxicity while hydrogen and chloro substitution does not showed the significant anticonvulsant activity. It was also found that the compounds '3-(4-methoxyphenyl)-1-(4- phenoxyphenyl)prop-2-en-1-one' **(57)** and '3-(3,4 dimethoxyphenyl)-1-(4-phenoxyphenyl)prop-2-en-1-one' **(58)** showed the most potent anticonvulsant activity without neurotoxicity.

Antioxidant activity

Vasil'ev et al[149] studied six anti-oxidants from the class of chalcones (ArOH), compounds from which flavonoids are obtained in nature. The antiradical activity of chalcones and a number of related compounds was determined by a chemiluminescence method using the scavenging of peroxide radicals $ROO^{\bullet} + ArOH \rightarrow ROOH + OAr^{\bullet}$ (with the rate constant k_7) in a model reaction of diphenylmethane (RH) oxidation. The structures and energies of the reagents and intermediates were determined by semi empirical quantum chemical (PM3, PM6) calculations. 3- (3,4-Dihydroxyphenyl)-1-phenylprop-2-en-1-one **(59)** and caffeic acid, which have a catechol structure, that is, two neighboring OH groups in phenyl ring A, exhibited high antioxidant activity ($k_7 \approx 107$ l/mol/s); this is consistent with the lowest bond strengths D(ArO–H) of 79.2 and 76.6 kcal/mol, respectively. The abstraction of a hydrogen atom by the $ROO^{\bullet}$ radical is the main reaction path of these compounds; however, the low stoichiometric co-efficients of inhibition (f = 0.3 0.7) suggested a contribution of secondary and/or side reactions of ArOH and $OAr^{\bullet}$. In the other chalcones, the ArO–H bond was stronger (D(ArO–H) = 83-88 kcal/mol) and the antioxidant activity was lower ($k7$ = 104-105 l/mol/s).

Sivakumar et al[150] synthesized 25 of chalcone derivatives and evaluated their antioxidant activity, and (QSAR). Antioxidant activity was evaluated through four different methods namely, superoxide radical-scavenging, hydrogen peroxide-scavenging, reducing power, and DPPH radical-scavenging assays at 50 µg/ml *in vitro*. The antioxidant potential of the compound was related to its *(i)* hydrogen or electron donation capacity, *(ii)* its ability to stabilize and delocalize the unpaired electron, and *(iii)* potential to chelate transition metal ions. These actions were achieved either by the hydrogen atom or single electron transfer. In

the case of ferric reducing anti-oxidant power (FRAP), it was due to the single electron transfer and in the cases of superoxide radical-scavenging, hydrogen peroxide-scavenging, and DPPH radical-scavenging activities, it was due to the transfer of hydrogen atom. The antioxidant activity of the flavonoids was due to the inhibition of the enzyme responsible for the superoxide radical production, chelation of the metal ions and scavenging of ROS. Generally, compounds with – SCH_3 and –OCH_3 in the *para* position of the ring A and OH in the ring B were most active than others. The chalcone '1-(4-hydroxyphenyl)-3-(4 (methylthio)phenyl)prop-2-en-1-one' **(60)** was showing the highest superoxide radical-scavenging activity (>50%), reducing power activity (>46%), DPPH scavenging activity (>20%). In few cases, some of the compounds were more active than ascorbic acid or butylated hydroxytoluene. QSAR was developed correlating the antioxidant activity with the structural features of the compounds and the predictive capability of the models was estimated using internal and external validation methods. All the predictions were within the 99% confidence level. Spatial, structural, and lipophilic properties of the compounds determined their antioxidant properties.

Vogel *et al*[151] established a general strategy for the synthesis of 3'-prenylated chalcones and synthesized a series of prenylated hydroxychalcones, including the hop *(Humulus lupulus L.)* secondary metabolites xanthohumol, desmethylxanthohumol, xanthogalenol, and 4-methylxanthohumol. They investigated the influence of the ring A hydroxylation pattern on the cytotoxic activity of the prenylated chalcones in a HeLa cell line and revealed that non-natural prenylated chalcones, like 2',3,4',5-tetrahydroxy 6'-methoxy-3'-prenylchalcone **(61)** (IC_{50} 3.2 ± 0.4 μM) as well as the phase I metabolite of xanthohumol, 3 hydroxyxanthohumol '1-(2,4-dihydroxy-6-methoxy-3-(3- methylbut-2-

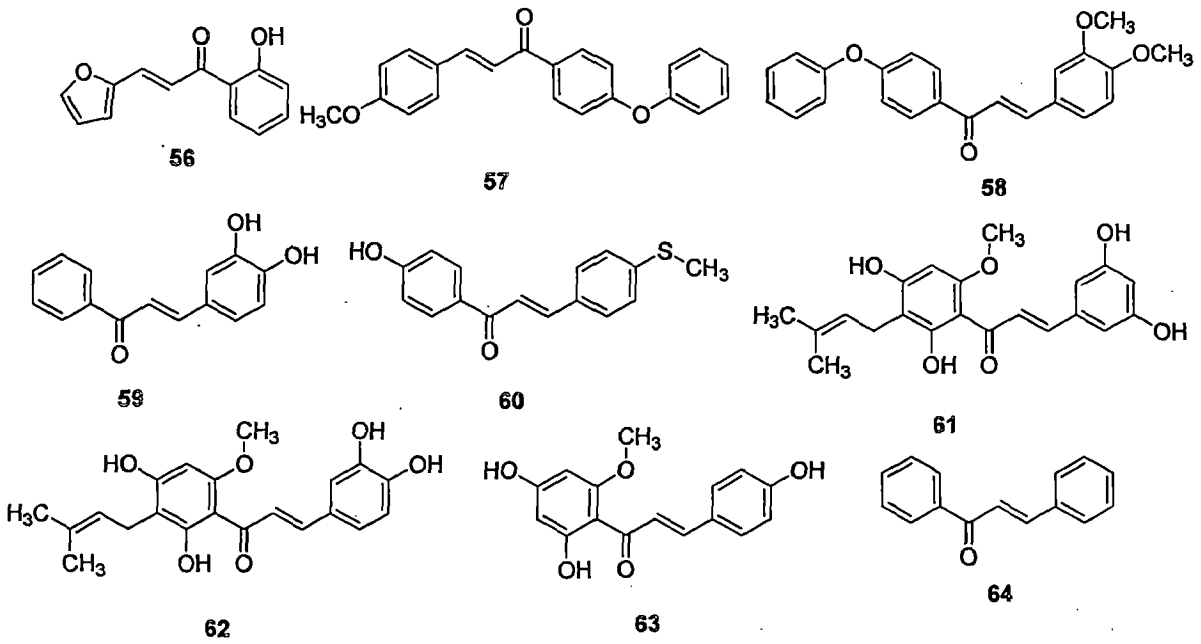


Fig.2.12. Chalcone derivatives used for anticonvulsant activity, antioxidant activity, mammalian alpha-amylase inhibitory activity and cyclooxygenase (COX) inhibitory activity.

enyl)phenyl)-3-(3,4 dihydroxyphenyl)prop-2-en-1-one' **(62)** (IC_{50} 2.5 ± 0.5 μM), were more active in comparison to xanthohumol (IC_{50} 9.4 ± 1.4 μM). A comparison of the cytotoxic activity of xanthohumol and 3- hydroxyxanthohumol with the non-prenylated analogs helichrysetin (IC_{50} 5.2 ± 0.8) and 3-hydroxyhelichrysetin (IC_{50} 14.8 ± 2.1) showed that the prenyl side chain at C-3' has an influence on the cytotoxicity against HeLa cells only for the dihydroxylated derivative. This offers interesting synthetic possibilities for the development of more potent compounds. The ORAC (Oxygen Radical Absorbance Capacity) fluorescein activity of the synthesized compounds was also investigated for their antioxidant activity evaluation and revealed the highest activity for the compounds helichrysetin '1-(2,4-dihydroxy-6-methoxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one' **(63)**, 4'-methylxanthohumol, and desmethylxanthohumol, with 4.4 ± 0.6, 3.8 ± 0.4, and 3.8 ± 0.5 Trolox equivalents, respectively.

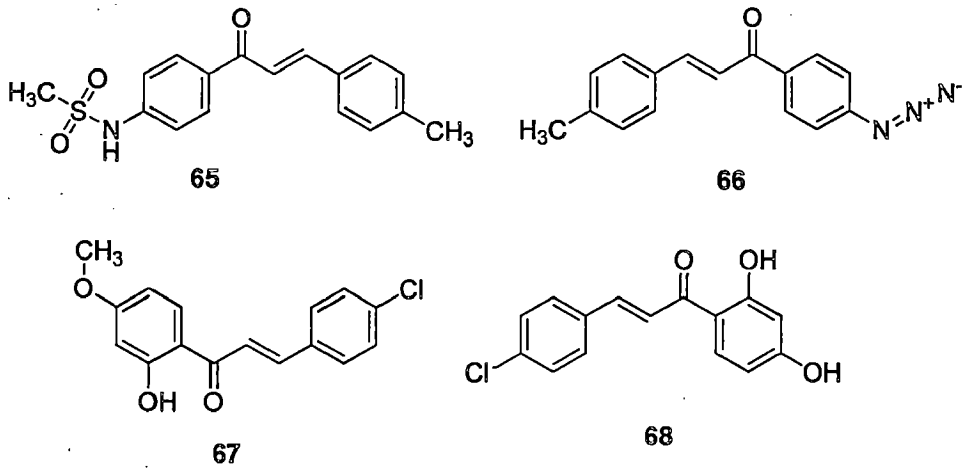


Fig.2.13. Chalcone derivatives used for mammalian alpha-amylase inhibitory activity and monoamine oxidases (MAOs) inhibitory activity.

Mammalian Alpha-Amylase inhibitory activity

Trans-chalcone (64), a biphenolic core structure of flavonoids precursor was tested for inhibitory activity toward alpha-amylase (1,4-α-D-glucan glucanohydrolase) using Bernfeld method by Najafian et al.[152] Porcine pancreatic alpha-amylase was observed to be effectively inhibited by this compound, which showed competitive behavior with a K_i of 48 μM and an IC_{50} of 96.44 μM as compared to flavonoids possessing IC_{50} values ranging typically from about 10 to about 30 μM for mammalian alpha-amylase. Soluble starch (the natural substrate of the enzyme) was used in this study in order to obtain more realistic results. The possible binding mode of the compound was assessed *in silico*, and the two residues Trp59, and Tyr62 were proposed as main interacting residues with transchalcone. In conclusion, this compound could be used to design effective inhibitors of alpha-amylase.

Zarghi et al[153] synthesized chalones possessing a methanesulfonamido ($MeSO_2NH$) or an azido (N3) pharmacophore at the *para*-position of the C-1 phenyl ring and evaluated their biological activity as cyclooxygenase-1/-2 inhibitors. *In vitro* COX-1/COX-2 structure-activity relationships were determined by varying the substituents on the C-3 phenyl ring (4-

H, 4-Me, 4-F, and 4-OMe). Among the chalones possessing a C-1 *para*- $MeSO_2NH$ COX-2 pharmacophore '1-(4-methanesulfonamidophenyl)-3-(4-methylphenyl)prop-2 en-1-one' **(65)** was identified as a selective COX-2 inhibitor (COX-2 IC_{50} = 1.0 μM; selectivity index >100) that was less potent than the reference drug rofecoxib (COX-2 IC_{50} = 0.50 μM; SI > 200). The corresponding chalcone analogue possessing a C-1 *para*-N3 COX-2 pharmacophore '1-(4-azidophenyl)-3-(4 methylphenyl)prop-2-en-1-one' **(66)**, exhibited potent and selective COX-2 inhibition (COX-1 IC_{50} = 22.2 μM; COX-2 IC_{50} = 0.3 μM; SI = 60). A molecular modeling study where these two chalcones were docked in the binding site of COX-2 showed that the *p*-$MeSO_2NH$ and N-3 substituents on the C-1 phenyl ring are oriented in the vicinity of the COX-2 secondary pocket (His90, Arg513, Phe518, and Val523). The structure-activity data acquired indicated that the propenone moiety constitutes a suitable scaffold to design new acyclic 1,3-diphenylprop-2-en-1-ones with selective COX-1 or COX-2 inhibitory activity.

Monoamine Oxidases (MAOs) inhibitory activity

Chimenti et al[154] synthesized a large series of substituted chalcones tested *in vitro* for their ability to inhibit human monoamine oxidases A and B (hMAO-A and hMAO-B). The potential effects of the test drugs on hMAO activity were investigated by measuring their effects on the production of hydrogen peroxide (H_2O_2) from *p*tyramine using the Amplex Red MAO assay kit and microsomal MAO isoforms prepared from insect cells infected with recombinant baculovirus containing cDNA inserts for hMAO-A or hMAO-B. While all the compounds showed hMAO-B selective activity in the micro- and nano-molar ranges, the best results were obtained in the presence of chlorine and hydroxyl or methoxyl substituents. The most active compounds, '3-(4-chlorophenyl)-1-(2-hydroxy-4- methoxyphenyl)prop-2-en-1-

one' (67) and '3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1-one' (68) (IC_{50}=0.0044±0.00027 μM and 0.0051±0.00019 μM, respectively), are disubstituted in the 2- and 4-position of the B aromatic moiety with two hydroxyls or hydroxyl and methoxy groups and in 4'-position of the A aromatic moiety with a chlorine atom. To better understand the enzyme-inhibitor interaction and to explain the selectivity of the most active compounds toward hMAO-B, molecular modeling studies were carried out on new, high resolution, hMAO-B crystallographic structures. For the only compound that also showed activity against hMAO-A as well as low selectivity, the molecular modeling study was also performed on the hMAO-A crystallographic structure. The docking technique provided new insight on the inhibition mechanism and the rational drug design of more potent/selective hMAO inhibitors based on the chalcone scaffold. In the reversibility and irreversibility tests, hMAO-B inhibition was found to be irreversible in presence of the compounds '3-(4-chlorophenyl)-1-(2 hydroxy-4- methoxyphenyl)prop-2-en-1-one' and '3-(4-chlorophenyl)-1-(2,4-dihydroxyphenyl)prop-2-en-1 one' (chosen for docking experiments).

2.5. Conclusions

From the above introduction, it can be said that chalcones and their derivatives display a wide range of applications in organic electronics, such as solar cells, organic light emitting diodes (OLEDs), thin film transistors (TFTs), sensors, bulk heterojunction solar cells, non linear optical devices (NLOs) and pharmacological activities, such as antimalarial, anticancer, antiprotozoal (antileishmanial and antitrypanosomal), antiinflammatory, antibacterial, antifilarial, antifungal, antimicrobial, larvicidal, anticonvulsant and antioxidant activities. They also show inhibition of the enzymes, especially mammalian alpha-amylase, cyclooxygenase (COX) and monoamine oxidase (MAO) and antimitotic activity too.

Because of this, chalcones and their derivatives have attracted increasing attention of the scientists for the search of new potent pharmacological activity in it.

2.6. References

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Chapter 3

Synthesis & Characterization

3.1. Introduction

A variety of methods are available for the synthesis of chalcones, the most convenient method is the one that involves the Claisen-Schmidt condensation of equimolar quantities of a substituted acetophenone with substituted aldehydes in the presence of aqueous alcoholic alkali.[1-8] In the Claisen-Schmidt reaction, the concentration of alkali used, usually ranges between 10 and 60 %. [9-10] The reaction is carried out at about 50 °C for 12-15 hours or at room temperature for one week. Under these conditions, the Cannizaro reaction[11] also takes place and thereby decreases the yield of the desired product. There are various condensing agents used for the synthesis of chalcones.

1. Alkali

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

2. Hydrochloric Acid

Dry hydrochloric gas in a suitable solvent like ethylacetate at 0 °C was used as a condensing agent in a few syntheses of chalcones from aromatic ketones. Methanolic

solution of dry hydrochloric acid gas at 0 °C was also used by Lyle, Paradis[21b] and Marathey.[21c]

3. **Other Condensing Agents**

Phosphorous oxychloride was used by Raval and Shah[12] for the synthesis of chalcones. Whereas Szell and Sipos[13] condensed 2-hydroxy-5-nitroacetophenone with benzaldehyde in presence of anhydrous $AlCl_3$. Similarily Kuroda, Matsukuma and Nakasmura[14] obtained chalcone by condensing acetophenone derived from anisole and other polymethoxy benzenes with some methoxy aldehydes in presence of anhydrous aluminium chloride. Besides the above, other condensing agents used in synthesis of chalcones are, Amino acid,[15] Aqueous solution of borax,[16] Perchloric acid,[17] Piperidine ,[18] Boron trifloride,[19] Alkali metal alkoxide,[20] Magnesium tert-butoxide,[21] Organocadmium compound.[22]

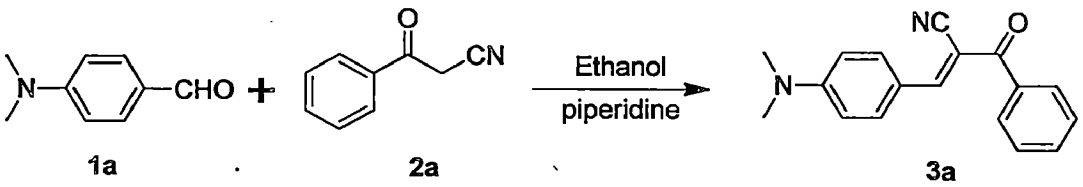
3.2. Materials and methods

All the reactions were carried out by using chemicals purchased from Sigma Aldrich, s. d. fine and Thomas Baker with purity of > 99% and using them as such. Solvents were dried by standard procedures. Column chromatography purifications were performed with the use of silica gel (100-200 mesh, Thomas Baker) as a stationary phase in a column with 40 cm long and 3.0 cm diameter. The IR spectra were recorded on a THERMO Nicolet spectrometer. The ^{1}H and ^{13}C NMR spectra were measured with Bruker AMX500 spectrometer operating at 500.13 and 125.77 MHz, respectively. Deuterated chloroform ($CDCl_3$) was used as solvent with residual peak at δ 7.26 for ^{1}H; 77.0 ^{13}C, respectively.

3.3. Synthesis of compounds

The synthesis of all of the compounds was accomplished by the base catalyzed condensation of appropriate arylaldehyde with 3-oxo-3-phenylpropanenitrile. These aldehydes (**1a-f**) are prepared by following the formylation of fused polyaromatic hydrocarbon or appropriate arylamine with the help of literature reported procedures.[23-24]

Synthesis of (*E*)-2-benzoyl-3-(4-(dimethylamino)phenyl)acrylonitrile (3a).

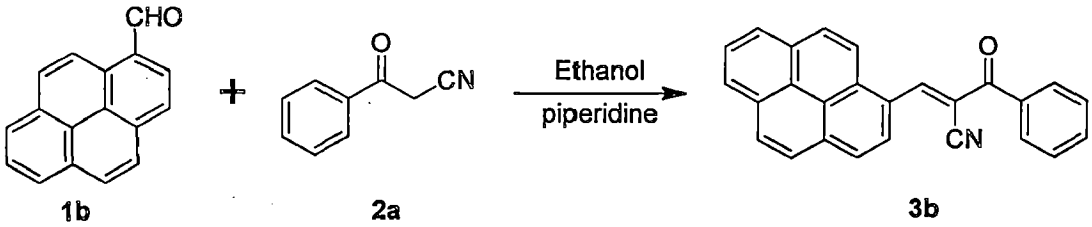


1a **2a** **3a**

In a 100 mL round bottom flask 4-(dimethylamino)benzaldehyde (0.5 mg, 3.3 mmol), 3-oxo-3-phenylpropanenitrile (0.479 g, 3.3 mmol), and ethanol (15-20 mL) were charged. Then 2-3 drops of piperidine was added and kept for reflux at 90°C for 1 h. A red colored solid formed. This was filtered and washed with little amount of ethanol and dried. Yield: 90%. m.p.: 140-143 °C, IR (KBr, cm^{-1}): 2200 ($\nu_{C\equiv N}$), 1651 ($\nu_{C=O}$). ^1H NMR ($CDCl_3$, 500.17 MHz): δ 3.09–3.17 (m, 6H), 6.72 (d, J = 9.0 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 2H), 8.00–8.02 (m, 3H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 190.14, 155.78, 153.88, 137.36, 124.55, 132.36, 128.96, 128.38, 119.75, 119.22, 111.64, 101.66, 40.08.

Synthesis of (*E*)-2-benzoyl-3-(pyren-1-yl)acrylonitrile (3b).

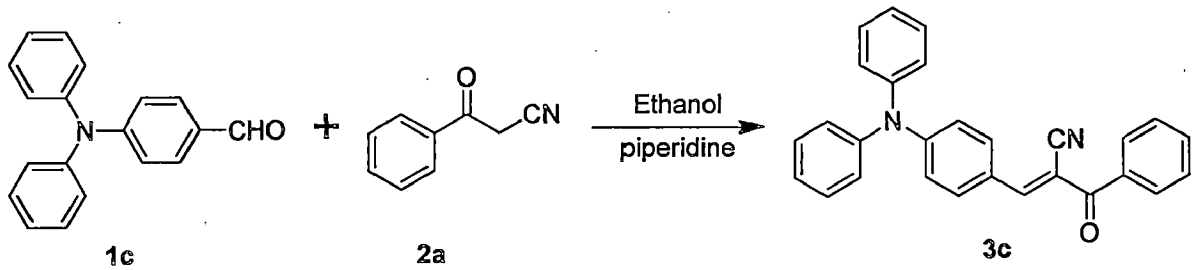
In a 100 mL round bottom flask pyrene-1-carbaldehyde (0.461 g, 2.0 mmol), 3-oxo-3-phenylpropanenitrile (0.290 g, 2.0 mmol), and ethanol (15-20 mL) were charged.



1b 2a 3b

Then 2-3 drops of piperidine was added and kept for reflux at 90 °C for 1 h. A Red-Orange colored solid formed. This was filtered and washed with little amount of ethanol and dried. Yield: 85%. m.p.: 177-180 °C, IR (KBr, cm^{-1}): 2205 ($\nu_{C\equiv N}$), 1649 ($\nu_{C=O}$). ^1H NMR ($CDCl_3$, 500.17 MHz): δ 6.99 (dd, J = 11.5 Hz, J_1 = 2.5 Hz, 2H), 7.19–7.22 (m, 6H), 7.35–7.39 (m, 4H), 7.48–7.51 (m, 2H), 7.58–7.61 (m, 1H), 7.85–7.86 (m, 2H), 7.91 (dd, J = 11.5 Hz, J_1 = 2.5 Hz, 2H), 8.00 (s, 1H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 189.13, 152.83, 136.23, 134.92, 133.48, 131.65, 131.11, 130.41, 130.37, 129.25, 129.43, 128.78, 127.42, 127.20, 126.99, 126.73, 126.32, 125.14, 125.11, 124.22, 121.62, 117.65, 111.24.

Synthesis of (*E*)-2-benzoyl-3-(4-(diphenylamino)phenyl)acrylonitrile (3c).

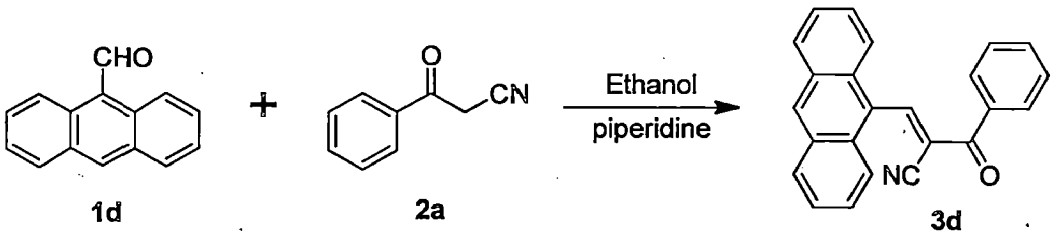


1c 2a 3c

In a 100 mL round bottom flask 4-(diphenylamino)benzaldehyde (0.547 g, 2.0 mmol), 3-oxo-3-phenylpropanenitrile (0.290 g, 2.0 mmol), and ethanol (15-20 mL) were charged. Then 2-3 drops of piperidine was added and kept for reflux at 90 °C for 1 h. A Orange colored solid formed. This was filtered and washed with little amount of ethanol and dried. Yield: 50%. m.p.: 142-144 °C, IR (KBr, cm^{-1}): 2215 ($\nu_{C\equiv N}$), 1642 ($\nu_{C=O}$). ^1H NMR ($CDCl_3$, 500.17

MHz): δ 7.56–7.65 (m, 6H), 7.68–7.72 (m, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.08–8.11 (m, 3H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 8.610 (s, 1H), 9.117 (s, 1H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 189.77, 155.12, 152.75, 145.56, 136.77, 133.57, 132.82, 129.87, 129.77, 129.12, 128.52, 126.54, 126.34, 125.69, 123.62, 119.06, 118.47, 104.49.

Synthesis of (*E*)-3-(anthracen-10-yl)-2-benzoylacrylonitrile (3d).

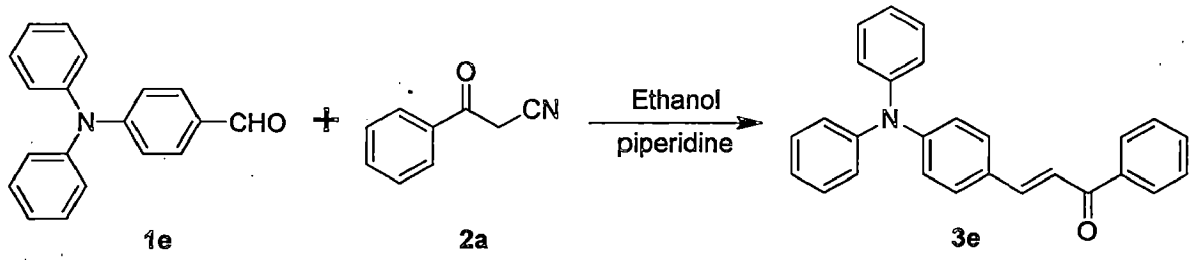


1d 2a 3d

In a 100 mL round bottom flask anthracene-10-carbaldehyde (0.619 g, 3.0 mmol), 3-oxo-3-phenylpropanenitrile (0.435 g, 3.0 mmol), and ethanol (15-20 mL) were charged. Then 2-3 drops of piperidine was added and kept for reflux at 90 °C for 1 h. A red colored solid formed. This was filtered and washed with little amount of ethanol and dried Pale yellow solid. Yield: 83%. m.p.: 167-169 °C, IR (KBr, cm^{-1}): 2222 ($\nu_{C\equiv N}$), 1658 ($\nu_{C=O}$). ^{1}H NMR ($CDCl_3$, 500.17 MHz): δ 7.58–7.61 (m, 2H), 7.68–7.71 (m, 1H), 8.03–8.05 (m, 2H), 8.09–8.15 (m, 2H), 8.23–8.32 (m, 6H), 9.00 (d, J = 8.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 187.72, 155.62, 135.59, 133.93, 131.11, 130.94, 129.55, 129.37, 129.11, 128.93, 127.54, 125.82, 125.62, 124.61, 119.89, 115.51.

Synthesis of (*E*)-3-(4-(diphenylamino)phenyl)-1-phenylprop-2-en-1-one (3e).

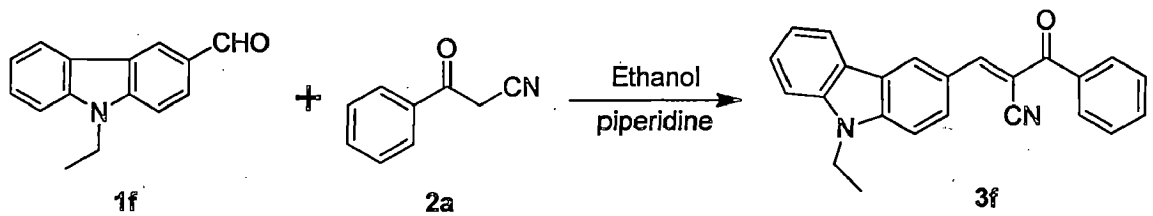
In a 100 mL round bottom flask 4-(diphenylamino)benzaldehyde (0.492 g, 1.8 mmol), 3-oxo-3-phenylpropanenitrile (0.261 g, 1.8 mmol), and ethanol (15-20 mL) were charged.



1e 2a 3e

Then 2-3 drops of piperidine was added and kept for reflux at 90 °C for 1 h. A Yellow colored solid formed. This was filtered and washed with little amount of ethanol and dried. Yield: 70%. m.p.: 110-113 °C, IR (KBr, cm^{-1}): 1686 ($\nu_{C=O}$). ^1H NMR ($CDCl_3$, 500.17 MHz): δ 7.02 (td, J = 9.0 Hz, J_1 = 2.0 Hz, 3H), 7.16–7.18 (m, 6H), 7.32–7.36 (m, 8H), 7.67 (td, J = 9.0 Hz, J_1 = 2.0 Hz, 3H), 9.81 (s, 1H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 190.45, 153.38, 146.18, 131.32, 129.75, 129.12, 126.33, 125.13, 119.36.

Synthesis of (*E*)-2-benzoyl-3-(9-ethyl-9*H*-carbazol-3-yl)acrylonitrile (3f).



1f 2a 3f

In a 100 mL round bottom flask 9-ethyl-9*H*-carbazole-3-carbaldehyde (0.335 g, 1.5 mmol), 3-oxo-3-phenylpropanenitrile (0.218 g, 1.5 mmol), and ethanol (15-20 mL) were charged. Then 2-3 drops of piperidine was added and kept for reflux at 90 °C for 1 h. A Yellow-Orange colored solid formed. This was filtered and washed with little amount of ethanol and dried. Yield: 65%. m.p.: 90-93 °C, IR (KBr, cm^{-1}): 2202 ($\nu_{C\equiv N}$), 1654 ($\nu_{C=O}$). ^1H NMR ($CDCl_3$, 500.17 MHz): δ 1.47–1.50 (m, 3H), 4.41 (dd, J = 14.5 Hz, J_1 = 7.0 Hz, 2H), 7.32–7.35 (m, 1H), 7.46–7.49 (m, 2H), 7.52–7.57 (m, 3H), 7.61–7.64 (m, 1H), 7.90–7.92

(m, 2H), 8.16 (d, J = 5 Hz, 1H), 8.28–8.30 (m, 2H), 8.78 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.770 MHz): δ 191.88, 189.97, 157.13, 145.59, 140.03, 140.66, 136.78, 132.86, 129.31, 129.19, 128.59, 128.49, 127.24, 127.06, 128.77, 125.79, 124.07, 123.72, 123.16, 123.07, 122.92, 122.84, 121.01, 120.83, 120.70, 120.34, 118.50, 109.33, 109.26, 109.19, 108.72, 105.20, 100.00, 38.05, 37.96, 13.92, 13.87.

3.4. Conclusions

Synthetic methodology was developed successfully for the preparation of novel chalcone derivatives having cyano substitution. The success of synthetic methodology attributes to the appropriate use of base and the presence of electron withdrawing cyano (-CN) group on the aromatic ketone, that help in the generation of carbanion. All the reactions were performed in lesser time when compare to literature reported method with good yield. Further the structural composition was established without doubt by spectral analysis. The presence of –CN and –C=O group was confirmed by IR spectroscopic analysis, where they shows a sharp peaks around 1650-1700 cm^{-1} and 2200-2250 cm^{-1}respectively. The presence of carbonyl carbon was also proved by the peak present around 190 ppm in ^{13}C NMR spectra.

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Chapter 4

Optical, electrochemical and thermal properties

4.1 Introduction

When a molecule absorbs a photon of sufficient energy, the photon energy is given to the electrons and the electron density rearranges in space. Since the nucleus is much heavier than the electrons, the electronic excitation process (~10^{-15}-10^{-16}s) is much faster than the geometrical relaxation time of the molecule (~10^{-14}-10^{-13}s). Hence, the electronic excitation takes place without a change in the molecular structure, this is known as vertical transition. The processes that change the nuclear geometry and/or modify the kinetic energy of the nuclei without changing the electronic potential energy surface that governs the nuclear motions are referred to as *adiabatic*. Due to the vertical transition, the photon energy is transferred to the electrons and to the nuclei. The additional nuclei energy is in the form of vibrational motion, while the additional electronic energy is related to the changes in electron density. In a single-electron picture, this electronic energy increase can be explained approximately as follows: one electron in the HOMO becomes excited to the LUMO upon light absorption. For this reason the molecule is excited to a vibrational excited state of the electronic excited state. The antibonding character of the LUMO results in an overall

reduction of bond strength, when it is occupied. Consequently the relative position of the nuclei changes after the excitation. The excited molecule strives to return to its ground state via various relaxation processes. In the single-electron picture, this is equivalent to the electron in the LUMO comes back to the HOMO. Since the lifetime of the excited electronic state is long, the molecule first relaxes down to the vibrational ground state of the excited electronic state. Relaxation down to the electronic ground state can either be through formation of heat (non-radiative decay, also called quenching), or by the emission of a photon, the latter called photoluminescence. The emitted photon has a lower energy than the excitation photon and the difference is known as Stokes shift.[1]

In a single-electron picture, upon excitation of the molecule a hole is left in the HOMO when the electron is excited to the LUMO. Since the hole is positive and the electron is negative, there will be a columbic attraction between the two charges – they form a bound electron-hole pair called an exciton and characterized by an exciton binding energy. The exciton is an uncharged particle in a molecular solid that can travel. Since it does not carry an effective charge, it does not migrate in an electric field, although it might diffuse due to concentration gradients. The onset energy for absorption (i.e. the optical gap) differs from the HOMO-LUMO gap with the exciton binding energy.

$h\nu = E_{LUMO} - E_{HOMO} - E_{be}$. Where E_{be} is the binding energy of the exciton.

$$I = I_0 e^{-\sigma l} = I_0 e^{-\varepsilon c l}$$

In absorption and emission spectra, light intensity is plotted as a function photon energy. In general absorption spectroscopy relies on the *Lambert-Beer law*, which relates the

intensity I of monochromatic light of wave number transmitted through a sample to the intensity I_0 incident on the sample.

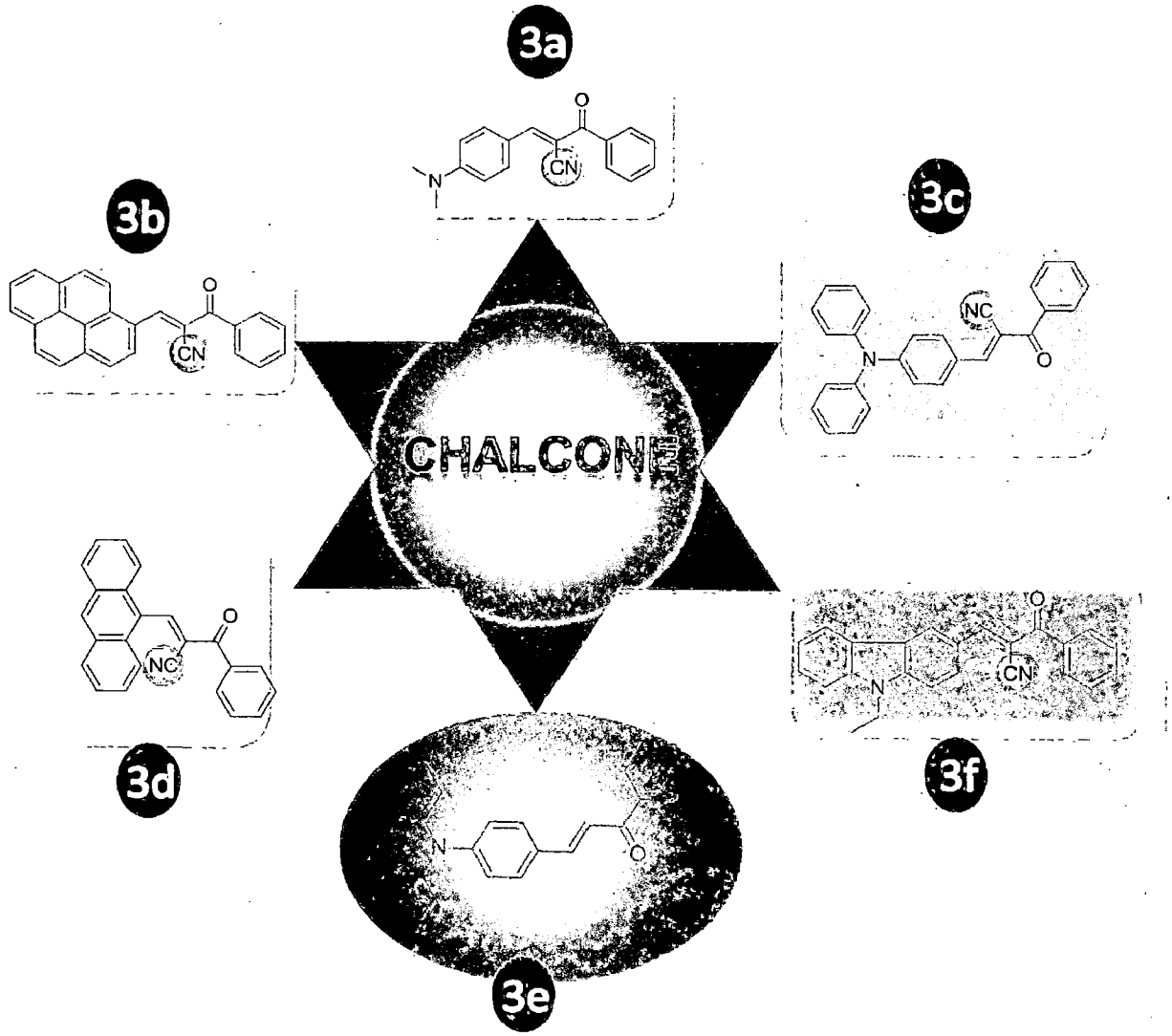

Fig.4.1. Pictorial representation of the compounds.

4.2 Materials and methods

All the solvents were distilled by standard procedures. Electronic absorption spectra were obtained on a UV-1800 SHIMADZU UV spectrophotometer. The fluorescence spectra were measured on a RF-5301 PC SHIMADZU spectrofluorophotometer. The TGA analysis was performed on a Perkin Elmer Pyris Diamond Analyser under nitrogen atmosphere with

heating rate 10 °C/ minute. Cyclic voltammetric experiments were performed with a CH Instruments electrochemical analyzer. All measurements were carried out at room temperature with a conventional three-electrode configuration consisting of a glassy carbon working electrode, a platinum wire auxiliary electrode, and a nonaqueous acetonitrile $Ag/AgNO_3$ reference electrode. The E_{ox} values were determined as $(E_p^a + E_p^c)/2$, where E_p^a and E_p^c are the anodic and cathodic peak potentials, respectively. The potentials are quoted against the ferrocene internal standard. The solvent in all experiments was dichloromethane, and the supporting electrolyte was 0.1 M tetrabutylammonium perchlorate.

4.3 Photophysical properties

Representative absorption spectra of the compounds recorded in dichloromethane solutions are displayed in Figure 4.1 and the data are compiled in Table 4.1. All the compounds exhibit two absorption bands in the UV-Visible region upon excitation. The absorption band lies around 290-350 nm is attributable to π-π* transitions. Another band at the region from 359-447 nm corresponds to superposition of delocalized π-π* transitions and charge transfer transitions. The λ_{max} value for the **3c** is greater than **3e**. This indicates that the insertion of cyano group in between the conjugation pathway increase the acceptor strength, consequently enhanced donor-acceptor interactions leads to red shifted absorption.

It is known that a π-π* transition band normally has a longer wavelength as the effective conjugation length increases, a charge-transfer band will be affected by the electron donor, electron acceptor. The λ_{max} value for charge transfer band is in order of **3e** < **3f** < **3b** < **3d** <**3a** < **3c**.

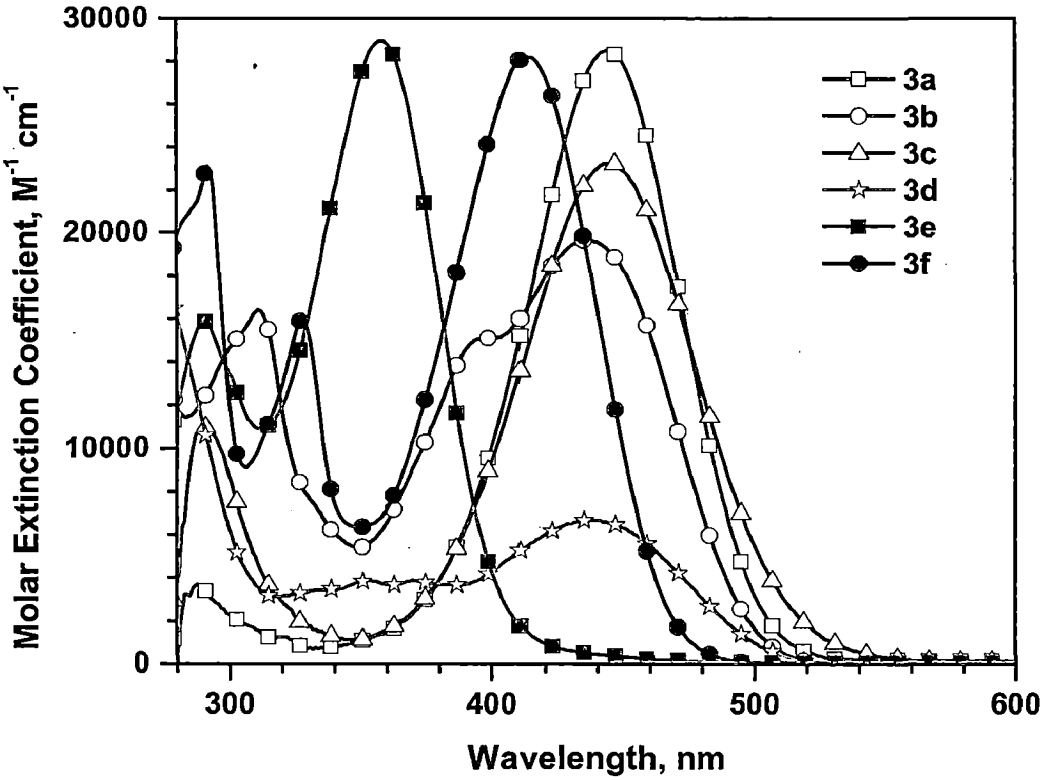

Fig.4.2. Absorption spectra of the dyes **(3a-f)** recorded in dichloromethane solutions.

Table 4.1. Optical and electrochemical data for the compounds recorded in dichloromethane.

Compounds	λ_{abs},nm ($\varepsilon \times 10^3$ M^{-1} cm^{-1})[a]	λ_{em}, nm	E_{ox}, mV[b]	HOMO, eV[c]	LUMO, eV[c]	$E_{0\text{-}0}$, eV	$E_{0\text{-}0}$*, V[d]
3a	444 (28.5), 288 (36.8)	513	684	5.484	3.193	2.392	-0.94
3b	438 (19.6), 311 (16.4)	533	956	5.756	3.370	2.386	-0.66
3c	447 (23.2), 292 (11.0)	575	712	5.512	3.202	2.310	-0.83
3d	441 (6.7), 371 (3.9), 354 (3.9)	-	904	5.704	3.302	2.402	-0.73
3e	359 (28.9), 290 (15.9)	505	712	5.512	2.555	2.957	-1.48
3f	415 (28.2), 328 (16.0), 292 (23.1)	499	952	5.752	3.202	2.550	-0.83

[a]measured for approximately 2.0×10^{-5} M dichloromethane solutions; [b]measured for dichloromethane solutions using tetrabutylammonium perchlorate (TBAP) as supporting electrolyte at a scan rate of 100 mV/s; [c]deduced from the equations HOMO = E_{ox}+ 4.8 and LUMO = HOMO- $E_{0\text{-}0}$. [d]excited state oxidation potential *vs* NHE.

Compared to **3a** and **3c**, **3b** and **3d** absorbs at shorter wavelength. This suggests that donor strength of aryamine unit is better as compared to fused polyaromatic hydrocarbon to shift

the charge transfer band to lower energy side. In between the arylamine donors triphenylamine is more electron rich when compare to 4-(*N*,*N*-dimethylamino)phenyl, therefore its donor strength is superior, this leads to bathochromic shift of absorption band. Similarly in case of **3b** and **3d**, **3b** that has pyrene unit which is more electron rich than anthracene, and this leads to red shifted absorption band. [2]Among all the cyano chalcones **3f** has blue shifted absorption; this shows lesser electron donating nature of carbazole. As shown in Table 4.1 molar extinction coefficienst for **3a**, **3c**, **3e** and **3f** are higher than **3b** and **3d**. This supports that arylamine donor have significant contribution to enhance the transition probability for the charge transfer transitions.

The phenomenon of solvatochromism arises when a solute dissolved in solvents of varying polarity apparent a pronounced change in position, intensity, and shape of an absorption band. A bathochromic (red) shift and a hypsochromic (blue) shift with increasing solvent polarity are called positive and negative solvatochromism, respectively. A change from bathochromic to hypsochromic, or vice versa, with increase in solvent polarity, is called reverse solvatochromism. The pronounced change in the position of the absorption band has been used as a probe to determine one of the properties of the solvent, namely, its polarity. However, the term solvent polarity is yet to be defined precisely although several attempts have been made so far. The important point concerning the so-called polarity of a solvent is its overall solvation capability, which is the cumulative effect of all the solvent-solute interactions, excluding those such as protonation, oxidation, reduction, complexation, etc., which might lead to a chemical change of the solute.[3] Solvatochromic compounds are those solutes that induce a change in the color of the solution with a change in solvent polarity. Typically, solvatochromic compounds can be described by two extreme resonance

contributing structures: one form is quinoidal, non- polarized, and formally nonaromatic; the other is zwitterionic, polarized, and fully aromatic. The change in the absorption band with solvent arises from variation in the contribution of these canonical forms to the overall resonance hybrid.[4]

Table 4.2. Absorption data for the dyes recorded in different solvents.

Compounds	λ_{abs}, nm ($\varepsilon \times 10^3$ M^{-1} cm^{-1})					
	TOL	EA	$CHCl_3$	DCM	ACN	MeOH
3a	433 (37.3)	430 (26.1), 325 (6.7),	442 (27.5), 334 (52.6), 332 (52.4), 324 (55.1), 264 (12.8)	444 (28.5), 288 (36.8)	438 (38.1), 323 (3.0), 308 (3.0), 263 (10.6)	444 (32.5), 267 (7.3)
3b	429 (16.6), 304 (15.1)	426 (21.0), 393 (18.9), 307 (18.1)	421 (16.0), 302 (14.6), 263 (22.9)	438 (19.6), 311 (16.4)	414 (17.8), 393 (16.9), 300 (16.1)	415 (10.4), 299 (9.8), 259 (15.6)
3c	444 (26.0), 296 (15.9)	434 (24.4), 291 (13.7)	454 (26.1), 294 (14.9), 266 (13.9)	447 (23.2), 292 (11.0)	438 (32.6), 287 (13.8)	445 (23.4), 287 (10.9)
3d	434 (5.3), 376 (3.6)	420 (5.9), 350 (4.1)	436 (4.4), 358 (3.7)	441 (6.7), 371 (3.9), 354 (3.9)	420 (4.6), 385 (4.1)	425 (4.0), 383 (3.2), 352 (3.0)
3e	357 (27.9), 292 (13.3)	351 (32.5), 289 (15.6), 253 (7.9)	362 (22.7), 292 (9.4)	359 (28.9), 290 (15.9)	351 (23.2), 289 (10.0)	357 (15.7), 288 (6.9)
3f	410 (19.8), 328 (11.5), 293 (19.9)	406 (25.9), 325 (14.8), 290 (22.8)	410 (12.8), 327 (128), 312 (13.5), 292 (25.6)	415 (28.2), 328 (16.0), 292 (23.1)	406 (17.7), 325 (13.3), 290 (23.3)	409 (8.0), 326 (6.5), 289 (12.1)

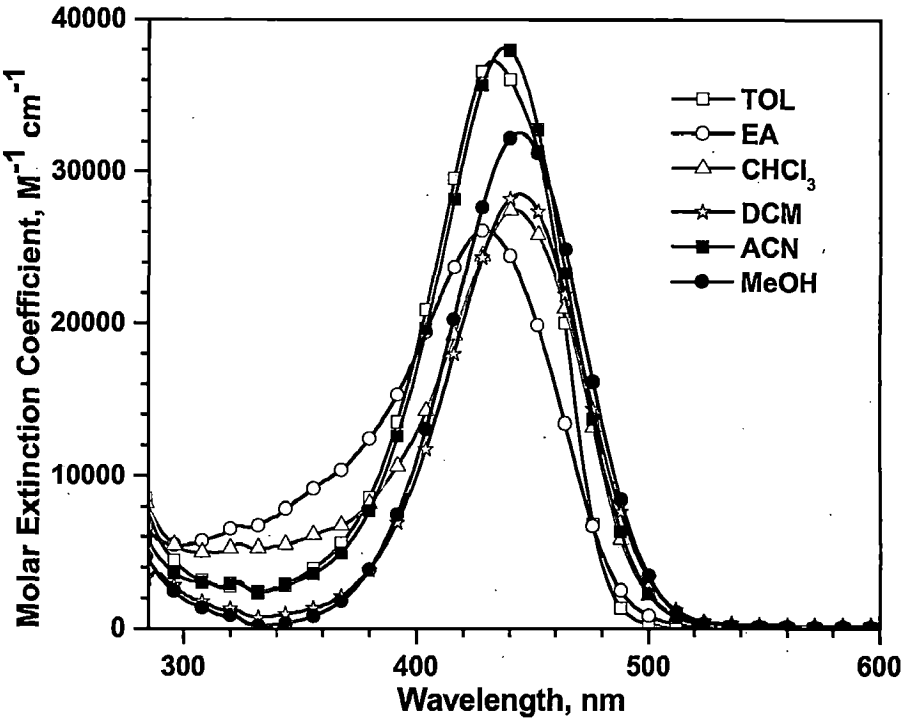

Fig.4.3. Absorption spectra of **3a** recorded in different solvents.

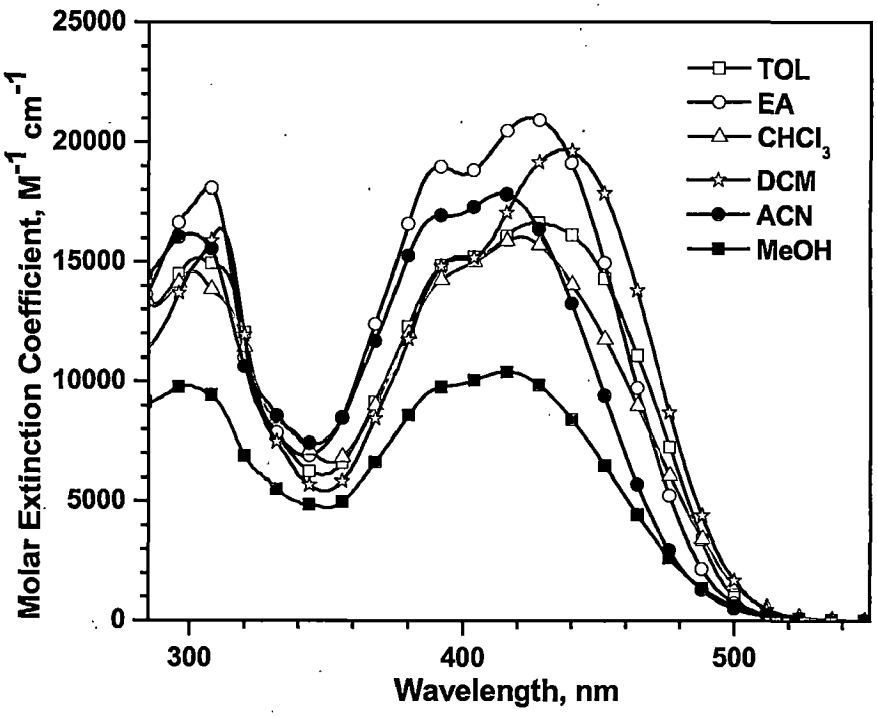

Fig.4.4. Absorption spectra of **3b** recorded in different solvents.

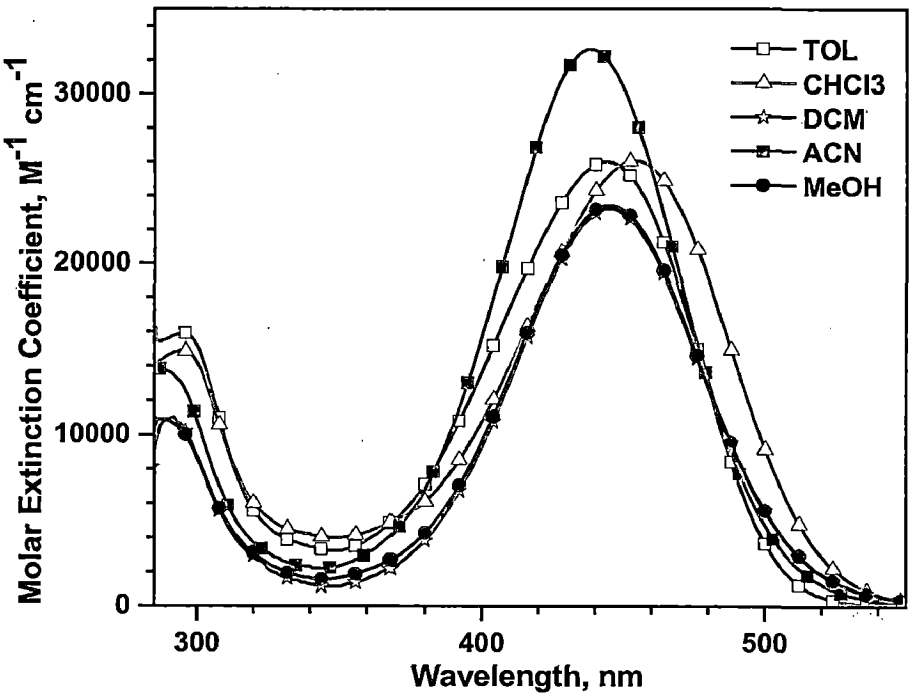

Fig.4.5. Absorption spectra of **3c** recorded in different solvents.

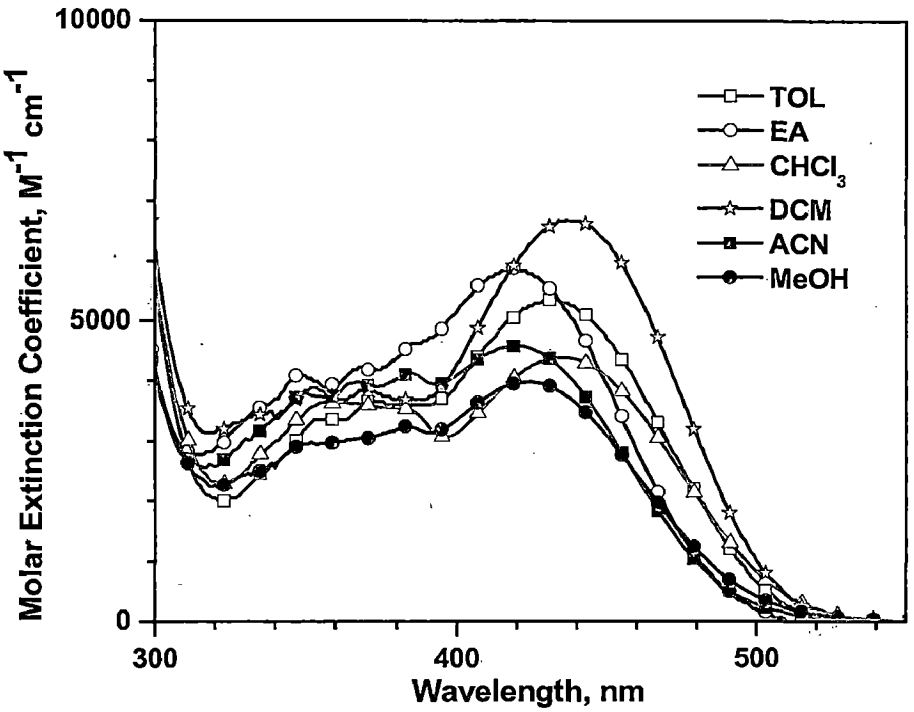

Fig.4.6. Absorption spectra of **3d** recorded in different solvents.

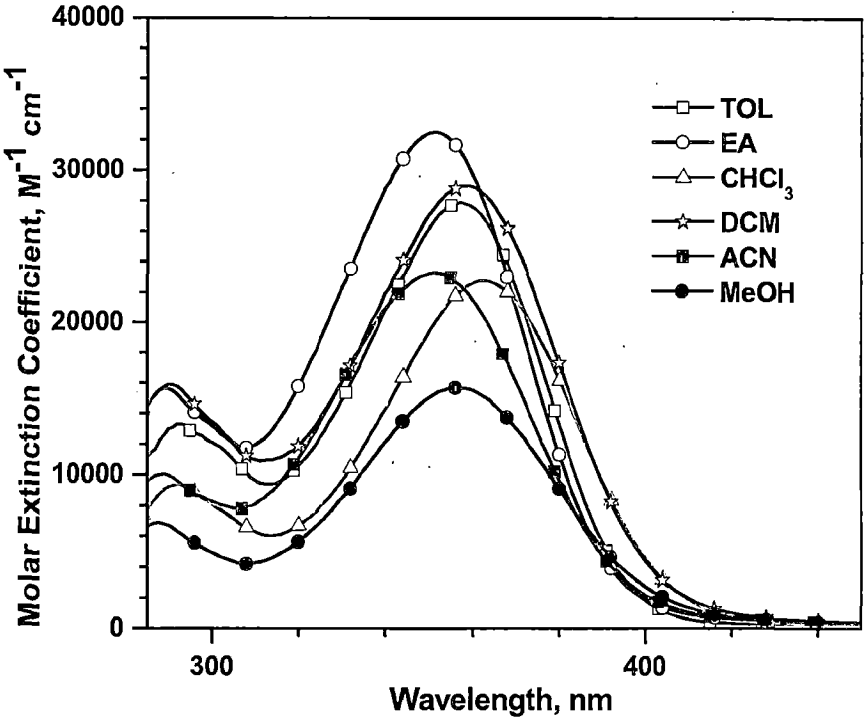

Fig.4.7. Absorption spectra of **3e** recorded in different solvents.

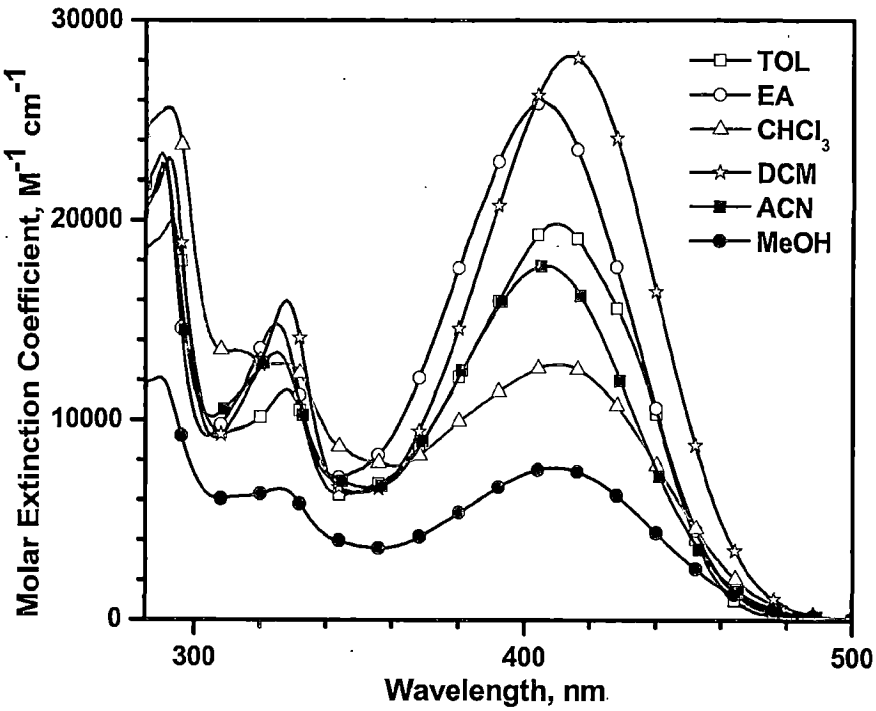

Fig.4.8. Absorption spectra of **3f** recorded in different solvents.

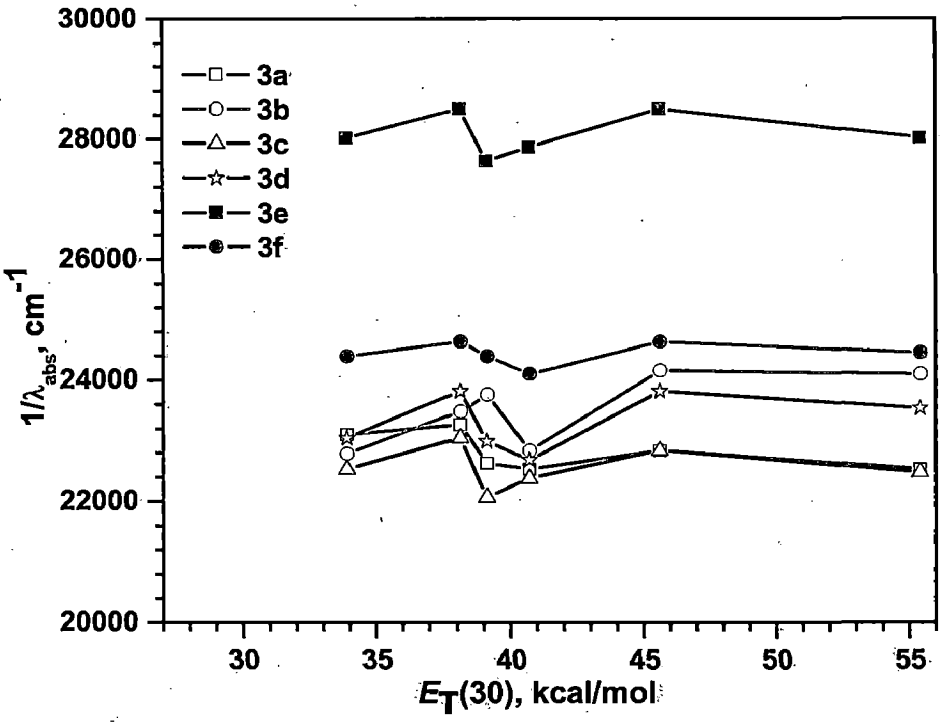

Fig.4.9. Variation of $1/\lambda_{abs}$ with solvent polarity parameter ($E_T(30)$).

Absorption spectra for these compounds were recorded in solvents of different polarity. It is observed that absorption maxima do not show much change in the peak position with changing the solvent polarity. This suggest that this band have major contribution from π-π* transitions. The absorption spectra of **3b** and **3d** are showing vibrionic bands in less polar solvents. This indicates that these compounds may aggregate in polar solvents. All the compounds are showing red shifted absorption in chloro solvents (chloroform, dichloromethane), this attributes to instant stabilization of polarizble electron in the excited state.[5] Further a plot between the absorption maxima and $E_T(30)$[6] shows that only in dichloromethane a small deviation is observed.

Emission spectra of the compounds recorded in dichloromethane are shown in Fig.4.10 and the data are complied in Table 4.1.

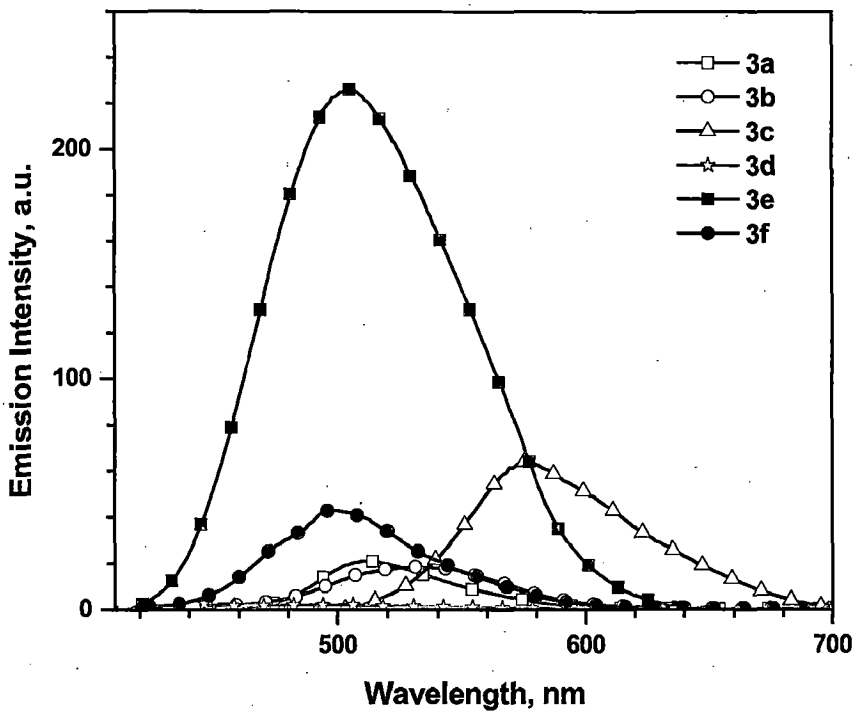

Fig.4.10. Emission spectra of all the compounds recorded in dichloromethane solutions.

The emission profile for **3e** shows a strong emission peak when compare to **3c**. This attributes to the presence of cyano group in the chalcones, that increase the dipolar character in the molecule and causes dipole-dipole interactions leads to decrease in emission intensity. The effect of donor strength is also observed on the emission profile of the compounds. Since the donor strength of pyreen and anthracene is lesser when compare to aryl amines , the emission intensity of **3b** and **3d** is very low.

Fluorescence spectra of the compounds were also examined in a series of solvents with varying polarity index ($E_T(30)$) to identify the impact of the polarity of the solvent on the excited state of the dyes and to identify the nature of the molecules in the excited state. It is found that with increasing the solvent polarity emission maxima is red shifted, this indicate the polar excited state for these compound that may undergo dipole-dipole realaxation.

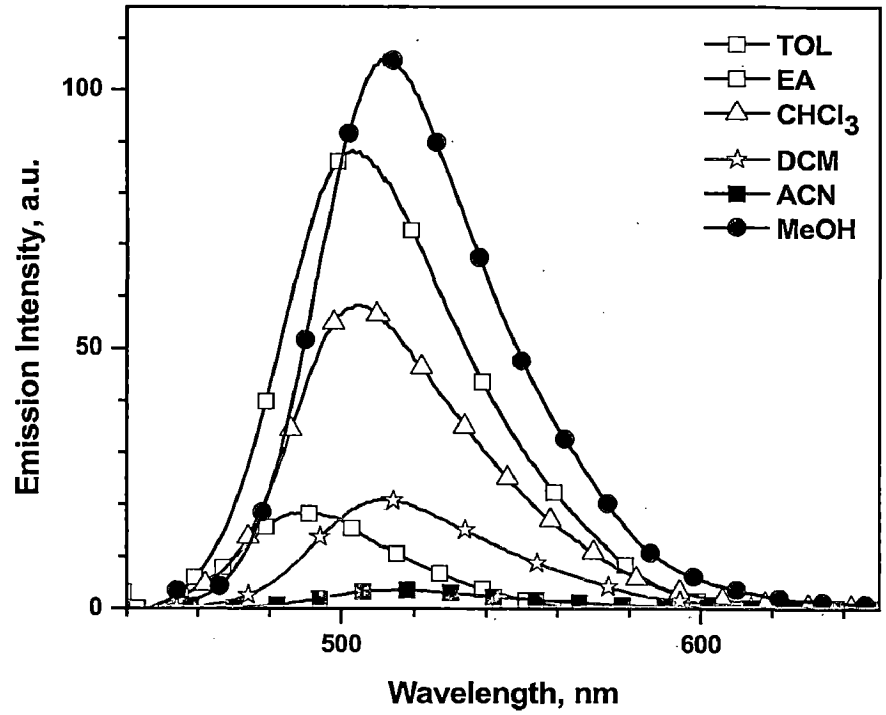

Fig.4.11. Emission spectra of **3a** recorded in different solvents.

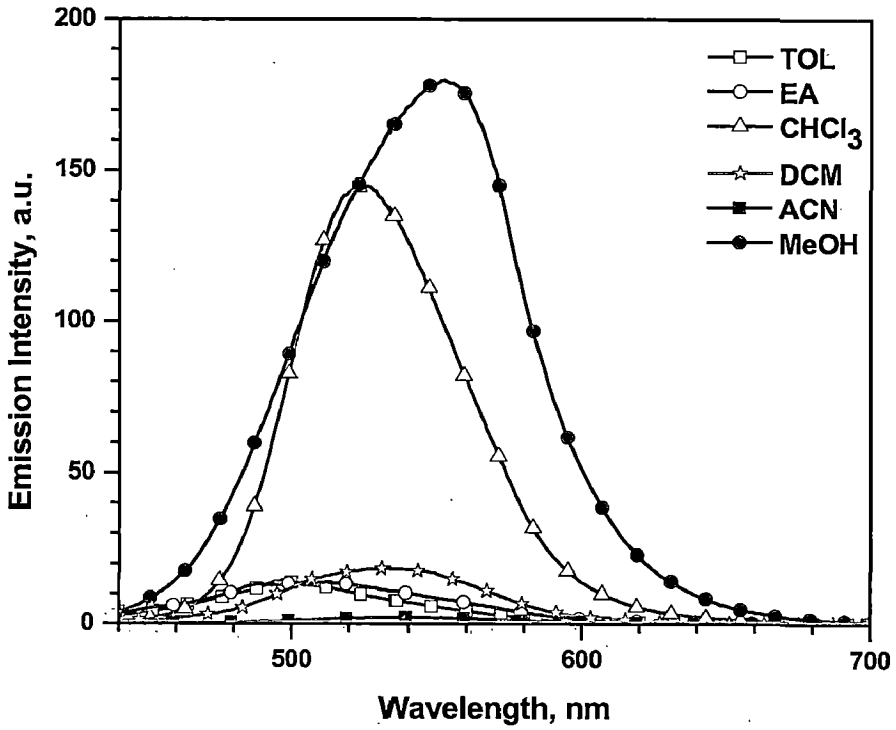

Fig.4.12. Emission spectra of **3b** recorded in different solvents.

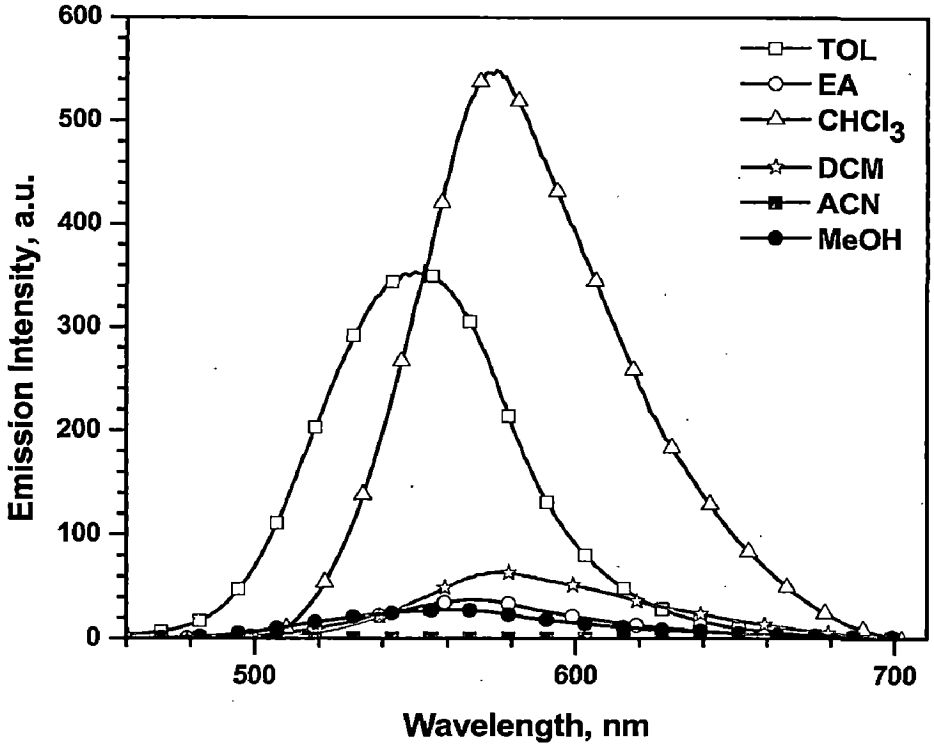

Fig.4.13. Emission spectra of **3c** recorded in different solvents.

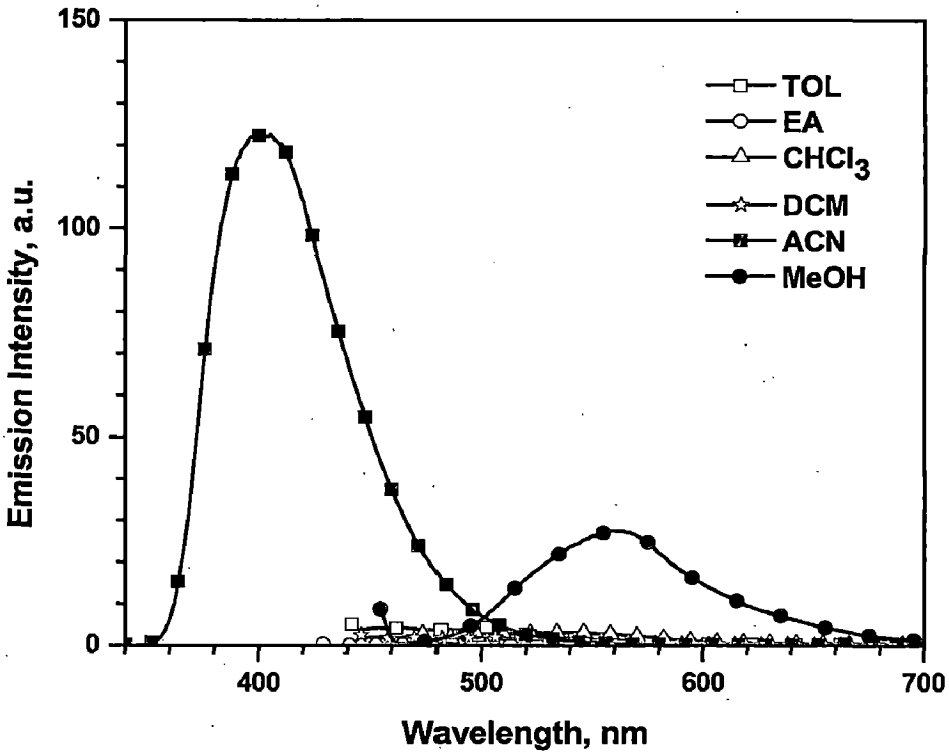

Fig.4.14. Emission spectra of **3d** recorded in different solvents.

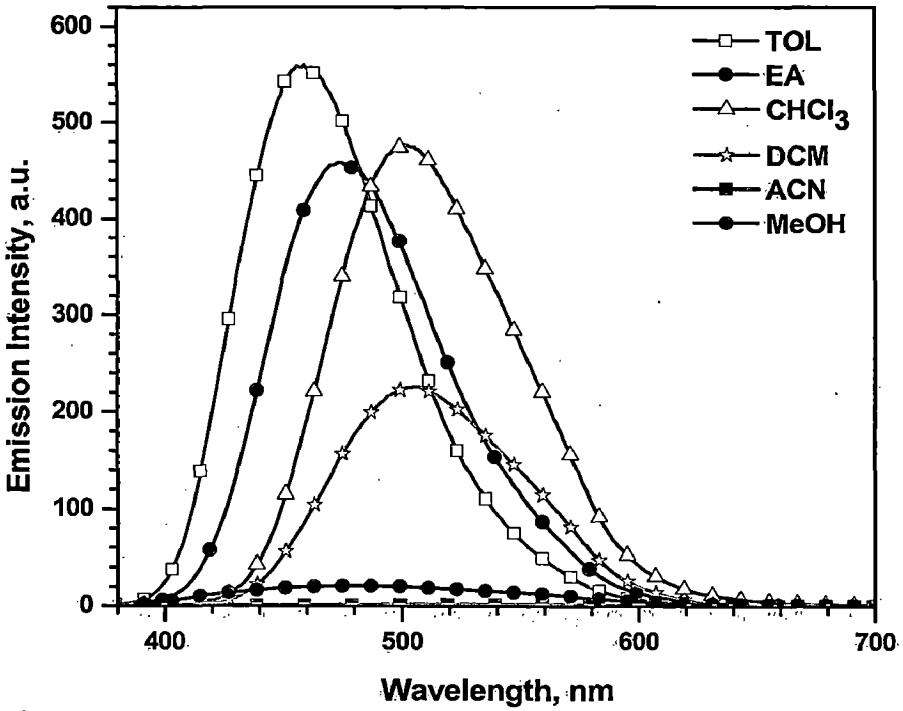

Fig.4.15. Emission spectra of **3e** recorded in different solvents.

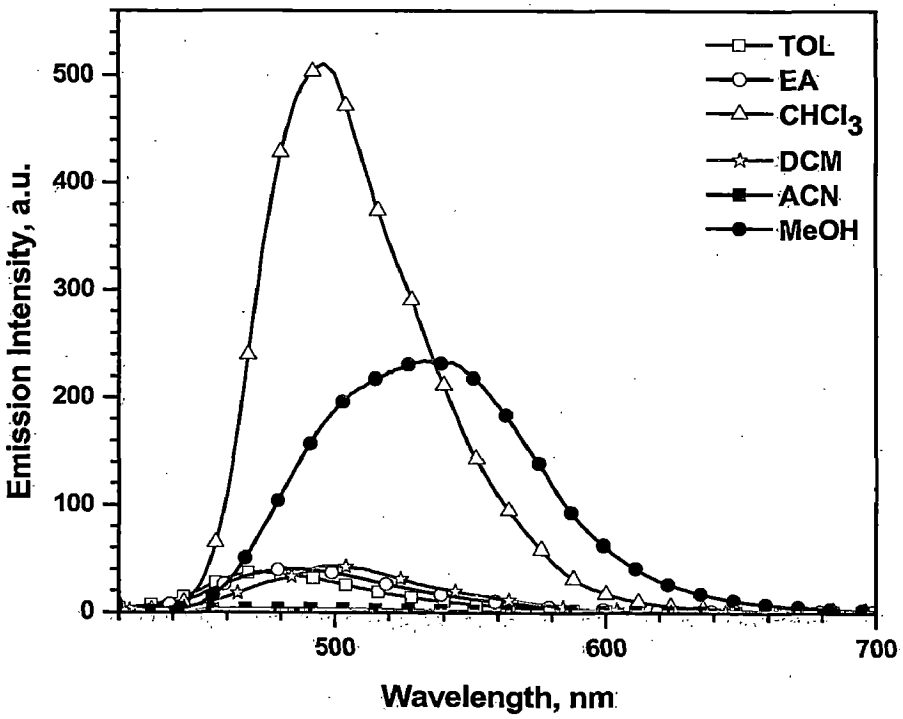

Fig.4.16. Emission spectra of **3f** recorded in different solvents.

Table 4.3. Emission spectral data for the compounds.

Compounds	λ_{em}, nm (Φ, %)						Stokes shift, cm^{-1}					
	TOL	EA	$CHCl_3$	DCM	ACN	MeOH	TOL	EA	$CHCl_3$	DCM	ACN	MeOH
3a	488 (4)	503 (10)	505 (14)	513 (5)	517 (3)	514 (25)	2663	3375	2822	3029	3489	3067
3b	497 (7)	512 (4)	526 (16)	533 (6)	-	552 (27)	2658	3943	4742	4069	-	5980
3c	550 (10)	568 (6)	575 (18)	575 (3)	-	558 (6)	4340	5436	4635	4960	-	4550
3d	401	-	-	-	-	528 (5)	-	-	-	-	-	
3e	459 (14)	474 (10)	500 (10)	505 (25)	-	515 (12)	6224	7569	7624	8053	-	7264
3f	471 (7)	485 (5)	496 (11)	499 (3)	433 (10)	-	3159	4012	4229	4056	3666	-

The observed quantum yield is low for the compounds, this suggest that these compounds are not very good emissive materials. Higher stoke shift is observed for the compound **3e**. This shows that introduction of cyano group increases the rigidity in the molecules.[7]

4.4. Electrochemical properties

The oxidation and reduction propensities of the compounds **3a-3f** were scrutinized by cyclic and differential pulse voltammetric methods. The redox potentials of the dyes are collected in Table 4.1. The excited state oxidation potential ($E_{0\text{-}0}$*) of the sensitizer is estimated by subtracting the 0–0 transition energy ($E_{0\text{–}0}$) from the first oxidation potential (Eox), whereas $E_{0\text{–}0}$ is derived from the absorption edge of the dyes since no reduction peakwas observed for the dyes. The HOMO values were deduced from the oxidation potential by referencing to ferrocene which was used as internal standard as given below.

$$HOMO = E_{ox} + 4.8$$

While the LUMO was obtained from the optical band gap derived from the absorption edge using the equation:

$$LUMO = HOMO - E_{0\text{-}0}$$

All of the dyes showed an irreversible oxidation wave corresponding to the removal of an electron from the donor segment.

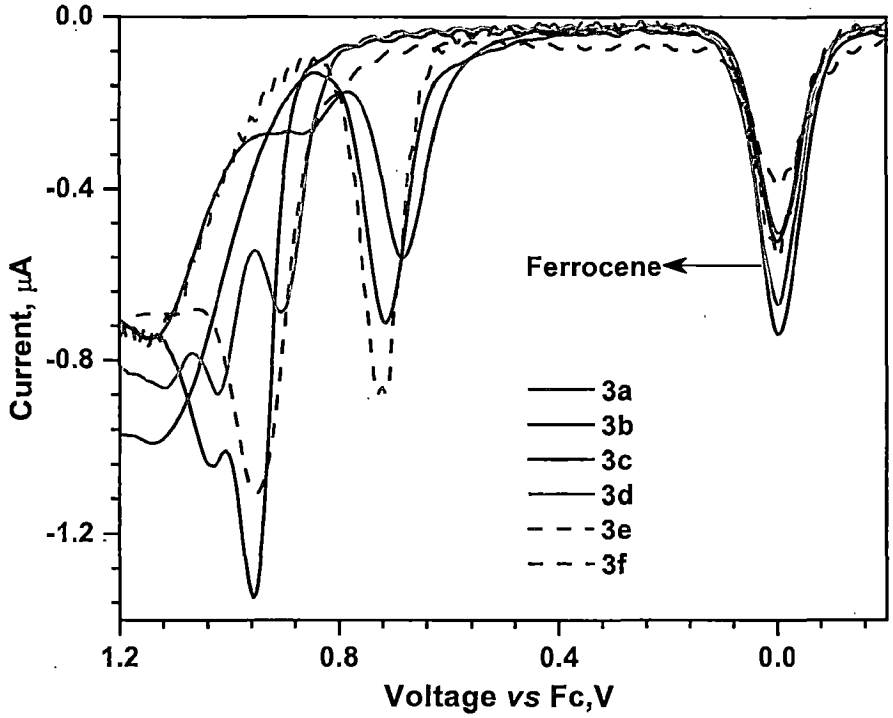

Fig.4.17. Differential pulse voltammograms for **3a-f** recorded indichloromethane solutions.

It is apparent that the nature of the electronic interaction between the donor and acceptor moieties affects the oxidation potentials.[8] As the spacer length is fixed in all the compounds, the alterations in the oxidation potentials of the dyes can be considered as the manifestations of the donor strength. Strong donors are expected to interact effectively with the acceptor moiety and lead to a reduction in the electrochemical bandgap. Thus lower oxidation potentials are expected for the strong donor (arylamine) containing derivatives **3a** and **3c** while larger oxidation potential for the anthracene, carbazole and pyrene derivative **3d**, **3f** and **3b** respectively. In agreement with these generalizations, the oxidation potentials of the dyes assumed the order: **3a** < **3c** ~**3e** < **3d** < **3f** < **3b**. The effect of cyano substitution is also observed in the electrochemical properties of the compounds. As the donor moiety is same in **3c** and **3e** the both oxidizes at same potential but a significant decrement in the band gap was

observed for **3c**. This indicates that cyano substitution may helpful in preparing low band gap materials.[9]

4.5. Thermal properties

The thermal stability and the decomposition temperatures of the compounds were determined by the thermal gravimetric analysis (TGA) under a nitrogen atmosphere, with a heating rate of 10 °C/ min.

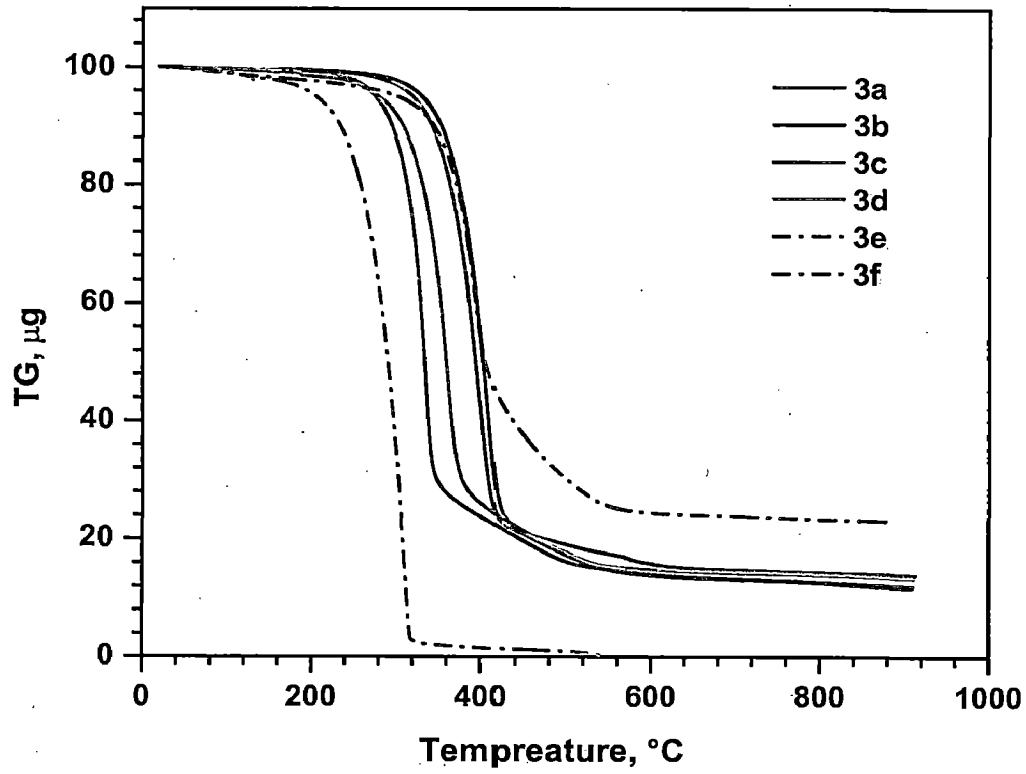

Fig.4.18. Thermogravimetric analysis curve.

The order of decomposition temperatures are found as **3b** > **3c** > **3f** > **3d** > **3a** > **3e**. Since the rigid structure of the planar fused-ring derivatives extends the π conjugation and facilitates the interchain π stacking, this increases the thermal stability, therefore **3b** shows higher thermal stability.

Table 4.4. Thermogravimetric analysis data for the compounds.

Compounds	T onset, ° C	T_d, ° C
3a	275	336
3b	330	409
3c	319	400
3d	279	361
3e	204	311
3f	299	394

As observed from the structure of dyes, **3c** and **3e** have same structural features except the presence of cyano (-CN) group in **3c**, the decomposition temperature for **3c** is higher than **3e**. This may be due to higher bond dissociation energy of C≡N (213 kcal/mol) when compare to C–H (98 kcal/mol) bond.[10] This indicates that the introduction of cyano (-CN) group is helpful to increases the thermal stability of the compounds.[11] As per the decrease in molecular weight thermal decomposition temperature of **3a** is lower among all the compounds. While the introduction of two benzene rings in **3c** makes a star shaped structure that increases its thermal stability.

4.6. Conclusions

The successfully synthesized chalcone derivatives were characterized and analyzed by different spectral techniques. These compounds are orange or red in color and freely soluble in common solvents including dichloromethane, ethylacetate, methanol, acetonitrile and toluene. The dilute solutions of the dyes appear intense yellow. The cyano substituted

chalcones displayed rich optical properties. It is found that nature of donor significantly affects the absorption, electrochemical and thermal properties. Although the absorption spectra are not much influenced by the nature of solvent a significant difference in the emission profile was observed. The incorporation of cyano groups at the vinylene moieties induces red shifts in the absorption and fluorescence spectra of the derivatives, due to the electron-acceptor properties of the cyano groups. On the other hand, the addition of csubstituents causes a strong reduction of fluorescence yields. The low yields are mainly a consequence of nonplanarity caused by steric hindrance, which enables torsional induced nonradiative deactivation. Similarly electrochemical properties were also influenced by the donor strength. The introduction of cyano unit effectively stabilizes the LUMO level and shift the electronic absorption band to the red as long as the molecular planarity is not severely distorted. All the compounds showed moderate thermal stability.

4.7. References

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Chapter 5

Summary

We have successfully developed methodology for the preparation of novel donor-acceptor architecture chalcones containing triarylamine/polyaromatic hydrocarbon donors and cyanovinyl acceptors. The yield of chalcone derivative was 50-90%. The success of the synthesis is attributed to the stoichiometrically controlled condensation reaction, appropriate use of base and presence of electron withdrawing group (-CN) at the aromatic ketone. The structural composition was established without doubt by spectral analysis.

The spectral properties of these molecules in solvents such as toluene, ethylacetate, chloroform, dichloromethane, acetonitrile, and methanol were measured. The nature of the conjugation as well as donor strength is demonstrated to significantly affect the optical, electrochemical and thermal properties of the dyes. The longest wavelength absorption band of cyanovinyl chalcones **3a-d** was in the range of 400-450 nm and did not appear to be influenced by the medium. This suggests a less polar ground state which will be less effectively solvated by polar solvents. The fluorescence of chalcones was red shifted in the range of 470-560 nm and was most intense in chloroform. The fluorescence maximum increases with an increase in solvent polarity. A strong electron withdrawing group cyano group increases the polarity that leads to the quenching of fluorescence in highly polar

solvents such as acetonitrile and methanol. The quantum yield of chalcone derivatives without cyano group **3e** is higher than the chalcone derivatives having cyanovinyl substitution. The Stokes shift is highest for **3e** in all the solvents, this indices that introduction of cyano substitution leads to rigidity in the molecule and favors for lesser aggregation in excited state.

All the compounds displayed an irreversible oxidation peak in cyclic voltammogram. This peak underwent shifts corresponding to electron donating strength of donor unit present in the chalcone derivatives. The introduction of cyano unit seems to stabilize the LUMO and make these compounds to be useful as low band gap materials. The highest thermal stability was observed for **3b** and lowest is for chalcone derivative (**3e**) without cyano substitution.

In outlook we believe that this novel class of cyanovinyl substituted chalcone derivatives can lead to potential design of optical sensor for probing the acivity of medium and in the presence of metal cation by the introduction of 2-pyridyl/thiophene/arylamine in the chemical structure. Since the biological activity of such cyanovinyl substituted chalcones are not known therefore a comparative study with other known chalcones having same structure scaffold can lead to new possibilities for drug designing in the field of medicinal chemistry.

Supporting Information

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Fig.S3.	^{1}H NMR spectra of **3b** recorded in $CDCl_3$.	S4
Fig.S4.	^{13}C NMR spectra of **3b** recorded in $CDCl_3$.	S5
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Fig.S6.	^{13}C NMR spectra of **3c** recorded in $CDCl_3$.	S7
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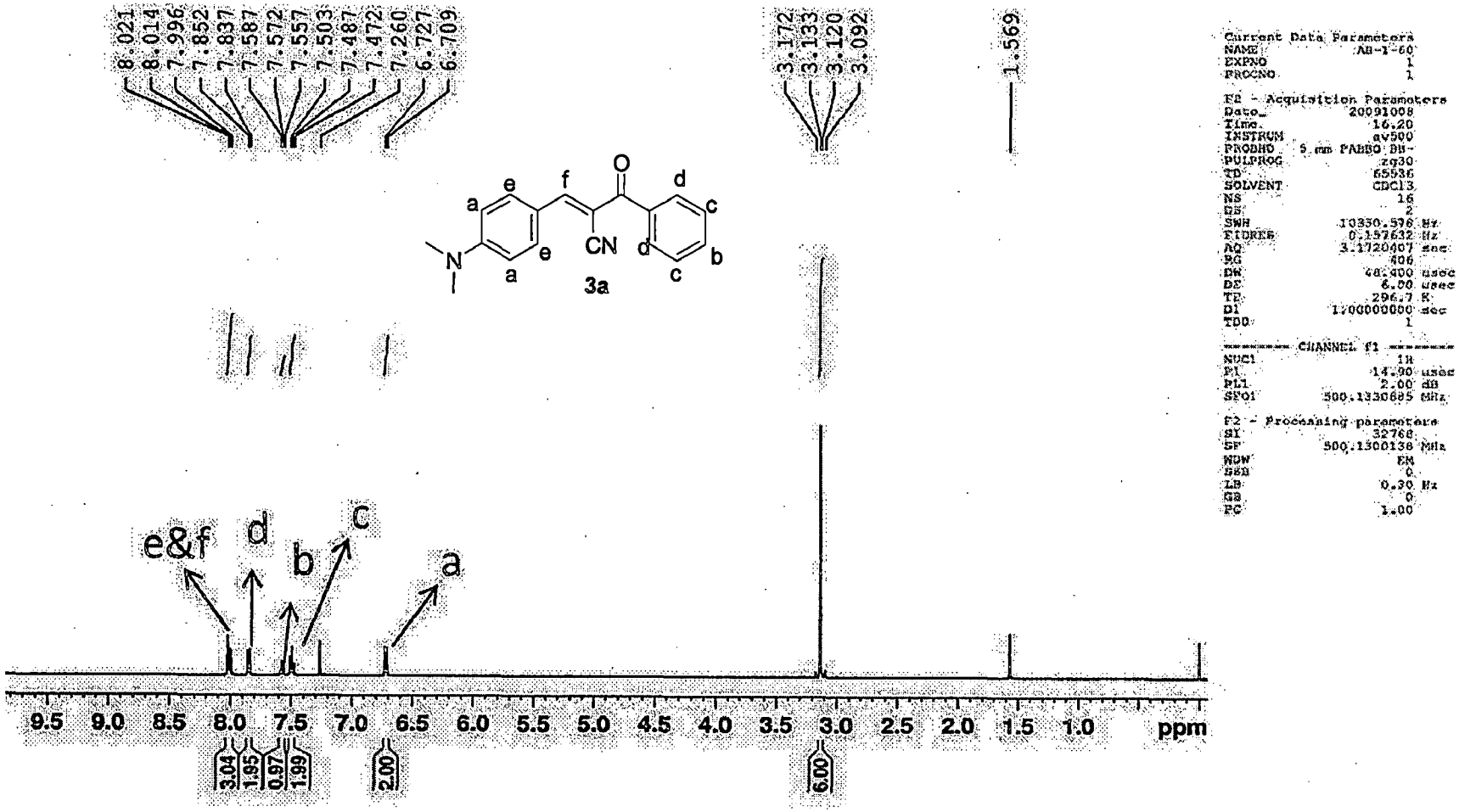

Fig.S1. ^{1}H NMR spectra of **3a** recorded in $CDCl_3$.

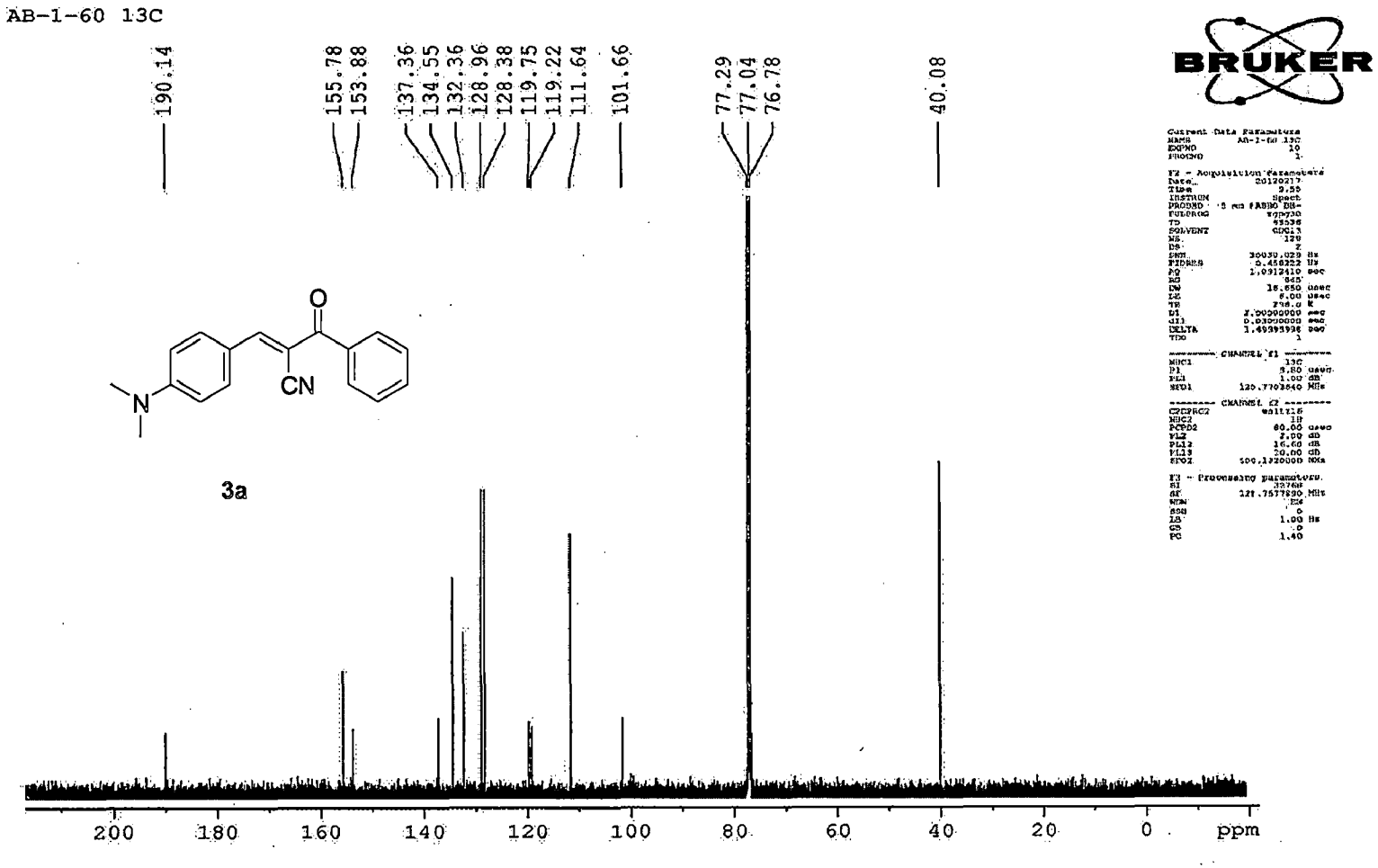

Fig.S2. ^{13}C NMR spectra of **3a** recorded in $CDCl_3$.

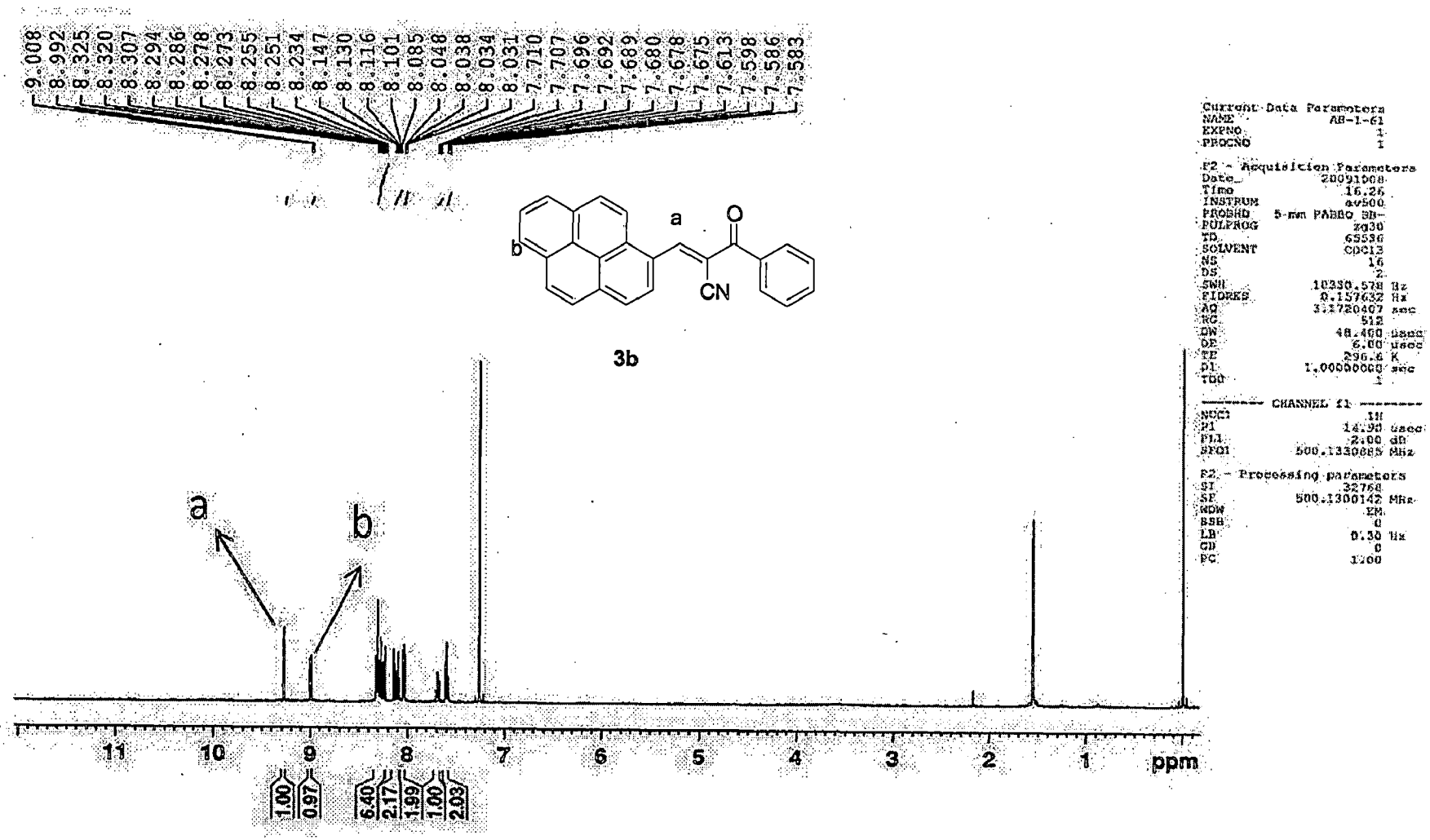

Fig.S3. ^{1}H NMR spectra of **3b** recorded in $CDCl_3$.

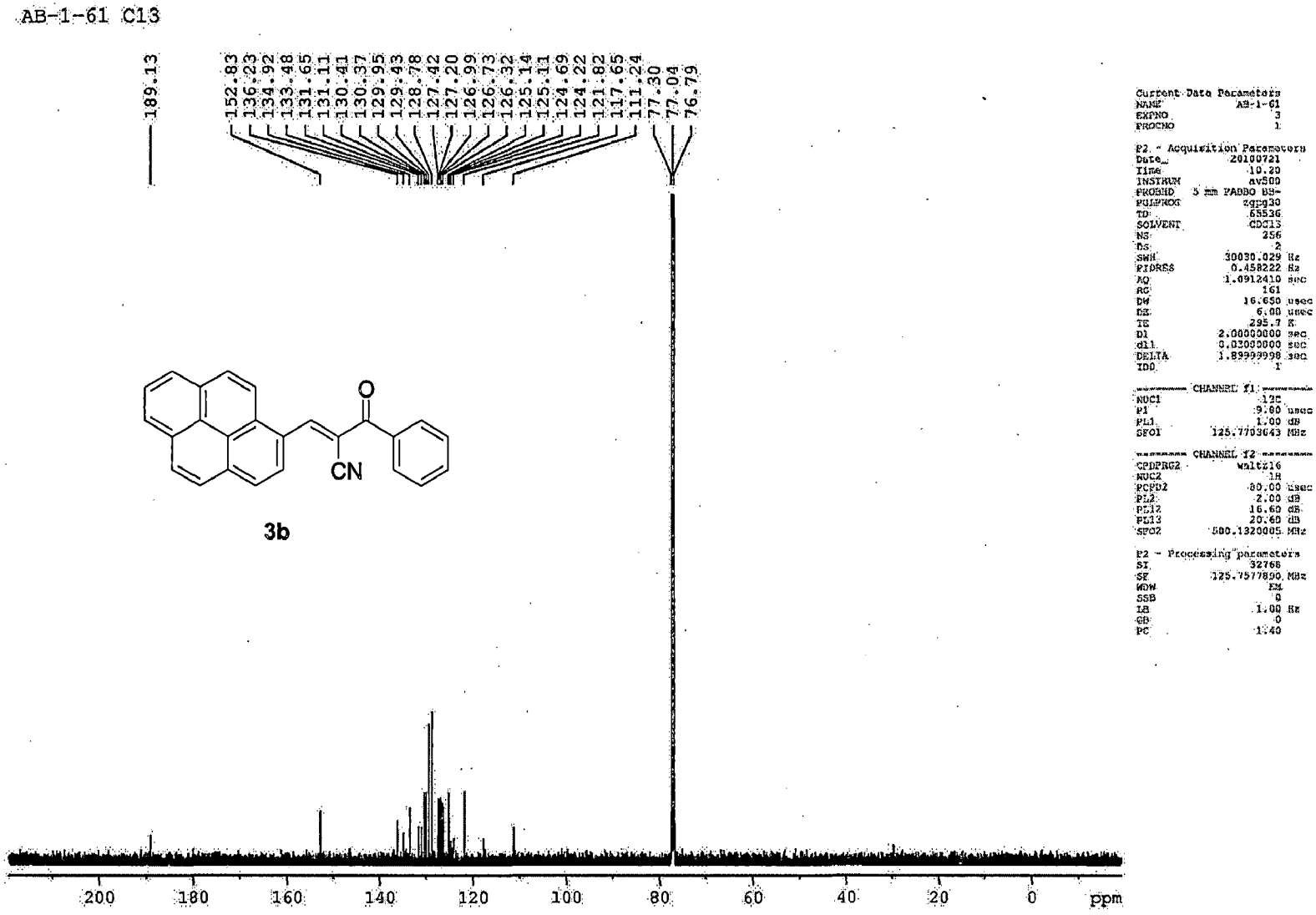

Fig.S4. ^{13}C NMR spectra of **3b** recorded in $CDCl_3$.

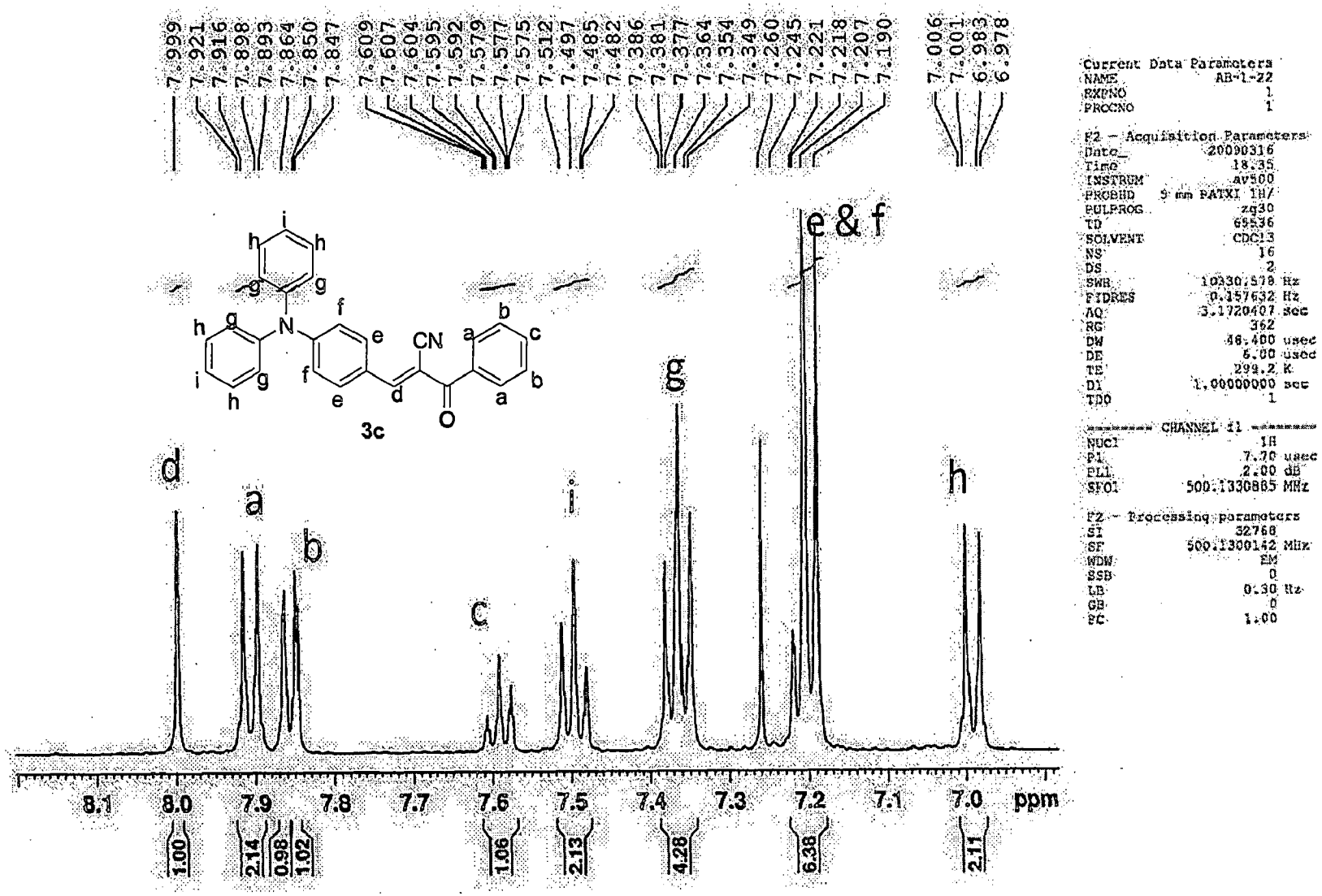

Fig.S5. ^{1}H NMR spectra of 3c recorded in $CDCl_3$.

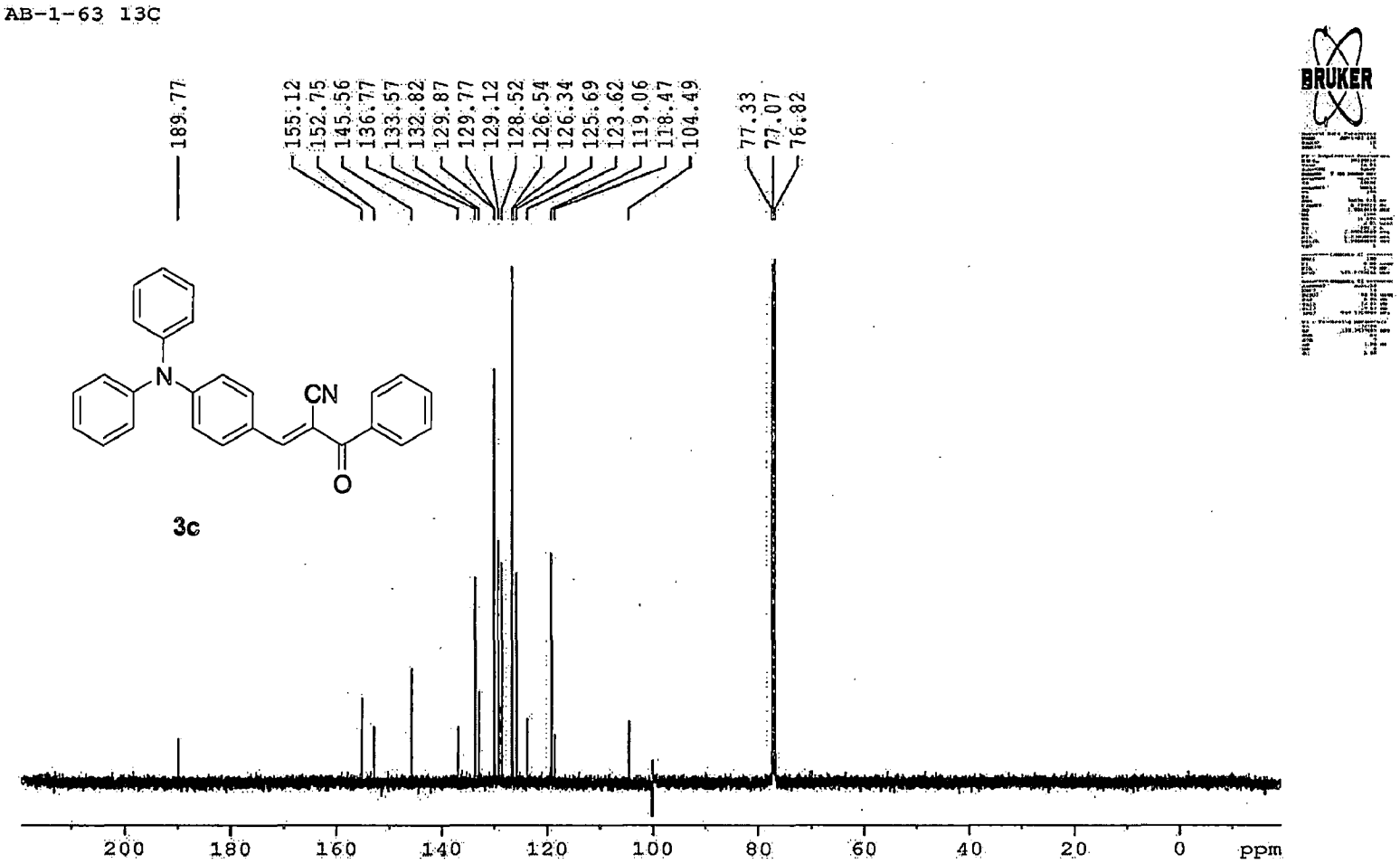

Fig.S6. ^{13}C NMR spectra of **3c** recorded in $CDCl_3$.

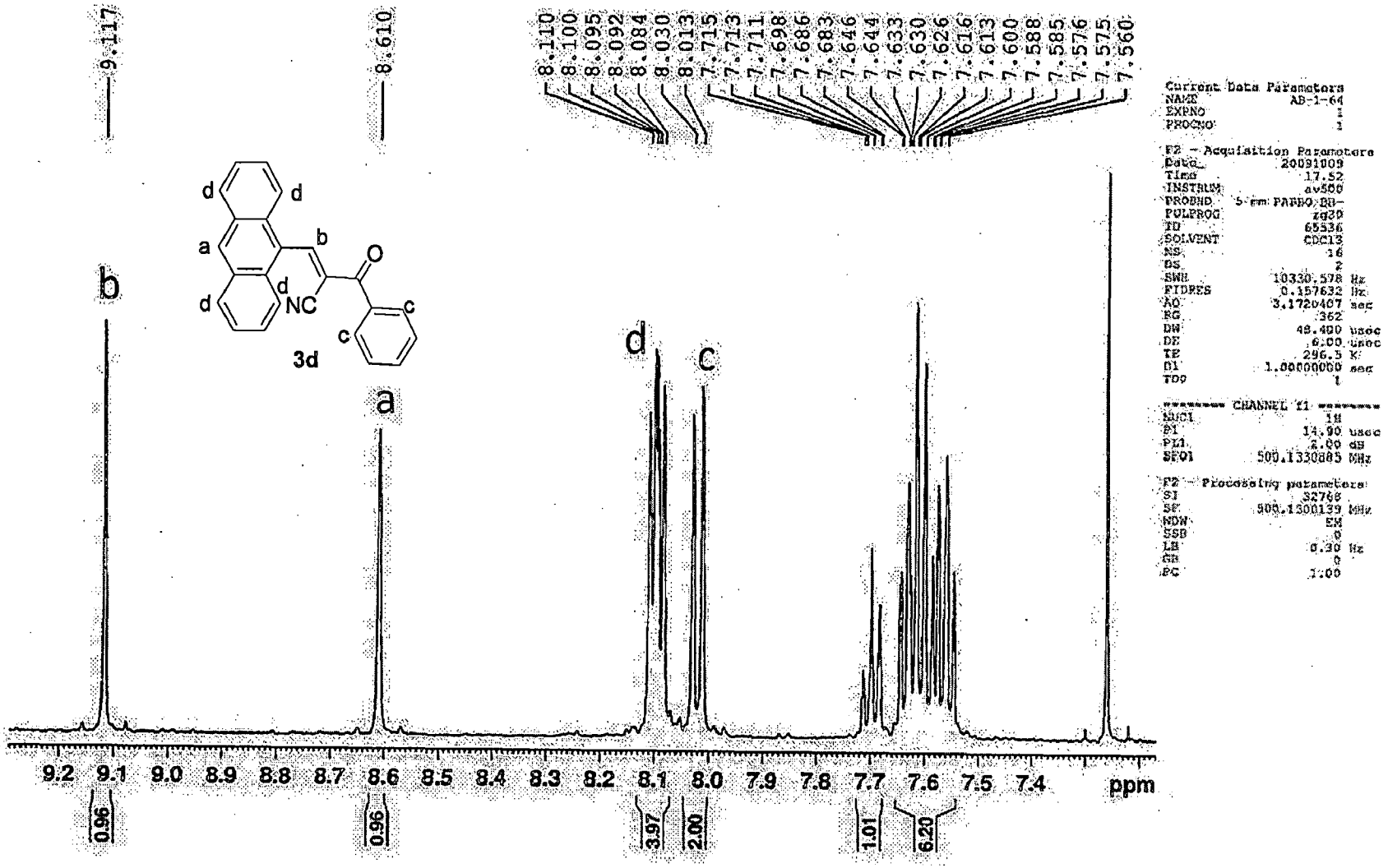

Fig.S7. ^{1}H NMR spectra of 3d recorded in $CDCl_3$.

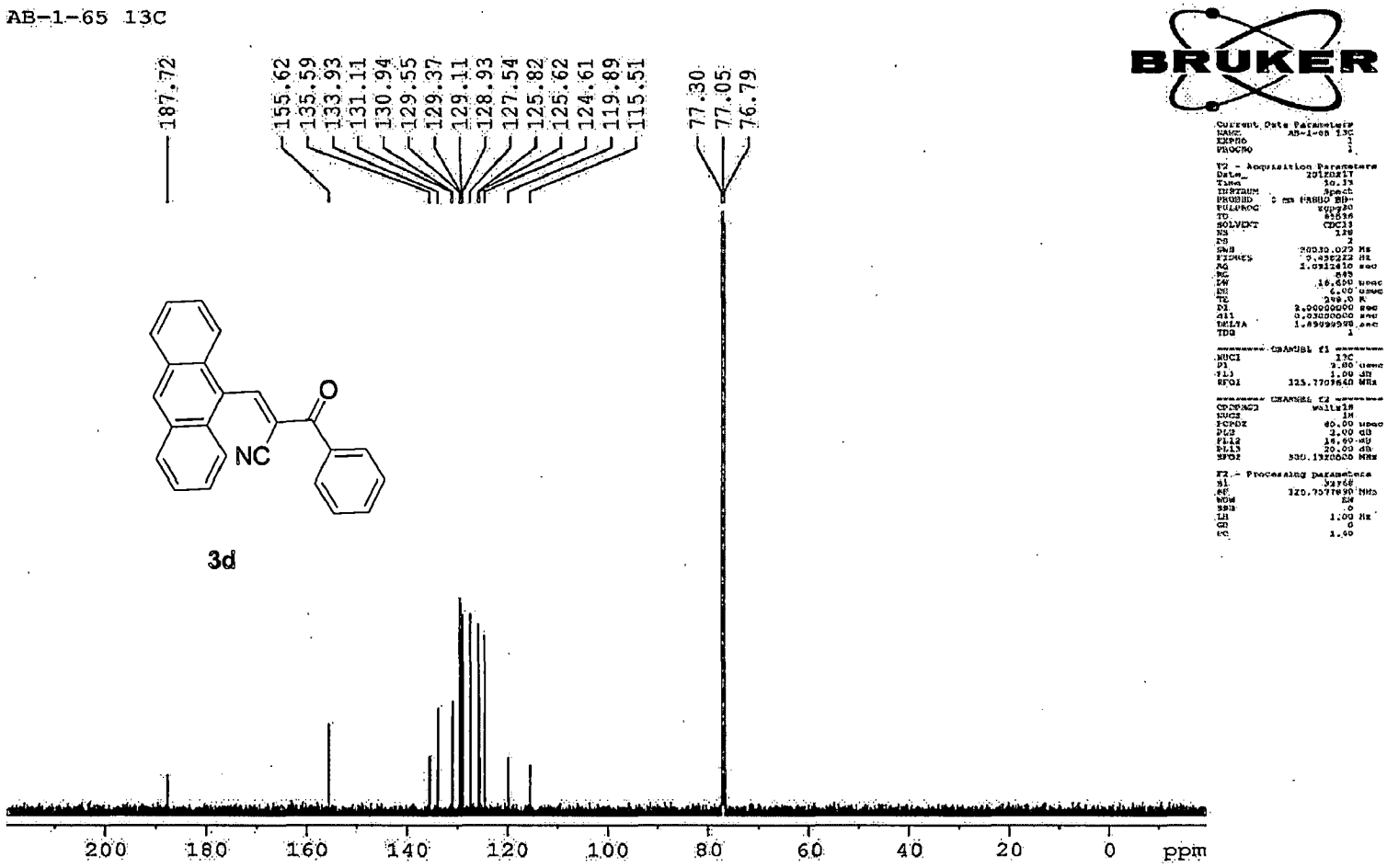

Fig.S8. ^{13}C NMR spectra of **3d** recorded in $CDCl_3$.

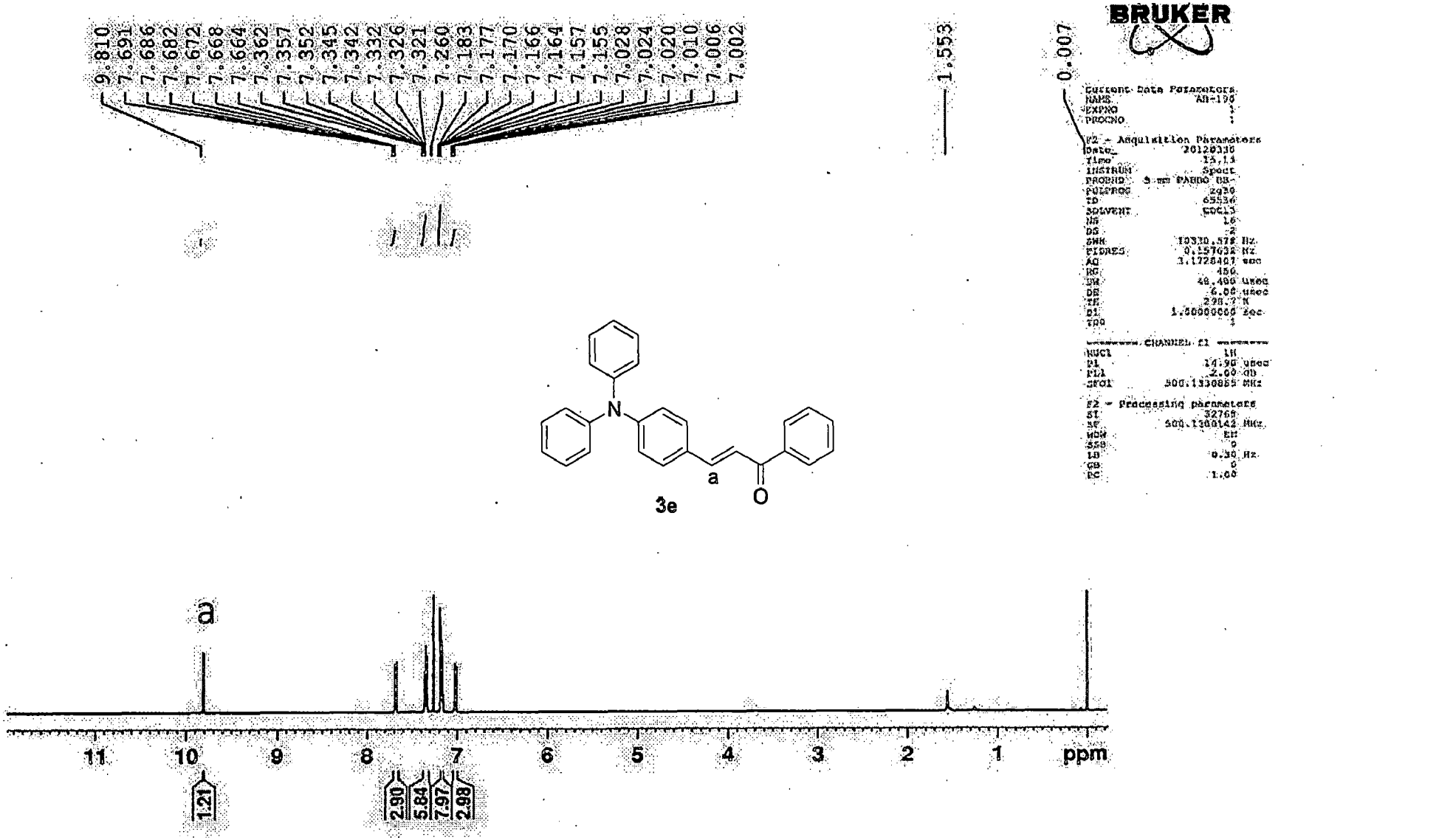

Fig.S9. ^{1}H NMR spectra of **3e** recorded in $CDCl_3$.

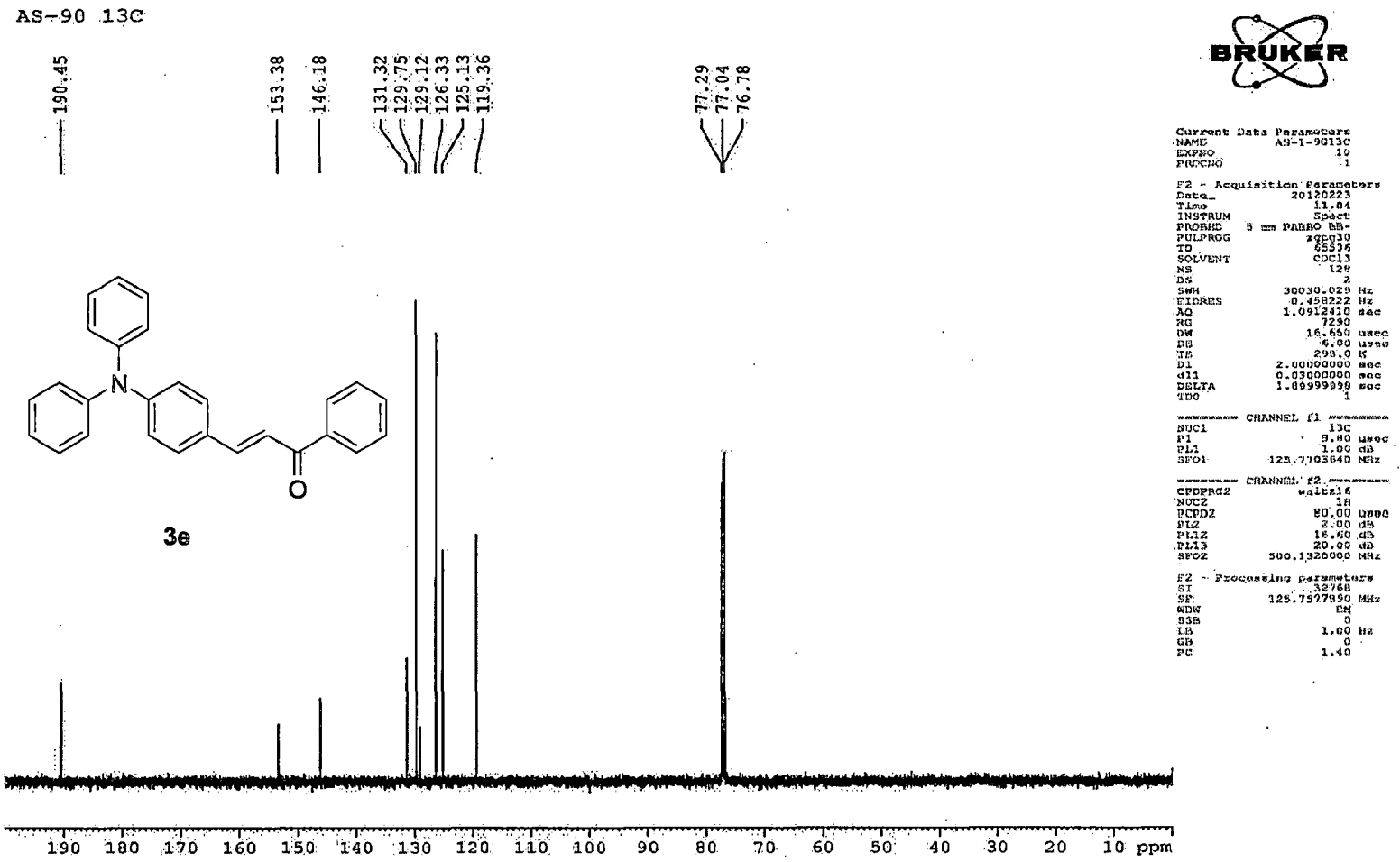

Fig.S10. ^{13}C NMR spectra of **3e** recorded in $CDCl_3$.

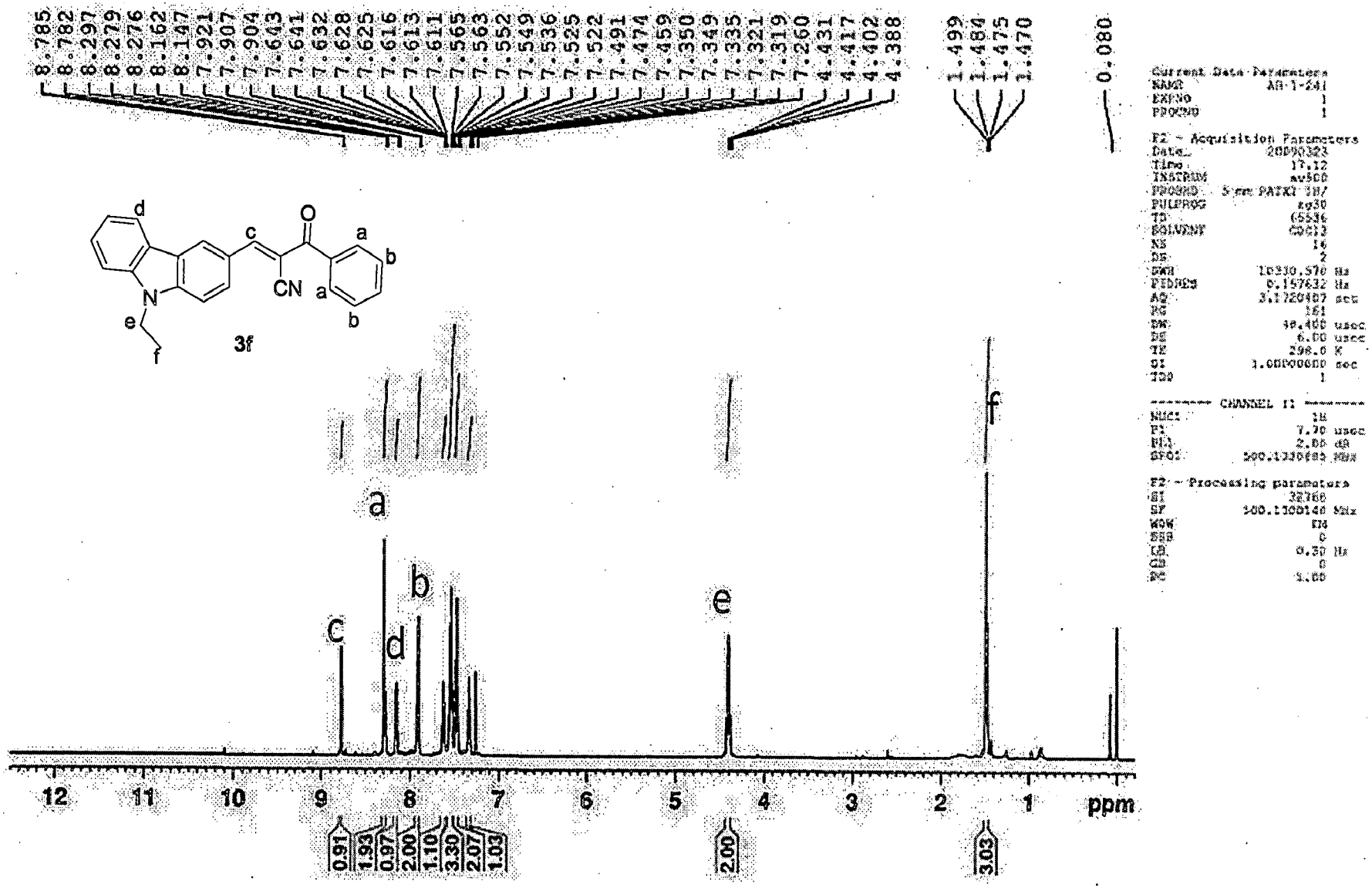

Fig.S11. ^{1}H NMR spectra of **3f** recorded in $CDCl_3$.

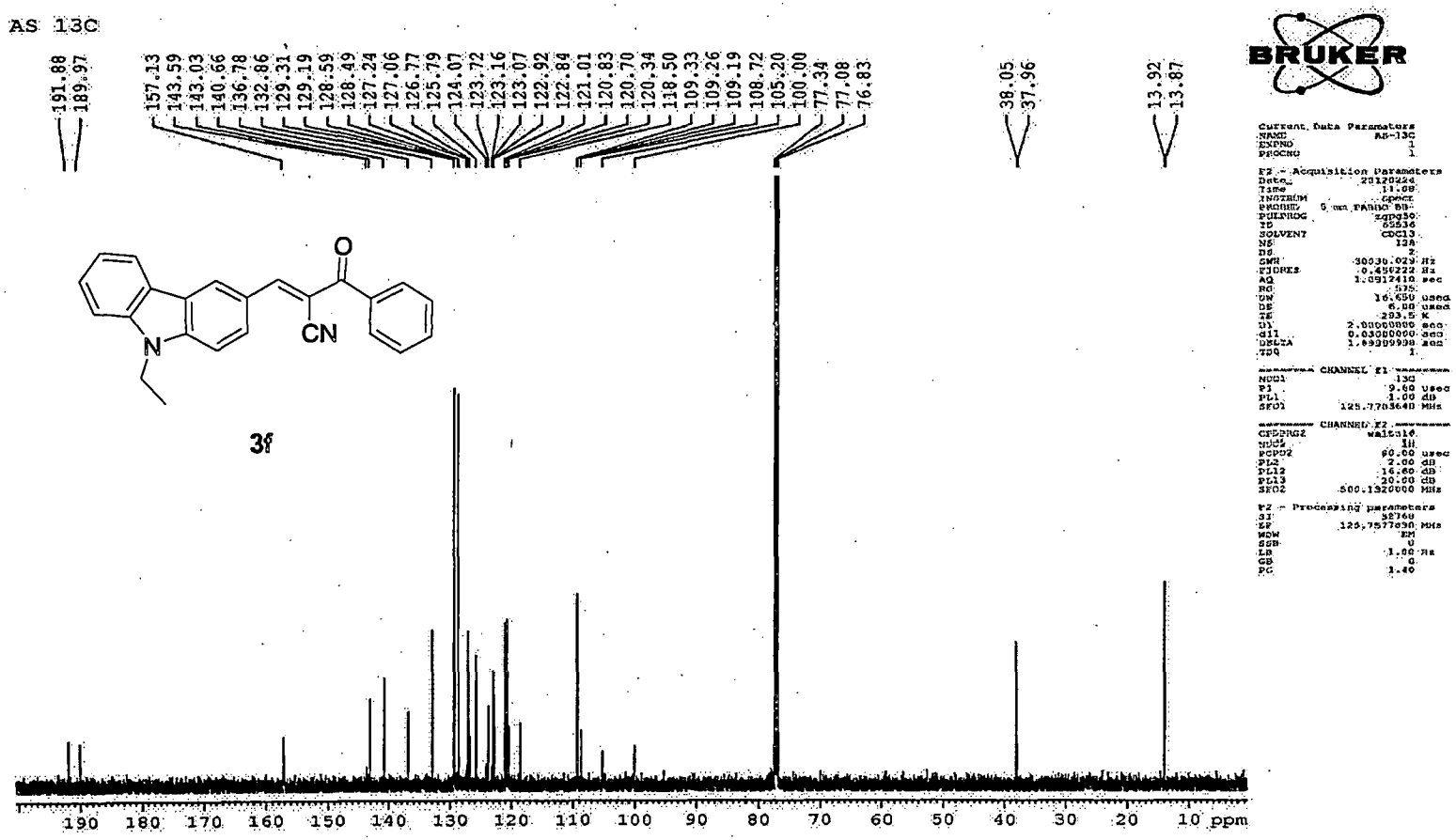

Fig.S12. ^{13}C NMR spectra of **3f** recorded in $CDCl_3$.

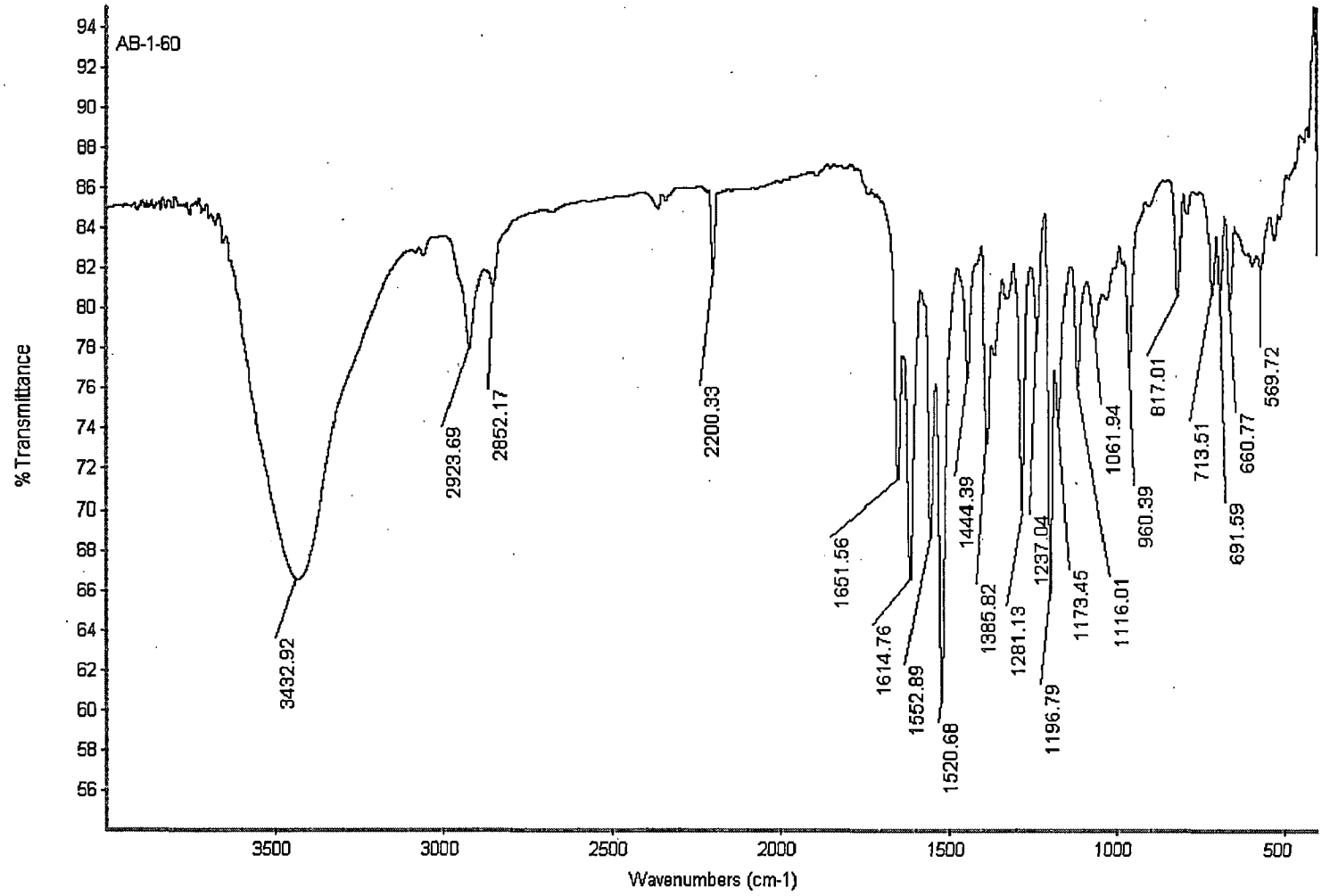

Fig.S13. IR spectrum of **3a**.

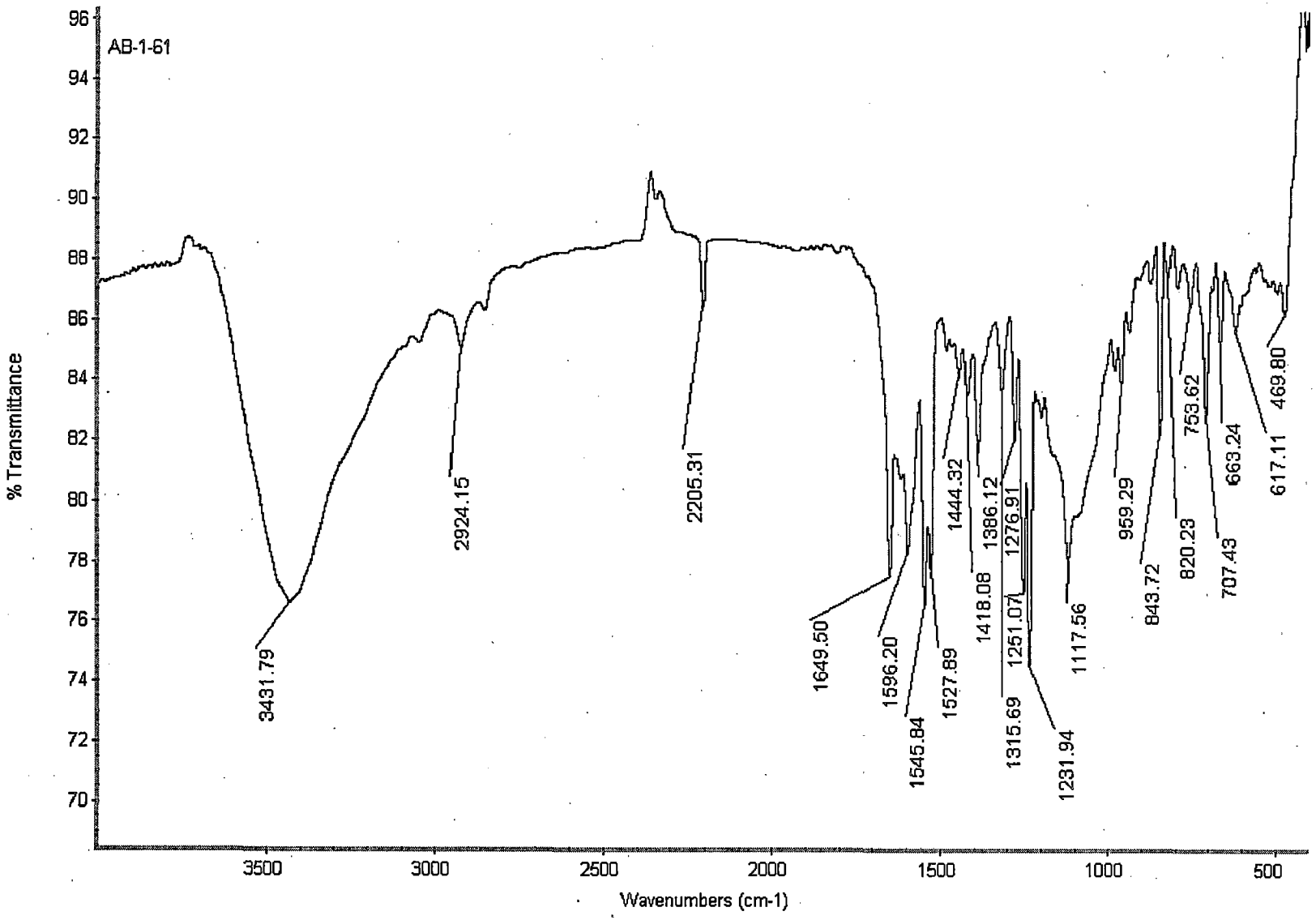

Fig.S14. IR spectrum of **3b**.

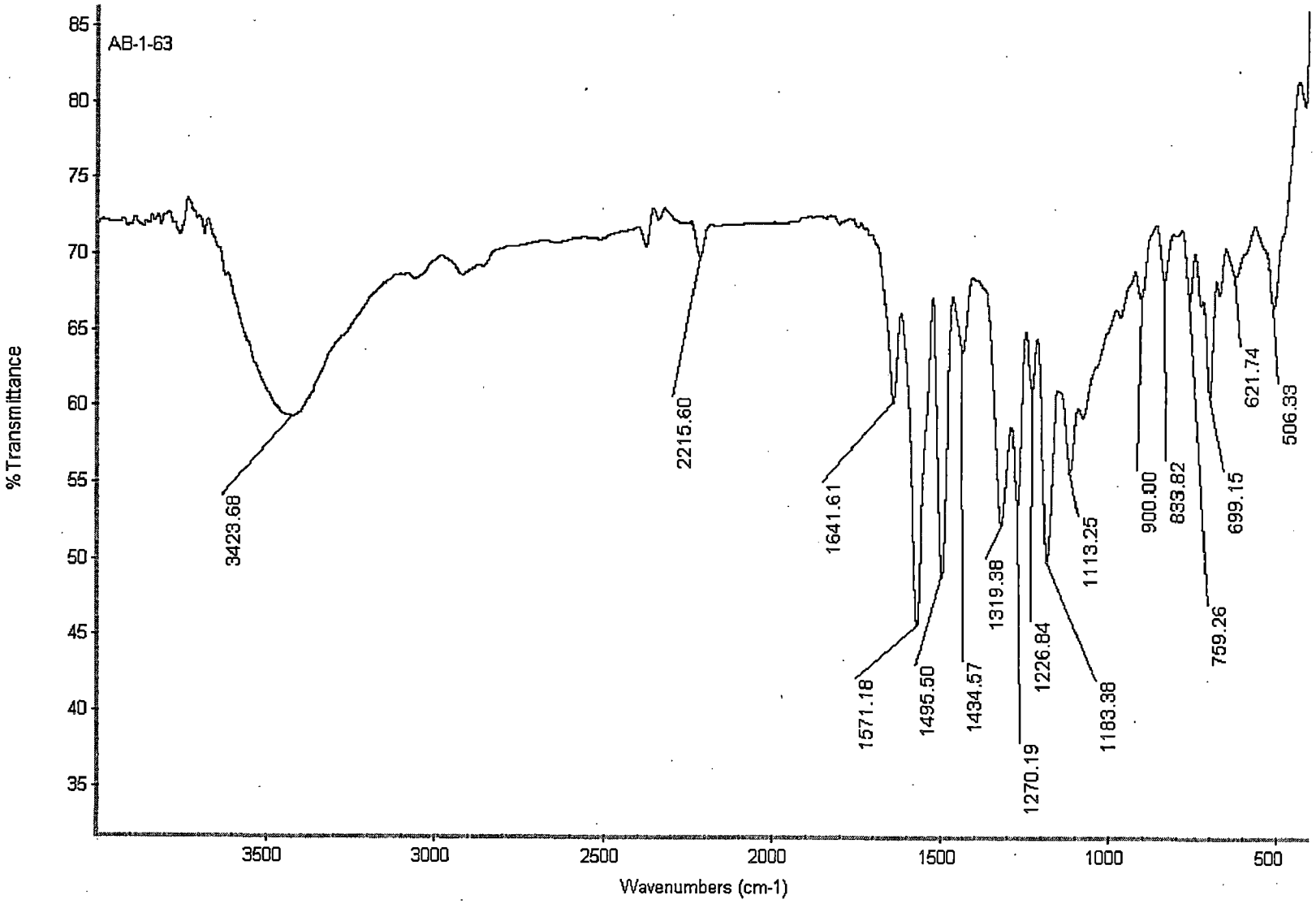

Fig.S15. IR spectrum of **3c**.

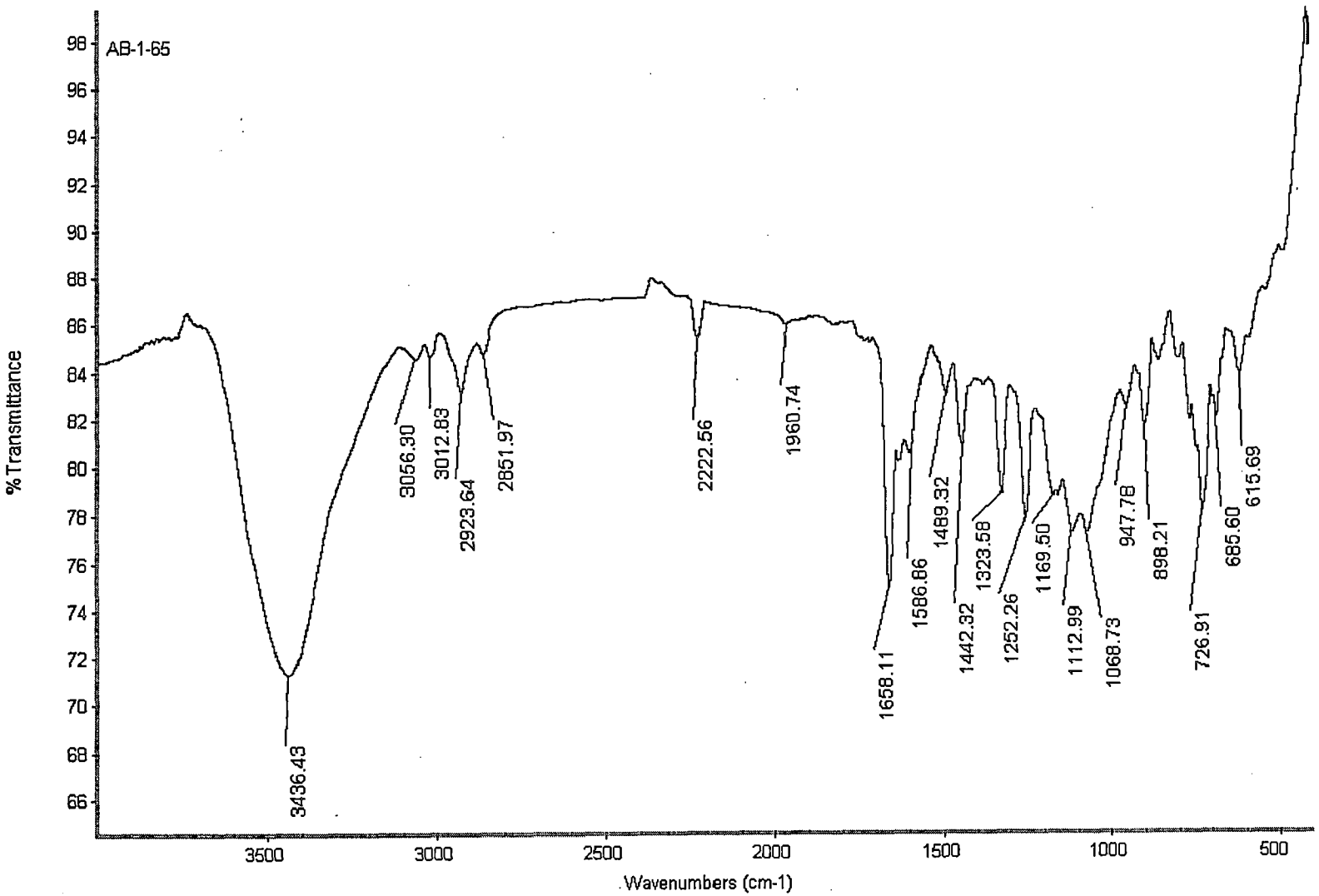

Fig.S16. IR spectrum of **3d**.

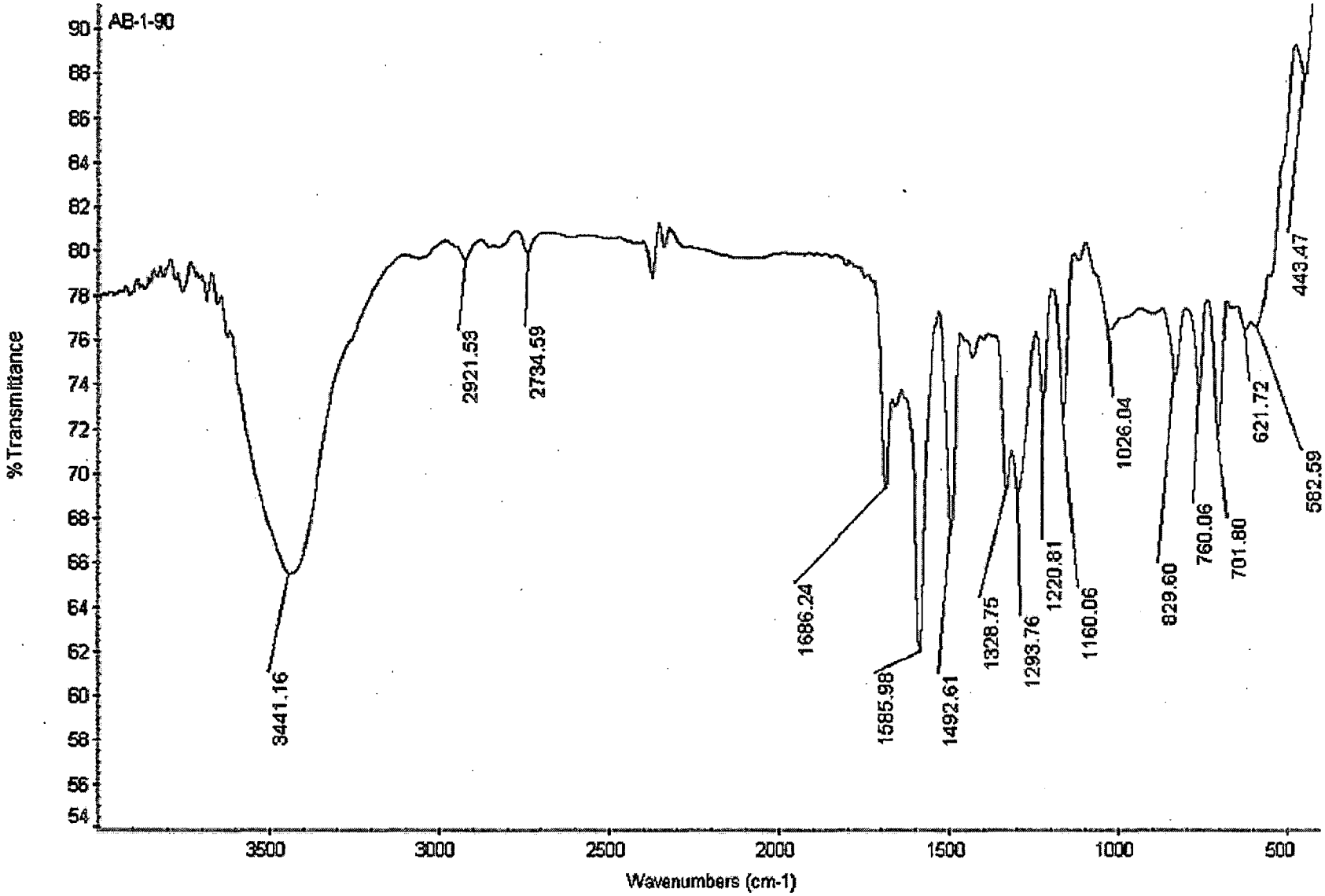

Fig.S17. IR spectrum of 3e.

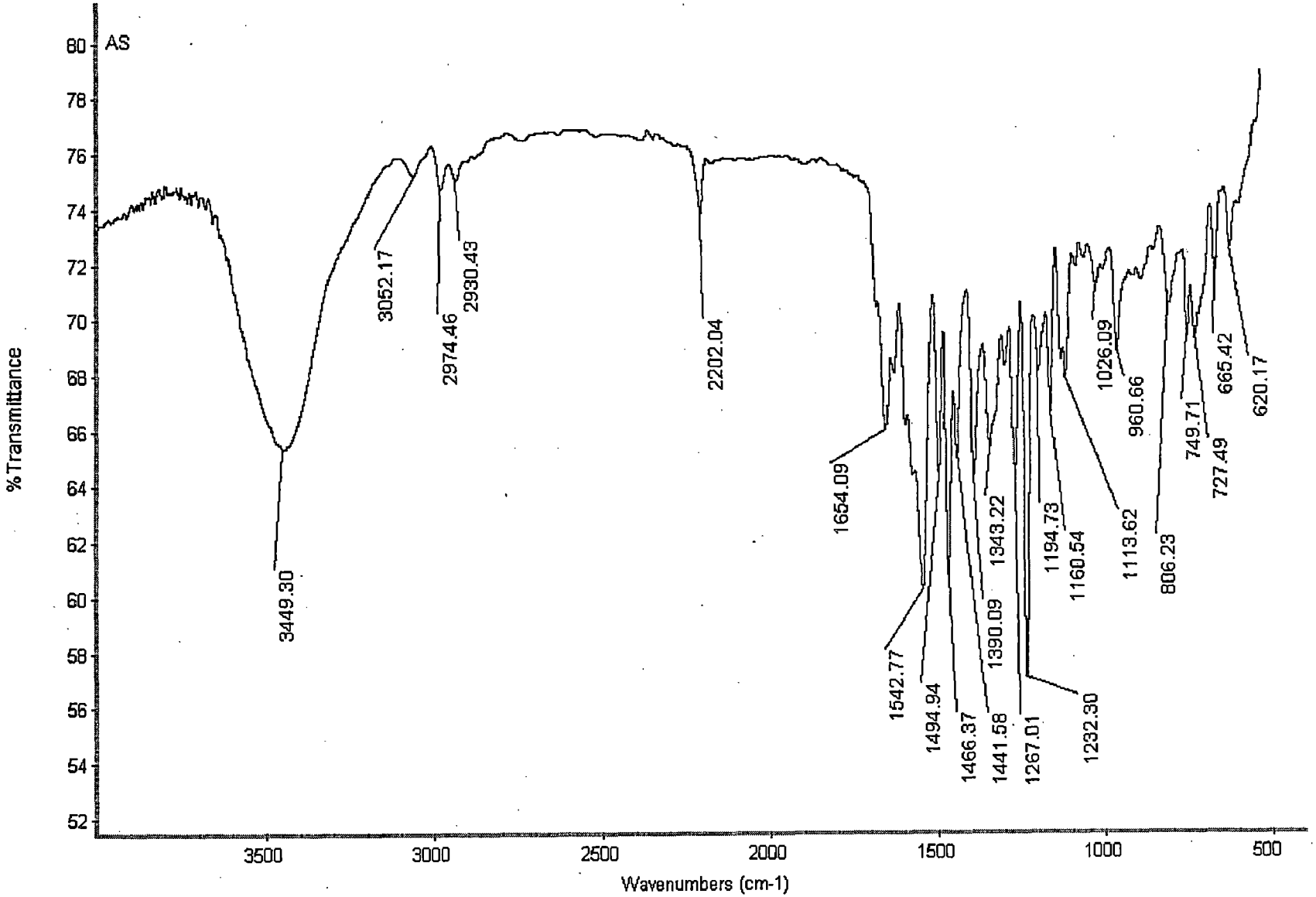

Fig.S18. IR spectrum of **3f**.

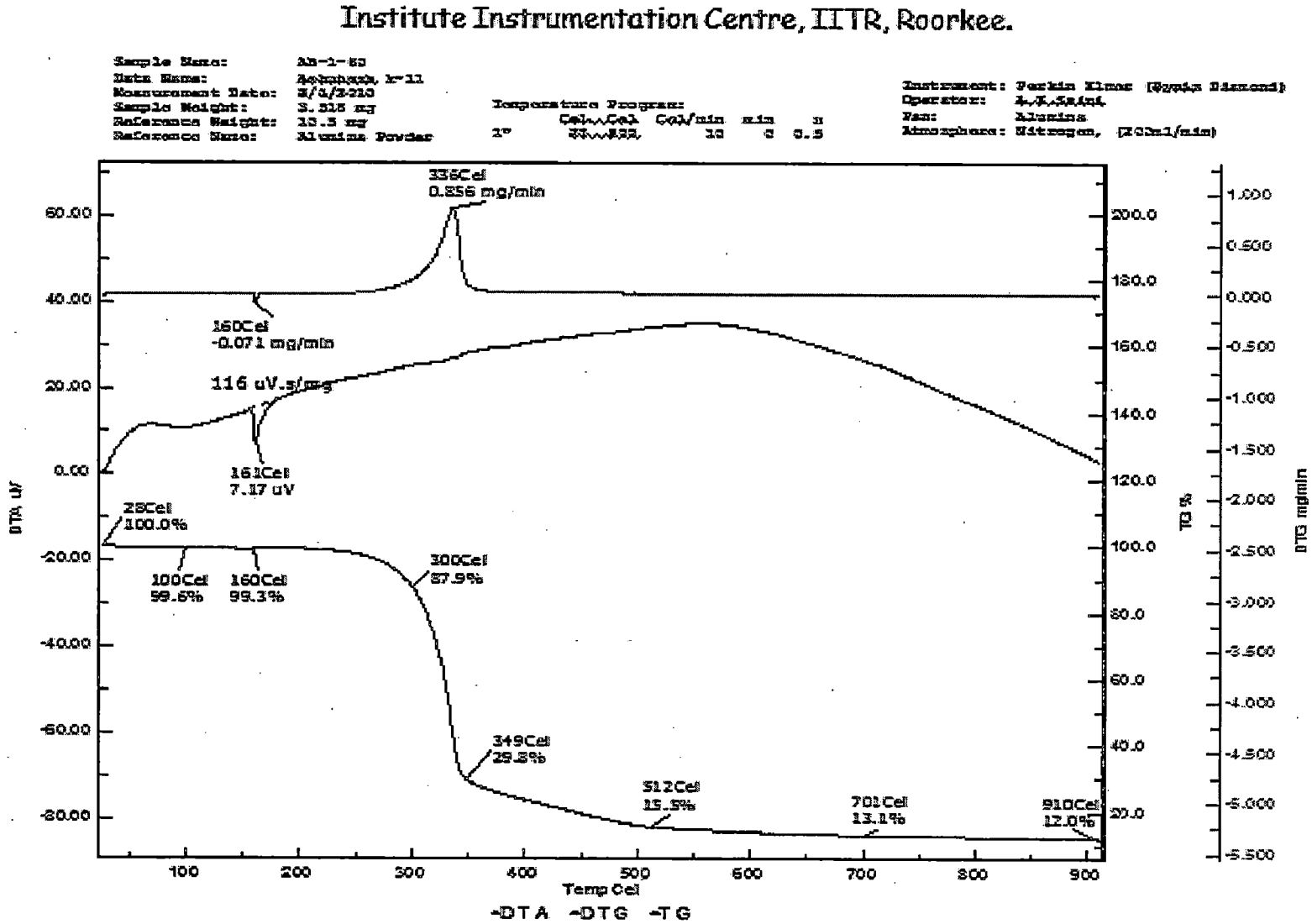

Fig.S19. TGA curve for **3a.**

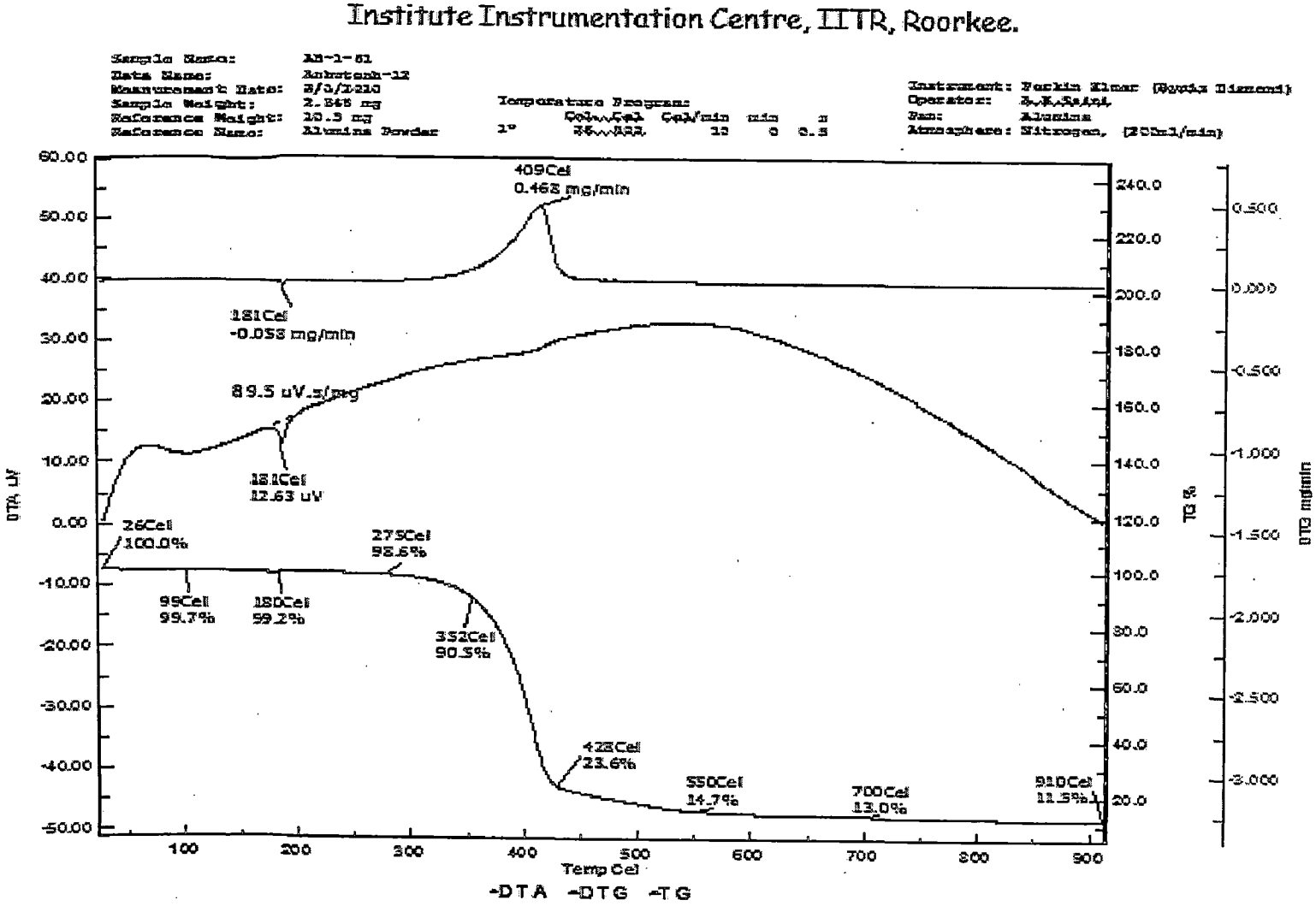

Fig.S20. TGA curve for **3b**.

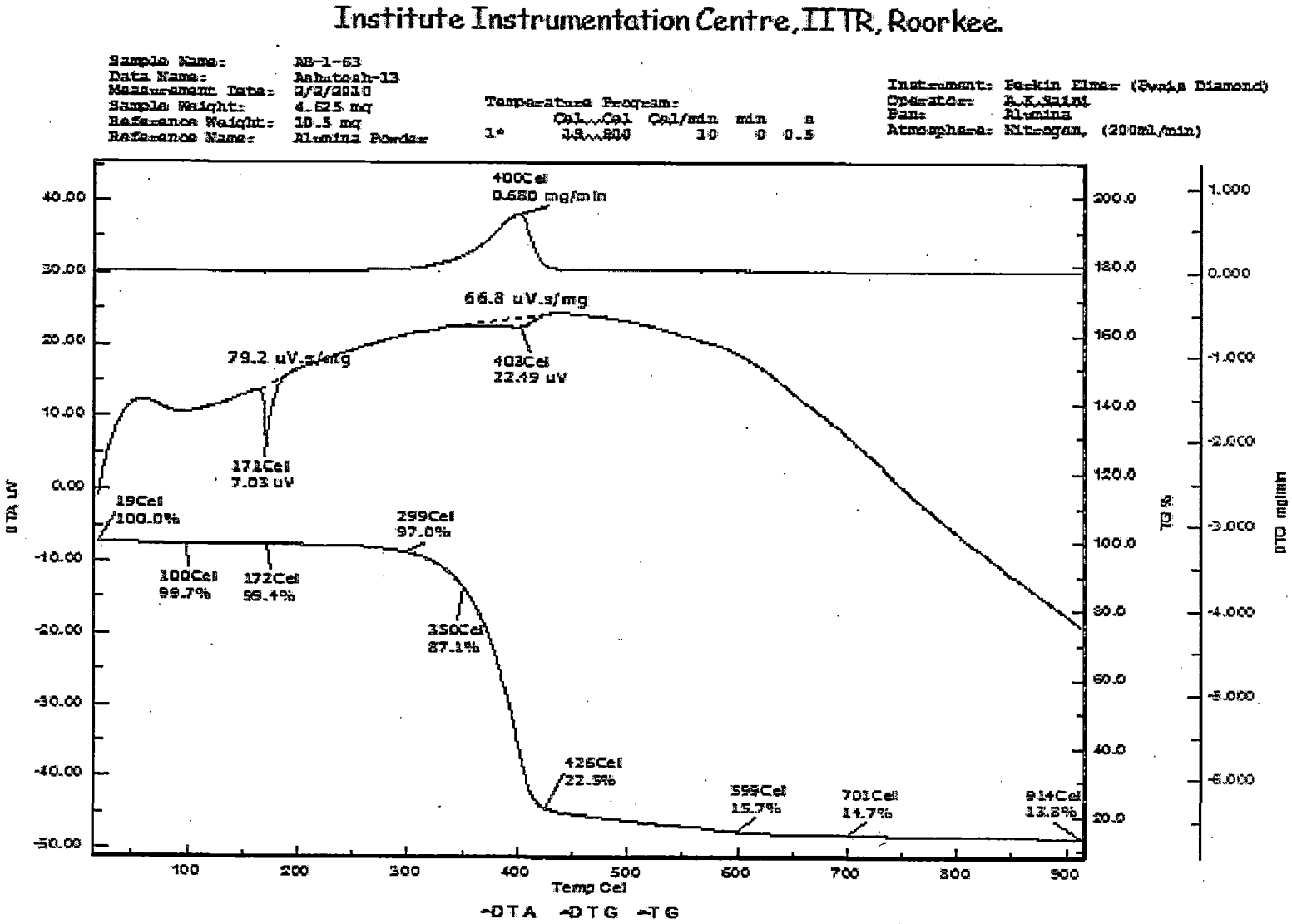

Fig.S21. TGA curve for **3c.**

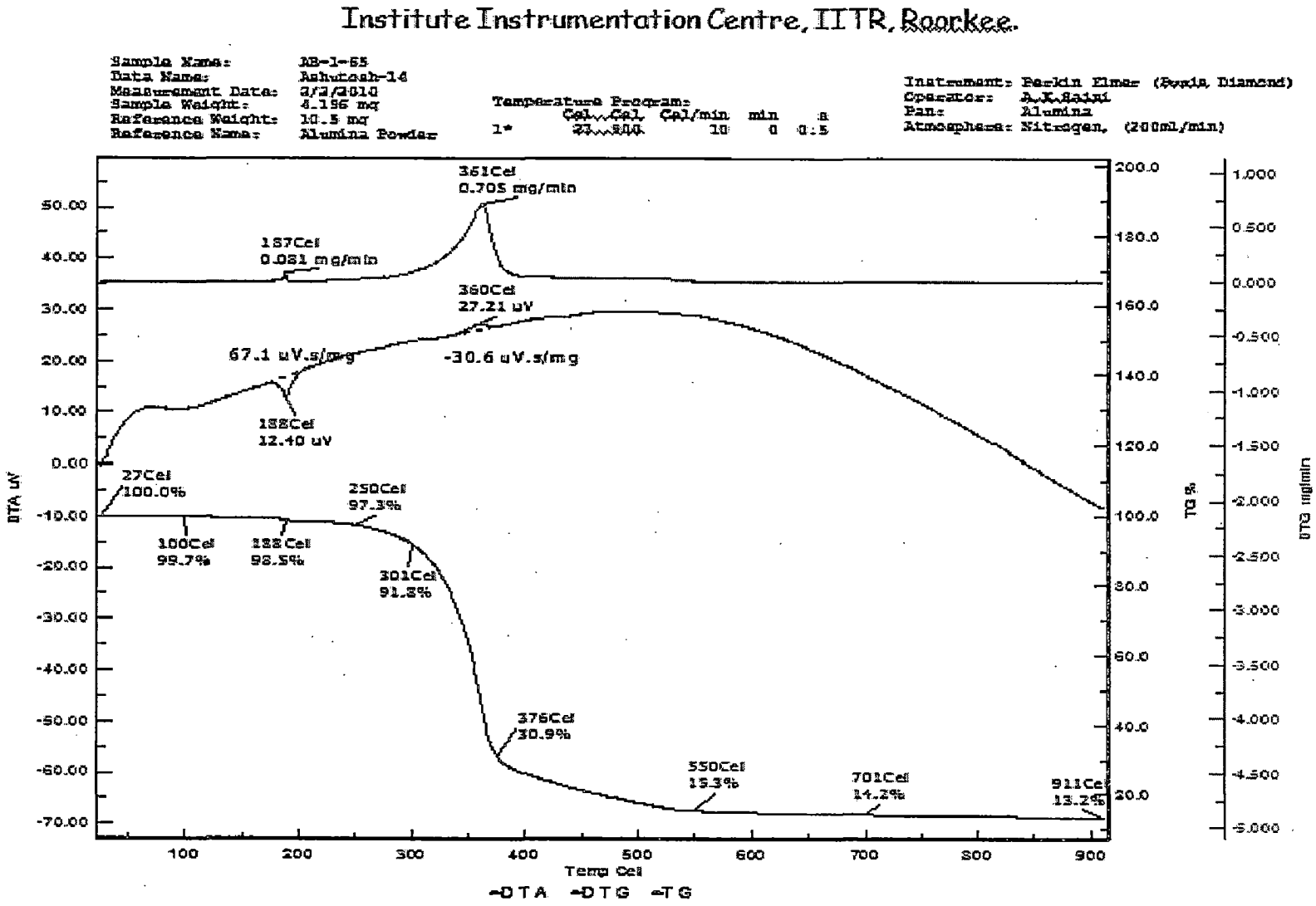

Fig.S22. TGA curve for **3d.**

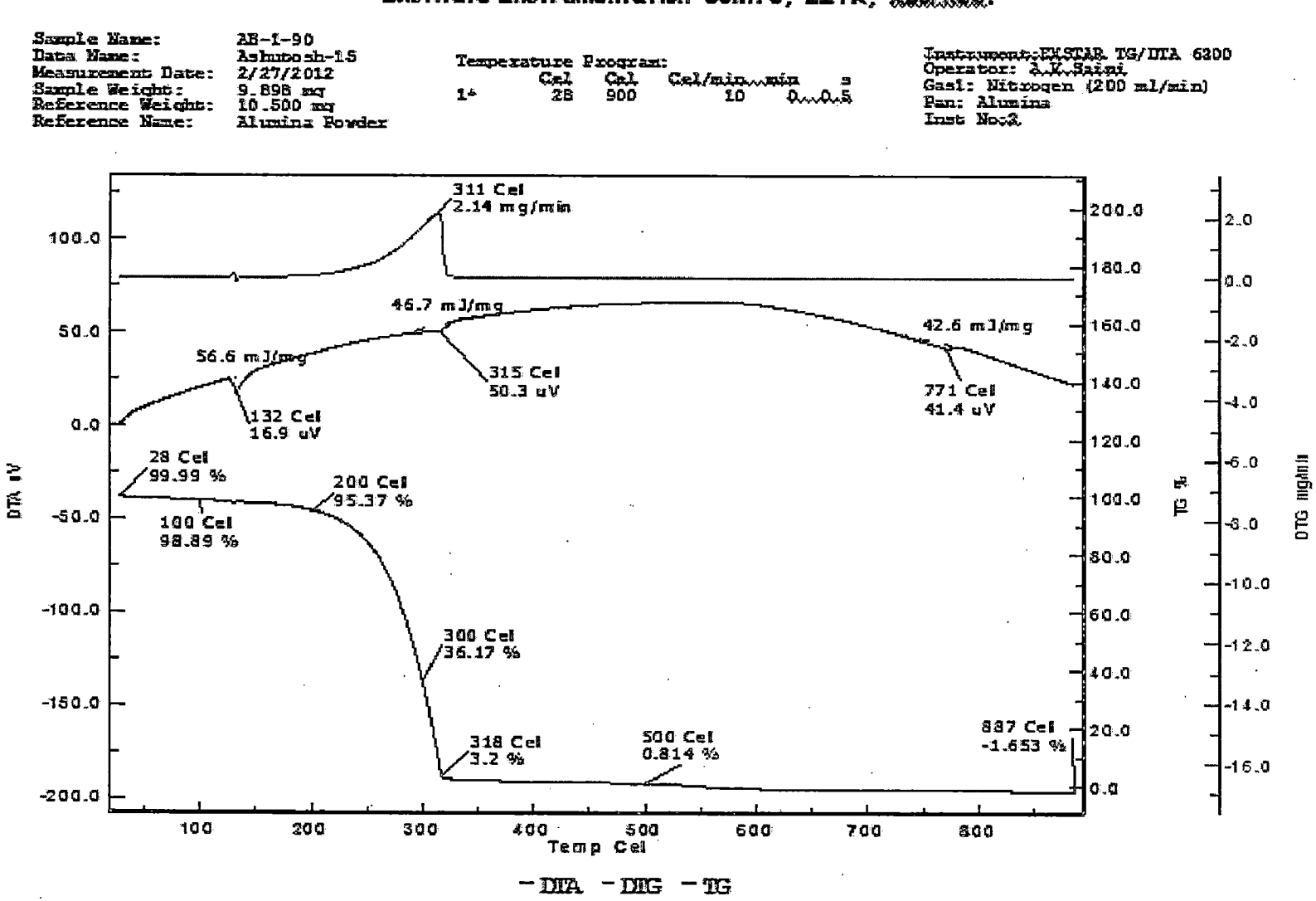

Fig.S23. TGA curve for 3e.