
Utility of 4-(4-acetoaminophenyl)-4-oxo-but-2-enoic acid to prepare Pyran and Pyridine derivatives as building blocks in Heterocyclic Synthesis

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Utilidad del ácido 4-(4-acetoaminofenil)-4-oxo-but-2-enoico en la preparación de derivados de Pirano y Piridina como unidades estructurales para la Síntesis de Heterociclos

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RESUMEN

El presente trabajo está dedicado al estudio de la interacción del derivado del ácido β -aróil acrílico (1) con malononitrilo en presencia de piperidina y/o acetato de amonio, y el uso de los compuestos formados como materias primas en la síntesis de sistemas heterocíclicos condensados o aislados. Se ha establecido que el ácido β -aróilacrilico (1) reacciona con malononitrilo en DMF en presencia de piperidina como catalizador formando el derivado 4H-piránico (2). Cambiando el catalizador por acetato de amonio, se obtiene el derivado de piridina (3). Cuando se hizo reaccionar el compuesto (2) con trietilortoformato se obtiene etoximetilenamino-4H-pirano (4). El compuesto (4) se utilizó como producto de partida clave en la síntesis de algunos sistemas anulares y heterocíclicos interesantes (5-8). Del mismo modo, los derivados del ácido maleámico (9) y (15) se han sintetizado vía interacción de (2) y (3) con anhídrido maléico para estudiar el comportamiento de los derivados del ácido maleámico como análogos del ácido β -aróilacrilico en la obtención de compuestos con metileno activos en la reacción de adición de Michael (10-14); (16-18).

Palabras clave: ácido β -aróilacrilico, adición de Michael, 2-aminopirano, 2-aminopiridina, pirimidina y ácido maleámico.

SUMMARY

The present work is devoted to study the interaction of β -aroylacrylic acid derivative (1) with malononitrile in the presence of piperidine and/or ammonium acetate, then using the formed compounds as a starting material for synthesizing fused and isolated heterocyclic system. It has been established that the β -aroylacrylic acid (1) react with malononitrile in (DMF) in the presence of piperidine

as catalyst with formation of 4H-pyran derivative (2). By changing the catalyst into ammonium acetate, pyridine derivative (3) has been obtained. When compound (2) was allowed to react with triethylorthoformate afforded ethoxymethyleneamino-4H-pyran (4). Compound (4) was used as key starting material for synthesizing some interesting annulated and heterocyclic systems (5-8). Also, the maleamic acid derivatives (9) and (15) have been synthesized via the interaction of (2) and (3) with maleic anhydride to study the behavior of the formed maleamic acid derivatives as analogies of β -aroylacrylic towards different active methylene compounds under Michael addition reaction (10-14); (16-18).

Keywords: β -aroylacrylic acid, Michael addition, 2-aminopyran, 2-aminopyridine, pyrimidine and maleamic acid

RESUM

Aquest treball està dedicat a l'estudi de la interacció del derivat de l'àcid β -aróilacrilic (1) amb malononitril en presència de piperidina i/o acetat d'amoni, i l'ús dels productes formats com a matèries primeres en la síntesi de sistemes heterocíclics condensats o aïllats. S'ha establert que l'àcid β -aróilacrilic (1) reacciona amb malononitril en DMF en presència de piperidina com a catalitzador formant el derivat 4H-pirànic (2). Canviant el catalitzador per acetat d'amoni, s'obté el derivat de piridina (3). Quan es va fer reaccionar el producte (2) amb trietilortoformat s'obté etoximetilenamino-4H-pirà (4). El producte (4) es va utilitzar com a producte de partida clau en la síntesi d'alguns sistemes anulars i heterocíclics interessants (5-8). De la mateixa manera, els derivats de l'àcid maleàmic (9) i (15) s'han sintetitzat via interacció de (2) i (3) amb anhídrid maléic per estudiar el comportament dels derivats

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de l'àcid maleàmic com a anàlegs de l'àcid β -aroilacrílic en l'obtenció de compostos amb metilens actius en la reacció d'addició de Michael (10-14); (16-18).

Paraules clau: àcid β -aroilacrílic, addició de Michael, 2-aminopirà, 2-aminopiridina, pirimidina i àcid maleàmic.

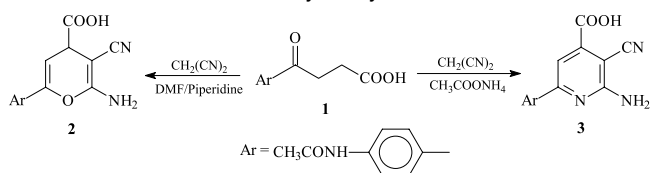
INTRODUCTION

The author aimed through this work to study the behavior of acid (1) towards some containing active methylene compounds. Also pyran and fused 4H-pyran derivatives have attracted a great deal of interest owing to their antimicrobial activity,^{1,2,3} inhibition of influenza, virus sialidases,⁴ mutagenic activity as antiviral,⁵ antiproliferation agents,⁶ sex pheromones activity,^{7,8} antitumor⁹ and anti-inflammatory agent.¹⁰ Moreover, pyran derivatives are well known for their antihistaminic activity.¹¹

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 in agrochemical and veterinary products¹²⁻¹⁵. This current pharmacological importance has stimulated our interest to synthesize several new and biologically active derivatives of these heterocyclic systems.

RESULT AND DISCUSSION

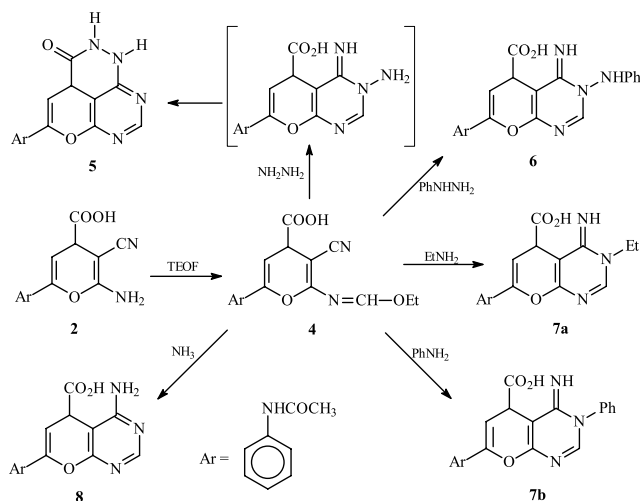
The interaction of 4-(4-acetoaminophenyl)-4-oxo-but-2-enoic acid (1) with malononitrile in dimethylformamide (DMF) in the presence of piperidine as catalyst afforded 2-amino-6-(4-acetoaminophenyl)-3-cyano-4H-pyran-4-carboxylic acid (2). On the other hand, when the reaction was subjected in the presence of ammonium acetate as catalyst yielded 2-amino-6-(4-acetoaminophenyl)-3-cyano-4H-pyridine-4-carboxylic acid (3). Both 2 and 3 were used as pre key starting material for synthesis of both fused and isolated heterocyclic system.



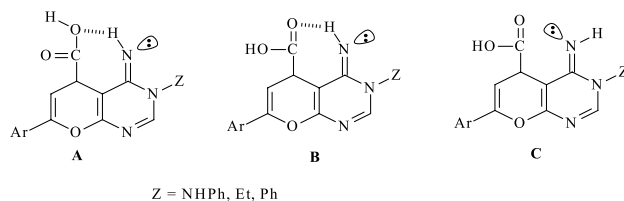
The EIMS of compound 2 exhibits $m/e = 298$ (M^+ , intensity 33%). EIMS of compound 3 exhibits $m/e = 296$ (M^+ , intensity 32%). The reaction takes place via nucleophilic addition of the carbanion derived from the malononitrile to the α,β -unsaturated carbonyl moiety in the acid 1 followed by cyclisation in case of 2 and ring closure and dehydration in case of 3. Refluxing of 2 with neat triethylorthoformate afforded 6-(4-acetoaminophenyl)-3-cyano-ethoxymethylene-amino-4H-pyran-4-carboxylic acid (4). Compound 4 was used as key starting material for synthesizing some interesting annulated and heterocyclic systems.

Interaction of compound 4 with hydrazine hydrate in boiling ethanol yielded 5-(4-acetoaminophenyl)-1,2,3-trihydro-6-oxo-1,2,7,9-tetra-azaphenalen-3-one (5) without isolation of imino derivative.¹⁶ This could be explained the formation of imino derivative first, which in the presence of

a base (hydrazine hydrate) underwent a Dimorth rearrangement to give the thermodynamically more stable hydrazine derivative, which underwent ring closure and yielded the desired product. EIMS of compound 5 exhibits $m/e = 322$ (M^+). Refluxing an ethanolic solution of 4 with phenylhydrazine yielded the corresponding 7-(4-acetoaminophenyl)-4-imino-3-phenylamino-4-hydro-5H-pyrano[2,3-d]pyrimidine-5-carboxylic acid (6). EIMS of compound 6 showed $m/e = 416$ (M^+). The reaction involves nucleophilic substitution on the carbon atom of methyldene moiety followed by ring closure. When compound 4 was submitted to react with primary amines namely, ethylamine and aniline led to the formation of 7-(4-acetoaminophenyl)-3-ethyl-4-imino-4-hydro-5H-pyrano[2,3-d]pyrimidine-5-carboxylic acid (7a) and/or 7-(4-acetoaminophenyl)-3-phenyl-4-imino-4-hydro-5H-pyrano[2,3-d]pyrimidine-5-carboxylic acid (7b). Ammonolysis of compound 4 gave 4-amino-7-(4-acetoaminophenyl)-5H-pyrano[2,3-d]pyrimidine-5-carboxylic acid (8). EIMS of compound 8 showed $m/e = 326$ (M^+). Also, the structure of compound 8 was established by an independent synthesis from the interaction of compound 2 with formamide. The reaction involved nucleophilic substitution on the unsaturated carbon atom followed by ring closure to afford the desired product 8.



The reaction products of compound 4 with phenyl hydrazine, ethyl amine and aniline can exist in one of three conformation A, B or C, both A and B are stabilized via hydrogen bond formation, so they are more stable than C, in case A hydrogen bond is formed by using one lone pair of electrons on the oxygen of hydroxyl group (OH, sp^3), while in case B the formed hydrogen bond will use lone pair on the oxygen of carbonyl moiety ($C=O$, sp^2), so hydrogen bond in case A is stronger than B.

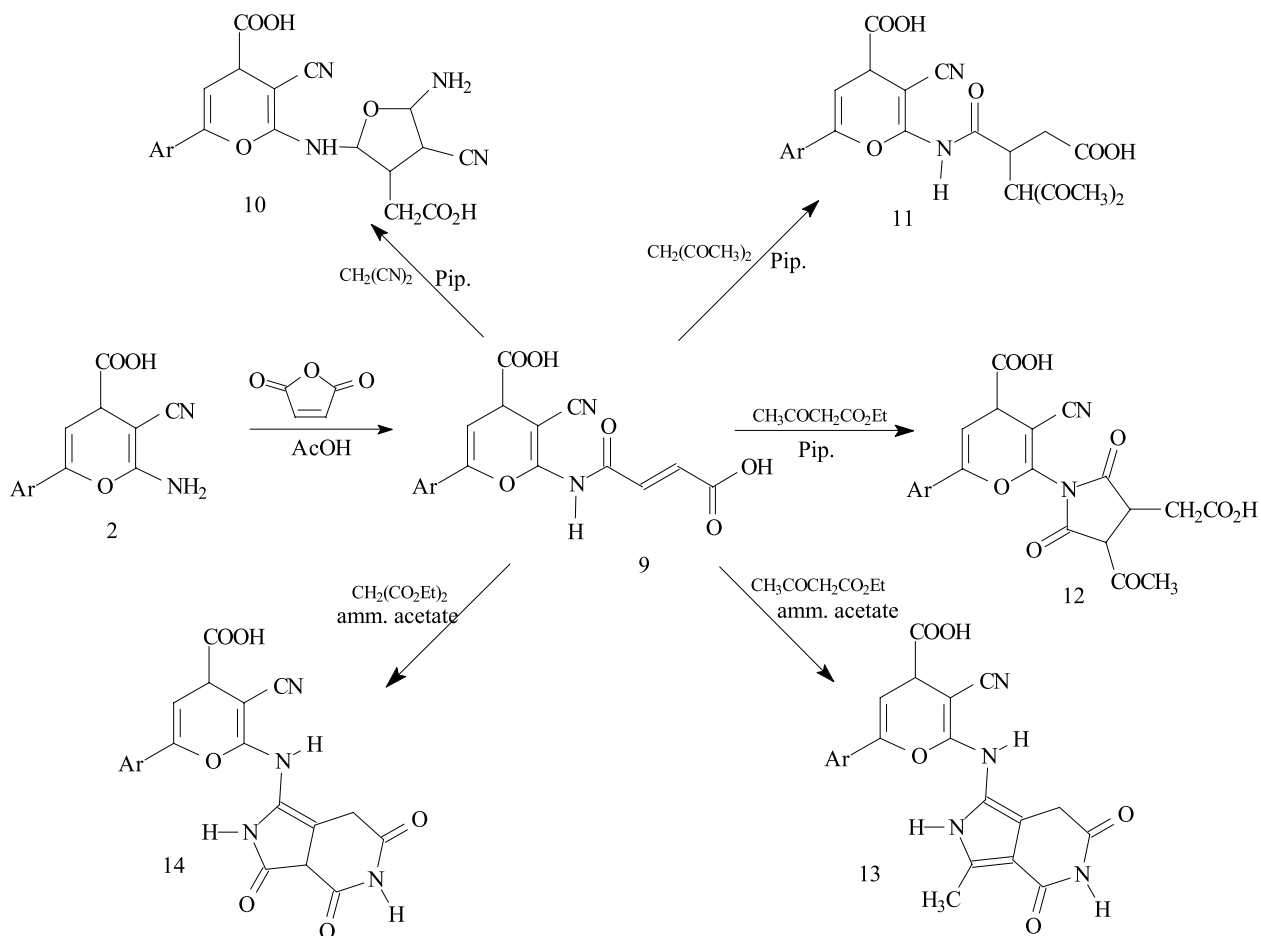


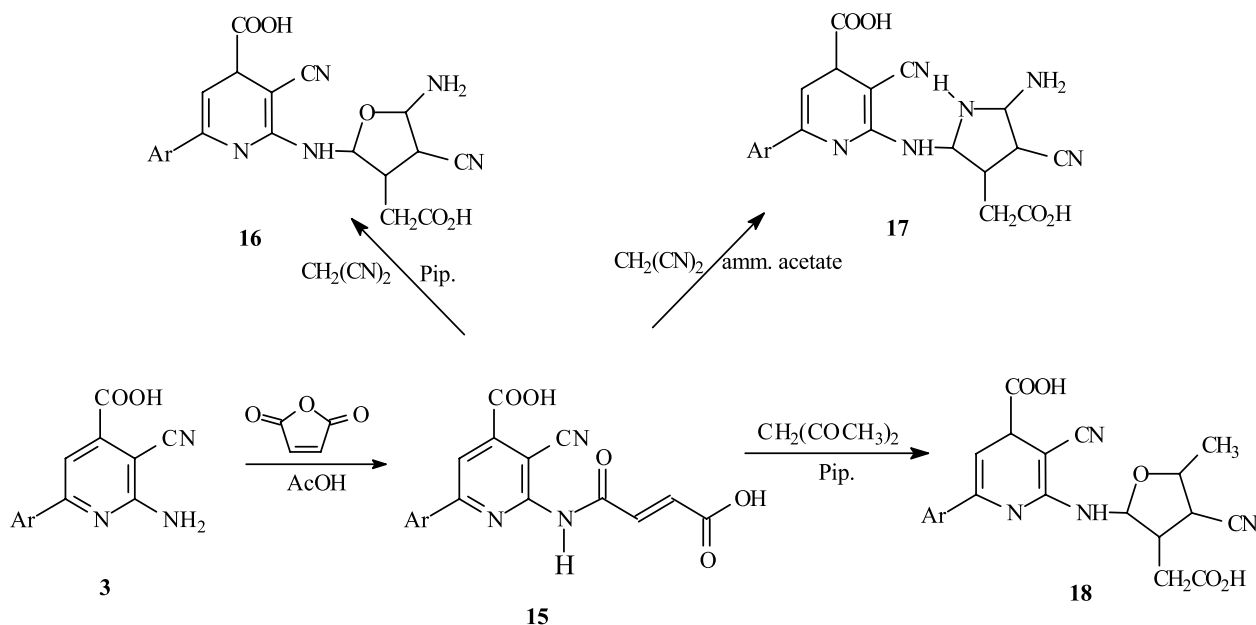
The N-cyclic maleamic acid¹⁷⁻¹⁹ (9) has been synthesized via interaction of compound 2 in refluxing acetic acid with maleic anhydride. The N-cyclic maleamic acid is constructed such that due to the ring-cleaved structure of

maleic anhydride ($-\text{COCH}=\text{CHCOOH}$) that bonded to the amino group (NH_2) of the starting N-cyclic amine via a maleamic bond ($-\text{NH}-\text{CO}-$). EIMS of compound **9** showed $m/e = 384$ (M^+).

In this investigation the author sought to investigate the behavior of maleamic acid derivative **9** 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 compounds. When maleamic acid derivative **9** was allowed to react with malononitrile in the presence of few drops of piperidine as a catalyst it yielded 2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-acetoaminophenyl)-3-cyano-4H-pyran-4-carboxylic acid (**10**). Compound **10** was obtained from Michael addition reaction (via α,β -unsaturated acid rather than α,β -unsaturated amide). EIMS of compound **10** showed $m/e = 463$ corresponding to (M^+). Interaction of maleamic acid derivatives **9** with acetyl acetone in the presence of piperidine as catalyst it yielded the Michael adduct 2-[3-acetyl-2-(carboxymethyl)-4-oxopentanamido]-6-(-acetoamino phenyl)-3-cyano-4H-pyran-4-carboxylic acid (**11**). Maleamic acid derivative **9** react with acetyl acetone under Michael reaction condition as α,β -unsaturated acid rather than α,β -unsaturated amide, this is due to the polarization by the carbonyl group of the carboxyl outweighs the po-

larization by the carbonyl of amide group, and the carbanion derivative from acetyl acetone is more bulky [we need more work on the bifunctional substrate to make the results more clear]. Interaction of the maleamic acid 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-acetoaminophenyl)-3-cyano-4H-pyran-4-carboxylic acid (**12**). The EIMS of compound **12** showed $m/e = 480$ (M^+) such spectral data consistent with the proposed structure. By changing the catalyst into ammonium acetate, maleamic acid derivative **9** interacted with ethyl acetoacetate and yielded the 6-(4-acetoaminophenyl)-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 (**13**). The reaction takes place via Michael addition reaction to α,β -unsaturated acid moiety followed by enolisation and amination with ring closure to afford the desired product. Refluxing maleamic acid derivative **9** with diethyl malonate in DMF in the presence of ammonium acetate afforded 6-(4-acetoaminophenyl)-3-cyano-2-[3,4,6-trioxo-3,3a,4,5,6,7-hexahydro-2H-pyrrolo[3,4-c]pyridine-1-ylamino]-4H-pyran-4-carboxylic acid (**14**). The reaction takes place via Michael addition reaction followed by amination and ring closure to give the desired product.





On the lights of the previous results, further investigation at the same reaction types was carried out on N-cyclic maleamic acid derivative **15**, which has been synthesized via the interaction of compound **3** in acetic acid with maleic anhydride. Interaction of the compound **15** with malononitrile in the presence of piperidine as catalyst afforded 2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-acetoaminophenyl)-3-cyano-pyridine-4-carboxylic acid **16**. On the other hand, refluxing compound **15** with malononitrile in the presence of ammonium acetate yielded 2-[5-amino-3-(carboxymethyl)-4-cyano-1H-pyrrolo-2-yl-amino]-6-(4-acetoaminophenyl)-3-cyano pyridine-4-carboxylic acid (**17**). The reaction takes place via Michael addition reaction to α,β -unsaturated acid moiety followed by ring closure to give the desired product. When compound **15** was allowed to react with acetyl acetone in presence of piperidine as catalyst it yielded 2-[4-acetyl-3-(carboxymethyl)-5-methylfuran-2-ylamino]-6-(4-acetoaminophenyl)-3-cyanopyridine-4-carboxylic acid (**18**). EIMS of compound **18** showed $m/e = 475$ corresponding to (M^+).

EXPERIMENTAL

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. Mass spectra were recorded on Shomadzu GC-MS (QP-1000EX) instrument operating at 70eV. Homogeneity of all compounds synthesized was checked by TLC.

6-(4-acetoaminophenyl)-2-amino-3-cyano-4H-pyran-4-carboxylic acid (**2**) and 6-(4-acetoaminophenyl)-2-amino-3-cyano-4H-pyridine-4-carboxylic acid (**3**)

To solution of 4-(4-acetaminophenyl)-4-oxobut-2-enoic acid (**1**) (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 2 hrs. The reaction mixture was allowed to cool at room temperature then poured into water (100 ml). The precipitate formed was filtered off

and washed with water, then dried and crystallized from the proper solvent to give 4H-Pyran derivative and/or pyridine derivative respectively. Compound **2** crystallized from EtOH/ H_2O as orange crystals; m.p. 170°C Elemental analysis for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_4$ (299.29): Calcd: C, 60.2; H, 4.38; N, 14.04. Found: C, 60.35; H, 4.43; N, 14.18. IR (KBr) ν_{max} (cm^{-1}): 1640, 1700, 2211, 2862, 2937, 3187 and 3317 cm^{-1} due to $\nu_{\text{C=O}}$, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} groups, respectively. Compound **3** crystallized from EtOH/ H_2O as pale yellow crystals; m.p. 180°C Elemental analysis for $\text{C}_{15}\text{H}_{12}\text{N}_4\text{O}_3$ (296.29): Calcd: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.95; H, 4.43; N, 18.99. IR (KBr) ν_{max} (cm^{-1}): 1634, 1672, 1728, 2213, 2928, 3113, 3384 and 3443 cm^{-1} due to $\nu_{\text{C=O}}$, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} groups, respectively.

6-(4-acetoaminophenyl)-3-cyano-2-ethoxy methyleneamino-4H-pyran-4-carboxylic acid (**4**)

4H-Pyran derivative (1.00 g, 3.4 mmol) in triethylorthoformate (10 ml) was stirred under reflux for 5 hrs. The reaction mixture was concentrated and the obtained brown precipitate was crystallized from ethanol/water to afford ethoxymethyleneamino-4H-pyran as white crystals; m.p. 195°C . Elemental analysis for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_5$ (355.35): Calcd: C, 60.84; H, 4.82; N, 11.82. Found: C, 60.95; H, 4.93; N, 11.94. IR (KBr) ν_{max} (cm^{-1}): 1640, 1680, 2208, 2863, 2936, 3310 cm^{-1} attributable to $\nu_{\text{C=O}}$, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} groups, respectively.

5-(4-acetoaminophenyl)-1,2,3-trihydro-6-oxo-1,2,7,9-tetraazaphenalen-3-one (**5**) and 7-(4-acetoaminophenyl)-4-imino-3-phenylamino-3,5-dihydro-4H-pyrano[2,3-d]pyrimidine-5-carboxylic acid (**6**)

A mixture of ethoxymethyleneamino-4H-pyran (**4**) (3.00 g, 8.70 mmol) and hydrazine hydrate (0.30 ml, 8.70 mmol) or phenylhydrazine (0.85 ml, 8.70 mmol) in absolute ethanol (30 ml) was refluxed for 7 hrs. 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 (**5**) and/or (**6**). Compound **5** crystallized from EtOH/ H_2O as white crystals; m.p. 225°C Elemental analysis for $\text{C}_{16}\text{H}_{12}\text{N}_5\text{O}_3$ (322.31): Calcd: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.54; H, 4.21; N, 21.74. IR

(KBr) $\nu_{\max}$ (cm^{-1}): 1660, 3400 cm^{-1} (broad) attributable to $\nu_{\text{C=O}}$, ν_{NH} , and devoid any band for ν_{CN} . EIMS exhibits $m/e = 322$ (M^+). Compound **6** crystallized from EtOH/ H_2O as white crystals; m.p. 150°C. Elemental analysis for $\text{C}_{22}\text{H}_{19}\text{N}_5\text{O}_4$ (417.43): Calcd: C, 63.3; H, 4.59; N, 16.78. Found: C, 63.45; H, 4.62; N, 16.89. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1631, 1693, 2937, 3100, 3400 cm^{-1} attributable to $\nu_{\text{C=O}}$, ν_{CH} , ν_{NH} and ν_{OH} groups, respectively. EIMS showed $m/e = 416$ (M^+).

7-(4-acetoaminophenyl)-3-ethyl-4-imino-3,5-dihydro-4H-pyrano[2,3-d]pyrimidine-5-carboxylic acid (7a) and/or 7-(4-acetoaminophenyl)-3-phenyl-4-imino-3,5-dihydro-4H-pyrano [2,3-d]pyrimidine-5-carboxylic acid (7b)

A mixture of ethoxymethyleneamino-4H-pyran (**4**) (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 5 hrs. 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 (**7a**) and/or (**7b**). Compound **7a** crystallized from EtOH/ H_2O as white crystals; m.p. 132°C. Elemental analysis for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{O}_4$ (354.37): Calcd: C, 61.01; H, 5.12; N, 15.81. Found: C, 61.21; H, 5.23; N, 15.94. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1630-1642, 1694-1695, 2937, 3282-3285, 3340-3360 attributable to $\nu_{\text{C=O}}$, ν_{CH} , ν_{NH} and ν_{OH} groups, respectively. Compound **7b** crystallized from EtOH/ H_2O as white crystals; m.p. 150°C. Elemental analysis for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_4$ (402.43): Calcd: C, 65.67; H, 4.51; N, 13.92. Found: C, 65.84; H, 4.62; N, 13.99. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1631-1641, 1695-1696, 2936, 3280-3286, 3340-3360 attributable to $\nu_{\text{C=O}}$, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} groups, respectively.

7-(4-acetoaminophenyl)-4-amino-5H-pyrano[2,3-d]pyrimidine-5-carboxylic acid 8

To a solution of ethoxymethyleneamino-4H-pyran (**4**) (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 2 hrs. After cooling, the reaction mixture was acidified with diluted solution of cold HCl, the precipitate formed was filtered off and washed with water, dried then crystallized from EtOH as white crystals; m.p. 140°C to afford the aminopyranopyrimidine (**8**). Elemental analysis for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_4$ (326): Calcd: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.94; H, 4.45; N, 17.28. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1638, 1690, 2925, 3200, 3400 attributable to $\nu_{\text{C=O}}$, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} groups, respectively. EIMS showed $m/e = 326$ (M^+).

4-[6-acetoamino-3-cyano-4-hydro-4-carboxy-pyran-2-yl] amino-4-oxobut-2-enoic acid (9)

Maleic anhydride (0.33 g, 3.4 mmol) was completely dissolved at room temperature in glacial acetic acid (30 ml), and then 4H-pyran derivative (**2**) (1.00 g, 3.4 mmol) was added to the solution; the resulting mixture was stirred under reflux for 1 hr. 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 MeOH as white crystals; m.p. 230°C to afford N-cyclic maleamic acid (**9**). Elemental analysis for $\text{C}_{19}\text{H}_{15}\text{N}_3\text{O}_7$ (397.35): Calcd: C, 57.43; H, 3.81; N, 10.58. Found: C, 57.52; H, 3.93; N, 10.64. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1635, 1695, 2210, 2862, 2936, 3110 and 3430

cm^{-1} attributable to $\nu_{\max}$ of amide and carbonyl group, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} , respectively. EIMS showed $m/e = 397$ (M^+).

2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-aceto aminophenyl)-3-cyano-4H-pyran-4-carboxylic acid (10)

To a solution of maleamic acid (**9**) (2.00 g, 5.15 mmol) and malononitrile (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 hrs. 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, crystallized from EtOH/ H_2O as white crystals; m.p. 190°C. Elemental analysis for $\text{C}_{22}\text{H}_{21}\text{N}_5\text{O}_7$ (467.42): Calcd: C, 56.53; H, 4.53; N, 14.98. Found: C, 56.99; H, 4.48; N, 15.21. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1631, 1697, 2211, 2864, 2938, 3284, 3300, 3400 cm^{-1} attributable to $\nu_{\max}$ of two carbonyl groups, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} , respectively. EIMS showed $m/e = 467$ corresponding to (M^+).

2-[3-acetyl-2-(carboxymethyl)-4-oxopentanamido]-6-(4-acetoaminophenyl)-3-cyano-4H-pyran-4-carboxylic acid (11)

To a solution of maleamic acid (**9**) (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 hrs. 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 MeOH/ H_2O as white crystals; m.p. 155°C. Elemental analysis for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_9$ (497.47): Calcd: C, 57.95; H, 4.66; N, 8.45. Found: C, 58.05; H, 4.76; N, 8.65. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1642, 1691, 2210, 2863, 2936, 3183, 3313 cm^{-1} attributable to $\nu_{\text{C=O}}$, ν_{CN} , ν_{CH} , ν_{NH} and ν_{OH} , respectively.

2-[(3-acetyl-4-carboxymethyl)-2,5-dioxopyrrolidin-1-yl]-6-(4-acetoaminophenyl)-3-cyano-4H-pyran-4-carboxylic acid (12)

A mixture of maleamic acid (**9**) (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 hrs. 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 (**12**) as white crystals; m.p. 180°C. Elemental analysis for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}_9$ (481.42): Calcd: C, 57.38; H, 3.98; N, 8.73. Found: C, 57.54; H, 4.06; N, 8.94. IR (KBr) $\nu_{\max}$ (cm^{-1}): 1631, 1697, 2210, 2864, 2938, 3283, 3400 cm^{-1} attributable to $\nu_{\text{C=O}}$, $\nu_{\text{C=N}}$, ν_{CH} , ν_{NH} and/or ν_{OH} respectively. EIMS showed $m/e = 481$ (M^+).

6-(4-acetoaminophenyl)-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 (13)

A mixture of maleamic acid (**9**) (2.00 g, 5.15 mmol) and ethyl acetoacetate (0.65 ml, 5.15 mmol) in dioxan (20 ml) in the presence of ammonium acetate was refluxed at 60°C for 10 hrs. The reaction mixture was allowed to cool at room temperature then poured into diluted solution of ace-

tic acid (200 ml). The solid formed was filtered off, washed with water, dried and crystallized from EtOH/H₂O as white crystals; m.p. 198°C. Elemental analysis for C₂₃H₁₉N₅O₆ (461.44): Calcd: C, 59.87; H, 4.15; N, 15.18. Found: C, 59.99; H, 4.31; N, 15.22. IR (KBr) $\nu_{\max}$ (cm⁻¹): 1644, 1695, 2205, 2864, 3280, 3421 cm⁻¹ attributable to $\nu_{\text{C=O}}$, ν_{CN} , ν_{NH} and ν_{OH} , respectively.

6-acetoaminophenyl-3-cyano-2-[3,4,6-trioxo-3,3a,4,5,6,7-hexahydro-2H-pyrrolo[3,4-c]pyridine-1-ylamino-4H-pyran-4-carboxylic acid (14)

A mixture of maleamic acid (**9**) (2.00 g, 5.15 mmol) and diethyl malonate (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 hrs. The reaction mixture was allowed to cool to 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 EtOH/H₂O as white crystals; m.p. 210°C. Elemental analysis for C₂₂H₁₇N₅O₇ (463.41): Calcd: C, 57.02; H, 3.7; N, 15.11. Found: C, 57.15; H, 3.85; N, 15.25. IR (KBr) $\nu_{\max}$ (cm⁻¹): 1632, 1695, 2210, 2863, 2937, 3186, 3315 and 3428 cm⁻¹ attributable to $\nu_{\max}$ of carbonyl groups, ν_{CN} , ν_{NH} , and ν_{OH} respectively.

4-[6-acetoamino-3-cyano-4-hydro-4-carboxy-pyridin-2-yl]amino-4-oxo-but-2-enoic acid (15)

Maleic anhydride (0.33 gm, 3.4 mmol) was completely dissolved at room temperature in glacial acetic acid or THF (30 ml), and then pyridine derivative (**3**) (1.00 g, 3.4 mmol) was added to the solution; the resulting mixture was stirred under reflux for 1 hr. The reaction mixture was allowed to cool to room temperature, and then poured into water (500 ml), the precipitate formed was filtered off, washed with water, dried and crystallized from MeOH/H₂O as white crystals; m.p. 240°C. Elemental analysis for C₁₉H₁₄N₄O₆ (394.23): Calcd: C, 57.87; H, 3.58; N, 14.21. Found: C, 57.98; H, 3.67; N, 14.41. IR (KBr) $\nu_{\max}$ (cm⁻¹): 1634, 1690, 1725, 2211, 3280, 3384, 3453 cm⁻¹ attributable to $\nu_{\max}$ of carbonyl groups, ν_{CN} , ν_{NH} , and ν_{OH} , respectively.

2-[5-amino-3-(carboxymethyl)-4-cyanofuran-2-ylamino]-6-(4-acetoamino-phenyl)-3-cyano-pyridine-4-carboxylic acid (16)

To a solution of N-cyclic maleamic acid (**15**) (2.00 g, 5.19 mmol) and malononitrile (0.34 g, 5.19 mmole) in DMF (15 ml) few drops of piperidine was added, the resulting mixture was refluxed at 60°C for 5 hrs. The reaction mixture was allowed to cool to room temperature then acidified with diluted acetic acid (200 ml), the solid formed was filtered off, washed with water, dried and crystallized from EtOH/H₂O as white crystals; m.p. 200°C. Elemental analysis for C₂₂H₂₂N₆O₆ (466.41): Calcd: C, 56.65; H, 4.75; N, 18.02. Found: C, 57.18; H, 4.61; N, 18.34. IR (KBr) $\nu_{\max}$ (cm⁻¹): 1634, 1690, 1725, 2211, 3280, 3384, 3453 cm⁻¹ attributable to $\nu_{\max}$ of carbonyl groups, ν_{CN} , ν_{NH} , and ν_{OH} , respectively.

2-[5-amino-3-(carboxymethyl)-4-cyano-1H-pyrrolo-2-yl-amino]-6-(4-acetoamino-phenyl)-3-cyanopyridine-4-carboxylic acid (17)

To a solution of N-cyclic maleamic acid (**15**) (2.00 g, 5.19 mmol) and malononitrile (0.34 g, 5.19 mmole) in DMF (15 ml) in the presence of ammonium acetate was added, the resulting mixture was refluxed at 60°C for 5 hrs. The reaction mixture was allowed to cool to room temperature then

acidified with diluted acetic acid (200 ml), the solid formed was filtered off, washed with water, dried and crystallized from EtOH/H₂O as white crystals; m.p. 210°C. Elemental analysis for C₂₂H₂₃N₇O₅ (465.46): Calcd: C, 56.77; H, 4.98; N, 21.66. Found: C, 57.21; H, 4.81; N, 21.54. IR (KBr) $\nu_{\max}$ (cm⁻¹): 1635, 1690, 1725, 2213, 2926, 3200, 3448 cm⁻¹ due to $\nu_{\max}$ of carbonyl groups, ν_{CN} , ν_{CH} , ν_{NH} and/or ν_{OH} , respectively. EIMS showed m/e = 465 corresponding to (M⁺).

2-[4-acetyl-3-(carboxymethyl)-5-methylfuran-2-ylamino]-6-(4-aceto-aminophenyl)-3-cyanopyridine-4-carboxylic acid (18)

A mixture of N-cyclic maleamic acid (**15**) (2.00g, 5.19 mmole) and acetylacetone (0.53 ml, 5.19 mmole) in DMF (20 ml) in the presence of piperidine was refluxed at 60°C for 3 hrs. The reaction mixture was allowed to cool to 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 EtOH/H₂O as white crystals; m.p. 220°C. Elemental analysis for C₂₄H₂₆N₄O₇ (482.48): Calcd: C, 59.74; H, 5.43; N, 11.61. Found: C, 60.04; H, 5.23; N, 11.94. IR (KBr) $\nu_{\max}$ (cm⁻¹): 1635, 1690, 1725, 2213, 2926, 3200, 3448 cm⁻¹ due to $\nu_{\max}$ of carbonyl groups, ν_{CN} , ν_{CH} , ν_{NH} and/or ν_{OH} , respectively. EIMS showed m/e = 482 corresponding to (M⁺).

BIBLIOGRAPHY

1. Bedair, A. H; El-Hady, N. A; Abd-Ellatif, M. S; Fakery, A. H; El-Agrody, A. M. *Farmaco* **2000**, 55, 708.
2. El-Agrody, A. M; El-Hakim, M. H; Abd-Ellatif, M. S; Fakery, A. H; El-Sayed, E. M; El-Ghareab, K. A. *Acetapharm.* **2000**, 50, 111.
3. El-Agrody, A. M; Abd-Ellatif, M. S; El-Hady, N. A; Fakery, A. H; Bedair, A. H. *Molecules* **2001**, 6, 519.
4. Taylor, R. N; Cleasby, A; Singh, D; Skarzynski, T. J. *Med. Chem.* **1988**, 41, 798.
5. Marteniz, A. G; Marco, L. J. *Bioorg. Med. Chem. Lett.* **1997**, 7, 3165.
6. Cromwell, N. H; Cook, K. E. *J. Org. Chem.* **1958**, 23, 1327.
7. Bianehi, G; Tava, A. *Agric. Biol. Chem.* **1987**, 51, 2001.
8. Hiramoto, K; Nasuhara, A; Michiloshi, K; Kato, T; Kikugawa, K. *Mutation Res.* **1997**, 395, 47.
9. Eiden, F; Denk, F; *Arch. Pharm.* **1991**, 324, 353.
10. Shishoo, C. J; Devani, M. B; Ullas, G. V; Ananthan, S; Bahadit, V. S. J. *Heterocycl. Chem.* **1981**, 18, 43.
11. Noda, K; Nakagawa, A; Nakajima, Y; Ide, H. *Japan. Kokai* 7,785,194. **1977**; C.A. **1978**, 88, 509089.
12. Brown, D. J; *Comprehensive Heterocyclic Chemistry*; A. R. Katrizky and C. W. Rees, Eds.; Vol 3 , Pergamon Press; Oxford **1984** ; P 443.
13. Matolcsy, G. *World Rev Pestic. Contr.* **1971**, 10, 50; C.A. **1972**, 76, 820315.
14. Pershin, G. N; Sherbakova, L. I; Zykova, T. N; Sokolova, V. N. *Farmakol. Toksikol. (Moscow)* **1972**, 35, 466.
15. Prikazchikova, L. P; Khutova, B. M; Vladimirtsev, I. F; Boldyrev, I. V; Zhuravskaya, N. I. *Fiziol. Akt. Veshchestva* **1975**, 7, 84; *Ref. Chem. Abstr.* **1975**, 127346m.
16. Glu, M. S; Ergün, B. C; Ünlü, S; Şhin, M. F; Kupel, E.; Lada, E. Y and Banoglu, E., *Arch. Pharm. Res.*, **2005**, 28, 5, 509.
17. El-Hashash, M. A; El-Sawy A. A; Eissa A. M. F and Sallam, M. S, *Journal of the Korean Chemical Society* **2009**, 53, 308.
18. Rich, D. H, Gesellchen, P. D, Tong, A, Cheung, Al; Buckner, C. K, *J. Med. Chem.* **1975**, 18, 1004.
19. Bhatti, M. H; Ali, S; Huma, F; Shahzadi, S. *Turk. J. Chem.* **2005**, 29, 463.