STUDIES ON THE SYNTHESIS OF *STRYCHNOS* ALKALOIDS WITH THE ASPIDOSPERMATAN SKELETON

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ABSTRACT

In recent year, organic chemist have paid great attention to the synthesis of uleine type alkaloids, because of their biological activity and being core structure for many biological active compounds (tubotaiwine (**4**), condyfoline (**5**) and tubotaiwinal (**6**)), Tetracyclic alkaloids of the uleine group and the more complex *Strychnos* alkaloids have the same core structure. Therefore, different synthetic strategies was applied in this study. The core structure of uleine group alkaloids and pentacyclic stychnos alkaloids, N-(Acetyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**), were synthesized. Many different new compounds (2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**), N-Methyl-2-(3-Ethyl-1-oxo-,2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**68**), 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3a]carbazol-2(10H)-one (**71**), 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3a]carbazol-2(10*bH*)-one (**73**), 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3a]carbazole-2,5(10*H*, 10*bH*)-dione (**74**) and 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)) were also synthesized successfully.

Keywords: Alkaloid*s, Aspidosperma* type alkaloids, Dasycarpidone, *Strychnos alkaloids*, Tetrahydrocarbazole derivatives, Uleine.

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ASPİDOSPERMATAN İSKELETİ İLE *STRYCHNOS* ALKALOİTLERİNİN SENTEZİ ÜZERİNE ÇALIŞMALAR

AYŞE UZGÖREN

ÖZ

Ulein tipi alkaloitler genellikle biyolojik aktif bileşiklerdir ve ayrıca birçok biyolojik aktif bileşiğin (tubotaiwine (**4**), condyfoline (**5**) ve tubotaiwinal (**6**)) temelini oluştururlar. Bu sebeple, son yıllarda sentetik organik kimyacıların oldukça ilgisini çekmektedir. Ulein grubu alkaloitleri ve daha kompleks yapıda olan “Strychnos” alkoloitlerinin temel yapıları aynıdır. Bu nedenle, bu çalışmada indol alkaloitlerinin sentezi için, farklı sentetik stratejiler oluşturulmuştur. Ulein grup alkaloitleri ve pentasiklik “Strychnos” alkaloitleri için temel yapı olan N-(Asetil)-12-etil-1,2,3,4,5,6-hekzahidro-1,5-metanoazokino[4,3-b]indol (**61**) bileşiği sentezlenmiştir. Bunun yanında, birçok yeni bileşik de (2-(3-Etil-1-okzo-2,3,4,9-tetrahidrokarbazol-2-il)asetik asit (**67**), N-Metil-2-(3-Etil-1-okzo-,2,3,4,9-tetrahidro-1H-karbazol-2-il)asetamit (**68**), 4-Etil-1-metil-3,3a,4,5,10,10b-hekzahidropirol[2,3a]karbazol-2(10H)-on (**71**), 4-Etil-3,3a,4,5-tetrahidro-10*H*-furo[2,3a]karbazol-2(10*bH*)-on (**73**), 4-Etil-3,3a,4,10-tetrahidro-3*H*-furo[2,3a]karbazol-2,5(10*H*, 10*bH*)-dion (**74**) ve 2-(3-Etil-1-hidroksi-4-okzo-2,3,4,9-tetrahidro-1H-karbazol-2-il)asetamit (**75**)) bu çalışmada ede edilmiştir.

Anahtar Kelimeler: Alkaloidler, *Aspidosperma* tipi alkaloidler, Dasykarpidon, *Strychnos* alkaloidleri, Tetrahidrokarbazol türeleri, Ulein.

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ABBREVIATIONS

^{1} H-NMR : Proton Nuclear Magnetic Resonance
^{13} C-NMR : Carbon Nuclear Magnetic Resonance
Bn : Benzyl
Boc$_2$O : Di-tert-butyldicarbonate
DDQ : 2.3-dichloro-5,6-dicyano-p-benzoquionone
DMSO : Dimethyl sulfoxide
HMPA : Hexamethylphosphoramide
IR : Infrared Spectroscopy
LAH : Lithium aluminum hydride
LC-MS : Liquid Chromatography - Mass Spectroscopy
m : Multiplet
Mp : Melting Point
MTBE : Methyl tertiary-butyl ether
Mw : Moleculer weigth
PCC : Pyridinium Chlorochromate
PDC : Pyridinium Dichromate
q : Quartet
Rf : Retardation factor
s : Singlet
t : Triplet
TFAA : Trifluoroacetamide
THF : Tetrahydrofuran
TLC : Thin Layer Chromatography
TMS : Tetramethylsilane
UV : Ultraviole Spectroscopy

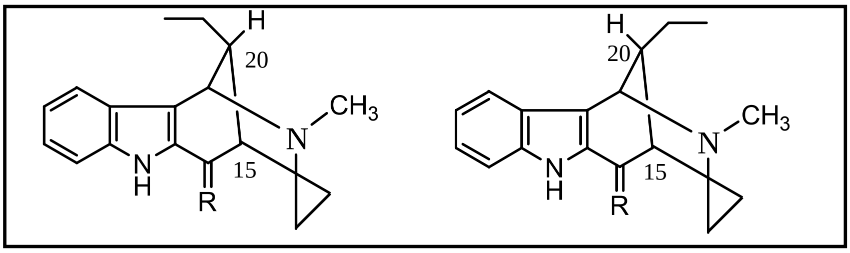
1 INTRODUCTION

The total synthesis of complex natural products remains the most difficult, daunting, and challenging endeavor in organic chemistry. It is also the most humbling, exhilarating, and formative entreprise in our science. The sizes and complexities of the natural products synthesized today bear no resemblance to the substrates that were targeted in the beginning (Wöhler, 1828). The assembly of complex natural products has stimulated the development of powerful synthetic methodologies that enable organic chemists to build, in a shorter time and more efficient manner, structures of previously undreamed complexity. The desire to imitate nature has led to the discovery and establishment of powerful biomimetic approaches, as examplified by the Johnson synthesis of steroids (Johnson, 1968).

The remarkable synthesis of vitamin B12 by Eschenmoser and Woodward marks starting of the modern natural product synthesis (Eschenmoser and Wintner, 1977; Woodward, 1968; Woodward and Hoffmann, 1969). Before this work, organic synthesis was performed primarily to nail down the structure of particular molecules. But the structure of vitamin B12 was known through the pioneering crystallographic work of Dorothy Crowford Hodgin. The emphasis thus shifted to exploring new synthetic routes to make this complex material from simple starting materials. The synthesis took 11 years and involved more than 90 separate reactions performed by over 100 co-workers. The sterochemical puzzles involved in the synthesis led to the Woodward-Hoffman rules, which spell out how the electronic structures of molecules reorganize during reactions. The vitamin B12 synthesis revolutionized theoretical chemistry, and the Woodward-Hoffman rules paved the way to the use of orbital theory by the chemical community (Woodward and Hoffmann, 1969).

The next milestone in organic chemistry was the discovery by Barton that organic molecules could be assigned a preferred conformation and that the chemical and physical properties of a molecule could be interpreted in terms of that preferred conformation (Eliel and Wilen, 1994). This discovery helped to guide synthetic pathways. Retrosynthetic analysis, which entails going backward from a target molecule to starting materials, was introduced by Corey and Cheng (Corey and Cheng,1989) and its relevance demonstrated by a number of exquisite total syntheses. The advent of organometallic chemistry and the realization that metal complexes could perform unique transformations resulted in a major leap forward in the complexity and size of the molecules that could be prepared (Nicolaou and Sorensen, 1996). Analytical tools have evolved in parallel. For example, powerful nuclear magnetic resonance spectrometers can now routinely detect microgram quantities of substances. But the challenges awaiting organic synthesis are unlimited as ever more complex biological structures are discovered. One of the these challenges is synthesis of alkaloids. Alkaloids are basic and nitrogen-containing compounds of plant origin. They have complex molecular structures and manifest significant pharmacological activity (Pelletier, 1970). Indol alkaloids comprise a large family of natural products. A great deal of research has gone into their structural elucidation, synthesis and biosynthesis (Kutney, 1973). Uleine and dasycarpidone are tetracyclic indole alkaloids. They were isolated from Aspidosperma species. Many scientist are interested in synthesis of these compounds because of their biological activity.

In 1959, Buchi and Wanhoff explained the structure of uleine using two-dimensional contitution (Buchi and Warnhoff, 1959). But the configuration of the ethyl group remained to be established. The first evidence concerning this point was provided by the reaction of the alkaloid with methyl iodide. The high rate of quarnization observed suggested that the ethyl group is situated equatorially away from the basic nitrogen atom (Shamma et al., 1967). An examination of Aspidosperma subincanum carried out in the same year led to the isolation of a nw alkaloid which proved to be epiuleine (Gaskell and Joule, 1967). In the nuclear magnetic resonance spectrum of epiueine, the C-methyl triplet appears at δ 1.08 while it's shifted upfield to δ 0.88 in uleine. This difference was attributed tol on-range shielding from the indole ring, and uleine and epiuleine were assigned the configurations **1a** and **1b**, respectively (Buchi et al., 1971) (Figure 1).



Normal series **20-Epi series**

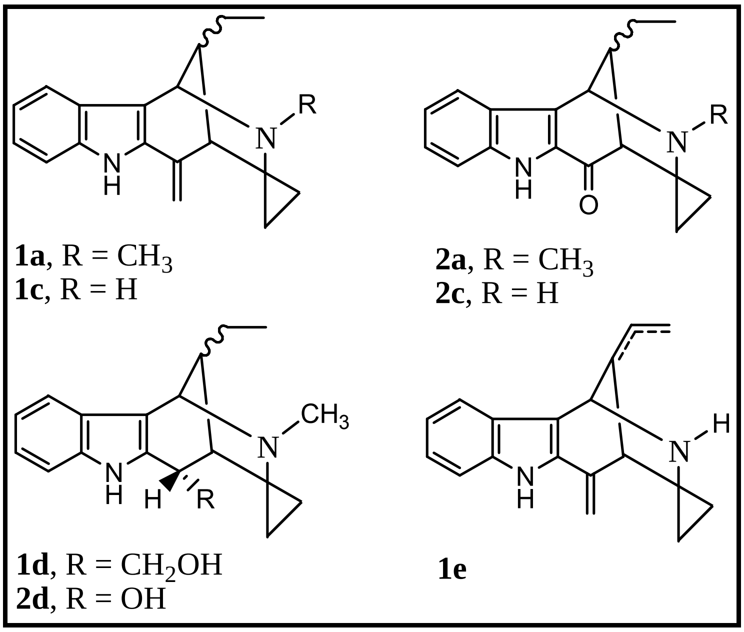
1a, R = CH_2 **1b,** R = CH_2

2a, R = O **2b**, R = O

Figure 1. Uleine-dasycarpidon and its epimers

Synthetic studies in this area have led to total synthesis of four natural products: uleine (**1a**) (Amat et al, 2004; Amat et al., 1997; Schmitt et al., 1997; Saito et al., 1997; Jackson et al., 1969; Wilson et al., 1968), epiuleine (**1b**) (Amat et al, 2004; Amat et al., 1997; Dolby and Biere, 1970,), dasycarpidone (**2a**) (Amat et al, 2004; Amat et al., 1997; Bonjoch et al., 1991; Jackson et al., 1969; Dolby and Biere, 1970; Dolby and Biere, 1968; Wilson et al., 1968) and epidasycarpidone (**2b**) (Dolby and Biere, 1970; Jackson et al., 1969; Dolby and Biere, 1968; Wilson et al., 1968).

The uleine group of indole alkaloids involves seven bases which have been chemically interrelated. Besides uleine (**1a**) itself, the group includes des-N-methyluleine (noruleine) (**1c**), 1,13-dihydro-13-hydroxyuleine (**1d**), dasycarpidone (**2a**), des-N-methyldasycarpidone (nordasycarpidone) (**2c**), dasycarpidol (**2d**) and des-N-methyldehydrouleine (**2e**) (Figure 2).



1a, R = CH_3
1c, R = H

2a, R = CH_3
2c, R = H

1d, R = CH_2OH
2d, R = OH

1e

Figure 2. Uleine group alkaloids

Aspidosermatan skeleton (**3**) is present in a large number of indole alkaloids belonging to different skeletal types such as as tubotaiwine (**4**), condyfoline (**5**), tubotaiwinal (**6**) and epicondyfoline (**7**) as well as in the alkaloids of the uleine group (Figure 3) skeleton (Bonjoch et al., 1991; Magnus et al., 1992). But most of them have some limitations because of their low yields.

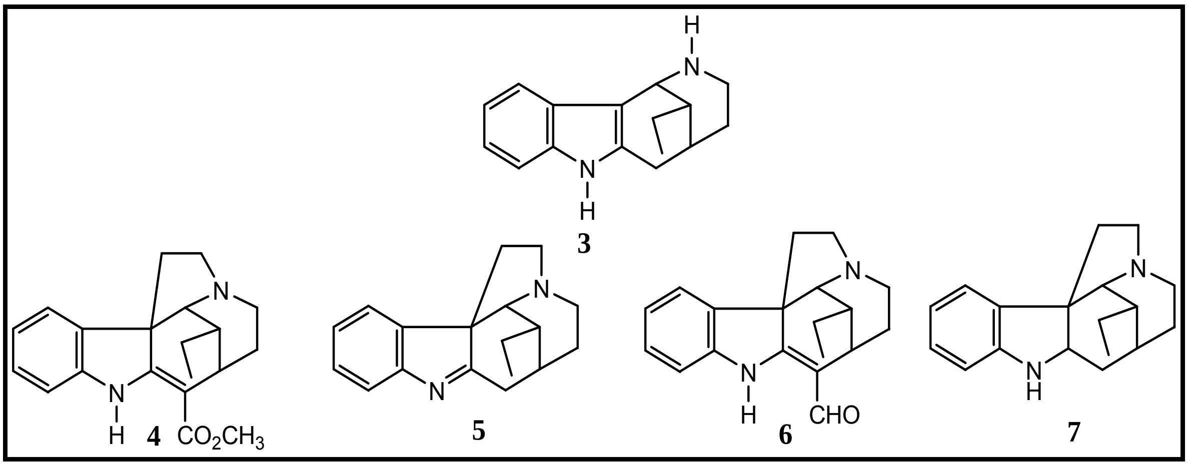


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Figure 3. Aspidospermatan skeleton and pentacyclic strychnos alkaloids

In our study, an alternative synthetic entry to the tetracyclic ring system of indole alkaloids of the uleine group is presented and many different new compounds are synthesized and characterized.

2 BACKGROUND

2.1 A Brief History of Natural Products Chemistry

The chemistry of the natural world has been used for hunting, euthanasia, execution, euphoria and medicines since the dawn of humanity. One of the first applications of natural products by primitive humans was the use of poisons for weapons, especially arrow poisons (Roberts et al., 1998). It has been identified that the people of South America, Asia and Africa all extensively used plant constituents for hunting and tribal warfare. The using these chemical weapons was an attempt by *Homo sapiens* to gain mastery over a hostile enviroment, which involved protecting themselves from both animal and human enemies, as well providing food through the use of more sophisticated hunting techniques. Although the arrow poisons from South America were generally made from *curare*, which is the crude extract of the plant, *Chondodendrum tomentosum* and various *Strychnos* species, a secreted residue from Columbian frogs of the genuses, *Phyllobates* and *Dendrobates*, was also used by local Indians as another source of arrow poison (Mann, 1989). While these toxic mixtures are stil used today in some parts of the world for hunting, they have also provided a source for both traditional and modern medicines. The modern medical world has isolated and purified various bioactive metabolites from the original arrow poisons, and used these natural products for effective therapies against disease or as tolls for research. Well known examples include, physostigmine (**8**) for glaucoma, (+)-tubocurarine (**9**) as a muscle relaxant in anesthesia, and reserpine (**10**) as an antihypertensive and psychotropic drug (Roberts et. al., 1998) (Figure 4).

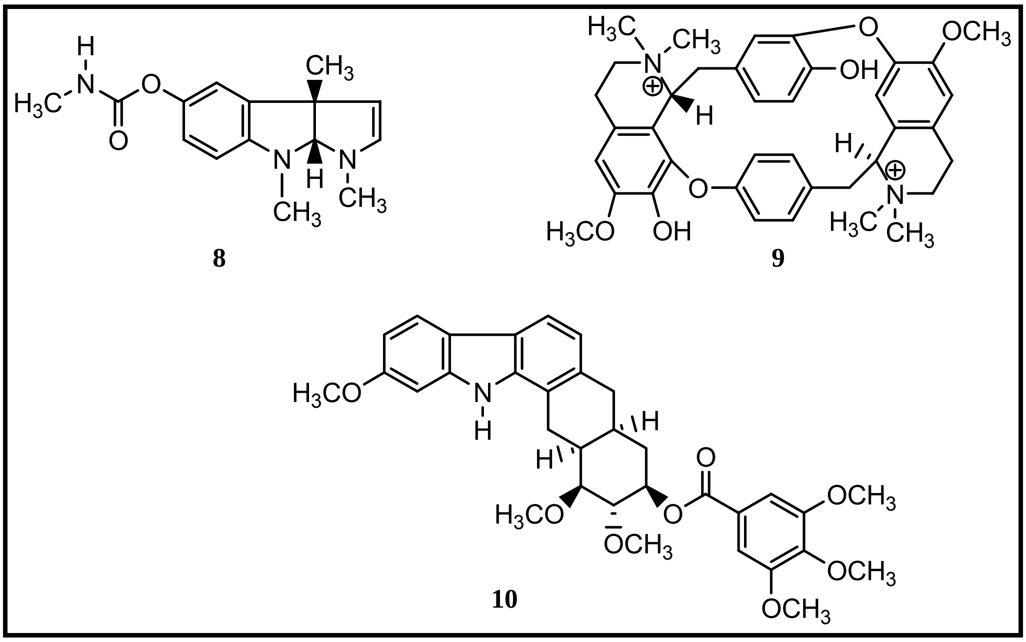

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Figure 4. Bioactive metabolites

While these examples highlight the use of natural products as drugs in the modern era, the use of plan tor animal material for healing has been used by many different civilisations over the millenia. The origin of traditional Chinese medicine can be traced back to around 2500 BC, with the Yellow Emperor recognised as the founding father. The classic text which bears his name, the Huang Ti Nei Ching Su Wen (or Yellow Emperor's Canon of Internal Medicine) is generally dated to only 1000 BC, however, this text could well represent the written work of a much older verbal tradition (Ody, 1993). The oldest compilation of Chinese herbs, is generally ragarded as the *Shen Nung Pen Ts'ao Ching* (or *Shen Nung's Catalogue of Herbs*). This text is believed to have been revised during the Han Dynasty (206 BC-220 AD), and contains a list of 365 plant materials used for healing purposes. Since that time the number of documented medicinal herbs used in China has increase to around 5300 (Barton, et. al., 1999).

Archaeological research has identified other ancient civilisations which used natural products for medicinal purposes. The Assyrians left behind 660 clay tablets describing 1000 medicinal plants used between 1900-400 BC, while the discovery of two papyrus scripts from ancient Egyot times have provided detail of the healers involvement in surgery, prescription, and the healing practices which used plant, animal and mineral material (Barton, et. al., 1999). Numerous individuals throught history have contributed to the use of natural products as therapeutic agents. The 2nd century Greek physician, Galen wrote extensively about the four *humours*-blood, phlegm, black bile and yellow bile-and classified herbs by their essential qualities as either hot or cold, (Ody, 1993). These theories were later expanded by the 7th century Arab doctor, Avicenna and were stil being used well into the 18th century. The Doctrine of Signatures was another medical principle which originated during the 11th century and was followed by the Western world up until the 18th century. This principle maintained that the outward appearance of a plant gave an indication of the ailments it would cure. With the birth of organic chemistry in the 19th century, scientists began examining bioactive plant samples in order to identify the individual active ingredients. The isolation and purification of bioactive compounds signaled the beginning of the scientific discipline, natural products chemistry.

2.2 Plants As a Source of Chemicals

Plant life is essential for human life. It maintains the delicate balance of pure air supply and supplies food, cloth and timber. Together with these, it has also been used as a source of chemicals for centuries. Among these the source of chemicals, which are important in healthcare and used as medicinals, agrochemicals and fine chemicals are only obtained from plants. Stimulants, narcotics and poisons are considered as medicinals.

At present there are approximately $2x10^4$ known plant-derived chemicals with an annual rate of about $1.6x10^3$ new additions (Fowler and Stepan-Sarkissian, 1983). About 10% of an estimated $7.5x10^5$ species of higher plants have been surveyed for biological activity (Floers, 1987). In spite of advances in synthetic organic chemistry, plants are the major source of these chemicals.

These plant-derived chemicals represent multibillion dolar industries; for example, an insecticide derived from Azadirachta indica the antitumor alkaloids vindlastine and vincristine found in the periwinkle (Catharanthus roseus) (Flores, 1987). The latter are the most effective chemical therapeutic agents for various forms of leukaemia and have a retail price of over $ 6000 g^{-1} (Flores, 1987).

In plants, these chemicals are usually present in small amounts. To get a few grams of desired compound, a large volume of raw material is necessary. To fulfill the high demand of these plant-derived chemicals, it is necessary to harvest the raw materials throught the year, which may result in the extinction of the plant species and finally to loss of the chemical forever. To overcome this problem and to get a continuous supply of these plant-derived products, development of an alternative method to the whole plant extraction was found to be important. Total synthesis of this compound may provide a competitive plant-derived chemical production system.

2.3 Alkaloids

2.3.1 “Alkali-like”

A natural product is a compound synthesised by plant or an animal. Substances containing a basic nitrogen atom isolated from natural sources are called alkaloids. Since alkaloids are often amines, they react more or less as bases and give soluble salts when treated with acids. Hence the term alkaloid, derived from “alkali-like”, was coined by the pharmacist W. Meissner in 1819 (Hosztafi,1997). This term was soon developed further and “true alkaloids” were long defined as compounds meeting four requirements:

The nitrogen atom is part of a heterocyclic system.
The compound has a complex molecular structure.
The compound manifests significant pharmacological activity.
The compound is restricted to the plant kingdom.

This definition is however not particularly valid today for several reasons (Pelletier, 1983; Snieckus,1980). Basicity, for example, is no longer as a necessary property of an alkaloid, despite the fact that the word stems from *alkali-like*. Piperine (**11**) (isolated from black pepper *Piper nigrum*) is a good example of a compound that is considered to be an alkaloid despite being a neutral amide. Although many early classified alkaloids contained nitrogen in a heterocyclic system. There are today too many exceptions for requirement to be mandatory, as exemplified by mescaline (**12**) (isolated from the cactus peyote, *Lophophora williamsii*) (Anderson, 1996). Also, vague concepts like *complexity* of molecular structure and *significant* pharmacological activity have no place in a modern definition. Furthermore, restriction to plant kingdom also seems inappropriate since too many compounds possessing classical alkaloid structures have been isolated from animal, fungal and bacterial sources. Thus, today the concept alkaloid has been expanded and it is generally considered to be a naturally occuring nitrogenous compound. However, a more specific definition has been proposed by Pelletier (Pelletier, 1983):

An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms.

The first alkaloid to be isolated in pure form was morphine (**13**) (from opium poppy seeds) in 1805 by W. Sertürner (Hosztafi,1997). Alkaloids typically have potent phsiological properties and are often toxic when the dose is large enough. In spite of this, many alkaloids have found use in medicine. Sometimes striking physiologial effects of alkaloids can be illustrated by the notoriously known alkaloids caffeine (**14**), nicotine (**15**) and cocaine (**16**), just to mention a few (Figure 5).

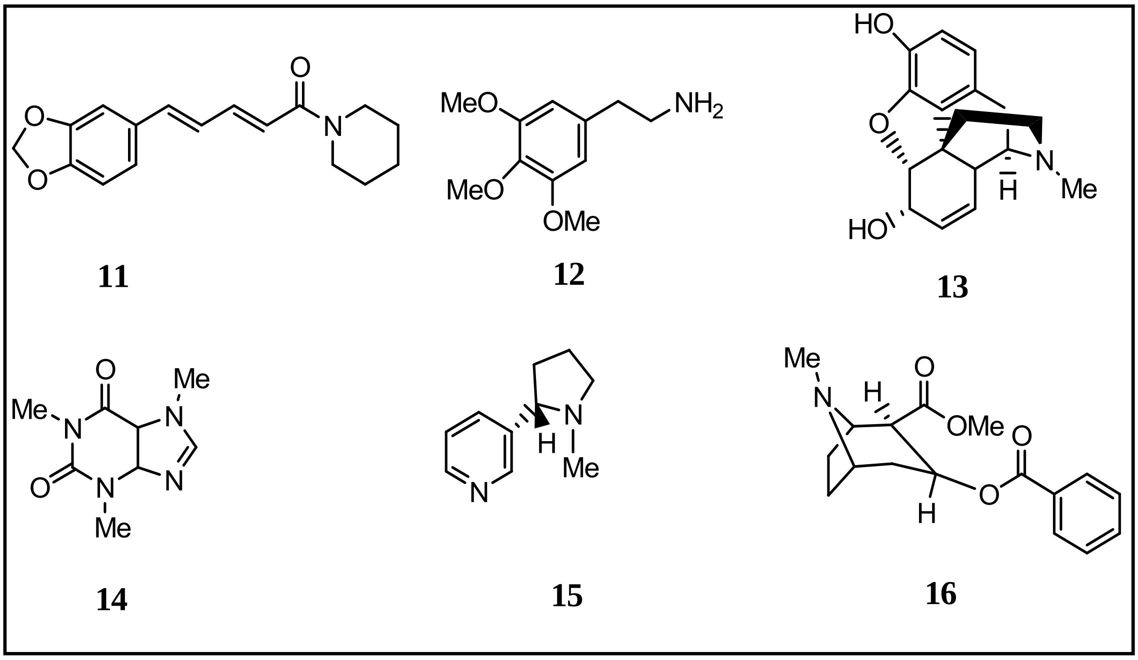


Figure 5. Some known alkaloids

2.3.2 Biological Significance of Alkaloids

Plants, animals, and microorganisms certainly do not produce alkaloids for the benefit of humans. It is much more likely that all these life forms have specific reasons to produce or store such a wealth of compounds (Hesse, 2002). These are;

_ Antifungal activity
_ Alkaloids as protectors against UV irradiation
_ Hydroxamic Acid as insecticides, herbicides, fungicides, and siderophores
_ Alkaloids as feeding deterrents
_ Alkaloids from animals

In addition, many animal species, especially insects and amphibians, synthesize alkaloids that, as far as we known, fulfill or may fulfill a number of different functions. These alkaloids include pheromones, poisons for paralyzing victims (to be stored as food resources), and spray reagents, which serve to deters hunters. The structural diversity of these compounds matches that of their vegetable counterparts in every way. Only a few examples have been picked (Hesse, 2002):

_ Poisons from spiders, wasps, and sponges
_ Poisons from amphibians

2.3.3 Alkaloids as Medicines

Chemistry, appearing on the scene at the start of the 19th century, also devoted itself principally to investigation of medicinal plants and drugs. Attempts were made to isolate the active principles and, later, to interpret their structures, so as to be able to synthesize them if necessary. The successes of extraction works slowly appeared, and many alkaloids were isolated from their natural sources and came onto the market. Some naturally occuring alkaloids are still isolated from plants in industrial quantities today, and are marketed as pharmaceuticals in pure form as either salts or derivatives.

According to the 1995 *International Drug Directory*, several alkaloids are still in use today (Index Nominum). *Ajmaline* (an antiadrenergic drug with a sedative effect in higher doses) and *sparteine* are used in the treatment of arrhythmia. *Atropine, hyoscyamine,* and *scopolamine* are parasympatholytics, substances that inhibit acetyl cholinergic neurotransmission at parasympathetic nerve endings and etc; Also many synthetic derivatives of natural alkaloids have also been manufactured, serving as medicines themselves, sometimes with similar or altered physiological effects.

Alkaloids that find application in the treatment of cancer have not yet been mentioned. *Catharanthus roseus* (Apocynaceae), long known as *Vinca rosea,* occurs in the tropics, although it seems to have originated in Madagascar. By 1963, after ca six years of research, 41 different alkaloids had already been isolated and then observed their activities. These important compounds are used today in the treatment of *Hodgkin's* disease. Since all of these substances from *Catharanthus roseus* are synthesized *in vivo* only in tiny amounts.

In summary, it can be seen that a number of natural alkaloids are still isolated from plants for direct medicinal application today. Also, innumerable structural modifications are carried out with the goal of removing or mitigating undesired side effects of drugs. A great many biologically active heterocycles can be viewed as spin-off products of earlier alkaloid research, and so it is hard not to conclude that the direct and indirect significance of alkaloids for medicine can scarcely be overstated (Hesse, 2002).

2.3.4 Classification of Alkaloids

Different methods had been used for classification of alkaloids. They are based on their biological distributions, physiological effect or chemical structure. According to the classification as a biological distrubition, the plants which contain alkaloids are estimated, however in physiological classification their effects on humans and animals are interested. Finally, in chemical clasification, included basic ring structures are considered. Structure unit is given as example for chemical classification;

indole type alkaloids,
pyrolidine type alkaloids,
pyridine-pyrolidine type alkaloids,
pyrolidine-piperidine type alkaloids,
quinoline type alkaloids,
isoquinoline type alkaloids,
imidazole type alkaloids,
pyridine type alkaloids (Pelletier, 1970).

2.3.4.1 Indole Alkaloids

Indole alkaloids can be relatively simple as exemplified by gramine (**17**), isolated from e.g. barley, or very complex such as strychnine (**18**), a highly poisonous compound isolated from the seeds of *Strychnos nux-vomica*. Lysergic acid diethylamide (LSD) (**19**) is another example of a synthetic derivative of an indole alkaloid well-known for its physiological activities (Rahman et. al., 1983) (Figure 6).

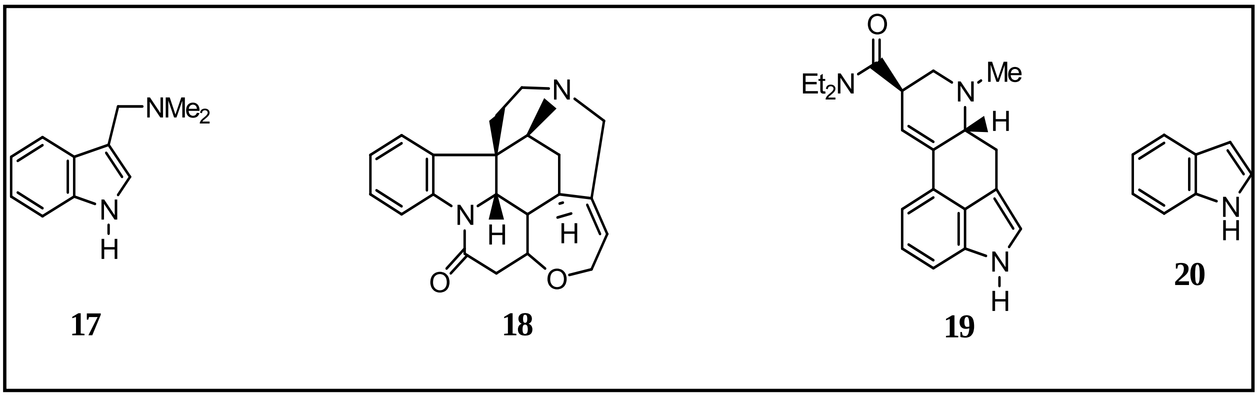


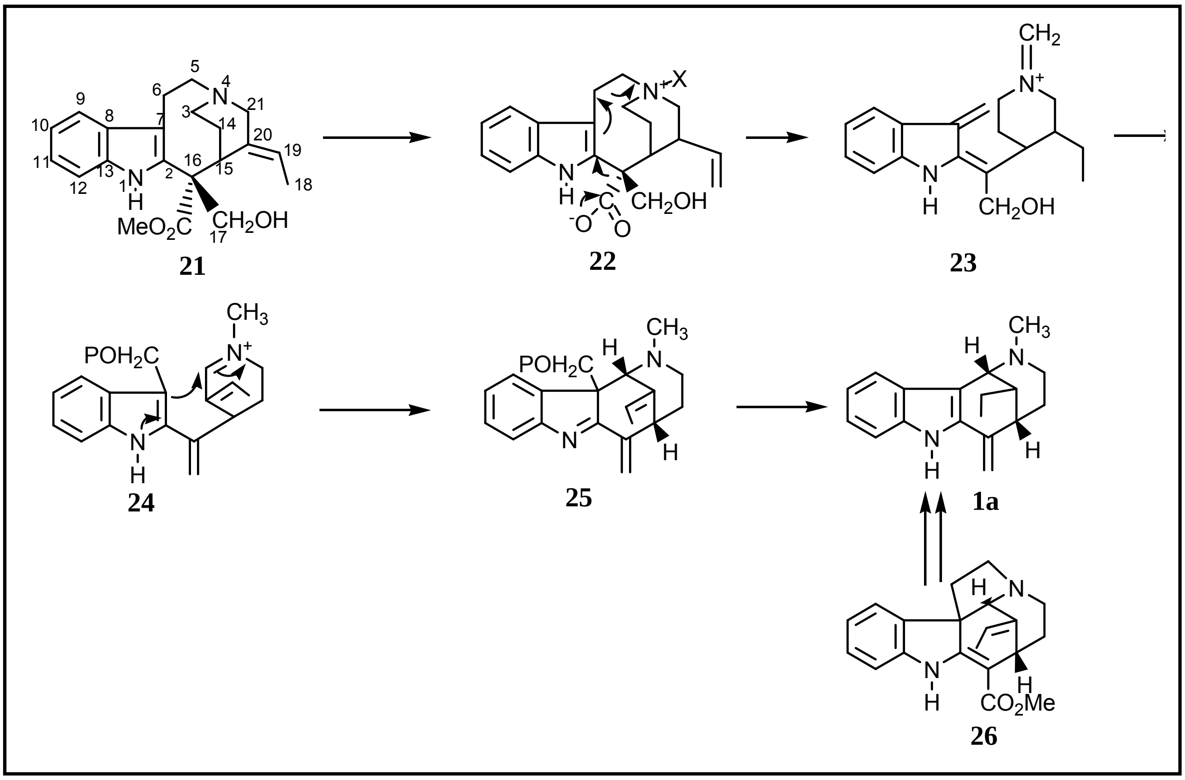
Figure 6. Indole alkaloids

Many commercially available indoles are colourless crystalline solids with a pronounced smell (Sundberg, 1970); they are reasonably stable in air. Indole itself is produced by high-temperature vapour-phase cyclising dehydogenation of 2-ethylaniline. Indole (**20**), first described by Baeyer in 1869, has been thoroughly studied over the years and continues to attract attentin from researchers all over the world (Baeyer, 1869). This focus on the indole ring system is partly due to its undisputable importance in nature, where this particular heterocycle is embedded in countless natural products and medicinally relevant compounds.

2.3.4.1.1 Uleine Alkaloids

The alkaloids of the uleine group constitute a comparatively small group of indole alkaloids lacking the two carbon link between the indole 3-position and the basic nitrogen atom, present in the greater part of monoterpenoid indole alkaloids (Joule , 1983). These alkaloids are characterized by the presence of a tetracyclic 1,5-methanoazocino-[4,3-*b*]indole framework bearing an ethyl substituent at the bridge carbon (Figure 1).

Biogenetically, the formation the uleine group of alkaloids from stemmadenine (**21)** may involve the initial generation of the coresponding N-oxide which could undergo a decarboxylative fragmentation of the C_5-C_6 bond. An alternative possibility to the biogenesis of uleine could be by oxidative removal of the tryptamine bridge from condylocarpine (**26)** (Rahman et. al., 1983) (Scheme 4).

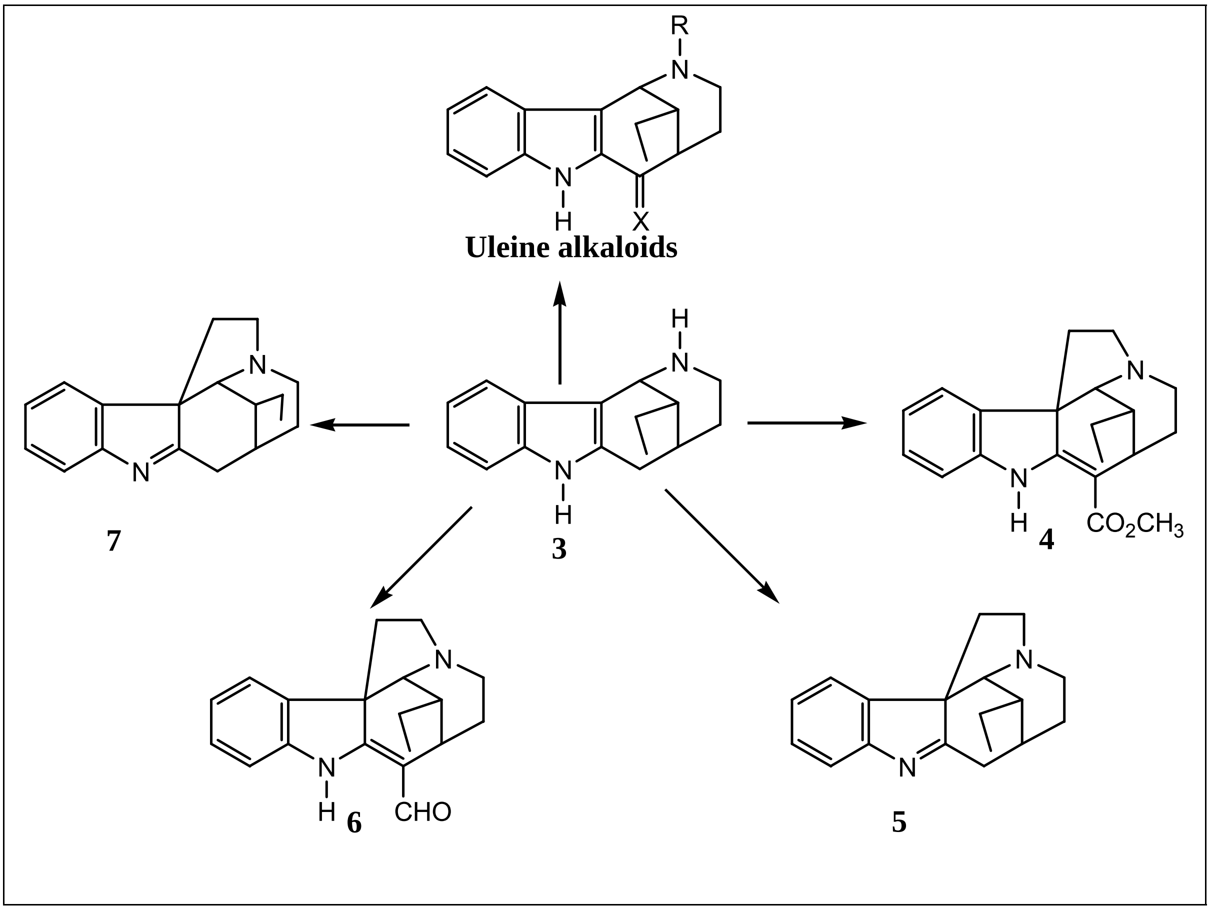


Scheme 1. Biosynthesis of Uleine Alkaloids

Absolute configurations of the bridgehead C-15 position results from their biogenetic origin from stemmadenine (**21)**. But there are two possible coniigurations at C-20. The first one is cis form of H_{15} and H_{20}, and consequently the ethyl substituent is equatorial with respect to the piperidine ring. The second one is the trans form in the 20-epi series (Figure 1).

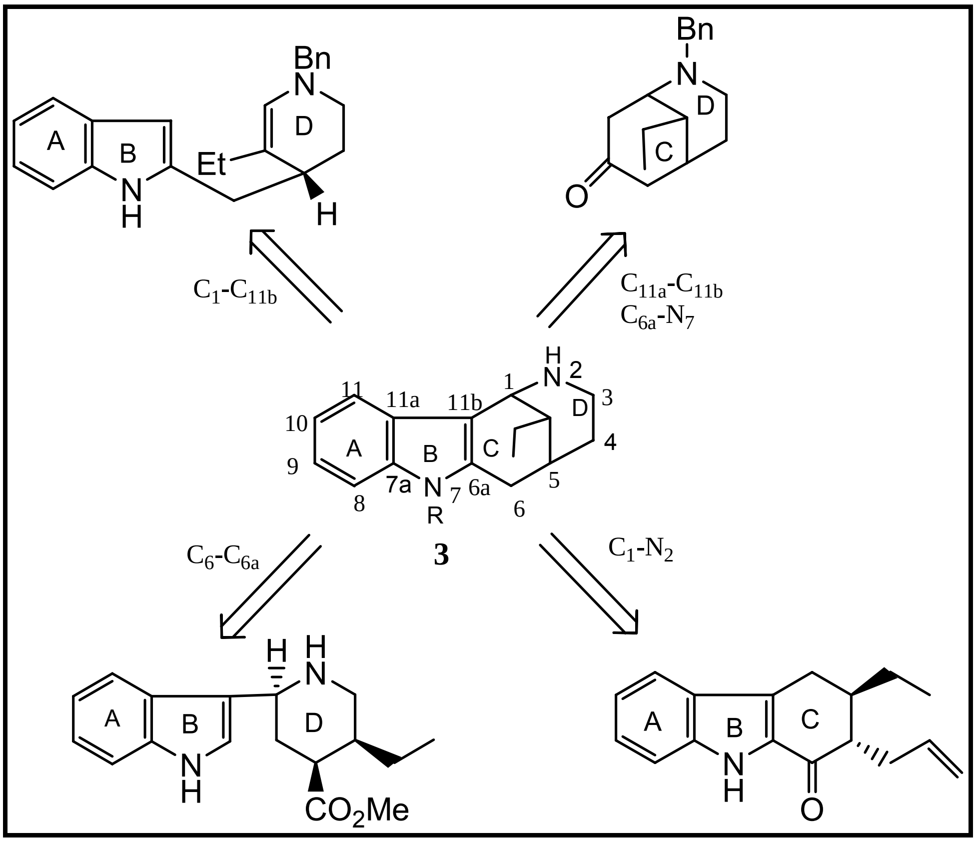
2.4 Synthetic Studies Related to theTetracyclic Structure

Hexahydro-1,5-methanoazocino [4,3-*b*] indole (**3**) skeleton which is the core structure for uleine (**1a**) , dasycarpidone (**2a**), noruleine (**1c**), nordasycarpidone (**2c**) and pentacyclic strychnos alkaloids such as tubotaiwine (**4**), condyfoline (**5**), tubotaiwinal (**6**) and epi condyfoline (**7**) (Scheme 2).



Scheme 2. Uleine and Pentacyclic Strychnos Alkaloids

Therefore the synthesis of tetracyclic structure is important for organic chemistry. Various synthesis strategies have been developed in order to form this system. These strategies has been collected in four groups (Scheme 3).

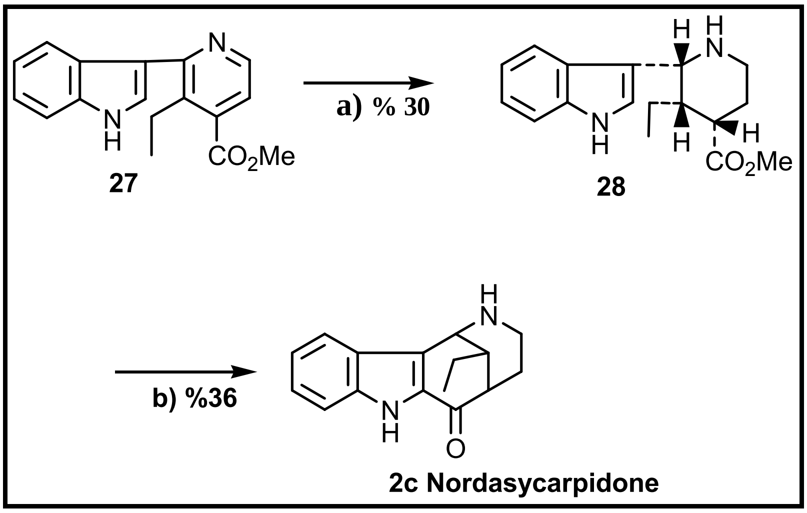


Scheme 3. Synthesis strategies for tetracyclic structure (**3**)

2.4.1 Formation of C_6-C_{6a} Bonds

2.4.1.1 Amat Approach

Amat, Bosch and co-workers described Pd(0) catalysed heteroarylation of indol-2- and -3-ylzinc derivatives and illustrated how such reactions could be applied to the synthesis of various classes of monoterpenoid indole alkaloids (Amat et al., 1997). **27** was converted into nordasycarpidone **1b**, which is a precursor to avariety of *Strychnos* type alkaloids (Scheme 4).

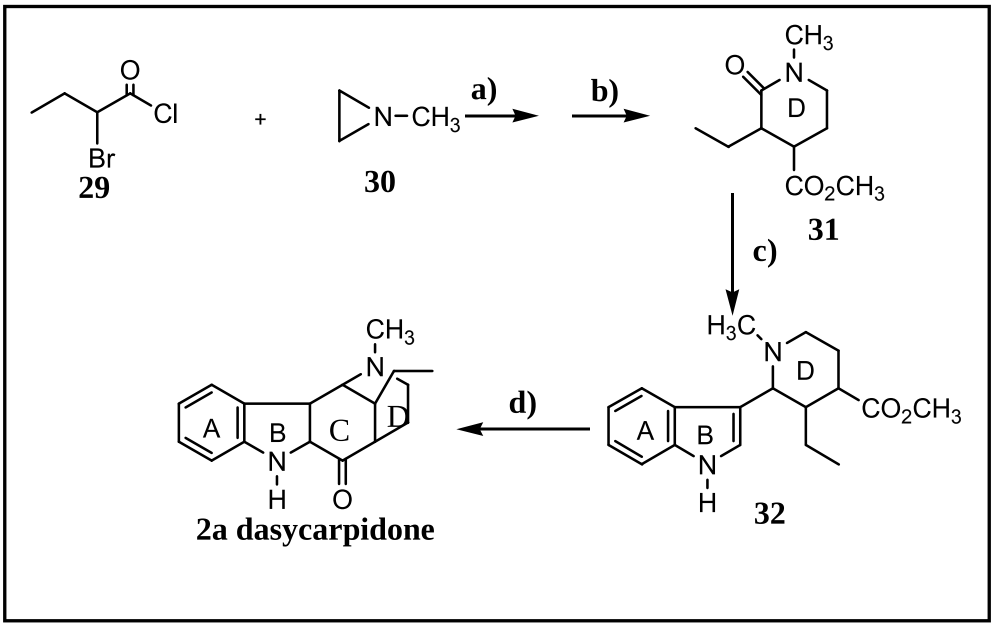


Reagents and conditions: a) HCl, MeOH, then H_2, PtO_2, MeOH, 60% b) $Ba(OH)_2$, H_2O–dioxane, then PPA (36%).

Scheme 4. Formation of C_6-C_{6a} bond type synthesis plan developed by Amat and co-workers

2.4.1.2 Dolby Approach

This type of synthetic strategies has been developed by Dolby (Dolby et al., 1968-1970). The synthetic studies consist of simply attaching an appropriately substitued piperidine derivative at β-position of indole itself. Dolby and co workers used N-methylaziridine and α-bromobutrylcloride as a starting metarial and synthesized tetracyclic ring structure (Scheme 5).



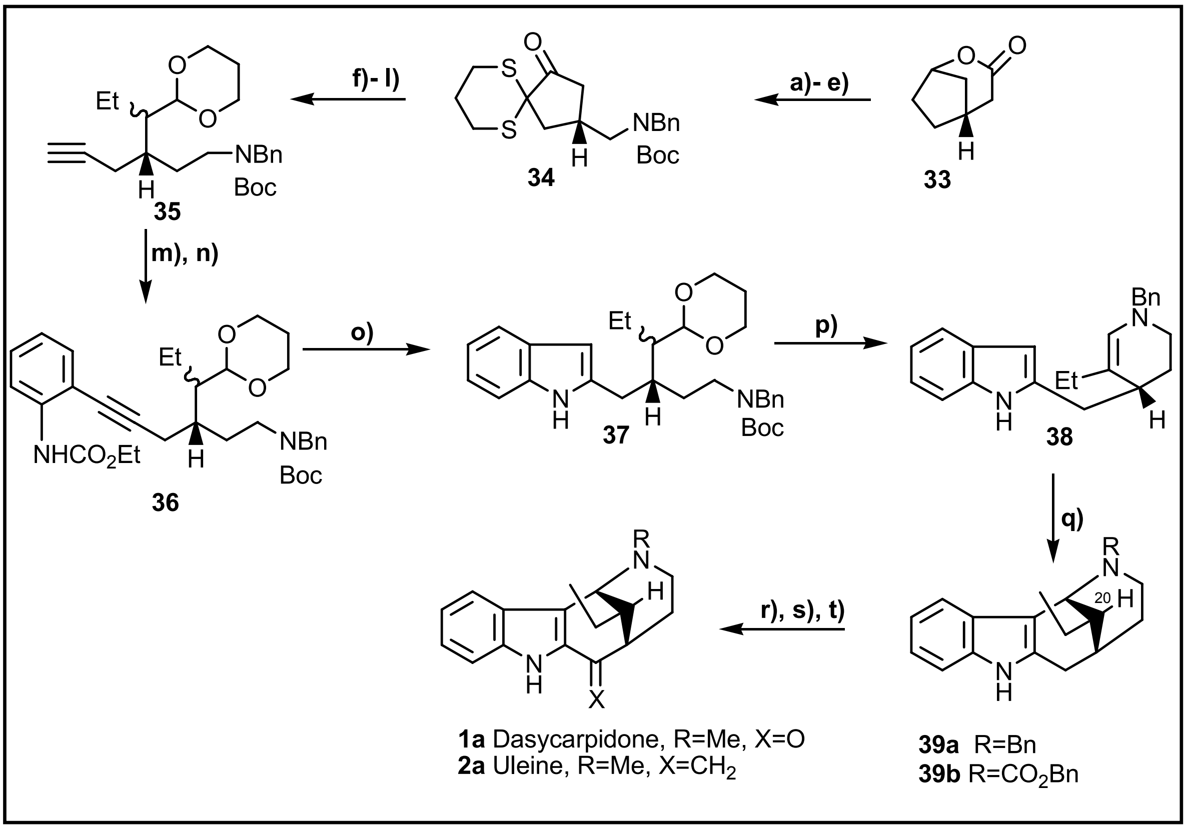
Reagents and conditions: a) benzene, 10 °C, sodium dimethyl malonate, acetic acid; b) NaCN, DMF; c) $POCl_3$, $NaBH_4$; d)poly-phosphoric acid, 75 °C (47 %).

Scheme 5. Formation of C_6-C_{6a} bonds type synthesis plan developed by Dolby and co workers

2.4.2 Formation of C_1-C_{11b} Bond

2.4.2.1 Ogasawara Approach

The first enantiospecific syntheses of (+)-uleine **1a** and (+)-dasycarpidone **2a** were reported by Ogasawara *and* co-workers (Saito et al., 1997). The starting material was d-lactone **33**, derived from (+)-norcamphor, which was converted into cyclopentanone **34** by a sequence of conventional steps. Following ring cleavage and functional group manipulation, the key steps in the synthesis were: palladium catalysed coupling of acetylene **35** to a protected iodoaniline; cyclisation of **36** to indole **37**; and the stereoselective, acid catalysed cyclisation of **38** to the uleine ring system **39**. Amine **39a** was obtained in 54% yield, together with 4% of the C-20 epimer, but had to be converted into carbamate **39b** prior to PDC oxidation to a ketone. *N*-Methylation then gave dasycarpidone **2a**, and subsequent methyllithium addition–dehydration gave uleine **1a** (Scheme 6).

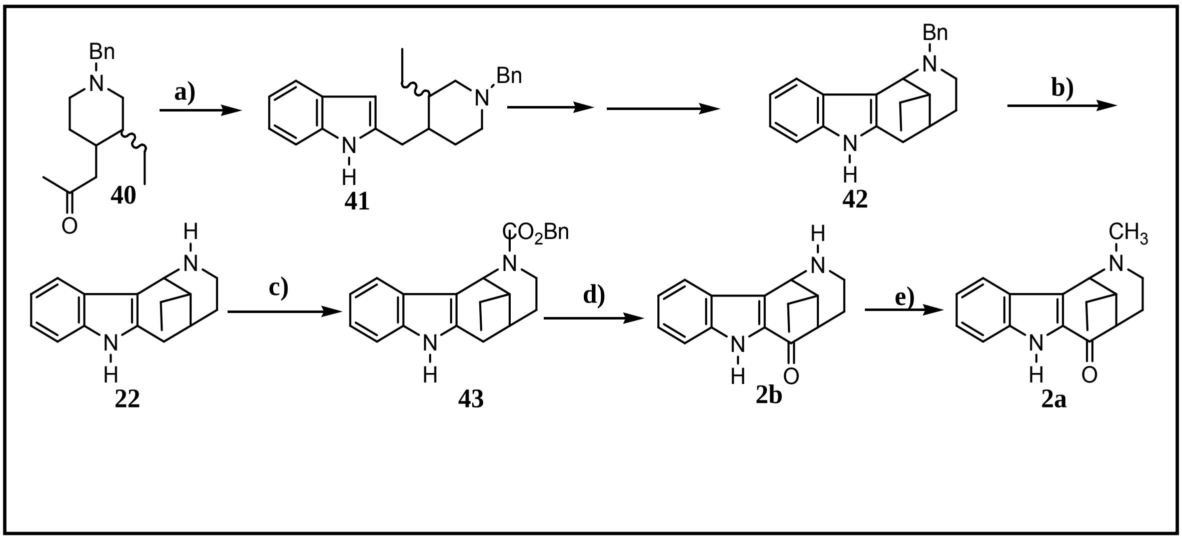


Reagents and conditions: a) $BnNH_2$, 180 °C, (75%); b) LAH, THF, reflux; c) Boc_2O, NaOH (95%); d) PCC, NaOAc, CH_2Cl_2 (95%); e) pyrrolidine, benzene, reflux, then $TsS(CH_2)_3STs$, Et_3N, MeCN (59%); f) KOH, tBuOH, 60°C, acid workup, then CH_2N_2 (99%); g) $NaN(TMS)_2$, EtI, THF, HMPA (73%); h) $Hg(ClO_4)_2$, $CaCO_3$, aq. THF (92%); i) AcC $(NN_2)PO(OMe)_2$, K_2CO_3, MeOH (90%); j) LAH, THF; k) Swern oxidation (87%); l) $Me_3SiO(CH_2)_3OSiMe_3$, Me_3SiOTf (cat.), THF (83%); m) $PdCl_2(PPh_3)_2$, CuI, 2-$IC_6H_4NHCO_2Et$, Et_3N (86%); n) NaOEt, EtOH (64% + 31% NH compd.); o) $ClCO_2Et$, pyr (81%); p) TFA, reflux (54% + 4% 20-epimer); q) Pd/C, HCO_2NH_4, MeOH, then $ClCO_2Bn$, K_2CO_3, CH_2Cl_2 (74%); r) PDC, Celite, TBHP, benzene (54%); s) Pd/C, H_2, formalin, MeOH (83%); t) MeLi, THF, then Al_2O_3, 120 °C (71%).

Scheme 6. Formation of C_1-C_{11b} bonds type synthesis plan developed by Ogasawara and co workers

2.4.2.2 Bosch Approach

In this approach, debenzylation of **42** by hydrogenolysis, followed by benzyloxycarbonylation of the resulting unstable secondary amine **22**, gave carbamate **43** in 50% overall yield. As expected, oxidation of **43** with SeO_2 furnished the 2-acylindole **43** without any degree of epimerization at C-20, and cleavage of the benzyl carbamate protecting group, either with BF_3-Me_2S or by hydrogenolysis with *in situ* methylation of the resulting secondary amine, gave the alkaloids nordasycarpidone (**2b**) and dasycarpidone (**2a**) in 73% and 76% yields, respectively (Bonjoch et. al., 1991)(Scheme 7).



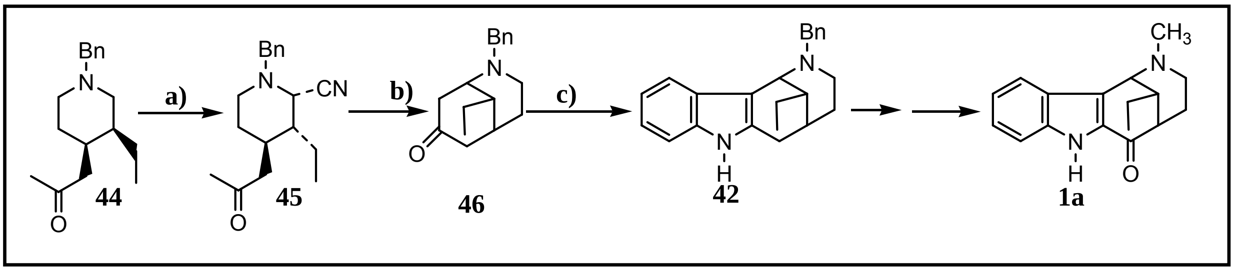
Reagents and conditions: a) Phenylhydrazine hydrochloride, Na_2CO_3, reflux; P_2O_5 in $MeSO_3H$, $NaHCO_3$; b)H_2 / $Pd(OH)_2$; c) CbzCl; d) SeO_2; e) $BF_3.Et_2O$-Me_2S.

Scheme 7. Formation of C_1-C_{11b} bonds type synthesis plan developed by Bosh and co workers

2.4.3 Formation of C $_{11a}$-C$_{11b}$ Bond

2.4.3.1 Bosch Approach

In this study C and D ring was accomplished. Then tetracyclic structure was obtained by indolization reaction. The method was applied succesfully by Gracia and his co-workers (Gracia et al., 1994). They synthesized 2-azabicyclo[3.3.1]nonane from 4-amino-2-ethyl substitued cyclohexanone, then reached tetracyclic structure via using Fischer indole synthesis (Scheme 8).



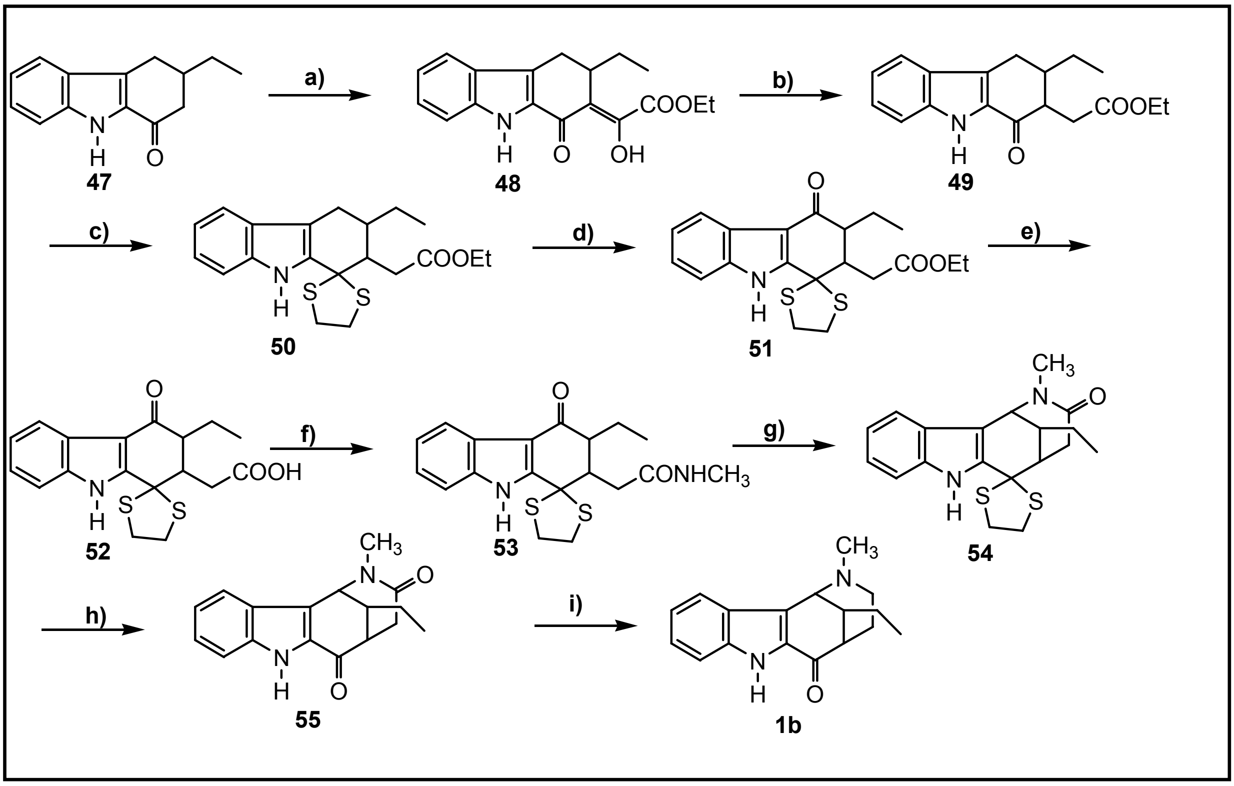
Reagents and conditions: a) m-CPBA, TFAA, KCN, pH 5; b) HCl, aq MeOH; c) $C_6H_5NHNH_2$, AcOH, 26%.

Scheme 8. Formation of C_{11a}-C_{11b} bond type synthesis plan developed by Bosh and co-workers

2.4.4 Formation of C_1-N_2 Bond

2.4.4.1 Patir Approach

In this study tetracyclic core structure (**54**) has been synthesized by D ring formation. In this strategy A and B rings are formed by Fischer indole reaction and tetracyclic structure is synthesized via using intramolecular cyclization (Uludağ et al., 2006) (Scheme 9).

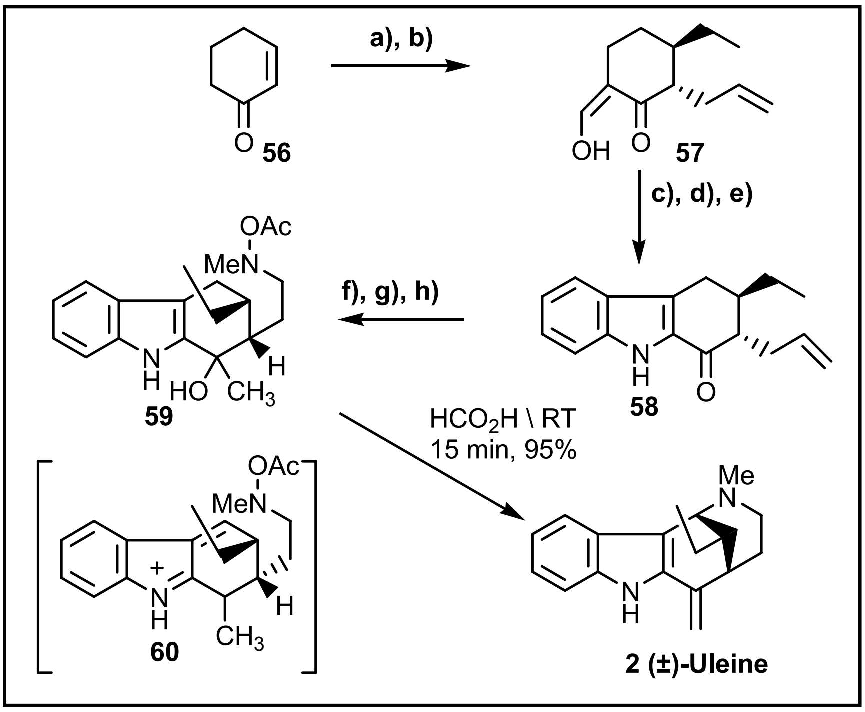


Reagents and conditions: a) THF, NaH, diethyl oxalate, 60°, 86%; b): CH_2Cl_2, triethylamine, CH_3SO_2Cl; then Zn, acetic acid, rt, 92%; c) $CHCl_3$, $HSCH_2CH_2SH$, Zn-triflate, reflux, 66%; d) THF, DDQ, 0°, 97%; e) CH_3OH-H_2O, KOH, rt, 84%; f) $CHCl_3$, $(C_2H_5)_3N$, ethyl chloroformate, CH_3NH_2, -10°, 77%; g) THF, $NaBH_4$, 55°; CH_2Cl_2, CF_3COOH, 5°, 77%; h) CH_3CN-H_2O, (90:10), $(CF_3CO_2)_2IPh$, rt, 74%; i) THF, Red-Al®, rt, 54%; CH_2Cl_2-THF, MnO_2, rt, 71%.

Scheme 9. Formation of C_1-N_2 bond type synthesis plan developed by Patir and co-workers

2.4.4.2 Blechert Approach

Another synthesis of uleine by Schmitt and Blechert involved a cationic 'domino' reaction as the key step (Schmitt and Blechert, 1997). Compound **59** was constructed from cyclohexenone by a fairly conventional sequence of reactions and upon simple treatment with formic acid at room temperature for 15 min it was transformed into uleine (**1a)** in 95% yield. It is believed that cation **60** is involved and a detailed mechanistic sequence is suggested in the below (Scheme 10).



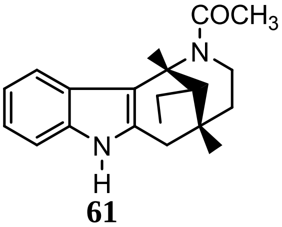
Reagents and conditions: a) i) EtMgBr, CuI, Me_2S, THF, ii) $H_2CNCHCH_2Br$, HMPA (60%); b) NaH, HCOOEt (95%); c) PhN_2Cl (85%); d) HCOOH (86%); e) NaOMe, MeOH (99%); f) i) OsO_4, $NaIO_4$, MTBE, H_2O, ii) MeNHOH, $NaBH_3CN$, iPrOH (85%); g) MeI, THF (98%); h) Ac_2O, pyr (99%).

Scheme 10. Formation of C_1-N_2 bond type synthesis plan developed by Blechert and co-workers

3 THE AIM OF THE WORK

Uleine (**1a**), 20-epiuleine (**1b**), dasycarpidone (**2a**), as well as their desalkyl, and dihydroforms, isolated from *Aspidosperma* sp. constitute a small family of Strychnos type indole alkaloids.

These alkaloids have same tetracyclic core structure (**61**). Although several methods exist for the synthesis of the tetracyclic core structure (**61**), most of them have some limitations because of their low yields. The synthesis of tetracyclic core structure (**61**) given in literature require a relatively large number of reaction steps. And syntheses of epi-form are predominant in these series. A crucial problem associated with the synthesis of these alkaloids is the control of the absolute (and relative) configuration at C15 and C20.



61

Figure 7. Tetracyclic core structure (**61**)

The aim of this work may be classified in four items.

1. To synthesize the tetracyclic core structure (**61**) without any degree of epimerization at C-20 in few steps given in literature,
2. To increase the yield of the tetracyclic core structure (**61**),
3. To synthesize possibly biologically active new compounds,
4. To develop new synthetic plan to synthesize the tetracyclic ring system for indole alkaloids of the uleine groups.

4 EXPERIMENTAL STUDY

4.1 General Procedures

All chemicals were purchased from Aldrich, Sigma and E. Merck. Solvents and all reagents were technical grade and were purified and dried by distillation from appropriate desiccant when necessary. Concentrations of solutions after reactions and extractions were achieved using a rotary evaporator at reduced pressure. Organic extracts were dried over anhydrous magnesium sulphate.

Analytical and preparative thin layer chromatography (TLC) was performed on silica gel HF-254 (Merck). Column chromatography was carried out by using 70-230 mesh silica gel (0.063-0.2 min, Merck).

The structure of the compounds in this study was done by the instruments mentioned below.

^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker instrument DPX-400, 400 MHz High Performance Digital FT-NMR Spectrometer by using $CDCl_3$ and DMSO as a solvent and tetramethylsilane (TMS) as internal standard respectively. Chemical shifts are as in part per million (δ) downfield from an internal standart TMS. Spin multiplicities are mentioned as: s (singlet), d (doublet), dd (doublet of doublet), t (triplet) m (multiplet), b (broad).

All melting points were measured in sealed tubes using an electrothermal digital melting point apparatus (Gallenkamp).

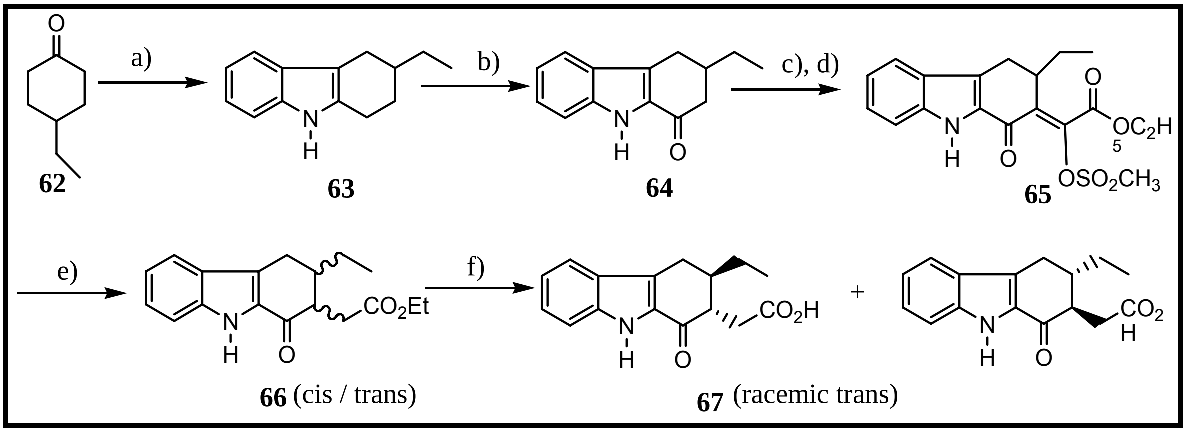
Infrared spectra were recorded with Mattson 1000 series FTIR spectrometer.

Mass spectra were recorded on AGILENT 1100 MSD LC-MS spectrometer.

4.2 EXPERIMENTS

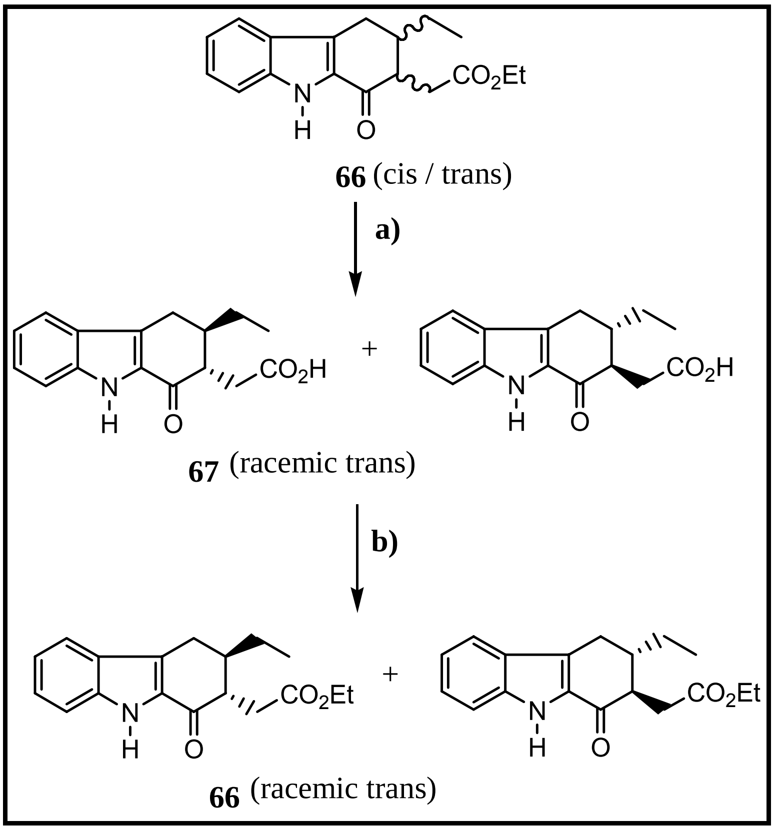
In this study, different synthetic strategies is developed to synthesize the target molecule (**61**). These synthetic strategies are given below (Ergun et al., 2000; Uludag et al., 2006).

4.2.1 Synthetic Plan-1



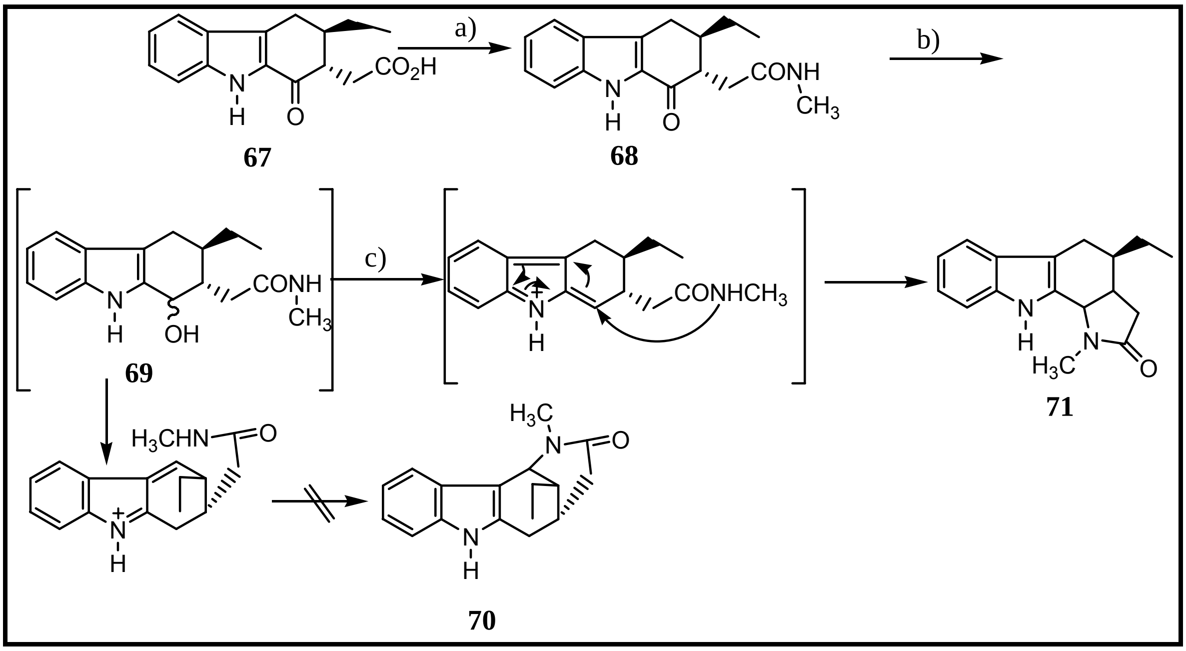
Reagents and conditions: a) Ethanol, Phenylhydrazine hydrochloride, b) methanol-water, periodic acid; c) THF, NaH, diethyl oxalate, 60°; d) CH_2Cl_2, triethylamine, CH_3SO_2Cl; e) Zn, acetic acid, rt ; f) CH_3OH-H_2O, KOH, rt.

Scheme 11. Synthesis of diastereomers of saturated ketoacid (**67**)



Reagents and conditions: a) CH_3OH-H_2O, KOH, rt., b) ethanol, p-toluene sulfonic acid, reflux.

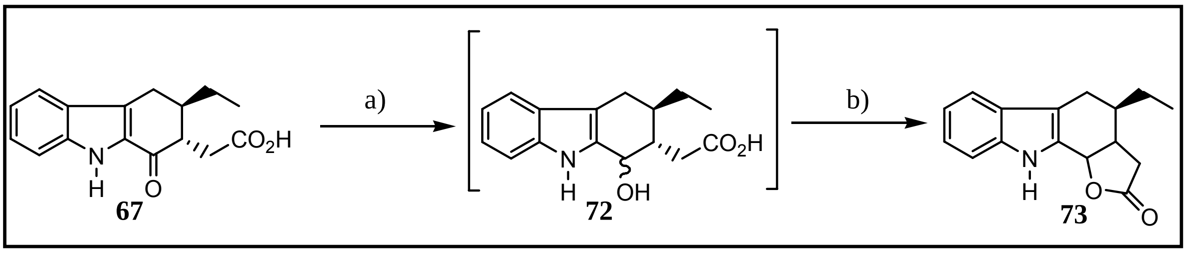
Scheme 12. Determination of structure of compound **67**



Reagents and conditions: a) $CHCl_3$, $(C_2H_5)_3N$, ethyl chloroformate, CH_3NH_2, -10º, b)THF, $NaBH_4$, 55º; c) HCl.

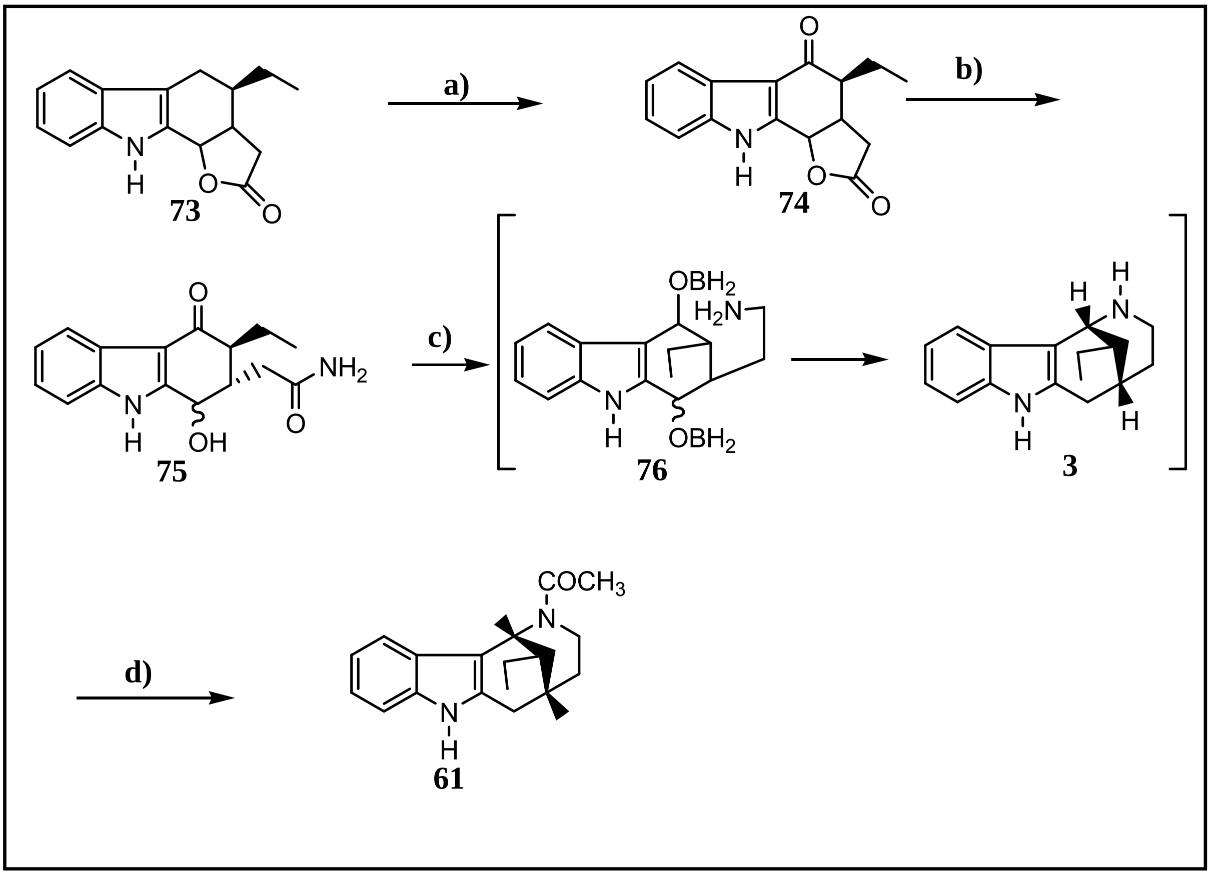
Scheme 13. Synthesis of compound (**71**)

4.2.2 Synthetic Plan-2



Reagents and conditions: a)THF, $NaBH_4$, 55°; b) HCl.

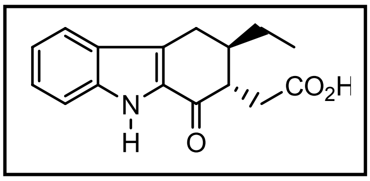
Scheme 14. Synthesis of compound (**73**)



Reagents and conditions: a) THF, DDQ, 0°; b) methanol-amonia, rt; c)THF, $BH_3.CH_3SCH_3$, acetic acid, d) CH_2Cl_2, acetanhydride.

Scheme 15. Synthesis of compound (**61**)

4.2.3 Synthesis of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl) acetic acid (67)



A solution of 5 g (16.72 mmoles) of compound **66** in 20 ml tetrahydrofurane and 100 ml 15 % potassium hydroxide solution (methanol-water (1:1)) is stirred for 4 hour. The organic solvent is evaporated under vacuum. The residue is acidified slowly with 100 ml of 10% hydrochloric acid. The mixture is cooled to 0 ^oC and the precipitate is filtrated. The product is washed with water and ether and recrystallized from ethyl acetate.

Yield : 4.37 g (96.4%)

Mp : 230.2 ^oC

Rf (ethyl acetate-methanol(20:1)) : 0.69

IR (potassium bromide), $\nu(cm^{-1})$: 3283 (N-H indol), 2959-2912 (C-H aliphatic), 1706 (C=O, acid), 1639 (C=O, ketone) (Figure 8).

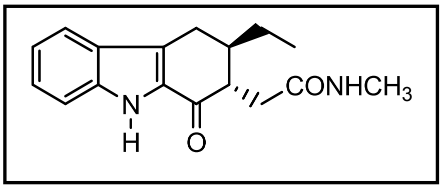
^1H NMR (DMSO, 400MHz) δ (ppm) : 0.98 (t, 3H, $CH_2\mathit{CH_3}$, J=7.37 Hz), 1.40-1.49 (m, 1H), 1.60-1.66 (m, 1H), 2.22-2.35 (m, 1H), 2.65-2.71 (m, 3H), 2.73-2.80 (m, 1H), 3.18 (dd, 1H, J_1=4.46 Hz ,J_2= 16.48 Hz), 7.07-7.10 (m, 1H, aromatic proton), 7.25-7.32 (m, 1H, aromatic proton), 7.41 (d, 1H, aromatic proton, J = 8.30 Hz), 7.70 (d, 1H, aromatic proton, J = 7.80 Hz), 11.72 (s, 1H, N-H), 12.13 (bs, 1H, OH) (Figure 9).

APT (DMSO, 100MHz) δ (ppm) : 11.06 (CH_3), 25.25 (CH_2), 25.41 (CH_2), 31.85 (CH_2), 41.84 (CH), 49.04 (CH), 113.25 (CH), 120.11 (CH), 121.59 (CH), 125.79 (C), 126.61 (CH), 126.74 (C), 130.80 (C), 137.60 (C), 173.85 (C=O, ketone), 191.143 (C=O, acid) (Figure 10).

UV (nm): 236, 308 (Figure 11).

LC-MS : 271,8 $[M]^+$, 253,8 $[M-H_2O]^+$, 225,7 $[M-CO_2H]^+$, 78,7 $[M-C_{10}H_{11}NO_3]^+$ (Figure 12).

4.2.4 Synthesis of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)-acetamide (68)



Compound **67** (1.5 g, 4.14 mmoles) and 0.83 g (8.2 mmoles) triethylamine are dissolved in 30 mL chloroform, and cool to –10º. To this mixture is added dropwise 0.91 g (8 mmoles) ethyl chloroformate, and the temperature is kept at –10º for 3 h. After 3h, 5 mL of 40% methylamine was added and stirred for 24 h. The organic solvent is evaporated under vacuum. The residue is poured into the water and cooled to 0°C. The precipitate is filtrated. The product is washed with water and ether and recrystallized from methanol.

Yield	: 83,7%
Mp	: 187.9 °C
Rf (ethyl acetate-methanol(20:1))	: 0,60

IR (potasyum bromür), ν(cm^{-1}) : 3264 (N-H indol), 2950(C-H alifatik), 1652 (C=O, amid, C=O, keton) (Figure 13).

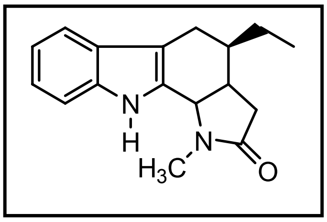
^{1}H NMR (DMSO, 400MHz) δ (ppm) : 0.94 (t, 3H, CH$_2$*CH$_3$*, J=7.04 Hz), 1.37-1.42 (m, 1H), 1.51-1.54 (m, 1H), 2.16-2.17 (m, 1H), 2,51-2.60 (m, 5H), 2.70-2.80 (m, 2H), 3.15-3.20 (dd, 1H, J$_1$=4,39 Hz, J$_2$=16,78 Hz), 7.08 (t, 1H, J=7,23 Hz, aromatic proton), 7.30 (t, 1H, J=7,73 Hz, aromatic proton), 7.40 (d, 1H, J=8.20 Hz, aromatic proton), 7.69 (d, 1H, aromatic proton, J = 7.88 Hz), 7.82 (s, N-H), 11.51 (s, 1H, N-H indol) (Figure 14).

APT (DMSO, 100MHz) δ (ppm) : 11.51 (CH$_3$), 24.40 (CH$_2$), 25.99 (CH$_2$), 26.02 (CH$_3$), 34.27(CH$_2$), 41.76 (CH), 49.09 (CH), 113.23 (CH), 120.07 (CH), 121.54 (CH), 125.85 (C), 125.99 (C), 126.53 (CH), 130.71 (C), 138.80 (C), 171.56 (C=O, keton), 191.83 (C=O, amide) (Figure 15).

UV (nm) : 236, 310 (Figure 16).

LC-MS : 284,8 $[M]^+$, 253,8 $[M-NHCH_3]^+$, 78,7$[M-C_{11}H_{14}N_2O_2]^+$, (Figure 17).

4.2.5 Synthesis of 4-Ethyl-1-methyl-3,3a,4,5,10,10b -hexahydropyrrolo[2,3-a] carbazol-2(10H)-one (71)



A solution of 1 g (35.21 mmoles) of compound **68** in 20 ml tetrahydrofuran is treated with 2 g of sodium borohydride and the mixture heated for 4 hours. The reaction mixture is poured into 50 ml of %10 hydrochloric acid solution and cooled to 0°C . Then the precipitate is filtrated and the product is recrystallized from ether.

Yield	: 75 %
Mp	: 251.4 °C
Rf (ethyl acetate)	: 0.30

IR (potassium bromide), ν(cm^{-1}) : 3430 (N-H indol), 2989-2877 (C-H aliphatic), 1725 (C=O) (Figure 18).

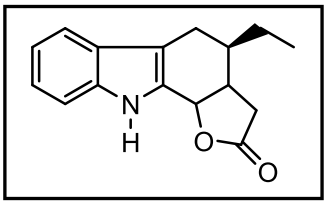
^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm) : 1.05 (t, 3H, CH_2CH_3, J=7.40), 1.29-1.38 (m, 1H), 1.59-1.65 (m, 1H), 1.85 (m, 1H), 2.51-2.59 (m,1H), 2.55 (m, 3H), 2.99-3.04 (dd, 1H, J_1=5.18 Hz, J_2= 16.20 Hz), 3.07 (s, 3H), 4.64 (d, 1H, J=3.54 Hz), 7.13-7.28 (m, 2H, aromatic proton), 7.37 (d, 1H, aromatic proton, J = 8.02 Hz), 7.58 (d, 1H, aromatic proton, J = 7.74 Hz), 8.71 (s, 1H, N-H) (Figure 19).

APT ($CDCl_3$, 100MHz) δ (ppm) : 11.64 (CH_3), 23.31 (CH_2), 25.90 (CH_2), 28.91 (CH_3), 35.12 (CH_2), 36.12 (CH), 37.67 (CH), 56.02 (CH), 111.15 (CH), 111.79 (C), 118.93 (CH), 119.57 (CH), 122.69 (CH), 126.73 (C), 129.33 (C), 136.89 (C), 174.52 (C=O) (Figure 21).

UV (nm) : 222, 308 (Figure 22).

LC-MS : 268,8 $[M]^+$, 236,7 $[M-CH_3NH_2]^+$, 195,7 $[M-CH_3CONHCH_3]^+$, 78,7$[M-C_{11}H_{14}N_2O]^+$, (Figure 23).

4.2.6 Synthesis of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (73)



A solution of 1 g (3.18 mmoles) of compound **67** in 20 ml tetrahydrofuran is treated with 2 g of sodium borohydride and the mixture is refluxed for 2 hours. The reaction mixture is poured into a solution of 50 ml of %10 hydrochloric acid and cooled to 0^oC . Then the precipitate is filtrated and the product is recrystallized from ether.

Yield	: 0.85 g (90.4%)
Mp	: 202.0 ^oC
Rf (ethyl acetate)	: 0.57

IR (potassium bromide), $\nu(cm^{-1})$: 3371 (N-H indol), 2959-2857 (C-H aliphatic), 1762 (C=O, lactone) (Figure 24).

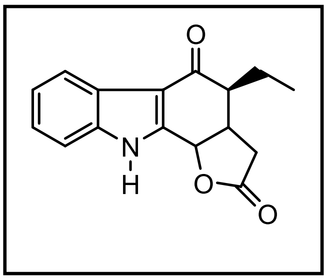
^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm) : 1.06 (t, 3H, CH_2CH_3, J=7.46), 1.32-1.44 (m, 1H), 1.62-1.73 (m, 1H), 1.77-1.86 (m, 1H), 2.46-2.52 (dd, 1H, J_1=7.79 Hz ,J_2= 16.20 Hz), 2.61-2.66 (dd, 1H, J_1=4.10 Hz ,J_2= 16.47 Hz), 2.69-2.82 (m, 2H), 3.04-3.09 (dd, 1H, J_1=4.94 Hz ,J_2= 16.18 Hz), 5.56 (d, 1H, J=5.95 Hz), 7.14-7.17 (m, 1H, aromatic proton), 7.24-7.28 (m, 1H, aromatic proton), 7.39 (d, 1H, aromatic proton, J = 8.73 Hz), 7.59 (d, 1H, aromatic proton, J = 7.88 Hz), 8.28 (s, 1H, N-H) (Figure 25).

APT ($CDCl_3$, 100MHz) δ (ppm) : 11.57 (CH_3), 23.41 (CH_2), 25.80 (CH_2), 33.37 (CH_2), 36.51 (CH), 40.17 (CH), 73.78 (CH), 111.45 (CH), 113.51 (C), 119.21 (CH), 119.77 (CH), 123.42 (CH), 126.22 (C), 127.98 (C), 137.22 (C), 176.55 (C=O, lactone) (Figure 26).

UV (nm) : 222, 278 (Figure 27).

LC-MS : 255,8 $[M]^+$, 196,7 $[M-CH_3CO_2H]^+$, 140,6 $[M-CH_3CO_2H-C_4H_8]^+$, 78,7$[M-C_{10}H_{11}NO_2]^+$ (Figure 28).

4.2.7 Synthesis of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (74)



To a solution of 1 g (3.92 mmoles) of compound **73** in 20 ml tetrahydrofuran (%90) is added dropwise 1.78 g (7.84 mmoles) of 2,3-dichloro-5,6-dicyano-p-benzoquinone in 5 ml tetrahydrofuran at 0 °C. The reaction mixture is stirred for 12 hours at room temmperature then the solution is poured into 5 % of potassium carbonate solution and extracted with ethyl acetate. The organic layer is dried with anhydrous magnesium sulfate and the solvent is removed. The residue is purified by chromatography using silica gel and ethyl acetate. The product is recrystallized from ether.

Yield	: 0.95 g (90.2%)
Mp	: 237.1 °C
Rf (ethyl acetate)	: 0.79

IR (potassium bromide), ν(cm^{-1}) : 3195 (N-H indol), 2964-2888 (C-H aliphatic), 1781 (C=O, lactone), 1644 (C=O, ketone) (Figure 29).

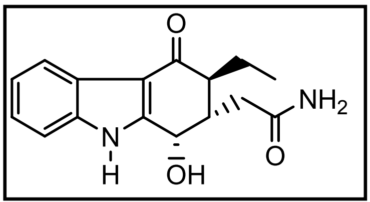
^{1}H NMR ($CDCl_3$, 400MHz) δ (ppm) : 0.94 (t, 3H, $CH_2\mathit{CH_3}$, J=7.30), 1.58-1.65 (m, 1H), 1.74-1.80 (m, 1H), 2.41-2.51 (m, 3H), 2.83-2.89 (dd, 1H, J_1=8.21 Hz, J_2=16.43 Hz), 6.05 (d, 1H, J=6.75 Hz), 7.21-7.31 (m, 2H, aromatic proton), 7.50 (d, 1H, aromatic proton, J = 7.95 Hz), 8.06 (d, 1H, aromatic proton, J = 7.61 Hz), 12.39 (s, 1H, N-H) (Figure 30).

APT ($CDCl_3$, 100MHz) δ (ppm) : 12.06 (CH_3), 24.13 (CH_2), 34.05 (CH_2), 39.38 (CH), 49.88 (CH), 71.92 (CH), 111.90 (C), 112.81 (CH), 122.62 (CH), 122.76 (CH), 123.93 (C), 124.42 (CH), 137.65 (C), 142.73 (C), 175.96 (C=O, ketone), 193.64 (C=O, lactone) (Figure 31).

UV (nm) : 212, 242, 294 (Figure 32).

LC-MS : 269,7 $[M]^+$, 223,7 $[M-CO_2H]^+$, 167,7 $[M-CO_2H-C_4H_8]^+$, 78,7$[M-C_{10}H_9NO_3]^+$, (Figure 33).

4.2.8 Synthesis of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl) acetamide (75)



A solution of 1 g (3.72 mmoles) of compound **74** in 30 ml of methanol and 30 ml of amonia is stirred for 4 hours at room temperature. The residue is poured into the water and cooled to 0°C. The precipitate is filtrated. The product is washed with water and ether and recrystallized from methanol.

Yield	: 80.2%
Mp	: 160.5 °C
Rf (etil asetat-methanol(20:1))	: 0.27

IR (potassium bromide), ν(cm^{-1}) : 3379 (N-H indol), 2953-2868 (C-H aliphatic), 1624 (C=O, ketone), 1624 (C=O, amide) (Figure 34).

^{1}H NMR (DMSO, 400MHz) δ (ppm) : 0.93 (t, 3H, CH_2CH_3, J=7.17), 1.56-1.64 (m, 1H), 1.75-1.83 (m, 1H), 1,94-2,09 (m, 1H), 2.31-2.34 (m, 2H), 2.79-2.83 (dd, 1H, J_1 = 4.50 Hz, J_2 = 4.19 Hz), 5.27 (d, 1H, J= 4,43 Hz), 5,95 (s,1H, OH), 6.83 (s, 1H, NH), 7.13-7.20 (m, 2H, aromatic proton), 7.32 (s, 1H, NH), 7.43 (d, 1H, aromatic proton, J = 8.01 Hz), 7.96 (d, 1H, aromatic proton, J = 7.50 Hz), 11.97 (s, 1H, N-H) (Figure 35).

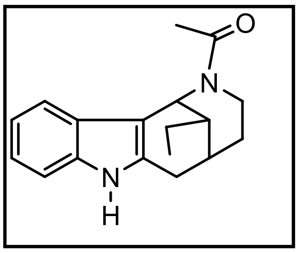
^{1}H NMR (DMSO-D_2O, 400MHz) δ (ppm) : 0.93 (t, 3H, CH_2CH_3, J=7.17), 1.56-1.64 (m, 1H), 1.75-1.83 (m, 1H), 1,94-2,09 (m, 1H), 2.31-2.34 (m, 2H), 2.79-2.83 (dd, 1H, J_1 = 4.50 Hz, J_2 = 4.19 Hz), 5.27 (d, 1H, J= 4,43 Hz), 7.13-7.20 (m, 2H, aromatic proton), 7.43 (d, 1H, aromatic proton, J = 8.01 Hz), 7.96 (d, 1H, aromatic proton, J = 7.50 Hz) (Figure 36).

APT ($CDCl_3$, 100MHz) δ (ppm) : 12.26 (CH_3), 22.51 (CH_2), 33.95 (CH_2), 42.38 (CH), 52.27 (CH), 62.86 (CH), 109.71 (C), 112.57 (CH), 120.94 (CH), 120.06 (CH), 123.06 (CH), 125.08 (C), 136.98 (C), 151.54 (C), 174.10 (C=O, ketone), 194.74 (C=O, amide) (Figure 37).

UV (nm) : 214, 242, 264, 298 (Figure 38).

LC-MS : 285,8 $[M]^+$, 268,8 $[M\text{-}OH]^+$, 251,8 $[M\text{-}OH\text{-}NH_3]^+$, 223,7 $[M\text{-}OH\text{-}NH_3\text{-}CO]^+$, 78,7$[M\text{-}C_{10}H_{11}N_2O_3]^+$, (Figure 39).

4.2.9 Synthesis of N-(Acetyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (61)



To solution of 1 g (3.50 mmoles) of compound **75** in 20 ml tetrahydrofuran (%90) is added 10 ml of 2 M $BH_3.CH_3SCH_3$ at room temperature is refluxed for 2 hours. To this mixture is added dropwise 10 ml acetic acid at 0 °C. Then the solution is poured into 10 % of sodium hydroxide solution and extracted with ethyl acetate and the solvent is removed. The residue is solved in dichloromethane and 5 ml acetanhydride is added dropwise to this solution. The solution is stirred for 1 hour at room temperature. Then the solution is washed with 5 % of sodium hydroxide solution. The organic layer is dried over anhydrous magnesium sulfate and the solvent is removed. The residue is purified by chromatography using silica gel and ethyl acetate-methanol (10:1). The product is recrystallized from ether-petrolium ether.

Yield	: 36%
Mp	:125,4 °C
Rf (etil asetat-methanol(10:1))	: 0,92

IR (potasium bromide), ν(cm^{-1}) : 3390 (N-H indol), 2950-2873 (C-H aliphatic), 1654 (C=O, ketone) (Figure 40)

^1H NMR (DMSO, 400MHz) δ (ppm) : 1.00 (t, 3H, CH_2CH_3, J=7.28 Hz), 1.34-1.43 (m, 1H), 1.49-1.59 (m, 2H), 1.70-1.80 (m, 1H), 1.91-1.96 (m, 1H), 1,99 (s, 3H, CH_3), 2.49-2.55 (m, 2H), 2.79-2.95 (m, 2H), 3.36-3.41 (dd, 1H), 5.39 (d, 1H), 7.09-7.14 (m, 2H, aromatik proton), 7.29-7.31 (m, 1H, aromatik proton), 7.46-7.49 (m, 1H, aromatik proton), 7.76 (s, 1H, N-H) (Figure 41).

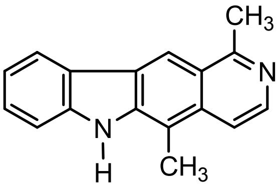
APT (DMSO, 100MHz) δ (ppm) : 11.67 (CH_3), 23.11 (CH_2), 23.34 (CH_3), 25.57 (CH_2), 32.97 (CH_2), 34.85 (CH), 37.73 (CH_2), 38.92 (CH), 39.08 (CH), 107.96 (C), 110.53 (CH), 117.63 (CH), 119.02 (CH), 120.95 (CH), 127.90 (C), 132.13 (C), 136.08 (C), 170.17 (C=O), (Figure 43).

UV : 228, 276 (Figure 44).

LC-MS : 284,9 $[M+2]^+$, 282,8 $[M]^+$, 239,8 $[COCH_3]^+$, 195,7 $[M-COCH_3-NH_2-C_2H_5]^+$, 78,7$[M-C_{12}H_{16}N_2O]^+$, (Figure 45).

5 EXPERIMENTAL RESULTS AND DISCUSSION

A relatively small number of the indole alkaloids, isolated mostly Aspidosperma, Tabernaemontana and Ochrosia species, lack the two carbon chain in which, in the others, is derived biogenetically from tryptophan (Snieckus V., 1968). Within this group, four distinct skeletal types have been identifed, represented by the alkaloids olivacine (**77**), ellipticine **(78**), uleine (**1a**) [and dasycarpidone (**2a**)], and finally vallesamine (**79a**), [and apparicine (**79b**)]. For the first two of these types synthetic pathways have been well worked out. We present here an approach which leads to the third skeletal type. An alternative and different approach has also recently been used to produce this skeletal type.



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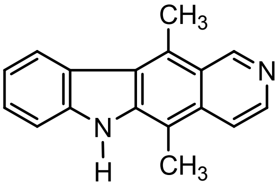

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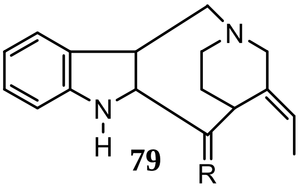

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a;R = CO_2Me, CH_2OH
b;R = CH_2

In this study, synthetic scheme 11-15 are given on page 24-26 were applied. Scheme 11 outlines the synthesis of intermediate **67**. In the first step, a succesful Fischer-Indole synthesis commencing with 4-ethylcyclohexanone led to the formation of compound **63**. Oxidation of this intermediate with periodic acid resulted in the formation of compound **64.** The 1-oxo-tetrahydrocarbazole **64** was then converted into ethoxalyl derivative **65** by using sodium hydride and diethyl oxalate in tetrahydrofuran. A mixture of diastereomers of saturated ketoester **66** was obtained by the reaction of **65** with triethylamine and methanesulfonyl chloride followed by the reduction of the resulting mesylate with zinc dust in acetic acid (Ergun et al., 2000; Uludag et al., 2006). For the compound **66**, the diastereomeric mixture was obtained. The ratio of these isomers (trans to cis) was found as 66:34 using GC-MS analysis. The separation of the diastereomers by column chromatography was unsuccessful. Therefore the diastereomers of **66** was hydrolysed by using 15% potassium hydroxide in methanol-water (3:1) at room temperature and only one saturated ketoacid **67** were obtained according to GC-MS analysis. Compound **67** was converted into compound **66** by using ethanol and p-toluene sulfonic acid. Only one keto ester **66** was obtained according to GC-MS analysis and this one is racemic trans according to literature datas (Uludağ et al., 2006) (Scheme 12).

The amide (**68**) was obtained by the treatment of **67** with triethylamine and ethyl chloroformate in chloroform, followed by the addition of methylamine. The reduction of the ketone **68** to the corresponding alcohol **69** was carried out with an excess of sodium borohydride in tetrahydrofuran at 55º. When the compound **69** treated with trifluoroacetic acid at 5°, the expected compound is compound **70,** according to Blechert Approach. In our that reaction, the compound **71** was obtained (Scheme 13).

Intermediate tetracyclic compound **70** couldn't synthesized by using synthetic plan-1. Therefore, at this point an alternative synthetic pathway (Synthetic Plan-2) was used. The reduction of the ketoacid **67** to the corresponding alcohol **72** was carried out with an excess of sodium borohydride in tetrahydrofuran at room temperature. The acid-catalyzed ring closure of the rather labile alcohol **72** was accomplished by using trifluoroacetic acid at 5º to give intermediate **73** (Scheme 14).

Compound **73** was oxidized with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone at 0º to the corresponding 4-oxo compound **74.** Compound **75** was obtained by the treatment of **74** with amonia-methanol (1:1). Compound **3** was obtained by the reaction of hydroxyl-amide (**75**) with boran dimethyl thio ether and acetic acid but had to be converted into acetyl derivative (**61**) by using acetanhydride. (Scheme 15).

The structural assignment of the compounds is made on the basis of the ^{1}H, APT NMR, IR, UV and LC-MS spectroscopy .

5.1 Synthesis of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (67)

Characterization of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**) was achieved by IR, UV, LC-MS, ^{1}H-NMR and APT spectroscopy.

The IR spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**) shows bands at 3283 cm^{-1} for N-H streching of indol, at 2959-2912 cm^{-1} for C-H streching, at 1706 cm^{-1} for C=O streching of carboxylic acid and at 1639 cm^{-1} for C=O streching of ketone (Figure 8).

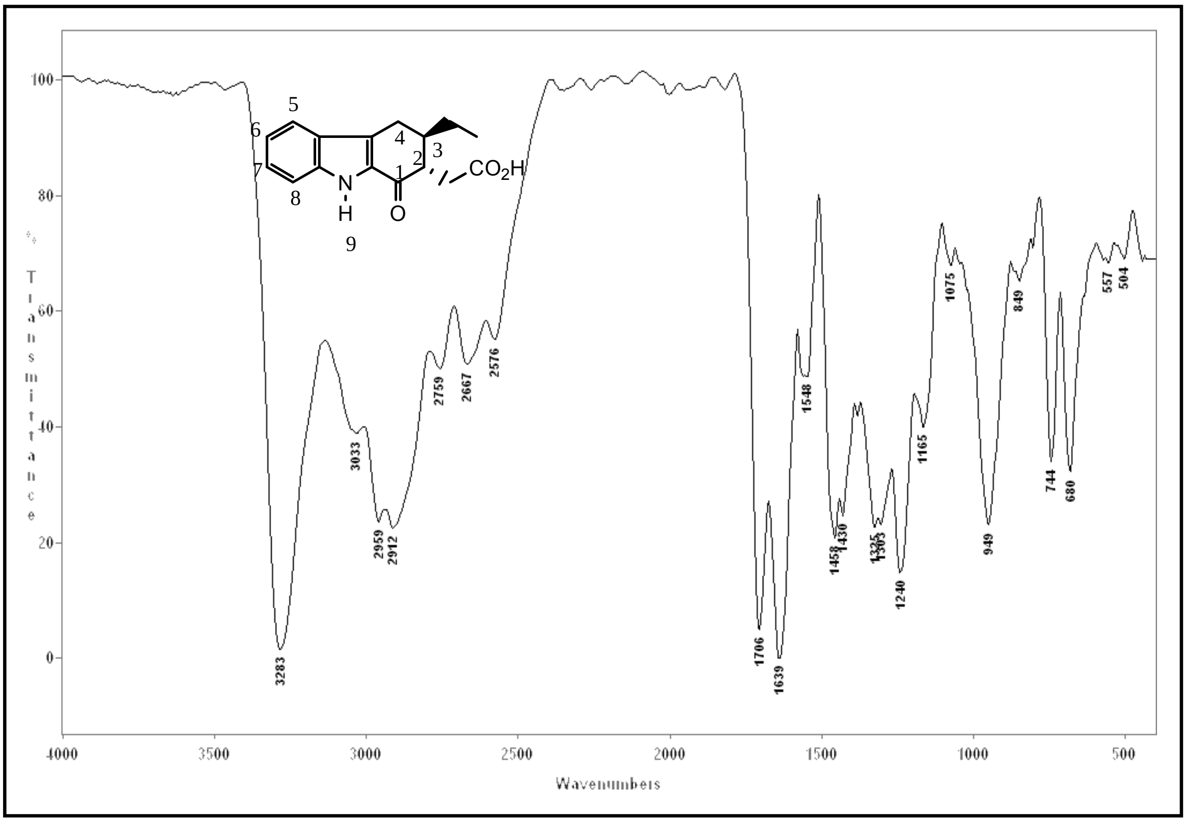

Figure 8. The IR spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**)

The ^{1}H-NMR spectrum of compound **67** shows a triplet between 0.96 ppm and 0.99 ppm for methyl protons of ethyl group. The multiplet between 1.40 ppm and 1.49 ppm is due to the methylene proton of ethyl group and the multiplet between 1.60 ppm and 1.66 ppm is due to the other methylene proton of ethyl group. The multiplet between 2.22 ppm and 2.35 ppm belong to proton of methine group attached to C(3). The multiplet between 2.65 ppm and 2.71 ppm is due to protons of methylene group of C(4) and the methylene proton of acetic acid group. The other methylene proton attached to acetic acid group give multiplet between 2.73 ppm and 2.80 ppm. The doublet of doublet at 3.18 ppm with 4.46 Hz and 16.48 Hz belong to methine proton attached to C(2). The multiplet between 7.07 ppm and 7.10 ppm, the multiplet between 7.25 ppm and 7.32 ppm, the doublet between 7.39 ppm and 7.42 ppm with 8.30 Hz and doublet between 7.69 ppm and 7.71 ppm with 7.80 Hz belong to the aromatic ring. The singlet at 11.72 ppm and the broad singlet at 12.13 ppm is due to the proton of NH group and OH group, respectively (Figure 9).

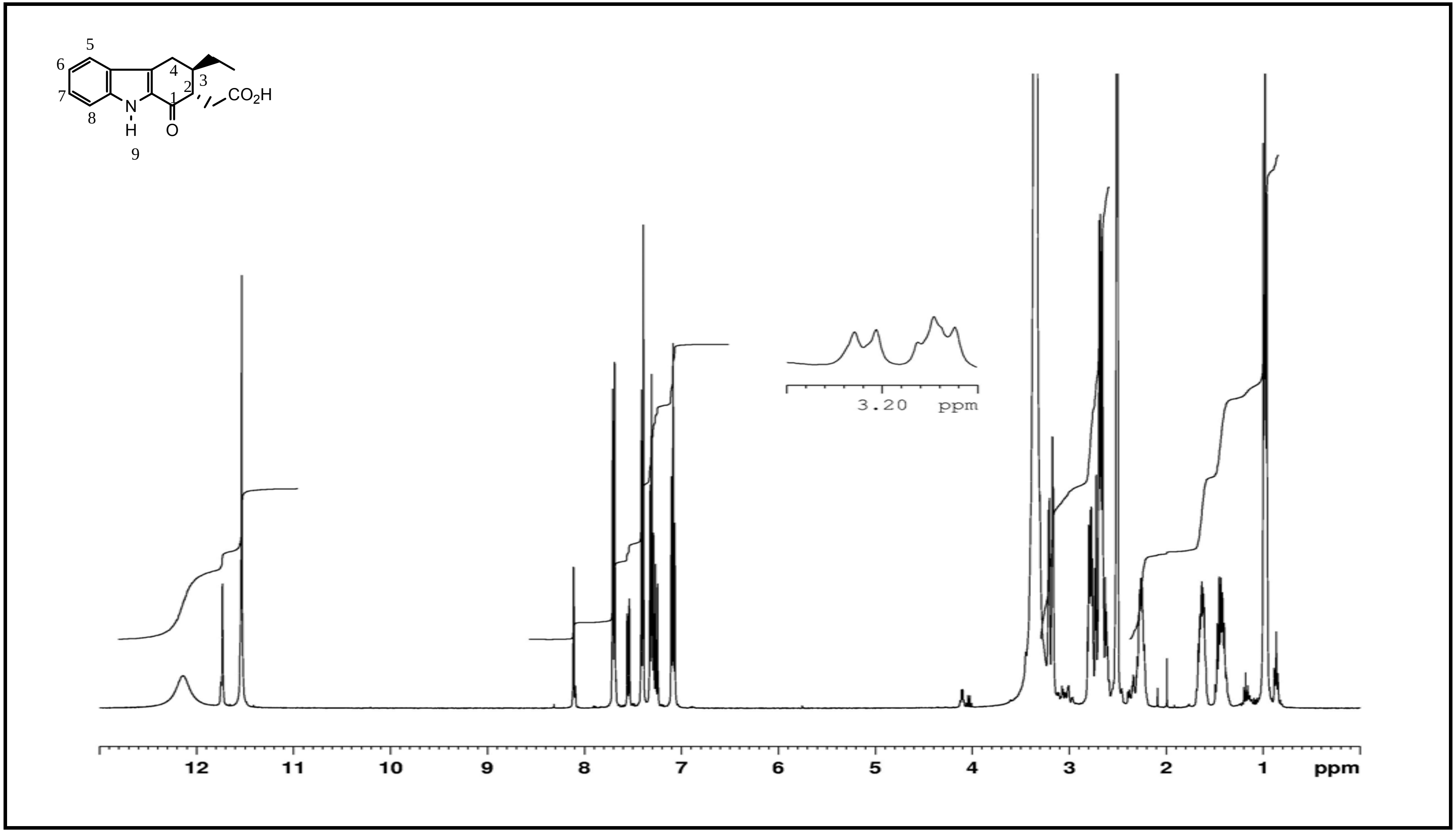

Figure 9. The ^{1}H-NMR spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**)

The APT spectrum of compound **67** exhibit signal at 11.06 ppm for the methyl carbon and 25.25 ppm for the methylene carbon of ethyl group. The signals at 25.41 ppm for C(4) and 31.85 ppm for acetic acid C is due to the methylene carbons. The methine carbons show signal at 41.84 ppm for C(3) and 49.04 ppm for C(2). The carbons of indole ring exhibit signals at 113.25 ppm, 120.11 ppm, 121.59 ppm and 125.79 ppm. The methine carbons of aromatic ring attached to C(6), C(7), C(5) and C(8) exhibit signal at 126.61 ppm, 126.74 ppm, 130.80 ppm and 137.60 ppm, respectively. The signal at 173.85 ppm is due to ketone carbon and the signal at 191.143 ppm belong to acid carbon (Figure 10).

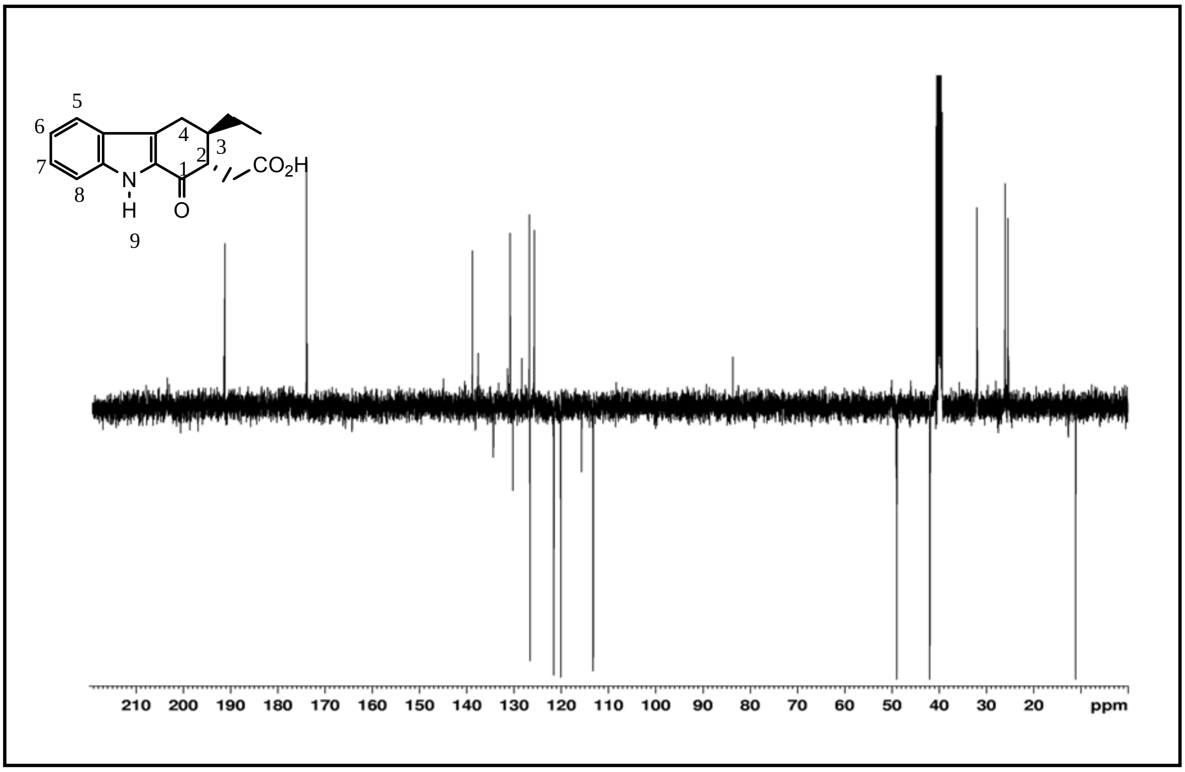

Figure 10. The APT spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**)

The UV spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**) has two bands at 236nm (π-π*) and 308 nm (n-π*) (Figure 11).

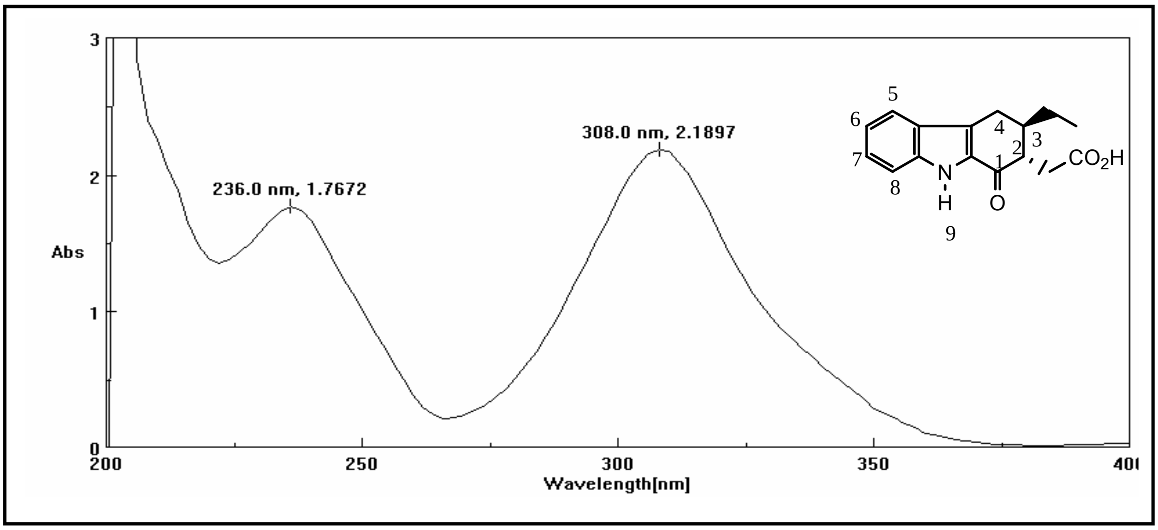

Figure 11. The UV spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**)

The LC-MS spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**) has four signals. The signal at 271.8 belong to molecular ion (M+). The loss of OH group from $[M+]_+$ is proved by the m/z: 253,8 $[M-H_2O]^+$, the loss of COOH group from $[M+]_+$ is proved by the m/z: 225,7 $[M-CO_2H]^+$. The signal at 78.7 belong to $[C_6H_6]$+ (Figure 12).

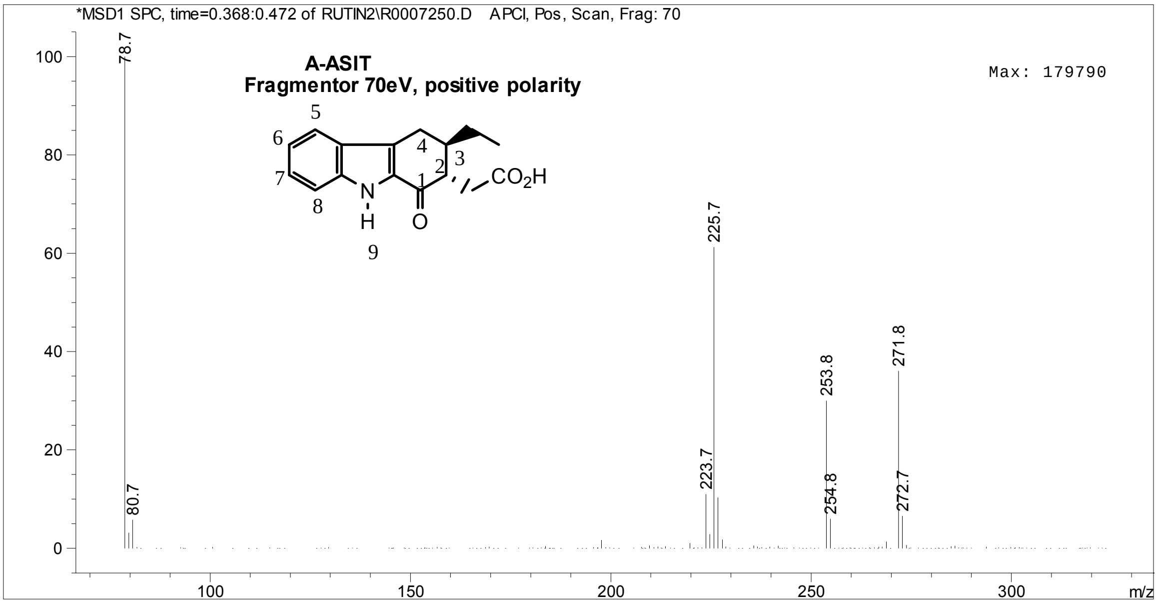

Figure 12. The LC-MS spectrum of 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**)

5.2 Synthesis of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)-acetamide (68)

Characterization of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**) was achieved by IR, UV, LC-MS, ^{1}H-NMR and APT spectroscopy.

The IR spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**) shows bands at 3264 cm^{-1} for N-H streching of indol, at 2950 cm^{-1} for C-H streching, at 1652 cm^{-1} for C=O streching of amide and ketone (Figure 13).

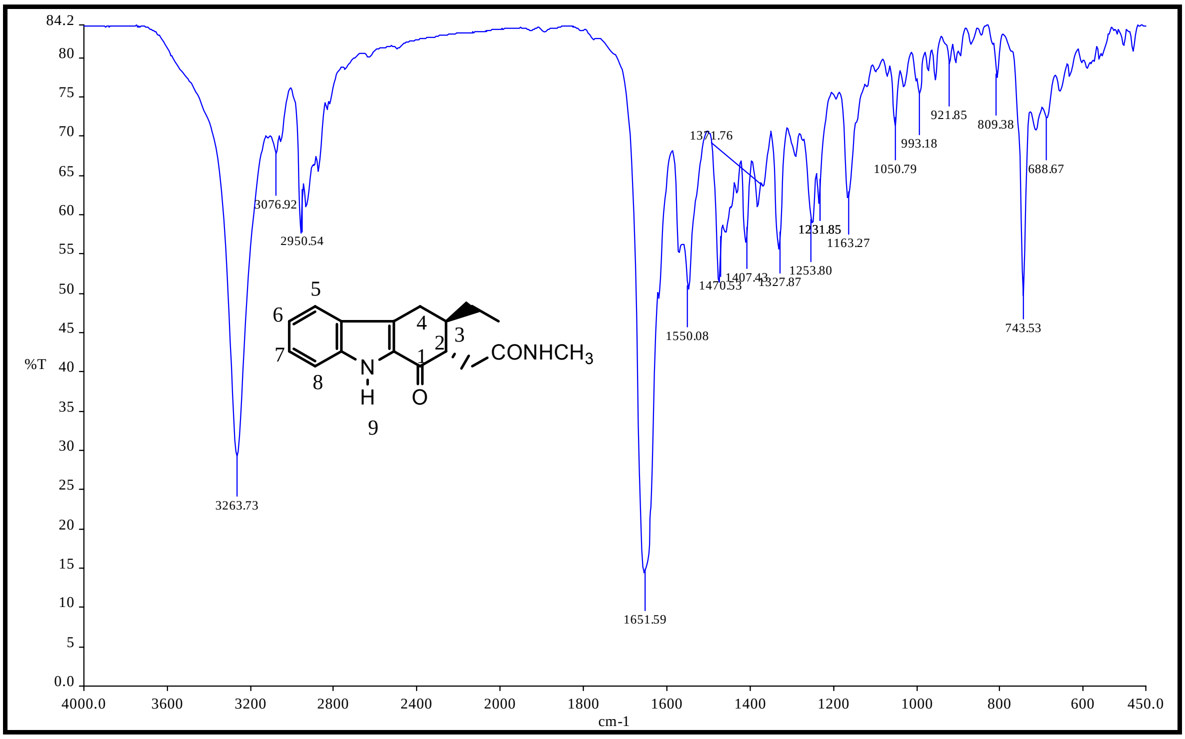

Figure 13. The IR spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**)

The ^{1}H-NMR spectrum of compound **68** shows a triplet between 0.92 ppm and 0.95 ppm with 7.04 Hz for methyl protons of ethyl group. The multiplet between 1.37 ppm and 1.42 ppm is due to the methylene proton of ethyl group and the multiplet between 1.51 ppm and 1.54 ppm is due to the other methylene proton of ethyl group. The multiplet between 2.16 ppm and 2.17 ppm belong to proton of methine group attached to C(3). The singlet at 2.60 ppm is due to the methyl protons attached to NH group. The multiplet between 2.51 ppm and 2.60 ppm is due to protons of methylene group of C(4). The multiplet between 2.70 ppm and 2.80 ppm is due to protons of methylene group of acetamide group. The doublet of doublet between 3.15 ppm and 3.20 ppm with 4.39 Hz and 16.48 Hz belong to methine proton attached to C(2). The multiplet between 7.06 ppm and 7.10 ppm, the multiplet between 7.28 ppm and 7.32 ppm, the doublet between 7.39 ppm and 7.40 ppm with 8.20 Hz and doublet between 7.68 ppm and 7.70 ppm with 7.88 Hz belong to the aromatic ring. The singlet at 7.82 ppm and at 11.51 ppm is due to the proton of NH group of amide and indol, respectively (Figure 14).

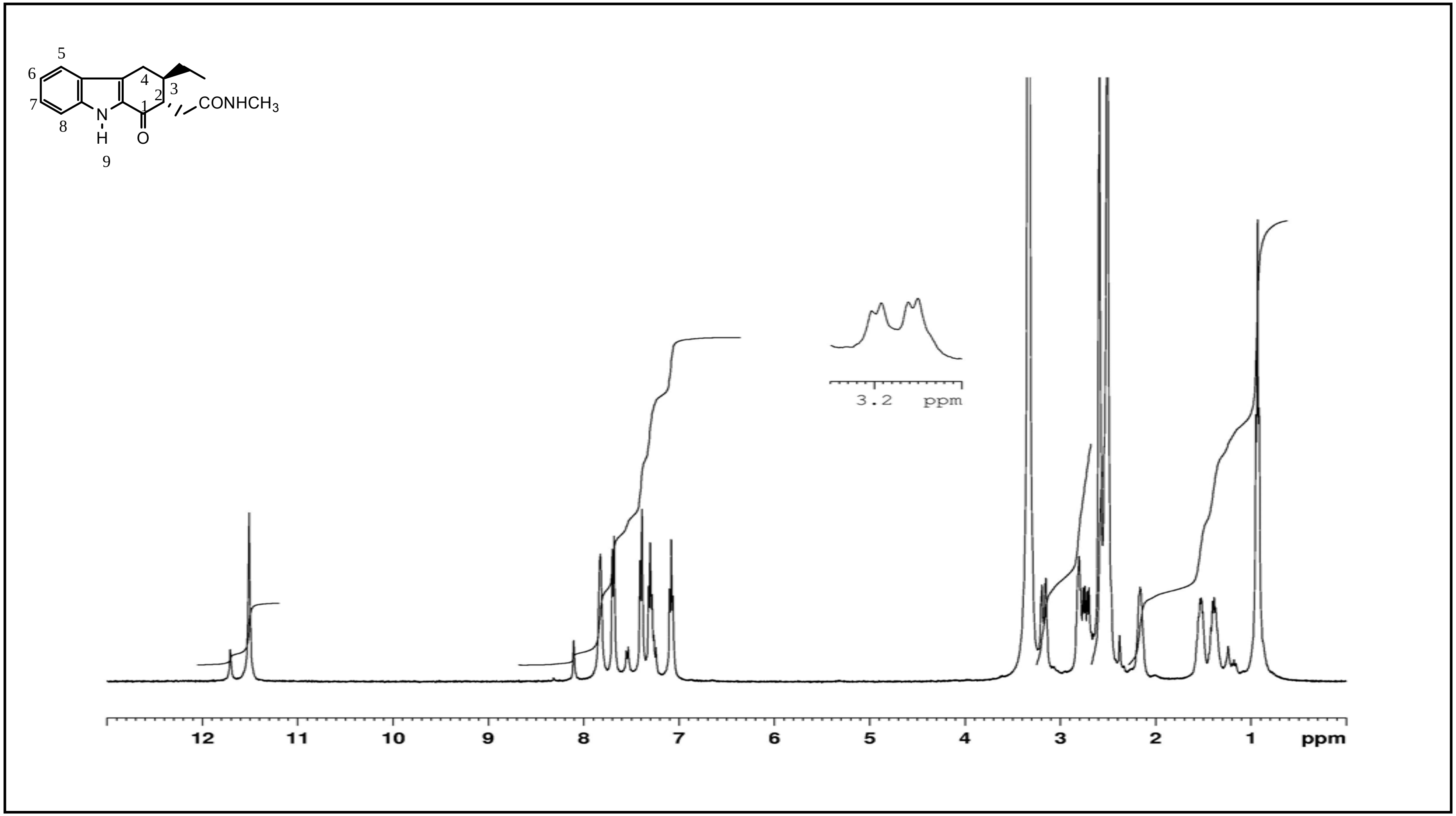

Figure 14. The ^{1}H-NMR spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**)

The APT spectrum of compound **68** exhibit signal at 11.51 ppm for the methyl carbon and 24.40 ppm for the methylene carbon of ethyl group. The signals at 25.98 ppm for C(4) and 34.27 ppm for C (acetamide) is due to the methylene carbons. The methine carbons show signal at 26.02 ppm for C(3) and 41.76 ppm for C(2). The signal at 49.09 ppm is due to the methyl carbon. The carbons of indole ring exhibit signals at 125.86 ppm, 125.99 ppm, 130.71 ppm and 138.79 ppm. The methine carbons of aromatic ring attached to C(6), C(7), C(5) and C(8) exhibit signal at 113.23 ppm, 120.07 ppm, 121.54 ppm and 126.53 ppm, respectively. The signal at 171.56 ppm is due to ketone carbon and the signal at 191.83 ppm belong to amide carbon (Figure 15).

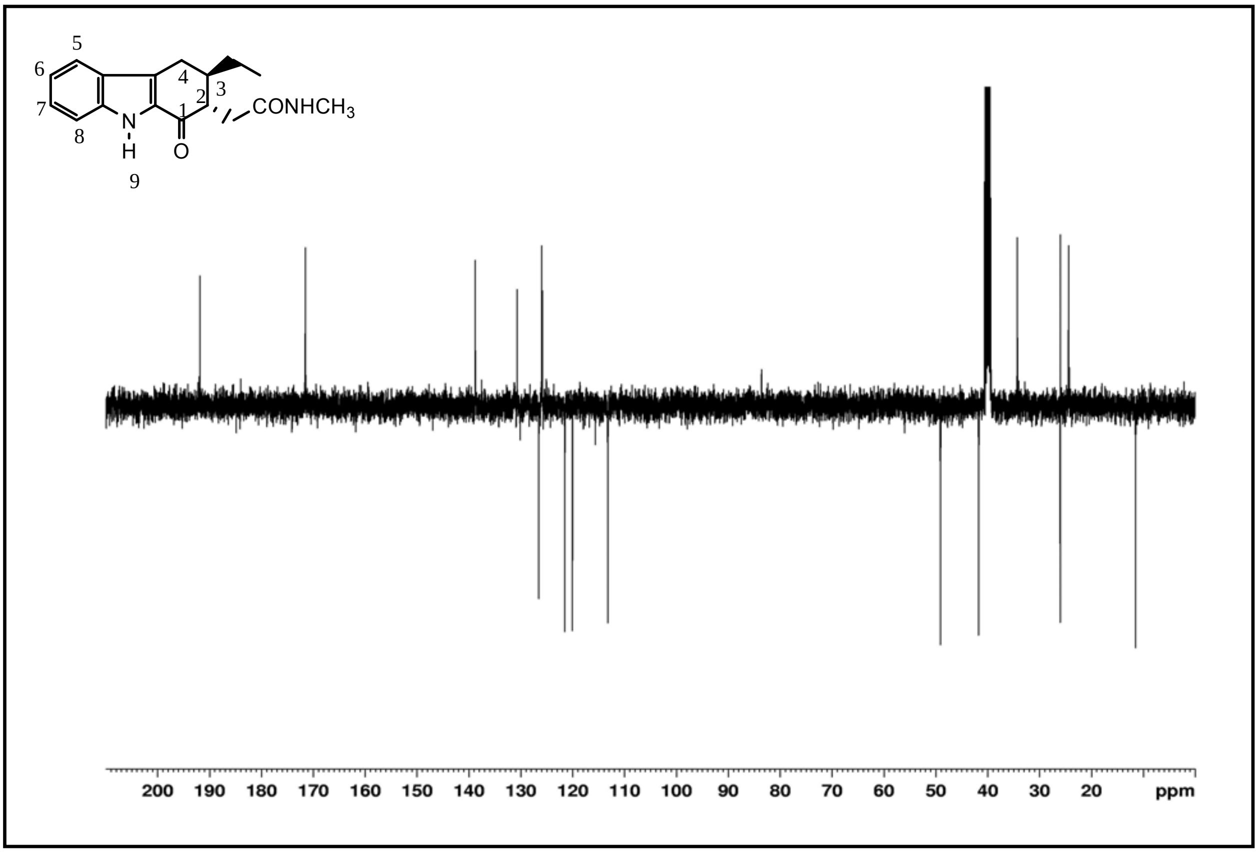

Figure 15. The APT spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**)

The UV spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**) has two bands at 236nm (π-π*) and 310 nm (n-π*) (Figure 16).

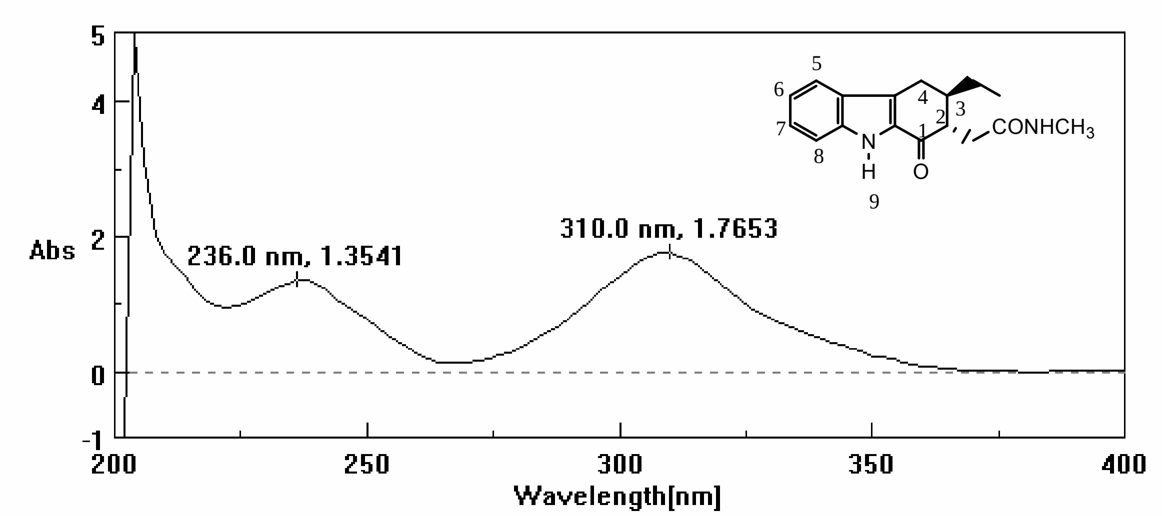

Figure 16. The UV spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**)

The LC-MS spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**) has three signals. The signal at 284.8 belong to molecular ion (M+). The loss of $NHCH_3$ group from [M+]+ is proved by the m/z: 253,8 $[M\text{-}NHCH_3]^+$, The signal at 78.6 belong to $[C_6H_6]$+ (Figure 17).

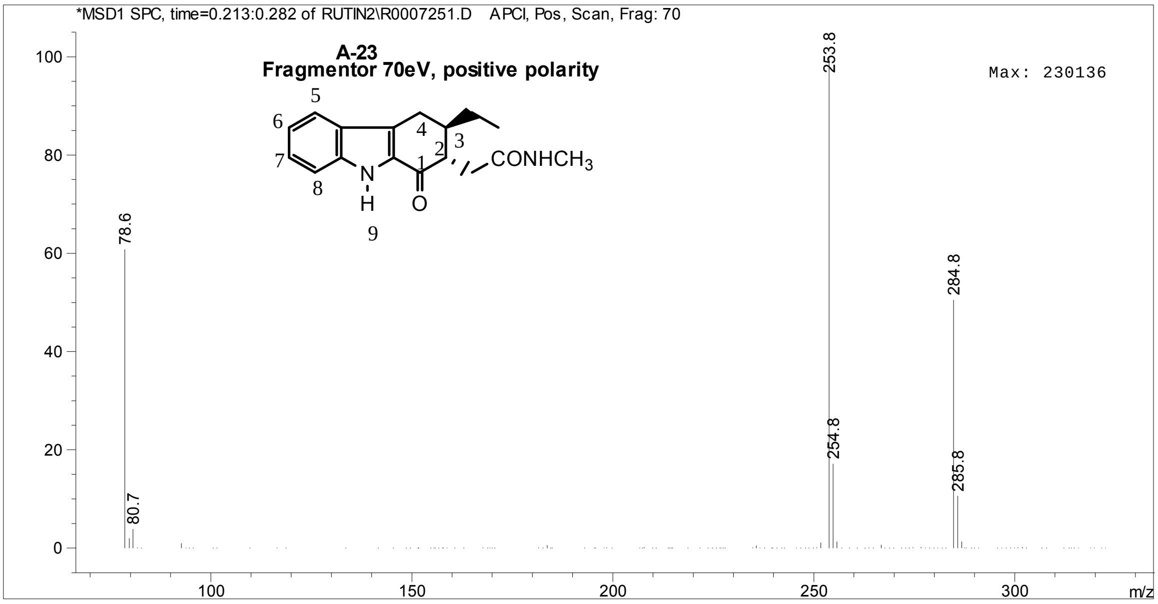

Figure 17. The LC-MS spectrum of N-methyl-2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)-acetamide (**68**)

5.3 Synthesis of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (71)

Characterization of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**) was achieved by IR, UV, LC-MS, ^{1}H-NMR and APT spectroscopy.

The IR spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**) shows bands at 3430 cm^{-1} for N-H streching of indol, at 2989-2877 cm^{-1} for C-H streching, at 1725 cm^{-1} for C=O streching of amide (Figure 18). The formation of compound **71** is proved by loss of C=O streching band of ketone.

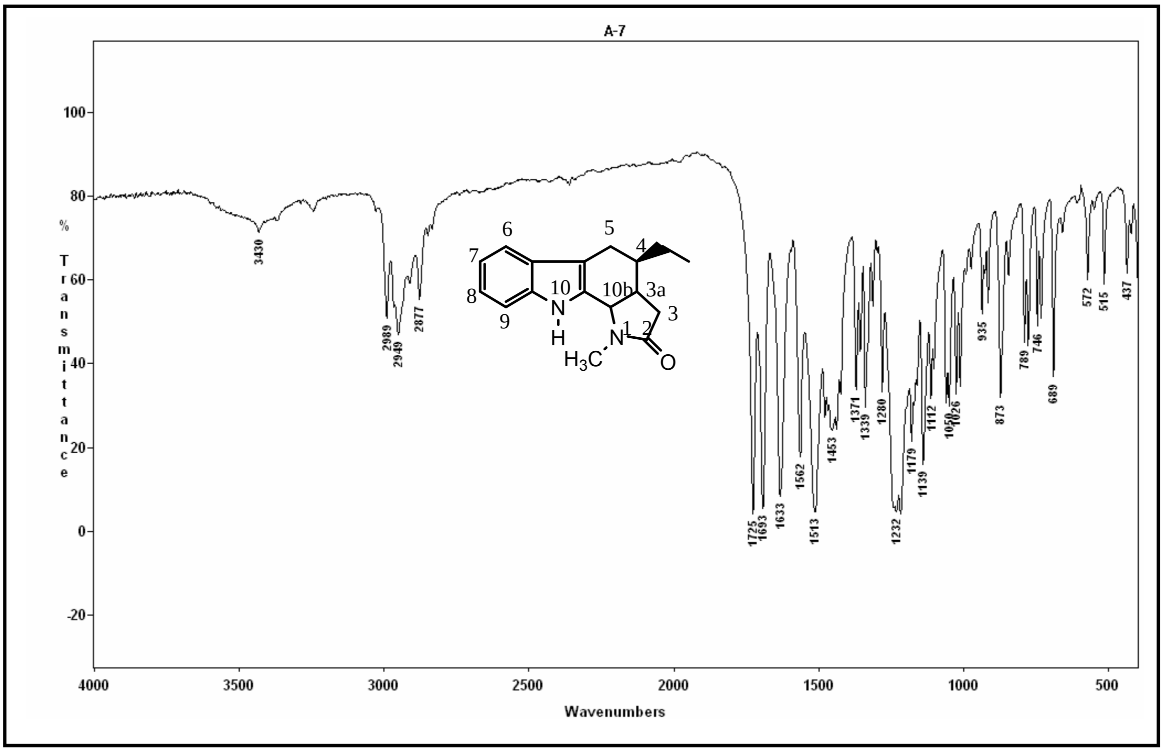

Figure 18. The IR spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**)

Formation of compound **71** is proved by the ^{1}H-NMR spectrum. The spectrum of compound **71** shows a triplet between 1.02 ppm and 1.07 ppm with 7.40 Hz for methyl protons of ethyl group. The multiplet between 1.29 ppm and 1.38 ppm is due to the methylene proton of ethyl group and the multiplet between 1.59 ppm and 1.65 ppm is due to the other methylene proton of ethyl group. The multiplet at 1.85 ppm belong to proton of methine group attached to C(4).The multiplet between 2.51 ppm and 2.59 ppm is due to the proton of methylene group of C(3). The multiplet at 2.55 ppm is due to protons of methylene group of C(5) and the methylene proton attached to C(3). The doublet of doublet between 2.99 ppm and 3.04 ppm with 5.18 Hz and 16.20 Hz belong to methine proton attached to C(3a). The singlet at 3.07 ppm is due to the methyl protons attached to NH group. The doublet at 4.64 ppm with 3.54 Hz belong to methine group attached to C(10b). The multiplet between 7.13 ppm and 7.28 ppm, the doublet at 7.37 ppm with 8.02 Hz and doublet at 7.58 ppm with 7.74 Hz belong to the aromatic ring. The singlet at 8.71 ppm is due to the proton of NH group of indol (Figure 19).

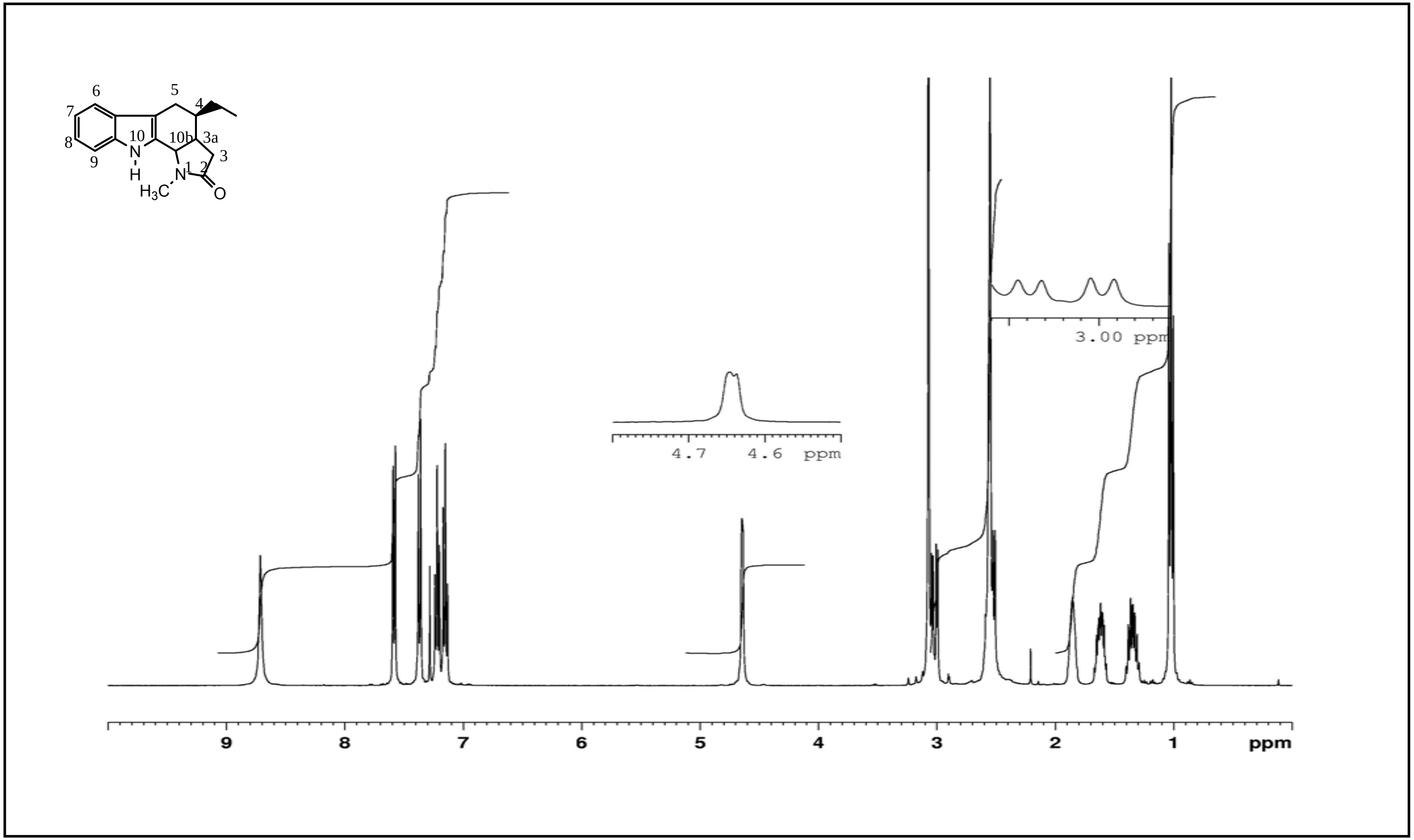

Figure 19. The ^{1}H-NMR spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b -hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**)

In order to determine the formylation position of D ring, COSY spectrum of the compounds were taken. As shown in Figure-20, C(10b) H at 4.64 ppm and C(3a) H at 3.04 ppm have interaction with each other.

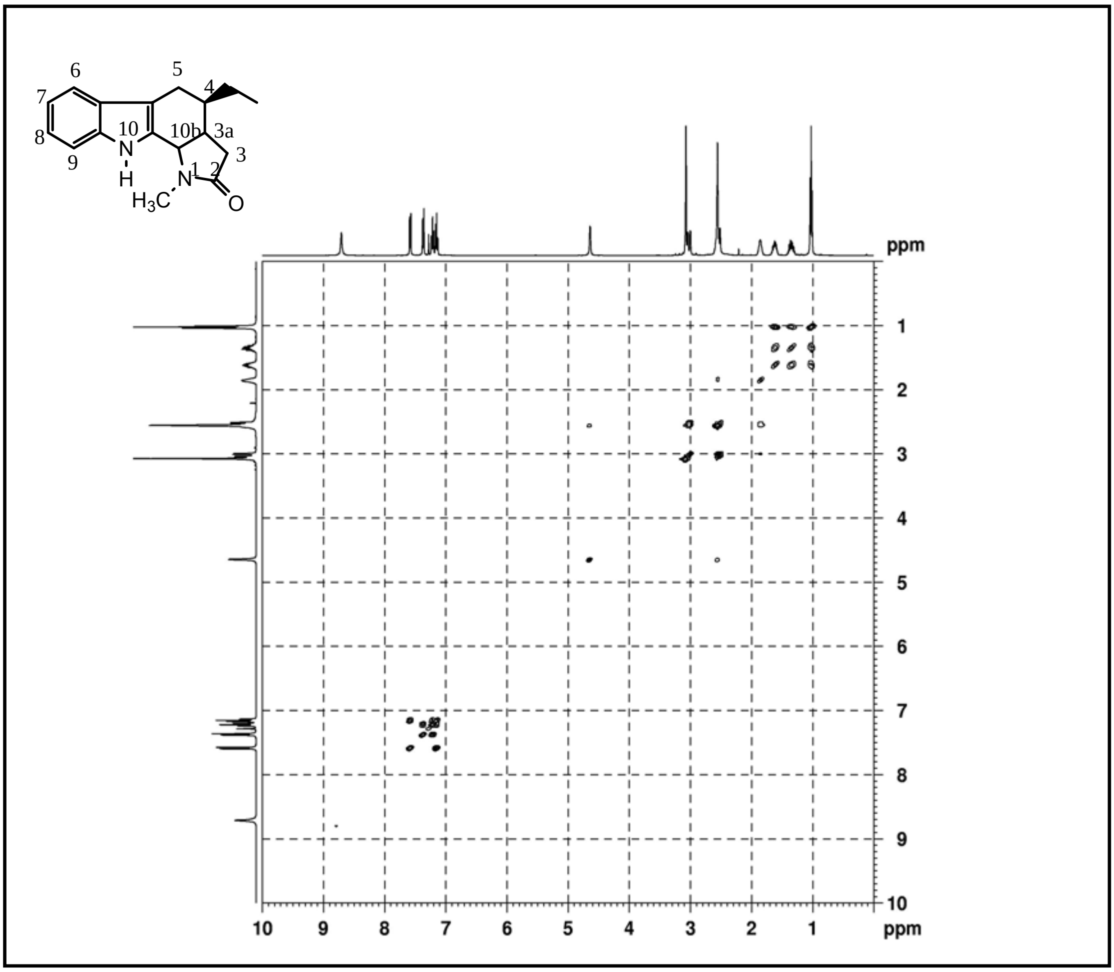

Figure 20. The COSY spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**)

^1H	δ (ppm)	H-H COSY
CH_3 (belong to ethyl)	1.02-1.07	CH_2 (belong to ethyl)
CH (α) (belong to ethyl)	1.29 -1.38	CH_3 (belong to ethyl), 4
CH (β) (belong to ethyl)	1.59 -1.65	CH_3 (belong to ethyl), 4
1	3.07	-
3	2.51-2.59	3a
3a	2.99-3.04	3,4,10b
4	1.85	3a,5,CH_2 (belong to ethyl)
5	2.55	4
6	7.37	8,9
7	7.13	8
8	7.28	6,7
9	7.58	6
10	8.71	
10b	4.64	3a

The APT spectrum of compound **71** exhibit signal at 11.64 ppm for the methyl carbon and 23.31 ppm for the methylene carbon of ethyl group. The signals at 25.90 ppm for C(5) and 35.12 ppm for C(3) is due to the methylene carbons. The signal at 28.91 ppm is due to the methyl carbon. The methine carbons show signal at 36.12 ppm for C(4), 37.67 ppm for C(3) and 56.02 ppm for C(10b). The carbons of indole ring exhibit signals at 111.79 ppm,126.73 ppm, 129.33 ppm and 136.89 ppm. The methine carbons of aromatic ring attached to C(7), C(8), C(6) and C(9) exhibit signal at 111.15 ppm, 118.93 ppm, 119.57 ppm and 122.69 ppm, respectively. The signal at 174.52 ppm belong to amide carbon (Figure 21).

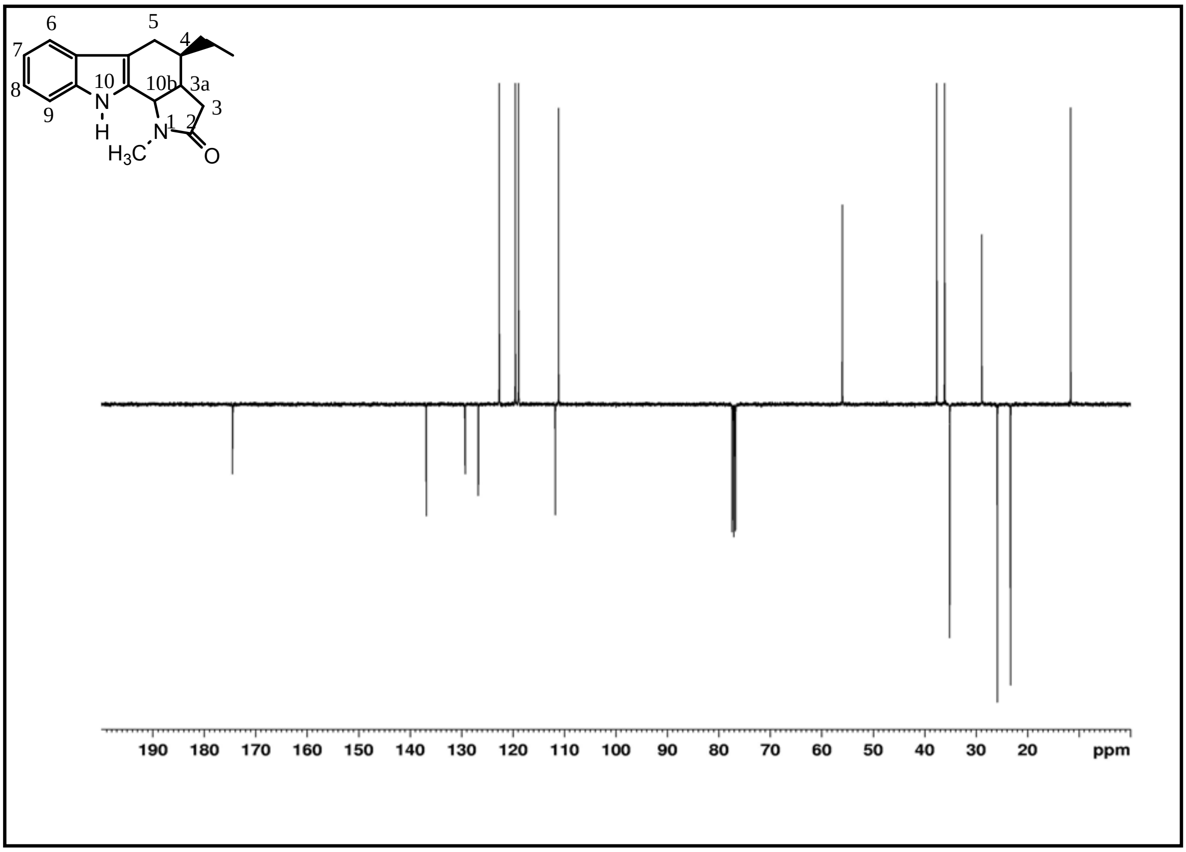

Figure 21. The APT spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**)

The UV spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**) has two bands at 222nm (π-π*) and 276 nm (n-π*) (Figure 22).

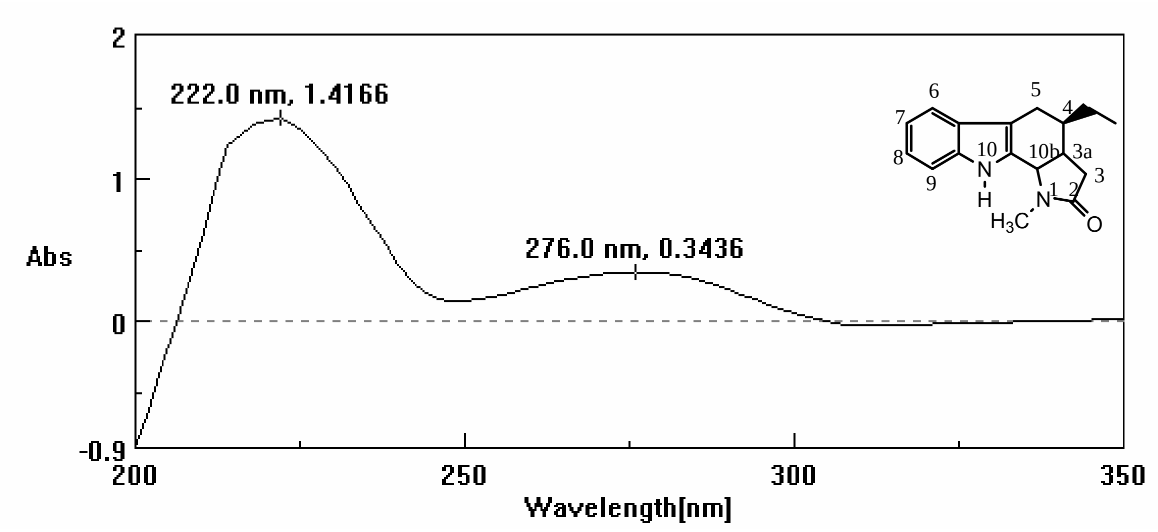

Figure 22. The UV spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**)

The LC-MS spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**) has four signals. The signal at 268.8 belong to molecular ion (M+). The loss of CH_3NH_2 group from [M]+ is proved by the m/z: 237,7 $[M- CH_3NH_2]^+$ and the loss of CO group from $[M- CH_3NH_2]$+ is proved by the m/z: 195,7 $[M- CH_3NH_2\text{-}CO]^+$ .The signal at 78.7 belong to $[C_6H_6]$+ (Figure 23).

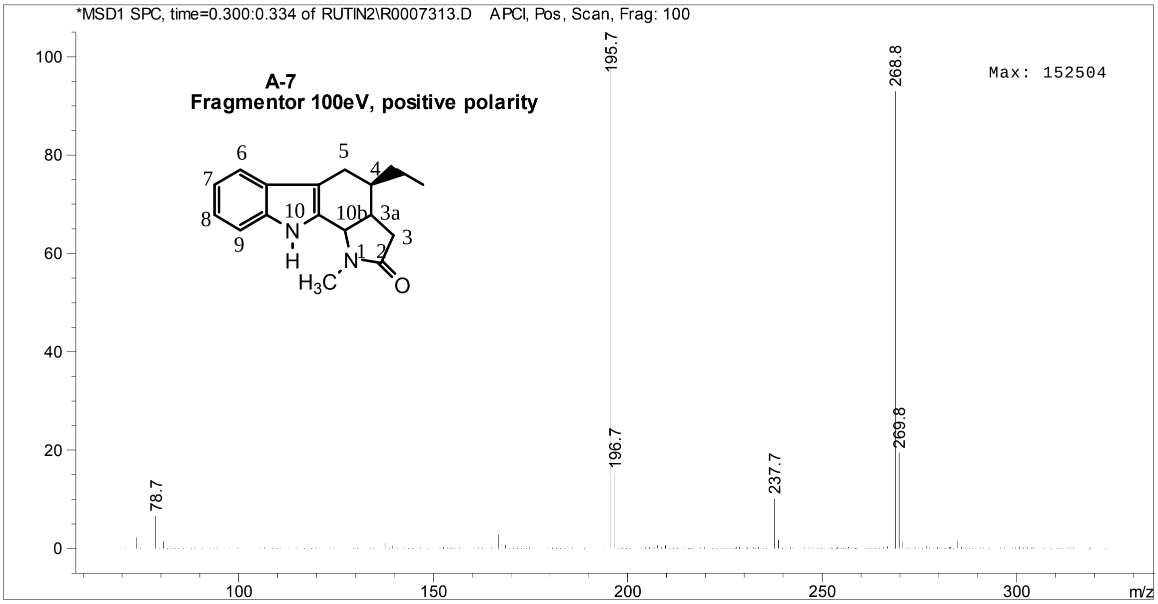

Figure 23. The LC-MS spectrum of 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3-a]carbazol-2(10H)-one (**71**)

5.4 Synthesis of 4-Ethyl-3,3a,4,5-tetraydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (73)

Characterization of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**) was achieved by IR, UV, LC-MS, ^{1}H-NMR and APT spectroscopy.

The IR spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**) shows bands at 3371 cm^{-1} for N-H streching of indol, at 2959-2857 cm^{-1} for C-H streching, at 1762 cm^{-1} for C=O streching of lactone (Figure 24). The formation of compound **73** is proved by loss of C=O streching band of ketone.

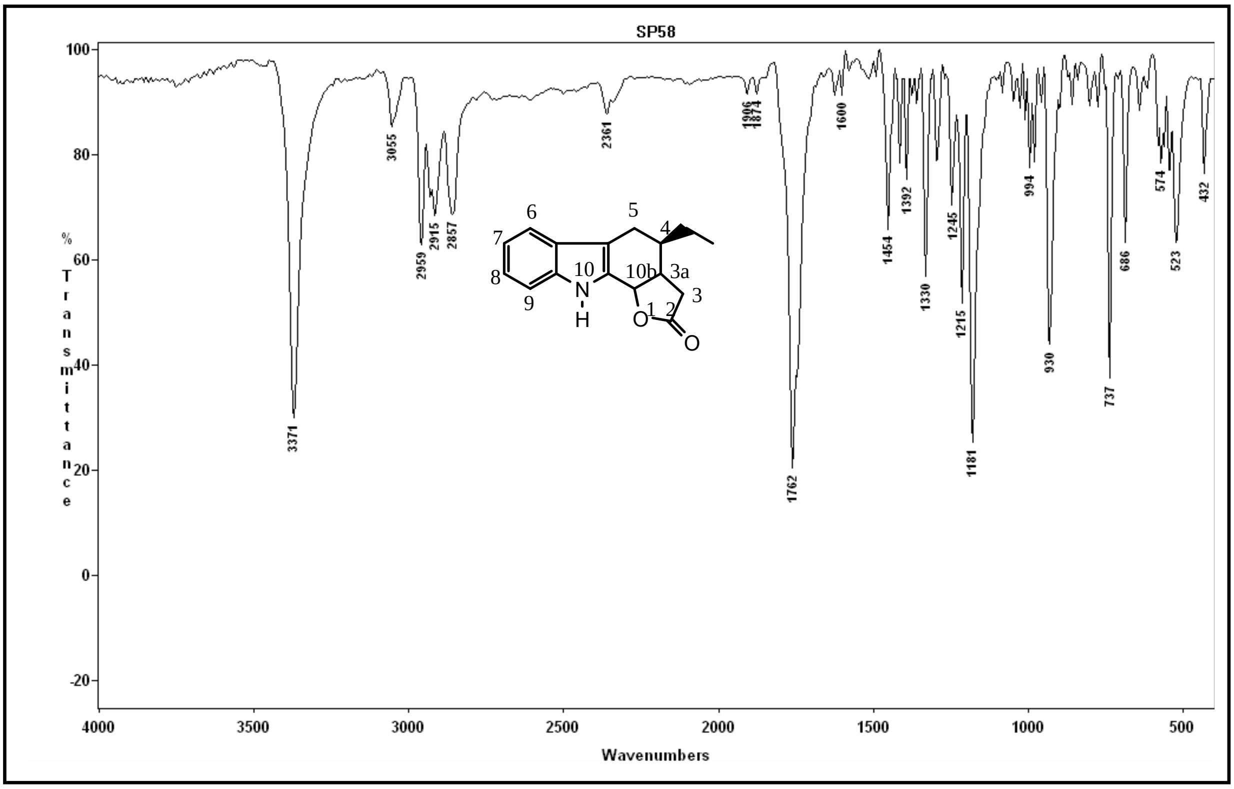

Figure 24. The IR spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**)

Formation of compound **73** is proved by the ^{1}H-NMR spectrum. The spectrum of compound **73** shows a triplet between 1.04 ppm and 1.08 ppm with 7.46 Hz for methyl protons of ethyl group. The multiplet between 1.32 ppm and 1.44 ppm is due to the methylene proton of ethyl group and the multiplet between 1.62 ppm and 1.73 ppm is due to the other methylene proton of ethyl group. The multiplet between 1.77 ppm and 1.86 ppm belong to proton of methine group attached to C(4). The doublet of doulet between 2.46 ppm and 2.52 ppm with 7.79 Hz and 16.20 Hz and the doublet of doulet between 2.61 ppm and 2.66 ppm with 4.10 Hz and 16.47 Hz belong to methylene protons of C(5). The multiplet between 2.69 ppm and 2.82 ppm is due to the protons of methylene group of C(3). The doublet of doublet between 3.04 ppm and 3.09 ppm with 4.94 Hz and 16.18 Hz belong to methine proton attached to C(3a). The doublet between 5.55 ppm and 5.56 ppm with 5.95 Hz belong to methine group attached to C(10b). The multiplet between 7.14 ppm and 7.17 ppm, the multiplet between 7.24 ppm and 7.28 ppm, the doublet between 7.38 ppm and 7.40 ppm with 8.73 Hz and doublet between 7.58 ppm and 7.60 ppm with 7.88 Hz belong to the aromatic ring. The singlet at 8.28 ppm is due to the proton of NH group of indol (Figure 25).

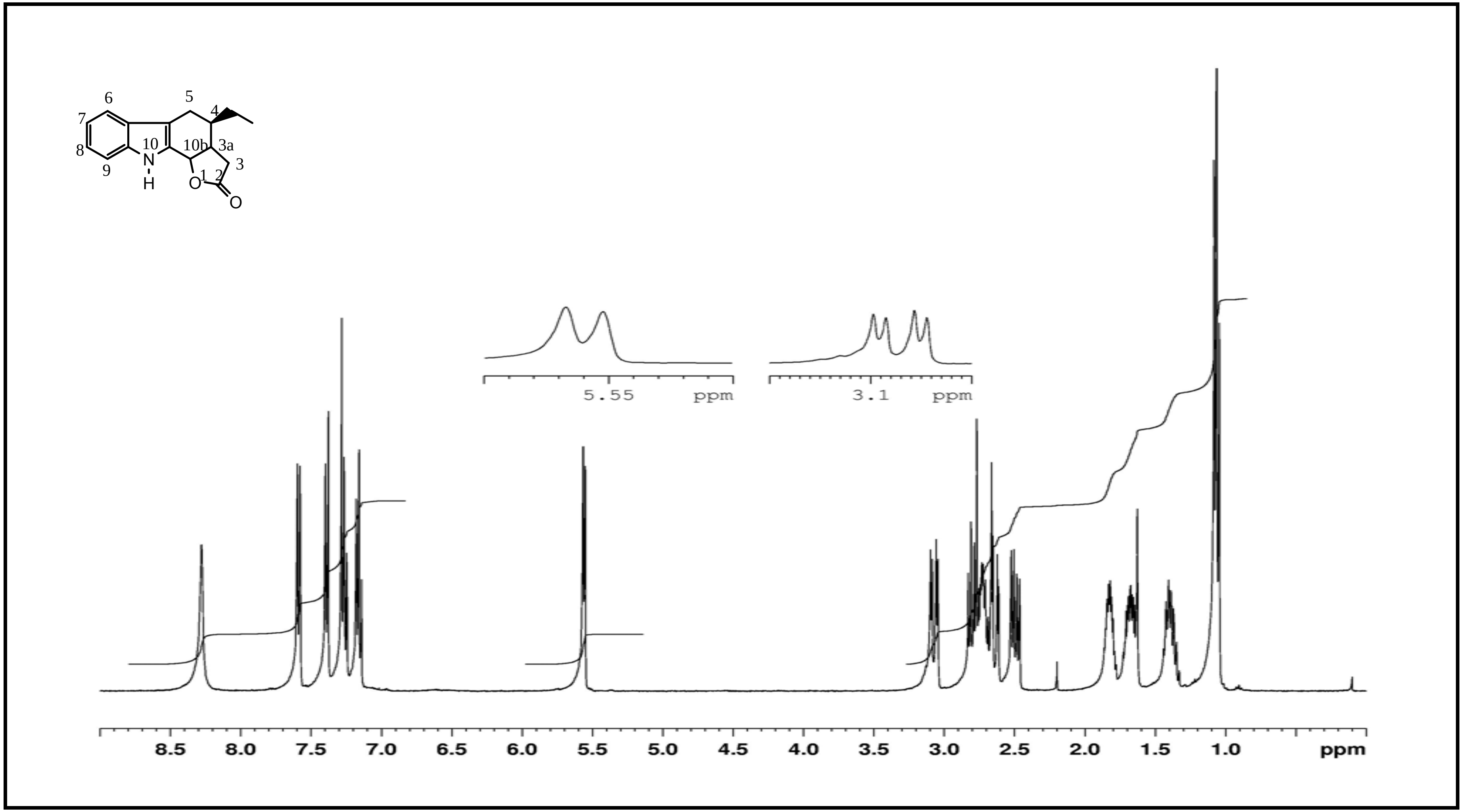

Figure 25. The ^{1}H-NMR spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**)

The APT spectrum of compound **73** exhibit signal at 11.57 ppm for the methyl carbon and 23.41 ppm for the methylene carbon of ethyl group. The signals at 25.80 ppm for C(5) and 33.37 ppm for C(3) is due to the methylene carbons. The methine carbons show signal at 36.51 ppm for C(4), 40.17 ppm for C(3a) and 73.78 ppm for C(10b). The carbons of indole ring exhibit signals at 113.51 ppm ,126.22 ppm, 127.98 ppm and 137.22 ppm. The methine carbons of aromatic ring attached to C(7), C(8), C(6) and C(9) exhibit signal at 111.45 ppm, 119.21 ppm, 119.77 ppm and 123.42 ppm, respectively. The signal at 176.55 ppm belong to lactone carbon (Figure 26).

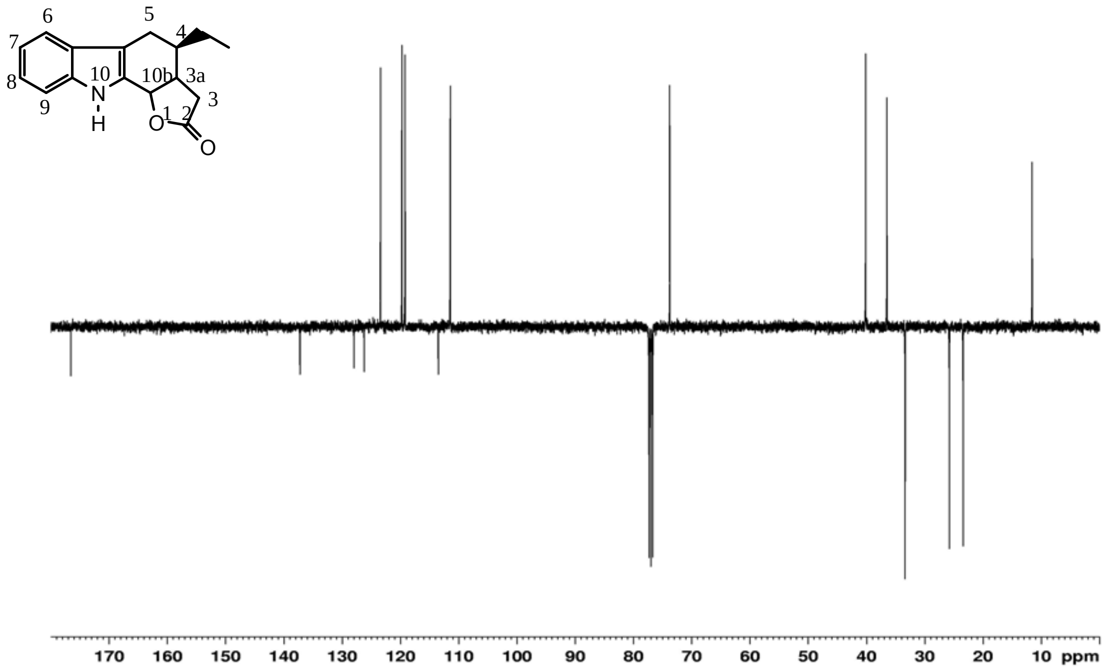

Figure 26. The APT spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**)

The UV spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**) has two bands at 222nm (π-π*) and 278 nm (n-π*) (Figure 27).

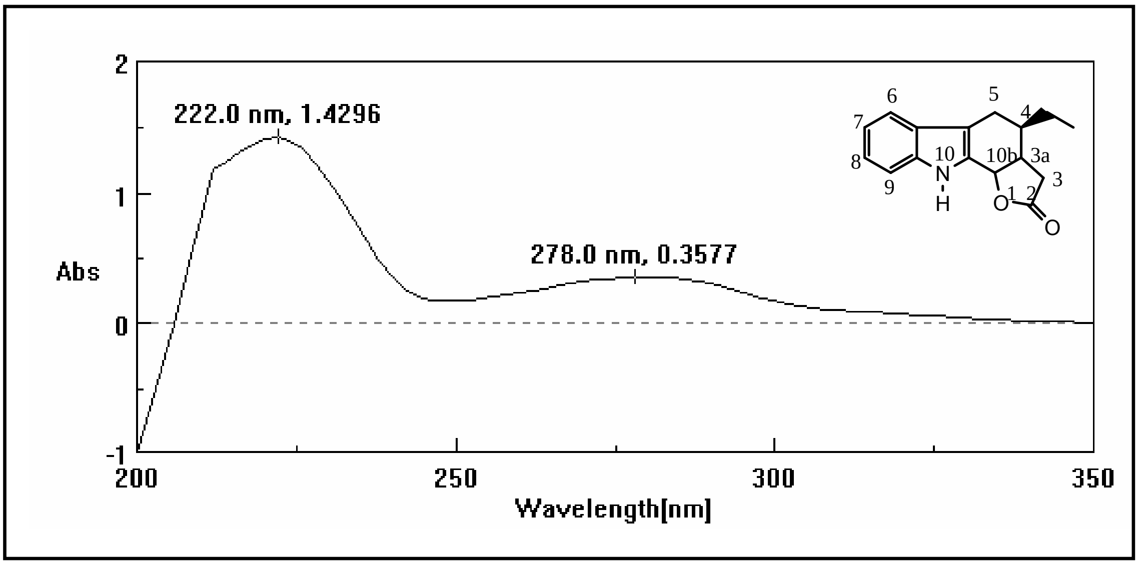

Figure 27. The UV spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**)

The LC-MS spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**) has four signals. The signal at 255.8 belong to molecular ion (M+). The loss of CH_3CO_2H group from [M]+ is proved by the m/z: 196,7 [M-$CH_3CO_2H]^+$ and the loss of C_4H_8 group from [M- CH_3CO_2H]+ is proved by the m/z: 140.6 [M- CH_3CO_2H- $C_4H_8]^+$. The signal at 78.7 belong to [C_6H_6]+ (Figure 28).

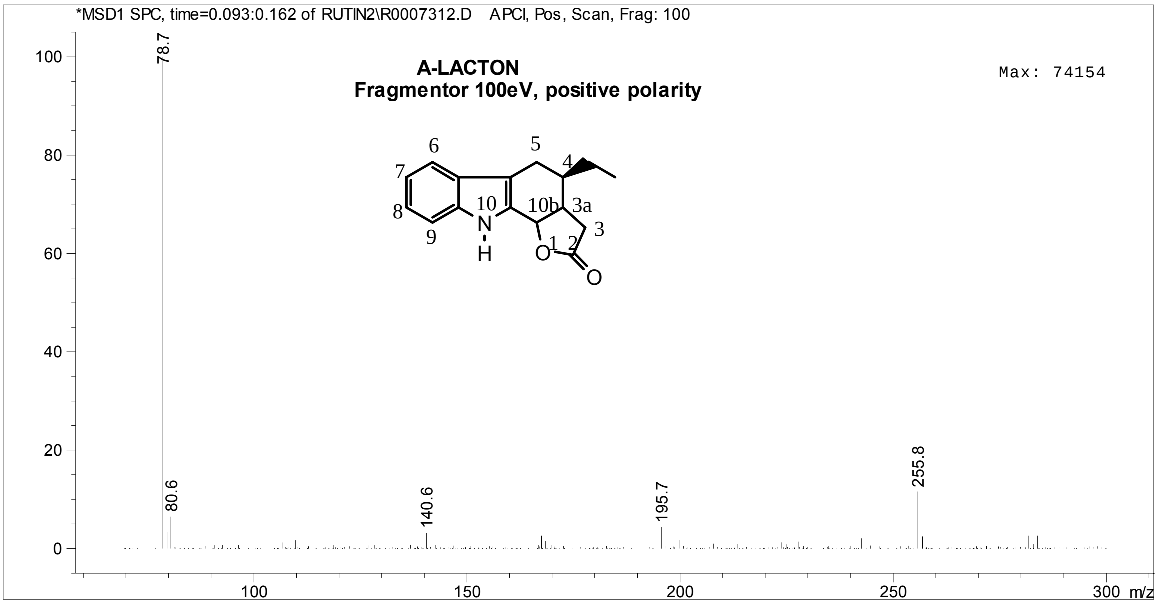

Figure 28. The LC-MS spectrum of 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3-a]carbazol-2(10b*H*)-one (**73**)

5.5 Synthesis of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (74)

Characterization of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**) was achieved by IR, UV, LC-MS, ^{1}H-NMR and APT spectroscopy.

The IR spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**) shows bands at 3195 cm^{-1} for N-H streching of indol, at 2964-2888 cm^{-1} for C-H streching, at 1781 cm^{-1} for C=O streching of lactone and 1644 cm^{-1} for C=O streching of ketone (Figure 29). The formation of compound **74** is proved by formtion of C=O streching band of ketone.

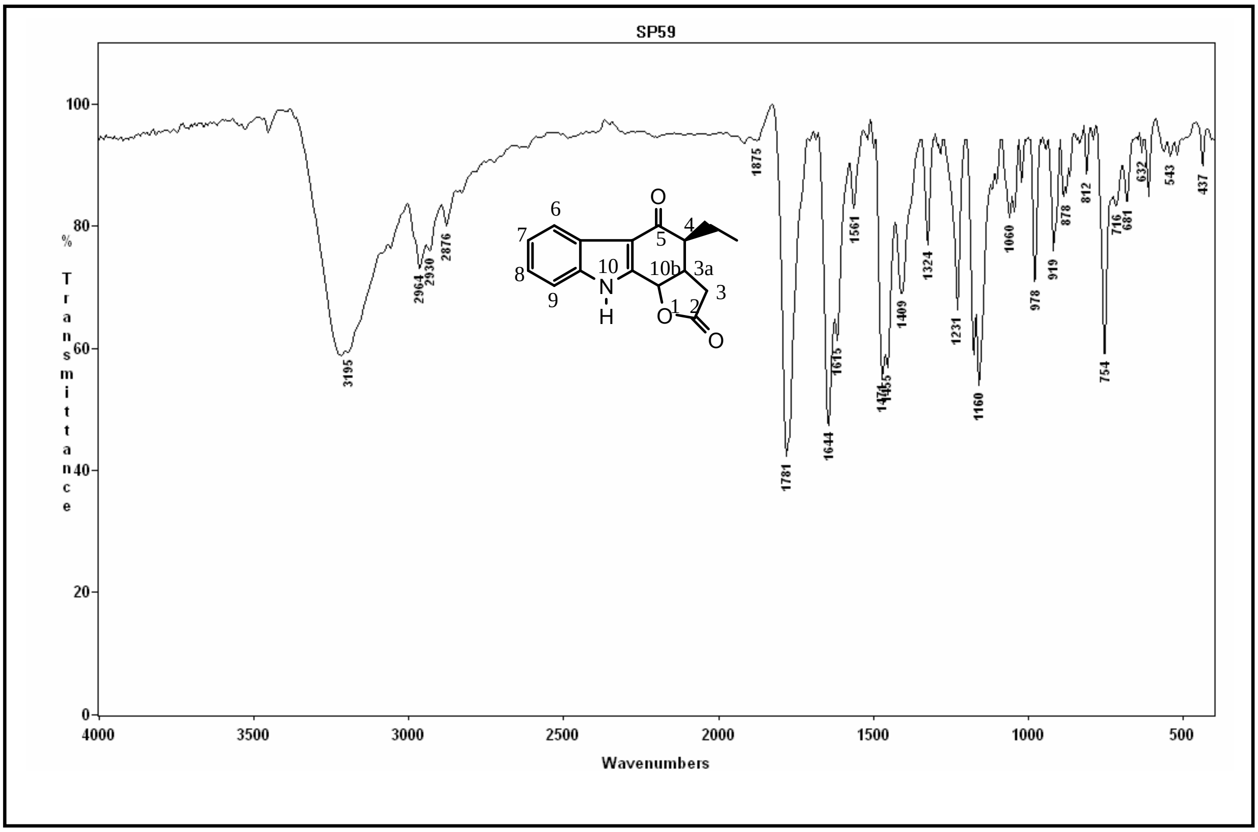

Figure 29. The IR spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**)

Formation of compound **74** is proved by the ^{1}H-NMR spectrum. The spectrum of compound **74** shows a triplet between 0.92 ppm and 0.95 ppm with 7.30 Hz for methyl protons of ethyl group. The multiplet between 1.58 ppm and 1.65 ppm is due to the methylene proton of ethyl group and the multiplet between 1.74 ppm and 1.80 ppm is due to the other methylene proton of ethyl group. The multiplet between 2.41 ppm and 2.51 ppm belong to methylene proton of C(3) and the methine protons attached to C(4). The doublet of doublet between 2.83 ppm and 2.89 ppm with 8.21 Hz and 16.43 Hz belong to methine proton attached to C(3a). The doublet at 6.05 ppm with 6.75 Hz belong to methine group attached to C(10b). The multiplet between 7.21 ppm and 7.31 ppm, the doublet at 7.50 ppm with 7.95 Hz and doublet at 8.06 ppm with 7.61 Hz belong to the aromatic ring. The singlet at 12.39 ppm is due to the proton of NH group of indol (Figure 30).

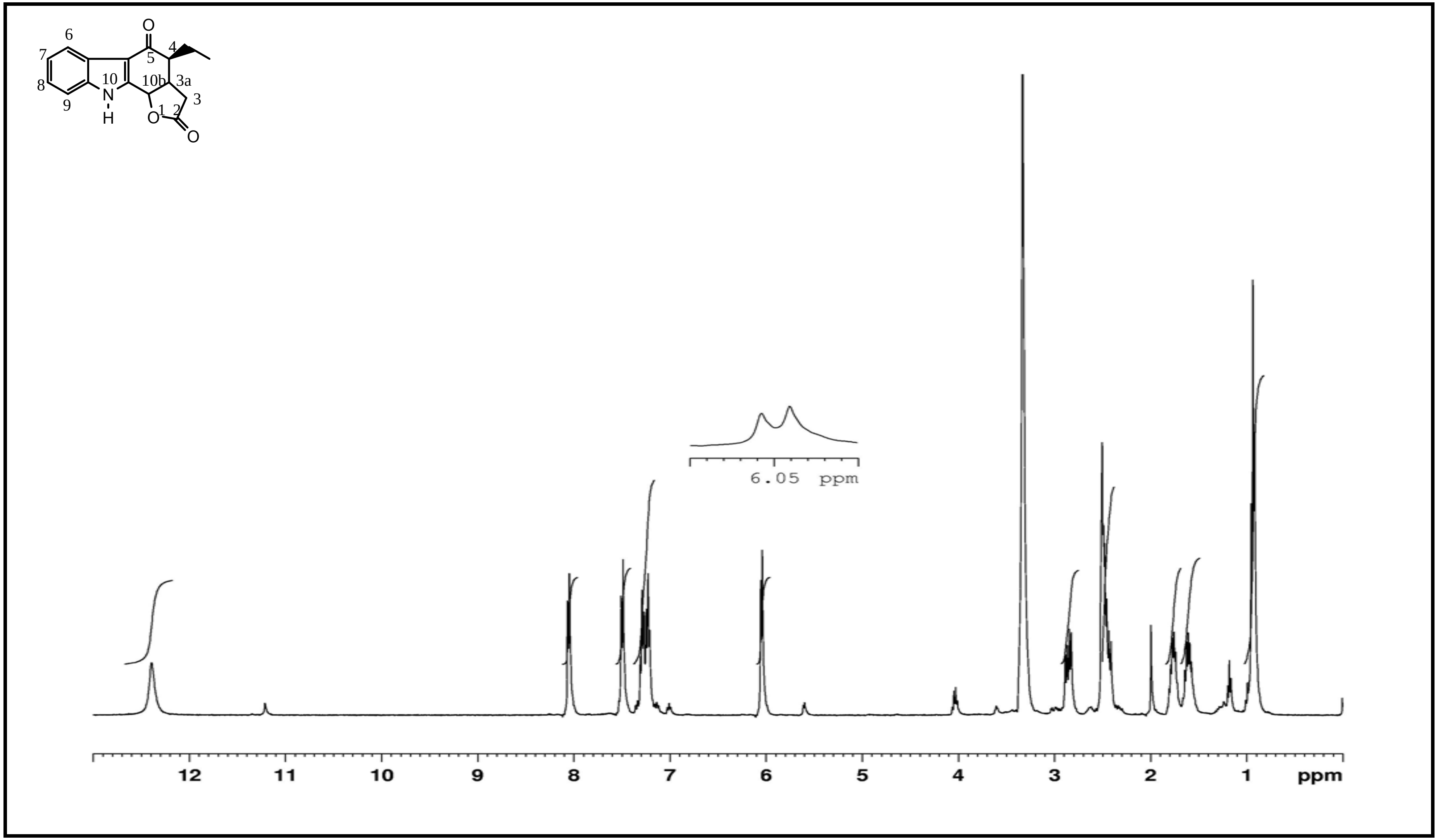

Figure 30. The ^{1}H-NMR spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**)

The APT spectrum of compound **74** exhibit signal at 12.06 ppm for the methyl carbon and 24.13 ppm for the methylene carbon of ethyl group. The signal at 34.05 ppm for C(3) is due to the methylene carbon. The methine carbons show signal at 39.38 ppm for C(4), 49.88 ppm for C(3a) and 71.92 ppm for C(10b). The carbons of indole ring exhibit signals at 111.90 ppm, 123.93 ppm, 137.65 ppm and 142.73 ppm. The methine carbons of aromatic ring attached to C(7), C(8), C(6) and C(9) exhibit signal at 112.81 ppm, 122.62 ppm, 122.76 ppm and124.42 ppm, respectively. The signal at 175.96 ppm belong to ketone carbon and the signal at 193.64 belong to lactone carbon (Figure 31).

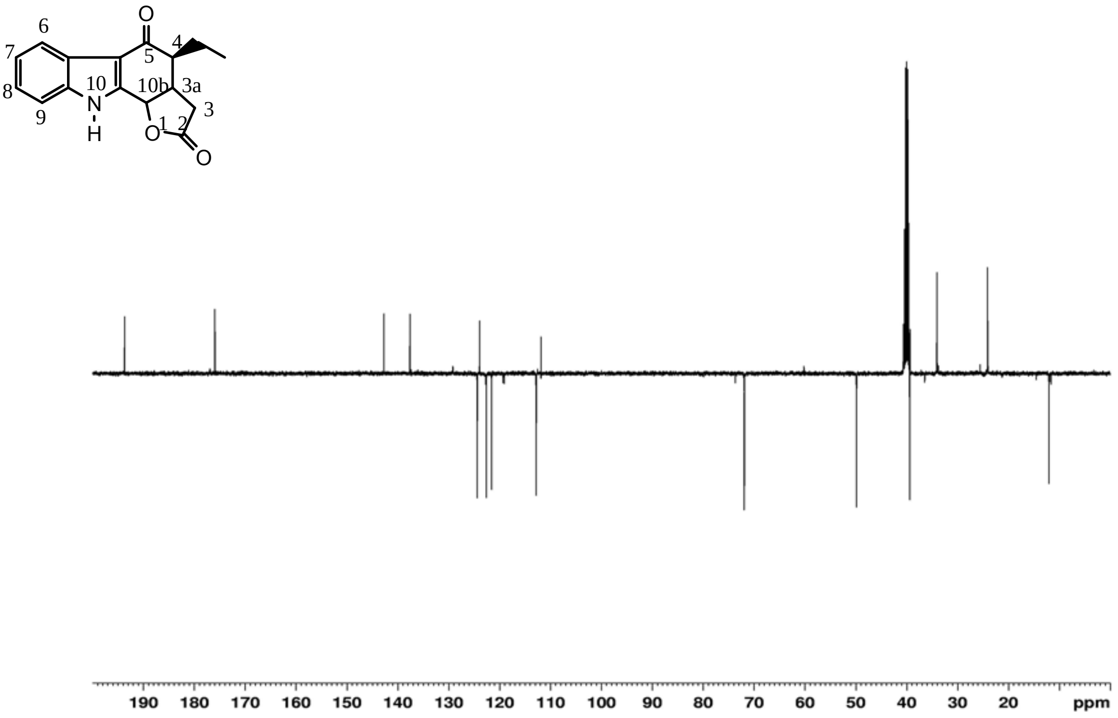

Figure 31. The APT spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**)

4-oxo-tetrahydrocarbazole derivative has different characteristic UV spectrum from tetrahydrocarbazole derivative. The UV spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**73**) has three bands at 212nm (π-π*), 242nm (π-π*), 262 nm (n-π*) and 294 nm (n-π*) (Figure 32).

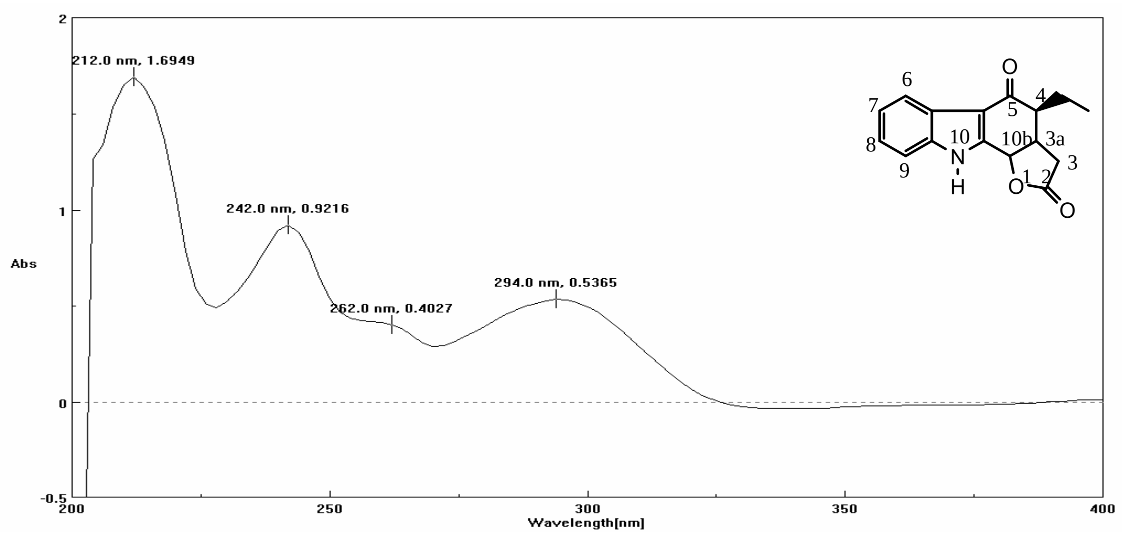

Figure 32. The UV spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**)

The LC-MS spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**) has four signals. The signals at 269.7 belong to molecular ion (M+). The loss of CO_2H group from [M]+ is proved by the m/z: 223,7 $[M- CO_2H]^+$ and the loss of C_4H_8 group from [M- CO_2H]+ is proved by the m/z: 167.7 $[M- CO_2H- C_4H_8]^+$. The signal at 78.7 belong to $[C_6H_6]$+ (Figure 33).

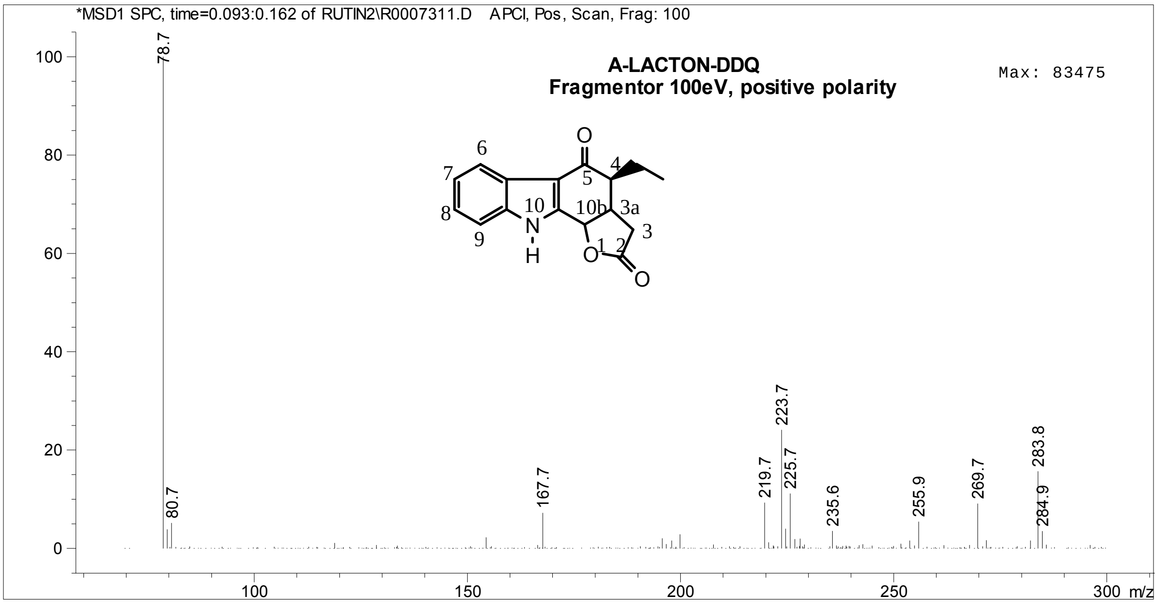

Figure 33. The LC-MS spectrum of 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3-a]carbazole-2,5(10*H*,10b*H*)-dione (**74**)

5.6 Synthesis of 2-(3-Ethyl-1-hydroxy-4-oxo-1,2,3,9-tetrahydro-1*H*-carbazol-2-yl)acetamide (75)

Characterization of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**) was achieved by IR, UV, LC-MS, ^{1}H-NMR and APT spectroscopy.

The IR spectrum of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-2-yl)acetamide (**75**) shows bands at 3379 cm^{-1} for N-H streching of indol, at 2953-2868 cm^{-1} for C-H streching, at 1624 cm^{-1} and 1602 cm^{-1} for C=O streching of ketones (Figure 34).

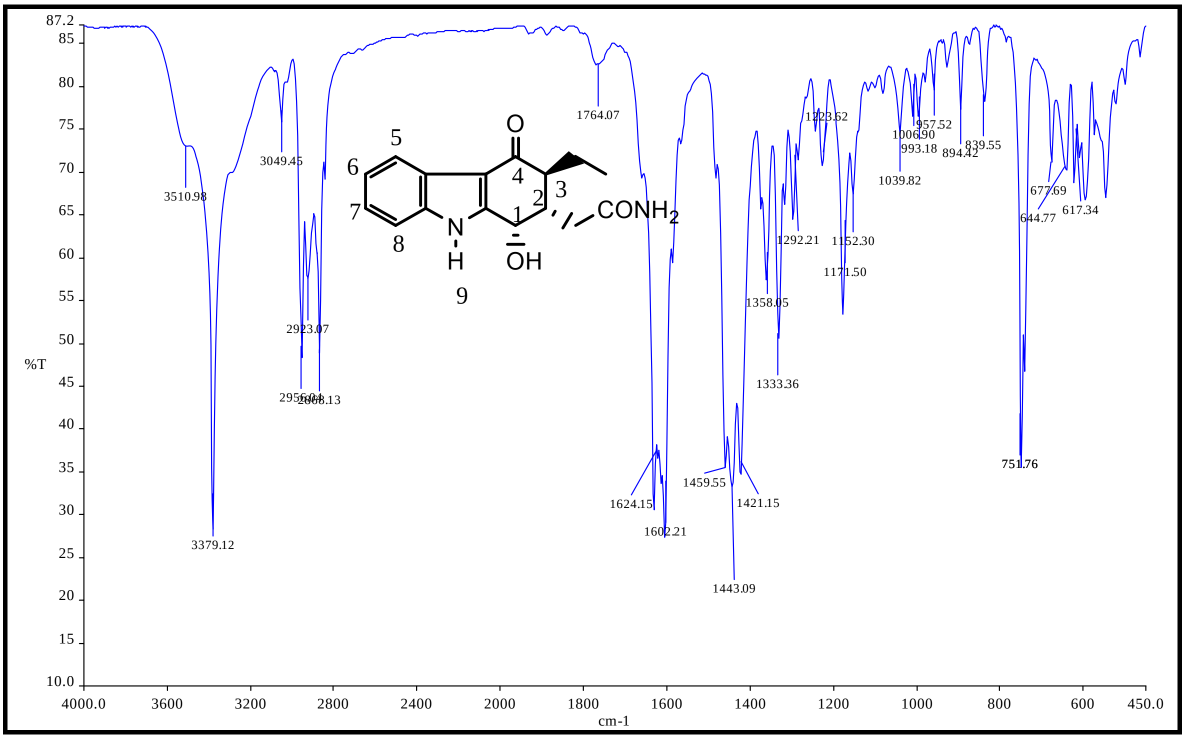

Figure 34. The IR spectrum of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)

Formation of compound **75** is proved by the ^{1}H-NMR spectrum. The spectrum of compound **75** shows a triplet between 0.91 ppm and 0.95 ppm with 7.17 Hz for methyl protons of ethyl group. The multiplet between 1.56 ppm and 1.64 ppm is due to the methylene proton of ethyl group and the multiplet between 1.75 ppm and 1.83 ppm is due to the other methylene proton of ethyl group. The multiplet between 1.94 ppm and 2.09 ppm belong to the methine proton attached to C(3). The multiplet between 2.31 ppm and 2.34 ppm belong to methylene protons of acetamide group. The doublet of doublet between 2.79 ppm and 2.83 ppm with 4.50 Hz and 4.19 Hz belong to methine proton attached to C(2). The doublet between 5.26 ppm and 5.27 ppm with 4.43 Hz belong to methine group attached to C(1). The singlet a 5.95 is due to the proton of OH group. The singlets at 6.83 ppm and 7.32 ppm are due to the proton of NH_2 group. The multiplet between 7.13 ppm and 7.20 ppm, the doublet at 7.44 ppm with 8.01 Hz and doublet between 7.95 ppm and 7.97 ppm with 7.50 Hz belong to the aromatic ring. The singlet at 11.97 ppm is due to the proton of NH group of indol (Figure 35).

In order to determine the O-H and N-H peaks, ^{1}H-NMR spectrum of the compounds were taken with mixture of DMSO-D_2O as a solvent. O-H peak at 5,95 ppm, NH_2 peaks at 6.83 ppm and 7.32 ppm and N-H peak at 11.97 ppm, as shown in Figure-35, diminish when döterium exchanged spectrum is taken and losing these peaks are proved the structure (Figure 36).

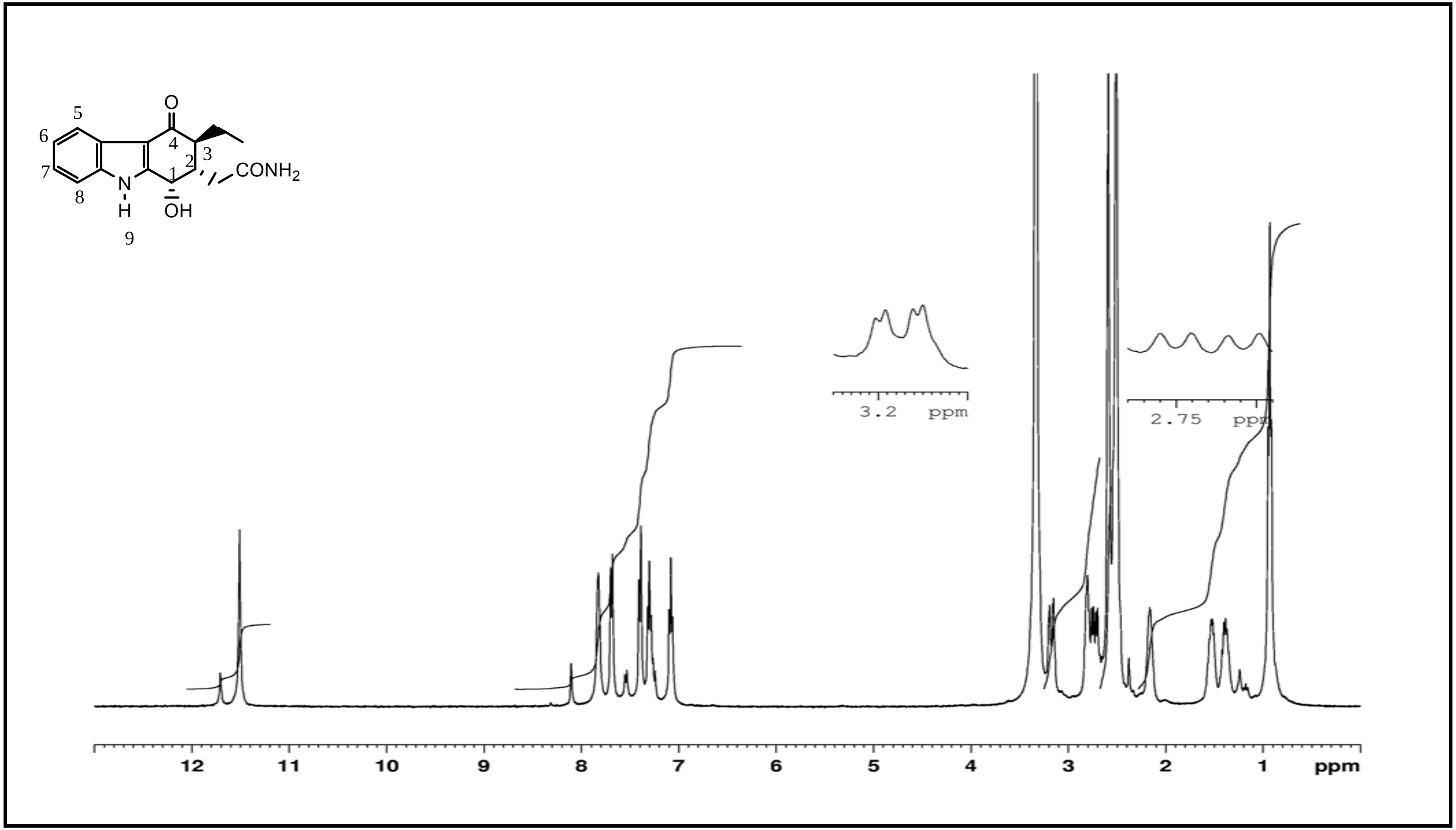

Figure 35. The ^{1}H-NMR spectrum of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)

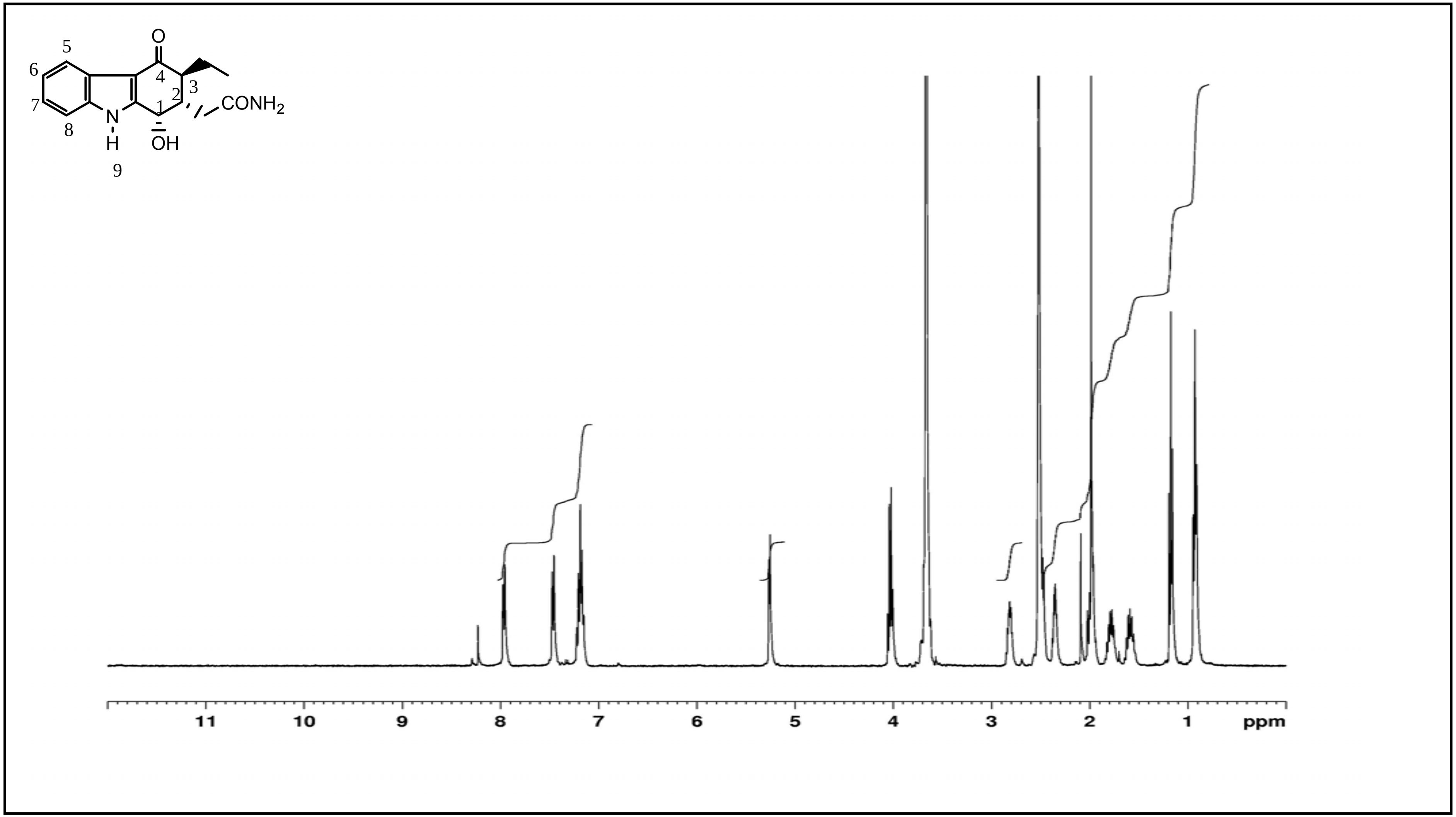

Figure 36. The ^{1}H-NMR spectrum of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**) in DMSO-D_2O

The APT spectrum of compound **75** exhibit signal at 12.26 ppm for the methyl carbon and 22.51 ppm for the methylene carbon of ethyl group. The signal at 33.95 ppm for C(acetamide group) is due to the methylene carbon. The methine carbons show signal at 42.38 ppm for C(3), 52.27 ppm for C(2) and 62.86 ppm for C(1). The carbons of indole ring exhibit signals at 109.71 ppm, 125.08 ppm, 136.98 ppm and 151.54 ppm. The methine carbons of aromatic ring attached to C(6), C(7), C(5) and C(8) exhibit signal at 112.57 ppm, 120.94 ppm, 120.06 ppm and 123.06 ppm, respectively. The signal at 174.10 ppm belong to ketone carbon and the signal at 194.74 belong to amide carbon (Figure 37).

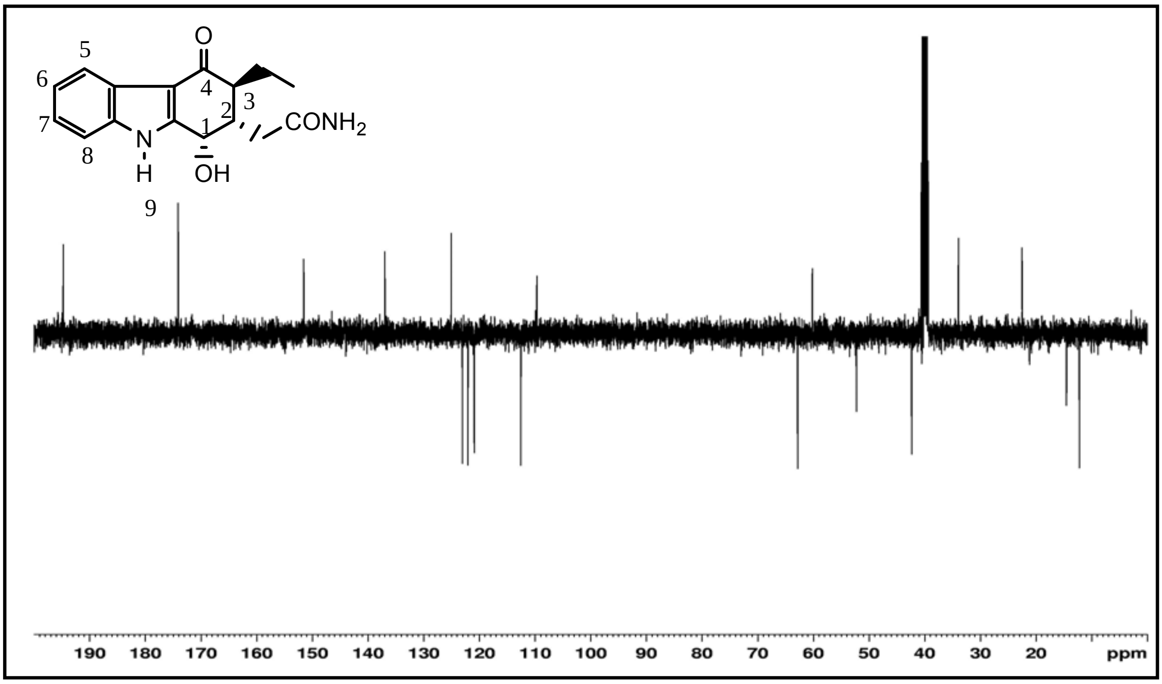

Figure 37. The APT spectrum of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)

4-oxo-tetrahydrocarbazole derivative has different characteristic UV spectrum from tetrahydrocarbazole derivative. The UV spectrum of 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**) has four bands at 214nm (π-π*), 242nm (π-π*) , 264nm (n-π*) and 298 nm (n-π*) (Figure 38).

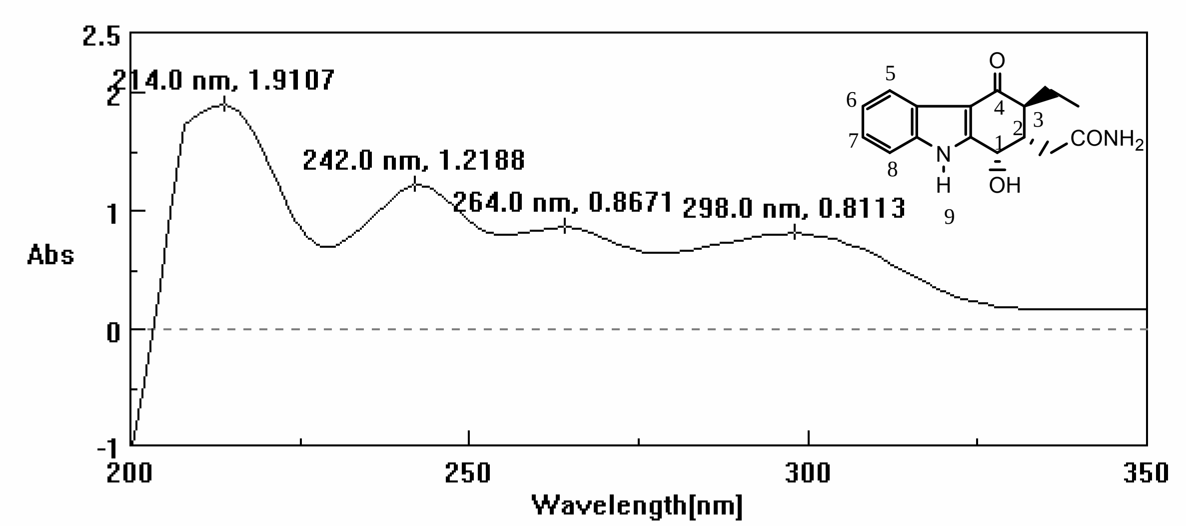

Figure 38. The UV spectrum of 2-(3-Ethyl-1hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)

The LC-MS spectrum of 2-(3-Ethyl-1hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**) has five signals. The signal at 285.8 belong to molecular ion (M+). The loss of OH group from [M]+ is proved by the m/z: 268,8 $[M- OH]^+$, the loss of NH_3 group from [M-OH]+ is proved by the m/z: 251.8 $[M-OH-NH_3]^+$ and the loss of CO group from $[M-OH-NH_3]$+ is proved by the m/z: 223.7 $[M-OH-NH_{3-}CO]^+$. The signal at 78.7 belong to $[C_6H_6]$+ (Figure 39).

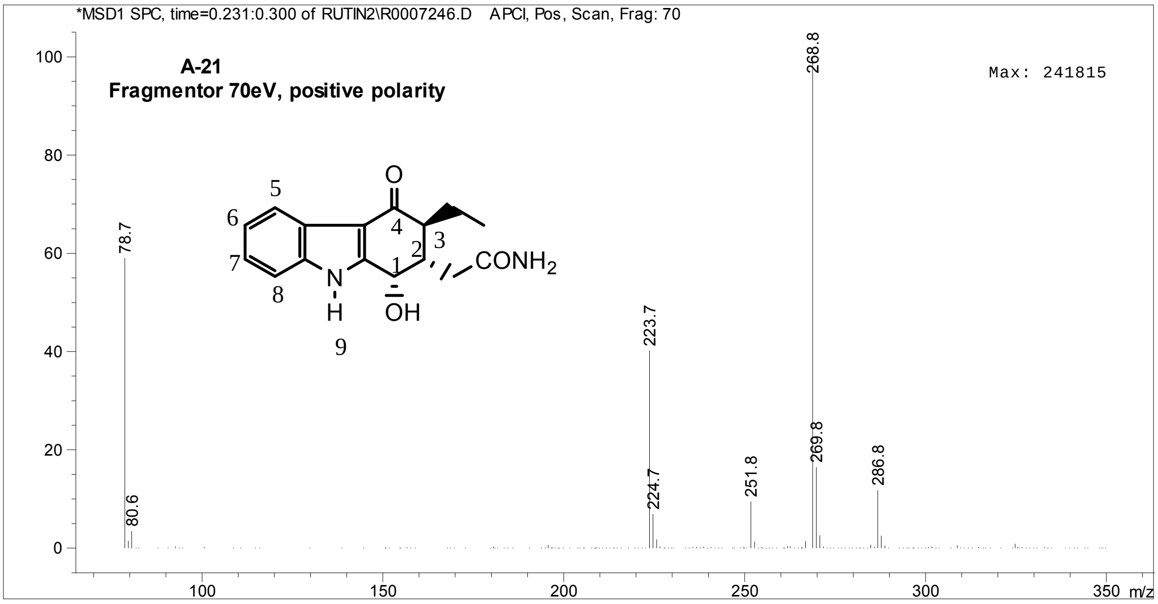

Figure 39. The LC-MS spectrum of 2-(3-Ethyl-1hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)

5.7 Synthesis of N-(Acetyl)-12-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (61)

Characterization of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**) was achieved by IR, UV, LC-MS, ^{1}H-NMR, COSY and APT spectroscopy.

The IR spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**) shows bands at 3390 cm^{-1} for N-H streching of indol, at 2950-2873 cm^{-1} for C-H streching, at 1654 cm^{-1} for C=O streching of ketone (Figure 40).

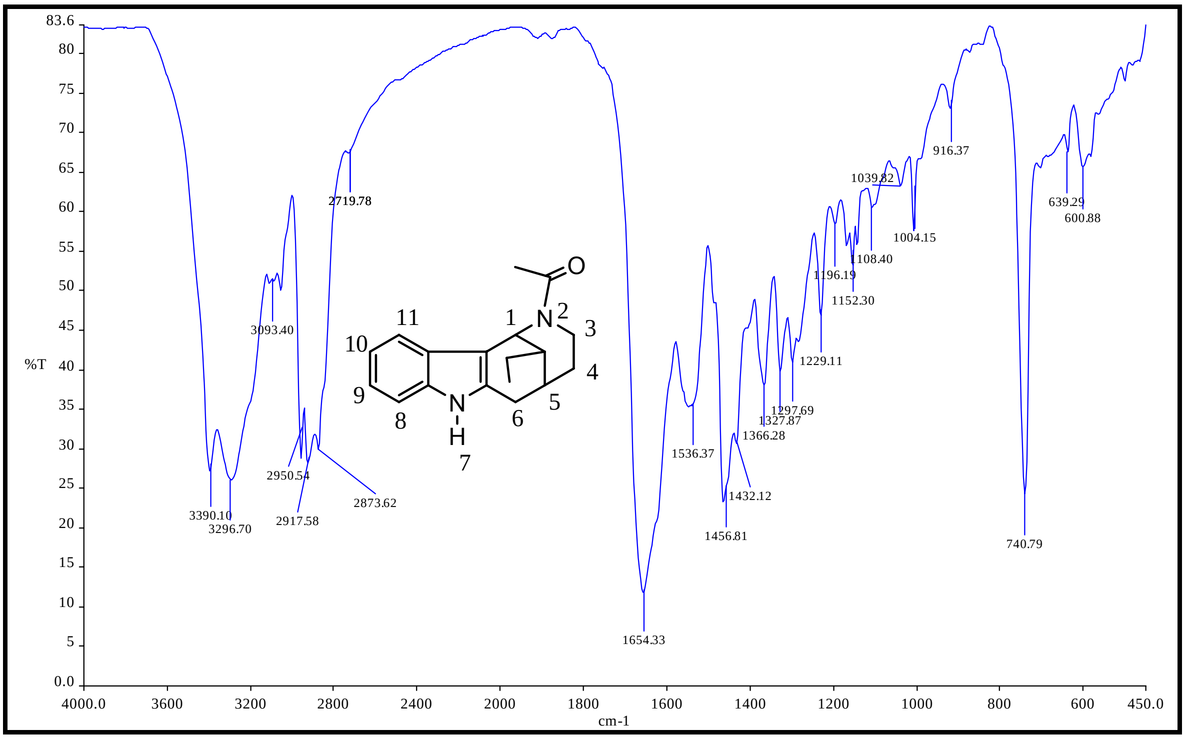

Figure 40. The IR spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**)

Formation of compound **61** is proved by the ^{1}H-NMR spectrum. The spectrum of compound **61** shows a triplet between 0.98 ppm and 1.01 ppm with 7.28 Hz for methyl protons of ethyl group. The multiplet between 1.34 ppm and 1.43 ppm is due to the methylene protons of ethyl group. The multiplet between 1.49 ppm and 159 ppm belong to the other methylene proton of ethyl group and C(4). He multiplet between 1.70 ppm and 1.80 ppm is due to the methylene proton of C(4). The multiplet between 1.92 ppm and 1.96 ppm belong to the methine proton attached to C(5). The singlet at 1.99 ppm is due to the methyl proton of acetyl group. The multiplet between 2.49 ppm and 2.55 ppm belong to methylene protons attached to C(3) and C(6). The multiplet between 2.79 ppm and 2.95 ppm belong to the other methylene protons attached to C(3) and C(6). The doublet of doublet between 3.36 ppm and 3.41 ppm belong to methine proton attached to C(12). The doublet between 5.32 ppm and 5.46 ppm belong to methine group attached to C(1). The multiplet between 7.09 ppm and 7.14 ppm, the doublet between 7.29 ppm and 7.31 ppm with 7.67 Hz and doublet between 7.46 ppm and 7.49 ppm with 6.04 Hz belong to the aromatic ring. The singlet at 7.74 ppm is due to the proton of NH group of indol (Figure 41).

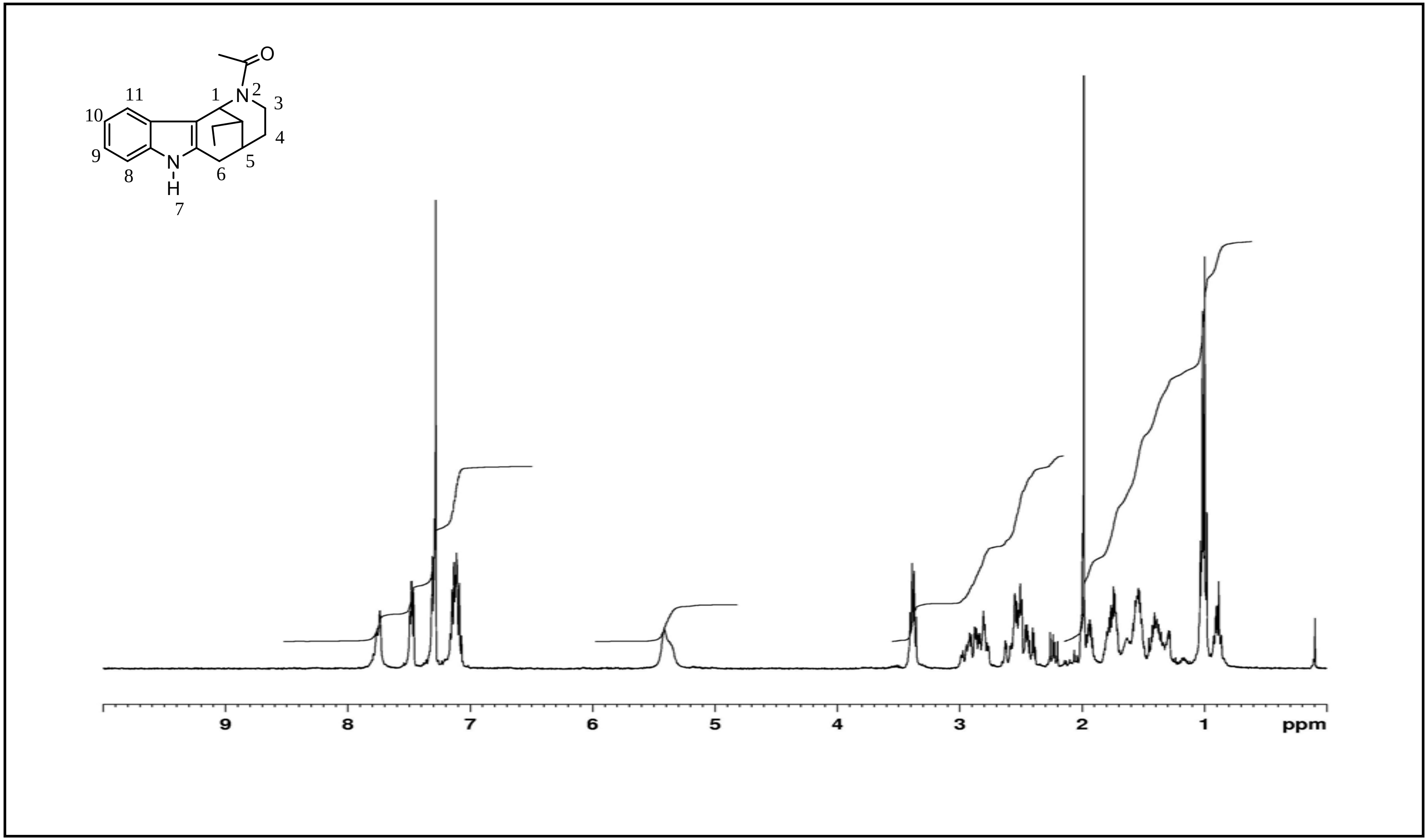

Figure 41. The ^{1}H-NMR spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**)

In order to determine the formylation position of D ring, COSY spectrum of the compounds were taken. As shown in Figure 42, C(1) H between 5.32 ppm and 5.46 pm and C(12) H between 3.36 ppm and 3.41 ppm have interaction with each other.

^1H	δ (ppm)	H-H COSY
CH_3 (belong to ethyl)	0.98-1.01	CH_2 (belong to ethyl)
CH (α) (belong to ethyl)	1.34-1.43	CH_3 (belong to ethyl), 12
CH (β) (belong to ethyl)	1.49 -1.59	CH_3 (belong to ethyl), 12
1	5.32-5.36	12
2	1.99	-
3 (α)	2.49-2.55	4
3 (β)	2.79-2.95	4
4(α)	1.49 -1.59	3,5
4 (β)	1.70-1.80	3,5
5	1.92-1.96	4,6,12
6 (α)	2.49-2.55	5
6 (β)	2.79-2.95	5
7	7.74	-
8	7.46-7.49	9
9	7.09-7.14	8,10
10	7.09-7.14	9,11
11	7.29-7.31	10
12	3.36-3.41	1,5, CH_2 (belong to ethyl)

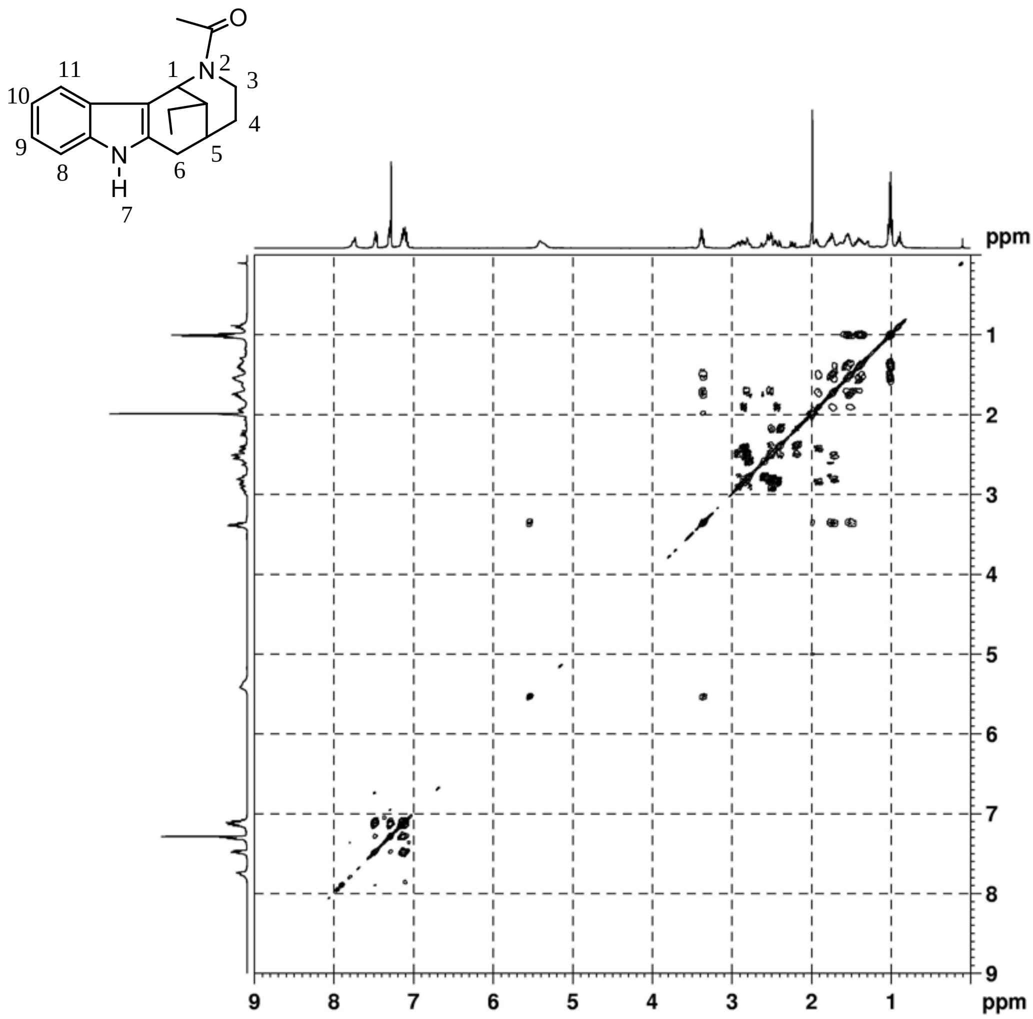

Figure 42. The COSY spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**)

The APT spectrum of compound **61** exhibit signal at 11.67 ppm for the methyl carbon and 23.11 ppm for the methylene carbon of ethyl group. The signal at 25.57 ppm for C (6), 32.97 ppm for C (4), and 37.73 ppm for C (3) and is due to the methylene carbons. The methine carbons show signal at 42.38 ppm for C(3), 52.27 ppm for C(2) and 62.86 ppm for C(1). The carbons of indole ring exhibit signals at 109.71 ppm, 125.08 ppm, 136.98 ppm and 151.54 ppm. The methine carbons of aromatic ring attached to C(6), C(7), C(5) and C(8) exhibit signal at 112.57 ppm, 120.94 ppm, 120.06 ppm and 123.06 ppm, respectively. The signal at 174.10 ppm belong to ketone carbon. (Figure 43).

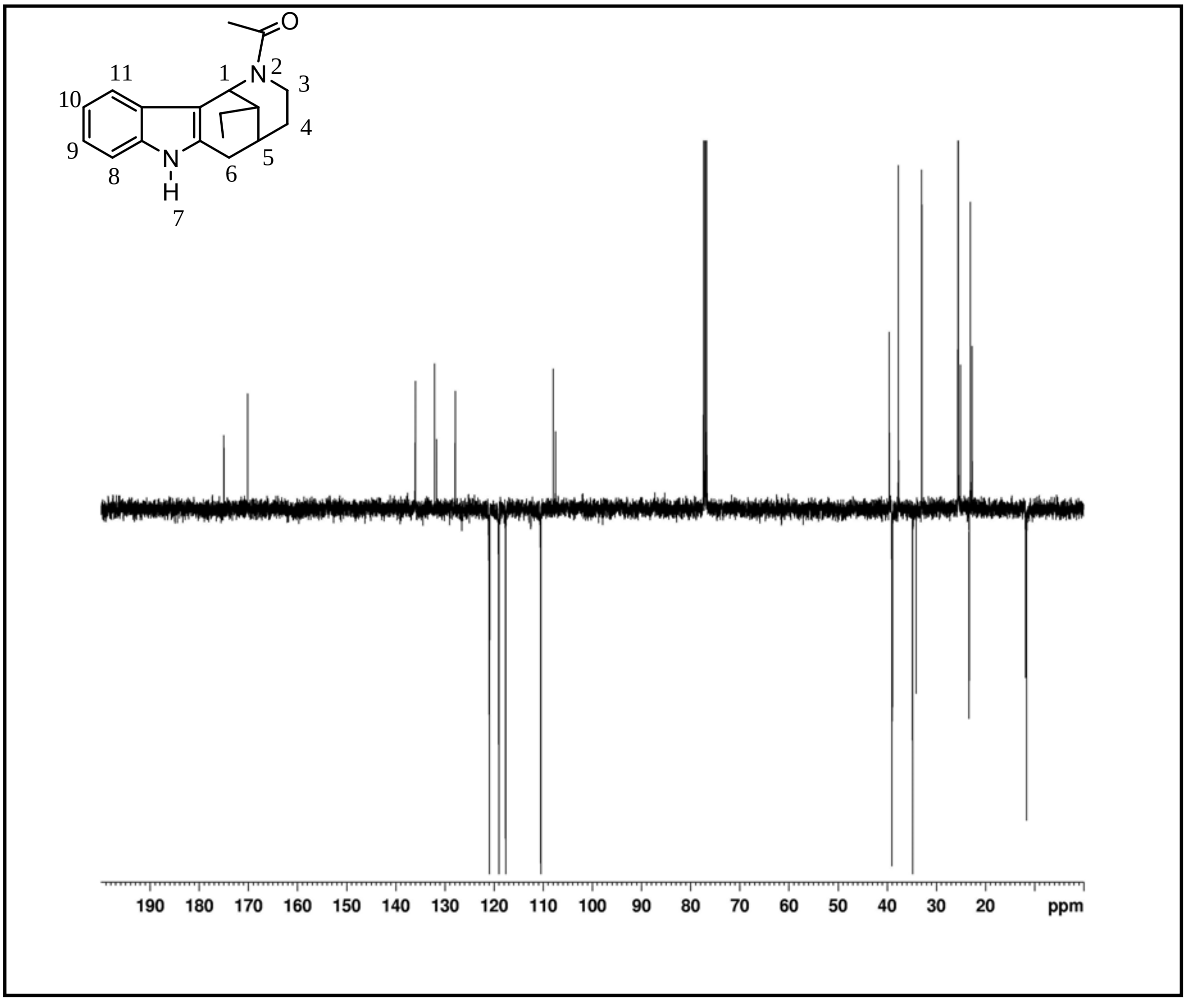

Figure 43. The APT spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**)

The UV spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**) has two bands at 228 nm (π-π*), and 276 nm (n-π*) (Figure 44).

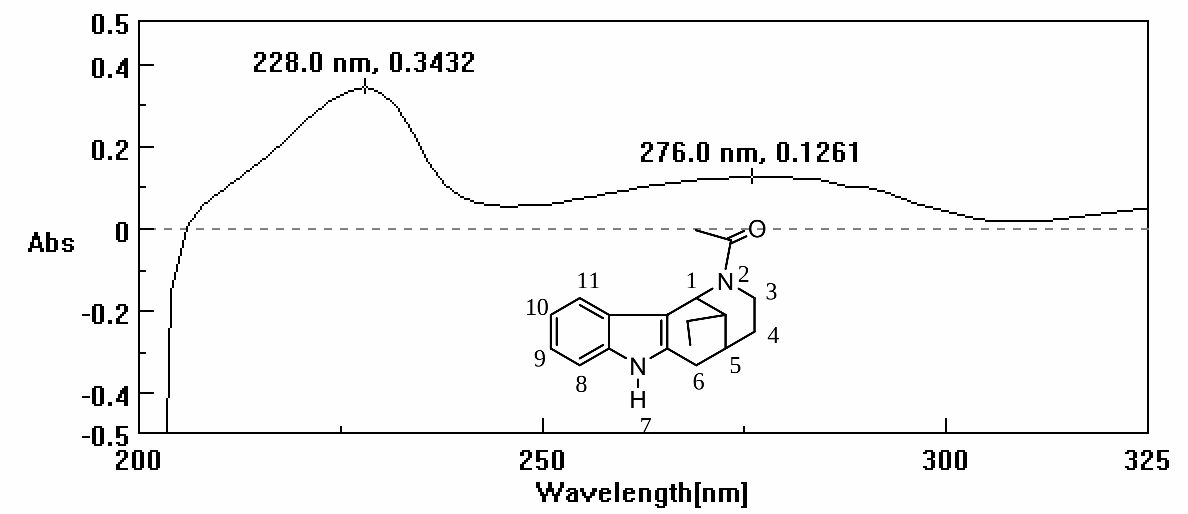

Figure 44. The UV spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**)

The LC-MS spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**) has five signals. The signal at 284.9 belong to [M+2]+ and the signal at 282.8 belong to molecular ion (M+). The loss of $COCH_3$ group from [M]+ is proved by the m/z: 239,8 $[M\text{-}COCH_3]^+$, the loss of $C_2H_5NH_2$ group from $[M\text{-}COCH_3]$+ is proved by the m/z: 195.7 $[M\text{-}COCH_3\text{-}C_2H_5NH_2]^+$. The signal at 78.7 belong to $[C_6H_6]$+ (Figure 45).

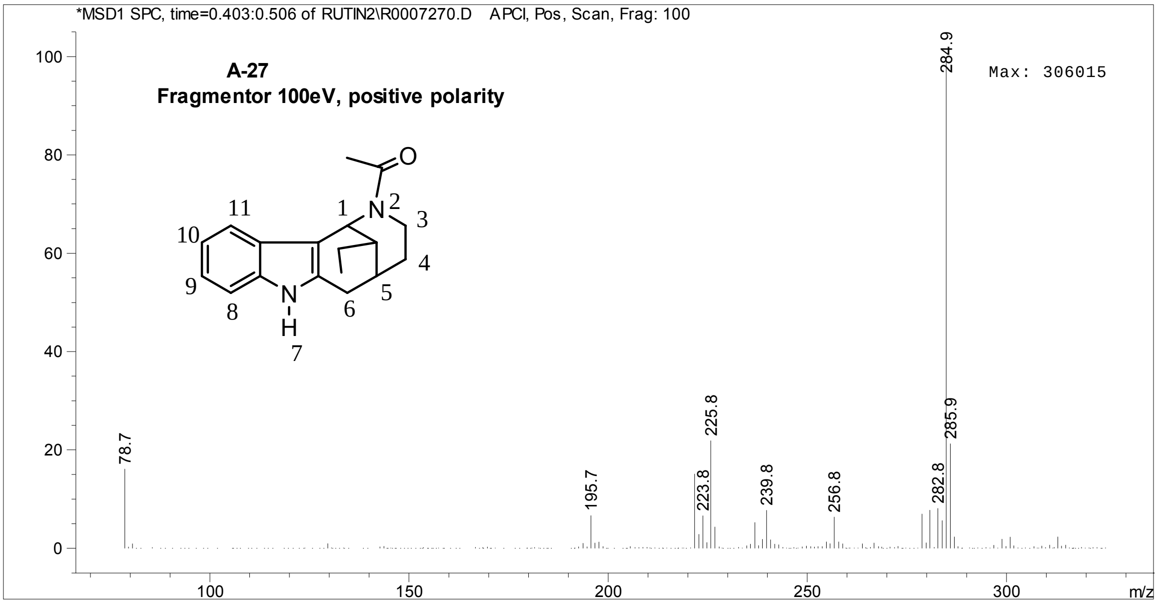

Figure 45. The LC-MS spectrum of N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**)

6 CONCLUSION

In this study many new compounds (N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**), 2-(3-Ethyl-1-oxo-2,3,4,9-tetrahydrocarbazole-2-yl)acetic acid (**67**), N-Methyl-2-(3-Ethyl-1-oxo-,2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**68**), 4-Ethyl-1-methyl-3,3a,4,5,10,10b-hexahydropyrrolo[2,3a]carbazol-2(10H)-one (**71**), 4-Ethyl-3,3a,4,5-tetrahydro-10*H*-furo[2,3a]carbazol-2(10*bH*)-one (**73**), 4-Ethyl-3,3a,4,10-tetrahydro-3*H*-furo[2,3a]carbazole-2,5(10*H*, 10*bH*)-dione (**74**) and 2-(3-Ethyl-1-hydroxy-4-oxo-2,3,4,9-tetrahydro-1H-carbazol-2-yl)acetamide (**75**)) have been obtained succesfully. Such compounds are not only of interest to medicinal chemists, but also useful synthetic intermediates in natural product synthesis. One of them, N-(Acetyl)-12-ethyl-1,2,3,4,5,6,-hexahydro-1,5-methanoazocino[4,3-b]indole (**61**), is very important intermediate products for synthesis of uleine type alkaloids and pentacyclic strychnos alkaloids. There are several total synthesis of this intermediate product. However, the overall yields are low and, with only a few exception, the epimer at C-20 is the predominant product. In this study tetracyclic compound **61** is synthesized without any degree of epimerization at C-20 and overall yield is 23 %.

REFERENCES

Amat, M., Hadida, S., Pshenichnyi, G. and Bosch, J., 1997, Palladium(0)-Catalyzed Heteroarylation of 2- and 3-Indolylzinc Derivatives. An Efficient General Method for the Preparation of (2-Pyridyl)indoles and Their Application to Indole Alkaloid Synthesis., Journal of Organic Chemistry, 62, 3158-3175.

Amat, M., Perez, M., Llor, N., Martinelli, M., Molins, E. and Bosch, J., 2004, Enantioselective formal synthesis of uleine alkaloids from phenylglycinol-derived bicyclic lactams., Chemical Communications (Cambridge, United Kingdom), 14, 1602-1603.

Anderson, E.F., 1996, Peyote, Divine Cactus, 2nd ed. The Universit of Arizona Pres.

Baeyer, A., Emmerling, A., 1869, Synthese des Indols , Chem. Ber., 2, 679.

Barton, D., Nakanishi, K., meth-Cohn, O.,1999, Editors Comprehensive Natural Products Chemistry; 1st ed.; Pergamo Pres, Vol. 1.

Bonjoch, J.; Casamitjana, N.; Gracia, J.; Bosch, J., 1991, A stereoselective total synthesis of dasycarpidan alkaloids: (±)- dasycarpidone , (±)-dasycarpidol, and (±)-nordasycarpidone, Journal of the Chemical Society, Chemical Communications, 23, 1687-8.

Buchi, G. and Warnhoff, E. W., 1959, The structure of uleine, J. Amer. Chem. Soc., 81, 4433.

Büchi, G., Gould, S. J. And Naef, F., 1971, Stereospecific syntheses of uleine and epiuleine., Journal of the American Chemical Society, 93, 2492-2501.

Corey, E. J. and Cheng, X.-M., 1989, The Logic of Chemical Synthesis (Wiley, New York.

Dolby L J. and Biere H., 1968, The total synthesis of (±)- dasycarpidone and (±)-epidasycarpidone. Journal of the American Chemical Society, 90, 2699-2700.

Dolby, L. J. and Biere, H., 1970, Total synthesis of (±)- dasycarpidone , (±)-epidasycarpidone, and (±)-epiuleine., Journal of Organic Chemistry, 35, 3843-5.

Eliel, E. L. and Wilen, S. H., 1994, Stereochemistry of Organic Compounds, (Wiley, New York, 1994), p. 20.

Ergun Y., Bayraktar N., Patir S. And Okay G., 2000, Intermediates for the synthesis of indole alkaloids. Synthesis of tetrahydrocarbazole derivatives, Journal of Heterocyclic Chemistry, 37 (1): 11-14.

Eschenmoser, A. , Wintner, C. E, 1977, Natural Product Synthesis and Vitamin B12 , Science, 196, 1410.

Floers, H. E., 1987, Use of plant cell and organ culture in the production of biological chemicals. In “Biotechnology in Agricultural Chemistry” (LeBaron, H. M., Mumma, R. O., Honeycutt, R. C., Duesing, J. H. eds), Acs Symposium Series 334, 66-86.

Fowler, M.W. and Stepan-Sarkissian, G., 1983, Chemicals from plant cell fermantation, In: *Advances in biotechnological processes* **2.,** 135-158.

Gaskell, A. J. and Joule, J. A., 1967, Structure of Uleine - Relative Stereochemistry, Chem. Ind. (London), 1089.

Gracia, J. Casamitjana, N., Bonjoch, J., Bosch, J., 1994, Total Synthesis of Uleine -Type and Strychnos Alkaloids through a Common Intermediate., Journal of Organic Chemistry, 59, 3939-51.

Hesse, M., 2002, Alkaloids, Wiley-Vhca, Weinhemin, 283-310.

Hosztafi, S., 1997, The Discovery of Alkaloids, Pharmazie, 52, 546-550.

Index Nominum, 1995, International Drug Directory, Medpharm, Stutgard.

Jackson, A., Wilson, N. D. V., Gaskell, A. J., Joule, J. A., 1969, Syntheses of (±)-dasycarpidone,(±)-3-epi-dasycarpidone,(±)- uleine , and(±)-3-epi-uleine., Journal of the Chemical Society [Section] C: Organic, 19, 2738-47.

Johnson, W. S., 1968, Non-enzymic Biogenetic-like Olefin Cyclizations, Acc. Chem. Res. 1, 1-8.

Joule, John A., 1983, The uleine -ellipticine-vallesamine group. Chemistry of Heterocyclic Compounds (Chichester, United Kingdom) 25(4), 265-92.

Kutney, J.P. 1973, Alkaloids, Wiesner, K. F. (ed.), Vol.9, chapter 9, University Park Press, p. 28-100.

Magnus, P., Sear, W. L., Kim, C. S., Vicker, N., 1992, Studies on the Synthesis of Strychnos Alkaloids. A New Entry into the Azocino [4-3-6]indole Core Structure and Related Studies, J. Org. Chem. 57, p. 70-78.

Mann, J., 1989, Chem. Br., 25, 478-482.

Nicolaou, K. C. and Sorensen, E. J., 1996, Classics in Total Synthesis (VCH, Weinheim, Germany).

Ody, P., 1993., The Complete Medicinal Herbal; 1st ed.; Darling Kindersley Limited,

Patir et al., 2006

Pelletier, S. W., 1983, The nature and definition of an alkaloid, In Alkaloids: Chemical and biological perspectives, Wiley, New York, vol.1, p. 1-5.

Pelletier, S.W., 1970, Chemistry of the Alkaloids, Department of Chemistry, Nastrond Reinhold Company, New York, 1-9.

Rahman, A. and Basha, A., 1983, Biosynthesis of Indole Alkaloids, Clarendon Press: Oxford.

Roberts, M. F. and Wink, M., 1998, Editors Alkaloids: Biochemistry, Ecology, and Medicinal Applications; 1st ed.; Plenum Pres.

Saito, M., Kawamura, M., Hiroya, K. and Ogasawara, K., 1997, First enantiocontrolled syntheses of (+)- uleine and (+)-dasycarpidone., Chemical Communications (Cambridge), 8, 765-766.

Schmitt, M. H. and Blechert, S., 1997, A new cationic domino process to (±)-uleine., Angewandte Chemie, International Edition in English, 36, 1474-1476.

Shamma, M., Weiss, J. A. And Shine, R. J., 1967, The stereochemistry of the C-3 ethyl side chain in uleine and its analogs, Tetrahedron Lett., 2489-2492.

Snieckus, V., 1980, Heterocyclic Compounds in Alkaloid Synthesis, In Survey of Progress in Chemistry, Scott, A. F. Ed.; Academic Pres, New York, vol. 9, p. 122.

Sundberg, R.J., 1970, The Chemistry of Indoles, Academic Pres, New York.

Uludag, N., Hokelek, T. and Patir, S., 2006, A New Approach to The Total Synthesis of (+/-)-20-Epidasycarpidone, Journal of Heterocyclıc Chemıstry 43 (3): 585-591.

Wilson, N. D. V., Jackson, A., Gaskell, A. J., and Joule, J. A., 1968, The syntheses of uleine and 3-epi-uleine, Chem. Commun., 584.ü

Woodward, R. B. and Hoffmann, R., 1969, The Conservation of Orbital Symmetry, Angew. Chem. Int. Ed. Engl. 8, 781-853.

Woodward, R. B., 1968 Recent advances in the chemistry of natural products, Pure Appl. Chem. 17, 519-547.

Wöhler, F., 1828, Ueber die künstliche Bildung des Harnstoffe. Poggendorfs , Ann. Phys. Chem. 12, 253-256.

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