

이중고리 합성에 블록제로서 이용된 피란과 피리딘

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(2009. 3. 13 접수)

Pyran and Pyridine as Building Blocks in Heterocyclic Synthesis

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(Received March 13, 2009)

요약. 현재 수행하는 작업은 피페리딘 또는 암모늄 아세테이트 존재하에서 malononitrile와 β -aroylacrylic acid 유도체의 DMF 용매조건에서 상호작용에 대한 연구이며, 형성된 화합물을 이용한 퓨즈되고 단리된 이중고리화 시스템의 합성에 관한 것이다. β -aroylacrylic acid (3)이 DMF 용매와 피페리딘 촉매조건에 malononitrile와 반응하여 4H-피란유도체(4)를 형성한다. 촉매를 암모늄 아세테이트로 바꿈으로써 피리딘 유도체를 얻었다. 또한 N-말레암산 유도체 (19)와 (27)은 말레 무수물과 함께 (4)와 (5)의 반응을 경유하여 합성되었다. 마이클 첨가 반응에서 이용되는 메틸렌화합물에 관한 이 연구는 β -aroylacrylic acid의 경우와 유사하게 형성된 말레암산 유도체의 반응성에 대한 것이다.

주제어: β -Aroylacrylic acid, 마이클 반응, 2-아미노피란, 2-아미노피리딘, 피리미딘, 말레암산

ABSTRACT. The present work is devoted to study the interaction of β -aroylacrylic acid derivative (3) with malononitrile in (DMF) in the presence of piperidine and/or ammonium acetate, then using the formed compounds as starting materials for synthesizing fused and isolated heterocyclic systems. It has been established that the β -aroylacrylic acid (3) reacts with malononitrile in (DMF) in the presence of piperidine as a catalyst with the formation of 4H-pyran derivative (4). By changing the catalyst into ammonium acetate, pyridine derivative (5) has been obtained. Also the N-maleamic acid derivatives (19) and (27) have been synthesized via the interaction of (4) and (5) with maleic anhydride. The purpose of this step is to study the behavior of the formed maleamic acid derivatives – as analogies of β -aroylacrylic acids – towards different active methylene compounds under Michael addition reaction.

Keywords: β -Aroylacrylic acid, Michael reaction, 2-aminopyran, 2-aminopyridine, Pyrimidine, Maleamic-acid.

INTRODUCTION

Compounds Containing the triazolo[1,5-c]pyrimidine moiety have attracted considerable attention due to their remarkable adenosine and benzodiazepine receptor affinity. Particularly, the 5-

amino- 9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-c]quinazoline (1) (Figure 1) was found to be a highly potent adenosine antagonist,¹ while the 9-chloro-2-(2-fluorophenyl)-1,2,4-triazolo[1,5-c]quinazolin-5(6H)-one (2) displayed a very significant benzodiazepine binding activity.²

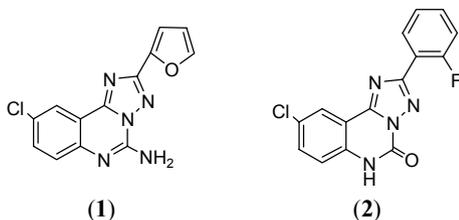


Fig. 1.

Also pyran and fused 4*H*-pyran derivatives have attracted a great deal of interest owing to their antimicrobial activity,^{3,4,5} inhibition of influenza, virus sialidases,⁶ mutagenic activity as antiviral,⁷ antiproliferation agents,⁸ sex pheromones activity,^{9,10} antitumor¹¹ and anti-inflammatory agent.¹² Moreover, pyran derivatives are well known for their antihistaminic activity.¹³

Also, pyrimidines and fused pyrimidines play an inertial role in several biological processes and have a considerable chemical and pharmacological importance. In particular pyrimidine nucleus can be found in a broad variety of antibacterial and antitumor agents as well as in agrochemical and veterinary products.¹⁴⁻¹⁷ This current pharmacological importance has stimulated our interest to synthesize several new and biologically active derivatives of these heterocyclic systems.

EXPERIMENTAL SECTION

All melting points are uncorrected and determined by the open capillary method using Gallen Kamp melting point apparatus. Microanalyses were carried out by the Micro Analytical Center at Cairo University. The IR spectra were recorded on FT/IR-300E Jasco spectrophotometer as (KBr) discs. The ¹H NMR spectra were measured on a Varian Gemini 200 MHz instrument with chemical shifts (δ) expressed in ppm downfield from TMS. Mass spectra were recorded on Shomadzu GC-MS (QP-1000EX) instrument operating at 70eV. (Tables 1&2).

(E)-2-amino-6-(4-chloro-3-methylphenyl)-3-cyano-4*H*-pyran-4-carboxylic acid (4) and (E)-2-amino-6-(4-chloro-3-methylphenyl)-3-cyanopyri-

dine-4-carboxylic acid (5).

To a solution of 4-(4-chloro-3-methylphenyl)-4-oxobut-2-enoic acid (**3**) (1.00 g, 4.47 mmol) and malononitrile (0.3 g, 4.47 mmol) in refluxing DMF (20 mL) few drops of piperidine or ammonium acetate (0.34 g, 4.47 mmol) were added; the resulting mixture was refluxed for (2h). The reaction mixture was allowed to cool at room temperature then poured into water (100 mL). The precipitate formed was filtered off and washed on the filter funnel with water, then dried and crystallized from the proper solvent to give 4*H*-Pyran derivative (**4**) and/or Pyridine derivative (**5**) respectively.

6-(4-chloro-3-methylphenyl)-3-cyano-2-(ethoxymethyleneamino)-4*H*-pyran-4-carboxylic acid (6).

4*H*-Pyran derivative (**4**) (1.00 g, 3.4 mmol) in triethylorthoformate^{18,19,20} (10 mL) was stirred under reflux for (5h). The reaction mixture was concentrated and the obtained brown precipitate then crystallized from ethanol/water to afford ethoxymethyleneamino-4*H*-pyran (**6**).

5-(4-chloro-3-methylphenyl)-1,2,3a-trihydro-6-oxa-1,2,7,9-tetrazaphenalen-3(3*H*)-one (7) and 7-(4-chloro-3-methylphenyl)-4-imino-3-(phenylamino)-4-hydro-5*H*-pyrano[2,3-*d*] pyrimidine-5-carboxylic acid (8).

A mixture of ethoxymethyleneamino-4*H*-pyran (**6**) (3.00 g, 8.70 mmol) and hydrazine hydrate²¹ (0.30 mL, 8.70 mmol) or phenylhydrazine (0.85 mL, 8.70 mmol) in absolute ethanol (30 mL) was refluxed for (7h). The reaction mixture was left to cool at room temperature then acidified with diluted HCl, the formed solid was filtered off, washed with cold water, dried and crystallized from the proper solvent to afford pyranopyrimidines (**7**) and/or (**8**).

7-(4-chloro-3-methylphenyl)-3-ethyl-4-imino-4-hydro-5*H*-pyrano[2,3-*d*] pyrimidine-5-carboxylic acid (9) and 7-(4-chloro-3-methylphenyl)-4-imino-3-phenyl-4hydro-5*H*-pyrano [2,3-*d*] pyrimidine-5-carboxylic acid (10).

A mixture of ethoxymethyleneamino-4*H*-pyran (**6**) (3.00 g, 8.70 mmol) and ethylamine (0.57 mL, 8.70 mmol) and/or aniline (0.75 mL, 8.70 mmol) in absolute ethanol (30 mL) was refluxed for (5h).

Table 1. Characterization and physical data of synthesized compounds

Comp. No.	M.P. °C Yield g (%)	Solvent	Formula mol. wt.	Analysis %Calc./Found		
				C	H	N
4	158	Ethanol/Water	C ₁₄ H ₁₁ ClN ₂ O ₃	57.84	3.81	9.64
	1.15g (89)		290	57.42	3.59	9.31
5	166	Ethanol/Water	C ₁₄ H ₁₀ ClN ₃ O ₂	58.45	3.50	14.61
	1.07g (84)		287	58.20	3.31	14.40
6	172	Ethanol/Water	C ₁₇ H ₁₅ ClN ₂ O ₄	58.88	4.36	8.08
	0.88g (75)		346	58.61	4.15	7.90
7	208	Ethanol/Water	C ₁₅ H ₁₁ ClN ₄ O ₂	57.24	3.52	17.80
	2.16g (79)		314	56.92	3.37	17.62
8	132	Ethanol/Water	C ₂₁ H ₁₇ ClN ₄ O ₃	61.69	4.19	13.70
	2.95g (83)		408	61.26	4.06	13.41
9	108	Ethanol/Water	C ₁₇ H ₁₆ ClN ₃ O ₃	59.05	4.66	12.15
	2.64g (88)		345	58.78	4.49	12.02
10	96	Ethanol/Water	C ₂₁ H ₁₆ ClN ₃ O ₃	64.05	4.09	10.67
	2.87g (84)		393	63.59	3.86	10.42
11	130	Ethanol	C ₁₅ H ₁₂ ClN ₃ O ₃	56.70	3.81	13.23
	2.40g (87)		317	56.42	3.65	12.92
12	112	Methanol/Water	C ₁₅ H ₁₁ ClN ₂ O ₃ S	53.82	3.31	8.37
	2.21g (76)		334	53.51	3.05	8.15
13	168	Ethanol/Water	C ₁₈ H ₁₂ ClN ₅ O ₃	56.63	3.17	18.34
	0.89g (73)		381	56.37	2.99	18.18
14	148	Ethanol/Water	C ₁₇ H ₁₂ Cl ₂ N ₄ O ₃	52.19	3.09	14.32
	1.1g (85)		391	51.70	2.96	14.09
15	156	Methanol/Water	C ₁₉ H ₁₅ ClN ₄ O ₄	57.22	3.79	14.05
	1.13g (89)		398	56.98	3.56	13.84
16	198	Methanol/Water	C ₁₈ H ₁₁ ClN ₄ O ₄	56.48	2.90	14.64
	0.90g (74)		382	56.13	2.72	14.36
17	162	Ethanol	C ₁₆ H ₁₁ ClN ₄ O ₃	56.07	3.23	16.35
	0.89g (81)		342	55.79	3.01	16.02
18	188	Ethanol/Water	C ₁₇ H ₁₃ ClN ₄ O ₃	57.23	3.67	15.70
	0.95g (83)		356	56.99	3.52	15.49
19	221	Methanol	C ₁₈ H ₁₃ ClN ₂ O ₆	55.61	3.37	7.21
	1.1g (83)		388	55.25	3.21	7.08
20	178	Ethanol/Water	C ₂₁ H ₁₅ ClN ₄ O ₆	55.46	3.32	12.32
	1.61g (69)		454	55.21	3.15	12.14
21	145	Methanol/Water	C ₂₃ H ₂₁ ClN ₂ O ₈	56.51	4.33	5.73
	2.16g (86)		488	56.09	4.20	5.58
22	160	Methanol/Water	C ₂₂ H ₁₇ ClN ₂ O ₈	55.88	3.62	5.92
	1.97g (81)		472	55.53	3.44	5.67
23	167	Ethanol/Water	C ₂₁ H ₁₆ ClN ₅ O ₅	55.58	3.55	15.43
	1.84g (79)		453	55.28	3.32	15.22
24	185	Ethanol/Water	C ₂₃ H ₁₉ ClN ₄ O ₄	61.27	4.25	12.43
	1.69g (73)		450	60.84	4.06	12.14

Table 2. IR, ¹HNM and Mass spectral data of synthesized compounds

Comp. No.	IR (KBr) cm ⁻¹	¹ H NMR (200 MHz, DMSO- <i>d</i> ₆), δ	Mass m/z
4	1712 (C=O, carboxyl), 2196 (C≡N) and 3280 (NH).	2.32 (3H, s, CH ₃), 3.93 (1H, d, <i>J</i> = 6.4, H-4 pyran), 5.19 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.52-7.60 (3H, m, aromatic protons), 8.37 (2H, brs, exchangeable NH ₂) and 11.74 (1H, brs, exchangeable OH)	288 (M ⁺ -H ₂), 152, 137, 125, 79.
5	1629 (C=N), 1718 (C=O, carboxyl), 2200 (C≡N) and 3285 (NH).	2.35 (3H, s, CH ₃), 6.91 (1H, s, H-5 pyridine), 7.63-7.71 (3H, m, aromatic protons), 7.97 (2H, brs, exchangeable NH ₂) and 11.54 (1H, brs, exchangeable OH).	287 (M ⁺), 153, 121, 105, 77.
6	1682(C=N), 1726 (C=O, carboxyl), 2210 (C≡N) and 3390 (OH).	1.33 (3H, t, <i>J</i> = 7.62Hz, OCH ₂ CH ₃), 2.38 (3H, s, CH ₃), 3.9 (1H, d, <i>J</i> = 6.4, H-4 pyran), 4.27 (2H, q, <i>J</i> = 7.62Hz, OCH ₂), 5.16 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.59-7.66 (3H, m, aromatic protons), 8.32 (1H, s, N=CH-O) and 11.59 (1H, brs, exchangeable OH).	
7	1610(C=N), 1651(C=O amide) and 3324 (broad band, N-H).	2.27 (3H, s, CH ₃), 3.91 (1H, d, <i>J</i> = 6.4, H-5 pyran), 4.56 (1H, s, exchangeable CONH-NH), 5.18 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.59-7.66 (3H, m, aromatic protons), 9.27 (1H, s, exchangeable CONH), 9.41 (1H, s, CH pyrimidine).	314 (M ⁺), 264, 152.
8	1600 (C=N), 1722 (C=O, carboxyl) and 3386 (basin peak, OH and NH).	2.21 (3H, s, CH ₃), 3.95 (1H, d, <i>J</i> = 6.4, H-5 pyran), 5.2 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.51-7.60 (3H, m, aromatic protons), 8.73 (1H, s, exchangeable -NHPh), 9.12 (1H, s, NH imino), 9.55 (1H, s, CH pyrimidine), 11.51 (1H, brs, exchangeable OH).	
9	1648 (C=N), 1720(C=O, carboxyl) and 3359 (NH and OH)	1.29 (3H, t, <i>J</i> = 7.4, N-CH ₂ CH ₃), 2.23 (3H, s, CH ₃), 3.88 (1H, d, <i>J</i> = 6.4, H-5 pyran), 4.87 (2H, q, <i>J</i> = 7.3, N-CH ₂ CH ₃), 5.14 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.54-7.62 (3H, m, aromatic protons), 9.08 (1H, s, NH imino), 9.45 (1H, s, CH pyrimidine) and 11.48 (1H, brs, exchangeable OH).	
10	1684(C=N), 1726(C=O, carboxyl) and 3351 (NH and OH)	2.26 (3H, s, CH ₃), 3.94 (1H, d, <i>J</i> = 6.4, H-5 pyran), 5.22 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.52-7.63 (3H, m, aromatic protons), 9.05 (1H, s, NH imino), 9.42 (1H, s, CH pyrimidine), 11.45 (1H, brs, exchangeable OH).	
11	1648(C=N), 1728 (C=O, carboxyl) and 3386 (NH or OH).	2.21 (3H, s, CH ₃), 3.89 (1H, d, <i>J</i> = 6.4, H-5 pyran), 5.16 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.31 (2H, s, exchangeable NH ₂), 7.53-7.61 (3H, m, aromatic protons), 9.22 (1H, s, CH pyrimidine) and 11.49 (1H, brs, exchangeable OH).	
12	1444 (C=S), 1682 (C=N), 1727 (C=O, carboxyl) and 3366 (NH or OH).	2.23 (3H, s, CH ₃), 3.1 (1H, brs, exchangeable SH), 3.9 (1H, d, <i>J</i> = 6.4, H-5 pyran), 5.17 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.51-7.59 (3H, m, aromatic protons), 8.41 (1H, s, CH pyrimidine), 9.25 (1H, brs, exchangeable NH) and 11.45 (1H, brs, exchangeable OH).	
13	1620 (C=N), 1650 (C=O, amide), 3300-3390 (NH).	2.25 (3H, s, CH ₃), 3.92 (1H, d, <i>J</i> = 6.4, H-5 pyran), 4.46 (1H, s, CH pyrazol), 5.21 (1H, d, <i>J</i> = 6.4, H-5 pyran), 6.35 (1H, brs, exchangeable NH ₂), 7.53-7.61 (3H, m, aromatic protons), 8.45 (1H, s, CH pyrimidine).	
14	1656 and 1670 (2 C=O, amide) and 3395 (NH).	2.18 (3H, s, CH ₃), 3.91 (1H, d, <i>J</i> = 6.4, H-5 pyran), 3.94 (2H, s, CH ₂ Cl), 5.2 (1H, d, <i>J</i> = 6.4, H-5 pyran), 7.51-7.64 (3H, m, aromatic protons), 8.44 (1H, s, CH pyrimidine), 9.26 (1H, brs, exchangeable CONH).	

Table 2.

Comp. No.	IR (KBr) cm^{-1}	^1H NMR (200 MHz, DMSO- d_6), δ	Mass m/z
15	1619 and 1705 (2 C=O), 2855 (CH aliphatic) and 3386 (NH).	2.23 (3H, s, CH ₃), 2.34 (3H, s, COCH ₃), 3.66 (2H, s, COCH ₂ CO), 3.94 (1H, d, $J=6.4$, H-5 pyran), 5.19 (1H, d, $J=6.4$, H-5 pyran), 7.55-7.63 (3H, m, aromatic protons), 8.43 (1H, s, CH pyrimidine), 9.21 (1H, brs, exchangeable CONH).	396 (M ⁺), 303, 286, 351, 153.
16	1626 and 1652 (2 C=O, amide), 2855-2922 (CH aliphatic) and 3420 (OH).	2.26 (3H, s, CH ₃), 3.92 (1H, d, $J=6.4$, H-5 pyran), 5.17 (1H, d, $J=6.4$, H-5 pyran), 5.21 (1H, s, CH pyrazole), 7.52-7.60 (m, aromatic protons, 3H), 8.45 (1H, s, CH pyrimidine), 11.98 (1H, brs, exchangeable OH pyrazole).	382 (M ⁺), 355, 301, 249.
17	1655 and 1680 (2 C=O), 2923 (CH aliphatic) and 3216 (NH).	2.24 (3H, s, CH ₃), 3.9 (1H, d, $J=6.4$, H-5 pyran), 5.19 (1H, d, $J=6.4$, H-5 pyran), 7.55-7.67 (3H, m, aromatic protons), 7.98 (1H, s, CHO), 8.41 (1H, s, CH pyrimidine), 9.23 (1H, brs, exchangeable CONH).	
18	1656 (C=N), 1735 (C=O, ester), 2855-2925 (CH aliphatic) and 3420 (NH).	2.20 (3H, s, CH ₃), 2.41 (3H, s, CH ₃ COO-), 3.87 (1H, d, $J=6.4$, H-5 pyran), 4.88 (1H, brs, exchangeable NH), 5.15 (1H, d, $J=6.4$, H-5 pyran), 7.54-7.62 (3H, m, aromatic protons), 8.43 (1H, s, CH pyrimidine).	
19	1653 (C=O, amide), 1690 and 1732 (2 C=O, carboxyl), 2207 (C=N), 2924 (CH aliphatic), 3088-3200 (OH) and 3423 (NH).	2.24 (3H, s, CH ₃), 3.93 (1H, d, $J=6.4$, H-5 pyran), 5.19 (1H, d, $J=6.4$, H-5 pyran), 6.62 (1H, d, $J=15.2$ Hz CH=), 7.12 (1H, d, $J=15.2$ Hz =CH), 7.51-7.59 (3H, m, aromatic protons), 9.56 (1H, brs, exchangeable NHCO, maleamic), 11.44 (1H, brs, exchangeable OH) and 12.08 (1H, brs, exchangeable OH).	344 (M ⁺ -CO ₂), 316, 279, 152.
20	1721 (C=O carboxylic), 2207 (C=N), 2924 (CH aliphatic), 3100, 3200, 3386, 3422 (NH) and (OH).	2.26 (3H, s, CH ₃), 3.92 (1H, d, $J=6.4$, H-5 pyran), 5.16 (1H, d, $J=6.4$, H-5 pyran), 7.53-7.62 (3H, m, aromatic protons), 8.93 (2H, brs, exchangeable NH ₂), 9.42 (1H, s, exchangeable NH, maleamic) and 11.45-11.47 (2H, brs, exchangeable 2 OH).	
21	1638 (C=O, amide), 1678 (C=O, ketonic), 1724 (C=O, carboxyl), 2218 (C=N), 3240 (NH) and 3386 (OH).	2.03 (6H, s, 2CH ₃), 2.21 (3H, s, CH ₃), 2.75-2.93 (2H, m, CH ₂), 3.72 (1H, s, CH), 3.89 (1H, d, $J=6.4$, H-5 pyran), 5.17 (1H, d, $J=6.4$, H-5 pyran), 7.53-7.61 (3H, m, aromatic protons), 9.51 (1H, brs, exchangeable NHCO), 11.47 (1H, brs, exchangeable OH) and 12.16 (1H, s, exchangeable OH).	
22	1636 (C=O, amide), 1685 (C=O, ketonic), 1723 (C=O carboxyl), 2208 (C=N), 3219 (NH) and 3381 (OH).	2.24 (3H, s, CH ₃), 2.36 (3H, d, CH ₃), 2.72-2.91 (2H, m, CH ₂), 3.92 (1H, d, $J=6.4$, H-5 pyran), 4.2 (1H, d, CH), 5.18 (1H, d, $J=6.4$, H-5 pyran), 7.55-7.64 (3H, m, aromatic protons), and 11.45 (1H, brs, exchangeable OH), 12.12 (1H, s, exchangeable OH).	
23	1635 (C=N), 1721 (C=O, carboxyl), 2206 (C=N), 3216 (NH) and 3347 (basin peak, OH).	2.19 (3H, s, CH ₃), 2.42-2.61 (2H, m, CH ₂), 3.1 (1H, d, CH), 3.72 (1H, s, CH), 3.89 (1H, d, $J=6.4$, H-5 pyran), 5.17 (1H, d, $J=6.4$, H-5 pyran), 7.53-7.60 (3H, m, aromatic protons), 8.37 (2H, s, exchangeable NH ₂), 11.43 (1H, brs, exchangeable OH) and 11.94 (1H, s, exchangeable OH).	

Table 2.

Comp. No.	IR (KBr) cm^{-1}	^1H NMR (200 MHz, DMSO- d_6), δ	Mass m/z
24	1630(C=N), 1655(C=O, amide), 1721 (C=O, carboxyl), 2206 (C \equiv N), 3216 (NH) and 3360(OH).	2.24 (3H, s, CH $_3$), 2.35 (3H, s, CH $_3$), 2.43 (3H, s, CH $_3$), 2.9 (2H, s, pyridinone protons), 3.72 (1H, s, CH), 3.88 (1H, d, $J = 6.4$, H-5 pyran), 5.18 (1H, d, $J = 6.4$, H-5 pyran), 7.52-7.63 (3H, m, aromatic protons), 8.45 (1H, brs, exchangeable NH), 9.63 (1H, brs, exchangeable NH) and 11.71 (1H, s, exchangeable OH).	
25	1653(C=O, amide), 1721 (C=O, carboxylic), 2205 (C \equiv N), 3214(NH) and 3342 (OH).	2.21 (3H, s, CH $_3$), 3.0 (2H, s, piperidinone protons), 3.72 (1H, s, CH), 3.91 (1H, d, $J = 6.4$, H-5 pyran), 5.19 (1H, d, $J = 6.4$, H-5 pyran), 7.54-7.66 (3H, m, aromatic protons), 9.21 (1H, brs, exchangeable NH), 9.61 (1H, brs, exchangeable NH), 9.82 (1H, brs, exchangeable NH) and 11.71 (1H, s, exchangeable OH).	
26	1634(C=O, amide), 1721 (C=O carboxyl), 2205 (C \equiv N), 3213(NH) and 3342 (OH).	2.20 (3H, s, CH $_3$), 2.35 (3H, s, CH $_3$), 3.2 (2H, s, piperidinone protons), 3.72 (1H, s, CH), 3.92 (1H, d, $J = 6.4$, H-5 pyran), 5.2 (1H, d, $J = 6.4$, H-5 pyran), 7.52-7.61 (3H, m, aromatic protons), 8.49 (1H, brs, exchangeable NH), 9.65 (1H, brs, exchangeable NH), 9.85 (1H, brs, exchangeable NH) and 11.76 (1H, s, exchangeable OH).	
27	1634 (C=O, amid), 1719 (C=O, carboxyl), 2209 (C \equiv N), 3217, 3347, 3445 (NH) and (OH).	2.19 (3H, s, CH $_3$), 6.68 (1H, d, $J = 15.2$ Hz CH=), 6.83 (1H, s, pyridine proton), 7.14 (1H, d, $J = 15.2$ Hz = CH), 7.55-7.64 (3H, m, aromatic protons), 10.16 (1H, brs, exchangeable NHCO, maleamic), 11.83 (1H, brs, exchangeable OH) and 12.13 (1H, brs, exchangeable OH).	385 (M^+), 341, 315, 277, 153.
28	1629 (C=N), 1719 (C=O carboxyl), 2207 (C \equiv N), 3220, 3372, 3447 (NH) or (OH).	2.22 (3H, s, CH $_3$), 3.83 (2H, s, CH $_2$), 6.99 (1H, s, pyridine proton), 7.54-7.62 (3H, m, aromatic protons), 8.21 (2H, brs, exchangeable NH $_2$), 10.48 (1H, brs, exchangeable NH), 11.83 (1H, s, exchangeable OH) and 12.17 (1H, s, exchangeable OH).	
29	1631(C=N), 1720 (C=O carboxyl), 2207 (C \equiv N), 3213, 3347, 3448 (NH) and (OH).	2.22 (3H, s, CH $_3$), 2.37 (3H, s, CH $_3$), 2.65 (3H, s, OCH $_3$), 3.81 (2H, s, CH $_2$), 7.1 (1H, s, pyridine proton), 7.51-7.59 (3H, m, aromatic protons), 10.45 (1H, brs, exchangeable NH), 11.81 (1H, s, exchangeable OH) and 12.19 (1H, s, exchangeable OH).	423 (M^+ -CO $_2$), 286, 152, 138.
30	1632(C=N), 1720 (C=O, carboxyl), 2210 (C \equiv N), 3217, 3354, 3451 (NH) and (OH).	2.24 (3H, s, CH $_3$), 3.86 (2H, s, CH $_2$), 6.85 (1H, s, pyridine proton), 7.56-7.64 (3H, m, aromatic protons), 8.26 (2H, brs, exchangeable NH $_2$), 8.42 (1H, brs, exchangeable NH), 10.61 (1H, brs, exchangeable NH), 11.89 (1H, s, exchangeable OH) and 12.21 (1H, s, exchangeable OH).	

After cooling, the reaction mixture was poured into diluted HCl, the precipitated product was filtered off and washed several times with cold water, dried and crystallized from the proper solvent to afford the iminopyranopyrimidines (**9**) and/or (**10**).

4-amino-7-(4-chloro-3-methylphenyl)-5H-pyrano [2,3-*d*]pyrimidine-5-carboxylic acid (11).

To a solution of ethoxymethyleneamino-4*H*-pyran (**6**) (3.00 g, 8.70 mmol) and absolute ethanol (30 mL), ammonia solution (0.31 mL, 8.70 mmol) was added; the resulting mixture was refluxed for (2h). After cooling, the reaction mixture was acidified with very diluted solution of cold HCl, the precipitate formed was filtered off and washed on the filter funnel with water, dried then crystallized

from ethanol/water to afford the aminopyrano-pyrimidine (**11**).

7-(4-chloro-3-methylphenyl)-4-mercapto-5H-pyran[2,3-d]pyrimidine-5-carboxylic acid (12).

A mixture of ethoxymethyleneamino-4H-pyran (**6**) (3.00 g, 8.70 mmol) in ethanol (30 mL) and sodium hydrogensulphide (0.48 g, 8.70 mmol) was stirred under reflux for (7h). The reaction mixture was allowed to cool at room temperature then poured into water. The solid product was collected by filtration and crystallized from methanol/water to afford mercaptopyranopyrimidine (**12**).

4-amino-3H-pyrazolo[1,2-a]-12-(4-chloro-3-methylphenyl)-1aH-pyran[3,4-d]pyrimido[4,5-e]-1a,2,3,4-tetrahydro-pyridazine-2,6-dione (13).

A mixture of pyranopyrimidine (**7**) (1.00 g, 3.20 mmol) and ethyl cyanoacetate^{22,23} (0.34 mL, 3.20 mmol) in absolute ethanol (15 mL) was refluxed for (7 h). The reaction mixture was allowed to cool at room temperature then poured into water (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford aminopyrazolinone (**13**).

5-(4-chloro-3-methylphenyl)-1-(1-oxo-2-chloroethyl)-2,3a-dihydro-6-oxa-1,2,7,9-tetrazaphenalen-3(3H)-one (14).

A solution of pyranopyrimidine (**7**) (1.00 g, 3.20 mmol) and ethyl chloroacetate (0.34 mL, 3.20 mmol) in absolute ethanol (15 mL) was refluxed for (10 h). The reaction mixture was allowed to cool at room temperature then poured into water (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford the non-cyclized oxo-chloro-ethyltetrazaphenalen (**14**).

5-(4-chloro-3-methylphenyl)-1-(1,3-dioxobutyl)-2,3a-dihydro-6-oxa-1,2,7,9-tetrazaphenalen-3(3H)-one (15).

A mixture of pyranopyrimidine (**7**) (1.00 g, 3.20 mmol) and ethyl acetoacetate²⁴ (0.40 mL, 3.20 mmol) in absolute ethanol (15 mL) was refluxed for (10 h). The reaction mixture was allowed to cool at room temperature then poured into water (200 mL), the solid formed was filtered

off, washed with water, dried and crystallized from methanol/water to afford dioxobutyltetrazaphenalen (**15**).

4-hydroxy-3H-pyrazolo[1,2-a]-12-(4-chloro-3-methylphenyl)-1aH-pyran[3,4-d]pyrimido[4,5-e]-1a,2,3,4-tetrahydro-pyridazine-2,6-dione (16).

A mixture of pyranopyrimidine (**7**) (1.00 g, 3.20 mmol) and diethylmalonate^{22,23,24} (0.48 mL, 3.20 mmol) in absolute ethanol (15 mL) was refluxed for (10 h). The reaction mixture was allowed to cool at room temperature then poured into water (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from methanol/water to afford pyrazolinedione derivative (**16**).

5-(4-chloro-3-methylphenyl)-1-formyl-2,3a-dihydro-6-oxa-1,2,7,9-tetrazaphenalen-3(3H)-one (17).

Pyranopyrimidine (**7**) (1.00 g, 3.20 mmol) in formic acid²⁵ (85%) (15 mL) was refluxed for (15 h). The reaction mixture was left to cool, then poured into water (300 mL) the formed precipitate was filtered off, washed thoroughly with water, dried and crystallized from absolute ethanol to afford formyl derivative (**17**).

5-(4-chloro-3-methylphenyl)-1,3a-dihydro-6-oxa-1,2,7,9-tetrazaphenalen-3-yl acetate (18).

In acetylchloride (15 mL), pyranopyrimidine (**7**) (1.00 g, 3.20 mmol) was refluxed in water bath for (2 h). The reaction mixture was concentrated, the separated brown solid crystallized from ethanol/water to afford acetoxy derivative (**18**).

(E)-2-(3-carboxyacrylamido)-6-(4-chloro-3-methylphenyl)-3-cyano-4H-pyran-4-carboxylic acid (19).

Maleic anhydride^{26,27} (0.33 g, 3.4 mmol) was completely dissolved at room temperature in glacial acetic acid (30 mL), and then 4H-pyran derivative (**4**) (1.00 g, 3.4 mmol) was added to the solution; the resulting mixture was stirred under reflux for (1 h). The reaction mixture was allowed to cool at room temperature, then poured into water (500 mL), the precipitate formed was filtered off, washed with water, dried and crystallized from methanol to afford N-cyclic maleamic acid (**19**).

2-amino-6-[4-carboxy-6-(4-chloro-3-methylphenyl)-3-cyano-4H-pyran-2-ylamino]-3-cyano-4H-pyran-4-carboxylic acid (20).

To a solution of maleamic acid (**19**) (2.00 g, 5.15 mmol) and malononitrile²⁸ (0.34 g, 5.15 mmol) in dioxan (20 mL) few drops of piperidine was added; the resulting mixture was refluxed at 60 °C for (7 h). The reaction mixture was allowed to cool at room temperature then acidified with diluted acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from the ethanol/water to afford bis compound (**20**).

2-[3-acetyl-2-(carboxymethyl)-4-oxopentanimido]-6-(4-chloro-3-methylphenyl)-3-cyano-4H-pyran-4-carboxylic acid (21).

To a solution of maleamic acid (**19**) (2.00 g, 5.15 mmol) and acetylacetone (0.53 mL, 5.15 mmol) in DMF (20 mL) few drops of piperidine was added; the resulting mixture was refluxed at 60 °C for (7 h). The reaction mixture was allowed to cool at room temperature then acidified with diluted acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from methanol/water to afford Michael adduct (**21**).

2-[3-acetyl-4-(carboxymethyl)-2,5-dioxopyrrolidin-1-yl]-6-(4-chloro-3-methylphenyl)-3-cyano-4H-pyran-4-carboxylic acid (22).

A mixture of maleamic acid (**19**) (2.00 g, 5.15 mmol) and ethyl acetoacetate (0.65 mL, 5.15 mmol) in dioxan (20 mL) in the presence of piperidine was refluxed at 60 °C for (10 h). The reaction mixture was allowed to cool at room temperature then poured into diluted solution of acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from methanol/water to afford N-cyclic maleimide (**22**).

2-[5-amino-3-(carboxymethyl)-4-cyano-3,4-dihydro-2H-pyrrol-2-ylideneamino]-6-(4-chloro-3-methylphenyl)-3-cyano-4H-pyran-4-carboxylic acid (23).

A mixture of maleamic acid (**19**) (2.00 g, 5.15 mmol) and malononitrile (0.34 g, 5.15 mmol) in DMF (30 mL) in the presence of ammonium

acetate was refluxed in water bath at 60 °C for (10 h). The reaction mixture was allowed to cool at room temperature then poured into diluted solution of acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford iminopyrrol derivative (**23**).

6-(4-chloro-3-methylphenyl)-3-cyano-2-[3,4-dimethyl-6-oxo-6,7-dihydro-2H-pyrrolo[3,4-c]pyridin-1-ylamino]-4H-pyran-4-carboxylic acid (24).

To a solution of maleamic acid (**19**) (2.00 g, 5.15 mmol) and acetylacetone²⁸ (0.53 mL, 5.15 mmol) in DMF (30 mL) ammonium acetate was added; the resulting mixture was refluxed in water bath at 60 °C for (8 h). The reaction mixture was allowed to cool at room temperature then acidified with diluted acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford pyridinopyrrol (**24**).

6-(4-chloro-3-methylphenyl)-3-cyano-2-[3,4,6-trioxo-3,3a,4,5,6,7-hexahydro-2H-pyrrolo-[3,4-c]pyridin-1-ylamino]-4H-pyran-4-carboxylic acid (25).

A mixture of maleamic acid (**19**) (2.00 g, 5.15 mmol) and diethylmalonate (0.78 mL, 5.15 mmol) in DMF (30 mL) in the presence of ammonium acetate was refluxed in water bath at 60 °C for (6 h). The reaction mixture was allowed to cool at room temperature then poured into diluted solution of acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford pyridinopyrrol (**25**).

6-(4-chloro-3-methylphenyl)-3-cyano-2-[3-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrrolo [3,4-c]pyridin-1-ylamino]-4H-pyran-4-carboxylic acid (26).

A mixture of maleamic acid (**19**) (2.00 g, 5.15 mmol) and ethyl acetoacetate (0.65 mL, 5.15 mmol) in DMF (30 mL) in the presence of ammonium acetate was refluxed in water bath at 60 °C for (3 h). The reaction mixture was allowed to cool at room temperature then poured into diluted solution of acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford pyridino-

pyrrol (26).

(E)-2-(3-carboxyacrylamido)-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (27).

Maleic anhydride^{26,27} (0.33 mL, 3.4 mmol) was completely dissolved at room temperature in glacial acetic acid or THF (30 mL), and then pyridine derivative (5) (1.00 g, 3.4 mmol) was added to the solution; the resulting mixture was stirred under reflux for (1 h). The reaction mixture was allowed to cool at room temperature, then poured into water (500 mL), the precipitate formed was filtered off, washed with water, dried and crystallized from methanol to afford N-cyclic maleamic acid (27).

2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (28).

To a solution of N-cyclic maleamic acid (27) (2.00 g, 5.19 mmol) and malononitrile (0.34 g, 5.19 mmol) in DMF (15 mL) few drops of piperidine was added; the resulting mixture was refluxed at 60 °C for (5h). The reaction mixture was allowed to cool at room temperature then acidified with diluted acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from methanol/water to afford furan derivative (28).

2-[4-acetyl-3-(carboxymethyl)-5-methylfuran-2-ylamino]-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (29).

A mixture of N-cyclic maleamic acid (27) (2.00 g, 5.19 mmol) and acetylacetone (0.53 mL, 5.19 mmol) in DMF (20 mL) in the presence of piperidine was refluxed at 60 °C for (3 h). The reaction mixture was allowed to cool at room temperature then poured into diluted solution of acetic acid

(200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford furan derivatives (29).

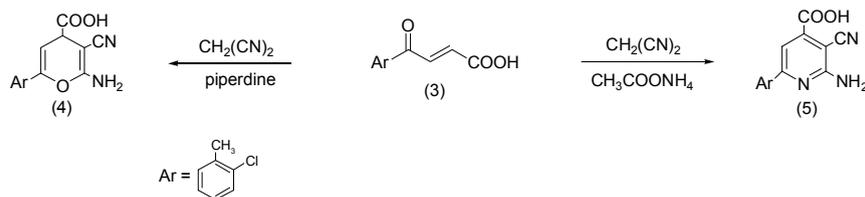
2-[5-amino-3-(carboxymethyl)-4-cyano-1H-pyrrol-2-ylamino]-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (30).

A mixture of N-cyclic maleamic acid (27) (2.00 g, 5.19 mmol) and malononitrile²⁸ (0.34 g, 5.19 mmol) in DMF (30 mL) in the presence of ammonium acetate was refluxed at 60 °C for (3 h). The reaction mixture was allowed to cool at room temperature then poured into diluted solution of acetic acid (200 mL), the solid formed was filtered off, washed with water, dried and crystallized from ethanol/water to afford aminopyrrol derivative (30).

RESULTS AND DISCUSSION

The β -aroylacrylic acid derivative 4-(4-chloro-3-methylphenyl)-4-oxo-but-2-enoic acid²⁹⁻³⁸ (3) has interacted with malononitrile in dimethylformamide (DMF) in the presence of piperidine as a catalyst to afford 2-amino-6-(4-chloro-3-methylphenyl)-3-cyano-4H-pyran-4-carboxylic acid (4). On the other hand, when the reaction was carried out in the presence of ammonium acetate it yielded 2-amino-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (5) (Scheme 1). Both (4) and (5) were used as pre-key starting materials for synthesizing both fused and isolated heterocyclic systems.

The structure of compounds (4) and (5) were established by their correct analytical data and their IR spectra which exhibited strong absorption bands at the regions 1649-1655, 1712-1720, 2196 and 3280-3285 attributable to $\nu_{C=N}$, $\nu_{C=O}$, $\nu_{C\equiv N}$ and ν_{NH}



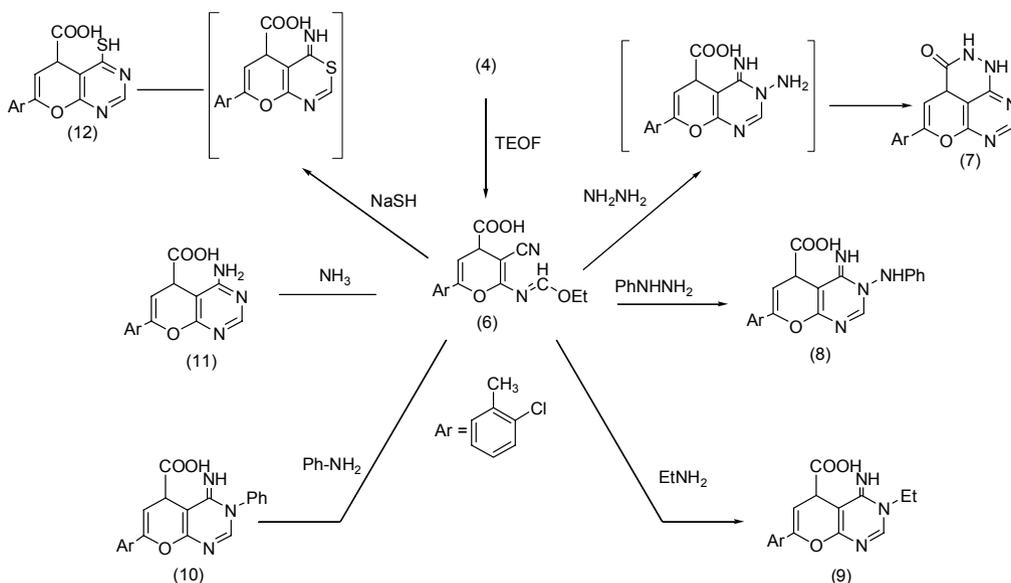
Scheme 1.

respectively. The ^1H NMR spectrum of compound (4) revealed two doublets at δ 3.93 and 5.19 assigned to pyran protons H-4 and H-5 respectively, multiplet at δ 7.52-7.60 assigned for aromatic protons, singlet at δ 2.32 ppm assigned for protons of methyl group and finally two exchangeable singlets at δ 8.37 and 11.74 ppm consistent with the protons of (NH_2) and (OH) respectively. The ^1H NMR spectrum of compound (5) exhibited multiple signal at δ 7.63-7.71 assigned for aromatic protons, singlet at δ 2.35 ppm assigned for protons of methyl group and finally two exchangeable singlets at δ 7.97 and 11.45 ppm consistent with the protons of (NH_2) and (OH) respectively. EI-MS for compounds (4) and (5) exhibited m/z 288 and 287 (M^+) respectively. The reaction takes place via nucleophilic addition of the carbanion derived from the malononitrile to the α,β -unsaturated carbonyl moiety in the acid (3) followed by cyclization in case of (4) and ring closure and dehydrogenation in case of (5).

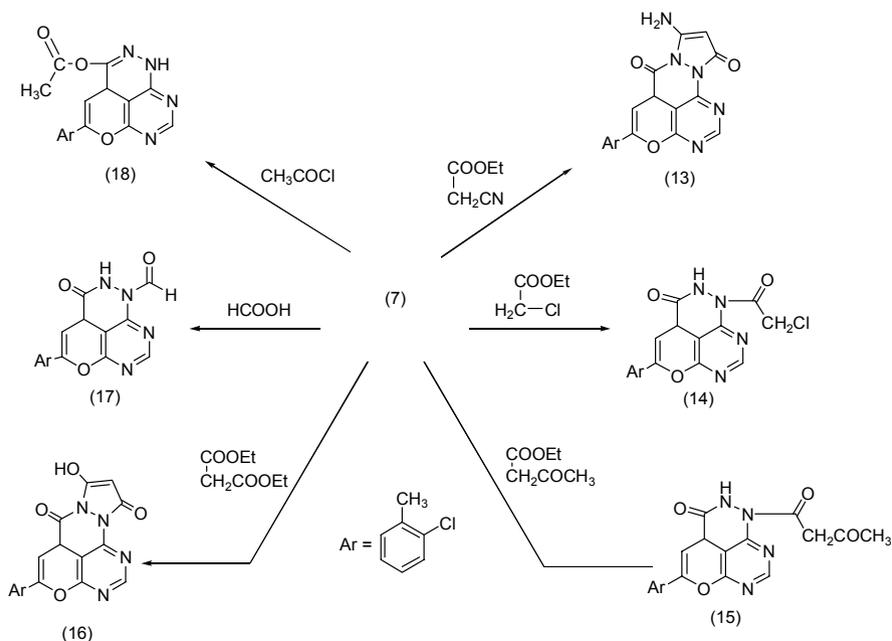
Refluxing of (4) with neat triethylorthoformate afforded 6-(4-chloro-3-methylphenyl)-3-cyano-2-(ethoxymethyleneamino)-4*H*-pyran-4-carboxylic acid (6). Its IR displayed an absorption bands at 1682, 1726, 2210 and 3390 attributable to $\nu_{\text{C}=\text{N}}$,

$\nu_{\text{C}=\text{O}}$, $\nu_{\text{C}=\text{N}}$ and ν_{OH} and showed no absorption frequency in the NH region. The ^1H NMR spectrum of compound showed singlet signal of the azamethine proton ($\text{N}=\text{CH}$) at δ 8.32, triplet at δ 1.33 assigned for terminal methyl protons (OCH_2CH_3) and quartet signal at δ 4.27 assigned with the two protons of methylene (OCH_2). Compound (6) was used as key-starting material for synthesizing some interesting annulated heterocyclic systems (Scheme 2).

Thus, interaction of compound (6) with hydrazine hydrate in boiling ethanol yielded 5-(4-chloro-3-methylphenyl)-1,2,3a-trihydro-6-oxa-1,2,7,9-tetraazaphenalen-3(3*H*)-one (7), without isolation of the imino derivative. This could be explained by the formation of the imino derivative first, which in the presence of a base (hydrazine hydrate) underwent a Dimroth rearrangement^{39,40,41} to give the thermodynamically more stable hydrazino derivate which underwent ring closure and yielded the desired product (7). IR spectrum of compound (7) exhibited strong absorption bands at 1610, 1651 and 3324 (broad band) attributable to $\nu_{\text{C}=\text{N}}$, $\nu_{\text{C}=\text{O}}$ (amide) and ν_{NH} devoid any band for $\nu_{\text{C}=\text{N}}$. The ^1H NMR spectrum revealed exchangeable two singlet signals at δ 9.27 and 4.56 ppm attributable to the protons



Scheme 2.



Scheme 3.

1a,2,3,4-tetrahydropyridazine-2,6-dione (**13**) was prepared via the interaction of compound (**7**) with ethyl cyanoacetate. The lactam form of compound (**7**) is more predominant in the solution due to the high polarity of ethanol, so the reaction possibly takes place via the acylation of more nucleophilic nitrogen of the pyridazinone moiety followed by ring closure to give the desired product (**13**) (Scheme 3). Structure of the compound (**13**) was established by microanalytical and spectral data. Its IR spectrum exhibited strong absorption bands at 1620, 1650, 3300 and 3391 attributable to $\nu_{\text{C}=\text{N}}$, $\nu_{\text{C}=\text{O}}$ and ν_{NH} respectively, and devoid any absorptions for $\nu_{\text{C}=\text{N}}$. The ^1H NMR spectrum of the compound showed two singlet signals at δ 4.46 and exchangeable one at δ 6.35 for protons of (CH) and (NH_2) at the pyrazole ring respectively.

When compound (**7**) was allowed to react with ethyl chloroacetate in boiling ethanol it yielded 5-(4-chloro-3-methylphenyl)-1-(1-oxo-2-chloroethyl)-2,3a-dihydro-6-oxa-1,2,7,9-tetrazaaphenalen-3(3H)-one (**14**). The reaction takes place via nucleophilic substitution involving the more nucleophilic nitrogen on the carbonyl group of the ethoxycar-

bonyl moiety (Tetrahedral Mechanism). The outputs of reading IR spectrum for compound (**14**) showed absorption vibrational bands at 1656, 1670 and 3395 attributable to ν_{max} of two carbonyl groups and ν_{NH} respectively.

Treating compound (**7**) with ethyl acetoacetate in boiling ethanol afforded 5-(4-chloro-3-methylphenyl)-(1,3-dioxobutyl)-2,3a-dihydro-6-oxa-1,2,7,9-tetrazaaphenalen-3(3H)-one (**15**). The structure of compound (**15**) was substantiated from its microanalytical and spectral data. The IR spectrum revealed strong absorption bands at 1619, 1705, 2855 and 3392 cm^{-1} attributable to ν_{max} of two carbonyl groups, aliphatic ν_{CH} and ν_{NH} respectively. The ^1H NMR spectrum revealed two singlet signals at δ 2.38 and 3.66 attributable to aliphatic methyl and methylene protons of ($\text{COCH}_2\text{COCH}_3$) respectively. EI-MS exhibits m/z 396 corresponding to (M^+). The reaction possibly takes place via nucleophilic attack by lone pair of N_1 (more nucleophile) on the carbonyl of the ethoxycarbonyl moiety in which (N-C) bond was formed between (NH) of pyridazinone moiety and carbonyl group of the ester moiety before (C-OEt) bond started to break

and consequently a lot of energy is accumulated in the reaction medium which decreases the activation energy of the reaction and facile conversion was occurred.

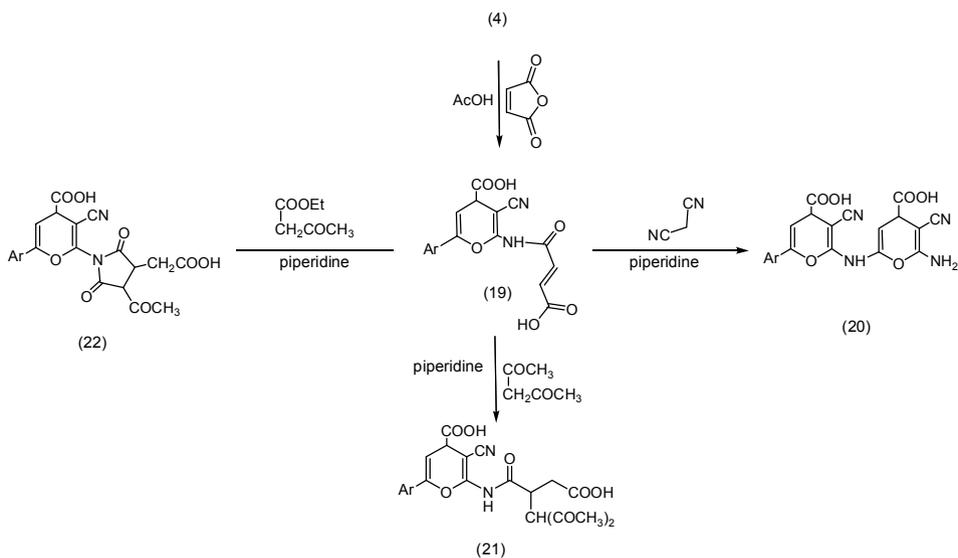
Reacting compound (7) with diethylmalonate in boiling ethanol afforded 4-hydroxy-3H-pyrazolo-[1,2-a]-12-(4-chloro-3-methylphenyl)-1aH-pyran o-[3,4-d]pyrimido[4,5-e]1a,2,3,4-tetrahydropyridazine-2,6-dione (16). Its IR spectrum exhibited strong absorption bands at 1626, 1652, 2855-2922 and 3420 attributable to ν_{\max} of two amide groups, aliphatic ν_{CH} and ν_{NH} respectively. The ^1H NMR spectrum revealed two singlet signals at δ 5.21 and exchangeable one at δ 11.98 consistent with protons of (CH) and (OH) at the pyrazole ring. EI-MS exhibited m/z at 382 corresponding to (M $^+$).

The formylated derivative 5-(4-chloro-3-methylphenyl)-1-formyl-2,3a-dihydro-6-oxa-1,2,7,9-tetraazaphenalen-3(3H)-one (17) was prepared by refluxing compound (7) with formic acid. Compound (7) exhibits lactam-lactim dynamic equilibrium in solution, (lactam form is more predominate), so the reaction takes place by formylating the more nucleophilic nitrogen of the pyridazinone moiety to give the desired product. The structure of compound (17) was substantiated from its micro-

analytical and spectral data. Its IR spectrum revealed strong absorption bands at 1655, 1680, 2923 and 3216 attributable to ν_{\max} of two carbonyl groups, ν_{CH} and ν_{NH} respectively.

Acylation of compound (7) by using acetylchloride afforded 5-(4-chloro-3-methylphenyl)-1,3a-dihydro-6-oxa-1,2,7,9-tetraazaphenalen-3-yl acetate (18). The reaction takes place via acylation of hydroxyl moiety of the lactim form of compound (7) which exhibits lactam-lactim dynamic equilibrium in the solution, (the lactim form in the presence of acetylchloride is more predominate due to the weak polarity of the later in comparison with ethanol or formic acid). The IR exhibited strong absorption bands at 1656, 1735, 2855, 2925-3420 cm^{-1} attributable to $\nu_{\text{C=N}}$, $\nu_{\text{C=O}}$ (ester), ν_{CH} and ν_{NH} respectively. The ^1H NMR spectrum of compound (18) showed singlet at δ 2.41 assigned for (CH₃COO-) at the pyridazine ring and exchangeable broad singlet at δ 4.88 for (NH) proton of the same ring.

The N-cyclic maleamic acid^{26,27} (19) has been synthesized via interaction of compound (4) in refluxing acetic acid with maleic anhydride (Scheme 4). The N-cyclic maleamic acid is constructed such that due to the ring-cleaved structure of maleic anhydride (-COCH=C- HCOOH) that



Scheme 4.

bonded to the amino group (NH₂) of the starting N-cyclic amine via a malemic bond (-NH-CO-). The structure of the N-cyclic maleamic acid (**19**) has confirmed by microanalytical and spectral data. Its IR spectrum revealed strong absorption bands at 1653, 1690, 1732, 2207, 2924, 3088, 3200, and basin peak centered at 3423 attributable to ν_{\max} of amide and two carboxylic carbonyls, $\nu_{C=N}$, ν_{CH} , ν_{NH} and ν_{OH} respectively. The ¹H NMR spectrum revealed two doublet signals for (CH=CH) protons in the downfield region at δ 6.62 and δ 7.12 with $J = 15.2$ Hz, also it showed exchangeable singlet signal at δ 9.56 for the proton of maleamic bond (NH-CO). EI-⁺MS exhibited m/e at 344 corresponding to (M -CO₂). In this investigation the author sought to investigate the behavior of maleamic acid derivative (**19**) towards active methylene compounds under Michael reaction conditions with the aim of obtaining more precise information about the course of the reaction and synthesizing some interesting heterocyclic compound.

When maleamic acid derivative (**19**) was allowed to react with malononitrile in the presence of few drops of piperidine as a catalyst it yielded 2-amino-6-[4-carboxy-6-(4-chloro-3-methylphenyl)-3-cyano-4*H*-pyran-2-ylamino]-3-cyano-4*H*-pyran-4-carboxylic acid (**20**). Compound (**20**) was obtained from Michael addition reaction (α,β -unsaturated amide rather than α,β -unsaturated acid) and gave an adduct through the fleeting intermediate which underwent ring closure to give the desired product. IR spectrum of (**20**) revealed strong absorption bands at 1721, 2207, 2924, 3100, 3200, 3386 and 3422 attributable to $\nu_{C=O}$, $\nu_{C=N}$, ν_{CH} , ν_{NH} and ν_{OH} respectively. The ¹H NMR spectrum exhibited two exchangeable singlet signals at δ 8.93 and 9.42 attributable to the protons of (NH₂), (NH maleamic) respectively.

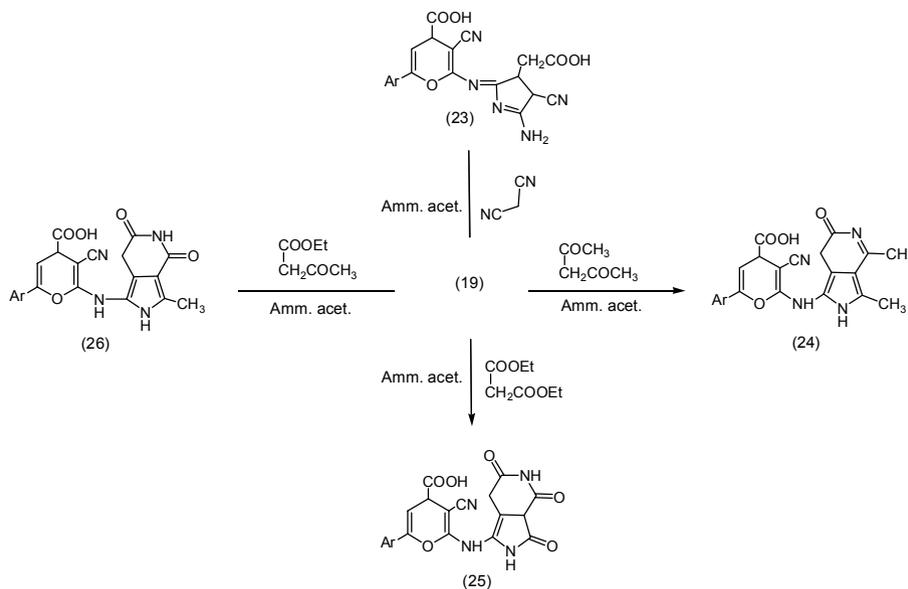
Treating compound (**19**) with acetylacetone in the presence of piperidine as a catalyst afforded the Michael adduct 2-[3-acetyl-2-(carboxymethyl)-4-oxopentanamido]-6-(4-chloro-3-methylphenyl)-3-cyano-4*H*-pyran-4-carboxylic acid (**21**). The structure of the compound (**21**) was evidenced from microanalytical and spectral data. Its IR spectrum

revealed strong absorption bands at 1638, 1678, 1724, 2218, 3240 and 3380 attributable to ν_{\max} of carbonyl groups (amide, ketonic and carboxylic), $\nu_{C=N}$, ν_{NH} and ν_{OH} respectively. Maleamic acid (**19**) reacts with acetylacetone under Michael reaction conditions as α,β -unsaturated acid rather than α,β -unsaturated amide, this is due to the polarization by the carbonyl of the carboxyl group outweighs the polarization by the carbonyl of amide group.

Interaction of the maleamic acid (**19**) with ethyl acetoacetate in the presence of piperidine as a catalyst yielded N-cyclic maleimide 2-[3-acetyl-4-(carboxymethyl)-2,5-dioxopyrrolidin-1-yl]-6-(4-chloro-3-methylphenyl)-3-cyano-4*H*-pyran-4-carboxylic acid (**22**). The structure of compound (**22**) was proved from microanalytical and spectral data. Its IR spectrum revealed strong absorption bands at 1636, 1685, 1723, 2208, 3219 and 3381 attributable to ν_{\max} of carbonyl groups, ν_{CN} , ν_{NH} and ν_{OH} respectively. The ¹H NMR spectrum of the compound showed absorption signals correlated with the (COCH₃) and (CH₂COOH) protons. Also the maleamic acid (**19**) reacts with ethyl acetoacetate under Michael reaction conditions as α,β -unsaturated acid rather than α,β -unsaturated amide, this is due to polarization by carbonyl of carboxyl group leads to more stable (less electrostatic repulsion) intermediate.

By changing the catalyst into ammonium acetate, maleamic acid derivative (**19**) interacted with malononitrile to afford 2-[5-amino-3-(carboxymethyl)-4-cyano-3,4-dihydro-2*H*-pyrrol-2-ylideneamino]-6-(4-chloro-3-methylphenyl)-3-cyano-4*H*-pyran-4-carboxylic acid (**23**) (Scheme 5). The structure of compound (**23**) was inferred from microanalytical and spectral data. Its IR spectrum revealed a strong absorption bands at 1635, 1721, 2206, 3216 and 3347 (basin peak) attributable to $\nu_{C=N}$, $\nu_{C=O}$, $\nu_{C=N}$, ν_{NH} and ν_{OH} respectively. Compound (**23**) was obtained from Michael addition of malononitrile and α,β -unsaturated acid followed by cyclization to give the desired product.

Interaction of maleamic acid derivative (**19**) with acetylacetone in the presence of ammonium acetate in water bath yielded 6-(4-chloro-3-methyl-



Scheme 5.

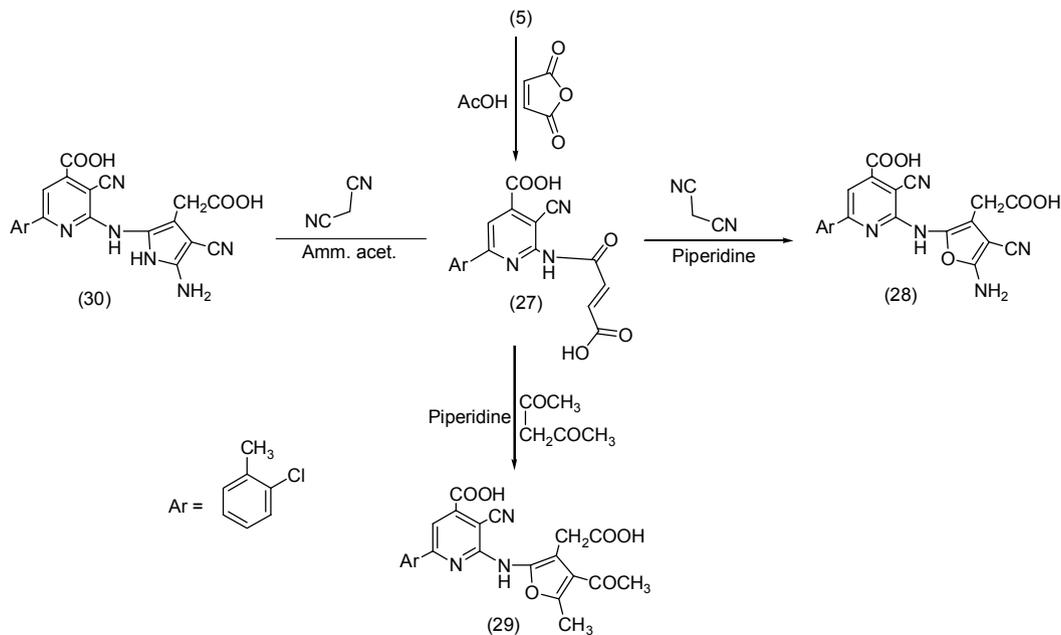
phenyl)-3-cyano-2-[3,4-dimethyl-6-oxo-6,7-dihydro-2H-pyrrolo[3,4-c]pyridin-1-ylamino]-4H-pyran-4-carboxylic acid (**24**). The structure of compound (**24**) was established from microanalytical and spectral data. Its IR spectrum revealed strong absorption bands at 1630, 1655, 1722, 2206, 3216 and 3360 cm^{-1} attributable to $\nu_{\text{C}=\text{N}}$, ν_{max} of carbonyl groups, $\nu_{\text{C}\equiv\text{N}}$, ν_{NH} and ν_{OH} respectively. The ^1H NMR spectrum of compound (**24**) revealed two singlet signals at δ 2.35 and δ 2.43 assigned for the protons of two methyl groups.

Refluxing maleamic acid derivative (**19**) with diethylmalonate in the presence of ammonium acetate in a water bath afforded 6-(4-chloro-3-methylphenyl)-3-cyano-2-[3,4,6-trioxo-3,3a,4,5,6,7-hexahydro-2H-pyrrolo[3,4-c]pyridin-1-ylamino]-4H-pyran-4-carboxylic acid (**25**). The structure of compound (**25**) was established on the basis of elemental analysis and spectra of ^1H NMR and IR which exhibited strong absorption bands at 1653, 1721, 2205, 3214 and 3342 (broad peak) attributable to ν_{max} of carbonyl groups, $\nu_{\text{C}=\text{N}}$, ν_{NH} and ν_{OH} respectively. Such IR data agreed well with the proposed structure.

Treatment of maleamic acid derivative (**19**) with ethyl acetoacetate in the presence of ammo-

nium acetate in a water bath yielded the 6-(4-chloro-3-methylphenyl)-3-cyano-2-[3-methyl-4,6-dioxo-4,5,6,7-tetrahydro-2H-pyrrolo[3,4-c]pyridine-1-ylamino]-4H-pyran-4-carboxylic acid (**26**). Further reactions with α -methyl group on pyrrol moiety of the obtained compound has not occurred due to the need of stronger base moreover, the expected conjugate base will not be stabilized as in case of α -alkyl pyridine (the nitrogen of pyridine has negative charge in one of the resonating structures).⁴² The structure of compound (**26**) was confirmed based on its elemental and spectral analyses. Thus IR spectrum of (**26**) revealed strong absorption bands at 1634, 1721, 2205, 3213 and 3342 (broad peak) attributable to $\nu_{\text{C}=\text{O}}$ groups, $\nu_{\text{C}\equiv\text{N}}$, ν_{NH} and ν_{OH} respectively.

On the lights of the previous results, further investigation at the same reaction type was carried out on N-cyclic maleamic acid derivative (**27**), which has been synthesized via the interaction of compound (**5**) in acetic acid with maleic anhydride (Scheme 6). This reaction involving the ring cleaved structure of maleic anhydride ($\text{COC}=\text{CH}-\text{COOH}$) is bonded to the amino group (NH_2) of the pyridine derivative via a maleamic bond ($-\text{NH}-\text{CO}-$). The structure of compound (**27**) was inferred from



Scheme 6.

analytical and spectral analyses. IR spectrum of compound (27) exhibited strong absorption bands at 1634, 1719, 2209, 3217, 3347 and 3445 attributable to $\nu_{C=O}$ (amide), $\nu_{C=O}$ (carboxyl), $\nu_{C\equiv N}$, ν_{NH} and ν_{OH} respectively.

Interaction of the compound (27) with malononitrile in the presence of piperidine afforded 2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-chloro-3-methylphenyl)-3-cyano-pyridine-4-carboxylic acid (28). IR spectrum of compound (28) revealed strong absorption bands at 1629, 1719, 2207, 3220, 3372 and 3447 due to $\nu_{C=N}$, $\nu_{C=O}$, $\nu_{C\equiv N}$ and ν_{NH} and/or ν_{OH} respectively. The reaction takes place via Michael addition to the α,β -unsaturated acid moiety followed by ring closure to give the desired product (28).

When compound (27) was allowed to react with acetylacetone in the presence of piperidine as catalyst it yielded 2-[4-acetyl-3-(carboxymethyl)-5-methylfuran-2-ylamino]-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (29). The IR spectrum of (29) revealed strong absorption bands at 1631, 1720, 2210, 3213, 3347 and 3448 attributable to $\nu_{C=N}$, $\nu_{C=O}$, $\nu_{C\equiv N}$, ν_{NH} , and ν_{OH}

respectively. The ¹H NMR spectrum exhibited absorption signals correlated with the (CH₃), (COCH₃) and (CH₂COOH) protons. EI-MS exhibited m/z 423 (M⁺ - CO₂).

Refluxing compound (27) with malononitrile in the presence of ammonium acetate yielded 2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-chloro-3-methylphenyl)-3-cyanopyridine-4-carboxylic acid (30). The reaction takes place via Michael addition followed by ring closure to give the desired product. Structure of compound (30) was inferred from microanalytical and spectral data. Its IR spectrum revealed strong absorption bands at 1632, 1720, 2210, 3217, 3354 and 3451 attributable to $\nu_{C=N}$, $\nu_{C=O}$, $\nu_{C\equiv N}$, ν_{NH} and/or ν_{OH} respectively.

The ¹H NMR spectrum showed exchangeable (NH₂) as well as singlet consistent with protons of methylene group of (CH₂COOH).

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