SYNTHESIS OF HETEROCYCLIC STEROIDS DERIVATIVES WITH DIFFERENTNITROGEN NUCLEOPHILES

Abdulmalik Shehu

Master Thesis

Department of Chemistry, Organic Chemistry

Supervisor: Prof. Dr. Süleyman Servi

JULY – 2017

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MASTERS THESIS

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DEDICATION

I dedicated this work to my beloved parents Malam Shehu Abubakar and Malama Amina Muhammad without their encouragement, prayers and support it would have not been possible to accomplish my dream and to my daughter Haneefa.

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ABSTRACT

Pyrazoline derivatives that are endocyclic or exocyclic substituted with the steroid molecule have significant biological activity. In this thesis, two different steroid such as Pregnenolone and *trans*-dehydroepiandrosten were used as starting compounds. Firstly, α,β-unsaturated carbonyl substituted steroid derivatives were obtained from Aldol condensation reaction with heteroaromatic aldehydes of the starting materials DHEA and Pregnenolone in basic medium. Various steroid substituted pyrazoline derivatives were synthesised from the reaction heteroaromatic substituted α,β-unsaturated carbonyl compounds with different nitrogen nucleophiles such as hydrazine and thiosemicarbazide. The structures of all the synthesized compound were characterized by using FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.

Keywords: Pregnenolone, *trans*-dehydroepiandrosterone, pyrazoline, hydrazine hydrate and thiosemicarbazide.

ÖZET

FARKLI AZOT NÜKLEOFİLLERİ İLE HETERO-HALKALI STEROİD TÜREVLERİNİN SENTEZİ

Steroid molekülü ile endosiklik ya da eksosiklik substitüe olmuş pirazolin türevleri önemli biyolojik aktivitelere sahiptir. Bu tezde, başlangıç bileşikleri olarak Pregnenolon ve *trans*-dehidroepiandrosten gibi iki farklı steroid kullanılmıştır. İlk olarak, α, β-doymamış karbonil substitüe steroid türevleri bazik ortamda başlangıç maddeleri DHEA ve Pregnenolon'un heteroaromatik aldehidler ile Aldol kondansasyon reaksiyonundan elde edildi. Çeşitli heteroaromatik substitüe α,β doymamış karbonil bileşiklerinin hidrazin ve tiyosemikarbazid gibi farklı nitrojen nükleofilleriyle reaksiyonundan çeşitli steroid substitue pirazolin türevleri sentezlenmiştir. Bütün sentezlenen bileşiklerinin yapıları, FT-IR, ^{1}H-NMR ve ^{13}C-NMR spektroskopisi kullanılarak karakterize edildi.

Anahtar Kelimeler: Pregnenolon, *trans*-dehidroepiandrosteron, pirazolin, hidrazin hidrat ve tiyosemikarbazid.

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SYMBOLS AND ABBREVIATION

AcO : Acetyl

AcOH : Acetic acid

Aq : Aqueous

AÜ : Adiyaman University

$CDCl_3$: Chloroform-D

d : doublet

DHEA : Dehydroepiandrosterone

DDQ : 2,3-Dichloro-5,6-dicyano-p-benzoquinone

EtOAc : Ethyl acetate

FÜ : Firat University

HCl : Hydrochloric acid

g : Gram

g/mol : Gram per moles

h : Hour

IR : Infrared

J : Coupling Constant

KCN : Potassium Cyanide

KOH : Potassium Hydroxide

L : Litre

M : Molar

M : Multiplet

$MgSO_4$: Magnesium Sulphate

MHz : Mega Hert

mL : Millitre

mmol : Millimoles

$NaBH_4$: Sodium Borohydride

NaOH : Sodium Hydroxide

Ni : Nickel

NMR : Nuclear Magnetic Resonance

Pd	**:** Pladium
ppm	**:** Part per million
Pt	**:** Platinum
s	**:** Singlet
t	**:** Triplet
TLC	**:** Thin Layer Chromatography
TBDMSCI	**:** Tert-butyldimethylsilylchloride
δ	**:** Chemical Shift

1. INTRODUCTION

Naturally occurring compounds like steroids has attract much attention of synthetic organic and medicinal chemist due to their tremendous number of biological activities. Researches were carried out on steroids which figured out their biological functions. Different pharmacological roles of natural compound like the steroids explore their different ring modifications. The biological functions of steroids increases potentially on modification by fused heterocyclic compounds such as pyrazole, indole, imidazole etc.

Steroids attracts much attention due to their special biological activities. With the exception of naturally occurring substances, most steroid drugs are semi-synthetic compounds prepared by adding specific functionality to the core structure of a steroid.

All over the world, cancer continues to become one of the most difficult diseases and among the most leading to human death. Development of new anti-cancer drugs and more effective strategic treatment for cancer is of great importance [1].

The new targets of the medicinal chemists are to obtain new specific and powerful drugs for cancer treatment [2]. Use of steroid is a common practice for cancer treatment.

In recent years, heterosteroids have received great interest by medicinal chemists for drug discovery. The steroid nucleus have attracted the attention of researchers due to its interesting structural and stereo chemical properties, and thus changes in the steroid skeleton are envisaged for the discovery of new chemical substances with some promising drug potential. The chemical properties of steroid are affected by incorporation of a heteroatom into a heterocyclic ring or a steroid skeleton and often results in useful changes in the biological activities. The products obtained by introducing heteroatoms into the steroid nuclei are called nuclear heterosteroids [3].

Other than endocrinologists and biochemists steroid is a source of inspiration for organic chemists because of their different biological activities.

1.1 Steroid

Steroids are complex polycyclic molecules found in all plants and animals. They are classified as simple lipids because they do not hydrolyze and form waxes like solid and liquid oils. Steroids are found in a wide variety of hormones, including emulsifiers and membrane components. Steroids are compounds based on the tetracyclic *androstane* ring system [4].

The four rings are identified by the letters A, B, C, and D starting with the lower left ring and the carbon atoms are numbered starting with ring A and ending with two "angled" (axial) methyl groups as shown in **Figure 1.1.** [5].

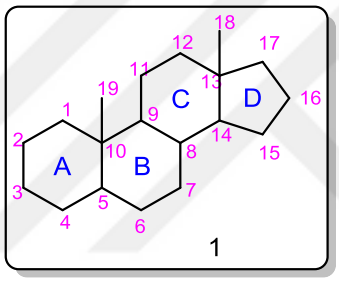


Figure 1.1 Demonstration of general steroid molecules

In many steroids B, C and C, D ring junctions are *trans*. The A, B ring link can be *cis* or *trans*, and the steroids with three-dimensional structure are shown in Figure 1.2. Form two general groups.

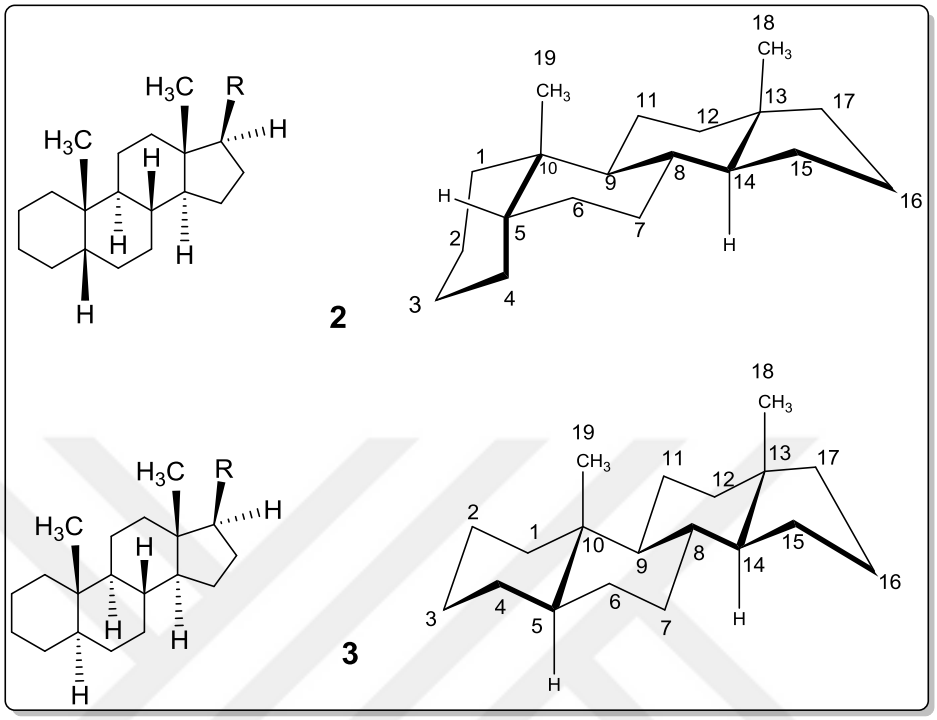


Figure 1.2 The *cis* and *trans* binding patterns of the A, B ring

The methyl groups on the ring bonds (i.e., groups 18 and 19) are used as important reference points in stereochemical nomenclature. These angular methyl groups are perpendicular to the general plane of the ring system, which is shown in Figure 1.2 above. Generally, groups on the same side as the angular methyl groups are called beta-substituents (β) and the groups on the opposite side of the angular methyl groups are called alpha-substituents (α). Adapting *α* and *β* nomenclature to the hydrogen atom at position 5, A - B ring junction connected as *cis* ring system it's called 5β series while 5α series when A - B ring junction connected as *trans* ring system [5]. Therefore, the R group in position 17 identifies the basic name of each steroid in the systematic nomenclature [6].

Steroids generally have a hydroxyl or an oxygen functional group (= O or -OH) at the C3 position and also an oxygen functional group or a side chain at the C17 position, and some steroid have a double bond at the C4 and C5 or C6 positions, like of *androsterone* **4** and *cholesterol* **5** structures. *Androsterone* **4** which is a male sex hormone and is obtained from the

simple *androstane* ring system. *Cholesterol* **5** is accepted as a common biological intermediate which is believed to be the biosynthetic precursor of other steroids [6].

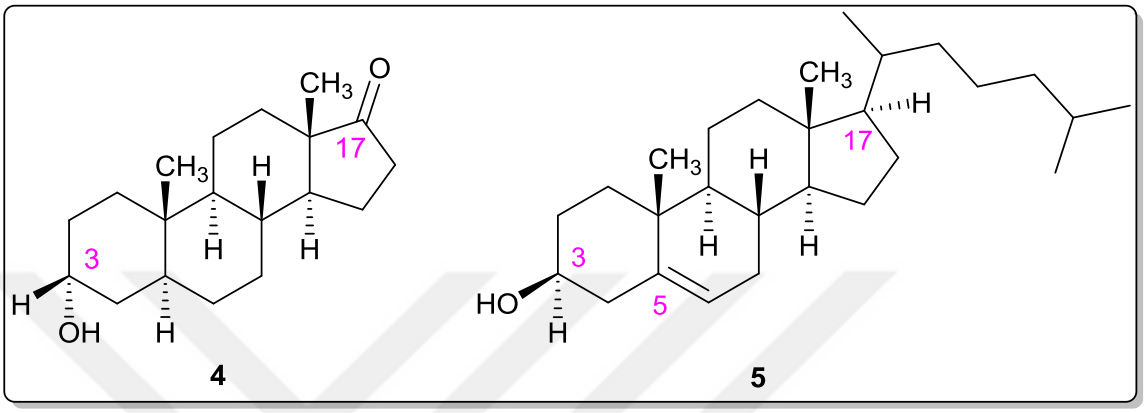


Figure 1.3 Androsterone and Cholesterol structure showing their difference at position 17 of the D ring

People could not believe that any synthetic hormone could compete the surprising power of natural steroids when steroid hormones were first isolated. However, many synthetic steroids have been developed over the past 50 years. Some of these synthetic hormones are hundreds or thousands times more powerful than natural steroids [7].

1.2 Pregnenolone

Pregnenolone is a steroid that is synthesized within the organism and it is a predecessor or metabolic intermediate in the biosynthesis of most of the steroid hormones, including the *progestogens*, *androgens*, *estrogens*, *glucocorticoids*, and *mineralocorticoids*, and its IUPAC nomenclature is pregn-5-en-3β-ol-20-one [8].

Pregnenolone is the main steroid produced from *Cholesterol*. It is produced in three main organs: the brain, gonads and adrenal glands [8, 9], but the salivary gland and white blood cells are also capable of producing pregnenolone [10].

In 1940s, it was reported that *Pregnenolone* have anti-stress and mood-elevating effects on factory workers, students, and pilots. Later when researches were carried out, pregnenolone was found to act as neurosteroid, neuroprotective and neurogenesis [11].

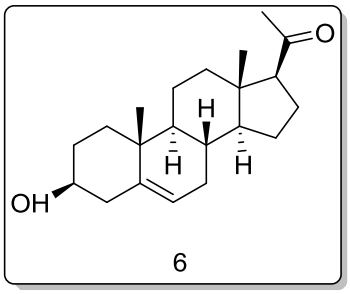


Figure 1.4 Structure of *Pregnenolone*

1.3 Dehydroepiandrosterone (DHEA)

Dehydroepiandrosterone (DHEA) is a sterol which is also known as *Androstenolone* or *Prasterone* [12, 13], its IUPA name is "3β-3-Hydroxyandrost-5-en-17-one" which is shown in (**Figure 1.5**) it is a steroid hormone produced in the adrenal gland and brain, which is the most flowing hormone in the human body.

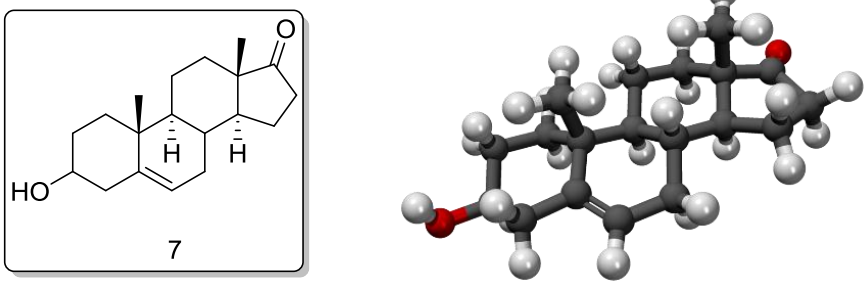


Figure 1.5 Structure and 3D view of DHEA

For the synthesis of many steroids with various biological functions, *Dehydroepiandrosterone* is used as starting material. Reports shows that new compound with numerous number of biological effect were produced such as anti-apoptotic cancer, anti-prostate cancer, neuroprotective etc. by modification of DHEA [14].

1.3.1 Some reactions of DHEA

DHEA undergoes Oppenauer oxidation with aluminium triisopropoxide as catalyst in excess ketone, to produce *Androst-4-ene-3, 17-dione* **8** by oxidizing position 3 hydroxyl group to ketone. In the synthesis of *Estranes* **9**, DHEA suffices as basic material which kick off by Oppenauer oxidation then accompanied by some steps. DHEA also react with phosphorous

pentachloride (PCl_5) by which chloride ions displaced the 3 position hydroxyl group **10**. In the design and synthesis of *17- methyl testosterone* **11** DHEA undergoes an interesting reaction with an excess Grignard reagent (CH_3MgBr). 17- Ethynyl derivatives **12** can also be synthesized by the use of lithium acetylide instead of CH_3MgBr by identical method with **11.** In acetic acid DHEA acetate also react with KCN to produce cyanohydrin, *16-dehydropregnenolone* **13** were obtained by dehydration of the cyanohydrin formed with addition of CH_3MgBr to the formed dehydrated product followed by hydroxylation of the imine compound. Synthesis and design of different DHEA containing heterocyclic compounds have been carried out and determined their biological activities, such as derivative of DHEA containing heteroaryl on C_{16} via Methine Bridge **14**, also galenterone **15** containing heteroaryl at the C_{17} were reported in the literature [15, 16].

A general schematic summary of those synthesis is shown in the figure below

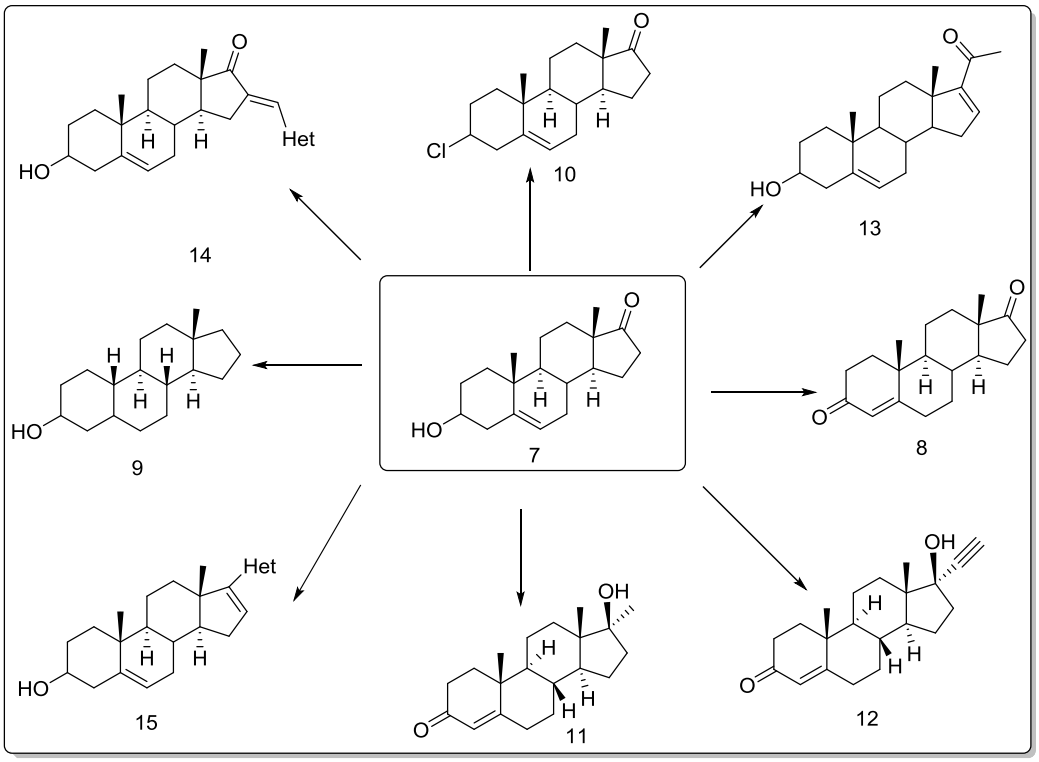


Figure 1.6 Synthesis of different compounds from DHEA

1.4 Cholesterol

One of the most commonly known steroids is cholesterol **5**, which can be obtained from almost all animal tissues. A rich source of *Cholesterol* are Gallstones [5, 6].

Cholesterol was first isolated in 1770. In the 1920s, two German chemists, Adolf Windaus and Heinrich Wieland revealed the structure of *Cholesterol*. For this reason they received the Nobel Prize in 1927 and 1928.

The correct structure of *Cholesterol* was found by British scientist Wieland, by taking advantage of Bernal's results. The presence of eight stereo centers in the cholesterol gives the difficulty in elucidating its structure. The stereoisomerism rule of 2^n proposed that cholesterol structure has 2^8 or 256 stereoisomers because of its eight chirality centers, and cholesterol is only one of these 256 structures [5].

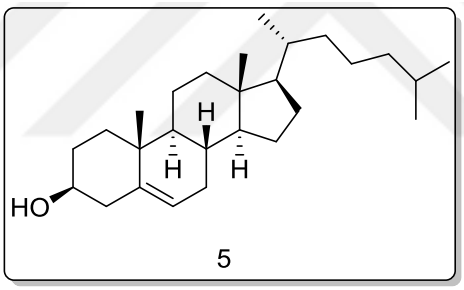


Figure 1.7 Structure of *Cholesterol*

Cholesterol is largely synthesized in the human body. *Cholesterol* is known to function as an intermediate in the biosynthesis of all of the body's steroids. Therefore *Cholesterol* is synthesized more than the necessary for steroid biosynthesis in our body. Elevated levels of cause arterial stiffness and heart attack [5,6].

So much work has been done in the field of *Cholesterol* metabolism wishing that its level can be lowered with diet and medication [6]

1.5 Vitamins D

In 1919 an intensive research began on the *Vitamin* D when it became clear that the sunlight helped to treat rickets, which is a childhood illness that is revealed by weak bones. Investigations revealed that *Vitamins* was involved in the sunlight, and it was finally

concluded that it's *Vitamin* D, one of the useful and numerous among D *Vitamins* is *Vitamin* D_3. *Vitamin* D_3 is composed of *7-dehydrocholesterol* with two reactions that take place in the *Vitamins* [6]. Firstly is the conversion *7-dehydrocholesterol* to pre-*Vitamin* D_3 obtained from the sunlight then the pre-*Vitamin* D_3 is spontaneously isomerized to afford *Vitamin* D_3. The structure of *Vitamin* D_3 is shown in (**Figure 1.7**) below.

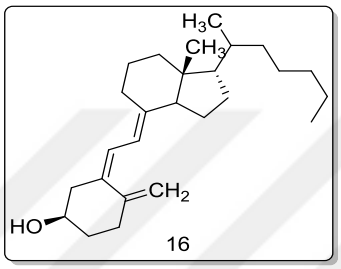


Figure 1.8 Structure of *Vitamin* D_3

Vitamin D_3 enables the absorption of Ca^{2+}, in the intestine, which is essential for health and necessary for bone growth. Inadequate *Vitamin* D_3 may be caused by insufficient of sunlight due to different factors, e.g. season of the year. Diets that will increase with vitamin D_3 are recommended for children and elderly people in many countries. Use of skin color, cloud and sunscreen are also factors that can affect the production of *Vitamin* D_3 in skin [6].

1.6 Adrenocortical Hormones

From a portion of the adrenal cortex at least 28 different hormones have been collected, which is, the adrenal glands that rest on the kidneys. *Cortisone* and *cortisol* are two of these hormones.

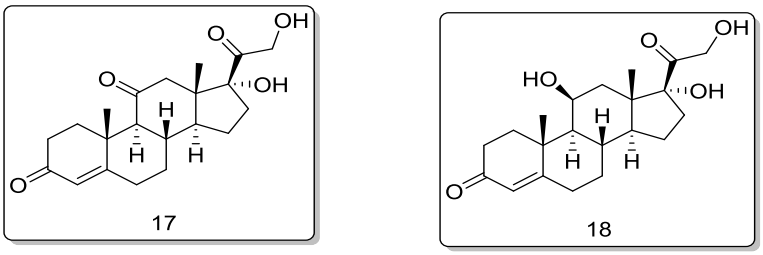


Figure 1.9 Structure of *Cortisone* and *Cortisol*

Adrenocortical hormones contain an oxygen functional group (like, a keto in cortisone and a *β*-hydroxyl group in cortisol) normally in 11-position. An important hormone that is synthesized by the human adrenal cortex is *Cortisol*.

Adrenocortical serves as a regulator of numerous biological activities which include carbohydrate, protein and lipid metabolism, water and electrolyte balance, allergic and inflammatory reactions. *Cortisone* is used in the treatment of rheumatoid arthritis (inflammatory rheumatism). Most of the steroids with oxygen functional group in position 11 are used in the treatment of many diseases such as asthma and skin inflammation [5,6].

1.7 Sex steroids

Sex steroid are responsible for reproduction in mammals and are classified into three groups, which are the female sex hormones (*Estrogens*), male sex hormones (*Androgens*), pregnancy hormones (*Progestins*).

1.7.1 Estrogens

The first female sex hormone isolated was *Estrogen*, and it was isolated by Adolf Butenandt and Edward Doisy by using urine of pregnant women to isolate *Estrone* **19**, the results obtained by these researchers was published in 1929. In the following years, Doisy had thrived in isolating *Estradiol*. In his study, 4 tons of female pig eggs were used to extract 12 mg *Estradiol* [6]. The real female sex hormone is *Estradiol* **20**, and the metabolized form secreted by the *Estradiol* is the *Estrogen*. *Estradiol* is the hormone that control the menstrual cycle and reproductive process of female and also it developed the female secondary sex characteristics [17].

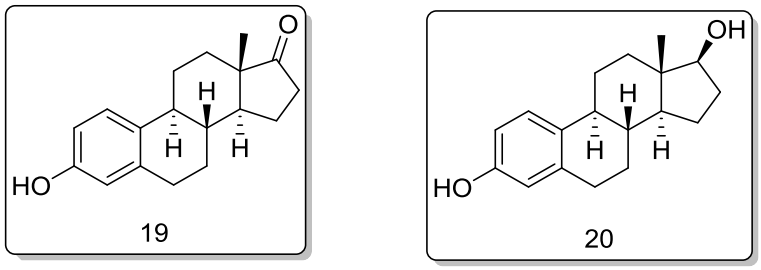


Figure 1.10 Structure of *Estrone* and *Estradiol*

1.7.2 Androgens

Butenandt and Kurt Tscherning in 1931 prospered in obtaining 15 mg of this homogeneous extract by taking 15,000L male urine from *Androsterone*, which is the first *Androgen*. In Netherlands Ernest Lacquer acquired the *Testosterone* which is another male sex hormone from the bull's testes. Later it was found that *Testosterone* is the real male sex hormone while the *Androsterone* was the metabolized form [5]. The development of secondary male characteristics are control by the *Testosterone* such as male sex organs, muscular buildout deepening of voice etc.

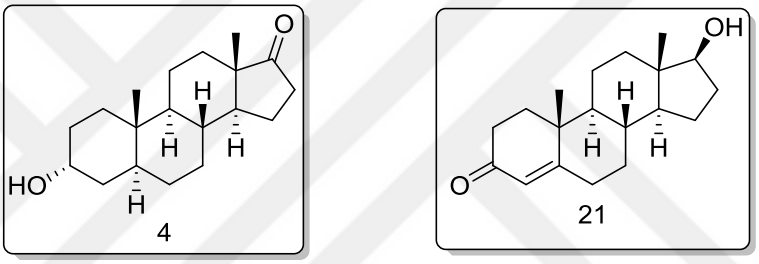


Figure 1.11 Structure *Androsterone* and *Testosterone*

Testosterone **21** and *Estradiol* **20** are chemical compounds that regulate "masculinity" and "femininity". Looking at their structural formulas, we can find out that these two compounds have a slight difference. An angular methyl group CH_3 at C_{10} and a keto group at C_3 are present on the **21** while **A** ring of **20** is aromatic without the angular methyl at C_{10} and a hydroxyl groups at C_3 and C_{17} [5].

1.7.3 Progestin

The most important progestin is *Progesterone* (pregnancy hormone) which is another female sex hormone. After breeding, the residue from the breakdown of the egg cell (corpus luteum) begins to secrete *Progesterone*. This hormone develops the uterine lining to hold the fertilized egg and constant *Progesterone* secretion is required for the pregnancy to complete. (The *Progesteron*e is secreted to the placenta when it is secreted by the corpus luteum.) [6]

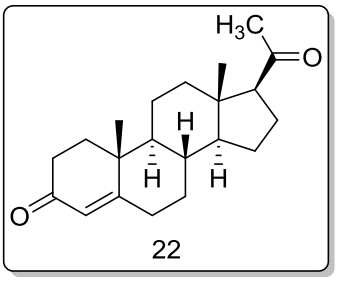


Figure 1.12 Structure of *Progesterone*

Ovulation is also prevented by *Progesterone* **22** and seemingly is a chemical agent which prevents pregnant women from being a pregnant again when impregnated. A series of such compounds have been developed and are now widely used. In addition to norethynodrel, another commonly used synthetic *Progestin* is the double-bond isomer, called norethindrone [6]

Development of synthetic *Estrogens* in combination with synthetic *Progestin* are now been used as a birth control pills. The compound called *Ethinylestradiol* or novesstrol is one of the very strong synthetic estrogens [6].

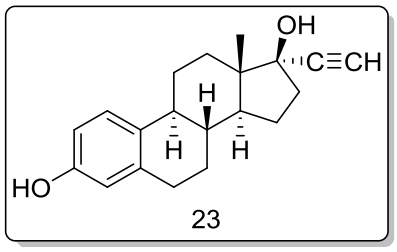


Figure 1.13 Structure of *Ethinylestradiol*

1.8 Other Steroids

The structure, sources and physiological characteristics of some of other important steroids are as follows.

1.8.1 Digitoxigenin

Since 1785 *Digitoxigenin* has been used to treat heart disease, which can be obtained by the hydrolysis. In the process, the sugar molecules are joined to the **OH** group of the C_3 position of the steroids as acetal linkages. It strengthens the venom of the heart muscle when it's taken in small dose while in larger doses it is poisonous to the heart. The structure is given below [6].

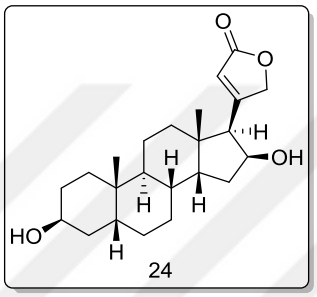


Figure 1.14 Structure of *Digitoxigenin*

1.8.2 Colic acid

This is the most abundant acid obtained from the hydrolysis of human *Bovine ile*. Liver produces the *Bile* and gallbladder stored it which is in high concentration. When food enters the small intestine, *Bile* travels through the common *Bile duct* to reach the *Duodenum*. So bile acts as a soap to the lipids which helps it in *Digestion* [6].

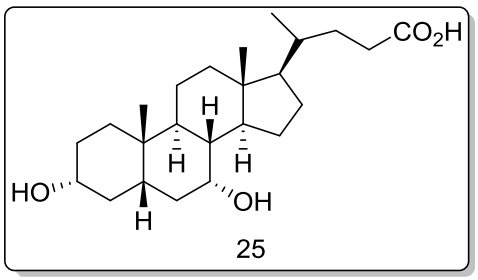


Figure 1.15 Structure of *Colic acid*

1.9 Some Reactions of Steroids

Possession of double bonds, hydroxyl groups, keto group etc. by steroids, make steroids to undergoes reactions that are observed in molecules with similar functional groups [5]. The complexity of the stereochemistry of steroid reactions are strongly influenced by steric hindrance of the angular methyl groups that are on the beta face. For many steroids reactive reactions that took place with the functional group close to the angular methyl group, and when the reactive steric hindrance entered, the reaction is favored by the relatively unobstructed α face. Examples showing this tendency are shown in the following reactions

1.9.1 Reduction of steroids

Steroids undergoes reduction in the presence of hydrogen gas in palladium as catalyst. The reduction take place through the α-face of the steroid molecule as it explained above .The equation for the reaction is shown below [5].

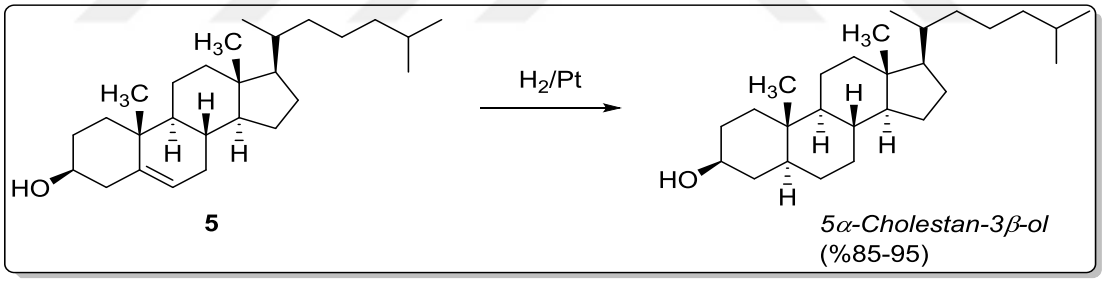


Figure 1.16 Reduction of steroid

1.9.2 Aldol Condensation

Aldol condensation reaction is the reaction of carbonyl compound enolates with aldehydes and ketones to form a *β-hydroxyl* carbonyl compound resulting in a hydration, from which the carbon chain of the carbonyl compound is increased by aldehydes or ketones which have an enolizable α-carbon, in an acidic or basic medium. Formation of the new carbon-carbon bond make these reaction synthetic value to be quite high. Using an aldehyde which have an *α*-hydrogen as the carbonyl compound, the first step of the reaction is an addition reaction in which an aldehyde molecule attack the carbonyl group of another aldehyde or keto molecule from the α-carbon. This product is the aldehyde (ald) and the other is the alcohol

(ol). For this reason, this product is called Aldol addition product. The first step of the reaction is given in equation below [18].

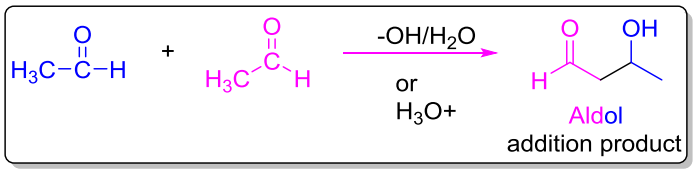


Figure. 1.17 Reaction showing aldol addition product

When the initial product of the reaction is heated (often without heat), a conjugate turns into a compound of enone (*α, β*-unsaturated carbonyl compound), losing one mole of water. This product is called Aldol condensation product. The second step of the reaction is give in the equation below.

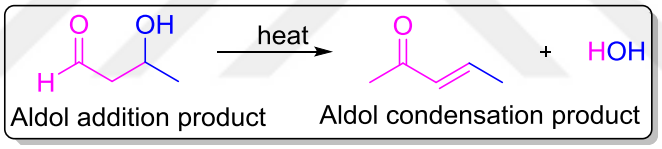


Figure 1.18 Aldol condensation product

Reaction Mechanism

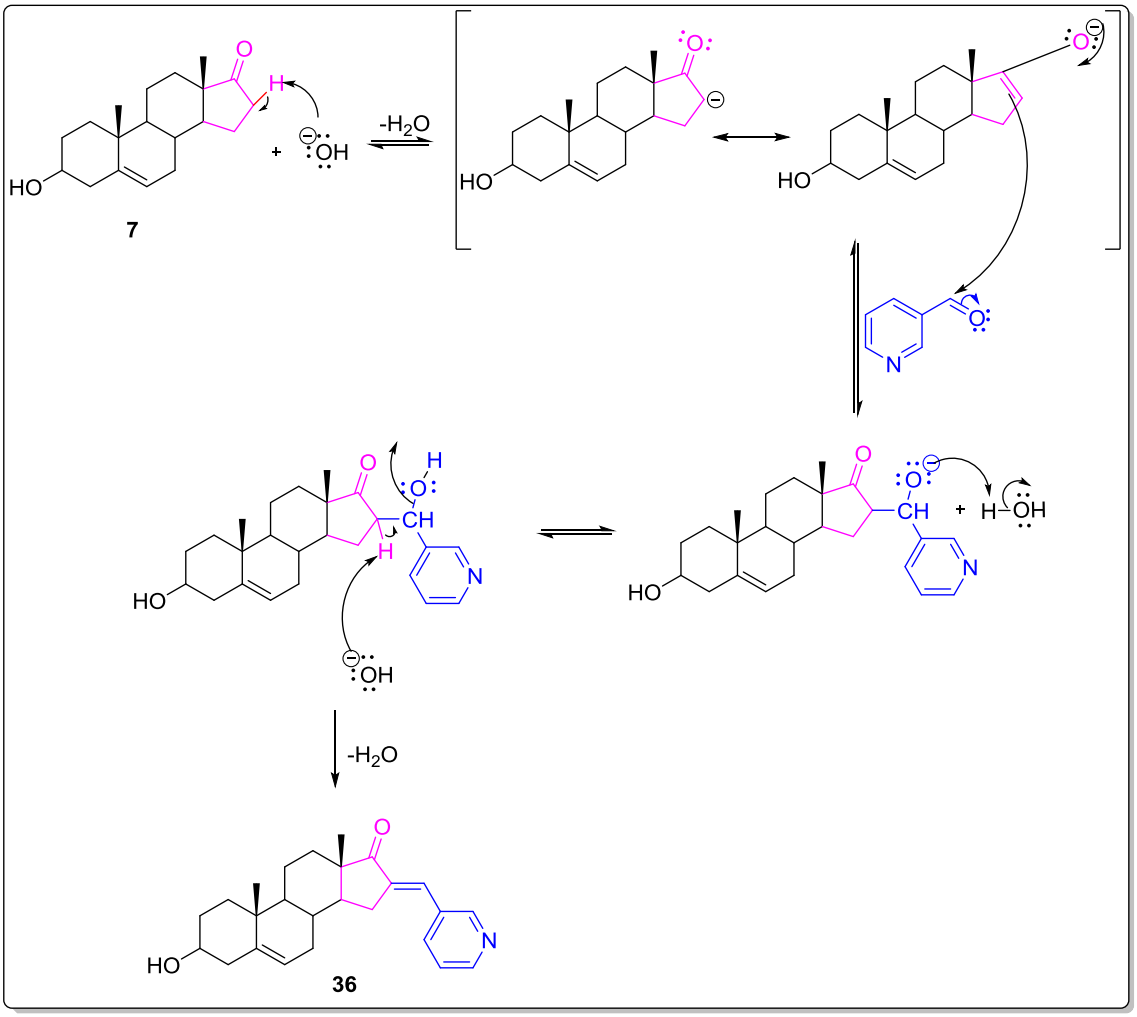


Figure 1.19 Aldol condensation reaction mechanism

The resulting aldol condensation product contains the -OH and CHO important functional groups, which can be converted into new species. Like the aldehyde group may be reduced to produce 1,3-diols, and also both the aldehyde and the alcohol functional group can be oxidized to produce *2-Oxocarboxylic acids*. Similarly, the condensation products are converted into very different compounds. The reduction reaction equation is give below [18].

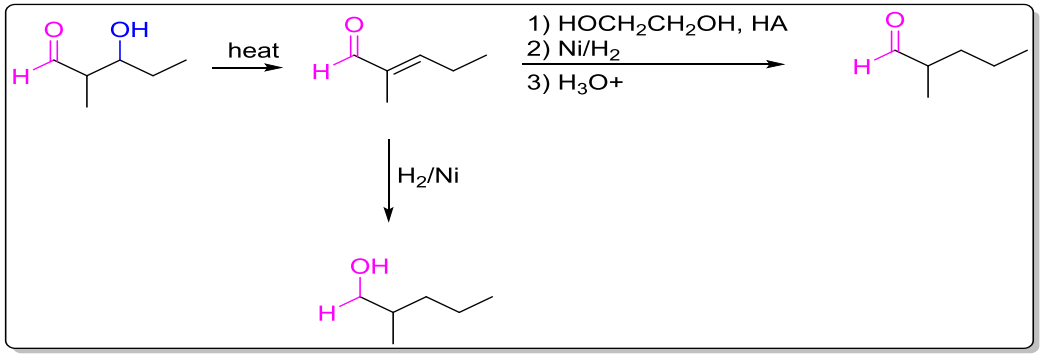


Figure 1.20 Reduction of Aldol condensation product

Aldol reactions are reversible reactions. And all those reactions may also be made by ketones, but in this case its reaction carried out in a basic medium, the return of ketone is mainly the equilibrium. These Aldol reactions on the reverse side are known as retro-aldol reactions [18].

1.9.3 Epoxidation Reaction

Epoxidation of steroids takes place in the presence of phenyl hydrogen carbonate which also attack the less sterically hindered side, which is the α-face of the steroid molecule. The equation for the reaction is given below [5]

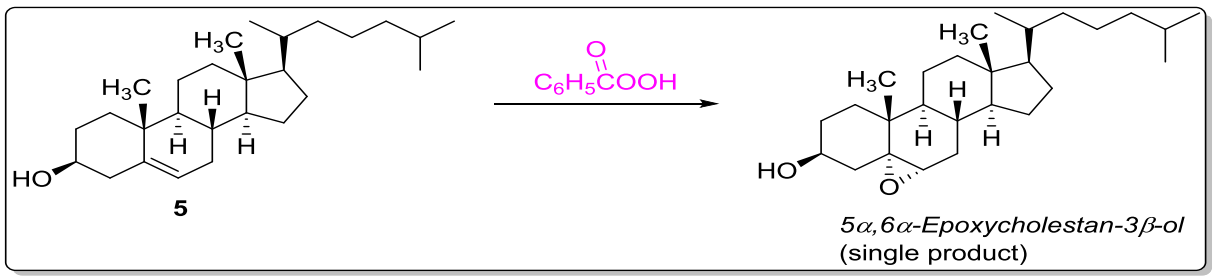


Figure 1.21 Epoxidation of steroid

When the epoxy ring in 5α, 6α-epoxycolestane-3β-ol is opened, the chloride ion must be from the β-surface, but the reaction takes place at the 6 open positions. So it should be noted that substituents 5 and 6 in the formula are diacylic [6].

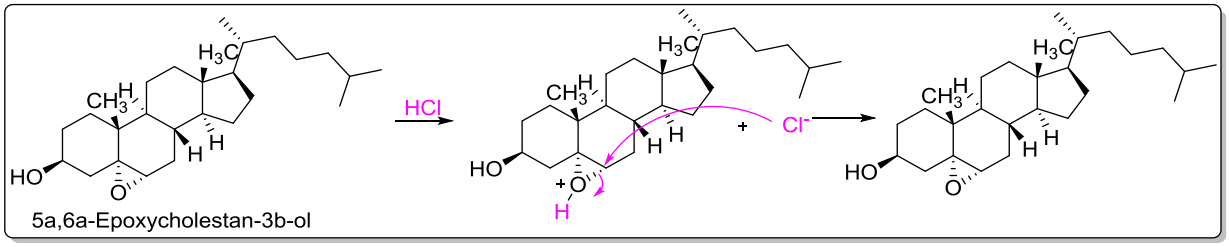


Figure 1.22 Reaction showing opening of the epoxy ring

1.9.4 Nitration Reaction

Also a nitration reaction can be carried out with a solution of *Estrone* in acetic acid which can be nitrated with nitric acid to produce *2-nitroestrane* **32** and *4-nitroestrone* **33**. When treated in sodium borohydride $NaBH_4$ these products are converted to nitro *Estradiol* **34** and **35** [15].

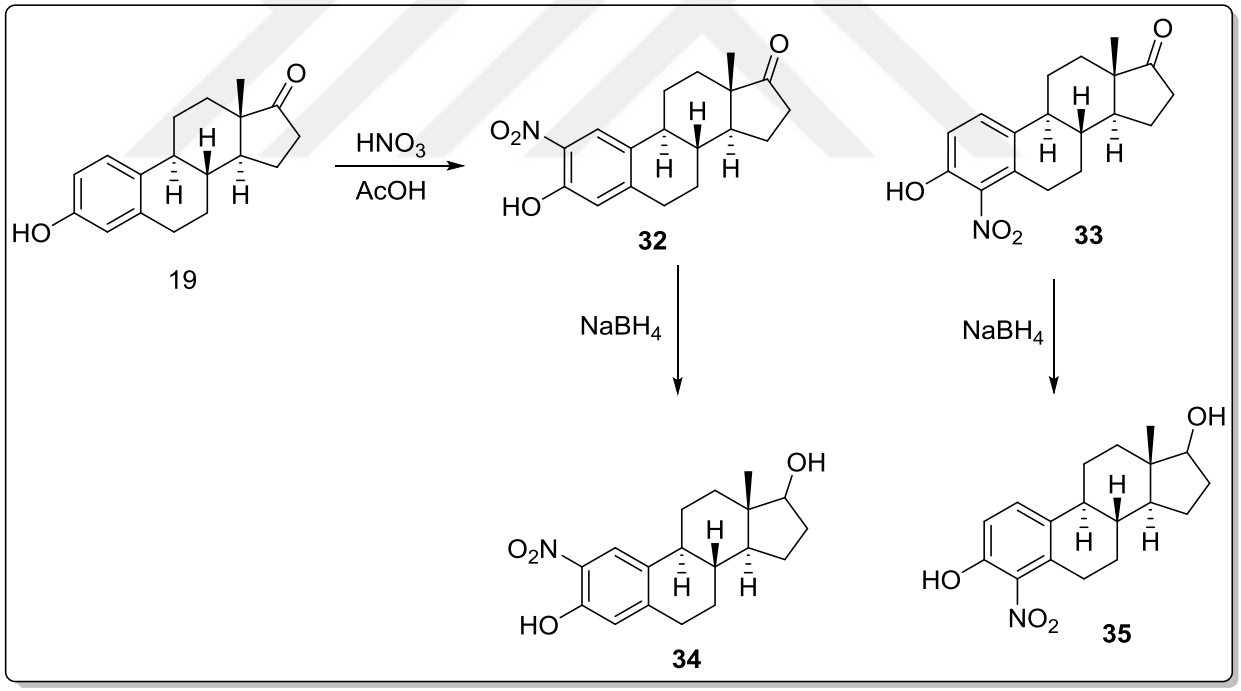


Figure 1.23 Nitration of steroid (DHEA)

1.9.5 Other reactions of some steroids

Heating of **5** with selenium at 300^{o}C produces Diels hydrocarbon as shown below [19].

Figure 1.24 Conversion of cholesterol to Diels hydrocarbon

After several steps of direct sequence of reaction starting with *Estradiol* **20** gives **27** and on reacting **27** with KOH lead to the cleavage of the bond between the carbon atoms bearing the two OH groups in the five membered ring and then oxidized to carboxylic acid in a suitable reaction condition to afford **28** as intermediate, on heating **28** with selenium make the COOH group leave as carbon (iv) oxide from which the six membered ring lose hydrogens and gives phenanthrol **29**, also treating **28** with acetic anhydride lead to the formation of anhydride **30** in the D ring as shown in the figure below [19].

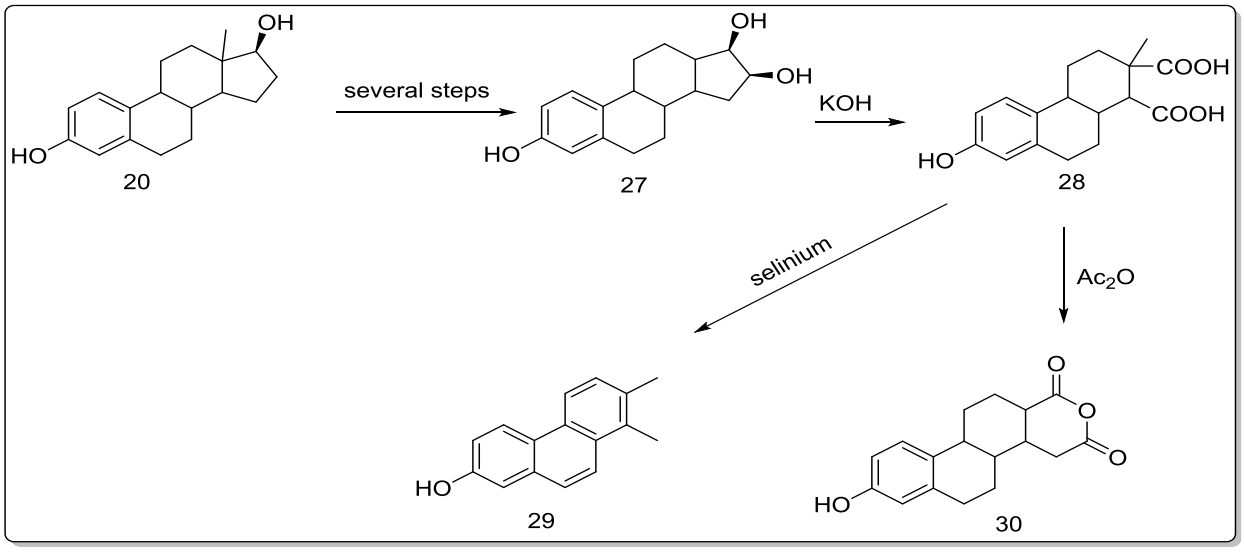


Figure 1.25 Conversion of estradiol to different compounds

Oppenauer oxidation of **7** lead to the formation of *Androst-4-ene-3,17-dione* **31**, on treating **31** with fermenting yeast produces *Testosterone* **21** which can be converted back to **31** by oxidation in chromium trioxide CrO_3 as shown in the figure below [19].

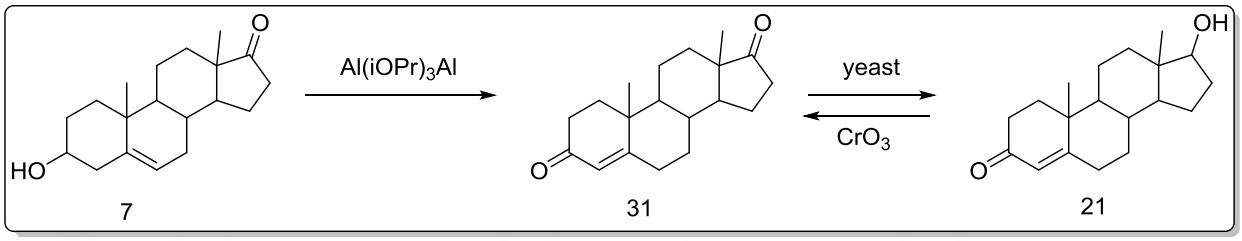


Figure 1.26 Synthesis of *Testosterone* from DHEA

1.10. Pyrazole, pyrazoline

Pyrazole belong to the five-membered heterocyclic ring with two heteroatoms and it's also called (1,2-diazole). They are classified as aromatic heterocycles and are π-excessive N-heteroaromatic compounds according to the classification of Alberts. But their aromaticity depends on the substituent attached to the ring [20]. In 1883, the first pyrazole derivative was synthesized from 3-oxybutanone and phenyl hydrazine, while its structure was determined in 1887 as 3-methyl-1-phenyl-1H-pyrazol-5-ol. 1*H*-pyrazole was prepared from decarboxylation of 1*H*-pyrazole-3,4,5-tricarboxylic acid [20].

Pyrazolines are less stable, stronger bases, and acting more as unsaturated compounds when compared to pyrazoles. They are colorless liquid with boiling point in the range of 120–150^{o}C. **Figure 1.27** below shows the structure of pyrazole and 2-pyrazoline.

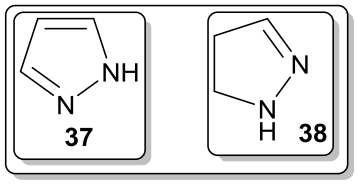


Figure 1.27 Structure of 1*H*-pyrazole and 2-pyrazoline

Pyrazolines are partially forms of pyrazole which has variable position of double bonds that are in equilibrium with each other. But among the pyrazoline derivatives, 2-pyrazoline is the derivative that has a monoimino character and it is the most stable among them. The figure below shows the equilibrium states of the derivatives [21].

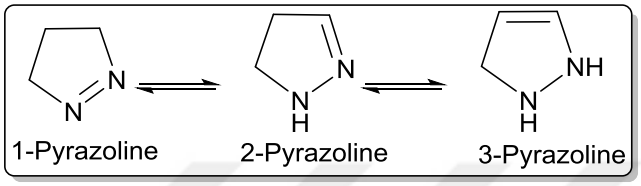


Figure 1.28 Equilibrium states of pyrazoline derivatives

1.10.1 Synthesis of pyrazoline

Many of the classical synthesis of pyrazole still belong to the selection of best methods available in the literature and new development have been incorporated. But using 1,3-dicarbonyl and hydrazine or its derivatives is likely to be the most widely and the most general method for pyrazole synthesis [20]. Pyrazoline is commonly synthesized from the reduction pyrazole by the use of hydrogen gas in the presence of palladium catalyst as presented in the figure below [22].

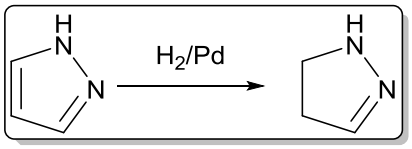


Figure 1.29 Reduction of pyrazole to pyrazoline

Different synthetic route were used for synthesis of pyrazoline, a summary for these synthetic methods were shown in the figure below [21, 23, 24, 25].

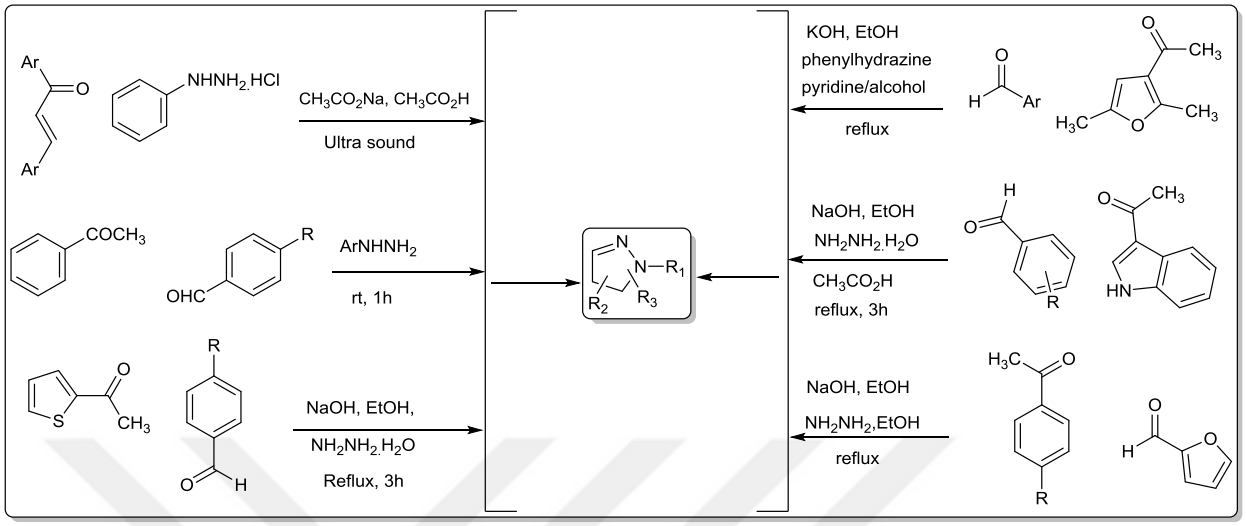


Figure 1.30 Summary of the synthetic route of pyrazoline

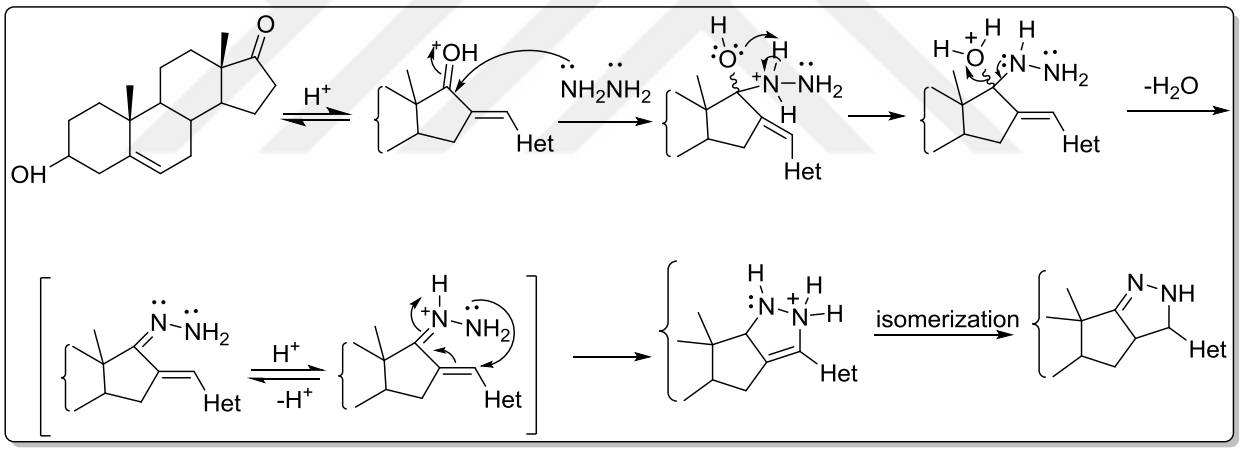


Figure 1.31 Mechanism for the formation pyrazoline ring

1.10.2 Biological activities of pyrazolines

Pyrazole derivatives biologically are less, having little significance, which is possibly due to the difficulty experienced for the living organisms to form the N-N bond, but it was found have an interesting pharmacological activities [20]. Some pyrazoles derivatives are reported as antipyretic (fever reduction), analgesic (pain killing) [26]. Pyrazoline were reported in the literature to possess a huge number of biological functions, most researches revealed that different substituent attached to pyrazoline core make it to have different biological activities [20,26].

Various type of activities possess by pyrazoline as drugs, dye are summarized in the figure below [20, 25, 26, 27].

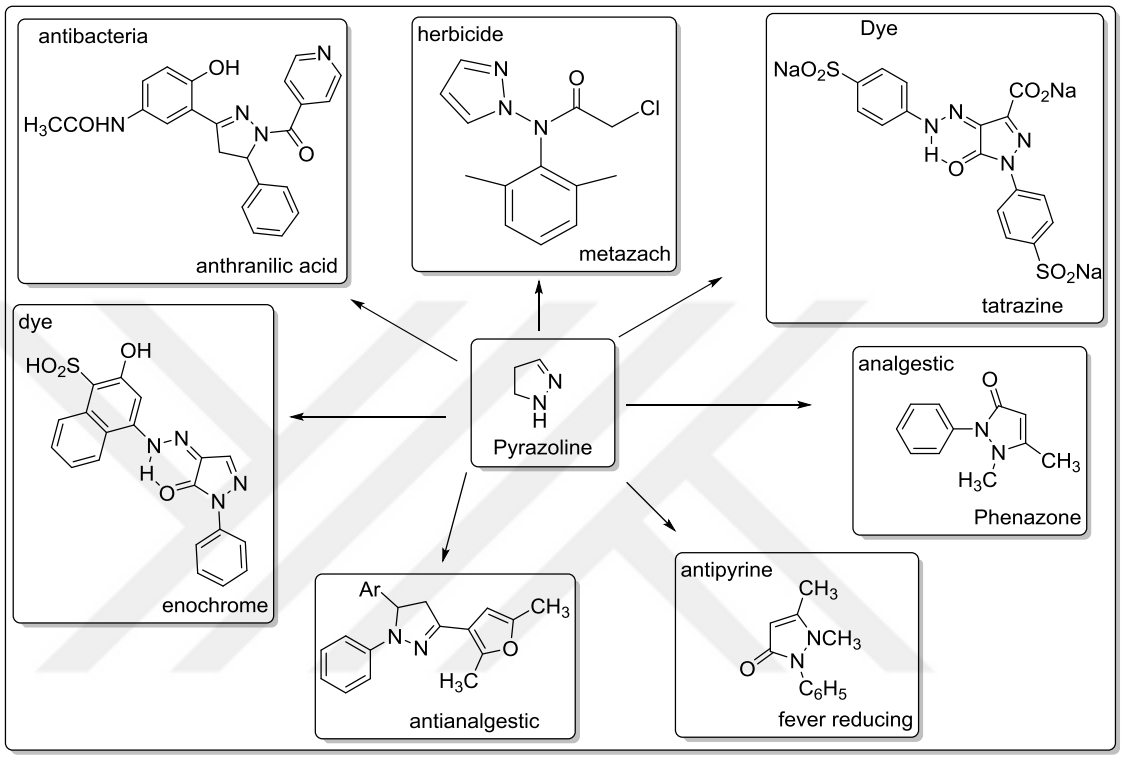


Figure 1.32 A summary of the bioactive pyrazoline derivatives

2. LITERATURE REVIEW

Pyrazole and its partially saturated derivative 2-pyrazoline assured to possess one of the most important scaffold among the five membered N-containing heterocycles. Different methods for their preparation and wide range of their pharmacological effect were emulated in the heterocyclic chemistry researches. Despite their scanty in nature and their limitations due to the difficulty of human body to form the N-N bond but incorporating their core structure plays a vital role towards the improving the bioactivity. Researches revealed that compounds containing these heterocycles moiety exert anti-inflammatory, anti-tubercular, antidepressant, anticonvulsant, antimicrobial, analgesic and other biological activities. So pyrazole/pyrazoline moiety becomes the focus of the scientific research interest [28].

A great pharmacological interest have been observed on steroid derivatives by which the D ring were modified by heterocyclic ring. So steroids and its derivatives are suitable to be elaborated as drugs for the treatment of numerous number of diseases such as autoimmune diseases, cardiovascular disease, brain tumor, prostate cancer and osteoarthritic [29].

It was discovered in the literature that, till 1930s a limited synthesis of steroidal pyrazole derivatives had been achieved. Perhaps, Ruzicka *et al* in 1938 obtained the first steroidal pyrazole as a single derivative of cholest-4-eno [3,2-c] pyrazole-5-carboxylic acid. Structure of the first synthesized steroidal pyrazole is given in the figure below [30].

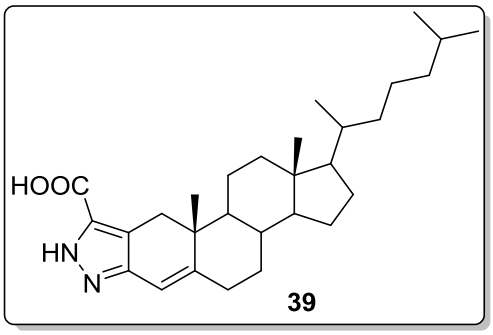


Figure 2.1 Structure of first synthesized steroidal pyrazole

Decades after, organic chemist put forward much attention towards the synthesis of steroidal pyrazoles and it was found that a number of biological activities are obtained by fusion the pyrazole ring into steroid nucleus [30].

2.1. Modification of steroids with heterocycles on the D ring

A.H. Bandy report the synthesis of two series of pyrazolinyl and pyrazolyl *Pregnenolone* by using different method in the journal of steroid (2014). Starting with pregnenolone **6** by aldol condensation to afford the α-β-unsaturated compound as the condensation product **45**. Refluxing **39** with hydrazine hydrate in acetic acid afford the pyrazoline derivative **46** in a diastereomeric mixture as shown in the figure below [29].

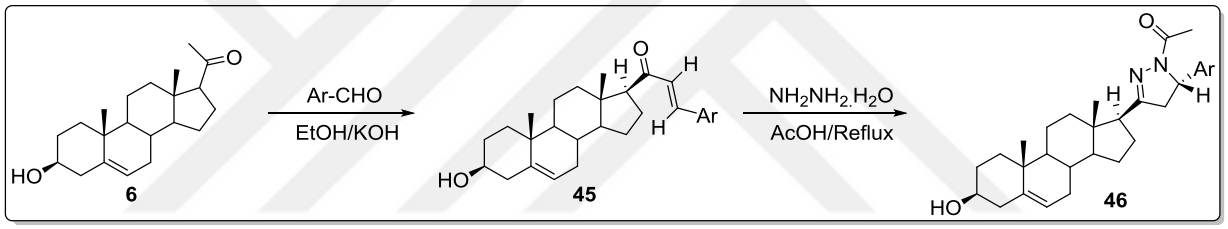


Figure 2.2 Synthesis of D-ring substituted pyrazolinyl pregnenolones

The pyrazolyl derivative were synthesized by starting with the **6** using the method portrayed in the literature by Schneider *et al*. to afford **47**, reacting **47** with phenyl hydrazine or its *p*-substituted derivative in dichloromethane followed by addition of BF_3OEt_2 in dropwise as catalyst afford **48** as shown below [29].

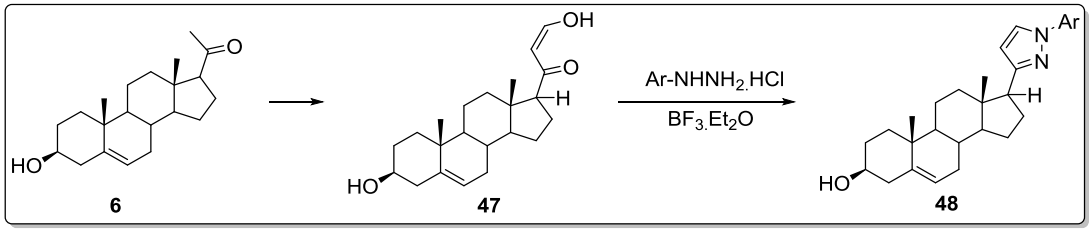


Figure 2.3 Synthesis of D-ring substitued pyrazolyl *Pregnenolones*

An interesting synthesis of stereo selective Novel *Androstenoarylpyrazolines* were reported in the Journal of Mol Divers (2015) by Gerg″o Mótyán *et al.* by the BF_3 induced intramolecular 1, 3-dipolar cycloaddition of alkenyl hydrazones that is produced from the steroidal D-seco-aldehyde in the presence of differently substituted arylhydrazines. The cyclizations are not pure combined mechanism to afford the primary products which is aryl pyrazolidines, rather it's a stepwise mechanism. Under the reaction conditions, spontaneous oxidation of the saturated N, N-heterocycles led to the formation of pyrazoline derivatives **53** and **54** in good to excellent yields. Some of the derivatives exerted in vitro anti proliferative activities against all utilized breast cancer panel which were higher or comparable to those of the reference cisplatin [28].

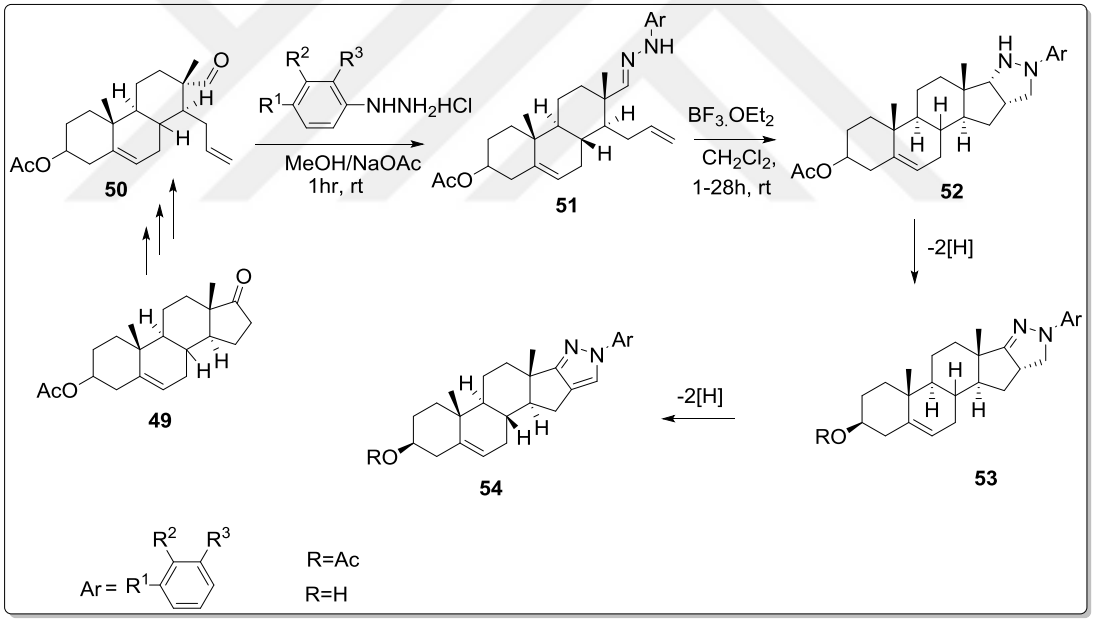


Figure 2.4 Syntheses of 5-androstenoarylpyrazolines

In an attempt to modify the D ring, an exocyclic synthesis of pyrazoline were reported in the European Journal of Medicinal Chemistry by N.J. Fan *et al*. Starting with *Pregnenolone* derivative **55**, epoxidation of **55** gives the epoxy compound **56**, when **56** were reacted with concentrated HCl in acetic acid the epoxy ring opens which afford **57**, treatment of **57** with TBDSCI in dioxane at reflux afford **58** which were also obtained by dehydrogenation of **6** with DDQ. Compound **59** was obtained by aldol condensation with different aromatic

aldehydes, then later **59** were reacted with hydrazine hydrate in acetic acid at reflux to afford **60**. The synthesized compound were tested for cytotoxic activity against brine shrimp (*Atemia Selina*) and three human cancer cell line (NCl-H460, Hela and HepG2) and it was found to possess a significant activity [31].

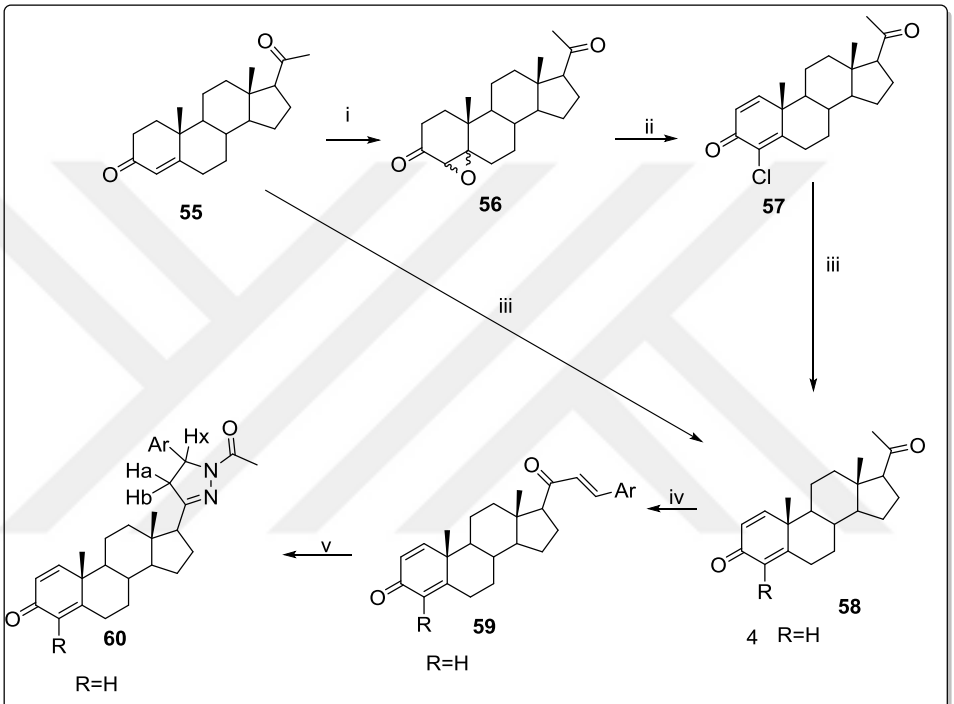


Figure 2.5 Synthesis of the steroidal C-17pyrazolinyl derivatives

In another report by M. Garrido et al. the cytotoxic effect of human cancer cells on three series of novel *Dehydroepiandrosterone* derivatives containing triazole or pyrazole rings at C-17 and an ester moiety at C-3 of the androstane skeleton were determined. The panel cancer cells: PC-3, MCF-7 and SKLU-1 were used.

From the result obtained, it shows the highest cytotoxic potency of the steroidal derivatives of the triazole. Due to the presence of three nitrogen atoms in the triazole which form stronger hydrogen bonds with the active site of the cell as compared to the pyrazole

group having two nitrogen atoms, but when free hydroxyl group at C-3 and a pyrazole ring at C-17 are used it showed a very high cytotoxic activity [32].

Bandy et al. also reported another synthesis of 17-pyrazolinyl derivatives of *Pregnenolone* and were evaluated as potential anticancer agents against various human cancer cell lines (panel of seven human cancer cell). The synthesis of the compound involve the transformation of the starting *Pregnenolone acetate* into *Pregnenolone*, then conversion of *Pregnenolone* to the corresponding benzylidine derivatives and finally the conversion of this derivative to the stable steroidal 17-pyrazoline [33].

Another interesting synthesis of pyrazoline and isoxazoline derivatives of *Androstane* series were reported by A.U. Siddiqui et al. using Claisen condensation of androstane derivative **61** with dimethylcarbonate to afford **62**, when **62** were reacted with hydrazine hydrate or its derivatives afforded the pyrazoline derivatives **63** while the isoxazoline derivative **64** was obtained by reacting **62** with hydroxylamine. And these synthesized compounds were reported tSo have a wide range of pharmacological activities [34].

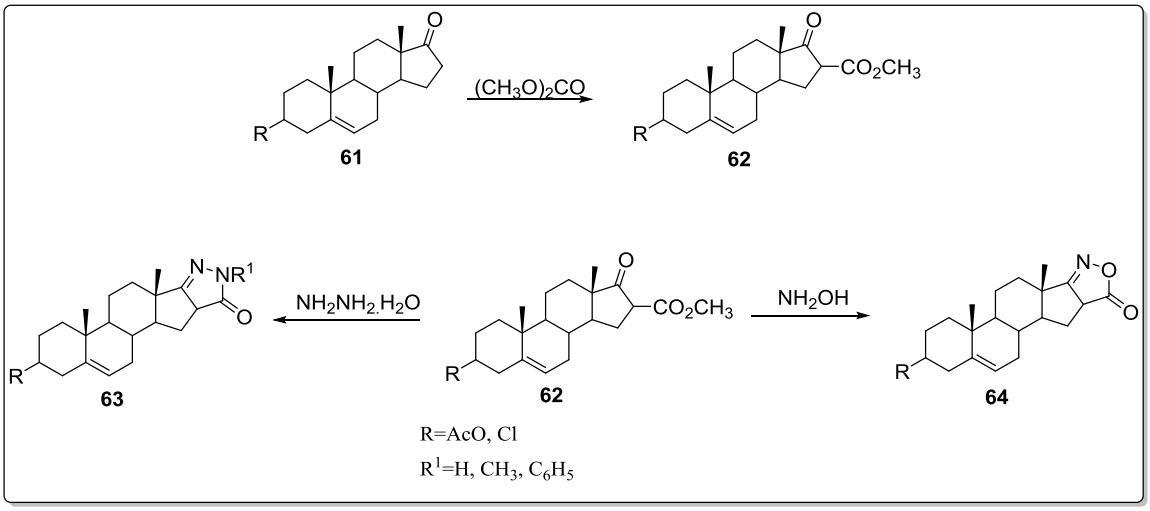


Figure 2.6 Synthesis of pyrazoline and isoxazoline derivatives

Z. Iványi et al report the synthesis of steroidal benzylidines from *Pregnenolone* **6** with benzaldehyde and p-substituted benzaldehydes. The 17β-chalconyl derivatives product of pregnenolone **65** formed from aldol condensation were reacted with hydrazine hydrate in acetic acid. The ring-closure reaction afforded a mixture of two steroidal pyrazoline epimers

66 and **67**. The pair of isomers are crucial epimers which could only be separated in acetylated form. The in vitro inhibition of rat testicular C17,20-lyase activity and the anti-proliferative effects on four human cancer cell lines were measured, and the results obtained from the two epimers series were compared [35].

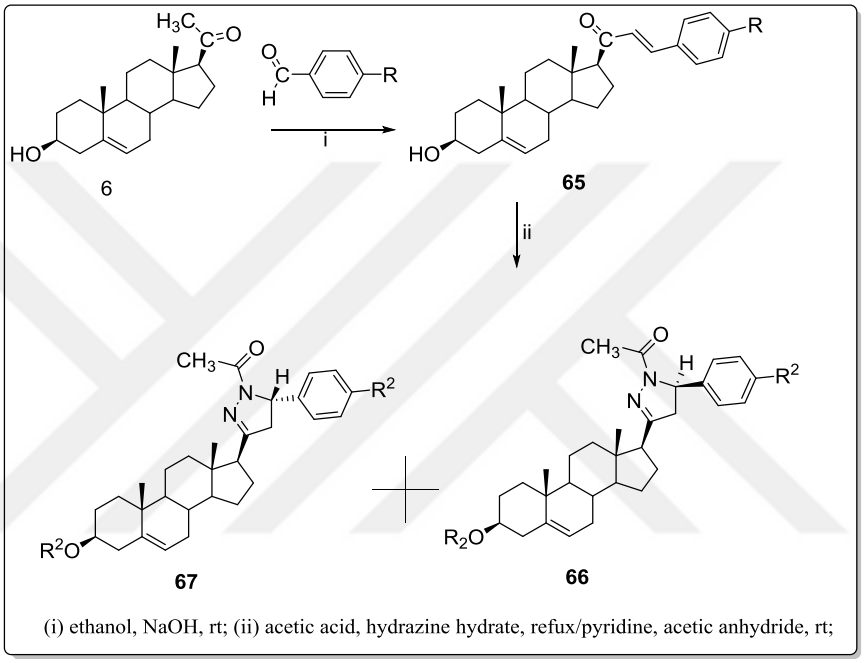


Figure 2.7 Synthesis of 5'R and 5'S Phenylpyrazolinylandrostene derivatives of pyrazoline

2.2 Non-steroidal pyrazolines

Synthesis and investigation of tautomerism of some pyrazoline derivatives were reported in the Journal of Molecular and Bio Mol. Spectroscopy by F. B. Miguel et al. starting by the reaction of O-alkylated aldehyde **59** with aceophenone **60** to afford the O-alkylated chalcone derivatives **61** in the presence of NaOH in ethanol using Claisen reaction. The pyrazoline was obtained by the reaction of carbazide or thiosemicarbazide with **61** to afford the carboxamide **62** and carbothioamide **63** respectively [36].

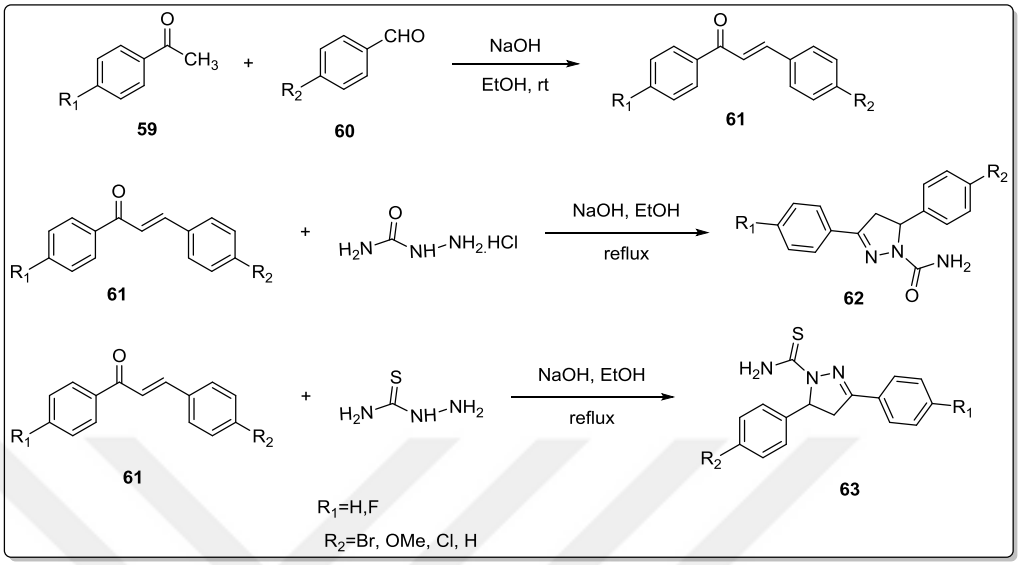


Figure 2.8 Synthesis of carboxamide and carbothioamide

From the result of the equilibrium between the tautomeric form of the synthesized pyrazoline derivatives, it was found that the compounds were exist in tautomers that tautomerized either in solid form or in solution and the compounds are stable [36].

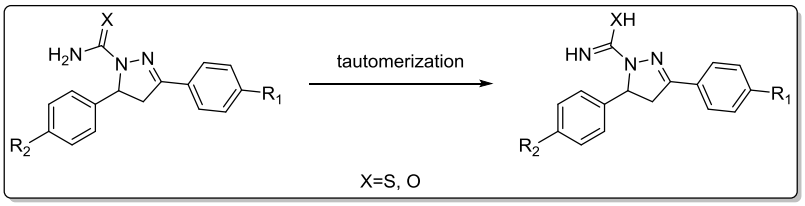


Figure 2.9 Tautomerisation of carboxamide carbothioamide

F. Chimenti *et al* report the synthesis of a series of 3,5-diarylpyrazoles by the reaction of epoxy chalcone formed from epoxidation of α,β-unsaturated ketone and aqueous hydrogen peroxide with hydrazine monohydrate and *p*-toluene sulfonic acid monohydrate and tested for the competency to inhibit reversible monoamine oxidase-A (MAO-A) and monoamine oxidase-B(MAO-B). It was found that all the tested derivatives possess a reversible mode of action [37].

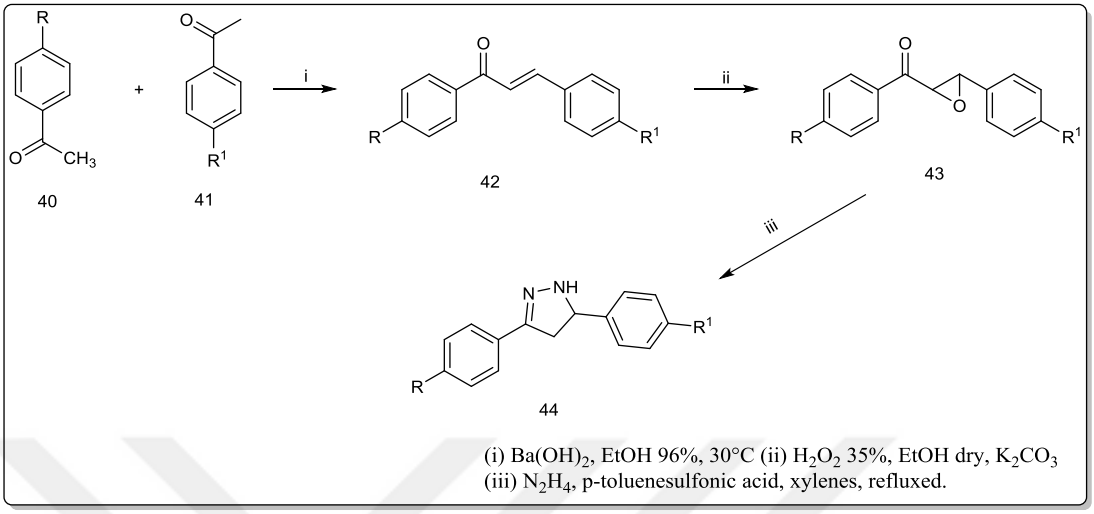


Figure 2.10 Synthesis of 3,5-diarylpyrazole derivatives

2.3. Aims of the study

Recently steroids, azasteroids, heterocyclic compounds and their derivatives considerably attract the attention of synthetic and medicinal chemist due to their numerous interesting biological activities. Our study immerses on modification of steroid D ring (*Dehydroepiandrosterone DHEA* and *pregnenolone*) with heterocyclic compound (pyrazoline) containing different heteroaromatic substituents, in which the heterocyclic compound fused with the steroid D ring. The first part of the study focuses on the modification of C16 and C17 carbon atoms of DHEA by different pyrazoline derivatives with novel heteroaromatic substituent fused at the steroid D ring using the nitrogen nucleophile (hydrazine hydrate) by endocyclic nucleophilic attack.

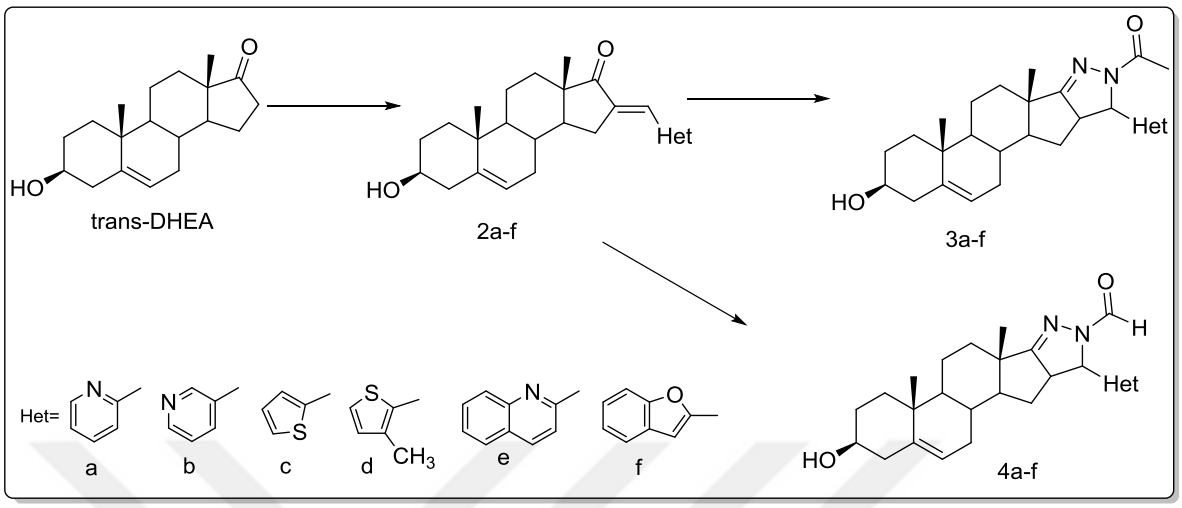


Figure 2.11 Synthesis of pyrazoline derivatives from *DHEA* (Aim of the study first part)

The last part of the study is the modification of C20 and C21 carbon atoms of *Pregnenolone* by two different pyrazoline derivatives with also novel heteroaromatic substituents fused with the steroid D ring using different nitrogen nucleophile (hydrazine hydrate and thiosemicarbazide) by exocyclic nucleophilic attack.

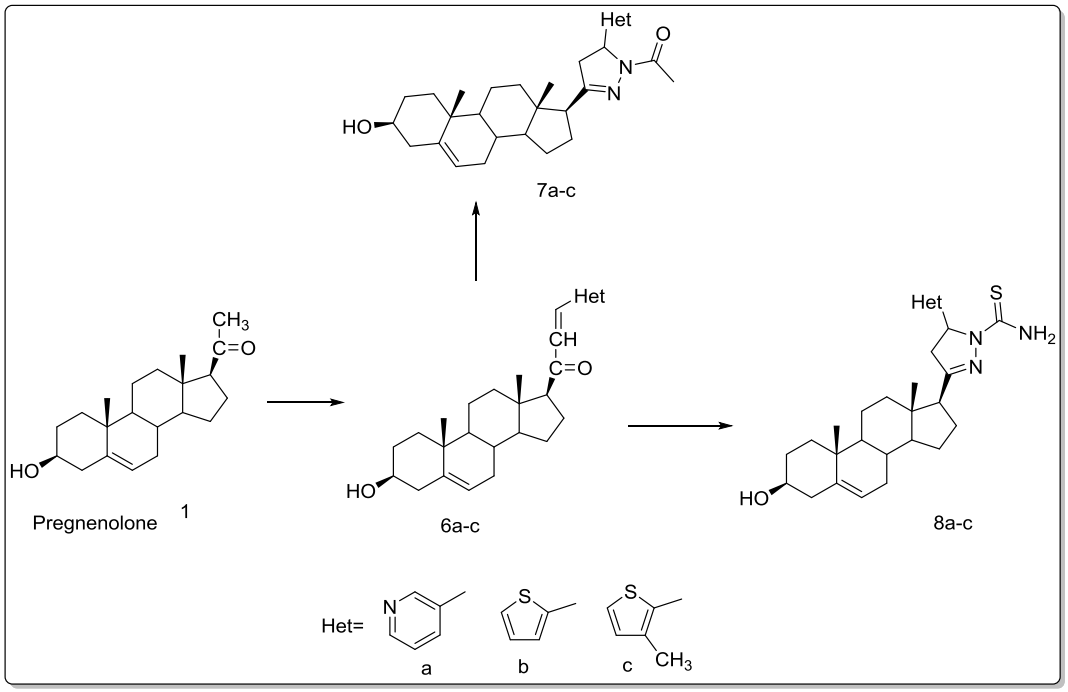


Figure 2.12 Synthesis of pyrazoline derivatives from *Pregnenolone* (Aim of the study last part)

3. MATERIAL AND METHODS

All weighing was made on Denver APX-200 digital scale, melting point were determined with SMP30 melting point apparatus, TLC were carried out on precoated silica gel plates, Heidolp 4001 Rotary Evaporator was used for evaporating solvents at reduced pressure.

Infrared spectra were recorded on Perkin Elmer Spectrum Two, ^{1}H and ^{13}C- NMR spectrums were recorded with BRUKER 400 MHz-NMR and 100 MHz-NMR spectrometer respectively with TMS as internal standard, all the spectrum stated were carried out in $CDCl_3$ and are reported in ppm.

Some of the apparatus used were conical flask, funnel, beaker, round bottom flask, filter paper, hot plate, magnetic stirrer, dropper, spatula, oven, measuring cylinder, separation funnel, condenser etc.

Reagents and solvents used in this thesis and their supplying company are sum up in the table below.

Table 3.1 Reagents and supplying company

Reagents (%)	Supplying Company
DHEA 99%	Acros Organic
Pregnenolone	Fubchem
Hydrazine hydrate 50%	Sigma Aldrich
Thiosemicarbazide	Merck
2-Pyridinecarboxaldehyde 99%	Acros Organic
3-Pyridinecarboxaldehyde 98%	Acros Organic
2-Thiophenecarboxaldehyde 98%	Alfa Aesar
2-Quinolinecarboxaldehyde 97%	Acros Organic
3-Methyl-2-Thiophenecarboxaldehyde 90%	
Phenyl hydrazine 98%	Merck
2-Formylbenzofuran 96%	Acros Organic
NaOH	Merck
KOH	Merck
Acetic Acid 99.8%	Scharlau
Formic Acid 98%	Scharlau
Ethanol 95%	Sigma Aldrich
Methanol 99.9%	Sigma Aldrich
Chloroform 99.4%	Sigma Aldrich
Benzene 99%	Sigma Aldrich
Pyridine 99%	Fisher Scientific
Acetic anhydride 98.5%	

3.1. Experimental

The reagents used in this thesis were all used as received from the manufacturer. And according to the method available for the standard purification, all the solvents used were purified and dried.

3.2. Summarized general procedure for the synthesis of endocyclic pyrazoline derivatives from DHEA

Compound **2** was obtained by aldol condensation of DHEA with heteroaromatic aldehyde followed by endocyclic reaction of **2** with hydrazine hydrate in acetic acid and formic acid afforded compounds **3** and **4** respectively.

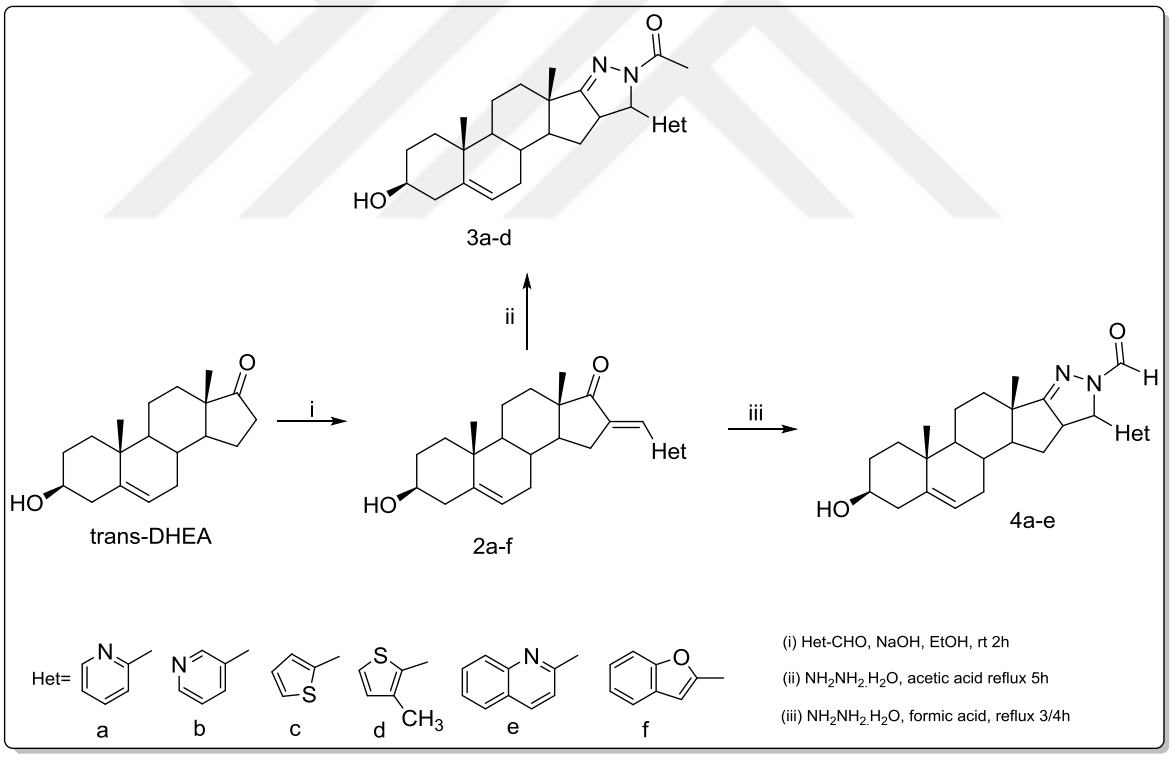


Figure 3.1 Summarized general procedure for the synthesis of endocyclic pyrazoline derivatives from DHEA

3.2.1 Synthesis of *16(E)*-(2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2a)

1.0 g (3.47 mmol, 99%) DHEA and 1.75 g (43. 68 mmol) NaOH was dissolved in 30 mL 95% ethanol in a round bottom flask and stirred for about 5 minutes, 0.71 mL (7.45 mmol, 1.13 g/ mL, 99%) 2-pyridine carboxaldehyde were added and stirred for 3 h at room temperature. The reaction mixture was poured onto ice water, the white precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as white powder (76.3%, mp 164-167^{o}C).

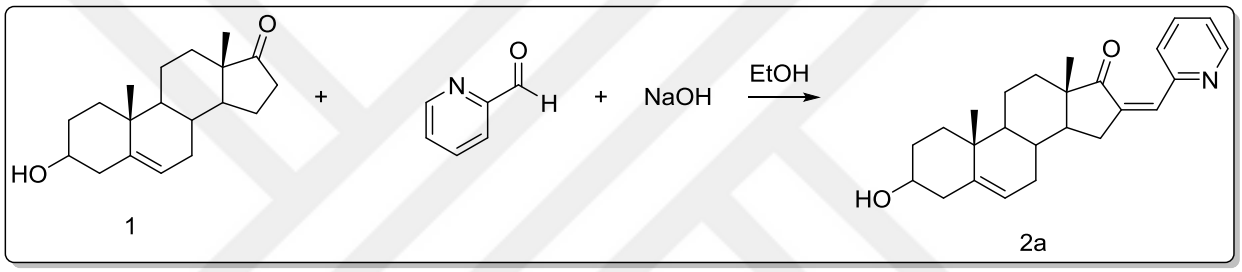


Figure 3.2 Synthesis of 16*(E)*- (2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2a)

3.2.2 Synthesis of 16*(E)*- (3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2b)

1.0 g (3.47 mmol, 99%) DHEA and 1.75 g (43. 68 mmol) NaOH was dissolved in 30 mL, 95% ethanol in a round bottom flask and stirred for about 5 minutes, 0.71 mL (7.49 mmol, 1.14 g/mL, 98%) 3-pyridine carboxaldehyde were added and stirred for 3 h at room temperature. The reaction mixture was precipitated under ice water and the white precipitate obtained were filtered and washed with and dried. The dried compound was crystallized from ethanol and were obtained as white powder (76.4%, mp 251-254^{o}C).

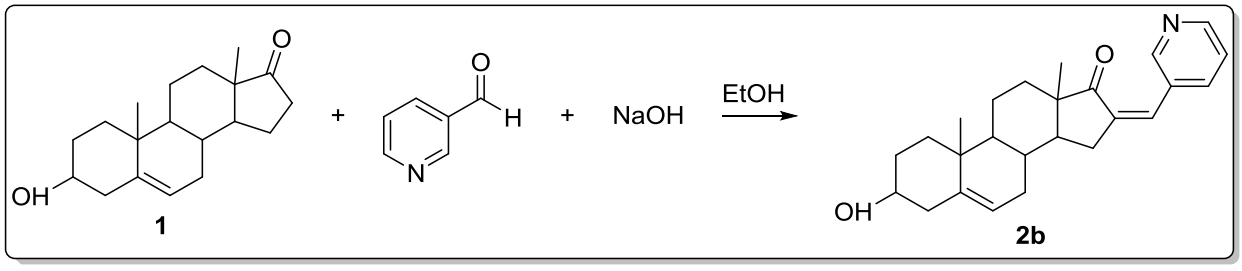


Figure 3.3 Synthesis of 16(*E*)- (3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2b)

3.2.3 Synthesis of *16(E)*- (2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2c)

1.0 g (3.47 mmol, 99%) DHEA and 1.75 g (43. 75 mmol) NaOH was dissolved in 30 mL, 95% ethanol in a round bottom flask and stirred for about 5 minutes, 0.7 mL (7.49 mmol, 1.22 g/mL, 98%) 2-thiophene carboxaldehyde were added and stirred for 3 h at room temperature. The reaction mixture was precipitated under ice water and the white precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as milk powder (75.2%, mp 220-222^{o}C).

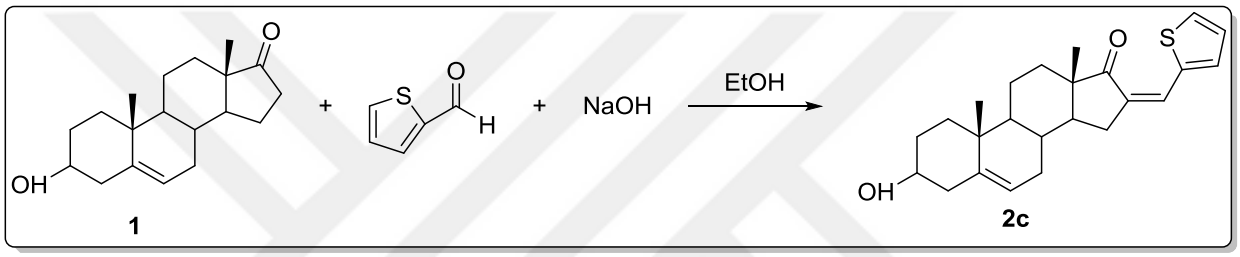


Figure 3.4 Synthesis of 16*(E)*- (2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2c)

3.2.4 Synthesis of *16(E)*- (3-methyl-2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2d)

1.0 g (3.47 mmol, 99%) DHEA and 1.75 g (43. 68 mmol) NaOH was dissolved in 30 mL, 99.9% methanol in a round bottom flask and stirred for about 5 minutes, 0.9 mL (7.49 mmol, 1.17 g/mL, 90%) 3-methyl-2-thiophene carboxaldehyde were added and stirred for 3 h at room temperature. The reaction mixture was precipitated under ice water and the milk precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as pale yellow solid (72.9%, 213-216^{o}C).

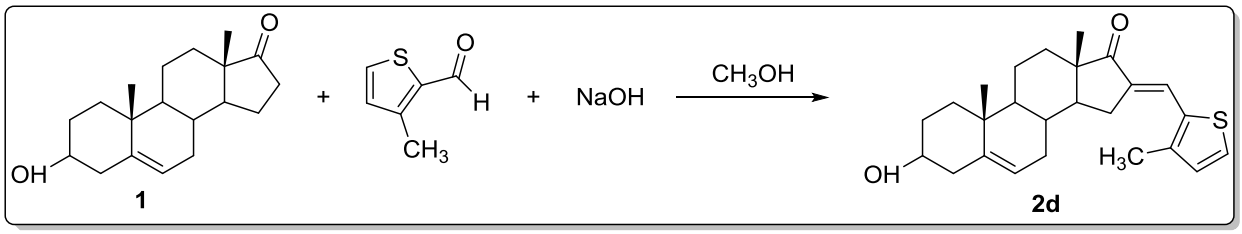


Figure 3.5 Synthesis of 16(*E*) - (3-methyl-2-thiophenyliden)-3β-hydroxyandrost-5-en-17- one (2d)

3.2.5 Synthesis of 16*(E)*- (2-quinolinyliden)-3β-hydroxyandrost-5-en-17-one (2e)

1.0 g (3.47 mmol, 99%) DHEA and 1.75 g (43. 68 mmol) NaOH was dissolved in 30 mL, 95% ethanol in a round bottom flask and stirred for about 5 minutes, 0.45 g (7.45 mmol, 97%) 2-quinoline carboxaldehyde were added and stirred for 3 h at room temperature. The reaction mixture was precipitated under ice water and the white precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as pale yellow powder (67.6%, mp 212-215^{o}C).

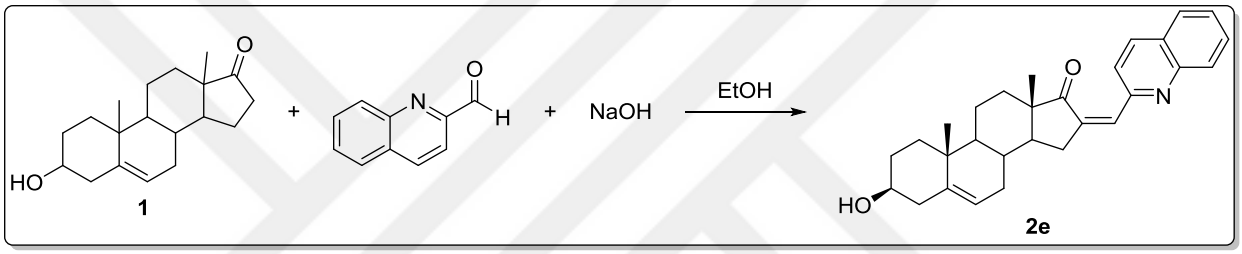


Figure 3.6 Synthesis of 16(*E*)- (2-quinolinyliden)-3β-hydroxyandrost-5-en-17-one (2e)

3.2.6 Synthesis of 16(E)- (2-benzofuranyliden)-3β-hydroxyandrost-5-en-17-one (2f)

0.925 g (3.21 mmol, 99%) DHEA and 1.26 g (31. 43 mmol) NaOH was dissolved in 30 mL, 95% ethanol in a round bottom flask and stirred for about 5 minutes, 0.9 mL (7.49 mmol, 1.21 g/mL, 96%) 2-benzofuran carboxaldehyde were added and stirred for 3 h at room temperature. The reaction mixture was precipitated under ice water and the milk precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as yellowish powder (74.6%, mp 219-221^{o}C).

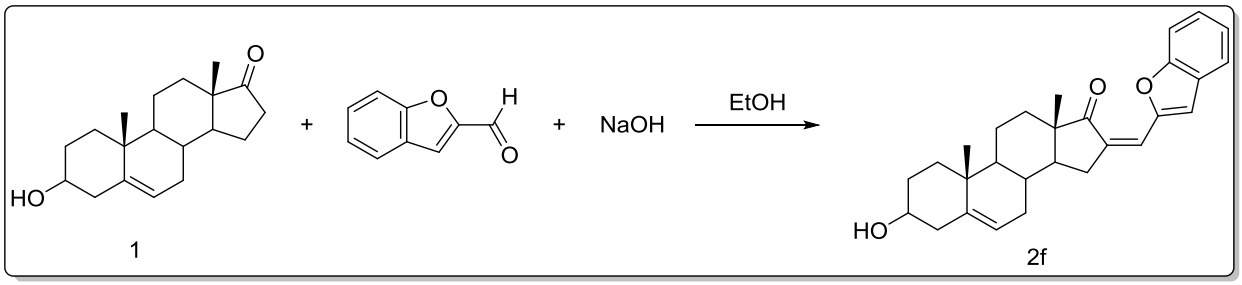


Figure 3.7 Synthesis of 16(*E*)-(2-benzofuranyliden)-3β-hydroxyandrost-5-en-17-one (2f)

3.2.7 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(2-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (3a)

30 mL, 99.8% acetic acid and 0.64 mL, (6.62 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.5 g (1.32 mmol) of **2a** in a round bottom flask. The mixture was heated at reflux for 5 h, the reaction progress was monitored using TLC. Upon the completion of the reaction, the reaction mixture was precipitated under ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as brownish powder. (87.1%, 103-106^{o}C)

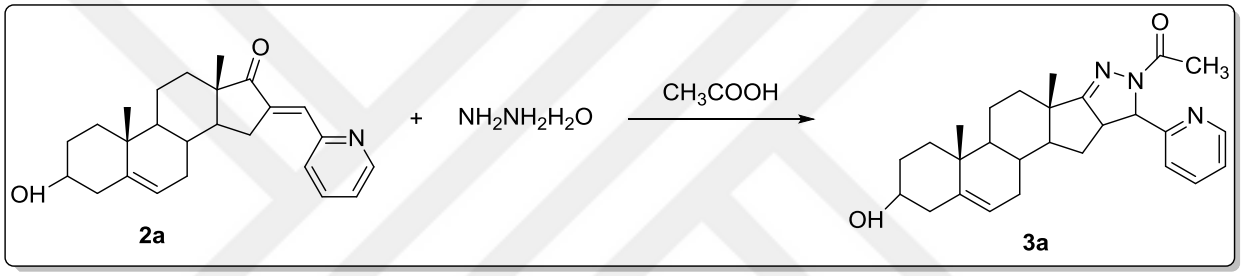


Figure 3.8 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(2-pyridinyl)-16, 17-pyrazolinyl) androst-5-ene (3a)

3.2.8 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(3-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (3b)

30 mL, 99.8% acetic acid and 0.64 mL (6.62 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.5 g (1.32 mmol) of **2b** in a round bottom flask. The mixture was heated at reflux for 5 h, the reaction progress was monitored using TLC. Upon the completion of the reaction, the reaction mixture was precipitated under ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as yellowish powder (87.1%, mp 195-198^{o}C).

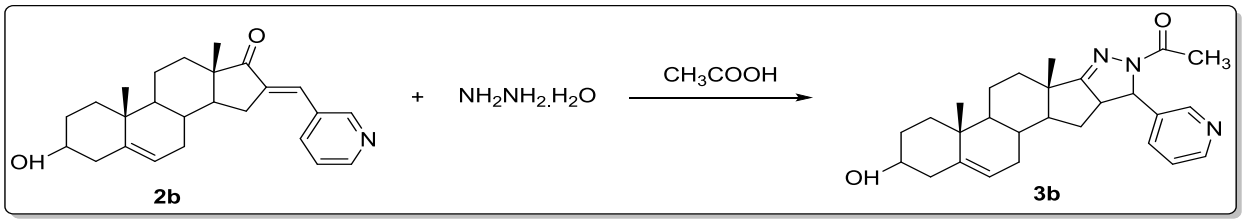


Figure 3.9 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(3-pyridinyl)-16, 17-pyrazolinyl) androst-5-ene (3b)

3.2.9 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (3c)

15 mL, 99.8% acetic acid and 0.32 mL, (3.27 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.25 g (0.653 mmol) of **2c** in a round bottom flask. The mixture was heated at reflux for 5 h, the reaction progress was monitored using TLC. Upon the completion of the reaction, the reaction mixture was precipitated under ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as yellowish powder (87.4%, mp 143-146^{o}C).

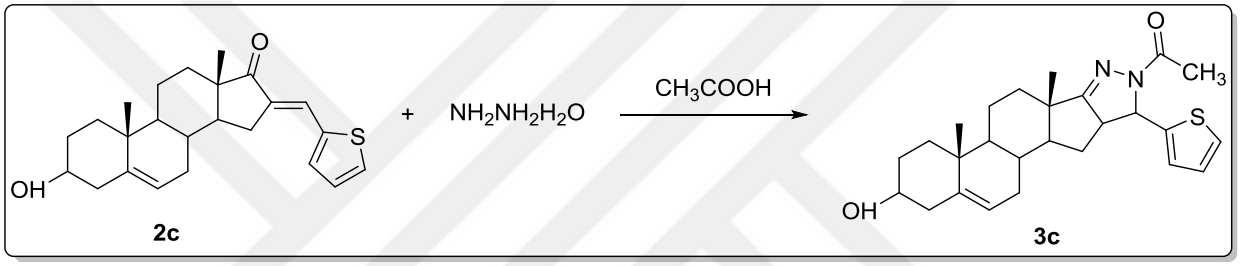


Figure 3.10 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (3c)

3.2.10 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (3d)

30 mL, 99.8% acetic acid and 0.61 mL (6.30 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.5 g (1.26 mmol) of **2d** in a round bottom flask. The mixture was heated at reflux for 5 h, the reaction progress was monitored using TLC. Upon the completion of the reaction, the reaction mixture was precipitated under ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from ethanol and were obtained as deep brown liquid (87.7%, *[oily]*).

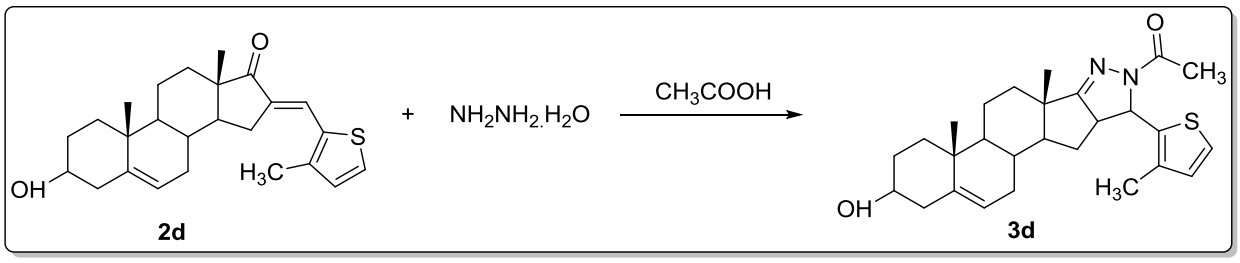


Figure 3.11 Synthesis of 3β-hydroxyl-(1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (3d)

3.2.11 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (4a)

10 mL, 98% formic acid and 0.97 mL (0.1 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.75 g (2.0 mmol) compound **2a** in a round bottom flask. The mixture was heated at reflux for about 4 h, the progress of the reaction was monitored using TLC. Upon the completion of the reaction, the reaction mixture was poured onto ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from methanol and chloroform in the ratio 1:1v/v and were obtained as light green shiny crystals (90%, mp 230-233^{o}C).

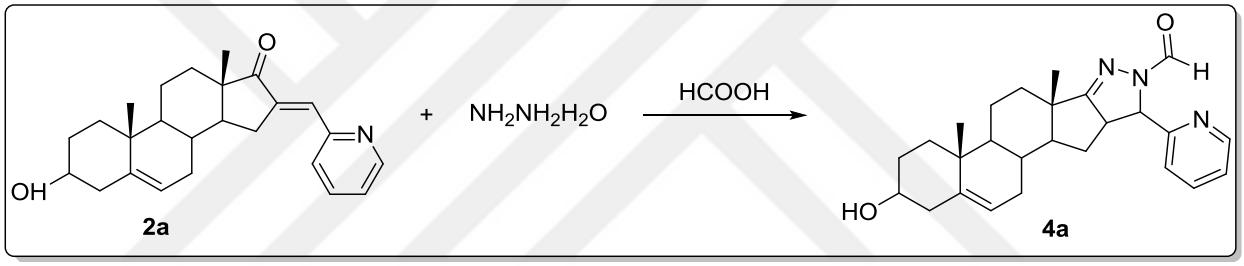


Figure 3.12 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (4a)

3.2.12 Synthesis of 3β-hydroxyl-(1-Formyl-5-(3-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (4b)

10 mL, 98% formic acid and 0.97 mL (0.1 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.75 g (2.0 mmol) compound **2b** in a round bottom flask. The mixture was heated at reflux for about 4 h, the progress of the reaction was monitored using TLC. Upon the completion of the reaction, the reaction mixture was poured onto ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from methanol and chloroform in the ratio 3:1v/v respectively and were obtained as milky powder (90%, mp 226-228^{o}C).

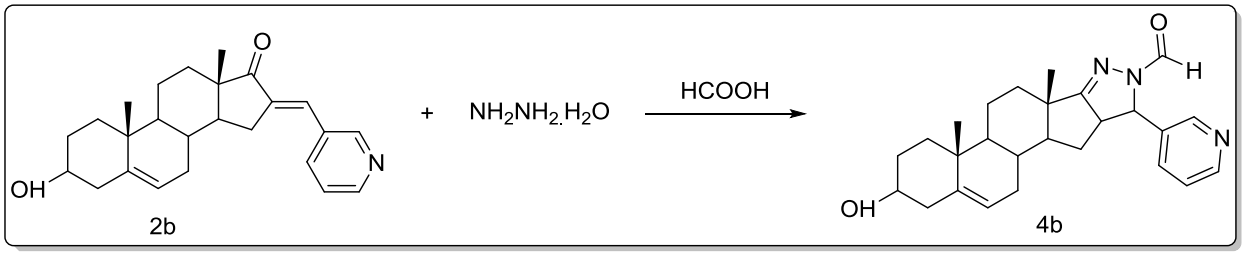


Figure 3.13 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (4b

3.2.13 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4c)

10 mL, 98% formic acid and 0.95 mL (0.980 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.75g (2.0 mmol) compound **2c** in a round bottom flask. The mixture was heated at reflux for about 4 h, the progress of the reaction was monitored using TLC. Upon the completion of the reaction, the reaction mixture was poured onto ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from methanol and chloroform in the ratio 1:1v/v respectively and were obtained as light brown powder (90%, mp 230-233.5^{o}C).

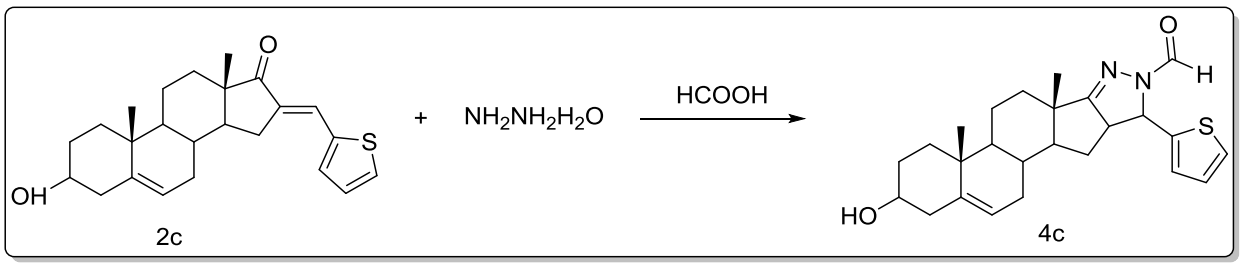


Figure 3.14 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4c)

3.2.14 Synthesis of 3β-hydroxyl-(1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4d)

10 mL, 98% formic acid and 0.92 mL (0.950 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.75 g (1.89 mmol) compound **2d** in a round bottom flask. The mixture was

heated at reflux for about 4 h, the progress of the reaction was monitored using TLC. Upon the completion of the reaction, the reaction mixture was poured onto ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from methanol and chloroform in the ratio 1:1v/v respectively and were obtained as yellow solid (90%, mp 164-167^{o}C).

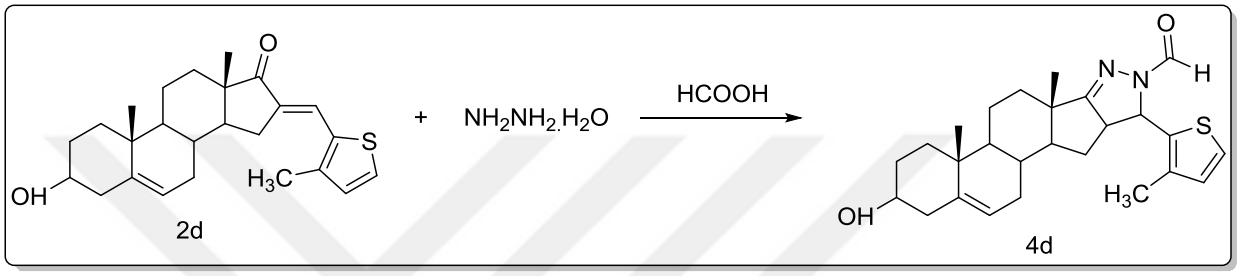


Figure 3.15 Synthesis of 3β-hydroxyl-(1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4d)

3.2.15 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl) androst-5-ene (4e)

10 mL, 98% formic acid and 0.28 mL (0.292 mmol, 1.03 g/mL, 50%) hydrazine hydrate were added to 0.25 g (0.585 mmol) compound **2e** in a round bottom flask. The mixture was heated at reflux for about 4 h, the progress of the reaction was monitored using TLC. Upon the completion of the reaction, the reaction mixture was poured onto ice water and the precipitate obtained were filtered and washed with water and dried. The dried compound was crystallized from methanol and chloroform in the ratio 1:3v/v respectively and were obtained as deep milk solid (91%, mp 145-148.5^{o}C).

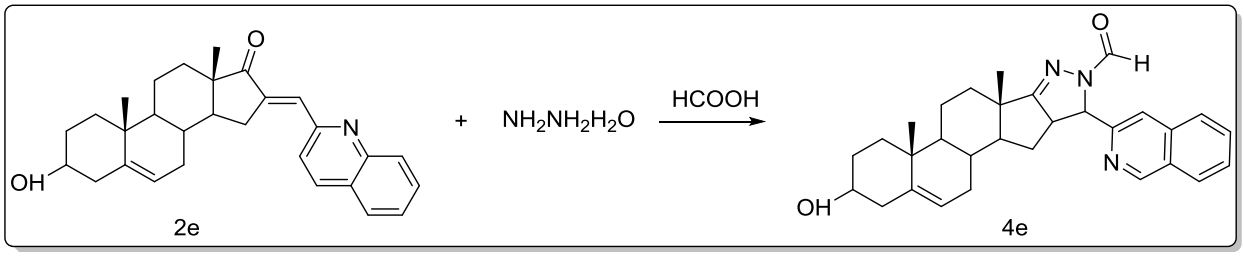


Figure 3.16 Synthesis of 3β-hydroxyl-(1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl) androst-5-ene (4e)

3.3 summarized general procedure for the synthesis of exocyclic pyrazoline derivatives from *Pregnenolone*

Compound **6** was obtained by aldol condensation of *Pregnenolone* with heteroaromatic aldehyde, reaction of **6** with hydrazine hydrate in acetic acid by affords **7** while compound **8** was prepared by the reaction of **6** with thiosemicarbazide in hydrochloric acid in the presence of ethanol.

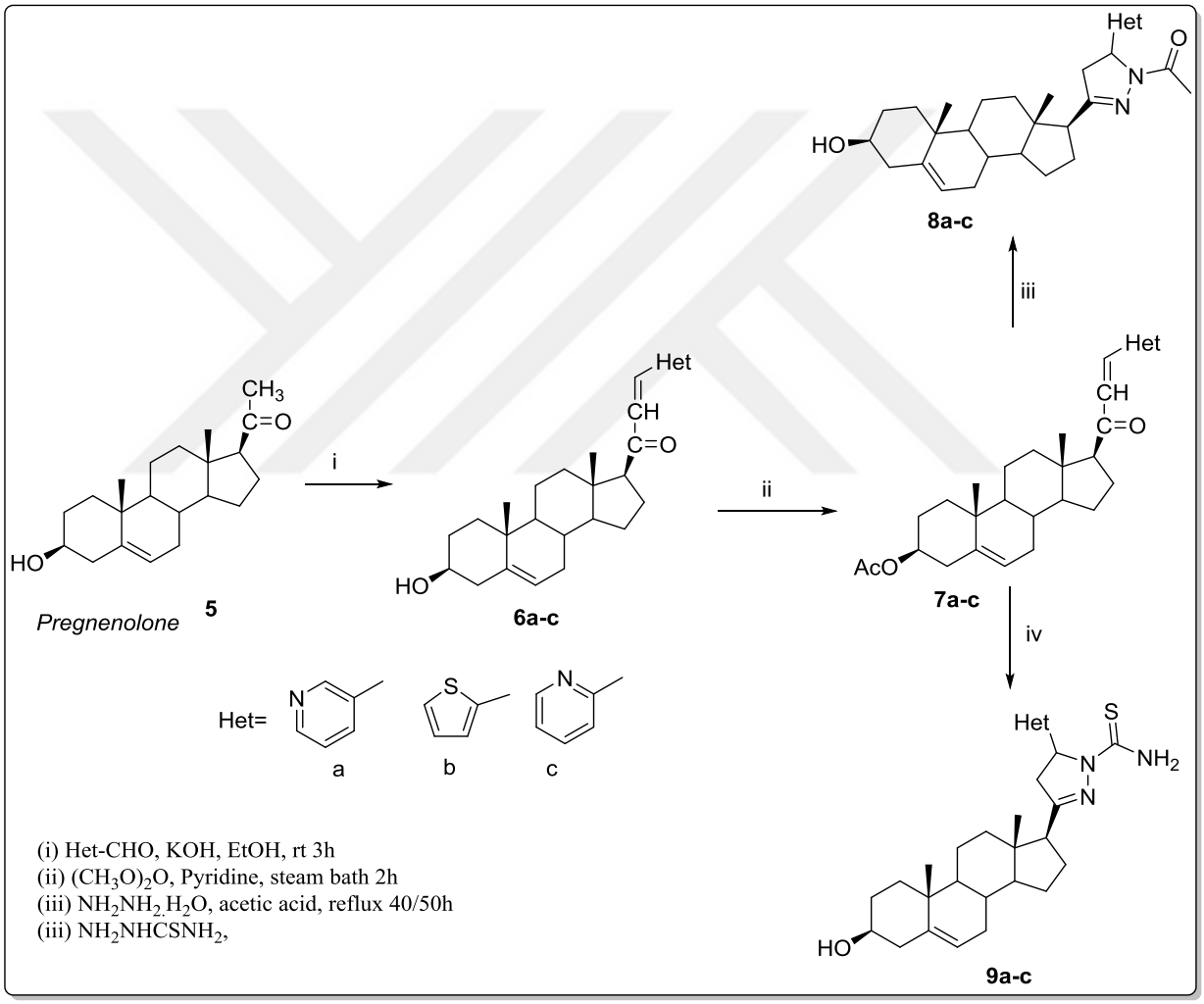


Figure 3.17 Summarized procedure for the synthesis of exocyclic pyrazoline derivatives from Pregnenolone

3.3.1 Synthesis of 21*(E)*- 3*β* - hydroxy-21-(3-pyridinylidene) pregn-5-en-20-one (6a)

To 2.00 g (6.32 mmol) *Pregnenolone* in 40 mL, 95% ethanol 0.71 g, (12.64 mmol) KOH were added and stirred until cleared solution is obtained, 0.72 mL (7.58 mmol, 1.14 g/mL, 98%) 3-pyridinecarboxaldehyde were added with continuous stirring for 3 h at room temperature. After the completion of the reaction, the yellow colored reaction mixture was precipitated under ice water and the precipitate were filtered off washed with water and dried. The dried compound was crystallized from ethanol and were obtained as light brown solid (78.1%, mp 119-121 ^{o}C).

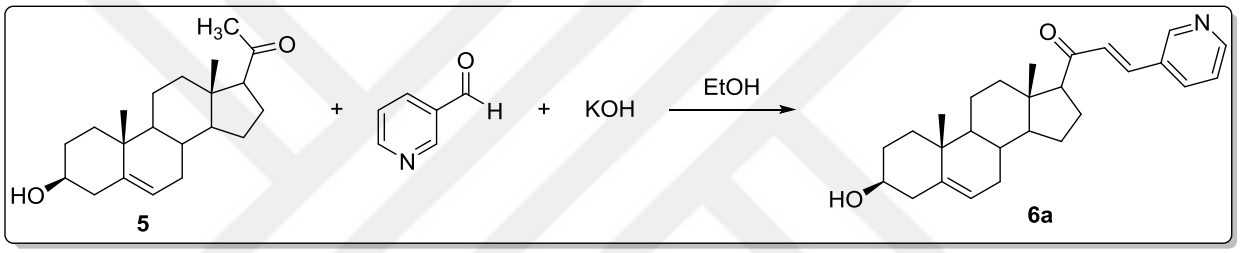


Figure 3.18 Synthesis of 21(E) -3β-hydroxy-21-(3-pyridinylidene) pregn-5-en-20-one (6a)

3.3.2 Synthesis of *(21E)*-3*β*-hydroxy-21-(2-thiophenylidene) pregn-5-en-20-one (6b)

To 2.00 g (6.32 mmol) *Pregnenolone* in 40 mL, 95% ethanol (0.71g, 12.64 mmol) KOH were added and stirred until cleared solution is obtained, 0.7 mL (7.58 mmol, 1.17 g/mL, 90%) 2-thiophenecarboxaldehyde were added with continuous stirring for 3 h at room temperature. After the completion of the reaction, the yellow colored reaction mixture was precipitated under ice water and the precipitate were filtered off washed with water and dried. The dried compound was crystallized from ethanol and were obtained as milk powder (77.2%, mp 115-118 ^{o}C).

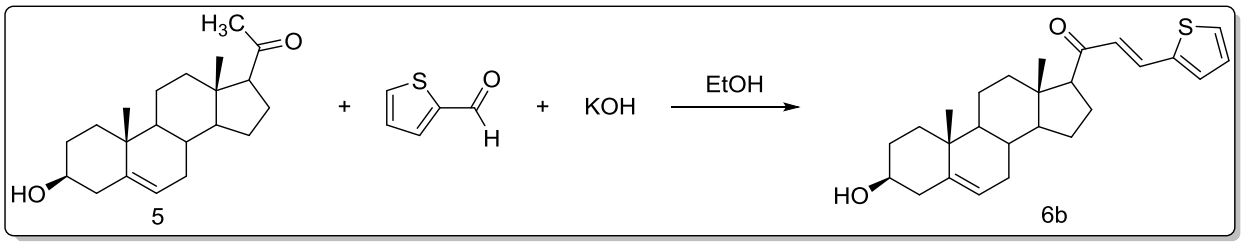


Figure 3.19 Synthesis of 21*(E)*-3*β*-hydroxy-21-(2-thiophenylidene) pregn-5-en-20-one (6b)

3.3.3 Synthesis of 21*(E)*- 3*β*-hydroxy-21-(2-pyridinylidene) pregn-5-en-20-one (6c)

To 2.00 g (6.32 mmol) *Pregnenolone* in 40 mL, 95% ethanol 0.71 g (12.64 mmol) KOH were added and stirred until cleared solution is obtained, 0.73 mL, (7.58 mmol, 1.13 g/mL, 99%) 2-pyridinecarboxaldehyde were added with continuous stirring for 3 h at room temperature. After the completion of the reaction, the yellow colored reaction mixture was precipitated under ice water and the precipitate were filtered off washed with water and dried. The dried compound was crystallized from ethanol and were obtained as white solid (78.1%, mp 115-118 ^{o}C).

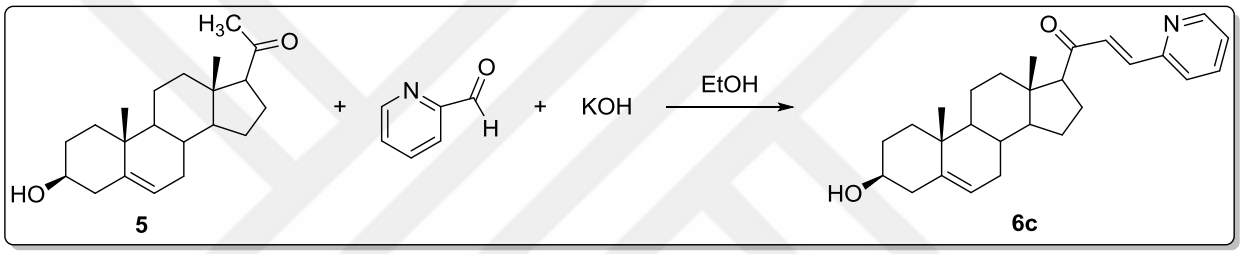


Figure 3.20 Synthesis of 21*(E)*- 3*β* - hydroxy-21-(2-pyridinylidene) pregn-5-en-20-one (6c)

3.3.4 Synthesis of 21*(E)*- 3*β* - acetoxy-21-(3-pyridinylidene) pregn-5-en-20-one (7a)

To a solution of **6a** 2.00 g (4.93 mmol) in 10 mL, (978 mg/mL, 99%) pyridine, 5 mL, (51.24 mmol, 1.08 g/mL, 98.5%) acetic anhydride was added in a round bottom flask and sealed. The mixture was heated in a steam bath for 2 h. The reaction mixture changes from yellow to brown, the brown solution were precipitated in ice water and ammonia solution were added drop wise until pH is 7, the precipitate obtained were filtered off washed with water and dried. The crude product was purified from chloroform and were obtained as light brown solid (90.5%, mp 170-174 ^{o}C).

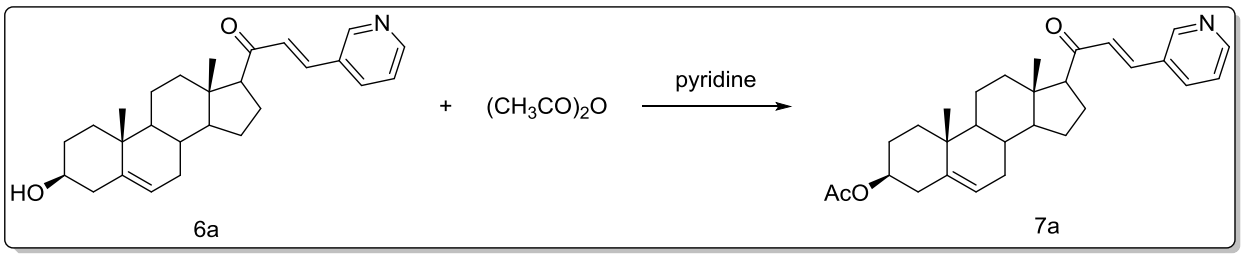


Figure 3.21 Synthesis of 21*(E)*- 3*β*-acetoxy-21-(3-pyridinylidene) pregn-5-en-20-one (7a)

3.3.5 Synthesis of 21*(E)* - 3*β*-acetoxy-21-(2-thiophenylidene) pregn-5-en-20-one (7b)

To a solution of **6b** 2.00 g (4.87 mmol) in 10 mL (978 mh/mL, 99%) pyridine, 5 mL (50.61 mmol, 1.08 g/mL, 98.5%) acetic anhydride was added in a round bottom flask and sealed. The mixture was heated in a steam bath for 2 h. The reaction mixture changes from yellow to brown, the brown solution were precipitated in ice water and ammonia solution were added drop wise until pH is 7, the precipitate obtained were filtered off washed with water and dried. The crude product was purified from chloroform and were obtained as milk powder (90.9%, mp173-176 ^{o}C).

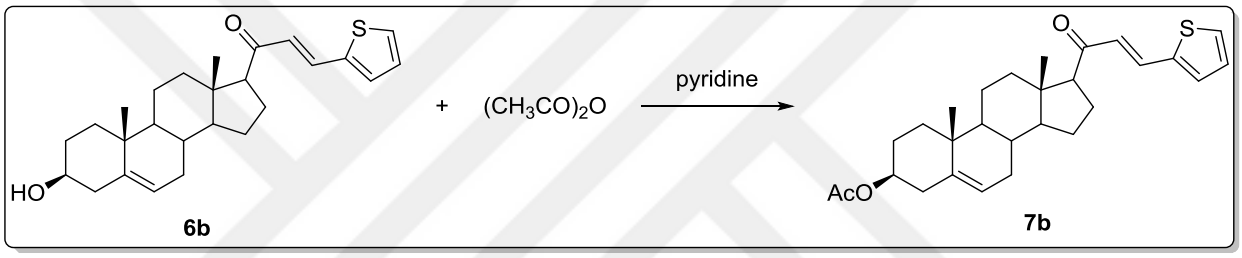


Figure 3.22 Synthesis of 21*(E)*- 3*β* - acetoxy-21-(2-thiophenylidene) pregn-5-en-20-one (7b)

3.3.6 Synthesis of 21*(E)*- 3*β*-acetoxy-21-(2-pyridinylidene) pregn-5-en-20-one (7c)

To a solution of **6c** 1.00 g (2.47 mmol) in 5 mL (978 g/mL, 99%) pyridine, 2.5 mL (25.62 mmol, 1.08 g/mL, 98.5%) acetic anhydride was added in a round bottom flask and sealed. The mixture was heated in a steam bath for 2 h. The reaction mixture changes from yellow to brown, the brown solution were precipitated in ice water and ammonia solution were added drop wise until pH is 7, the precipitate obtained were filtered off washed with water and dried. The crude product was purified from chloroform and were obtained as white solid (90.9%, 179-183 ^{o}C).

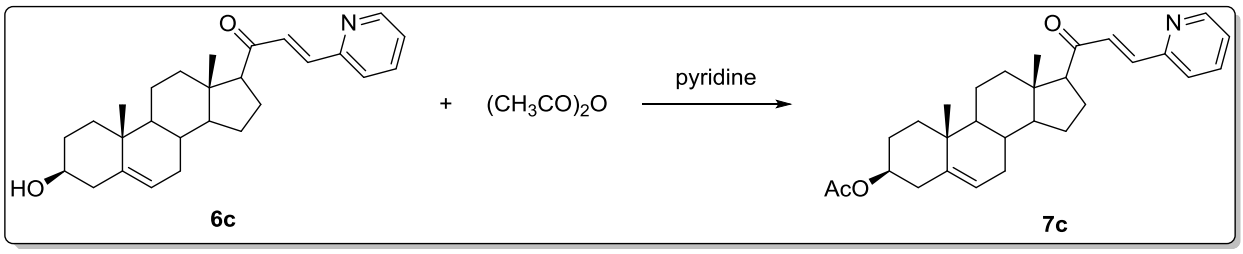


Figure 3.23 Synthesis of 21*(E)*- *3β* - acetoxy-21-(2-pyridinylidene) pregn-5-en-20-one (7c)

3.3.7 Synthesis of 3β-acetoxy-17β-(1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (8a)

To a solution of **7a** 0.5 g (1.12 mmol) in 23 mL 99.8% acetic acid, 1.1 mL (11.17 mmol, 1.03 g/mL, 50%) hydrazine hydrate was added and heated at reflux for 2 h, the reaction progress was monitored by TLC. Upon the completion of the reaction, the reaction mixture changes from yellow colored to purple. The reaction mixture was precipitated in ice water and ammonia solution were added drop wise until pH is 7, the precipitate was filtered off washed with water and dried. The crude product was crystallized from ethanol and were obtained as purple powder (88.8%, mp 75-79 ^{o}C)**.**

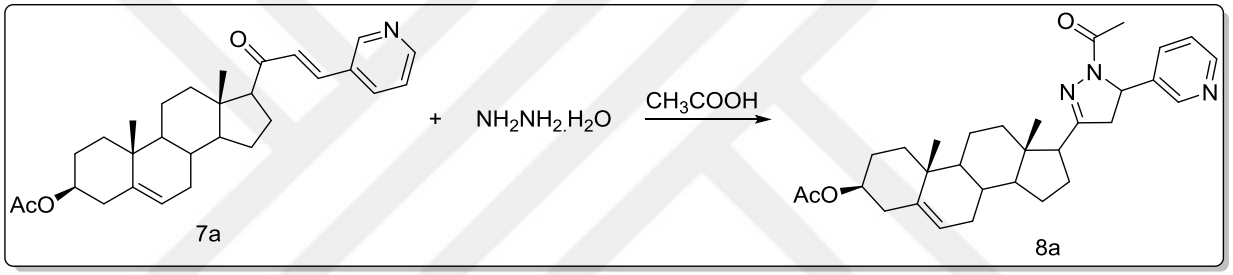


Figure 3.24 Synthesis of 3β-acetoxy-17β-(1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-en-3β-ol (8a)

3.3.8 Synthesis of 3β-acetoxy-17β-(1-Acetyl-5-(2-thiophenyl)-3-pyrazolinyl) androat-5-ene (8b)

To a solution of **7b** 0.5 g (1.10 mmol) in 23 mL, 99.8% acetic acid 1.1 mL (11.05 mmol, 1.03 g/mL, 50%) hydrazine hydrate was added and heated at reflux for 2 h, the reaction progress was monitored by TLC. Upon the completion of the reaction, the reaction mixture changes from yellow to orange. The reaction mixture was precipitated in ice water and the precipitate were filtered off washed with water and dried. The crude product was crystallized from ethanol and were obtained as white solid (89.0%, mp 79-82 ^{o}C).

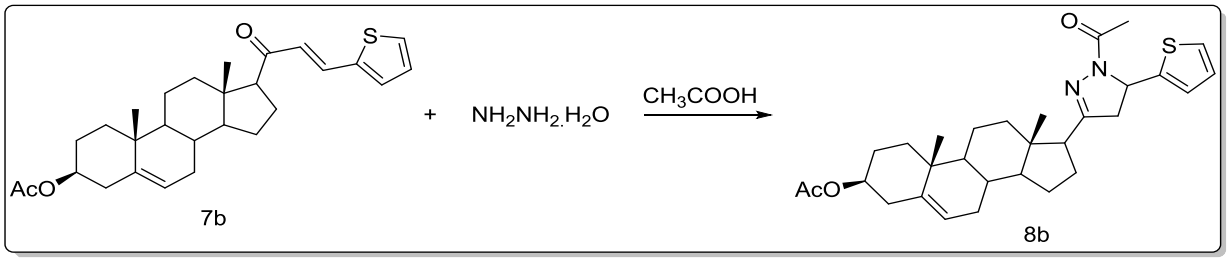


Figure 3.25 Synthesis of 3β-acetoxy-17β-(1-Acetyl-5-(2-thiophenyl)-3-pyrazolinyl) androat-5-en-3β-ol (8b)

3.3.9 Synthesis of 3β-acetoxy-17β-(1-Acetyl-5-(2-pyridinyl)-3-pyrazolinyl) androat-5-ene (8c)

To a solution of **7c** 0.35 g (0.782 mmol) in 16 mL, 99.8% acetic acid 0.76 mL (7.82 mmol, 1.03 g/mL, 50) hydrazine hydrate were added and heated at reflux for 2 h, the reaction progress was monitored by TLC. Upon the completion of the reaction, the reaction mixture changes from yellow colored to purple. The reaction mixture was precipitated under ice water and the precipitate were filtered off washed with water and dried. The dried compound was crystallized from ethanol and were obtained as purple powder (88.8%, mp 68-72 ^{o}C).

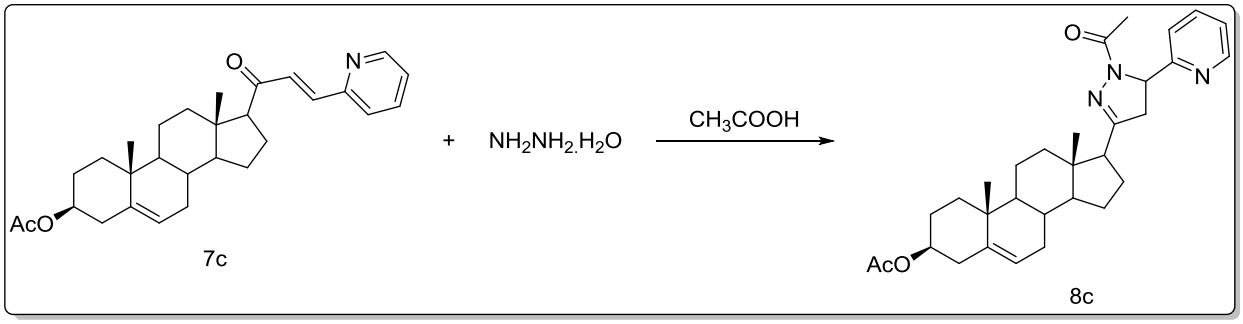


Figure 3.26 Synthesis of 3β-acetoxy-17β-(1-Acetyl-5-(2-pyridinyl)-3-pyrazolinyl) androat-5-en-3β-ol (8c)

3.3.10 Synthesis of 3β-acetoxy-17β-(-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (9a)

0.5 g (1.12 mml) **7a** in 20 mL, 99.8% absolute ethanol, 0.21 g (2.23 mmol) thiosemicarbazide were treated with 0.11 g (2.79 mmol) sodium hydroxide in 10 mL ethanol. The mixture was heated at reflux for about 5 h, the reaction mixture changes from brown to deep yellow and the reaction were monitored by IR. The deep yellow solution was kept in refrigerator for 1day, a pale brown precipitate was formed and filtered off. Then the filtrate was precipitated in ice water, the precipitate was filtered off washed with cold mixture of water and ethanol and dried. The crude product was purified from ethanol and were obtained as white shiny crystals (85.9%, mp 269 – 270.5 ^{o}C).

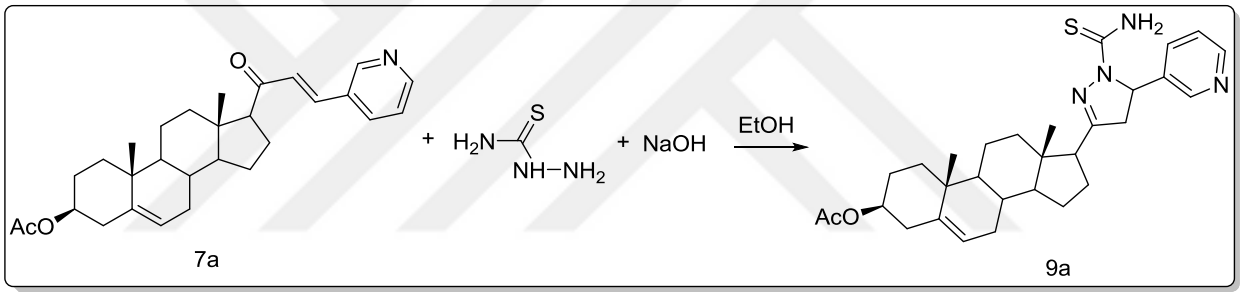


Figure 3.27 Synthesis of 3β-acetoxy-17β-(-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (9a)

3.3.11 Synthesis of 3β-acetoxy-17β-(-1-carbothioamide-5-(2-thiophenyl)-3-pyrazolinyl) androat-5-ene (9b)

0.5 g (1.10 mmol) **7b** in 20 mL, 99.8% absolute ethanol, 0.21 g (2.21 mmol) thiosemicarbazide were treated with 0.11 g (2.76 mmol) sodium hydroxide in 10 mL ethanol. The mixture was heated at reflux for about 5 h, the reaction mixture changes from yellow to orange and the reaction were monitored by IR. The solution was kept in refrigerator for 1day, a little precipitate was formed and filtered off. Then the filtrate was precipitated in ice water, the precipitate was filtered off washed with cold mixture of water and ethanol and dried. The crude product was purified from ethanol and were obtained as white liquid (86.1% [*oily*]).

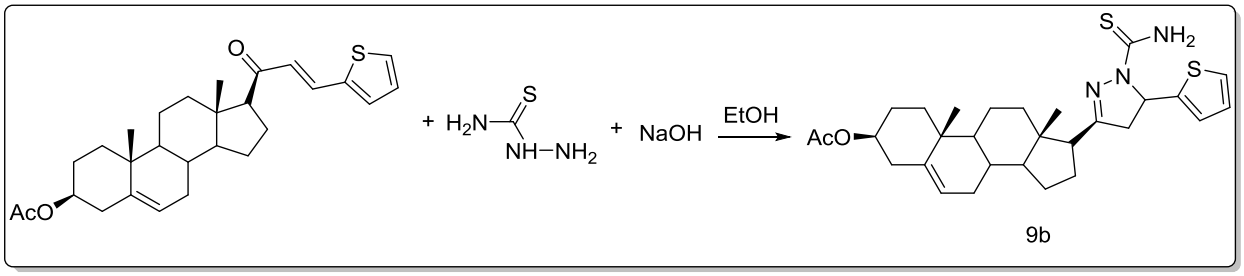


Figure 3.28 Synthesis of 3β-acetoxy-17β-(-1-carbothioamide-5-(2-thiophenyl)-3-pyrazolinyl) androat-5-ene (9b)

3.3.12 Synthesis of 3β-acetoxy-17β-(-1-carbothioamide-5-(2-pyridinyl)-3-pyrazolinyl) androat-5-ene (9c)

0.5 g (1.12 mmol) **7c** in 20 mL, 99.8% absolute ethanol, 0.21 g (2.23 mmol) thiosemicarbazide were treated with 0.11 g (2.79 mmol) sodium hydroxide in 10 mL ethanol. The mixture was heated at reflux for about 5 h, the reaction was monitored by IR. The solution was kept in refrigerator for 1day, a little precipitate was formed and filtered off. Then the filtrate was precipitated in ice water, the precipitate was filtered off washed with cold mixture of water and ethanol and dried. The crude product was purified from ethanol and were obtained as white shiny crystals (85.9%, mp 266-268 ^{o}C).

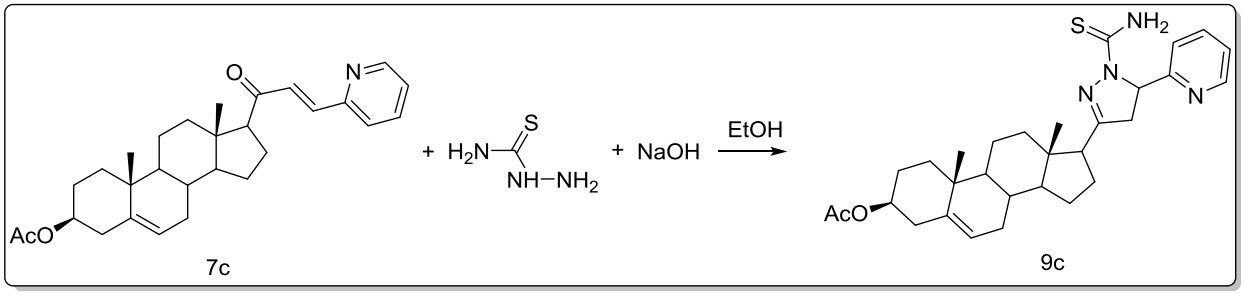


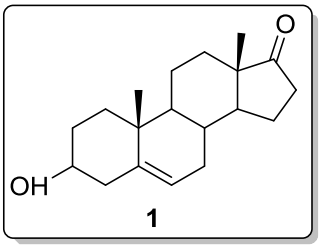
Figure 3.29 Synthesis of 3β-acetoxy-17β-(-1-carbothioamide-5-(2-pyridinyl)-3-pyrazolinyl) androat-5-ene (9c)

4. RESULTS

All the ^{1}H-NMR and ^{13}C-NMR spectrum were taken in CCl_3D else specified. IR spectrum were taking with PERKIN ELMER Spectrum Two on ATR unit. Characterization of infrared spectrum, NMR spectrum, melting point and percentage yields of all synthesized compounds in this thesis are given in this chapter below. The appendix section contain the spectral data of all the synthesized compounds.

4.1 Characterization of 3β-hydroxyandrost-5-en-17-one (1)

All the synthesized compounds in this thesis are derived from 3β-hydroxyandrost-5-en-17-one *(DHEA)* and *Pregnenolone,* IR, ^{1}H-NMR and ^{13}C-NMR spectrum of this derivation material are given in **Figure (4.1-4.3).** Investigating the ^{1}H-NMR and ^{13}C-NMR of **1**, showed a complexity in the spectra as such it is difficult to analyses all the peaks, so here only the clearly seen peaks will be studied.



Melting Point: 148.5^{O}C

Chemical Formula: $C_{19}H_{28}O_2$

Molecular Weight: 288.43

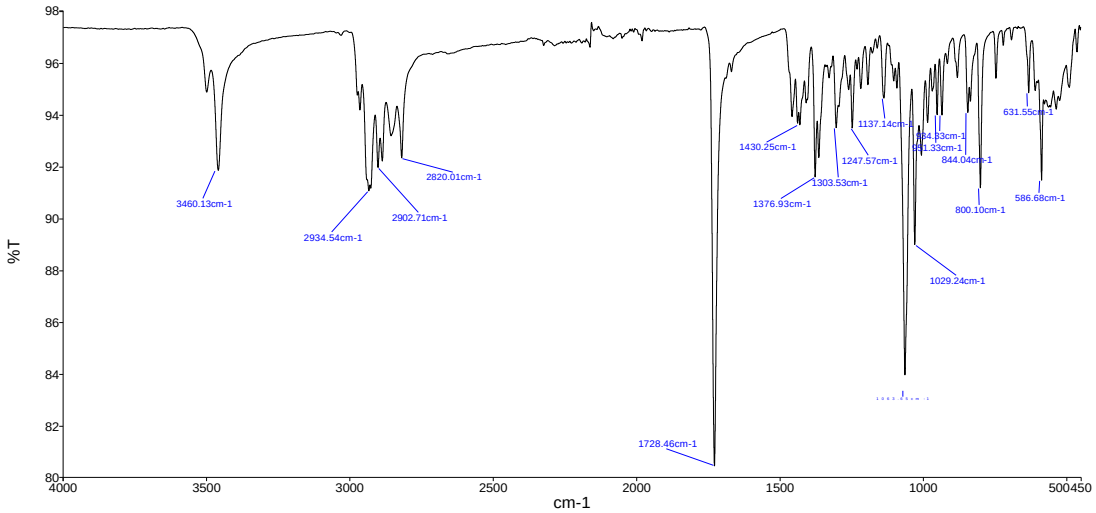


Figure 4.1 Infrared spectrum of 3β-hydroxyandrost-5-en-17-one

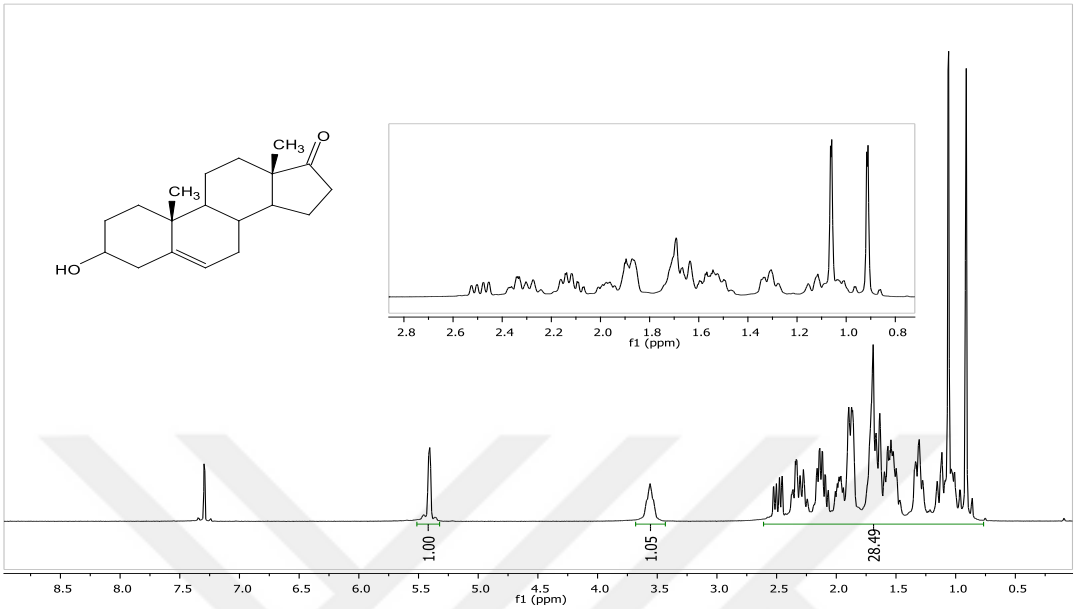


Figure 4.2 ^{1}H-NMR spectrum of 3β-hydroxyandrost-5-en-17-one

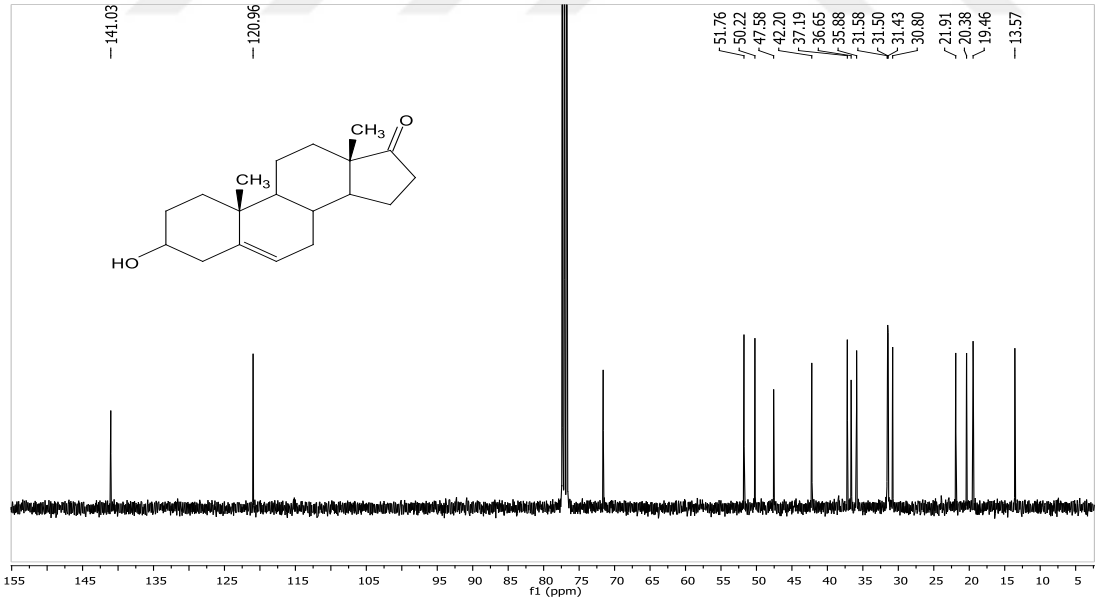
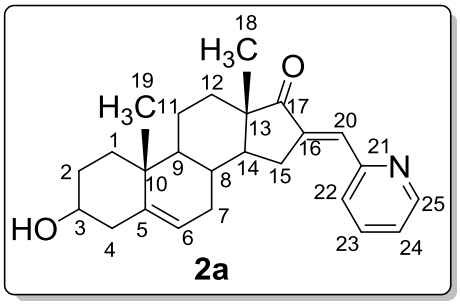


Figure 4.3 ^{13}C-NMR spectrum of 3β-hydroxyandrost-5-en-17-one

4.2 Characterization of 16*(E)* - 16-(2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2a)



2a

Melting Point: 164-167^{O}C

% Yield: 76.3%

Chemical Formula: $C_{25}H_{31}NO_2$

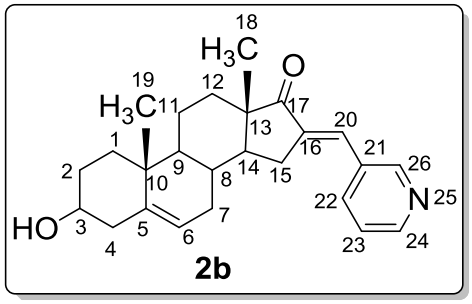
Molecular Weight: 377.53

IR (ATR, cm^{-1}): 3261.70 (stretching vibration, 3β-hydroxyl OH), 2929.10 (stretching vibration, aliphatic C-H), 1706.20 (stretching vibration, C=O, D ring ketone), 1613.02 (stretching vibration, C=N, pyridine ring), 1417.69 (stretching vibration, aromatic C=C), 1047.45 (stretching vibration, C-O, C_3), 1093.44 (stretching vibration, C-N).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.99 (s, 3H, CH_3-18), 1.08 (s, 3H, CH_3- 9), 2.55 - 1.35 (m, 15H, aliphatic CH and CH_2 steroid ring), 3.33 (d, *J* = 19.1 Hz, 1H, CH-15), 3.55 (s, 1H, CH-3), 5.41 (d, *J* = 5.2 Hz, 1H, endocyclic CH–6 proton), 7.34–7.22 (m, 1H, CH-24), 7.55 – 7.34 (m, 2H, CH-22 and CH-23), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H, CH-20), 8.73 (s, 1H, CH-25).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.23 (CH_3-18), 19.50 (CH_3-19), 20.45 (CH_2-11), 30.74 (CH_2-15), 30.97 (CH_2-7), 31.21 (CH_2-12), 31.56 (CH_2-2), 32.63 (CH-8), 36.72 (CH_2-1), 37.16 (C-10), 42.21 (C-4), 49.53 (C-14), 50.07 (C-13), 50.34 (C-9), 71.56 (C-3), 121.00 (C-6), 122.86 (C-24), 126.63 (C-22), 136.35 (C-20), 140.23 (C-23), 141.04 (C-5), 148.96 (C-16), 149.94 (C-25), 154.94 (C-21), 210.32 (C-17).

4.3 Characterization of 16*(E)* - 16-(3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2b)



2b

Melting Point: 251-254^{O}C

% Yield: 76.4%

Chemical Formula: $C_{25}H_{31}NO_2$

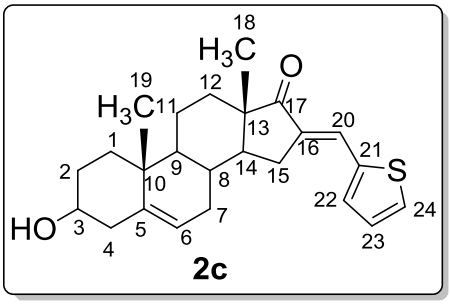
Molecular Weight: 377.53

IR (ATR, cm^{-1}): 3308.14 (stretching vibration, 3β-hydroxyl OH), 2917.17-2829.74 (stretching vibration, aliphatic C-H), 1717.15 (stretching vibration, C=O, D ring ketone), 1631.60 (stretching vibration, C=N, pyridine ring), 1569.03 (stretching vibration, aromatic C=C), 1071.90 (stretching vibration, C-O, C_3), 1056.47 (stretching vibration, C-N).

^{1}H-NMR: 400 MHz, $CDCl_3$ - d) δ 1.02 (s, 3H, CH_3-18), 1.10 (s, 3H, CH_3-19), 2.53 - 1.42 (m, 16H, aliphatic, CH and CH_2 steroid ring), 2.90 (dd, *J* = 15.9, 6.3 Hz, 1H, CH-9), 3.57 (dd, *J* = 15.2, 10.8 Hz, 1H, CH-3), 5.42 (s, 1H, endocyclic CH–6 proton), 7.43 (dd, *J* = 10.8, 5.9 Hz, 2H, CH-20 and 23), 7.86 (d, *J* = 7.8 Hz, 1H, CH-22), 8.61 (d, *J* = 4.6 Hz, 1H, CH-24), 8.82 (d, *J* = 19.2 Hz, 1H, CH-26). Solvent peak at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.22 (C-18), 19.50 (C-19), 20.39 (C-11), 29.42 (C-15), 30.91 (C-7), 31.19 (C-12), 31.56 (C-2), 32.89 (C-8), 36.73 (C-1), 37.1 3 (C-10), 42.23 (C- 4), 49.73 (C- 14), 50.07 (C-13), 50.27 (C-9), 71.55 (C-3), 120.75 (C-6), 123.62 (C-23), 129.32 (C-20), 131.54 (C-21), 136.86 (C-22), 138.20 (C-5), 141.20 (C-16), 149.70 (C-24), 151.21 (C-26), 209.04 (C-17).

4.4 Characterization of 16*(E)* - 16-(2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2c)



2c

Melting Point: 220-222^{o}C

%Yield: 75.2%

Chemical Formula: $C_{24}H_{30}O_2S$

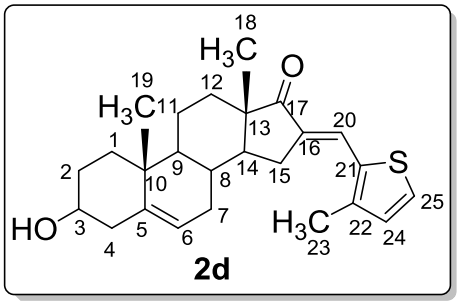
Molecular Weight: 382.56

IR (ATR, cm^{-1}): 3268.30 (stretching vibration, 3β-hydroxyl OH), 2931.30-2857.20 (stretching vibration, aliphatic C-H), 1718.58 (stretching vibration, C=O, D ring ketone), 1585.33 (stretching vibration, aromatic C=C), 1059.09 (stretching vibration, C-O, C_3), 1007.96 (stretching vibration, C-S).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.98 (s, 3H, CH_3-18), 1.10 (s, 3H, CH_3-19), 2.48 – 1.14 (m, 15H, aliphatic, CH and CH_2 steroid ring), 3.02 – 2.79 (m, 1H, CH-9), 3.57 (d, *J* = 4.5 Hz, 1H, CH-3), 3.86 – 3.66 (m, 2H, CH-15), 5.46 (d, *J* = 20.0 Hz, 1H, endocyclic CH – 6 proton), 7.17 – 7.11 (m, 1H, CH-23), 7.50 – 7.31 (m, 1H, CH -20), 7.53 (t, *J* = 9.9 Hz, 1H, CH-24), 7.65 – 7.55 (m, 1H, CH-22). Solvent peak appear at 7.29ppm.

. **^{13}C-NMR:** (100 MHz, $CDCl_3$ - d) δ 14.42 (C-18), 19.50 (C-19), 20.42 (C-11), 29.08 (C-15), 30.96 (C-7), 31.05 (C-2), 31.55 (C-8), 36.75 (C-1), 37.14 (C-10), 42.22 (C-4), 47.76 (C-14), 49.61 (C-13), 50.35 (C-9), 71.60 (C-3), 120.87 (C-6), 125.85 (C-20), 127.93 (C-23), 129.74 (C-22), 132.38 (C-24), 133.68 (C-21), 139.97 (C-16), 141.18 (C-5), 209.58 (C-17).

4.5 Characterization of 16*(E)* - 16-(3-methyl-2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2d)



2d

Melting Point: 213-216^{o}C

%Yield: 72.9%

Chemical Formula: $C_{25}H_{32}O_2S$

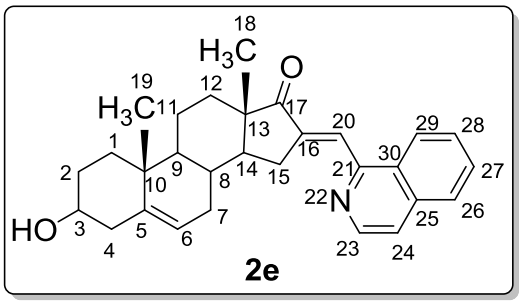
Molecular Weight: 396.59

IR (ATR, cm^{-1}): 3426.30 (stretching vibration, 3β-hydroxyl OH), 2927.80 (stretching vibration, aliphatic C-H), 1694.14 (stretching vibration, C=O, D ring ketone), 1595.49 (stretching vibration, aromatic C=C), 1057.09 (stretching vibration, C - O, C_3), 1091.70 (stretching vibration, C - S).

^{1}H-NMR: NMR (400 MHz, $CDCl_3$ - d) δ0.94 (s, 3H, CH_3-18), 1.06 (s, 3H, CH_3-19), 2.27-1.39 (m, 15H, aliphatic, CH and CH_2 steroid ring), 2.39 (s, 3H, CH_3-23), 2.87 (m, 2H, CH_2-15), 3.54 (m, 1H, CH-3), 5.40 (d, *J* = 3.5 Hz, 1H, endocyclic CH–6 proton), 6.95 (m, 1H, CH-24), 7.43 (m, 1H, CH-20), 7.69 (d, *J* = 20.0 Hz, 1H, CH-25).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.43 (C-23), 14.48 (C-18), 19.50 (C-19), 20.41 (C-11), 30.72 (C-15), 31.11 (C-7), 31.50 (C-12), 31.57 (C-2), 36.74 (C-1), 37.16 (C-10), 42.16 (C-4), 47.72 (C-14), 49.67 (C - 13), 50.01 (C-9), 71.45 (C-3), 120.79 (C-6), 128.37 (C-24), 130.79 (C-25), 132.46 (C-20), 133.80 (C-21), 141.26 (C-16 and C-5), 142.32 (C- 22), 209.92 (C-17).

4.6 Characterization of 16*(E)* - 16-(2-quinolinyliden)-3β-hydroxyandrost-5-en-17 one (2e)



2e

Melting Point: 212-215^{o}C

%Yield: 67.6%

Chemical Formula: $C_{29}H_{33}NO_2$

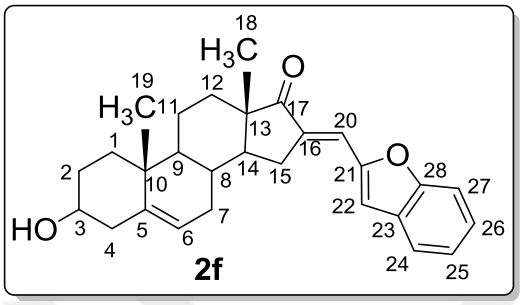
Molecular Weight: 427.59

IR (ATR, cm^{-1}): 3312.19 (stretching vibration, 3β-hydroxyl OH), 2933.24 (stretching vibration, aliphatic C-H), 1718.25 (stretching vibration, C=O, D ring ketone), 1636.31 (stretching vibration, C=N, quinoline ring), 1593.47 (stretching vibration, aromatic C=C), 1053.77 (stretching vibration, C-O, C_3). 1007.66 (stretching vibration, C-N).

^{1}H-NMR: ^{1}H NMR (400 MHz, $CDCl_3$ - d) δ 1.06 (s, 3H, CH3-18), 1.12 (s, 3H, CH_3-19), 2.70– 1.26 (m, 15H, aliphatic, CH and CH_2 steroid ring), 3.57 – 3.51 (m, 1H, CH-3), 3.76 – 3.43 (m, 2H, CH-15), 5.45 (m, 1H, endocyclic CH–6 proton), 7.59 (s, 1H, CH-20), 7.60 (m, 1H, C-28),), 7.61 (m, CH-24), 7.75 (m, 1H, CH–27), 7.77 (m, 1H, CH-26), 7.85 – 7.78 (m, 1H, CH-29), 8.21 – 8.14 (m, 1H, CH-23),

^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 14.29 (CH_3-18), 19.53 (CH_3-19), 29.97 (C-11), 31.28 (C-15), 31.567 (C-7), 31.61 C-13), 36.61 C-1), 37.16 (C-10), 42.25 (C-4), 47.76 (C-14), 49.52 (C-13), 50.35 (C-9), 71.65 (C-3), 120.88 (C-6), 121.03 (C-24), 123.65 (C-29), 127.15 (C-28), 127.54 (C-30), 129.84 (C-26), 129.88 (C-27), 131.01 (C-20), 136.26 (C-25), 141.08 (C-5), 148.15 (C-23), 155.04 (C-21), 209.94 (C-17).

4.7 Characterization of 16*(E)* – 16 - (2-benzofuranyliden) - 3β – hydroxyandrost - 5- en – 17 - one (2f)



Melting Point: 219-221^{o}C

%Yield: 74.6%

Chemical Formula: $C_{28}H_{32}O_3$

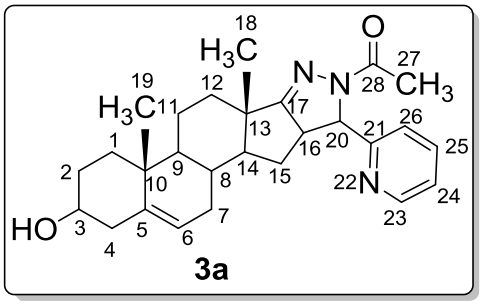
Molecular Weight: 416.56

IR (ATR, cm^{-1}): 3312.4 (stretching vibration, 3β-hydroxyl OH), 2933.2 (stretching vibration, aliphatic C-H), 1718.2 (stretching vibration, C=O, D ring ketone), 1636.3 (stretching vibration, C=N, quinoline ring), 1593.5 (stretching vibration, aromatic C=C).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ1.00 (s, 3H, CH_3-18), 1.11 (s, 3H, CH_3-19), 2.53-1.27 (m, 15H, aliphatic, CH and CH_2 steroid ring), 3.25 (d, *J* = 17.0 Hz, 2H, CH-15), (s, 1H, CH-3), 5.46 (m, 1H, endocyclic CH-6 proton), 7.01 (s, 1H, CH-25), 7.29 (1H, CH-26 coincides with solvent peak), 7.33 (m, 1H, CH-22), 7.38 (ddd, *J* = 16.2, 7.6, 1.6 Hz, 1H, CH-27), 7.53 (dd, *J* = 8.3, 0.7 Hz, 1H, CH-24), 7.64 (d, *J* = 7.5 Hz, 1H, CH-20),

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.35 (C-18), 18.46 (C-19), 20.44 (C-11), 29.26 (C-15), 31.01 (C-7), 31.20 (C-12), 31.52 (C-2), 31.59 (C-8), 36.75 (C-1), 37.15 (C-10), 42.23 (C-4), 47.56 (C - 14), 49.34 (C-13), 50.34 (C-9), 71.62 (C-3), 111.47 (C-22), 11I.88 (C-27), 119.94 (C-6), 120.95 (C-25), 121.64 (C-24), 123.34 (C-26), 126.03 (C-20), 128.36 (C-23), 141.13 (C-16 and C-5), 154.02 (C-21), 155.98 (C-28), 209.63 (C-17).

4.8 Characterization of 3β – hydroxyl - (1-Acetyl-5-(2-pyridinyl) - 16,17-pyrazolinyl) androst-5-ene (3a)



3a

Melting Point: 103-106^{o}C

%Yield: 87.1%

Chemical Formula: $C_{27}H_{35}N_3O_2$

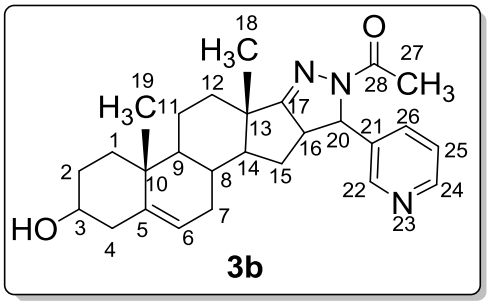
Molecular Weight: 433.60

IR (ATR, cm^{-1}): 3321.40 (stretching vibration, 3β-hydroxyl OH), 2937.93 (stretching vibration, aliphatic C-H), 1720.40 (stretching vibration, C=O, $\underline{CO}CH_3$), 1658.61 (stretching vibration, C=N), 1575.38 (stretching vibration, aromatic C=C), 1248.20 (stretching vibration, C-O, C_3), 1031.97 (stretching vibration, C-N).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.99 (s, 3H, CH_3-18), 1.00 (s, 3H, CH_3-19), 2.07 (s, 3H, CH_3-27), 2.43-1.11 (m, 17H, aliphatic, CH and CH_2 steroid ring), 3.65 – 3.32 (m, 1H, CH-3), 4.13 (m, 1H, CH - 9), 4.54 (m, 1H, CH-20), 5.45 (d, *J* = 5.1 Hz, 1H, endocyclic CH-6 proton), 7.23 (m, 1H, CH-24), 7.46 (m, 1H, CH-26), 7.73 (m, 1H, CH-25), 8.65 (ddd, *J* = 9.1, 4.9, 2.5 Hz, 1H, CH-23) Solvent peak appears at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ14.22 (C-18), 19.40 (C-19), 20.39 (C-20), 21.47 (C-25), 27.70 (C-15), 30.95 (C-7), 31.17 (C-2), 31.25 (C-8), 31.49 (C-12), 36.79 (C-1), 3.89 (C-10), 38.09 (C-4), 48.63 (C-13), 49.45 (C-16), 49.64 (C-9), 50.24 (C-14), 73.85 (C-3), 121.56 (C-24), 122.01 (C-6), 126.67 (C-26), 139.74 (C-25), 140.90 (C-5), 149.94 (C-23), 154.95 (C-21), 170.59 (C-17), 210.84 (C-28).

4.9 Characterization of 3β – hydroxyl - (1-Acetyl-5-(3-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (3b)



3b

Melting Point: 195-198^{o}C

%Yield: 87.1%

Chemical Formula: $C_{27}H_{35}N_3O_2$

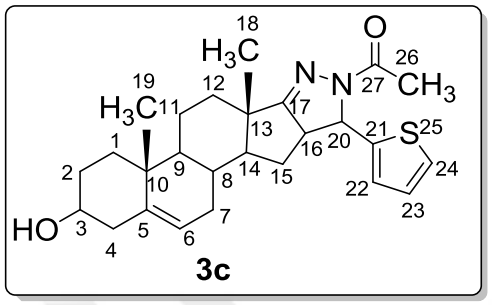
Molecular Weight: 433.60

IR (ATR, cm^{-1}): 3420.23 (stretching vibration, 3β-hydroxyl OH), 2940.55-2854.08 (stretching vibration, aliphatic C-H), 1727.70 (stretching vibration, C=O, $\underline{CO}CH_3$), 1633.98 (stretching vibration, C=N), 1586.45 (stretching vibration, aromatic C=C), 1248.47 (stretching vibration, C-O, C_3), 1032.31 (stretching vibration, C-N).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.61 (s, 3H, CH_3-18), 1.04 (s, 3H, CH_3-19), 2.17 – 1.08 (m, 17H, aliphatic, CH and CH_2 steroid ring), 2.21 (s, 3H, CH_3–27), 3.43 (m, 1H, CH-3), 4.14 – 3.85 (m, 1H, CH-16), 5.37 (s, 1H, endocyclic CH-6), 7.34 (m, 1H, CH-20), 7.98 (m, 1H, CH-25), 8.65 (d, *J* = 3.4 Hz, 1H, CH-24), 8.87 (d, *J* = 43.6 Hz, 1H, CH-22). Solvent peak appears at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 12.32 (C-18), 14.22 (C-11), 19.41 (C-19), 21.67 (C-27), 27.66 (C-15), 30.86 (C-12), 31.65 (C-1), 38.76 (C-10), 42.19 (C-4), 45.85 (C-13), 49.13 (C-9), 49.63 (C-14), 54.75 (C-16), 71.61 (C-20), 72.85 (C-3), 120.78 (C -6), 123.66 (C-25), 133.88 (C-21), 136.83 (C-26), 141.18 (C -5), 148.20 (C-24), 150.66 (C-22), 169.51 (C-17), 209.20 (C-28).

4.10 Characterization of 3β – hydroxyl - (1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (3c)



3c

Melting Point: 143-146^{o}C

%Yield: 87.4%

Chemical Formula: $C_{26}H_{34}N_2O_2S$

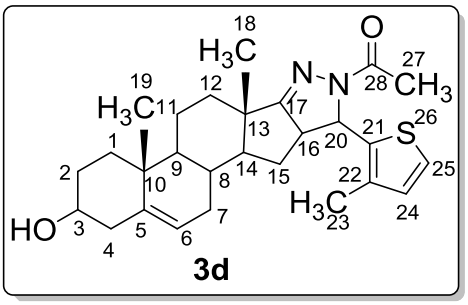
Molecular Weight: 438.63

IR (ATR, cm^{-1}): 3413.00 (stretching vibration, 3β-hydroxyl OH), 2932.60-2857.50 (stretching vibration, aliphatic C-H), 1709.21 (stretching vibration, C=O, $\underline{CO}CH_3$), 1616.37 (stretching vibration, C=N), 1453.04 (stretching vibration, aromatic C=C), 1240.55 (stretching vibration, C-O, C_3), 1055.43 (C-S).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.96 (s, 3H, CH_3-18), 1.10 (s, 3H, CH_3-19), 2.07 (s, 3H, CH_3-26), 2.39-1.11 (m, 17H, aliphatic CH and CH2 steroid protons), 3.43 (m,1H, CH-16), 3.52 (m, 1H, CH-3), 5.44 (m, 1H, endocyclic CH-6 proton), 7.16 (m, 1H, CH-22), 7.36 (d, *J* = 3.6 Hz, 1H, CH-23), 7.55 (d, *J* = 5.1 Hz, 1H, CH-24), 7.65 (s, 1H CH-20). Solvent peak appears at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.40 (C-18), 19.47 (C-11), 21.45 (C-26), 27.18 (C-15), 30.95 (C-7), 31.18 (C-2), 31.56 (C-8), 31.62 (C-12), 37.16 (C-1), 38.11 (C-10), 42.25 (C-4), 47.76 (C-14), 49.66 (C-14), 50.40 (C-16), 71.60 (C-20), 73.60 (C-3), 121.31 (C-6), 123.74 (C-22), 125.78 (C-23), 128.74 (C-24), 140.04 (C-5), 141.19 (C-21), 170.49 (C-17), 209.53 (C-27), 20.43 (C-19).

4.11 Characterization of 3β – hydroxyl - (1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (3d)



3d

Melting Point: *[oily]*).

%Yield: 87.7%

Chemical Formula: $C_{27}H_{36}N_2O_2S$

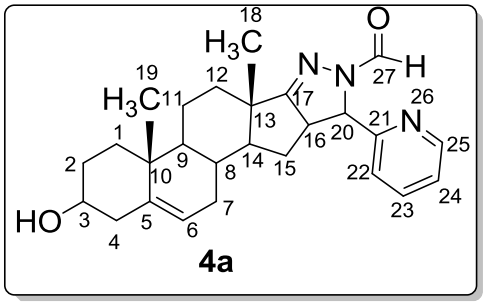
Molecular Weight: 452.66

IR (ATR, cm^{-1}): 3405.80 (stretching vibration, 3β-hydroxyl OH), 2933.31 (stretching vibration, aliphatic C-H), 1707.37 (stretching vibration, C=O, COCH_3), 1610.38 (stretching vibration, C=N), 1507.10 (stretching vibration, aromatic C=C), 1246.94 (stretching vibration, C-O, C_3), 1031.89 (stretching vibration, C-N), 1044.7 (stretching vibration, C-S).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.94 (s, 3H, CH_3-18), 1.07 (s, 3H, CH_3-19), 2.04 (s, 3H, CH_3-23), 2.35-1.24 (m, 16H, aliphatic CH and CH_2 steroid ring), 2.39 (s, 3H, CH_3-27), 2.87 (d, *J* = 6.5 Hz, 1H, CH-9), 3.71 (d, *J* = 7.0 Hz, 1H, CH-3), 4.75 – 4.47 (m, 1H, CH-16), 5.42 (dd, *J* = 14.4, 5.1 Hz, 1H, endocyclic CH-6 proton), 6.95 (d, *J* = 5.1 Hz, 1H, CH-20), 7.42 (d, *J* = 5.1 Hz, 1H, CH-24). Solvent peak appears at 7.69 ppm,

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.40 (CH_3-23), 1.38 (CH_3-18), 20.35 (CH_3-19), 21.45 (CH_3-27), 27.69 (C-15), 29.07 (C-7), 30.92 (C-2), 30.94 (C-8), 31.07 (C-12), 31.13 (C-10), 31.52 (C-1), 36.81 (C-4), 36.86 (C-13), 38.09 (C-10), 49.60 (C-14), 49.69 (C-16), 50.25 (C-20), 73.78 (C-3), 121.87 (C-6), 124.23 (C-25), 128.30 (C-24), 130.77 (C-21), 139.92 (C-22), 141.25 (C-5), 170.74 (C-17), 209.69 (C-28).

4.12 Characterization of 3β – hydroxyl - (1-Formyl-5-(2-pyridinyl)-16, 17-pyrazolinyl) androst-5-ene (4a)



4a

Melting Point: 230-233^{o}C

%Yield: 90%

Chemical Formula: $C_{26}H_{33}N_3O_2$

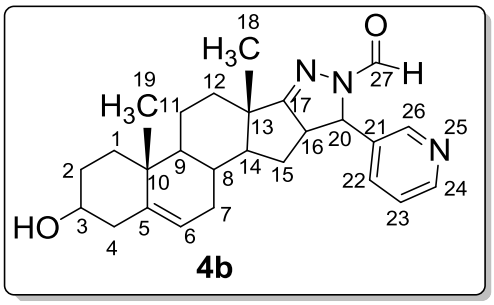
Molecular Weight: 419.57

IR (ATR, cm^{-1}): 3414.52 (stretching vibration, 3β-hydroxyl OH), 2967.70-2908.40 (stretching vibration, aliphatic C-H), 2855.12 (stretching vibration, C-H, aldehyde), 1715.80 (stretching vibration, C=O, aldehyde), 1630.82 (stretching vibration, C=N), 1581.87 (stretching vibration, aromatic C=C), 1193.45 (stretching vibration, C-O, C-3), 1082.22 (stretching vibration, C-N).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 1.02 (s, 3H, CH_3-18), 1.02 (s, 3H, CH_3-19), 2.54 (m, 1H, CH-16), 2.43-1.14 (m, 18H, aliphatic CH and CH_2 steroid ring), 3.34 (m, 1H, CH-3), 4.77 (ddd, *J* = 11.6, 10.1, 4.0 Hz, 2H, CH-20 and 3β-OH), 5.48 (d, *J* = 4.0 Hz, 1H, endocyclic CH-6 proton), 7.22 (m, 1H, CH-24), 7.46 (m, 1H, CH-22), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H, CH-23), 8.07 (d, *J* = 0.8 Hz, 1H, aldehyde proton), 8.73 (dd, *J* = 4.7, 1.0 Hz, 1H, CH-25).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.23 (CH_3-18), 19.41 (CH_3-19), 20.41 (C-11), 27.70 (C-15), 29.75 (C-7), 30.97 (C-2), 31.17 (C–8), 31.50 (C–12), 36.79 (C–61), 36.84 (C–10), 38.04 (C–4 and C-13), 47.46 (C-9), 49.47 (C–14), 50.23 (C–16), 73.72 (C-20), 75.75 (C-3), 122.37 (C-24), 122.86 (C-6), 126.72 (C–22), 136.37 (C-23), 149.94 (C–5), 149.94 (C–25), 154.97 (C–21), 160.66 (C-27), 210.21 (C-17).

4.13 Characterization of 3β – hydroxyl - (1-Formyl-5-(3-pyridinyl)-16,17-pyrazolinyl) androst-5-ene (4b)



4b

Melting Point: 226-228^{o}C

%Yield: 90%

Chemical Formula: $C_{26}H_{33}N_3O_2$

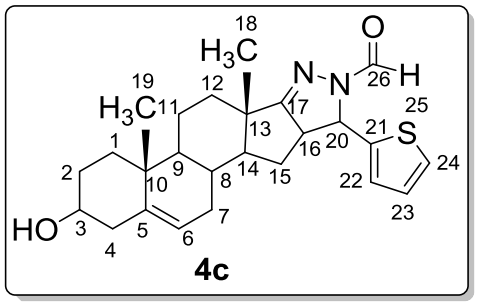
Molecular Weight: 419.57

IR (ATR, cm^{-1}): 3321.00 (stretching vibration, 3β-hydroxyl OH), 2942.01 (stretching vibration, aliphatic C-H), 1714.74 (stretching vibration, C=O, aldehyde), 1632.54 (stretching vibration, C=N), 1565.39 (stretching vibration, aromatic C=C), 1164.98 (stretching vibration, C-O, C-3), 1095.41 (stretching vibration, C-N).

^{1}H-NMR: 400 MHz, $CDCl_3$ -d) δ 0.96 (s, 3H, CH_3–18), 1.09 (s, 3H, CH_3-19), 2.57–1.17 (m, 17H, aliphatic CH and CH_2 steroid ring), 2.88 (m, 1H, CH–16), 3.55 (ddd, *J* = 19.4, 12.0, 6.4 Hz, 1H, CH-3), 4.75 (d, *J* = 8.6 Hz, 1H, CH-20), 5.41 (m, 1H, endocyclic CH-6), 7.41 (m, 1H, CH-23), 7.84 (d, *J* = 8.0 Hz, 1H, CH-22), 8.05 (d, *J* = 0.8 Hz, 1H, aldehyde proton), 8.58 (d, *J* = 4.4 Hz, 1H, CH-24), 8.80 (s, 1H, CH-26), solvent peak appears at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 19.39 (C-18), 19.50 (C–11), 20.33 (C-19), 27.72 (C-15), 30.90 (C–7), 31.18 (C-2), 31.50 (C-8), 36.73 (C-12), 36.78 (C-1), 37.14 (C-10), 42.25 (C–4), 49.64 (C– 13), 49.72 (C-9), 50.13 (C–14), 50.27 (C–C16), 71.44 (C-20), 73.62 (C–3), 120.67 (C-6), 123.66 (C-23), 131.55 (C-21), 136.83 (C-22), 141.28 (C-5), 149.64 (C-24), 151.13 (C-26), 160.64 (C- 27), 209.01 (C-17).

4.14 Characterization of 3β – hydroxyl - (1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst – 5 - ene (4c)



4c

Melting Point: 230-233.5^{o}C

%Yield: 90%

Chemical Formula: $C_{25}H_{32}N_2O_2S$

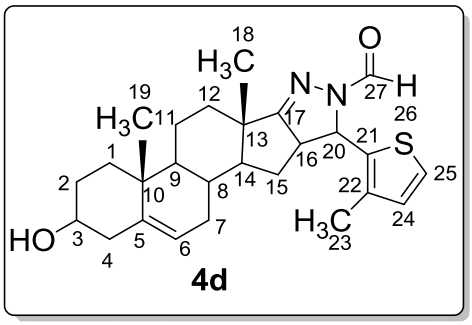
Molecular Weight: 424.60

IR (ATR, cm^{-1}): 3106.20 (stretching vibration, 3β-hydroxyl OH), 2943.27 (stretching vibration, aliphatic C-H), 1711.59 (stretching vibration, C=O, aldehyde), 1617.97 (stretching vibration, C=N), 1443.84 (stretching vibration, aromatic C=C), 1185.57 (stretching vibration, C-O, C-3), 1093.00 (stretching vibration, C-N), 1010.09 (stretching vibration, C-S).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.97 (s, 3H, CH_3-18), 1.06 (s, 3H, CH_3-19), 2.37–1.15 (m, 17H, aliphatic CH and CH_2 steroid ring), 2.90 (ddd, *J* = 16.1, 6.6, 1.7 Hz, 1H, CH-16), 3.50 (s, 1H, CH-3), 4.76 (m, 1H, CH-20), 5.47 (s, 1H, endocyclic CH-6), 7.14 (dd, *J* = 5.1, 3.7 Hz, 1H, CH-22), 7.35 (d, *J* = 3.5 Hz, 1H, CH-23), 7.53 (d, *J* = 5.1 Hz, 1H, CH-24), 8.06 (s,1H, aldehyde proton), solvent peak appears at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.42 (C-18), 19.40 (C-11), 20.37 (C-19), 27. 69 (C–15) 29.05 (C-7), 30.93 (C-7), 3.08 (C–2), 31.47 (C–8 and C-12), 36.81 (C–1 and C-10), 38.04 (C-4), 47.71 (C-13), 49.52 (C–9 and C–14), 50.22 (C-16), 73.68 (C–3 and C-20), 122.17 (C-6), 125.86 (C-22), 127.94 (C-23), 129.75 (C-24), 139.70 (C-5), 160.64 (C-26), 209.33 (C-17).

4.15 Characterization of 3β - hydroxy - (1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4d)



4d

Melting Point: 164-167^{o}C

%Yield: 90%

Chemical Formula: $C_{26}H_{34}N_2O_2S$

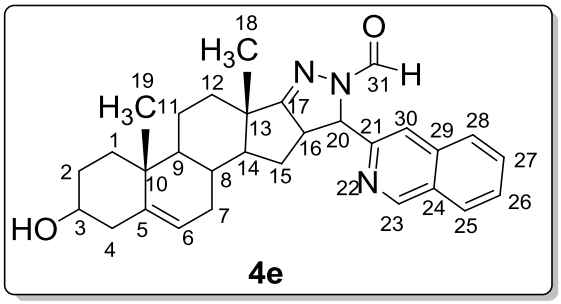
Molecular Weight: 438.63

IR (ATR, cm^{-1}): 3415.30 (stretching vibration, 3β-hydroxyl OH), 2940.71 (stretching vibration, aliphatic C-H), 1709.12 (stretching vibration, C=O, aldehyde), 1613.52 (stretching vibration, C=N), 1443.15 (stretching vibration, aromatic C=C), 1176.73 (stretching vibration, C-O, C-3), 1085.87 (stretching vibration, C-N), 1008.92 (stretching vibration, C-S).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.96 (s, 3H, CH_3-18), 1.10 (s, 3H, CH_3-19), 2.33 – 1.19 (m, 17H, aliphatic CH and CH_2 steroid ring), 2.42 (s, 3H, CH_3-23), 2.95 (m, 1H, CH-16), 3.56 (m, 1H, CH–3), 4.77 (s, 1H, 3β-OH), 5.48 (s, 1H, endocyclic CH-6), 6.97 (t, *J* = 6.2 Hz, 1H, CH-24), 7.44 (d, *J* = 5.1 Hz, 1H, CH-25), 8.07 (s, 1H, aldehyde proton).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ14.48 (C-23), 19.39 (C–18), 20.18 (C-11), 20.38 (C-19), 27.70 (C-15), 29.07 (C-7), 30.94 (C-2), 31.07 (C–8), 31.52 (C–12), 36.81 (C-1), 38.04 (C-10), 42.33 (C–4), 47.67 (C-13), 49.93 (C–9 and C-14), 50.24 (C–16), 71.57 (C-3), 122.23 (C-6), 124.20(C-25), 128.27 (C-21), 130.79 (C-24), 139.50 (C-5), 160.66 (C-27), 209.74 (C-17).

4.16 Characterization of 3β – hydroxyl - (1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl) androst-5-ene (4e)



4e

Melting Point: 145-148.5^{o}C

%Yield: 91%

Chemical Formula: $C_{30}H_{35}N_3O_2$

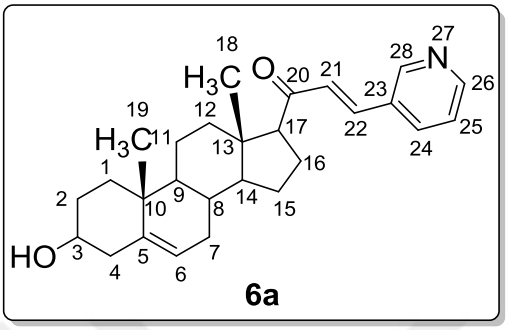
Molecular Weight: 469.63

IR (ATR, cm^{-1}): 3426.24 (stretching vibration, 3β-hydroxyl OH), 2944.91-2855.21 (stretching vibration, aliphatic C-H), 1721.03 (stretching vibration, C=O, aldehyde), 1638.33 (stretching vibration, C=N), 1553.9-1593.00 (stretching vibration, aromatic C=C), 1192.46 (stretching vibration, C-O, C-3), 1092.30 (stretching vibration, C-N).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 1.06 (s, 3H, CH_3-18), 1.14 (s, 3H, CH_3-19), 2.43 – 1.20 (m, 17H, aliphatic CH and CH_2 steroid ring), 2.78 (m, 1H, CH-16), 3.52 (ddd, *J* = 17.4, 6.4, 1.8 Hz, 1H, CH-3), 4.78 (d, *J* = 8.6 Hz, 1H, CH-20), 5.50 (d, *J* = 4.8 Hz, 1H, endocyclic C–6 proton), 7.58 (m, 2H, CH–30), 7.60 (m, 1H, CH-26), 7.76 (m, 1H, CH-27), 7.84 (d, *J* = 8.1 Hz, 1H, CH-28), 8.08 (s, 1H, aldehyde proton), 8.14 (m, 1H, CH-25), 8.32 (s, 1H, CH–23), solvent peak appears at 7.29 ppm.

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 14.29 (C-18), 19.42 (C-11), 20.45 (C-19), 27.70 (C-15), 29.96 (C-7), 30.97 (C-2), 31.89 (C–8), 31.51 (C–12), 36.82 (C–1 and C-10), 38.05 (C-4), 47.56 (C-13), 49.43 (C–9 and C-14), 50.22 (C–16), 73.72 (C–20), 76.29 (C-3), 122.31 (C-6), 123.67 (C-30), 127.14 (C-24), 127.53 (C–26), 129.82 (C-25), 129.87 (C–28), 131.07 (C-27), 136.25 (C-29), 141.66 (C-5), 154.74 (C-23), 160.80 (C-31), 210.08 (C-17).

4.17 Characterization of 21*(E)* - 3β – hydroxyl – 21 - (3-pyridinylidene) pregn-5-en-20-one (6a)



Melting Point: 119-121 ^{o}C

%Yield: 78.1%

Chemical Formula: $C_{27}H_{35}NO_2$

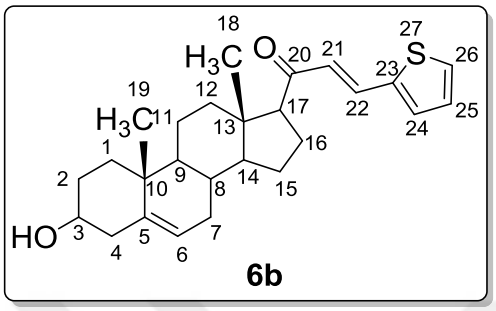
Molecular Weight: 405.58

IR (ATR, cm^{-1}): 3395.98 (stretching vibration, 3β-hydroxyl OH), 2968.58-2935.45 (stretching vibration, aliphatic C-H), 1682.66 (stretching vibration, C=O), 1609.71 (stretching vibration, C=N, pyridine ring), 1586.32 (stretching vibration, aromatic C=C), 1049.29 (stretching vibration, C-O, C-3), 1096.12 (stretching vibration, C-N).

^{1}H-NMR: NMR (400 MHz, $CDCl_3$ - d) δ 0.63 (s, 3H, CH_3-18), 0.99 (m, 3H, CH_3-19), 2.03 ((d, *J* = 12.9 Hz, 1H, CH-17),244 – 1.06 (m, 19H, aliphatic, CH and CH_2 steroid ring), 3.55 (m, 1H, CH-3), 5.33 (d, *J* = 4.9 Hz, 1H, endocyclic CH-6), 7.25 (s, 1H, CH-21), 7.49 – 7.44 (dd, *J* = 23.5, 11.7 Hz, 2H,coinsiding CH–22 and CH-25), 7.52 (d, *J* = 4.2 Hz, 1H, CH–24), 7.71 (d, *J* = 4.2 Hz,, 1H, CH-26), 8.63 (s, 1H, CH-27).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 13.49 (C-18), 19.39 (C-19), 21.10 (C-11), 22.73 (C-15), 24.67 (C-16), 31.54 (C-2), 31.82 (C–7), 31.99 (C–8), 36.15 (C–1), 37.26 (C-12), 39.04 (C-10), 42.20 (C-4), 45.12 (C-13), 50.01 (C-9), 57.14 (C-14), 62.28 (C-17), 71.49 (C-3), 121.28 (C-6), 124.27 (C-25), 124.87 (C-21), 130.16 (C-23), 136.91 (C-24), 139.94 (C-5), 140.89 (C-22), 150.07 (C-26), 153.28 (C-28), 201.00 (C-20).

4.18 Characterization of 21*(E)* - 3β-hydroxy – 21 - (2-thiophenylidene) pregn-5-en-20-one (6b)



6b

Melting Point: 115-118 ^{o}C

%Yield: 77.2%,

Chemical Formula: $C_{26}H_{34}O_2S$

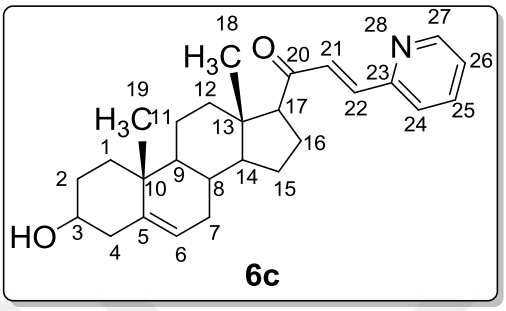
Molecular Weight: 410.23

IR (ATR, cm^{-1}): 3396.10 (stretching vibration, 3β-hydroxyl OH), 2935.77 (stretching vibration, aliphatic C-H), 1673.97 (stretching vibration, C=O), 1437.88 (stretching vibration, aromatic C=C), 1093.51 (stretching vibration, C-S), 1046.37 (stretching vibration, C-O, C-3).

^{1}H-NMR: (400 MHz, $CDCl_3$ - d) δ 0.64 (s, 3H, CH_3-18), 1.00 (s, 3H, CH_3-19), 2.16 (d, *J* = 1.2 Hz, 1H, CH-17), 2. 21 – 1.06 (m, 19H, aliphatic, CH and CH_2 steroid ring), 3.54 (s, 1H, CH-3), 3.54 (s, 1H, endocyclic CH-6), 6.58 (d, *J* = 15.6 Hz, 1H, CH-21), 7.07 (dd, *J* = 5.0, 3.6 Hz, 1H, CH-25), 7.36 – 7.27 (d, *J* = 15.6 Hz 1H, CH-22), 7.38 (d, *J* = 5.0 Hz, 1H, CH-24), 7.68 (d, *J* = 15.6 Hz, 1H, CH-26).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 13.43 (C-18), 19.53 (C-19), 21.12 (C-11), 22.71 (C-15), 24.68 (C-16), 31.56 (C-2), 31.85 (C–7), 32.27 (C-8), 36.54 (C–1), 37.27 (C–12), 39.02 (C-10), 42.22 (C 4), 45.09 (C-13), 50.05 (C-9), 57.16 (C-14), 62.16 (C-17), 72.17 (C-17), 121.35 (C–21), 121.36 (C-6), 125.60 (C-24), 128.06 (C-25), 131.67 (C-26), 134.00 (C-22), 139.88 (C-21), 140.65 (C–5), 200.02 (C–20).

4.19 Characterization of 21*(E)* - 3β – hydroxyl – 21 - (3-methyl-2-thiophenylidene) pregn-5-en-20-one (6c)



6c

Melting Point: 115-118 ^{o}C

%Yield: 78.1%,

Chemical Formula: $C_{27}H_{35}NO_2$

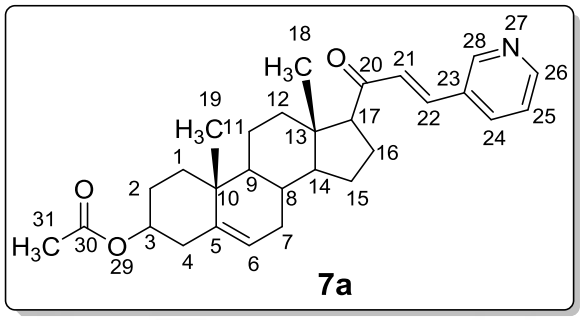
Molecular Weight: 405.58

IR (ATR, cm^{-1}): 3298.61 (stretching vibration, 3β-hydroxyl OH), 2904.22 (stretching vibration, aliphatic C-H), 1682.85 (stretching vibration, C=O), 1647.94 – 1609. 61 (C 0 N), 1535.93 (stretching vibration, aromatic C=C), 1048.29 (stretching vibration, C-O, C-3), 1096.27 (stretching vibration, C - N).

^{1}H NMR (400 MHz, $CDCl_3$-d): 0.65 (s, 3H, CH_3-18), 1.00 (s,3H, CH_3-19), 2.17 (s, H, CH - 17), 2.48 – 1.08 (m, 19H, aliphatic, CH and CH_2 steroid ring), 3.71 (q, *J* = 7.0 Hz, 1H CH-3), 5.35 (d, *J* = 5.1 Hz, 1H, endocyclic CH-6), 7.26 (d, *J* = 15.6 Hz, 2H, CH–25 and CH-26) 7.48 (d, *J* = 15.4 Hz, 2H, coinciding protons CH-21 and C-24), 7.60 (s, 1H, CH-22), 8.64 (d, *J* = 3.6 Hz, 1H, CH-27).

^{13}C-NMR: (100 MHz, $CDCl_3$ - d) δ 13.48 (C–18), 19.37 (C-19), 21.07 (C-11), 22.76 (C-15), 24.68 (C-16), 31.74 (C-2), 31.83 (C–7), 32.01 (C–8), 36.52 (C-1), 37.26 (C-12), 39.07 (C-10), 42.24 (C-4), 45.10 (C-13), 50.04 (C-9), 57.17 (C–14), 62.30 (C-17), 71.54 C-3), 121.32 (C-5), 124.22 (C-26), 125.83 (C-24), 130.18 (C-21), 136.84 (C-25), 139.93 (C-5), 140.88 (C-22), 150.11 (C-27), 153.35 (C-23), 200.91 (C-20).

4.20 Characterization of 21*(E)* - 3*β* – acetoxy – 21 - (3-pyridinylidene) pregn-5-en-20-one (7a)



7a

Melting Point: 170-174 ^{o}C

%Yield: 90.5%

Chemical Formula: $C_{29}H_{37}NO_3$

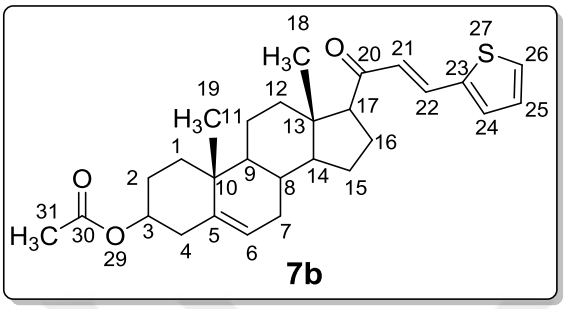
Molecular Weight: 447.62

IR (ATR, cm^{-1}): 2941.32 – 2905.06 (stretching vibration, aliphatic C-H), 1730.02 (stretching vibration, C = O), 1682.20 (stretching vibration, C = N), 1585.99 (stretching vibration, aromatic C = C), 1246.69 (stretching vibration, C - O, C - 3), 1036.10 (stretching vibration, C - N).

^{1}H NMR (400 MHz, $CDCl_3$ - d) δ 0.62 (s, 3H, CH_3-18), 0.97 (s, 3H, CH_3-19), 2.00 (s, 3H, CH_3-31), 2.06 (m, H, CH-17), 2.47 – 1.03 (m, 16H, aliphatic , CH and CH_2 steroid ring), 3.45 (m, 1H, CH-3), 5.35 (d, *J* = 5.1 Hz, 1H, endocyclic CH-6), 7.34 – 7.15 (m, 2H, coinciding protons CH–21 and CH-25), 7.56 – 7.37 (m, 2H, coinciding protons CH–22 and CH-24), 7.69 – 7.52 (m, 1H, CH-26), 8.63 (*J* = 3.6 Hz, 1H, CH-27).

^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 13.45 (C-18), 19.28 (C-19), 21.39 (C-31), 22.71 (C-11), 24.65 (C-15), 27.71 (C-16), 31.93 (C-2), 36.57 (C–7), 36.95 (C-8), 38.06 (C-1), 45.00 (C- 10), 46.48 (C–12), 49.90 (C-4), 50.90 (C–13), 57.04 (C-9), 57.04 (C-14), 62.25 (C-17), 73.79 (C-3), 122.31 (C-6), 124.16 (C-25), 124.78(C-21), 130.10 (C-23), 136.73 (C-24), 139.94 (C-5), 150.11 (C-28), 153.36 (C-26), 170.42 (C-30), 200.68 (C-31).

4.21 Characterization of 21(*E*) - 3*β* – acetoxy – 21 - (2-thiophenylidene) pregn-5-en-20-one (7b)



7b

Melting Point: 73-176 ^{o}C

%Yield: 90.9%

Chemical Formula: $C_{28}H_{36}O_3S$

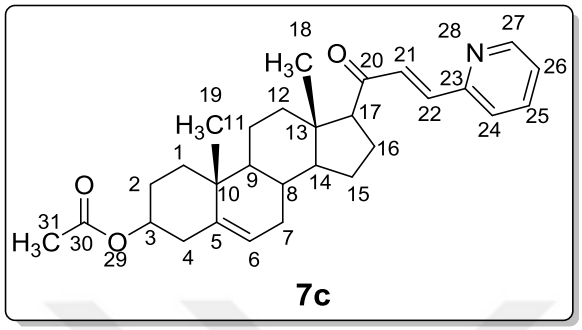
Molecular Weight: 452.65

IR (ATR, cm^{-1}): 2941.25 (stretching vibration, aliphatic C-H), 1586.54 (stretching vibration, C=O), 1440.90 (stretching vibration, aromatic C=C), 1247.03 (stretching vibration, C-O, C - 3), 1094.90 (stretching vibration, C-S).

^{1}H NMR (400 MHz, $CDCl_3$ - d) δ 0.64 (s, 3H, CH_3-18), 1.00 (s, 3H, CH_3-19), 2.04 (s, 3H, CH_3-30), 2.12 (d, *J* = 8.8 Hz, 1H, CH-17), 2.33 – 1.07 (m, 19H aliphatic, CH and CH_2 steroid ring), 4.62 (m, 1H, CH-3), 5.39 (d, *J* = 4.3 Hz, 1H, endocyclic CH-6), 6.60 – 6.56 (m, 1H, CH-21), 7.07 (m, 1H, CH-25), 7.29 (d, *J* = 2.4 Hz, 1H, CH–24), 7.37 (d, *J* = 4.9 Hz, 1H, CH-26), 7.67 (d, *J* = 15.6 Hz, 1H, CH-22).

^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 13.41 (C-18), 19.31 (C-19), 21.42 (C-30), 22.73 (C-11), 24.66 (C-15), 26.50 (C–16), 27.75 (C-2), 31.84 (C-7), 31.96 (C-8), 37.0 (C-1), 38.09 (C-12), 38.97 (C-10), 45.00 (C–4), 49.39 (C-13), 50.82 (C-9), 57.07 (C-14), 62.08 (C-17), 73.82 (C-3), 122.35(C–21), 122.61 (C–6), 126.78 (C-24), 128.25 (C-25), 131.46 (C-26), 139.66 (C-22), 140.25 (C-5), 170.48 (C-29), 199.73 (C-20).

4.22 Characterization of 21*(E)* - 3*β* - acetoxy – 21 - (2-pyridinylidine) pregn-5-en-20-one (7c)



7c

Melting Point: 179-183 ^{o}C

%Yield: 90.9%

Chemical Formula: $C_{29}H_{37}NO_3$

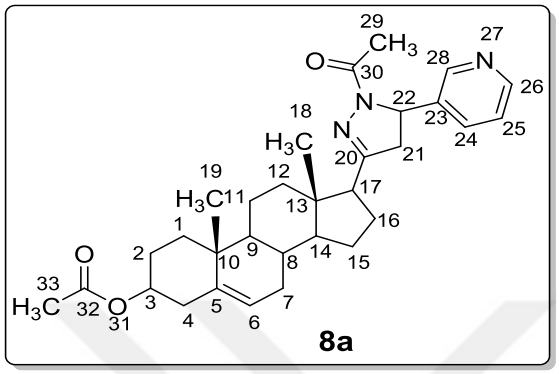
Molecular Weight: 447.62

IR (ATR, cm^{-1}): 2941.63 (stretching vibration, aliphatic C-H), 1730.02 (stretching vibration, C=O), 1682.09 (stretching vibration, C=N), 1585.95 (stretching vibration, aromatic C=C), 1246.94 (stretching vibration, C-O, C-3), 103626 (stretching vibration, C-N).

^{1}H NMR (400 MHz, $CDCl_3$ - d) δ 0.56 (s, 3H, CH_3-18), 0.92 (s, 3H, CH_3-19), 1.94 (s, 3H, CH_3-31), 2.25 (dd, *J* = 14.8, 8.8 Hz, 1H, CH-17), 2.82 - 1.06 (m, 19H, aliphatic CH and CH_2 steroid ring), 4.68 – 4.30 (m, 1H, CH-3), 5.29 (d, *J* = 4.9 Hz, 1H, endocyclic CH-6), 7.19 (d, *J* = 15.6 Hz, 2H, CH–25 and CH-26), 7.42 (s, 2H, CH-21 and CH-24), 7.63 (d, *J* = 1.8 Hz, 1H, CH-22), 8.56 (s, 1H, CH-27).

^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 13.39 (C-18), 19.21 (C-19), 20.94 (C-31), 21.30 (C-11), 22.67 (C-15), 24.59 (C-16), 27.66 (C-2), 30. 63 (C–7), 31.88 (C-8), 36.51 (C-1), 36.90 (C–12), 38.01 (C-10), 39.12 (C–4), 44.92 (C-13), 49.86 (C-9), 56.98 (C-14), 62.15 (C-17), 73.72 (C-3), 122.24 (C-6), 124.11 (C–26), 124.40 (C-26), 130.07 (C-21), 136.69 (C-25), 139.59 (C-5), 139.89(C–22), 170.30 (C-30), 200.53 (C-17).

4.23 Characterization of 3β – acetoxy - 17β - (1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (8a)



Melting Point: 75-79 ^{o}C

%Yield: 88.8%

Chemical Formula: $C_{31}H_{41}N_3O_3$

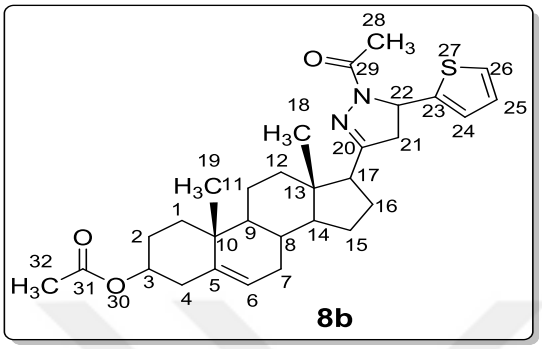
Molecular Weight: 503.69

IR (ATR, cm^{-1}): 2939.66 (stretching vibration, aliphatic C-H), 1731.22 (stretching vibration, C=O), 1660.08 (stretching vibration, C=N), 1591.57 (stretching vibration, aromatic C=C), 1239.79 (stretching vibration, C-O, C-3), 1029.33 (stretching vibration, C-N).

^{1}H NMR (400 MHz, $CDCl_3$ - d) δ0.70 (s, 3H, CH_3-18), 1.04 (s, 3H, CH_3-19), 2.04 (s, 3H, CH_3-29), 2.10 (m, 1H, CH–17), 2.33 (s, 3H, CH_3-34), 2.34 – 1.16 (m, 19H, aliphatic CH and CH_2 steroid ring), 3.24 – 2.92 (m, 2H, CH_2-21), 4.74 – 4.48 (m, 1H, CH-22), 5.40 (d, *J* = 4.3 Hz, 1H, endocyclic CH-6), 7.19 (m, 1H, CH–25), 7.65 (d, *J* = 1.4 Hz, 1H, CH-24), 8.57 (d, *J* = 4.5 Hz, 2H, coinciding protons CH–26 and CH-28), solvent peak appears at 7.29 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 13.18 (C-18), 19.34 (C-19), 21.42 (C-33), 24.44 (C–11), 24.47 (C–29), 27.74 (C-15), 31.74 (C-2), 32.00 (C-16), 37.02 (C–7), 38.09 (C–8), 43.04(C–1), 49.79 (C–21), 50 (C–10), 51.73 (C-12), 51.81 (C–13), 56.30 (C-9), 56.41 (C–17), 60.25 (C-14), 60.37 (C–22), 73.84 (C-3), 121.18 (C-26), 122.22 (C-6), 122.42 (C–28), 136.67 (C-27), 139.70 (C-5), 149.71 (C-25), 149.73 (C-23), 162.52 (C-31), 169.03 (C–20), 170.53 (C-33).

4.24 Characterization of 3β – acetoxy - 17β - (1-Acetyl-5-(2- thiophenyl)-3-pyrazolinyl) androat-5-ene (8b)



8b

Melting Point: 79-82 ^{o}C

%Yield: 89.0%

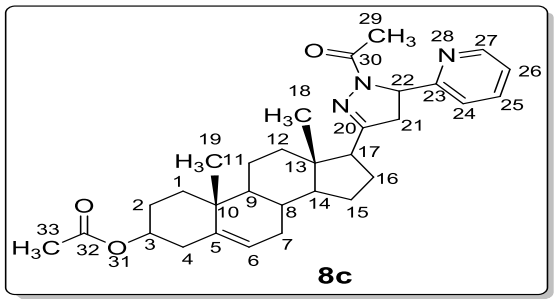
Chemical Formula: $C_{30}H_{40}N_2O_3S$

Molecular Weight: 508.28

IR (ATR, cm^{-1}): 2940.71 (stretching vibration, aliphatic C-H), 1731.08 (stretching vibration, C=O), 1664.41 (stretching vibration, C=N), 1437.88 (stretching vibration, aromatic C=C), 1243.82 (stretching vibration, C-O, C-3), 1033.47 (stretching vibration, C-S).

^{1}H NMR (400 MHz, $CDCl_3$ - d) δ0.69 (s, 3H, CH_3-18), 1.00 (s, 3H, CH_3-19), 1.95(s, 3H, CH_3-28), 2.30 (s, 3H, CH_3-32), 2.31 – 1.10 (m, 19H, aliphatic CH and CH_2 steroid ring), 2.87 (ddd, *J* = 49.3, 17.9, 3.7 Hz, 2H, CH-21), 3.64 (q, *J* = 7.0 Hz, 1H, CH-17), 4.57 (m, 1H, CH-3), 5.36 (d, *J* = 4.0 Hz, 1H, endocyclic CH-6), 6.54 (dd, *J* = 15.6, 8.5 Hz, 1H, CH-22), 6.90 – 6.79 (m, 1H, CH-24), 6.95 (dd, *J* = 10.3, 3.1 Hz, 1H, CH-25), 7.13 (d, *J* = 4.7 Hz, 1H, CH-26).
^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 13.41 (C-18), 19.31 (C-19), 20.96 (C–32), 21.37 (C-11), 24.32(C-28), 24.32 (C–15), 24.61 (C-2), 27.69 (C–16), 31.70 (C-7), 31.94(C–8), 36.59 (C-21), 36.98 (C–1), 38.05 (C-12), 43.95 (C-10), 45.81 (C-4), 49.97 (C-13), 51.71 (C-17), 51.83 (C-9), 56.41 (C–14), 73.83 (C-3), 76.93 (C–22), 122.37 (C-6), 124.53 (C-24), 126.69 (C-25), 139.56 (C-23), 139.67 (C-5), 159.87 (C-20), 168.87 (C–29), 20), 170.56 (C-31).

4.25 Characterization of 3β – acetoxy - 17β - (1-Acetyl-5-(2- pyridinyl)-3-pyrazolinyl) androat-5-ene (8c)



Melting Point: 68-72 ^{o}C

%Yield: 88.8%,

Chemical Formula: $C_{31}H_{41}N_3O_3$

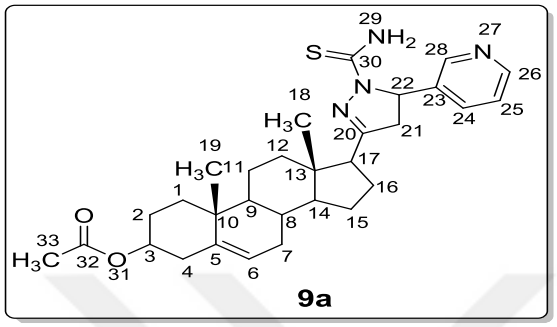
Molecular Weight: 503.69

IR (ATR, cm^{-1}): 2939.44 (stretching vibration, aliphatic C-H), 1731.16 (stretching vibration, C=O), 1659.85 (stretching vibration, C=N), 1591.58 (stretching vibration, aromatic C=C), 1239.60 (stretching vibration, C-O, C-3), 1029.06 (stretching vibration, C-N).

^{1}H NMR (400 MHz, $CDCl_3$-d) δ0.68 (s, 3H, CH_3-18), 1.11 (s, 3H, CH_3-19), 2.05 (s, 3H, CH_3-29), (s, 3H, CH_3-32), 2.46 –1.08 (m, 17H), 3.41 – 2.93 (m, 2H, CH-15), 3.70 (d, *J* = 7.0 Hz, 1H, CH-17), 4.61 (m, 1H, CH-3), 5.39 (d, *J* = 4.0 Hz, 1H, endocyclic CH-6), 5.63 – 5.45 (m, 1H, CH-22), 7.21 – 7.09 (m, 1H, CH-26), 7.35 – 7.23 (m, 1H, CH-28), 7.64 (dd, *J* = 10.9, 4.3 Hz, 1H, CH-27), 8.56 (d, *J* = 4.4 Hz, 1H, CH-25).

^{13}C NMR (100 MHz, $CDCl_3$-d) δ13.16 (C-18), 19.35 (C-19), 20.90 (C-33), 21.46 (C-11), 24.38 (C-29), 24.38 (C-15), 25.65 (C-2), 27.18 (C-16), 31.72 (C-7), 31.753 (C-8), 31.97 (C-1), 37.02 (C-21), 38.07 (C-10), 38.33 (C-12), 43.35 (C-4), 44.32 (C-13), 49.96 (C-9), 51.75 (C-10), 56.32 (C-14), 60.29 (C-22), 73.84 (C-3), 121.17 (C-26), 122.34 (C-6), 122.45 (C-28), 136.68 (C-27), 139.68 (C-5), 149.72 (C-25), 159.61 (C-23), 160.26 (C-29), 168.92 (C-17), 170.56 (C-32).

4.26 Characterization of 3β – acetoxy - 17β - (-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (9a)



9a

Melting Point: 269 – 270.5 ^{o}C

%Yield: 85.9%

Chemical Formula: $C_{30}H_{40}N_4O_2S$

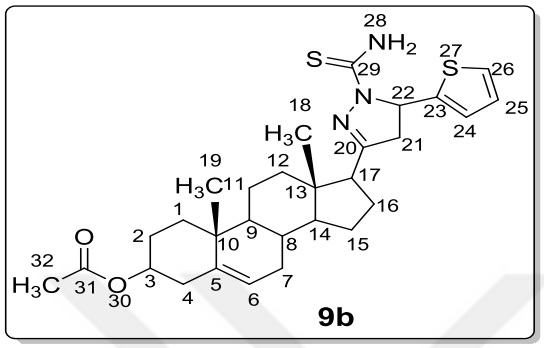
Molecular Weight: 520.74

IR (ATR, cm^{-1}): 3421.30 – 3283.66 (stretching vibration N–H), 2939.44 (stretching vibration, aliphatic C-H), 1601.65 (stretching vibration, C=O), 1570.80 (stretching vibration, C=N), 1487.38 (stretching vibration, aromatic C=C), 1044.77 (stretching vibration, C=S), 1330.00 (stretching vibration, C-O), 994.44 (C–N).

^{1}H NMR (400 MHz, DMSO – d_6) δ 0.56 (s, 3H, CH_3-18), 0.94 (s, 3H, s, 3H, CH_3-19), 2.11 (s, 3H, CH_3-32), 2.32 – 1.07 (m, 17H, aliphatic CH and CH_2 steroid ring), 2.81 (d, *J* = 18.2 Hz, 2H, CH_2-16), 3.36 (dd, *J* = 4.1, 1.5 Hz, 1H, CH-17), 5.27 (s, 1H, CH-3), 5.78 (d, *J* = 11.0 Hz, 1H, endocyclic CH-6 proton), 7.33 – 7.15 (m, 2H, NH_2, protons), 7.40 (s, 1H, CH-22), 7.72 (d, *J* = 6.8 Hz, 1H, CH–27), 7.82 (s, 1H, CH-28), 8.50 (s, 2H, CH–24 and CH-26).

^{13}C NMR (100 MHz, DMSO – d_6) δ 13.40 (C-18), 19.61 (C-19), 21.08 (C-32), 24.25 (C-15), 31.98 (C-16), 40.43 (C–2), 40.23 (C–7), 36.98 (C-8), 39.57 (C–1), 39.79 (C-12), 40.00 (C–10), 40.32 (C-4), 43.97 (C-21), 44.91 (C-13), 50.04 (C-17), 51.36 (C-9), 56.28 (C-14), 63.47 (C–22), 70.46 (C-3), 120.71 (C-6), 121.46 (C-27), 122.73 (C-22), 136.76 (C-28), 141.76 (C–6), 149.80 (C-26), 161.05 (C-20), 161.9 (C-32), 176.11 (C-29).

4.27 Characterization of 3β-acetoxy - 17β - (-1-carbothioamide-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (9b)



Melting Point: [*oily*].

%Yield: 86.1%

Chemical Formula: $C_{29}H_{39}N_3O_2S_2$

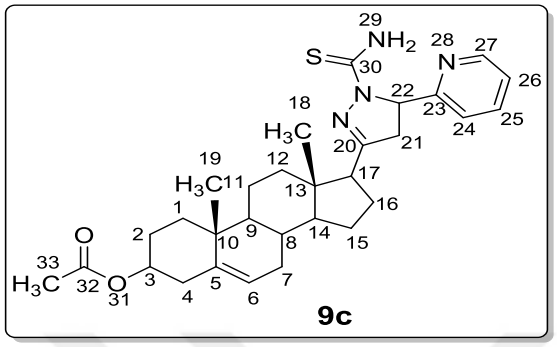
Molecular Weight: 525.77

IR (ATR, cm^{-1}): 3439.00–3297.06 (stretching vibration N–H), 2939.44 (stretching vibration, aliphatic C-H), 1700.96 (stretching vibration, C=O), 1586.40 (stretching vibration, C=N), 1471.58 (stretching vibration, aromatic C=C), 1119.04 (stretching vibration, C=S), 1081.13 (stretching vibration, C-S), 1047.73 (stretching vibration, C–N).

^{1}H NMR (400 MHz, $CDCl_3$ - d) δ 0.66 (s, 3H, CH_3-18), 0.9 (s, 3H, CH_3-19), 2.07 (s, 3H, CH_3- 31), 2.15 - 1.20 ((m, 19H, aliphatic CH and CH_2 steroid ring), 3.51 (dd, *J* = 4.1, 1.5 Hz, 1H, CH - 17), 3.69 (m, 1H, CH-3), 5.34 (s, 1H, endocyclic CH–6 proton), 6.15 (dd, *J* = 10.7, 2.3 Hz, 2H, NH_2 , protons), 6.95 – 6.86 (m, 1H, CH-24), 6.99 (dd, *J* = 6.4, 3.3 Hz, 1H, CH-25), 7.17 (m, 1H, CH-26), 7.29 (s, 1H, CH-22).

^{13}C NMR (100 MHz, $CDCl_3$ - d) δ 13.37 (C-18), 19.43 (C-19), 20.90 (C-31), 20.99 (C–11), 24.31 (C-15), 24.40 (C-2), 24.46 (C–16), 31.82 (C-7), 31.71 (C–8), 36.55 (C-21), 37.28 (C–1), 42.17 (C–12), 44 .26 (C–10), 50.00 (C–4), 50.03 (C-13), 56.39 (C-17), 58.17 (C–9), 58.59 (C–14), 71.51 (C-3), 74.72 (C-22), 121 .26 (C–6), 124.32 (C–24), 124.88 (C–25), 126.72 (C–26), 140.92 (C–23), 140.94 (C–5), 162.27 (C–20), 175.99 (C–30), 176.28 (C–28).

4.28 Characterization of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - pyridinyl)-3-pyrazolinyl) androat-5-ene (9c)



9c

Melting Point: 266-268 ^{o}C

%Yield: 85.9%

Chemical Formula: $C_{30}H_{40}N_4O_2S$

Molecular Weight: 520.74

IR (ATR, cm^{-1}): 3414.90 – 3275.58 (stretching vibration N–H), 2928.26 (stretching vibration, aliphatic C-H), 1600.85 (stretching vibration, C=O), 1571.40 (stretching vibration, C=N), 1485.04 (stretching vibration, aromatic C=C), 1055.80 (stretching vibration, C=S), 2031.00 (stretching vibration, C-N) 1046.00 (stretching vibration, C-O).

^{1}H NMR (400 MHz, DMSO – d_6) δ0.66 (s, 3H, CH_3-18), 0.99 (s, 3H, CH_3-19), 2.01 (s, Hz, 3H, CH_3-33), 2.45 – 1.20 (m, 19H, aliphatic CH and CH_2 steroid ring), 2.91 (ddd, *J* = 20.2, 18.0, 2.7 Hz, 2H, CH-21), 3.51 ((d, *J* = 4.2 Hz, 1H, CH-17), 3.38 (s, 1H, CH-3), 5.34 (s, 1H, endocyclic CH–6 proton), 6.15 (dd, *J* = 10.7, 2.3 Hz, 2H, NH_2 protons), 6.34 (s, 1H, CH-22), 6.92 (m, H, CH–26), 6.99 (dd, *J* = 6.4, 3.3 Hz, 1H, CH-28), 7.17 (m, 1H, CH-27), 7.29 (s, 1H, CH–25).

^{13}C NMR (100 MHz, DMSO – d_6) δ 18.38 (C-18), 19.43 (C-19), 20.90 (C-33), 20.99 (C-11), 24.31 (C-15), 24 - 72 (C-2), 31.52 (C-16), 31.71 (C-7), 32.00 (C-8), 32.05 (C-1), 36.53 (C-12), 36.55 (C-5), 37.28 (C-4), 42.17 (C-13), 50.00 (C-17), 50.03 (C-9), 56.39 (C-14), 58.59 (C-22), 71.51 (C-3), 121.16 (C-26), 121.26 (C-6), 124.29 (C-28), 140.92 (C-27), 140.94 (C-5), 144.77 (C-25), 162.27 (C–20), 162.68 (C–23), 175.99 (C-32), 176.28 (C-30).

5. DISCUSSION

C-16 and C-17 of DHEA were modified with pyrazoline derivative containing different heteroaromatic substituents using the methods available in the literature as first part of this study. Starting with DHEA we synthesized the heteroaromatic α, β-unsaturated derivatives **(2a-f)**. Then endocyclic nucleophilic attack of hydrazine hydrate on **(2a-f)** in presence of acetic acid and formic acid produces the 3β-hydroxy-(1-Acetyl-5-aza-16,17-pyrazolinyl) androst-5-ene **(3a-e)** and 3β-hydroxy-(1-Formyl-5-aza-16,17-pyrazolinyl) androst-5-ene **(4a-f)** respectively in good yield.

Synthesis of **3d** in the 1-Acetyl derivatives were unsuccessful, even though the reaction conditions and the time taken for the reaction as reported in the literature were changed but still unsuccessful, this is may be due to steric hindrance on the α, β-unsaturated derivatives of quinoline compared to the other derivatives used in this thesis as well as benzaldehyde derivative as reported in the literature.

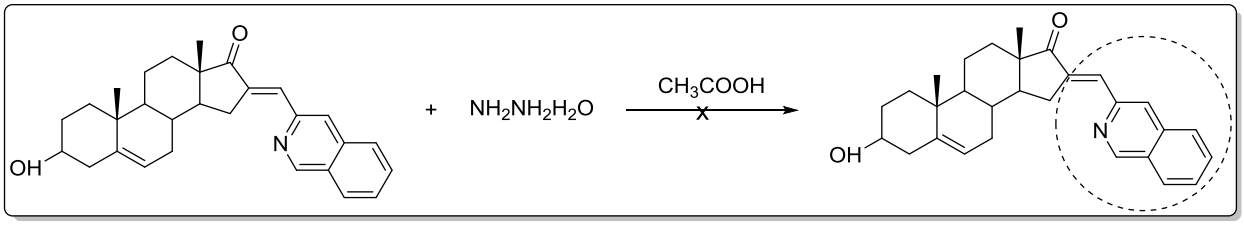


Figure 5.1 Unsuccessful reaction of α, β-unsaturated quinoline derivative

Also synthesis of **4f** in the 1- Formyl derivatives were unsuccessful using the method described by A.U. Siddiqui *et al*, in the New journal of organic synthesis (1993). Possibly due to steric hindrance.

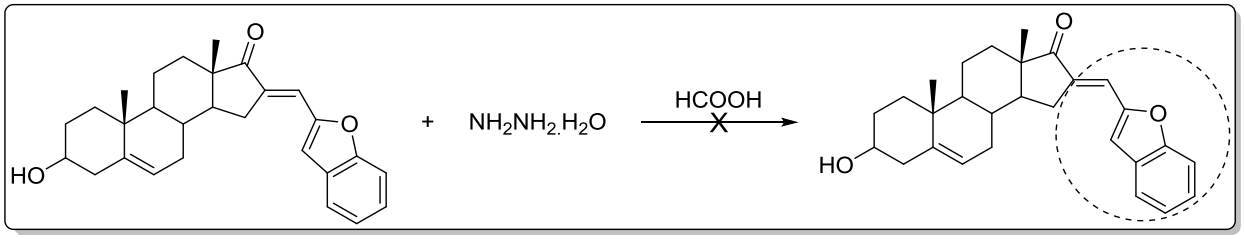


Figure 5.2 Unsuccessful reaction of 1-Formyl-(2-benzofuran) derivative

In the last part of this study C-17 of pregnenolone were modified with two different pyrazoline derivatives with novel heterocycle substituents. We started with aldol condensation of pregnenolone which afford the heteroaromatic α, β-unsaturated derivatives **(6a-c)**, compound (6a – c) were acetylated at the 3β-hydroxy then converted to pyrazolines derivatives by exocyclic nucleophilic attack of hydarzin hydrate in acetic acid produces the 17β-hydroxy-(1-Acetyl-5-aza-3-pyrazolinyl) androst-5-en-3β-ol derivatives **(8a-c)** and in thiosemicarbazide produces **9a-c** successfully in good yield.

All the pyrazoline derivatives synthesized in this thesis were characterized by infrared, ^{1}H-NMR and ^{13}C-NMR spectroscopy. Melting point of all the derivatives synthesized were determined unless for the compound that formed an oily product or decomposed before their expected melting point.

In conclusion all the pyrazoline derivatives synthesized in this thesis, we are certainly assured to have biological functions, since their analogous compounds were reported in the literature to have biological functions.

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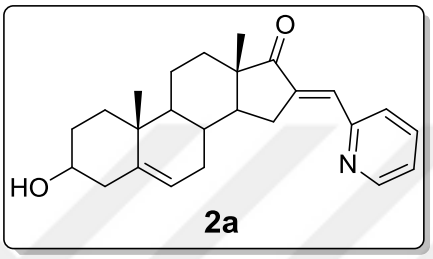
APPENDIX

Spectral data

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 16*(E)* – 16 - (2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one **(2a)**



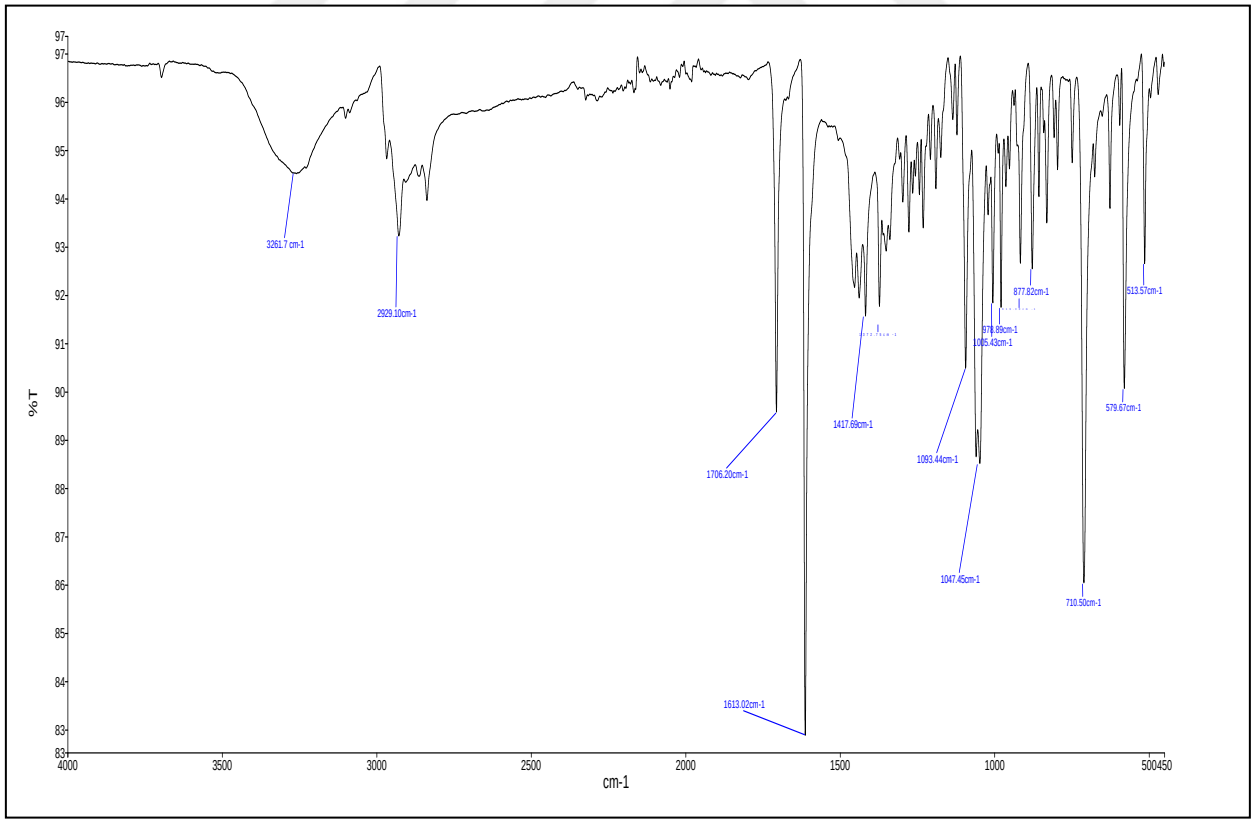


Figure A.1 IR spectrum of 16*(E)* – 16 - (2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2a)

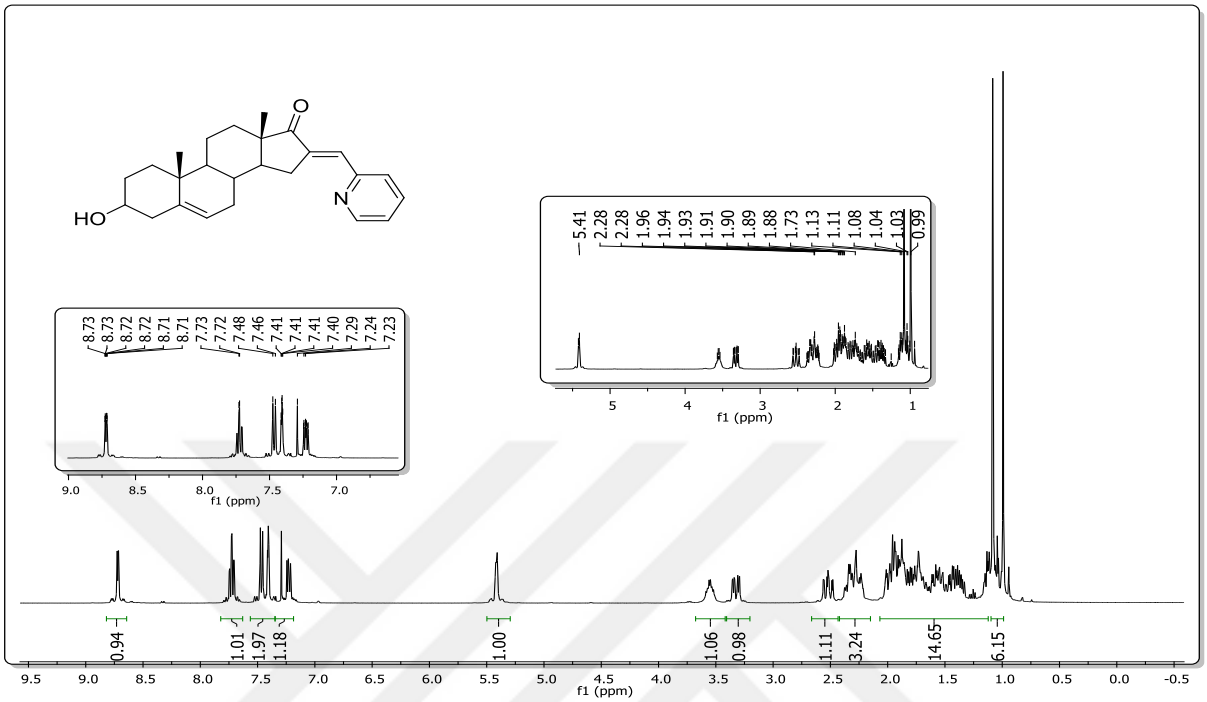


Figure A.2 1H-NMR spectrum of 16(E) – 16 - (2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one

(2a)

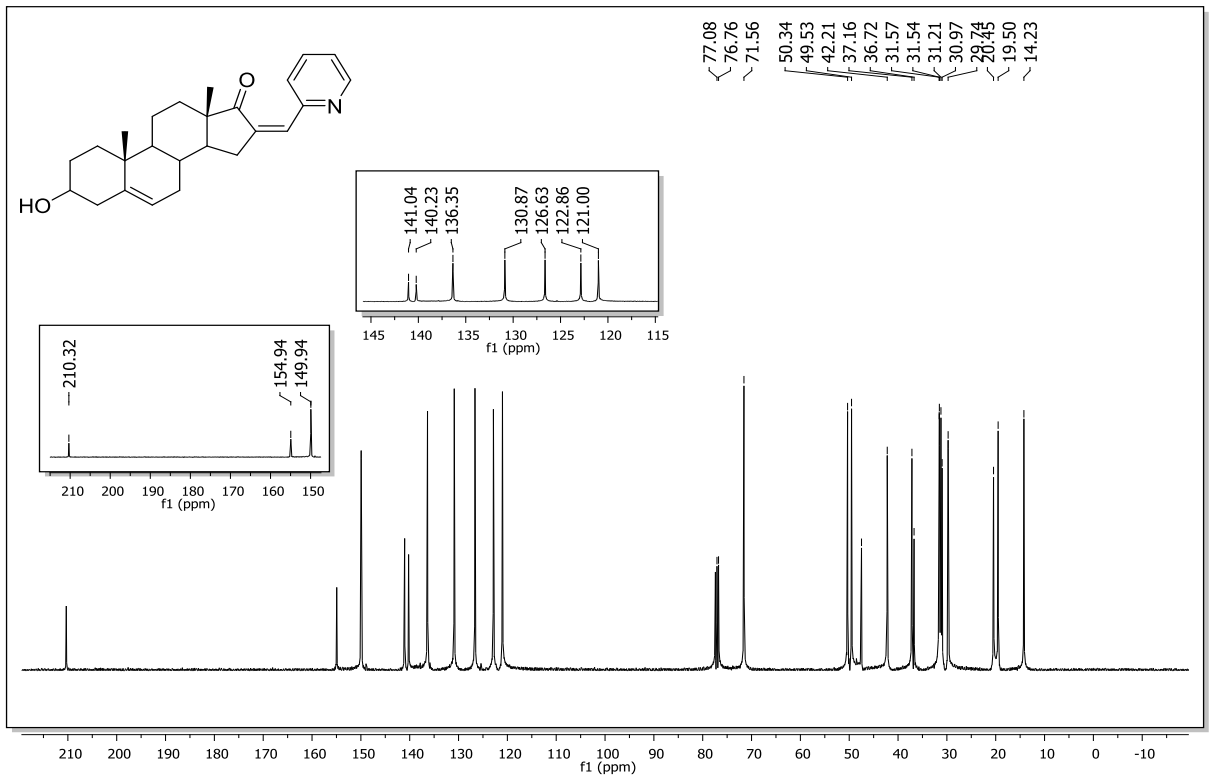
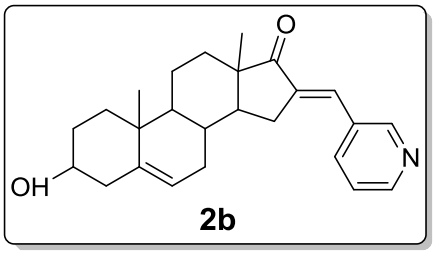


Figure A.3 13C-NMR spectrum of 16(E) – 16 - (2-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 16*(E)* – 16 - (3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one **(2b)**



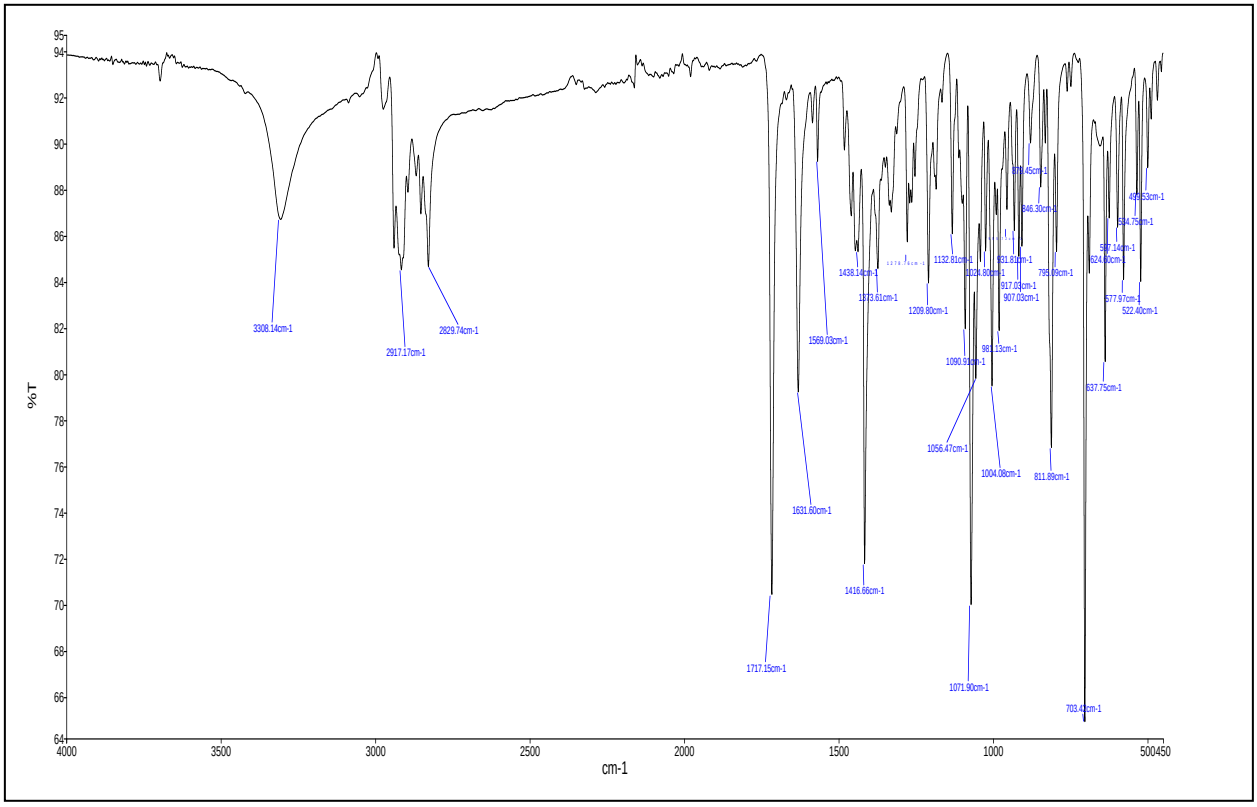


Figure A.4 IR spectrum of (16*(E)* -16-(3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2b)

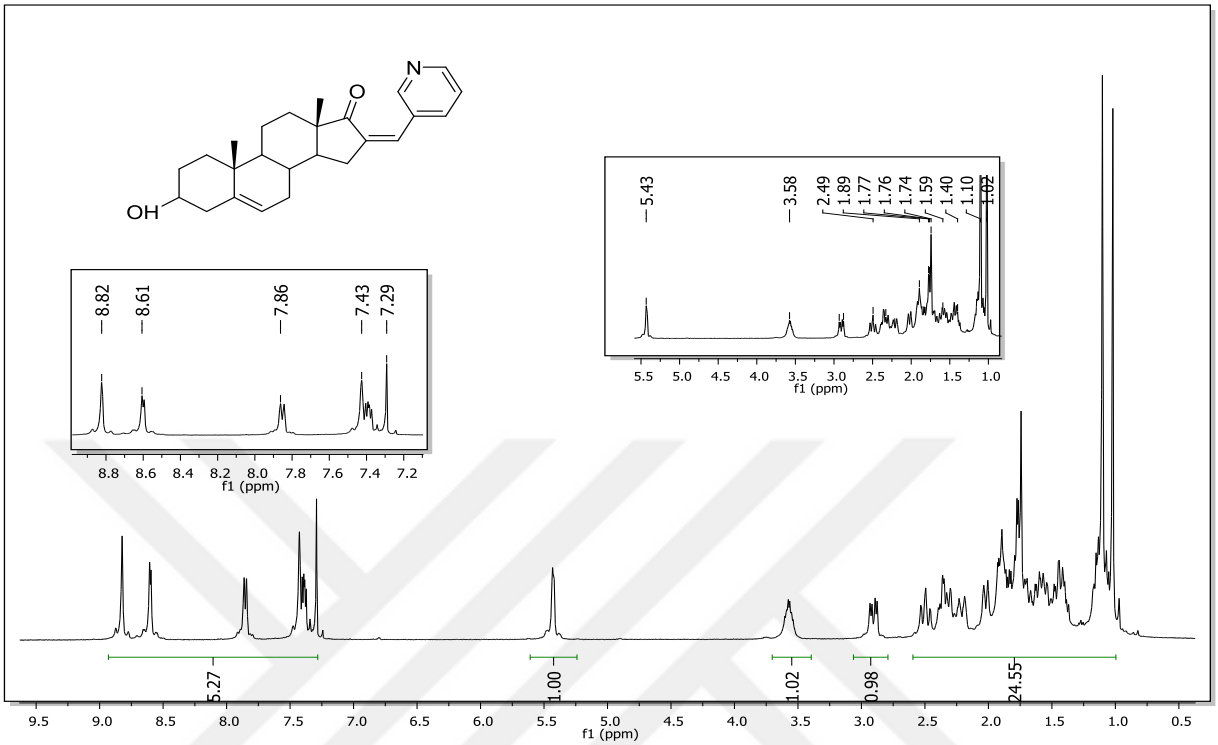


Figure A.5 ^{1}H-NMR spectrum of 16*(E)* -16-(3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2b)

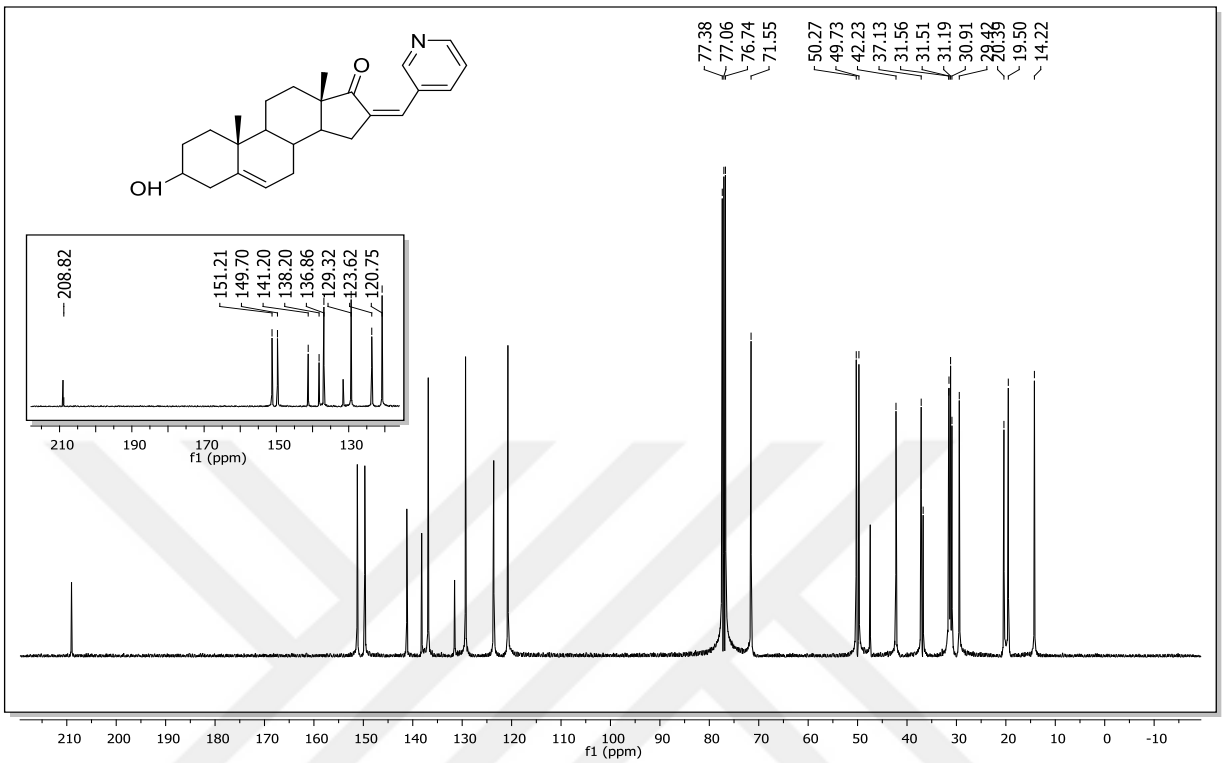
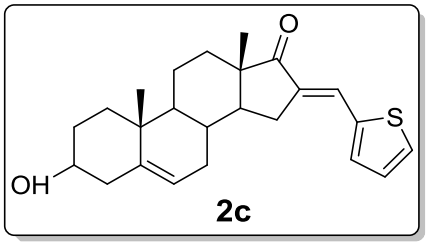


Figure A.6 13C-NMR spectrum of 16(E) – 16 - (3-pyridinyliden)-3β-hydroxyandrost-5-en-17-one (2b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 16*(E)* – 16 - (2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one **(2c)**



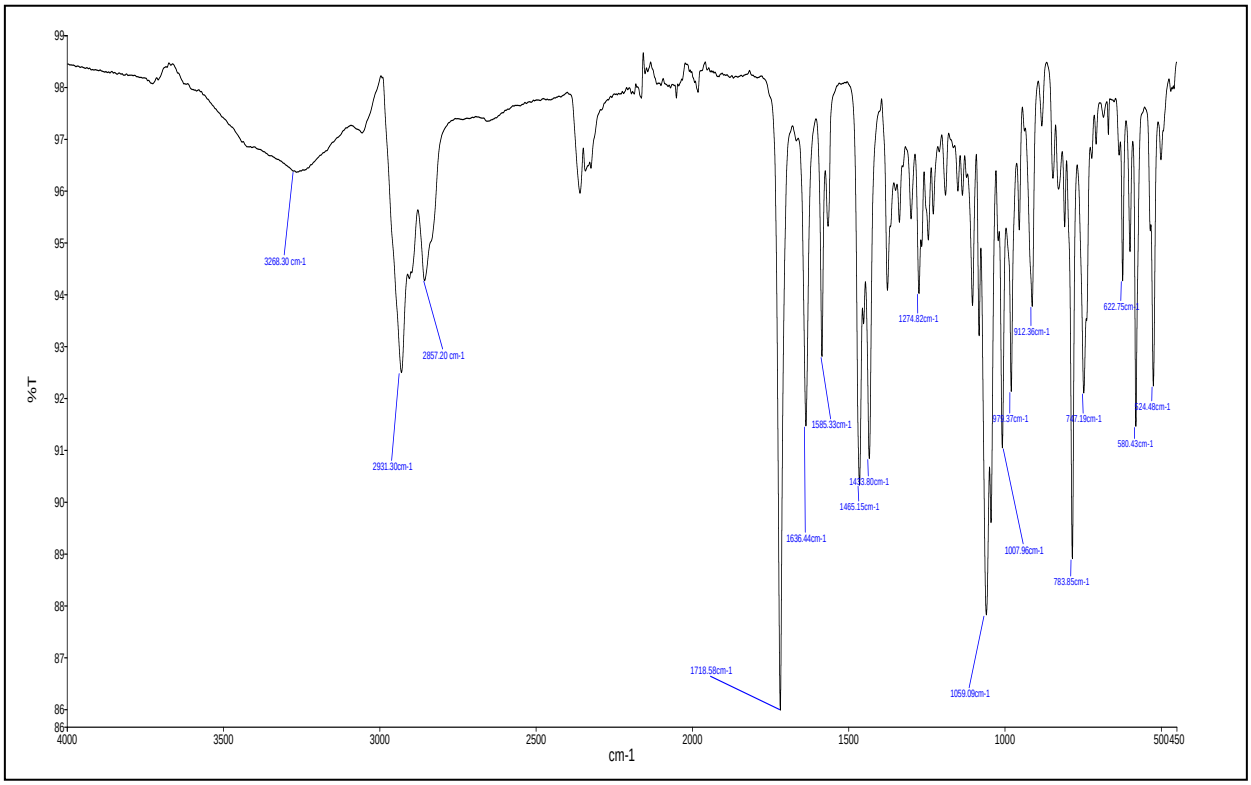


Figure A.7 IR spectrum of 16*(E)* – 16 - (2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2c)

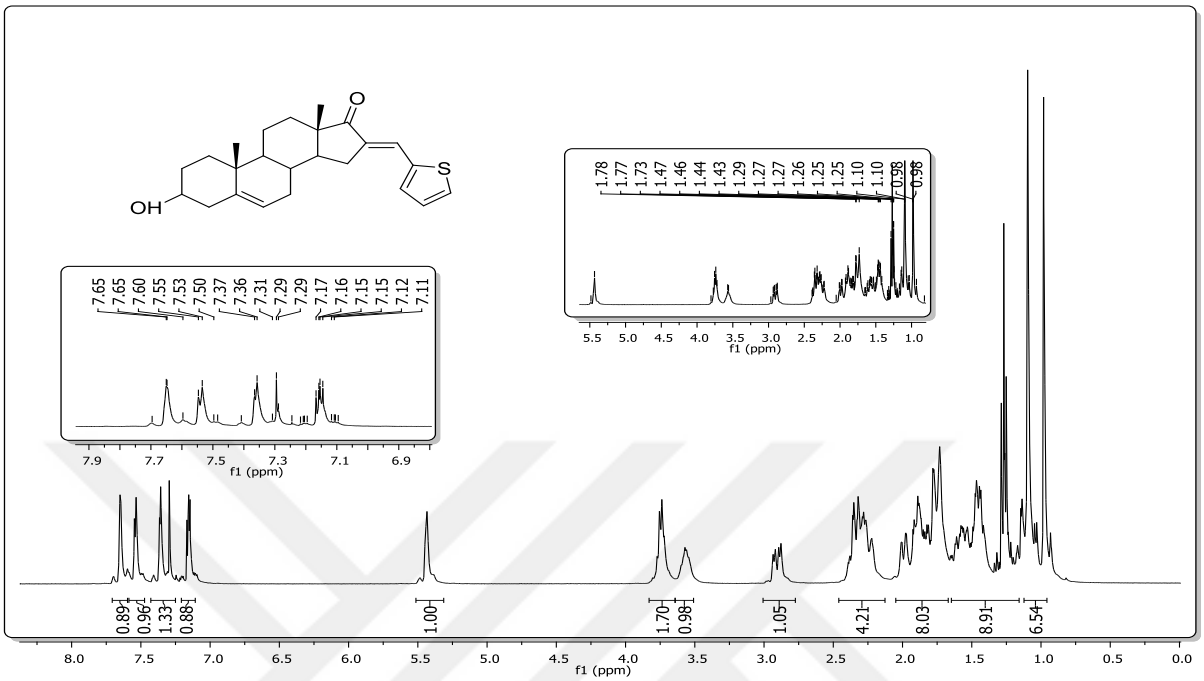


Figure A.8 ^{1}H-NMR spectrum of 16*(E)* – 16 - (2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2c)

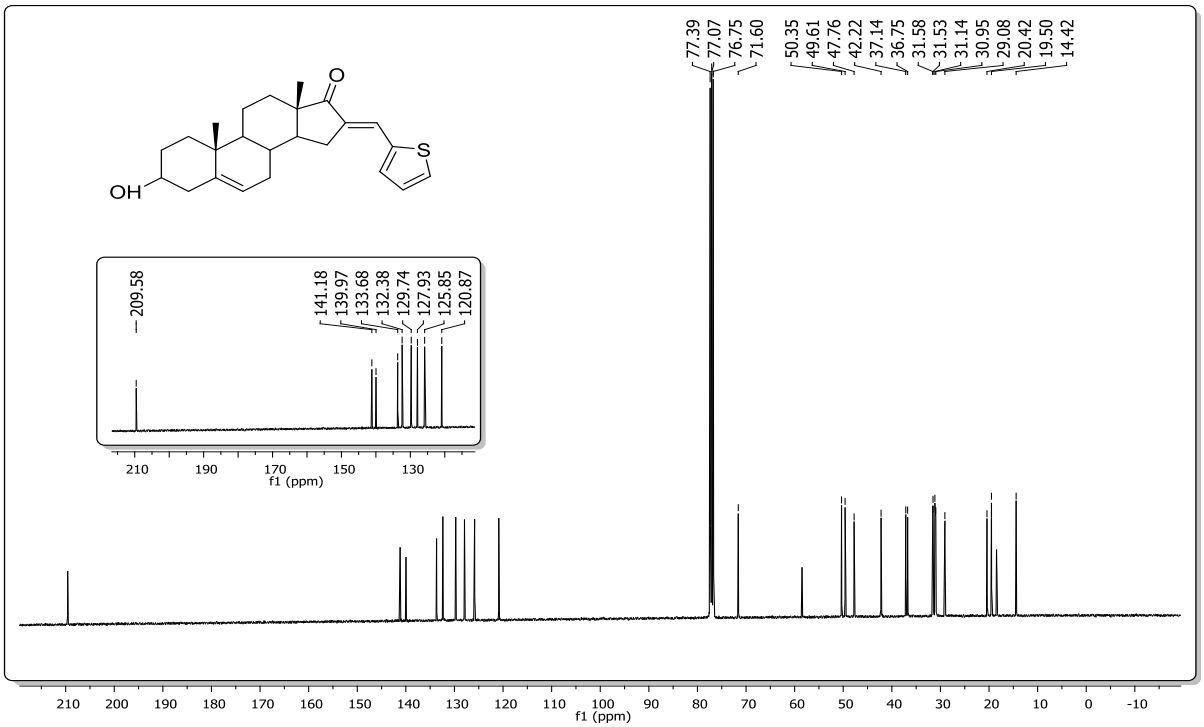
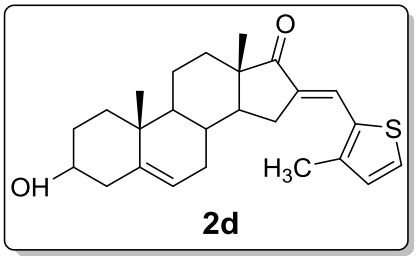


Figure A.9 ^{13}C-NMR spectrum of 16*(E)* – 16 - (2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2c)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 16*(E)* – 16 - (3-methyl-2-thiophenyliden)-3β - hydroxyandrost-5-en-17-one **(2d)**



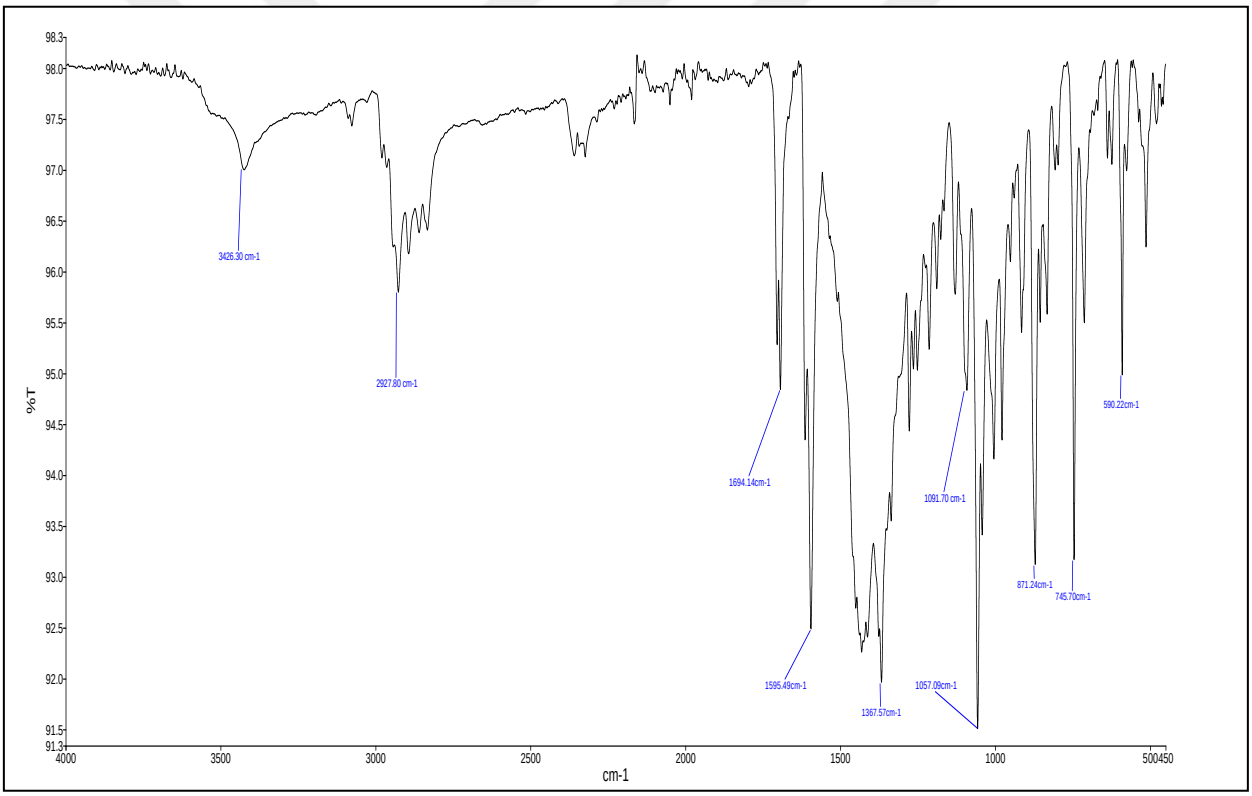


Figure A.10 IR spectrum of 16*(E)* – 16 - (3-methyl-2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2d)

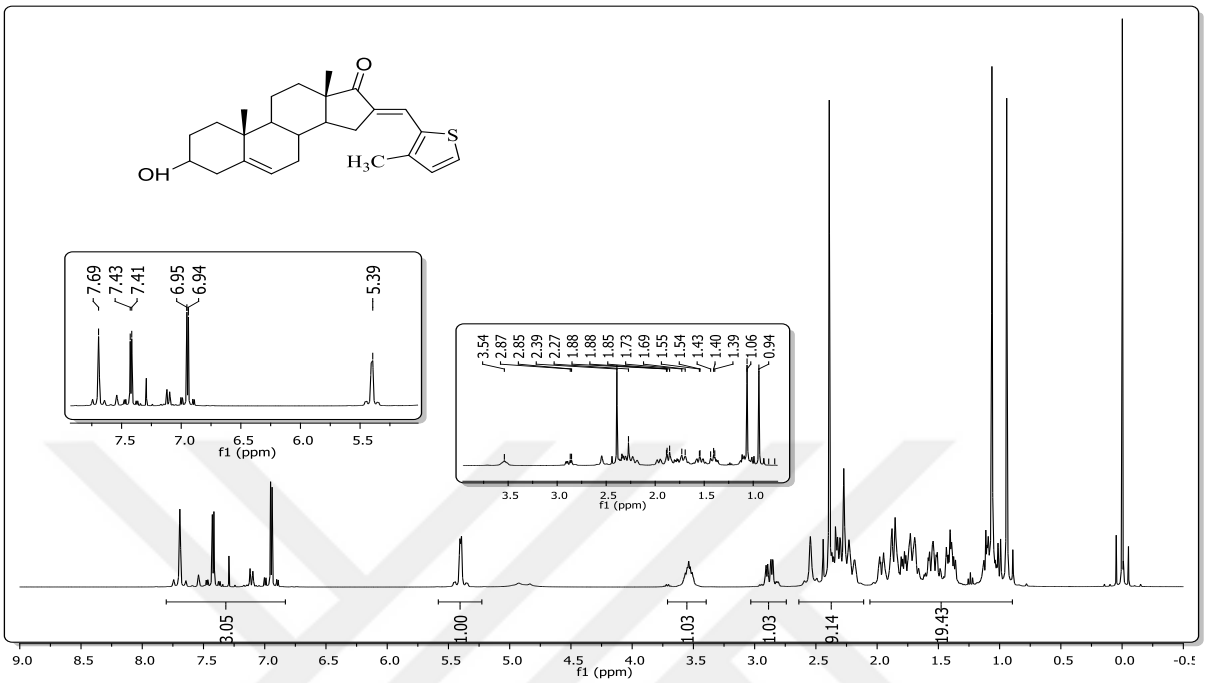


Figure A.11 1H-NMR spectrum of 16(E) – 16 - (3-methyl-2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2d)

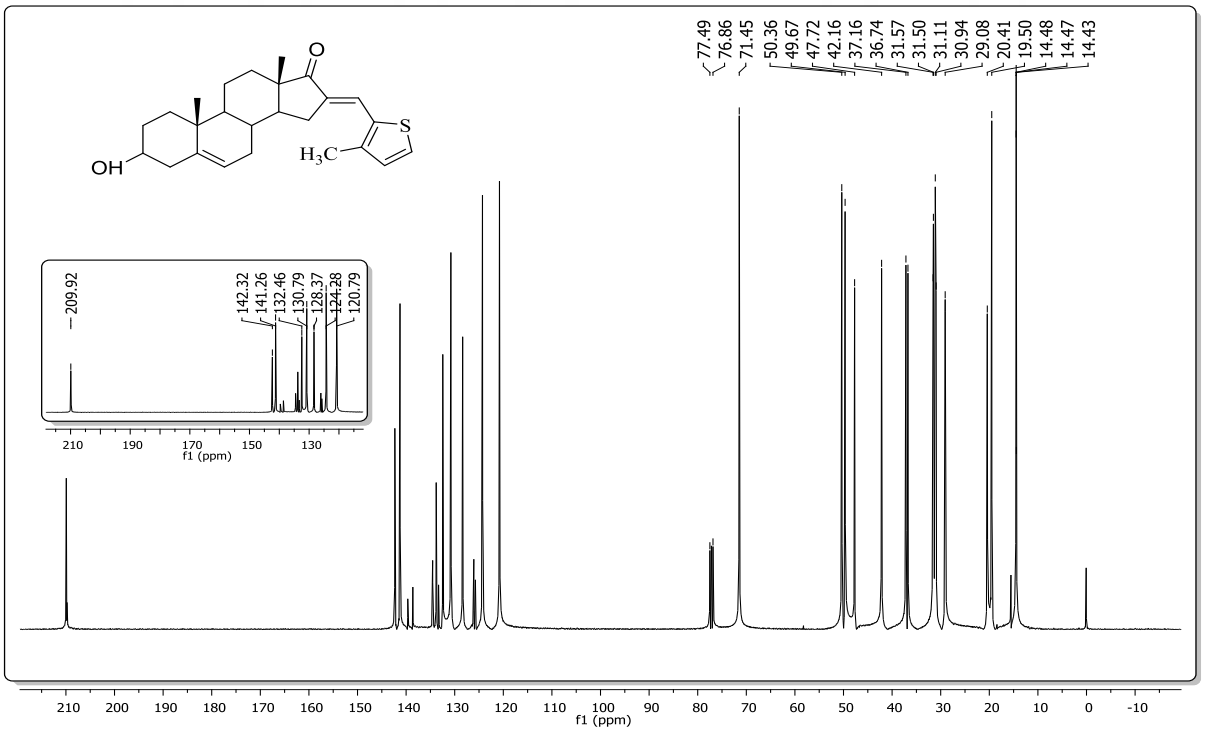
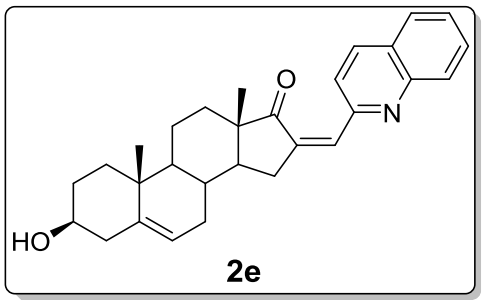


Figure A.12 ^{13}C-NMR spectrum of 16*(E)* – 16 - (3-methyl-2-thiophenyliden)-3β-hydroxyandrost-5-en-17-one (2d)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 16*(E)* -16 - (2-quinolinyliden)-3β-hydroxyandrost-5-en-17-one **(2e)**



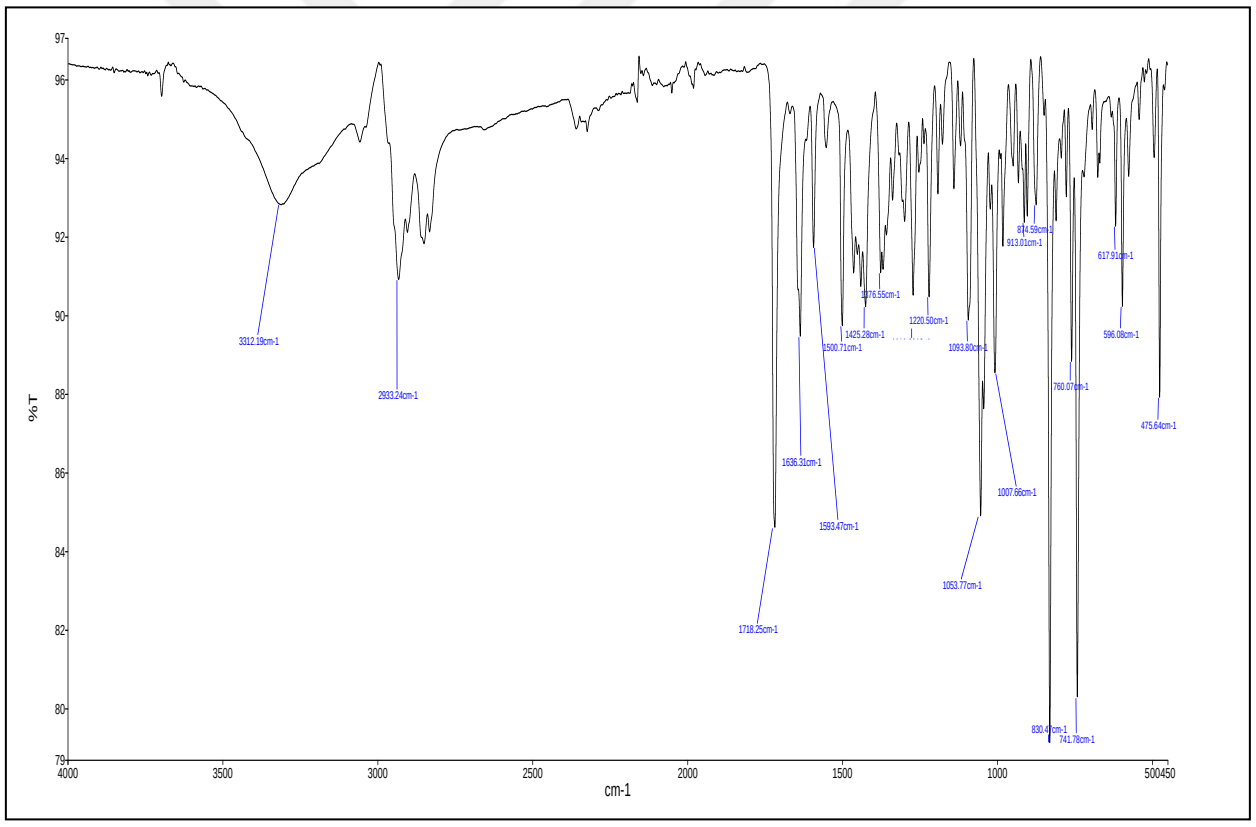


Figure A.13 IR spectrum of 16*(E)* – 16 - (2-quinolinyliden)-3β-hydroxyandrost-5-en-17-one (2e)

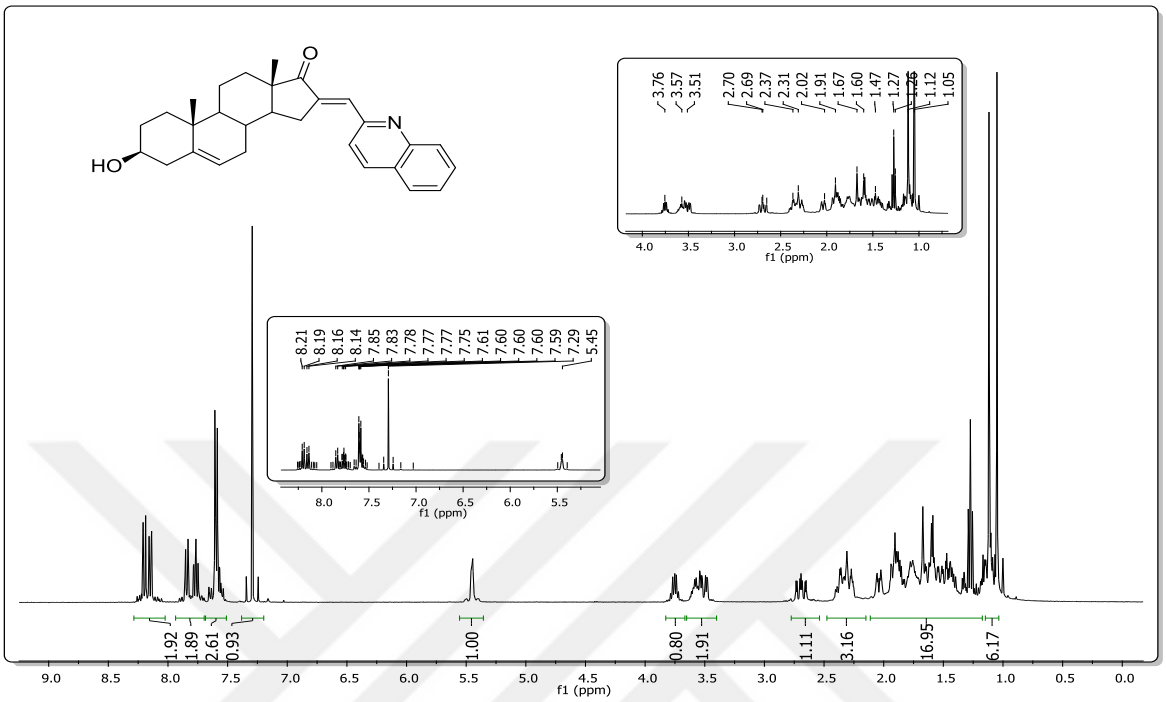


Figure A.14 1H-NMR spectrum of 16(E) – 16 - (2-quinolinyliden)-3β-hydroxyandrost-5-en-17-one (2e)

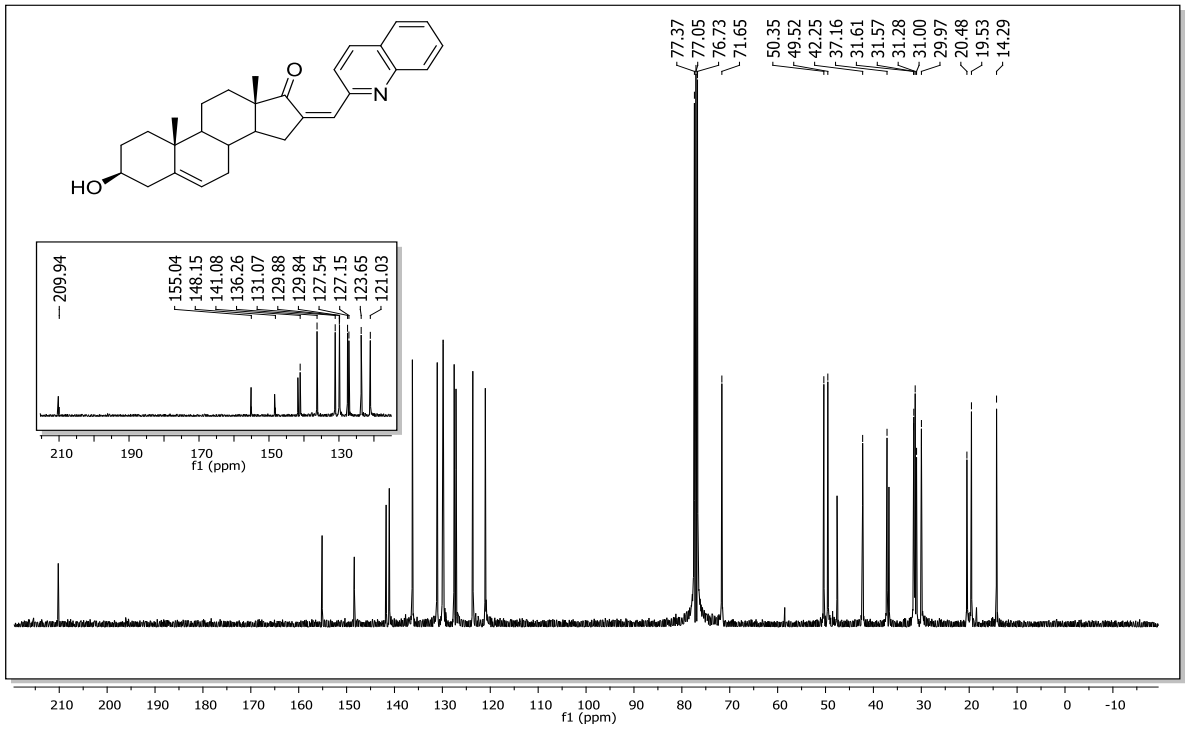
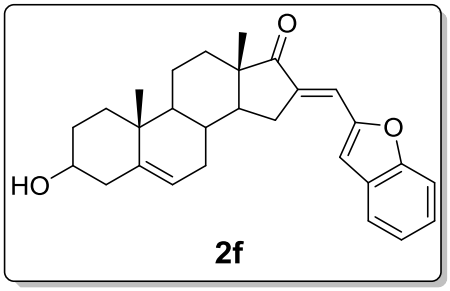


Figure A.15 ^{13}C-NMR spectrum of 16*(E)* – 16 - (2-quinolinyliden)-3β-hydroxyandrost-5-en-17-one (2e)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 16*(E)* – 16 - (2-benzofuranyliden)-3β-hydroxyandrost-5-en-17-one **(2f)**



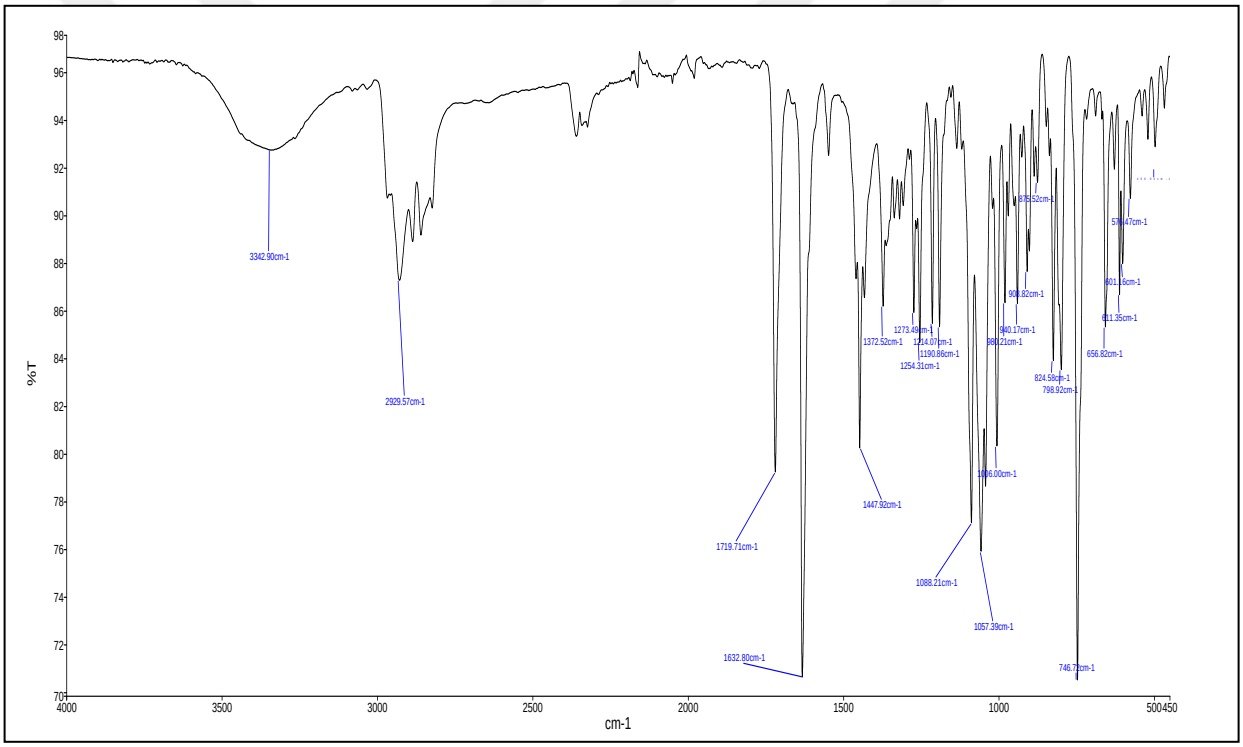


Figure A.16 IR spectrum of 16*(E)* – 16 - (2-benzofuranyliden)-3β-hydroxyandrost-5-en-17-one (2f)

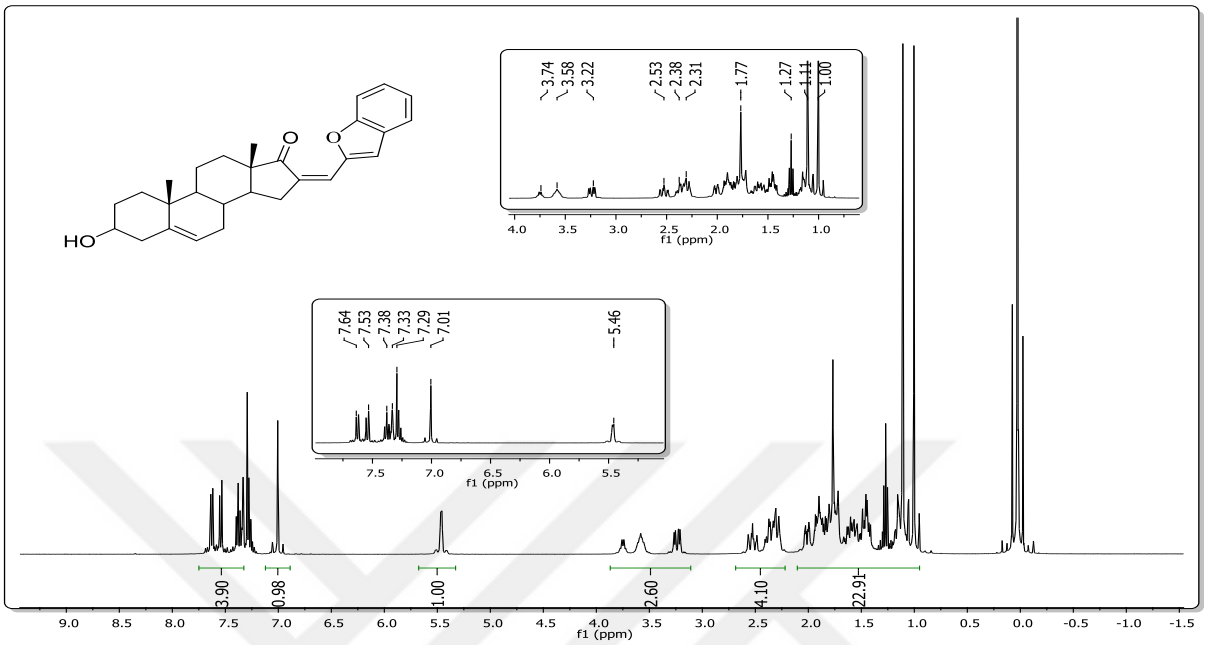


Figure A.17 ^{1}H-NMR spectrum of 16*(E)* – 16 - (2-benzofuranyliden)-3β-hydroxyandrost-5-en-17-one (2f)

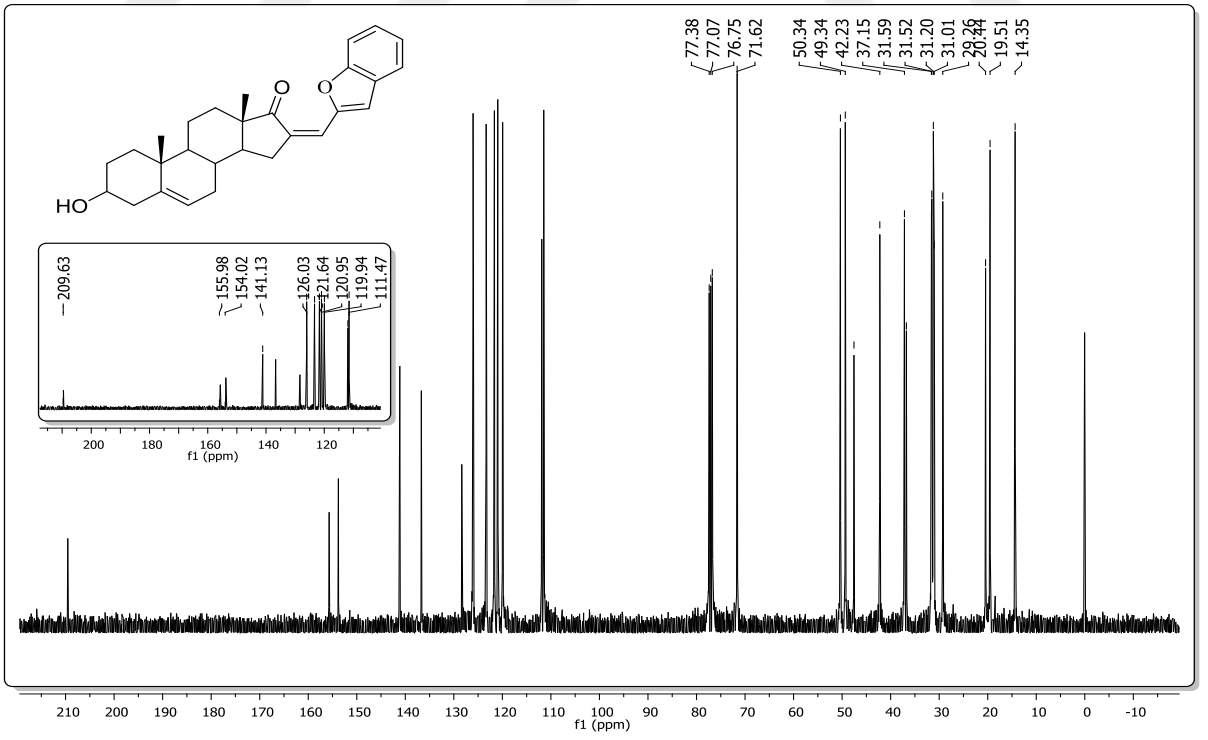
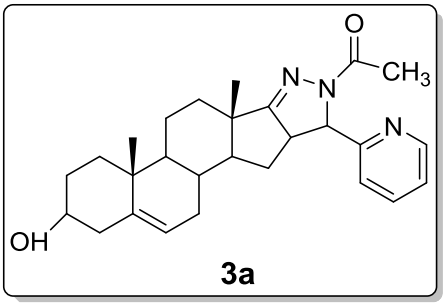


Figure A.18 ^{13}C-NMR spectrum of 16*(E)* – 16 - (2-benzofuranyliden)-3β-hydroxyandrost-5-en-17-one (2f)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene **(3a)**



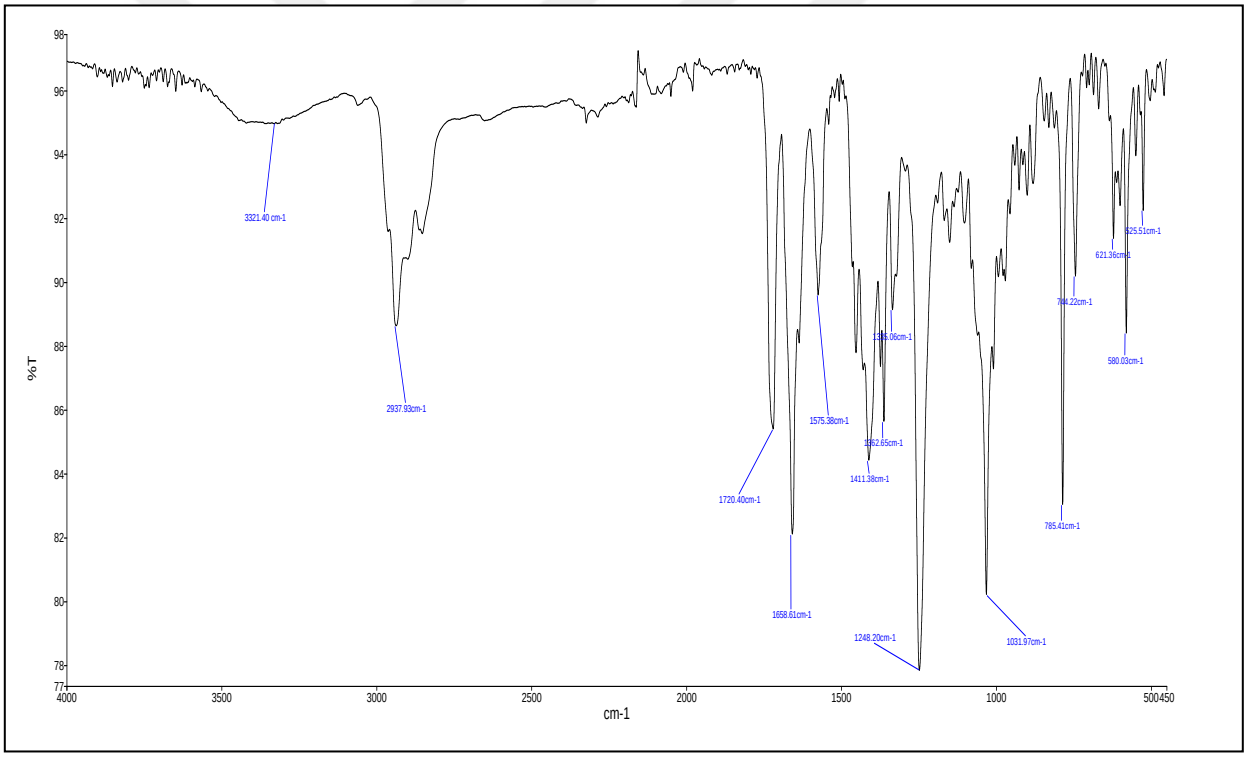


Figure A.19 IR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (3a)

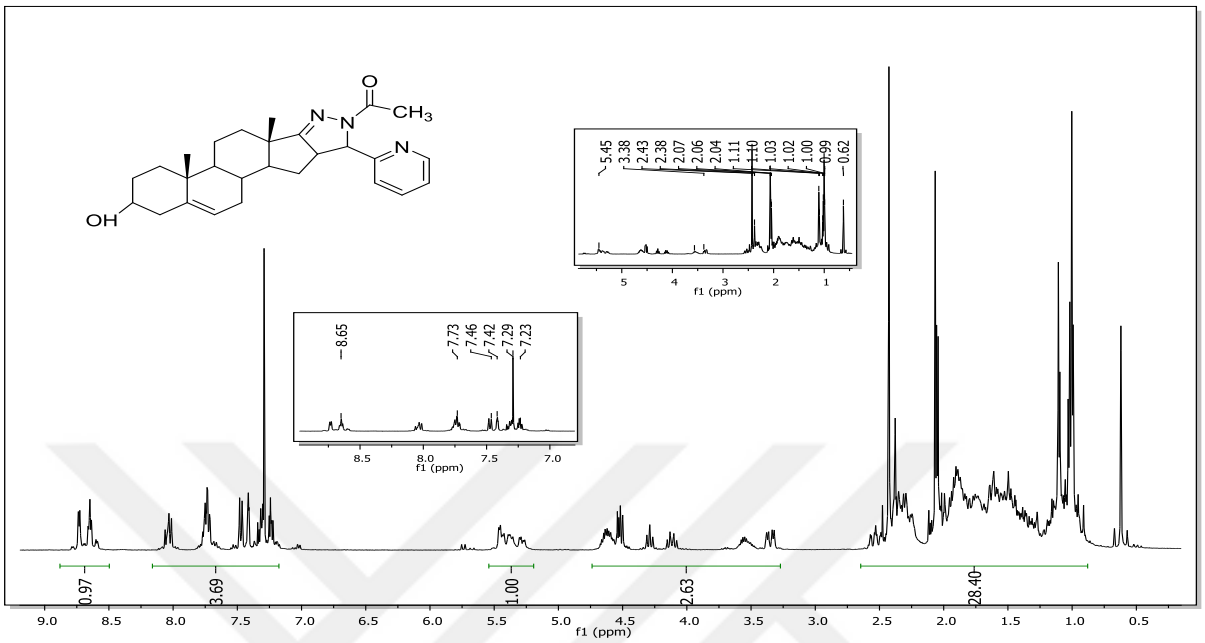


Figure A.20 ^{1}H-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (3a)

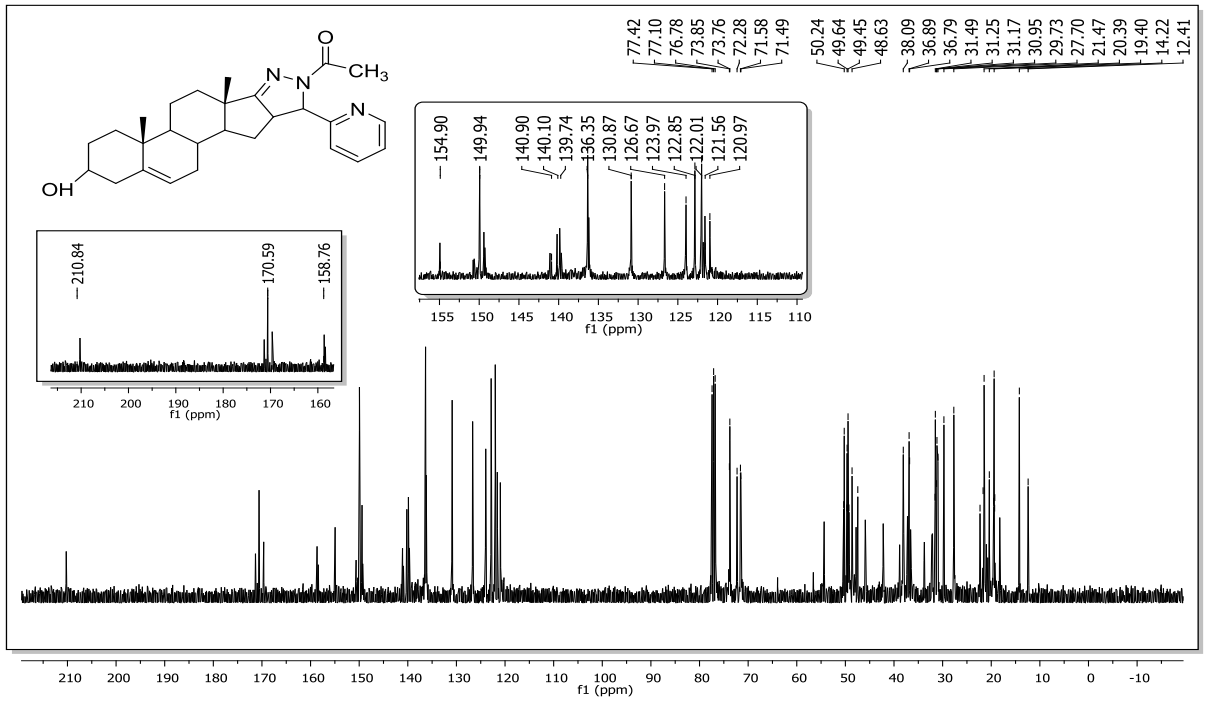
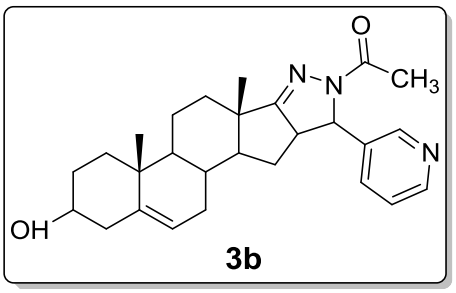


Figure A.21 ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (3a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene **(3b)**



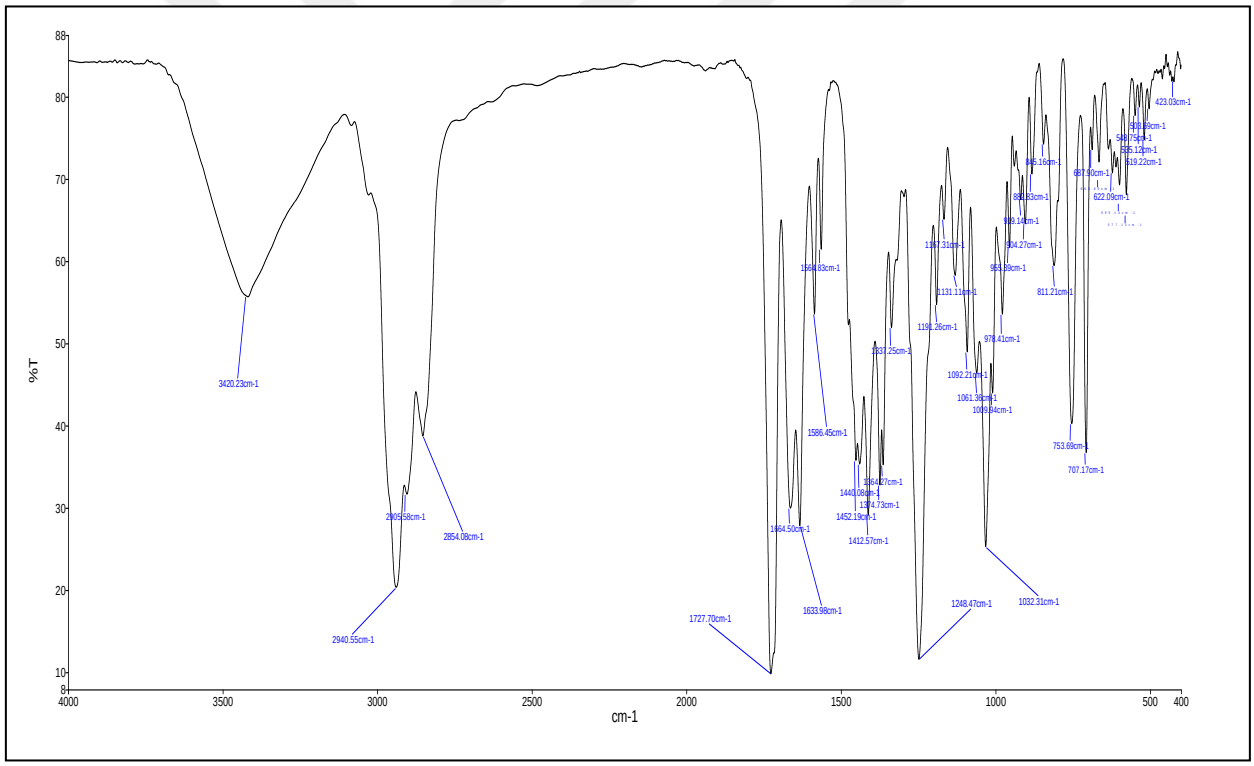


Figure A.22 IR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (3b)

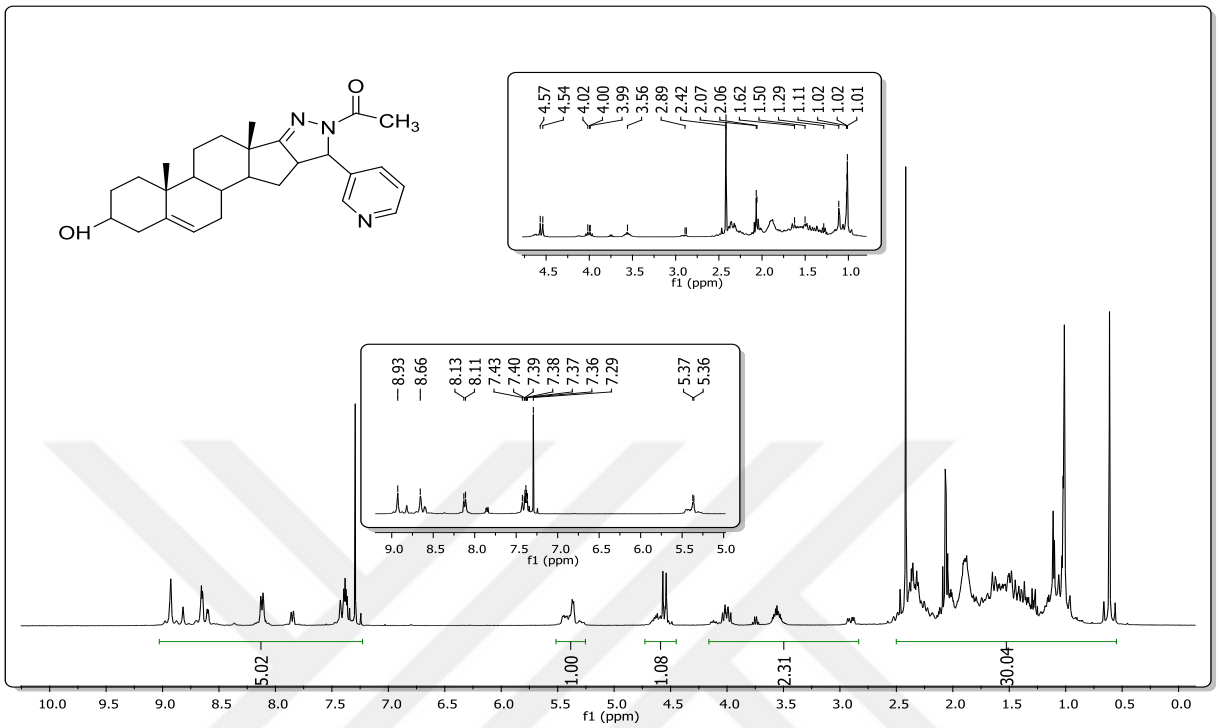


Figure A.23 1H-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (3b)

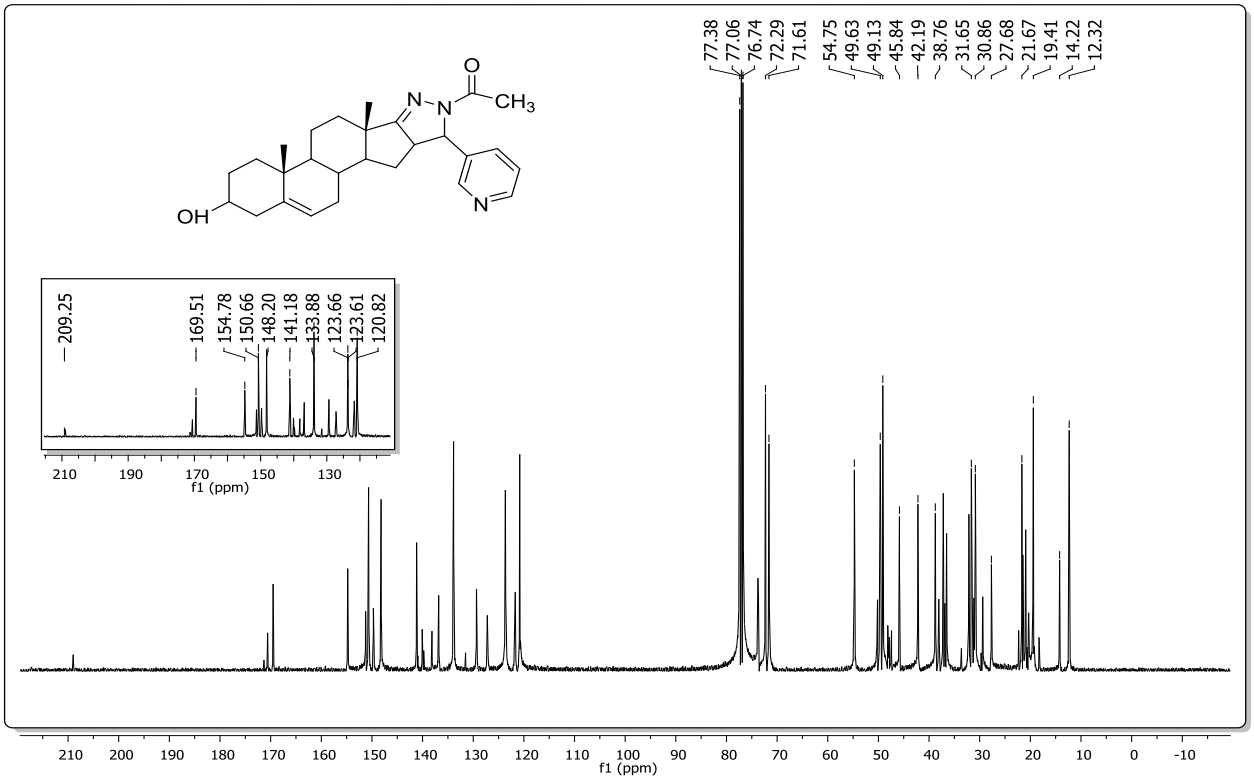
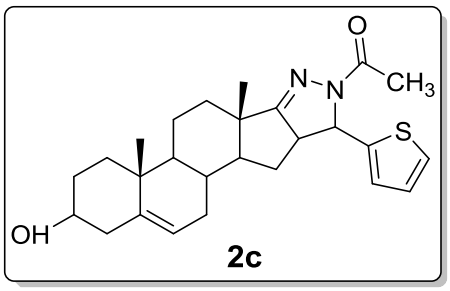


Figure A.24 13C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (3b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene **(3c)**



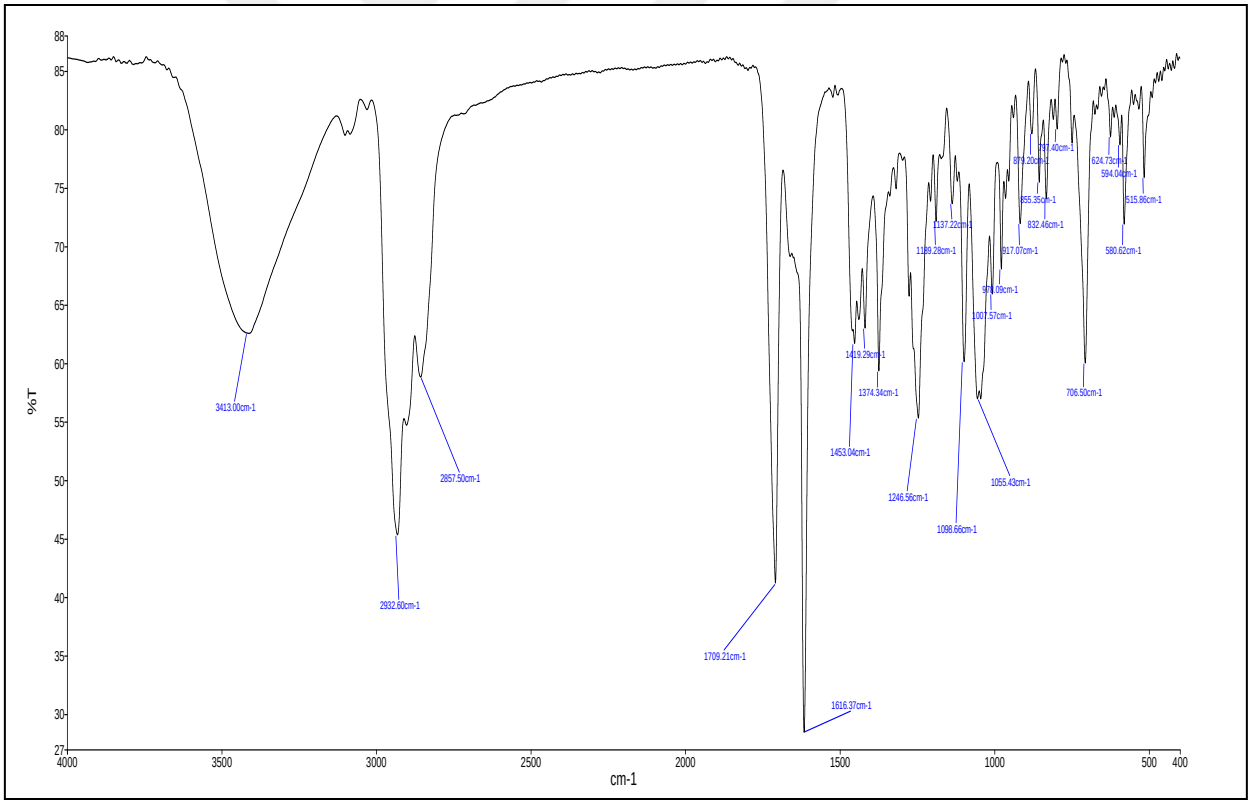


Figure A.25 IR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (3

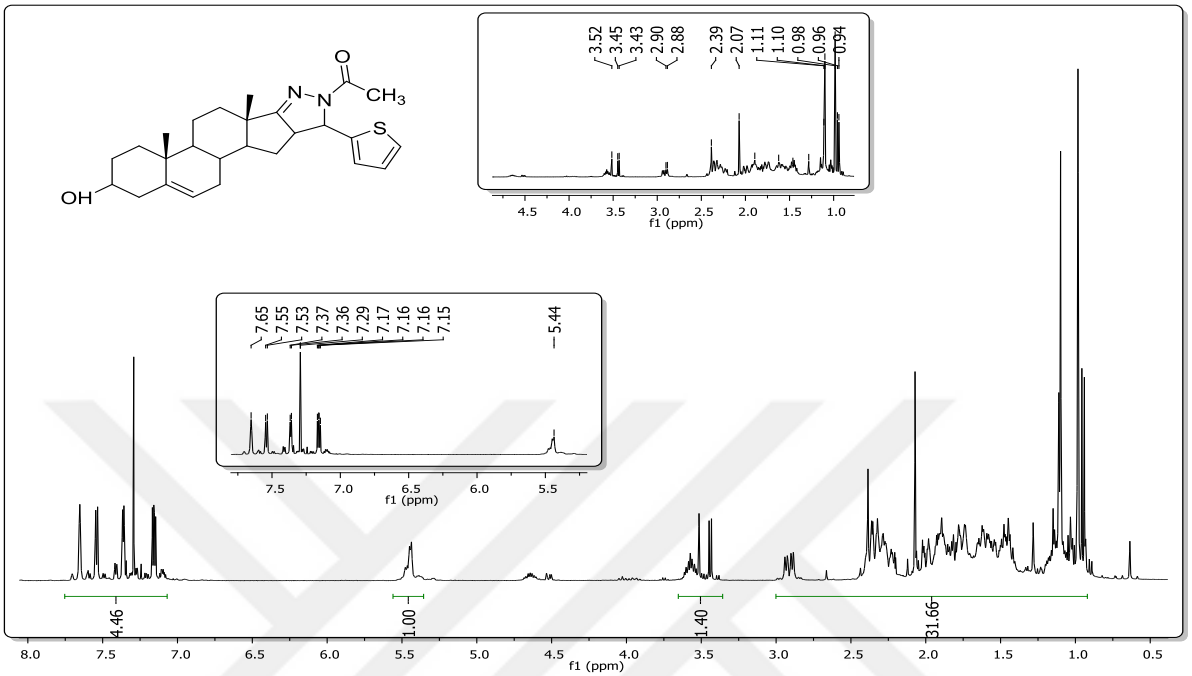


Figure A.26 1H-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (3c)

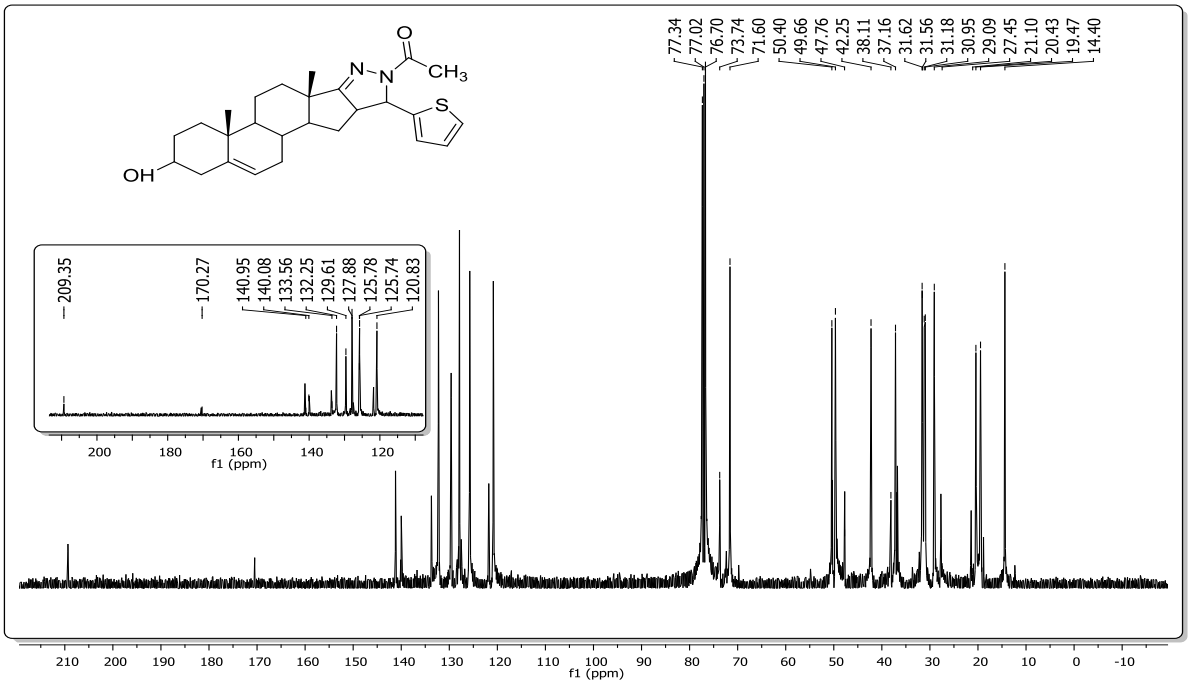
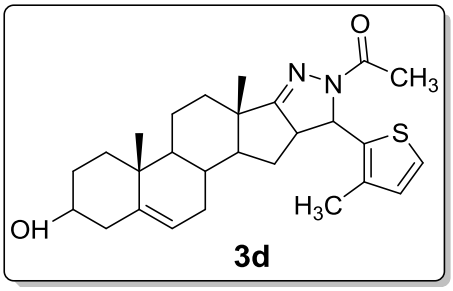


Figure A.27 ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (3c)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene **(3d)**



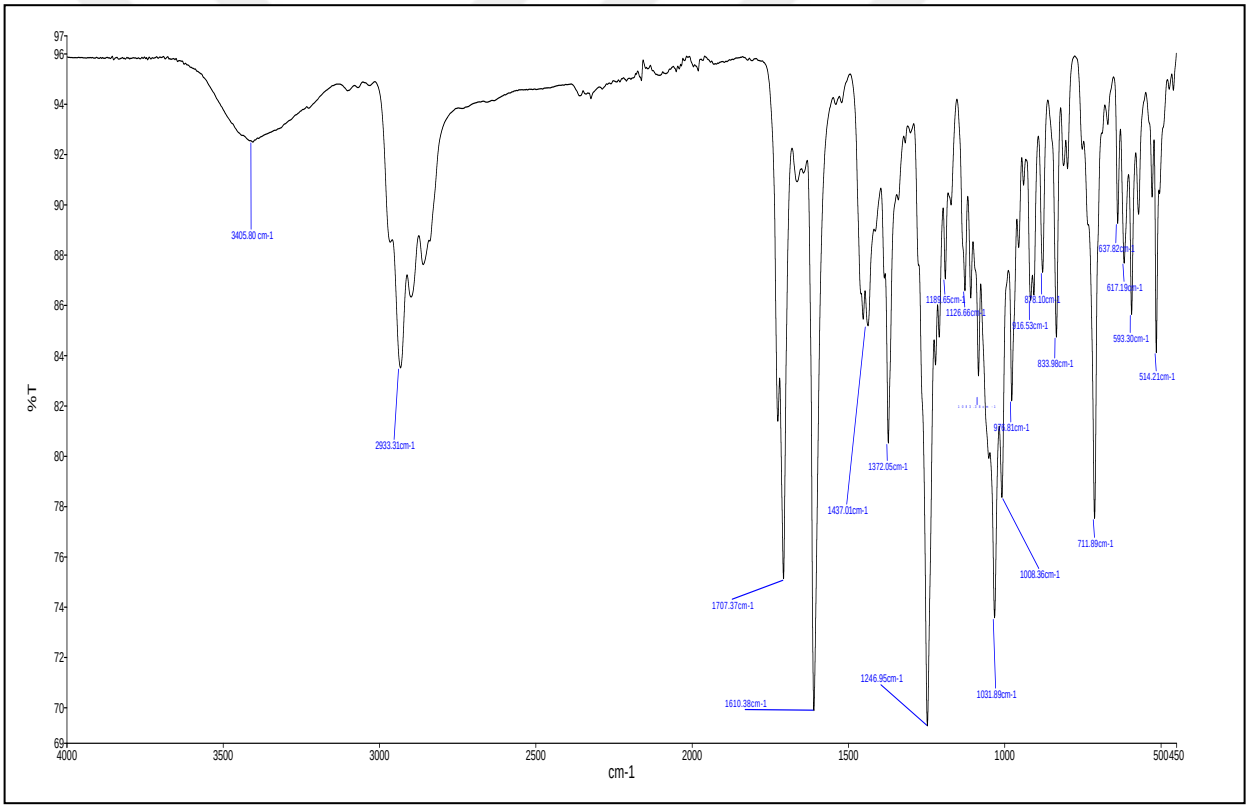


Figure A.28 IR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (3d)

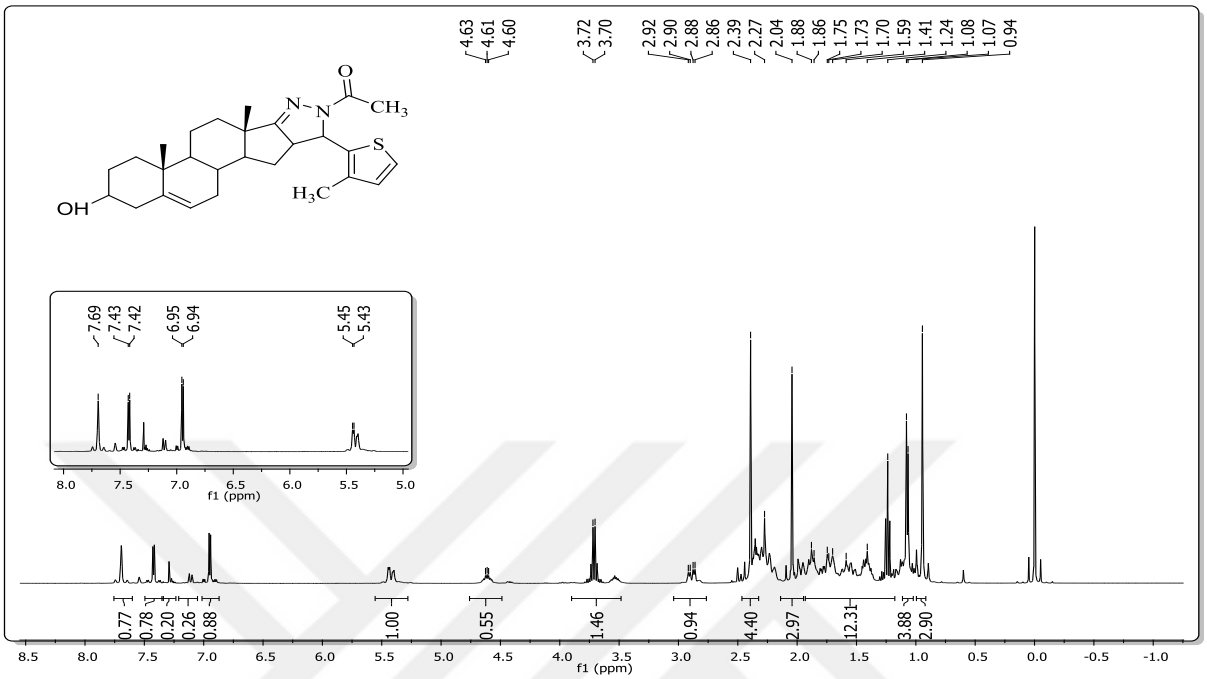


Figure A.29 ^{1}H-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (3d)

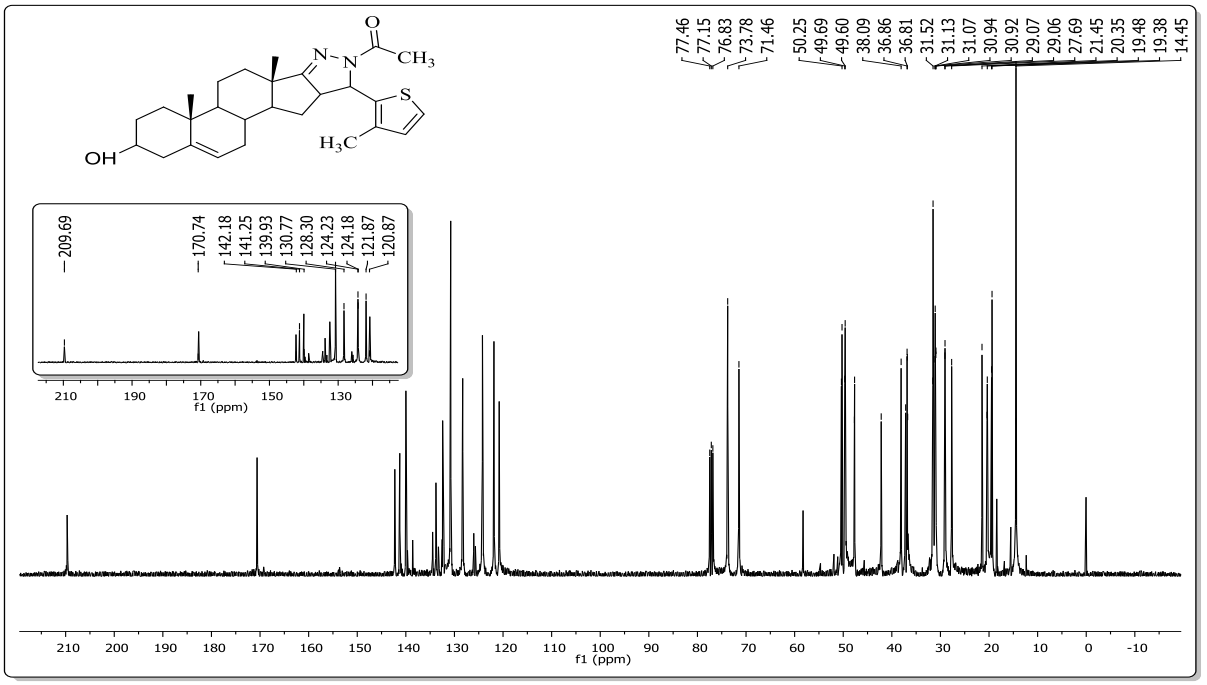
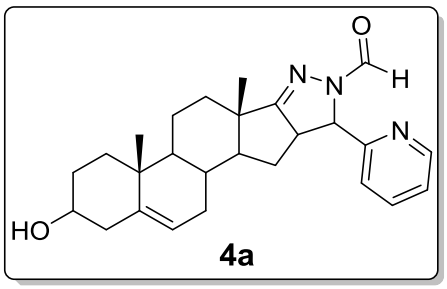


Figure A.30 ^{13}C-NMR spectrum of 3β-hydroxy-(1-Acetyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (3d)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene **(4a)**



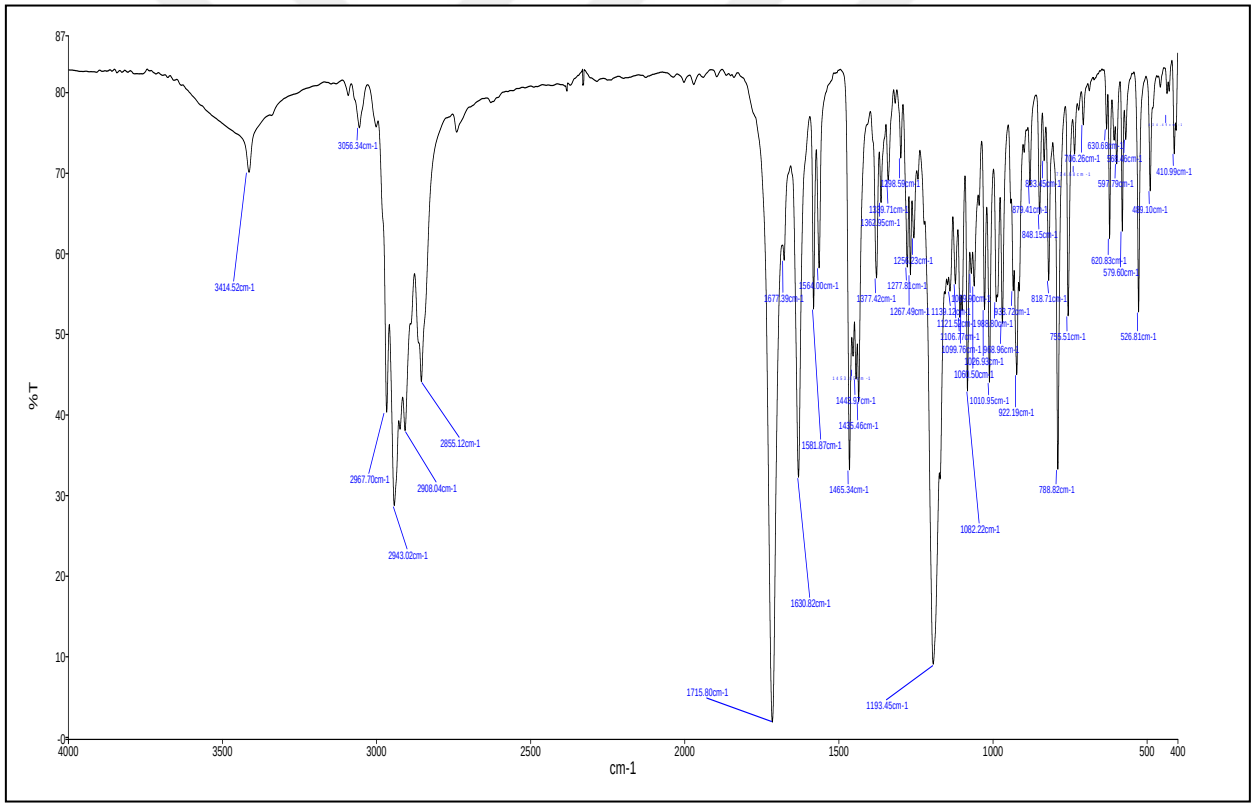


Figure A.31 IR spectrum of 3β-hydroxy-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (4a)

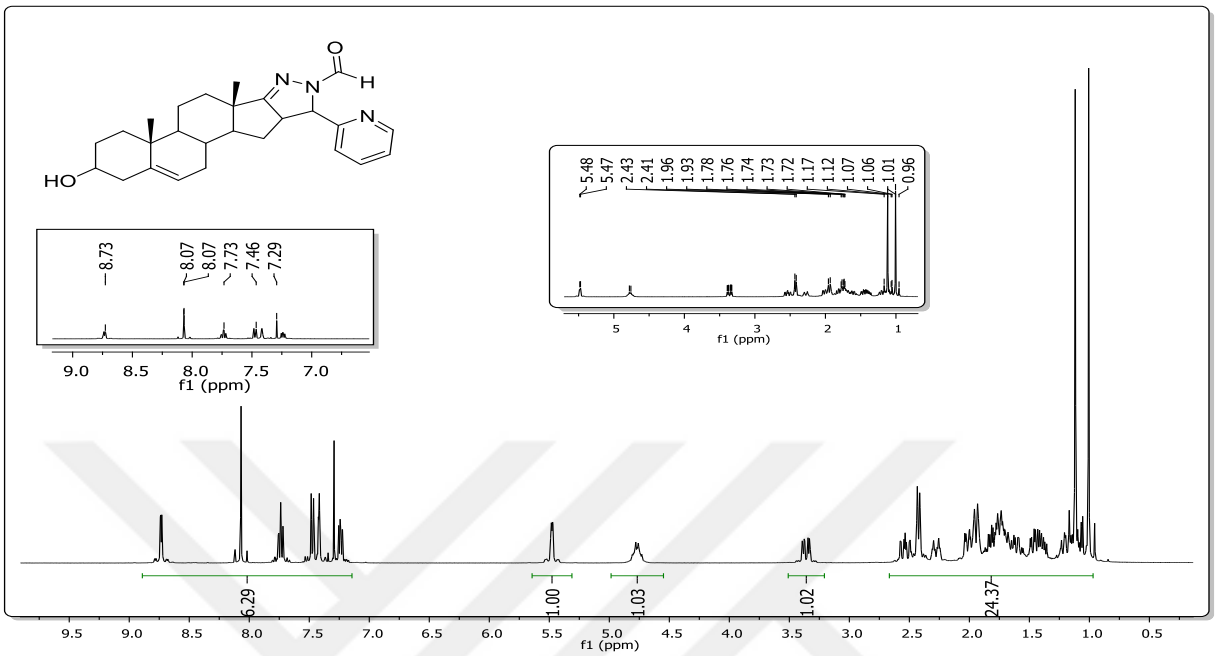


Figure A.32 1H-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (4a)

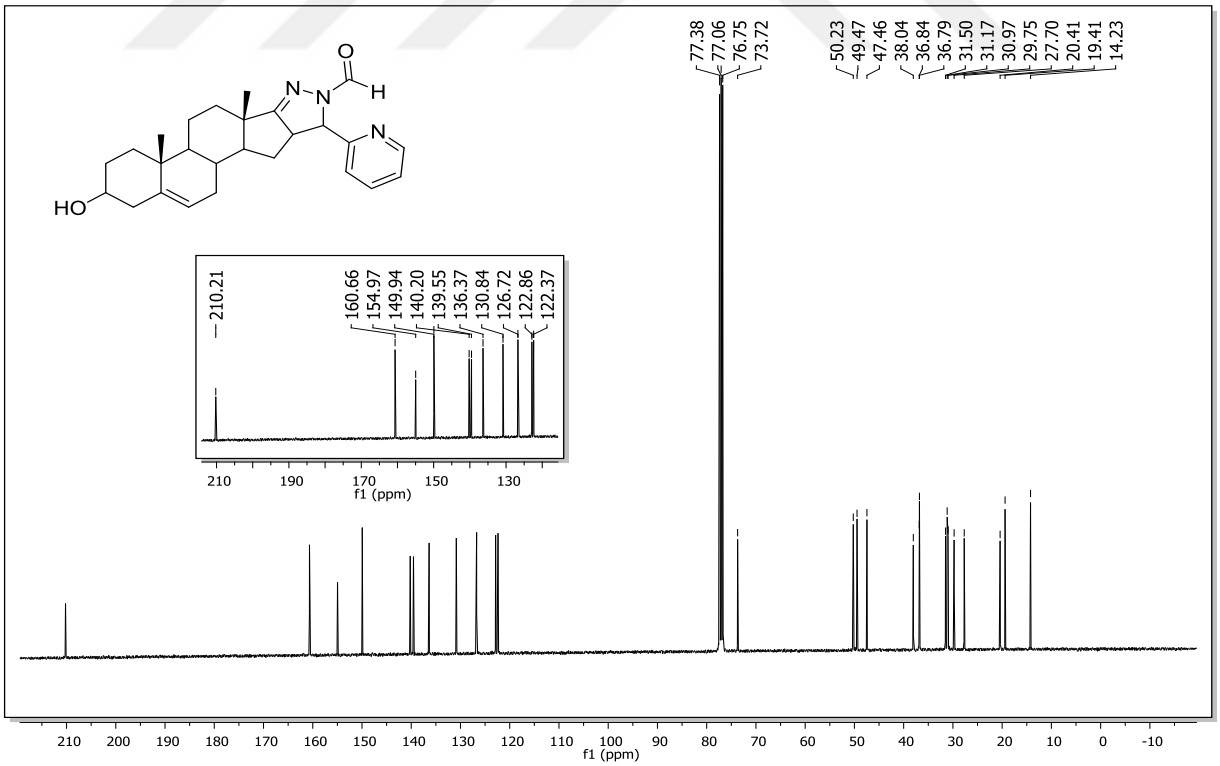
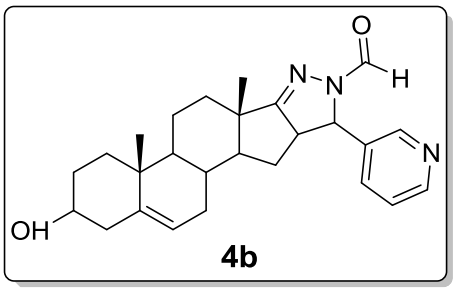


Figure A.33 13C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (4a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene **(4b)**



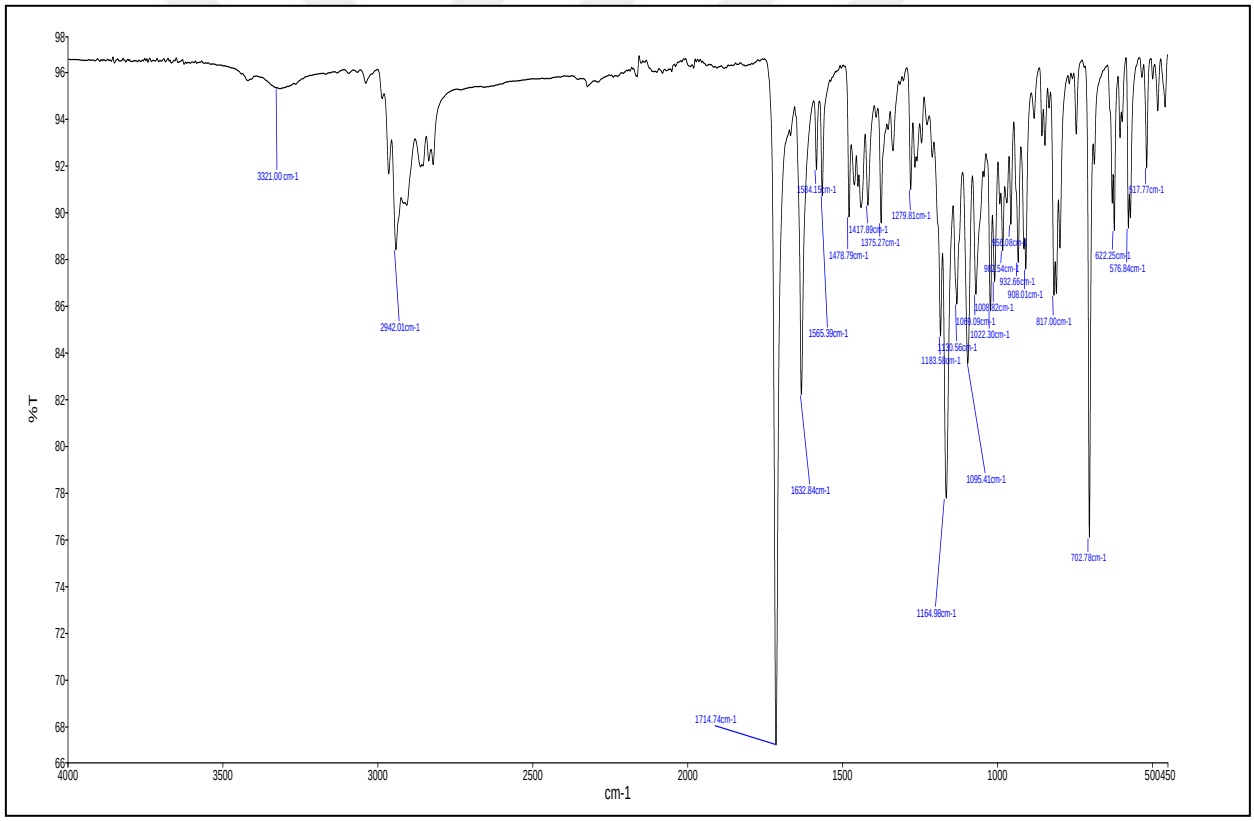


Figure A.34 IR spectrum of 3β-hydroxy-(1-Formyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (4b)

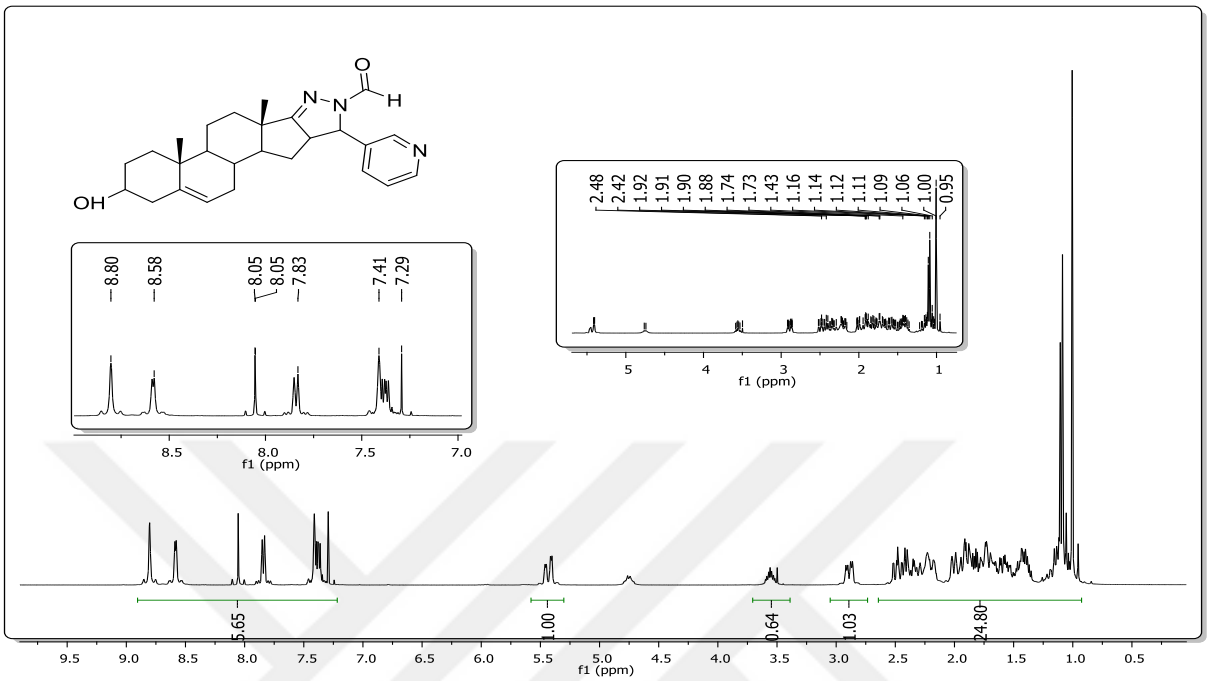


Figure A.35 ^{1}H-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (4b)

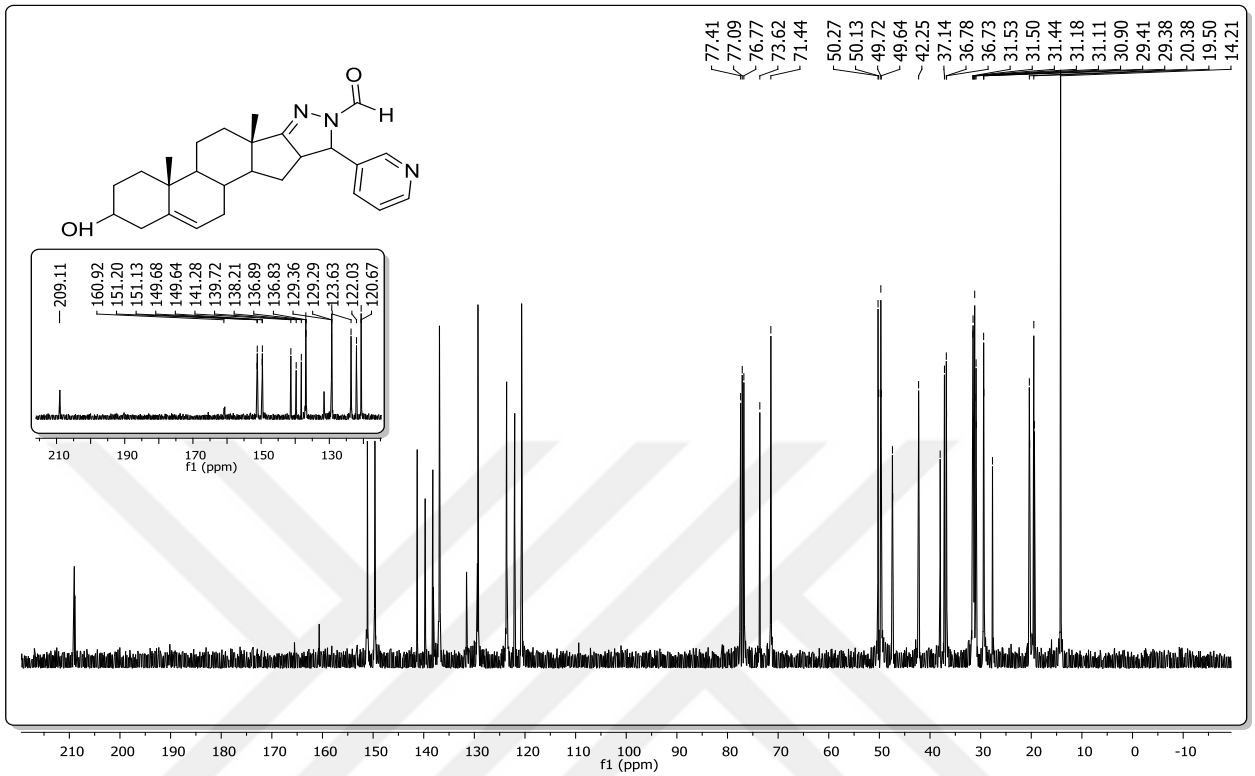
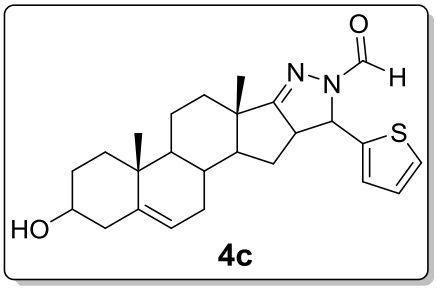


Figure A.36 13C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(3-pyridinyl)-16,17-pyrazolinyl)androst-5-ene (4b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene **(4c)**



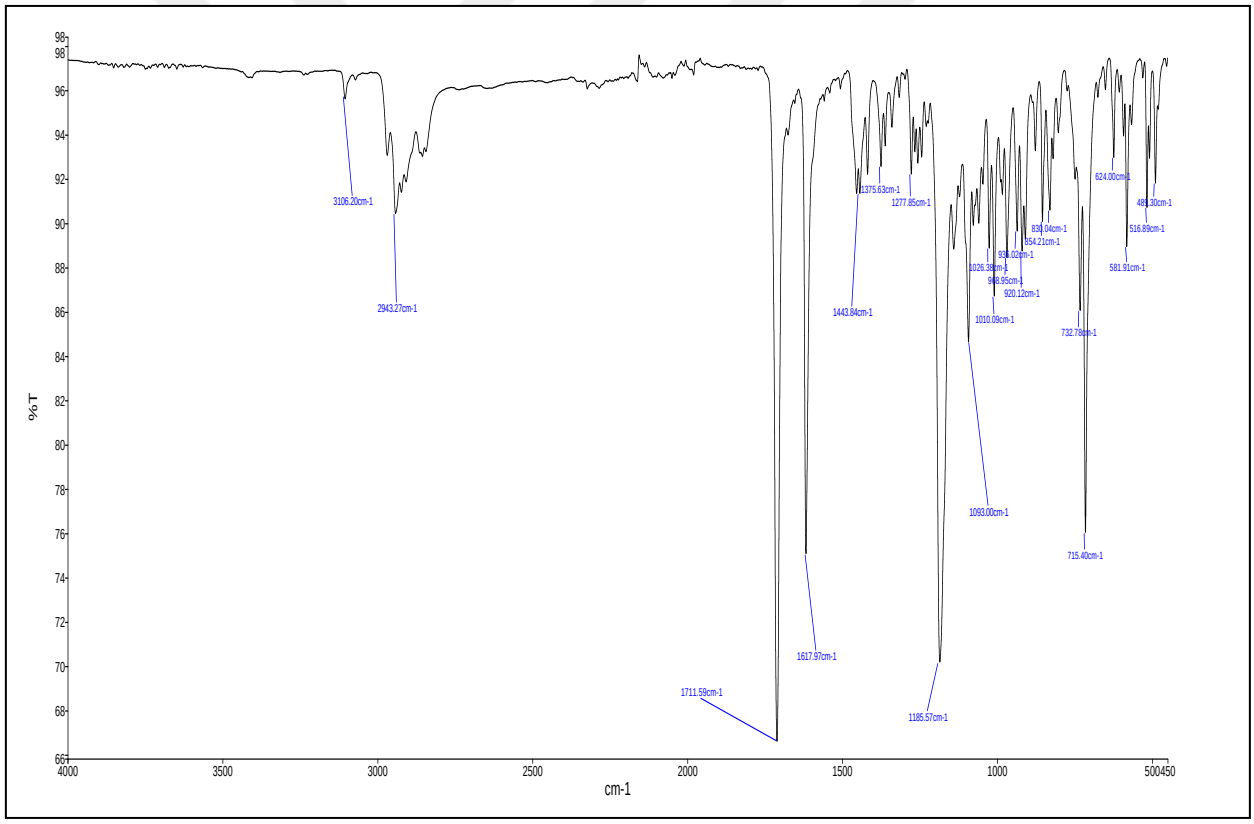


Figure A.37 IR spectrum of 3β-hydroxy-(1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4c)

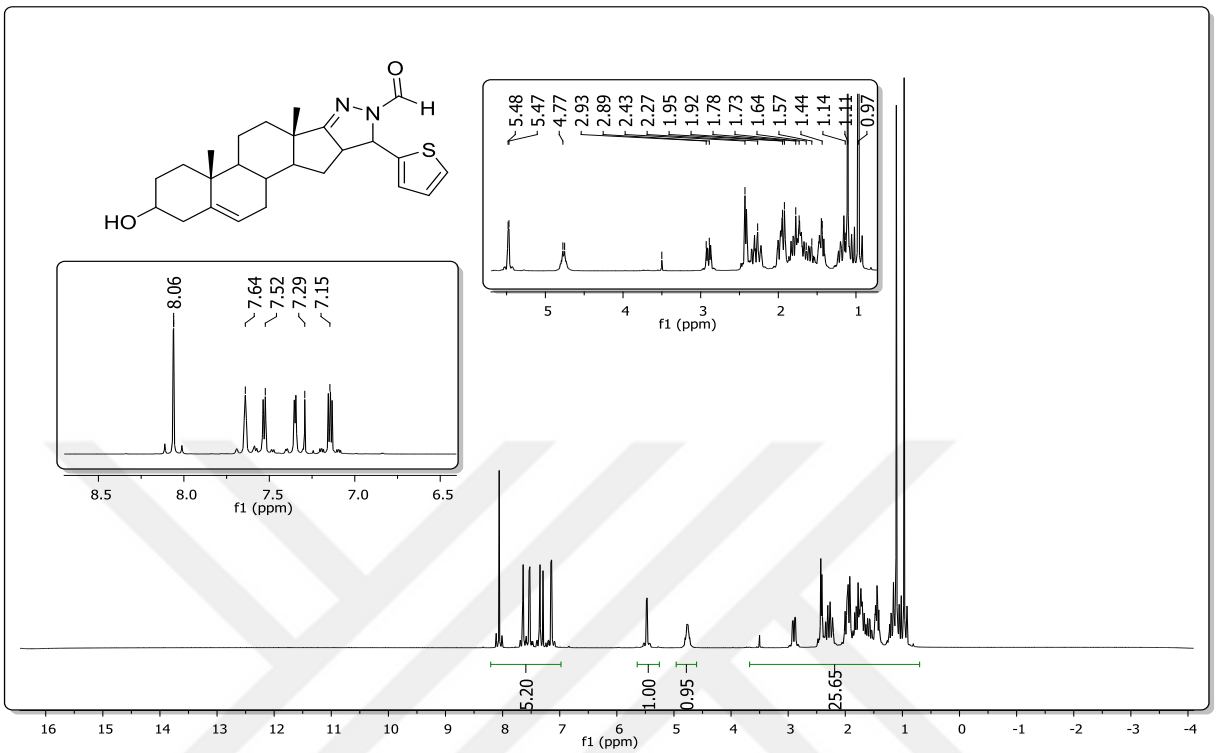


Figure A.38 ^{1}H-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4c)

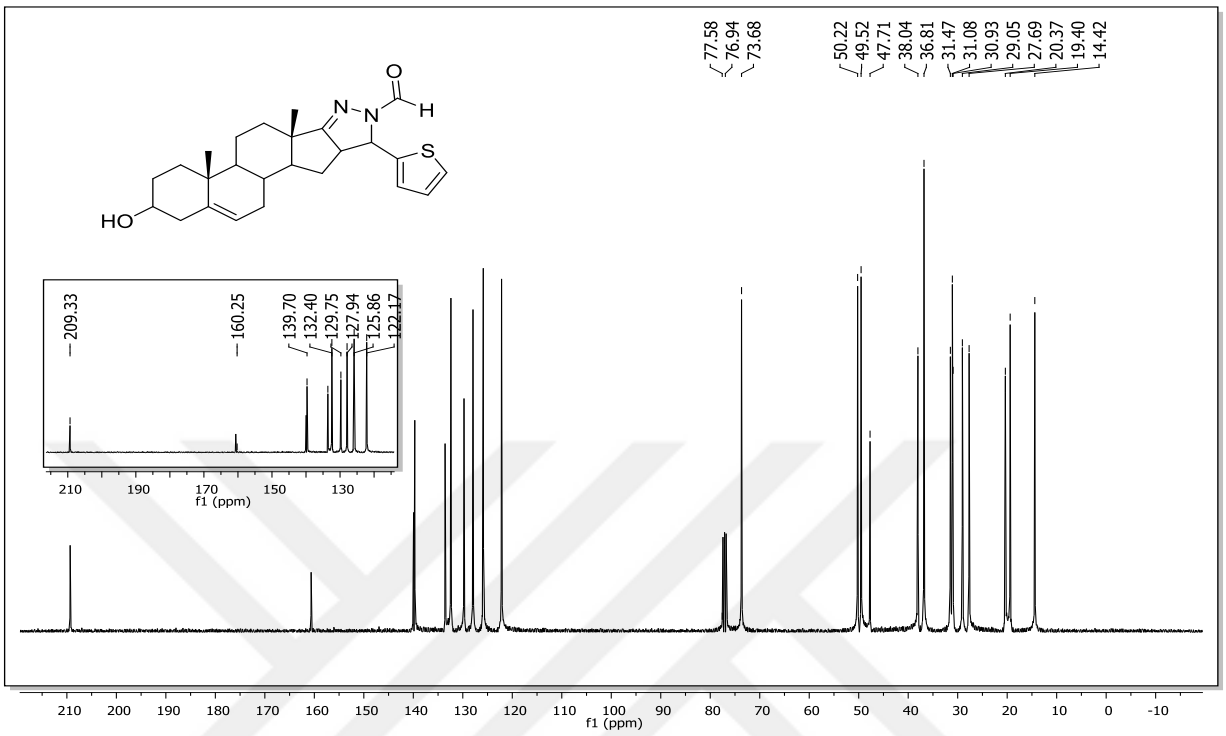
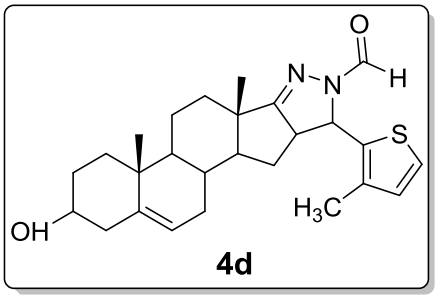


Figure A.39 ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-thiophenyl)-16,17-pyrazolinyl) androst-5-ene (4c)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene **(4d)**



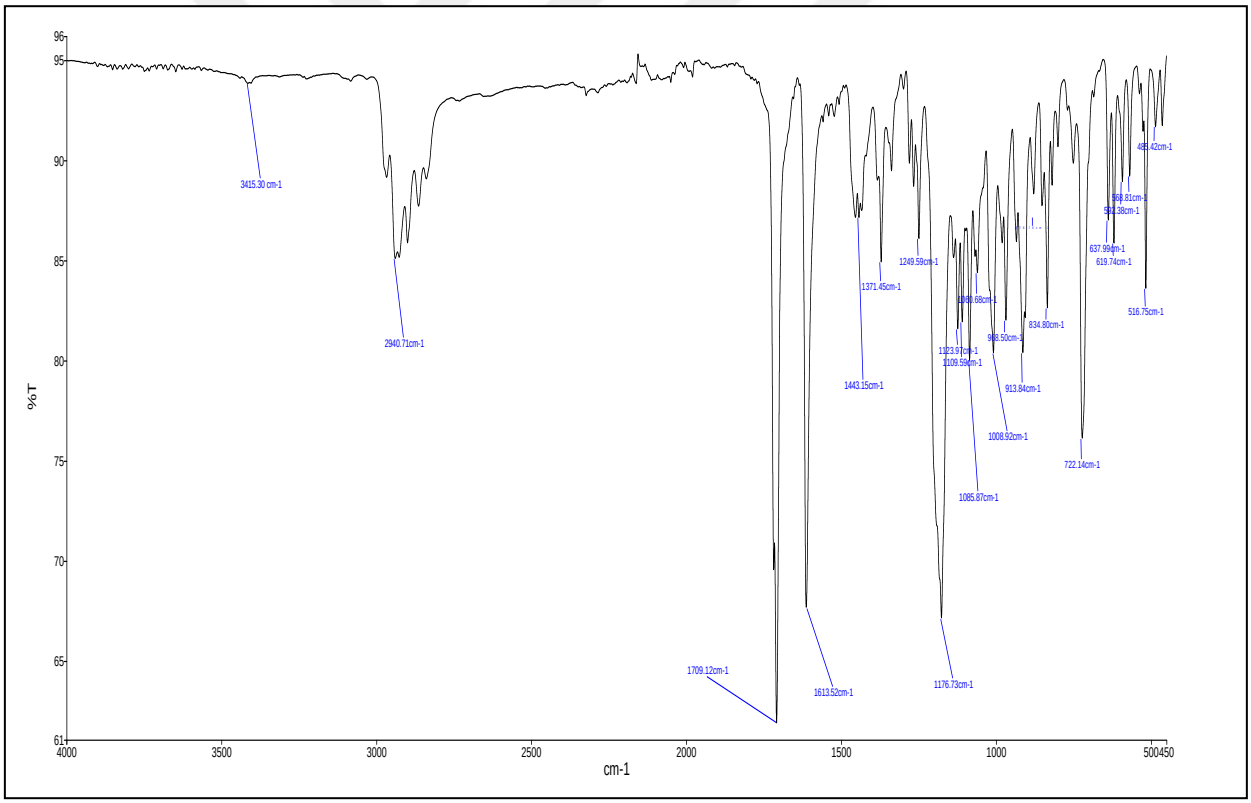


Figure A.40 IR spectrum of 3β-hydroxy-(1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (4d)

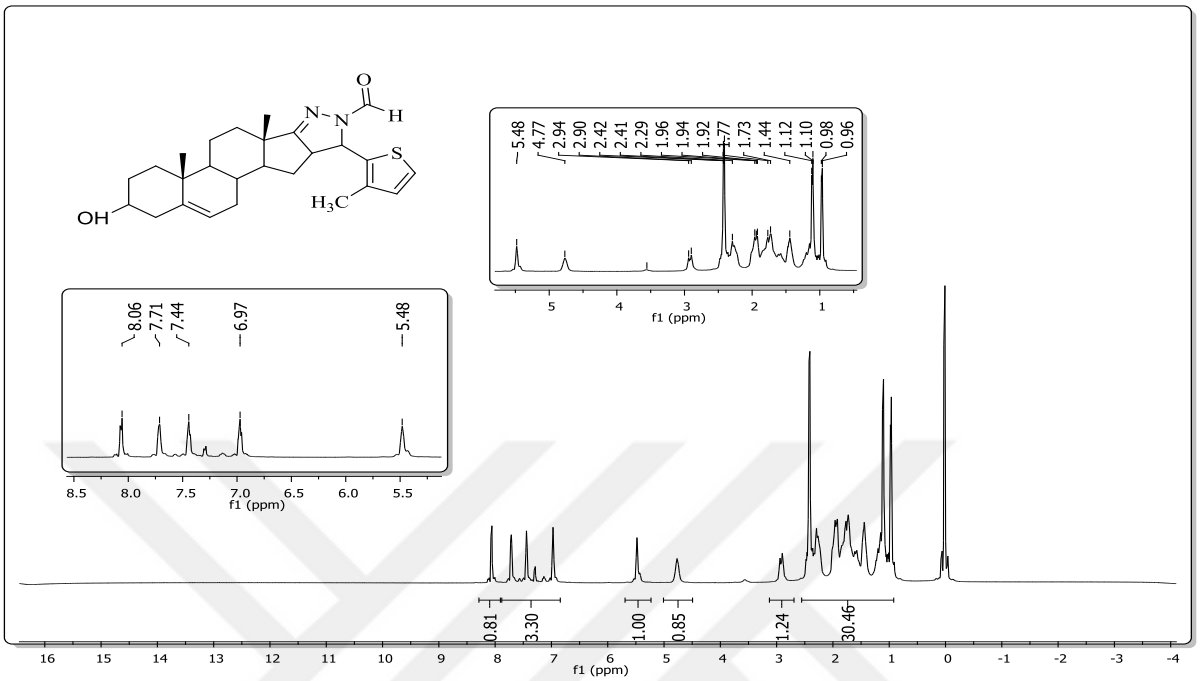


Figure A.41 ^{1}H-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (4d)

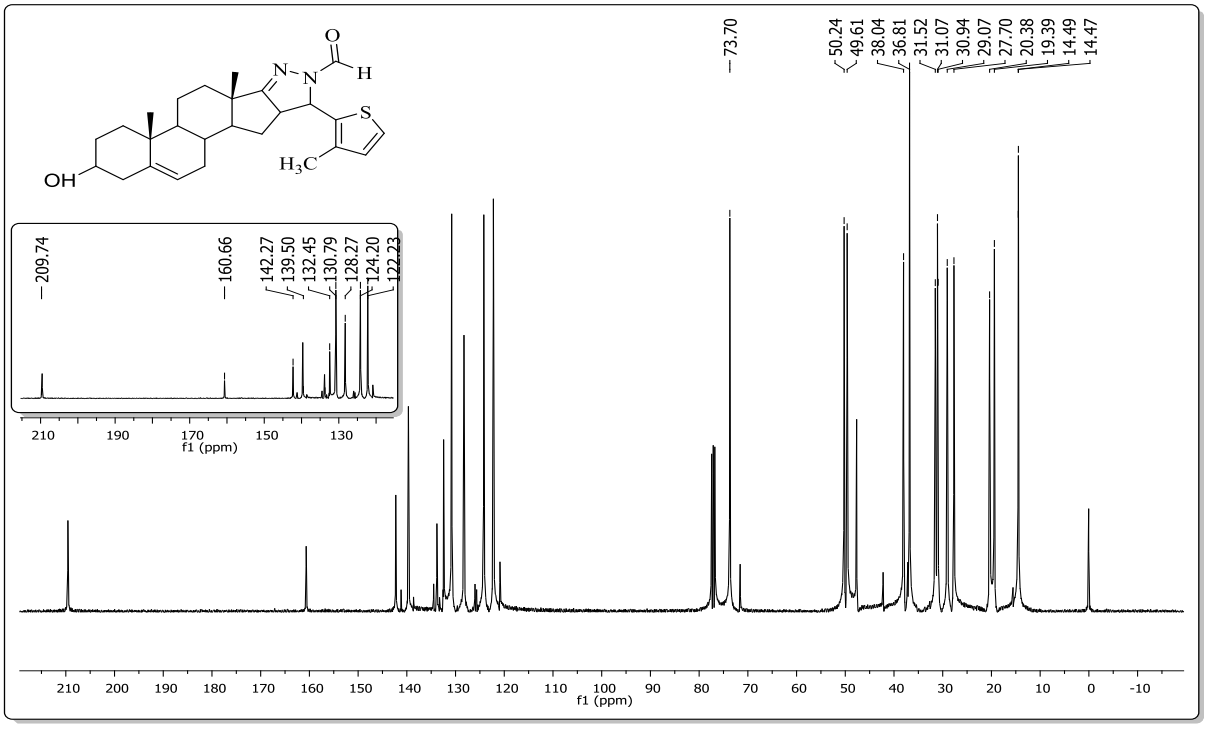
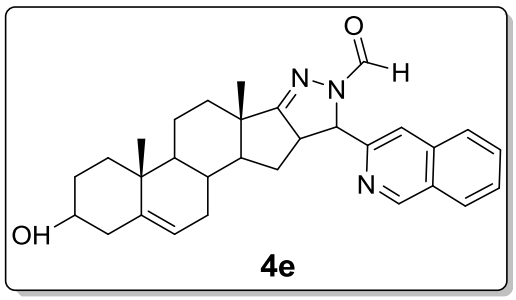


Figure A.42 ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(3-methyl-2-thiophenyl)-16,17-pyrazolinyl)androst-5-ene (4d)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl)androst-5-ene **(4e)**



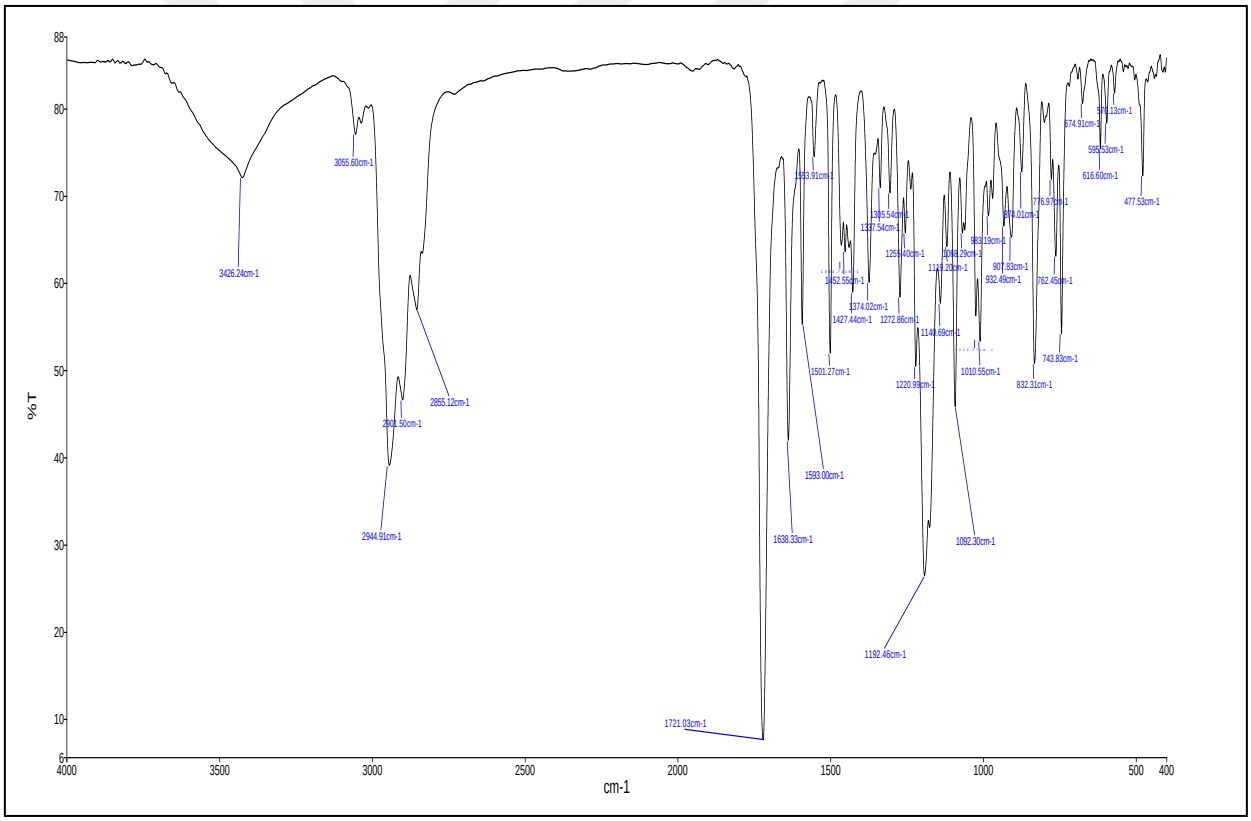


Figure A.43 IR spectrum of 3β-hydroxy-(1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl)androst-5-ene (4e)

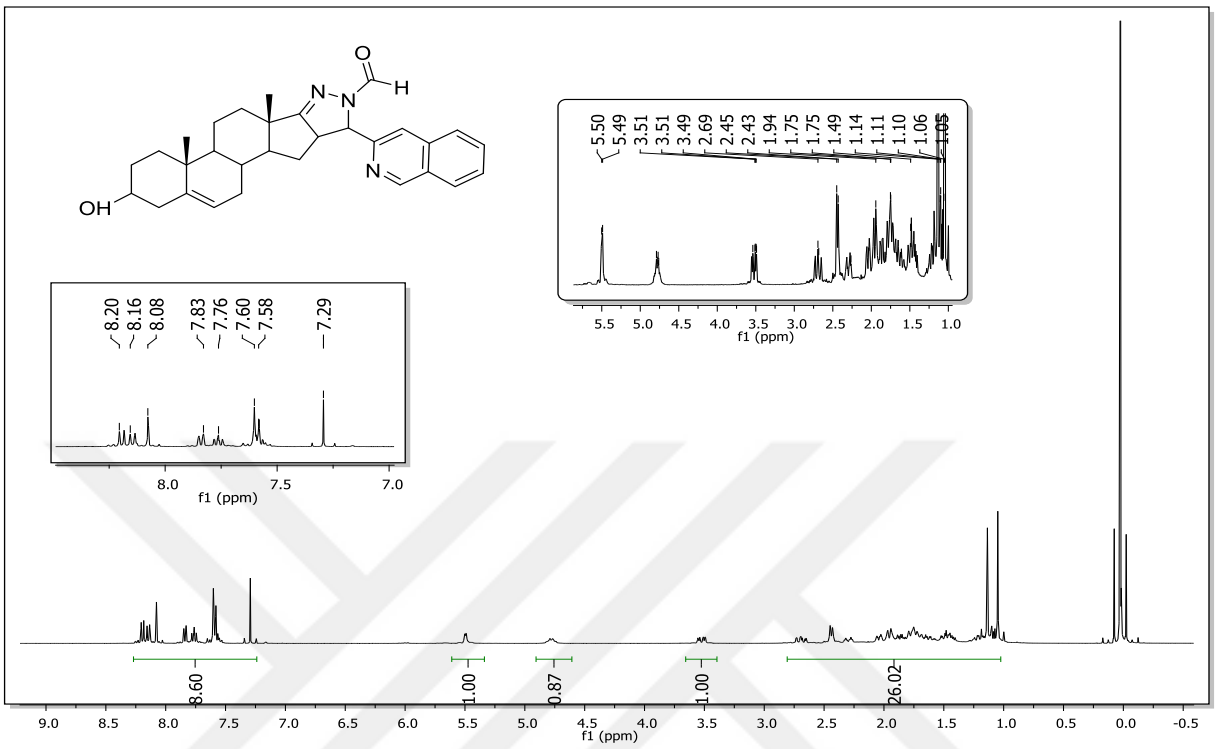


Figure A.44 ^{1}H-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl)androst-5-ene (4e)

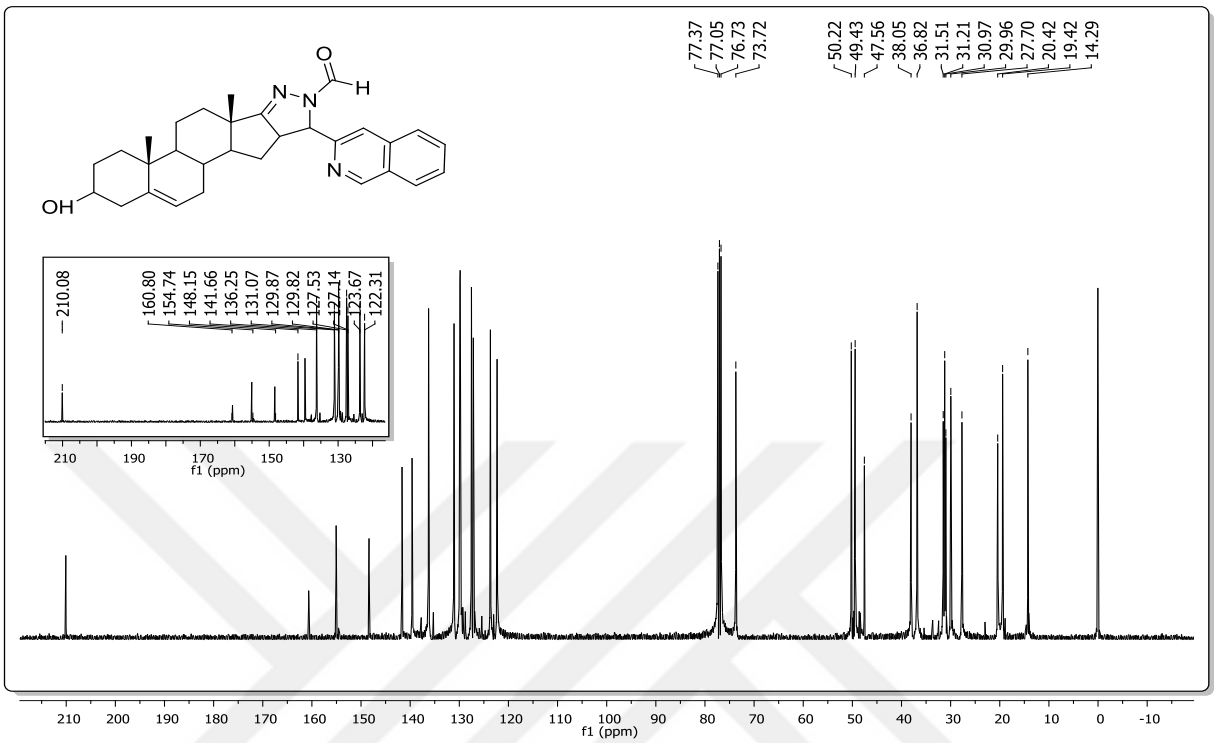
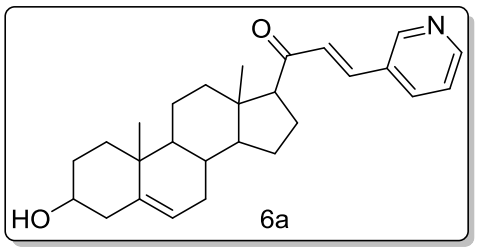


Figure A.45 ^{13}C-NMR spectrum of 3β-hydroxy-(1-Formyl-5-(2-quinolinyl)-16,17-pyrazolinyl)androst-5-ene (4e)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 21*(E)* - 3β - hydroxy-21-(3-pyridinylidene) pregn-5-en-20-one **(6a)**



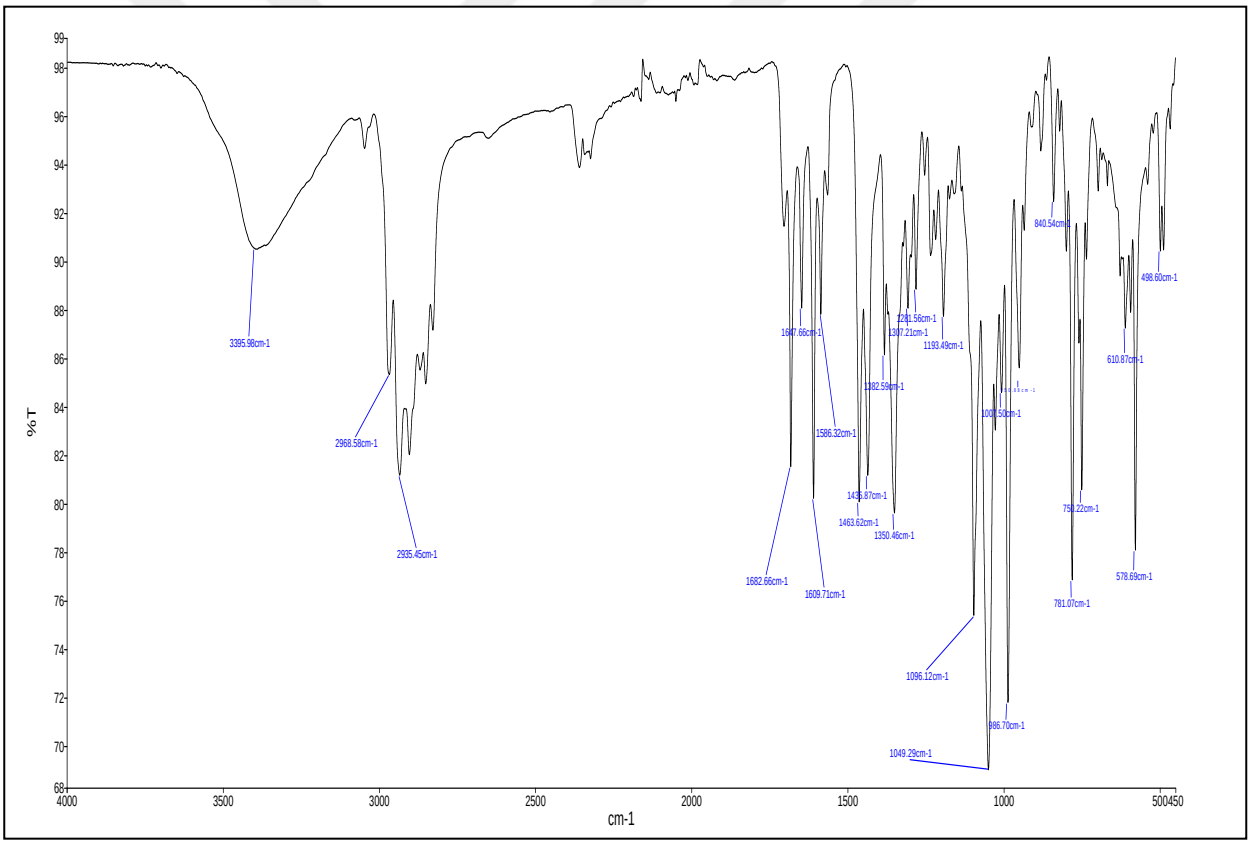


Figure A.46 IR spectrum of 21*(E)* - 3β – hydroxyl -21 - (3-pyridinylidene) pregn-5-en-20-one (6a)

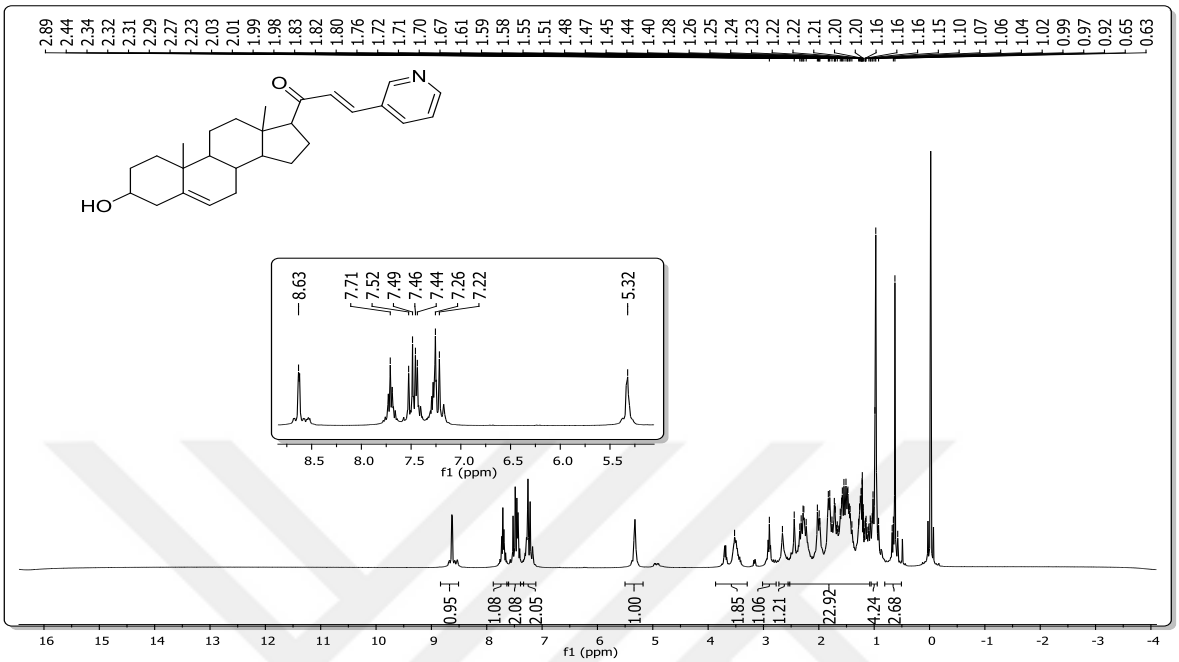


Figure A.47 ^{1}H-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (3-pyridinylidene) pregn-5-en-20-one (6a)

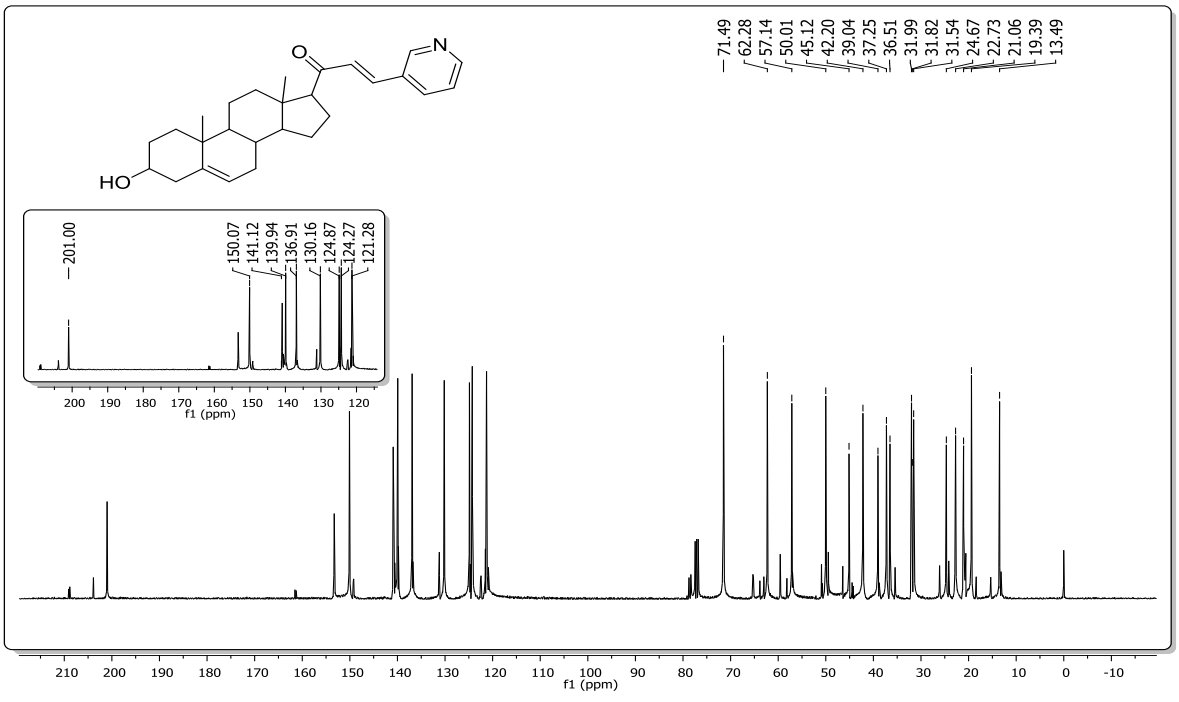
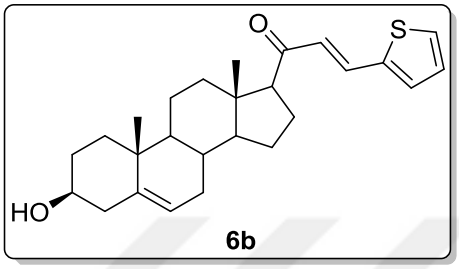


Figure A.48 ^{13}C-NMR spectrum of 21*(E)* - 3β –hydroxy -21 - (3-pyridinylidene) pregn-5-en-20-one (6a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2-thiophenylidene) pregn-5-en-20-one **(6b)**



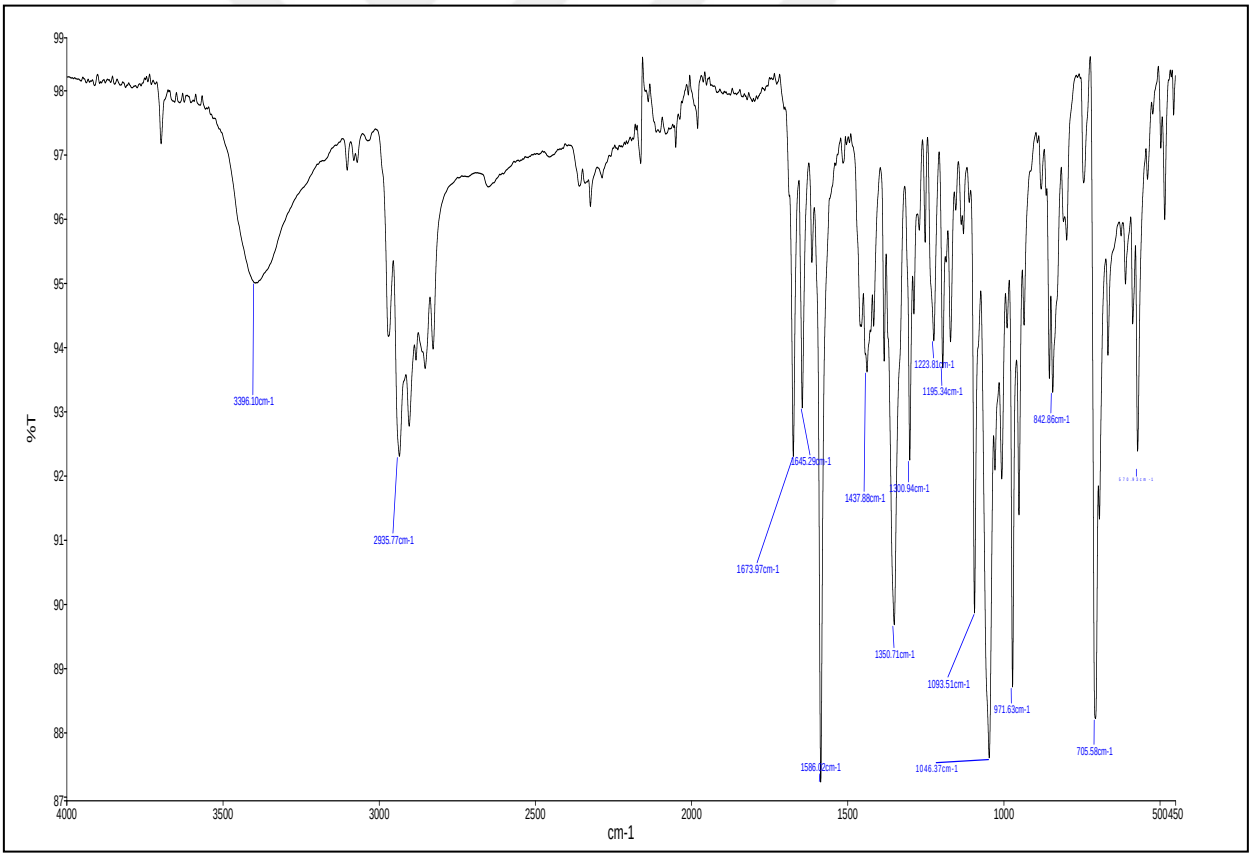


Figure A.49 IR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2-thiophenylidene) pregn-5-en-20-one (6b)

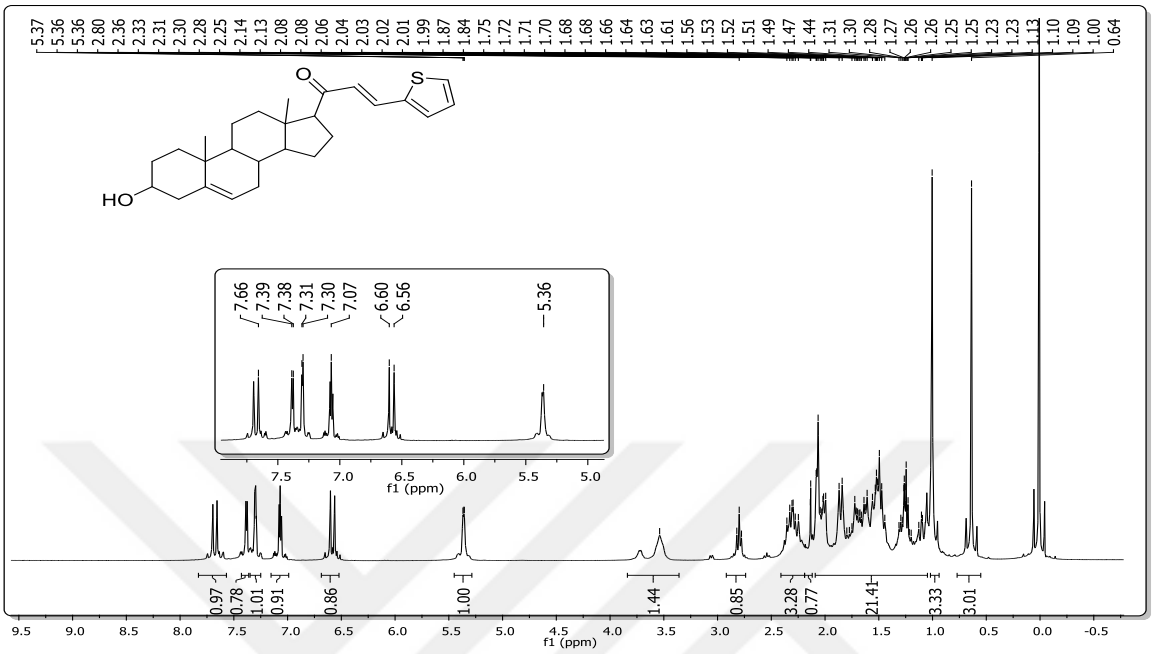


Figure A.50 ^{1}H-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2-thiophenylidene) pregn-5-en-20-one (6b)

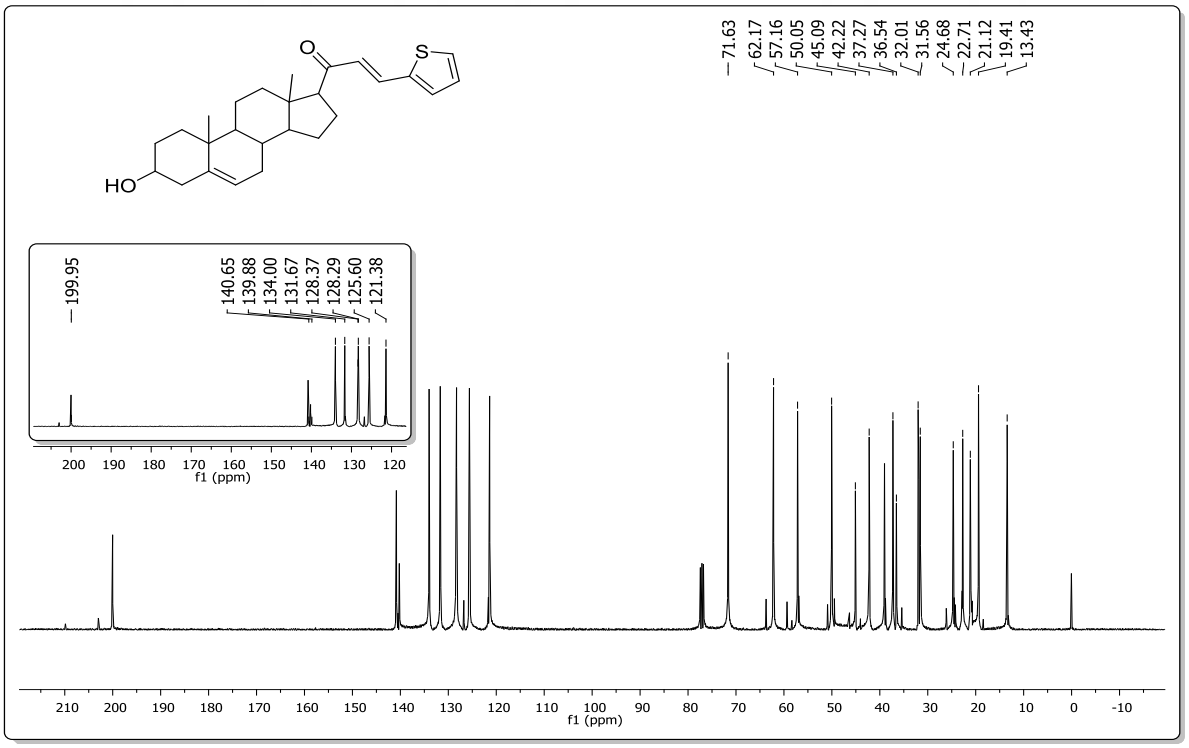
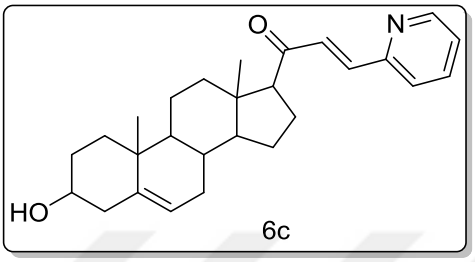


Figure A.51 ^{13}C-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2-thiophenylidene) pregn-5-en-20-one (6b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2 - pyridinylidene) pregn-5-en-20-one **(6c)**



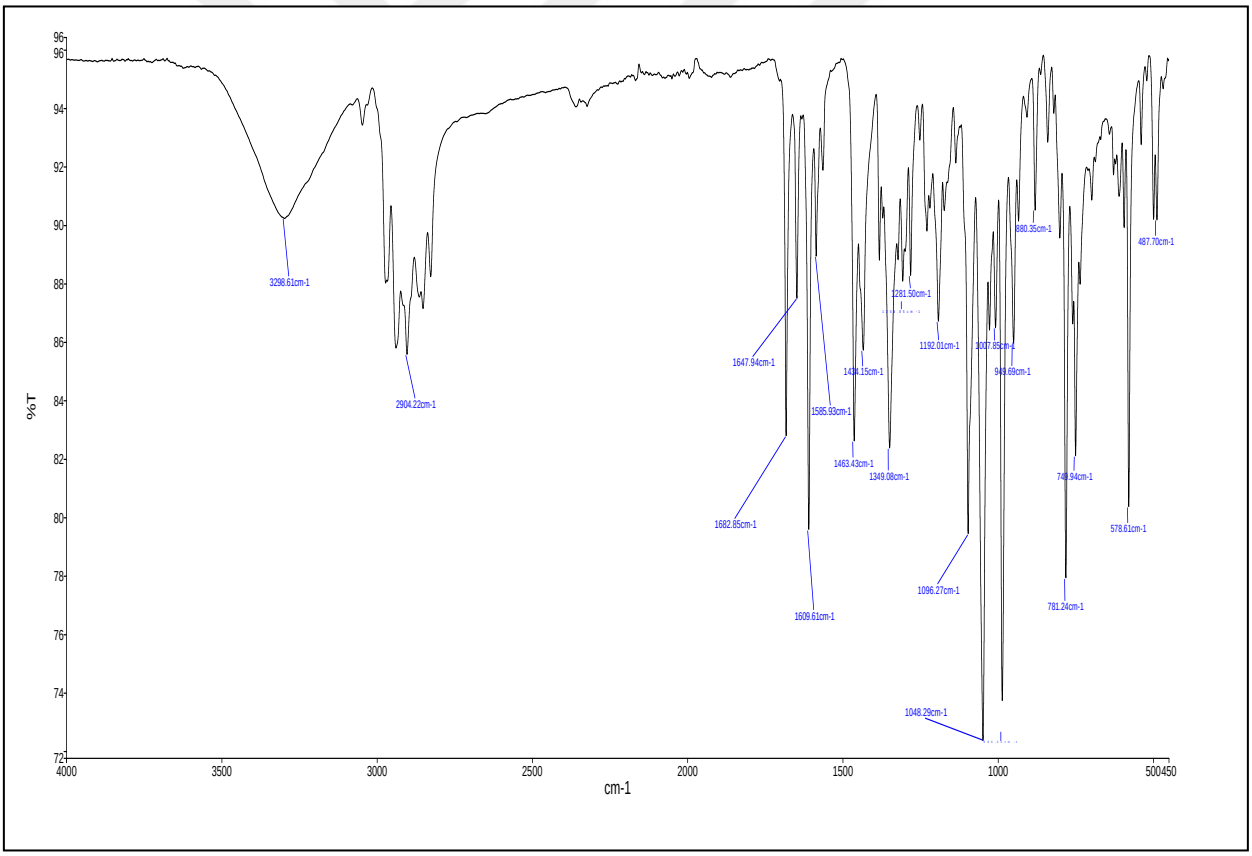


Figure A.52 IR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2 - pyridinylidene) pregn-5-en-20-one (6c)

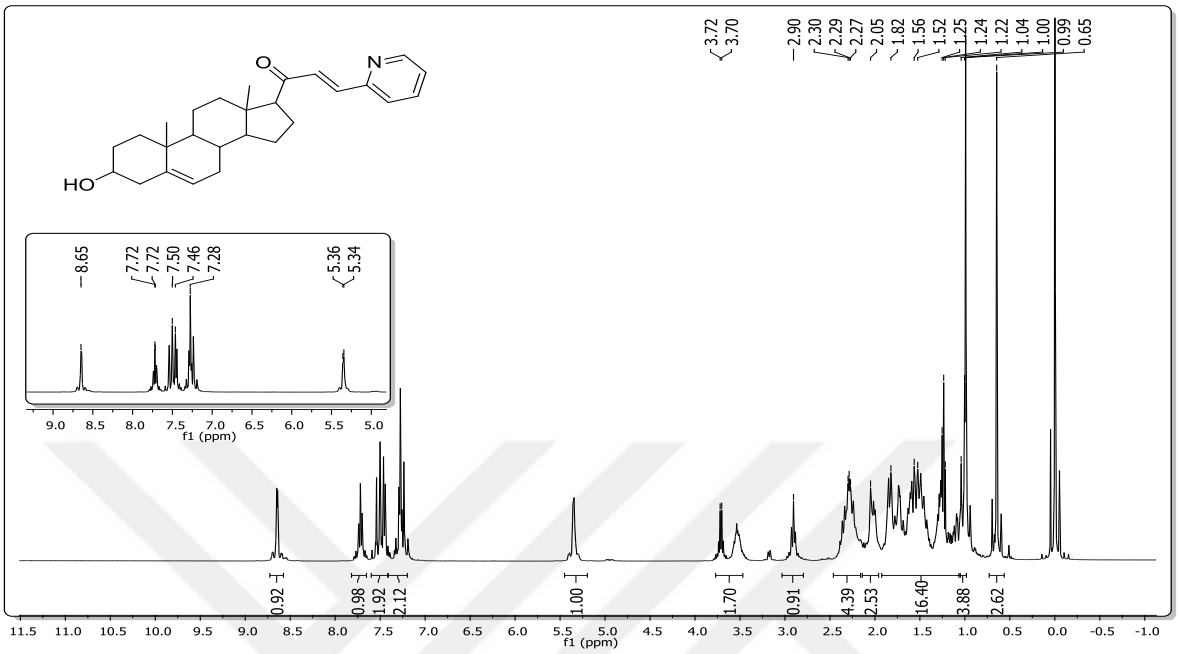


Figure A.53 ^{1}H-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2 - pyridinylidene) pregn-5-en-20-one (6c)

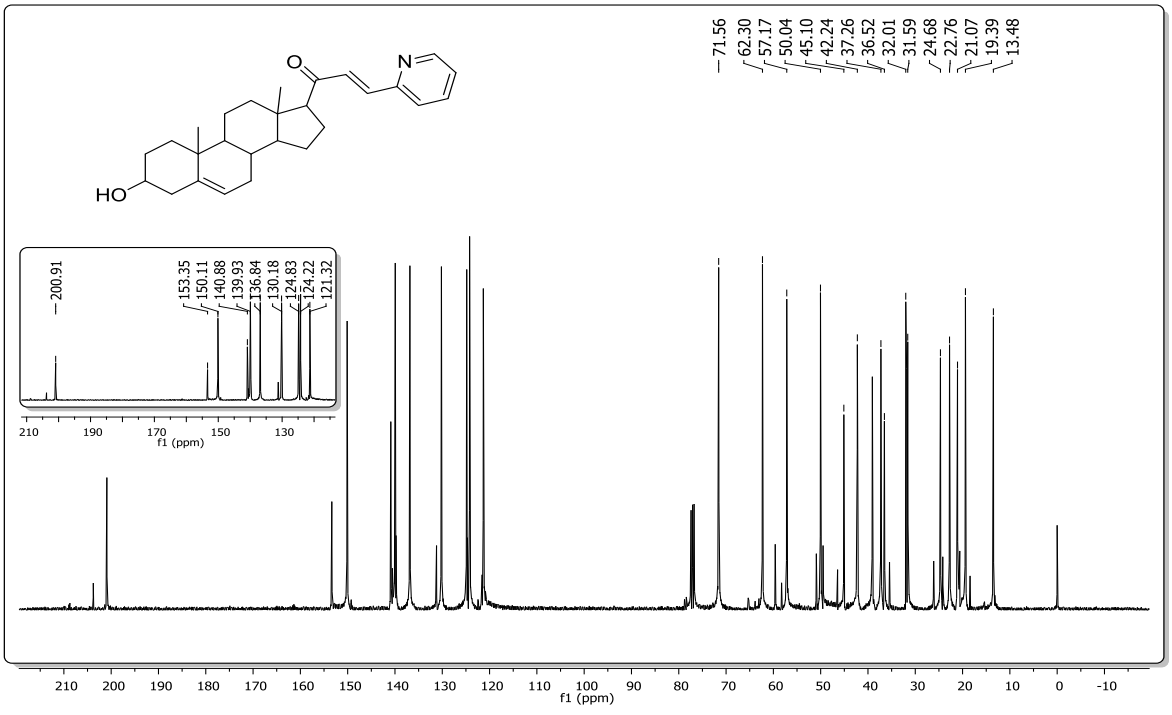
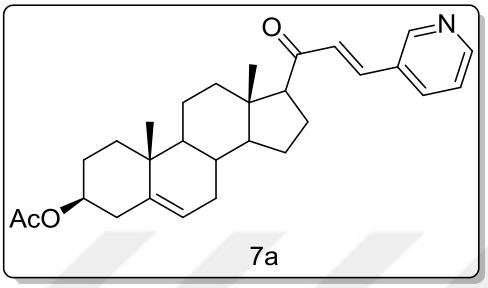


Figure A.54 ^{13}C-NMR spectrum of 21*(E)* - 3β – hydroxyl – 21 - (2 - pyridinylidene) pregn-5-en-20-one (6c)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 21*(E)* - 3β – acetoxy – 21 - (3 - pyridinylidene) pregn-5-en-20-one **(7a)**



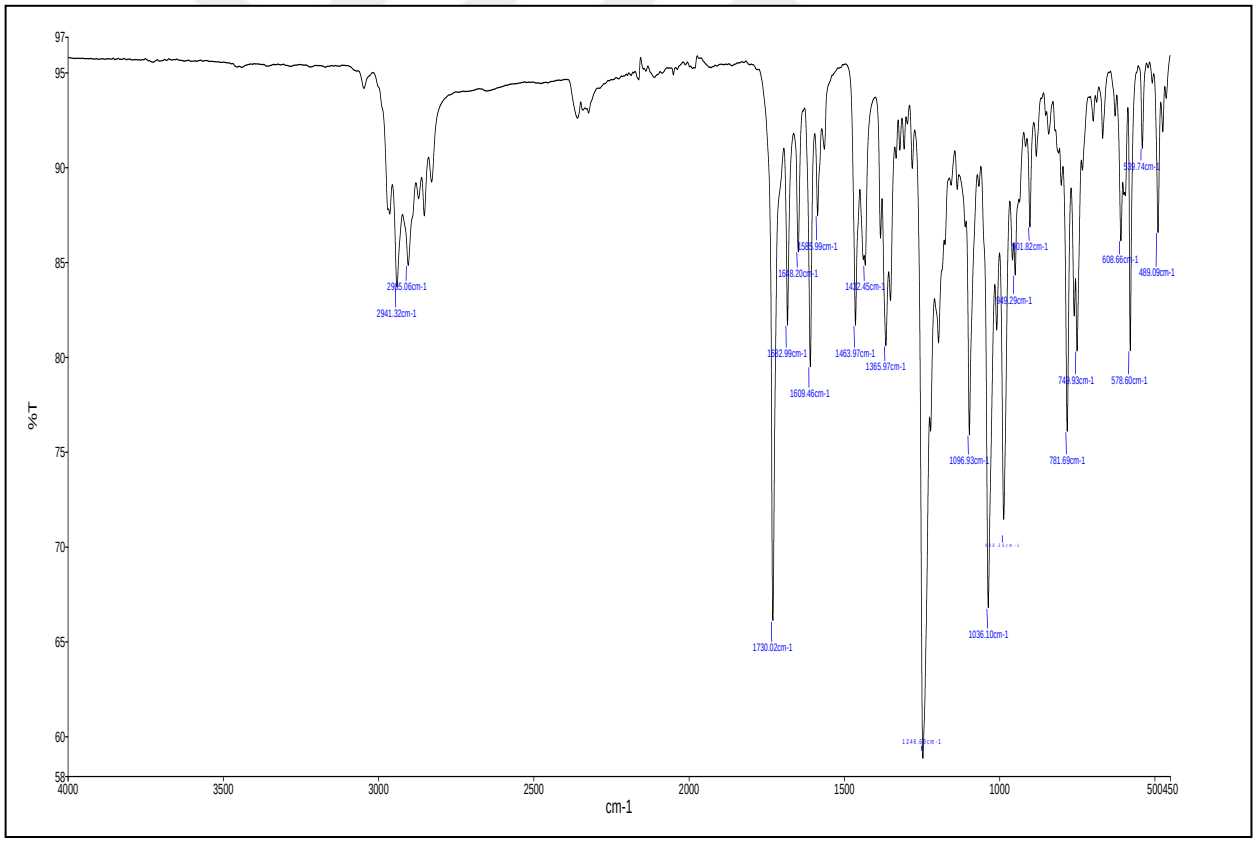


Figure A.55 IR spectrum of 21*(E)* - 3β – acetoxy – 21 - (3 - pyridinylidene) pregn-5-en-20-one (7a)

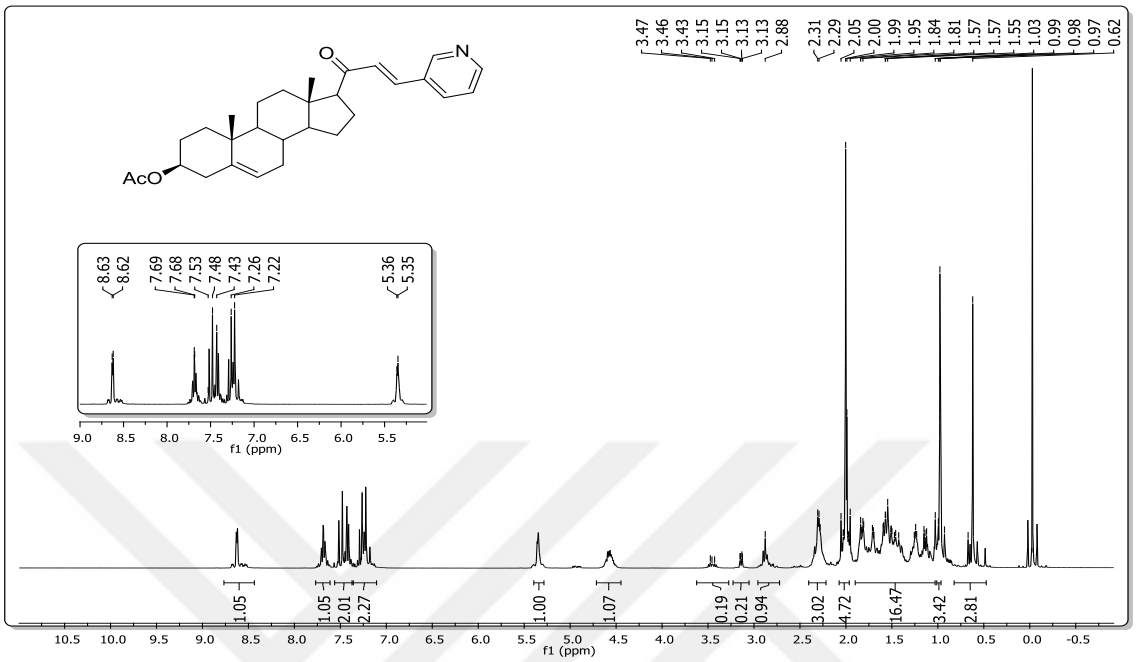


Figure A.56 ^{1}H-NMR spectrum of 21*(E)* - 3β – acetoxy – 21 - (3 - pyridinylidene) pregn-5-en-20-one (7a)

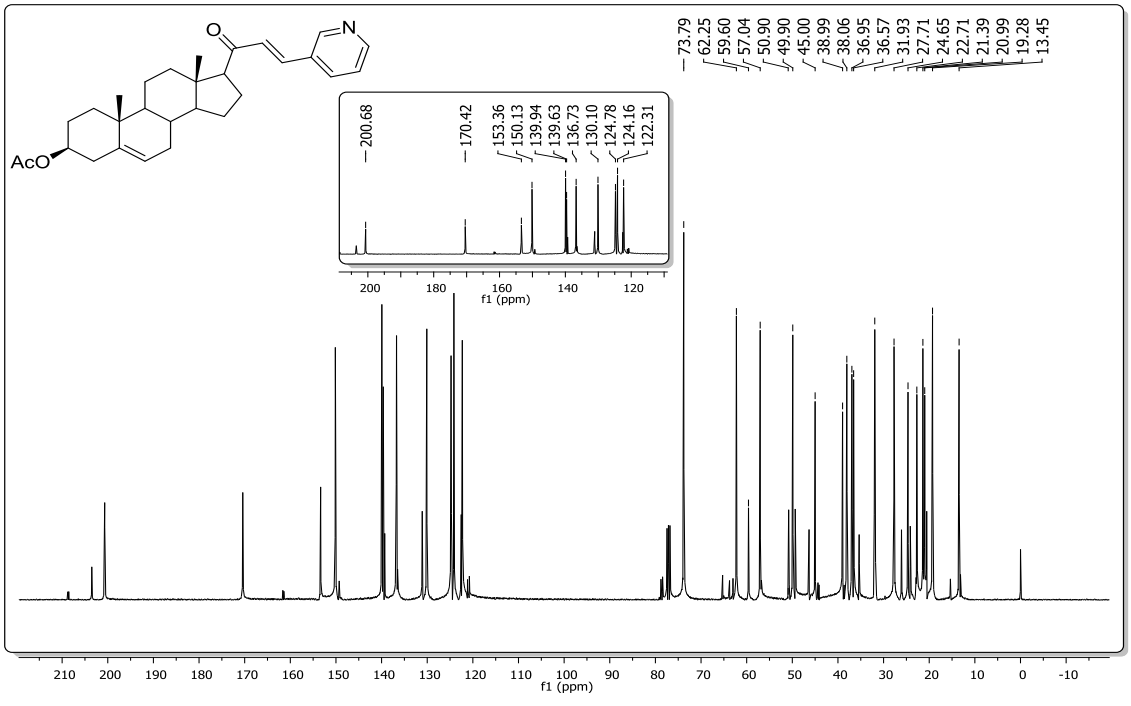
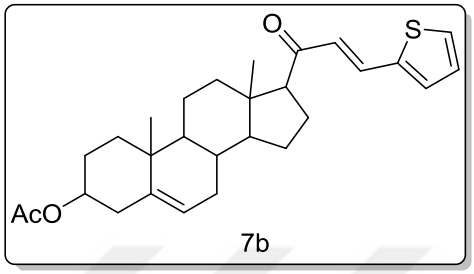


Figure A.57 ^{13}C-NMR spectrum of 21*(E)* - 3β – acetoxy – 21 - (3 - pyridinylidene) pregn-5-en-20-one (7a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 21*(E)* - 3β – acetoxy – 21 - (2 - thiophenylidene) pregn-5-en-20-one **(7b)**



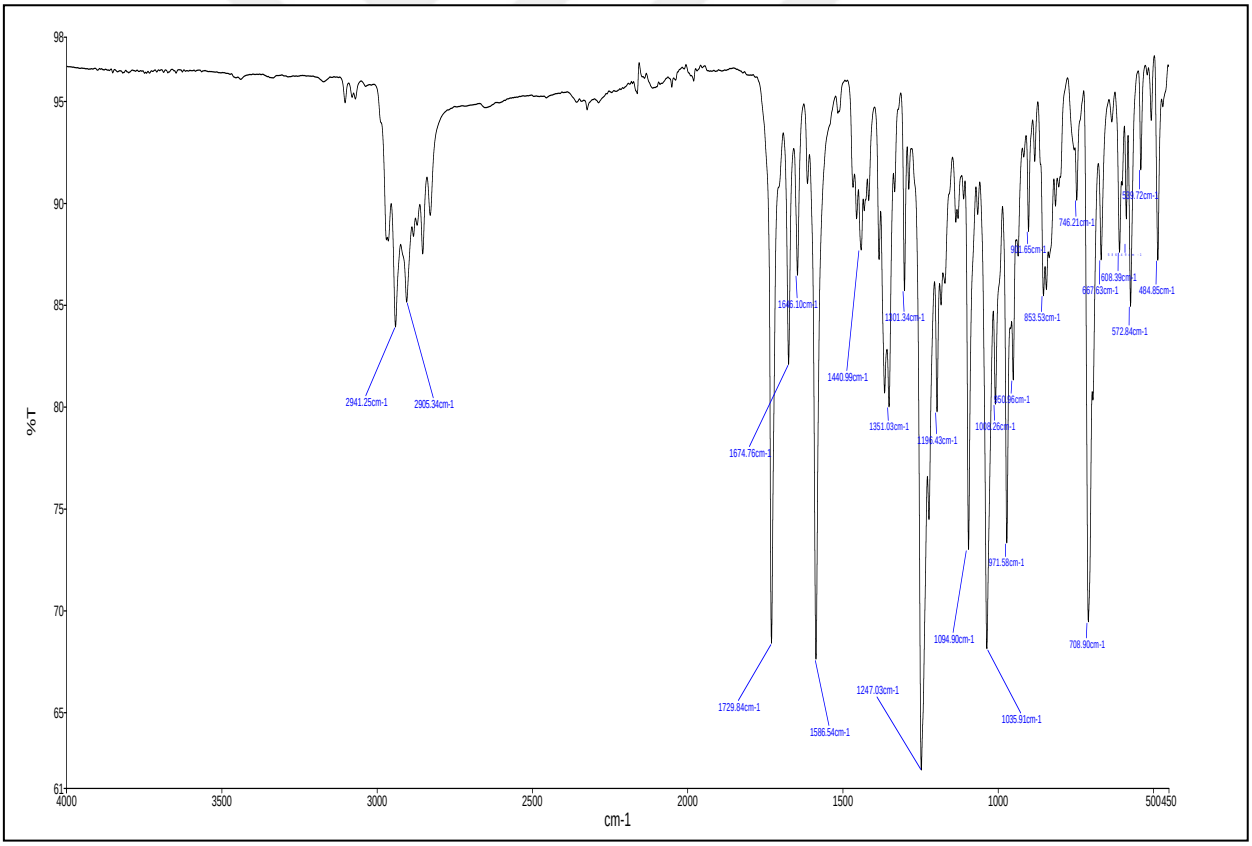


Figure A.58 1R spectrum of 21*(E)* - 3β – acetoxy – 21 - (2 - thiophenylidene) pregn-5-en-20-one (7b)

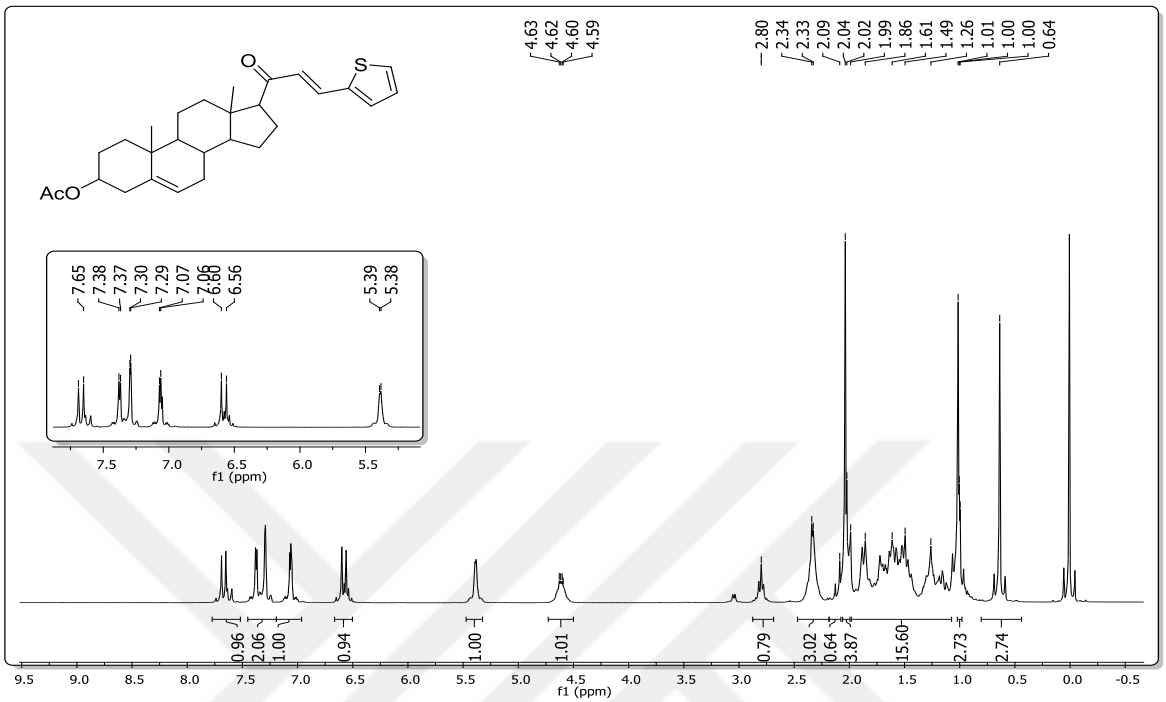


Figure A.59 ^{1}H-NMR spectrum of 21*(E)* - 3β – acetoxy – 21 - (2 - thiophenylidene) pregn-5-en-20-one (7b**)**

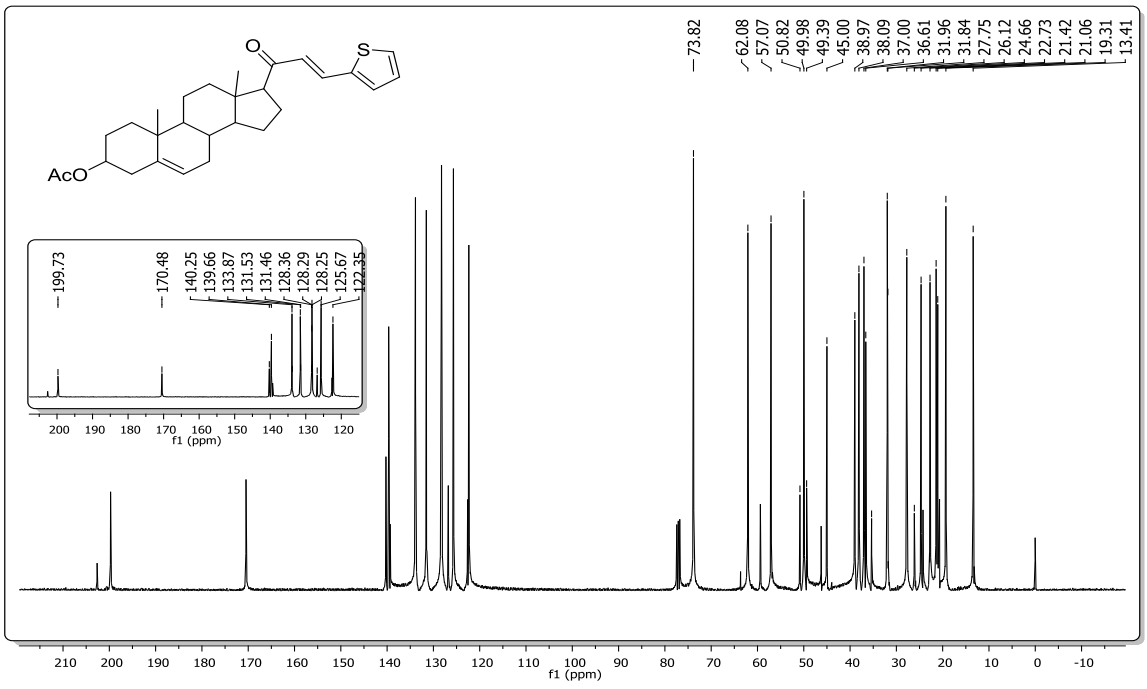
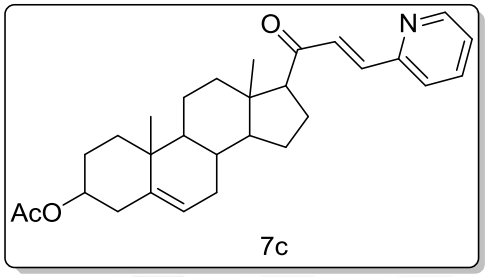


Figure A.60 ^{13}C-NMR spectrum of *(21E)* - 3β – acetoxy – 21 - (2 - thiophenylidene) pregn-5-en-20-one (7b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum 21*(E)* - 3β – acetoxy – 21 - (2 - pyridinylidene) pregn-5-en-20-one **(7c)**



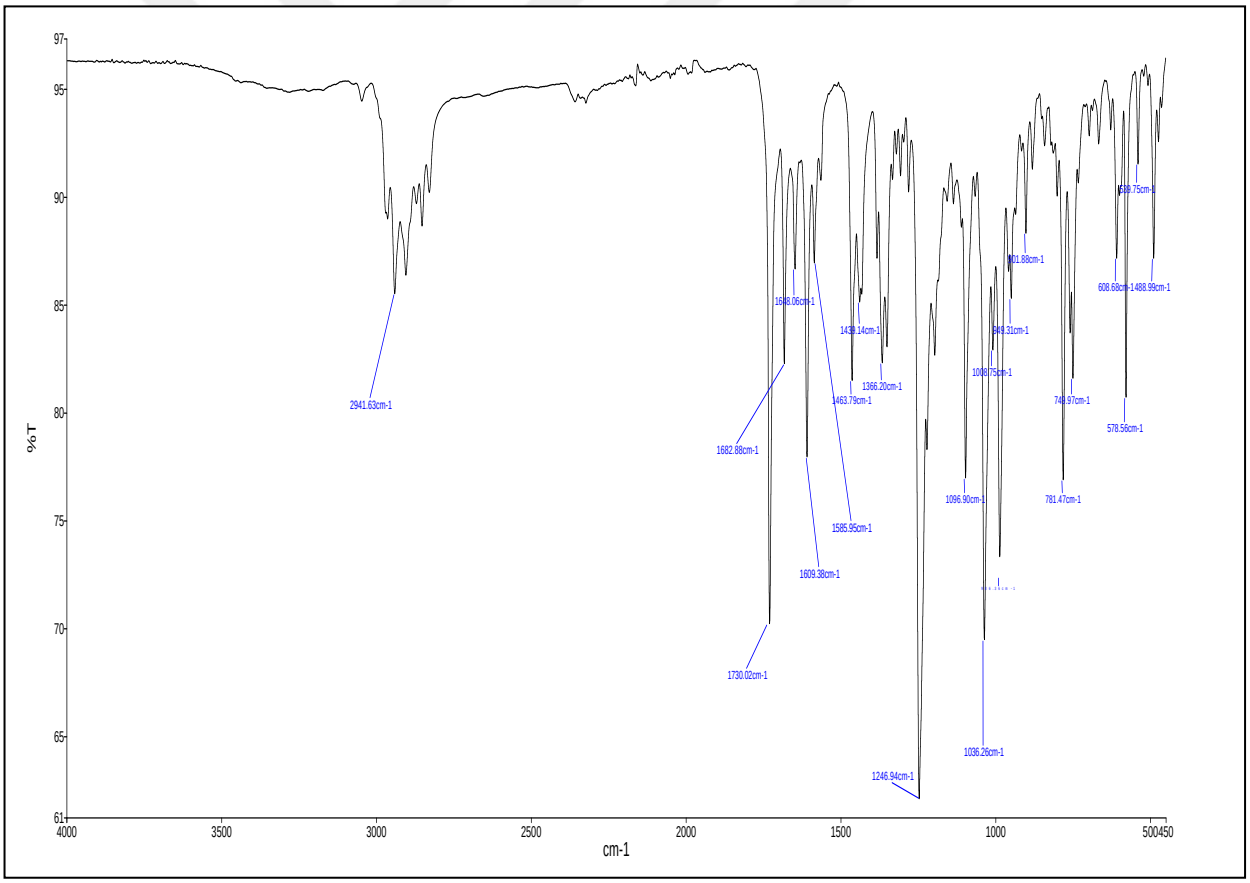


Figure A.61 1R spectrum of 21*(E)* - 3β – acetoxy – 21 - (2 - pyridinylidene) pregn-5-en-20-one (7c)

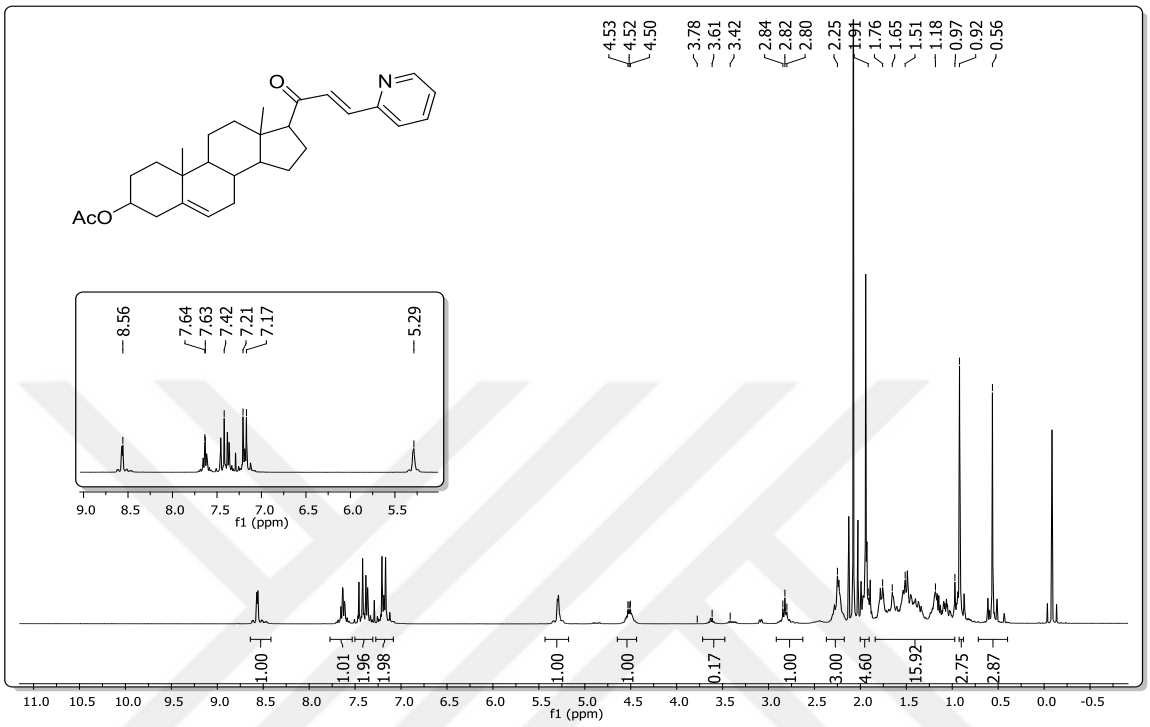


Figure A.59 ^{1}H-NMR spectrum of 21*(E)* - 3β – hydroxyl -21 - (2 - pyridinylidene) pregn-5-en-20-one (7c)

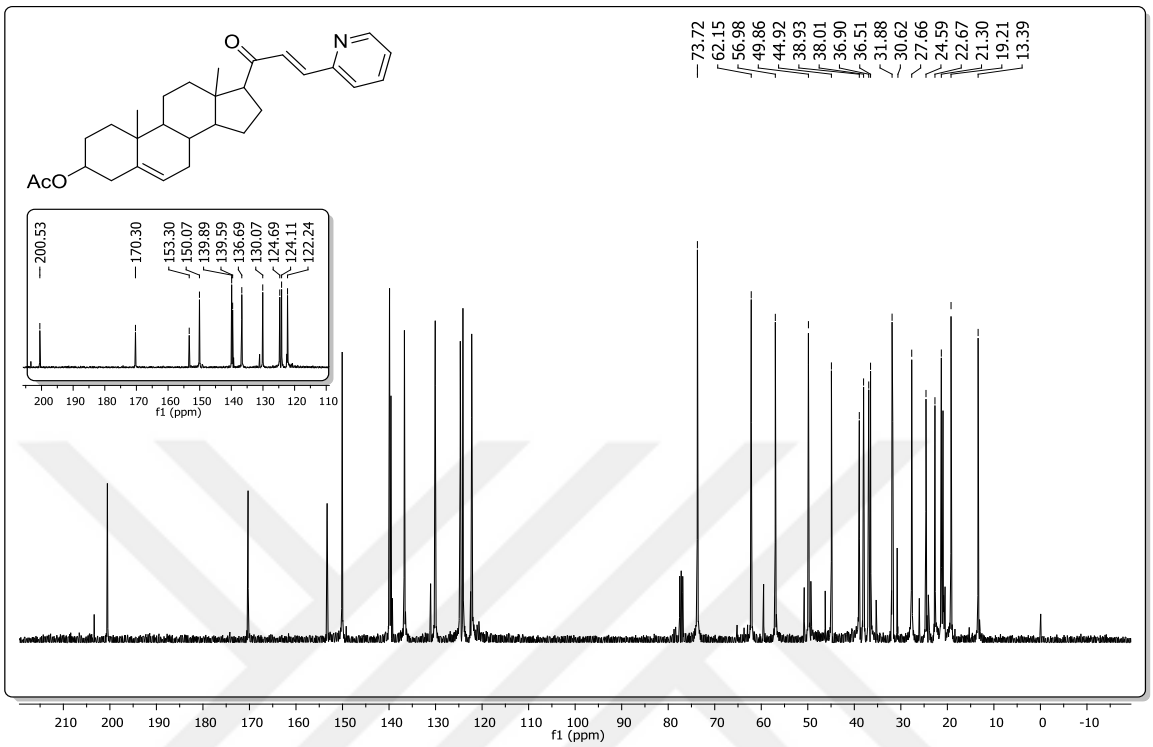
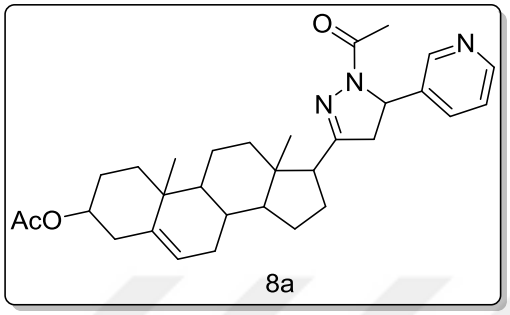


Figure A.60 ^{13}C-NMR spectrum of 21*(E)* - 3β – acetoxy – 21 - (2 - pyridinylidene) pregn-5-en-20-one (7c)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene **(8a)**



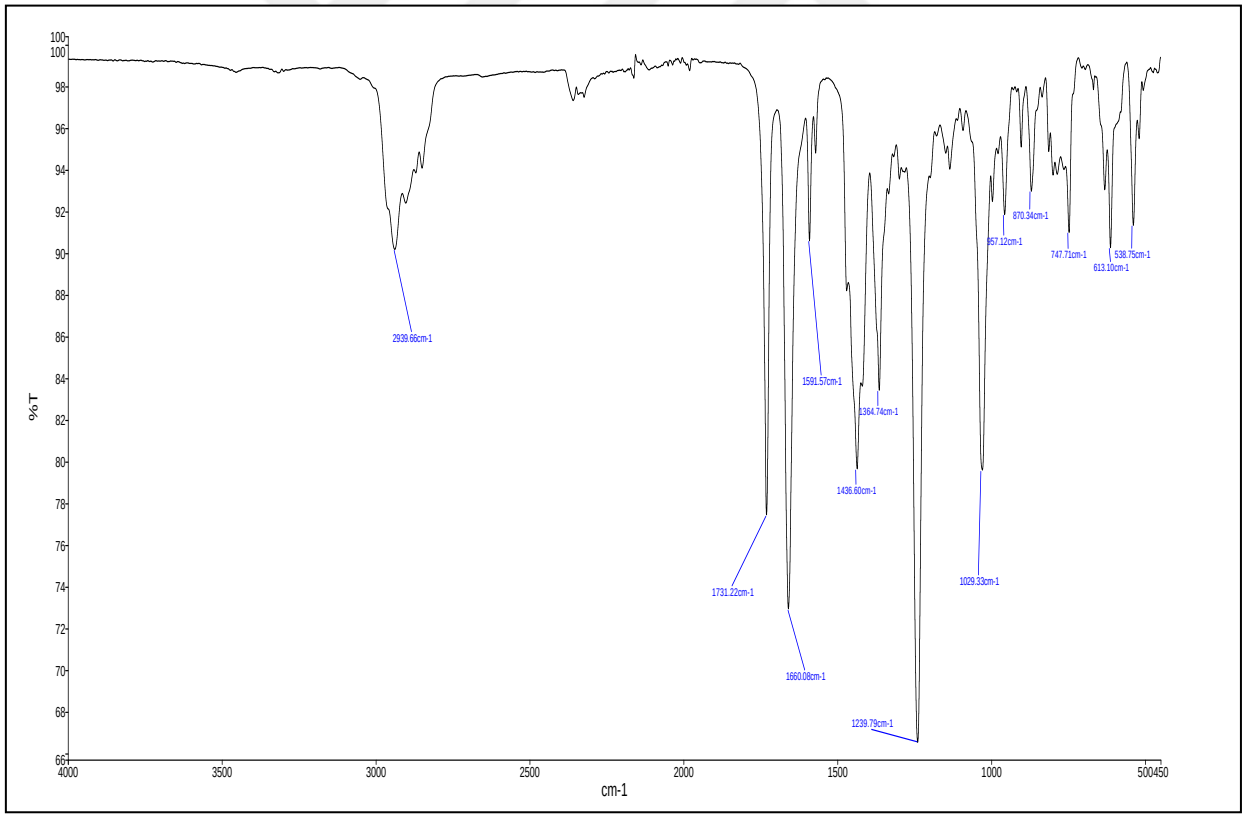


Figure A.61 1R spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat - 5- ene (8a)

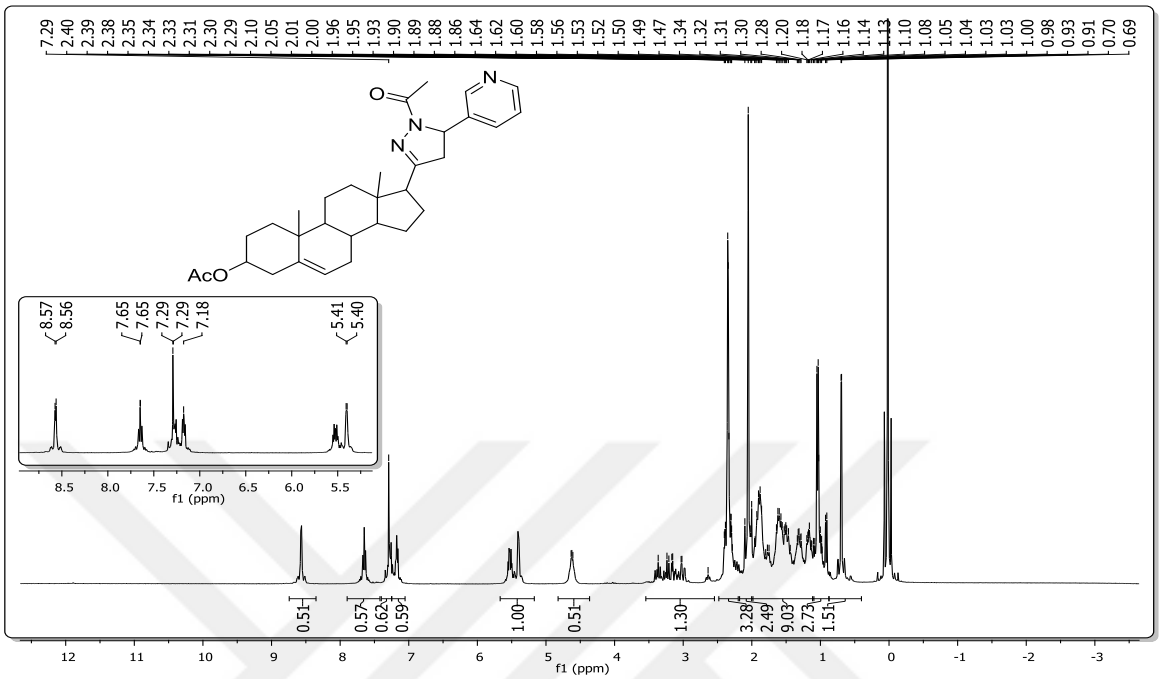


Figure A.62 ^{1}H-NMR spectrum of spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (8a)

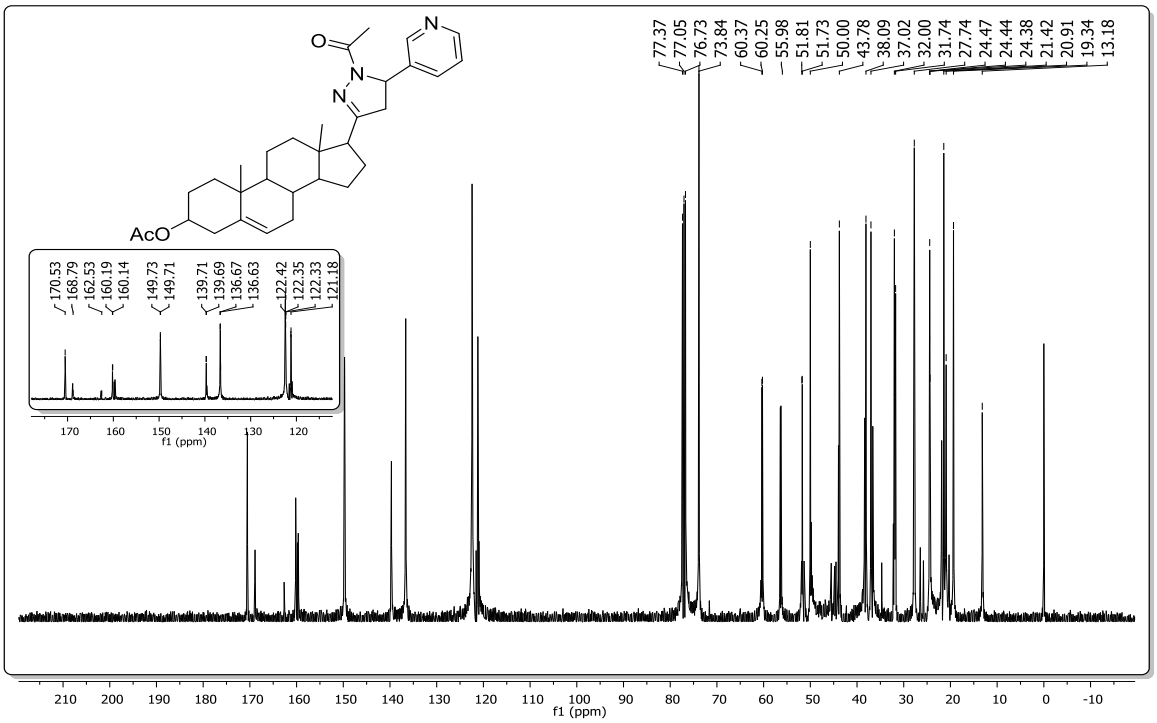
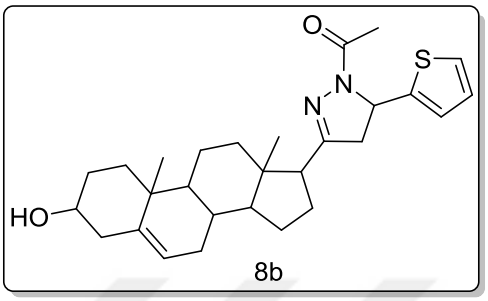


Figure A.63 ^{13}C-NMR spectrum of spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (8a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene **(8b)**



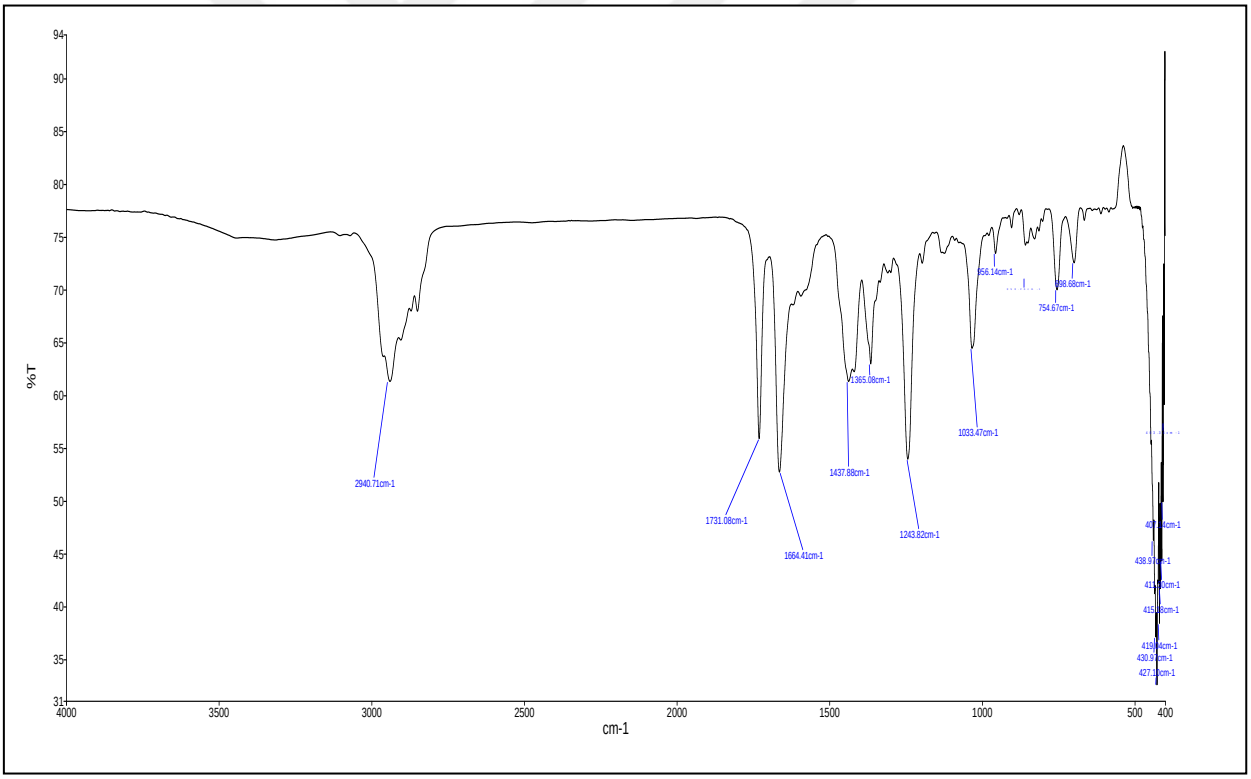


Figure A.64 1R spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (8b)

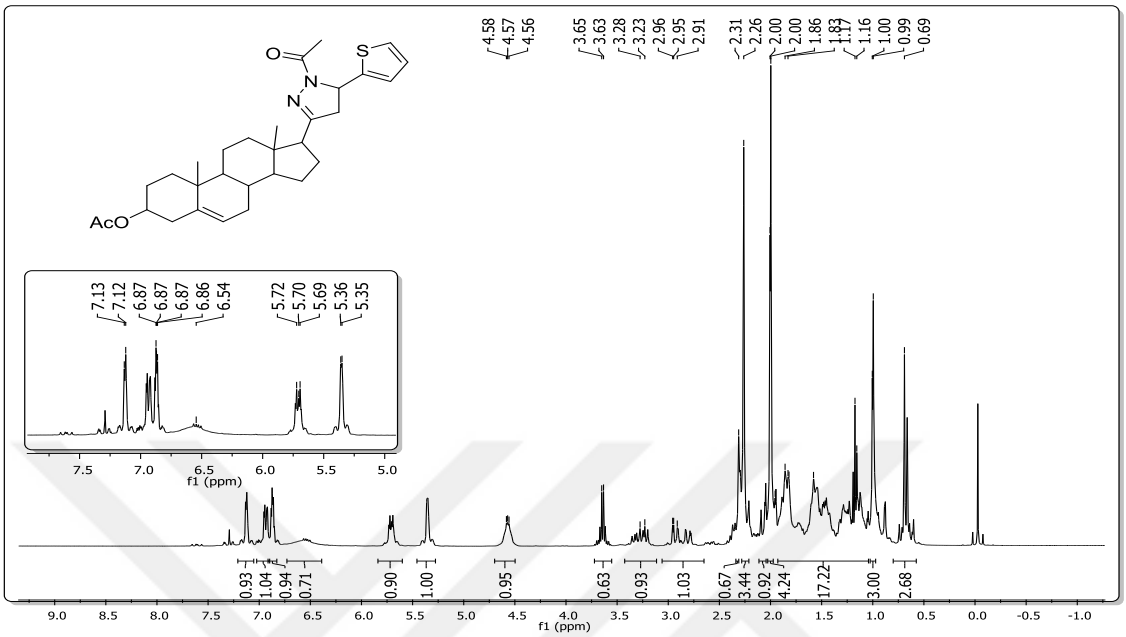


Figure A.65 ^{1}H-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (8b)

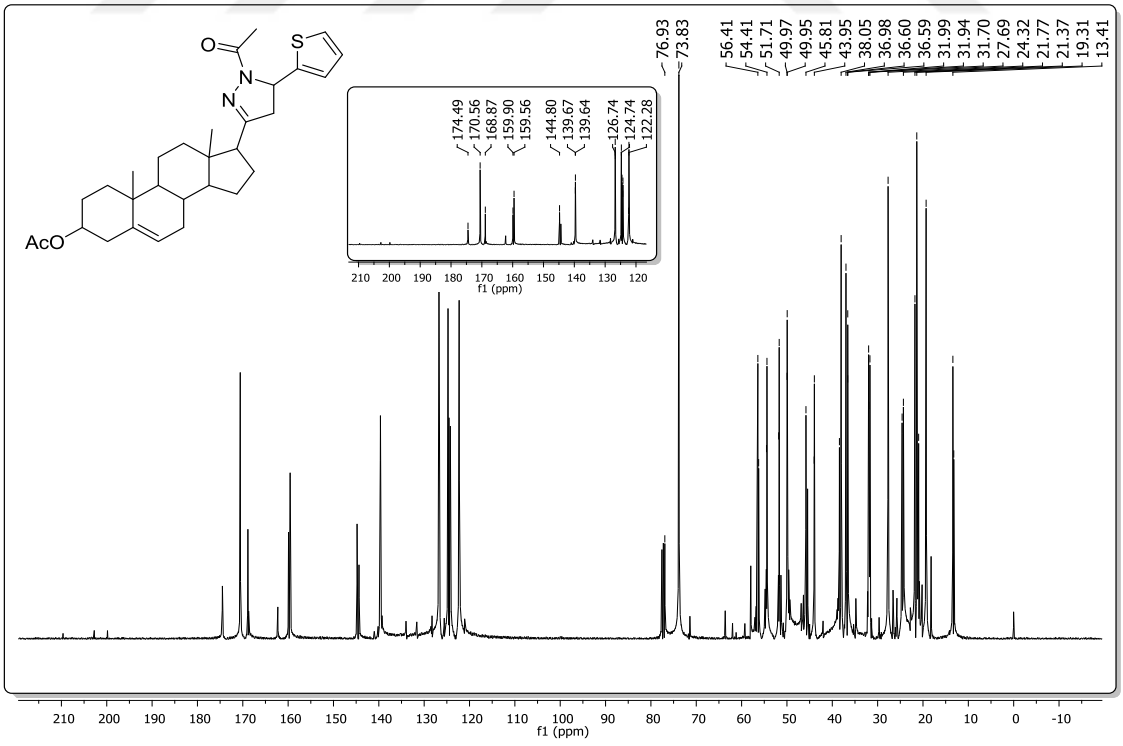
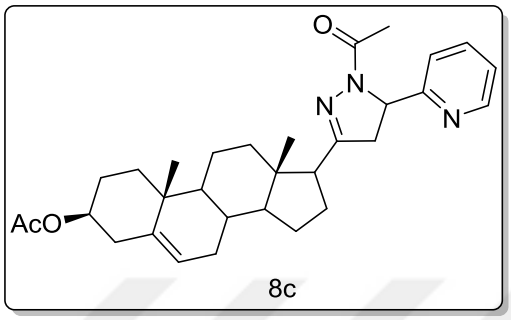


Figure A.66 ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (8b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - pyridinyl)-3-pyrazolinyl) androat-5-ene **(8c)**



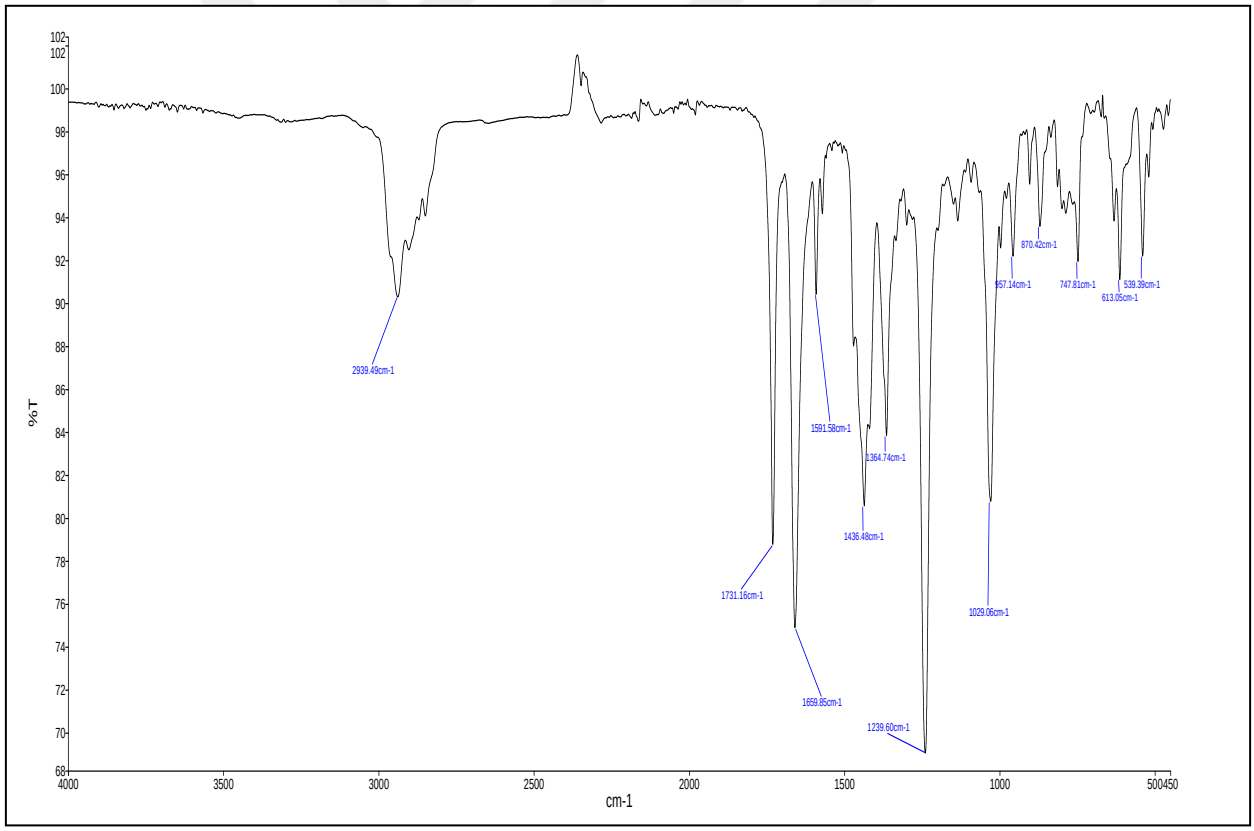


Figure A.67 1R spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - pyridinyl)-3-pyrazolinyl) androat-5-ene (8c)

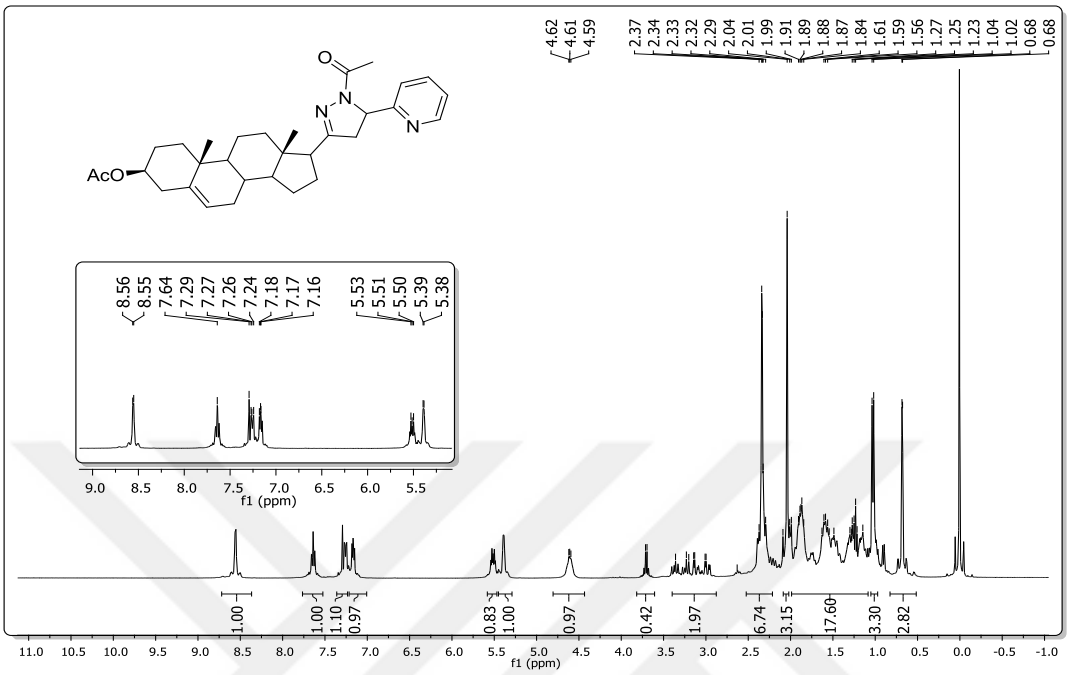


Figure A.68 ^{1}H-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - pyridinyl)-3-pyrazolinyl) androat-5-ene (8c)

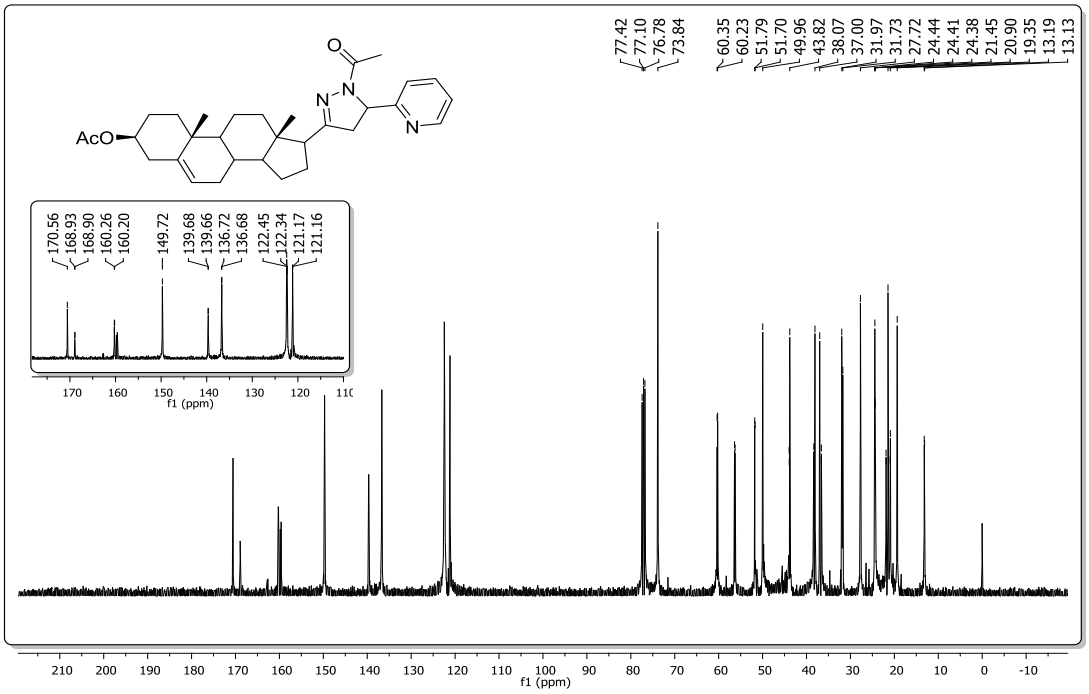
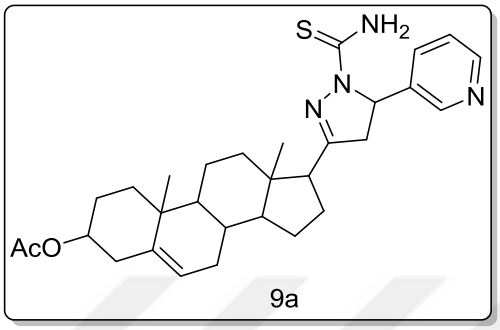


Figure A.69 ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (1-Acetyl-5-(2 - pyridinyl)-3-pyrazolinyl) androat-5-ene (8c)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene **(9a)**



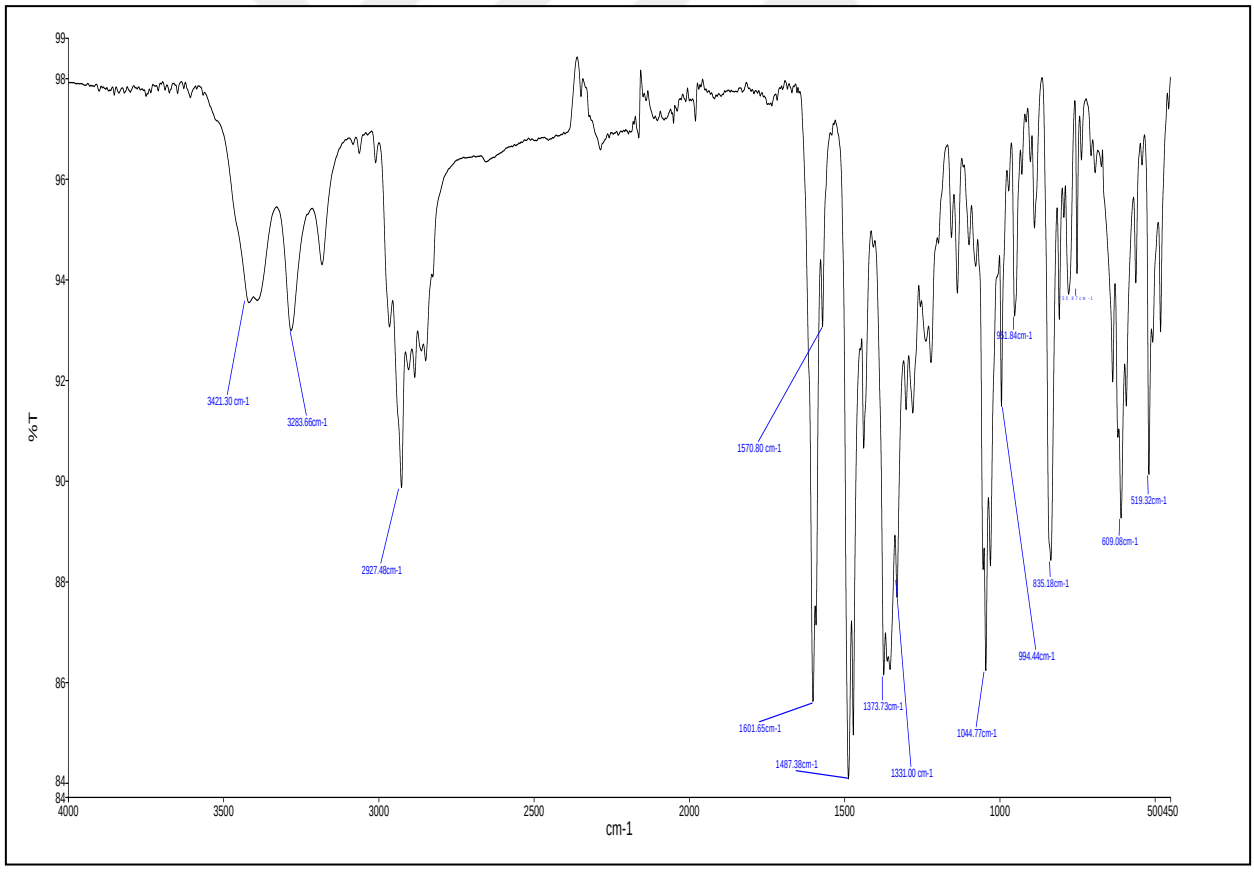


Figure A.70 1R spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (9a)

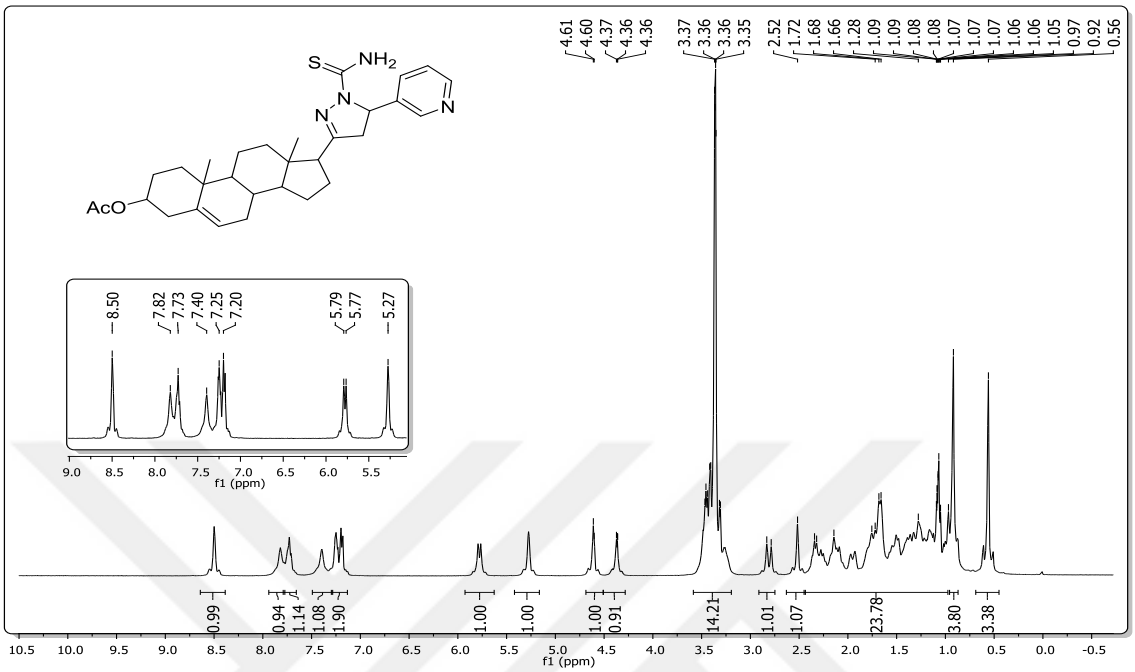


Figure A.71 ^{1}H-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (9a)

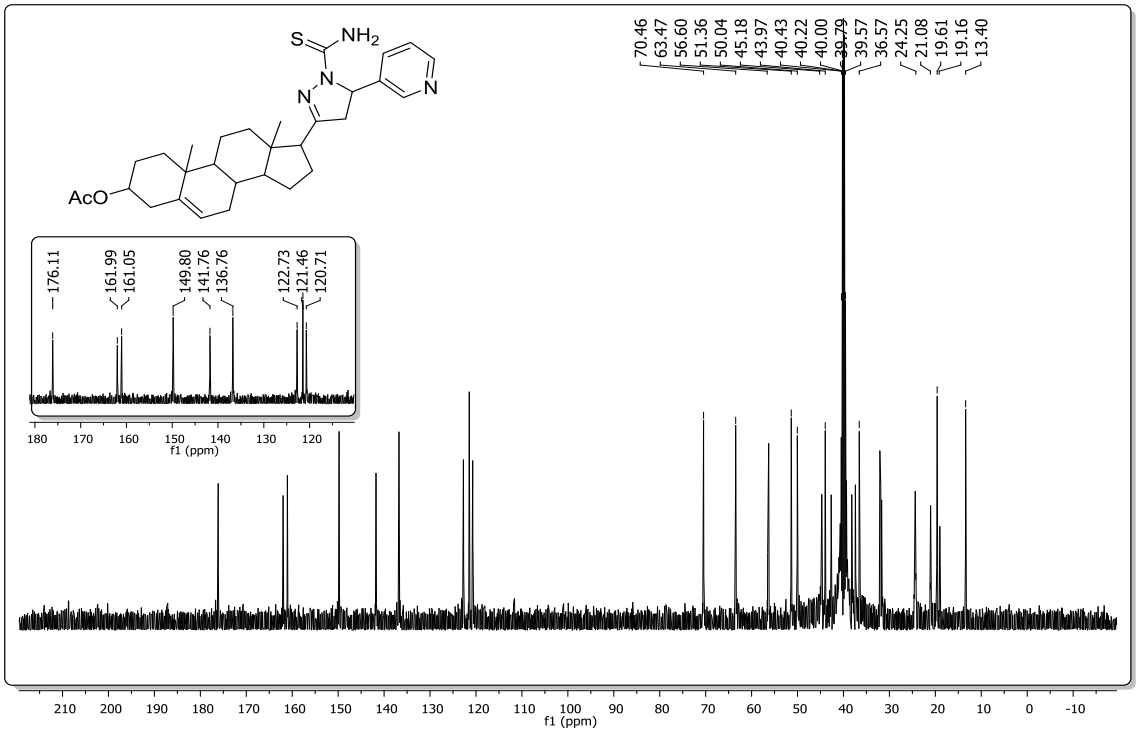
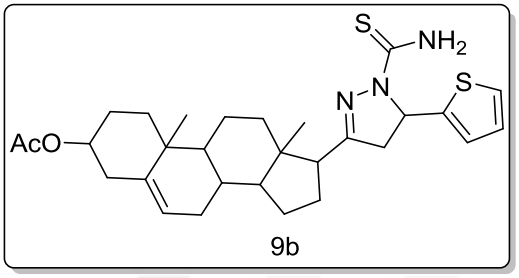


Figure A.72 ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(3-pyridinyl)-3-pyrazolinyl) androat-5-ene (9a)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene **(9b)**



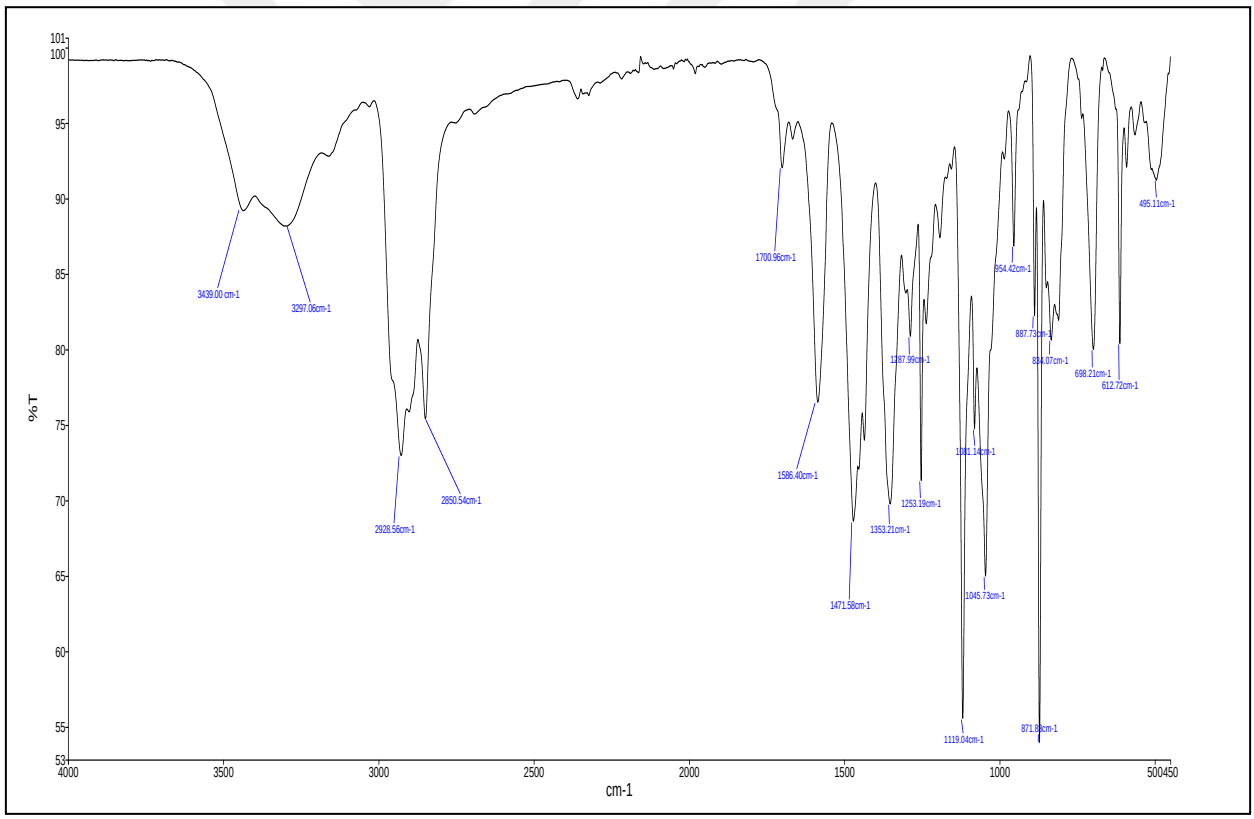


Figure A.73 1R spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (9b)

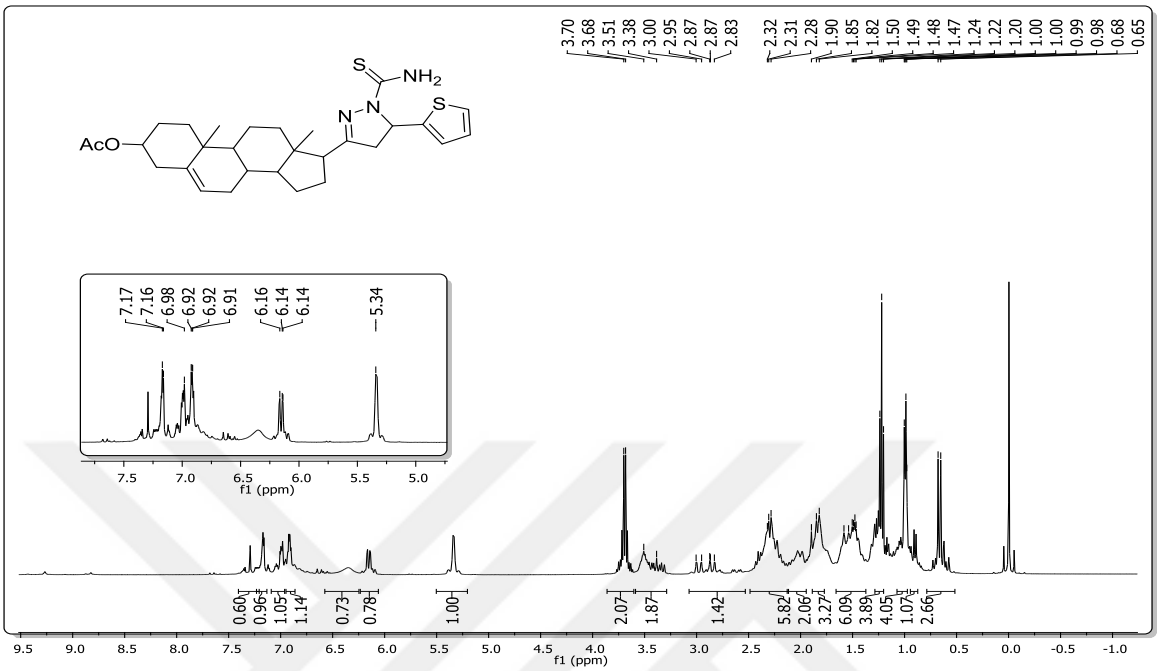


Figure A.74 ^{1}H-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (9b)

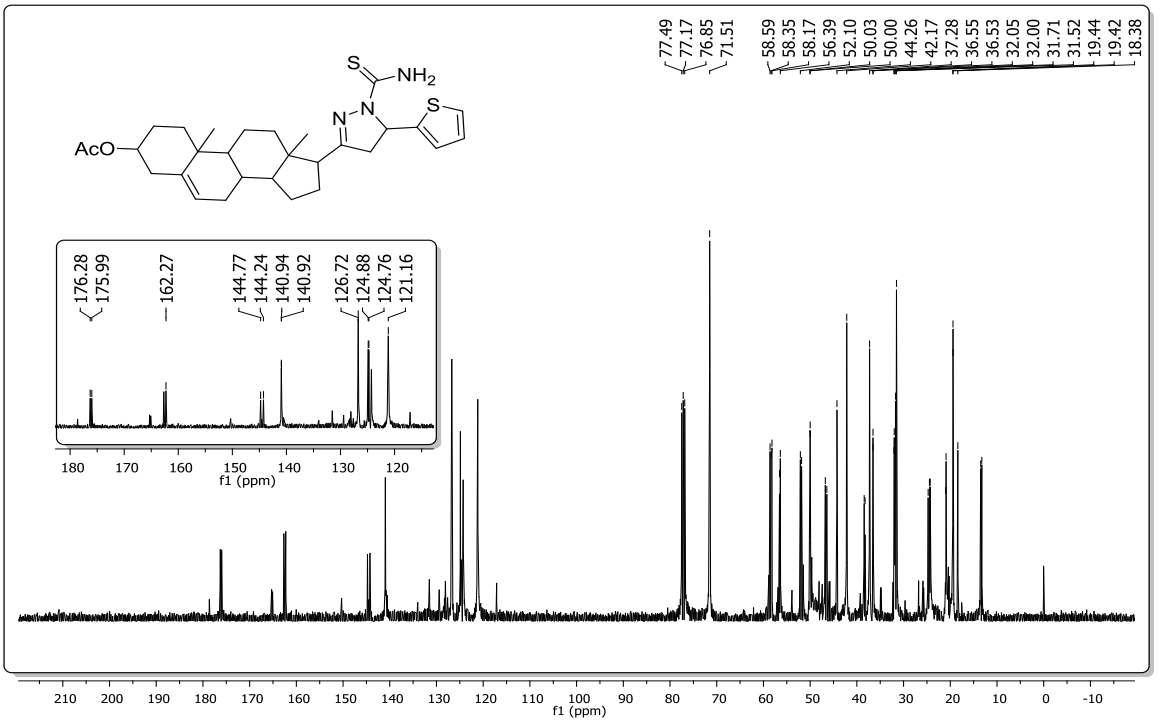
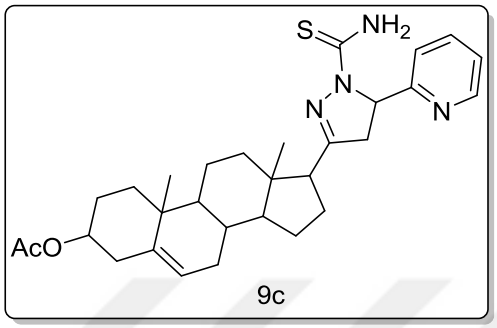


Figure A.75^{13}C-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - thiophenyl)-3-pyrazolinyl) androat-5-ene (9b)

IR, ^{1}H-NMR and ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - pyridinyll)-3-pyrazolinyl) androat-5-ene **(9c)**



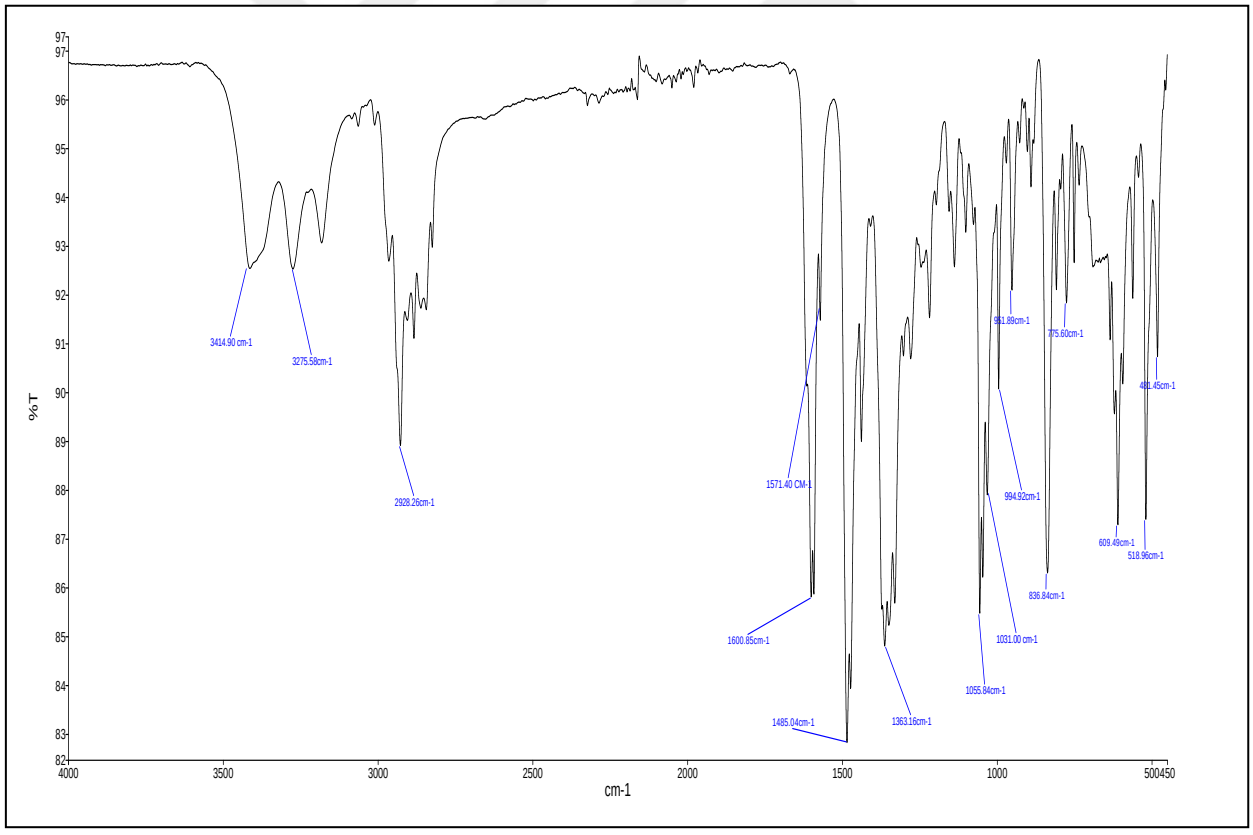


Figure A.76 1R spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - pyridinyll)-3-pyrazolinyl) androat-5-ene (9c)

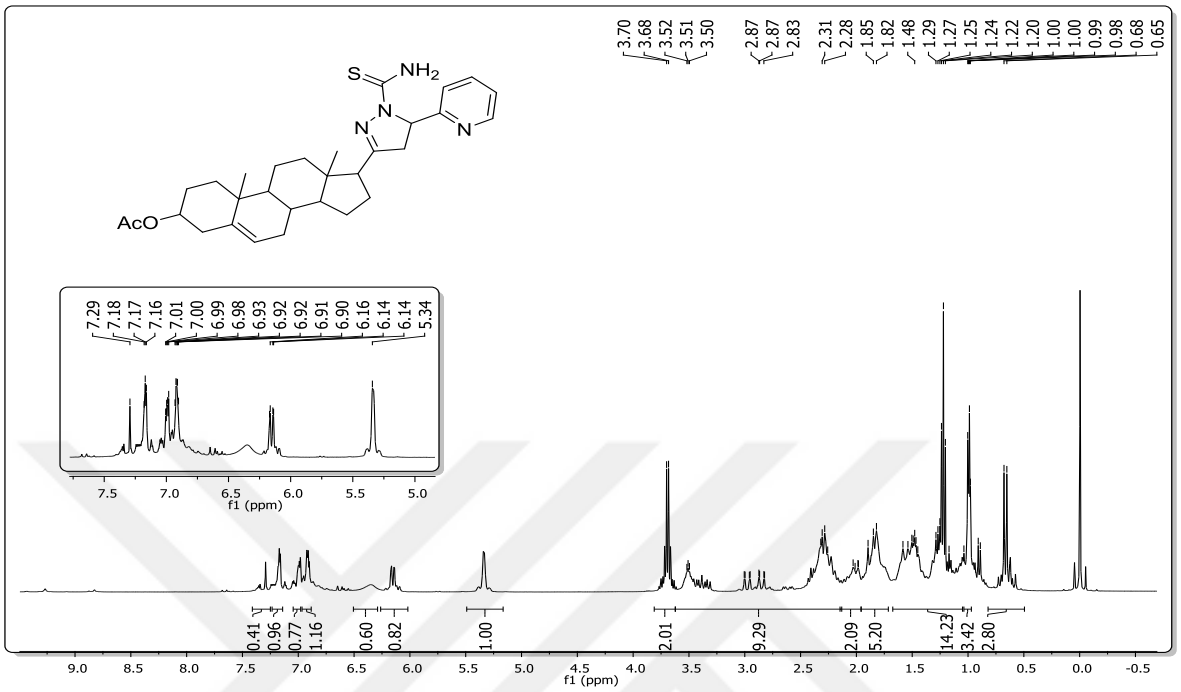


Figure A.77 ^{1}H-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - pyridinyll)-3-pyrazolinyl) androat-5-ene (9c)

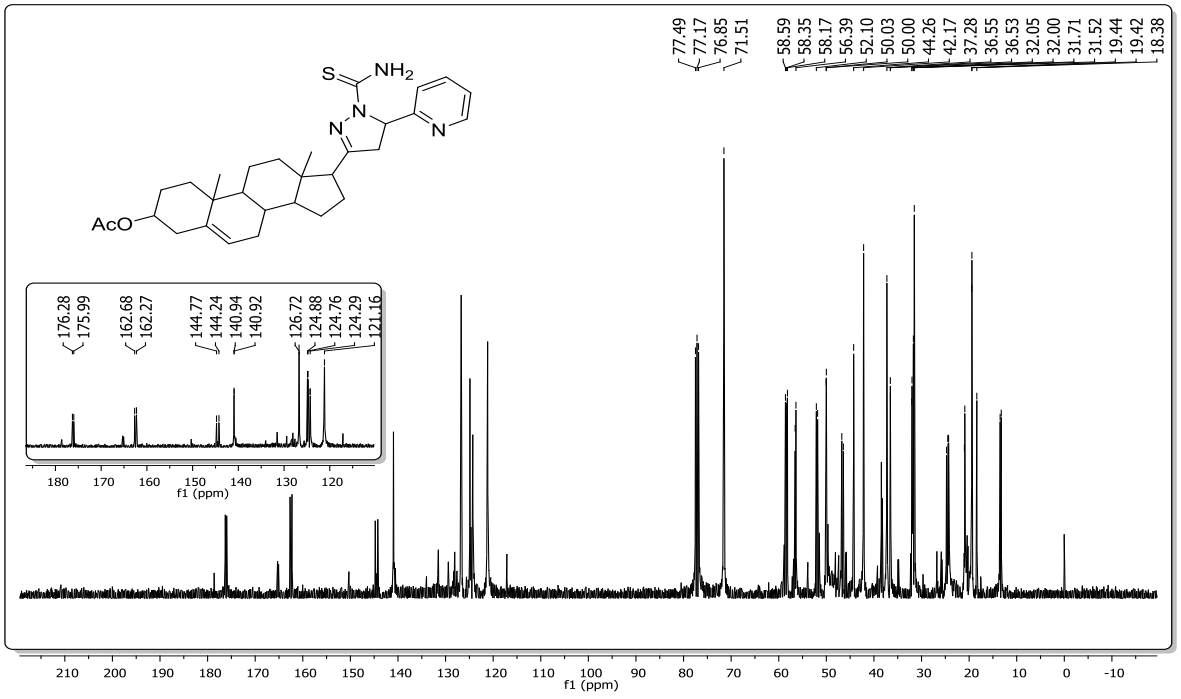


Figure A.78 ^{13}C-NMR spectrum of 3β – acetoxy - 17β - (-1-carbothioamide-5-(2 - pyridinyll)-3-pyrazolinyl) androat-5-ene (9c)

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➢ Senior Science Secondary School Lautai Gumel	2002	2005 SSCE Certificate
➢ Kano university of science and technology Wudil	2007	2012 BSc. Chemistry

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