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Efficient Synthesis of Novel Coumarin Derivatives Containing Pyridine Moiety with Expected Biological Activity.

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Abstract: The 2-acetyl-3H-benzo[f]chromen-3-one 1 was used as a key intermediates for the synthesis of 3-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl) - but-2-enenitrile derivatives 3a-d. *via* condensation reactions with activated nitiles derivatives in presence ammonium acetate. Moreover the 3a-d undergoes interamolecular cyclization to form 3-alkyl-2-amino-4-methyl-5-oxo-5H-benzo [5, 6]chromeno[4,3-b]pyridine 4a-d. Otherwise 1 reacts with acetophenone and cyclohexanone in presence of cyanoacetamide to afford the benzo[5,6]chromeno[3,4-c]pyridin-5-one derivatives 5 and 6, respectively.

Also, 4-aryl-6-[benzo[h]coumarin-3-yl]-3-cyano-2-pyridone derivatives 8a-d were prepared by an efficient and convenient method by the one-pot reaction of 1 with aromatic aldehydes 7a-d and malononitrile, in the presence of sodium hydroxide under solvent free condition. This method has the advantages, mild reaction conditions, easy workup, and inexpensive reagents. Moreover, 2-(4,6-diphenylpyridin-2-yl)-3H-benzo[f]chromen-3-one 11 was prepared via reaction of α-pyrdinium salt of methyl ketone of 1 with benzalacetophenone in presence of ammonium acetate. The structures of the synthesized compounds were confirmed by spectral data and elemental analyses. Compounds were tested for *in vitro* cytotoxicity against heptacelluar carcinoma (HepG2) and breast cancer (MCF-7) in addition to antibacterial.

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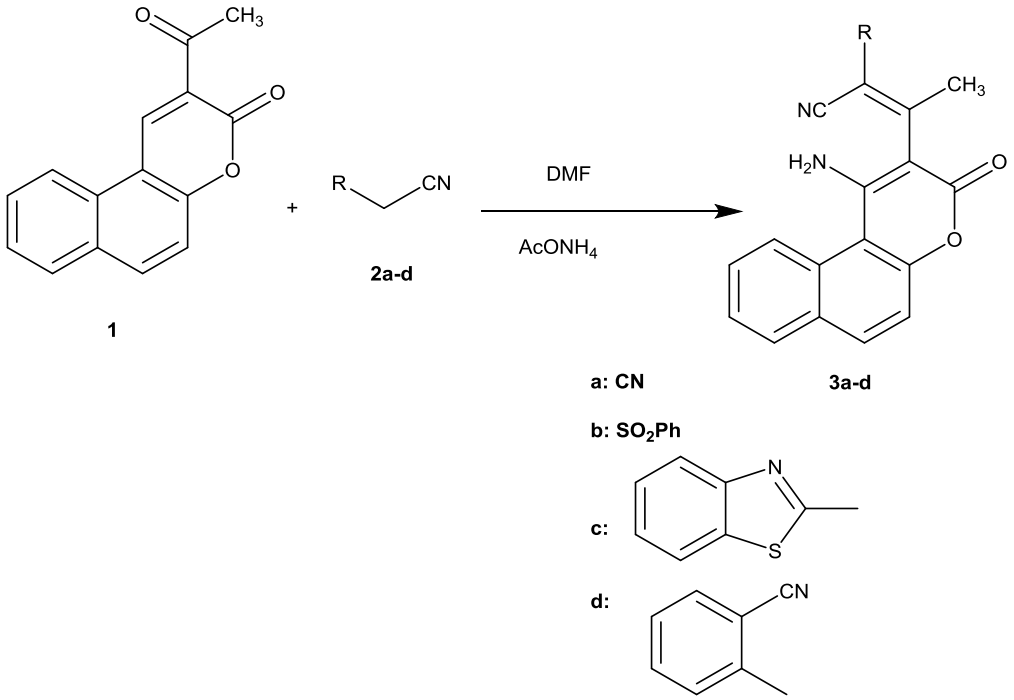
Introduction:

Various coumarin derivatives particularly fused with other heterocycles, have attracted much attention in recent years due to their biological activities (Ukawa K. and Heber D., 1986), and encouraged research to improve the availability of these compounds regard to procedures and substrates. Coumarins condensed pyridine ring (5-oxo-chromeno [4,3-b] pyridine) are also under investigation as the constitute the backbone of naturally occurring alkaloids, e.g. santiagonaminc (Valencia E. and Patra A ., 1984) .Some of them both natural and non -natural products are currently in clinical trials(Cheney I. *et al.*, 2007).

Results and Discussion

In the present work, we have developed the synthesis of new 2-amino-4-methyl-5-oxo-5H-benzo[5,6]chromeno[4,3-b]pyridine derivatives **4a-d** via interamolecular cyclization of 3-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)- but-2-enenitrile derivatives **3a-d.**

When compound **1** was allowed to react with activated nitriles **2 a-d** in refluxing dimethylformamide containing a catalytic amount of ammonium acetate to give 3-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)- 2-alkylbut-2-enenitrile derivatives **3a-d**.



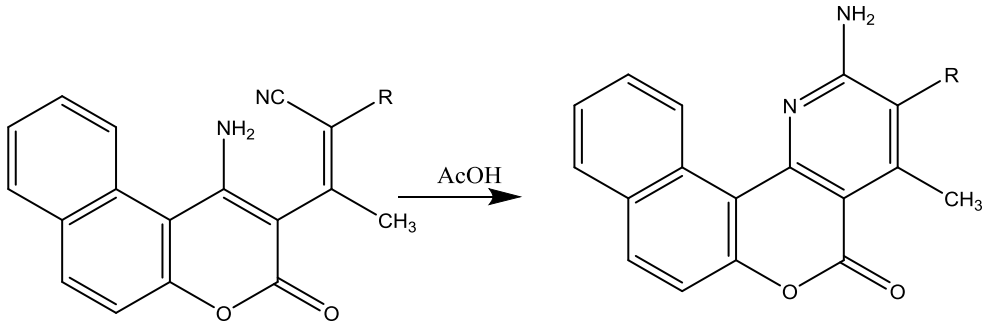
Scheme 1

The structures of the products **3a-d** were indicated by IR and ^{1}H-NMR spectroscopy, mass spectrometry and elemental analyses. The IR spectra of compounds **3a-d** showed a characteristic absorption band in the region between 2000-2200 cm^{-1} corresponding to the stretching vibration of the cyano group. The high frequency region of the spectra showed two strong absorption bands at 3300, 3400 cm^{-1} due to the stretching vibrations of the NH_2 group. In addition to strong absorption band in the region 1710-1722 cm^{-1} corresponding to the stretching vibration of the carbonyl group in the coumarin ring.

The ^{1}H-NMR spectra of **3a-d** showed the presence of a singlet signal within the region δ 2.15-2.30 ppm due to the methyl protons and a multiplet signal within the region δ 7.28-8.20 ppm due to aromatic protons, in addition to broad singlet signal (D_2O exchangeable) in the region 6.00-6.20 ppm due to amino group.

Also, the structures of compounds 3a-d were confirmed by its mass spectroscopic measurement.

When compounds **3a-d** refluxed on glacial acetic acid, afforded 3-alkyl-2-amino-4-methyl-5-oxo-5H-benzo[5,6]chromeno[4,3-b]pyridine **4a-d (scheme 2).**

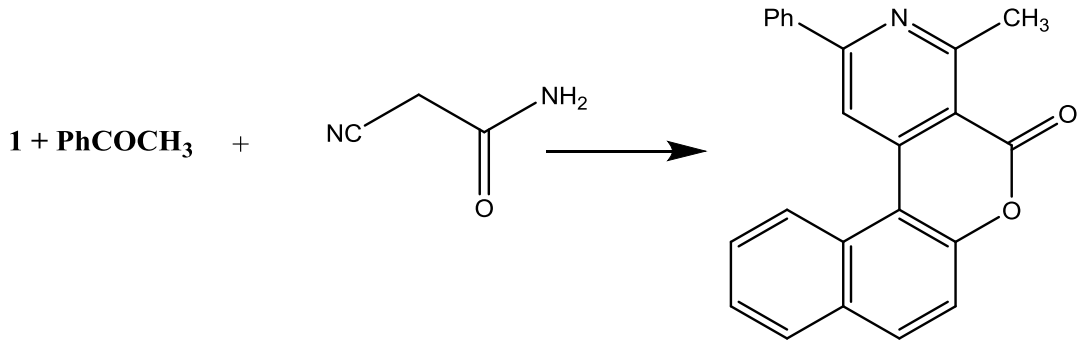


3a-d **4a-d**

Scheme 2

The structures of compounds **4b and 4c** was established on the basis of their IR spectra which showed absence of any peak around 2100-2250 cm^{-1} due to cyano group, which confirm that cyano group was involved in the reaction, while structures of compounds **4a and 4d** was established on the basis of their IR spectra which showed presence one absorption band in the region 2100-2250 cm^{-1} due to cyano group instead of two absorption bands in the region 2100-2250 cm^{-1} due to cyano groups in **3a** and **3d.** Also, structure of compounds **4a-d** were established on the basis of their ^{1} H-NMR .

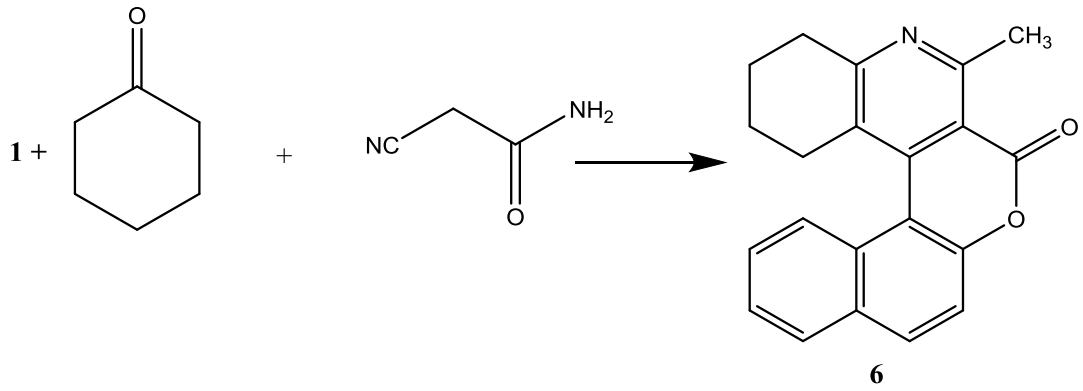
In continuation of our ongoing research program to synthesize potentially biologically active new benzo[5,6]chromeno[3,4-c]pyridin-5-one derivatives. When **1** is treated with cyanoacetamide and acetophenone , the latter substance takes part in the reaction, the cyanoacetamide simply furnishes ammonia instead of ammonium acetate, forming 2-phenyl-4-methyl-5H-benzo[5,6]chromeno[3,4-c]pyridin-5-one (**5) (scheme 3).**



5

Scheme 3

The structure of the product **5** was inferred from its analytical and spectral data. Thus, their IR spectra showed characteristic absorption bands at 1718 cm^{-1} due to carbonyl group. The ^{1}H-NMR spectra of **5** exhibited singlet signal at δ 2.43 ppm due to methyl protons in addition to multiplet signal in the region 7.10-8.40 ppm due to aromatic protons. By the same manner, on treatment **1** with cyclohexanone and cyanoacetamide as ammonia source gave 2-methyl-11,12,13,14-tetrahydro-3H-benzo[5,6]chromeno[3,4-c]quinolin-3-one **(6).**



6

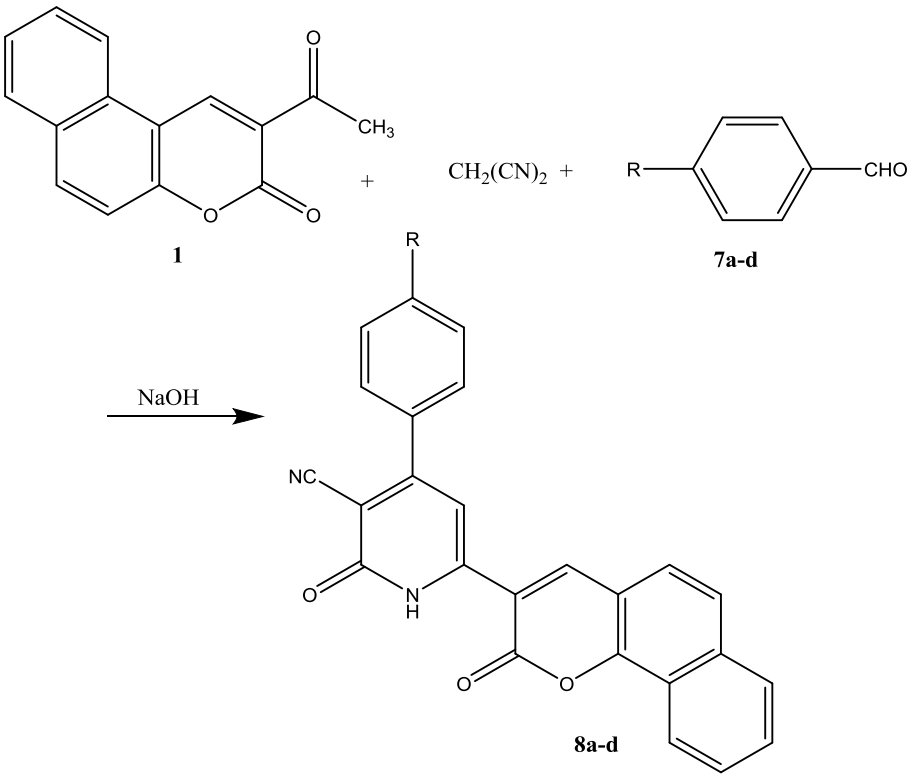
Scheme 4

Newly synthesized compound **6** was characterized on the basis of elemental analysis, IR, ^{1}H-NMR and mass spectral data. The IR spectrum of compound **6** showed absorption bands in the range from 3090–2890 cm^{-1} due to –CH_2- stretching and CH aromatic, the strong band at 1725 $cm^{-}1$ is attributed to the C=O stretching vibration. The absorption band seen at a 1610 cm^{-1} could be attributed to the C=N stretching. The ^{1}H-NMR spectrum of **6** showed multiplet signal at δ 1.60 ppm due to CH_2-12 and CH_2-13, singlet signal at δ 2.50 ppm due to methyl group, triplet signal at δ 2.60 ppm due to CH_2-11 and triplet signal at δ 3.10 ppm due to CH_2-14, in addition to multiplet signals in region 7.20-8.40 ppm. The mass spectrum gave molecular ion peak at m/z = 315 which confirm with the proposed structure. The combined spectral data gave strong support to the proposed structure

The nucleus of 2-pyridone occurs widely in the structures of biologically natural alkaloids (Jayaraman M . and Fox B. M., 2002). Many derivatives of 2-pyridone are frequently used as intermediates for the construction of alkaloids (Murry T. J. and Zimmerman S. C., 1995). Even some derivatives of 4,6-diaryl-2-pyridone, such as the simple structural related 2-pyridones, are recognized as potent LTB4 antagonist (Carles L. and Narkunan K., 2002). Numerous methods (Wang S. Z. and Yu G., 2003) have been reported for the synthesis of 2-pyridone derivatives, because of the biological importance associated with these compounds. However, these methods suffer from several drawbacks such as a long reaction time, an excess of volatile organic solvent, lower product yields, and harsh refluxing conditions. Therefore, the development of a simple and efficient method for the preparation of 2-pyridone derivatives is an active area of research and there is scope for further improvement involving milder reaction conditions and higher product yields.

In recent years, solvent-free organic reactions (Tanaka K and Toda F., 2000) have caused great interests, which have many advantages such as high efficiency and selectivity, easy separation and purification, mild reaction conditions, and benefit to industry as well as environment. Some solvent-free reactions can be carried out with just heating. In continuation to our ongoing endeavor on the application of solvent-free condition for the synthesis of organic compounds (Rong L. C. and Li X. Y., 2006), we herein describe a practical and simple method to prepare 4-aryl-6-[benzo[h]coumarin-3-yl]-3-cyano-2-pyridone **8a-d** with heating raw material under dry conditions.

The synthesis of 4-aryl-6-[benzo[h]coumarin-3-yl]-3-cyano-2-pyridone 8a-**d** is illustrated in **(scheme 5).**



8a: R=H
8b: R = OH
8c: R = OCH_3
8d: R = NMe_2

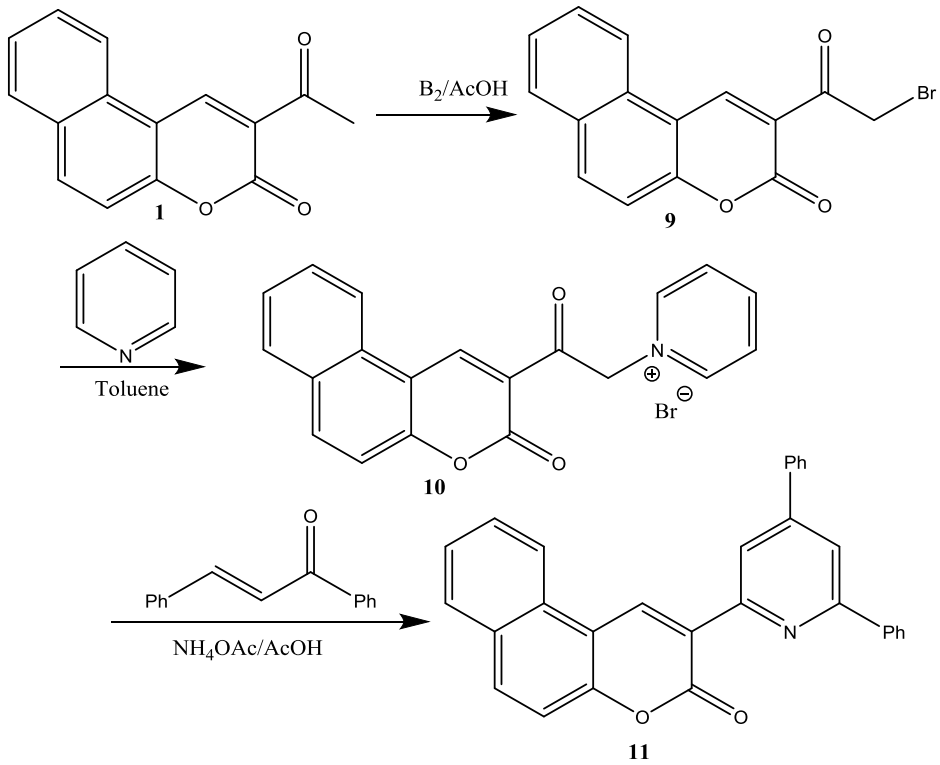
Scheme 5

In the presence of NaOH, the reactions of various aromatic aldehydes **7a-d** and **3** with malononitrile were carried out respectively to afford the corresponding products **8a-d**. All reactions were completed in about 45 min and the yields of products were high.

Because the reaction worked under solvent-free condition, the handling procedure of reaction was very simple. The structure of compounds **8a-d** was established on the basis of elemental and spectroscopic data. IR spectra of compounds **8a-d** showed strong absorption peak in the region 3180-3210 cm^{-1} due to NH group, 2100-2250 cm^{-1} attributable to cyano group, 1625-1640 cm^{-1} due to C=O. ^{1}H NMR showed siglet signal 11.88-12.60 ppm due to NH, 6.70-6.90 ppm due to CH-5 pyridine, in addition to multiplet in the region of 7.20-8.30 ppm due to aromatic protons and CH-4 in benzo[h]coumarin ring .

In conclusion, we have developed a simple and novel method for the synthesis of 4,6-diaryl-2-pyridone under solvent-free condition by one-pot reactions of aromatic aldehydes, **3**, and malononitrile. Because of avoiding the use of toxic organic solvent, this protocol has advantages of cheap starting materials, excellent yield, mild reaction conditions, simple experimental procedure and friendly environment. We believe that the present methodology addresses the current devise toward green chemistry.

2-(4,6-diphenylpyridin-2-yl)-3H-benzo[f]chromen-3-one (**11**) was synthesized via Kröhnke pyridine synthesis by formation α-pyridinium methyl ketone salt of **1**(Pitts W. J. and Jetter J. W., 1998) **,** then reaction of the product with chalcone in the presence of ammonium acetate as shown in **(scheme 6)**



Scheme 6

The structure of **11** was established on the basis of basis of the elemental and spectral data.

Biological evaluation

Antibacterial Studies

The newly synthesized compounds were checked for their *invitro* against various microorganisms such as *Bacillus subtills, Enterococcus faecalis E61* **(*Gram* positive bacteria)**, *Salmonella typhi, and Escherichia coli* **(Gram negative bacteria)** in order to establish their bioactivities. In these tests Ampicillin and Chloramphenicol were used as the standard drug . Disk diffusion technique was used for the determination of the antibacterial.

The results obtained against these microorganisms are given in Table 1

Table 1

compound no.	Inhibition zone (mm)			
	Gram Positive bacteria			Gram Negative bacteria
	Bacillus subtilis		*Enterococcus faecalis E61*	*Salmonella typhimurium T*
	876	*E.coli*		
3a	13	13	--	38
3b	12	7	--	--
3c	13	10	--	--
3d	11	12	--	10
4a	8	14	--	29
4b	11	14	--	34
4c	10	14	--	--
4d	8	13	--	--
5	7	12	--	--
6	--	10	--	--
8a	12	11	--	--
8b	13	9	8	--
8c	12	10	12	--
8d	10	10	11	--
11	9	8	--	--
Reference drugs				
Ampicillin	25	20	13	19
Chloramphenicol	24	23	18	21

The results obtained clearly show the efficiency of some of the new compounds, even at low concentrations. The results indicated that some of the synthesized compounds have higher activity than the standard.

We found that the activity of the synthesized compounds depends on their concentration and the strain of tested bacteria. Gram positive bacteria were more susceptible to the synthesized compounds than Gram negative ones.

This effect can be attributed in part to the great complexity of the double membrane-containing cell envelope in Gram negative bacteria, compared to the single membrane structure of positive ones.

The results depicted in Table 1 revealed that the most of tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive and Gram-negative bacterial strains.

The compounds **3a, 3b, 3c, 8a, 8b and 8c** showed relative activity towards Gram positive bacteria but less than the reference drugs. Regarding the structure-activity relationship revealed that all compounds of higher activity than the other contain either polar group as NH_2 (**3a, 3b, 3c)** or NH as other compounds**.**

Compounds **3a, 4a** and **4b** raveled mean diameters of the clear inhibition zones 29 and 34 mm against E.Coli Gram negative bacteria respectively i.e. greater clear inhibition zones than obtained by two references drugs Ampicilin and chloroamphincol 19 and 21 mm respectively.

Cytotoxic Screening

The In vitro Cytotoxicity **IC50 (µmol/L)** of the new synthesized compounds were studied using the 5-fluorouracil as reference drug, including MCF-7 (breast) and **HePG2** (liver)

The results are listed in Table 2

Table 2 Cytotoxic activity of the newly synthesized compounds.

Compounds	*In vitro* Cytotoxicity IC50 (µmol/L)	
	HePG2	MCF-7
5-FU	**9.30**	**13.1**
3a	**8.5**	**100**
3b	**69.2**	**73.4**
3c	**13.4**	**29.5**
3d	**22.0**	**22.4**
4a	**48.7**	**47.1**
4b	**67.5**	**94.7**
4c	**67.4**	**70.3**
4d	**69.3**	**70.4**
8a	**77.6**	**78.3**
8b	**58.1**	**59.9**
8c	**53.6**	**56.3**
8d	**57.8**	**58.0**

IC_{50} (µmol/L): (1-10) very strong, 11-25 (strong), 26-50 (moderate), 51-100 (very weak), 200 (noncytotoxicity) , 5-fu= 5 florocurcil.

All compounds showed cytotoxity against **MCF-7** (breast) and **HePG2** (liver), compound **3a** showed very strong cytotoxity against **HePG2** (liver) even more strong than 5-FC, while compound 3a showed very weak cytotoxity against **MCF-7** (breast) **.**Compound **3c** and **3d** showed strong cytotoxity against **HePG2** (liver)**,** also compound **3d** showed strong cytotoxity against **MCF-7** (breast) . Compound **3c** showed moderate cytotoxity against **MCF-7** and also **4a** showed moderate cytotoxity against **MCF-7** (breast) and **HePG2** (liver)**.** Other compounds showed weak cytotoxity against **MCF-7** (breast) and **HePG2** (liver)**.**

Experimental

Melting points were recorded on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, Great Britain, London) and are uncorrected. Infrared spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer (Thermoelectron Co. Egelsbach, Germany) using a KBr wafer technique. The ^{1}H NMR spectra were determined on Varian Gemini 200 MHz (Varian Co., Fort Collins, USA). DMSO-d_6 was used as solvent, TMS was used as internal standard and chemical shifts were measured in δ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Shimadzu (Japan). Elemental analyses were recorded on Perkin-Elmer 2400 Elemental analyzer at the Microanalytical Center at Cairo University, Cairo, Egypt.

Synthesis of 3-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)- but-2-enenitrile derivatives 3a-d.

A mixture of each of **1** (2.38 g, 0.01 mol.) and malononitrile (0.66 g, 0.01 mol.) in the presence of ammonium acetate (1.54 g, 0.02 mol.) was heated in an oil-bath at 150^{o}C for 30 min. The reaction mixture was poured onto ice/HCl. The solid that separated out was filtered, dried and recrystallized from the proper solvents to give compounds **3 a-d**.

2-(1-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)ethylidene)malononitrile (3a)

Yield: 85%; Dark brown solid; mp = 200 °C; IR (KBr): ν cm^{-1} 3312, 3558 (NH_2), 2189, 2203(two CN),1720 (C=O). ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 6.10 (broad s, 2H, NH_2), 7.28-8.20 (m, 6H, ArH); MS (EI): *m/z* =301 (M^+). Anal. Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found C, 71.72; H, 3.70; N, 13.97.

3-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)-2-(phenylsulfonyl)but-2-enenitrile (3b)

Yield: 88%; Dark brown solid; mp = 104 °C; IR (KBr): ν cm^{-1} 3315, 3554 (NH_2), 2187(CN),1718(C=O),. ^{1}H-NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 6.14 (broad s, 2H, NH_2), 7.28-8.20 (m, 11H, ArH); MS (EI): *m/z* = 390 (M^+- CN). Anal. Calcd for $C_{23}H_{16}N_2O_4S$: C, 66.34; H, 3.87; N, 6.73; S, 7.70 . Found C, 66.35; H, 3.84; N, 6.70; S, 7.70 .

3-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)-2-(benzo[d]thiazol-2-yl)but-2-enenitrile (3c)
Yield: 70%; yellow solid; mp = 233 °C; IR (KBr): ν cm^{-1} 3323, 3497 (NH_2), 2200(CN),1721(C=O). ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 6.20 (broad s, 2H, NH_2), 7.28-8.20 (m, 10H, ArH); MS (EI): *m/z* = 393 (M^+-NH_2). Anal. Calcd for $C_{24}H_{15}N_3O_2S$: C, 70.40; H, 3.69; N, 10.26; S, 7.83 . Found C, 70.42; H, 3.70; N, 10.26; S, 7.84

2-(2-(1-amino-3-oxo-3H-benzo[f]chromen-2-yl)-1-cyanoprop-1-en-1-yl)benzonitrile (3d)
Yield: 80%; Brown solid; mp = 118 °C; IR (KBr): ν cm^{-1} 3344, 3448 (NH_2), 2199, 2203(two CN),1720 (C=O). ^{1}H-NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 6.20 (broad s, 2H, NH_2), 7.28-8.20 (m, 10H, ArH); MS (EI): *m/z* = 377. Anal. Calcd for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.13 . Found C, 76.30; H, 3.99; N, 11.10.

Synthesis of 3-alkyl-2-amino-4-methyl-5-oxo-5H-benzo[5,6]chromeno[4,3-b]pyridine 4a-d
A solution of **3**a-c (0.01 mol.) in glacial acetic acid (30 mL) was refluxed for 3 hrs. The solids that separated on concentration and cooling were filtered off and recrystallized from the proper solvents as compounds

2-amino-4-methyl-5-oxo-5H-benzo[5,6]chromeno[4,3-b]pyridine-3-carbonitrile (4a)
Yield: 30%; Dark brown solid; mp > 300 °C; IR (KBr): ν cm^{-1} 3315, 3554 (NH_2), 2202(CN),1722(C=O),. ^{1}H-NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.10 (broad s, 2H, NH_2), 7.28-8.20 (m, 6H, ArH); MS (EI): *m/z* =301 (M^+). Anal. Calcd for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68; N, 13.95. Found C, 71.74; H, 3.67; N, 13.97.

2-amino-4-methyl-3-(phenylsulfonyl)-5H-benzo[5,6]chromeno[4,3-b]pyridin-5-one (4b)
Yield: 55%; Dark brown solid; mp >300 °C; IR (KBr): ν cm^{-1} 3346, 3444 (NH_2), 1725(C=O),. ^{1}H-NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.04 (broad s, 2H, NH_2), 7.28-8.20 (m, 11H, ArH); MS (EI): *m/z* = 416 (M^+). Anal. Calcd for $C_{23}H_{16}N_2O_4S$: C, 66.34; H, 3.87; N, 6.73; S, 7.70 . Found C, 66.35; H, 3.84; N, 6.70; S ,7.70 .

2-amino-3-(benzo[d]thiazol-2-yl)-4-methyl-5H-benzo[5,6]chromeno[4,3-b]pyridin-5-one (4c)
Yield: 30%; dark red solid; mp = 280 °C; IR (KBr): ν cm^{-1} 3356, 3412 (NH_2), 1725(C=O). ^{1}H-NMR (DMSO-d_6): δ 2.51 (s, 3H, CH_3), 6.98 (broad s, 2H, NH_2), 7.28-8.20 (m, 10H, ArH); MS (EI): *m/z* = 409 (M^+). Anal. Calcd for $C_{24}H_{15}N_3O_2S$: C, 70.40; H, 3.69; N, 10.26; S, 7.83 . Found C, 70.42; H, 3.70; N, 10.26; S, 7.84

2-(2-amino-4-methyl-5-oxo-5H-benzo[5,6]chromeno[4,3-b]pyridin-3-yl)benzonitrile (4d)
Yield: 35%; Brown solid; mp >300 °C; IR (KBr): ν cm^{-1} 3323, 3403 (NH_2), 2208(CN),1724 (C=O). ^{1}H-NMR (DMSO-d_6): δ 2.51 (s, 3H, CH_3), 7.10 (broad s, 2H, NH_2), 7.28-8.20 (m, 10H, ArH); MS (EI): *m/z* = 377. Anal. Calcd for $C_{24}H_{15}N_3O_2$: C, 76.38; H, 4.01; N, 11.13 . Found C, 76.36; H,4.04; N, 11.14.

Synthesis of 2-phenyl-4-methyl-5H-benzo[5,6]chromeno[3,4-c]pyridin-5-one (5).
A solution of compound **1**(1.19 g, 5 mmol) and 2-cyanoacetamide (0.42 g, 5 mmol) was heated to reflux in 20 ml acetophenone for 1 hr on oil bath in 170^{0}C (monitored by TLC). The solid product was filtered off and recrystallized from EtOH-DMF to give compound **5**

Yield: 60%; Dark yellow solid; mp = 257 °C; IR (KBr): ν cm^{-1} 1718 (C=O) ; ^{1}H-NMR (DMSO-d_6): δ 2,43 (s, 3H, CH_3), 7.10-8.40 (m, 12H, ArH); MS m/z =337 Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.88; H, 4.48; N, 4.15. Found C, 81.79; H,4.45; N , 4.13 .

Synthesis of 2-methyl-11,12,13,14-tetrahydro-3H-benzo[5,6]chromeno[3,4-c]quinolin-3-one (6).

A solution of compound **1** (1.19 g, 5 mmol) and 2-cyanoacetamide (0.42 g, 5 mmol) was heated to reflux in 20 ml cyclohecanone for 8 hr on oil bath in 170^{0}C (monitored by TLC). The solid product was filtered off and recrystallized from EtOH-DMF to give compound **6.**

Yield: 65%; Dark yellow solid; mp = 216 °C; IR (KBr): ν cm^{-1} 2890-3000 (CH_2 aliphatic) 3000- 3090-2890 (CH Aromatic), 1610(C=N), 1725(C=O) ; ^{1}H-NMR (DMSO-d_6): δ 1.6 (m, 4H, CH_2 -12,CH_2 -13), 2.50 (s, 3H, CH_3), 2.60 (t, 2H, CH_2-11),3.1(t, 2H, CH_2-14) , 7.20-8.40 (m, 12H, ArH); MS m/z = 315 . Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found C, 79.96; H, 5.46; N, 4.43.

Synthesis of 4-aryl-6-[benzo[h]coumarin-3-yl]-3-cyano-2-pyridone (8a-d)

General Procedure.

A mixture of aromatic aldehydes **7a-d** (1 mmol), **1** (1 mmol), malononitrile **3** (1.5 mmol) and NaOH (1.5 mmol) was put in a reaction flask and heated to a temperature of 75 °C for about 45 min. After completing the reaction, the reaction mixture was poured into water, and then washed with water thoroughly. The product was collected by filtration, dried, and recrystallized from 95% ethanol.

2-oxo-6-(2-oxo-2H-benzo[h]chromen-3-yl)-4-phenyl-1,2-dihydropyridine-3-carbonitrile (8a)

Yield : 60%; Dark brown solid; mp = 80 °C; IR (KBr): ν cm^{-1} 3188 (NH), 2200 (CN), 1633, 1724(two C=O) ; ^{1}H-NMR (DMSO-d_6): δ 6.80 (s, 1H, CH-5 pyridine), 7.20-8.30 (m, 12H, aromatic protons), 12.55 (s, 1H, NH) ; MS m/z = 390. Anal.Calcd for $C_{25}H_{14}N_2O_3$: C, 76.92; H, 3.61; N, 7.18. Found C, 76.95; H, 3.58; N, 7.15.

4-(4-hydroxyphenyl)-2-oxo-6-(2-oxo-2H-benzo[h]chromen-3-yl)-1,2-dihydropyridine-3-carbonitrile (8b)

Yield : 85%; Dark brown solid; mp =143 °C; IR (KBr): ν cm^{-1} br 3400 (OH), 3200 (NH), 2190 (CN), 1636, 1725(two C=O) ; ^{1}H-NMR (DMSO-d_6): δ 6.80 (s, 1H, CH-5 pyridine), 7.20-8.30 (m, 11H, aromatic protons), 10.20 (s, 1H, OH) , 12.24 (s, 1H, NH) ; MS m/z = 406 . Anal. Calcd for $C_{25}H_{14}N_2O_4$: C, 73.89; H, 3.47; N, 6.89. Found C, 73.90; H, 3.44; N, 6.86.

4-(4-methoxyphenyl)-2-oxo-6-(2-oxo-2H-benzo[h]chromen-3-yl)-1,2-dihydropyridine-3-carbonitrile (8c)

Yield : 85%; Dark brown solid; mp = 110 °C; IR (KBr): ν cm^{-1} 3198 (NH), 2200 (CN), 1635, 1725(two C=O) ; ^{1}H-NMR (DMSO-d_6): δ 3.90 (s, 3H, CH_3), 6.80 (s, 1H, CH-5 pyridine), 7.20-8.30 (m, 11H, aromatic protons), 11.98 (s, 1H, NH) ; MS m/z = 420 . Anal. Calcd for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found C, 74.26; H, 3.85; N, 6.64.

4-(4-(dimethylamino)phenyl)-2-oxo-6-(2-oxo-2H-benzo[h]chromen-3-yl)-1,2-dihydropyridine-3-carbonitrile (8d)

Yield : 60%; red solid; mp = 136 °C; IR (KBr): ν cm^{-1} 3188 (NH), 2200 (CN), 1640, 1725 (two C=O); ^{1}H-NMR (DMSO-d_6): δ 3.10 (s, 6H, $2CH_3$), 6.80 (s, 1H, CH-5 pyridine), 7.20-8.30 (m, 12H, aromatic protons), 11.90 (s, 1H, NH) ; MS m/z = 433. Anal. Calcd for $C_{27}H_{19}N_3O_3$: C, 74.81; H, 4.42; N, 9.69. Found C, 74.80; H, 4.44; N, 9.70.

Synthesis of 2-(4,6-diphenylpyridin-2-yl)-3H-benzo[f]chromen-3-one (11) .

A solution of **1** (0.238g, 1 mmol), benzalacetophenone (0.208 g, 1 mmol) and ammonium acetate (0.77 g, 1 mmol) in 10 ml glacial acetic acid was refluxed for about 6 h. The solid product was isolated by filtration. The solid product was washed with ethanol. The crude product is dried and crystallized from DMF-EtOH to furnish pure solid product.

2-(4,6-diphenylpyridin-2-yl)-3H-benzo[f]chromen-3-one (11).

Yield: 42%; Dark brown solid; mp = 255 °C; IR (KBr): ν cm^{-1} 3000-3090 (CH aromatic), 1725 (C=O), 1623 (C=N); ^{1}H-NMR (DMSO-d_6): δ 7.20-8.40 (m, 19H, aromatic protons) ; MS m/z = 425. Anal. Calcd for $C_{30}H_{19}NO_2$: C, 84.69; H, 4.50; N, 3.29. Found C, 84.68; H, 4.52; N, 3.31.

References

Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. "2-Pyridones from Cyanoacetamides and Enecarbonyl Compounds: Application to the Synthesis of Nothapodytine B" *J. Org. Chem*. 2002, **67**, 4304.

Cheney I. W., Yan S., Appleby T., Walker H., Vo T., Yao N., Hamatake R., Z. Hong, and Wu J. Z. "Identification and structure-activity relationships of substituted pyridones as inhibitors of Pim-1 kinase", *Bioorg. Med. Chem. Lett*., **17**, 1679 (2007).

Heber D. and Berghaus T. "Synthesis of 5*H*-[1]Benzopyrano[4,3-b]pyridin-5-ones Containing an Azacannabinoidal Structure", *J. Heterocycl. Chem*., **31**, 1353 (1994).

Jayaraman, M.; Fox, B. M.; Hollingshead, M.; Kohllhgen, G.; Pommioer, Y.Synthesis of new dihydroindeno[1,2-c]isoquinoline and indenoisoquinolinium chloride topoisomerase I inhibitors having high in vivo anticancer activity in the hollow fiber animal model *J. Med. Chem*. (2002), **45**, 242.

Johnston P. A., Foster C. A., Shun T. Y., Skoko J. J., Shinde S., Wipf P., and Lazo J. S. "Development and implementation of a 384-well homogeneous fluorescence intensity high-throughput screening assay to identify mitogen-activated protein kinase phosphatase-1 dual-specificity protein phosphatase inhibitors" , *Assay Drug Dev. Technol*., **5**, 319 (2007).

Moustapha, Chahid *et al,* "Reactions with Hydrazonoyl Halides 40: Synthesis of some new 1,3,4-thiadiazoles, Pyrrolo[3,4-c]pyrazoles, pyrazoles and pyrazolo[4,3-d]pyridazines" *Synthetic Communications*, **35**(2), 249-261; 2005.

Murry, T. J.; Zimmerman, S. C. "Synthesis of Heterocyclic Compounds Containing Three Contiguous Hydrogen Bonding Sites in All Possible Arrangements" *Tetrahedron Lett*. 1995, **36**, 7627.

Pitts W. J., Jetter J. W., Pinto D. J., Orwat M. J., Batt D. G., Sherk S. R., Petraitis J. J., Jacobson I. C., Copeland R. A., Dowling R. L., Jaffee B. D., Gardner T. L., Jones E. A., and Magolda R. L., *Bioorg*. "Heteroatom- and carbon-linked biphenyl analogs of Brequinar as immunosuppressive agents" *Med. Chem. Lett*., **8**, 307 (1998).

Rong, L. C.; Li, X. Y.; Wang, H. Y.; Shi, D. Q.; Tu, S. J.; Zhuang, Q. Y. "Efficient Synthesis of Tetrahydrobenzo[*b*]pyrans under Solvent-Free Conditions at Room Temperature" *Synth. Commun*. 2006, ***36,*** 2363.

Tanaka, K.; Toda, F. **"**Solvent-Free Organic Synthesis" *Chem. Rev*. 2000, **100**, 1025.

Ukawa K., Ishiguro T., Wada Y., and Nohara A., "Synthesis of 5-Oxo-5H-[1]benzopyrano[4,3-b]pyridine Derivatives" *Heterocycles*, **24**, 1931 (1986).

Valencia E., Patra A., A. J. Freyer, M. Shamma, and V. Fajardo, "Santiagonamine: a new aporphinoid alkaloid incorporating a phenanthridine skeleton" *Tetrahedron Lett*., **25**, 3163 **(1984).**

Wang, S. Z.; Yu, G.; Lu, J.; Xiao, K.; Hu, Y. F.; Hu, H. W. "A Regioselective Tandem Reaction between Chalcones and 2-Acetamido-acetamide Promoted by Cs_2CO_3 for the Preparation of 3-Unsubstituted 2-Pyridones" *Synthesis* 2003, 487.

تشييد بعض مشتقات الكيومارين الجديده المحتويه على مجموعات البيريدين وتقييم نشاطها الحيوى

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٢-اسيتيل -3H-بنزو [f] كرومين -٣- اون (١) كانت تستخدم بوصفها وسيطه رئيسيه لتشييد مشتقات ٣-(١-الامينيه -٣-اوكسو -٣H- بينزو [f] كرومين -٢- يل)بيوت-٢-انين نيتريل **١٣-د** عبر تفاعلات التكثيف **مع** مركبات النيتريل النشطه بالغليان مع تنائ مثيل فورماميد المحتوى على كميه الحافز من خلات الامونيوم زعلاوه على ذالك عند غليان المركبات ١٣ – د فى حمض الخليك التلجى اعطت ٣-الكيل -٢- امينو -٤- مثيل -٥-اكسو -٥ هيدروجين – بنزو [٥,٦] كرومينو [٣,٤-b] بيريدين **١٤-د**

و بنفس الطريقة عندما يتفاعل المركب **١** مع الهكسان الحلقى و اسيتوفينون و السيانو أسيتاميد كمصدر للأمونيا أعطى بينزو [٥,٦] كرومينو [٣,٤- c] بيريدين -٥- أون احد مشتقات ٥و٦ على التوالى .

في استمرار للسعي المتواصل على تخليق بعض المركبات العضوية الجديدة بدون استخدام المذيبات ، تم تخليق مركبات ٤، ٦-ثنائي الأريل – بنزو [h] ٣-كومارينيل- ٣-سيانو-٢-بيردون عن طريق تسخين المواد المتفاعلة بدون مذيب و في وجود هيدروكسيد الصوديوم ليعطي المركبات **١٨-د** في زمن لا يتجاوز ٤٥ دقيقة و بنسبة ناتج عالية.

تم تحضير المركب ٢-(٤،٦-ثنائي الفنيل-بيردين-٢-يل)-3H -بنزو[f]كرومون-٣-اون(**١١**) من خلال تفاعل كرونك و ذلك بتحضير املاح الفا – بيريدنيم ميثيل كيتون للمركب **١** ثم مفاعلتها الشالكون في وجود خلات الأمونيوم.

هذا و قد تم اثبات التراكيب البنائيه للمركبات بناءا على نتائج التحاليل الدقيقه للعناصر و القياسات الطيفيه المختلفه مثل طيف الاشعه تحت حمراء و طيف الرنين النووى المغناطيسى و كذالك مطياف الكتله .و ايضا تم الفعاليه البيولوجيه لبعض المركبات الجديده كمضادات للبكتيريا و الفطريات و كذالك الاورام