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Synthesis of New Analogues of drug 'Monastrol' *via* Biginelli Reaction.

Nadhir NA Jafar*, Abbas Noor Mohammed, and Ammar K Madlool.

Department of Chemistry, College of Science, Babylon University, Hilla, Iraq.

ABSTRACT

Ethyl-4-(4-(4-chlorophenylcarbamoyl)-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrmidine-5-carboxylate **14,** which is an analogous compound of Monastrol, has been synthesized within three steps. The first step was done by synthesizing each of *N*-(4-chlorophenyl)-2-methoxy-4-methylbenzamide **10** and 2-methoxy-*N*-(4-methoxyphenyl)-4-methylbenzamide **11** by means of coupling reaction that is used *N,N´*-dicyclohexylcarbodiimide **2** (DCC) and 1-hydroxybenzotriazole **5** (HOBt) as coupling reagents. The methyl group of the compounds **10** and **12,** which have a *para* position, was oxidized to aldehyde by using selenium dioxide as an oxidizing agent to form *N*-(4-chlorophenyl)-4-formyl-2-methoxybenzamide **12** and 4-formyl-2-methoxy-*N*-(4-methoxyphenyl)benzamide **13**. The compound **14** was synthesized in a one-pot reaction comprised of aldehyde product **12**, ethyl acetoacetate, and urea which is called Biginelli reaction. The synthesized compounds were being identified by different ways included the melting point, TLC technique, IR spectra, ^{1}H-NMR spectrophotometer, and Elemental analysis.

Keywords: Monastrol, Biginelli reaction, Coupling reagent, isoacylurea

Corresponding author

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INTRODUCTION

Monastrol is a small cell-preamble molecule, which was discovered by Thomas U. Mayer in 1999, being used as an anticancer drug. It is arrested the cancer cells via mitosis by inhibition the mitotic motor Eg5 belonging to Kinesin-5 family, Kinesins are a group of the related molecular motor proteins which move along microtubule since it considers as meaning to transport chromosomes and vesicles throughout the hydrolysis of the chemical energy (ATP) [1,2], where Eg5 plays a significant role of information of bipolar spindle [3,4].

Monastrol, which contains Dihydropyrimide, was synthesized by a well-known reaction is called Biginelli reaction. PietroBiginelli is an Italian chemist who invented the Biginelli reaction in 1893. The cyclocondensation reaction of ethylacetoacetate and benzaldehyde, which are in equimolar ratios, as well as urea were put in a one pot to accomplish the Biginelli reaction, where ethanol and hydrochloride (HCl) were used as a solvent and an acid catalyst respectively at a reflux temperature [5,6]. This reaction mainly experienced considerable developments due to the interesting pharmacological properties associated with Dihydropyrimidines which do not only have the activity of anti-tumor but Dihydropyrimidines have a wide range of biological activities such as anti-inflammatory as 2-(4,6-bis(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-acetic acid **I** [7,8,9] anti-bacterial as isopropyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate **II** [10,11,12], antitubercular as ethyl 4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrmidines-5-carboxylate **III** [13,14], calcium channel blockers as methyl 6-ethyl-4-(2-nitrophenyl)-2-oxo1,2,3,4-tetrahydropyrimidine-5-carboxylate **IV** [15,16,17], antiproliferativeas 2-(5-(4-fluorophenyl)-3-*p*-tolyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-methyl-6-oxo-4-phenyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (**V**) [18], diabetes as ethyl 6-methyl-2-oxo-4-*p*-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **VI** [19], and anti-ulcer as ethyl 6-methyl-2-(methylthio)-4-(3-nitrophenyl)-1,4,5,6-tetrahydropyrimidine-5-carboxylate **VII** [20].

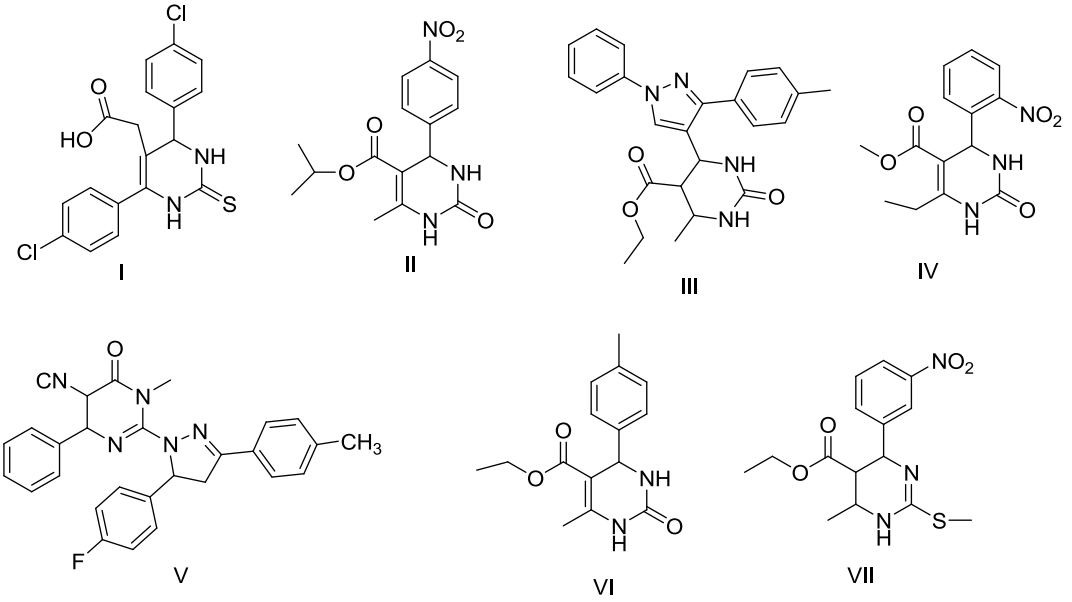

Figure 1: Dihydropyrimidines having biological activity

There are two drawbacks in the classical Biginelli reaction which are the long reaction time and the low yield. The immediate reason of both drawbacks was due to the acid catalyst. Given the increasing attention of this reaction, other methods were used to improve it as a microwave irradiation [21, 22, 23] and an ultrasonic irradiation [24, 25] as well as Lewis acid catalysts such as H_3BO_3 [26], Caf_2 [27], $Cu(OTf)_2$ [28], $InBr_3$ [29], $LiCl_3.7H_2O$ [30], and LiBr [31]. In our previous work, we also synthesized many pyrimidine derivatives and we recently prepared a new dihydropyrimidine by using the same Biginelli method [32-34].

In this paper, analogous of Monastrol contains an amide bond, where the amide bond is an entirely important bond in the field of organic chemistry because it exists in many areas of it, particularly in medicinal chemistry. According to the knowledge of medicinal chemistry, more than 25% of the known drugs contain an

amide bond [35]. There are many methods to comprise this bond, where coupling reagent by *N,N´*-dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) [36,37] is one of them.

MATERIAL AND METHODS

Melting point is uncorrected and was examined with a Stuart melting point (SMP 30, England). Infrared spectra (FT-IR) were screened by an IR Prestige-21 spectrophotometer as a KBr disk. NMR data carried out 500 MHz (^{1}HNMR) spectrometer (Avance III, Bruker, Iran) with a scale in ppm and TMS as an internal standard. All ^{1}H-NMR spectra were examined in dimethyl sulfoxide d_6. TLC-Silica plates GOF254 (0.2mm) out of the Merck Company were used to achieve the thin layer chromatography (TLC), while column chromatography has been done by Silica gel (0.040-0.063 mm). All materials were purchased from Sigma-Aldrich.

Experimental

Synthesis

General procedure of amide formation.

A mixture of 2-methoxy-4-methylbenzoic acid (500mg, 3.01mmole) in MeCN (30 ml), *N,N´*-dicyclohexylcarbodiimide (DCC) (621mg, 3.01 mmole), 1-hydroxybezotriazole (HOBt) (404mg, 3.01mmole), and substituted aniline (3.01mmole) were added successively. This mixture reaction was stirred with different temperatures, particularly at -5^{o}C for 1h, at 0^{o}C for 1h, at 5^{o}C for 1h, and at 23^{o}C for 33h. Dicyclohexylurea (DCU) was precipitated in a round bottom and then filtered. The filtrate was evaporated to dryness, and the residue was being dissolved in ethyl acetate and washed with a saturated NaCl solution, 5% $NaHCO_3$ solution, 1.0 M HCl respectively. Having done that, it was being followed by washing with a saturated NaCl solution and with water in turn. $MgSO_4$ was being used all the time to dry the residue, whereas after evaporation to dryness the residue was purified with decantation and recrystallized with MeCN.

Synthesisof N-(4-Chlorophenyl)-2-methoxy-4-methylbenzamide 10.[38]

From 4-chloro aniline **8** 380 mg**,** it yielded 320.mg (38.6%), M.P = (123-126 ^{o}C), phase = crystalline solid, color = colorless, R_f = 0.67 (ethyl acetate: hexane) (4:2). IR, *ύ* = cm^{-1} , N-H = 3346.61 , C-O = 1236.4 , C-Cl =1087.9, C=O = 1664, $CH_{aliphatic}$ = 2939.61 cm^{-1}, $CH_{aromatic}$ = 3039.91.^{1}H NMR (DMSO-d_6): δ 10.15 (s, 1H, NH), 7.88 (dd, 1H, *J* = 2.3Hz, 2.5Hz, $H5_{arom}$ + $H5'_{arom}$), 7.57 (d, 1H,*j* = 2.4Hz, $H4_{arom}$), 7.39 (dd, 2H, *J*=2.5Hz, 2.5Hz, $H3_{arom}$ + $H3'_{arom}$) , 7.01 (s, 1H, $H2_{arom}$), 6.89 (d, 1H, J = 7.6Hz, $H1_{arom}$), 3.89 (s, 3H, OMe), 2.36 (s, 3H, Me).Elemental analysis, Anal.Calcd for $C_{15}H_{14}NClO_2$ (275.73): C, 65.34; H, 5.12; N, 5.08. Found C, 65.24; H, 5.02; N, 5.06.

Synthesis of 2-methoxy- N-(4-methoxyphenyl) -4-methylbenzamide (11).

From 4-methoxy aniline **9** 370mg, it yielded 326mg (40%), M.P = (121-124^{o}C), phase = crystalline solid, color = colorless, R_f = 0.81 (ethyl acetate: hexane) (4:1). IR,*ύ* = cm^{-1}, N-H =3342.7, C-O 1234.48,C=O =1654.98, $CH_{aliphatic}$ = 2986.55, $CH_{aromatic}$ = 3072.^{1}H NMR (DMSO-d_6): δ 9.89 (s, 1H, NH), 7.64 (dd, 2H, *J* = 9Hz, for $H5_{arom}$ + $H5'_{arom}$), 7.60 (dd, 2H, *j* = 7.75Hz, for $H3_{arom}$ + $H3'_{arom}$), 7.00 (s, 1H, $H2_{arom}$), 6.91 (d, 1H, J = 9.0Hz, $H1_{arom}$), 6.88 (d, 1H, $H4_{arom}$), 3.85 (s, 3H, OMe_2), 3.73 (s, 3H, OMe_1), 2.36 (s, 3H, Me).Elemental analysis Anal.Calcd for $C_{16}H_{17}NO_3$ (271.31): C, 70.83; H, 6.16; N, 5.16.Found C, 70.64; H, 6.08; N, 5.12.

General procedure for oxidizing methyl group

A mixture consists of selenium dioxide (SeO_2) (332.7mg, 3mmole) with 4 drops of water and 20 ml of 1,4-dioxane had been heated at 50^{0}C while it stirred until dissolution. *N*-(4-substitutedphenyl)-2-methoxy-4-methylbenzamide (1mmole) was added to 20ml of 1,4-dioxane successively. Following this, the mixture was stirred by stirrer while it had been refluxing for 48 hours. Then, while the SeO_2 was precipitated the mixture had cooled to room temperature then filtered through a pad of celite-silica gel. After that, the filtrated substance was evaporated to give a residue, and subsequently the residue was purified on a silica gel column (20g).The eluents were ethyl acetate: hexane (3:1).

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Synthesis of N-(4-Chlorophenyl)-4-formayl-2-methoxybenzamide 12.

275.5 mg being taken from *N*-(4-Chlorophenyl)-2-methoxy-4-methylbenzamide **10** yielded 165 mg (57%), M.P = (114-116 ^{o}C), phase = crystalline solid, color = light yellow, R_f = 0.72 (ethyl acetate: hexane) (4:1). IR,*ύ* = cm^{-1}, N-H =3346.6, C-O 1238.48, C=O_{amide} =1662.68,C=$O_{aldehyde}$= 1734.06 $cm^{-1}$$CH_{aliphatic}$ = 2986.55 cm^{-1}, $CH_{aldehyde}$ = 2852.7 cm^{-1}, $CH_{aromatic}$ = 3032.20 Cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 10.62 (s, 1H, H_{aldey}), 10.13 (s, 1H, NH), 7.77 (dd, 2H, *J* = 8.6 Hz for$H5_{arom}$ + $H5'_{arom}$), 7.57 (dd, 2H, *j* = 7.7 Hz for $H3_{arom}$ + $H3'_{arom}$), 7.39 (d, 1H, *J* = 8.6 Hz, $H4_{arom}$) , 7.01 (s, 1H, $H2_{arom}$), 6.89 (d, 1H, *J* = 7.6Hz, $H1_{arom}$), 3.89 (s, 3H, OMe).Elemental analysis, Anal.Calcd for $C_{15}H_{12}NO_3$ (289.05): C, 62.19; H, 4.17; N, 4.83. Found C, 62.09; H, 4.14; N, 4.82.

Synthesis of 4-formyl-2-methoxy-N-(4-methoxyphenyl)benzamide 13.

271mg being taken from 2-methoxy- N-(4-methoxyphenyl) -4-methylbenzamide **11** produced 135mg (47%), M.P = (106-108 ^{o}C), phase = crystalline solid, color = light red, R_f = 0.83 (ethyl acetate: hexane) (5:1). IR,*ύ*= cm^{-1}, N-H =3342.6, C-O 1234.48, C=O amide =1654.98, C=$O_{aldehyde}$= 1722.43 CH = 2986.55 cm^{-1}, $CH_{aldehyde=}$ 2852.7. ^{1}H NMR (DMSO-d_6): δ 10.52 (s, 1H, H_{aldey}), 9.88 (s, 1H, NH), 7.65 (d, 2H, *J* = 8.9Hz, for $H5_{arom}$ + $H5'_{arom}$), 7.61 (d, 2H, *j* = 7.7 for $H3_{arom}$ + $H3'_{arom}$), 7.0 (s, 1H, $H2_{arom}$), 6.91 (d, 1H, *J* = 8.9 Hz, $H4_{arom}$), 6.88 (d, 1H,), *J* = 8.15 Hz, H1*arom*), 3.90, 3H, OMe_2), 3.73 (s, 3H, OMe_1). Elemental analysis, Anal.Calcd for $C_{16}H_{15}NO_4$ (285.10): C, 67.36; H, 5.30; N, 4.91. Found C, 67.35; H, 5.30; N, 4.89

Synthesis of ethyl-4-(4-(4-chlorophenylcarbamoyl)-3-methoxyphenyl)-6-methyl-2-oxo-tetrahydro pyrmidine-5-carboxylate (Biginelli product) **14**.

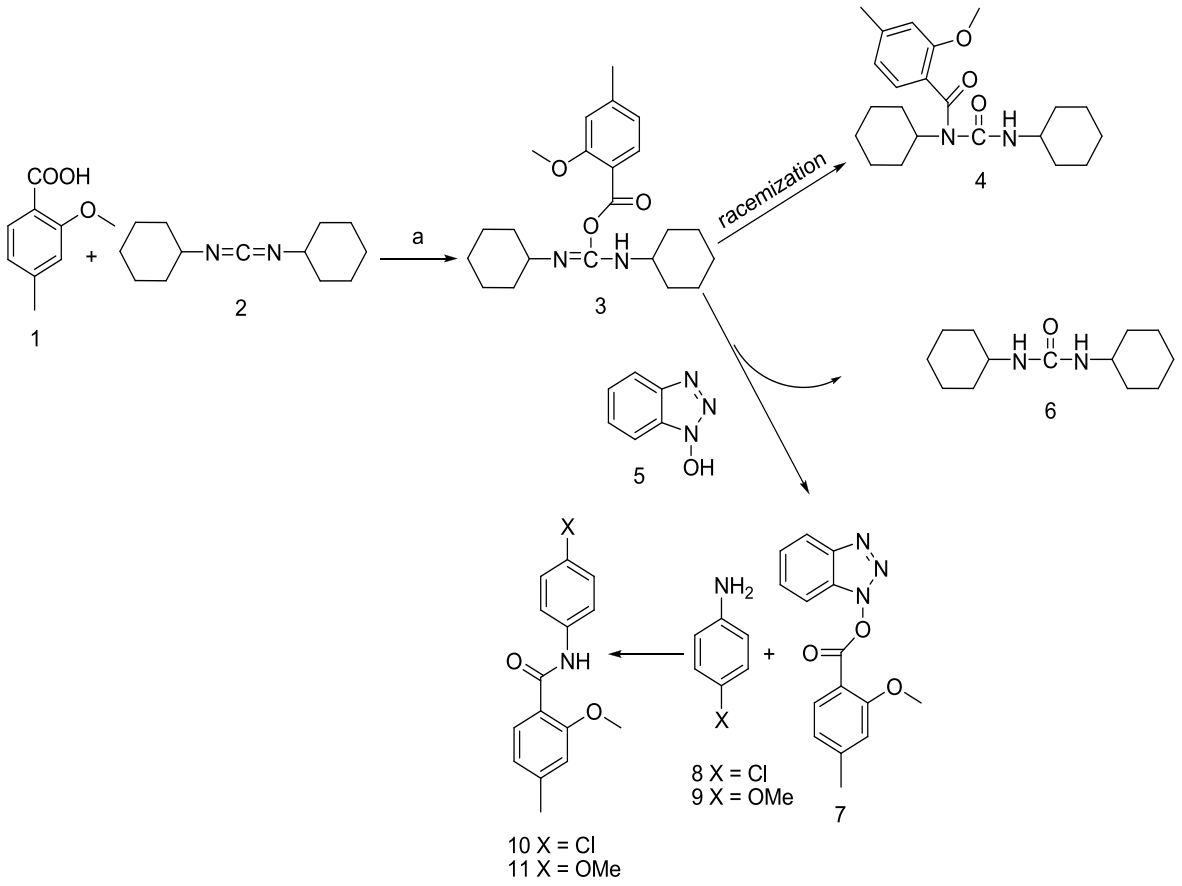
A mixture of *N*-(4-Chlorophenyl)-4-formayl-2-methoxybenzamide **12** (0.6mmol, 171 mg), ethyl acetoaacetate (0.6mmol, 78 mg), and urea (0.9 mmol, 54 mg) in absolute ethanol (20 ml) were refluxing for 18hr at 80^{o}C in presence of catalytic amount of conc. HCl. After completion the TLC examination, the mixture of reaction was poured into crushed ice and stirred. Following this step, it extracted with chloroform and washed with water. The organic phase was then dried over (Na_2SO_4) and concentrated under vacuum, whereas the obtainable residue had purified by column chromatography. Here, methanol in chloroform was used as an eluent solvent system (2:1) to produce a pure Monastrol-analogue compound. Yield 111mg (42%), M.P = (245-247 ^{o}C), color = white powder, R_f = 0.78 (methanol:Chloroform) (2:1), IR,*ύ*= cm^{-1}, O-H = 3421, $CH_{aromatic}$ = 3192 , $CH_{aliphatic}$ = 2956, C=O_{ester} = 1720 , C=O_{amide} = 1681.^{1}H NMR (DMSO-d_6): δ10.13 (s, 1H, NH), 7.78 (d, 2H, *J* = 13.4Hz, for $H5_{arom}$ + $H5'_{arom}$), 7.57 (d, 2H, *j* = 7.7 for $H3_{arom}$ + $H3'_{arom}$), 7.01 (s, 1H, $H2_{arom}$), 7.39 (d, 1H, *J* = 8.6 Hz, $H4_{arom}$), 6.89 (d, 1H,), *J* = 5.05 Hz, H1*arom*), 4.89 (s, 2H, NH), 4.36, (s, 3H, OMe $_{heterocyclic\ ring}$), 3.89 (s, 1H, $_{heterocyclic\ ring}$), 3.36 (q, 2H, *J* = 9.6 Hz, CH2), 1.26 (t, 3H, j = 5.5 Hz, 5.05 Hz, CH_{3ester}).Elemental analysis, Anal.Calcad for $C_{22}H_{22}N_3O_5$ (443.1): C, 59.53; H, 5.00; N, 9.47; Found C, 59,40; H, 4.98; N. 9.37.

RESULT AND DISCUSSION

There are three steps to synthesize the Biginelli product, where 2-methoxy-4-methylbenzoic **1** acid has been chosen as a starting material. The first step has involved the formation of an amide bond by coupling reaction which was composed as a result of *N,N´*-dicyclohexylcarbodiimide **2** (DCC) and 1-hydroxybenzotriazole **5** (HOBt). *N*-(4-chlorophenyl)-2-methoxy-4-methylbenzamide **10** and 2-methoxy-N-(4-methoxyphenyl)-4-methylbenzamide **11** were prepared from the reaction of carboxylic acid **1** with 4-chloroaniline **8** and 4-methoxyaniline **9** respectively (scheme 1). The low temperature was an essential factor for this reaction, where -5^{0}C at 1 hour, 0^{0}C at 1 hour, 5^{0}C at 1 hour, and 23^{0}C at 33 hours were applied. At the beginning, DCC added into the compound **1** to activate the carboxylic group by transferring proton into it. This transferring depends on the polarity of an used solvent being followed-up by the addition of carboxylate to form an intermediate is called *O*-acylisourea **3**. Because of the reactivity of *O*-acylisourea, it can possibly undergo a racemization giving *N*-acylisourea which is not potent and racemization, therefore, should largely be banned by adding HOBt **5** through 70s after appending DCC into the compound **1**. Here, as HOBt uses to reduce racemization, it leads to forming the OBt active ester **7** with dicyclohexylurea **6**, where DCU is an insoluble by-product in various solvents can easily be removed by filtration. OBt active ester **7** is apparently more stable than *O*-acylisourea and less susceptible to the racemization. Finally, OBt active ester reacts with the amino group of the compounds **8** and **9** leading to the compounds **10** and **11** which they are shown by the scheme 2. The compounds **10** and **11** were diagnosed by IR and ^{1}H-NMR. In IR spectra, it has been shown that the IR spectrum clearly peaks at region (v = cm^{-1}) 3346 and 1662 assigning to N-H and C=O bonds respectively of the

compound **10**, whereas the appearance of compound **11** patently peaks at regions 3338 and 1651 belonging to N-H and C=O bonds respectively. In ^{1}H-NMR spectra, for the compound **10**, it is observed that the emergent peak at the deshield region (10.15 ppm) belongs to N-H amide, 6.87-7.78 ppm refers to seven protons of the aromatic system, 3.896 ppm attributes to the three protons of methoxy group, and the peak of shield region (2.5 ppm) signalizes to the three protons of methyl group. As for compound **11**, the appearance peaks at region 9.894 ppm for N-H, but 6.8-7.63 ppm points to protons of the aromatic system, while 2.4 ppm has determined for three protons of the methyl group.

The second step involves the oxidation of methyl group by Selenium dioxide (SeO_2). SeO_2 is a good selective oxidant for a methyl group, where it converts a methyl group into aldehyde [39]. The first paper explained the use of SeO2 as an oxidizing agent being introduced in 1932 by Riley *et al*. [40]



Scheme 1: Formation of amide bond (a) CH_3CN, cooling -5, 0, 5, and 23^{o}C

(4-chlorophenyl)-4-formyl-2-methoxybenzamide **12** and 4-formyl-2-methoxy-*N*-(4-methoxyphenyl)bezamide **13** were prepared by reacting SeO_2 with the compound **10** and **11** respectively by using 1,4-dioxane as a solvent with refluxing for 48 hours which is explained in the scheme 2 . It has used an additional amount of SeO_2 in about three times than more of compounds **10** and (11) (3:1) mole to ensure the oxidation is done. After completing the reaction, selenium was precipitated on a round bottom as a by-product, removed by filtration with a pad of celite-silica gel, and purified by using column chromatography. In IR spectra, it has peaked at region (v = cm^{-1}) 1734 and 2854 belong to C=O aldehyde and C-H aldehyde bonds respectively of the compound **12**, whilst the peak of compound **13** has emerged at region 1722.43 and 2852.72 for C=O aldehyde and C-H aldehyde bonds in turn. In ^{1}H-NMR spectra, superficially, the appearance of proton aldehyde for compounds **12** and **13** have valued at 10.628 ppm and 10.52 ppm respectively.

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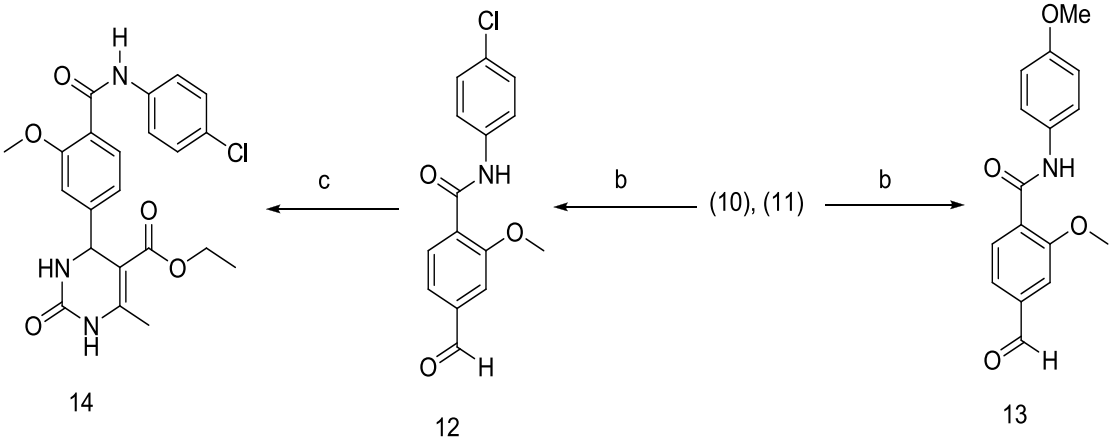

Scheme 2: Formation of Biginelli product. (b) 1,4 Dioxane, SeO_2, reflux 48 h. (c) ethanol, HCl, reflux 18h.

The final step has included the most important stage to attain our target. Simply, Ethyl4-(4-(4-chlorophenylcarbamoyl)-3-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrmidine-5-carboxylate **14** has been prepared by a classical method is called a Biginelli method which has involved a condensation of the compound **12**, ethylacetoacetate, and urea in one-pot under a strongly acidic condition. Additionally, the reaction was performed by heating the mixture of three components being dissolved in ethanol with an amount of HCl as well as reflux for 18h which is shown in the scheme 2. It has been appeared that there is a new peak at region (v = cm^{-1}) 1721 belong to C=O ester, and the same time, in 1H-NMR spectrum, N-H primidine ring has peaked at region 4.89 ppm with disappearing of aldehyde proton.

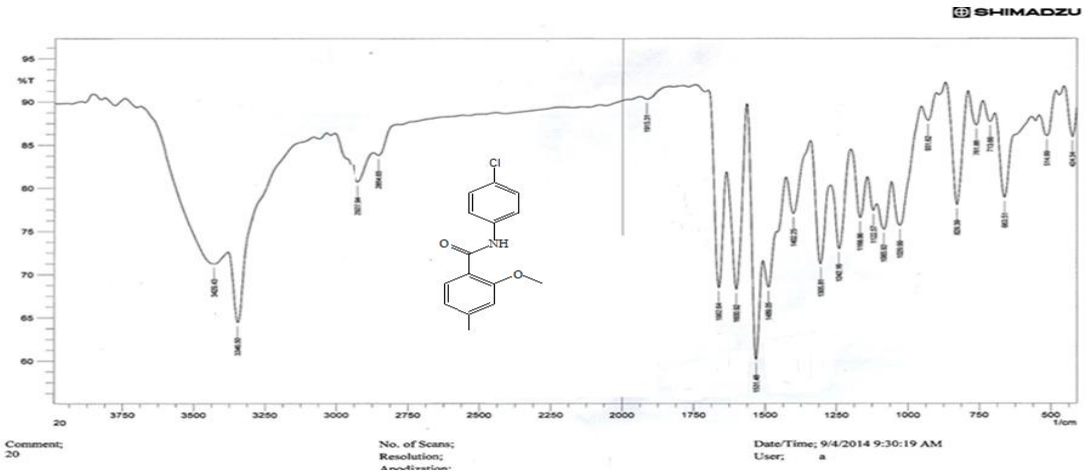

Figure 2: IR spectrum of compound (10).

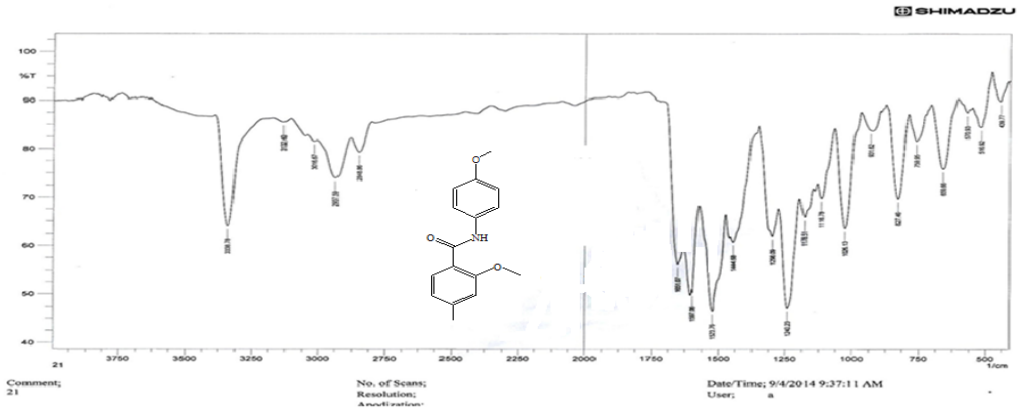

Figure 3: IR spectrum of compound (11).

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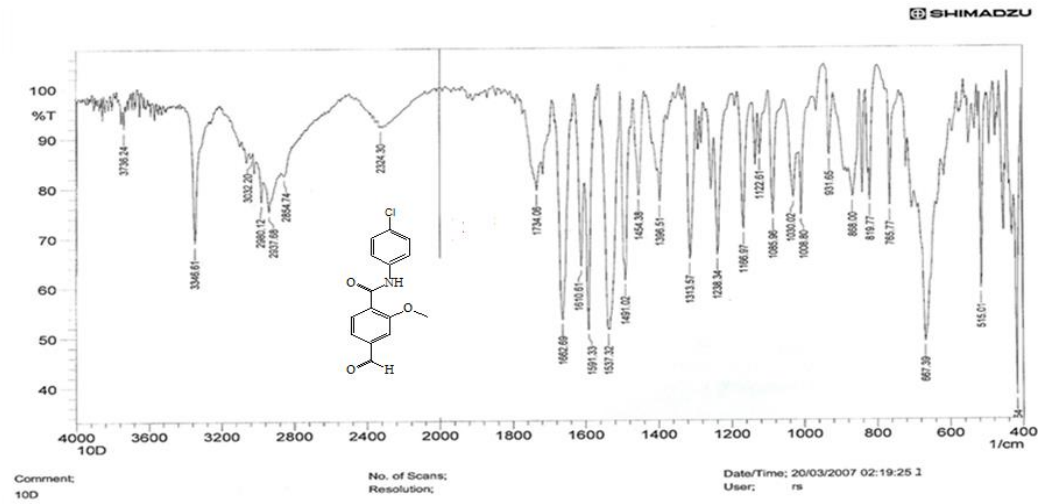

Figure 4: IR spectrum of compound (12).

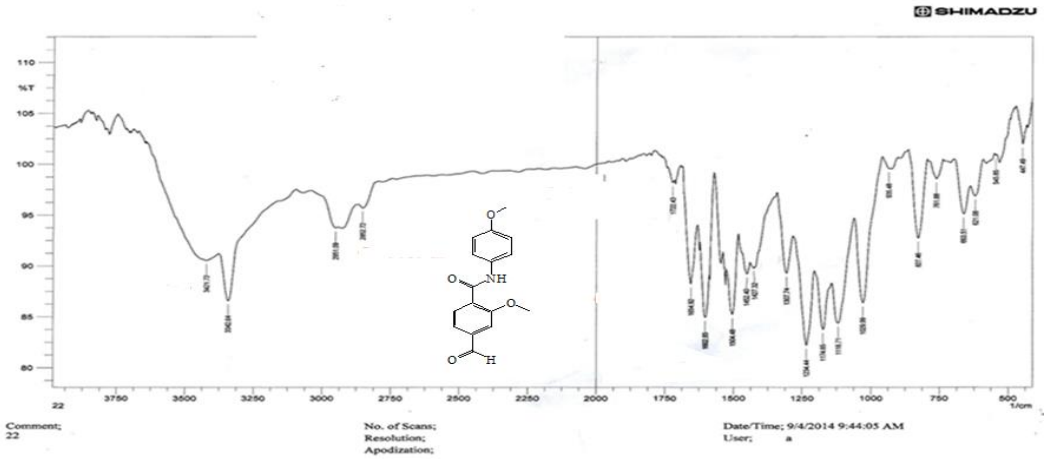

Figure 5: IR spectrum of compound (13)

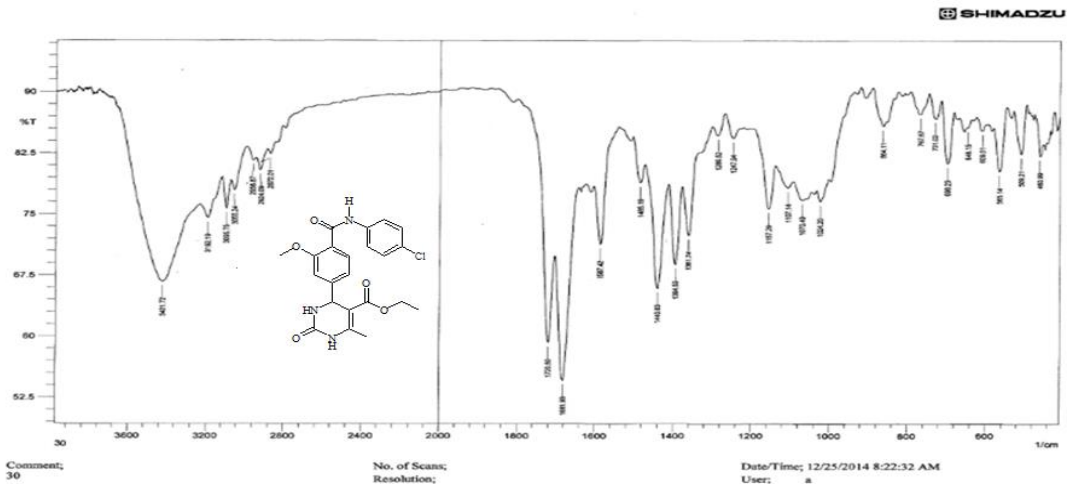

Figure 6: IR spectrum of compound (14)

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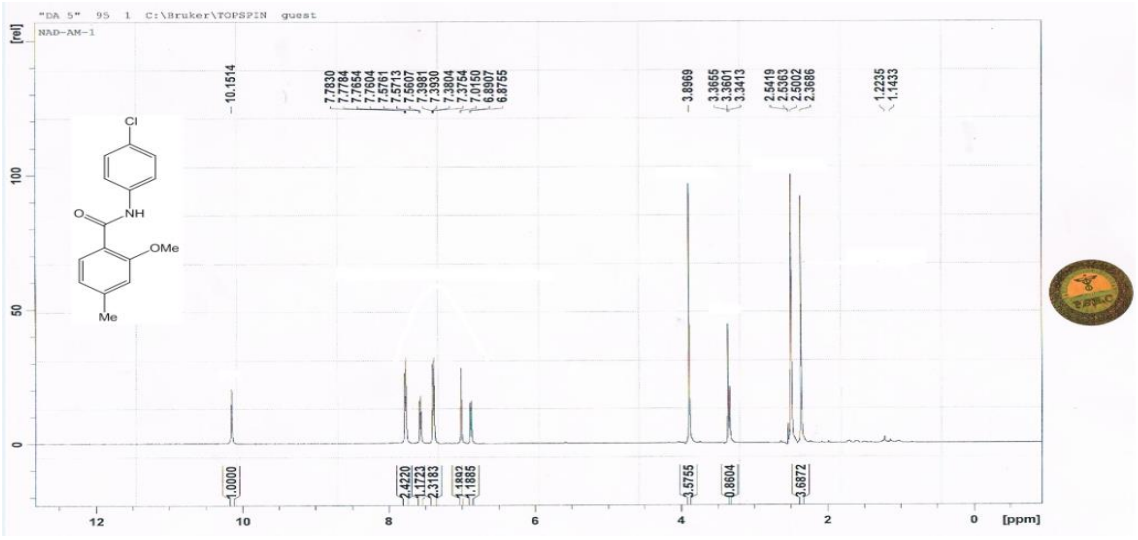

Figure 7: ^{1}H-NMR spectrum of compound (10)

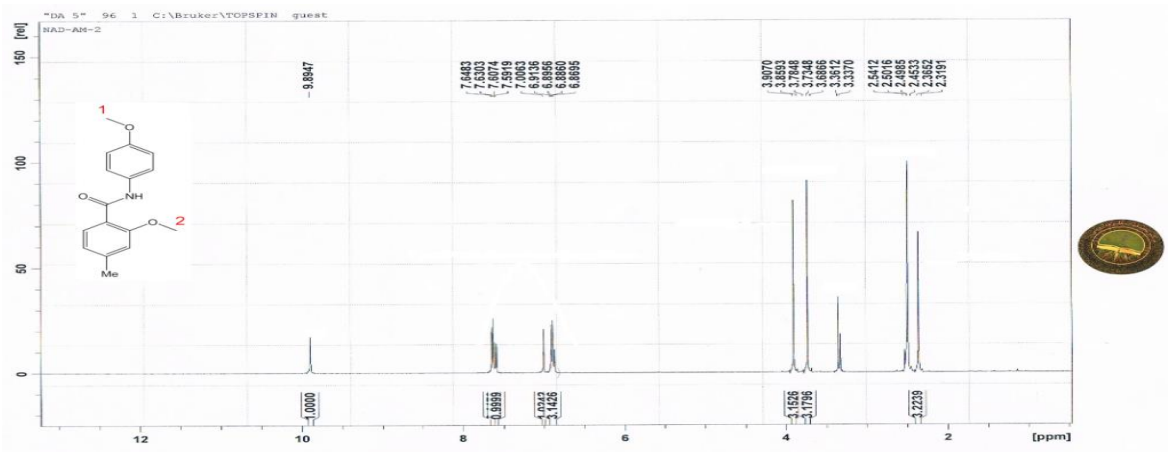

Figure 8: ^{1}H-NMR spectrum of compound (11).

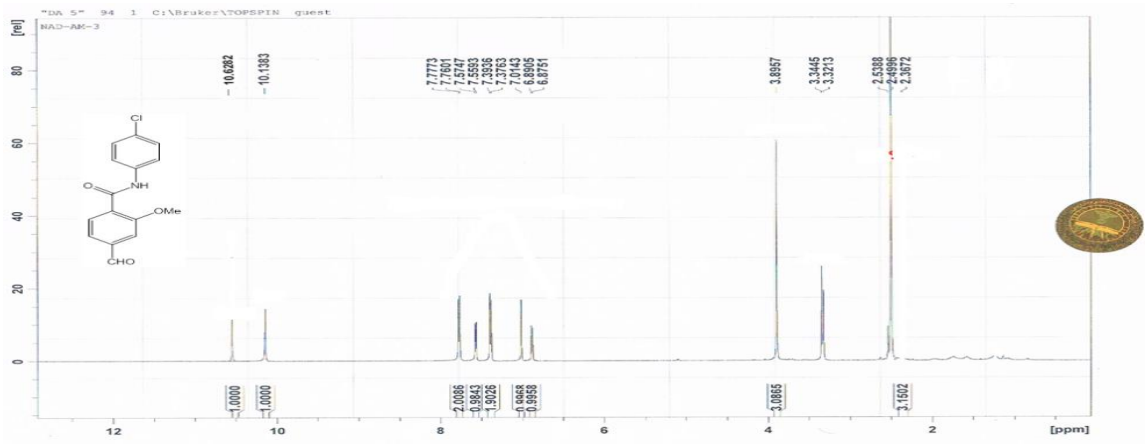

Figure 9: ^{1}H-NMR spectrum of compound (12).

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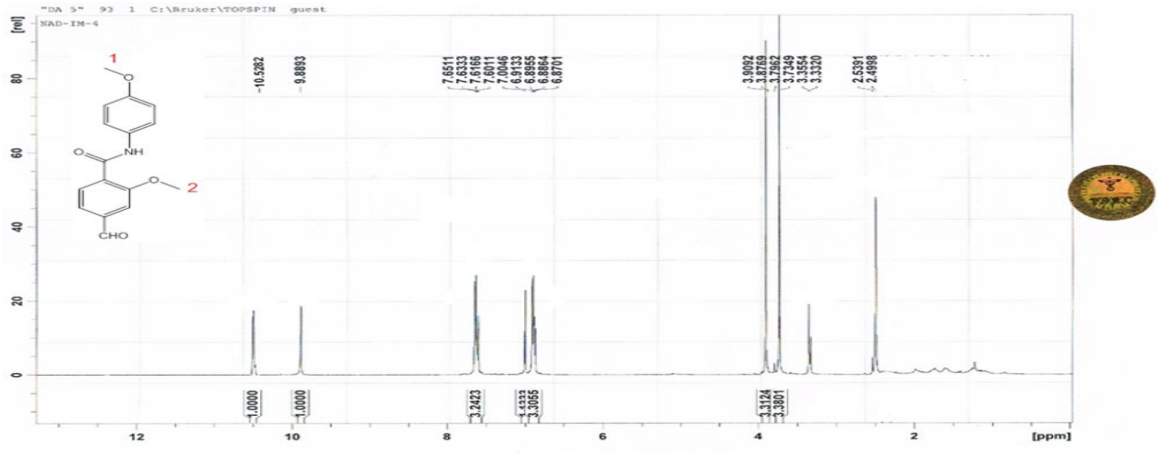

Figure 10: ^{1}H-NMR spectrum of compound (13).

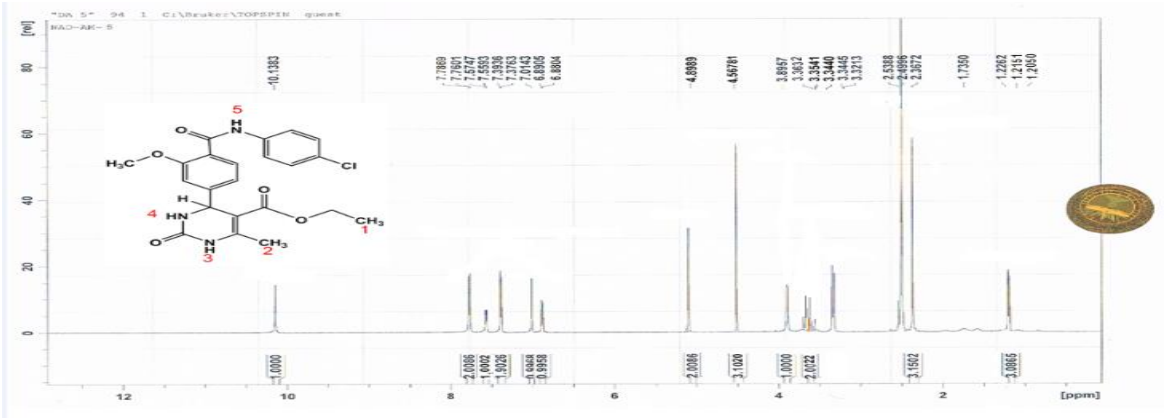

Figure 11: ^{1}H-NMR spectrum of compound (14).

CONCLUSIONS

The immediate purpose of this project was primarily to synthesize amide compounds by means the coupling method and convert a methyl group in *para* position to an aldehyde group that uses as a starting material in synthesis of compound **14**. Following this, the compound **14** was synthesized using the Biginelli reaction by mixing three components in one-pot. The yield of the compound **14** was good when using HCl as an acid catalyst. All synthesized compounds had been screened by IR, ^{1}H-NMR, and elemental analysis and all the results were entirely exacted.

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