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## THE UTILITY OF BENZOYLCHROMENE AND 2-IMINOCHROMENE-3-CARBOXAMIDE DERIVATIVES FOR THE SYNTHESIS OF PYRANOCHROMENES, CHROMENOPYRANO(PYRIMIDINE)PYRIDINE, CHROMENO(PYRIDINES)QUINOLINE AND THEIR ANTIMICROBIAL EVALUATION

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**THE UTILITY OF BENZOYLCHROMENE AND 2-IMINOCHROMENE-3-CARBOXAMIDE DERIVATIVES FOR THE SYNTHESIS OF PYRANOCHROMENES, CHROMENOPYRANO(PYRIMIDINE)PYRIDINE, CHROMENO(PYRIDINES)QUINOLINE AND THEIR ANTIMICROBIAL EVALUATION**

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**Abstract**

Some new pyrano[3,4-c]chromene derivatives (**4,5,9,13,14**), bispyrano[3,4-c]chromene derivative (**18**) were synthesized via Michael addition of different active methylene compounds to benzoylchromenes **1a,b** under different reaction conditions. Chromeno[4',3':4,5]pyrano[2,3-d]pyrimidine and Chromeno[4',3':4,5]pyrano[2,3-b]pyridine (**24,28**) derivatives were obtained from the condensation of **4** with formic acid and benzylidene malononitrile respectively. Novel chromeno[3,4-c]pyridine derivatives (**34,37,40,43**) and chromeno[3,4-c]tetrahydroquinolinedione (**47**) were obtained via treatment of 2-iminochromene-3-(4-ethoxyphenyl)-carboxamide (**31**) with acetonitrile derivatives and cyclohexanone respectively. The structures of the titled compounds cited in this article were elucidated by spectroscopic data (IR, <sup>1</sup>HNMR and mass spectra). The antimicrobial activities of the synthesized compounds were performed and some of them display significant results.

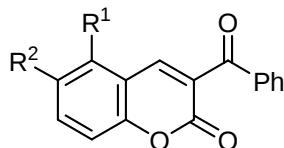
**Keywords:** Chromenes; Michael reaction, pyrano[3,4-c]chromenes, chromeno[3,4-c]pyridines, chromeno[4',3':4,5]pyrano[2,3-d]pyrimidine, chromeno[4',3':4,5]pyrano[2,3-b]pyridine, antimicrobial activity.

**Introduction**

Chromene derivatives have exhibited biomedical applications including anti-hyperglycemic, anti-dyslipidemia, cytotoxic, molluscicidal, anti-inflammatory, anti-cancer, anti-leukemic and anti-fungal activities [1-9]. Also, chromene derivatives were found useful as antimicrobial [10–12], inhibitors of influenza virus [13,14], anti-hypertensive, anti-allergic, anti-viral, anti-coagulants, antitumor, sex pheromone and anti-HIV agents [15–25]. Some chromene derivatives were used as pigments, photoactive materials, biodegradable, agrochemicals and were utilized in the synthesis of macrocyclic ligands [26–29]. In continuation of our work for the synthesis of new heterocyclic derivatives of potential biological activities [30-33] and in view of the above aforementioned facts, the authors report herein the

synthesis of some newly chromene derivatives fused onto different heterocyclic nuclei. Such derivatives might possess interesting and useful biological properties.

### Results and Discussion

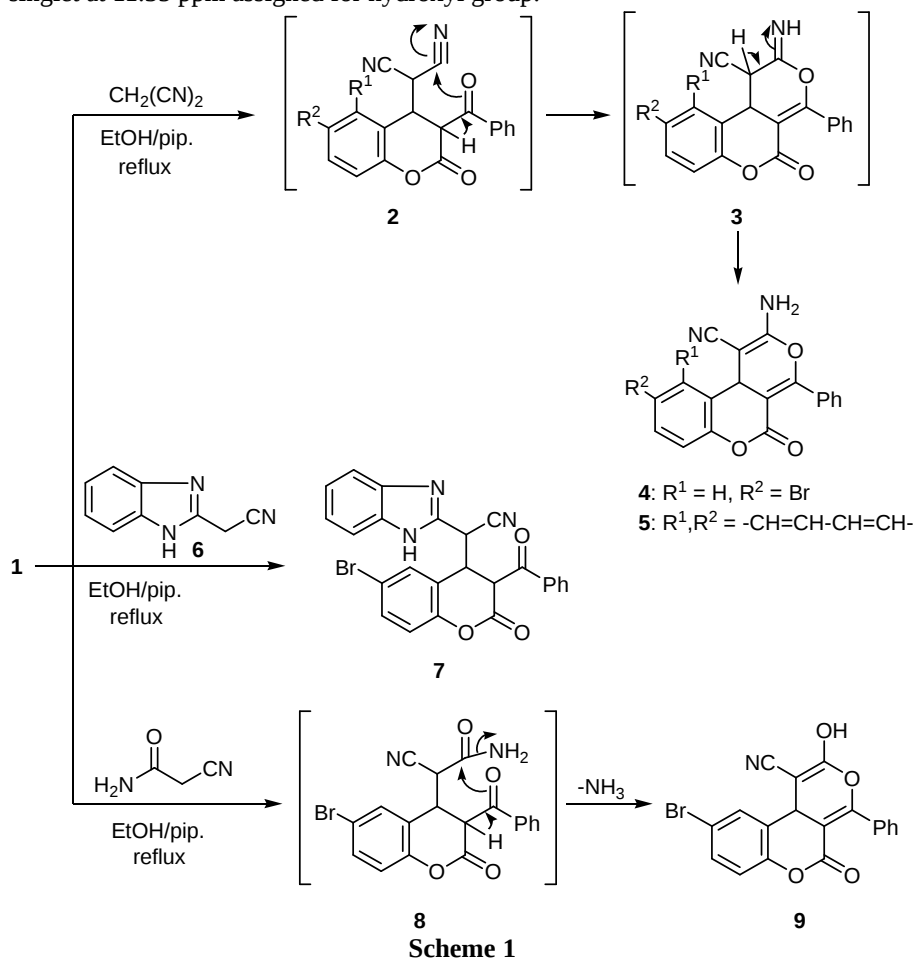


- 1 a**;  $R^1 = H$ ,  $R^2 = Br$   
**b**;  $R^1, R^2 = -CH=CH-CH=CH-$

**Figure 1**

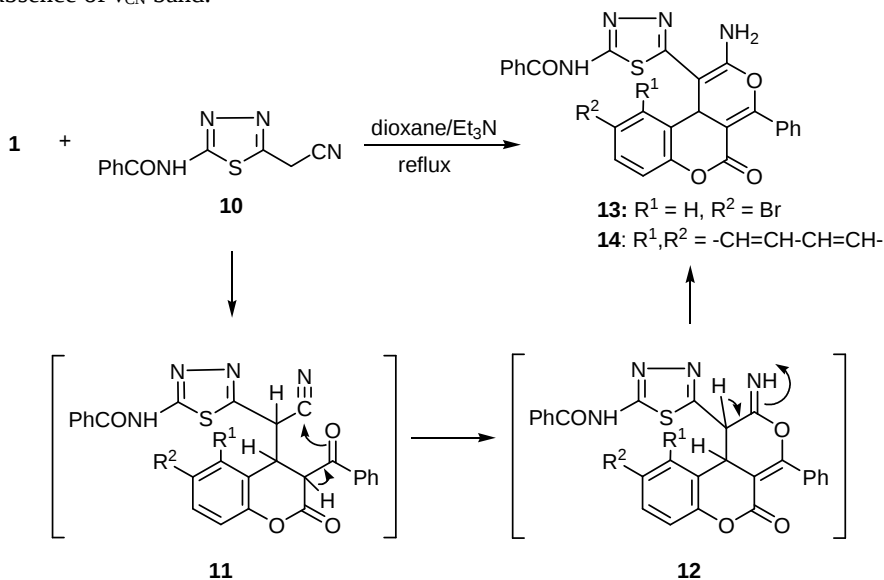
Benzoylchromenes **1a,b**, **Figure 1** [34] were allowed to react with active methylene compounds to give pyrano[3,4-c]chromene and benzo[f]pyrano[3,4-c]chromene derivatives. Thus, treatment of chromene derivatives **1a,b** with malononitrile in ethanol in the presence of a catalytic amounts of piperidine gave the corresponding 2-aminopyrano[3,4-c]chromene-1-carbonitrile **4** and benzo[f]pyrano[3,4-c]chromene analogue **5**, respectively, (Scheme 1). The reaction pathway is assumed to proceed via Michael addition of the active methylene group to the activated double bond of compound **1** to give Michael adduct **2** followed by intramolecular cyclization through nucleophilic addition of the hydroxyl group to the cyano group and tautomerization to afford the pyrano[3,4-c]chromene-5-one derivatives **4,5**. The infrared spectrum of compound **4** showed absorption bands at 3344, 3210  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 2210  $\text{cm}^{-1}$  ( $\text{C}\equiv\text{N}$ ), 1648  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ). The mass spectrum of compound **4** showed a molecular ion peak at  $m/z$  394 together with a base peak at  $m/z$  77. The  $^1\text{H}$ NMR spectrum of compound **5** revealed a singlet at 3.56 ppm assigned to chromene-H4. The reaction of compound **1a** with 2-cyanomethylbenzimidazole (**6**) in refluxing ethanol in the presence of piperidine as a catalyst led to the formation of Michael adduct **7** as the only isolable product, (Scheme 1). The infrared spectrum of the reaction product showed the presence of 2222  $\text{cm}^{-1}$  ( $\text{C}\equiv\text{N}$ ) which ruled out the possibility of intramolecular cyclization reaction. The  $^1\text{H}$ NMR spectrum of compound **7** revealed a triplet at 3.56 ppm assigned to chromene-H4, doublet at 4.75 ppm assigned to chromene-H3, doublet at 5.89 ppm assigned to  $\text{CH-CN}$ . Treatment of compound **1a** with cyanoacetamide in refluxing ethanol in the presence of piperidine resulted in the formation of pyrano[3,4-c]chromene derivative **9**. The formation of compound **9** may be assumed to proceed via initial addition of active methylene group to the highly conjugated double bond at C-4 under Michael reaction conditions to give Michael adduct **8** followed by intramolecular cyclization

through loss of ammonia molecule and tautomerization, (Scheme 1). The structure of compound **9** was supported by its  $^1\text{H}$ NMR spectrum ( $\text{DMSO-}d_6$ ) which revealed the presence of singlet signal at  $\delta$  3.56 ppm assigned to 4H-pyran and downfield singlet at 11.35 ppm assigned for hydroxyl group.



Condensation of chromene derivatives **1a,b** with N-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide (**10**) in dioxane- $\text{Et}_3\text{N}$  at reflux temperature resulted in 1:1 adducts **13&14**, respectively (Scheme 2). The formation of **13&14** indicated that the anionic carbon of **10** attacked the most activated electrophilic carbon of **1** at position-4 to yield an acyclic Michael adduct **11** which underwent cyclization (Scheme 2). The  $^1\text{H}$ NMR spectrum ( $\text{DMSO-}d_6$ ) of **13&14** indicated the presence of

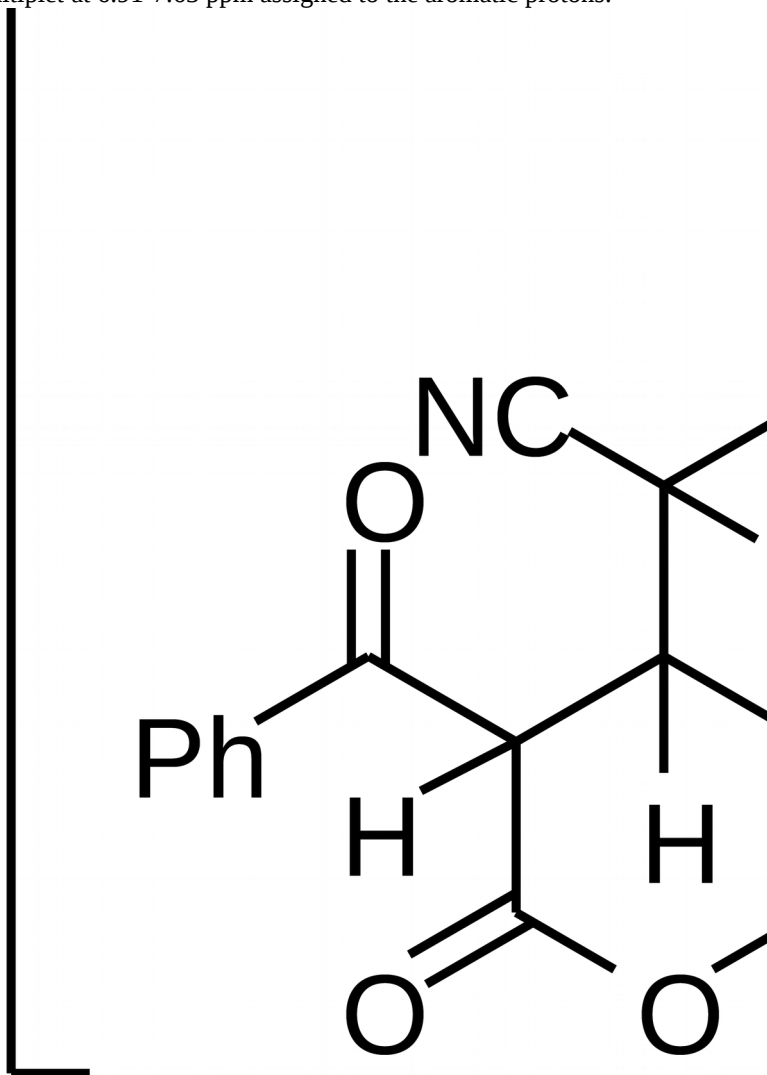
singlet at  $\delta$  3.56 ppm assigned to 4H-pyran nucleus and infrared spectra showed the absence of  $\nu_{\text{CN}}$  band.



**Scheme 2**

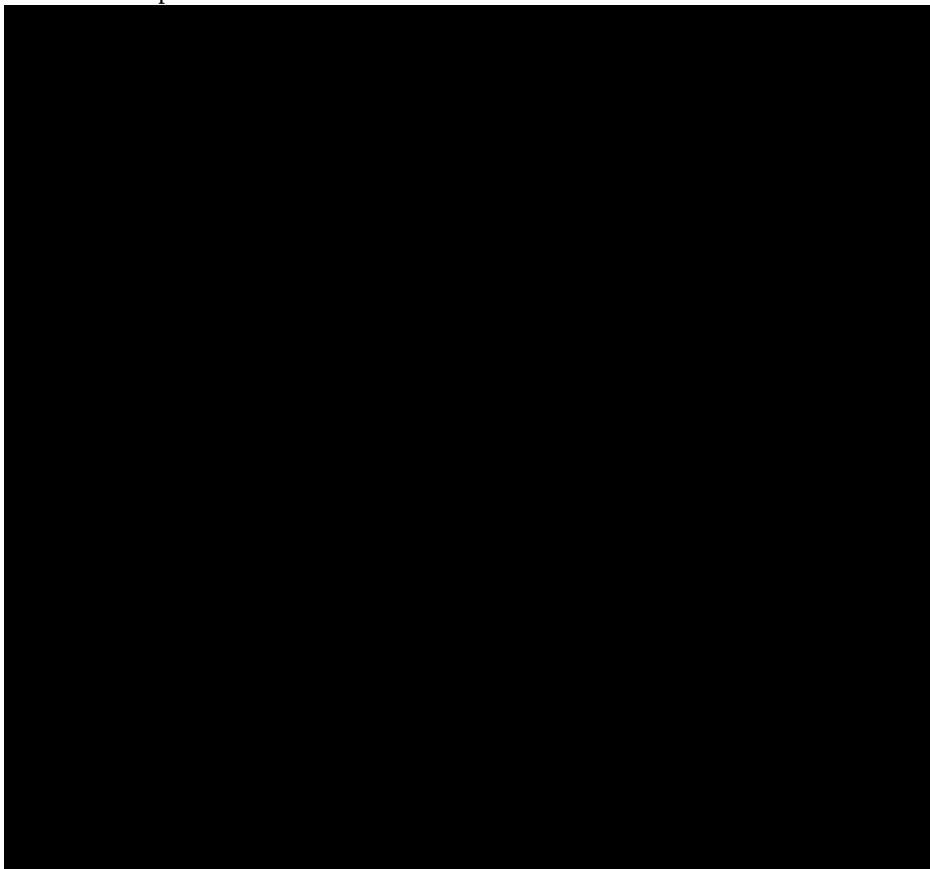
Treatment of compound **1a** with bis-cyanoacetamide derivative **15** in dioxane in the presence of triethylamine as a catalyst afforded bis pyrano[3,4-c]chromene derivative **18** and the other possible structure **19** was excluded on the basis of elemental analysis and spectral data, (Scheme 3). The infrared spectrum of compound **18** showed absorption band at 3412, 3304  $\text{cm}^{-1}$  for amino group and its mass spectrum display a molecular ion peak at  $m/z$  850 (50%) with a base peak at  $m/z$  77. The formation of compound **18** is assumed to proceed via nucleophilic addition of activated methylene of the cyanoacetamide derivative to the activated double bond to give Michael adduct **16** followed by intramolecular cyclization through nucleophilic addition of the hydroxyl group to the cyano group and tautomerization. Refluxing of compound **1a** with malononitrile dimer (2-aminoprop-1-ene-1,1,3-tricarbonitrile) **20** in ethanol-piperidine gave the addition product tricarbonitrile derivative **21** through nucleophilic attack of anionic carbon of **20** to the activated double bond at 4-position of **1a** and the two other possible structures, chromeno[3,4-c]pyridine **22** and pyrano[3,4-c]chromene **23** were ruled out (Scheme 3). The structure of compound **21** was supported by infrared spectrum which showed absorption bands at 3308, 3164  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 2206 ( $\text{C}\equiv\text{N}$ ), 1692, 1640 ( $\text{C}=\text{O}$ ). The  $^1\text{H}$ NMR spectrum ( $\text{DMSO}-d_6$ ) of the reaction product showed the presence of downfield singlet at 10.59 ppm for the one amino group protons ( $\text{D}_2\text{O}$  exchangeable) in addition to the presence of a triplet at 2.64 ppm assigned for the chromene-H4,

doublet at 3.56 ppm assigned for CH-CN, doublet at 4.34 assigned for chromene-H3 and a multiplet at 6.91-7.63 ppm assigned to the aromatic protons.



Scheme 3

Refluxing of pyrano[3,4-c]chromene derivative **4** with boiling formic acid gave the chromeno[4',3':4,5]pyrano[2,3-d]pyrimidine derivative **24**, (Scheme 4). The mass spectrum of compound **24** showed a molecular ion peak at  $m/z$  422 together with a base peak at  $m/z$  105 corresponding to cationic benzoyl fragment. The chromeno[4',3':4,5]pyrano[2,3-b]pyridine derivative **28** was synthesized through condensation of **4** with 2-(4-methoxybenzylidene)malononitrile **25** in boiling dioxane-piperidine mixture. The formation of the reaction product indicated that amino group of **4** attacked at  $\beta$ -carbon of **25** to yield an acyclic Michael adduct **26** which underwent cyclization to give **28**, with elimination of HCN molecule and aromatization (Scheme 4). The mass spectrum of this compound showed a molecular ion peak at  $m/z$  551.



**Scheme 4**

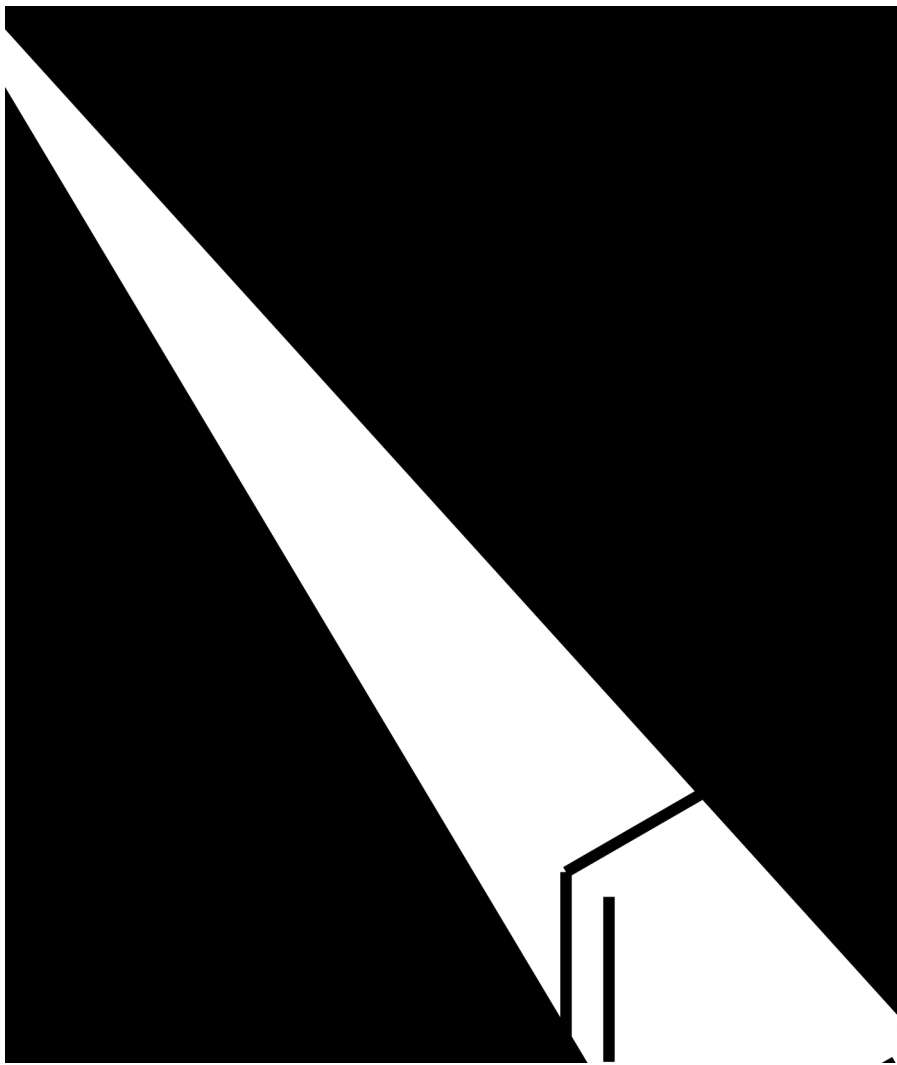
In the same manner, this study was extended to synthesize a series of novel compounds containing chromeno[3,4-c]pyridine with the aim of obtaining new biologically active compounds. Thus, The reaction of cyanoacetamide derivative **30**

[35] with 5-bromosalicylaldehyde **29** in ethanol containing a catalytic amount of piperidine gave the 2-imino-chromene-3-carboxamide derivative **31** (Scheme 5). The infrared spectrum of compound **31** showed absorption bands at  $3272\text{ cm}^{-1}$  (NH),  $2980\text{ cm}^{-1}$  (CH-aliph.),  $1664\text{ cm}^{-1}$  (C=O). In addition, the structure of compound **31** was supported by  $^1\text{H}$ NMR spectrum (DMSO- $d_6$ ) which revealed a triplet and quartet at  $\delta$  1.31, 4.02 for the methyl and methylene protons, a multiplet at  $\delta$  6.89-8.08 ppm for the aromatic protons and three singlets at  $\delta$  8.50, 9.33, 12.51 ppm for chromene-H4 and two NH groups. The reactivity of 2-imino-chromene-3-carboxamide derivative **31** towards active methylene compounds was also explored. Thus, treatment of compound **31** with malononitrile, ethyl cyanoacetate and cyanoacetamide in dioxane-piperidine under reflux gave a novel chromeno[3,4-c]pyridine derivatives **34,37** respectively (Scheme 5). The infrared spectrum of compound **34** showed absorption bands at  $3342$ ,  $3312$ ,  $3210\text{ cm}^{-1}$  ( $\text{NH}_2$ , NH),  $2208$  ( $\text{C}\equiv\text{N}$ ),  $1648\text{ cm}^{-1}$  (C=O). Its mass spectrum revealed a molecular ion peak at  $m/z$  450 (26.17%) with a base peak at  $m/z$  69. The formation of **34** may be assumed to proceed via the Michael addition of malononitrile carbanion to  $\text{C}_3\text{-C}_4$  double bond in **31** to yield the acyclic Michael adduct **32** followed by intramolecular cyclization and dehydrogenation under reaction conditions. However, the reaction of compound **31** with ethyl cyanoacetate and cyanoacetamide gave a compound proved to be identical (mp, and mixed mp) with the chromeno[3,4-c]pyridine derivative **37**. The infrared spectrum of the reaction product exhibited the absorption bands at  $3408\text{ cm}^{-1}$  (OH),  $3310\text{ cm}^{-1}$  (NH),  $2206\text{ cm}^{-1}$  ( $\text{C}\equiv\text{N}$ ),  $1724\text{ cm}^{-1}$  (C=O). The  $^1\text{H}$ NMR spectrum of **37** in DMSO- $d_6$  exhibited a triplet at  $\delta$  1.51 ppm characteristic for  $\text{CH}_3$  protons and a quartet at  $\delta$  3.04 ppm for  $\text{CH}_2$  protons, multiplet at 7.19-8.34 ppm assigned to aromatic protons, in addition to presence of two singlets at 9.12, 10.82 ppm assigned to NH and OH, respectively. Also, the structure of **37** was supported by its mass spectrum which revealed a molecular ion peak at  $m/z$  451 together with a base peak at  $m/z$  55. The formation of **37** was assumed to proceed via Michael adduct **35** followed by intramolecular cyclization through the loss of ethanol and/or ammonia molecule and autoxidation under reaction conditions.



### Scheme 5

Also, refluxing of compound **31** with 2-cyanomethylbenzimidazole (**6**) and/or N-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide (**10**) in dioxane containing piperidine as catalyst afforded a novel chromeno[3,4-c]pyridine derivatives **40,43** respectively (Scheme 6). The infrared spectrum of these compounds showed the absence of the absorption band of cyano group. In addition, <sup>1</sup>HNMR spectrum gave analytical figures compatible with the proposed structural formula. The formation of compounds **40,43** were rationalized by the addition of methine carbanion to the activated double bond of **31** to give Michael adducts **38,41** which undergo intramolecular cyclization through nucleophilic addition of carboxamide nitrogen followed by aromatization by autoxidation (Scheme 6).



Scheme 6

Finally, spectroscopic analyses revealed that 2-bromo-8-(4-ethoxyphenyl)-9,10,11,12-tetrahydro-6H-chromeno[3,4-c]quinoline-6,7 (8H)-dione (**47**) was obtained from the reaction of compound **31** with cyclohexanone in refluxing ethanol containing sodium acetate as a catalyst (Scheme 7). The infrared spectrum of the reaction product showed the characteristic bands at 2940, 2870  $\text{cm}^{-1}$  for the aliphatic-H and at 1668  $\text{cm}^{-1}$  for the carbonyl group. Also, the  $^1\text{H}$ NMR spectrum (DMSO- $d_6$ ) of the reaction product showed triplet at  $\delta$  1.33 assigned to  $\text{CH}_3$ , and at  $\delta$  1.47-1.64 ppm assigned to the cyclohexyl protons in addition to the presence of signals at  $\delta$  4.04 and  $\delta$  6.96-7.55 ppm which were readily assigned to the quartet

CH<sub>2</sub> and aromatic protons, respectively. The formation of chromeno[3,4-c]quinoline-6,7-dione derivative **47** is assumed to proceed through the formation of Michael adduct **44** followed by ring closure with spontaneous elimination of water molecule, autoxidation and hydrolysis of imino function to carbonyl group under the reaction conditions.

S

### Scheme 7

#### Antimicrobial Screening:

The synthesized compounds were tested for their antimicrobial activities in vitro by agar diffusion method using "Mueller–Hinton" agar medium for bacteria and "Sabouraud's" agar medium for yeasts.

The assayed collection included two Gram-positive bacteria: *Bacillus subtilis* (NCIB 3610) and *Staphylococcus aureus* (NCTC 7447); two Gram-negative bacteria: *Escherichia coli* (NCTC 10416) and *Pseudomonas aeruginosa* (NCIB 9016); Unicellular fungi: *Candida albicans* (IMRU 3669) and Filamentous fungi: *Aspergillus niger* (ATCC 16404) using Ampicillin 25 µg/ml as a reference compound. The inhibition zone diameters were recorded and rounded up to the nearest whole number (mm) for analysis. The inhibitory effects of the synthesized compounds against these organisms are given in **Table (1)** and depicted graphically in **Figures (2-3)**.

Table (1):Biological activity of the newly synthesized compounds

Inhibition-zone diameter (mm/mg sample)						
Compound No.	Gram-positive		Gram-negative		Fungi	
	<i>B. Subtilis</i> (NCIB 3610)	<i>S. aureus</i> (NCTC 7447)	<i>E. Coli</i> (NCTC 10416)	<i>P. aeruginosa</i> (NCIB 9016)	<i>A. niger</i> (ATCC16404)	<i>C.albicans</i> (IMRU 3669)
4	25	20	40	20	30	25
5	30	20	40	20	30	30
7	31	33	35	15	30	30
9	30	30	35	21	30	30
13	28	25	35	20	30	30
14	25	26	35	15	30	25
18	25	25	32	15	32	30
21	28	25	40	15	35	25
24	32	30	40	15	35	25
28	30	25	40	25	25	30
31	25	25	35	15	30	25
34	28	30	35	15	30	30
37	25	25	45	22	30	30
40	30	30	35	15	32	28
43	25	28	35	15	35	25
47	30	20	30	25	25	30
Ampicillin	36	34	47	27	38	34

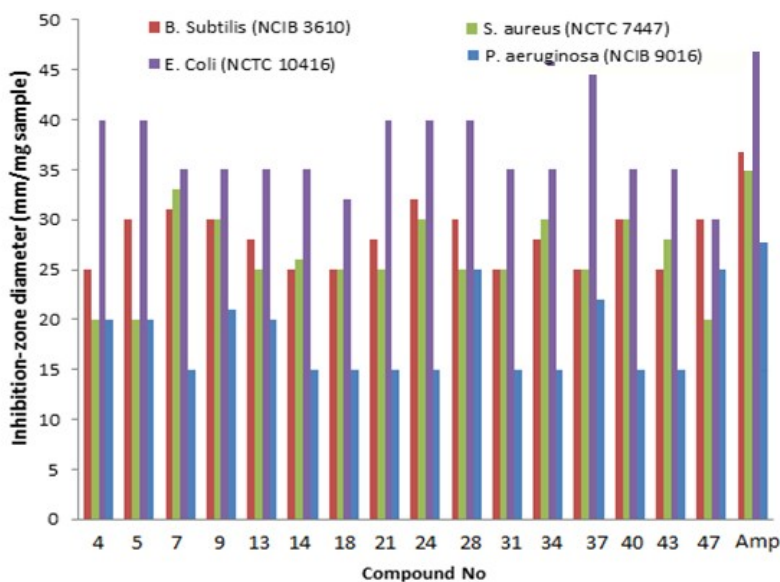


Figure (2) : Graphical representation of the antibacterial activity of the tested compounds, compared with Ampicillin.

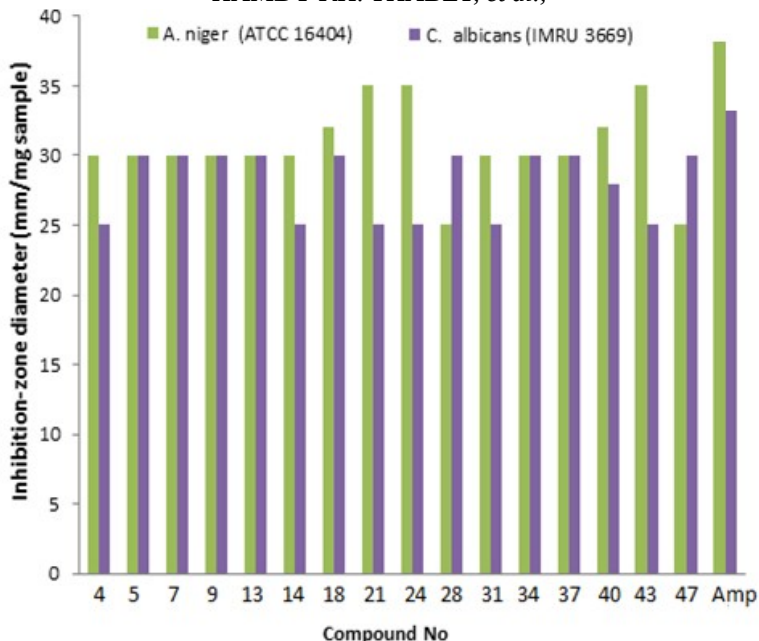


Figure (3) : Graphical representation of the antifungal activity of the tested compounds, compared with Ampicillin.

The screening results from **Table (1)** and **Figures (2-3)** indicate that: all compounds under investigation have moderate activity against all the tested bacterial strains than the standard drug Ampicillin.

## Experimental

### General methods

Melting points were determined on a Stuart melting point apparatus and are uncorrected; IR spectra were recorded in KBr on a Shimadzu 440 spectrometer ( $\nu$ ,  $\text{cm}^{-1}$ ). The  $^1\text{H}$  NMR spectra at 300 MHz were recorded in  $\text{DMSO}-d_6$  on a Varian Mercury VX-300 NMR spectrometer. Chemical shifts ( $\delta$ ) are related to that of the solvent. Mass spectra were measured on a Shimadzu GMMS-QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Microanalytical Center, Cairo University, Cairo (Egypt).

**Synthesis of pyrano[3,4-c]chromene derivatives 4,5,7 and 9: General procedure:** A mixture of chromene derivative **1a** and/or **1b** (0.01 mol), malononitrile, 2-cyanomethylbenzimidazole (**6**), or cyanoacetamide (0.01 mol), piperidine (0.5 ml) in ethanol (30 mL) was heated under reflux for 4 hours, The

resulting solid that obtained on hot was filtered off and recrystallized from dioxane to give **4**, **5**, **7** and **9**, respectively.

**2-Amino-9-bromo-5-oxo-4-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (4)**

Yellow crystals: Yield 90%, mp 330-32°C; Anal. Calcd. for C<sub>19</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 57.74; H, 2.81; N, 7.09. Found: C, 57.61; H, 2.66; N, 6.94.; IR (KBr, cm<sup>-1</sup>): 3344, 3210 (NH<sub>2</sub>), 2210 (C≡N), 1648 (C=O); MS *m/z* (% relative intensity): 394 (27.44), 330 (37.56), 328 (M-CH<sub>2</sub>(CN)<sub>2</sub>, 27.41), 272 (33.50), 251 (32.99), 213 (36.04), 161 (42.64), 77 (100).

**2-Amino-5-oxo-4-phenyl-5,12cH-benzo[f]pyrano[3,4-c]chromene-1-carbonitrile (5)**. Brown crystals: Yield 88%, mp 250-52°C; Anal. Calcd. for C<sub>23</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 75.40; H, 3.85; N, 7.65. Found: C, 75.28; H, 3.77; N, 7.51; IR (KBr, cm<sup>-1</sup>): 3326, 3222 (NH<sub>2</sub>), 2204 (C≡N), 1666 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 3.56 (s, 1H, chromene-H4), 7.26-9.22 (m, 13H, Ar-H + NH<sub>2</sub>-exchangeable with D<sub>2</sub>O).

**2-(1H-Benzo[d]imidazol-2-yl)-2-(3-benzoyl-6-bromo-2-oxochroman-4-yl)acetonitrile (7)**. Yellow crystals: Yield 75%, mp 265-67°C; Anal. Calcd. for C<sub>25</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>3</sub>: C, 61.74; H, 3.32; N, 8.64. Found: C, 61.63; H, 3.26; N, 8.49; IR (KBr, cm<sup>-1</sup>): 3194 (NH), 2960, 2904 (CH-aliphatic), 2222 (CN), 1662 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 3.56 (t, 1H, Chromene-H4), 4.75 (d, 1H, chromene-H3), 5.90 (d, 1H, CH-CN), 6.95-7.48 (m, 12H, Ar-H), 10.65 (s, 1H, NH).

**9-Bromo-2-hydroxy-5-oxo-4-phenyl-5H,10bH-pyrano[3,4-c]chromene-1-carbonitrile (9)**. Yellow crystals: Yield 62%, mp 348-50°C; Anal. Calcd. for C<sub>19</sub>H<sub>10</sub>BrNO<sub>4</sub>: C, 57.60; H, 2.54; N, 3.54. Found: C, 57.45; H, 2.40; N, 3.46; IR (KBr, cm<sup>-1</sup>): 3336 (OH), 2204 (C≡N), 1670 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 3.56 (d, 1H, chromene-H4), 7.31-7.97 (m, 8H, Ar-H), 11.35 (s, 1H, OH-exchangeable with D<sub>2</sub>O).

**Synthesis of pyrano[3,4-c]chromene derivatives 13,14: General procedure:** A mixture of chromene derivative **1a** and/or **1b** (0.01 mol), *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)benzamide (**10**), triethylamine (0.5 ml) in ethanol (30 mL) was heated under reflux for 4hours, The resulting solid that obtained on hot was filtered off and recrystallized from dioxane/DMF to give **13** and **14**.

***N*-(5-(2-Amino-9-bromo-5-oxo-4-phenyl-5H,10bH-pyrano[3,4-c]chromen-1-yl)-1,3,4-thiadiazol-2-yl)benzamide (13)**. Yellow crystals: Yield 58%, mp 338-

40°C; Anal. Calcd. for  $C_{27}H_{17}BrN_4O_4S$ : C, 56.55; H, 2.99; N, 9.77. Found: C, 56.38; H, 2.82; N, 9.65; IR (KBr,  $cm^{-1}$ ): 3302, 3156 ( $NH_2/NH$ ), 1660 (C=O);  $^1H$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta/ppm$ ): 3.56 (s, 1H, chromene-H4), 7.19-8.62 (m, 13H, Ar-H), 9.21, 13.01 (2s, 3H,  $NH_2$  and NHCO-exchangeable with  $D_2O$ ).

***N*-(5-(2-amino-5-oxo-4-phenyl-5H,12cH-benzof[*f*]pyrano[3,4-*c*]-chromen-1-yl)-1,3,4-thiadiazol-2-yl)benzamide (14).** Yellow crystals: Yield 60%, mp 294-96°C; Anal. Calcd. for  $C_{31}H_{20}N_4O_4S$ : C, 68.37; H, 3.70; N, 10.29. Found: C, 68.25; H, 3.64; N, 10.15; IR (KBr,  $cm^{-1}$ ): 3268, 3126 ( $NH_2/NH$ ), 2922 (CH-aliph.), 1658 (C=O);  $^1H$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta/ppm$ ): 3.56 (s, 1H, chromene-H4), 7.45-8.57 (m, 16H, Ar-H), 9.26, 12.99 (2s, 3H,  $NH_2$  and NHCO).

**Synthesis of *N,N'*-(ethane-1,2-diyl)bis[2-amino-9-bromo-5-oxo-4-phenyl-5H,10bH-pyrano[3,4-*c*]chromene-1-carboxamide] (18).**

To a solution of chromene derivative **1a** (0.02 mol), *N,N'*-(ethane-1,2-diyl)bis(2-cyanoacetamide) (**15**) (0.01 mol) and piperidine (0.5 ml) were added in dioxane (30 mL). The reaction mixture was refluxed for 6 hours, The resulting solid that obtained on hot was filtered off and recrystallized from dioxane/DMF to give **18**.

Yellow crystals: Yield 55%, mp 280-82°C; Anal. Calcd. for  $C_{40}H_{28}Br_2N_4O_8$ : C, 56.36; H, 3.31; N, 6.57. Found: C, 56.24; H, 3.27; N, 6.48; IR (KBr,  $cm^{-1}$ ): 3412, 3304 ( $NH_2$ ), 2936, 2854 (CH-aliph.), 1646 (C=O); MS *m/z* (% relative intensity): 850 (50.18), 813 (41.14), 786 (62.03), 764 (54.43), 667 (81.65), 624 (51.90), 573 (71.52), 563 (65.19), 439 (59.95), 378 (92.25), 78 (100).

**Synthesis of 2-Amino-3-(3-benzoyl-6-bromo-2-oxochroman-4-yl)prop-1-ene-1,1,3-tricarbonitrile (21).**

To a solution of chromene derivative **1a** (0.01 mol), 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**20**) (0.01 mol) and piperidine (0.5 ml) were added in ethanol (30 mL). The reaction mixture was refluxed for 4 hours, The resulting solid that obtained on hot was filtered off and recrystallized from dioxane to give **21**.

Yellow crystals: Yield 72%, mp 344-46°C; Anal. Calcd. for  $C_{22}H_{13}BrN_4O_3$ : C, 57.29; H, 2.84; N, 12.15. Found: C, 57.32; H, 2.74; N, 12.06; IR (KBr,  $cm^{-1}$ ): 3308, 3164 ( $NH_2$ ), 2206 (C $\equiv$ N), 1692, 1640 (C=O);  $^1H$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta/ppm$ ): 2.64 (t, 1H, chromene-H4), 3.56 (d, 1H, CH-CN), 4.34 (d, 1H, chromene-H3), 6.91-7.63 (m, 8H, Ar-H), 10.59 (s, 2H,  $NH_2$ -exchangeable with  $D_2O$ ).

**11-Bromo-6-phenyl-2,12b-dihydro-1H,7H-chromeno[4',3':4,5]pyrano-[2,3-**

**d]pyrimidine-1,7-dione (24).** To a solution of compound **4** (0.01 mol) formic acid (20 mL) was added. The reaction mixture was heated under reflux for 5h. The solid product formed was collected by filtration and recrystallized from dioxane to give **24**.

Brown crystals: Yield 63%, mp 180-82°C; Anal. Calcd. for C<sub>20</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>4</sub>: C, 56.76; H, 2.62; N, 6.62. Found: C, 56.59; H, 2.53; N, 6.54; IR (KBr, cm<sup>-1</sup>): 3332 (NH), 1678, 1650 (C=O); MS *m/z* (% relative intensity): 422 (53.02), 408 (46.98), 327 (53.02), 283 (34.90), 235 (52.35), 173 (52.35), 165 (42.28), 135 (63.09), 105 (100), 77 (89.93).

**1-Amino-11-bromo-3-(4-methoxyphenyl)-7-oxo-6-phenyl-7H,12bH-chromeno[4',3':4,5]pyrano[2,3-b]pyridine-2-carbonitrile (28).**

A solution of compound **4** (0.01 mol), 4-methoxybenzylidenemalononitrile (**25**) (0.01 mol) and piperidine (0.5 mL) in dioxane (30 mL) was heated under reflux for 6h. The solid product formed on heating was collected by filtration to give **28**.

Brown crystals: Yield 77%, mp 320-22°C; Anal. Calcd. for C<sub>29</sub>H<sub>18</sub>BrN<sub>3</sub>O<sub>4</sub>: C, 63.06; H, 3.28; N, 7.61. Found: C, 62.92; H, 3.14; N, 7.48; IR (KBr, cm<sup>-1</sup>): 3294, 3233 (NH<sub>2</sub>), 2212 (C≡N), 1650 (C=O); MS *m/z* (% relative intensity): 551 (68.97), 485 (65.25), 435 (75.56), 288 (85.47), 77 (100).

**6-Bromo-N-(4-ethoxyphenyl)-2-imino-2H-chromene-3-carboxamide (31):**

A mixture of cyanoacetamide derivative **30** (0.01 mol) and 5-bromo salicylaldehyde (**29**) (0.01 mol), few drops of piperidine as a catalyst was refluxed in ethanol (30 ml) for 3h. The resulting solid that obtained on hot was filtered off and recrystallized from dioxane to give **31**.

Yellow crystals: Yield 85%, mp 165-67°C; Anal. Calcd. for C<sub>18</sub>H<sub>15</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.72; H, 3.85; N, 7.15; IR (KBr, cm<sup>-1</sup>): 3272 (NH), 2950 (CH-aliph.), 1664 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 1.31 (t, 3H, CH<sub>3</sub>), 4.02 (q, 2H, CH<sub>2</sub>), 6.89-8.08 (m, 7H, Ar-H), 8.50 (s, 1H, chromene-H4), 9.33, 12.51 (2s, 2H, 2NH exchangeable with D<sub>2</sub>O).

**Synthesis of chromeno[3,4-c]pyridine derivatives 34, 37, 40, 43: General procedure:** A mixture of chromene derivative **31** (0.01 mol), and active methylene compound namely [malononitrile, ethyl cyanoacetate, cyanoacetamide, 2-cyanomethyl-benzimidazole (**6**), and/or *N*-(5-(cyanomethyl)-1,3,4-thiadiazol-2-yl)-benzamide (**10**) (0.01 mol), piperidine (0.5 mL) in dioxane (30 mL) was heated under



reflux for 6 hours, The resulting solid that obtained on hot was filtered off and recrystallized from dioxane/DMF to give **34**, **37**, **40**, **43**, respectively.

**2-Amino-9-bromo-1-cyano-3-(4-ethoxyphenyl)-5-imino-3,5-dihydro-4H-chromeno[3,4-c]pyridin-4-one (34)**. Brown crystals: Yield 90%, mp 340-42°C; Anal. Calcd. for C<sub>21</sub>H<sub>15</sub>BrN<sub>4</sub>O<sub>3</sub>: C, 55.89; H, 3.35; N, 12.42. Found: C, 55.70; H, 3.24; N, 12.29; IR (KBr, cm<sup>-1</sup>): 3342, 3312, 3210 (NH<sub>2</sub>/NH), 2208 (C≡N), 1648 (C=O); MS *m/z* (% relative intensity): 450 (26.17), 329 (16.82), 263 (19.63), 221 (24.30), 153 (29.60), 81 (47.66), 69 (100), 55 (67.60).

**9-Bromo-1-cyano-3-(4-ethoxyphenyl)-2-hydroxy-5-imino-3,5-dihydro-4H-chromeno[3,4-c]pyridin-4-one (37)**. Yellow crystals: Yield 80%, mp 210-12°C; Anal. Calcd. for C<sub>21</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>4</sub>: C, 55.77; H, 3.12; N, 9.29. Found: C, 55.61; H, 3.04; N, 9.20; IR (KBr, cm<sup>-1</sup>): 3408 (OH), 3310 (NH), 3060 (CH-arom.), 2950 (CH-aliph.), 2206 (C≡N), 1724 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 1.51 (t, 3H, CH<sub>3</sub>), 3.04 (q, 2H, CH<sub>2</sub>), 7.19-8.34 (m, 7H, Ar-H), 9.12 (s, 1H, NH), 10.82 (s, 1H, OH). MS *m/z* (% relative intensity): 451 (27.61), 429 (33.26), 325 (31.36), 285 (29.95), 208 (28.66), 178 (34.72), 137 (75.56), 69 (98.72), 55 (100).

**2-Amino-1-(1H-benzo[d]imidazol-2-yl)-9-bromo-3-(4-ethoxyphenyl)-5-imino-3,5-dihydro-4H-chromeno[3,4-c]pyridin-4-one (40)**. Brown crystals: Yield 65%, mp 230-32°C; Anal. Calcd. for C<sub>27</sub>H<sub>20</sub>BrN<sub>5</sub>O<sub>3</sub>: C, 59.79; H, 3.72; N, 12.91. Found: C, 59.65; H, 3.61; N, 12.84; IR (KBr, cm<sup>-1</sup>): 3396, 3260 (NH<sub>2</sub>/NH), 2972 (CH-aliph.), 1710 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 1.31 (t, 3H, CH<sub>3</sub>), 4.02 (q, 2H, CH<sub>2</sub>), 6.91-8.26 (m, 11H, Ar-H), 9.14 (s, 2H, NH<sub>2</sub>-exchangeable with D<sub>2</sub>O), 8.82, 10.45 (2s, 2H, 2NH exchangeable with D<sub>2</sub>O).

**2-Amino-9-bromo-1-(2-benzamido-1,3,4-thiazol-5-yl)-3-(4-ethoxy-phenyl)-5-imino-3,5-dihydro-4H-chromeno[3,4-c]pyridin-4-one (43)**. Brown crystals: Yield 60%, mp 275-77°C; Anal. Calcd. for C<sub>29</sub>H<sub>21</sub>BrN<sub>6</sub>O<sub>4</sub>S: C, 55.33; H, 3.36; N, 13.35. Found: C, 55.27; H, 3.29; N, 13.24; IR (KBr, cm<sup>-1</sup>): 3340, 3156 (NH<sub>2</sub>/NH), 2976 (CH-aliph.), 1728, 1666 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 1.35 (t, 3H, CH<sub>3</sub>), 4.06 (q, 2H, CH<sub>2</sub>), 6.97-8.23 (m, 12H, Ar-H), 8.61 (s, 2H, NH<sub>2</sub>), 9.08 (s, 1H, NH), 12.96 (s, 1H, NHCO).

**2-Bromo-8-(4-ethoxyphenyl)-9,10,11,12-tetrahydro-6H-chromeno-[3,4-c]quinoline-6,7(8H)-dione (47)**. A mixture of chromene derivative **31** (0.01 mol), cyclohexanone (0.01 mol), sodium acetate (0.5 g) in ethanol (30 mL) was heated under reflux for 6 hours, The resulting solid that obtained on hot was filtered off and recrystallized from dioxane to give **47**.

## THE UTILITY OF BENZOYLCHROMENE AND 2-IMINOCHR ..... 129

White crystals: Yield 70%, mp 290-92°C; Anal. Calcd. for C<sub>24</sub>H<sub>20</sub>BrNO<sub>4</sub>: C, 61.82; H, 4.32; N, 3.00. Found: C, 61.69; H, 4.21; N, 2.89; IR (KBr, cm<sup>-1</sup>): 3260 (NH), 2940, 2870 (CH-aliph.), 1668 (C=O); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ/ppm): 1.33 (t, 3H, CH<sub>3</sub>), 1.47-1.64 (m, 8H, cyclohexyl-H), 4.04 (q, 2H, CH<sub>2</sub>), 6.96-7.55 (m, 7H, Ar-H).

### Antimicrobial Assay :

In the agar diffusion method [36-37] compounds dissolved in dimethylformamide (DMF) at a concentration of 100 mg/mL were used. Agar media seeded with the tested microorganisms were poured in Petri dishes and were allowed to solidify, and then holes of about 7 mm were punched in the agar using a sterile cork porrer. A 50-μl volume of the dissolved compounds were added to the pores and DMF was included as solvent control. Plates were allowed to stand in a refrigerator for two hours before incubation to allow the tested compounds to diffuse through the agar. The plates containing bacterial cultures were incubated at 37°C for 24 h and those containing yeasts were incubated at 30°C for 48h. After incubation, the growth inhibition zones around the holes were observed, indicating that the examined compound inhibits the growth of microorganism. The tested microorganisms were obtained from the Regional Center for Mycology & Biotechnology (RCMP), Al-Azhar University.

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THE UTILITY OF BENZOYLCHROMENE AND 2-IMINOCHR ..... 131

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