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Synthesis and antibacterial activity of 2-amino chromenes arising cyanoiminocoumarins and *β*-naphthol

Lamia Dammak[1], Mariem Kammoun[1], Noureddine Allouche[2], Houcine Ammar[*1] and Souhir Abid[1]

[1]*Laboratoire de Chimie Appliquée: Hétérocycles, Corps Gras et Polymères, Faculté des Sciences de Sfax, Université de Sfax, Route Soukra, BP1171, 3000 Sfax, Tunisie*

[2]*Laboratoire de Chimie des Substances Naturelles (UR11/ES74), Faculté des Sciences de Sfax, Université de Sfax, Route Soukra, BP1171, 3000 Sfax, Tunisie*

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Abstract: The synthesis of 2-amino chromene, reported in our previous paper, has been accomplished by the reaction of cyanoiminocoumarin and *β*-naphthol. The obtained compound was reacted with various electrophilic or nucleophilic reagents. All the new homologous 2-amino-4*H*-chromenes have been characterized on the basis of their spectral (IR, ^{1}H and ^{13}C NMR) data and microanalysis. Four compounds were evaluated *in vitro* for their preliminary antibacterial activities against five different pathogenic bacterial strains such as *Bacillus thuringiensis*, *Escherichia coli*, *Staphylococcus aureus*, *klebsiella pneumonia and Salmonella Sp.* Antibacterial activity of each compound was compared with standard drug, Penicillin.

Keywords: Cyanoiminocoumarins; 2-amino-4*H*-chromene; *β*-naphtol; antibacterial activity.

1. Introduction

In recent years, there has been increasing interest in chromenes not only because they constitute a group among the major classes of naturally occurring compounds such as natural alkaloids, flavonoids, tocopherols and anthocyanins [1-4], but also because of their versatility as synthones in organic transformations to give molecules having value as human therapeutic agents [5-6]. Among different types of chromene systems, 2-amino-4*H*-chromenes are of particular utility due to highly pronounced spasmolitic-, diuretic-, anticoagulant- and antianaphylactic activities [7-9]. They have also been widely employed as cosmetics, pigments, laser dyes, optical brighteners fluorescence markers and potent biodegradable agrochemicals [10-14]. In addition, they can be used to privileged medicinal scaffolds serving for generation of small-molecule ligands [7].

More specifically, 2-amino-4*H*-chromene-3-carbonitrile derivatives are of broad pharmaceutical interest and significance because they provide a promising lead for the development of

* Corresponding author. E-Mail: houcine_fss@yahoo.fr

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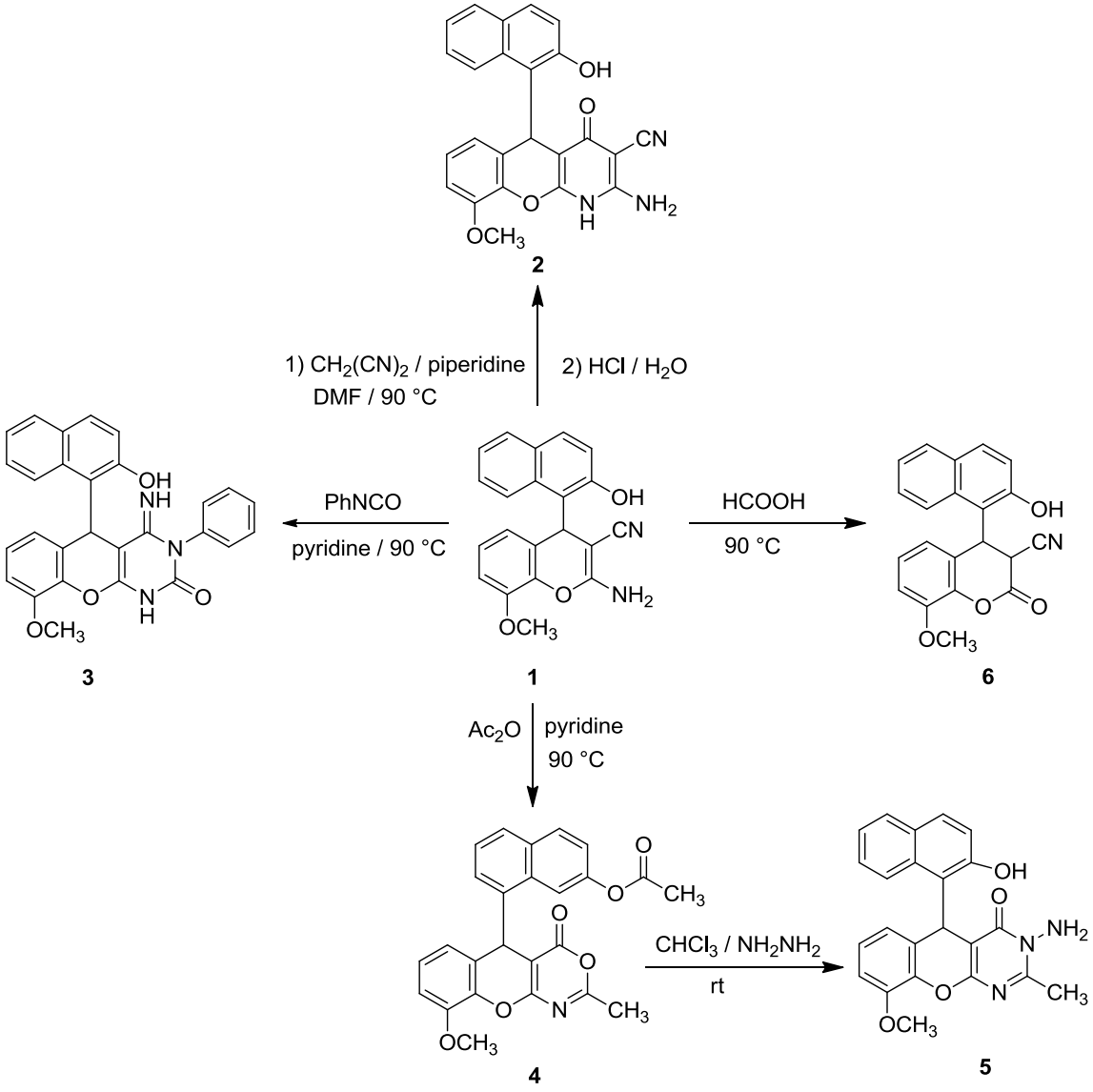
new analogues as potential anti-cancer anticoagulant and antibacterial agents [15-17]. Moreover, they are convenient synthons in the synthesis of densely substituted nitrogen heterocycles displaying remarkable effects as pharmaceuticals, which justifies our continuing efforts in designing novel heterocyclic molecules of biological importance.

In this context, our team in a recent study investigated a facile route for the formation of novel 2-amino-4-(2-hydroxynaphthyl)-4*H*-chromene-3-carbonitriles via Michael addition of various 3-cyanoiminocoumarins and *β*-naphthol [18]. We found that these compounds are convenient starting materials to provide various polyheterocyclic systems.

Herein, we have extended this study to develop new simpler methods for the synthesis of functionally substituted heterocycles with anticipated broad spectrum of biological activity by using an 8-methoxy-substituted 2-amino-4-(2-hydroxynaphthyl)-4*H*-chromene-3-carbonitrile 1 as a building block for synthesis of additional heterocycles (Scheme 1).

Compound **1** is of particular interest as the cyano and amino groups, in combination with chromene double bond, and the presence of hydroxyl group provide a rich opportunity for heterocyclic construction. Herein, we thus describe our study on the reaction of chromene 1 with malonitrile, phenyl isocyanate, acetic anhydride and formic acid.



Scheme 1. Synthesis of polycyclic compounds **2-6**

2. Experimental

2.1. Chemistry

2-Amino-4-(2-hydroxynaphthyl)-8-methoxy-4*H*-chromene-3-carbonitrile **1** was prepared as previously described [18]. All reagents were purchased from commercial sources and used without further purification. All solvents were dried and distilled prior to their use. The melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were registered on a Jasco FT-IR 420 spectrophotometer apparatus using Perkin Elmer 100. ^{1}H and ^{13}C spectra were recorded on a Bruker WP 200 spectrometer operating at 300 and 75 MHz, respectively, in DMSO-d_6 with TMS as internal standard (chemical shifts in ppm). Elemental microanalysis were performed on a EA 1112 analyzer from CE Instruments. All compounds are recrystallized in ethanol.

*2-Amino-5-(2-hydroxynaphthalen-1-yl)-9-methoxy-4-oxo-4,5-dihydro-1H-chromeno [2,3-b] pyridine-3-carbonitrile (**2**):* To a mixture of the 2-Amino-4-(2-hydroxynaphthyl)-8-methoxy-4*H*-chromene-3-carbonitrile **1** (1mmol) and malonitrile (1mmol) in DMF (5 mL) was added a few drops of piperidine. After refluxing for 24h, the resulting mixture was allowed to cool at room temperature and then diluted with cold water. A few drops of concentrated HCl were added and the resulting solid filtered off, washed several times with cold water and dried furnishing compound **2** in 50% yield as a brown solid, m.p. 228 °C. IR (cm^{-1}): ν = 3519 (OH), 3452 (NH_2), 3344 (NH), 2186 (C≡N), 1771 (C=O). ^{1}H NMR: δ 3.77 (s, 3H, OCH_3), 5.61 (s, 1H, H_5), 6.41 (d, *J* = 7.60 Hz, 1H, H_6), 6.59 (t, *J* = 8.00 Hz, 1H, H_7), 6.70 (d, *J* = 8.00 Hz, 1H, H_8), 6.91 (2H, NH_2), 7.30 (d, *J* = 9,20 Hz, 1H, H_{Ar}), 7.40-7.45 (m, 2H, H_{Ar}), 7.87 -7.95 (m, 3H, H_{Ar}), 9.06 (OH). ^{13}C NMR: δ 36.2, 56.0, 57.6, 109.8, 117.1, 117.2, 119.7, 120.9, 121.0, 123.6, 123.6, 125.3, 127.5, 128.8, 129.4, 129.4, 130.9, 131.0, 132.6, 142.8, 147.3, 147.6, 160.5, 162.8. Anal. Calcd for $C_{24}H_{17}N_3O_4$: C, 70.07, H, 4.16, N, 10.21. Found: C, 70.14, H, 4.10, N, 10.18.

*5-(2-Hydroxynaphthalen-1-yl)-4-imino-9-methoxy-3-phenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidin-2(5H)-one **(3):*** To the solution of the 2-amino-4-(2-hydroxynaphthyl)-8-methoxy-4*H*-chromene-3-carbonitrile **1** (1mmol) in pyridine (10 mL) was added phenyl isocyanate (1mmol) and the mixture was refluxed for 24h. After cooling, ethyl acetate (20 mL) was added and the yellow solid **3** obtained was filtered and washed several times with ether and dried.The compound was obtained in 80% yield as a yellow solid, m.p. > 260 °C. IR (cm^{-1}): ν = 3438 (OH), 3198-3326 (NH), 1687 (C=O), 1638 (C=C). ^{1}H NMR: δ 3.79 (s, 3H, OCH_3), 5.84 (s, 1H, H_5), 5.95 (s, 1H, NH), 6.13 (s, 1H, NH), 6.41 (dd, *J* = 6.80 Hz, *J* = 1.20 Hz, 1H, H_6), 6.62 (t, *J* = 7.60 Hz, 1H, H_7), 6.73 (dd, *J* = 6.80 Hz, *J* = 1.20 Hz, 1H, H_8), 6.97 (t, *J* = 7.20 Hz, 1H, H_{Ph}), 7.28 (t, *J* = 7.60 Hz, 2H, H_{Ph}), 7.43-7.46 (m, 5H, $2H_{Ph,}$ $3H_{Ar}$), 7.90-7.92 (m, 3H, H_{Ar}), 8.64 (OH). ^{13}C NMR: δ 21.9, 64.6, 99.5, 113.2, 118.9, 119.2, 120.6, 121.9, 122.1, 122.5, 123.2, 123.7, 125.4, 126.3, 127.9, 128.3, 128.3, 128.8, 129.3, 129.3, 130.6, 133.5, 136.3, 148.9, 150.7, 162.8. Anal. Calcd for $C_{28}H_{21}N_3O_4$: C, 72.57, H, 4.53, N, 9.07. Found: C, 71.75, H, 4.74, N, 9.35.

*1-(9-Methoxy-2-methyl-4-oxo-4,5-dihydrochromeno[2,3-d][1,3]oxazin-5-yl)naphthalen-2-yl acetate (**4**):* To a solution of the 2-Amino-4-(2-hydroxynaphthyl)-8-methoxy-4*H*-chromene-3-carbonitrile **1** (1 mmol) in pyridine (5 mL), was added acetic anhydride (10 mL). After refluxing for 24h, the reaction mixture was cooled and ethyl acetate (15 mL) was added. The green solid **4** obtained was filtered and washed with water and dried. The compound was obtained in 75% yield as a green solid, m.p. > 260 °C. IR (cm^{-1}): ν = 1742-1761 (C=O), 1654 (C=N), 1605 (C=C). ^{1}H NMR: δ 2.16 (s, 3H, CH_3), 2.30 (s, 3H, $OCOCH_3$), 3.60 (s, 3H, OCH_3), 5.82 (s, 1H, H_5), 6.87 (d, *J* = 8.10 Hz, 1H, H_6), 7.12 (t, *J* = 8.10 Hz, 1H, H_7), 7.23 (d, *J* = 7.50 Hz, 1H, H_8),7.38-7.51 (m, 3H, H_{Ar}), 7.87-7.92 (m, 2H, H_{Ar}), 8.04 (d, *J* = 8,40 Hz, 1H, H_{Ar}). ^{13}C NMR: δ 14.0, 20.3, 20.7, 55.7, 98.6, 111.0, 115.1, 117.0, 123.1, 123.8, 124.6, 125.3, 127.0, 128.5, 129.4, 130.7, 130.8, 135.7, 136.0, 147.6, 149.5, 151.1, 158.3,

160.9, 162.0. Anal. Calcd for $C_{25}H_{19}NO_6$: C, 69.92, H, 4.46, N, 3.26. Found: C, 69.97, H, 4.40, N, 3.29.

*(3-Amino-5-(2-hydroxynaphthalen-1-yl)-9-methoxy-2-methyl-3H-chromeno[2,3-d]pyrimidin-4(5H)-one (**5**):* (1 mmol) of compound **4** was dissolved in 10 ml of chloroform and stirred for 15 min. To the above solution, (2 mmol) of hydrazine hydrate was added. The mixture was stirred at room temperature for 5h, and the white solid was precipitated. After filtration, the solid was collected, washed with chloroform and dried to give compound **5**. The compound was obtained in 85% yield as a white solid, m.p. 240 °C. IR (cm^{-1}): ν = 3452 (OH), 3255-3196 (NH_2), 1645 (C=O), 1625 (C=N), 1595 (C=C). ^{1}H NMR: δ 2.30 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 5.95 (s, 1H, H_5), 6.44 (d, *J* = 7.60 Hz, 1H, H_6), 6.56 (t, *J* = 7.60 Hz, 1H, H_7), 6.67 (dd, *J* = 8.00 Hz, *J* = 1.20 Hz, 1H, H_8), 7.40-7.50 (m, 3H, H_{Ar}), 7.89 -7.93 (m, 2H, H_{Ar}), 8.02 (d, *J* = 8,40 Hz, 1H, H_{Ar}), 8.32 (2H, NH_2), 9.37 (OH). ^{13}C NMR: δ 21.4, 31.1, 55.9, 100.8, 110.3, 117.3, 117.7, 119.9, 121.5, 123.7, 125.3, 127.5, 128.9, 129.5, 131.2, 131.3, 132.2, 143.4, 148.3, 148.7, 158.6, 161.8, 164.0. Anal. Calcd for $C_{23}H_{19}N_3O_4$: C, 68.82, H, 4.77, N, 10.47. Found: C, 68.77, H, 4.81, N, 10.50.

*4-(2-Hydroxynaphthalen-1-yl)-8-methoxy-2-oxochroman-3-carbonitrile (**6**):* A mixture of the 2-Amino-4-(2-hydroxynaphthyl)-8-methoxy-4*H*-chromene-3-carbonitrile **1** (1mmol) and formic acid (5mL) was refluxed for 24h as a solid started to form. After cooling to room temperature, yellow solid was collected by filtration, washed with ethanol and dried to give compound **6**. The compound was obtained in 70% yield as a yellow solid, m.p. 240 °C. IR (cm^{-1}): ν = 3402 (OH), 2258 (C≡N), 1753 (C=O), 1627 (C=C). ^{1}H NMR: δ 3.79 (s, 3H, OCH_3), 5.49 (d, *J* = 7.60 Hz, 1H, H_4), 5.75 (d, *J* = 6.80 Hz, 1H, H_3), 6.55 (d, *J* = 7.60 Hz, 1H, H_5), 6.69 (t, *J* = 8.00 Hz, 1H, H_6), 6.87 (dd, *J* = 8.00 Hz, *J* = 0.80 Hz, 1H, H_7), 7.43 (d, *J* = 9,2 Hz, 1H, H_{Ar}), 7.49 (t, *J* = 7.20 Hz, 1H, H_{Ar}), 7.56 (dd, *J* = 7.20 Hz, *J* = 1.20 Hz, 1H, H_{Ar}), 7.91-8.02 (m, 3H, H_{Ar}), 9.41 (OH). ^{13}C NMR: δ 34.8, 43.7, 56.1, 111.8, 115.3, 117.1, 117.5, 120.0, 120.1, 123.4, 124.5, 126.0, 128.1, 129.1, 130.5, 131.1, 144.4, 148.1, 148.8, 162.2, 173.8. Anal. Calcd for $C_{21}H_{15}NO_4$: C, 73.03, H, 4.38, N, 4.06. Found: C, 73.11, H, 4.34, N, 4.03.

2.2. Biological

The antibacterial assays were carried out by the agar diffusion and microdilution methods in order to determine the antibacterial activity of the 4 synthesized molecules according to the method described by Berghe and Vlietinck[19]. The bacterial suspensions were adjusted with sterile saline to a concentration of 1.0×10^5 cfu/mL. The inocula were prepared daily and stored at +4 °C until use.

2.2.1. Agar diffusion test

The 4 molecules were dissolved in 100 % DMSO and filtered through a 0.22 µm Nylon membrane filter. The bacterial strains were cultured in a nutriment broth Muller Hinton (MH) for 24 hours. Then, 200 µL of each suspension bacteria (10^6 cfu) (estimated by absorbance at 600 nm) was spread on Muller Hinton agar (MHG). Bores were made by using a sterile borer and were loaded with 50 µL of each sample extract. Penicillin (10 µg/well) was used as positive reference standard. All the plates were incubated at 37 °C for 24 hours. Antibacterial activity was evaluated by measuring the inhibition zone (IZ) in millimeters.

2.2.2. Microdilution test

The minimum inhibitory concentrations (MICs) were determined using 96-well microtitre plates. The bacterial suspension was adjusted with sterile saline to a concentration of 1.0×10^5cfu/mL.Compounds to be investigated were dissolved in broth LB medium (100 mL) with bacterial inoculum (1.0×10^4 cfu per well) to achieve the wanted concentrations (0.02–15.0 µg/mL). The microplates were incubated for 24 h at 28 °C. The lowest concentrations without visible growth (at the

binocular microscope) were defined as concentrations that completely inhibited bacterial growth (MICs). The optical density of each well was measured at a wavelength of 655 nm by Microplate manager 4.0 (Bio-Rad Laboratories) and compared with a blank and the positive control. Penicillin was used as a positive control using the same concentrations as in the disc diffusion test.

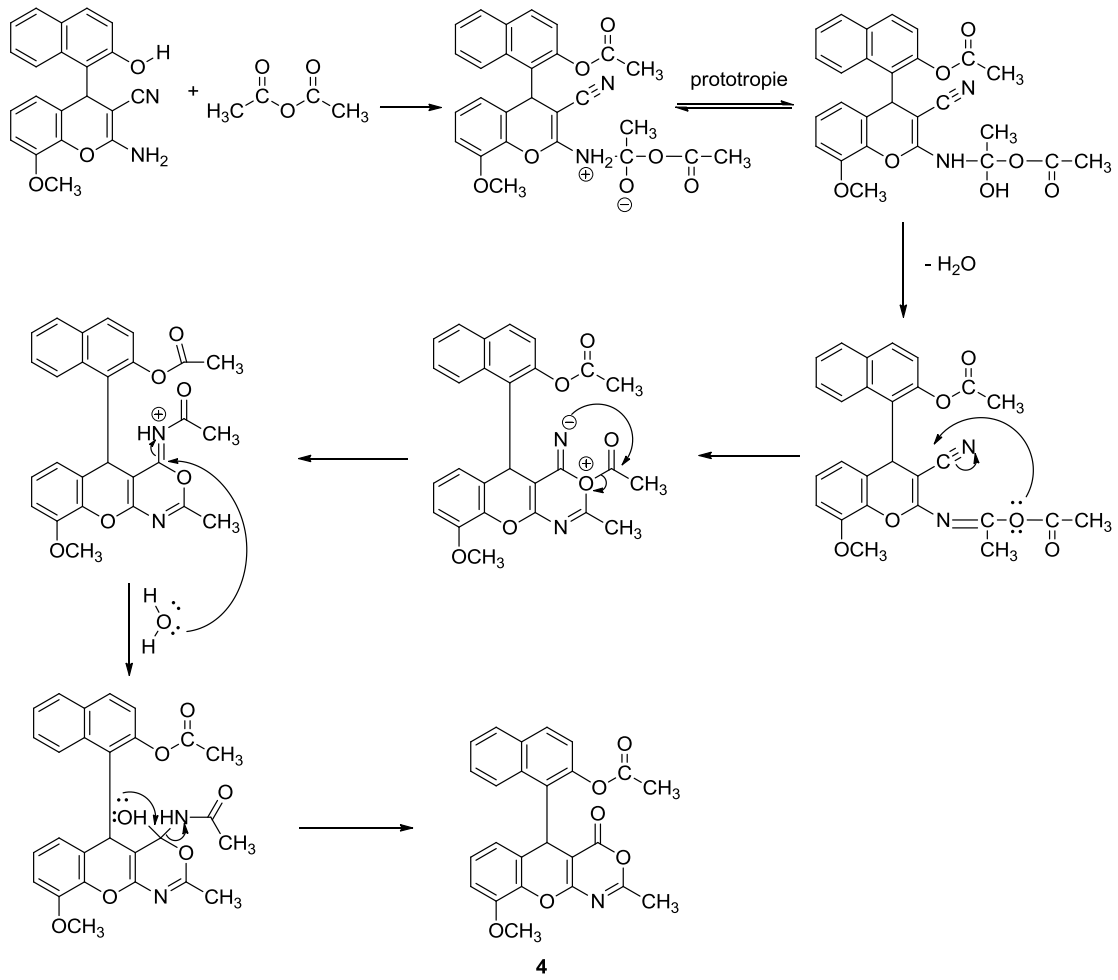
3. Results and Discussion

In the first experiment, a cyclocondensation of chromene **1** with malonitrile in boiling dimethyl formamide containing a catalytic amount of piperidine afforded after hydrolysis in a HCl solution, 2-amino-3-cyano-4-oxo-pyrimidine 2 in moderate yield. The structure of **2** was established on the basis of spectral and elemental data. In particular, the IR spectra is marked by the appearance of two new bands at 1771 cm^{-1} and 3344 cm^{-1} due to C=O and NH groups respectively. When chromene **1** and phenyl isocyanate were heated together at 90 °C in pyridine for 24 hours, 4-imino-2-oxo-*N*-phényl-pyrimidine **3** was isolated after precipitation in ethyl acetate in good yield. The structure was confirmed by spectral and elemental data. In the IR spectrum, no absorption band was detected at about 2180 cm^{-1} indicating the absence of the nitrile group, while the appearance of a strong band at 1687 cm^{-1} attributed to a C=O group confirmed the conversion of compound **1** to compound **3**. In the ^{1}H NMR spectrum of **3**, the -NH_2 resonance of starting chromene **1** at 6.88 ppm is no longer present and two NH resonances appeared at 5.95 ppm and 6.13 ppm. In the ^{13}C NMR spectrum, a resonance at 162.8 ppm confirms the presence of a C=O group. Mechanistically, it is presumed that the amino group of chromene **1** reacts with the isocyanate to give the corresponding urea, which can then undergo cyclisation onto the cyano function.

The reaction mixture of chromene **1** in pyridine with two equivalents of acetic anhydride was refluxed at 90 °C for 24h (Scheme 2). After cooling, ethyl acetate was added leading to the isolation of acylated polycyclic oxazinone **4** in 75% yield. The absence of cyano and amino absorption bands and the appearance of a broad absorption band at 1761 cm^{-1} corresponding to two C=O groups in the IR spectrum confirmed the product. This result was also confirmed by the presence, in the ^{13}C NMR spectrum, of signals at 162 ppm and 160.9 ppm due to the two carbonyl groups. The ^{1}H NMR spectrum showed the presence of two resonances in the 2.16 and 2.30 ppm assignable to two CH_3 protons. Hydrazine hydrate was then added to compound 4 to give the phenolic *N*-aminopyrimidinone **5** in good yield. The IR spectra of compound **5** showed a strong absorption bands at 1645, 3255, 3452 cm^{-1} corresponding to conjugated cyclic amide, amino and hydroxyl group respectively. The ^{1}H NMR spectrum of **5** showed in particular two singlet peaks at 8.32 and 9.37 ppm due to the NH_2 and OH groups respectively. Finally, the treatment of chromene **1** with hot formic acid afforded after several hours 3-cyano-3,4-dihydrocoumarin **6**. In this case, the IR spectrum of product **6** showed the disappearance of an original peak at 3450-3341cm^{-1} due to NH_2 group and the appearance of an intensive broad band of coumarinic carbonyl at 1753 cm^{-1}. The ^{1}H NMR spectrum of **6** showed a characteristic peak (doublet) of H_3 on the pyranic ring at 5.75 ppm and a second doublet H_4 peak at 5.49 ppm. Additional and complete characterization of products 2-6 is provided in the experimental section.

The results of the antibacterial assay of the compounds **1**, **4** and **5** against a range of microorganisms are presented in Table 1. All of the tested compounds showed variable inhibitory activities against different microorganisms. Compound **1** exhibited the highest inhibitory activity against various microorganisms, mainly *klebsiella pneumoniae* (16.5 mm, 0.25 μg/mL), followed by compound 5 (15 mm, 0.5 μg/mL). This activity is greater than that of penicillin (11 mm, 1.5 μg/mL). On the other hand, except for compound **4** (12 mm, 1 μg/mL), all other compounds were inactive against *Salmonella Sp.* In addition, compound 4 was active against all tested bacteria except *Escherichia coli.* The potent activity exhibited by **1** and **4** would likely be caused by the presence of phenolic moiety in their structures. In this way, previous studies have established that the antimicrobial action of phenolic compounds is related to their ability to denaturize proteins. They act by causing the leakage of cytoplasmic constituents such as proteins or minerals and testifying their

ability to cross the cells wall. Polyphenols are also known to bind to the peptidoglycan leading to the breaking of the bacterial cell-wall integrity [20-21].



Scheme 2. Mechanism of compound **4**

Table 1. Antibacterial activity of compounds

		Bacillus thuringiensis	*Escherichia coli*	*Staphylococcus aureus*	*Klebsiella pneumoniae*	*Salmonella Sp*
1	IZ	15 mm	13 mm	14 mm	16,5 mm	NA
	MIC	0.5 µg/mL	0.75 µg/mL	0.5 µg/mL	0.25 µg/mL	NA
4	IZ	13,5 mm	Inactive	13 mm	11,25 mm	12 mm
	MIC	0.5 µg/mL	Inactive	0.75 µg/mL	1.5 µg/mL	1 µg/mL
5	IZ	14 mm	14 mm	12 mm	15 mm	NA
	MIC	0.5 µg/mL	0.5 µg/mL	1 µg/mL	0.5 µg/mL	NA
Penicillin	IZ	11 mm	12 mm	10 mm	11 mm	13 mm
	MIC	1.5 µg/mL	1 µg/mL	2 µg/mL	1.5 µg/mL	0.75 µg/mL

IZ: Inhibition Zone; MIC: Minimum Inhibitory Concentration; NA: Non active

4. Conclusion

In conclusion, we have developed a simple procedure for the synthesis five new polycyclic compounds initiated by the condensation of different reagents with 2-Amino-4-(2-hydroxynaphthyl)-8-methoxy-4*H*-chromene-3-carbonitrile. These compounds are obtained in moderate to good yields. Their antibacterial activities were also evaluated by the microdilution method.

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Supporting Information

Supporting information accompanies with this paper on http://www.acgpubs.org/OC

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