Synthesis and Antimicrobial Activity of Some New Nitrogen Bridge-head Pyrido[1,2-*b*][1,2,4]triazepines Incorporating 6-Methylchromone Moiety

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Abstract:

Some new nitrogen bridge-head pyrido[1,2-*b*][1,2,4]triazepines incorporating 6-methylchromone moiety have been synthesized from the reaction of 1,6-diamino-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4**) with some α,γ-bifunctional electrophiles including 2-cyano-3,3-*bis*(methylthio)acrylonitrile, 2-cyano-3,3-*bis*(methylthio)prop-2-enamide, 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde, 2-chloro-3-formylquinoline, *p*-methoxybenzylidene-malononitrile, ethyl 2-cyano-3-(4-methoxyphenyl)prop-2-enoate, chromone-3-carbonitrile. Structures of the newly synthesized products have been deduced upon the help of elemental analysis and spectral data. The synthesized compounds were screened for their antimicrobial activity.

Keywords: Chromone; 1,6-diaminopyridone; pyrido[1,2-*b*][1,2,4]triazepines.

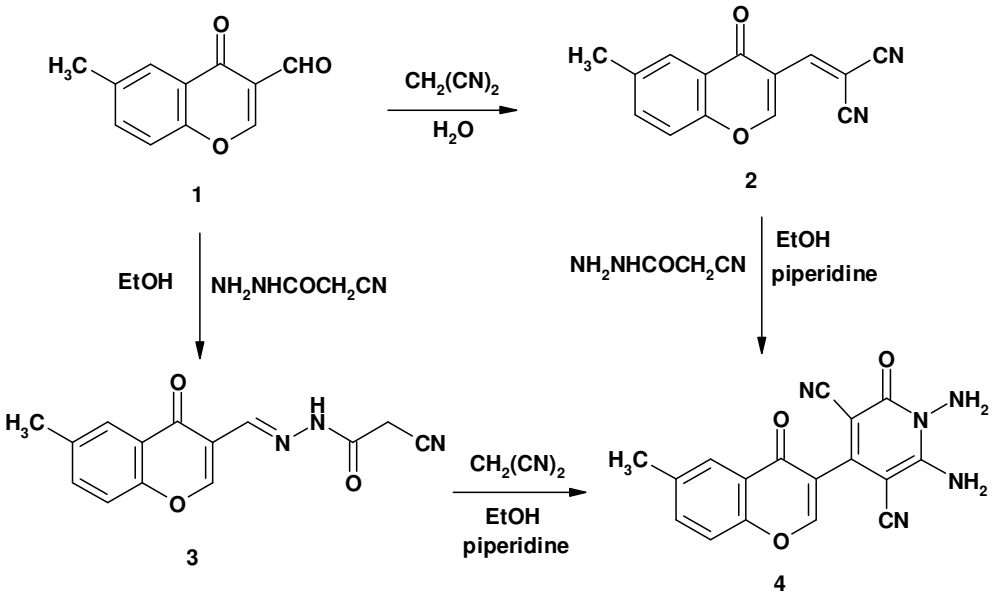
INTRODUCTION

Chromone derivatives exhibited significant biological activities such as anticancer [1,2], antitumor [3,4], antiviral [5], antibiotic [6], antimicrobial [7], antifungal [8], antioxidant [9,10], plant growth inhibitors [11], and physiological activity [12]. Polyfunctional pyridines are highly reactive intermediates that have been extensively used in heterocyclic synthesis [13-15]. On the other hand, 1,2,4-triazepines [16] are considered as important nitrogen heterocyclic rings due to their interested biological activity. *o*-Diamines are very active substrates for building of various heterocyclic systems [17,18]. In symmetrical diamines, the product will be the same irrespective of which amine participates

first in the reaction. In the case of unsymmetrical diamines, the electron withdrawing/donating nature of substituents influence the initial participation of a particular amino group in the reaction, resulting in chemoselective products. On the basis of above observations and as a part of our aforementioned work directed for the synthesis of new polynuclear bioactive heterocyclic systems [19,20], the present work aims to study the chemical reactivity of 1,6-diamino-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4**) towards various 1,3-bifunctional electrophiles to furnish some new nitrogen bridgehead pyrido[1,2-*b*][1,2,4]triazepines linked 6-methyl chromone moiety.

RESULTS AND DISCUSSION

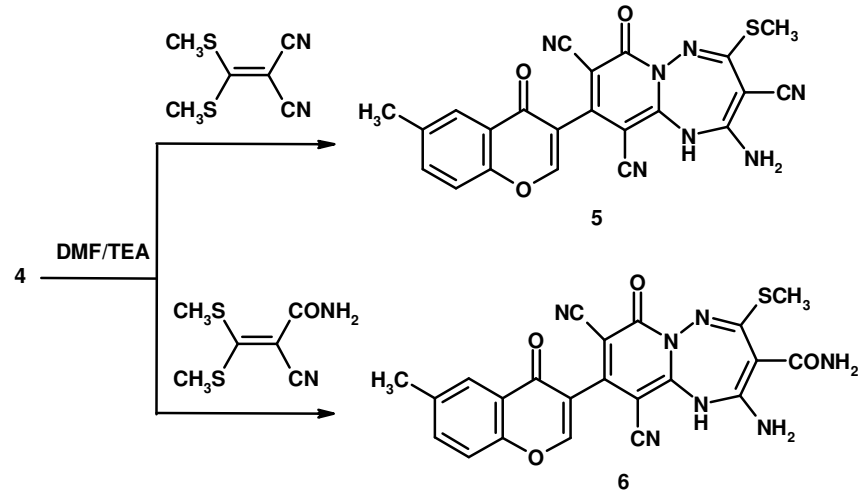
The starting compound 1,6-diamino-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4**) was prepared by refluxing an alcoholic solution of [(6-methyl-4-oxo-4*H*-chromen-3-yl)methylene]malononitrile (**2**) [21] with cyanoaceto-hydrazide or *N*`-[6-methyl-4-oxo-4*H*-chromone-3-yl]-2-cyanoacetohydrazide (**3**) [22] with malononitrile in the presence of piperidine as a catalyst (Scheme 1) [23]. The IR spectrum of compound **4** showed characteristic absorption bands at 3418, 3313 (2 NH_2), 2262 (2 C≡N), 1680 ($C=O_{pyridone}$) and 1634 cm^{-1} ($C=O_{\gamma\text{-pyrone}}$). Also, the ^1H NMR spectrum of compound **4** revealed three characteristic singlet signals at 2.26, 8.50 and 9.40 ppm attributed to the CH_3, H-$5_{chromone}$ and H-$2_{chromone}$, respectively. In addition, the ^1H NMR spectrum showed two exchangeable signals at 4.59 and 10.22 ppm due to the *N*-NH_2 and *C*-NH_2 protons, respectively, these results confirm the difference in nucleophilicity between the two amino groups. Thus, it is expected that the hydrazide β-nitrogen (*N*-NH_2) is more nucleophilic and will react more rapidly with the electron deficient carbon than the second amino group (*C*-NH_2). Compound **4** was further deduced from its mass spectrum which showed the molecular ion peak at m/z 333 which agree well with the molecular formula $C_{17}H_{11}N_5O_3$ and supports the identity of the structure.



Scheme 1. Formation of 1,6-diaminopyridone **4**.

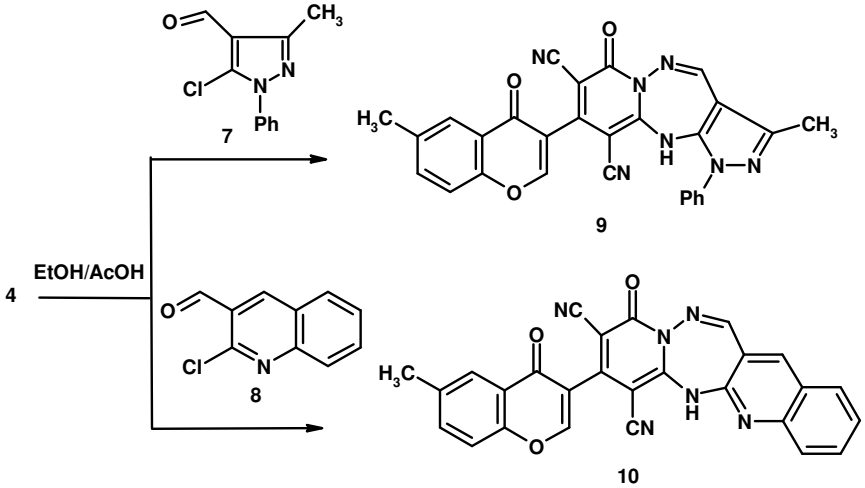
o-Diamines are ready-made nucleophilic centers for the synthesis of fused nitrogen heterocyclic rings [17,18]. Thus, diaminopyridone **4** is a useful building block for nitrogen bridge-head pyrido[1,2-*b*][1,2,4]triazepine derivatives of expected biological activity, *via* ring closure reactions with some α,γ-bifunctional electrophiles. Thus, heterocyclization of compound **4** with 2-cyano-3,3-*bis*(methylthio)acrylonitrile afforded 2-amino-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4-methylthio-7-oxo-5*H*-pyrido[1,2-*b*][1,2,4]triazepine-3,8,10-tricarbonitrile (**5**) (Scheme 2). The reaction may proceed *via* nucleophilic displacement of SCH_3 group by the more nucleophilic amino group (*N*-NH_2) with concomitant cycloaddition of the other amino group (*C*-NH_2) onto nitrile function to produce the target product **5**. The IR spectrum of compound **5** showed absorption bands at 3434, 3156 (NH_2, NH), 2263, 2230 (3 C≡N), 1685 ($C{=}O_{pyridone}$), 1632 ($C{=}O_{\gamma\text{-pyrone}}$), 1599 cm^{-1} (C=N and C=C). Also, its ^1H NMR spectrum exhibited characteristic signals assigned to two methyl groups at 2.24 ($CH_{3\ chromone}$) and 2.76 ppm (SCH_3), in addition to two exchangeable signals at 7.93 and 10.05 ppm attributed to NH_2 and NH protons, respectively.

Similarly, condensation of compound **4** with 2-cyano-3,3-*bis*(methylthio)prop-2-enamide under similar conditions gave 2-amino-8,10-dicyano-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4-(methylthio)-7-oxo-1,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-3-carboxamide (**6**) (Scheme 2).



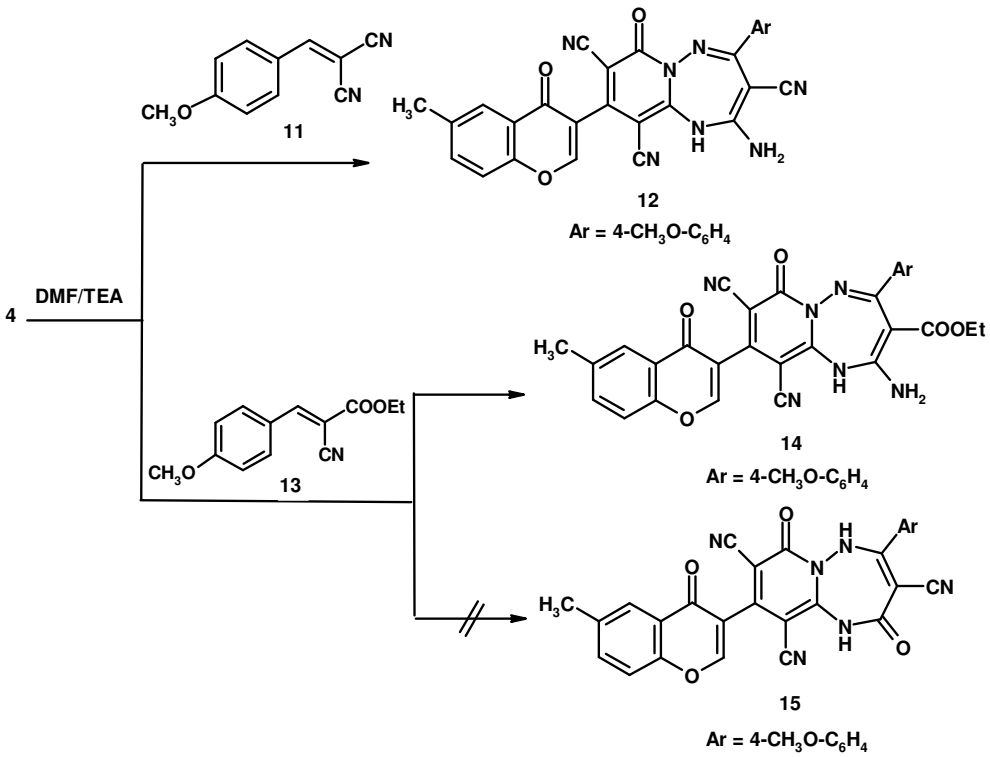
Scheme 2. Formation of pyrido[1,2-*b*][1,2,4]triazepine derivatives **5** and **6**.

1,6-Diaminopyridone **4** was allowed to react with some heterocyclic *o*-chloroaldehydes [24]. Thus, condensation of **4** with 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (**7**) [25] and 2-chloro-3-formylquinoline (**8**) [26] in ethanol containing few drops of acetic acid afforded the heteroannulated pyrido[1,2-*b*][1,2,4]triazepines **9** and **10**, respectively (Scheme 3). The ^{1}H NMR spectra of compounds **9** and **10** showed characteristic singlet signals due to H-7$_{\text{triazepine}}$ at 8.56 and 8.55 ppm, respectively. Also, the spectrum of compound **10** showed characteristic singlet at 8.90 ppm attributed to the H-4 of the quinoline nucleus. Further, the mass spectrum of compound **10** revealed the molecular ion peak at m/z 469 (M-1) corresponding to the molecular formula $C_{27}H_{14}N_6O_3$, which is coincident with the formula weight (470.45) and supports the identity of the structure.



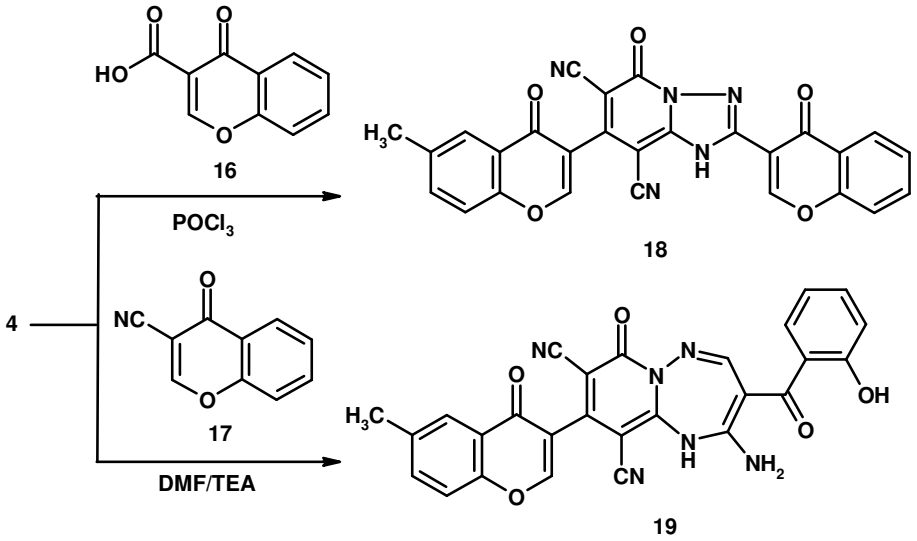
Scheme 3. Formation of pyrido[1,2-*b*][1,2,4]triazepine derivatives **9** and **10**.

Next, we aimed to study the chemical reactivity of compound **4** towards some arylidenenitriles. Thus, treating diaminopyridone **4** with *p*-methoxybenzylidene-malononitrile (**11**) in DMF containing two drops of triethylamine gave 2-amino-4-(4-methoxyphenyl)-7-oxo-5,7-dihydro-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-pyrido[1,2-*b*] [1,2,4]triazepine-3,8,10-tricarbonitrile (**12**) (Scheme 4). The ^{1}H NMR spectrum of compounds **12** showed characteristic singlet signals at 3.87 ppm attributed to methoxy protons. The mass spectrum of compound **12** did not recorded the molecular ion peak at m/z 515 but record a peak at m/e 484 (M-31) corresponding to the molecular weight after loss of the methoxy group. Also, condensation of **4** with ethyl 2-cyano-3-(4-methoxyphenyl)prop-2-enoate (**13**) under the same reaction conditions yielded ethyl 2-amino-8,10-dicyano-4-(4-methoxyphenyl)-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-7-oxo-5,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-3-carboxylate (**14**) and not the other possible product **15** (Scheme 4), the reaction may proceed nucleophilic addition of amino group (*N*-NH_2) to the activate double bond followed by cycloaddition of the other amino group (*C*-NH_2) to the nitrile function with concomitant aromatization to produce the target compound **14**. The ^{1}H NMR spectrum showed triplet and quartet signals at 1.28 and 4.28 ppm attributed to the ethoxy protons, the spectrum also revealed characteristic singlet at 3.85 ppm assigned to the methoxy protons.



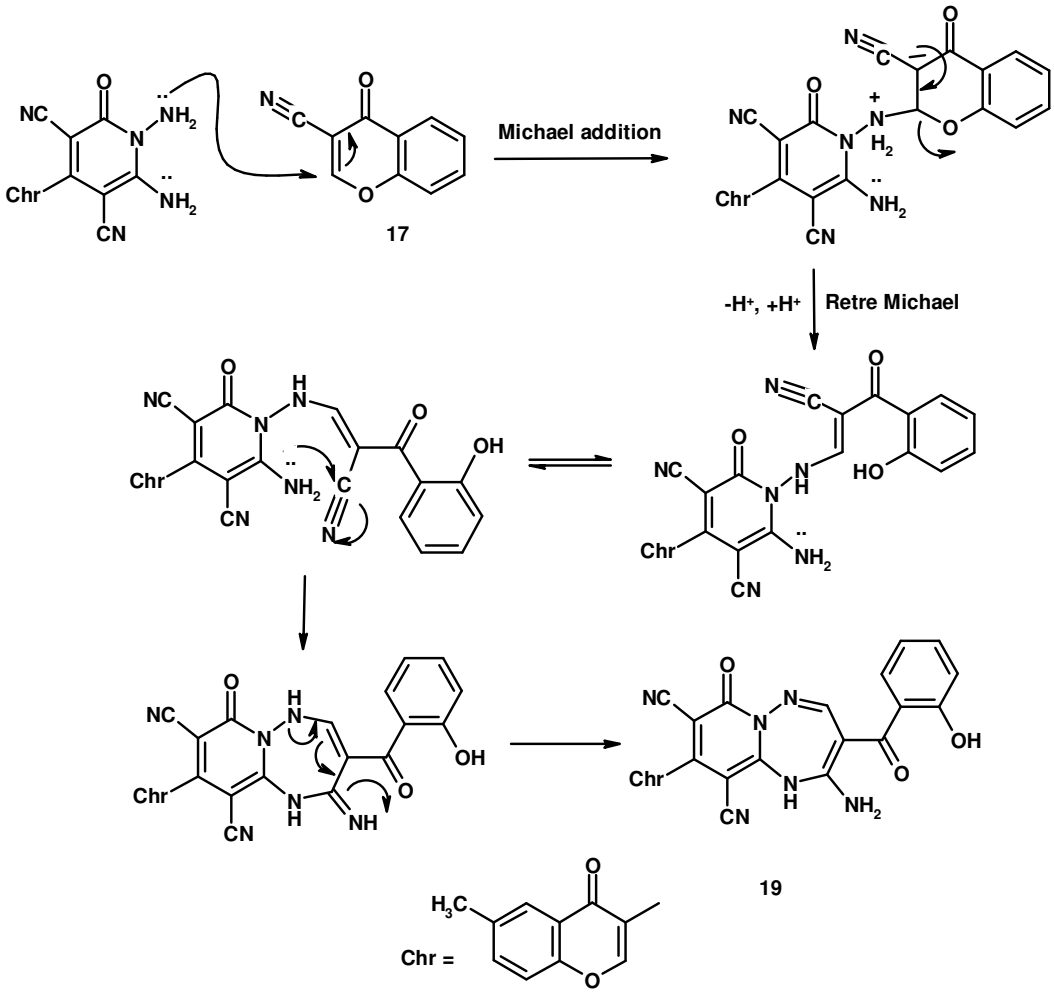
Scheme 4. Condensation of diaminopyridone **4** with arylidinenitriles **11** and **13**.

The chemical behavior of diaminopyridone **4** was studied towards chromone-3-carboxylic acid (**16**) [27] and chromone-3-carbonitrile (**17**) [28]. Thus, treatment of compound **4** with chromon-3-carboxylic acid (**16**) in $POCl_3$ produced 7-(6-methyl-4-oxo-4*H*-chromene-3-yl)-2-(4-oxo-4*H*-chromene-3-yl)-5-oxo-3,5-dihydro-1,2,4-triazolo[1,5-*a*] pyridine-6,8-dicarbonitrile (**18**) (Scheme 5). The IR spectrum of compound **18** recorded characteristic absorption bands at 3402 (NH), 2219 (2 C≡N), 1670 ($C=O_{pyridone}$), 1650 (2 $C=O_{\gamma\text{-pyrone}}$) and 1601 cm^{-1} (C=N and C=C). Also, its ^1H NMR spectrum showed characteristic signals at 9.23 ($H–2`_{chromone}$), 9.44 ($H–2_{chromone}$), in addition to an exchangeable signal at 10.20 ppm attributed to $NH_{triazole}$.



Scheme 5. Reaction of **4** with chromone-3-carboxylic acid (**16**) and chromone-3-carbonitrile (**17**).

Finally, treatment of **4** with chromone-3-carbonitrile (**17**) gave pyridotriazepine derivative **19** (Scheme 5). The reaction may proceed *via* ring opening of the γ-pyrone ring by the more nucleophilic amino group with concomitant cycloaddition of the other amino group to the nitrile function. The proposed mechanism for the formation of compound **19** is depicted in Scheme 6. The IR spectrum of compound **19** showed characteristic absorption bands at 3405, 3315, 3211 (OH, NH_2, NH), 2259, 2220 (2 C≡N), 1684 ($C=O_{pyridone}$), 1629 ($C=O_{\gamma\text{-pyrone}}$ and $C=O_{hydrogen\ bonded}$) and 1600 cm^{-1} (C=C and C=N). The ^1H NMR spectrum of compound **19** showed characteristic singlet at 8.46 ppm due to the $H\text{-}7_{triazepine}$ [29].



Scheme 6. The proposed mechanism for the formation of pyridotriazepine **19**.

ANTIMICROBIAL ACTIVITY

The standardized disc agar diffusion method [30] was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* as Gram positive bacteria, *Proteus vulgaris* as Gram negative bacteria and *Candida albicans* as fungus starin. The antibiotic Doxymycin and Fluconazole were purchased from Egyptian markets and used in concentrations 100 µg mL^{-1} as references for antibacterial and antifungal activities.

The compounds were dissolved in DMSO which has no inhibition activity to get concentration of 100 µg mL^{-1}. The results depicted in Table 1 showed various activities against all species of microorganisms which suggest that the variations in the structures affect on the growth of the microorganisms. Thus, we can conclude from these results:

1) The prepared compounds showed a variable antimicrobial activity towards all species of bacteria and fungi (Table 1). They showed antifungal activity higher than antibacterial activity.
2) Compounds **18** showed a good antimicrobial activity. This high effect may attribute to the presence of two skeletons of chromone moieties beside the triazolopyridone moiety.

Table 1. The antimicrobial activity of the newly synthesized Compounds.

Compound No.	Diameter of inhibition zone (mm) conc. (100 µg mL^{-1})		
	S.aureus (Gram +ve)	*P. vulgaris* (Gram -ve)	*C. albicans* (Fungal strain)
4	5	-	5
5	-	5	9
6	5	4	6
9	-	5	8
10	6	-	4
12	5	-	5
14	6	4	6
18	11	7	10
19	4	-	6
Doxymycin	15	10	-
Fluconazole	-	-	16

CONCLUSION

We have successfully synthesized a new series of nitrogen bridge-head pyrido[1,2-*b*] [1,2,4]triazepines linked with a 6-methylchromone moiety *via* ring closure reactions of the key intermediate 1,6-diamino-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydro pyridine-3,5-dicarbonitrile (**4**) with some α,γ-bifunctional electrophiles.

EXPERIMENTAL

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300MHz) were measured on Mercury-300BB, using DMSO-d_6 as a solvent and TMS (δ) as the internal standard. Mass spectra were obtained using Jeol-AMS-AX-500 instrument

mass spectrometer (70 eV). Elemental microanalyses were performed at microanalysis unit in National Research Center, Dokki, Giza, Egypt.

1,6-Diamino-4-(6-methyl-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (4).

Method A:

A mixture of (6-methyl-4-oxo-4*H*-chromen-3-yl)methylenemalononitrile (**2**) (2.36 g, 10 mmol) and cyanoacetohydrazide, (0.99 g, 10 mmol), in absolute ethanol (50 mL) containing two drops of piperidine, was heated under reflux for 3h. The orange-yellow precipitate obtained during heating was filtered and crystallized from ethanol to give **4** as orange-yellow crystals, yield (2.33 g, 70%), mp 242-243 ºC.

Method B:

A mixture of *N*'-[(6-methyl-4-oxo-4*H*-chromen-3-yl)methylene]-2-cyano acetohydrazide (**3**) (1.35, 5 mmol) and malononitrile (0.33 g, 5 mmol), in absolute ethanol (50 mL) containing two drops of piperidine, was heated under reflux for 3h. The orange-yellow precipitate obtained during heating was filtered and crystallized from ethanol to give **4** as orange-yellow crystals, yield (1.1 g, 68%), mp 242-243 ºC. IR (KBr, cm^{-1}): 3418, 3313 (2 NH_2), 3050 ($CH_{arom.}$), 2924 ($CH_{aliph.}$), 2262 (2 C≡N), 1680 ($C=O_{pyridone}$), 1634 ($C=O_{\gamma\text{-}pyrone}$), 1591 (C=C). ^{1}H NMR (DMSO-d_6, δ): 2.26 (s, 3H, CH_3), 4.59 (bs, 2H, N-NH_2 exchangeable with D_2O), 6.92 (d, 1H, *J*=8.4 Hz, H-$8_{chromone}$), 7.31 (d, 1H, *J*=8.4 Hz, H-$7_{chromone}$), 8.50 (s, 1H, H-$5_{chromone}$), 9.40 (s, 1H, H-$2_{chromone}$), 10.22 (bs, 2H, C-NH_2 exchangeable with D_2O). M/z (*I* %): 333 (4), 319 (4), 209 (3), 184 (6), 170 (7), 134 (45), 130 (7), 116 (12), 108 (19), 88 (100), 68 (76). Analysis Calcd for $C_{17}H_{11}N_5O_3$ (333.31); C, 61.26; H, 3.33; N, 21.01%. Found: C, 60.90; H, 3.40; N, 20.70%

2-Amino-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4-methylthio-7-oxo-5*H*-pyrido[1,2-*b*][1,2,4]triazepine-3,8,10-tricarbonitrile (5).

A mixture of compound **4** (0.67 g, 2 mmol) and 2-cyano-3,3-*bis*(methylthio) acrylonitrile (0.34 g, 2 mmol) in DMF (30 mL) containing two drops of triethylamine was heated under reflux for 4h. The solid obtained after cooling was filtered, washed with ethanol and crystallized from DMF/EtOH to give **5** as yellow crystals, yield (0.47 g, 52 %), m.p. 242 ºC. IR (KBr, cm^{-1}): 3434, 3156 (NH_2, NH), 3049 ($CH_{arom.}$), 2926 (CH_{aliph}), 2263,

2230 (3 C≡N), 1685 ($C=O_{pyridone}$), 1632 $C=O_{\gamma\text{-pyrone}}$), 1599 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 2.24 (s, 3H, $CH_{3chromone}$), 2.76 (s, 3H, SCH_3), 6.90 (d, 1H, *J*=8.4 Hz, H-$8_{chromone}$), 7.22 (d, 1H, *J*=8.1 Hz, H-$7_{chromone}$), 7.93 (bs, 2H, NH_2 exchangeable with D_2O), 8.49 (s, 1H, H-$5_{chromone}$), 9.31 (s, 1H, H-$2_{chromone}$), 10.05 (bs, 1H, NH exchangeable with D_2O). M/z (*I* %): 453 (M-2; 4), 439 (3), 409 (2), 390 (5), 317 (9), 302 (4), 289 (15), 274 (3), 263 (6), 237 (6), 209 (5), 159 (4), 134 (12), 116 (6), 107 (13), 91 (5), 78 (45), 73 (100), 50 (12). Analysis Calcd for $C_{22}H_{13}N_7O_3S$ (455.46): C, 58.02; H, 2.88; N, 21.53; S, 7.04 %. Found: C, 57.80; H, 2.80; N, 21.30; S, 6.90%.

2-Amino-8,10-dicyano-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4-(methylthio)-7-oxo-1,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-3-carboxamide (6).

A mixture of compound **4** (0.67 g, 2 mmol) and 2-cyano-3,3-*bis*(methylthio)prop-2-enamide (0.38 g, 2 mmol) in DMF (30 mL) containing two drops of triethylamine was heated under reflux for 4h. The solid obtained after cooling was filtered, washed with ethanol and crystallized from DMF to give **6** as yellow crystals, yield (0.39 g, 41 %), mp 142 ºC. IR (KBr, cm^{-1}): 3428, 3200 ($2NH_2$, NH), 2925 (CH_{aliph}), 2194 (2 C≡N), 1695 ($C=O_{carboxamide}$), 1682 ($C=O_{pyridone}$), 1652 ($C=O_{\gamma\text{-pyrone}}$), 1600 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 2.23 (s, 3H, $CH_{3\ chromone}$), 2.72 (s, 3H, SCH_3), 6.87 (d, 1H, *J*=7.2 Hz, H-$8_{chromone}$), 7.15 (d, 1H, *J*=7.8 Hz, H-$7_{chromone}$), 7.60 (bs, 2H, NH_2), 7.94 (bs, 2H, NH_2), 8.55 (s, 1H, H-$5_{chromone}$), 8.74 (s, 1H, H-$2_{chromone}$), 10.02 (bs, 1H, NH). Analysis Calcd for $C_{22}H_{15}N_7O_4S$ (473.46): C, 55.81; H, 3.19; N, 20.71; S, 6.77 %. Found: C, 55.81; H, 3.19; N, 20.71; S, 6.77 %.

3-Methyl-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-7-oxo-7,11-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*e*]pyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (9).

A mixture of compound **4** (0.67 g, 2 mmol) and 5-chloro-3-methyl-1-phenylpyrazole-4-carbaldehyde (**7**) (0.44 g, 2 mmol) in ethanol (20 mL) containing few drops of acetic acid was heated under reflux for 4h. The solid obtained during heating was filtered and crystallized from DMF to give **9** as yellow crystals, yield (0.56 g, 56%), mp 281 ºC. IR (KBr, cm^{-1}): 3332 (NH,), 3063 ($CH_{arom.}$), 2933 ($CH_{aliph.}$), 2226 (2 C≡N), 1681 ($C=O_{pyridone}$), 1633 ($C=O_{\gamma\text{-pyrone}}$), 1589 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 2.07 (s, 3H, $CH_{3\ pyrazole}$), 2.38 (s, 3H, $CH_{3\ chromone}$), 6.90-7.80 (m, 7H, Ar-H), 8.15 (s, 1H, H-$5_{chromone}$), 8.56 (s, 1H, H-$7_{triazepine}$), 9.35 (s, 1H, H-$2_{chromone}$), 11.41 (bs, 1H, NH

exchangeable with D_2O). Analysis Calcd for $C_{28}H_{17}N_7O_3$ (499.49): C, 67.33; H, 3.43; N, 19.63%. Found: C, 67.10; H, 3.30; N, 19.40%.

2-(6-Methyl-4-oxo-4*H*-chromen-3-yl)-4-oxo-4*H*-quinolinyl[2,3-*e*]pyrido[1,2-*b*] [1,2,4]triazepine-1,3-dicarbonitrile (10).

A mixture of compound **4** (0.67 g, 2 mmol) and 3-formyl-2-chloroquinoline (**8**) (0.38 g, 2 mmol) in ethanol (20 mL) containing few drops of acetic acid was heated under reflux for 4h. The solid obtained during heating was filtered and crystallized from ethanol to give **10** as yellow crystals, yield (0.38 g, 54%), mp 290 ºC. IR (KBr, cm^{-1}): 3401 (NH), 3063 ($CH_{arom.}$), 2922, 2860 ($CH_{aliph.}$), 2226 (2 C≡N), 1681 ($C=O_{pyridone}$), 1630 $C=O_{\gamma\text{-}pyrone}$), 1590 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 2.27 (s, 3H, CH_3), 6.93 (d, 1H, *J*=8.7 Hz, H-$8_{chromone}$), 7.32 (d, 1H, *J*=6.9 Hz, H-$7_{chromone}$), 7.76 (t, 1H, *J*=7.2 Hz, H-$7_{quinoline}$), 7.78 (t, 1H, *J*=7.2 Hz, H-$6_{quinoline}$), 8.01 (d, 1H, *J*=7.5 Hz, H-$8_{quinoline}$), 8.17 (d, 1H, *J*=7.8 Hz, H-$5_{quinoline}$), 8.31 (s, 1H, H-$5_{chromone}$), 8.55 (s, 1H, H-$7_{triazepine}$), 8.90 (s, 1H, H-$4_{quinoline}$), 9.12 (bs, 1H, NH exchangeable with D_2O), 9.23 (s, 1H, H-$2_{chromone}$). M/z (*I* %): 469 (M-1; 6), 413 (5), 334 (74), 316 (33), 290 (21), 288 (84), 259 (17), 234 (15), 220 (27), 209 (18), 168 (20).152 (21), 135 (39), 107 (28), 91 (17), 88 (21), 77 (78), 73 (12), 62 (100). Analysis Calcd for $C_{27}H_{14}N_6O_3$ (470.45): C, 68.93; H, 3.00; N, 17.86%. Found: C, 68.80; H, 3.40; N, 17.90%.

2-Amino-4-(4-methoxyphenyl)-7-oxo-5,7-dihydro-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-pyrido[1,2-*b*][1,2,4]triazepine-3,8,10-tricarbonitrile (12).

A mixture of compound **4** (0.67 g, 2 mmol) and *p*-methoxybenzylidene-malononitrile (**11**) (0.36 g, 2 mmol) in DMF (15 mL) containing two drops of triethylamine was heated under reflux for 4h. The solid obtained during heating was filtered and crystallized from DMF/MeOH to give **12** as orange crystals, yield (0.58 g, 56 %), m.p. 268 ºC. IR (KBr, cm^{-1}): 3399, 3197 (NH_2, NH), 3024 ($CH_{arom.}$), 2850 ($CH_{aliph.}$), 2217 (3 C≡N), 1682 ($C=O_{pyridone}$), 1630 ($C=O_{\gamma\text{-pyrone}}$), 1596 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 2.26 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.95 (d, 1H, H-$8_{chromone}$), 7.15 (d, 2H, Ar-H), 7.31 (d, 1H, H-$7_{chromone}$), 8.01 (d, 2H, Ar-H), 8.26 (s, 1H, H-$5_{chromone}$), 8.67 (bs, 2H, NH_2 exchangeable with D_2O), 9.32 (s, 1H, H-$2_{chromone}$), 10.22 (bs, 1H, NH exchangeable with D_2O). M/z (*I* %): 515 (not recorded), 484 (M-OCH_3; 5), 457 (42), 409 (44), 393 (10), 317 (7), 288 (4), 259

(3), 209 (3), 182 (6), 168 (6), 121 (63), 107 (19), 76 (12), 43 (100). Analysis Calcd for $C_{28}H_{17}N_7O_4$ (515.49): C, 65.24; H, 3.32; N, 19.02%. Found: C, 65.20; H, 3.4; N, 19.00%.

Ethyl 2-amino-8,10-dicyano-4-(4-methoxyphenyl)-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-7-oxo-5,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-3-carboxylate (14).

A mixture of compound **4** (0.67 g, 2 mmol) and ethyl 2-cyano-3-(4-methoxyphenyl)prop-2-enoate (**13**) (0.46 g, 2 mmol) in DMF (30 mL) containing two drops of triethylamine was heated under reflux for 4h. The solid obtained during heating was filtered and crystallized from DMF/H_2O to give **14** as reddish orange crystals, yield (0.39 g, 35%), m.p. 285 ºC. IR (KBr, cm^{-1}): 3377, 3200 (NH_2, NH), 3032 ($CH_{arom.}$), 2933, 2841 ($CH_{aliph.}$), 2220 (2 C≡N), 1710 ($C=O_{ester}$), 1685 ($C=O_{pyridone}$), 1634 ($C=O_{\gamma\text{-pyrone}}$), 1593 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 1.28 (t, 3H, *J*=7.2 Hz, $CH_2\mathit{CH_3}$), 2.26 (s, 3H, $CH_{3\ chromone}$), 3.85 (s, 3H, OCH_3), 4.28 (q, 2H, *J*=7.2 Hz, $\mathit{CH_2}CH_3$), 6.93 (d, 1H, *J*=8.7 Hz, H-$8_{chromone}$), 7.12 (d, 2H, Ar-H), 7.33 (d, 1H, *J*=8.7 Hz, H-$7_{chromone}$), 8.05 (d, 2H, Ar-H), 8.26 (s, 1H, H-$5_{chromone}$), 8.44 (bs, 1H, NH exchangeable with D_2O), 8.52 (bs, 1H, NH exchangeable with D_2O), 9.32 (s, 1H, H-$2_{chromone}$), 10.24 (bs, 1H, NH exchangeable with D_2O). Analysis Calcd for $C_{30}H_{22}N_6O_6$ (562.55): C, 64.05; H, 3.94; N, 14.94%. Found: C, 64.09; H, 4.05; N, 14.72%.

7-(6-Methyl-4-oxo-4*H*-chromen-3-yl)-2-(4-oxo-4*H*-chromen-3-yl)-5-oxo-3,5-dihydro[1,2,4]triazolo[1,5-*a*]pyridine-6,8-dicarbonitrile (18).

A mixture of compound **4** (0.67 g, 2 mmol) and chromone-3-carboxylic acid (**16**) (0.38 g, 2 mmol) in phosphorus oxychloride (30 mL) was heated under reflux on a water bath for 4h. After cooling, the reaction mixture was poured onto ice/water. The precipitated solid was filtered, washed with water, air dried and crystallized from ethanol to give **18** as yellow crystals, yield (0.53 g, 54%), mp > 300 ºC. IR (KBr, cm^{-1}): 3402 (NH), 3039 ($CH_{arom.}$), 2925 ($CH_{aliph.}$), 2219 (2 C≡N), 1670 ($C=O_{pyridone}$), 1650 (2 $C=O_{\gamma\text{-pyrone}}$), 1601 (C=N and C=C). ^{1}H NMR (DMSO-d_6, δ): 2.28 (s, 3H, CH_3), 6.92 (d, 1H, *J*=8.7 Hz, H-$8_{chromone}$), 7.33 (d, 1H, *J*=6.6 Hz, H-$7_{chromone}$), 7.57 (t, 1H, *J*=7.2 Hz, H-6`$_{chromone}$), 7.77 (d, 1H, *J*=8.1 Hz, H-8`$_{chromone}$), 7.89 (t, 1H, *J*=7.5 Hz, H-7`$_{chromone}$), 8.15 (s, 1H, *J*=7.8 Hz, H-5`$_{chromone}$), 8.34 (s, 1H, H-$5_{chromone}$), 9.23 (s, 1H, H-2`$_{chromone}$), 9.44 (s, 1H, H-$2_{chromone}$), 10.20 (bs, 1H, NH exchangeable with D_2O). Analysis .Calcd for $C_{27}H_{13}N_5O_5$ (487.44): C, 66.53; H, 2.69; N, 14.37%. Found: C, 66.20; H, 3.00; N, 14.10%.

2-Amino-3-(2-hyroxyphenyl)carbonyl-7-oxo-9-(6-methyl-4-oxo-4*H*-chromen-3-yl)-5*H*-pyrido[1,2-*b*][1,2,4]triazepine-8,10-dicarbonitrile (19).

A mixture of compound **4** (0.67 g, 2 mmol) and chromone-3-carbonitrile (**17**) (0.34 g, 2 mmol) in DMF (30 mL) was heated under reflux for 4h. The solid obtained after cooling was filtered, washed with cold ethanol and crystallized from DMF to give **19** as yellow crystals, yield (0.39 g, 39%), mp > 300 ºC. IR (KBr, cm^{-1}): 3405, 3315, 3211 (NH_2, NH, OH), 3050 ($CH_{arom.}$), 2968, 2922 ($CH_{aliph.}$), 2259, 2220 (2 C≡N), 1684 ($C=O_{pyridone}$), 1629 ($C=O_{\gamma\text{-pyrone}}$ and $C=O_{hydrogen\ bonded}$), 1600 (C=C). ^{1}H NMR (DMSO-d_6, δ): 2.24 (s, 3H, CH_3), 6.89 (d, 1H, H-$8_{chromone}$), 7.26 (d, 1H, H-$7_{chromone}$), 7.40-7.90 (m, 4H, A-H), 8.24 (s, 1H, H-$5_{chromone}$), 8.46 (s 1H, H-$7_{triazepine}$), 8.58 (bs, 1H, NH), 9.03 (bs, 1H, NH), 9.34 (s, 1H, H-$2_{chromone}$), 10.13 (bs, 1H, NH). Analysis Calcd for $C_{27}H_{15}N_6O_5$ (504.47): C, 64.29; H, 3.20; N, 10.66%. Found: C, 64.30; H, 3.10; N, 10.38%.

REFERENCES

[1] Nam, D. H.; Lee, K. Y.; Moon, C. S.; Lee, Y. S. *Eur J Med Chem* **2010**, *45*, 4288.

[2] Horton, D. A.; Bourne, G. T.; Smyth, M. L. *Chem Rev* **2003**, *103*, 893.

[3] Lim. L.- C.; Kuo, Y.-C.; Chou, C. -J. *J Nat Prod* **2000**, *63*, 627.

[4] Huang, W.; Liu, M.-Z.; Li, Y.; Tan, Y.; Yang, G.-Fu. *Bioorg Med Chem* **2007**, *15*, 5191.

[5] Ghosh, C. K. *Heterocycles* **2004**, *63*, 2875.

[6] Zhao, P.-L.; Li. J.; Yang, G.-Fu. *Bioorg Med Chem* **2007**, *15*, 1888.

[7] Albrecht, U.; Lalk, M.; Langer, P. *Bioorg Med Chem* **2005**, *13*, 1531.

[8] Chornous, V. A.; Bratenko, M. K.; Vovk, M. V.; Sidorchuk, I. I. *Pharmaceut Chem J* **2001**, *35*, 203.

[9] Li, Y.; Yang, Z.; Li, T.; Liu, Z.; Wang, B. *J Fluoresc* **2011**, *21*, 1091.

[10] Kim, S. H.; Lee, Y. H.; Jung, S. Y.; Kim, H. Ja; Jin, C.; Lee, Y. S. *Eur J Med Chem* **2011**, *46*, 1721.

[11] Nawrot–Modranka, J.; Nawrot, E.; Graczyk, J. *Eur J Med Chem* **2006**, *41*, 1301.

[12] Ishar, M. P. S.; Singh, G.; Singh, S.; Sreenivasan, K. K.; Singh, G. *Bioorg Med Chem Lett* **2006**, *16*, 1366.

[13] Pawar, R. P.; *Tetrahedron Lett* **2005**, *46*, 7183.

[14] Harb, A. A.; *Chem Pap* **2004**, *58*, 260.

[15] Kuethe, J. T.; Wong, A.; Davies, I. W. *J Org Chem* **2004**, *69*, 7752.

[16] Gupta, M.; Paul, S.; Gupta, R. *Eur J Med Chem* **2011**, *46*, 631.

[17] Fronabarger, J. W.; Chapman, R. D.; Gilardi, R. D. *Tetrahedron Lett* **2006**, *47*, 7707.

[18] Bhosale, R. S.; Sarda, S. R.; Ardhapure, S. S.; Jadhav, W. N.; Bhusare, S. R.; Pawar, R. P. *Tetrahedron Lett* **2005**, *46*, 7183.

[19] Ali, T. E.; Ibrahim, M. A. *J Braz Chem Soc* **2010**, *21*, 1007.

[20] Ibrahim, M. A.; Abdel-Rahman, R. M.; Abdel-Halim, A. M.; Ibrahim, S. S.; Allimony, H. A. *J Braz Chem Soc* **2009**, *20*, 1275.

[21] Hangarge, R. V.; Sonwane, S. A.; Jarikote, D. V.; Shingare, M. S. *Green Chem.* **2001**, *3*, 310.

[22] El-Shaaer, H. M.; Foltínová, P.; Lácová, M.; Chovancová, J.; Stankovičová, H.; *Il Farmaco* **1998**, *53*, 224.

[23] Al-Najjar, A. A. A.; Amer, S.A.; Riad, M.; Elghamy, I.; Elnagdi, M. H. *J Chem Res(S)* **1996**, 296.

[24] El-Rady, E. A. *Phosphorus, Sulfur and silicon* **2008**, *183*, 1659.

[25] Becher, J.; Olesen, P. H.; Knudsen, N. A.; Toftlund, H. *Sulfur Lett* **1986**, *4*, 175.

[26] Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J Chem Soc Perkin Trans 1*, **1981**, 1520.

[27] Machida, Y.; Nomoto, S.; Negi, S.; Jkuta, H.; Saito, I. *Synth Commun* **1980**, *10*, 889.

[28] Petersen, U.; Heitzer, H. *Liebigs Ann Chem* **1976**, 1659.

[29] Abdel-Megid, M. *Chem Heterocycl Compd* **2009**, *45*, 1523.

[30] Rahman, A.U.; Choudhary, M.I.; Thomsen, W.J.; *Bioassay Techniques for Drug Development*, Harwood Academic Publishers: The Netherlands, **2001**.

[31] Khan, K. M.; Saify, Z. S.; Zeesha, A. K.; Ahmed, M.; Saeed, M; Schick, M.; Kohlbau, H. J.; Voelter, W. *Arzneim Forsch* **2000**, *50*, 915.