Synthesis and Antimicrobial Evaluation of the Novel Heteroannulated Furo[3`,2`:6,7]chromeno[2,3-*b*]pyridines: Part 1

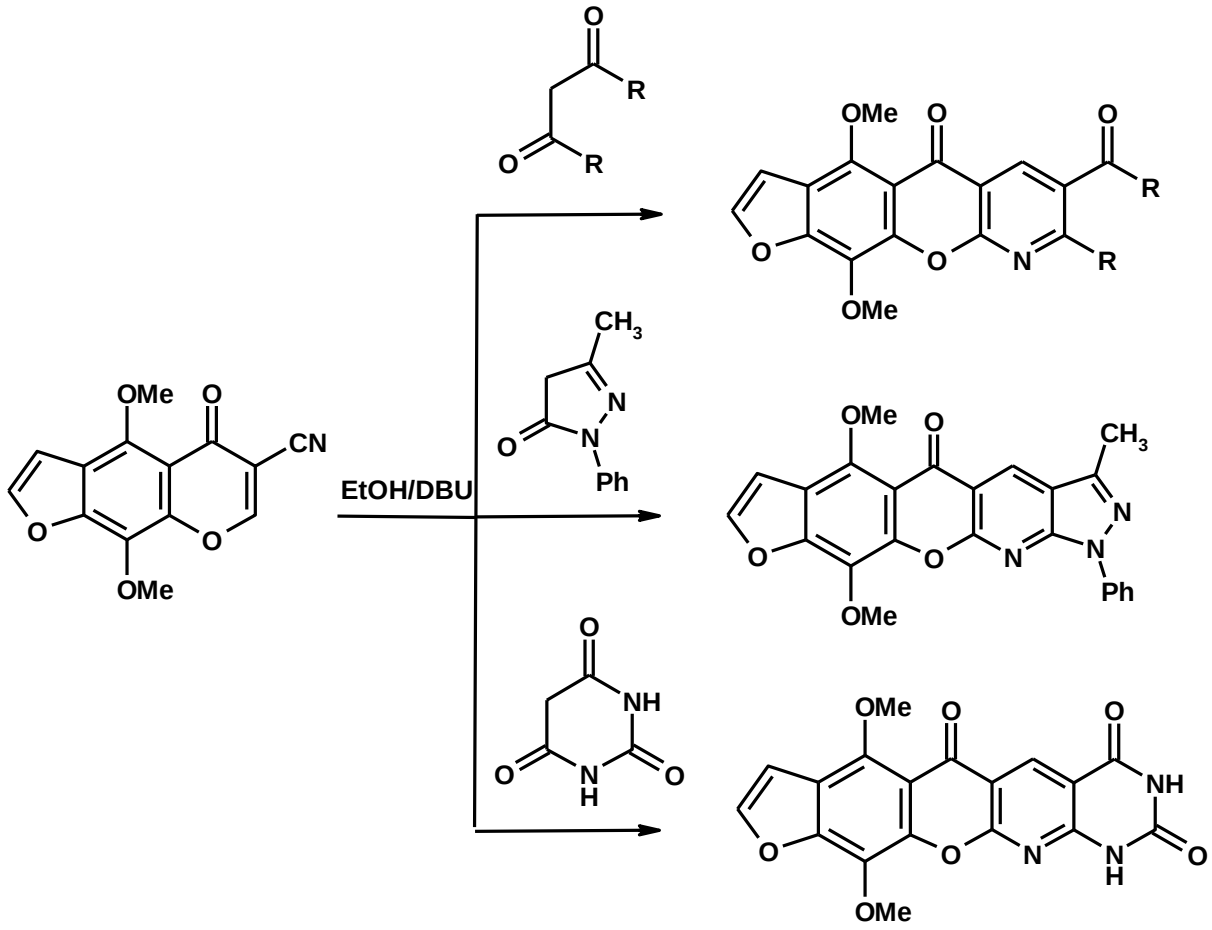
Magdy A. Ibrahim,* Sami A. Al-Harbi[b] and Esam Allehyani[b]

[a] *Department of Chemistry, Faculty of Education, Ain Shams University, Heliopolis 11757, Cairo, Egypt.*

[b] *Department of Chemistry, University College in Al-Jamoum, Umm Al-Qura University, Makkah, Saudi Arabia*

*****E-mail: magdy_ahmed1977@yahoo.com

Graphical abstract:



Author to whom correspondence should be addressed; Magdy A. Ibrahim. E-mail address: magdy_ahmed1977@yahoo.com

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Abstract

The chemical behavior of 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) was investigated towards some acyclic and cyclic active methylene ketones namely; acetylacetone, ethyl acetoacetate, ethyl benzoylacetate, acetoacetanilide, dimedone, indanedione, pyrazolidine-3,5-dione and 5-methyl-2- phenyl-2,4-dihydro-3*H*-pyrazol-3-one, barbituric acid and 1-allylthiobarbituric acid and hippuric acid. A variety of novel heteroannulated furochromenopyridines were efficiently synthesized through a cascade reactions between 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) and the carbon nucleophilic reagents. Structures of the new products were inferred based on their analytical and spectral data.

Keywords: Khellin-6-carbonitrile, RORC, cascade reactions, furochromenopyridines, furochromenopyridopyrimidines**,** cyclocondensation.

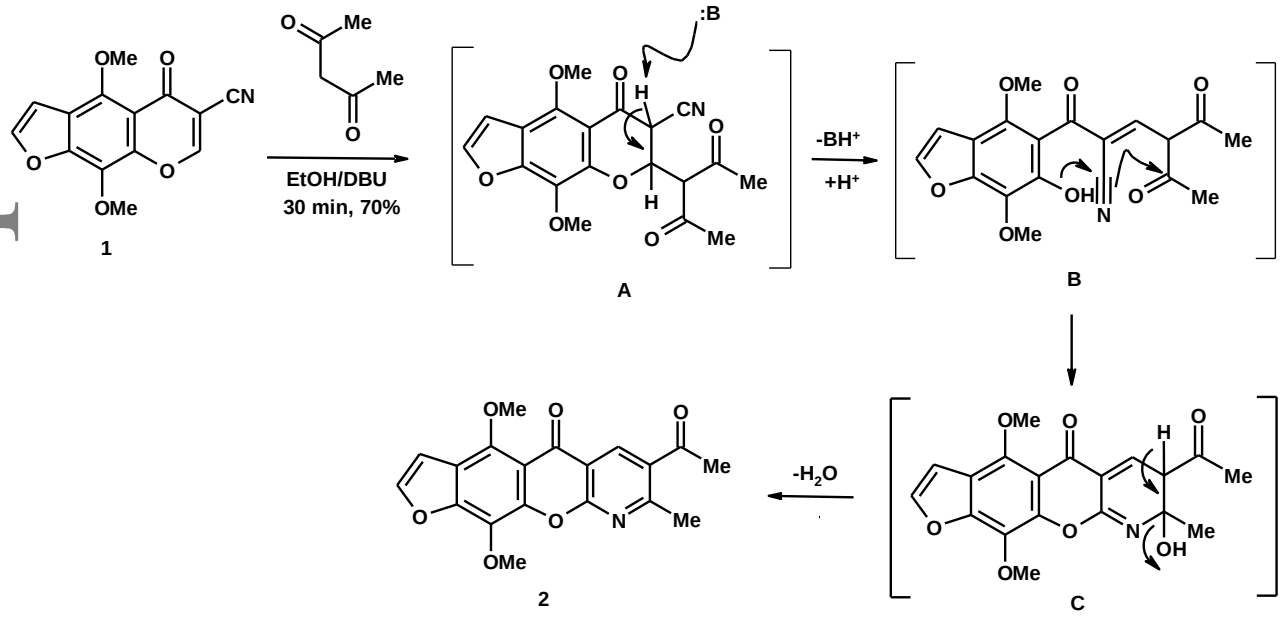
1. INTRODUCTION

Khellin (4,9-dimethoxy-7-methyl-5*H*-furo[3,2-g]chromen-5-one) is a furochromone derivative extracted from the seeds of *Ammi visnaga* [1]. Khellin used in the photochemotherapy of dermatoses such as vitiligo and psoriasis [2], and possess a high antiatherosclerotic activity [3,4]. Determination of khellin in *Ammi visnaga* fruits was achieved by using capillary electrophoresis [5]. Khellin used for the treatment of angina [6], and kidney stone as well as a spasmolytic agent [7]. The interaction and binding properties of khellin with DNA have been studied [8, 9]. Khellin prevent cell damage caused by oxalate in renal epithelial cells [10]. DFT-theoretical calculations were used for inspection of the optimized geometries of some furo[3,2-g]chromenes [11-13]. In addition, the spectral properties, photoelectrical, photosensitivity, and photodiode studies were performed for a diversity furo[3,2-g]chromenes [14-16]. Biological activity is well known for furo[3,2-g]chromenes such as antimicrobial [17], anticancer [18], antitumor [19], anti-HIV [20], analgesic and anti-inflammatory activities [21-23]. The ring-opening ring closure (RORC) reactions of chromone-3-carbonitrile are well known [24-27]. Khellin-6-carbonitrile (4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile) [28] may represent a good precursor for building of novel heterocyclic systems fused furo[3,2-g]chromenes due to the unique position of carbonitrile functional group in khellin-6-carbonitrile which is typically similar to chromone-3-carbonitrile. The present work is devoted to study the chemical transformations of 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) towards a variety of acyclic and cyclic active methylene compounds, bearing $–CH_2$-

CO- group, hoping to construct a series of novel heteroannulated furo[3`,2`:6,7]chromeno[2,3-*b*] pyridines and evaluate their antimicrobial activity.

2. RESULTS AND DISCUSSION

Treatment of 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) with acetylacetone, in boiling ethanol containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a basic catalyst, yielded 7-acetyl-4,11-dimethoxy-8-methyl-5-oxo-5*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyridine (**2**) (Scheme 1). The reaction may occur through *Michael* addition at C-7 position giving intermediate **A** followed by retro-*Michael* reaction with ring opening giving intermediate **B** which underwent two successive cycloaddition reactions forming intermediate **C**. Dehydration of the later intermediate afforded the target product **2** as described in Scheme 1. Characteristic absorption bands appeared in the IR spectrum at 1694 ($C{=}O_{acetyl}$), 1651 ($C{=}O_{\gamma\text{-pyrone}}$) and 1608 cm^{-1} (C=N). Also, specific singlet signals observed in the ^1H NMR spectrum at δ 2.67 ($CH_{3\ pyridine}$), 2.88 ($CH_{3\ acetyl}$) and 8.56 ppm (H-6). The ^{13}C NMR spectrum of compound **2** showed specific signals at δ 19.8 ($CH_{3\ pyridine}$), 28.1 ($CH_{3\ acetyl}$), 176.6 ($C{=}O_{\gamma\text{-pyrone}}$) and 192.9 ($C{=}O_{acetyl}$). The structure of compound **2** was also confirmed from its mass spectrum which recorded the molecular ion peak at m/z 353.

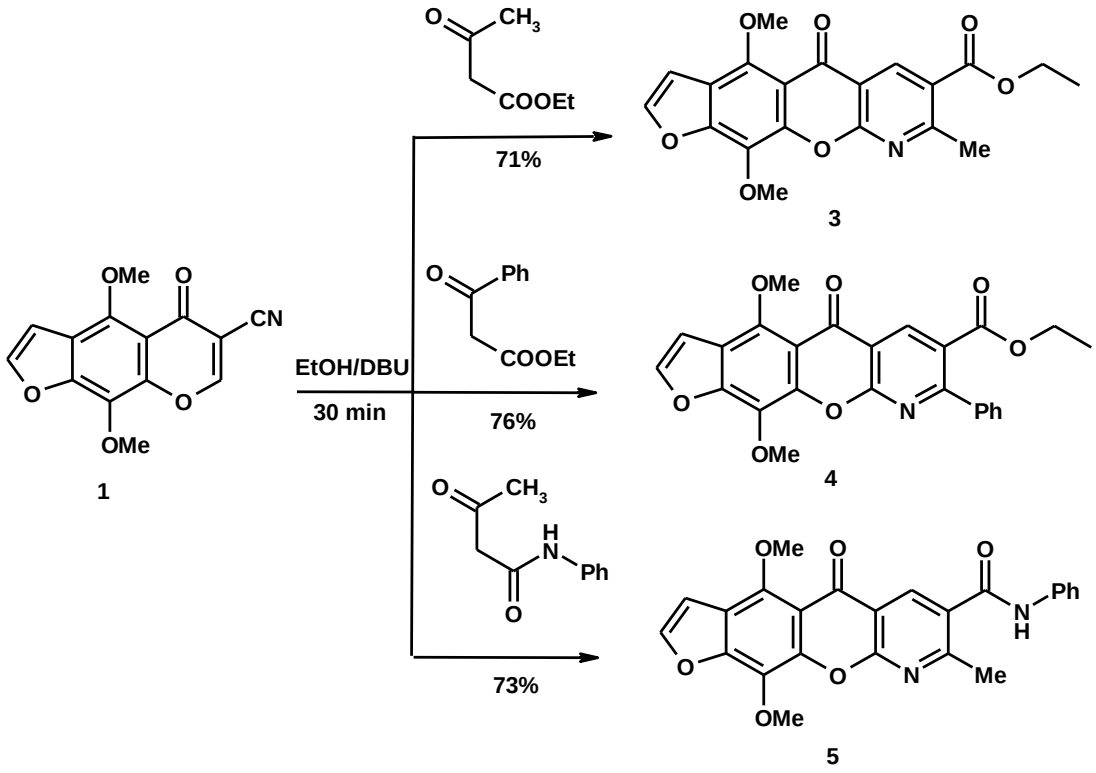


Scheme 1: The suggested mechanism for reaction of carbonitrile **1** with acetylacetone.

Furochromenopyridine-6-carboxylates **3** and **4** were similarly prepared from reactions of substrate **1** with ethyl acetoacetate and ethyl benzoylacetate (Scheme 2) [29]. Compounds **3** and **4** showed typical absorption bands in their IR spectra at 1690/1696 ($C{=}O_{ester}$), 1656/1659 ($C{=}O_{\gamma\text{-pyrone}}$)

and 1612/1611 cm^{-1} (C=N), respectively. A distinctive singlet appeared in their ^1H NMR spectra at δ 8.75 and 8.78 ppm, assignable to H-6. The spectrum of compound **3** revealed specific singlet attributed to $CH_{3\ pyridine}$ at δ 2.75 ppm.

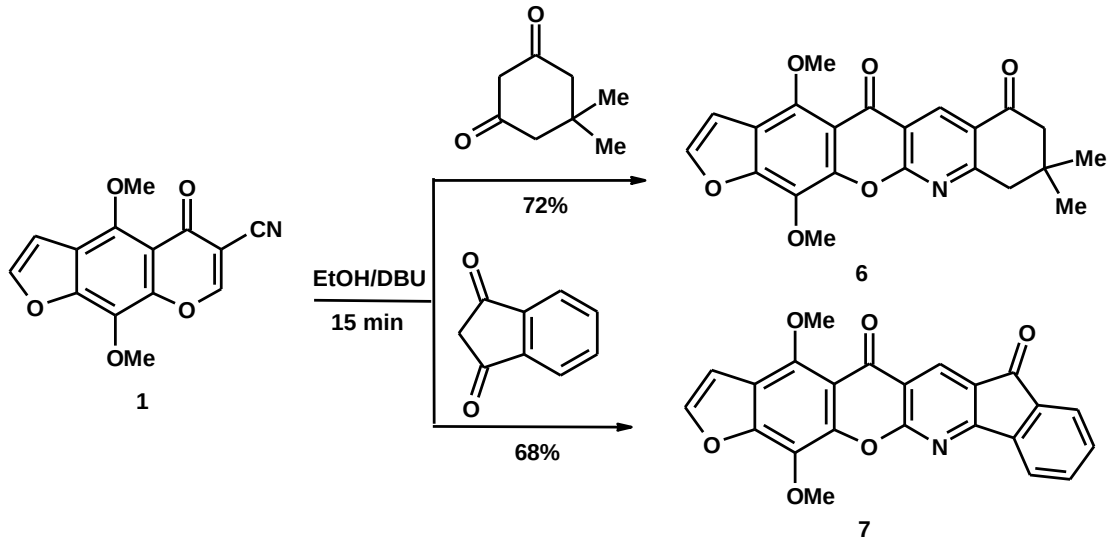
Under the previous reaction conditions, treatment of carbonitrile **1** with acetoacetanilide produced furo[3`,2`:6,7]chromeno[2,3-*b*]pyridine-7-carboxamide **5** (Scheme 2). The IR spectrum of compound **5** showed distinctive absorption bands at 1667 ($C=O_{amide}$), 1655 ($C=O_{\gamma\text{-pyrone}}$) and 1613 (C=N) cm^{-1}. The ^{13}C NMR spectrum of compound **5** revealed typical signals at δ 19.3 ($CH_{3\ pyridine}$), 168.9 ($C=O_{amide}$) and 176.2 ($C=O_{\gamma\text{-pyrone}}$). Its mass spectrum exhibited the parent ion peak at m/z 430 which approves the proposed molecular formula $C_{24}H_{18}N_2O_6$.



Scheme 2: Formation of furo[3`,2`:6,7]chromeno[2,3-*b*]pyridines **3-5**.

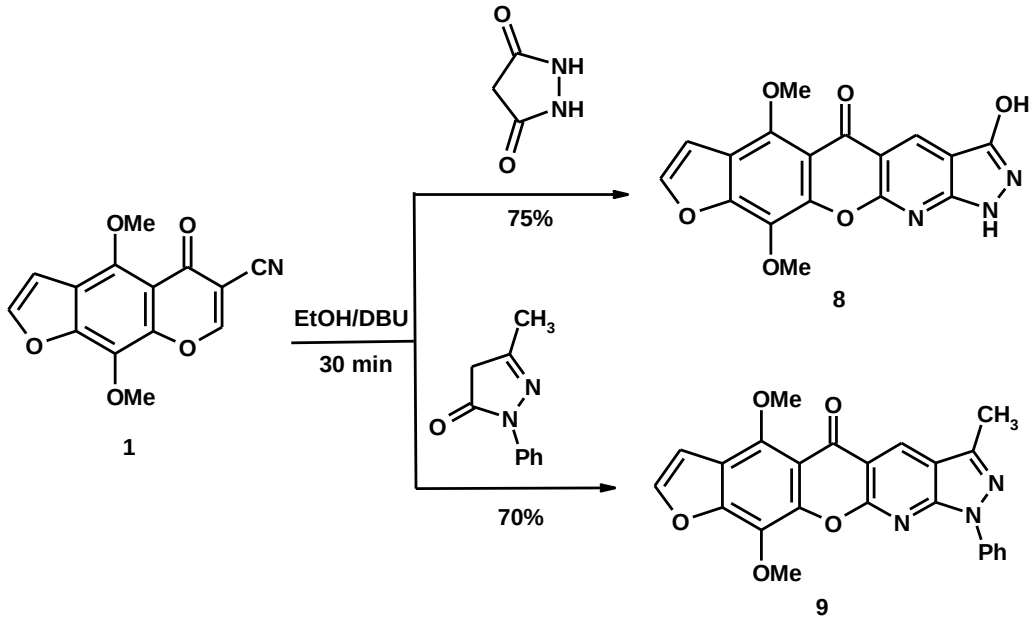
Also, the present research was extended to study the behavior of carbonitrile **1** towards some cyclic carbon nucleophiles aiming to construct a variety of novel heteroannulated furochromenes. Therefore, reaction of dimedone with carbonitrile **1**, gave furochromenoquinoline derivative **6**, in 72% yield (Scheme 3) [30]. Distinctive absorption bands observed in the IR spectrum at 1683 ($C=O_{quinolinone}$), 1659 ($C=O_{\gamma\text{-pyrone}}$) and 1605 cm^{-1} (C=N). Its ^1H NMR spectrum exhibited singlet signal assigned to H-6 at δ 8.76. Structure of compound **6** was also deduced from its mass spectrum which revealed the molecular ion peak at m/z 393, and the base peak at m/z 365 corresponding to the molecular ion after loss of CO molecule.

In the same manner, the linear heteroannulated hexafused furo[3`,2`:6,7]chromeno[2,3-*b*]indeno[2,1-*e*]pyridine derivative **7** was synthesized by reacting carbonitrile **1** with 1,3-indanedione in absolute ethanol (Scheme 3) [31]. The IR spectrum of compound **7** showed distinctive absorption bands at 1720 ($C=O_{indanone}$), 1661 ($C=O_{\gamma\text{-pyrone}}$) and 1612 cm^{-1} (C=N). Its ^1H NMR spectrum showed specific singlet at δ 8.57 assigned to $H\text{-}4_{pyridine}$. The mass spectrum of compound **7** exhibited the parent ion peak at m/z 399, as the base peak, which agrees well with the suggested molecular formula $C_{23}H_{13}NO_6$ and supports the structure.



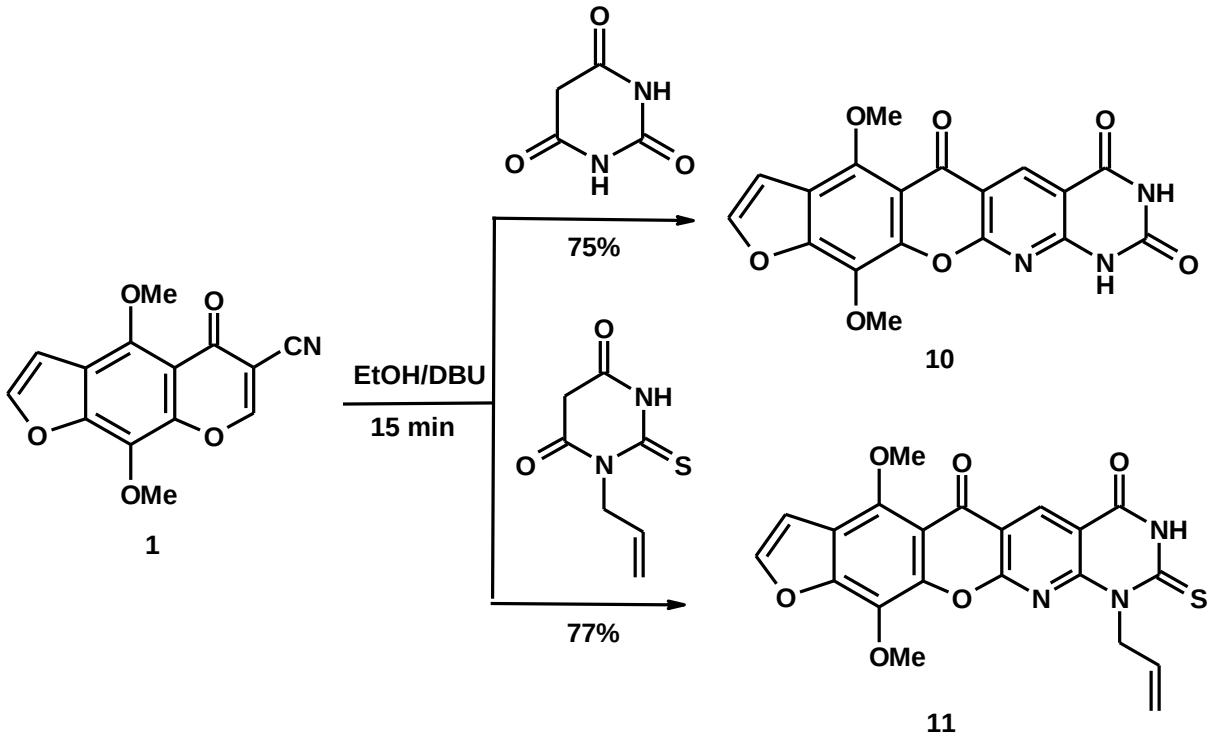
Scheme 3. Formation of linear heteroannulated furochromenes **6** and **7**.

Next, carbonitrile **1** was allowed to react with some heterocyclic compounds containing active methylene group aiming to build a novel linear heteroannulated systems containing furochromenes. Boiling substrate **1** with pyrazolidine-3,5-dione and 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one, in absolute ethanol containing DBU, furnished the novel furo[3`,2`:6,7]chromeno[2,3-*b*]pyrazolo[4,3-*e*]pyridines **8** and **9**, respectively (Scheme 4). The IR spectra of compounds **8** and **9** showed specific bands corresponding to $C=O_{\gamma\text{-pyrone}}$ at 1653 and 1664 cm^{-1}, respectively. The ^1H NMR spectra of compounds **8** and **9** showed distinctive singlet signal assignable to H-6 at δ 8.71 and 8.69, respectively. The spectrum of compound **9** showed upfield singlet signal assigned to $CH_{3pyrazole}$ at δ 2.12, while the spectrum of compound **8** showed two D_2O-exchangeable signals attributed to NH and OH protons at δ 11.21 and 13.64, respectively. Furthermore, the mass spectra for compounds **8** and **9** recorded their molecular ion peaks that agree with the proposed formula weights at 353.29 and 427.41, respectively.



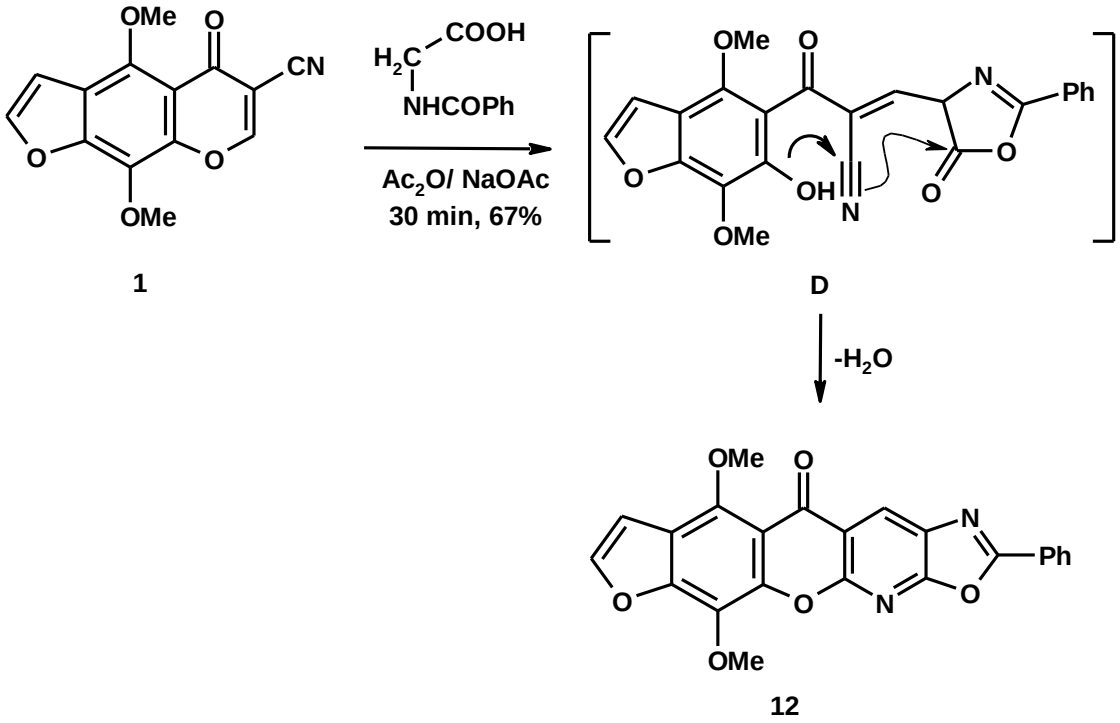
Scheme 4. Formation of furo[3`,2`:6,7]chromeno[2,3-*b*]pyrazolo[4,3-*e*]pyridines **8** and **9**.

Also, the novel furo[3``,2``:6`,7`]chromeno[3`,2`:5,6]pyrido[2,3-*d*]pyrimidines **10** and **11** were efficently prepared from base catalysed ring opening ring closure reactions of carbonitrile **1** with barbituric acid and 1-allylthiobarbituric acid, respectively (Scheme 5) [31]. The IR spectra of compounds **10** and **11** showed specific absorption bands at 1692/1707 and 1656/1649 cm^{-1} assigned to $C{=}O_{pyrimidinone}$ and $C{=}O_{\gamma\text{-}pyrone}$, respectively. Definite singlet observed in ^{1}H NMR spectra of compounds **10** and **11**, attributed to H-6 at δ 8.82 and 8.85, respectively. The parent ion peaks appeared in the mass spectra of compounds **10** and **11** at m/z 381 and 437 that agree well with the proposed molecular formula weights $C_{18}H_{11}N_3O_7$ and $C_{21}H_{15}N_3O_6S$ and confirm the proposed structures.



Scheme 5. Formation of furo[3``,2``:6`,7`]chromeno[3`,2`:5,6]pyrido[2,3-*d*]pyrimidines **10** and **11**.

Finally, reaction of compound **1** with hippuric acid in boiling acetic anhydride in the presence of freshly fused sodium acetate produced the novel linear furo[3`,2`:6,7]chromeno[2,3-*b*][1,3]oxazolo[4,5-*e*]pyridine **12** (Scheme 6) [29]. The reaction occurs *via* the preliminary formation of 2-phenyloxazol-5-one (as a non-isolable intermediate) which reacted with compound **1** giving intermediate **D** which cyclized through cycloaddition and cyclocondensation reactions leading to the final product **12**. In the IR spectrum, specific absorption band for only one carbonyl group appeared at 1653 cm^{-1} ($C=O_{\gamma\text{-pyrone}}$). The ^{1}H NMR spectrum showed typical singlet signal attributable to H-6 at δ 8.75. Compound **12** was also confirmed from its mass spectrum which revealed the parent ion peak at m/z 414 that coincident well with the suggested formula weight (414.37).



Scheme 6: Formation of furo[3`,2`:6,7]chromeno[2,3-*b*][1,3]oxazolo[4,5-*e*]pyridine **12**.

3. ANTIMICROBIAL EVALUATION

The prepared compounds were tested for their in *vitro* antibacterial activity against Gram-positive bacteria namely *Staphylococcus aureus* (ATCC25923) and *Bacillus subtilis* (ATCC6635), and Gram-negative bacteria namely *Salmonella typhimurium* (ATCC 14028) and *Escherichia coli* (ATCC 25922). They were also estimated against yeast (*Candida albicans* ATCC 10231) and fungus (*Asperigillus fumigatus*). The test was performed on medium potato dextrose agar (PDA) which contained infusion of 200 g potatoes, 6 g dextrose and 15 g agar [32]. Uniform size filter paper disks (3 disks per compound) were impregnated by equal volume (10 µl) from the concentrations of 500 and 1000 µg/mL dissolved compounds in dimethylformamide (DMF) and carefully placed on inoculated agar surface. After incubation for 36 h at 27 °C in the case of bacteria and for 48 h at 24°C in the case of fungi. The obtained results were recorded for each tested compound as average diameter of inhibition zones of the bacteria and fungus around the disks in mm at the concentrations 500 and 1000 µg/mL. The antimicrobial activities were determined by measuring the inhibition zones, including the diameter of the disc (6 mm) (Table 1). The results represented in Table 1 appeared that:

[1] Most of the investigated compounds presented different inhibitory effects on the growth of the tested microorganisms, and the antimicrobial activity varies from low to high activities.

[2] Compounds **5** and **8** recorded high activity against *Bacillus subtilis* as Gram-positive bacteria, *Escherichia coli* as Gram-negative bacteria and *Asperigillus fumigatus* as the fungal strain. Also, compounds **9-11** revealed high antifungal activity towards *Asperigillus fumigatus*. In addition, compound **11** recorded high antimicrobial activity against the Gram-negative bacteria, *Escherichia coli*.

[3] The high activity of some of the prepared compounds **5** and **8-11** towards certain microorganisms, may attribute to the presence of additional electron rich nitrogen and oxygen heteroatoms (NH, C=O and OH) within the molecule.

[4] The above results appeared that, some of the prepared compounds recorded high antimicrobial activity as comparable with the reference drugs and may serve as antimicrobial agents.

Table 1: In *vitro* antimicrobial evaluations of the prepared compounds at 500 and 1000 μg/mL by disc diffusion assay**.**

	Mean* of zone diameter(mm)											
	Gram - positive bacteria				**Gram - negative bacteria**				**Yeasts and Fungi**			
	Staphylococcus aureus		*Bacillus subtilis*		*Salmonella typhimurium*		*Escherichia coli*		*Candida albicans*		*Asperigillus fumigatus*	
Compd. No.	1000 μg/ml	500μg/ml	1000 μg/ml	500 μg/ml	1000 μg/ml	500 μg/ml	1000 μg/ml	500 μg/ml	1000 μg/ml	500 μg/ml	1000 μg/ml	500 μg/ml
2	9 L	6 L	11 L	7 L	14 I	10 I	18 I	13 I	18 I	14 I	15 I	10 I
3	11 L	7 L	10 L	6 L	18 I	14 I	16 I	11 I	17 I	12 I	17 I	12 I
4	10 L	6 L	14 I	8 L	16 I	11 I	17 I	11 I	20 I	14 I	16 I	10 I
5	17 I	12 I	**24 H**	**19 H**	17 I	13 I	**25 H**	**19 H**	18 I	13 I	**27 H**	**20 H**
6	18 I	13 I	13 I	7 L	16 I	10 I	15 I	9 I	15 I	10 I	14 I	9 I
7	10 L	7 L	10 L	6 L	13 I	10 I	14 I	9 I	16 I	11 I	15 I	9 I
8	16 I	11 I	**16 H**	**20 H**	16 I	11 I	**29 H**	**22 H**	15 I	10 I	**26 H**	**21 H**
9	17 I	13 I	20 I	13 I	19 I	14 I	19 I	12 I	16 I	12 I	**28 H**	**22 H**
10	14 I	10 I	18 I	11 I	21 I	15 I	18 I	14 I	19 I	14 I	**25 H**	**19 H**
11	16 I	10 I	19 I	14 I	19 I	13 I	**27 H**	**21 H**	21 I	15 I	**26 H**	**19 H**
12	11 L	8 L	10 L	6 L	19 I	16 I	17 I	12 I	16 I	11 I	19 I	14 I
S	35	26	35	25	36	28	38	27	35	28	37	26

* Calculated from 3 values.

L = Low activity, I = Intermediate activity, H = High activity, S: Standard drug

S: Standard drug such as Chloramphencol in the case of Gram-positive bacteria, Cephalothinin the case of Gram-negative bacteria and cycloheximide in the case of yeast and fungi.

4. CONCLUSIONS

In conclusion, the chemical transformations of electron deficient; 4,9-dimethoxy-5-oxo-5*H*-furo [3,2-*g*]chromene-3-carbonitrile (**1**) was investigated towards some acyclic and cyclic active methylene ketones containing –CH_2CO– moiety. Khellin-6-carbonitrile (**1**) represents a key intermediate for construction of a new category of heteroannulated furochromens. A novel series of linear furo[3`,2`:6,7]chromeno[2,3-*b*]pyridines, furo[3`,2`:6,7]chromeno[2,3-*b*]pyrazolo[4,3-*e*]pyridines, furo[3``,2``:6`,7`]chromeno[3',2':5,6]pyrido[2,3-*d*]pyrimidines and furo[3`,2`:6,7]chromeno[2,3-*b*][1,3]oxazolo[4,5-*e*]pyridine were efficiently synthesized. Reactions of 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) with carbon nucleophilic reagents occur throughout a cascade reactions involving ring opening followed by a diversity of ring closure (RORC) reactions.

5. EXPERIMENTAL

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on FTIR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using GC-2010 Shimadzu Gas chromatography instrument mass spectrometer (70 eV). Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer. The purity of the synthesized compounds was tested using TLC. 4,9-Dimethoxy-5-oxo-5*H*- furo[3,2-*g*]chromene-3-carbonitrile (**1**) was prepared according to literature [28].

General procedures for reaction of carbonitrile 1 with active methylene nucleophiles: Formation of heteroannulated furochromenopyridines 2-11.

A mixture of carbonitrile **1** (0.54 g, 2 mmol) and the active methylene nucleophiles namely acetylacetone, ethyl acetoacetate, ethyl benzoylacetate, acetoacetanilide, dimedone, indane-1,3-dione, pyrazolidine-3,5-dione, 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one**,** barbituric acid and 1-allylbarbituric acid (2 mmol) in absolute ethanol (20 mL) in the presence of DBU (0.1 mL) was heated under reflux for 30 min.

7-Acetyl-4,11-dimethoxy-8-methyl-5-oxo-5*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyridine (2). Crystallized from EtOH as pale yellow crystals, mp 285-286 ºC, yield (0.51 g, 72%). IR (KBr, cm^{-1}): 3115 (CH_{furan}), 2962, 2933 ($CH_{aliph.}$), 1694 ($C=O_{acetyl}$), 1651 ($C=O_{\gamma\text{-pyrone}}$), 1608 (C=N), 1575 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.67 (s, 3H, $CH_{3\ pyridine}$), 2.88 (s, 3H, $CH_{3\ acetyl}$), 3.86 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.14 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.92 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.56 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 19.8 ($CH_{3\ pyridine}$), 28.1 ($CH_{3\ acetyl}$), 58.2 (OCH_3), 59.1 (OCH_3), 104.6, 106.1, 108.4, 114.6, 115.0, 126.4, 128.2, 140.3, 141.9, 145.4, 147.6, 152.8, 158.3, 176.6, 192.9. Mass spectrum (*m/z*, *I* %): 353 (M^+; 29), 325 (100), 295 (41), 280 (23), 236 (28), 220 (47), 205 (16), 191 (28), 177 (7), 147 (10), 118 (21), 77 (63), 64 (38). Anal. Calcd for $C_{19}H_{15}NO_6$ (353.33): C, 64.59; H, 4.28; N, 3.96%. Found: C, 64.43; H, 4.04; N, 3.86%.

Ethyl 8-methyl-4,11-dimethoxy-5-oxo-5*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyridine-7-carboxylate (3). Crystallized from AcOH as white crystals, mp 275-276 ºC, yield (0.55 g, 71%). IR (KBr, cm^{-1}): 3117 (CH_{furan}), 2974, 2926 ($CH_{aliph.}$), 1690 ($C=O_{ester}$), 1656 ($C=O_{\gamma\text{-pyrone}}$), 1612 (C=N), 1567 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.43 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 2.75 (s, 3H, $CH_{3\ pyridine}$), 3.84 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.27 (q, 2H, *J* =7.2 Hz, CH_2CH_3), 7.18 (d, 1H, *J*=2.1 Hz, H-3_{furan}), 7.96 (d, 1H, *J*=2.1 Hz, H-2_{furan}), 8.75 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 15.7 (CH_3), 18.7 ($CH_{3\ pyridine}$), 58.4 (OCH_3), 59.6 (OCH_3), 60.4 (CH_2), 105.6, 107.4, 112.5, 114.8, 119.4, 128.2, 140.2, 142.5, 144.8, 147.5, 152.3, 159.8, 160.7, 165.3, 176.2. Mass spectrum (*m/z*, *I* %): 383 (M^+; 34), 353 (52), 338 (100), 310 (14), 282 (25), 242 (43), 220 (65), 205 (6), 147 (14), 134 (32), 118 (72), 77 (38), 64 (66). Anal. Calcd for $C_{20}H_{17}NO_7$ (383.35): C, 62.66; H, 4.47; N, 3.65%. Found: C, 62.42; H, 4.25; N, 3.39%.

Ethyl 8-phenyl-4,11-dimethoxy-5-oxo-5*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyridine-7-carboxylate (4). Crystallized from DMF/EtOH as pale yellow crystals, mp> 300 ºC, yield (0.68 g, 76%). IR (KBr, cm^{-1}): 3124 (CH_{furan}), 3061 ($CH_{arom.}$), 2948, 2915 ($CH_{aliph.}$), 1696 ($C=O_{ester}$), 1659 ($C=O_{\gamma\text{-pyrone}}$), 1611 (C=N), 1584 (C=C).^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.28 (t, 3H, *J* = 6.6 Hz, CH_2CH_3), 3.86 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.25 (q, 2H, *J* =6.6 Hz, CH_2CH_3), 6.85-7.11 (m, 5H, Ph-H), 7.24 (d, 1H, *J*=2.4 Hz, H-3_{furan}), 7.93 (d, 1H, *J*=2.4 Hz, H-2_{furan}), 8.78 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 15.7 (CH_3), 57.9 (OCH_3), 58.8 (OCH_3), 61.2 (CH_2), 105.3, 107.5, 110.7, 112.4, 114.7, 126.3, 127.8, 128.3, 130.5, 136.2, 140.4, 142.1, 144.7, 147.2, 151.6, 152.8, 158.3, 166.1, 176.9. Mass spectrum (*m/z*, *I* %): 445 (M^+; 100), 400 (39), 372 (33), 342 (51), 265 (17), 242 (100), 220 (43), 205 (11), 147 (8), 134 (43), 118 (24), 77 (14), 64 (51). Anal. Calcd for $C_{25}H_{19}NO_7$ (445.42): C, 67.41; H, 4.30; N, 3.14%. Found: C, 67.30; H, 4.05; N, 2.91%.

4,11-Dimethoxy-8-methyl-*N*-phenyl-5-oxo-5*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyridine-7-carboxamide (5). Crystallized from DMF as yellow crystals, mp> 300 ºC, yield (0.63 g, 73%). IR (KBr, cm^{-1}): 3258 (NH), 3122 (CH_{furan}), 3065 ($CH_{arom.}$), 2969, 2925 ($CH_{aliph.}$), 1667 ($C=O_{amide}$), 1655 ($C=O_{\gamma\text{-pyrone}}$), 1613 (C=N), 1571 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.63 (s, 3H, $CH_{3\ pyridine}$), 3.84 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.23 (d, 1H, *J*=2.4 Hz, H-3_{furan}), 7.39-7.52 (m, 5H, Ph-H), 7.94 (d, 1H, *J*=2.4 Hz, H-2_{furan}), 8.67 (s, 1H, H-$4_{pyridine}$), 9.58 (bs, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 19.3 ($CH_{3\ pyridine}$), 58.5 (OCH_3), 59.9 (OCH_3), 105.8, 114.2, 115.6, 121.8, 123.7, 125,4, 128.1, 130.3, 135,9, 140.3, 141.9, 144.5, 146.2, 147.6, 152.1, 158.6, 163.8, 168.9, 176.2. Mass spectrum (*m/z*, *I* %): 430 (M^+; 29), 338 (100), 308 (28), 280 (8), 235 (16), 220 (60), 205 (27), 191 (39), 177 (22), 147 (19), 135 (25), 119 (11), 92 (100), 77 (19), 64 (51). Anal. Calcd for $C_{24}H_{18}N_2O_6$ (430.41): C, 66.97; H, 4.22; N, 6.51%. Found: C, 66.60; H, 3.88; N, 6.25%.

9,9-Dimethyl-4,13-dimethoxyfuro[3`,2`:6,7]chromeno[2,3-*b*]quinoline-5,7(5*H*,7*H*)-dione (6). Crystallized from DMF/MeOH as white crystals, mp 290-291 ºC, yield (0.58 g, 72%).IR (KBr, cm^{-1}): 3109 (CH_{furan}), 2963, 2913 ($CH_{aliph.}$), 1683 ($C=O_{quinolinone}$), 1659 ($C=O_{\gamma\text{-pyrone}}$), 1605 (C=N), 1579 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 1.07 (s, 6H, $2CH_3$), 2.65 (s, 2H, CH_2), 3.06 (s, 2H, CH_2), 3.94 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 7.19 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.96 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.76 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 26.6, 27.1, 34.5, 46.2, 51.9, 58.9 (OCH_3), 60.1 (OCH_3), 105.4, 107.2, 112.6, 114.7, 126.9, 129.5, 140.7, 142.6, 145.5, 147.3, 152.6, 159.4, 169.8, 179.3, 195.8. Mass spectrum (*m/z*, *I* %): 393 (78), 365 (100), 337 (63), 307 (13), 265 (18), 239 (8), 215 (12), 202 (35), 187 (9), 103 (8), 80 (13), 65 (18). Anal. Calcd for $C_{22}H_{19}NO_6$ (393.39): C, 67.17; H, 4.87; N, 3.56%. Found: C, 66.80; H, 4.72; N, 3.25%.

4,14-Dimethoxyfuro[3`,2`:6,7]chromeno[2,3-*b*]indeno[2,1-*e*]pyridine-5,7(5*H*,7*H*)-dione (7). Crystallized from DMF/MeOH as white crystals, mp> 300 ºC, yield (0.54 g, 68%).IR (KBr, cm^{-1}): 3118 (CH_{furan}), 3066 ($CH_{arom.}$), 2968, 2924 ($CH_{aliph.}$), 1720 ($C=O_{indanone}$), 1661 ($C=O_{\gamma\text{-pyrone}}$), 1612 (C=N), 1584 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 4.03 (s, 3H, OCH_3), 4.12 (s, 3H, OCH_3), 7.10 (d, 1H, *J*=2.1 Hz, H-3_{furan}), 7.41-7.53 (m, 4H, Ar-H), 7.93 (d, 1H, *J*=2.1 Hz, H-2_{furan}), 8.57 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 59.4 (OCH_3), 60.2 (OCH_3), 105.8, 107.3, 113.9, 115.7, 117.9, 125.3, 126.4, 127.1, 128.6, 130.2, 132.8, 135.3, 140.0, 142.2, 144.3, 145.9, 152.6, 159.0, 163.4, 178.5, 191.4. Mass spectrum (*m/z*, *I* %): 399 (100), 369 (28), 312 (22), 242 (33), 228 (18), 205 (12), 191 (7), 118 (41), 102 (62), 77 (24), 64 (11). Anal. Calcd for $C_{23}H_{13}NO_6$ (399.35): C, 69.17; H, 3.28; N, 3.51%. Found: C, 68.87; H, 3.03; N, 3.38%.

6,10-Dimethoxy-3-hydroxy-5-oxo-5*H*-1-hydrofuro[3`,2`:6,7]chromeno[2,3-*b*]pyrazolo[4,3-*e*] pyridine (8). Crystallized from DMF as pale yellow, mp> 300 ºC, yield (0.53 g, 75%). IR (KBr, cm^{-1}): 3441 (OH), 3263 (NH), 3112 (CH_{furan}), 1653 ($C=O_{\gamma\text{-pyrone}}$), 1616 (C=N), 1573 (C=C). ^1H NMR (DMSO-d_6, δ, 300 MHz): 3.88 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 7.22 (d, 1H, *J*=2.1 Hz, H-3_{furan}), 7.87 (d, 1H, *J*=2.1 Hz, H-2_{furan}), 8.71 (s, 1H, H-$4_{pyridine}$), 11.21 (bs, 1H, NH exchangeable with D_2O), 13.64 (bs, 1H, OH exchangeable with D_2O).^{13}C NMR (DMSO-d_6, δ, 75 MHz): 59.1 (OCH_3), 59.7 (OCH_3), 103.8, 105.6, 107.2, 113.8, 117.4, 128.3, 139.8, 140.7, 143.4, 145.6, 151.8, 152.7, 156.2, 161.6, 177.8. Mass spectrum (*m/z*, *I* %): 353 (27), 325 (42), 308 (100), 278 (35), 252 (21), 226 (13), 188 (9), 147 (11), 118 (15), 104 (25), 76 (11), 65 (21). Anal. Calcd for $C_{17}H_{11}N_3O_6$ (353.29): C, 57.80; H, 3.14; N, 11.89%. Found: C, 57.55; H, 3.00; N, 11.63%.

6,10-Dimethoxy-3-methyl-1-phenyl-5-oxo-5*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyrazolo[4,3-*e*] pyridine (9). Crystallized from DMF as pale yellow crystals, mp> 300 ºC, yield (0.60 g, 70%). IR (KBr, cm^{-1}): 3124 (CH_{furan}), 3046 ($CH_{arom.}$), 2958, 2923 ($CH_{aliph.}$), 1664 ($C=O_{\gamma\text{-pyrone}}$), 1622 (C=N), 1594 (C=C). ^1H NMR (DMSO-d_6, δ, 300 MHz): 2.12 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.87 (t, 1H, *J*=6.9 Hz, Ar-H), 7.18 (d, 1H, *J*=2.4 Hz, H-3_{furan}), 7.29-7.52 (m, 4H, Ar-H), 7.96 (d, 1H, *J*=2.4 Hz, H-2_{furan}), 8.69 (s, 1H, H-$4_{pyridine}$).^{13}C NMR (DMSO-d_6, δ, 75 MHz): 18.3 (CH_3), 59.4 (OCH_3), 60.1 (OCH_3), 105.9, 107.6, 114.1, 117.8, 120.4, 121.3, 126.7, 128.2, 130.0, 139.6, 140.9, 141.5, 144.3, 146.2, 147.8, 150.5, 152.8, 159.7, 177.2. Anal. Calcd for $C_{24}H_{17}N_3O_5$ (427.41): C, 67.44; H, 4.01; N, 9.83%. Found: C, 67.32; H, 3.86; N, 9.51%.

7,11-Dimethoxy-6*H*-furo[3``,2``:6`,7`]chromeno[3`,2`:5,6]pyrido[2,3-*d*]pyrimidine-2,4,6(1*H*,3*H*)- trione (10). Crystallized from DMF/H_2O as yellow crystals, mp> 300 ºC, yield (0.57 g, 75%). IR (KBr, cm^{-1}): 3365 (2NH), 3124 (CH_{furan}), 2958, 2911 ($CH_{aliph.}$), 1692 ($C=O_{pyrimidinone}$), 1656 ($C=O_{\gamma\text{-pyrone}}$), 1614 (C=N), 1588 (C=C). ^1H NMR (DMSO-d_6, δ, 300 MHz): 3.94 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3), 7.19 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.84 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.82 (s, 1H, H-$4_{pyridine}$), 11.52 (bs, 2H, 2NH exchangeable with D_2O). Mass spectrum (*m/z*, *I* %): 381 (100), 353 (22), 310 (19), 280 (62), 242 (31), 220 (27), 205 (11), 177 (8), 120 (35), 77 (14), 66 (14). Anal. Calcd for $C_{18}H_{11}N_3O_7$ (381.29): C, 56.70; H, 2.91; N, 11.02%. Found: C, 56.51; H, 2.73; N, 10.88%.

1-Allyl-7,11-dimethoxy-2-thioxo-furo[3``,2``:6`,7`]chromeno[3`,2`:5,6]pyrido[2,3-*d*]pyrimidine-4,6(4*H*,6*H*)-dione (11). Crystallized from DMF as orange crystals, mp 296-297 ºC, yield (0.68 g, 77%). IR (KBr, cm^{-1}): 3235 (NH), 3104 (CH_{furan}), 1707 ($C=O_{pyrimidinone}$), 1649 ($C=O_{\gamma\text{-pyrone}}$), 1612

(C=N), 1572 (C=C), 1226 (C=S). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.02 (s, 2H, CH_2, H-1`), 3.87 (s, 3H, $OCH_3$), 3.98 (s, 3H, $OCH_3$), 4.89-4.93 (m, 2H, H-3`), 5.78-5.84 (m, 1H, H-2`), 7.15 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.92 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.85 (s, 1H, H-6), 11.13 (bs, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 37.9, 59.5 (OCH_3), 60.2 (OCH_3), 104.6, 105.9, 107.3, 109.0, 114.3, 115.4, 117.3, 127.6, 134.7, 140.5, 144.9, 146.1, 151.6, 155.9, 158.3, 162.2, 168.4, 177.3. Mass spectrum (*m/z*, *I* %): 437 (32), 410 (13), 382 (100), 349 (41), 276 (18), 228 (33), 191 (13), 147 (7), 116 (21), 77 (43), 65 (18). Anal. Calcd for $C_{21}H_{15}N_3O_6S$ (437.43): C, 57.66; H, 3.46; N, 9.61; S, 7.33%. Found: C, 57.51; H, 3.20; N, 9.47; S, 7.10%.

6,10-Dimethoxy-2-phenyl-11-oxo-11*H*-furo[3`,2`:6,7]chromeno[2,3-*b*][1,3]oxazolo[4,5-*e*] pyridine (12).

Hippuric acid (0.36 g, 2 mmol) dissolved in acetic anhydride (10 mL) and fused sodium acetate (0.5 g) was heated under reflux for 15 min, then compound **1** (0.54 g, 2 mmol) was added. The reaction mixture was heated under reflux for 30 min. The yellow crystals obtained after cooling were filtered and crystallized from AcOH, mp 281-282 ºC, yield (0.56 g, 67%). IR (KBr, cm^{-1}): 3120 (CH_{furan}), 3060 ($CH_{arom.}$), 2946, 2912 ($CH_{aliph.}$), 1653 ($C{=}O_{\gamma\text{-pyrone}}$), 1621 (C=N), 1576 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.89 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 7.20 (d, 1H, *J*=2.1 Hz, H-3_{furan}), 7.30-7.47 (m, 5H, Ph-H), 7.90 (d, 1H, *J*=2.1 Hz, H-2_{furan}), 8.75 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 59.7 (OCH_3), 60.5 (OCH_3), 105.5, 107.1, 114.5, 117.6, 125.9, 127.4, 128.5, 129.4, 130.2, 133.6, 140.7, 142.6, 144.6, 146.3, 147.3, 151.8, 159.4, 161.6, 177.9. Mass spectrum (*m/z*, *I* %): 414 (21), 386 (45), 309 (15), 283 (23), 242 (100), 220 (32), 171 (12), 118 (14), 103 (9), 90 (6), 77 (48), 64 (21). Anal. Calcd for $C_{23}H_{14}N_2O_6$ (414.37): C, 66.67; H, 3.41; N, 6.76%. Found: C, 66.30; H, 3.22; N, 6.48%.

6. REFERENCES

[1] D. Vedaldi, S. Caflleri, F. Dall'Acqua, L. Andrea, L. Bovalini, P. Martelli, *Farmaco* 1988, 4, 333-346.

[2] B. Marconi, F. Mancini, P. Colombo, F. Allegra, F. Giordano, A. Gazzaniga, G. Orecchia, P. Santi, *J. Controlled Release*, 1999, 60, 261-268.

[3] A.A. Abu-Hashem, M. El-Shazly, *Eur. J. Med. Chem.*, 2015, 90, 633-665.

[4] R.B. Gammill, C.E. Day, P.E. Schurr, *J. Med. Chem.*, 1983, 26, 1672-1674.

[5] K. Gunaydin, F.B. Erim, *J. Chromatogr. A*, 2002, 954, 291-294.

[6] H. A. Dewar, T.A. Grimson, *Br. Heart J*., 1950, 12, 54-60.

[7] P. Vanachayangkul, K. Byer, S. Khan, V. Butterweck, *Phytomed*., 2010, 17, 653-658.

[8] L. Trabalzini, P. Martelli, L. Bovalini, F. Dall'Acqua, E. Sage, *J. Photochem. Photobiol. B: Bid,* 1990, 7, 317-336.

[9] N. Beyazit, K. Kaya, P. Senel, A. D. Ozdemir, A. Golcu, *J. Mol. Struct.*, 2019, 1197, 450-457.

[10] P. Vanachayangkul, K. Byer, S. Khan, V. Butterweck, *Phytomed*., 2010, 17, 653-658.

[11] S. Turbay, O.E. Piro, G.A. Echeverra, A. Navarro, M.P. Fernndez-Liencres, M. Fortuna, M.E. Tuttolomondo, *Spectrochim. Acta A*, 2014, 123, 71-77.

[12] I. O. Akchurin, A. I. Yakhutina, A. Y. Bochkov, N. P. Solovjova, M. G. Medvedev, V. F. Traven, *J. Mol. Struct.*, 2018, 1160, 215-221.

[13] M.A. Ibrahim, S. Abdel Halim, N. Roushdy, A.A.M. Farag, N.M. El-Gohary, *Opt. Mater.*, 2017, 73, 290-305.

[14] N. Roushdy, A.A.M. Farag, M.A. Ibrahim, S. Abdel Halim, N.M. El-Gohary, *Optik*, 2019, 178, 1163–1176.

[15] M.A. Ibrahim, S. Abdel Halim, N. Roushdy, A.A.M. Farag, N.M. El-Gohary, *Optik*, 2018, 166, 294–306.

[16] A.A.M. Farag, M.A. Ibrahim, S. Abdel Halim, N. Roushdy, N.M. El-Gohary, *J. Mol. Struct.*, 2018, 1156, 516-523.

[17] H. Regaila, A. Gohar, G. Abdel Sadek, *Egypt J. Pharm. Sci.*, 1988, 29, 343-347.

[18] K. M. Amin, Y. M. Syam, M. M. Anwar, H. I. Ali, T. M. Abdel-Ghani, A. M. Serry, *Bioorg. Chem.*, 2018, 76, 487-500.

[19] I.F. Zaeid, A.M. Nasef, N.M. Fawzy, A.M. Soliman, M.M. E-Baroudy, *Int. J. Pharm. Sci. Rev. Res.*, 2015, 30, 306-314.

[20] A.E. Amr, M.M. Abdalla, S.A. Essaouy, M.M.H. Areef, M.H. Elgamal, T.A. Nassear, A.E. Haschich, M.A. Al-Omar, *Russ. J. Gen. Chem.*, 2017, 87, 1591–1600.

[21] M. S. Frasinyuk, S. V. Gorelov, S. P. Bondarenko, V. P. Khilya, *Chem. Heterocycl. Compds.*, 2009, 45, 1261-1269.

[22] M. Ghate, M. V. Kulkarni, *Indian J. Chem*., 2005, 44B, 1674-1678.

[23] A.A. Abu-Hashem, M.M. Youssef, *Molecules*, 2011, 16, 1956-1972.

[24] M. A. Ibrahim, A. Badran, S. H. Hashiem, *J. Heterocycl. Chem*., 2018, 55, 2844-2851.

[25] N. M. El-Gohary, M. A. Ibrahim, S. Said, *Heterocycles*, 2018, 96, 690-704.

[26] M. A. Ibrahim, N. M. El-Gohary, *J. Heterocycl. Chem.*, 2016, 53, 859-864.

[27] M. A. Ibrahim, N. M. El-Gohary, S. S. Ibrahim, S. Said, *Chem. Heterocycl. Compds*., 2015, 50, 1624-1633.

[28] F. Eiden, J. Schünemzinn, *Arch. Pharm.*, 1983, 316, 201-209.

[29] M.A. Ibrahim, *Synth. Commun.*, 2009, 39, 3527-3545.

[30] A.A.M. Farag, N. Roushdy, S. Abdel Halim, N. M. El-Gohary, M. A. Ibrahim, S. Said, *Spectrochim. Acta Part A*, 2018, 191, 478-490.

[31] M. A. Ibrahim, A. M. El-Kazak, *J. Heterocycl. Chem.*, 2019, 56, 1075-1085.

[32] A. U. Rahman, M. I. Choudhary, W. J. Thomsen, *Bioassay Techniques for drug development*, 16 the Netherlands: Harwood Academic Publishers, **2001**.

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