HETEROCYCLES, Vol. 100, No. 9, 2020, pp. 1450 - 1462. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 1st June, 2020, Accepted, 30th June, 2020, Published online, 8th July, 2020
DOI: 10.3987/COM-20-14294

SYNTHETIC APPROACH FOR BUILDING HETEROANNULATED FURO[3,2-*g*]CHROMENES USING 4,9-DIMETHOXY-5-OXO-5*H*-FURO-[3,2-*g*]CHROMENE-6-CARBONITRILE AND CYCLIC CARBON NUCLEOPHILES

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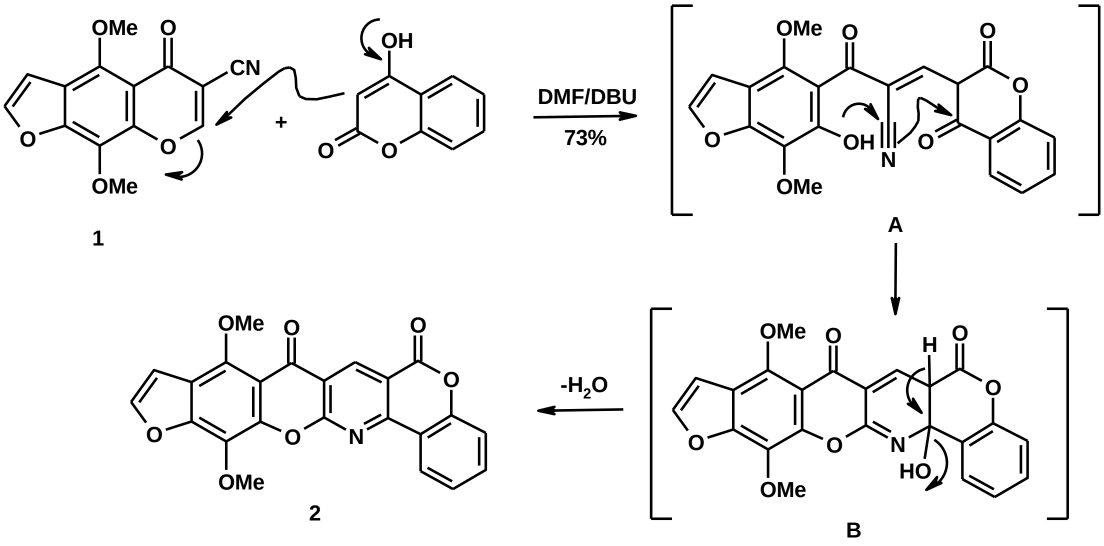
Abstract – A novel series of polyfused heterocyclic systems containing furo[3,2-*g*]chromenes were efficiently synthesized. The reactivity of 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) was studied towards a variety of carbon nucleophilic reagents such as heterocyclic enols, heterocyclic enamines and cyclic active methylene compounds. Treatment of carbonitrile **1** with 4-hydroxycoumarin, 4-hydroxy-1-methylquinolin-2(1*H*)-one (**3**), 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**) afforded furodichromeno-pyridine **2**, furochromenonaphthyridine **5**, furochromenodipyridopyrimidine **6**. Reaction of carbonitrile **1** with 4(6)-aminouracil and 5-amino-3-methyl-1*H*-pyrazole proceed through ring opening followed by cycloaddition into the nitrile group giving pyrido[2,3-*d*]pyrimidine **7** and pyrazolo[3,4-*b*]pyridine **8**. Also, reaction of carbonitrile **1** with 5-amino-2,4-dihydro-3*H*-pyrazol-3-one (**9**), 2-(phenylimino)-1,3-thiazolidin-4- one (**11**), thiobarbituric acid and cyclohexane-1,3-dione produced the novel annulated furo[3,2-*g*]chromenes **10**, **12**-**14**, respectively. Cyclohexane-1,2-dione reacted with carbonitrile **1** in 1:2 molar ratio afforded *bis*-(furochromeno)[1,10]phenanthroline **15**. The prepared compounds were screened in *vitro* for their antimicrobial activity and some of them appeared notable activity against the tested microorganisms.

The natural occurring furochromones (khellin and visnagin) are present in the fruits and seeds of *Ammi visnaga* L.[1] Furochromones have attracted a great consideration because of their several applications including antimicrobial,[2] anticancer,[3] anti-inflammatory,[4] anticonvulsant,[5] antitubercular[6] and analgesic.[7] Structures of some furo[3,2-*g*]chromenes were optimized using DFT-theoretical calculations.[8] Variable applications were investigated for furo[3,2-*g*]chromene derivatives including photodiode, photovoltaic, photoelectrical and photosensitivity.[9] Also, khellin contains γ-pyrone ring in its structure and therefore, revealed significant reactivity towards nucleophilic reactions.[10] Boiling khellin in 10% potassium hydroxide solution resulted in destroying of γ-pyrone ring giving khellinone which upon *Vielsmeier–Haack* formylation gave 6-formylkhellin.[11] 4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]-chromene-6-carbonitrile (khellin-6-carbonitrile) (**1**)[12] may represent a building block substrate for the synthesis of novel heteroannulated furo[3,2-g]chromenes due to the existence of the cyano group at position 3 of the γ-pyrone ring.[13] The current research work aims to investigate the chemical behavior of khellin-6-carbonitrile (**1**) towards a diversity of cyclic carbon nucleophiles include cyclic enols, cyclic enamines and cyclic active methylene compounds and evaluate their antimicrobial activity of the newly prepared compounds.

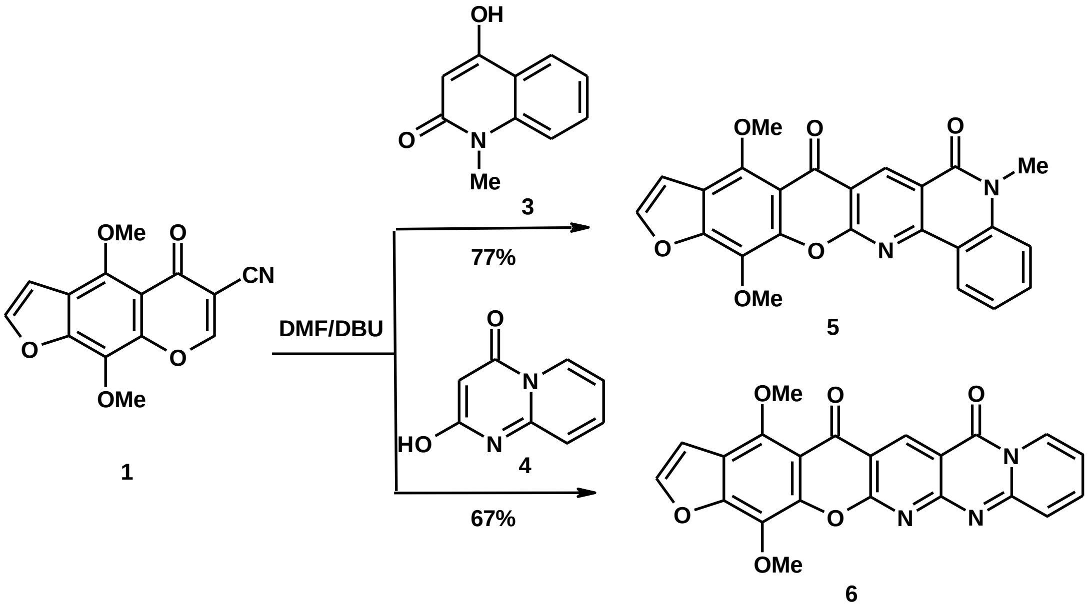
Treatment of khellin-6-carbonitrile (**1**) with 4-hydroxycoumarin in boiling DMF containing 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) afforded the novel annulated 4,15-dimethylfuro[3``,2``:6`,7`]-dichromeno[2`,3`-*b*:3,4-*e*]pyridine-5,7(5*H*,7*H*)-dione (**2**). The reaction proceeds *via* nucleophilic attack at C-7 with γ-pyrone ring opening producing intermediate **A** followed by cycloaddition reactions giving intermedite **B** which dehydrated to the target product **2** (Scheme 1).[14]



Scheme 1. Formation of the novel furodichromenopyridine derivative **2**

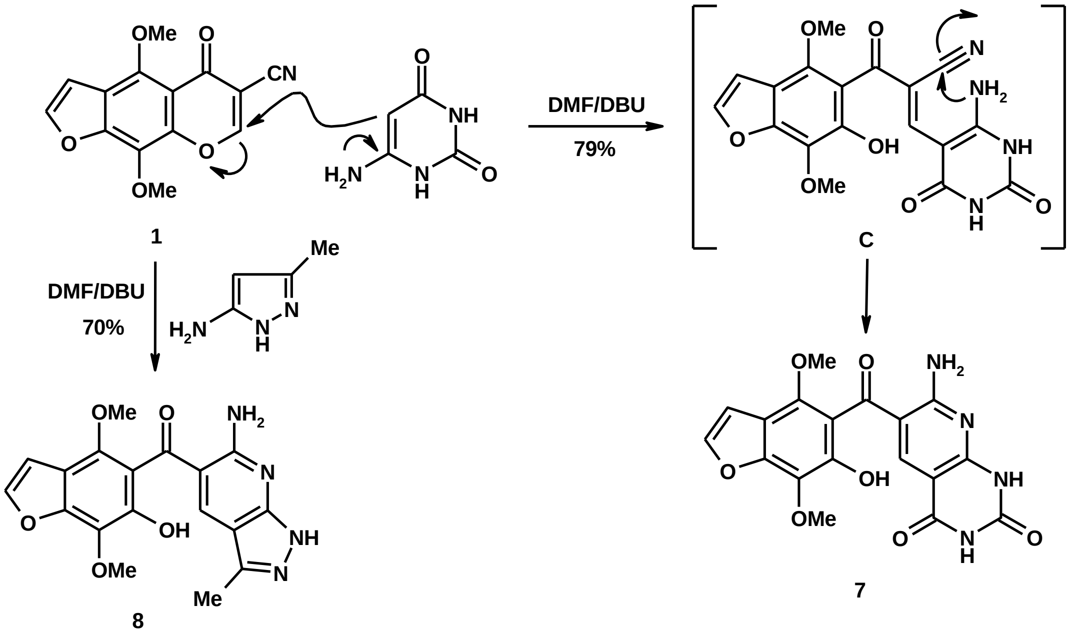
Characteristic two doublet signals assignable to H-3$_{furan}$ and H-2$_{furan}$ observed in the ^{1}H NMR spectrum of compound **2** at δ 7.16 and 7.89 (*J*=2.1 Hz), as well specific singlet appeared at δ 8.66 attributed to H-4$_{pyridine}$. The parent ion peak of compound **2** appeared in the mass spectrum at *m/z* 415 which is coincident with its molecular formula $C_{23}H_{13}NO_7$. Distinctive absorption bands observed in the IR spectrum at $\tilde{\nu}$ 1741 (C=O$_{\alpha\text{-pyrone}}$), 1659 (C=O$_{\gamma\text{-pyrone}}$) and 1609 cm^{-1} (C=N). The ^{13}C NMR spectrum showed downfield signals at δ 160.2 and 177.2 corresponding to C=O$_{\alpha\text{-pyrone}}$ and C=O$_{\gamma\text{-pyrone}}$, respectively.

Similarly, reaction of khellin-6-carbonitrile (**1**) with 4-hydroxy-1-methylquinolin-2(1*H*)-one (**3**) and 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**) produced the polycyclic 4,15-dimethyl-8-methyl-5*H*-benzo[*h*]furo[3`,2`:6,7]chromeno[2,3-*b*][1,6]naphthyridine-5,7(8*H*)-dione (**5**) and 4,16-dimethylfuro-[3```,2```:6``,7``]chromeno[3``,2``:5`,6`]dipyrido[1,2-*a*:2`,3`-*d*]pyrimidine-5,7(5*H*,7*H*)-dione (**6**) (Scheme 2).[15] The ^{1}H NMR spectra of compounds **5** and **6** displayed specific singlet signals assignable to H-4 pyridine at δ 8.71 and 8.78, respectively. The molecular ion peaks appeared in the mass spectra at *m/z* 428 and 415 and confirm the proposed structures.



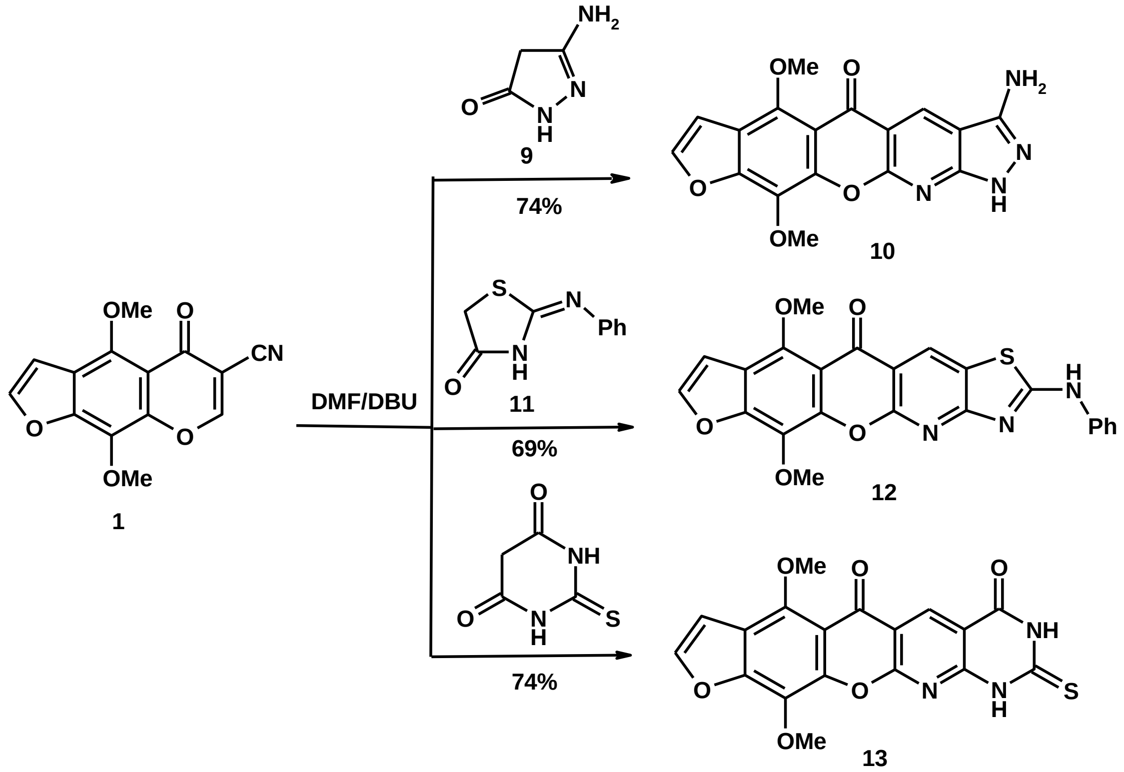
Scheme 2. Formation of heteroannulated furochromene derivatives **5** and **6**

On the other hand, reaction of carbonitrile **1** with cyclic enamine such as 4(6)-aminouracil proceed through nucleophilic attack at C-7 position with ring opening giving intermediate **C** which underwent cycloaddition of the amino group into the nitrile function producing pyrido[2,3-*d*]pyrimidine derivative **7** (Scheme 3). In this reaction, the cycloaddition into the nitrile group occurs by the nitrogen atom of the amino group not the oxygen atom of the hydroxy group; due to the higher nucleogilicity of nitrogen as compare with oxygen. Also, treating carbonitrile **1** with 5-amino-3-methyl-1*H*-pyrazole gave pyrazolo[3,4-*b*]pyridine derivative **8** (Scheme 3). Compounds **7** and **8** presented red color with $FeCl_3$ solution; confirming the existence of free phenolic OH group. Distinctive absorption band observed in the IR spectra of compounds **7** and **8** at $\tilde{\nu}$ 1638/1640 cm^{-1} ($C=O_{ketone}$). Characteristic singlet assignable to $H\text{-}4_{pyridine}$ observed in the ^1H NMR spectra of compounds **7** and **8** at δ 8.83 and 8.79. The NH_2 protons appeared as D_2O-exchangeable signals at δ 7.68 and 7.75, respectively. In the mass spectra, the molecular ion peaks appeared at *m/z* 398 and 368 that agree with the suggested formula weights 398.33 and 368.34, respectively.



Scheme 3. Formation of pyrido[2,3-*d*]pyrimidine **7** and pyrazolo[3,4-*b*]pyridine **8**

After that, the reactivity of carbonitrile **1** was tested towards some cyclic active methylene compounds.[16] Thus, treatment of compound **1** with 5-amino-2,4-dihydro-3*H*-pyrazol-3-one (**9**) in boiling DMF containing DBU produced annulated 3-amino-6,10-dimethoxy-1*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]-pyrazolo[4,3-*e*]pyridin-5(5*H*)-one (**10**) (Scheme 4). In the IR spectrum, typical absorption bands appeared at $\tilde{\nu}$ 3365, 3279, 3235 (NH_2, NH), 1658 ($C=O_{\gamma\text{-pyrone}}$) and 1611 cm^{-1} (C=N). In the ^1H NMR spectrum, characteristic singlet assignable to $H\text{-}4_{pyridine}$ observed at δ 8.82, in addition, D_2O-exchangeable signals attributed to NH_2 and NH appeared at δ 8.26 and 11.45, respectively. The mass spectrum showed the parent ion peak as the base peak at *m/z* 352 and approves the suggested molecular formula ($C_{17}H_{12}N_4O_5$).

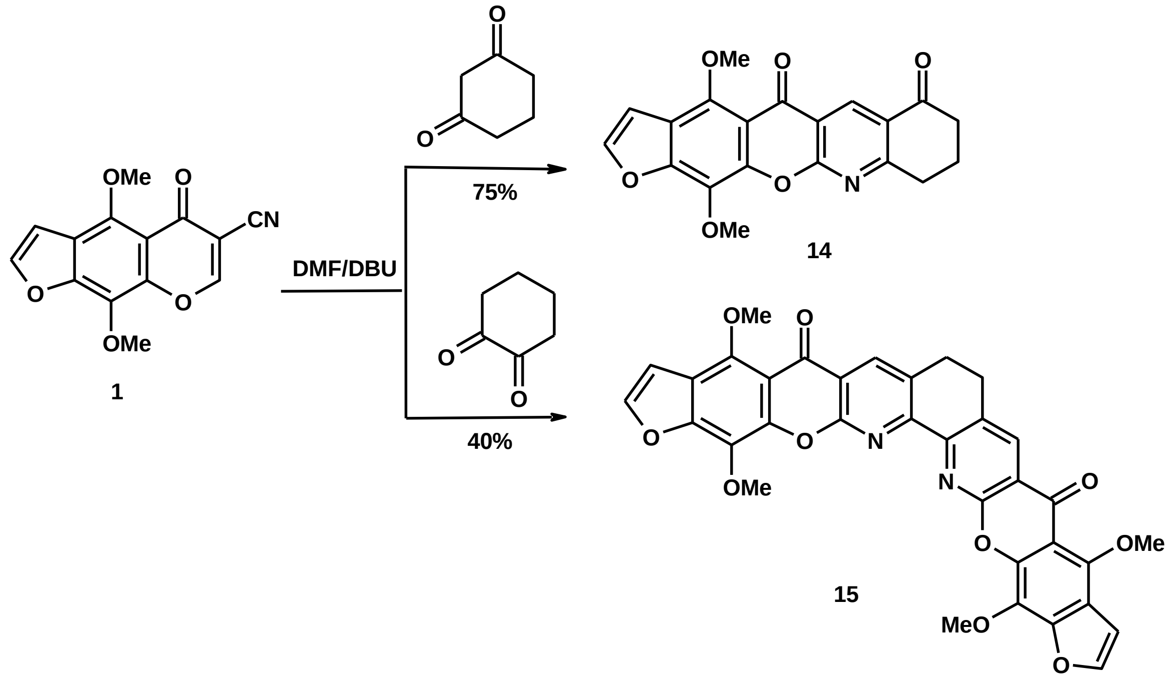


Scheme 4. Reaction of carbonitrile **1** with cyclic active methylene compounds

In the same manner, boiling compound **1** with 2-(phenylimino)-1,3-thiazolidin-4-one (**11**) and thiobarbituric acid in DMF containing DBU gave linear heteroannulated furochromenothiazolopyridine **12** and furochromenopyridopyrimidine **13**, respectively (Scheme 4). The mass spectra of compounds **12** and **13** proved the assigned structures and revealed the parent ion peaks at *m/z* 445 and 397, respectively. The important feature in the ^{1}H NMR spectra of compounds **12** and **13** is the existence of specific singlet characteristic to H-4$_{\text{pyridine}}$ at δ 8.69 and 8.80, respectively.

Next, the behavior of compound **1** was investigated towards 1,3-cyclohexanedione under the previous conditions producing furo[3`,2`:6,7]chromeno[2,3-*b*]quinoline (**14**) (Scheme 5).[17] The mass spectrum confirmed the structure and recorded the molecular ion peak at *m/z* 365. In the IR spectrum, typical absorption bands attributed to C=O$_{\text{quinolinone}}$ and C=O$_{\gamma\text{-pyrone}}$ appeared at $\tilde{\nu}$ 1681 and 1654, respectively. The ^{1}H NMR spectrum showed three triplet signals attributable to three CH$_2$ protons at 2.17, 2.73 and 3.21, in addition the H-4$_{\text{pyridine}}$ appeared as specific singlet at δ 8.89.

Finally, 1,2-cyclohexanedione reacted with carbonitrile **1** in 1:2 molar ratio giving *bis*-furo[3`,2`:6,7]-chromeno[2,3-*b*:3`,2`-*j*][1,10]phenanthroline (**15**) (Scheme 5).[17] Characteristic absorption bands appeared in the IR spectrum at $\tilde{\nu}$ 1663 (C=O$_{\gamma\text{-pyrone}}$) and 1618 cm^{-1} (C=N). The molecular ion peak observed as the base peak in mass spectrum of compound **15** at *m/z* 618 and proves the suggested structure.



Scheme 5. Reaction of carbonitrile **1** with 1,3-cyclohexanedione and 1,2-cyclohexanedione

ANTIMICROBIAL EVALUATION

The standardized disc agar diffusion method[18] was followed to determine the antimicrobial activity of the prepared compounds against the sensitive microorganisms which are: Gram-positive bacteria *Staphylococcus aureus* (ATCC 25923) and *Bacillus subtilis* (ATCC 6635), Gram-negative bacteria *Escherichia coli* (ATCC 25922) and *Salmonella typhimurium* (ATCC 14028), yeast *Candida albicans* (ATCC 10231) and fungus *Asperigillus fumigatus*. The antimicrobial activities were determined by measuring the inhibition zones, including the diameter of the disc (6 mm) as shown in Table 1. The data of the antimicrobial activity presented in Table 1 reported that:

[1] The investigated compounds offered different inhibitory effects on growing of the tested microorganisms, and the antimicrobial activity differs from moderate to high activities.

[2] Compounds **7** and **8** recorded high inhibitory effects against all types of microorganisms and this may attribute to the existence of 4,7-dimethoxy-6-hydroxy-1-benzofuran linked with pyrido[2,3-*d*]-pyrimidine and pyrazolo[3,4-*b*]pyridine in the same molecular frame. Also, compound **15** recorded high activity against the tested microorganisms and this may due to the presence of annulated *bis*-(furochromeno)[1,10]phenanthroline.

[3] Compound **6** recorded high antimicrobial effects against *Bacillus subtilis* and *Salmonella typhimurium*, in addition to high antifungal activity against *Asperigillus fumigatus*. Compound **5** revealed high inhibitory effects against *Bacillus subtilis* as Gram-positive bacteria. While, compound **12** showed high antimicrobial activity against the two selected Gram-positive bacteria. Also, compound **14**

appeared high activity towards *Candida albicans* as the yeast.

[4] The high inhibitory effects of some of the synthesized compounds **5-8**, **12** and **15** towards certain microorganisms, may attribute to the presence of heterocyclic systems annulated furo[3,2-*g*]chromenes as well as benzofuran bearing different functional groups. These compounds of comparable activity 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**.**

Compd. No.	**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*	
	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	1000 μg/ml	500 μg/ml
2	21 I	14 I	17 I	12 I	16 I	11 I	17 I	14 I	15 I	9 L	15 I	10 I
5	19 I	14 I	**24 H**	**19 H**	18 I	14 I	15 I	10 I	16 I	12 I	14 I	8 L
6	20 I	15 I	**27 H**	**20 H**	**26 H**	**20 H**	18 I	13 I	18 I	13 I	**26 H**	**18 H**
7	**27 H**	**20 H**	**25 H**	**19 H**	**24 H**	**19 H**	**26 H**	**21 H**	**25 H**	17 I	**25 H**	16 I
8	**29 H**	**21 H**	**28 H**	**20 H**	**31 H**	**22 H**	**28 H**	**20 H**	**27 H**	**19 H**	**32 H**	**21 H**
10	19 I	13 I	16 I	11 I	18 I	13 I	14 I	10 I	18 I	12 I	16 I	9 I
12	**26 H**	**19 H**	**24 H**	**18 H**	16 I	11 I	18 I	11 I	19 I	14 I	20 I	16 I
13	13 I	8 L	21 I	15 I	17 I	13 I	16 I	12 I	17 I	12 I	15 I	10 I
14	15 I	9 I	14 I	10 I	15 I	11 I	19 I	12 I	**26 H**	**20 H**	17 I	11 I
15	**28 H**	**21 H**	**28 H**	**20 H**	**25 H**	**19 H**	**27 H**	**21 H**	**30 H**	**22 H**	**25 H**	**18 H**
S	35	26	35	25	36	28	38	27	35	28	37	26

* Calculated from 3 values.
S: Standard drug, H = High activity, I = Intermediate activity, L = Low activity,
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.

The chemical behavior of 4,9-dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (khellin-6-carbonitrile) (**1**) was investigated towards a variety of carbon nucleophilic reagents involving cyclic enols, cyclic enamines and cyclic active methylene compounds. A novel heteroannulated systems including furo[3,2-*g*]chromenes were efficiently synthesized from reaction of carbonitrile **1** with cyclic enols; 4-hydroxycoumarin**,** 4-hydroxy-1-methylquinolin-2(1*H*)-one (**3**) and 2-hydroxy-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (**4**). 4,7-Dimethoxy-6-hydroxy-1-benzofuran linked pyrido[2,3-*d*]pyrimidine **7** and pyrazolo[3,4-*b*]pyridine **8** were prepared from reaction of carbonitrile **1** with 4(6)-aminouracil and

5-amino-3-methyl-1*H*-pyrazole. A diversity of novel heteroannulated furo[3,2-*g*]chromenes were obtained from reaction of compound **1** with cyclic active methylene compounds namely 5-amino-2,4-dihydro-3*H*-pyrazol-3-one (**9**), 2-(phenylimino)-1,3-thiazolidin-4-one (**11**), thiobarbituric acid and cyclohexane-1,3-dione and cyclohexane-1,2-dione. The used nucleophilic reagents reacted with the starting substrate **1** through a domino process initiated by nucleophilic attack at C-7 with ring opening followed by different types of cyclization depending on the nucleophile used.

EXPERIMENTAL

General. 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 were tested using TLC. 4,9-Dimethoxy-5-oxo-5*H*-furo[3,2-*g*]chromene-6-carbonitrile (**1**) was prepared according to literature.[12]

Biological method. The test for the antimicrobial activity was performed on medium potato dextrose agar (PDA) which contained infusion of 200 g potatoes, 6 g dextrose and 15 g agar. Uniform size filter paper disks (6 mm diameter, 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.[18]

4,15-Dimethylfuro[3``,2``:6`,7`]dichromeno[2`,3`-*b*:3,4-*e*]pyridine-5,7(5*H*,7*H*)-dione (2). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 4-hydroxycoumarin (0.32 g, 2 mmol), in DMF (10 mL) containing DBU (0.1 mL), was heated under reflux for 2 h. The yellow crystals deposited during heating were filtered off and crystallized from AcOH, mp 285-286 ºC, yield 0.61 g (73%). IR (KBr, cm^{-1}): 3117 (CH_{furan}), 3053 ($CH_{arom.}$), 2965, 2898 ($CH_{aliph.}$), 1741 ($C{=}O_{\alpha\text{-pyrone}}$), 1659 ($C{=}O_{\gamma\text{-pyrone}}$), 1609 (C=N) and 1595 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.88 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 7.16 (d, 1H, *J*=2.1 Hz, H-3_{furan}), 7.48-7.53 (m, 2H, Ar-H), 7.67 (t, 1H, *J*=7.8 Hz, Ar-H), 7.80 (d, 1H, *J*=7.8 Hz, Ar-H), 7.89 (d, 1H, *J*=2.1 Hz, H-2_{furan}), 8.66 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 57.6 (OCH_3), 58.4 (OCH_3), 105.5 (C-3_{furan}), 108.1 (C-4a), 111.3 (C-6a), 114.0 (C-3a), 114.9 (C-5a), 122.6 (C-9), 125.4 (C-11), 126.9 (C-10), 127.9 (C-12), 128.4 (C-15), 130.1 (C-12a), 139.5 (C-14a), 143.3 (C-6), 146.1 (C-

2furan), 147.8 (C-4), 150.9 (C-8a), 152.2 (C-15a), 152.9 (C-12b), 159.6 (C-7 as OC=O), 162.7 (C-13a), 177.3 (C-5 as C=O). Mass spectrum (*m/z*, *I* %): 415 (100), 387 (61), 347 (12), 319 (7), 220 (54), 205 (30), 148 (26), 118 (9), 77 (22), 64 (17). Anal. Calcd for $C_{23}H_{13}NO_7$ (415.35): C, 66.51; H, 3.15; N, 3.37%. Found: C, C, 66.47; H, 3.08; N, 3.10%.

4,15-Dimethyl-8-methyl-5*H*-benzo[*h*]furo[3`,2`:6,7]chromeno[2,3-*b*][1,6]naphthyridine-5,7(8*H*)-dione (5). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 4-hydroxy-1-methylquinolin-2(1*H*)-one (**3**) (0.35 g, 2 mmol), in DMF (10 mL) containing DBU (0.1 mL), was heated under reflux for 2 h. The pale yellow crystals obtained during heating were filtered off and crystallized from DMF/H_2O, mp 300-301 ºC, yield 0.66 g (77%). IR (KBr, cm^{-1}): 3108 (CH_{furan}), 3074 ($CH_{arom.}$), 2949, 2922 ($CH_{aliph.}$),1669 ($C{=}O_{quinolinone}$), 1657 ($C{=}O_{\gamma\text{-pyrone}}$), 1606 (C=N), 1581 (C=C). ^1H NMR (DMSO-d_6, δ, 300 MHz): 3.62 (s, 3H, *N*-CH_3), 3.91 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.18 (d, 1H, *J*=2.4 Hz, H-3_{furan}), 7.50-7.62 (m, 3H, Ar-H), 7.85 (d, 1H, *J*=8.4 Hz, Ar-H), 7.90 (d, 1H, *J*=2.4 Hz, H-2_{furan}), 8.71 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 29.4 (*N*-CH_3), 57.5 (OCH_3), 58.6 (OCH_3), 105.7 (C-3_{furan}), 108.0 (C-4a), 112.1 (C-6a), 114.5 (C-3a), 119.8 (C-5a), 122.0 (C-12a), 123.3 (C-9), 125.7 (C-11), 127.5 (C-10), 128.1 (C-12), 129.7 (C-15), 133.6 (-8), 139.3 (C-14a), 143.4 (C-6), 145.9 (C-2_{furan}), 147.5 (C-4), 151.7 (C-15a), 154.3 (C-12b), 157.4 (C-13a), 160.2 (C-7 as C=O), 177.2 (C-5 as C=O). Mass spectrum (*m/z*, *I* %): 428 (100), 400 (44), 372 (31), 342 (16), 242 (50), 220 (72), 205 (22), 133 (23), 118 (14), 102 (10), 77 (15), 63 (6). Anal. Calcd for $C_{24}H_{16}N_2O_6$ (428.39): C, 67.29; H, 3.76; N, 6.54%. Found: C, 67.21; H, 3.50; N, 6.38%.

4,16-Dimethylfuro[3```,2```:6``,7``]chromeno[3``,2``:5`,6`]dipyrido[1,2-*a*:2`,3`-*d*]pyrimidine-5,7(5*H*, 7*H*)-dione (6). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 2-hydroxy-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**4**) (0.32 g, 2 mmol), in DMF (10 mL) containing DBU (0.1 mL), was heated under reflux for 2 h. The white crystals obtained after cooling were filtered off and crystallized from EtOH, mp 264-265 ºC, yield 0.56 g (67%). IR (KBr, cm^{-1}): 3112 (CH_{furan}), 3057 ($CH_{arom.}$), 2954, 2928 ($CH_{aliph.}$), 1666 ($C{=}O_{pyrimidinone}$), 1654 ($C{=}O_{\gamma\text{-pyrone}}$), 1613 (C=N), 1584 (C=C). ^1H NMR (DMSO-d_6, δ, 300 MHz): 3.92 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.22 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.61-7.78 (m, 4H, Ar-H), 7.93 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.78 (s, 1H, H-$4_{pyridine}$). Mass spectrum (*m/z*, *I* %): 415 (28), 387 (17), 359 (13), 333 (7), 242 (36), 220 (100), 205 (62), 191 (11), 177 (21), 135 (7), 117 (8), 77 (13), 63 (7). Anal. Calcd for $C_{22}H_{13}N_3O_6$ (415.35): C, 63.62; H, 3.15; N, 10.12%. Found: C, 63.38; H, 2.87; N, 9.92%.

7-Amino-6-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl]pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (7). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 4(6)-aminouracil (0.26 g, 2 mmol), in DMF (10 mL) containing DBU (0.1 mL), was heated under reflux for 2 h. The pale yellow crystals obtained during heating were filtered off and crystallized from DMF/H_2O, mp > 300 ºC, yield 0.63 g

(79%). IR (KBr, cm^{-1}): 3418 (OH), 3387, 3312, 3259 (NH_2, 2NH), 3104 (CH_{furan}), 3038 ($CH_{arom.}$), 2932, 2895 ($CH_{aliph.}$), 1724, 1703 (2C=$O_{pyrimidinedione}$), 1638 (C=O_{ketone}), 1601 (C=N) and 1577 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.94 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 7.20 (d, 1H, *J*=2.4 Hz, H-3_{furan}), 7.68 (bs NH_2 exchanged with D_2O), 7.98 (d, 1H, *J*=2.1 Hz, H-2_{furan}), 8.83 (s, 1H, H-5), 10.84 (bs, 1H, NH exchanged with D_2O), 11.06 (bs, 1H, NH exchanged with D_2O), 12.26 (bs, 1H, OH exchanged with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 57.8 (OCH_3), 59.4 (OCH_3), 102.3 (′C-5), 105.6 (′C-3_{furan}), 108.7 (C-4a), 112.1 (C-6), 111.3 (′C-3a), 123.0 (′C-7), 142.6 (C-5), 145.8 (′C-2_{furan}), 147.2 (′C-4), 151.2 (′C-7a), 153.4 (C-2 as C=O), 155.2 (C-7), 156.8 (C-8a), 158.5 (C-4 as C=O), 160.2 (′C-6-as C-OH), 193.4 (C=O). Mass spectrum (*m/z, I* %): 398 (48), 382 (10), 352 (8), 221 (100), 205 (66), 177 (21), 134 (18), 124 (7), 118 (13), 89 (11), 77 (30), 64 (18). Anal. Calcd for $C_{18}H_{14}N_4O_7$ (398.33): C, 54.28; H, 3.54; N, 14.07%. Found: C, 54.15; H, 3.33; N, 13.75%.

6-Amino-3-methyl-5-[(6-hydroxy-4,7-dimethoxy-1-benzofuran-5-yl)carbonyl]-1*H*-pyrazolo[3,4-*b*]-pyridine (8). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 5-amino-3-methyl-1*H*-pyrazole (0.20 g, 2 mmol), in DMF (10 mL) containing DBU (0.1 mL), was heated under reflux for 2 h. The pale yellow crystals formed after cooling were filtered off and crystallized from *n*-butanol, mp 255-256 ºC, yield 0.52 g (70%). IR (KBr, cm^{-1}): 3421 (OH), 3374, 3289, 3243 (NH_2, NH), 3120 (CH_{furan}), 3054 ($CH_{arom.}$), 1640 (C=O_{ketone}), 1607 (C=N) and 1590 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.92 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 7.23 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.75 (bs, 2H, NH_2 exchanged with D_2O), 7.95 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.79 (s, 1H, H-4), 11.32 (bs, 1H, NH exchanged with D_2O), 12.41 (bs, 1H, OH exchanged with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 15.2 (CH_3), 57.3 (OCH_3), 58.8 (OCH_3), 101.8 (′C-5), 105.9 (′C-3_{furan}), 110.7 (′C-3a), 115.1 (C-3a), 118.2 (C-5), 123.3 (′C-7), 138.2 (C-3), 141.8 (C-4), 146.1 (′C-2_{furan}), 147.5 (′C-4), 151.3 (′C-7a), 154.8 (C-7), 156.4 (C-7a), 159.9 (′C-6-as C-OH), 192.7 (C=O). Mass spectrum (*m/z, I* %): 368 (63), 352 (35), 337 (20), 220 (100), 205 (54), 147 (27), 160 (9), 134 (23), 107 (15), 77 (36), 64 (12). Anal. Calcd for $C_{18}H_{16}N_4O_5$ (368.34): C, 58.69; H, 4.38; N, 15.21%. Found: C, 58.50; H, 4.21; N, 15.03%.

3-Amino-6,10-dimethoxy-1*H*-furo[3`,2`:6,7]chromeno[2,3-*b*]pyrazolo[4,3-*e*]pyridin-5(5*H*)-one (10). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 5-amino-2,4-dihydro-3*H*-pyrazol-3-one (**9**) (0.20 g, 2 mmol) in DMF (10 mL) containing DBU (0.1 mL) was heated under reflux for 2 h. The yellow crystals obtained during heating were filtered and recrystallized from *n*-butanol, mp > 300 ºC, yield 0.52 g (74%). IR (KBr, cm^{-1}): 3365, 3279, 3235 (NH_2, NH), 3113 (CH_{furan}), 3063 ($CH_{arom.}$), 2974, 2949 ($CH_{aliph.}$), 1658 (C=$O_{\gamma\text{-pyrone}}$), 1611 (C=N), 1588 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.91 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 7.21 (d, 1H, *J*=2.4 Hz, H-3_{furan}), 7.87 (d, 1H, *J*=2.4 Hz, H-2_{furan}), 8.26 (bs, 2H, NH_2

exchangeable with D_2O), 8.82 (s, 1H, H-4$_{pyridine}$), 11.45 (bs, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 57.9 (OCH_3), 58.7 (OCH_3), 93.1 (C-3a), 105.9 (C-7), 108.3 (C-5a), 112.8 (C-6a), 116.2 (C-4a), 127.8 (C-10), 139.8 (C-10a), 142.3 (C-4), 145.7 (C-8), 147.3 (C-6), 149.2 (C-3), 150.8 (C-12a), 152.2 (C-9a), 157.3 (C-11a), 177.5 (C-5 as C=O). Mass spectrum (*m/z*, *I* %): 352 (100), 324 (71), 309 (6), 294 (8), 279 (10), 242 (26), 220 (43), 205 (14), 177 (19), 147 (34), 118 (26), 103 (9), 77 (15), 63 (6). Anal. Calcd for $C_{17}H_{12}N_4O_5$ (352.30): C, 57.96; H, 3.43; N, 15.90%. Found: C, 57.65; H, 3.30; N, 15.78%.

6,10-Dimethoxy-2-phenylaminofuro[3``,2``:6`,7`]chromeno[2,3-*b*][1,3]thiazolo[5,4-*e*]pyridin-5(5*H*)-one (12). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and 2-(phenylimino)-1,3-thiazolidin-4-one (**11**) (0.69 g, 2 mmol) in DMF (20 mL) containing DBU (0.1 mL), was refluxed for 2 h. The solid obtained during heating was filtered and recrystallized from DMF/EtOH, mp > 300 ºC, yield 0.62 g (69%). IR (KBr, cm^{-1}): 3360 (NH), 3101 (CH$_{furan}$), 3048 (CH$_{arom.}$), 2987, 2958 (CH$_{aliph.}$), 1663 C=O$_{\gamma\text{-pyrone}}$), 1611 (C=N). ^{1}H NMR (DMSO, δ, 300 MHz): 3.86 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.19 (d, 1H, *J*=1.8 Hz, H-3$_{furan}$), 7.46-7.53 (m, 5H, Ar-H), 7.90 (d, 1H, *J*=1.8 Hz, H-2$_{furan}$), 8.69 (s, 1H, H-4$_{pyridine}$), 9.97 (bs, 1H, NH exchangeable with D_2O). Mass spectrum (*m/z, I* %): 445 (40), 417 (22), 340 (18), 310 (9), 296 (7), 242 (48), 220 (100), 205 (31), 177 (14), 148 (29), 134 (12), 117 (8), 104 (13), 77 (25), 64 (13). Anal. Calcd for $C_{23}H_{15}N_3O_5S$ (445.45): C, 62.02; H, 3.39; N, 9.43; S, 7.20%. Found: C, 61.86; H, 3.10; N, 9.22; S, 6.92%.

7,11-Dimethoxy-6*H*-2-thioxofuro[3``,2``:6`,7`]chromeno[3`,2`:5,6]pyrido[2,3-*d*]pyrimidine-4,6(1*H*, 3*H*)-dione (13). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and thiobarbituric acid (0.26 g, 2 mmol) in absolute EtOH (20 mL) containing DBU (0.1 mL) was heated under reflux for 2 h. The yellow crystals deposited during heating were filtered and recrystallized from DMF/H_2O, mp > 300 ºC, yield 0.59 g (74%). IR (KBr, cm^{-1}): 3370, 3345 (2NH), 3116 (CH$_{furan}$), 2963, 2917 (CH$_{aliph.}$), 1684 (C=O$_{pyrimidinone}$), 1651 (C=O$_{\gamma\text{-pyrone}}$), 1610 (C=N), 1572 (C=C), 1217 (C=S). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 3.89 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.18 (d, 1H, *J*=2.1 Hz, H-3$_{furan}$), 7.86 (d, 1H, *J*=2.1 Hz, H-2$_{furan}$), 8.80 (s, 1H, H-4$_{pyridine}$), 10.94 (bs, 1H, NH exchangeable with D_2O), 11.36 (bs, 1H, NH exchangeable with D_2O). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 58.1 (OCH_3), 59.3 (OCH_3), 103.4 (C-4a), 106.1 (C-8), 107.8 (C-6a), 108.8 (C-5a), 113.1 (C-7a), 128.6 (C-11), 139.5 (C-11a), 143.8 (C-5), 145.8 (C-9), 147.6 (C-7), 151.6 (C-10a), 153.5 (C-13a), 155.8 (C-12a), 161.2 (C-4 as C=O), 177.9 (C-6 as C=O), 190.4 (C-2 as C=S). Mass spectrum (*m/z, I* %): 397 (100), 369 (64), 341 (48), 308 (17), 278 (11), 242 (37), 220 (31), 205 (19), 177 (14), 148 (26), 133 (12), 117 (7), 77 (14), 64 (9). Anal. Calcd for $C_{18}H_{11}N_3O_6S$ (397.36): C, 54.41; H, 2.79; N, 10.57; S, 8.07%. Found: C, 54.20; H, 2.48; N, 10.27; S, 7.85%.

9,10-Dihydro-4,13-dimethoxyfuro[3`,2`:6,7]chromeno[2,3-*b*]quinoline-5,7(5H,8*H*)-dione (14). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and cyclohexane-1,3-dione (0.22 g, 2 mmol) in absolute EtOH (20 mL) containing DBU (0.1 mL) was heated under reflux for 2 h. The white crystals obtained after cooling were filtered and recrystallized from AcOH, mp 295-296 ºC, yield 0.55 g (75%). IR (KBr, cm^{-1}): 3105 (CH_{furan}), 2970, 2941 ($CH_{aliph.}$), 1681 ($C=O_{quinolinone}$), 1654 ($C=O_{\gamma\text{-pyrone}}$), 1602 (C=N), 1585 (C=C). ^{1}H NMR (DMSO-d_6, δ, 300 MHz): 2.17 (t, 2H, *J*= 6.1 Hz, CH_2), 2.73 (t, 2H, *J*= 6.1 Hz, CH_2), 3.21 (t, 2H, *J*= 6.1 Hz, CH_2), 3.91 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 7.24 (d, 1H, *J*=1.8 Hz, H-3_{furan}), 7.92 (d, 1H, *J*=1.8 Hz, H-2_{furan}), 8.89 (s, 1H, H-$4_{pyridine}$). ^{13}C NMR (DMSO-d_6, δ, 75 MHz): 23.8 (C-9 as CH_2), 26.4 (C-10 as CH_2), 34.2 (C-8 as CH_2), 57.7 (OCH_3), 58.9 (OCH_3), 106.0 (C-3), 108.4 (C-4a), 113.2 (C-3a), 115.7 (C-5a), 126.1 (C-6a), 128.5 (C-13), 139.8 (C-12a), 143.7 (C-6), 145.9 (C-2), 147.4 (C-4), 151.3 (C-13a), 154.2 (C-10a), 157.2 (C-11a), 177.8 (C-5 as C=O), 193.7 (C-7 as C=O). Mass spectrum (*m/z*, *I* %): 365 (70), 337 (100), 309 (65), 242 (40), 220 (56), 205 (23), 148 (19), 133 (9), 117 (6), 77 (10), 64 (8). Anal. Calcd for $C_{20}H_{15}NO_6$ (365.34): C, 65.75; H, 4.14; N, 3.83%. Found: C, 65.60; H, 4.01; N, 3.54%.

7,8-Dihydro-4,11,15,20-tetramethoxy-*bis*-furo[3`,2`:6,7]chromeno[2,3-*b*:3`,2`-*j*][1,10]-phenanthroline-5,10(5*H*,10*H*)-dione (15). A mixture of carbonitrile **1** (0.54 g, 2 mmol) and cyclohexane-1,2-dione (0.22 g, 2 mmol), in absolute EtOH (20 mL) containing DBU (0.1 mL), was heated at reflux for 20 min. The pale yellow crystals obtained during heating were filtered off and crystallized from DMF, mp > 300 ºC, yield 0.49 g (40%). IR (KBr, cm^{-1}): 3101 (CH_{furan}), 3008 ($CH_{arom.}$), 2976, 2913 ($CH_{aliph.}$), 1663 ($C=O_{\gamma\text{-pyrone}}$), 1618 (C=N), 1562 (C=C). ^{1}H-NMR (DMSO-d_6, δ, 300 MHz): 2.13 (s, 4H, $2CH_2$), 3.96 (s, 6H, $2OCH_3$), 4.12 (s, 6H, $2OCH_3$), 7.22 (d, 2H, *J*=2.1 Hz, 2H-3_{furan}), 7.97 (d, 2H, *J*=2.1 Hz, H-2_{furan}), 8.83 (s, 2H, 2H-$4_{pyridine}$). Mass spectrum, *m/z* (I_r %): 618 (100), 562 (42), 242 (65), 220 (37), 205 (15), 148 (28), 134 (12), 117 (6), 77 (36), 64 (19). Anal. Calcd for $C_{34}H_{22}N_2O_{10}$ (618.551): C, 66.02; H, 3.58; N, 4.53%. Found: C, 65.83; H, 3.29; N, 4.42%.

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