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Synthesis of Some Substituted Pyrimidines Derived from 3-Acetyl Coumarin

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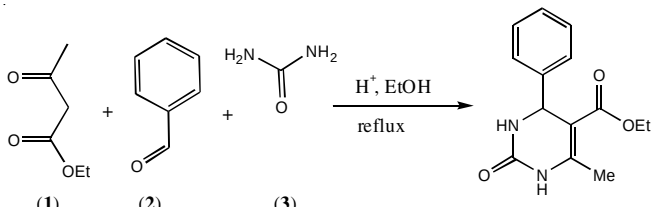
This study targets mainly the synthesis of a number of derivatives of coumarin containing ring pyrimidin-2-one substitutes different aromatic rings, taking advantage of the Biginelli reaction which includes the reaction of 3-acetyl coumarin with suitable aromatic aldehydes and urea in the presence of $AlCl_3$ and absolute ethanol as a solvent. It has been indicated that the biological activity is important and diverse to these kinds of compounds, which is the preparation of compound 3-acetyl coumarin (**7**) to be used as a compound base. The compounds having heterocyclic ring are expected to have various important biological and therapeutic applications. This proves structural formulae for each of new synthetic compounds on the basis of chemical reactions, analysis of the elements, the infrared spectra and nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR).

Keywords: Coumarin derivatives, Substituted pyrimidines, 4,3-Dihydro-(4-aryl-6-coumarin)pyrimidin-2-one.

INTRODUCTION

Coumarin derivatives received considerable attention by researchers as one of the compounds that possess medical and biological activities as well as industrial uses, where many of the products that contain coumarin units showed a number of pharmacological activities[1-4]. It is also found that compounds containing pyrimidine ring play an important role in many biological systems such as vitamins, enzymes assistance and many antibiotics as well as its presence in the nucleic acids[5], which attracted multiple biological activities of compounds pyrimidine much attention in the past few years, so the researchers worked in the preparation of these compounds because of its great diversity in the effectiveness of biological and pharmaceutical critria[6,7]. The pyrimidine derivatives are major intermediate of a large number of pharmaceutical manufactured which show a group of derivatives pyrimidine activity as antimicrobial[8], analgesic, antiviral, anti-inflammatory[9], also anti-HIV[10], antitubercular[11], antitumor[12], antimalarial[13] and diuretic[14], in addition to the pyrimidine compounds are also used as hypnotic drugs for the nervous system[15]. It can also prepare this type of compounds through many reactions as well as Biginelli reaction[16]. They includes this reaction blending ethyl acetoacetate (**1**) or its derivatives with benzaldehyde (**2**) or its derivatives, urea (**3**) and that the process occurs, the reaction is heating mixture of the three components dissolved in the solvent particularly with the availability of acidic conditions to produce through this method new derivatives pyrimidine known as 4,3-dihydro-pyrimidin-2-one (**4**) as shown in the following equation:

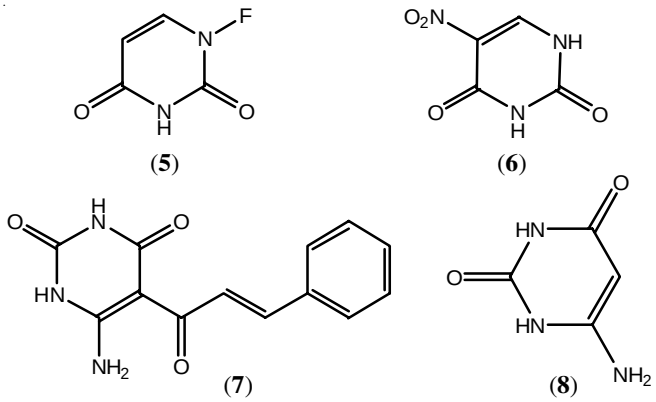


(**1**) (**2**) (**3**) (**4**)

Uracil is an important class of pyrimidine derivatives[17a], where exhibit various pharmacological and biological activity[17b], for example, fluorouracil (**5**) is used widely as an anticancer[18]. While the compound 5-nitrouracil (**6**) used to inhibition of the enzyme thymidine phosphorylase[19] and also its derivative showed antibacterial activity[20]. Also 5-cinnamoyl-6-aminouracil (**7**) derivatives are used as agents inhibition against the growth of cancer cells[21]. While 6-aminouracils (**8**) find wide application as starting materials for the preparation of many of the active compounds and biologically important as well as, its derivatives can be used as a coupling component in dye chemistry[22]. In addition to the above mentioned properties, it was prepared a series of coumarin derivatives containing on pyrimidine ring (**Scheme-I**) and so by taking advantage of Biginelli condensing[23].

EXPERIMENTAL

The chemicals used in the synthesis of all compounds were purchased from Aldrich, Merck and BDH Chemical



Companies and used without further purification. The melting points were measured on an Electrothermal Melting point/SMP (Gallenkamp) and are uncorrected.

The spectral measurements are infrared spectroscopy of type FT-IR spectrophotometer (Shimadzu). Nuclear magnetic resonance spectroscopy of the proton and carbon-type Biospin Auance III and 400 MHz (Germany) 600 MHz using (DMSO-d_6) as solvent and TMS as a reference. Thin layer chromatography (TLC) was performed on Alumina plates covered with silica gel layer and the spots were developed with iodine vapour. Elemental analyses (CHN) were carried out by using Vario Elemental Anlayzer 3000 (Shimadzu, Japan).

Synthesis of compound 3-acetyl coumarin[24] **(7):** Added (12.21 g/0.1 mol) of salicyldehyde to (13.0 g/0.1 mol) of ethyl acetoacetate, then put the mixture in a beaker capacity (100 mL) containing (20 mL) absolute ethanol and then added (5) drops from catalyst (piperidine). The mixture was stirred for 0.5 h at 5-10 °C. The yellow solid separated was filtered off subsequently washed with ethanol, dried and recrystallized from ethanol to give 3-acetyl coumarin as yellow crystals. Yield: 15.7 g (83 %), m.p. =116-118 °C (sawn 119-121 °C), R_f = 0.42.

Preparation of a series of compounds 3,4-dihydro(4-aryl-6-coumarin)pyrimidin-2-one[23] **(8-13):** A solution of 3-acetylcoumarin (5 mmol) in absolute ethanol (20 mL) containing $AlCl_3$ (10 mol %) was refluxed with the appropriate substituted benzaldehyde (5 mmol) and urea (5 mmol) for about 8-12 h. The progress of reaction was monitored by TLC. After the completion of reaction, the reaction mixture was allowed to reach ambient temperature and then the precipitate formed was filtered, washed with water, dried and recrystallized from ethanol to get pure powder.

Synthesis of 3,4-dihydro-4-(4-hydroxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyrimidin-2(1*H*)-one (8): The compound **8** was prepared according to general method where taking (0.56 g, 3 mmol) of compound **7** with (0.36 g, 3 mmol) of 4-hydroxybenzadehyde and (0.18 g, 3 mmol) of urea. After reflux the mix for 10 h, the compound **8** was obtained as brown precipitate, after recrystallization. Yield: 0.65 g (64 %), m.p. =193-195 °C, R_f = 0.66. Anal. calcd. (%) for $C_{19}H_{14}N_2O_4$ (334.33): C, 68.26; H, 4.22; N, 8.38. Found (%): C, 67.96; H, 4.12; N, 8.11.

Synthesis of 3,4-dihydro-4-(4-methoxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyrimidin-2(1*H*)-one (9): The compound **9** was prepared according to general method where taking (0.56 g, 3 mmol) of compound **7** with (0.4 g, 3 mmol) of 4-methoxybenzadehyde and (0.18 g, 3 mmol) of urea. After reflux the mix for 8.5 h. The compound **9** was obtained as reddish brown precipitate, after recrystallization. Yield: 0.62 g (59 %), m.p. = 117-119 °C, R_f = 0.64. Anal. calcd. (%) for $C_{20}H_{16}N_2O_4$ (348.35): C, 68.96; H, 4.63; N, 8.04. Found (%): C, 68.72; H, 4.48; N, 7.85.

Synthesis of 3,4-dihydro-4-(4-chlorophenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyrimidin-2(1*H*)-one (10): The compound **10** was prepared according to general method where taking (0.56 g, 3 mmol) of compound **7** with (0.42 g, 3 mmol) of 4-chlorobenzadehyde and (0.18 g, 3 mmol) of urea. After reflux in the mixture for 11 h, compound **10** was obtained as brown precipitate, after recrystallization. Yield: 0.74 g (69 %), m.p. = 241-243 °C, R_f = 0.56. Anal. calcd. (%) for $C_{19}H_{13}N_2O_3Cl$ (352.77): C, 64.69; H, 3.71; N, 7.94. Found (%): C, 64.41; H, 3.56; N, 7.73.

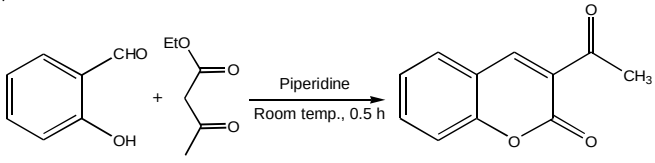
Synthesis of 3,4-dihydro-4-(2,4-dichlorophenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyrimidin-2(1*H*)-one (11): The compound **11** was prepared according to general method where taking (0.56 g, 3 mmol) of compound **7** with (0.52 g, 3 mmol) of 2,4-dichlorobenzadehyde and (0.18 g, 3 mmol) of urea. After reflux the reaction mixture for 9 h, the compound **11** was obtained as white precipitate, after recrystallization. Yield: 0.68 g (58 %), m.p. = 263-265 °C, R_f = 0.62. Anal. calcd. (%) for $C_{19}H_{12}N_2O_3Cl_2$ (387.22): C, 58.93; H, 3.12; N, 7.23. Found (%): C, 58.72; H, 2.94; N, 7.07.

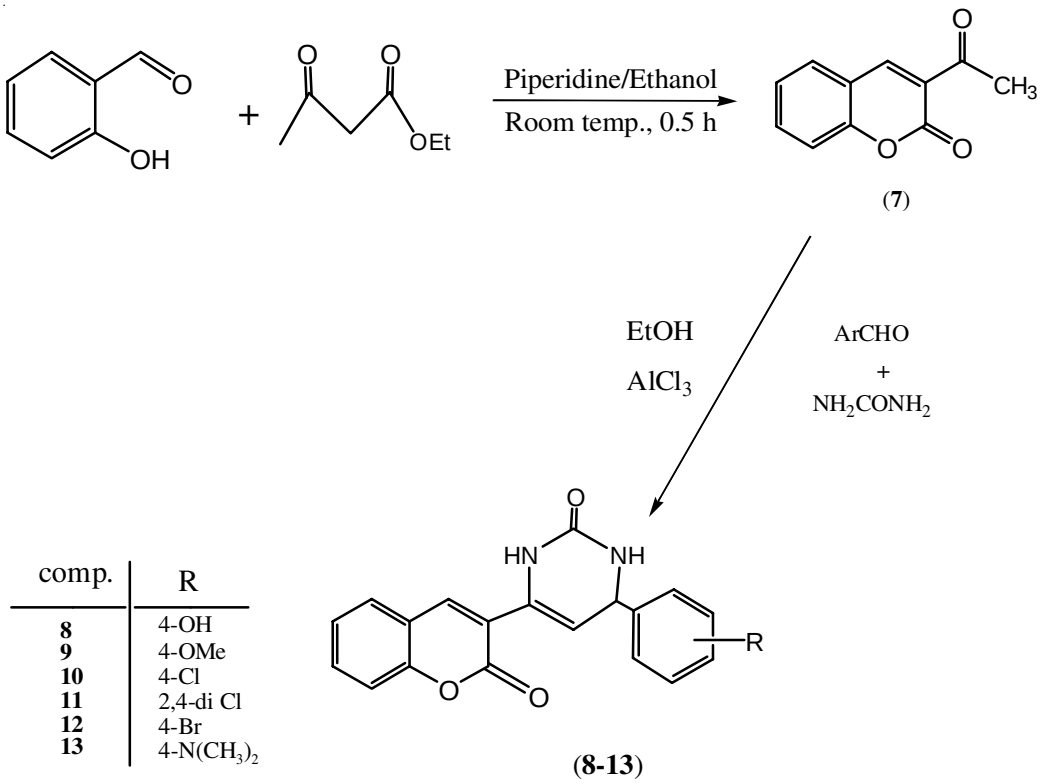
Synthesis of 3,4-dihydro-4-(4-bromophenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyrimidin-2(1*H*)-one (12): The compound **12** was prepared according to general method where taking (0.56 g, 3 mmol) of compound **7** with (0.55 g, 3 mmol) of 4-bromobenzadehyde and (0.18 g, 3 mmol) of urea. After reflux the mix for 12 h. Compound **12** was obtained as brown precipitate, after recrystallization. Yield: 0.72 g (60 %), m.p. = 237-239 °C, R_f = 0.45. Anal. calcd. (%) for $C_{19}H_{13}N_2O_3Br$ (397.22): C, 57.45; H, 3.30; N, 7.05. Found (%): C, 57.32; H, 3.14; N, 6.84.

Synthesis of3,4-dihydro-4-(4-bromophenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyrimidin-2(1*H*)-one (13): The compound **13** was prepared according to general method where taking (0.56 g, 3 mmol) of compound **7** with (0.44 g, 3 mmol) of 4-bromobenzadehyde and (0.18 g, 3 mmol) of urea. After reflux the mix for 9 h. Compound **13** was obtained as greenish yellow precipitate, after recrystallization. Yield: 0.67 g (62 %), m.p. = 209-211 °C, R_f = 0.54. Anal. calcd. (%) for $C_{21}H_{19}N_3O_4$ (361.39): C, 69.79; H, 5.30; N, 11.63. Found (%): C, 69.58; H, 5.16; N, 11.47.

RESULTS AND DISCUSSION

The synthetic strategies adopted in the synthesis of the intermediate and target compounds are depicted in the **Scheme-I**. The base compound 3-acetyl coumarin **7** was prepared from reaction of salicyldehyde with ethyl acetoacetate and a few drops of piperdine as catalyst and ethanol as solvent according to the following equation:

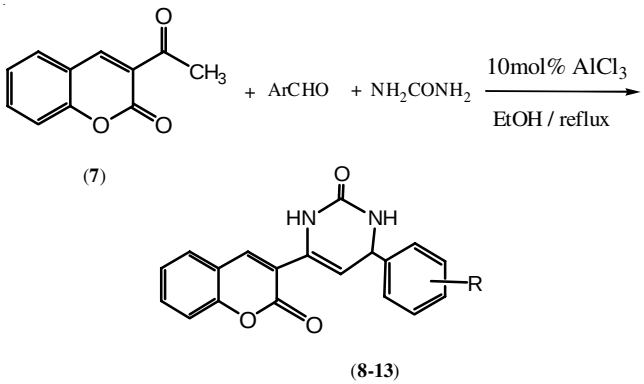




Scheme-I: Synthetic pathway for the compounds **7-13** and their structures

The structure compound **7** was determined on the basis of spectral data, as well as elemental analysis, according to the literature[25].

Coumarin derivatives (**8-13**) were synthesized through of condensation 3-acetyl coumarin (**7**) with number of substituted aromatic aldehydes and urea with a small amount of $AlCl_3$ as catalyst and ethanol absolute as solvent. According to the following equation:



R = **8**: 4-OH , **9**: 4-OMe , **10**; 4-Cl , **11**; 2,4-$(Cl)_2$, **12**; 4-Br , **13**; 4-$N(CH_3)_2$

The mechanism proposed for this reaction includes two steps[26]: The first aldol condensation between benzaldeyde and methyl group to form a stabilized carbenium ion. A second step is the nucleophilic addition of urea gives the intermediate, which quickly dehydrates to give the desired product (**Scheme-II**).

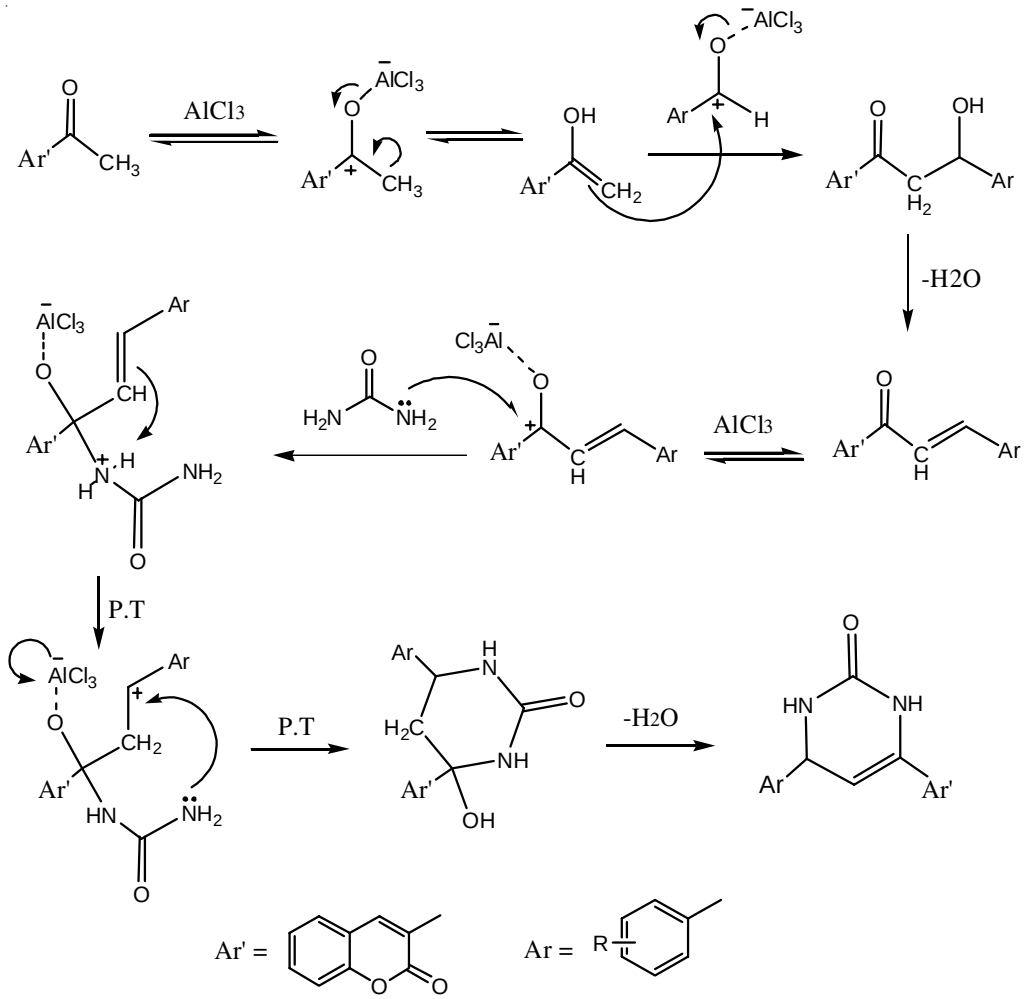
The melting point was uncorrected which determined by open capillary tube and was listed in the Table-1 as well as other physical properties. The synthesized compounds were characterized by their elemental analysis, IR, ^1H NMR, ^{13}C NMR. The IR spectra of the compounds **8-13** showed characteristic absorption bands at 3440-3172 cm^{-1} (OH; NH) stretching, 1751-1712 cm^{-1} due to (lactone C=O) and1697-1643 cm^{-1}

TABLE-1
PHYSICO-CHEMICAL DATA OF THE COMPOUNDS **8-13**

Comp. No.	R	m.p. (°C)	Yield (%)	Colour	R_f
8	OH-4	193-195	64	Brown powder	0.66
9	OMe-4	217-219	59	Reddish brown	0.70
10	4-Cl	241-243	69	Brown powder	0.56
11	2,4-Di(Cl)	263-265	58	White powder	0.62
12	4-Br	237-239	60	Brown powder	0.45
13	4-$N(CH_3)_2$	209-211	62	Powder yellow	0.52

TABLE-2
FT-IR SPECTRA DATA (cm^{-1}) OF THE COMPOUNDS **8-13**

Comp. No.	N-H	C-H aromatic	C=O lactone	C=O amide	C=C Olfe.	Other
8	3386	3070	1725	1697	1565	OH 3440
9	3326	3039	1720	1676	1573	O-CH_3 1056
10	3354	3018	1743	1687	1567	C-Cl 726
11	3332	3008	1751	1650	1589	C-Cl 640, 684
12	3178	3024	1720	1650	1596	C-Br 663
13	3201	3070	1712	1643	1593	–



[79]=R=4-OH , [80]=R=4-OMe , [81]=R=4-Cl , [82]=R=2,4-$(Cl)_2$, [83]=R=4-Br , [84]=R=4-$N(CH_3)_2$

Scheme-II

attributed to the (amide C=O) stretching vibration. The absorption bands at 1596-1565 cm^{-1} region could be attributed to the (C=C) stretching and other absorption bands were listed in Table-2. The ^1H NMR spectra of the compounds **8-13** showed singlet in the range 11.18-9.81 ppm, which is characteristic for N-H and singlet in the range 9.01-8.22 ppm due to H-4 for coumarin, as well as aromatic protons which is showed at range 7.98-7.00 ppm and other singles were listed in Table-3. The ^{13}C NMR spectra of the compounds **8-13** showed singlet in the range 167.75-162.05 ppm which is characteristic of (lactone C=O) and singlet in the range 160.02-156.71 ppm attributed to (amid C=O), as well as aromatic atoms carbon which is showed at range 139.6-116.06 ppm and other singles were listed in Table-4. Elemental analysis (C-H-N) was listed in Table-5.

TABLE-3
^1H NMR SPECTRA DATA (ppm) OF COMPOUNDS **8-13**

Comp. No.	H-4 coumarin	H-5' pyrimidine	Ar-H	N-H (2H)d	H-4' pyrimidine	Other
8	8.79	8.07	7.98-7.16	6.86	6.74	OH 5.27
9	8.67	7.97	7.80-7.01	6.90	6.11	O-CH_3 3.87
10	8.72	8.52	7.38-7.23	6.81	5.83	–
11	8.79	8.75	7.65.7.17	6.96	5.93	–
12	8.22	8.19	8.08-7.67	6.44	5.58	–
13	9.01	8.27	7.71-7.00	96.6	5.93	N-$(CH_3)_2$ 3.22

TABLE-4
^{13}C NMR SPECTRA DATA (ppm) OF COMPOUNDS **8-13**

Comp. No.	C=O lactone	C=O amide	C4"-arom. phenyl	C8a coum.	C1"-arom. phenyl	C-arom.	C5'-pyri.	C4'-pyri.	Other
8	167.75	158.12	158.93	157.67	154.92	134.6-116.6	116.33	64.95	–
9	165.45	157.56	157.52	160.80	139.26	133.3-118.2	112.58	61.15	OMe 60.42
10	162.43	160.02	137.63	154.34	149.18	134.5-116.6	112.86	81.22	–
11	164.58	156.71	150.12	150.90	150.82	139.6-119.7	116.29	85.44	–
12	162.24	157.85	142.70	156.62	145.97	132.9-118.8	115.20	56.70	–
13	162.05	156.88	150.62	153.25	146.02	137.6-128.3	108.40	62.05	N-$(CH_3)_2$ 40.05

TABLE-5
ELEMENTAL ANALYSIS OF COMPOUNDS **8-13**

Comp. No.	Elemental analysis (%): Calcd. (Found)		
	C	H	N
8	68.26 (67.96)	4.22 (4.12)	8.38 (8.11)
9	68.96 (68.72)	4.63 (4.48)	8.04 (7.85)
10	64.69 (64.41)	3.71 (3.56)	7.94 (7.73)
11	58.93 (58.72)	3.12 (2.94)	7.23 (7.07)
12	57.45 (57.32)	3.30 (3.14)	7.05 (6.84)
13	69.79 (69.58)	5.30 (5.16)	11.63 (11.47)

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