

## Synthesis and Antimicrobial Activity of Chromone-linked 2-Pyridone Fused with 1,2,4-Triazoles, 1,2,4-Triazines and 1,2,4-Triazepines Ring Systems

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Três novas séries de sistemas heterocíclicos nitrogênio fundidos como o 1,2,4-triazol[1,5-*a*] piridinas (**5-7** e **9**), pirido[1,2-*b*][1,2,4]triazinas (**10**, **11**, **13** e **15**), e também pirido[1,2-*b*][1,2,4] triazepinas (**17**, **18**, **20** e **22**) ligadas a um fragmento cromona foram sintetizadas a partir do intermediário-chave 1,6-diamino-(6-cloro-4-oxo-4*H*-chromen-3-il)-2-oxo-1,2-diidropiridina-3,5-dicarbonitrila (**4**) com alguns reagentes eletrofilicos. As estruturas dos compostos inéditos foram estabelecidas por análise elementar e dados espectrais. Todos os produtos foram testados quanto à sua atividade antimicrobiana *in vitro*. Os compostos **7**, **9** e **15** mostraram as maiores atividades quando comparadas às drogas de referência.

Three series of novel fused nitrogen heterocyclic systems such as 1,2,4-triazolo[1,5-*a*] pyridines (**5-7** and **9**), pyrido[1,2-*b*][1,2,4]triazines (**10**, **11**, **13** and **15**), and pyrido[1,2-*b*][1,2,4]triazepines (**17**, **18**, **20** and **22**) linked with a chromone moiety were synthesized from the key intermediate 1,6-diamino-(6-chloro-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4**) with some electrophilic reagents. The structures of the novel compounds were established by elemental analyses and spectral data. All the products were also screened *in vitro* for their antimicrobial activity. Compounds **7**, **9** and **15** showed the highest activities when compared with the reference drugs.

**Keywords:** chromone, *o*-diamine, triazolopyridone, pyridotriazine, pyridotriazepine, antimicrobial activity

### Introduction

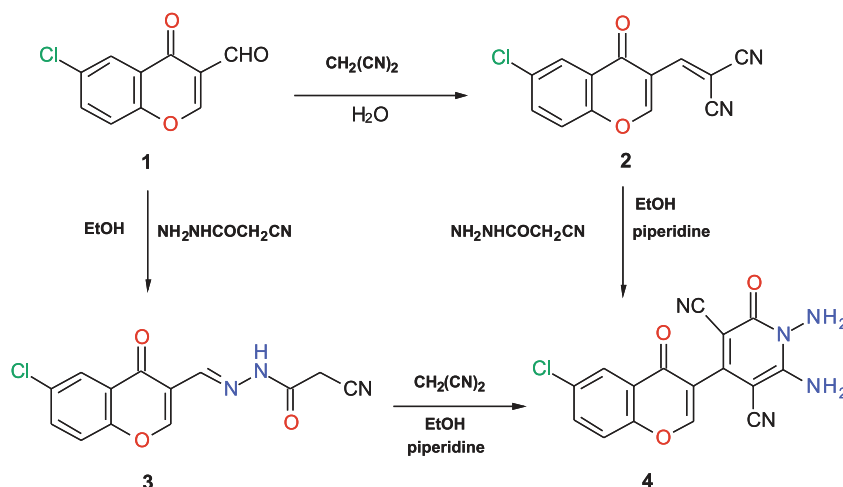
The pharmacodynamic versatility of 4-oxo-4*H*-chromene moiety has been documented not only in many of its synthetic derivatives but also in several naturally occurring flavones and khellins.<sup>1-3</sup> These synthesized and isolated derivatives were found to have a wide range of biological properties including antiinflammatory,<sup>4</sup> analgesic,<sup>5</sup> antimicrobial,<sup>6-8</sup> antitumor<sup>9</sup> and anticancer.<sup>10</sup> Pyridines are an important class of heterocycles due to their practical and synthetic applications.<sup>11</sup> In particular, some 2-pyridone derivatives possess diverse bioactivities such as analgesic,<sup>12</sup> antiinflammatory<sup>13</sup> and anticancer.<sup>14</sup> On the other hand, 1,2,4-triazoles, 1,2,4-triazines and 1,2,4-triazepines have been found to possess a wide spectrum of pharmacological, medicinal and biological activities.<sup>15-20</sup> As part of our research work aiming to the synthesis of a variety of fused heterocyclic systems for biological evaluation, we report here efficient and convenient synthetic methods of different

biodynamic nitrogen heterocycles such as 1,2,4-triazoles, 1,2,4-triazines and 1,2,4-triazepines fused with 2-pyridone ring containing a chromone moiety.

### Results and Discussion

1,6-Diamino-(6-chloro-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4**) was prepared in good yield by refluxing alcoholic solution of [6-chloro-4-oxo-4*H*-chromen-3-yl)methylene] malononitrile (**2**) with cyanoacetohydrazide or *N'*-[(6-chloro-4-oxo-4*H*-chromen-3-yl)-2-cyanoacetohydrazide (**3**) with malononitrile in the presence of a catalytic amount of piperidine (Scheme 1). The IR spectrum of compound **4** showed characteristic absorption bands at 3401, 3308 (2 NH<sub>2</sub>), 2259 (2 C≡N), 1681 (C=O<sub>pyridone</sub>) and 1641 cm<sup>-1</sup> (C=O<sub>pyrone</sub>). Also, the <sup>1</sup>H NMR spectrum of **4** exhibited two characteristic singlet signals at δ 4.61 (N-NH<sub>2</sub>) and 10.78 ppm (C-NH<sub>2</sub>). These results indicated the difference in nucleophilicity between the two amino groups. Thus, it is expected that the hydrazide β-nitrogen (N-NH<sub>2</sub>) is

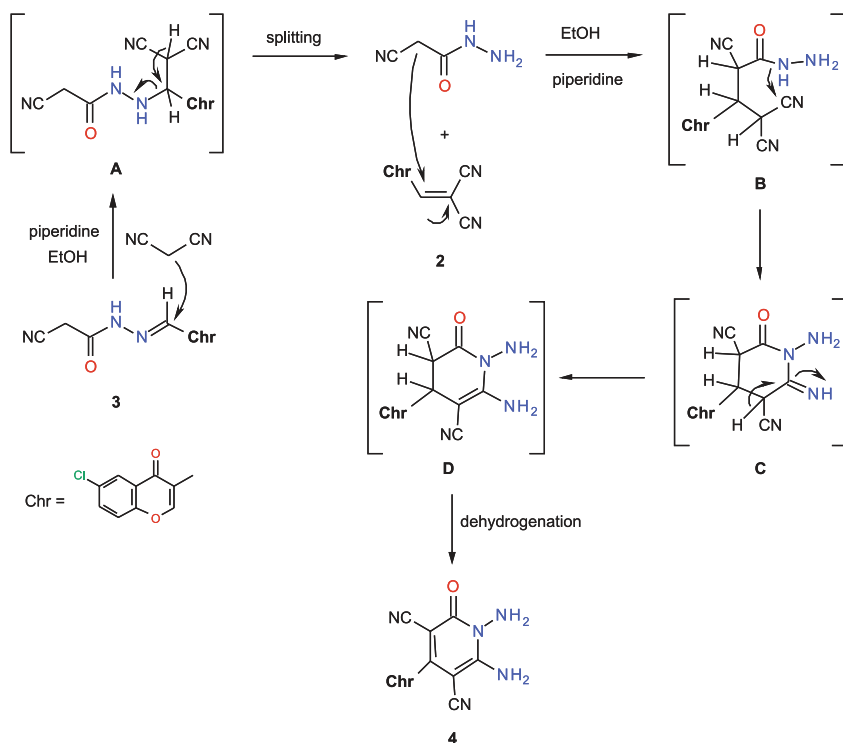
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**Scheme 1.** Synthetic pathways for the formation of compound **4**.

more nucleophilic and will react more rapidly with the electron deficient carbon than the second amino group (C–NH<sub>2</sub>). Product **4** was assumed to be formed *via* an initial addition of the active methylene of malononitrile to the hydrazone linkage in **3** to yield a Michael adduct **A**. This adduct dissociates into 2-cyanoacetohydrazide and **2**, which then further react in the way described earlier by El-Najar and co-workers<sup>21</sup> to yield an intermediate tricyanobutyrohydrazide **B** that cyclizes to intermediates **C** then **D**. The intermediate **D** underwent dehydrogenation to afford the isolated product **4** (Scheme 2).

The 1,6-diamino groups are ready-made nucleophilic centers for the synthesis of fused nitrogen heterocyclic rings.<sup>22</sup> Thus, compound **4** is a useful intermediate for the synthesis of new triazolopyridone, pyridotriazine and pyridotriazepine derivatives. Heterocyclization of compound **4** with ethyl formate and acetic anhydride afforded the triazolo[1,5-*a*]pyridine derivatives **5** and **6**, respectively (Scheme 3). The IR and <sup>1</sup>H NMR spectra of the latter compounds confirmed the absence of the two NH<sub>2</sub> groups. Furthermore, their <sup>1</sup>H NMR spectra showed characteristic singlet signal at δ 8.61 ppm for H–3 of



**Scheme 2.** The proposed mechanism for the formation of compound **4**.

triazole moiety in compound **5** and two singlet signals at  $\delta$  2.75 and 2.91 ppm corresponding to the two methyl groups in compound **6**.

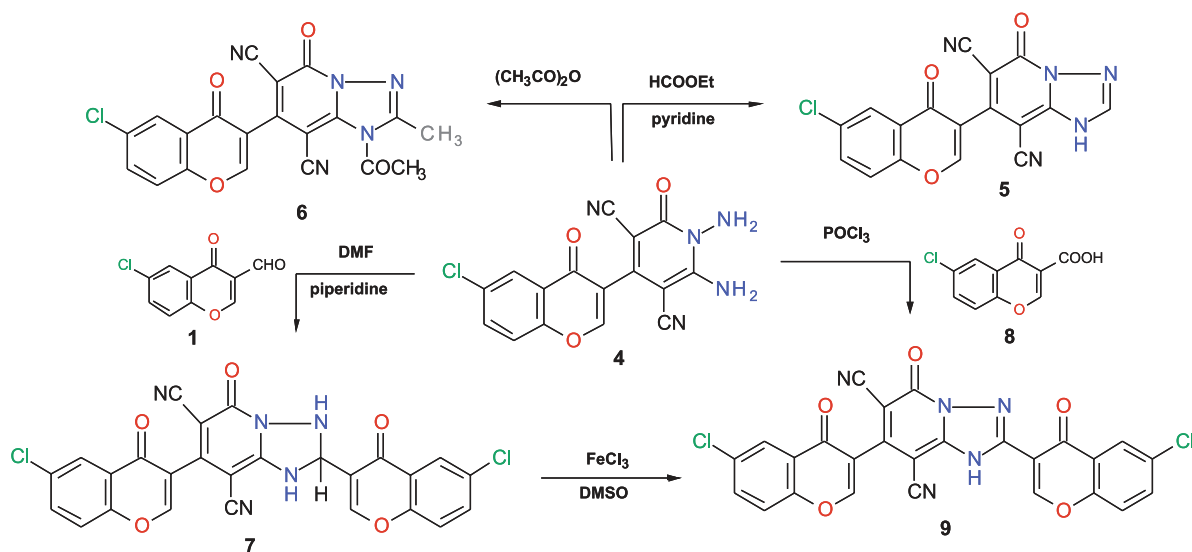
In continuation to our interest in the synthesis of chromone derivatives containing nitrogen heterocyclic systems,<sup>7,8,23</sup> compound **4** was allowed to react with some chromone derivatives. Thus, cyclocondensation of **4** with 6-chloro-3-formylchromone (**1**) in DMF under reflux containing few drops of piperidine afforded the 1,2,3,5-tetrahydro[1,2,4] triazolo[1,5-*a*]pyridine derivative **7**. Oxidation of the latter compound by ferric chloride in boiling DMSO yielded 2,7-*bis*(6-chloro-4-oxo-4*H*-chromen-3-yl)-5-oxo-1,5-dihydro-1,2,4-triazolo [1,5-*a*]pyridine-6,8-dicarbonitrile (**9**). Compound **9** was also obtained by refluxing **4** with 6-chloro-chromone-3-carboxylic acid (**8**) in phosphorus oxychloride (Scheme 3). The analytical and spectral data of **7** and **9** are in agreement with the proposed structures. Thus, the <sup>1</sup>H NMR spectrum of **7** showed a triplet signal at  $\delta$  6.99 ppm corresponding to N-CH-N hydrogen of triazole moiety and a doublet signal at  $\delta$  10.51 ppm due to N<sup>2</sup>-H hydrogen of the triazole moiety. These two hydrogens were absent in the <sup>1</sup>H NMR spectrum of compound **9** that confirmed the oxidation process of its dihydroanalogue **7**.

Next, we allowed compound **4** to react with 1,2-dielectrophilic reagents to develop a facile and convenient route to polysubstituted pyrido[1,2-*b*][1,2,4] triazine derivatives with an expected wide spectra of biological activities.<sup>24</sup> Thus, cyclocondensation of **4** with ethyl 2-chloro-3-oxobutanoate in DMF containing a catalytic amount of piperidine under reflux produced the pyrido[1,2-*b*][1,2,4]triazine-2-carboxylate derivative **10**, which was transformed to the pyrido[1,2-*b*][1,2,4]

triazino[4,5-*d*][1,2,4]triazine derivative **11** upon fusion with benzoic acid hydrazide (Scheme 4). The IR spectrum of compound **11** exhibited characteristic absorption bands at 3335, 3197 (OH, NH), 2265, 2221 (2 C≡N), 1672 (C=O<sub>pyridone</sub>) and 1633 cm<sup>-1</sup> (C=O<sub>pyrone</sub>). Also, its <sup>1</sup>H NMR spectrum displayed signals at  $\delta$  1.91, 10.53 and 13.27 ppm corresponding to methyl, NH and OH hydrogens, respectively. The absence of the triplet and quartet signals corresponding to the ethoxycarbonyl hydrogens of compound **10** supported the formation of compound **11**.

On the other hand, the interaction of **4** with 2,3-dichloroquinoxaline (**12**) and 3-chloro-7,8-diphenyl-4*H*-1,2,4-triazino[4,3-*b*][1,2,4]triazine (**14**) in pyridine led to the formation of the corresponding quinoxalino[2,3-*e*]pyrido[1,2-*b*][1,2,4]triazine **13** and pyrido[1,2-*b*][1,2,4]triazino[3',2':3,4]triazino[5,6-*e*][1,2,4]triazine **15**, respectively (Scheme 4). The <sup>1</sup>H NMR spectrum of **13** showed four broad signals at  $\delta$  10.72, 11.28, 11.94 and 12.21 ppm assignable to four NH hydrogens which confirmed that the product **13** exists in two tautomeric forms **13A** and **13B** due to amino-imino tautomerism.

The study was extended to investigate the behavior of 1,6-diaminopyridone derivative **4** towards some 1,3-dielectrophilic reagents which represents a new, simple and efficient synthetic route to prepare pyrido[1,2-*b*][1,2,4]triazepine derivatives. Therefore, refluxing **4** with acetylacetone and arylidene malononitrile **16** in DMF containing few drops of piperidine as a basic catalyst furnished the pyrido[1,2-*b*][1,2,4]triazepine derivatives **17** and **18**, respectively (Scheme 5). The <sup>1</sup>H NMR spectrum of **17** showed a singlet signal at  $\delta$  4.63 ppm due to CH<sub>2</sub> hydrogens while compound **18** displayed broad signals at

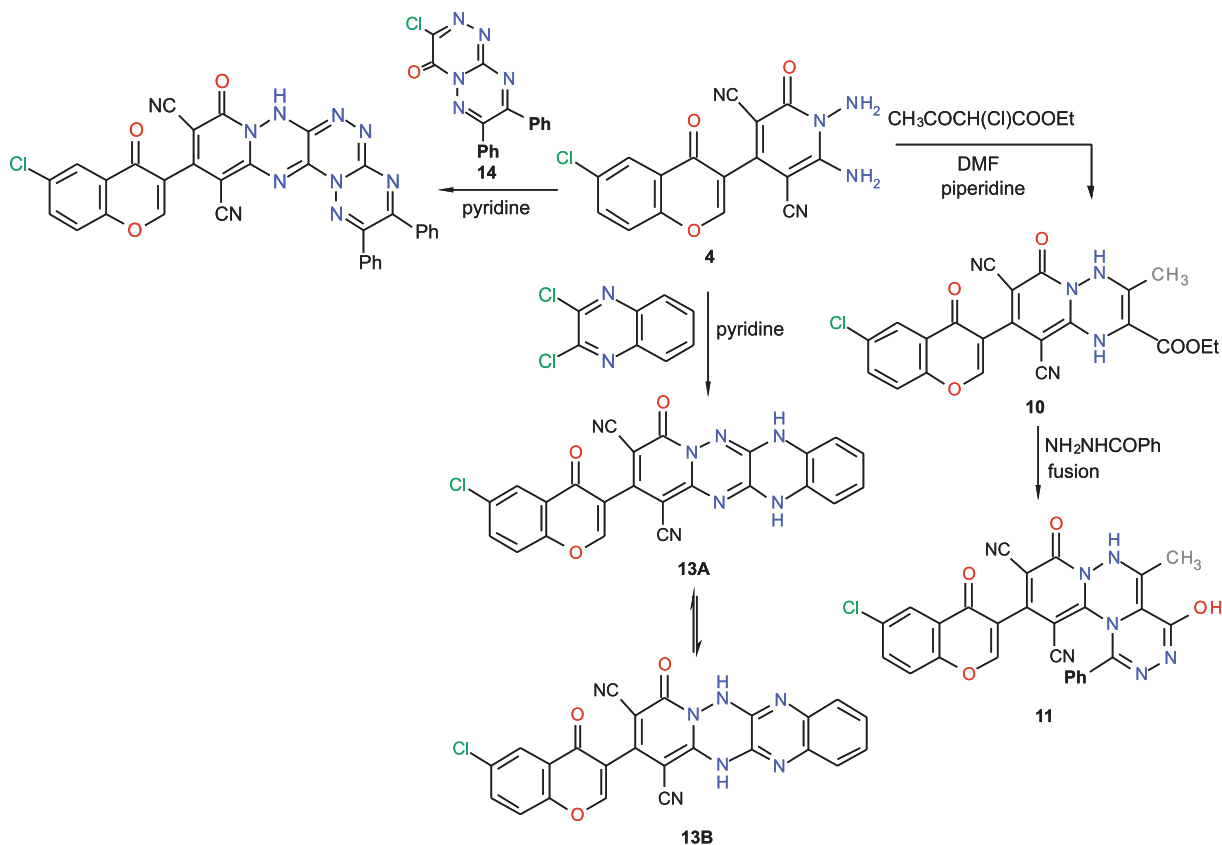


Scheme 3. Synthetic pathway for the formation of 1,2,4-triazolo[1,5-*a*]pyridines.

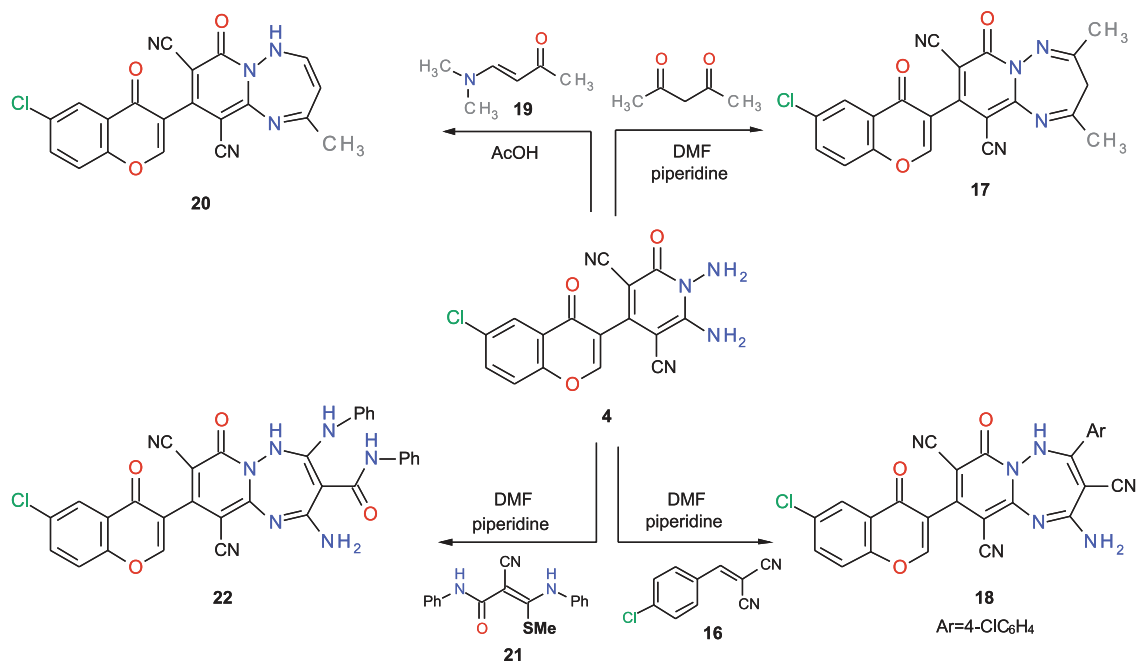
$\delta$  8.89 and 10.67 ppm assigned to  $\text{NH}_2$  and NH hydrogens, respectively.

Furthermore, we also investigated the reactivity of **4** towards enaminone and ketene *N,S*-acetal. Thus, reaction

of **4** with 4-(dimethylamino)but-3-en-2-one (**19**) in glacial acetic acid afforded the 5,7-dihydropyrido[1,2-*b*] [1,2,4]triazepine derivative **20** (Scheme 5). The structure of the latter product was confirmed from its elemental



**Scheme 4.** Synthetic pathway for the formation of pyrido[1,2-*b*][1,2,4]triazines.



**Scheme 5.** Synthetic pathway for the formation of pyrido[1,2-*b*][1,2,4]triazepines.

analysis which agreed well with the molecular formula  $C_{20}H_{10}ClN_5O_3$ . Also, its  $^1H$  NMR spectrum showed a singlet signal at  $\delta$  2.34 ppm corresponding to the methyl hydrogens, besides a doublet signal at  $\delta$  7.94 ppm assigned to  $C_7-H$  hydrogen of triazepine ring. The formation of compound **20** was assumed to take place *via* an initial Michael addition of the hydrazide  $\beta$ -nitrogen ( $N-NH_2$ ) group in **4** to the activated double bond in enaminone followed by cyclization *via* loss of both dimethylamine and water molecules.<sup>24</sup>

Finally, treatment of **4** with ketene *N,S*-acetal derivative **21** in DMF under reflux containing few drops of piperidine produced 2-amino-9-(6-chloro-4-oxo-4*H*-chromen-3-yl)-8,10-dicyano-*N*-phenyl-4-(phenylamino)-7-oxo-5,7-dihydropyrido[1,2-*b*][1,2,4]triazepine-3-carboxamide (**22**) (Scheme 5). The formation of **22** was assumed to take place *via* nucleophilic attack of ( $N-NH_2$ ) on compound **21** to remove methanethiol followed by cycloaddition of the second amino group ( $C-NH_2$ ) on the nitrile group. The IR spectrum of **22** showed absorption bands for  $NH_2$ ,  $NH$  and  $C=O_{amide}$  groups at 3375-3325, 3152 and 1648  $cm^{-1}$ , respectively, while its  $^1H$  NMR spectrum showed signals at  $\delta$  8.08, 9.91, 10.63 and 11.08 ppm assigned to the  $NH_2$  and three  $NH$  hydrogens, respectively.

### Antimicrobial activity

The standardized disc agar diffusion method<sup>25</sup> was followed to determine the activity of the synthesized compounds against the sensitive organisms *Staphylococcus aureus* (ATCC 25923) and *Streptococcus pyogenes* (ATCC 19615) as Gram positive bacteria, *Pseudomonas fluorescens* (S 97) and *Pseudomonas phaseolicola* (GSPB 2828) as Gram negative bacteria and two species of fungi, namely *Fusarium oxysporum* and *Aspergillus fumigatus*. The antibiotic chloramphenicol was used as reference in the case of Gram negative bacteria, while cephalothin was used in the case of Gram positive bacteria and cycloheximide was used as antifungal reference.

The compounds were dissolved in DMF which has no inhibition activity to get concentration of 2 mg  $mL^{-1}$ . The test was performed on medium potato dextrose agars (PDA) which contain infusion of 200 g potatoes, 6 g dextrose and 15 g agar.<sup>26</sup> Uniform size filter paper disks (3 disks per compound) were impregnated with equal volume (10  $\mu L$ ) from the specific concentration of dissolved tested compounds 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

**Table 1.** The antimicrobial activity of compounds **4-7**, **9-11**, **13**, **15**, **17**, **18**, **20** and **22**

Compd. No.	Diameter of the inhibition zone in mm <sup>a,b</sup> (activity index) <sup>c</sup>					
	Gram positive bacteria		Gram negative bacteria		Fungal strains	
	<i>S. aureus</i>	<i>S. pyogenes</i>	<i>P. phaseolicola</i>	<i>P. fluorescens</i>	<i>F. oxysporum</i>	<i>A. fumigatus</i>
<b>4</b>	4 (0.14)	3 (0.10)	8 (0.32)	9 (0.30)	6 (0.21)	7 (0.22)
<b>5</b>	12 (0.43)	13 (0.43)	14 (0.56)	22 (0.73)	14 (0.50)	15 (0.48)
<b>6</b>	18 (0.64)	16 (0.53)	16 (0.64)	13 (0.43)	10 (0.36)	13 (0.43)
<b>7</b>	23 (0.82)	21 (0.70)	17 (0.68)	21 (0.70)	16 (0.57)	21 (0.68)
<b>9</b>	25 (0.89)	26 (0.87)	15 (0.60)	18 (0.60)	20 (0.71)	19 (0.61)
<b>10</b>	7 (0.25)	6 (0.20)	4 (0.16)	10 (0.33)	8 (0.28)	5 (0.16)
<b>11</b>	11 (0.39)	13 (0.43)	16 (0.64)	10 (0.33)	10 (0.36)	12 (0.39)
<b>13</b>	10 (0.36)	13 (0.43)	12 (0.48)	17 (0.57)	8 (0.28)	6 (0.19)
<b>15</b>	24 (0.86)	23 (0.77)	18 (0.72)	22 (0.73)	21 (0.75)	27 (0.87)
<b>17</b>	5 (0.18)	7 (0.23)	7 (0.28)	10 (0.33)	5 (0.18)	8 (0.25)
<b>18</b>	6 (0.21)	6 (0.20)	7 (0.28)	12 (0.40)	20 (0.71)	14 (0.45)
<b>20</b>	12 (0.43)	14 (0.47)	15 (0.60)	22 (0.73)	14 (0.50)	15 (0.48)
<b>22</b>	4 (0.14)	7 (0.23)	7 (0.28)	10 (0.33)	8 (0.28)	4 (0.13)
chloramphenicol	–	–	25	30	–	–
cephalothin	28	30	–	–	–	–
cycloheximide	–	–	–	–	28	31

<sup>a</sup>Calculated from 3 values; <sup>b</sup>Identified depending on morphological and microscopical characteristics: Low activity = mean of zone diameter  $\leq 0.33$  of mean zone diameter of reference. Moderate activity = mean of zone diameter  $> 0.33 \leq 0.66$  of mean zone diameter of the reference compound. High activity = mean of zone diameter  $\geq 0.67$  of mean zone diameter of the reference compound; <sup>c</sup>Activity index: inhibition zone of the sample /inhibition zone of the reference compound.

of fungi, inhibition of the organisms was measured and used to calculate mean of inhibition zones. Activity index of all the synthesized compounds was also calculated against the corresponding standard drug (Table 1). The products 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: *i*) The prepared compounds showed a moderate to high antimicrobial activity towards all species of bacteria and fungi (Table 1); *ii*) It is known that compounds having oxygen heterocycles and active hydrogen at nitrogen groups (NH) can be preferable in the design of good bioregulators with desirable prompt biological activity. Also, the chromon-3-yl residue can simultaneously increase the activity and decrease the toxicity of nitrogen heterocycles.<sup>27</sup> Thus, the building up of compounds containing more nitrogen heterocycles on the 1,6-diamino-(6-chloro-4-oxo-4*H*-chromen-3-yl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**4**) may enhance the biological activities in most of the products in comparison with compound **4**; *iii*) Compounds which have 1,2,4-triazole ring fused with 2-pyridone showed greater activity than that of 1,2,4-triazine and 1,2,4-triazepine; *iv*) Compounds **7** and **9** showed the highest antimicrobial activity. This high effect may due to the presence of two chromone moieties besides the triazolopyridone moiety. Also, compound **15** has the same effect which may be attributed to the presence of polyfused bioactive 1,2,4-triazine systems.<sup>28</sup> Therefore, these compounds may be considered promising for the development of new antimicrobial agents.

## Conclusion

We have successfully synthesized three series of novel fused nitrogen heterocyclic systems such as 1,2,4-triazolo[1,5-*a*]pyridines, pyrido[1,2-*b*][1,2,4]triazines and pyrido[1,2-*b*][1,2,4]triazepines linked with a chromone moiety. The antimicrobial activities of the prepared compounds showed that polyheterocyclic systems **7**, **9** and **15** have good inhibitory effects when compared with the starting material.

## Experimental

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer using KBr disks. <sup>1</sup>H NMR spectra were measured on Gemini-200 spectrometer (200 MHz), using DMSO-*d*<sub>6</sub> as solvent and TMS ( $\delta$  in ppm) as an internal standard. Elemental microanalyses

were performed at Microanalysis Unit in National Research Center. Evaluation of antimicrobial activities was carried out in the Faculty of Agriculture, Al-Azhar University for Girls, Nasr-City, Cairo, Egypt. 6-Chloro-3-formylchromone (**1**),<sup>29</sup> [(6-chloro-4-oxo-4*H*-chromen-3-yl)methylene] malononitrile (**2**),<sup>30</sup> *N'*-[(6-chloro-4-oxo-4*H*-chromen-3-yl)methylene]-2-cyanoacetohydrazide (**3**),<sup>31</sup> 6-chloro-chromone-3-carboxylic acid (**8**),<sup>32</sup> 3-chloro-7,8-diphenyl-4*H*-[1,2,4]triazino[4,3-*b*][1,2,4] triazin-4-one (**14**)<sup>33</sup> and 2-cyano-3-(methylsulfanyl)-*N*-phenyl-3-(phenylamino)prop-2-enamide (**21**)<sup>34</sup> were prepared by published methods in literature.

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

#### Method A

A mixture of [(6-chloro-4-oxo-4*H*-chromen-3-yl)methylene]malononitrile (**2**) (1280 mg, 5 mmol) and cyanoacetohydrazide (500 mg, 5 mmol), in absolute ethanol (30 mL) containing few drops of piperidine, was refluxed for 3 h. After cooling, the formed solid was filtered and recrystallized from DMF to afford **4** as beige crystals, yield 74%, mp 288-289 °C.

#### Method B

A mixture of *N'*-[(6-chloro-4-oxo-4*H*-chromen-3-yl)methylene]-2-cyanoaceto-hydrazide (**3**) (1450 mg, 5 mmol) and malononitrile (330 mg, 5 mmol), in absolute ethanol (30 mL) containing few drops of piperidine, was refluxed for 3 h. After cooling, the formed solid was filtered and crystallized from DMF to afford **4** as beige crystals, yield 77%, mp 288-290 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3401, 3308 (2 NH<sub>2</sub>), 3058 (C-H<sub>arom</sub>), 2259 (2 C≡N), 1681 (C=O<sub>pyridone</sub>), 1641 (C=O<sub>pyrone</sub>), 1468 (NH<sub>2</sub> def.). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  4.61 (s, 2H, N-NH<sub>2</sub>), 7.13 (d, 1H, *J* 8 Hz, H-8), 7.54 (d, 1H, *J* 8 Hz, H-7), 8.53 (s, 1H, H-5), 9.48 (s, 1H, H-2), 10.78 (s, 2H, C-NH<sub>2</sub>). Anal. Calc. for C<sub>16</sub>H<sub>8</sub>ClN<sub>5</sub>O<sub>3</sub> (353.71): C, 54.33; H, 2.28; N, 19.80; Cl, 10.02. Found: C, 54.01; H, 2.02; N, 19.54; Cl, 9.69%.

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

A mixture of compound **4** (1710 mg, 5 mmol) and ethyl formate (370 mg, 5 mmol) in dry pyridine (30 mL) was refluxed for 10 h. After cooling the reaction mixture was poured onto ice and neutralized with concentrated HCl. The formed solid was filtered, washed several times with water and crystallized from DMF/H<sub>2</sub>O to give **5** as brown crystals, yield 68%, mp 274-276 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>:



3261 (NH), 3037 (C–H<sub>arom</sub>), 2261 (2 C≡N), 1683 (C=O<sub>pyridone</sub>), 1638 (C=O<sub>pyrone</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.10 (d, 1H, *J* 8.2 Hz, H-8), 7.55 (d, 1H, *J* 8.2 Hz, H-7), 8.53 (s, 1H, H-5), 8.61 (s, 1H, H-3<sub>triazole</sub>), 9.50 (s, 1H, H-2), 10.74 (br, 1H, NH). Anal. Calc. for C<sub>17</sub>H<sub>6</sub>ClN<sub>5</sub>O<sub>3</sub> (363.71): C, 56.14; H, 1.66; N, 19.26; Cl, 9.75. Found: C, 55.78; H, 1.52; N, 18.89; Cl, 9.41%.

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

A solution of compound **4** (1710 mg, 5 mmol) in acetic anhydride (10 mL) was refluxed for 6 h. The excess solvent was removed under vacuum to give a solid which was crystallized from ethanol to afford **6** as brown crystals, yield 47%, mp 297-299 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3073 (C–H<sub>arom</sub>), 2926 (C–H<sub>aliph</sub>), 2239 (2 C≡N), 1722 (C=O<sub>acetyl</sub>), 1675 (C=O<sub>pyridone</sub>), 1622 (C=O<sub>pyrone</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 2.75 (s, 3H, CH<sub>3</sub>), 2.91 (s, 3H, CH<sub>3</sub>), 7.07-7.97 (m, 2H, H-8 and H-7), 8.66 (s, 1H, H-5), 9.51 (s, 1H, H-2). Anal. Calc. for C<sub>20</sub>H<sub>10</sub>ClN<sub>5</sub>O<sub>4</sub> (419.77): C, 57.22; H, 2.40; N, 16.68; Cl, 8.44. Found: C, 56.94; H, 2.12; N, 16.32; Cl, 8.07%.

*2,7-Bis(6-chloro-4-oxo-4H-chromen-3-yl)-5-oxo-1,2,3,5-tetrahydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (7)*

A mixture of compound **4** (1710 mg, 5 mmol) and 6-chloro-3-formylchromone (**1**) (1040 mg, 5 mmol), in DMF (30 mL) containing few drops of piperidine, was refluxed for 5 h. After cooling, the reaction mixture was poured onto ice. The formed solid was filtered and crystallized from DMF/ethanol to afford **7** as yellow crystals, yield 93%, mp > 300 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3395, 3186 (2 NH), 3075 (C–H<sub>arom</sub>), 2928 (C–H<sub>aliph</sub>), 2263 (2 C≡N), 1680 (C=O<sub>pyridone</sub>), 1632 (2 C=O<sub>pyrone</sub>). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 6.99 (t, 1H, N–CH–N<sub>triazole</sub>), 7.37-7.96 (m, 4H, H-8, H-8', H-7 and H-7'), 8.35 (s, 1H, H-5), 8.53 (s, 1H, H-5'), 8.78 (s, 1H, H-2), 9.47 (s, 1H, H-2'), 10.51 (d, 1H, NH), 12.72 (br, 1H, NH). Anal. Calc. for C<sub>26</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>5</sub> (544.30): C, 57.37; H, 2.04; N, 12.87; Cl, 13.02. Found: C, 57.02; H, 1.75; N, 12.58; Cl, 12.71%.

*2,7-Bis(6-chloro-4-oxo-4H-chromen-3-yl)-5-oxo-1,5-dihydro[1,2,4]triazolo[1,5-a]pyridine-6,8-dicarbonitrile (9)*

*Method A*

A mixture of compound **4** (1710 mg, 5 mmol) and 6-chloro-chromone-3-carboxylic acid (**8**) (1070 mg, 5 mmol) in POCl<sub>3</sub> (10 mL) was refluxed on water bath for 3 h. After cooling, the reaction mixture was poured onto ice. The formed solid was filtered and crystallized from

DMF/ethanol to afford **9** as pale brown crystals, yield 88%; mp > 300 °C.

*Method B*

A mixture of compound **7** (1360 mg, 5 mmol) and ferric chloride (2500 mg) in DMSO (25 mL) was refluxed for 4 h. After cooling, the reaction mixture was poured onto 10% aqueous sodium carbonate solution (75 mL) and stirred for 1 h at room temperature. The formed solid was filtered and crystallized from DMF/ethanol to afford **9** as pale brown crystals, yield 82%, mp > 300 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3402 (NH), 3059 (C–H<sub>arom</sub>), 2258 (2 C≡N), 1682 (C=O<sub>pyridone</sub>), 1641 (2 C=O<sub>pyrone</sub>), 1598 (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 7.07-7.79 (m, 4H, H-8, H-8', H-7 and H-7'), 8.35 (s, 1H, H-5), 8.54 (s, 1H, H-5'), 8.68 (s, 1H, H-2), 9.51 (s, 1H, H-2'), 11.64 (br, 1H, NH). Anal. Calc. for C<sub>26</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>5</sub> (542.28): C, 57.59; H, 1.67; N, 12.91; Cl, 13.07. Found: C, 57.22; H, 1.34; N, 12.64; Cl, 12.76%.

*Ethyl 8-(6-chloro-4-oxo-4H-chromen-3-yl)-7,9-dicyano-3-methyl-6-oxo-1,6-dihydro-4H-pyrido[1,2-b][1,2,4]triazine-2-carboxylate (10)*

A mixture of compound **4** (1710 mg, 5 mmol) and ethyl 2-chloro-3-oxobutanoate (820 mg, 5 mmol), in DMF (30 mL) containing few drops of piperidine, was refluxed for 8 h. After cooling, the reaction mixture was onto ice-water. The formed solid was filtered and crystallized from AcOH/H<sub>2</sub>O to afford **10** as brown crystals, yield 69%, mp 188-190 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3394, 3199 (2 NH), 3044 (C–H<sub>arom</sub>), 2978, 2925 (C–H<sub>aliph</sub>), 2260, 2198 (2 C≡N), 1734 (C=O<sub>ester</sub>), 1683 (C=O<sub>pyridone</sub>), 1635 (C=O<sub>pyrone</sub>), 1103 (C–O–C). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>) δ 1.24 (t, 3H, *J* 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 2.23 (s, 3H, CH<sub>3</sub>), 3.77 (br, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 7.03-7.93 (m, 2H, H-8 and H-7), 8.53 (s, 1H, H-5), 9.51 (s, 1H, H-2), 10.64 (s, 1H, NH), 11.02 (br, 1H, NH). Anal. Calc. for C<sub>22</sub>H<sub>14</sub>ClN<sub>5</sub>O<sub>5</sub> (463.83): C, 56.97; H, 3.04; N, 15.10; Cl, 7.64. Found: C, 56.69; H, 2.79; N, 14.78; Cl, 7.28%.

*1-Phenyl-10-(6-chloro-4-oxo-4H-chromen-3-yl)-4-hydroxy-5-methyl-8-oxo-6H,8H-pyrido [1,2-b][1,2,4]triazino[4,5-d][1,2,4]triazine-9,11-dicarbonitrile (11)*

A mixture of compound **10** (2310 mg, 5 mmol) and benzoic acid hydrazide (680 mg, 5 mmol), containing few drops of triethylamine, was fused for 15 min at 190-200 °C. The reaction mixture was cooled at room temperature and treated with ethanol (5 mL). The formed solid was filtered and crystallized from ethanol to afford **11** as brown crystals, yield 44%, mp 262-264 °C. IR (KBr)  $\nu_{\max}$ /cm<sup>-1</sup>: 3335 (br, OH), 3197 (NH), 3050 (C–H<sub>arom</sub>), 2930 (C–H<sub>aliph</sub>), 2265, 2221 (2 C≡N), 1672 (C=O<sub>pyridone</sub>), 1633 (C=O<sub>pyrone</sub>), 1601

(C=N).  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  1.91 (br, 3H, CH<sub>3</sub>), 7.05-7.95 (m, 7H, H-8, H-7 and Ph-H), 8.52 (s, 1H, H-5), 9.50 (s, 1H, H-2), 10.53 (s, 1H, NH), 13.27 (br, 1H, OH). Anal. Calc. for C<sub>27</sub>H<sub>14</sub>ClN<sub>7</sub>O<sub>4</sub> (535.89): C, 60.51; H, 2.63; N, 18.30; Cl, 6.61. Found: C, 60.23; H, 2.41; N, 17.98; Cl, 6.29%.

*11-(6-Chloro-4-oxo-4H-chromen-3-yl)-9-oxo-9,13-dihydro-7H-quinoxalino[2,3-e]pyrido [1,2-b][1,2,4]triazine-10,12-dicarbonitrile (13)*

A mixture of compound **4** (1710 mg, 5 mmol) and 2,3-dichloroquinoxaline (**12**) (1000 mg, 5 mmol) in dry pyridine (30 mL) was refluxed for 4 h. After cooling, the reaction mixture was poured onto ice-water and neutralized with diluted HCl. The formed solid was filtered and crystallized from DMF/H<sub>2</sub>O to afford **13** as pale brown crystals, yield 45%, mp > 300 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3394, (br, NH), 3101 (NH), 3040 (C-H<sub>arom</sub>), 2241 (2 C≡N), 1675 (C=O<sub>pyridone</sub>), 1619 (C=O<sub>pyrone</sub>), 1556 (C=N).  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.01-8.07 (m, 6H, Ar-H), 8.68 (s, 1H, H-5), 9.53 (s, 1H, H-2), 10.72 (br, 1H, NH<sub>triazine</sub>), 11.28 (br, 1H, NH<sub>quinoxaline</sub>), 11.94 (br, 1H, NH<sub>triazine</sub>), 12.21 (br, 1H, NH<sub>quinoxaline</sub>). Anal. Calc. for C<sub>24</sub>H<sub>10</sub>ClN<sub>7</sub>O<sub>3</sub> (479.83): C, 60.07; H, 2.10; N, 20.43; Cl, 7.38. Found: C, 59.69; H, 1.86; N, 20.07; Cl, 7.02%.

*11-(6-Chloro-4-oxo-4H-chromen-3-yl)-9-oxo-2,3-diphenyl-7H-pyrido[1,2-b][1,2,4]triazino[3',2':3,4]triazino[5,6-e][1,2,4]triazine-10,12-dicarbonitrile (15)*

A mixture of compound **4** (1710 mg, 5 mmol) and 3-chloro-7,8-diphenyl-4H-[1,2,4]triazino[4,3-b][1,2,4]triazin-4-one (**14**) (1720 mg, 5 mmol) in dry pyridine (30 mL) was refluxed for 12 h. After cooling, the reaction mixture was poured onto ice-water, and neutralized with diluted HCl. The formed solid was filtered and crystallized from acetic acid to afford **15** as brown crystals, yield 49%, mp 225-227 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3200 (br, NH), 3064 (C-H<sub>arom</sub>), 2224 (2 C≡N), 1675 (C=O<sub>pyridone</sub>), 1636 (C=O<sub>pyrone</sub>), 1600 (C=N).  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.14-8.37 (m, 12H, Ar-H), 8.52 (s, 1H, H-5), 9.46 (s, 1H, H-2), 10.82 (s, 1H, NH). Anal. Calc. for C<sub>33</sub>H<sub>15</sub>ClN<sub>10</sub>O<sub>3</sub> (634.99): C, 62.42; H, 2.38; N, 22.06; Cl, 5.58. Found: C, 62.16; H, 2.07; N, 21.78; Cl, 5.19%.

*9-(6-Chloro-4-oxo-4H-chromen-3-yl)-2,4-dimethyl-7-oxo-3,7-dihydropyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile (17)*

A mixture of compound **4** (1710 mg, 5 mmol) and acetylacetone (500 mg, 5 mmol), in DMF (30 mL) containing few drops of piperidine, was refluxed for 10 h. After cooling, the reaction mixture was poured onto ice-water. The formed solid was filtered and crystallized from ethanol to afford **17**

as brown crystals, yield 59%, mp 182-184 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3042 (C-H<sub>arom</sub>), 2977 (C-H<sub>aliph</sub>), 2261, 2219 (2 C≡N), 1683 (C=O<sub>pyridone</sub>), 1637 (C=O<sub>pyrone</sub>), 1600 (C=N).  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  2.94 (s, 3H, CH<sub>3</sub>), 3.16 (s, 3H, CH<sub>3</sub>), 4.63 (br, 2H, CH<sub>2</sub>), 6.90-7.45 (m, 2H, H-8 and H-7), 8.51 (s, 1H, H-5), 8.96 (s, 1H, H-2). Anal. Calc. for C<sub>21</sub>H<sub>12</sub>ClN<sub>5</sub>O<sub>3</sub> (417.80): C, 60.37; H, 2.89; N, 16.76; Cl, 8.48. Found: C, 60.03; H, 2.57; N, 16.43; Cl, 8.19%.

*2-Amino-9-(6-chloro-4-oxo-4H-chromen-3-yl)-4-(4-chlorophenyl)-7-oxo-dihydro-pyrido [1,2-b][1,2,4]triazepine-3,8,10-tricarbonitrile (18)*

A mixture of compound **4** (1710 mg, 5 mmol) and (4-chlorobenzylidene) malononitrile (**16**) (940 mg, 5 mmol), in DMF (30 mL) containing a few drops of piperidine, was refluxed for 10 h. After cooling, the reaction mixture was poured onto ice-water. The formed solid was filtered and crystallized from DMF to afford **18** as red crystals, yield 39%, mp > 300 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3276, 3199 (NH<sub>2</sub>, NH), 3070 (C-H<sub>arom</sub>), 2276 (2 C≡N), 2216 (C≡N), 1676 (C=O<sub>pyridone</sub>), 1619 (C=O<sub>pyrone</sub>), 1592 (C=N), 1466 (NH<sub>2</sub> def).  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  7.10-8.19 (m, 6H, Ar-H), 8.61 (s, 1H, H-5), 8.89 (br, 2H, NH<sub>2</sub>), 9.54 (s, 1H, H-2), 10.67 (br, 1H, NH). Anal. Calc. for C<sub>26</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>7</sub>O<sub>3</sub> (540.31): C, 57.80; H, 2.05; N, 18.15; Cl, 13.12. Found: C, 57.52; H, 1.78; N, 17.77; Cl, 12.94%.

*9-(6-Chloro-4-oxo-4H-chromen-3-yl)-2-methyl-7-oxo-5,7-dihydropyrido[1,2-b][1,2,4]triazepine-8,10-dicarbonitrile (20)*

A mixture of compound **4** (1710 mg, 5 mmol) and 4-(dimethylamino)but-3-en-2-one (**19**) (570 mg, 5 mmol) in glacial acetic acid (30 mL) was refluxed for 10 h. After cooling, the reaction mixture was poured onto ice-water. The formed solid was filtered and crystallized from DMF/ethanol to afford **20** as pale brown crystals, yield 96%, mp 200-202 °C. IR (KBr)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 3394 (NH), 3039 (C-H<sub>arom</sub>), 2925 (C-H<sub>aliph</sub>), 2260 (2 C≡N), 1683 (C=O<sub>pyridone</sub>), 1625 (C=O<sub>pyrone</sub>), 1597 (C=N).  $^1\text{H NMR}$  (DMSO- $d_6$ )  $\delta$  2.34 (s, 3H, CH<sub>3</sub>), 6.91-7.42 (m, 2H, H-8 and C<sub>6</sub>-H<sub>triazepine</sub>), 7.49 (d, 1H, *J* 7.8 Hz, H-7), 7.94 (d, 1H, *J* 8 Hz, C<sub>7</sub>-H<sub>triazepine</sub>), 8.52 (s, 1H, H-5), 9.46 (s, 1H, H-2), 10.67 (s, 1H, NH). Anal. Calc. for C<sub>20</sub>H<sub>10</sub>ClN<sub>5</sub>O<sub>3</sub> (403.77): C, 59.49; H, 2.50; N, 17.34; Cl, 8.78. Found: C, 59.13; H, 2.37; N, 16.97; Cl, 8.43%.

*2-Amino-9-(6-chloro-4-oxo-4H-chromen-3-yl)-8,10-dicyano-N-phenyl-4-(phenylamino)-7-oxo-5,7-dihydropyrido[1,2-b][1,2,4]triazepine-3-carboxamide (22)*

A mixture of compound **4** (1710 mg, 5 mmol) and 2-cyano-3-(methylsulfanyl)-*N*-phenyl-3-(phenylamino)



prop-2-enamide (**21**) (1550 mg, 5 mmol), in DMF (30 mL) containing few drops of piperidine, was refluxed for 10 h. After cooling, the reaction mixture was poured onto ice-water. The formed solid was filtered and crystallized from DMF/ethanol to afford **22** as pale brown crystals, yield 61%, mp 263-265 °C. IR (KBr)  $\nu_{\max}/\text{cm}^{-1}$ : 3375, 3325, 3152 (NH<sub>2</sub>, 3NH), 3071 (C-H<sub>arom</sub>), 2221 (2 C≡N), 1669 (C=O<sub>pyridone</sub>), 1648 (C=O<sub>amide</sub>), 1630 (C=O<sub>pyrone</sub>), 1600 (C=N). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  6.94-7.68 (m, 12H, Ar-H), 8.08 (br, 2H, NH<sub>2</sub>), 8.66 (s, 1H, H-5), 9.21 (s, 1H, H-2), 9.91 (s, 1H, NH), 10.63 (s, 1H, NH), 11.08 (br, 1H, NH). Anal. Calc. for C<sub>32</sub>H<sub>19</sub>ClN<sub>8</sub>O<sub>4</sub> (614.99): C, 62.49; H, 3.11; N, 18.22; Cl, 5.76. Found: C, 62.09; H, 2.78; N, 17.81; Cl, 5.43%.

## Supplementary Information

Supplementary data are available free of charge at <http://jbcs.sbg.org.br>, as pdf file.

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## Synthesis and Antimicrobial Activity of Chromone-linked 2-Pyridone Fused with 1,2,4-Triazoles, 1,2,4-Triazines and 1,2,4-Triazepines Ring Systems

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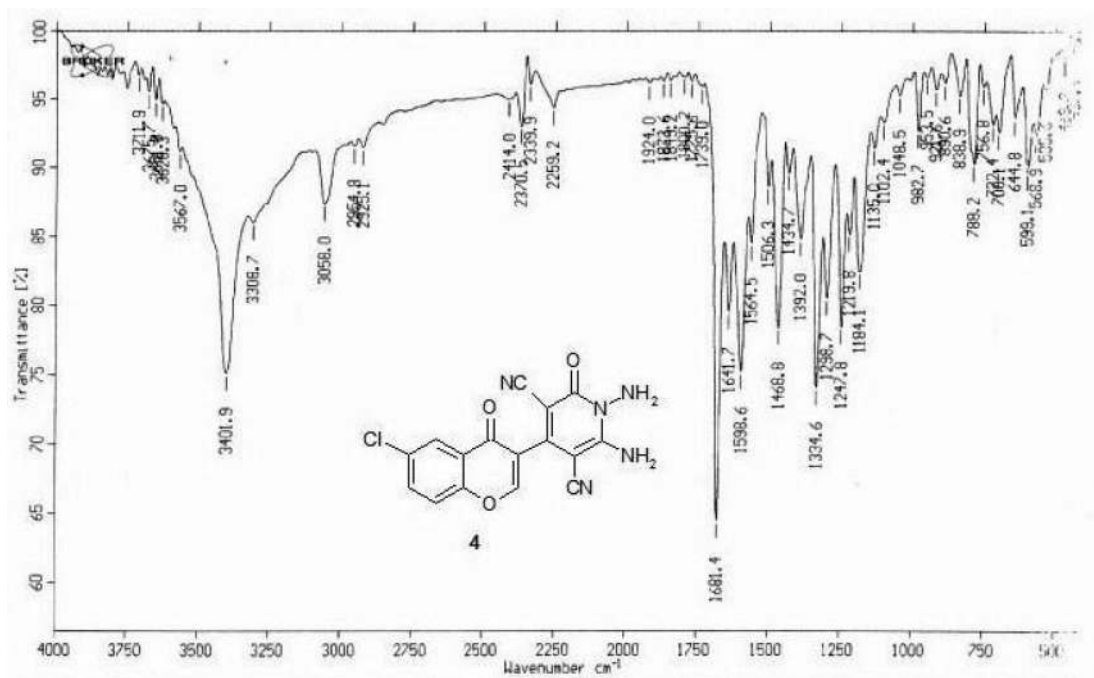


Figure S1. IR spectrum of compound 4.

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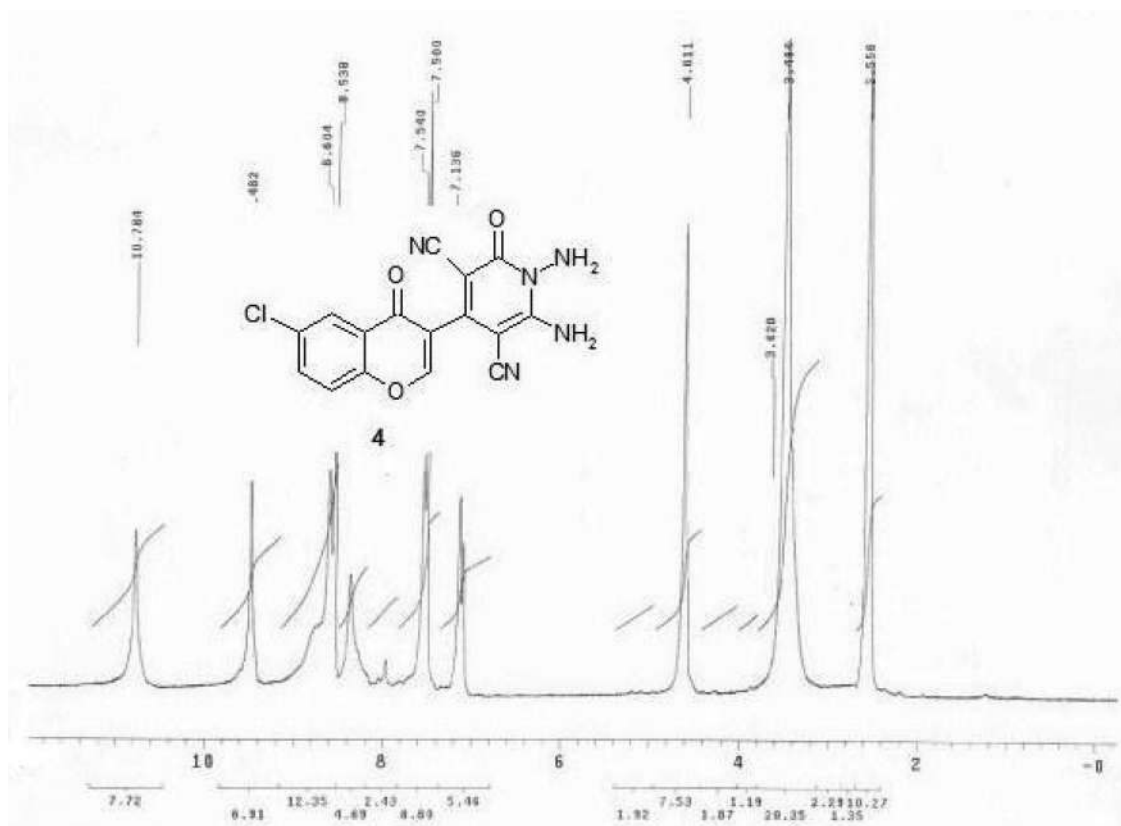
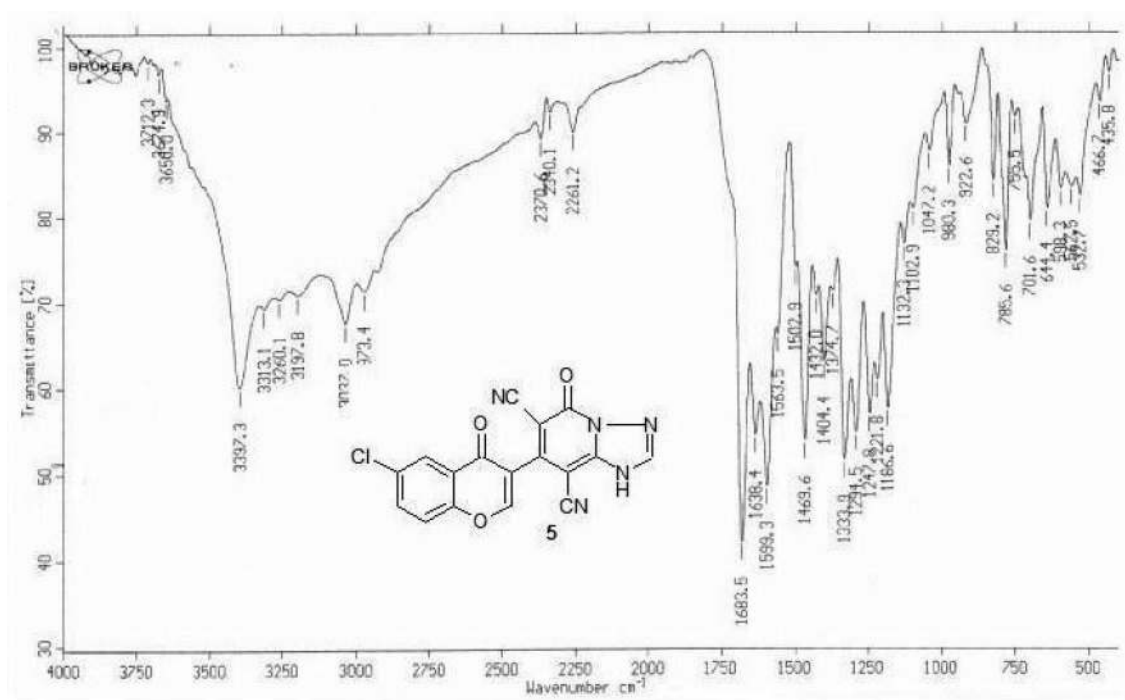
Figure S2. <sup>1</sup>H NMR spectrum of compound 4.

Figure S3. IR spectrum of compound 5.

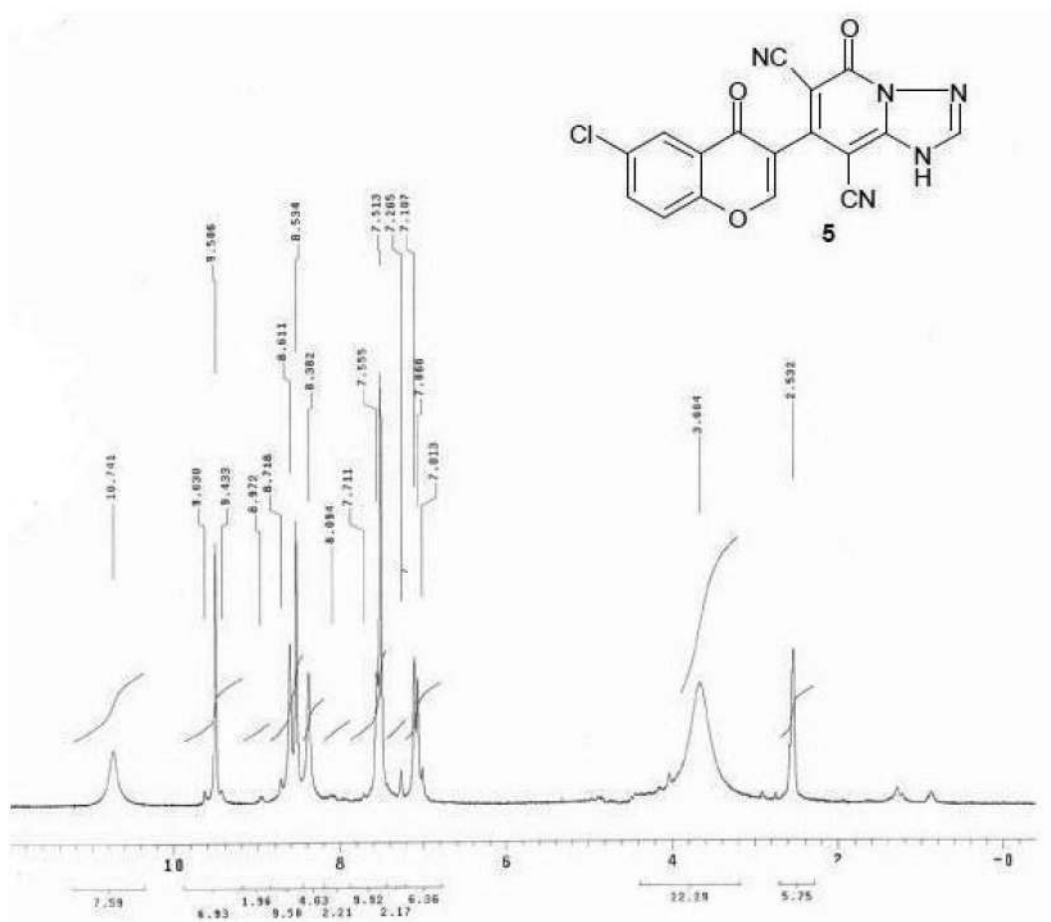
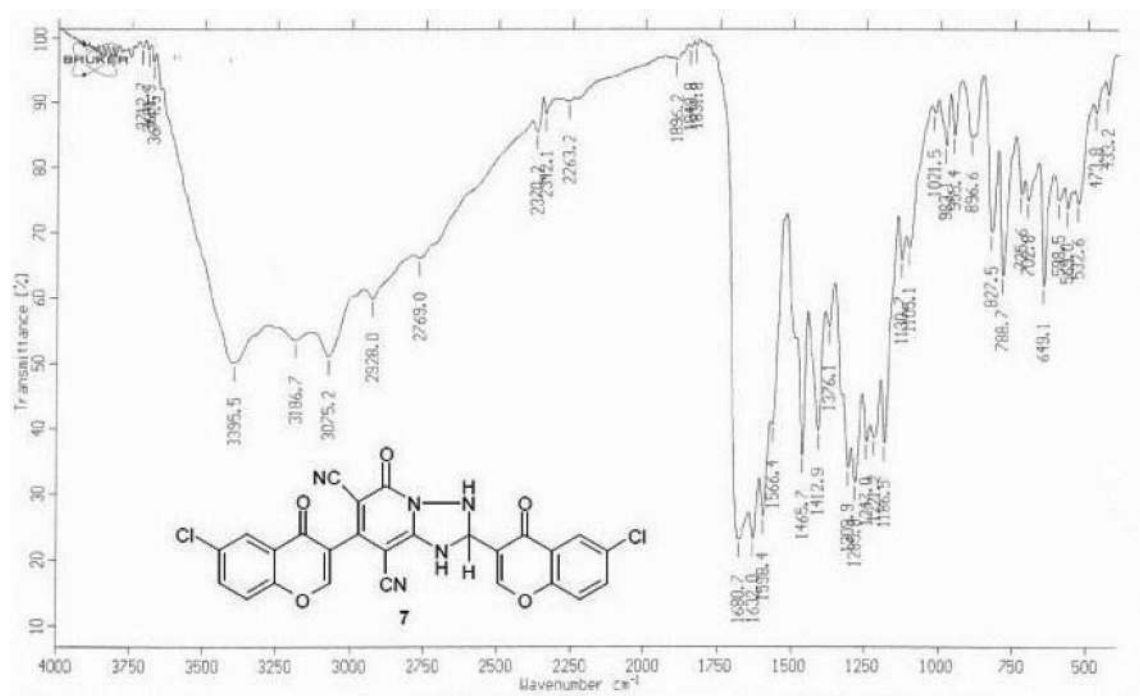
Figure S4. <sup>1</sup>H NMR spectrum of compound 5.

Figure S5. IR spectrum of compound 7.



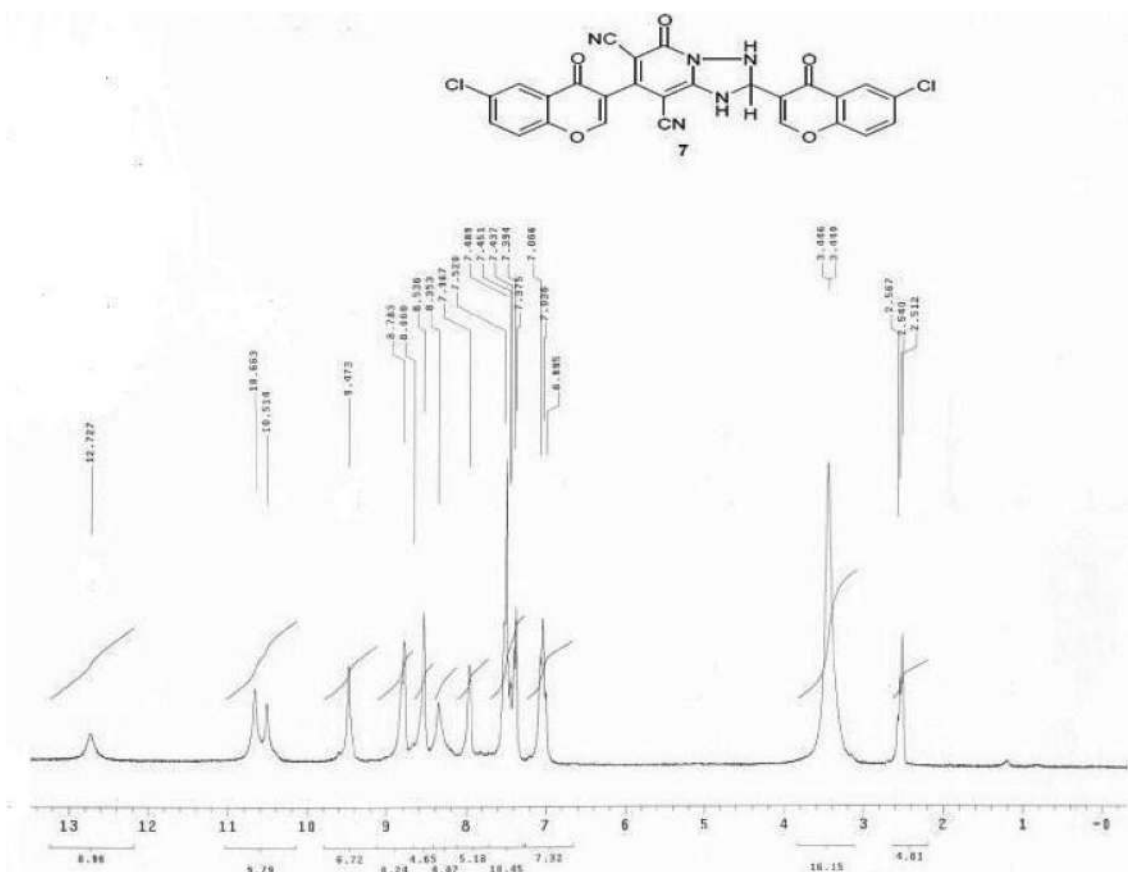
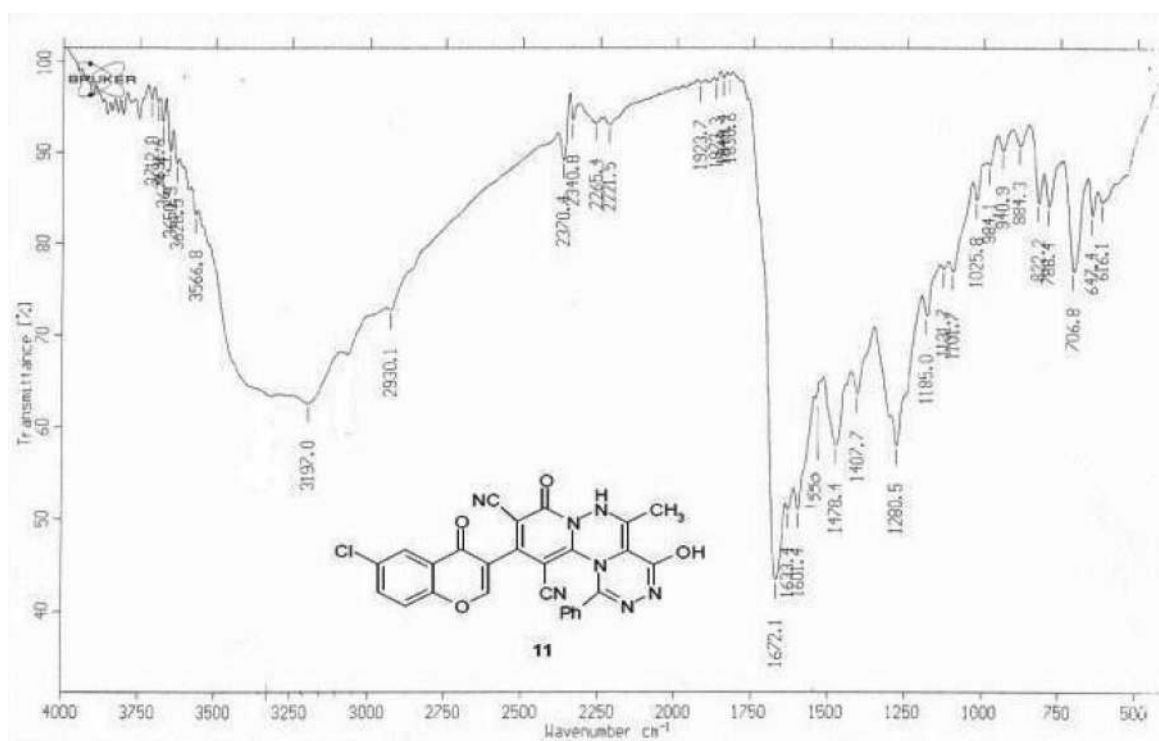
Figure S6. <sup>1</sup>H NMR spectrum of compound 7.

Figure S7. IR spectrum of compound 11.

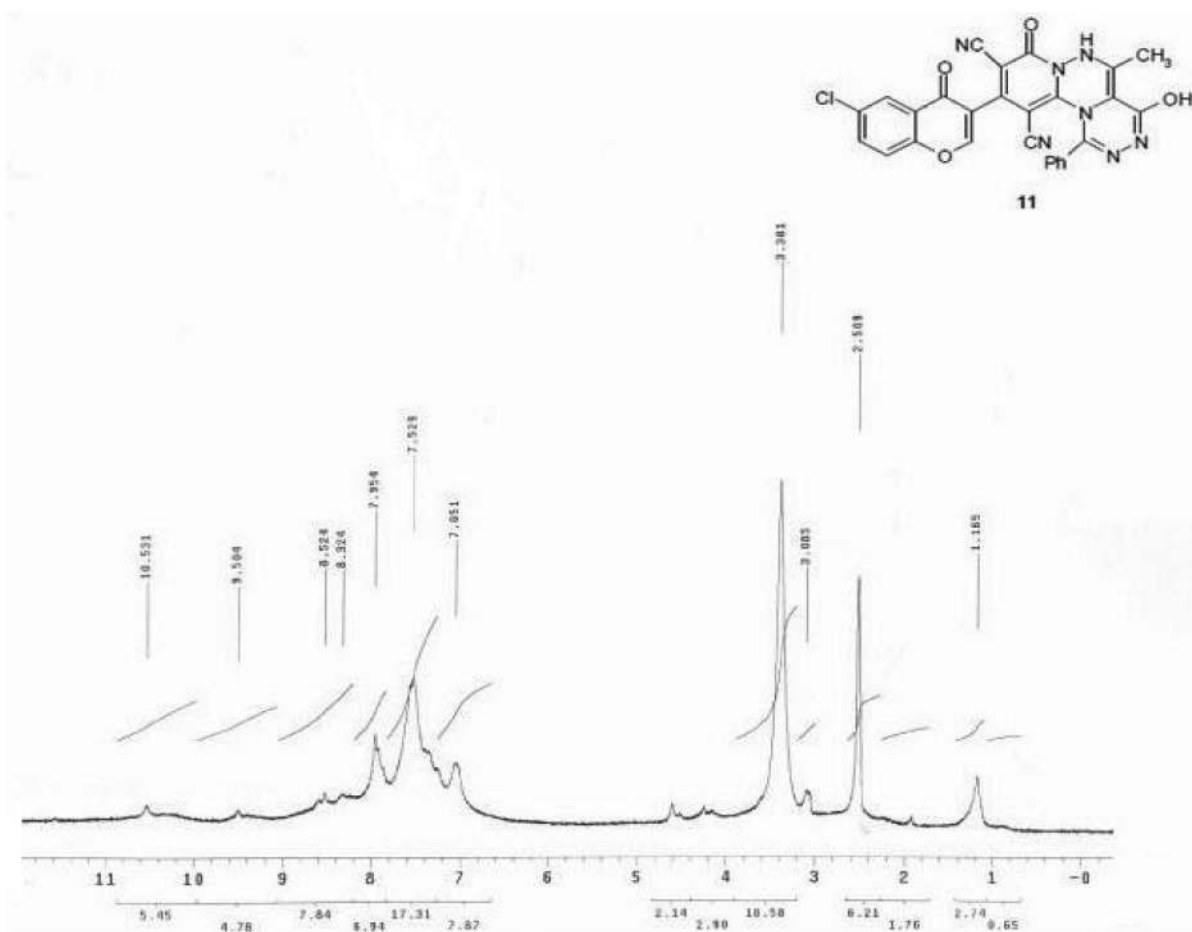
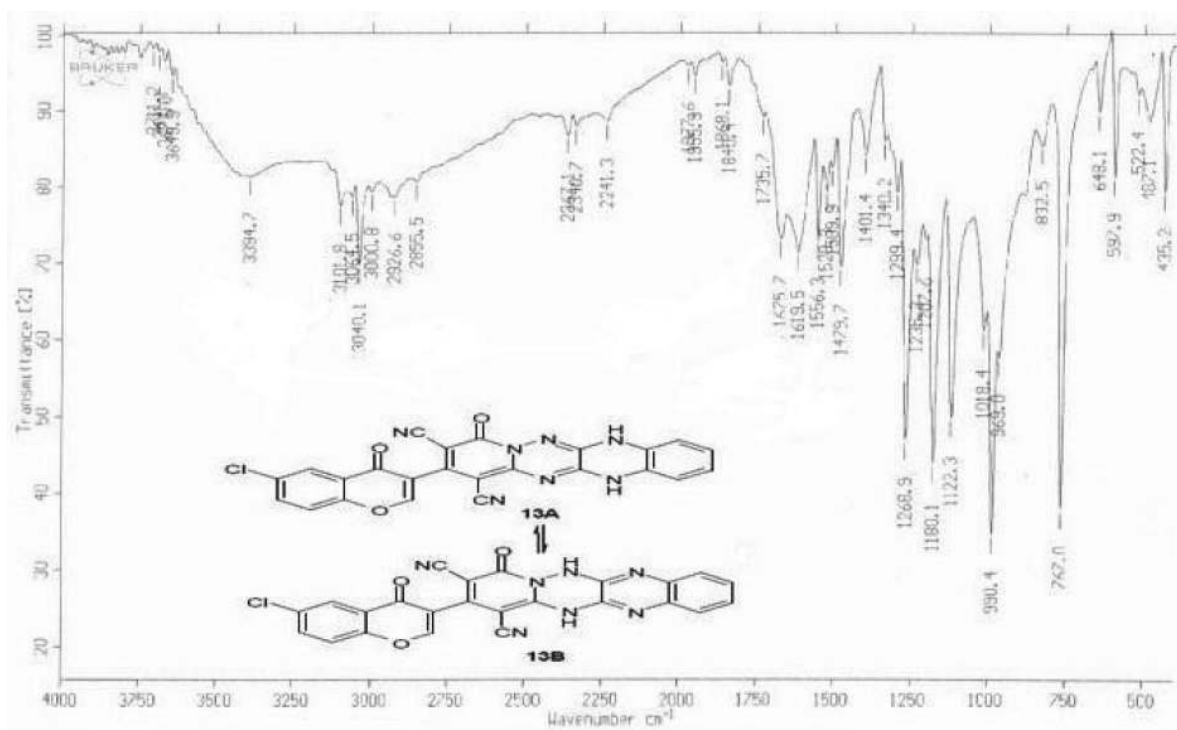
Figure S8. <sup>1</sup>H NMR spectrum of compound 11.

Figure S9. IR spectrum of compound 13.

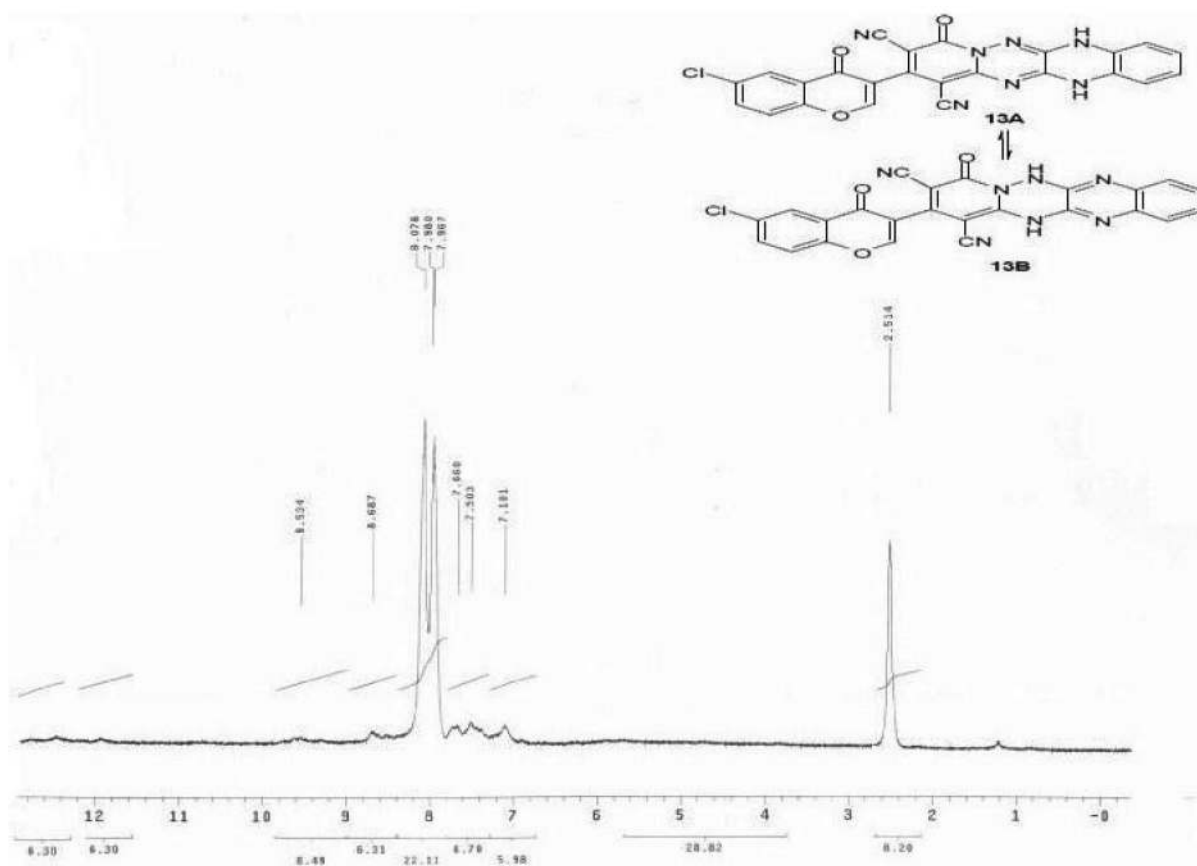
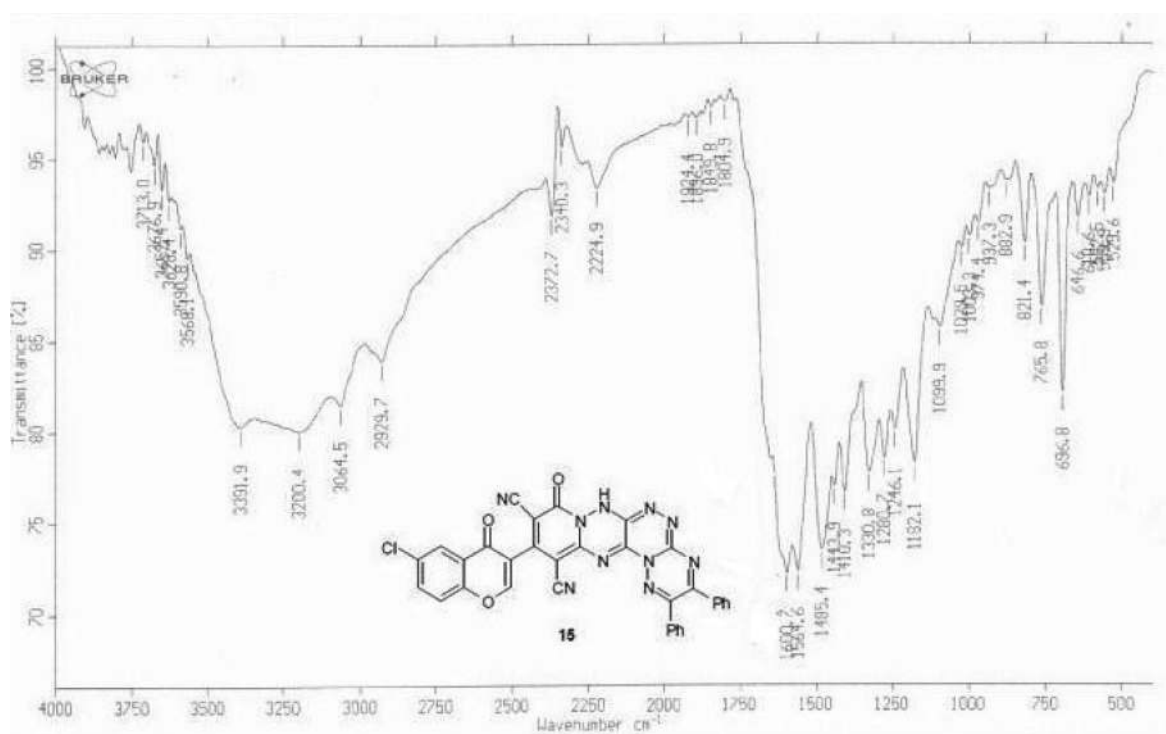
Figure S10. <sup>1</sup>H NMR spectrum of compound 13.

Figure S11. IR spectrum of compound 15.

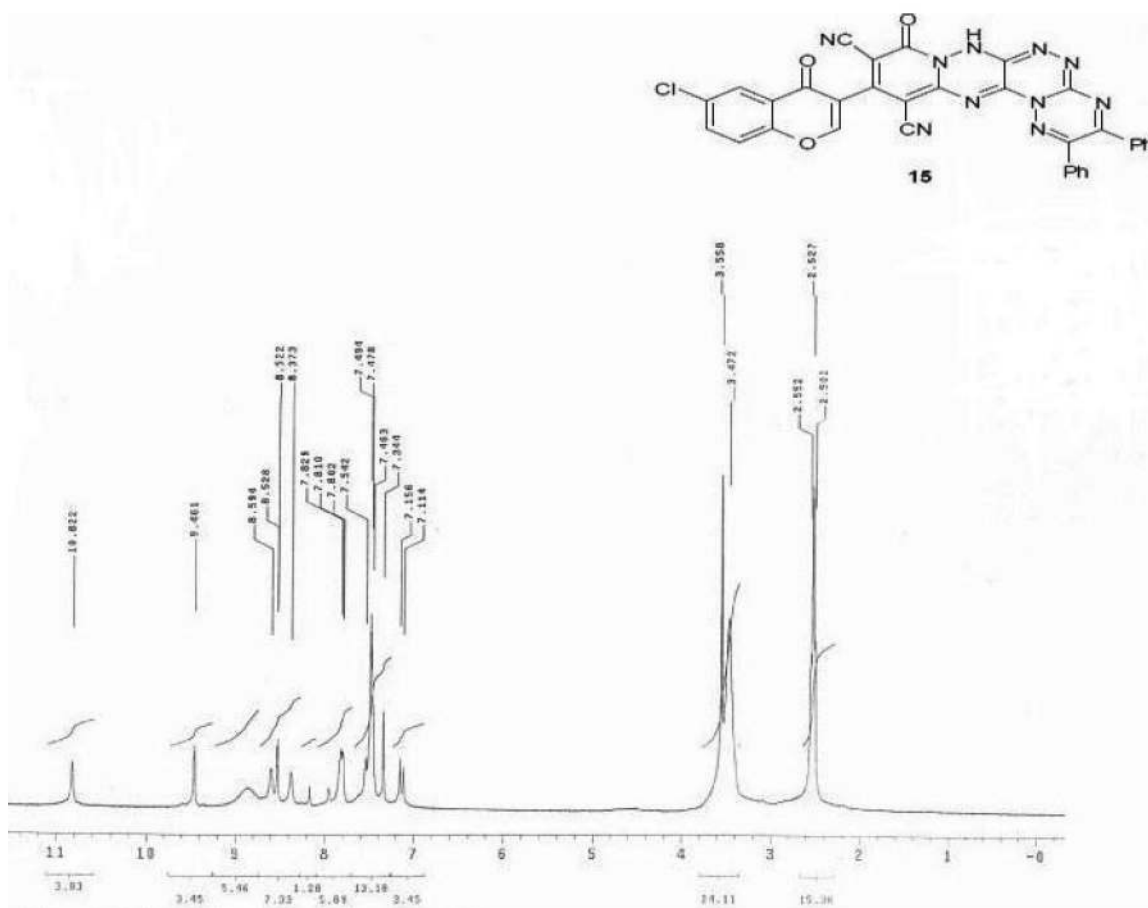
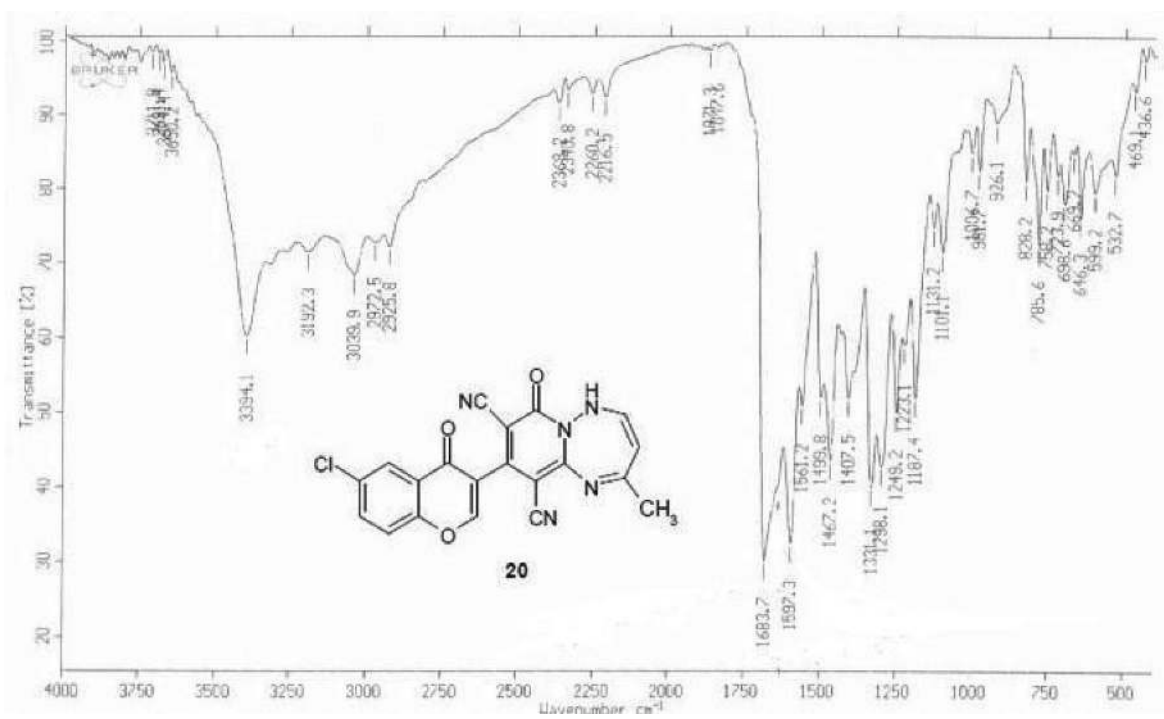
Figure S12. <sup>1</sup>H NMR spectrum of compound 15.

Figure S13. IR spectrum of compound 20.

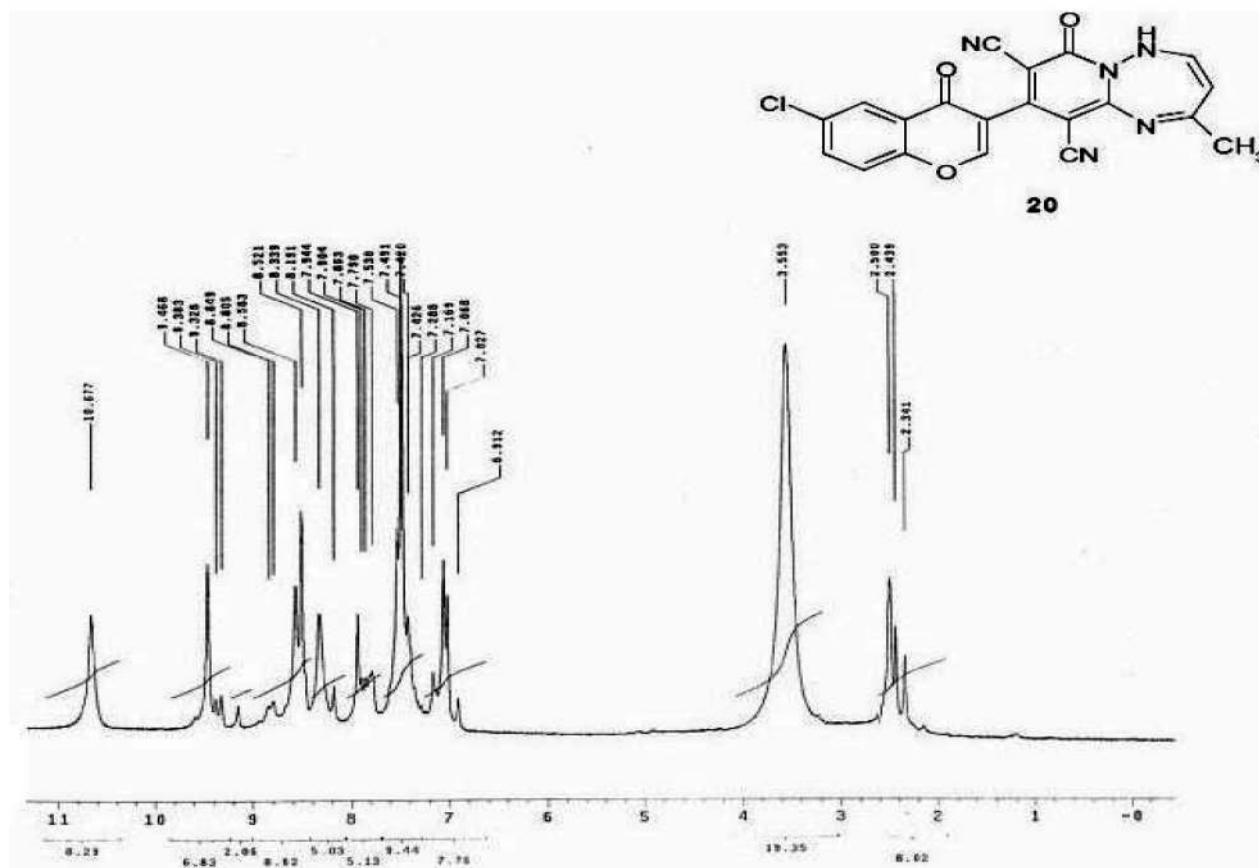


Figure S14. <sup>1</sup>H NMR spectrum of compound 20.