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Synthesis of Pyranopyrimidine Derivatives Using a Practical One-Pot Three-Component Reaction in the Presence of L-Proline Catalyst

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ABSTRACT

In the current research, different derivatives of pyranopyrimidine were synthesized using a three-component reaction between thiobarbituric acid derivative, aldehyde and Malononitrile in the presence of L-proline catalyst and water/ethanol (80/20) solvent. This method offers some benefits including easy separation of products, high efficiency, and absence of dangerous, expensive and toxic reagents.

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INTRODUCTION

Multi-component reactions have been known for more than 150 years. In 1850 the first multi-component reaction was reported by Stryker in the synthesis of α- amino cyanides. Among the advantages of multi-component reactions is their usefulness in the design and production of drugs. [2] Multi-component reactions are very powerful tools since the synthesis of complex organic molecules from simple and available materials can be done with a quick and easy method and without the isolation of intermediates. This type of reaction have a lot of advantages including high speed and high efficiency, low reaction time, low cost, selectivity, lack of impurities and reduction of the by product. Another advantage of these reactions is the ease with which their products are purified, because all the ingredients appear in the final product. These reactions can be used for the synthesis of heterocyclic compounds.

Heterocyclic compounds are cyclic compounds in which one or more carbon ring atoms have been replaced with non-carbon atoms such as Nitrogen, oxygen, sulfur, metal atoms, etc. The most common heterocyclic compounds have nitrogen or oxygen or both of them combined in a ring [6]. Pyranopyrimidine is a heterocyclic compound which is formed from a pyrano ring with pyrimidine .In this combination an oxygen atom is placed at position 8 and two Nitrogen atoms are placed at positions 1 and 3. [7]. Given the importance of pyranopyrimidine derivatives in pharmaceutical chemistry and organic reactions various methods and reagents have been reported for their synthesis and chemists are always looking for new ways to produce these compounds. Among these methods are synthesis of these compounds in the presence of various catalysts, microwave and use of ionic liquids [8-11]. Each of these methods has its own advantages and disadvantages.

On the other hand, amino acids play an important role in biochemical studies and are frequently used in various industries such as food processing, pharmaceutical industry and the production of chiral catalysts [12].

Among chiral catalysts, L- proline can be mentioned (Figure 1). Proline has a second amino group and an acidic group and is one of the α-amino acids that are derived from the amino acid L- glutamate. This amino acid is not produced by the human body. Its L form, which is the more common chirality, has a space chemistry of S. Since this compound has a polar nature, substituent groups have an important effect in their solubility [13,14,15].

Given the importance of this class of compounds in this study we investigate the catalytic effect of L – proline in synthesis of this class of heterocyclic compounds.

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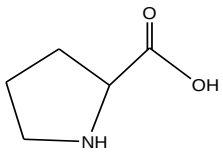

Fig. 1: Catalyst L – proline.

Experimental section:

General information of devices and materials:

The reported melting points are uncorrected and are reported in centigrade degrees. Determination of melting point in open capillary tubes was performed through using the melting point measurement Electro thermd 9100. The C^{13} NMR and H^{1} NMR spectrums of the products were prepared using BRUKER NMR-Spectrometer FX 400Q. The NMR chemical shifts of the spectra were calculated in relation to internal standard of TMS and were reported in ppm. Solvents and chemicals material and TLC plates were purchased from Fluka, Merck and Aldrich and were used as purchased.

General method for the preparation of Pyrano pyrimidine derivatives:

A mixture of thiobarbituric acid derivative (1 mmol), aldehyde (1.2 mmol) and Malononitrile (1 mmol) was solved in a mixture of ethanol and water (20:80, V/V) and was kept at room temperature for ten minutes. Then 1 mmol of the catalyst (L- proline) was added to the reaction mixture and the reaction was stirred by a magnetic stirrer at 80°C for 90 min under reflux conditions. Reaction progress was investigated using thin layer chromatography (TLC) using a mixture of ethyl acetate and n- hexane (2:3, V/V) as solvent. After completion of the reaction, the reaction mixture was cooled to the room temperature.

Afterwards, cold distilled water was added to the reaction mixture and the resulting sediments were separated using a filter paper. Then the solid products were washed with ethanol and were placed for 12 hours in an oven at 100°C to dry. Then, the dried products were solved in the dimethyl sulfoxide (DMSO) solvent and the desired compound was separated and purified by comparable plate chromatography or TLC.

Discussion and Conclusion:

Optimization of catalysts for the synthesis of Pyrano pyrimidine derivatives:

The reaction of para-chloroethyl benzaldehyde (1.2 mmol) with thiobarbituric acid (1 mmol) and Malononitrile (1 mmol) was investigated in the presence of various catalysts (1 mmol). Reactions were performed under the same conditions and at two different temperatures including room temperature and 50 ^{0}C and in the presence of acetic acid solvent (5 mL) (Table 1) (Figure 2).

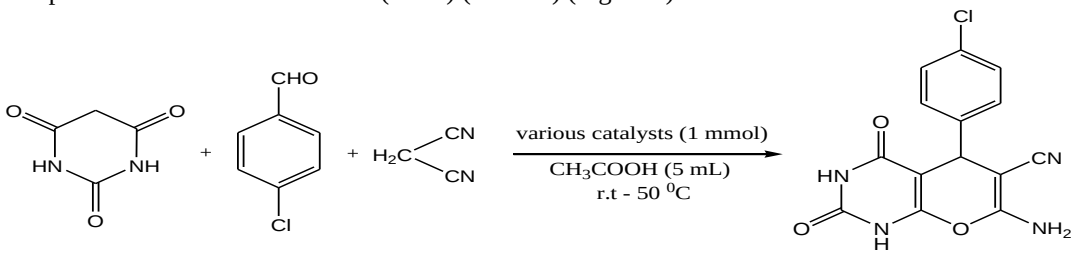

Fig. 2:

Various catalysts were investigated in the reaction (Table 1, rows 5-1). Also, at room temperature, the reaction rate and products yield were low (Table 1, row 4). At 50 ^{0}C, the best results were obtained when the L-proline was used as a catalyst (Table 1, row 9).

Table 1: The Effect of different catalysts in the synthesis of para-chloroethyl phenyl pyrimidine pyrano.

row	Catalyst type	Temperature(^{0}C)	Time(minute)	efficiency%
1	Boric acid	r.t	400	31
2	L- aspartic	r.t	370	60
3	HZS -5	r.t	380	54
4	L- proline	r.t	330	65
5	β- anilin	r.t	385	44
6	Boric acid	^{0}C50	320	49
7	L- aspartic	^{0}C50	300	69
8	HZS -5	^{0}C50	310	66
9	L- proline	^{0}C50	270	77
10	β- aniline	^{0}C50	305	58

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Optimizing the solvent and temperature for synthesis of Pyrano pyrimidine derivative:

After selecting L- proline as the best catalyst for this reaction, this time the reaction of para-chloroethyl benzaldehyde (1.2 mmol) with barbituric acid (1 mmol) and Malononitrile (1 mmol) was examined in the presence of different solvents. As can be seen in Table 2, the water/ethanol (5 mL) solvent was selected as the best solvent for this reaction (Table 2, row 3).

For optimizing of the reaction temperature, the reaction was studied in the presence of water/ethanol (50/50, V/V) solvent in the temperatures from 50 to 90 C (Table 2, rows 3-8). As can be seen in Table 2, with increases in the temperature the efficiency and speed of reaction was increased (Table 2, rows 3-7). However, when the reaction was carried out at a temperature of 90ºC, speed and reaction efficiency was decreased due to evaporation of ethanol at this temperature (Table 2, row 8). As a result, the temperature of 80ºC was chosen as the best temperature for the reaction (Table 2, row 7).

Table 2: Examination of the Effect of different solvents and temperatures in the synthesis of para-chloroethyl phenyl pyrimidine.

row	Solvent type	temperature (^{0}C)	Time(minute)	efficiency%
1	Acetic acid	^{0}C50	270	77
2	Aceto nitrile	^{0}C50	370	60
3	Water / ethanol(50/50)	^{0}C50	240	80
4	Water / ethanol(50/50)	^{0}C60	235	81
5	Water / ethanol(50/50)	^{0}C70	220	81
7	Water / ethanol(50/50)	^{0}C80	210	82
8	Water / ethanol(50/50)	^{0}C90	350	76

In order to determine the optimal water/ethanol ratio in the solvent, the ethanol content of the solvent was increased which led to increase in reaction efficiency and rate (Table 3, row 1) however increasing the water content decreased both speed and efficiency of the reaction (Table 3, rows 2-5). When the reaction was performed in the presence of water / ethanol solvent with ratio of (90/10) the reaction rate and efficiency was reduced (Table 3, row 6). As a result, 5 mL mixture of water/ethanol with ratio of (80/20, V/V) was selected as the best solvent for the reaction (Table 3, row 5).

Table 3: Examining the effects of different ratios of a mixture of water / ethanol as a solvent in the synthesis of para-chloroethyl phenyl pyrimidine.

row	Solvent type	Temperature(^{0}C)	Time(minute)	efficiency%
1	Water / ethanol(60/40)	^{0}C80	280	78
2	Water / ethanol(50/50)	^{0}C80	190	80
3	Water / ethanol(40/60)	^{0}C80	180	82
4	Water / ethanol(30/70)	^{0}C80	170	83
5	Water / ethanol(20/80)	^{0}C80	150	87
6	Water / ethanol(10/90)	^{0}C80	180	76

Optimizing the amount of catalyst L - Proline for synthesis of Pyrano pyrimidine derivatives:

After optimization of the effect of solvent and temperature and the selection of L- proline as the best catalyst for performing the reaction, for obtaining optimum amount of catalyst, different amounts of L- proline (1 mmol) was used in the presence of water/ethanol (80/20) solvent at 80 C. The best result was obtained when the 1 mmol of L- proline catalyst was used (Table 4, row 5).

Table 4: Examining the effect of the catalyst L- proline amount on para-chloroethyl phenyl pyrimidine synthesis.

row	L- proline catalyst amount (mmol)	Time(minute)	efficiency%
1	0/1	400	72
2	0/25	320	76
3	0/5	230	79
4	0/75	190	82
5	1	150	87

Base on the results of the tables (1, 2, 3, 4) ,other Pyrano pyrimidine derivatives were desirably synthesized under single container conditions through using 1 mmol of L- proline catalyst in the presence of water / ethanol (5 mL) solvent with ratio of (80/20) at 80ºC. (Figure 3).

As can be seen in Table 5, various derivatives of Pyrano pyrimidine were synthesized from reaction of different derivatives of benzaldehyde and thiobarbituric acid, thiosulfate thiobarbituric acid or dimethyl thiobarbituric acid with Malononitrile.

The efficiency of Thiobarbituric acid reaction of with the benzaldehyde derivative (Table 5, rows 1-7) was much better than that of thiosulfate thiobarbituric acid and dimethyl thiobarbituric acid (Table 5, No. 8-10). Generally, when an electron donor group was present the para position of benzaldehyde, the reaction was much better than when the electron acceptor group was in the para position of benzaldehyde. The best results were obtained when the para-methoxy benzaldehyde was used (Table 5, row 5,9), although the product resulting from

the reaction of para-chloroethyl benzaldehyde with thiobarbituric acid in the presence of Malononitrile also has a high efficiency (Table 5, row 1). The worst results were obtained when the para-nitro-benzaldehyde was used as the nitro group is a powerful electron acceptor which reduces the efficiency of the reaction (Table 5, row 8,2).

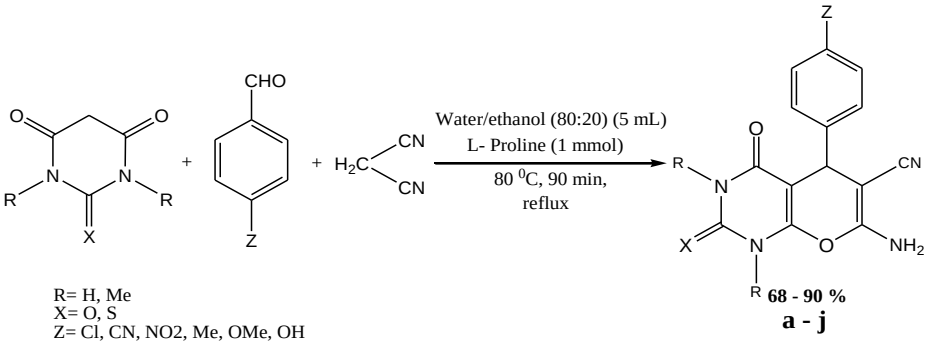
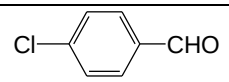
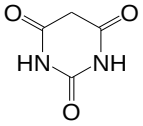
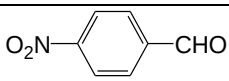
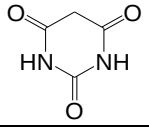
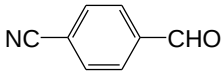
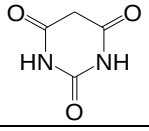
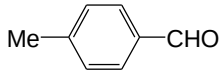
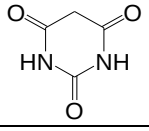
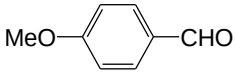
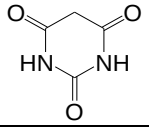
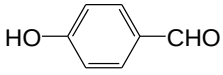
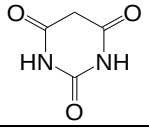
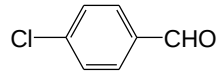
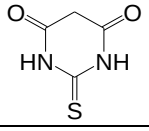
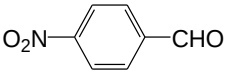
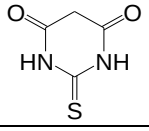
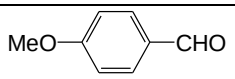
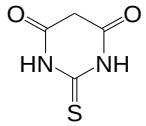
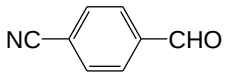
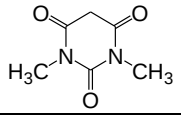


Fig. 3: Synthesizing different derivatives from pyrano pyrimidine in the presence of L- proline catalyst under optimal conditions.

Table 5: Pyrano pyrimidine derivatives synthesized via benzaldehyde derivatives reaction with thiobarbituric acid derivatives in the presence Malononitrile.

row	Nitrile	Benzaldehyde	Thiobarbituric acid	products	Efficiency (%)	Melting point(^{0}C)	Melting points recorded in sources(^{o}C)
1	$CH_2(CN)_2$			**a**	87	233	235
2	$CH_2(CN)_2$			**b**	70	235	235
3	$CH_2(CN)_2$			**c**	84	242	255
4	$CH_2(CN)_2$			**d**	73	230	230
5	$CH_2(CN)_2$			**e**	90	279	280
6	$CH_2(CN)_2$			**f**	72	288	290
7	$CH_2(CN)_2$			**g**	76	236	235
8	$CH_2(CN)_2$			**h**	68	220	220

9	$H_2(CN)_2$			**i**	85	270	270
10	$CH_2(CN)_2$			**j**	71	264	265

Also, six new compounds were synthesized from the reaction of 2-pyridine Carbaldehyde and Terephthaldehyde with thiobarbituric acid derivatives with high efficiencies. For this purpose, 2 mmol of Malononitrile and other reagents were used (Table 6, rows 1-3) (Fig. 4).

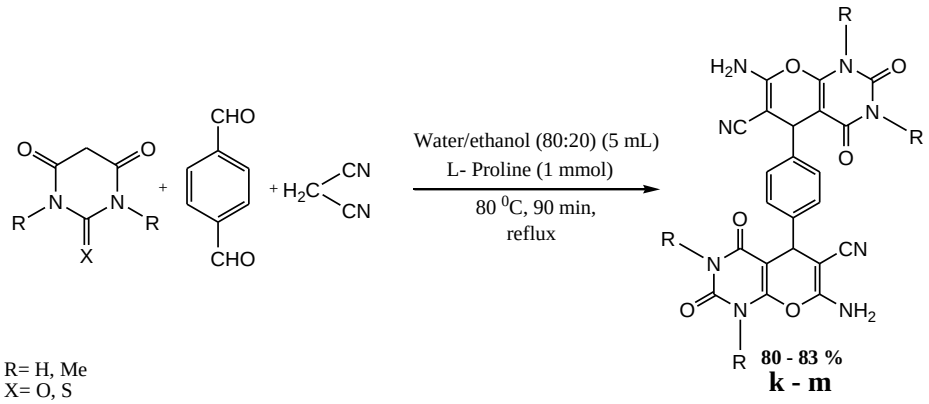


Fig. 4:

In addition, in this project, three other new derivatives of Pyranopyrimidine were synthesized with good efficiency. These derivatives were synthesized from reaction of 2-pyridine Carbaldehyde with thiobarbituric acid, barbituric acid and dimethyl thiobarbituric acid in the presence of malononitrile (Table 6, rows 4-6) (Fig. 5).

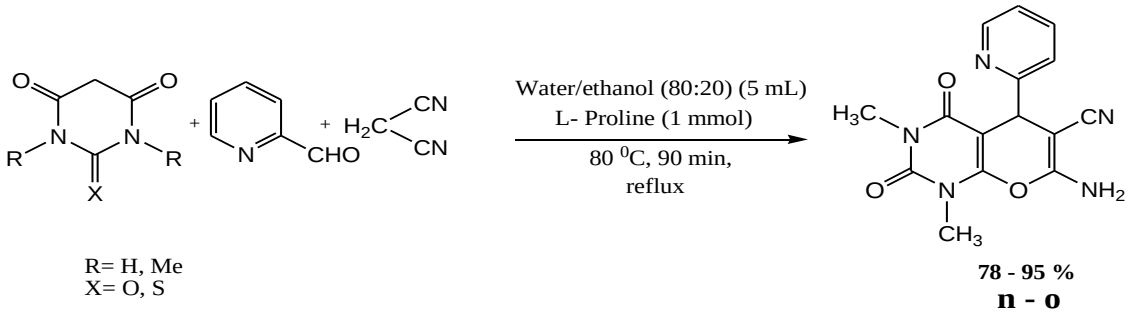
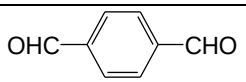
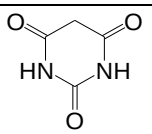
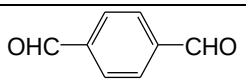
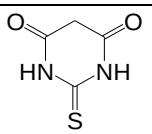
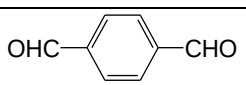
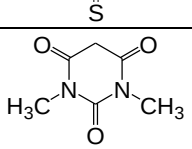
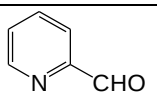
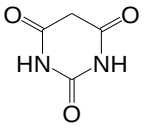
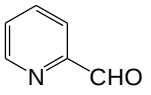
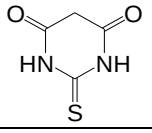
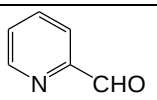
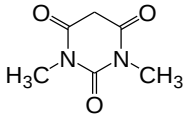


Fig. 5:

Table 6: Synthesis of Pyrano Pyrimidine derivatives through reaction of Terephthaldehyde and 2- Pyrimidine Carbaldehyde with derivatives of thiobarbituric acid in the presence of malononitrile.

Row	Nitrile	Aldehyde	Thiobarbituric acid	Product	Efficiency (%)	A taken melting point (0C)
1	$CH_2(CN)_2$			**k**	80	270
2	$CH_2(CN)_2$			**l**	73	210
3	$CH_2(CN)_2$			**m**	83	270

4	$CH_2(CN)_2$			**n**	85	325
5	$CH_2(CN)_2$			**o**	95	327
6	$CH_2(CN)_2$			**p**	78	320

The proposed mechanism for synthesis of Pyrano pyrimidine derivatives:

According to the proposed mechanism for this reaction, intermediate **a** is formed after addition of 1 mmol of L- proline to 1.2 mmol of aldehyde. Then intermediate **b** is formed by reaction between **a** and 1mmol of malononitrile. Then carboxylate anion attacks the acidic hydrogen between the two Nitrile groups and intermediate **c** is formed. In the next phase of reaction between 1 mmol of L- proline and 1 mmol of thiobarbituric acid in a dehydration process, intermediate **d** is formed. Then from the reaction between intermediate **d** and intermediate **c**, **e** compound is formed. During the process of ring creation, intermediate **e** converts to compound **f**. In the final step of the reaction, intermediates **f** reacts with water and L- proline is separated, producing the desired product of **g** which is Pyrano pyrimidinde (Figure 6).

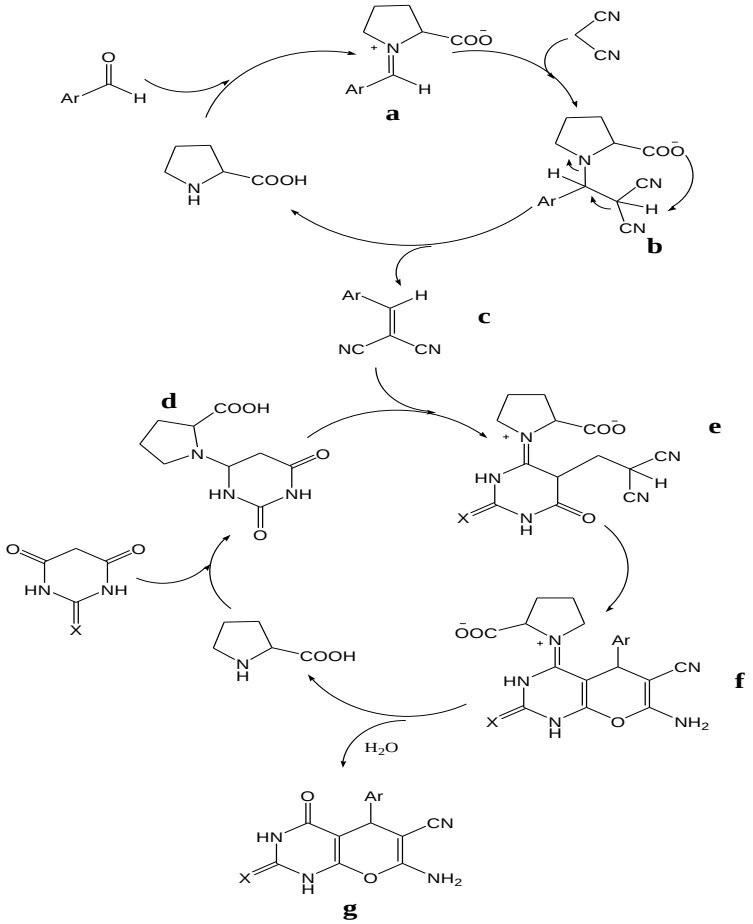


Fig. 6:

4.4- Spectral data for the samples of derivatives of synthesized Pyrano Pyrimidine:

Spectral data of derived **n** and its interpretation

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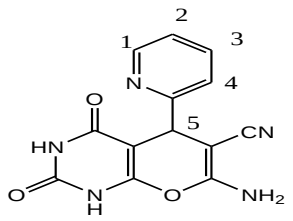
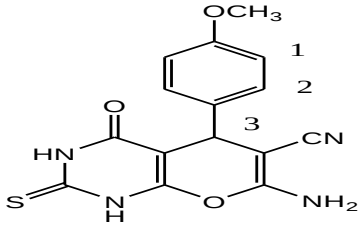


n

In IR spectrum of this compound, in the positions of 3420 cm^{-1} and 2205 cm^{-1} the peaks of the amine and Cyano groups were observed respectively. It also shows two peaks of the two carbonyl groups. In the compound's ^{1}HMR spectrum, a flaw peak is seen at the δ =4.03 which is related to CH (C-5) of Pyrano ring. In δ = 9.44 there is a splinted peak related to NH_2 group. Also, in δ =10.06 and δ =10.69, two splinted peaks are seen which are related to two groups of NH. Between δ = 8.92 and δ = 8.94 there is a binary peak from the CH (C-1) group of Pyridine ring that has a coupling constant equal to 8.8 Hz. Also between δ = 7.68 and δ = 7.72 there is a ternary peak from the CH (C- 3) group of Pyridine ring that has a coupling constant equal to 7.6 Hz. There is also a multiple Peak at δ =7/35 and δ =7/28 that is related to splitting of the pyridine ring (C-4 and 2). The coupled spectrum of C^{13}-NMR shows thirteen peaks which confirm the proposed structure. In this spectrum, in δ =24.9 and δ =118.3, there are peaks related to CH (C-5) and Cyano groups. Also five peaks of carbons from pyridine ring can be seen in the spectra. Resonance of the carbonyl group in coupled spectrum of C^{13}-NMR at δ =167.4 and δ =150.3 is also observed.

MS(EI,70 ev)M/Z%.282(29), 235(61), 143(67), 130(96), 119(33), 103(84), 91(98), 70(84), 44(100).

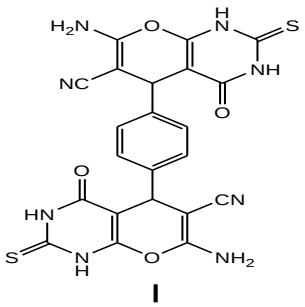
Spectral data of derived **i** and its interpretation



i

In ^{1}H-NMR spectrum of this compound, two flaw peaks are seen at δ =4.26 and δ =4.07 which are related to the methoxy and CH (C-3) of Pyran ring groups. At δ =7.71 a broad peak can be seen which is related to the NH_2 group, also at δ =8.30 and δ =9.03 two broad peaks can be seen that are related to the two NH groups. At δ =6.97 and δ = 6.99 a binary peak from the CH (C-1) group of the benzene ring can be seen that has coupling constant equal to 8Hz. In addition, between δ =7.18 and δ =7.20 another binary peak with a coupling constant equal to 8Hz can be seen that is related to the CH (CO 2) group of benzene ring. In the paired spectrum of ^{13}C-NMR, by showing thirteen messages, presented structure is confirmed. In this spectrum, the peaks in the positions δ =30.37 and δ = 53.68 are related to CH (C-3) and methoxy groups .The peak of Cyano group is visible at δ=119.5. Furthermore, in this composition, four peaks of the carbons of benzene ring can be seen, from which the peaks of the carbon 1 and 2 are longer. Resonant of carbonyl group in coupled ^{13}C-NMR spectrum is observed at δ =152.6 and δ=180.1.

Spectral data of derived **l** and its interpretation



l

In ^{1}H-NMR spectrum of this compound, at δ = 4.20 position a broad single peak can be seen which is related to CH group of the Pyran ring. At δ =7.42, a broad peak can be seen which is related to the NH_2 group, moreover at δ =9.02 and δ =10.98, two broad peaks are seen which are related to two groups of NH. Since the whole shape is symmetrical and interchangeable with a plane of symmetry, all hydrogen atoms of benzene ring are equivalent and at δ=7.13 a peak for the hydrogen atoms of the benzene ring can be seen. In the coupled ^{13}C-

NMR spectrum by showing ten messages, the proposed architecture is confirmed. In this spectrum, the peaks at δ = 121.5 and δ = 40.96, are related to the CH group of Pyran and Cyano rings. The peak of the Cyano Group is visible at δ =119.5. Also, in this compound, three peaks of the carbons of benzene ring can be seen from which the peaks of the equivalent carbon (non- substituted carbons of benzene ring) are longer. Resonant of carbonyl group in coupled ^{13}C-NMR spectrum is observed at δ =152.6 and δ=179.8.

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