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# Synthesis of Novel [1,2,4]Triazolo[1,5-a]Pyridines via concerted reactions between 2-cinnamoyl-2-cyanoacetohydrazide and α-cyanocinamonitriles

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**الخلاصـــة :-**

بخطوة واحدة حديثة لم يسبق لها مثيل على صعيد تحضير مشتقات [1,2,4]triazolo[1,5-a]pyridnide ما عدا المركبات التي تم انتاجها من قبلنا تحت المصادر (10-12) . تحضير هذه المركبات ناتج عن تفاعل المادتين (**3**) و (**2**). هذا التفاعل مصحوب بتكوين الحلقة السداسية ثم يتبع بتكوين الحلقة الخماسية في خطوة واحدة متعاقبة. هذا التفاعل يقود الى تكوين المركب (**6**) على شكل ملح وعند معاملة المركب (**6**) بمحلول حامض الهيدروكلوريك 10% يؤدي الى تكوين المركب المتعادل (**7**). كنا نتوقع من خلال تفاعل المادتين المذكورتين اعلاه (**2**) و (**3**) الى اتجاه التفاعل الى طريق اخر وتحضير المركب (**5**) حسب ماموجود في المخطط 4. وهذا التوقع ناتج عن سلوك التفاعل المعقول والمنطقي علميا. ولكن بعد التلاعب بضروف التفاعل لم نحصل عمليا سوى المركب (**6**) و (**7**).

## Abstract:

A novel one step synthesis of derivatives [1,2,4]triazolo[1,5-a]pyridines (**6**) from 2′-cinnamoyl-2-cyanoacetohydrazide (**3**) and α-cyanocinnamonitriles (**2**) is described. The reaction takes place by *6-exo-dig* cyclization followed by an *5-exo-trig* process to afford salts **6**. Compound **7** were solated from the reaction mixture as the corresponding piperidinium salts due to the high stability of the heterocyclic anion. Acidification with dilute hydrochloric acid yielded the neutral [1,2,4]triazolo [1,5-a]pyridines. Now, an alternative *7-endo trig* cyclization can take place and, in addition to the [1,2,4]triazolo[1,5-a] pyridines **6**, the novel heterocyclic compound of seven membered ring are obtained.

## Introduction:

The known preparative methods for the synthesis of [1,2,4]triazolo[1,5-a]pyridines involve: (a) reaction of 1,2-diaminopyridine derivatives with compounds such as carboxylic acids and esters [1], 1,3-diketones [2] and acetylene derivatives [3]. (b) Cyclization of 2(*N*-substituted amino) pyridines [4]. (c) Reaction of 1-aminopyridinium salts with nitriles [5]. (d) From 3-cyanomethyl[1,2,4]triazolo derivatives by reaction with ketomethylene compounds [6]. (e) Ring transformation of triazolo[4,3-a]pyridines and 2-thioxopyrones [7]. (f) Reaction of *N*-amino-α-pyridones with amides [8]. One step intramolecular synthesis of the title compounds are unusual [9] and most of these consist in intermolecular multistep processes in low overall yield.

## Experimental:

Melting point were determined in capillary tubes in a Electrothermal 9200 apparatus and are uncorrected. $^{1}$H-nmr and $^{13}$C-nmr spectra were recorded at 300 MHz and 75 MHz respectively on a Varian VXR 300s spectrometer. All nmr spectra were recorded as dimethyl sulfoxide solutions, chemical shifts being given as δ values with respect to tetramethylsilane as the internal standard. The ir spectra were measured with a Perkin-Elmer 781 instrument as potassium bromide pellets. Mass spectra were obtained with a Varian MAT 711 machine, all instruments which are exist in the University of Complutense-College of organic chemistry. Microanalyses were performed by the Universidad

Complutense Microanalytical Service. The reactions were monitored by tlc performed on silica gel plates (Merck 60-F) and using chloroform-methanol or toluene-ethyl acetate as eluant.

Cyanoacetohydrazide, malononitrile, and piperidine were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. Benzylidenemalononitrile was also a commercial product, but the remaining arylidenemalononitriles were prepared from aromatic aldehydes and malononitrile following the standard procedure [16].

**2′-Cinnamoyl-2-cyanoacetohydrazide (3).**

To a stirred solution of 2-cyanoacetohydrazide (**1**) (1.98g, 18.8 mmoles) in 5 ml of water at 0 $^0$C, 3-phenylpropenoyl chloride (30 mmoles) from a dropping funnel and a solution of potassium carbonate (1.29g) in 1.5 ml of water were added. After 20 minutes a precipitate was formed. The solid was collected by filtration and recrystallized from ethanol to yield white crystals (65% yield), mp 216-218$^0$; ir: 3200 (NH), 2260 (CN), 1680 (C=O), 1640 (C=O), cm$^{-1}$; $^1$H-nmr: δ 3.78 (2H, s, $CH_2$), 6.65 (1H, d, CH=, J= 16.2 Hz), 7.38 (3H, m, ArH), 7.53 (1H, d, =CH, J= 16.2 Hz) 7.58 (2H, m, ArH), 10.35 (1H, bs, NH), and 10.48 (1H, bs, NH).

*Anal*. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.90; H, 4.80; N, 18.35
Found: C, 62.70; H, 4.75; N, 18.45

6-Amino-1-cinnamoylamino-2-oxo-4-phenyl-1,2,3,4-teterahydropyridine-3,5- dicarbonitrile (**4a**).

To a solution of 2′-cinnamoyl-2-cyanoacetohydrazide (**3**) (2mmoles) and benzyli-denemalononitrile (**2a**) (2mmoles) were suspended in 10 ml of dry ethanol. The reaction mixture was stirred either at room temperature or at reflux temperature, until tlc showed no starting material left. The solid that precipitated was collected by filtration as (**4a**). The filterate was recrystallized from the appropriate solvent. (70% yield), mp 236-238$^0$ (ethanol); ir: 3460 ($NH_2$), 3300 (NH), 2260 (CN), 2200 (CN), 1680 (C=O), 1660 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ (diastereoisomeric mixture, major isomer) 4.12 (1H, d, CH), 5.42 (1H, d, CH), 6.75 (1H, d, CH=), 7.00-7.80 (13H, m, ArH, CH=, $NH_2$), 10.69 (1H, s, NH).

*Anal*. Calcd. for $C_{22}H_{17}N_5O_2$: C, 68.85; H, 4.55; N, 18.25
Found: C, 68.95; H, 4.45; N, 18.30

Piperidinium 7-Aryl-6,8-dicyano-2-cinnamyl-5-oxo[1,2,4]triazolo[1,5-a]pyridinides **(6).** General Procedure.

A suspension of equimolar amount of 2′-cinnamoyl-2-cyanoacetohydrazide (**3**) (4 mmoles) and the corresponding α-substituted cinnamonitrile **2** (4 mmoles) in 10-15 ml of dry ethanol and the equimolar amount of piperidine (4 mmoles), the mixture of the reaction was refluxed for avariable time (3-8 hours) until tlc showed the absence of starting material. The mixture of the reaction were concentrated to half of volume and after cooling, by left in a refrigenrator (2-3 hours). The solid that precipitated out was collected by filtration and recrystallized from a suitable solvent. This compound was found to be the corresponding to **6**.

7-Aryl-6,8-dicyano-2-cinnamyl-5-oxo[1,2,4]triazolo[1,5-a]pyridines **7.**
General Procedure**.**

To the mother liquors of the corresponding salt **6** was added a solution of 10% hydrochloric acid (10-15ml), and the mixture was stirred for 15 minutes, and then the mixture was left at room temperature for 24 hours. A white solid corresponding to the 7-aryl-6,8-dicyano-2-cinnamyl-5-oxo[1,2,4]triazolo[1,5-a]pyridines **7** precipitated. The solid precipitated was collected by filtration and

washed with plenty of water (neutral PH). Further purification was accomplished by recrystallization from the appropriate solvent.

Piperidinium 6,8-dicyano-2-cinnamyl-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a]pyridinide (**6a).**

This compound was obtained in 40% yield, mp 240-242$^0$ (ethanol); ir: 3200-2300 (wide-band), 2200 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 1.54 (2H, m, $CH_2$, piperidinium), 1.64 (4H, m, $2CH_2$, piperidinium), 3.02 (4H, m, $2CH_2$ piperidinium), 7.29 (1H, d, CH=, J=16.2 Hz), 7.36-7.61 (8H, m, ArH), 7.70 (1H, d, =CH, J=16.2 Hz), 7.75 (2H, m, ArH).

*Anal*. Calcd. for $C_{27}H_{24}N_6O$: C, 72.30; H, 5.35; N, 18.75
Found: C, 72.30; H, 5.55; N, 19.00

Piperidinium 6,8-dicyano-2-cinnamyl-7-(*p*-methylphenyl)-5-oxo[1,2,4]triazolo[1,5-a] pyridinide (**6b).**

This compound was obtained in 48% yield, mp 272-274$^0$ (ethanol); ir: 3100-2300 (wide-band), 2220 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 1.50 (2H, m, $CH_2$, piperidinium), 1.59 (4H, m, $2CH_2$ piperidinium), 2.37 (3H, s, $CH_3$), 2.97 (4H, m, piperidinium), 7.20-7.37 (8H, m, ArH, CH=), 7.60-7.71 (3H, m, ArH, =CH).

*Anal*. Calcd. for $C_{28}H_{26}N_6O$: C, 72.75; H, 5.65; N, 18.20
Found: C, 72.50; H, 5.95; N, 18.20

Piperidinium 6,8-dicyano-2-cinnamyl-7-(*p*-methoxyphenyl)-5-oxo[1,2,4]triazolo[1,5-a] pyridinide (**6c).**

This compound was obtained in 61% yield, mp 291-293$^0$ (ethanol); ir: 3100-2300 (wide-band), 2200 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 1.56 (2H, m, $CH_2$, piperidinium), 1.64 (4H, m, $2CH_2$ piperidinium), 3.02 (4H, m, $2CH_2$ piperidinium), 3.85 (3H, s, $CH_3O$), 7.09 (2H, d, ArH, J=8.4 Hz), 7.27 (1H, d, CH=, J=16.2 Hz), 7.32-7.46 (3H, m, ArH,), 7.49 (2H, d, ArH, J=8.4 Hz), 7.69 (1H, d, =CH, J=16.2 Hz), 7.74 (2H, m, ArH,).

*Anal*. Calcd. for $C_{28}H_{26}N_6O_2$: C, 70.30; H, 5.45; N, 17.55
Found: C, 70.10; H, 5.40; N, 17.65

Piperidinium 6,8-dicyano-7-(*p*-chlorophenyl)-2-cinnamyl-5-oxo[1,2,4]triazolo[1,5-a]- pyridinide (**6d).**

This compound was obtained in 53% yield, mp 268-270$^0$ (ethanol); ir: 3100-2300 (wide-band), 2220 (CN), 1630 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 1.49 (2H, m, $CH_2$, piperidinium), 1.62 (4H, m, $2CH_2$ piperidinium), 3.00 (4H, m, $2CH_2$ piperidinium), 7.24 (1H, d, =CH, J=16.2 Hz), 7.31-7.41 (3H, m, ArH), 7.56, (4H, q, ArH), 7.65 (1H, d, CH=, J=16.2 Hz), 7.69-7.72 (2H, m, ArH). 8.20 (1H, br s, ArH).

*Anal*. Calcd. for $C_{27}H_{23}ClN_6O$: C, 67.15; H, 4.75; N, 17.40
Found: C, 66.90; H, 4.90; N, 17.25

Piperidinium 6,8-dicyano-2-cinnamyl-7-(*p*-nitrophenyl)-5-oxo[1,2,4]triazolo[1,5-a] pyridinide (**6e).**

This compound was obtained in 68% yield, mp 284-286$^0$ (ethanol); ir: 3000-2300 (wide-band), 2220 (CN),1610 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 1.53 (2H, m, $CH_2$ piperidinium), 1.64 (4H, m, $2CH_2$ piperidinium), 3.04 (4H, m, $2CH_2$ piperidinium), 7.29 (1H, d, CH=, J=16.2 Hz), 7.36-7.46 (3H, m, ArH), 7.72 (1H, d, =CH, J=16.2 Hz), 7.76 (2H, m, ArH). 7.86 (2H, d, ArH, J=8.7 Hz), 8.24 (1H, br s, ArH), 8.42 (2H, d, ArH, J=8.7 Hz); $^{13}$C nmr: δ 21.82 (γ-$CH_2$, piperidinium), 22.43 (β-$CH_2$, piperidinium), 43.99 (α-$CH_2$, piperidinium), 77.23, 82.83 (6-C, 8-C), 116.84, 118.17, 118.24 (2CN, ArH), 123.81 (2C), 127.46 (2C), 129.05 (2C), 129.15 (ArH), 130.58 (2C) 135.82, 136.02, 142.73, 148. 24 (ArH, CH=CH), 153.00, 153.14, 156.17 (7-C, 8a-C, 2-C), 162.30 (CO).

*Anal*. Calcd. for $C_{27}H_{23}N_7O_3$: C, 65.70; H, 4.65; N, 19.90
Found: C, 65.55; H, 4.80; N, 19.80

6,8-Dicyano-2-cinnamyl-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a]pyridine (**7a).**

This compound was obtained in 27% yield, mp >350$^0$ (ethanol); ir: 3200-2300 (wide-band), 2200 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$, 7.28 (1H, d, CH=, J=16.2 Hz), 7.36-7.47 (3H, m, ArH), 7.54 (5H, S, ArH), 7.72 (1H, d, =CH, J=16.2 Hz), 7.76 (2H, m, ArH); $^{13}$C nmr: δ 77.20, 98.38 (6-C, 8-C), 115.84 (ArH), 117.01, 117.59 (2CN), 127.52 (2C), 128.63 (2C), 128.81 (2C), 129.12 (2C), 129.18, 129.74, 135.95, 136.06, 136.22 (ArH, CH=CH), 152.83, 155.67, 156.16 (7-C, 8a-C, 2-C), 161.10 (CO).

*Anal*. Calcd. for $C_{22}H_{13}N_5O$: C, 72.75; H, 3.60; N, 19.30
Found: C, 72.60; H, 3.65; N, 19.15

6,8-Dicyano-2-cinnamyl-7-(*p*-methylphenyl)-5-oxo[1,2,4]triazolo[1,5-a] pyridine (**7b).**

This compound was obtained in 16% yield, mp >380$^0$ (ethanol and acetonitrile); ir: 3100-2300 (wide-band), 2220 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 2.27 (3H, s, $CH_3$), 7.0-7.37 (8H, m, ArH, CH=), 7.6 (3H, m, ArH, =CH).

*Anal*. Calcd. for $C_{23}H_{15}N_5O$: C, 73.20; H, 4.00; N, 18.55
Found: C, 72.95; H, 4.15; N, 18.35

6,8-Dicyano-2-cinnamyl-7-(*p*-methoxyphenyl)-5-oxo[1,2,4]triazolo[1,5-a] pyridine (**7c).**

This compound was obtained in 12% yield, mp 364-366$^0$ (ethanol); ir: 3100-2300 (wide-band), 2200 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 3.85 (3H, s, $CH_3O$), 7.10 (2H, d, ArH), 7.27 (1H, d, CH=, J=16.2 Hz), 7.38-7.52 (5H, m, ArH,), 7.70 (1H, d, =CH, J=16.2 Hz), 7.75 (2H, m, ArH,).

*Anal*. Calcd. for $C_{23}H_{15}N_5O_2$: C, 70.25; H, 3.80; N, 17.80
Found: C, 69.95; H, 3.75; N, 17.90

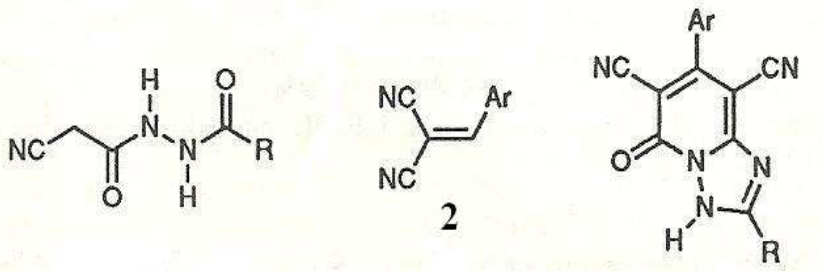
6,8-Dicyano-7-(*p*-chlorophenyl)-2-cinnamyl-5-oxo[1,2,4]triazolo[1,5-a]- pyridine (**7d).**

This compound was obtained in 10% yield, mp >380$^0$ (ethanol and acetonitrile); ir:3100-2300 (wide-band), 2220 (CN), 1650 (C=O) cm$^{-1}$; $^1$H nmr: $\delta_H$ 7.24 (1H, d, CH=, J=16.2 Hz), 7.32-7.42 (3H, m, ArH,), 7.56 (4H, q, ArH), 7.67 (1H, d, =CH, J=16.2 Hz), 7.72 (2H, m, ArH,), $^{13}$C nmr: δ 76.92, 83.68 (6-C, 8-C), 116.87 (CN) 117.8 (ArH), 118.26 (CN), 127.47 (2C), 128.74 (2C), 129.07 (2C), 130.76 (2C), 134.55, 135.06, 136.05, 136.11 (ArH, CH=CH), 152.9, 154.27, 156.08 (7-C, 8a-C, 2-C), 161.38 (CO).

*Anal*. Calcd. for $C_{22}H_{12}ClN_5O$: C, 66.40; H, 3.05; N, 17.60
Found: C, 66.30; H, 3.25; N, 17.70

## Results and Discussion:

We have previously reported the reaction of 2-acetyl-2-cyanoacetohydrazide **8**, 2-benzoyl-2-cyanoacetohydrazide **9** and, 2-cyano-2-phenylacetylacetohydrazide **10** with arylidenemalononitrile **2**, as a very convenient, one-step method to synthesis the very important [1,2,4]triazolo[1,5-a]pyridinones **7** [10-12]. Which have proved their usefull-ness in many applications such as pharmaceuticals, complexing agents, or fluorescent brighteners[13].



8 R=Me
9 R=Ph
10 R=$CH_2Ph$

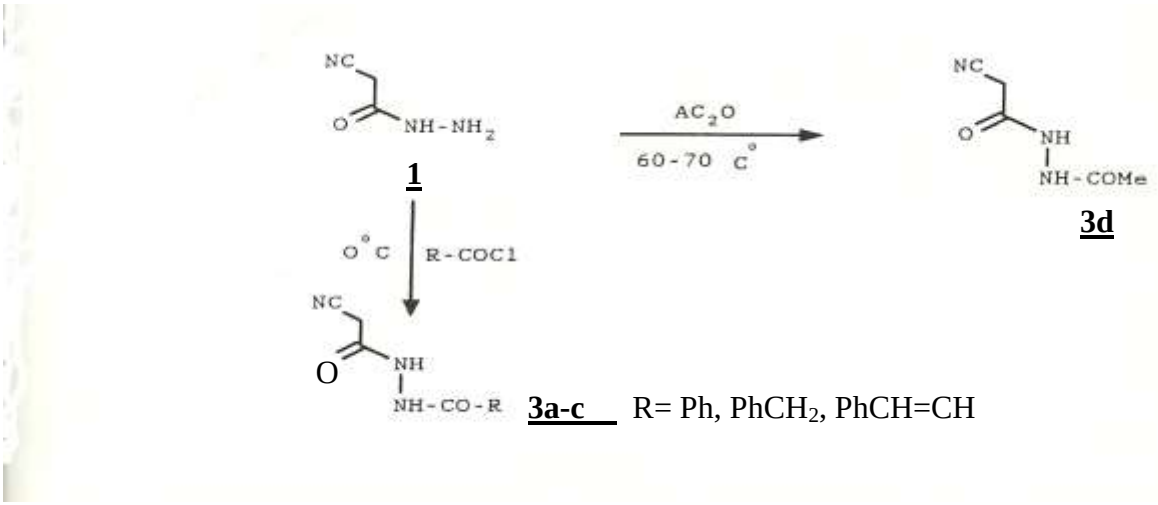
**2**

7
R=Me, Ph, $CH_2Ph$

(Scheme I)

In this paper we report the approach through the intramolecular nucleophilic substitution at 2-cyanocinnamonitriles (**2**)

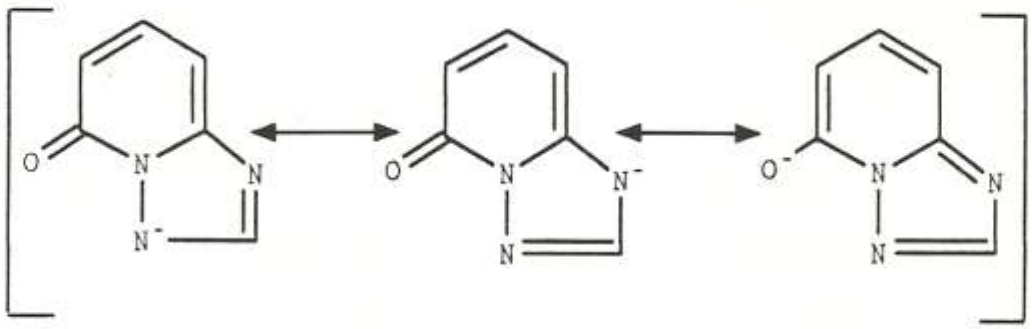
Thus, by reaction of cyanoacetohydrazide **1** (Scheme 2) with 3-phenylpropenyl chloride at $0^0$, the corresponding N-substituted 2-cyanoacetohydrazides **3** was obtained in good yield.




(Scheme 2)

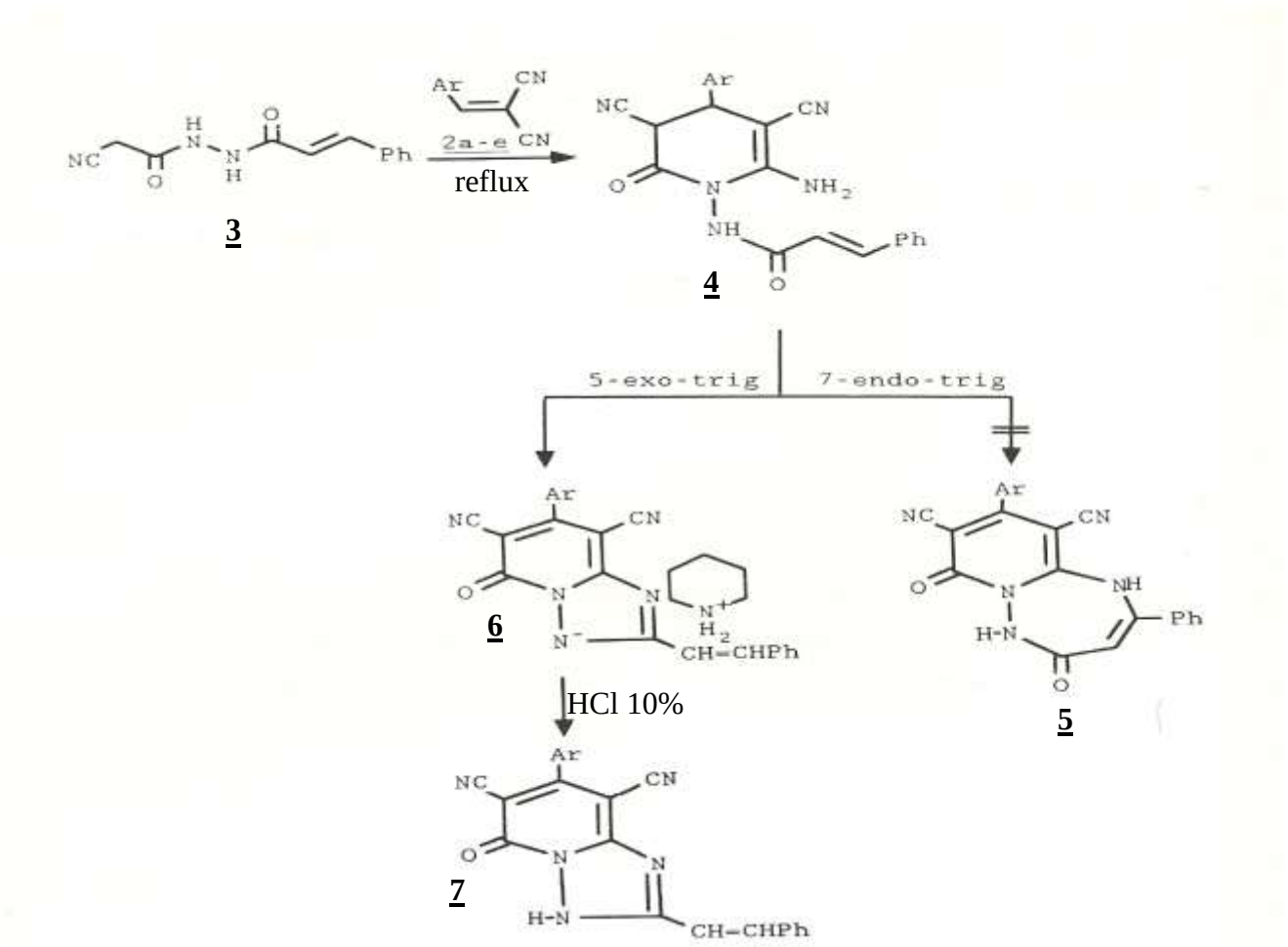
Reaction of this compound **3** with α-substituted cinnamonitriles **2** and piperidine in alcoholic solution led to the *6-exo-dig* cyclization [14] to yield the intermediate *N*-cinnamoylamino-3,4-dihydro-2-pyridones **4**. The subsequent *5-exo-trig* cyclization by attack of the primary amino group to the low reactivity amide carbonyl group led to the [1,2,4]triazolo[1,5-a]pyridones that were isolated as the piperidinium salts due to the high acidity of the ring proton [15], in moderate to good yields.

Formation of the piperidinium salt in the triazolo[1,5-a]pyridinone is due to the anion's stability, resulting from charge delocalization involving the two triazolo nitrogens and the pyridine oxygen in compounds **6** (Scheme 3)



(Scheme 3)

Several attempts were performed to obtain the neutral [1,2,4]triazolo[1,5-a]pyridones **7.** Thus, when the reaction of 2′-cinnamoyl-2-cyanoacetohydrazide **3** with α-cyanocinnamonitrile **2a** (Ar= $C_6H_5$) was carried out in the absence of piperidine, no evidence of formation of neutral compound **7** was observed. Compound **4a** (Ar=$C_6H_5$ ) was obtained in 50% yield as the only isolated as a mixture of diastereomers due to the presence of the two chiral carbons in the ring (Scheme 4).




(Scheme 4)

This fact could be evidence that the driving force in the formation of the bicyclic system is the formation of the salt, resulting in a very stable anion due to the charge delocalization in the two fused heterocyclic rings. However, the neutral compounds **7** could be finally obtained from the piperidinium salt **6** by treatment with hydrochloric acid (Scheme 4). The acid conditions used did not affect the other functional groups present in the molecule and the procedure to synthesize compounds **7**. Proved to be of a wide scope.

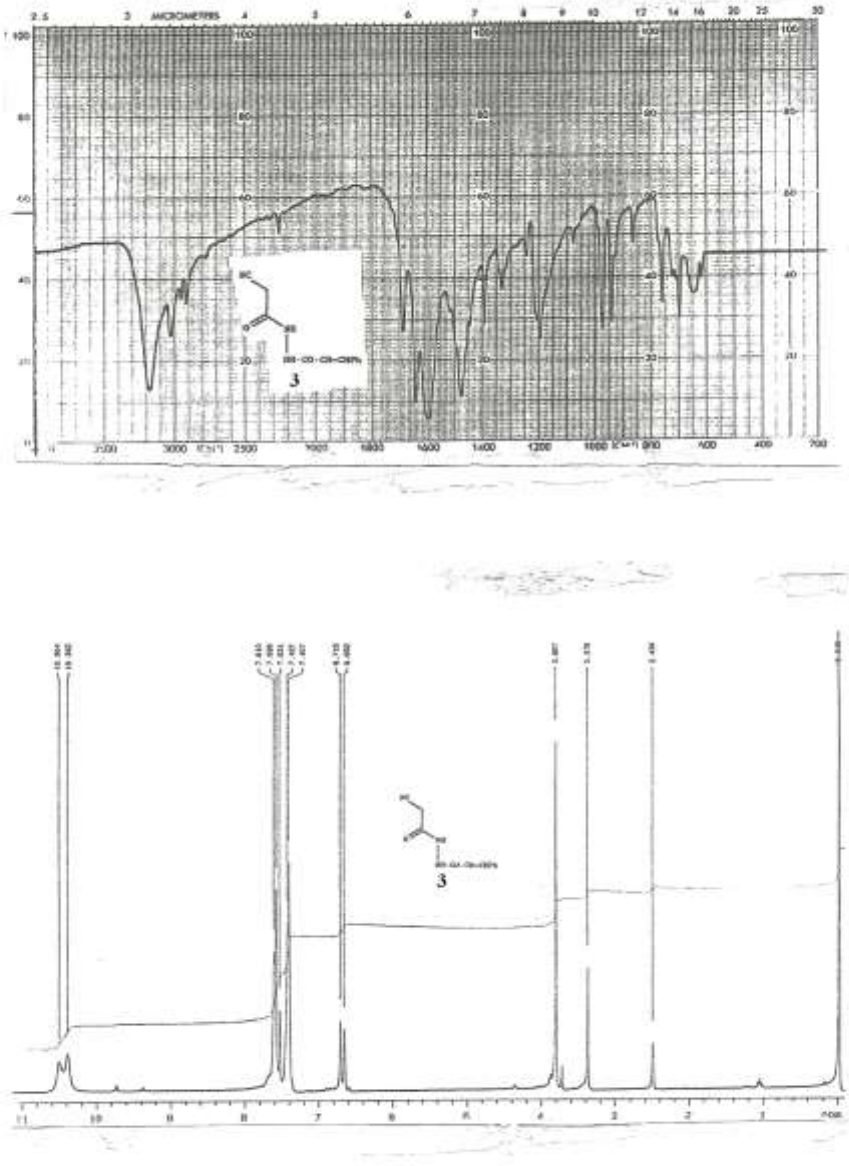



Fig.(1)

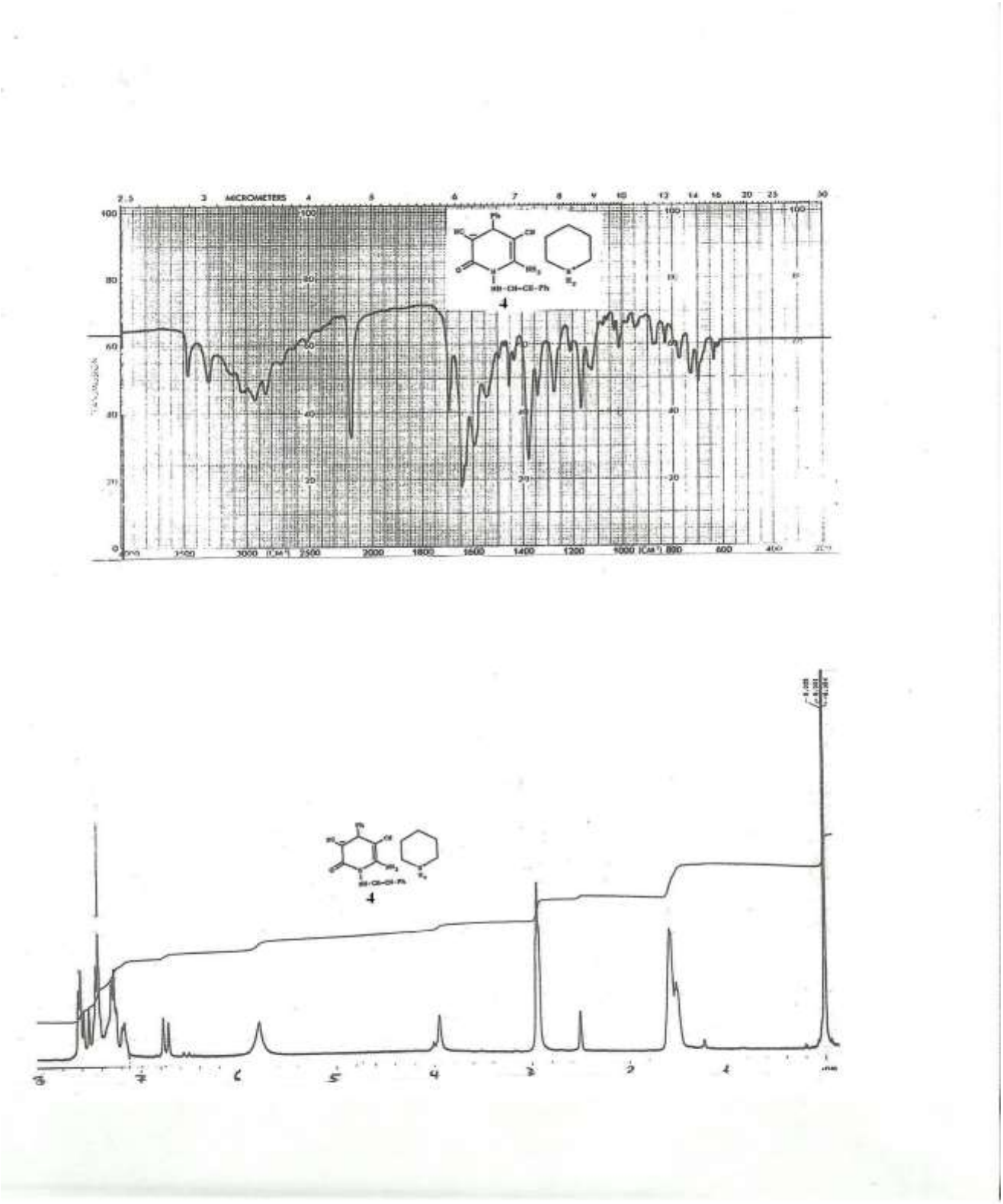


Fig.(2)

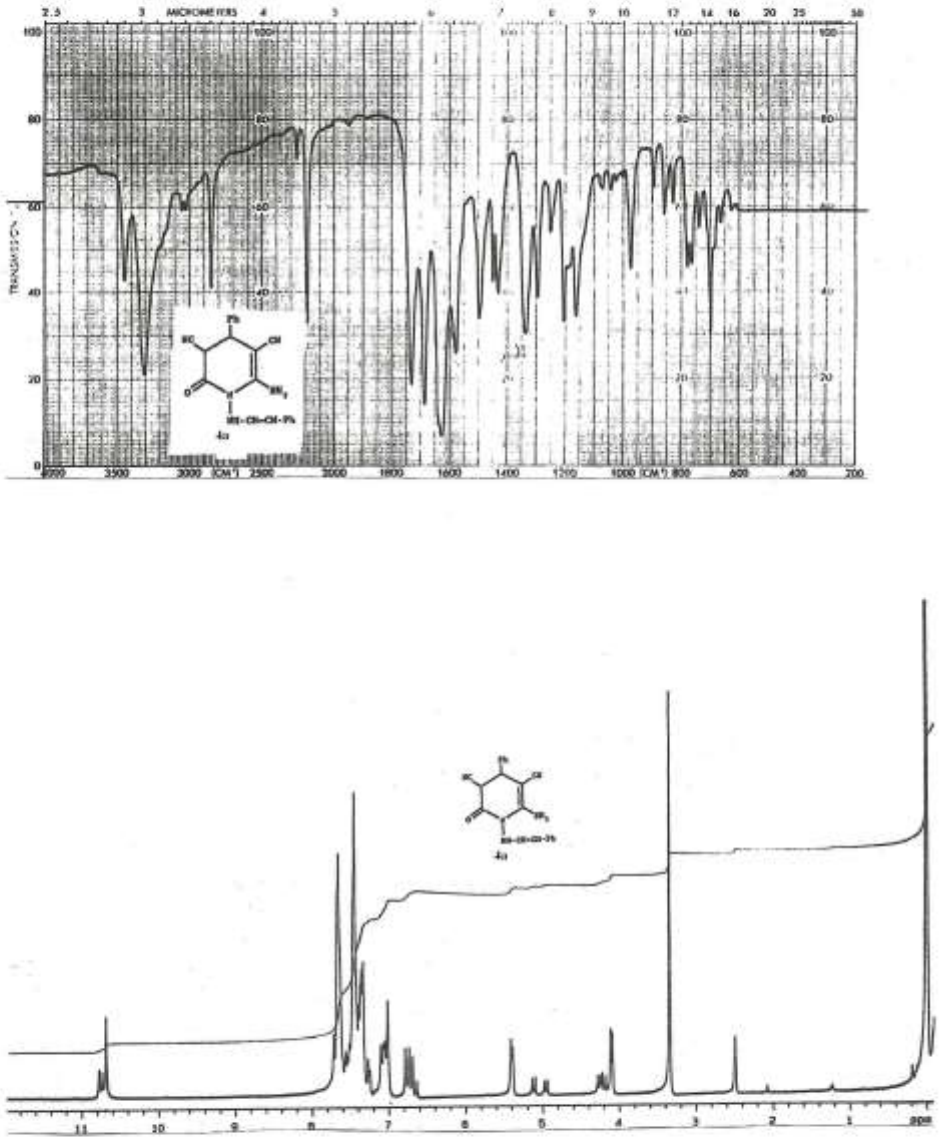


Fig.(3)

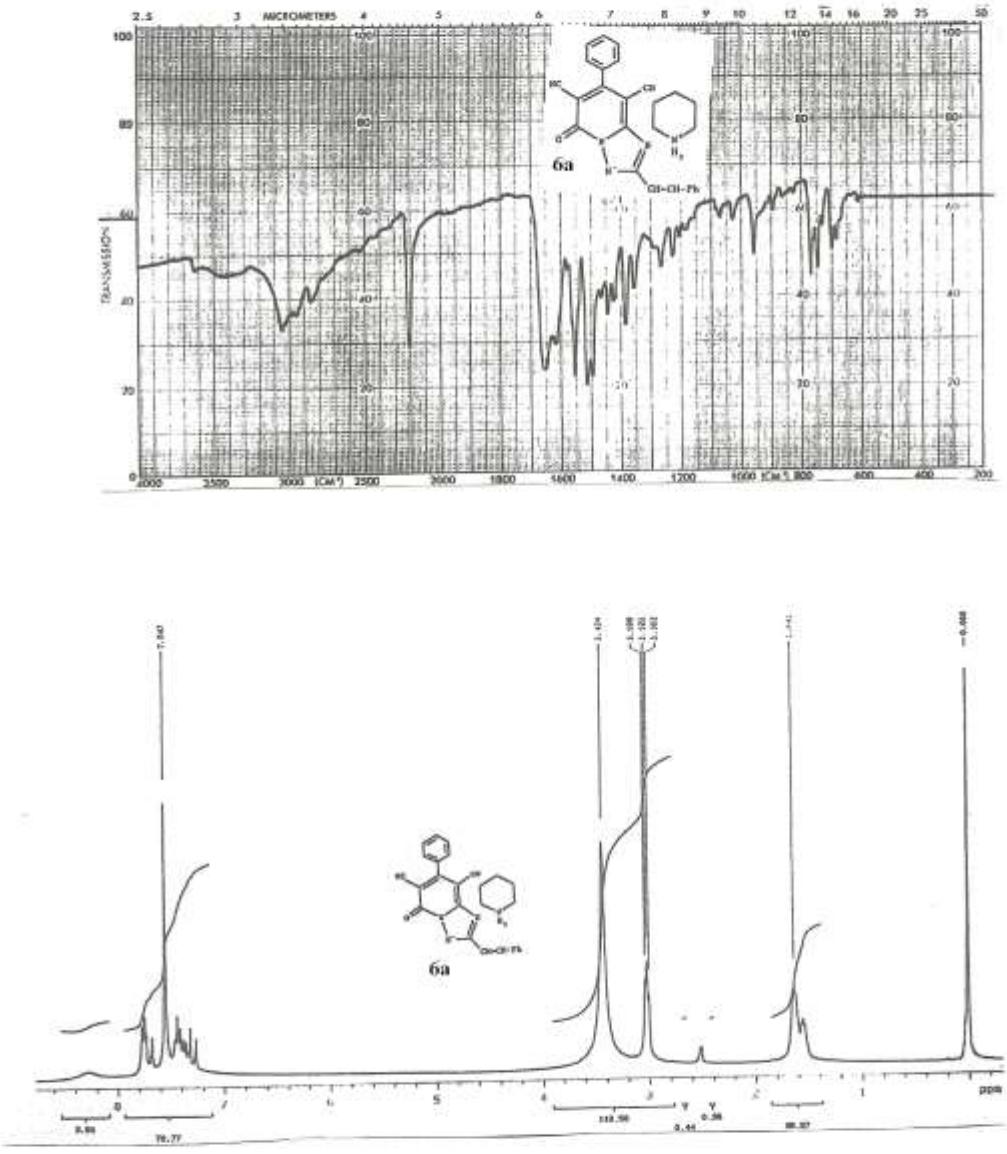



Fig.(4)

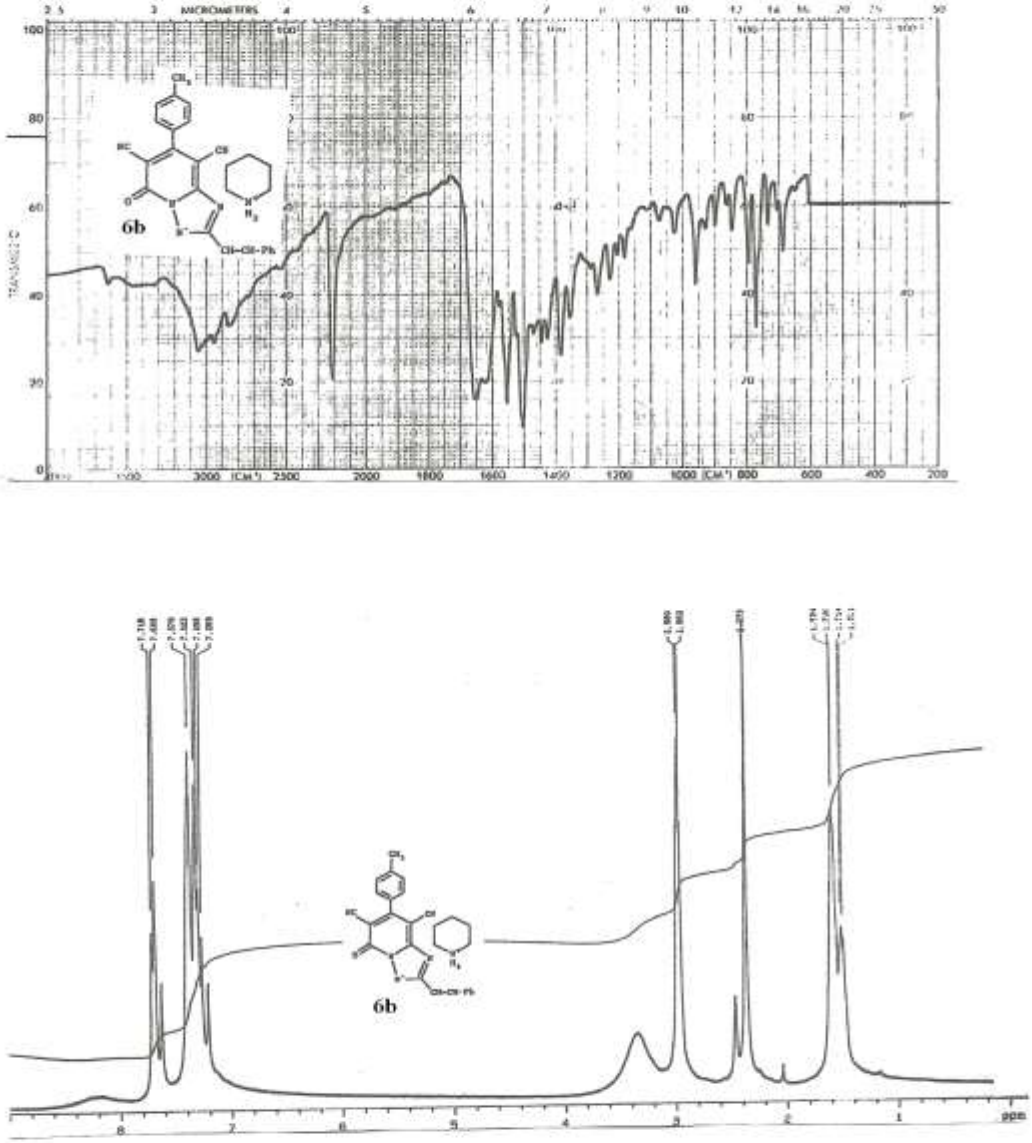



Fig.(5)

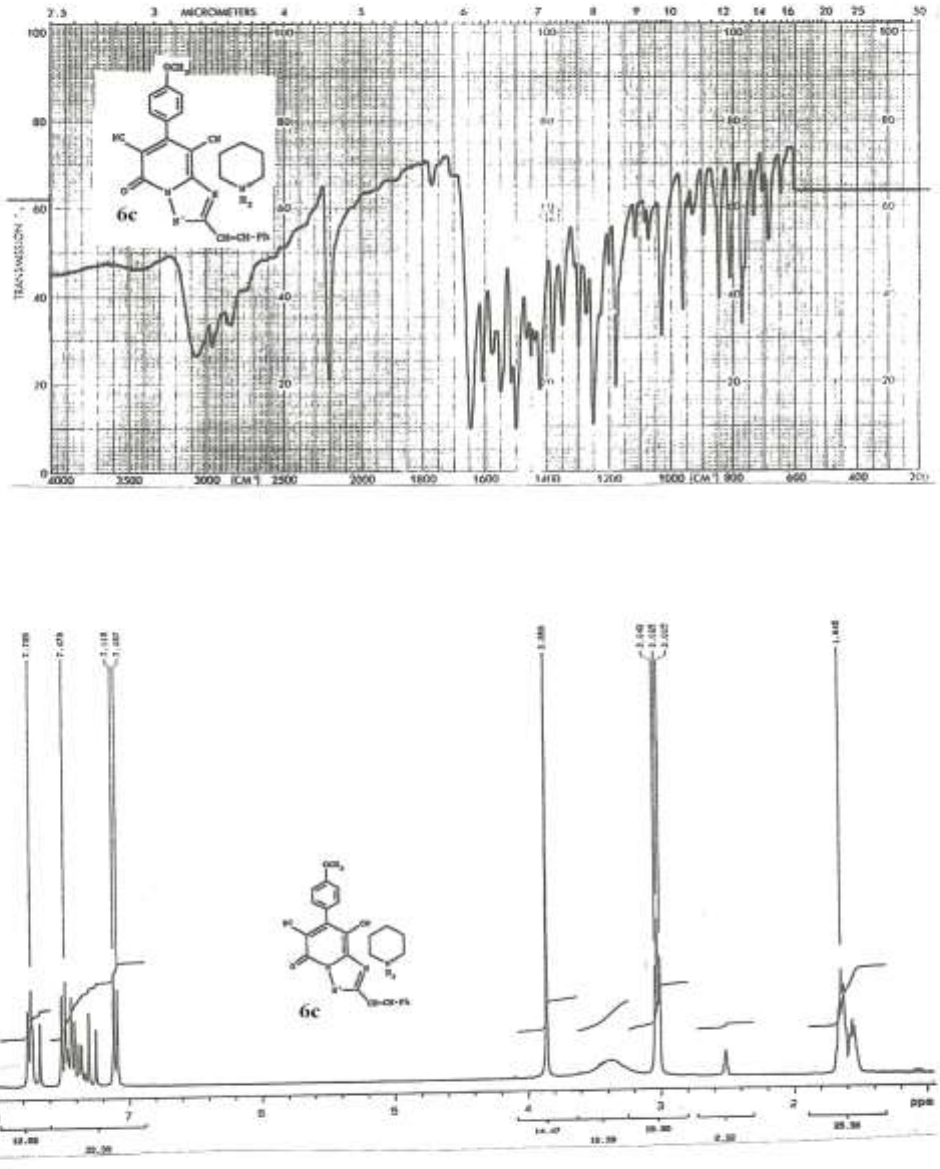
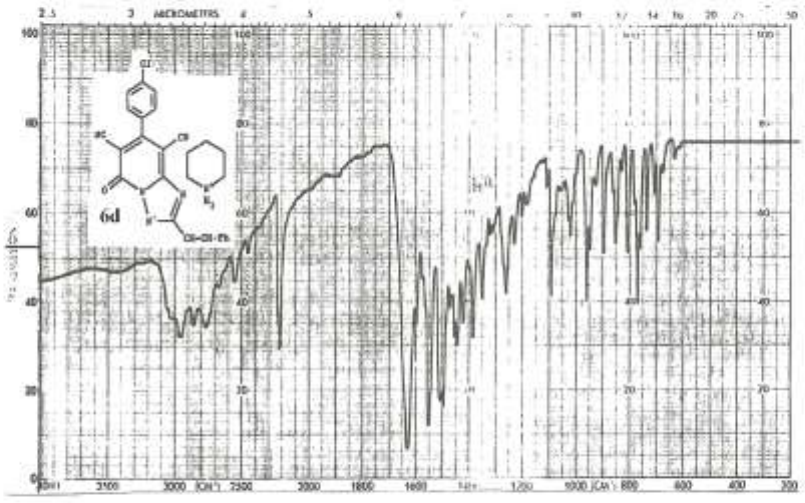



Fig.(6)



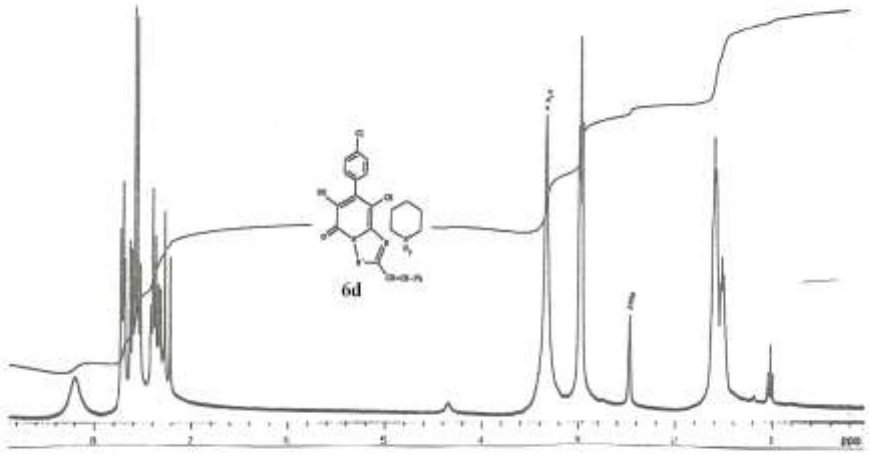
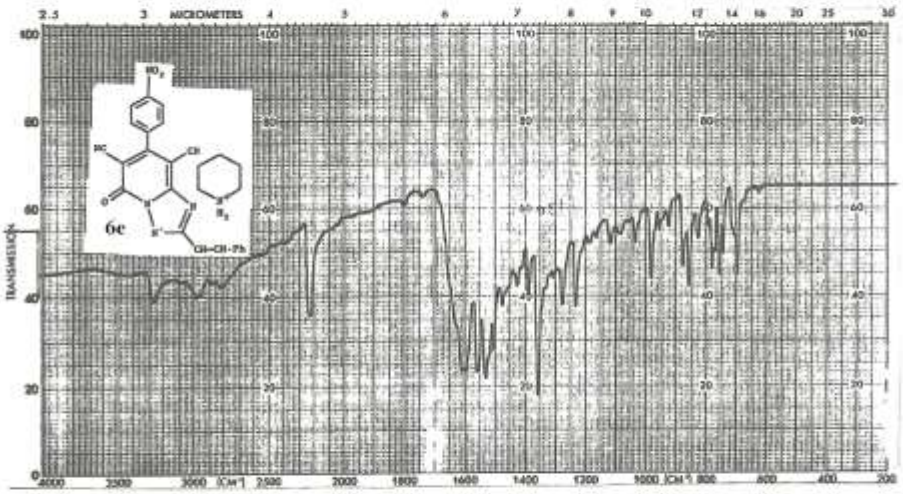




Fig.(7)



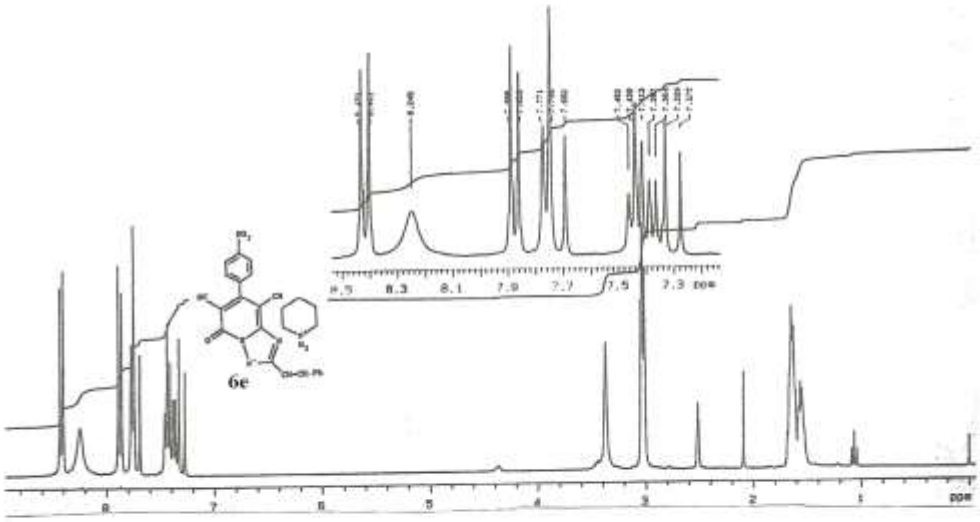




Fig.(8)

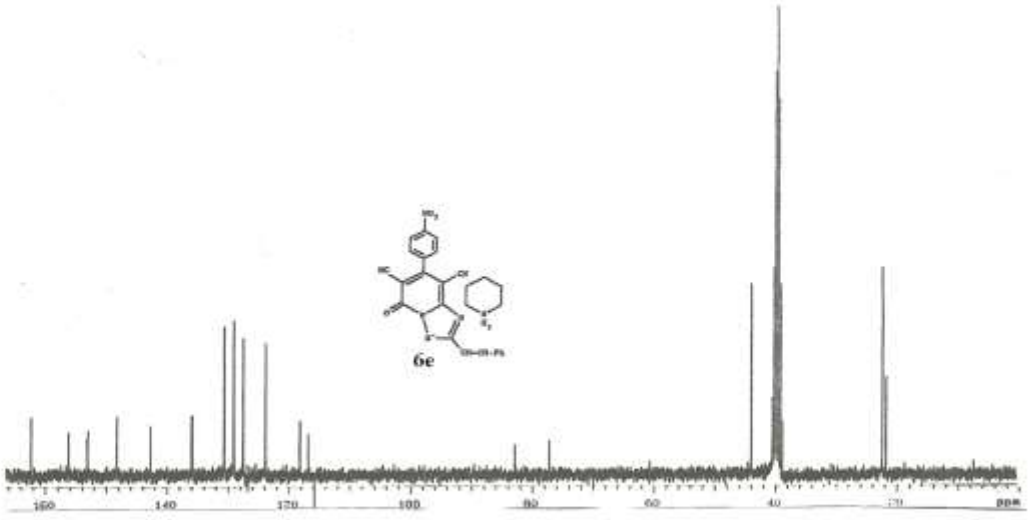



Fig.(9)

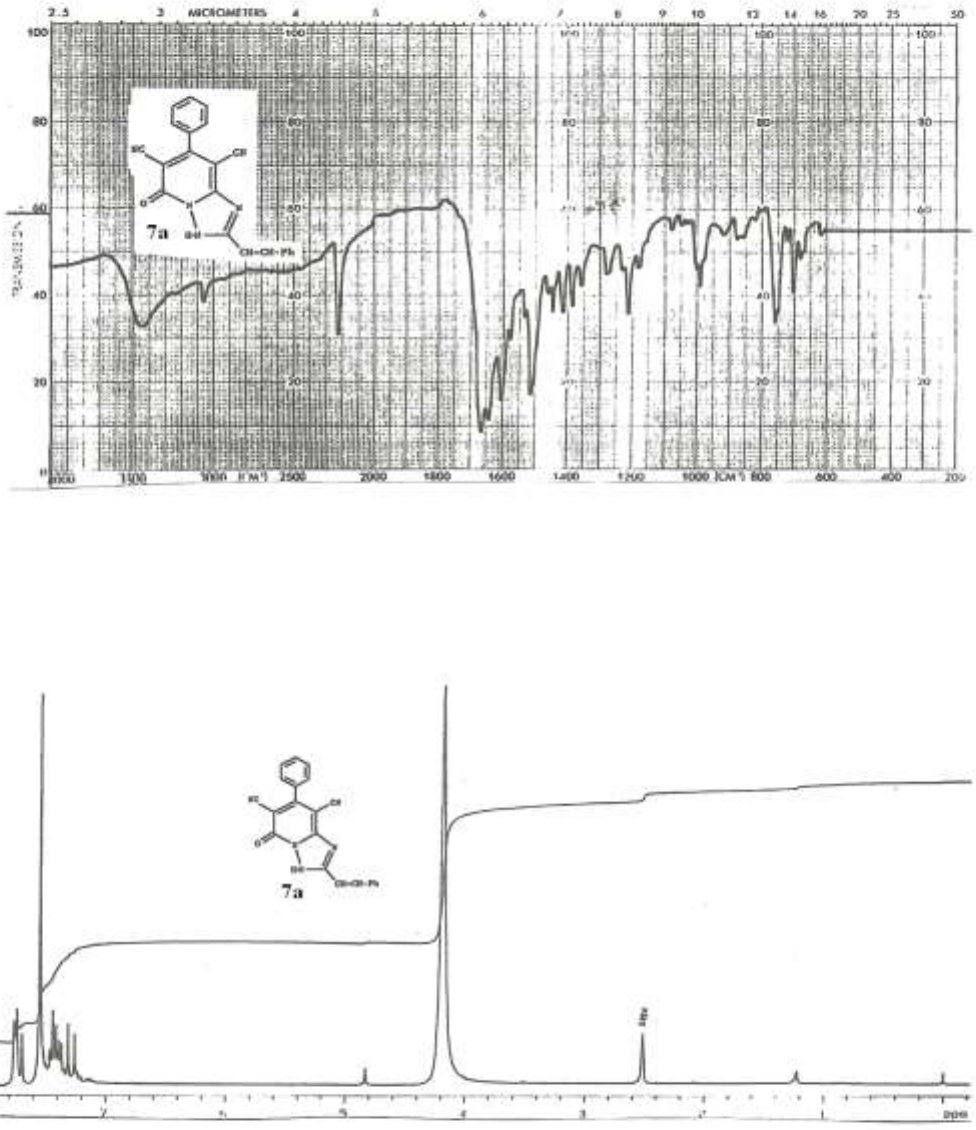



Fig.(10)

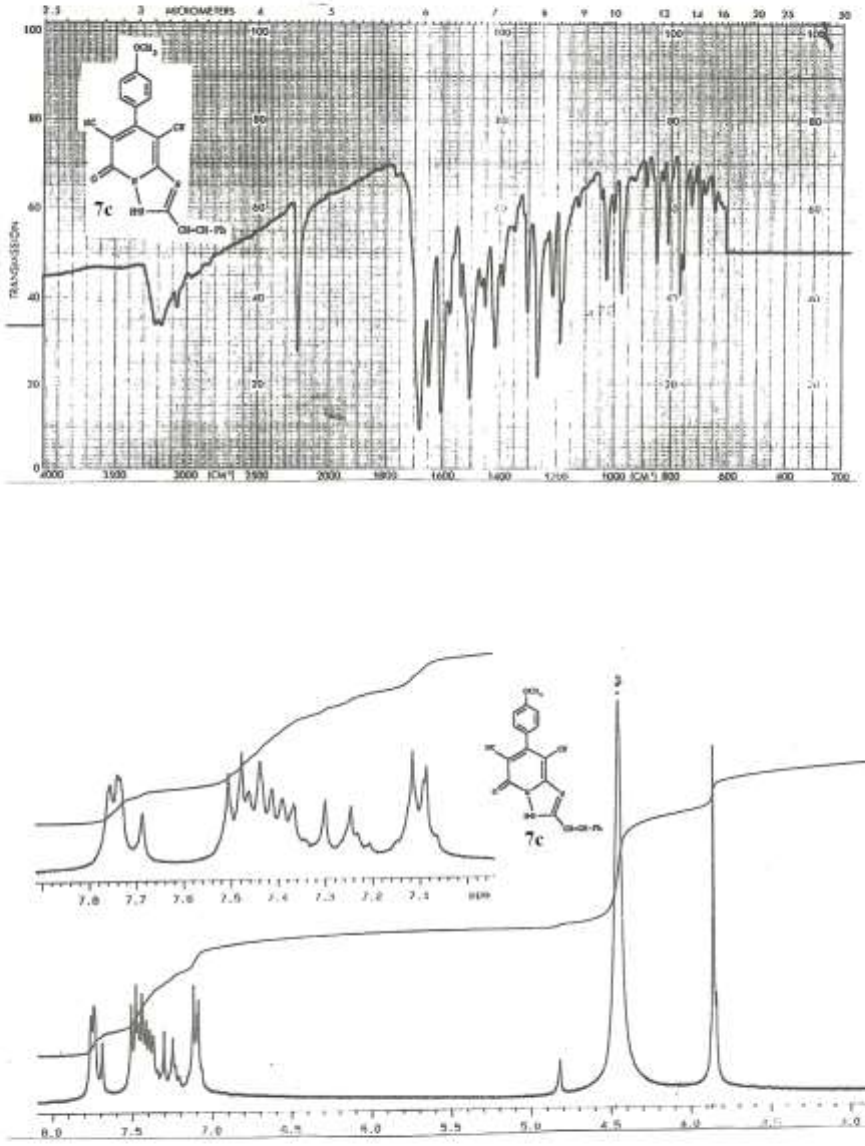



Fig.(11)

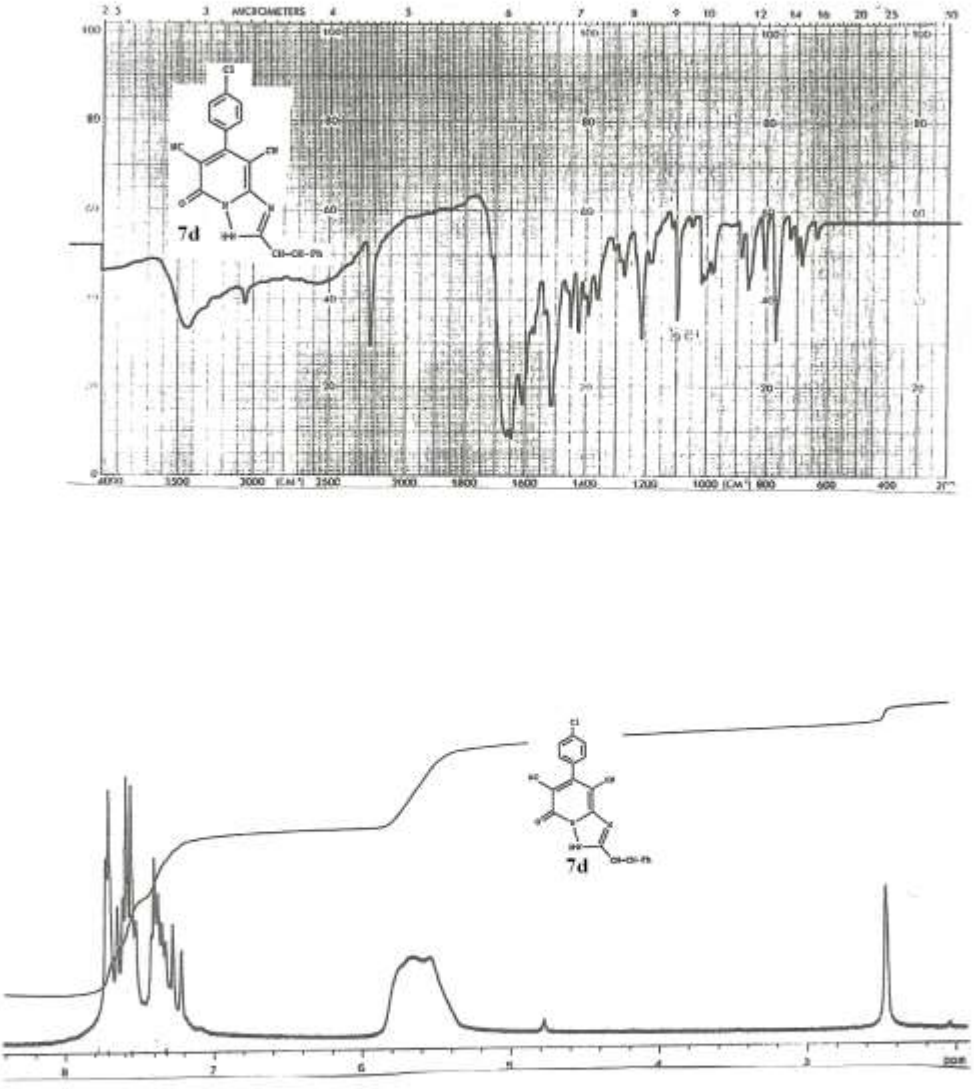



Fig.(12)

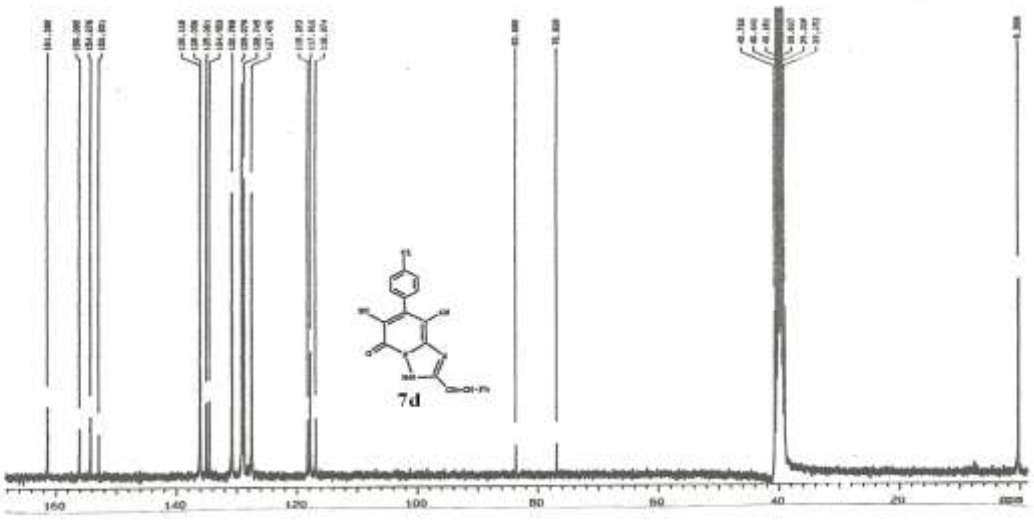



Fig.(13)

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