Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(22): 50-71
(http://www.derpharmachemica.com/archive.html)

Efficient Synthesis of Pharmaceutically Important Intermediates via Knoevenagel, Aldol Type Condensation by Using Aqueous Extract of *Acacia concinna* pods as a Green Chemistry Catalyst Approach

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ABSTRACT

The employment of green chemistry technique is significantly reducing chemical waste and reaction time has been proven in several organic synthesis and chemical transformation. Synthesis of pharmaceutically important intermediates via knoevenagel and aldol type condensation of substituted aromatic aldehyde with active methylene compounds has been achieved by using aqueous extract of Acacia concinna pods as a green surfactant type catalyst. The low cost, easy availability of the catalyst and simple reaction conditions suggest the possible use of present method for large scale preparations. Moreover, fruits are inexpensive and easily available in the market, and its juice can be extracted easily which can be used as catalyst in the organic transformations. Structures of the compounds were confirmed satisfactorily by spectral analyses such as FT-IR, ^{1}H, ^{13}C-NMR, and Mass.

Keywords: Fruit juice, *Acacia concinna* pods, Condensation, Natural catalyst

The role of naturally available fruit juice in organic synthesis has attracted the interest of scientist, essentially from the view of green chemistry. Development of new non-hazardous synthetic methodologies for various organic reactions is one of the latest challenges to the organic chemists. *Acacia concinna* juice as natural catalyst, due to its acidic nature has been found to be a suitable catalyst for various homogeneous acid catalysts. The green chemistry interest of fruit juice in organic synthesis is mainly due to their acidic nature, enzymatic activity, inexpensive, commercial availability, eco-friendly and economic processes.

In addition, novel catalytic procedures are necessary to produce the emerging classes of organic compounds that are becoming the targets of molecular and biomedical research. Several types of substances such as fruit juice, enzymes, surfactants, ionic liquids, clays and supercritical solvents are now widely recognized as practical alternatives to traditional organic synthesis, and as convenient solutions to certain intractable synthetic problems. This is due to problems associated with prevailing catalysts like hazardous nature, expensive, unsafe to handle, difficult to work up, requirement of hazardous organic solvents and elevated temperature conditions, and above all, with their adverse effects on environment. To overcome these disadvantages, the synthetic transformations using these materials are more efficient and generate less waste than the conventional chemical methods. Nowadays, many organic transformations have been carried out in water [1,2]. It is universal solvent because it is easily available, inexpensive, nontoxic, safer, and environmentally benign. The applications of an aqueous extract of different fruit juice have witnessed a rapid development. This growing interest in fruit juice is mainly because of its biocatalysts, environmentally benign character, non-hazardous and cost effectiveness.

In literature, numbers of organic reactions are reported in which natural catalysts like fruit juice; surfactants, clay, and animal bone are reported. Due to acidic nature aqueous fruit juice like lemon [3-6], pineapple [7,8], *Tamarindus indica* [9,10], Star fruit Juice [11], Coconut [12], Peanut shell [13] and *A. concinna* [14,15], fruits have been found to be a suitable replacement for various homogeneous acid catalysts and also clay [16,17], natural phosphates [18-20], animal bone [21] and reaction without solvent as a green chemistry approach [22].

Shikakai literature gives as 'fruit for the hair', wherein meaning of Shika is 'Hair' & Kai means 'Fruit'. Shikakai belongs to climbing shrub native to Asia, common in the warm plains of central and south India. The plants are medium fast growing and which is bushy cum creeper. These plants having curvy thorns, once the plants are developed big wild animals like elephant cannot able to cross. The benefits of Shikakai (*A. concinna*) are extracted from the pods of the shrub found in abundance in the hot, dry climates of Central Asia and the Far East. The pods contain rich in saponins which are foam forming substances, dried pods are powdered, which is considered as a superior cleanser for 'lustrous long hair' and has been reported as ' hair growth promoter', preventing dandruff and premature graying of hair. Leaves are used to treat against malarial fever and decoction of the pods for to relieve biliousness and acts as a purgative. An ointment, prepared from the ground pods, is good for skin diseases, use in herbal treatment for curing black fever (Visceral Leishmaniasis) and malarial fever, also advantageous in curing psoriasis (genetic disease) and the spreadable diseases like eczema. It provides a relief in scabies, rashes, cuts, and bruises and cures them. It is

effectual in curing oral ailments [23]. Growing a diversity of plants emulating woodland, we can grow fruit and nut trees, under- planted with smaller trees and shrubs, herbaceous, ground cover and climbing plants. This way it is possible to produce fruits, nuts, seeds, leaves and roots throughout the year. Unlike the majority of cultivated food plants these have not been selectively bred to increase size of yield, reduce bitterness or increase sweetness, yet many of them are delicious and highly nutritious.

In recent years, organic research is mainly focused on the development of greener and ecofriendly processes which involve in the use of alternative reaction media to replace toxic and expensive catalysts and hazardous solvents like benzene, methanol, commonly used in organic synthesis. Naturally occurring fruit juice are used as a green catalyst in organic synthesis as homogeneous or heterogeneous catalysts for various selective transformations of simple and complex molecules.

Being a part of heterocyclic chemistry indole derivatives have been a topic of substantial research interest and one of the most active areas due to their natural occurrence and pharmacological activities. Even though indole moiety is very small but is weight aged by scientists because of the diverse biological activities by not only indole but its various substituted derivatives as well [24-28]. Substituted indoles have been referred as advantaged structures since they are capable of binding to various receptors with high affinity. Due to wide range of biological and pharmacological activities of indole skeleton works like most attractive frameworks, physiologically important nucleus is abundantly found in therapeutic agents as well as in natural products which exhibit a broad range of applications in the pharmaceutical, perfume and cosmetic industries (Figure 1). Many synthetic and natural indoline derivatives (Figure 2) have shown interesting properties such as anticancer, antihypertensive, antidepressant, antipsychotic, Nonsteroidal Anti-inflammatory Drugs ($NSAID_S$), antiemetic, analgesic, antiasthmatic, antiviral, antiarrhythmic, b-blocker, toxins, inhibitor of RNA polymerase-11 and sexual dysfunction [26-29]. Many well-known marketed drugs such as vincamine, reserpine, binedaline, amedalin, siramesine, indalpine, yohimbine and ateviridine contains indoline nucleus as a basic scaffold and recently, silodosin were investigated as novel antidysuria agents on urethral contractions (Figure 1). They are also exploited as intermediates and building blocks in organic synthesis [25]. Reaction similar to 2a and 2b with Wittig reagent Ph3P=C(Me)CO2Et provided alpha beta -unsaturated carboxylic acid ethyl ester, followed by hydrolysis with sodium hydroxide in methanol to give alpha-beta -unsaturated carboxylic acid in 86% yield [30]. This has enthused us to search new and more convenient methods for the preparation of Indoline derivatives. Here we report an economic and efficient synthesis (Scheme 1) for Indoline derivatives (1b and 2b) by condensation of 3-(5-formylindolin-1-yl)propyl benzoate with nitroethane via Knoevenagel condensation by using aqueous extract of *A. concinna* pods with better yield (92-95%).

Sugimoto and co-workers [31,32] accomplished the synthesis of donepezil with an overall yield of 27.4%, where in the Aldol condensation of 5,6-dimethoxyindan-1-one, 1-benzyl piperidine-4-carboxaldehyde served as a key step of synthesis to yield compound (3), This process has additional obstacles for the large-scale production because of subzero temperature requirements (-78°C) and hazardous chemicals such as n-butyl lithium. Several other syntheses of donepezil intermediate (3a) have been reported [33-35] which are either too long or contain unacceptable operations and thus are not suitable for large scale preparation. Darzens condensation [36] was reported to afford (3a) by using n-butyl lithium, as unsafe condition and also giving the mix of diasteriomers. Here in our synthesis commenced from commercially available 5, 6-dimethoxy-indan-1-one, which was condensed with isonicotinaldehyde by using aqueous extract of *A. concinna*, pods in a modification of a literature procedure [37] to furnish the known intermediate (3a) in 95.8% yield (Scheme 1).

Bendroflumethiazide is a thiazide diuretic; also reduce the high blood pressure, treating excess fluid retention (oedema), for example like heart failure, liver cirrhosis or kidney disease. It works by helping the kidneys to eliminate excess fluid from the body by increasing the production of urine, fluid from the body, treating excess fluid buildup in the body caused by definite situation or medicines. Diuretics are sometimes referred to as 'water tablets'. Synthetic process of bendroflumethiazide and related derivatives was also disclosed in recent literature by using different solvents and acid catalysts like ethanol in the presence of hydrogen chloride [38], Methanol: Water in presence of acetic acid [39], dioxane/n-butanol in presence of a catalytic amount of p-toluene sulfonic acid [40]. Here we report an economic and efficient synthesis of Bendroflumethiazide (4) by Cyclocondensation of 5-trifluoromethyl-2, 4-disulfamylaniline with phenylacetaldehyde which is dissolved in Methanol by using aqueous extract of *A. concinna* pods with better yield (90-95%).

Trimethoprim exerts antimicrobial activity has recently been marketed as a single-entity product for the treatment of initial episodes of uncomplicated symptomatic urinary tract infections; it was previously available only in combination with sulfamethoxazole. Reported synthesis of trimethoprim intermediate [41] by using Potassium Hydroxide (KOH) or Dimethyl Sulfoxide (DMSO) but in our synthesis for Trimethoprim Intermediate (5) by condensation of 3,4,5-trimethoxy benzaldehyde with 3-(dimethylamino) propane nitrile in Methanol by using aqueous extract of *A. concinna* pods with better yield (92-95%).

Amlodipine belongs to a group of medicines called calcium antagonists. It is used to treat high blood pressure (hypertension) and angina pectoris (pain in the chest caused by blockages in the arteries leading to the heart) or chest pain classed as vasospastic angina pectoris (or Prinzmetal's angina). Amlodipine related intermediate (6b) reported by using 2-(2-(2, 4-dioxobutyloxy)-4 ethoxy, ethyl) isoindoline-1, 3-dione and 2-Chloro benzaldehyde in acetic acid [42] but in our synthesis used different aldehyde in presence of aqueous extract of *A. concinna* pods in toluene (6a-b) with 80-85% yield.

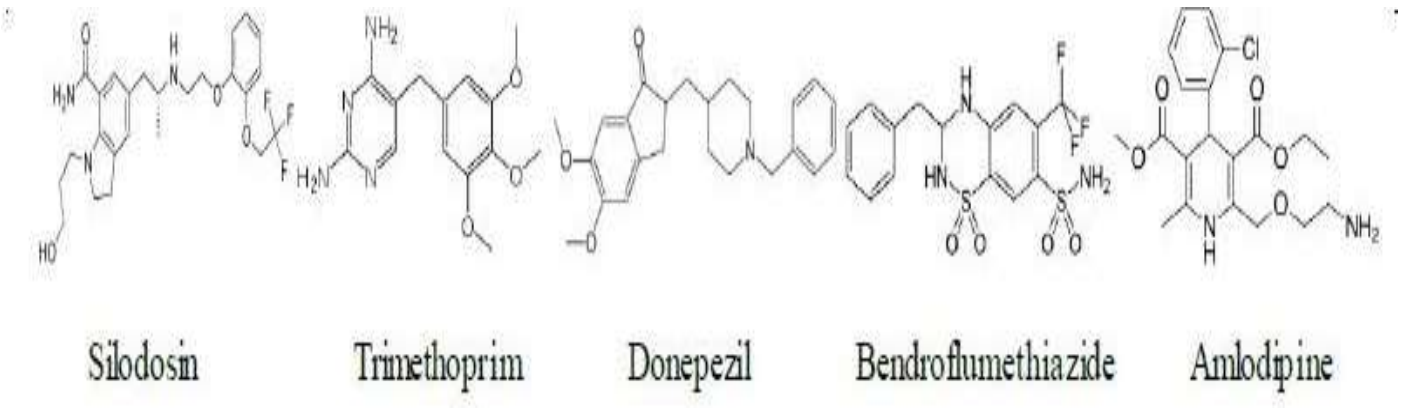


Figure 1: Synthesized biologically active indoline and other derivatives

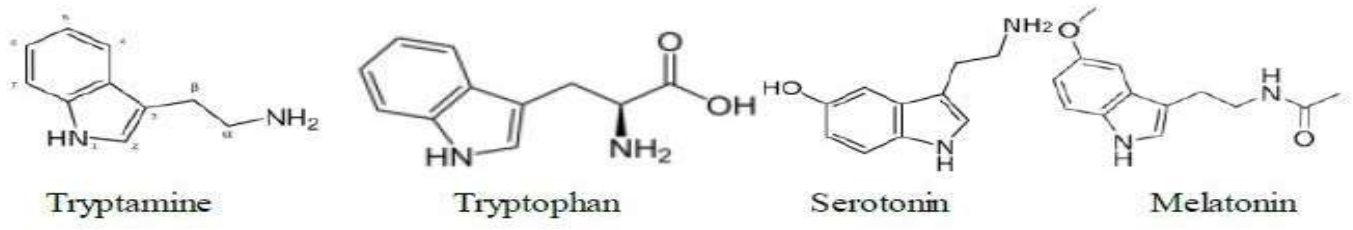


Figure 2: Structures of some naturally occurring biologically active Indoline derivatives

MATERIALS AND METHODS

Materials

All the chemicals and solvents used were of synthetic grade unless otherwise noted. Benzoic acid, 1-bromo-3-chloro propane, indoline, 2,3-dihydro-5,6-dimethoxyinden-1-one, 3,4,5-trimethoxy benzaldehyde, 3-(dimethylamino) propanenitrile, benzaldehyde, 2-(2-(2,4-dioxobutyloxy)-4 ethoxy, ethyl)isoindoline-1,3-dione, ammonium formate, sodium bicarbonate, 2-chloro benzaldehyde, 3-chloro benzaldehyde, 4-chloro benzaldehyde and isonicotinaldehyde were purchased from Sigma Aldrich, nitroethane, isonicotinaldehyde, phenylacetaldehyde, 1-(2,2-dimethoxyethyl) benzene and triethylamine were purchased from Acros organics. Preparation of 5-trifluoromethylaniline-2, 4-disulfonylchloride and 5-trifluoromethyl-2, 4-disulfamylaniline was done as per the process described in U.S. Patent-3,392,168. Conc. HCl, methanol, isopropyl alcohol, Dichloromethane (MDC), Dimethylformamide (DMF), DMSO, ethyl acetate, hexane, dioxane, toluene and acetone were used from Merck and DM water from commercial source.

Instrumentation

TLC: Merck TLC silica gel 60 F254, (0.25 mm) detection: UV light at 254 nm, HPLC: Column: Inertsil ODS-3, Temp 25-30°C, (150 mm × 4.60 mm × 5 µm), flow rate 1.0 ml/min, wavelength 225 λ, Diluent: ACN:WATER (50:50), Detector: *Waters 2487 Dual* λ Absorbance, ^{1}H-NMR: Bruker Avance 400 MHz NMR Spectrometer, chemical shifts are reported in ppm downfield from Tetramethylsilane (TMS). Flash chromatography: Teledyne Isco Combiflash Rf+ Lumen (230-400 mesh), detector: ELSD, IR: Thermo Scientific Nicolet iS50 FT-IR Spectrometer and MS: Thermo Scientific LC-MS Orbitrap-based systems.

Documentation of plant

Common name: Shikakai, Scientific Name: *Acacia concinna.* Shikakai belongs to climbing shrub native to Asia, common in the warm plains of central, south India, central Asia and the Far East. The plants are medium fast growing and which is bushy cum creeper. The pods contain rich in saponins of acacic acid, trihydroxy monocarboxylic triterpenic acid of either tetracyclic or α-amyrin group corresponding to pentacyclic triterpenes [43-48].

General procedure for the preparation of catalyst

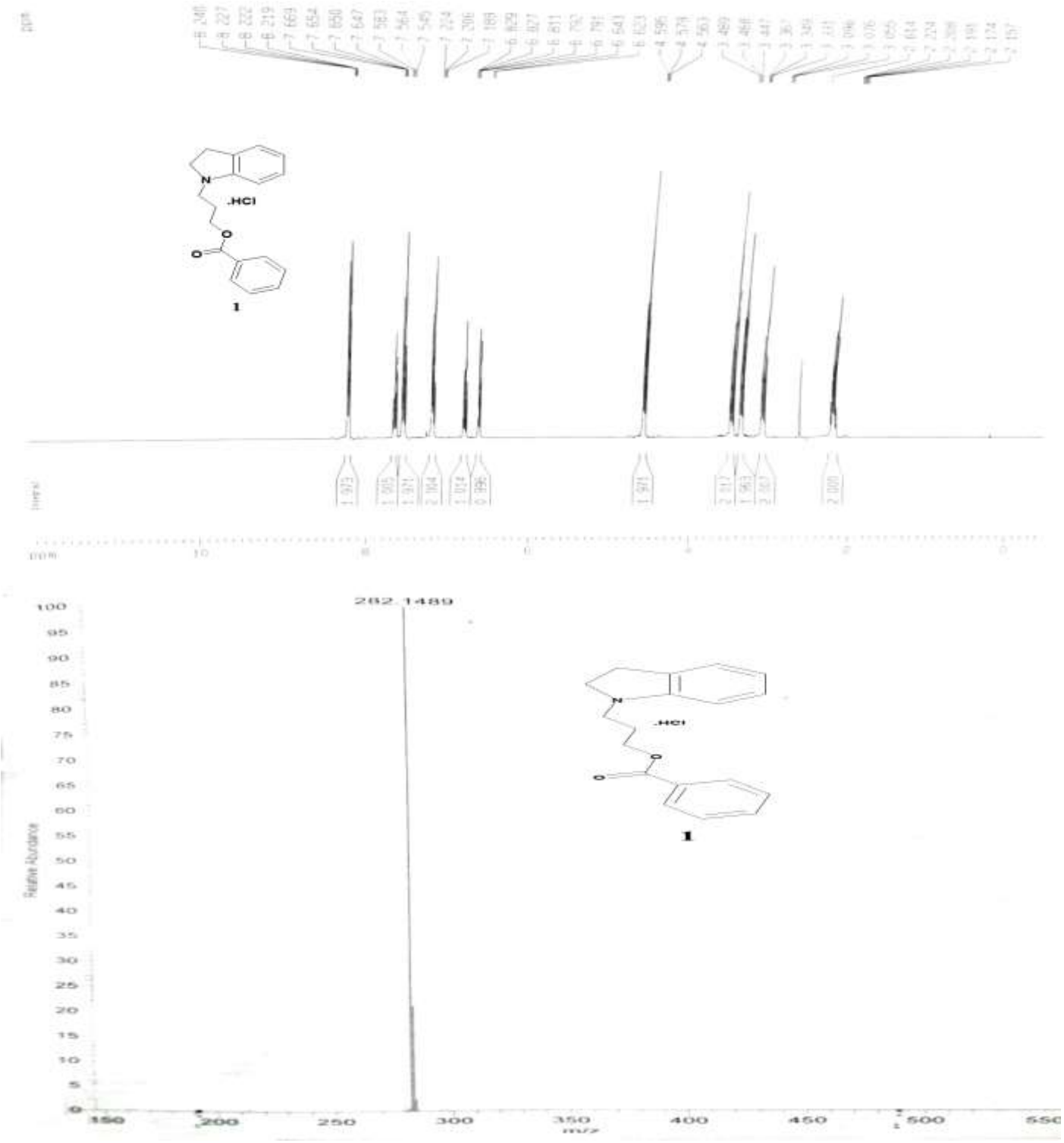
Powdered pods of *A. concinna* fruit (10 g) and water (100 ml) in a 250 ml conical flask was boiled for 15-20 mints. The material was then filtered off and the aqueous extract was employed as a catalyst (10%, w/v) for the synthesis of following compounds.

Figure 3: Photography of *Acacia concinna* fruit

SYNTHESIS

Preparation of 3-(indolin-1-yl) propyl benzoate hydrochloride (1)

Add benzoic acid (20 g), triethyl amine (25 g) and 1-bromo-3-chloro propane (25.8 g) in Dimethylformamide (DMF) (50 ml) at 25-30°C and maintained for 10 h. Heated it at 60°C for 4 h, then add again triethyl amine (25 g) and indoline (19.6 g) in reaction mass at 60°C and maintain for 15 h at 100°C. Quench the reaction mass in water (200 ml) and extract in ethyl acetate 140 ml, ethyl acetate layer washed by 5% sodium bicarbonate solution and evaporate the ethyl acetate layer. Degassed mass dissolved in Acetone 80 ml and added conc. HCl (18 ml) at 0-5°C and stir for 15 h at 25-30°C. Chill at 0-5°C and filter to get pure 3-(indolin-1-yl)propyl benzoate hydrochloride (1) Yield 45.65 g (88%). Anal. Calc. for $C_{18}H_{20}Cl_1N_1O_2$, C: 68.03; H: 6.34; Cl: 11.16; N: 4.41; O: 10.07, Found C: 68.30; H: 6.10; Cl: 11.07; N: 4.20; O: 10.33, HPLC: 99.77%, ^{1}H-NMR 400 MHz, $CDCl_3$: δ ppm: 2.15-2.22 (m, 2H, -CH_2-), 3.05-3.09 (t, 2H, -CH_2-indolin), 3.33-3.36 (t, 2H, -CH_2-indolin), 3.44-3.48 (t, 2H, -N-CH_2-), 4.56-4.59 (t, 2H, -OCH_2-), 6.62-6.64 (d, 1H, H-Ar-indolin), 6.79-6.82 (t, 1H, H-Ar-indolin), 7.18-7.22 (m, 2H, H-Ar-indolin), 7.54-7.58 (m, 2H, H-Ar), 7.64-7.69 (m, 1H, H-Ar), 8.21-8.24 (m, 2H, H-Ar), MS: $[M+H]^+$ (282.14 100%).

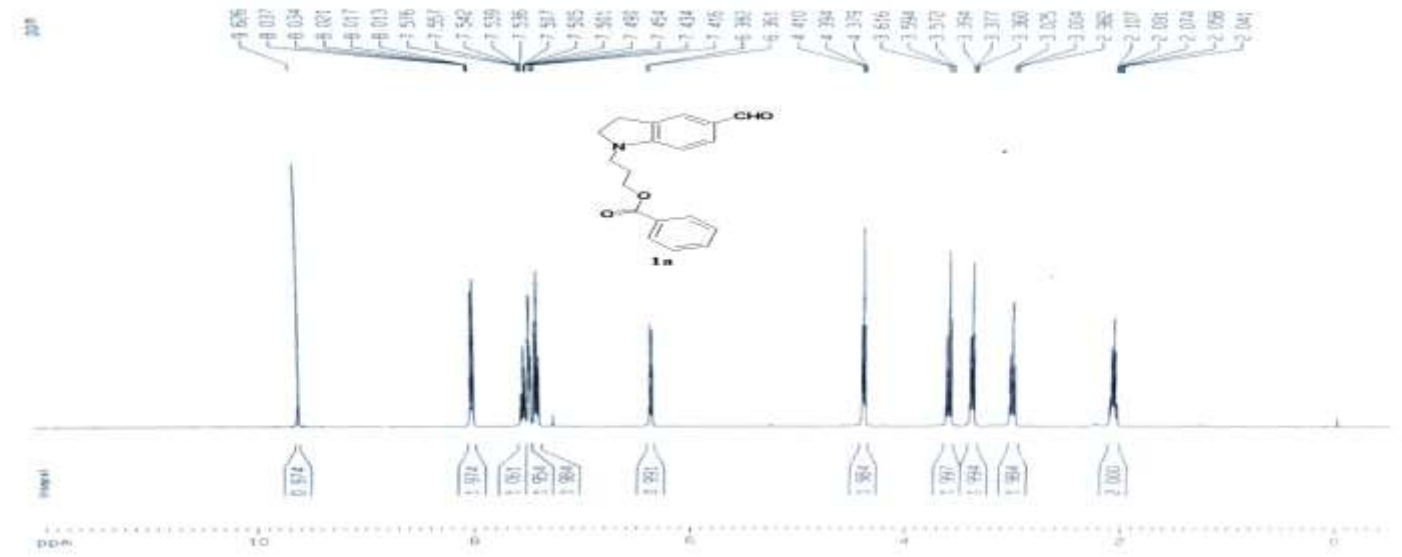


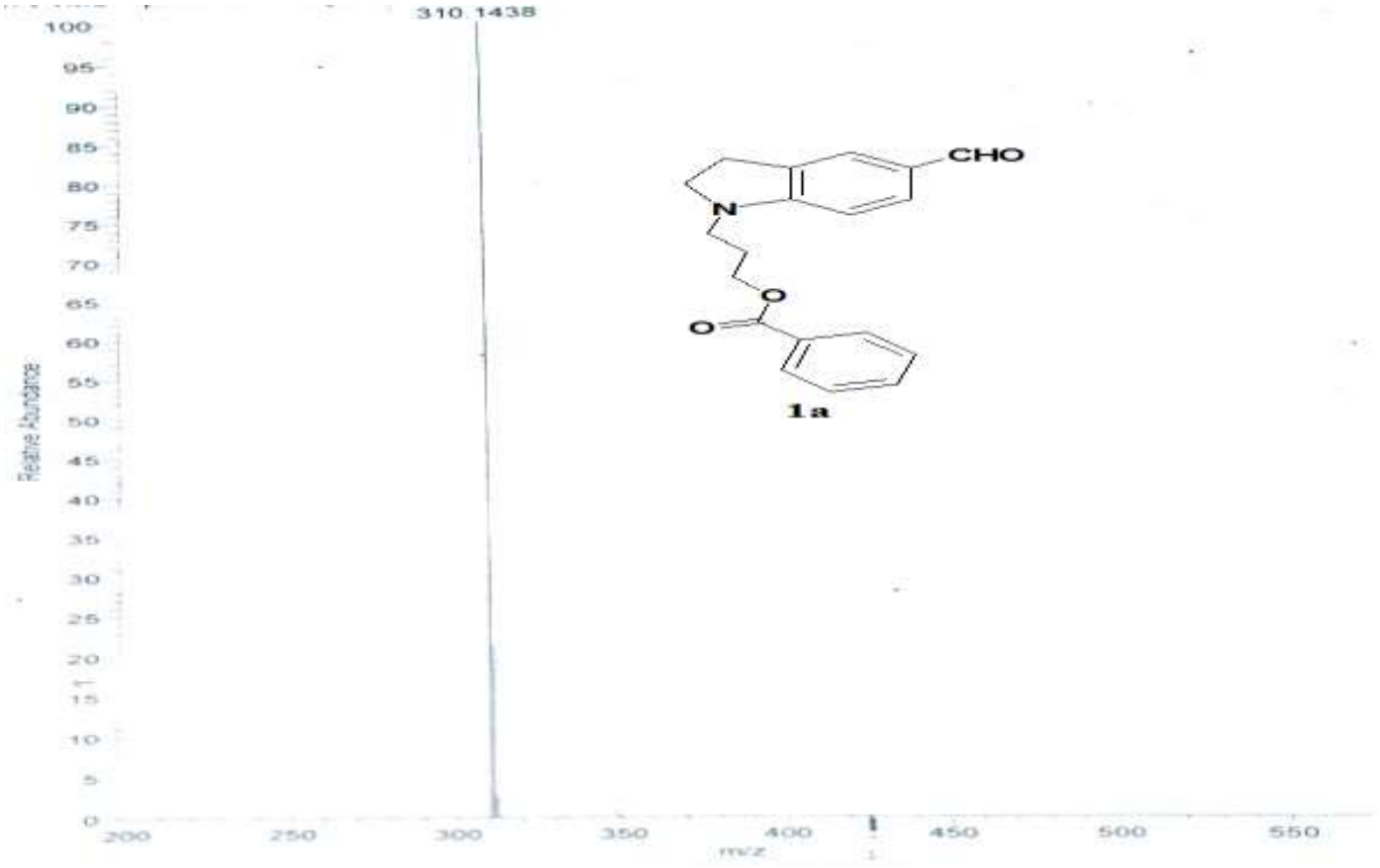
Preparation of 3-(5-(2-nitroprop-1-enyl) indolin-1-yl) propyl benzoate (2a)

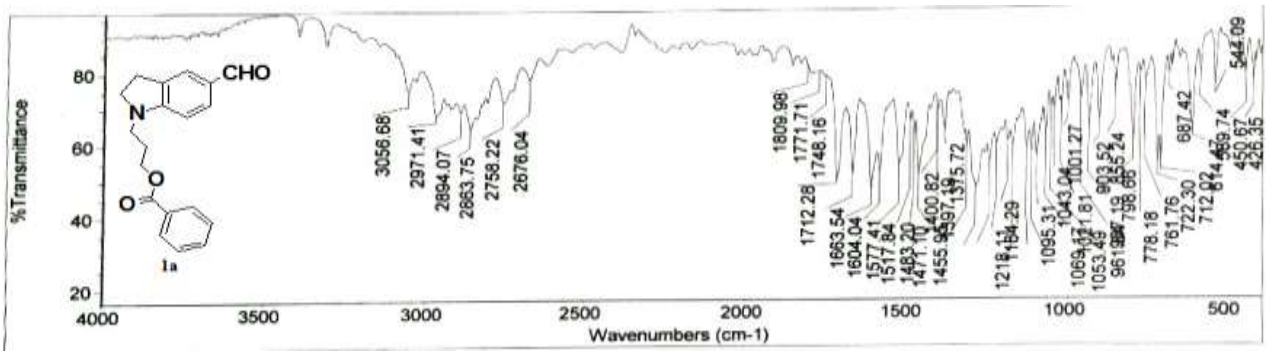
Add Phosphorus oxychloride (9.2 g) dropwise in chilled dimethylformamide (65 ml) at 0-5°C and stir for 25-30 min, then added 3-(indolin-1-yl)propyl benzoate hydrochloride (1) (10.0 g) in 3 equal lots at 0-5^{0}C. Slowly raise temp to 45-50°C for 6 h. Quench the reaction mass in ice water (120 ml), raise the temp at 25-30°C, neutralized by using 15% sodium carbonate solution and extract in toluene (1a). Add nitroethane (4.5 g) in the above toluene layer (1a) and aqueous extract of *A. concinna* pods 10 ml (10%) at 25-30°C to carry out *in situ* next step via Knoevenagel condensation. Raise the temp to reflux at 105-110°C for 7 h to remove the water azeotropically, reaction completion monitored by TLC, and then neutralized by 5% sodium carbonate solution. Separate both layers and evaporate the toluene, charged isopropyl alcohol and heated at 65-70°C, slowly cool down to at 25-30°C and stir for 24 h. Filter to get pure orange coloured Solid 3-(5-(2-nitroprop-1-enyl) indolin-1-yl)propyl benzoate (2a) Yield: 10.95 g (95%).

3-(5-formylindolin-1-yl)propyl benzoate (1a): HPLC: 99.57%, Anal. Calc. for $C_{19}H_{19}NO_3$, C: 73.77; H: 6.19; N: 4.53; O: 15.52, Found C: 73.42; H: 6.02; N: 4.81; O: 15.75, ^{1}H-NMR 400 MHz, $CDCl_3$: δ ppm: 2.04-2.10 (m, 2H, -CH_2-), 2.98-3.02 (t, 2H, -CH_2- indolin), 3.36-3.39 (t, 2H, -CH_2-indolin), 3.57-3.61 (t, 2H, -NCH_2-), 4.37-4.41 (t, 2H, -OCH_2-), 6.36-6.38 (d, 1H, H-Ar-indolin), 7.41-7.50 (m, 2H, H-Ar-indolin), 7.50-7.53 (m, 2H, H-Ar), 7.53-7.55 (m, 1H, H-Ar), 8.01-8.03 (d, 2H, H-Ar), 9.626 (s, 1H, indolin-5-CHO), IR: ν(cm^{-1}), 544w, 589w, 687w,

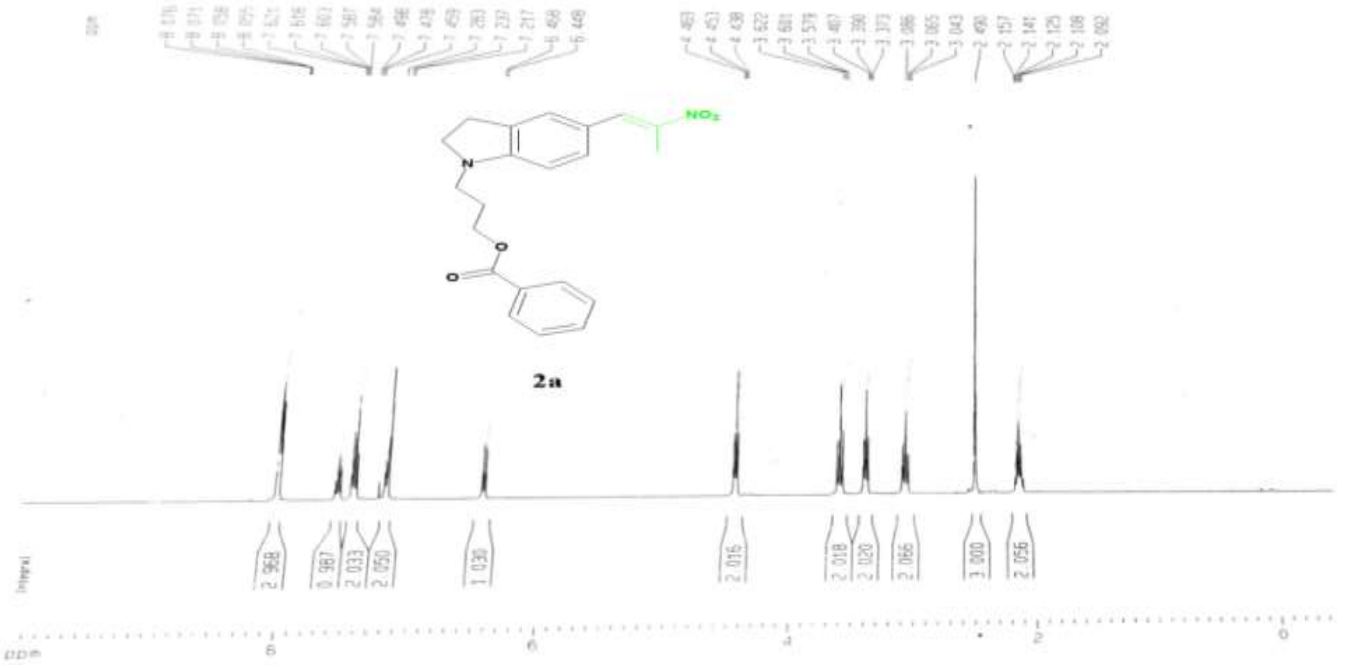
761s, 778w, 855w, 961w, 1043m, 1053m, 1095m, 1184w, 1218s, 1375s, 1455w, 1471m, 1483w, 1517m, 1577s, 1604s, 1654s, 1712s, 2676m, 2758m, 2883s, 2894m, 2971m, 3056m, MS: $[M+H]^+$ (310.14 100%).

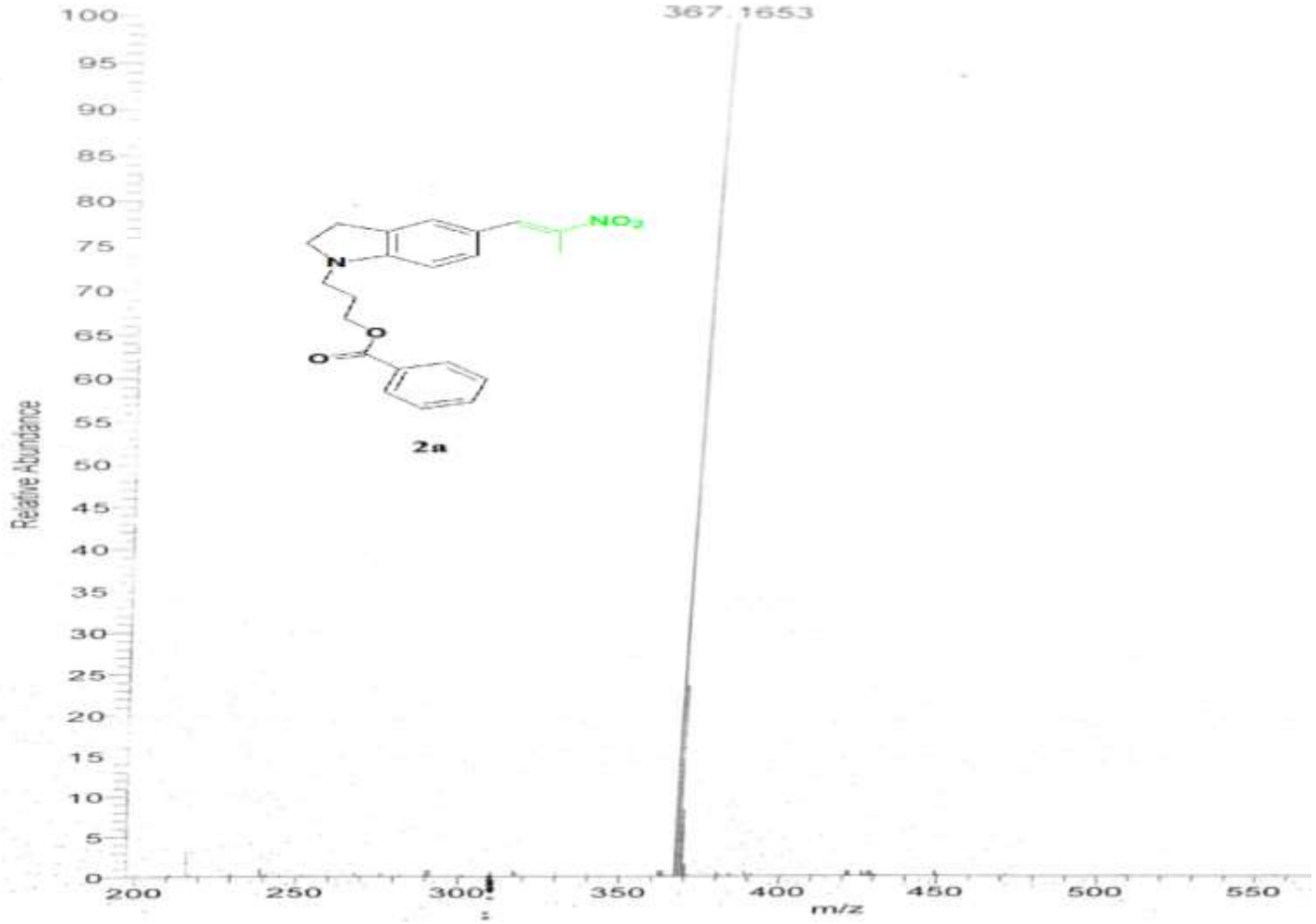


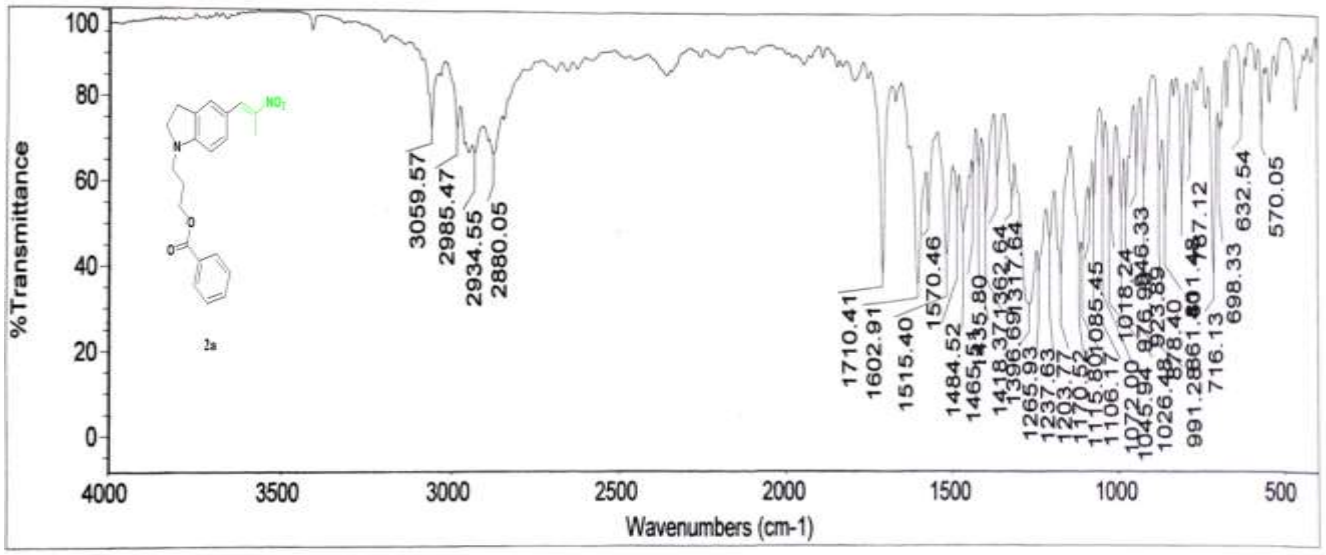




3-(5-(2-nitroprop-1-enyl) indolin-1-yl)propyl benzoate (2a): HPLC:96.14%, Yield (95%), Anal. Calc. for $C_{21}H_{22}N_2O_4$, C: 68.84; H: 6.05; N: 7.65; O: 17.47, Found C: 68.36; H: 6.52; N: 7.41; O: 17.71, ^{1}H-NMR 400 MHz, $CDCl_3$: δ ppm: 2.09-2.15 (m, 2H, -CH_2-), 2.49 (s, 3H, -CH_3), 3.04-3.08 (t, 2H, -CH_2-indolin), 3.37-3.40 (t, 2H, -CH_2-indolin), 3.57-3.62 (t, 2H, -NCH_2-), 4.43-4.46 (t, 2H, -OCH_2-), 6.44-6.46 (S, 1H, -HC-), 7.21-8.07 (m, 8H, H-Ar), IR: ν (cm^{-1}), 570w, 632w, 716s, 878m, 1026m, 1170s, 1203s, 1265s, 1418m, 1484w, 1515m, 1602s, 1710s, 2880m, 2934s, 2984w, 3059m, MS: $[M+H]^+$ (367.16. 100%).

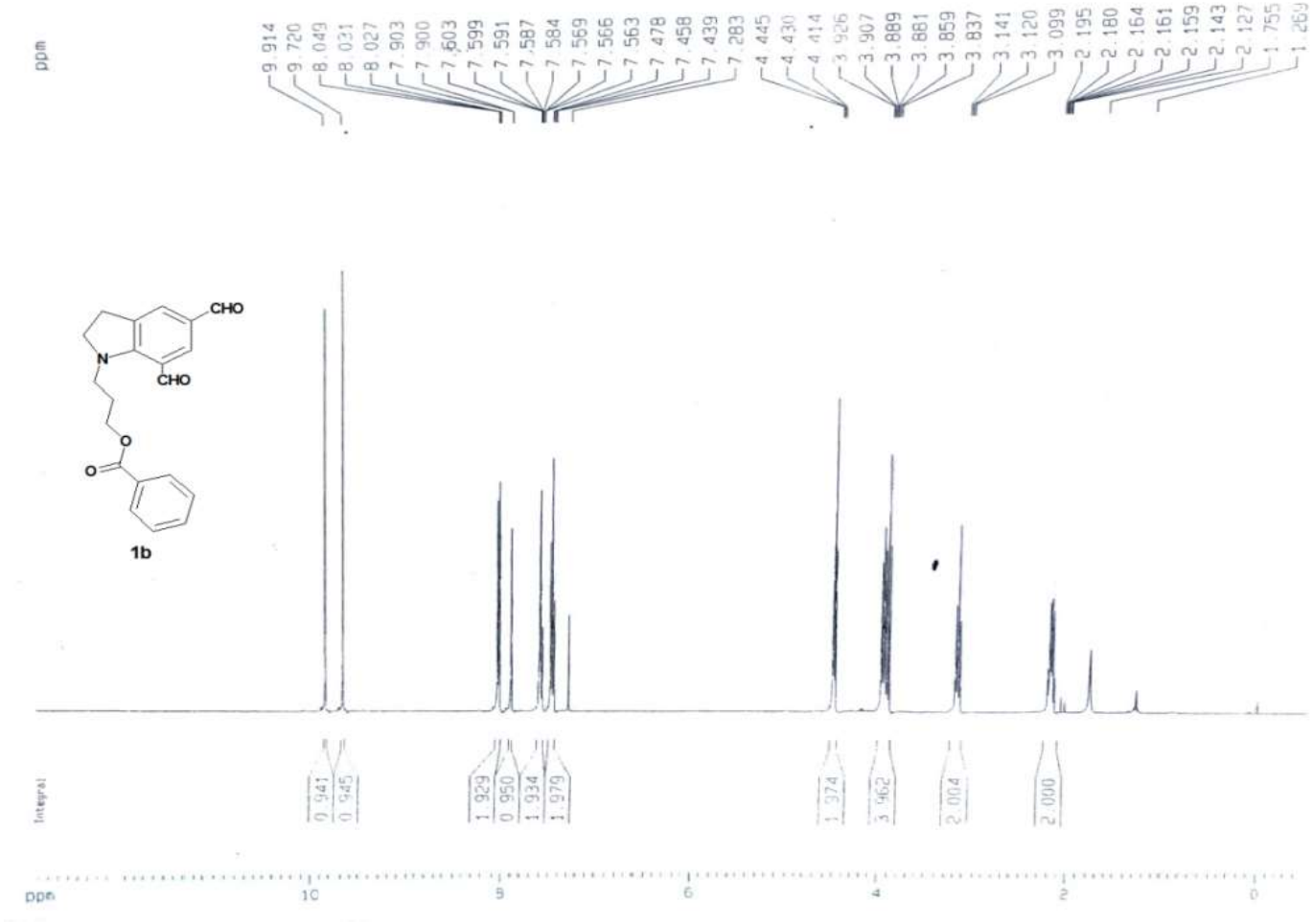


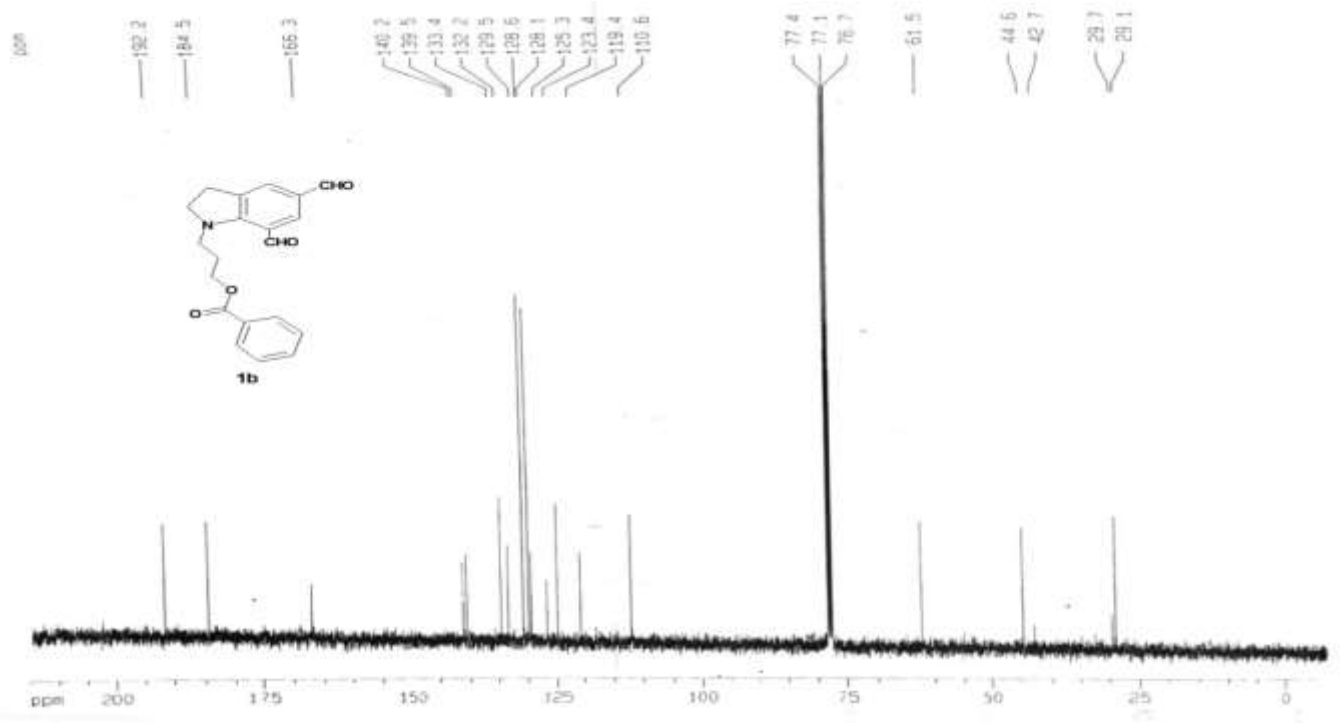




Preparation of 3-(5, 7-diformylindolin-1-yl) propyl benzoate (1b)

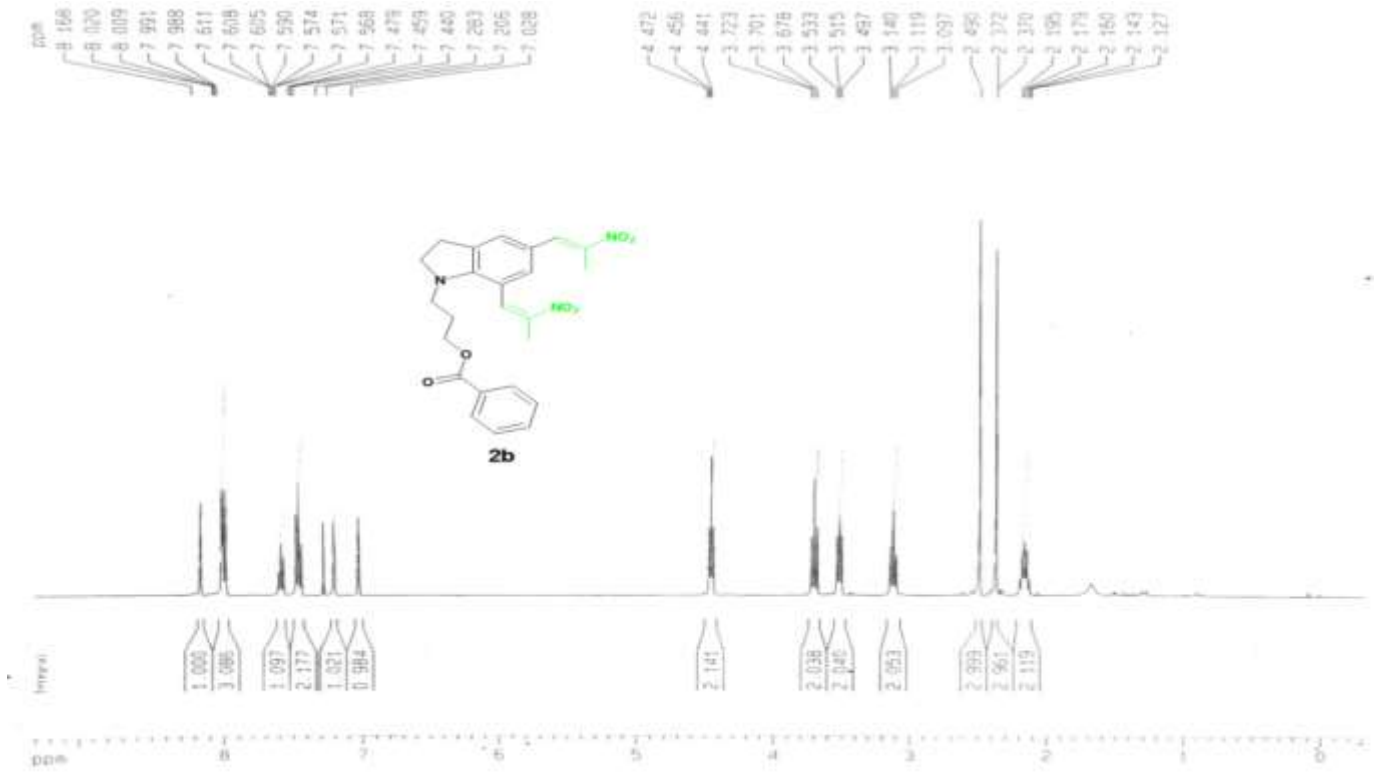
Add phosphorus oxychloride (9.2 g) dropwise in chilled DMF (65 ml) at 0-5°C and stir for 25-30 min, then added 3-(indolin-1-yl) propyl benzoate hydrochloride (1) (5.0 g) in 3 equal lots at 0-5°C. Slowly raise temp to 45-50°C for 15 h. Quench the reaction mass in ice water (120 ml), raise the temp at 25-30°C, neutralized by using 15% sodium carbonate solution and extract in ethyl acetate, evaporate ethyl acetate and purify the obtained crude oily mass by silica column in Hexane: Ethyl acetate (7:3) to get the pure 3-(5,7-diformylindolin-1-yl) propyl benzoate (1b) yield:4.5 g (85%), HPLC: 99.07%, Anal. Calc. for $C_{20}H_{19}NO_4$, C: 71.20; H: 5.68; N: 4.15; O: 18.97, Found C: 71.45; H: 5.55; N: 4.01; O: 18.99, ^{1}H-NMR 400 MHz, $CDCl_3$: δ ppm: 2.12-2.19 (m, 2H, -CH_2-), 3.09-3.14 (t, 2H, -CH_2-indolin), 3.83-3.88 (t, 2H, -CH_2-indolin), 3.88-3.92 (t, 2H, -NCH_2-), 4.41-4.44 (t, 2H, -OCH_2-), 7.28-8.04 (m, 7H, H-Ar), 9.72 (s, 1H, indolin-5, CHO), 9.91 (s, 1H, indolin-7, CHO), ^{13}C-NMR 400 MHz, $CDCl_3$: δ ppm: 29.1-29.7, 44.6, 61.5, 110.7, 123.4, 128.1, 128.6, 129.5, 133.4, 139.5, 184.5, 192.2, IR: ν(cm1), 563m, 711s, 905m, 1014m, 1074w, 1174s, 1176s, 1278w, 1321s, 1349s, 1365w, 1377w, 1440w, 1508s, 1567s, 1619w, 1660s, 1691s, 1711s, 2800w, 2826w, 2883m, 2962m, MS: $[M+H]^+$ (338.05 100%).

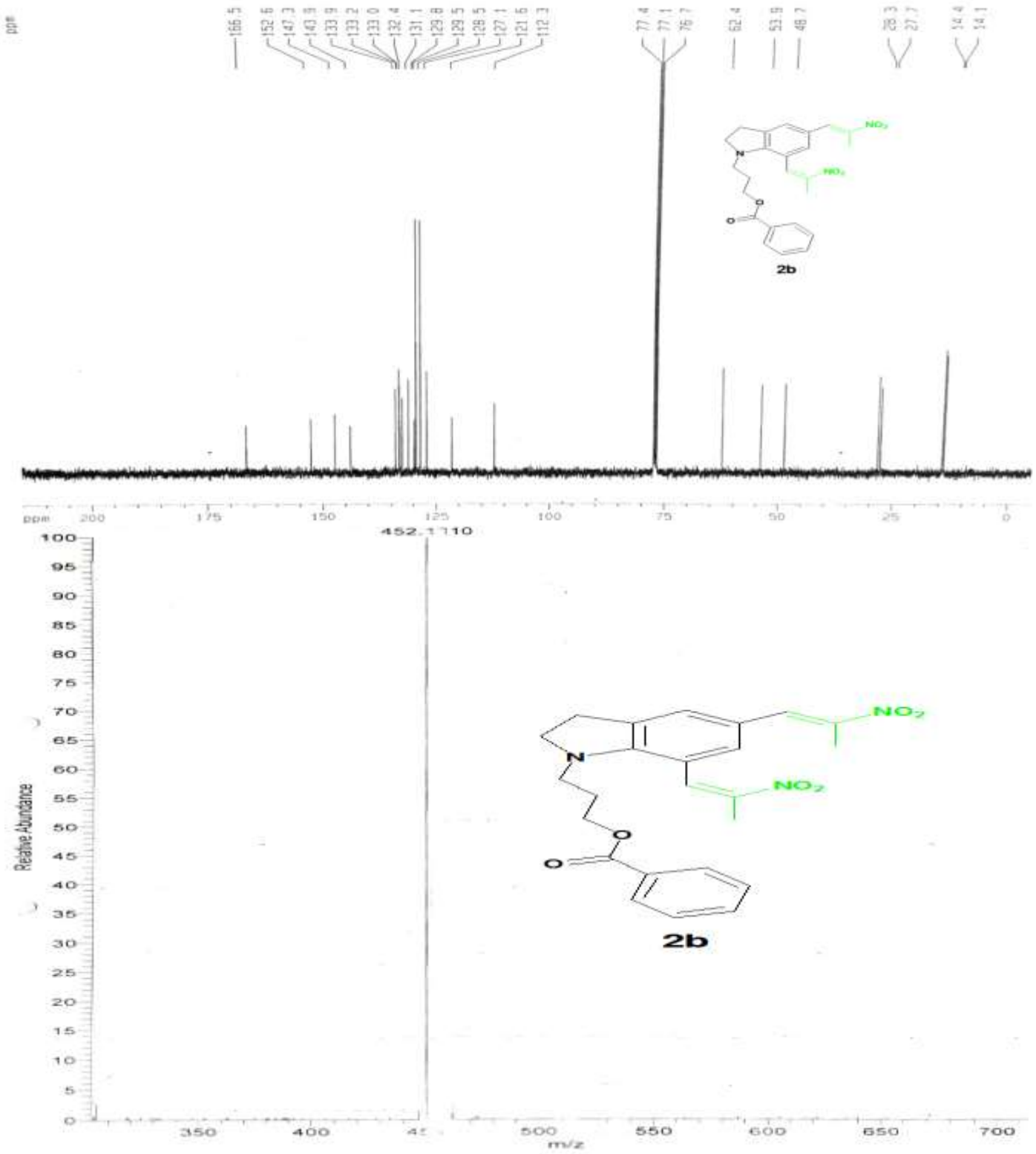




Knoevenagel condensation of 3-(5, 7-diformylindolin-1-yl) propyl benzoate (1b) with nitroethane to prepare 3-(5-(2-nitroprop-1-enyl)-7-(-2-nitroprop -1-enyl) indolin-1-yl) propyl benzoate (2b)

Add nitroethane (3.56 g) in above oily mass (1b) (4.0 g) dissolved in toluene (40 ml) and aqueous extract of *A. concinna* pods 8 ml (25%) at 25-30°C. Raise the temp of reaction mass to reflux at 105-110°C for 15 h to remove the water azeotropically, reaction completion monitored by TLC, and cool, add water (50 ml) then neutralized by 5% sodium carbonate solution at 25-30°C. Separate both layers and evaporate the toluene, charged Isopropyl alcohol and heated at 65-70°C, slowly cool down to at 25-30°C and stir for 24 h. Filter to get pure orange coloured solid 3-(5-(2-nitroprop-1-enyl)-7-(2-nitroprop-1-enyl) indolin-1-yl) propyl benzoate (2b) 4.92 g Yield (92%), Anal. Calc. for $C_{24}H_{25}N_3O_6$, C: 63.85; H 5.58; N: 9.31; O: 21.26, Found C: 63.41; H 5.80; N: 9.33; O: 21.46, ^{1}H-NMR 400 MHz, $CDCl_3$: δ ppm: 2.12-2.19 (m, 2H, -CH_2-), 2.37 (s, 3H, -CH_3), 2.49 (s, 3H, -CH_3), 3.09-3.14 (t, 2H, -CH_2-indolin), 3.49-3.53 (t, 2H, -CH_2-indolin), 3.67-3.72 (t, 2H, -NCH_2-), 4.44-4.47 (t, 2H, -OCH_2-), 7.02-8.16 (m, 9H, H-Ar), ^{13}C-NMR 400 MHz, $CDCl_3$: δ ppm: 14.1-14.4, 27.7-28.3, 48.7, 53.9, 62.4, 112.3, 121.6, 127.1-129.8, 131.1, 132.4, 133-133.2, 133.9, 143.9, 147.3, 152.6, 166.5, MS: $[M+H]^+$ (452.18. 100%).

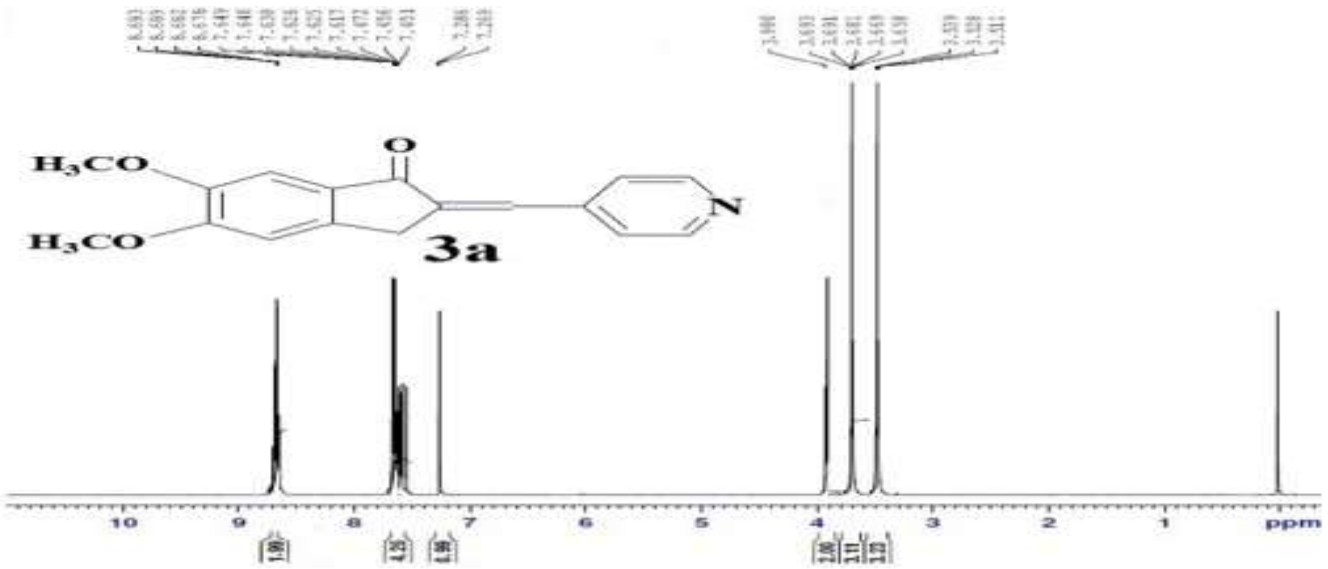


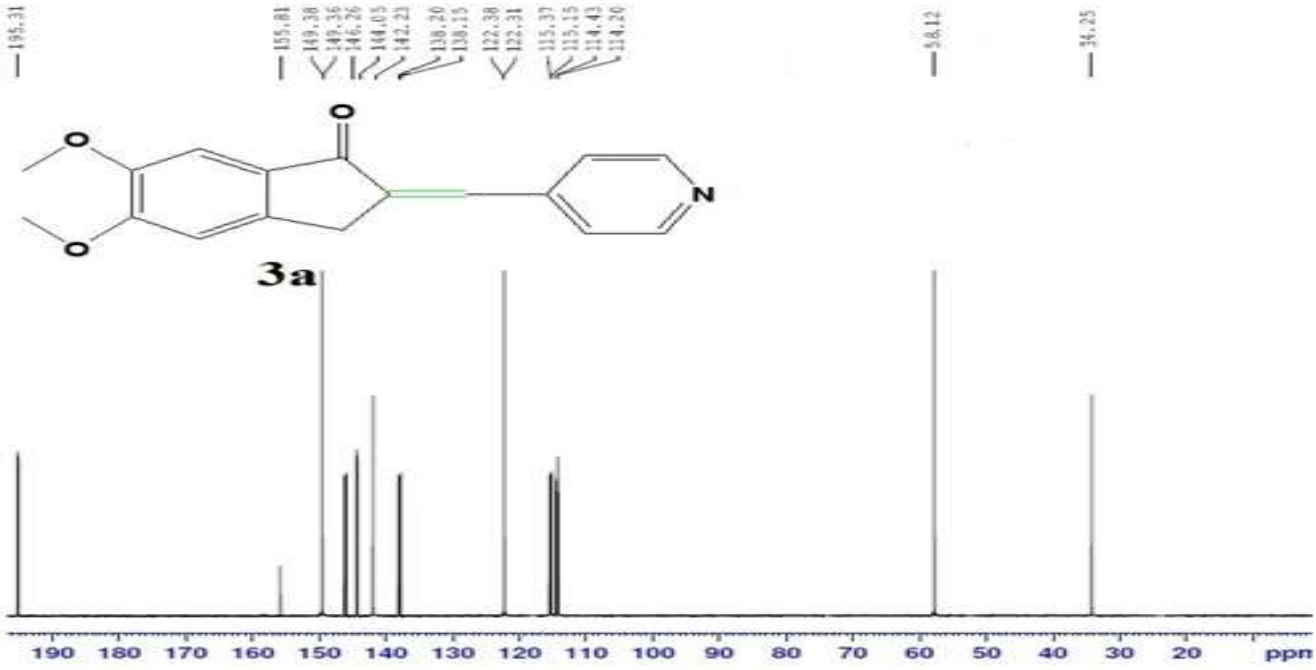


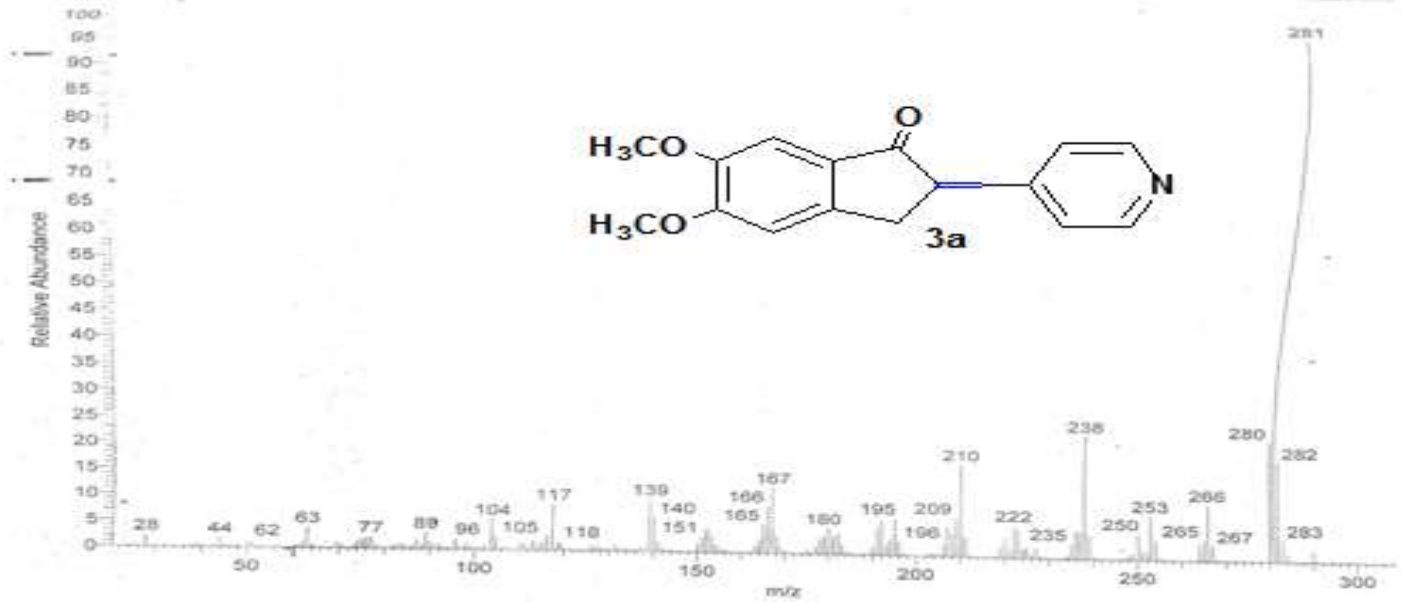
Aldol condensation of 2, 3-dihydro-5, 6-dimethoxyinden-1-one (3) with isonicotinaldehyde to prepare 2, 3-dihydro-5, and 6-dimethoxy-2-(pyridin-4-yl) methylene inden-1-ones (3a-d)

A mixture of compounds 2,3-dihydro-5,6-dimethoxyinden-1-one (3) (10. 0 g, 0.052 mol) and isonicotinaldehyde (6.69 g, 0.062 mol) were dissolved in toluene (100 ml) at 50-55°C and aqueous extract of *A. concinna* pods (10%, 10 ml) were added, further heated 7 h to remove water azeotropically at 105-110°C. The resulting solid was filtered and slurred in 8% sodium carbonate solution (100 ml) and filtered. The filter cake was washed with water (100 ml) and dried at 75°C to afford pure (3a) as pale yellow solid (14.20 g, yield 97%).

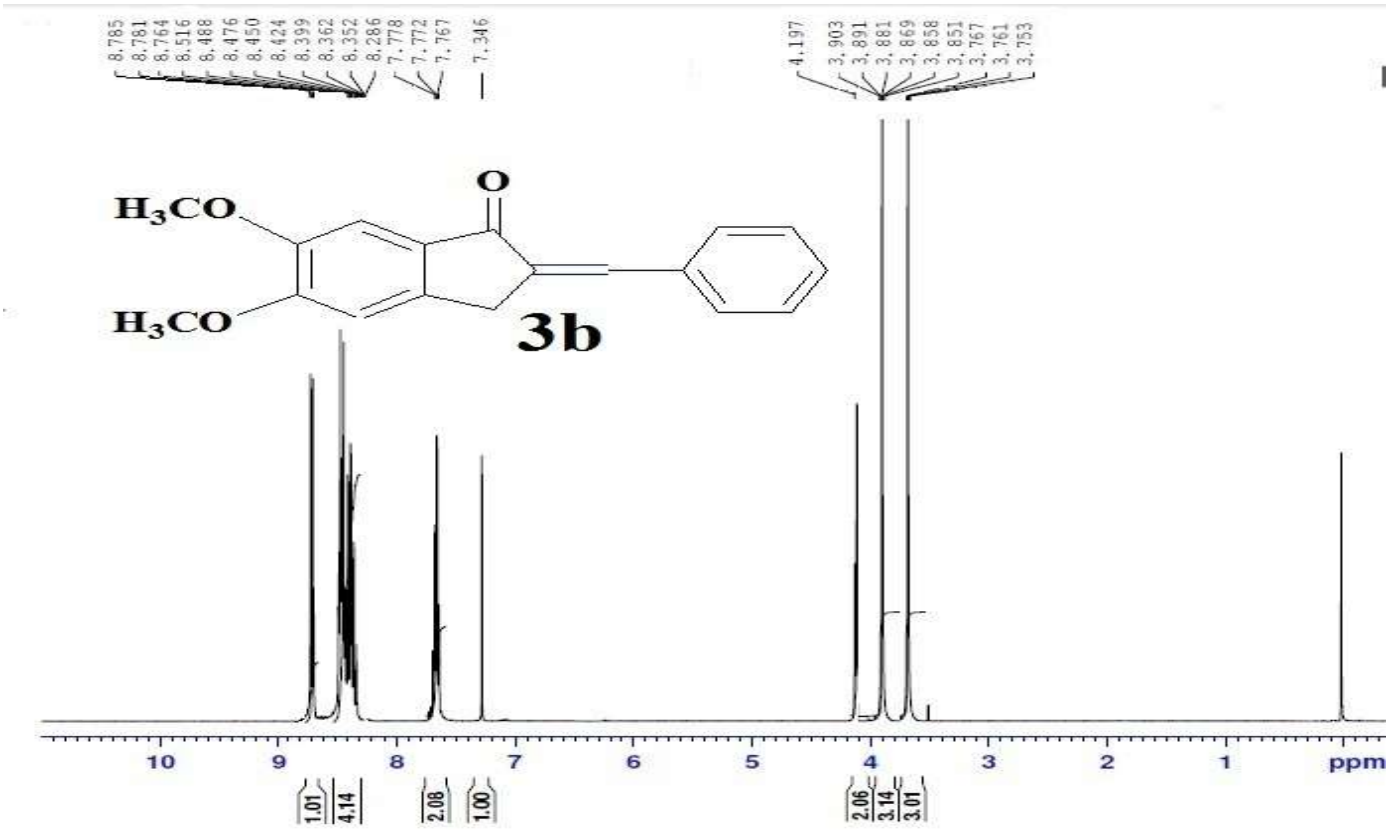
2,3-dihydro-5,6-dimethoxy-2-((pyridin-4-yl)methylene)inden-1-one (3a): pale yellow solid, yield 97%, Anal. Calc. for $C_{17}H_{15}NO_3$, C: 72.58; H: 5.37; N: 4.98; O: 17.06, Found C: 72.34; H: 5.35; N: 4.99; O: 17.32, ^{1}H-NMR 400 MHz, DMSO: δ ppm: 3.51-3.53 (s, 3H, -CH_3), 3.65-3.69 (s, 3H, -CH_3), 3.98 (s, 2H, -CH_2-), 7.26-7.28 (s, 1H, H-C-), 7.45-7.64 (m, 4H, H-Pyridine), 8.67-8.69 (dd, 2H, H-Ar-inden), ^{13}C-NMR: 400 MHz, DMSO: δ ppm: 34.25, 58.12, 114.20-114.43, 115.15-115.37, 122.31-122.38, 138.15-138.20, 142.23, 14405, 146.26, 149.36-149.38, 155.81, 195.31, MS: $[M+H]^+$ (281, 100%).

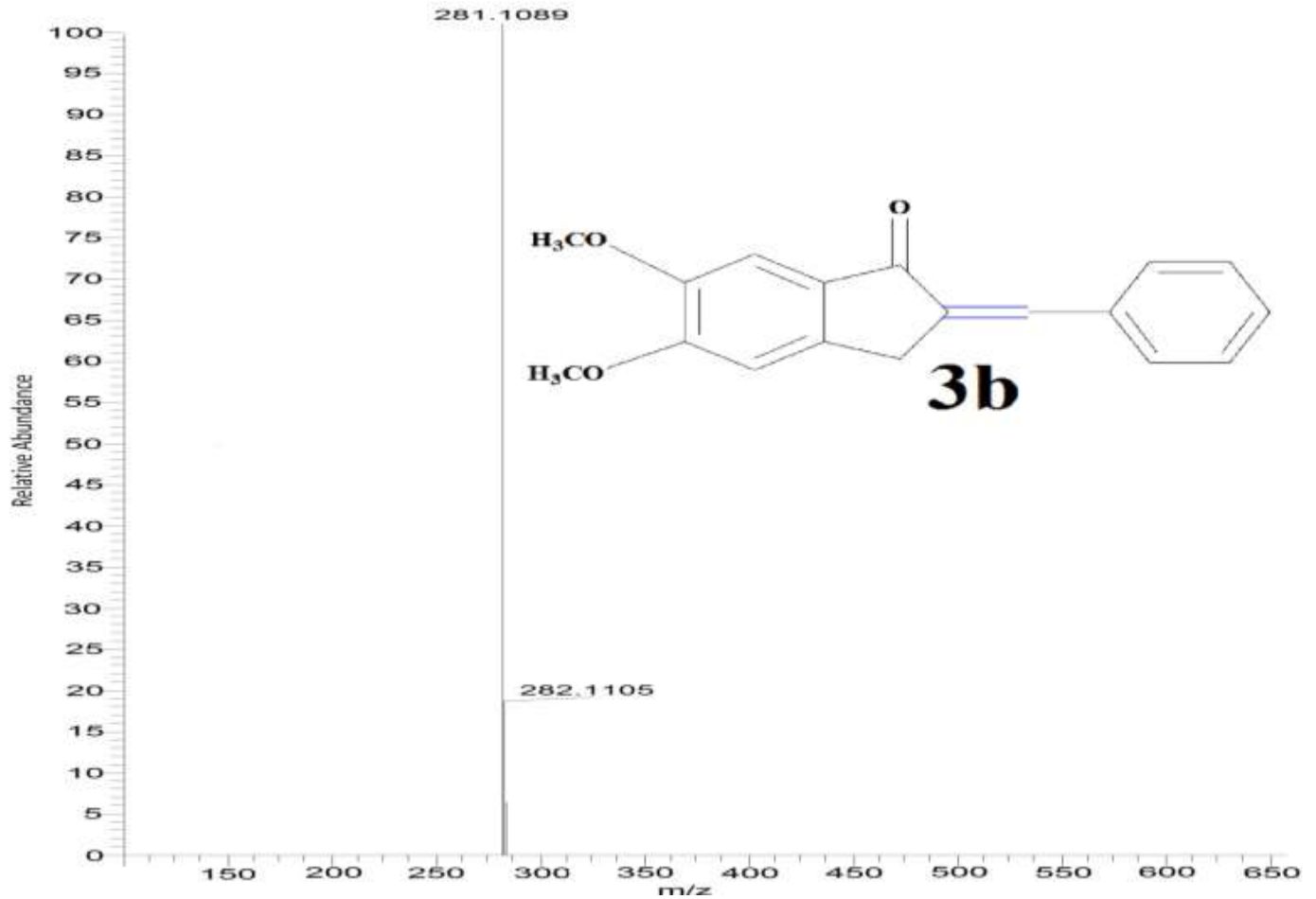

H3CO
H3CO
O
N
3a
ppm


O
O
N
3a
ppn

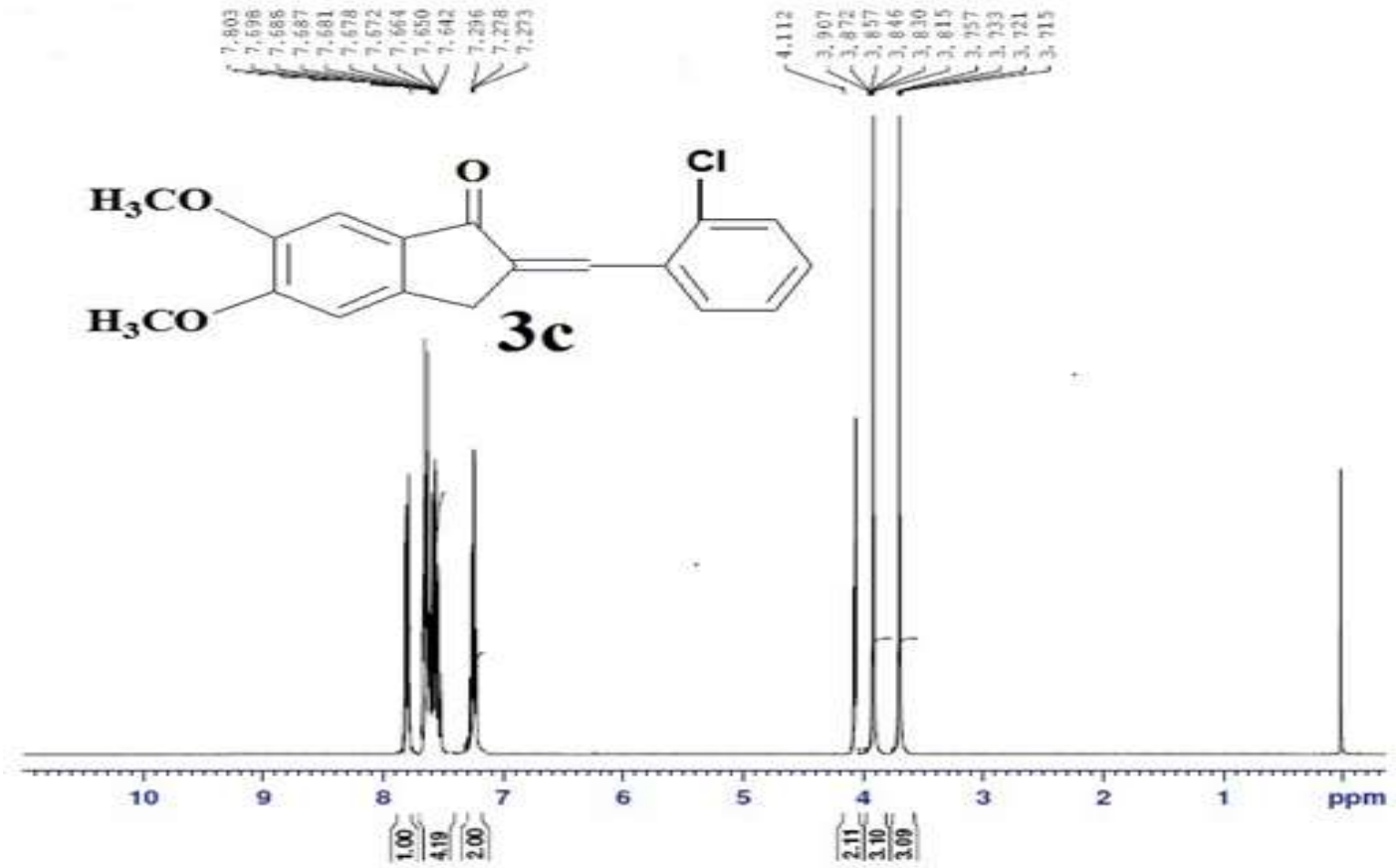

H3CO
H3CO
O
N
3a
Relative Abundance
m/z

2-benzylidene-2,3-dihydro-5,6-dimethoxyinden-1-one (3b): Yield (88%), Anal. Calc. for $C_{18}H_{16}O_3$, C: 77.12; H:5.75; O:17.12, Found C: 77.39; H:5.50; O:17.10, ^{1}H-NMR 400 MHz, DMSO: δ ppm: 3.75-3.76 (s, 3H, -CH_3), 3.85-3.90 (s, 3H, -CH_3), 4.19 (s, 2H, -CH_2-inden), 7.34 (s, H, H-C-), 7.76-7.77 (dd, 2H, H-inden), 8.28-8.76 (m, 4H, H-Ar), 8.78-8.78 (s, 1H, H-Ar), MS: $[M+H]^+$ (281.10, 100%).

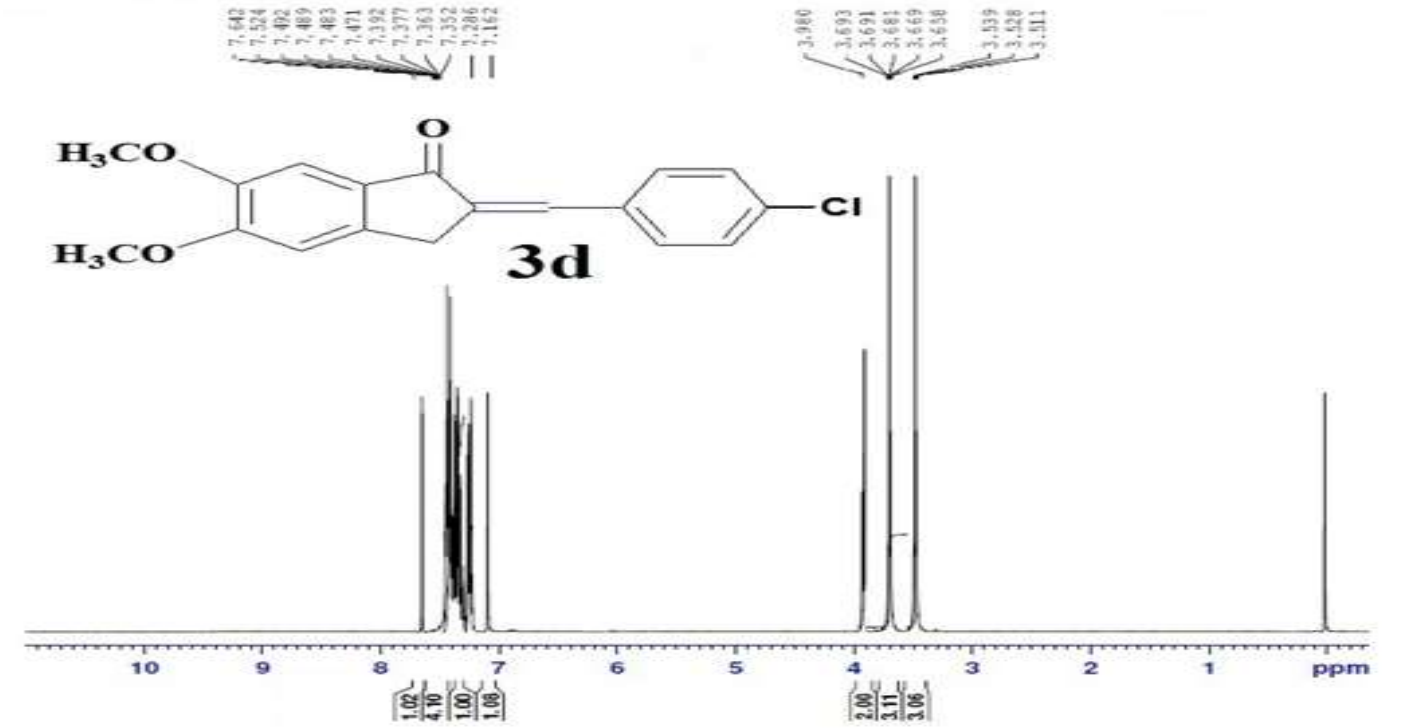


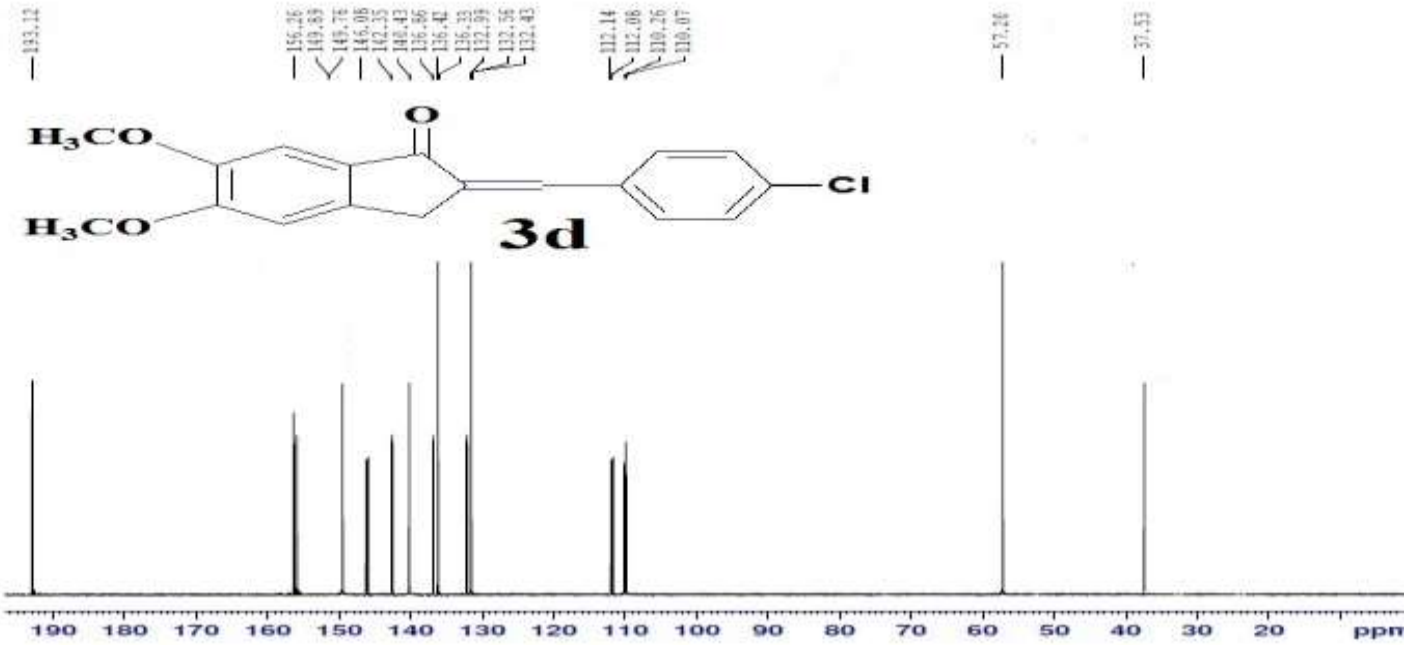


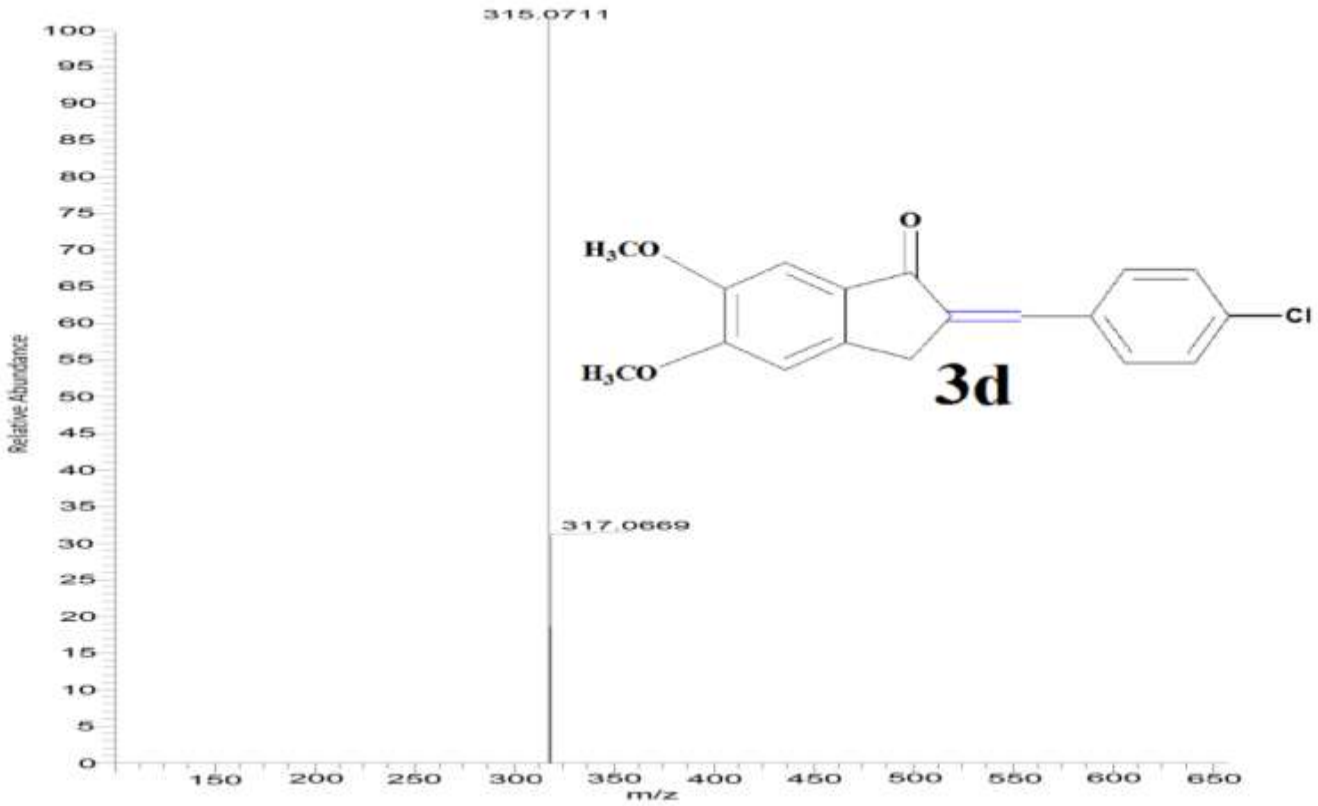
2-(2-chlorobenzylidene)-2,3-dihydro-5,6-dimethoxyinden-1-one (3c): Yield (90%), Anal. Calc. for $C_{18}H_{15}O_3$, C: 68.68; H: 4.80; Cl: 11.26; O: 15.25, Found C: 68.32; H: 4.96; Cl: 11.11; O: 15.61, ^{1}H NMR 400 MHz, DMSO: δ ppm: 3.71-3.75 (s, 3H, -CH3), 3.81-3.90 (s, 3H, -CH_3), 4.11(s, 2H, -CH_2-inden), 7.27-7.29 (s, 2H, H-inden), 7.64-7.688 (m, 4H, H-Ar), 7.69-7.80 (s, 1H, H-C-), MS: $[M+H]^+$ (315.07, 100%).



2-(4-chlorobenzylidene)-2, 3-dihydro-5,6-dimethoxyinden-1-one (3d): Yield (92%), Anal. Calc. for $C_{18}H_{15}O_3$**:** C: 68.68; H: 4.80; Cl: 11.26; O: 15.25, Found C: 68.42; H: 4.95; Cl: 11.45; O: 15.18, ^{1}H-NMR 400 MHz, DMSO: δ ppm: 3.51-3.53 (s, 3H, -CH_3), 3.65-3.69 (s, 3H, -CH_3), 3.98 (s, 2H, -CH_2-inden), 7.16 (s, 1H, H-inden), 7.28 (s, 1H, H-inden), 7.35-7.49 (m, 4H, H-Ar), 7.52-7.64 (s, 1H, H-C-), ^{13}C-NMR: 400 MHz, DMSO: δ ppm: 37.53, 57.20, 110.07-110.26, 112.08-112.14, 132.43-132.99, 136.33-136.42, 136.86, 140.43, 142.35, 146.07, 149.76-149.89, 156.26, 193.12, MS: $[M+H]^+$ (315.07, 100%).





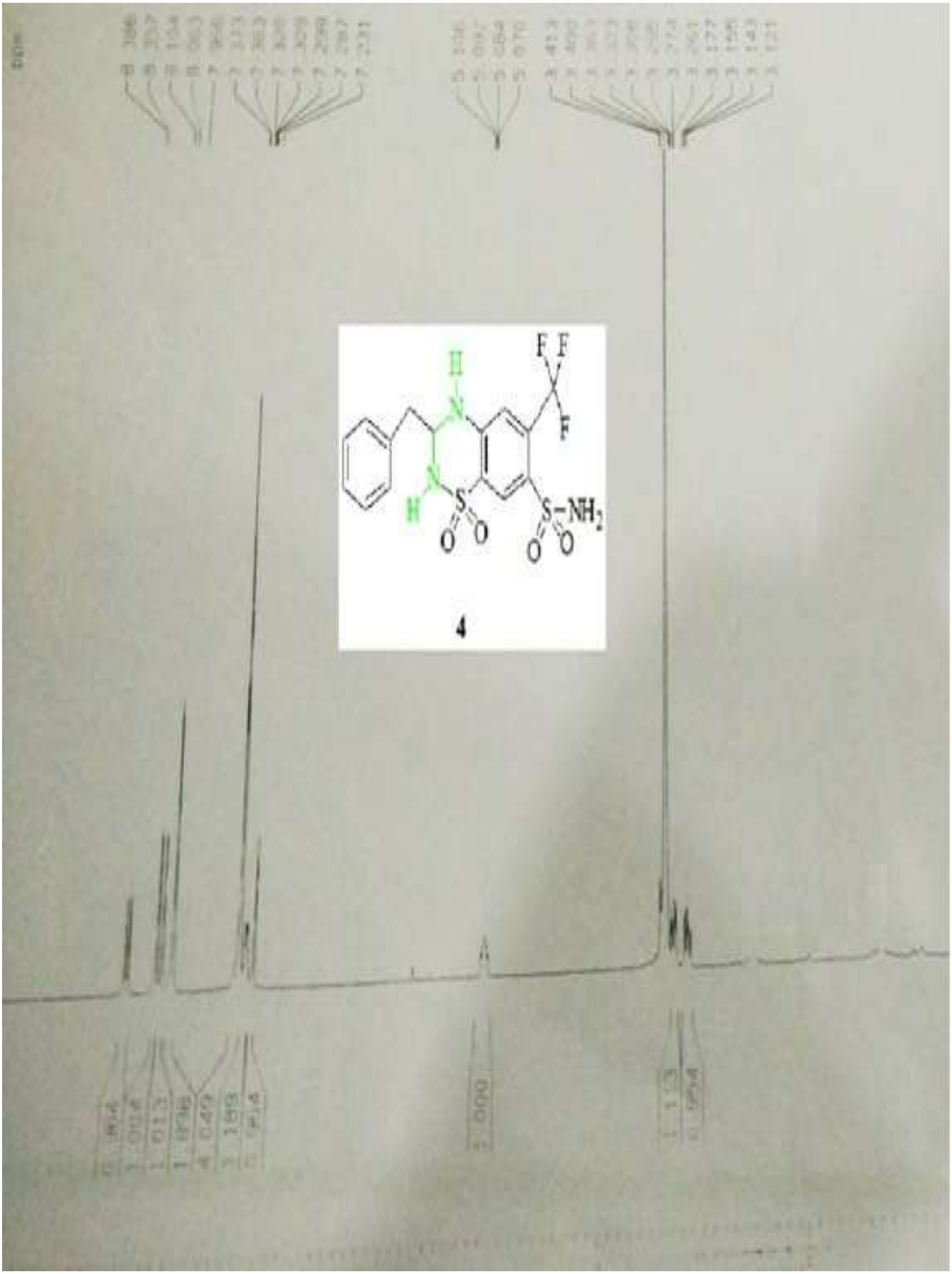


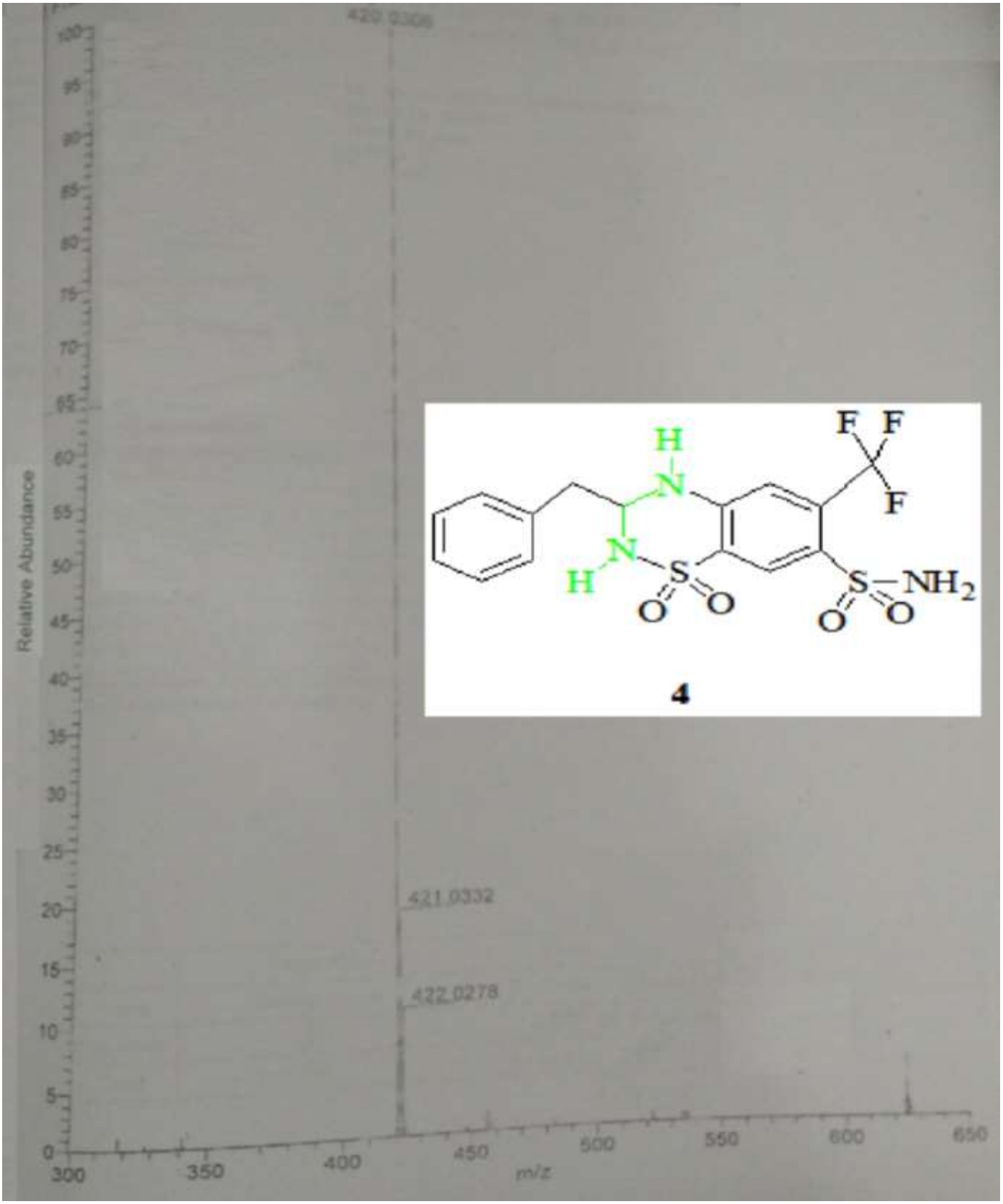
Preparation of 5-trifluoromethylaniline-2, 4-disulfonylchloride and 5-trifluoromethyl-2, 4-disulfamylaniline [34]

Preparation done as per the process described in U.S. Patent 3,392,168

Preparation of 3-benzyl-6-trifluoromethyl-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide (4)

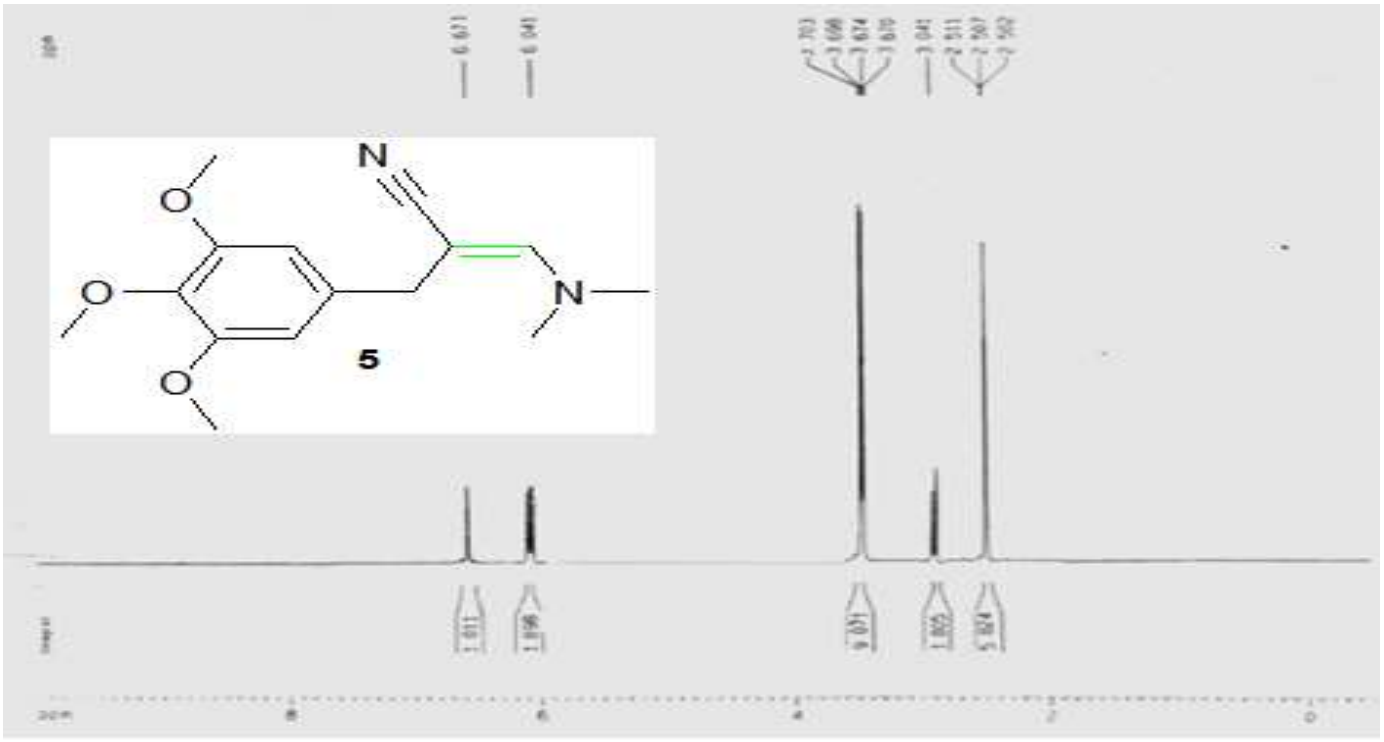
5-trifluoromethyl-2, 4-disulfamylaniline (5 g) and phenylacetaldehyde (2 g) or 1-(2,2-dimethoxyethyl)benzene (2.86 g) dissolved in methanol (30 ml) and a catalyst aqueous extract of *A. concinna* pods (10%, 10 ml) were heated for 6 h at 60-65°C and completion of reaction was monitored by using TLC (Hexane: Ethyl acetate 9:1). Reaction mixture was cool at 25-30°C for 1 h. and filtered crude product was recrystallized from dioxane, to get the pure desired product (4) 6.0 g (Yield 91%) with M.P. 224°C, Anal. Calc. for $C_{15}H_{14}F_3N_3O_4S_2$, C: 42.75; H:3.35; F:13.52; N:9.97; O:15.19; S:15.22 Found C: 42.47; H:3.53; F:13.87; N:9.72; O:15.26; S:15.15, ^{1}H-NMR 400 MHz, DMSO: δ ppm: 3.12-3.17 (dd, 1H, H-N-), 3.26-3.31 (dd, 1H, H-C-), 5.05-5.12 (m, 1H, H-N-), 7.23 (s, 1H,-CH_2), 7.29-7.30 (s, 1H, -CH_2), 7.36-7.38 (m, 4H, H-Ar), 7.97 (s, 2H, -NH_2), 8.06 (s, 1H, H-Ar), 8.10 (s, 1H, H-Ar), 8.36-8.39 (d, 1H, H-Ar), ^{13}C-NMR: 400 MHz, DMSO: δ ppm: 39.3-406, 67.8, 123.4, 125.6, 127.5, 127.8, 129.0, 129.4, 130.1, 135.7, 142.4, MS: [M-H] (420.03. 100%).

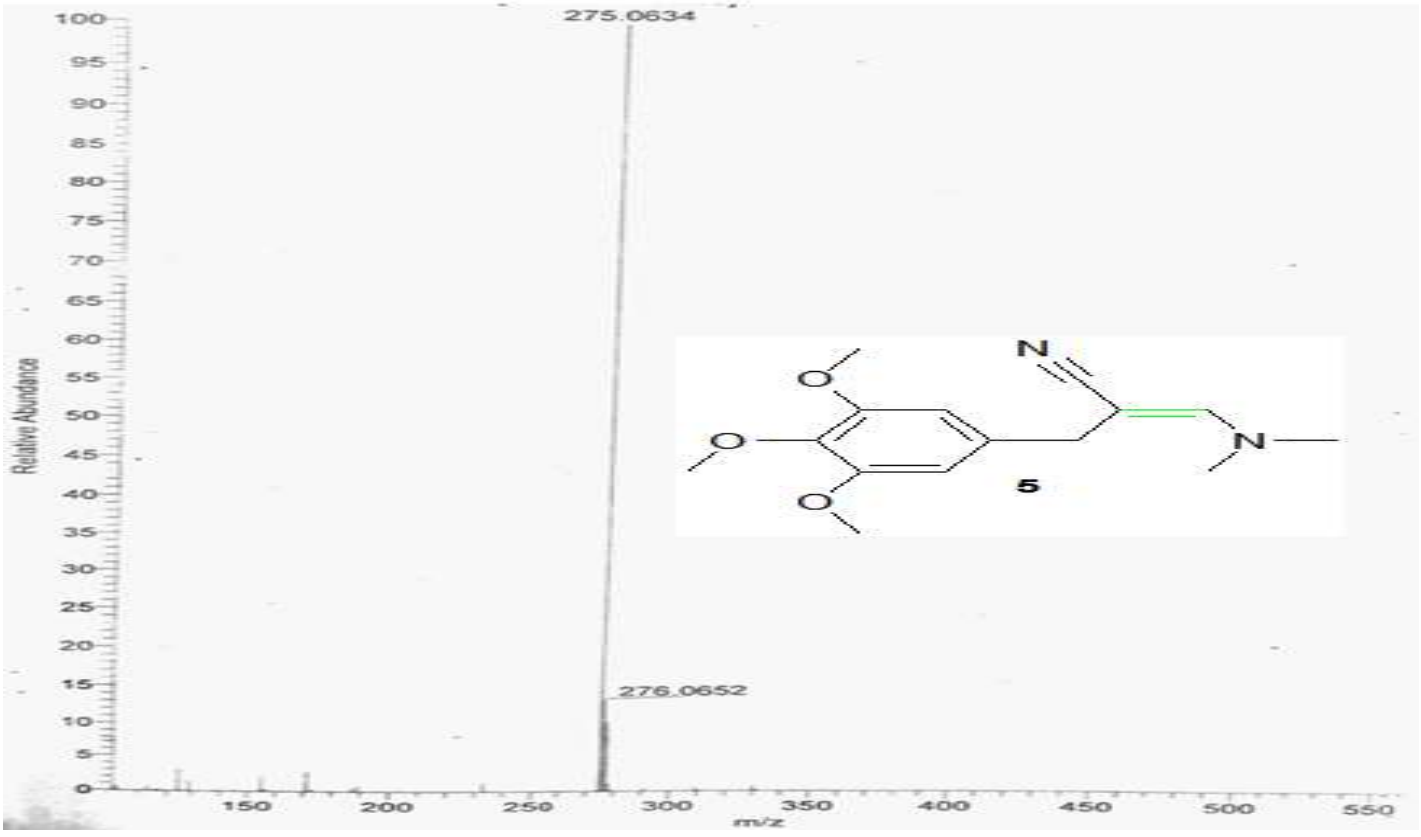

F F
F
H
N
N
H
S
O O
S-NH2
O O
4



Preparation of 2-(3, 4, 5-trimethoxybenzyl)-3-(dimethylamino) acrylonitrile (5)

3,4,5-trimethoxy benzaldehyde (5 g) and 3-(dimethylamino) propanenitrile (2.62 g) in methanol (30 ml) and a catalyst aqueous extract of *A. concinna* pods (10%, 10 ml) were heated for 8 h at 60-65°C and completion of reaction was monitored by using TLC (Hexane: Ethyl acetate 9:1). Reaction mixture was cool at 25-30°C for 1 h. and filtered crude product was recrystallized from DMSO: IPA, to get the pure desired product (5). Yield 6.68 g (95%), Anal. Calc. for $C_{15}H_{20}N_2O_3$, C: 65.20; H: 7.30; N: 10.14; O: 17.37 Found C: 65.38; H: 7.19; N: 10.29; O: 17.14, ^{1}H-NMR 400 MHz, DMSO: δ ppm: 2.502-2.511 (s, 6H, N-CH_3), 3.041 (s, 2H, -CH_2), 3.670-3.703 (s, 9H, O-CH_3), 6.041 (s, 2H, H-Ar), 6.671 (s, 1H, H-C-), MS: [M-H] (275.06 100%).

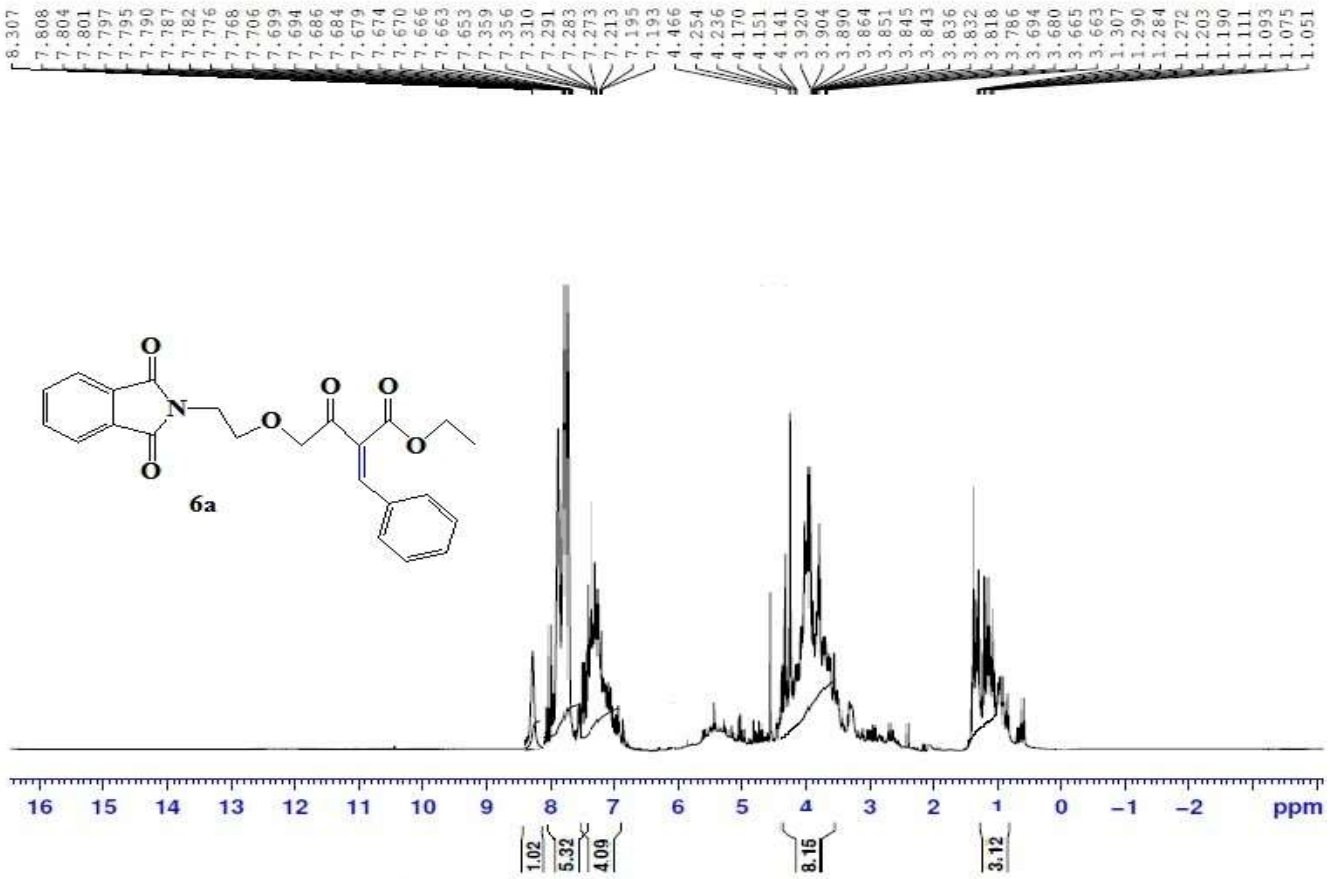




Preparation of (6a)

Benzaldehyde 1.16 g (1.1 mmol) and 2-(2-(2,4-dioxobutyloxy)-4 ethoxy, ethyl)isoindoline-1,3-dione (Ethyl 4-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-3-oxobutanoate) 3.19 g (1.0 mmol) in toluene (30 ml) and a catalyst aqueous extract of *A. concinna* pods (10%, 10 ml) were heated for 5 h azeotropically at 105-110°C and completion of reaction was monitored by using TLC (Hexane: Ethyl acetate 9:1). Reaction mixture was cooled at 45-50°C, added water 50 ml, separated layers and evaporated toluene layer was purified from column in Hexane: Ethyl acetate, to get the desired pure product light brown oily mass ethyl 2-benzylidene-4-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-3-oxobutanoate (6a).

Ethyl 2-benzylidene-4-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-3-oxobutanoate 6a: Yield 3.34 g (85%), Anal. Calc. for $C_{23}H_{23}NO_5$: C: 70.21; H: 5.89; N: 3.56; O: 20.33, Found C: 70.65; H: 5.55; N: 3.32; O: 20.48, 400 MHz, $CDCl_3$: δ ppm: 1.05-1.30 (t, 3H, $-CH_3$), 3.36-4.46 (m, 8H, 4^* - CH_2), 7.19-7.35 (dd, 4H, H-1,3-dioxoisoindolin), 7.65-7.80 (m, 5H, H-Ar), 8.30 (dd, 1H, -CH), MS: $[M+H]^+$ (408.13 100%).


8.307
7.808
7.804
7.801
7.797
7.795
7.790
7.787
7.782
7.776
7.768
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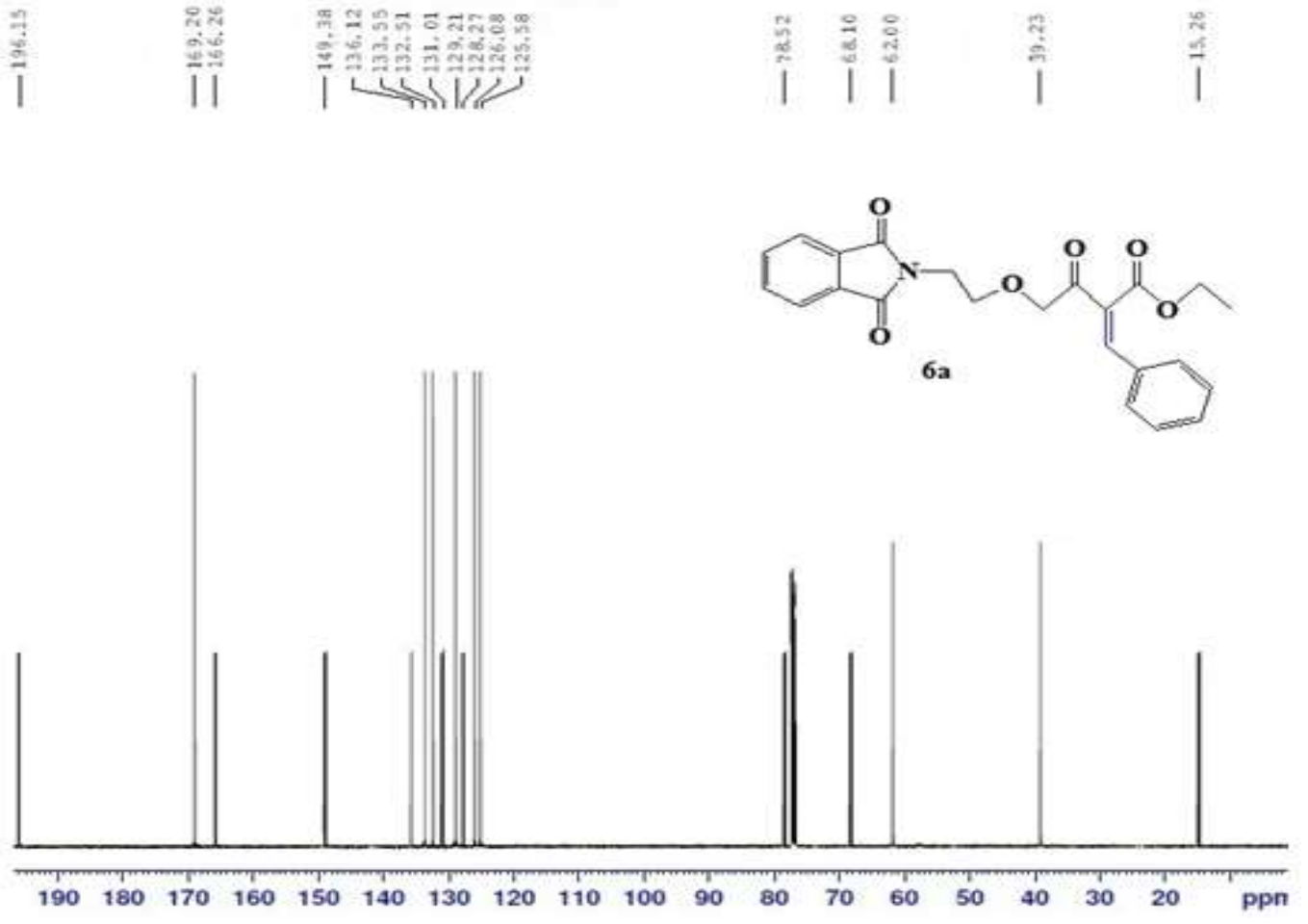
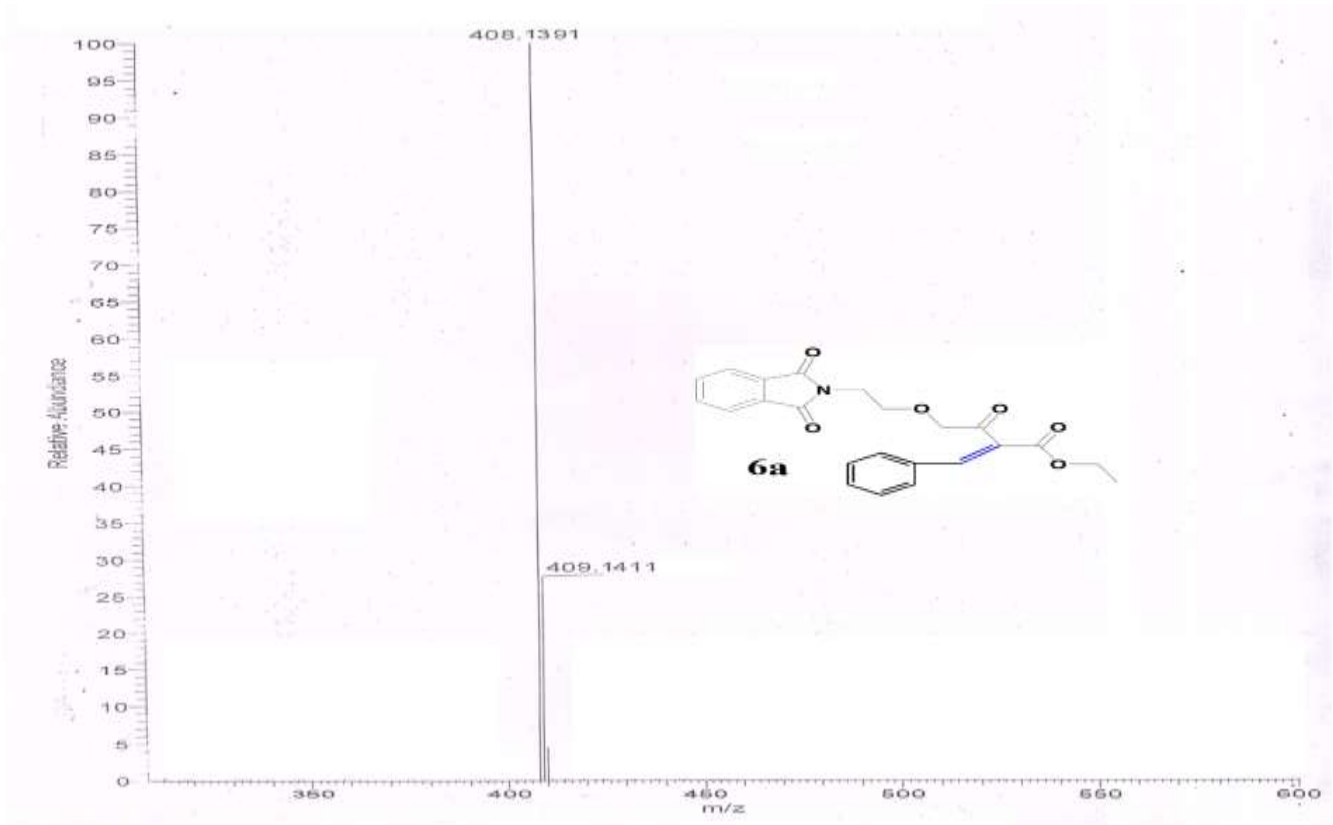
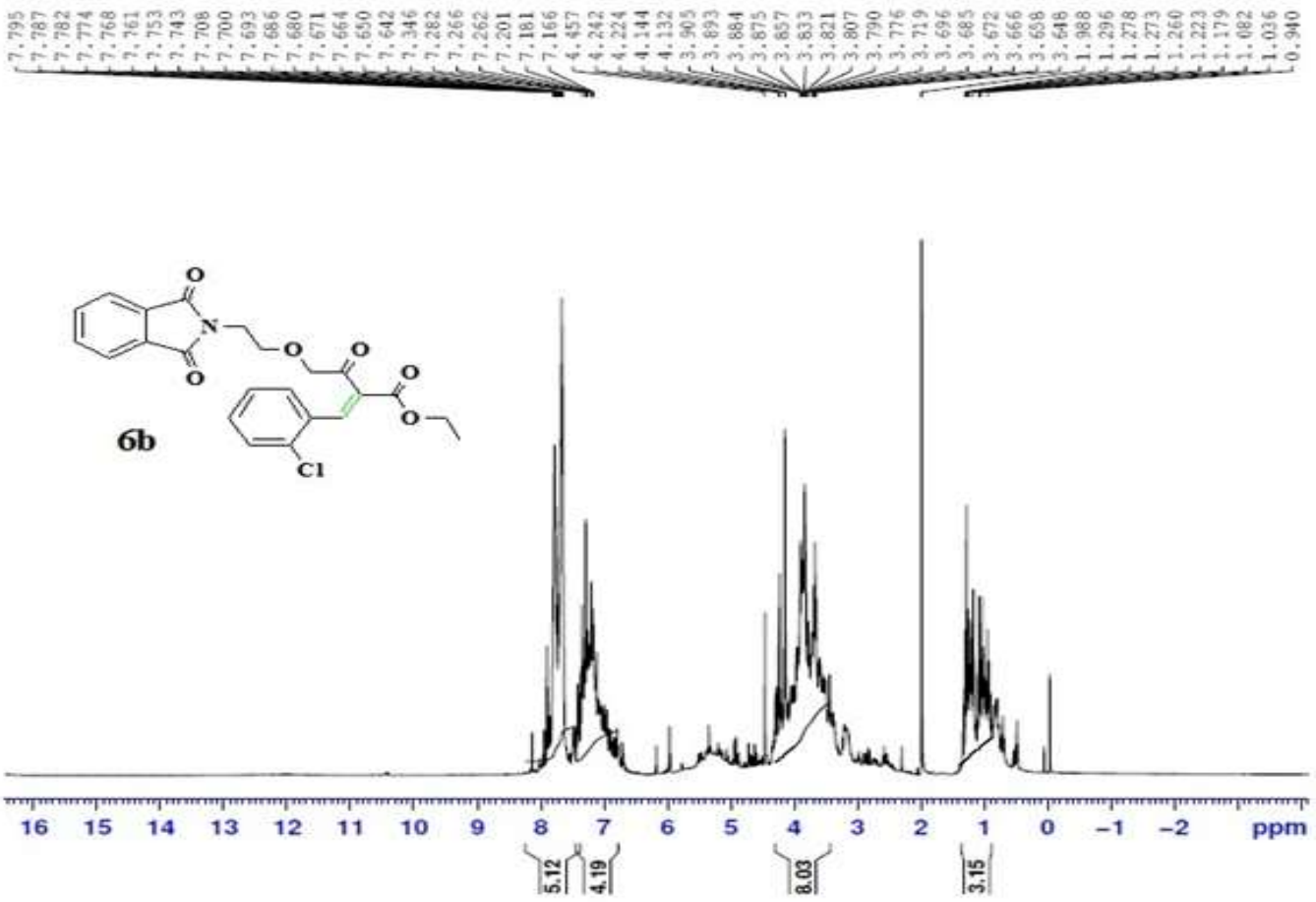
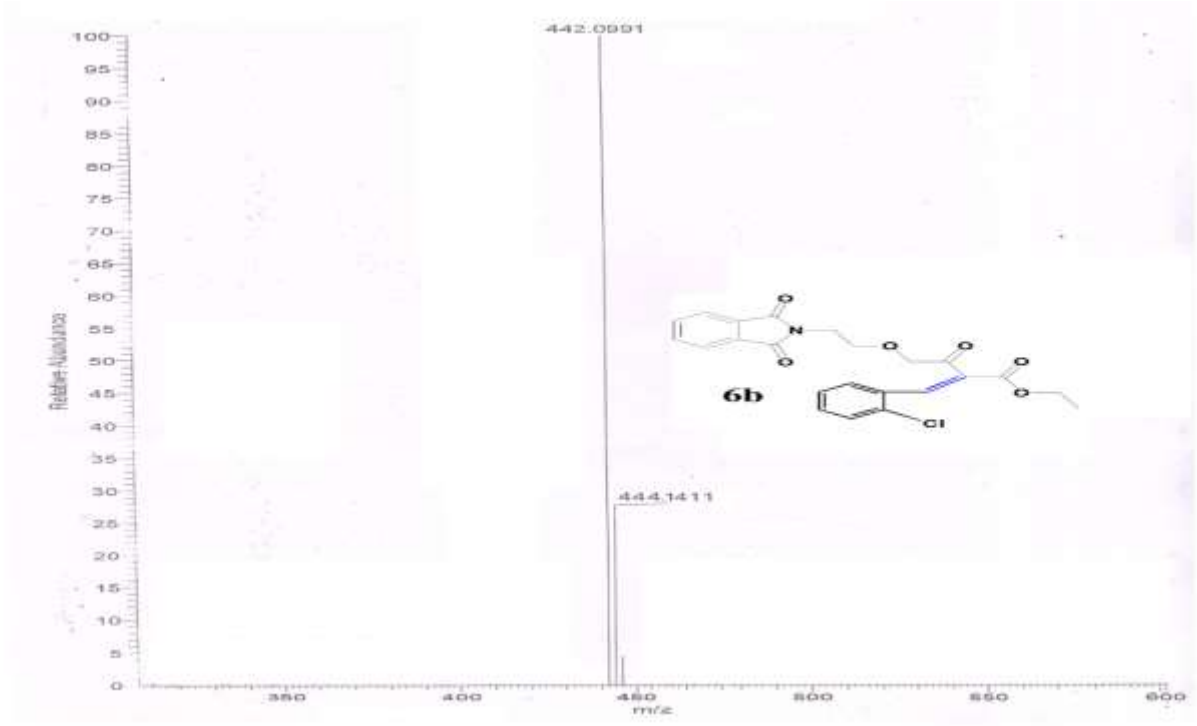
7.699
7.694
7.686
7.684
7.679
7.674
7.670
7.666
7.663
7.653
7.359
7.356
7.310
7.291
7.283
7.273
7.213
7.195
7.193
4.466
4.254
4.236
4.170
4.151
4.141
3.920
3.904
3.890
3.864
3.851
3.845
3.843
3.836
3.832
3.818
3.786
3.694
3.680
3.665
3.663
1.307
1.290
1.284
1.272
1.203
1.190
1.111
1.093
1.075
1.051
6a
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1 −2 ppm
1.02
5.32
4.09
8.15
3.12


196.15
169.20
166.26
149.38
136.12
133.55
132.51
131.01
129.21
128.27
126.08
125.58
78.52
68.10
62.00
39.23
15.26
6a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



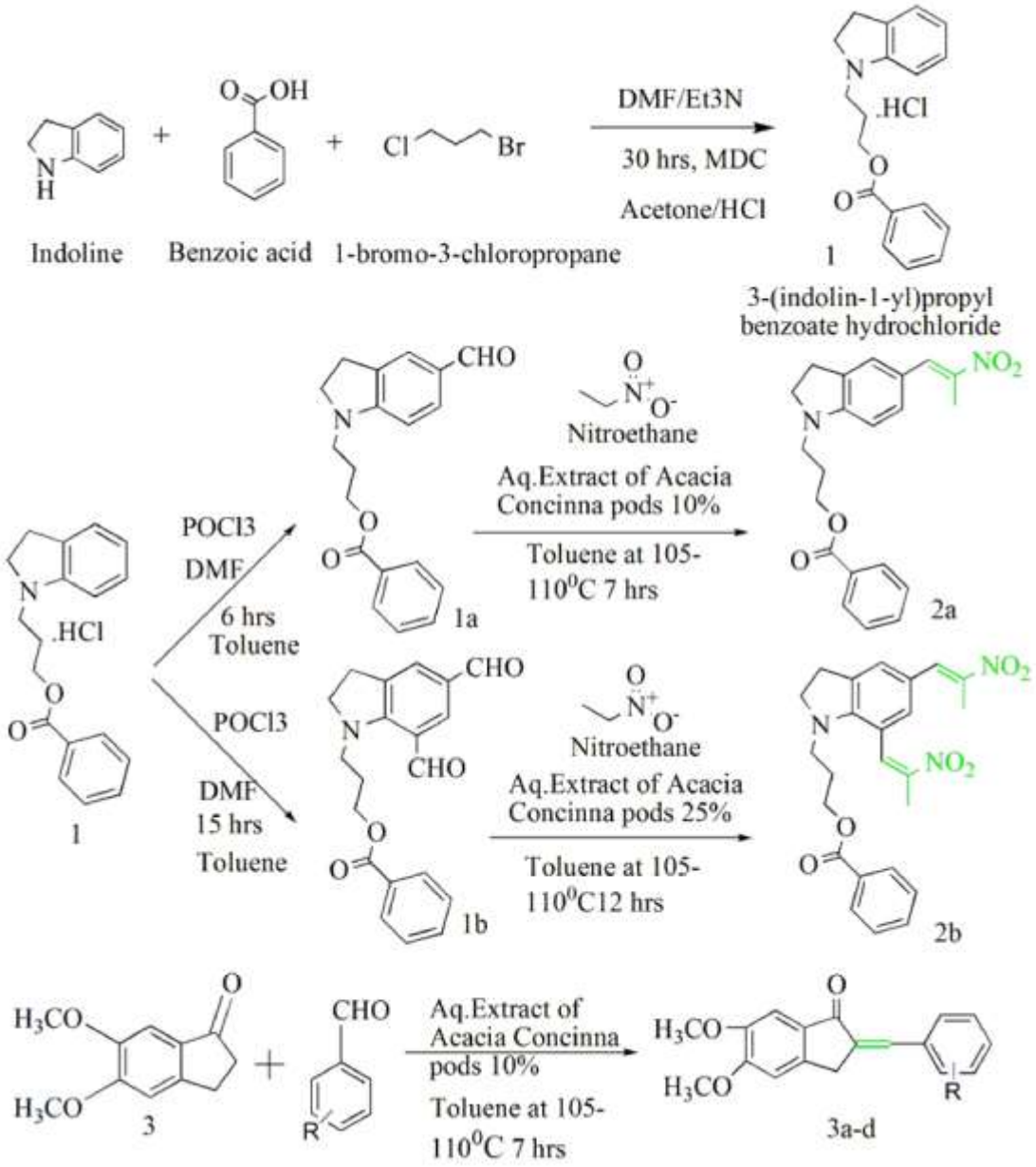
Ethyl 2-(2-chlorobenzylidene)-4-(2-(1,3-dioxoisoindolin-2-yl)ethoxy)-3-oxobutanoate (6b): Yield 3.64 g (85%), Anal. Calc. for $C_{23}H_{22}ClNO_5$: C: 64.56; H: 5.18; Cl: 8.29; N: 3.27; O: 18.70, Found C: 64.22; H: 5.52; Cl: 8.33; N: 3.40; O: 18.53, ^{1}H-NMR 400 MHz, $CDCl_3$ δ ppm: 0.94-1.29 (t, 3H, -CH_3), 3.65-4.45(m, 8H, 4*-CH_2), 7.16-7.34 (dd, 4H, H-1,3-dioxoisoindolin), 7.64-7.79 (m, 5H, H-Ar, -CH), MS: $[M+H]^+$ (442.10 100%).





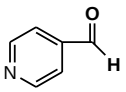
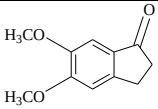
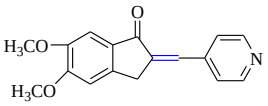
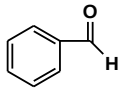
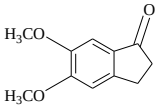
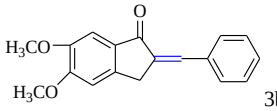
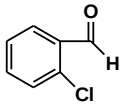
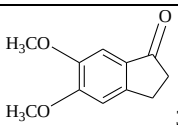
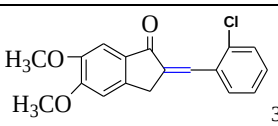
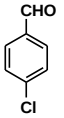
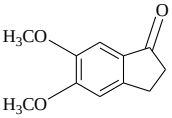
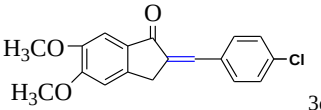
RESULTS AND DISCUSSION

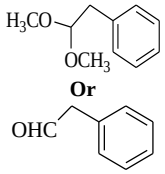
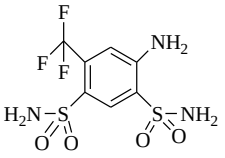
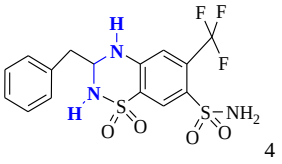
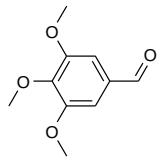
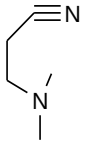
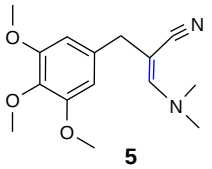
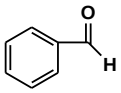
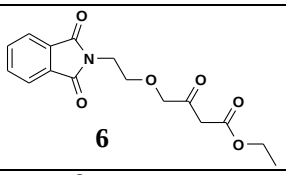
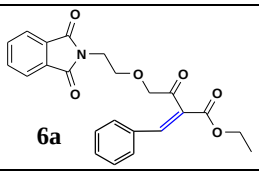
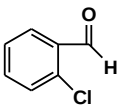
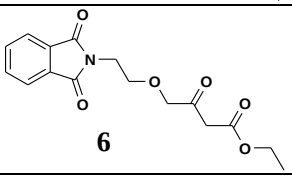
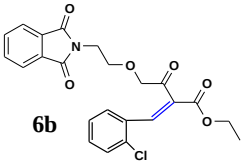
In continuation of our research and interest in the development of novel synthetic methodologies using fruit juice [3-10], herein we would like to report an synthesis of 3-(5-(2-nitroprop-1-enyl)indolin-1-yl)propyl benzoate from 3-(5-formylindolin-1-yl)propyl benzoate (Substituted aromatic aldehyde) and nitroethane via Knoevenagel condensation has been achieved by using aqueous extract of *A. concinna* pods as a green surfactant type catalyst Scheme 1. The condensation between indole substituted aldehyde and nitroethane takes place smoothly in presence of aqueous extract of *A. concinna* in toluene by azeotropic distillation at reflux temperature. The structures of different saponins present in the fruit have been recently established [37-40]. These saponins have surfactant properties similar to dodecyl benzene sulphonates [41]. The pods of *A. concinna* (Figure 3) have been found to contain the saponins of acacic acid. Acacic acid was found to be a trihydroxy monocarboxylic triterpenic acid of either tetracyclic or α-amyrin group [42]. The aqueous extract of these pods of fruit shows acidic pH (2.1) which is due to presence of a acaciac acid is a trihydroxy-monocarboxylic acid with molecular formula $C_{30}H_{48}O_5$ corresponding to pentacyclic triterpenes [43]. These interesting properties of aqueous extract of *A. concinna* pods allow us to use it as an eco-friendly acidic surfactant type catalyst for organic synthesis (Scheme 1) (Table 1).



Scheme 1: Synthesis of 1b and 2b from 1a and 2a with nitroethane via Knoevenagel condensation and Synthesis of 3a-d from 3 with substituted benzaldehyde via Aldol condensation

Table 1: Preparation of Knoevenagel, Aldol type condensation and cyclocondensation compounds by using aqueous extract of *Acacia concinna* pods

Entry	Aromatic Aldehyde	Active methylene compound	Product	% Yield[a]
1.		 3	 3a	97
2.		 3	 3b	88
3.		 3	 3c	90
4.		 3	 3d	92

5.			 4	91
6.			 **5**	95
7.		 **6**	 **6a**	85
8.		 **6**	 **6b**	85

The reaction was accompanied having green chemistry approach, shorter reaction time, mild reaction conditions and simple workup procedure along with excellent yield. As compared to other catalyst used under different conditions as depicted in Table 2. The scope of the presented method is demonstrated by using the substituted aromatic aldehyde to react with active methylene compound by using aq. extract of *A. concinna* via corresponding Knoevenagel, Aldol type condensation and cyclocondensation reactions with 80-97% yield as depicted in Table 3.

Table 2: Effect of surfactant on yield of 3-(5-(2-nitroprop-1-enyl) indolin-1-yl) propyl benzoate

Entry	Catalyst	Time (h)	% yield
1	TBAB	24	50
2	TBAF	22	48
3	p-TSA	26	52
4	$ZnCl_2$	20	70
5	Citric acid	25	72
6	Sodium acetate	18	65
7	Sodium benzoate	20	54
8	Sodium methoxide	15	38
9	Sodium ethoxide	17	40
10	Ammonium formate	17	64
11	Ammonium acetate	16	74
12	Aq. extract of *A. concinna* pods	15	95

Table 3: Optimization of % concentration of aq. extracts of *Acacia concinna* for Knoevenagel, Aldol type condensation and cyclocondensation reactions

Entry	% conc. of Aq. extract of *A. concinna* (w/v)	Time in h for compounds in brackets	% yield
1	5	12 (2a)	85
		9 (3a-d)	80-88
		9 (4)	85
		12 (5)	82
		8(6a-b)	70-75
2	10	7 (2a)	95
		7 (3a-d)	88-97
		6 (4)	91
		8 (5)	95
		5(6a-b)	80-85
3	15	7 (2a)	94
		20 (2b)	87
		7 (3a-d)	85-95
		6 (4)	90
4	20	6 (2a)	92
		17 (2b)	88
5	25	15 (2b)	92
6	30	14 (2b)	91

7	40	12 (2b)	90

CONCLUSIONS

We have developed an eco-friendly and economic process for the synthesis of pharmaceutically important Intermediates via Knoevenagel, Aldol type condensation by using aqueous extract of *A. concinna* pods as a catalyst green chemistry approach with several advantages such as shorter reaction time, mild reaction conditions, and simple work-up and reduces environmental impact with good quality and yield of the product.

ACKNOWLEDGEMENT

Authors are gratefully acknowledge the Director school of chemical sciences, thankful to Coordinator, Instrument Centre, Solapur University for their kind cooperation, inspiration, encouragement and constant support to complete the current work.

REFERENCES

[1] R. Maggi, F. Bigi, S. Carloni, A. Mazzacani, *Green Chemistry*., **2001**, 3, 173-174.
[2] A.K. Mallik, R. Pal, C. Guha, H. Mallik, *Green Chem. Lett. Rev*., **2012**, 5(3), 321-327.
[3] R. Pal, *Open J Organic Chem*., **2013**, 1(4), 47-56.
[4] M. B. Deshmukh, S.S. Patil, S.D. Jadhav, P.B. Pawar, *Synth. Commun*., **2012**, 42, 1177.
[5] S. Patil, S.D. Jadhav, M.B. Deshmukh, *Arch. Appl. Sci. Res*., **2011**, 3 (1), 203-208.
[6] R. Pal, *Int. J. Org. Chem*., **2013**, 3(2), 136-142.
[7] S. Patil, S.D. Jadhav, S. Mane, *J. Org. Chem*., **2011**, 1(3), 125.
[8] S. Patil, S.D. Jadhav, M.B. Deshmukh, *Indian J. Chem. Section B*., **2013**, 52(8), 1172.
[9] G.M. Nazeruddin, Y.I. Shaikh, *Der Pharmacia Sinica*., **2014**, 5(6), 64-68.
[10] R. Pal, *Int. J. Adv. Chem*., **2014**, 2(1), 27-33.
[11] R. Pal, T. Sarkar, *Int. J. Org. Chem*., **2014**, 4, 106-115.
[12] A.M. Fonseca, F.J. Monte, M.C.F. Oliveira, M.C.M. Mattos, G.A. Cordell, R. Braz-Filho, T.L.G. Lemos, *J. Mol. Catal. B: Enz*., **2009**, 57(1-4), 78.
[13] X. Wei, Z. Hepan, Y. Jie, L. Fang, W. Yanji, *Chinese J. Catal*., **2016**, 37, 769-777.
[14] K. Mote, S. Pore, G. Rashinkar, S. Kambale, A. Kumbhar, R. Salunkhe, *Arch. Appl. Sci. Res*., **2010**, 2(3), 74-80.
[15] H.V. Chavan, B.P. Bandgar, *ACS Sustain. Chem. Engin*., **2013**, 1(8), 929-936.
[16] E. Ramesh, R. Raghunathan, *Synth. Commun*., **2009**, 39(4), 613.
[17] D. Habibi, O. Marvi, *Arkivoc*., **2006**, 13, 8.
[18] M. Zahouily, B. Mounir, H. Charki, A. Mezdar, B. Bahlaouan, M. Ouammou, *Arkivoc*., **2006**, 13, 178.
[19] M. Zahouily, B. Bahlaouan, A. Rayadh, S. Sebti, *Tetrahedr. Lett*., **2004**, 45(21), 4135.
[20] S. Sebti, A. Smahi, A. Solly, *Tetrahedr. Lett*., **2002**, 43(10), 1813.
[21] Y. Riadi, R. Mamouni, R. Azzalou, R. Boulahjar, Y. Abrouki, M.E. Haddad, S. Routier, G. Guillaumet, S. Lazar S, *Tetrahedr. Lett*., **2010**, 51(51), 6715.
[22] J.L. Scott, C.L. Taston, *Green Chem*., **2000**, 2, 245-247.
[23] Johnson, *Int. J. Toxicol.*, **2005**, 24, 75-118.
[24] R.J. Sundberg, Academic Press: New York., **1996**, 7-11.
[25] V. Sharma, P. Kumar, D. Pathak, *J. Heterocyc. Chem*., **2010**, 47, 491.
[26] S. Biswal, U. Sahoo, S. Sethy, H.K.S. Kumar, M. Banerjee, *Asian J. Pharm. Clin. Res*., **2012**, 5(1), 1-6.
[27] N.K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C.H. Kim, A.K. Verma, E.H. Choi, *Molecules*., **2013**, 18, 6620-6662.
[28] M. Kitazawa, M. Ban, K. Okazaki, M. Ozawa, T. Yazaki, R. Yamagishi, USOO5387603A, Kissei Pharmaceutical Co., Ltd., feb 7, **1995**.
[29] A.A. Ghanwat, B.B. Kashid, V.M. Gugwad, D.J. Kesarkar, *World J. Phar. Pharmac. Sci*., **2016**, 5(7), 1127-1137.
[30] P.C. Yan, X.Y. Zhang, X.W. Hu, B. Zhang, X.D. Zhang, M. Zhao, D.Q. Che, Y.Q. Li, Q.L Zhou, *Tetrahedr. Lett*., **2013**, 54, 1449-1451.
[31] H. Sugimoto, Y. Iimura, Y. Yamanishi, K. Yamatsu, *J. Med. Chem*., **1995**, 38, 4821-4829.
[32] S. Hachiro, T. Yutaka, H. Kunizou, K. Norio, L. Youichi, S. Atsushi, Y. Yoshiharu, O. Hiroo, A. Shin, K. Takashi, K Atsuhiko, K. Michiko, Y. Kiyomi, US patent-4895841, **1990**.
[33] K.M. Devries, WO patent-22584, **1997**.
[34] L.A. Gutman, E. Shkolnik, B. Tishin, G. Nisnevich, I. Zaltzman, WO patent-09483, **2000**.
[35] I. Yoichi, US patent-6252081, **2001**.
[36] S.K. Dubey, M. Kharbanda, S.K. Dubey, C.S. Mathela, *Chem. Pharm. Bull*., **2010**, 58(9), 1157-1160.
[37] C.R. Elati, N. Kolla, S.R. Chalamala, P.J. Vankawala, V. Sundaram, H. Vurimidi, V.T. Mathad, *Synthetic Communications: An International J. for Rapid Communication of Synthetic Organic Chem*., **2006** 36(2), 169-174.
[38] J.G. Topliss, M.H. Sherlock, F.H. Clarke, M.C. Daly, B.W. Pettersen, J. Lipski, N. Sperber, *J. Org. Chem*., **1961**, 26(10), 3842-3850.
[39] E. Schonfeldt, H.T. Thorsteinsson, GB-879592, March 21, **1960**.
[40] F. Lund, K. Lyngby, W.O.G. Sen, U.S. Patent-3392168, July 9, **1968**.
[41] Y.F. Ji, J.A. Jiang, H.W. Liu, D.H. Liao, X.Y. Wei, *Synthetic Communications: An International J. for Rapid Communication of Synthetic Organic Chem*., **2013**, 43(11), 1517-1522.
[42] J.E. Arrowsmith, S.F. Campbell, P.E. Cross, J.K. Stubbs, R.A. Burges, D.G. Gardiner, K.J. Blackburnt, *J. Med. Chem*., **1986**, 29, 1696-1702.
[43] Y. Tezuka, K. Honda, A.H. Banskota,, M.M. Thet, S. Kinmoonosides, AC Kadota, *J. Nat. Prod*., **2000**, 63, 1658.
[44] A.S.R. Anjaneyulu, M. Bapuji, L.R. Rao, A. Sree, *Phytochemistry*., **1979**, 18, 463.
[45] M.O. Farook, I.P. Varshney, Z. Naim, *Arch. Pharm*., **1961**, 294, 133.
[46] G. Pratap, V.S. Bhaskar Rao, F. Wiss, *Technol*., **1987**, 89, 205-208.
[47] I.P. Varshney, K.M. Shamsuddin, *Tetrahedr. Lett*., **1964**, 5, 2055-2058.
[48] I. P. Varshney, K.M. Shamsuddin, *Bull. Chem. Soc. Jpn*., **1970**, 43, 3830-3840.