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A CONVENIENT SYNTHESIS OF NOVEL COUMARIN DERIVATIVES WITH ANTICIPATED ANTIMICROBIAL ACTIVITIES

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Abstract – Chalcone and coumarin are two substantial classes of natural products possessing significant antimicrobial activities. Hybrid compounds containing both structures have been synthesized in a good yield using Claisen-Schmidt aldolic condensation. The reaction of the new chalcones with active methylene compounds under different reaction conditions led to the construction of pyridine, pyran, pyrazole and pyridinone containing coumarin moiety with different functional groups. Investigating the antimicrobial activity of the new synthesized heterocycles, displays that 3-(2′-amino-3′-cyano-4′-(4-hydroxy-3-methoxyphenyly)pyrid-6′-yl)-coumarin **2a** has the highest antimicrobial activity toward both Gram-positive and Gram-negative bacteria. Consequently, it was utilized as starting material for synthesis of more new fused heterocycles with anticipated high biological activity. All the new compounds are well characterized using, elemental analysis, FT-IR, ^{1}H NMR, ESI-Mass Spectrum and tested for their antimicrobial activity.

INTRODUCTION

Coumarins (2*H*-1-benzopyran-2-ones) represent a class of naturally and synthetically attained compounds that possess a wide variety of biological activities.[1-4] Natural coumarins have been used in medicine (anticoagulants), foods, and fragrances. These compounds possess several types of pharmacological properties such as antibacterial,[5-7] antifungal,[8,9] antioxidant,[10,11] anticancer,[12-14] anti-HIV,[15] anticoagulant,[16] antiarthritic,[17,18] anti-inflammatory,[19,20] antipyretic,[21] and antiviral.[22] In addition, many of these compounds have been used as additives in food, perfumes, cosmetics, pharmaceuticals,[23] optical brighteners,[24] dispersed fluorescent and laser dyes.[25-27] Additionally, chalcones are one of the major families of naturally occurring compounds with widespread distribution in many natural products, and they have been subject of great interest for their remarkable pharmacological activities.[28-30]

Some coumarin derivatives can be utilized efficiently for the synthesis of valuable heterocyclic ring systems. In this context, chalcones are essential building blocks and valuable reactive intermediates for the synthesis of various heterocyclic compounds as well as metal complexes of high-biological relevance. As a part of our on-going endeavour to create novel heterocyclic scaffolds through simple and straightforward convenient routes,[31,32] we have explored the use of 3-acetylcoumarin to construct some new chalcones bearing the coumarin scaffold. Moreover, the chalcones have been used as substrate for synthesizing more coumarin derivatives, targeting to increase the synthetic potential of coumarin and studying the antibacterial activities of the new synthesized compounds.

RESULTS AND DISCUSSION

Different chalcones **1a-e** have been synthesized according to reported procedures.[33] Many attempts were made to utilize compounds **1a-c** as starting materials for synthesis of new heterocycles containing coumarin moiety. It is well known that chalcone reacts with malononitrile giving different products depending on the reaction conditions.[34] Thus, when compounds **1a,b** were reacted with malononitrile in ethanol in the presence of excess ammonium acetate afforded 3-(2′-amino-3′-cyano-4′-arylpyrid-6′-yl)-coumarin derivatives **2a,b**. Also, the one-pot four-component reaction of 3-acetylcoumarin, aromatic aldehydes, malononitrile and ammonium acetate in absolute ethanol afforded the same products (Scheme 1). IR spectrum of compound **2a** showed a strong absorption bands for OH and NH_2 at 3546, 3347, 3221 cm^{-1} and for the nitrile group at 2210 cm^{-1}. Moreover, IR spectrum of compound **2b** showed a strong absorption bands for NH_2 group at 3352, 3218 cm^{-1} and for the nitrile group at 2208 cm^{-1}. The ^1H NMR (DMSO-d_6) spectrum of compound **2a** showed signals at δ; 3.72 (s, 3H, OCH_3), 5.62 (s, 1H, O*H*), 7.19 (s, 2H, NH_2), 6.90-7.85 (m, 8H, ArH and Pyr-H) and 8.80 (s, 1H, coumarin 4-H). The mass spectrum of compound **2a** revealed ion peak at *m/z* = 385 equivalent to molecular formula $C_{22}H_{15}N_3O_4$.

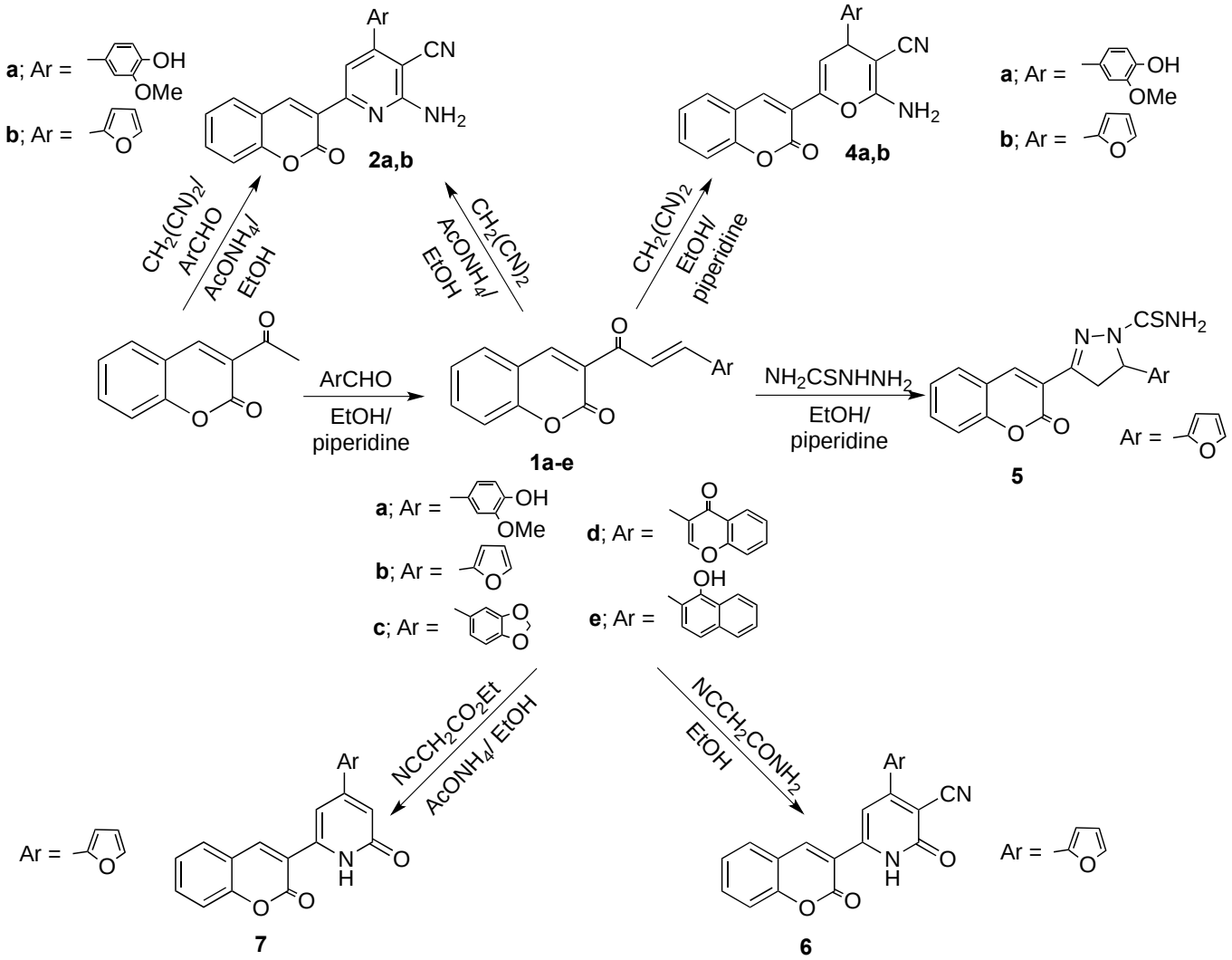
Although chalcones **1a,b**, bearing 4-hydroxy-3-methoxyphenyl and 2-furyl, react with malononitrile in presence of ammonium acetate afforded 2-amino-3-cyano-4-arylpyridine derivatives, chalcone **1c** shows a reaction-time dependence. Therefore, when the reaction was performed for 3 h only it gave compound **2c**,[35] whereas if the reaction was continued for longer time, under the same reaction condition, hydrolysis of nitrile group followed by its decarboxylation occurs to afford the compound **3** (Scheme 2). This could be attributed to electronic/steric effect exerted by benzodioxole moiety. The IR spectrum of compound **3** is devoid from absorption band for the cyano group, and it also showed two bands for NH_2 group at 3240, 3179 cm^{-1}. Another evidence for the formation of compound **3** was gained from ^1H NMR data which revealed two singlet peaks at 6.84 and 6.94 ppm characteristic for protons at C3 and C5 of pyridine ring. More confirmation for the structure was obtained from MS (EI) which showed an ion at *m/z* = 357 equivalents to (M-1).

An approach for 3-(pyran-6′-yl)coumarin derivatives was achieved by fusion of chalcones **1a,b** with malononitrile in presence of a catalytic amount of piperidine to give 3-(2′-amino-3′-cyano-4′-arylpyran-6′-yl)coumarin derivatives **4a,b** (Scheme 1).[36] It is worth mentioning that, initial trials of refluxing the chalcone with malononitrile in ethanol in presence of piperidine failed to afford the anticipated product and instead the starting materials were obtained. The IR spectra of compounds **4a,b** showed strong absorption bands for NH_2 group at 3342, 3225 cm^{-1} and 3340, 3227 cm^{-1} and for cyano group at 2212, 2210 cm^{-1} respectively. The ^1H NMR of compound **4b** displayed two doublet peaks at 3.94 and 4.61 ppm (each integrating for one proton) correspond to C4 and C5 of pyran ring and broad bands at 8.50 ppm which suggest two exchangeable protons (NH_2). The mass spectrum of compound **4b** revealed ion peak at *m/z* = 331, equivalent to (M-1).

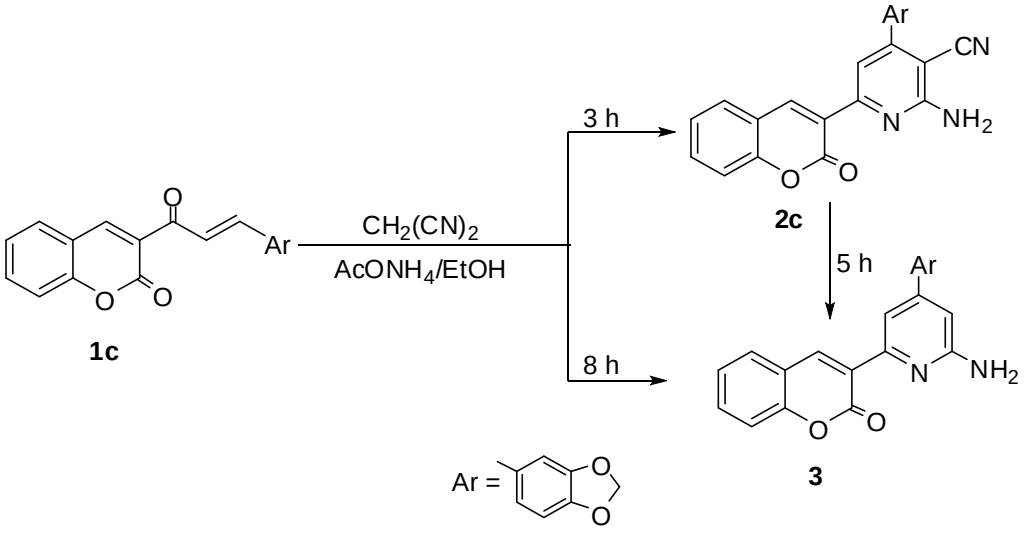
The reaction of chalcone **1b** with thiosemicarbazide under reflux for 10 h in boiling ethanol containing a catalytic amount of piperidine afforded 5-aryl-3-(2′-oxo-2′*H*-chromen-3′-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **5** (Scheme 1).[35]

Structure proof of compound **5** was based on its spectral data. IR revealed strong absorption bands at 3438, 3249 cm^{-1} characteristic for NH_2 group and at 1252 cm^{-1} due to C=S group. Additionally, ^1H NMR data displayed doublet peak at 3.32 ppm integrating for two protons (CH_2 of pyrazole), triplet peak at 3.78 ppm (CH of pyrazole) and a broad band at 11.15 ppm confirming the existence of exchangeable protons (NH_2). The mass spectrum of compound **5** afforded an ion peak at *m/z* = 340 equivalent to (M+1).

Fusion of chalcone **1b** with cyanoacetamide followed by refluxing in absolute ethanol gave 4-(aryl)-2-oxo-6-(2′-oxo-2′*H*-chromen-3′-yl)-1,2-dihydropyridine-3-carbonitrile **6** in 73% yield (Scheme 1). The IR spectrum of compound **6** showed the presence of nitrile and amide carbonyl groups indicated from absorption bands at 2221 and 1684 cm^{-1} respectively, it also showed absorption band for NH group at 3127 cm^{-1}. Additionally, ^1H NMR revealed a resonance at 5.97 ppm, a singlet characteristic for the proton at C5 and broad bands at 11.85 ppm, confirming the existence of exchangeable proton (NH). Interestingly, attempts to have the same product through reaction of chalcone **1b** with ethyl cyanoacetate afforded instead pyridin-2(1*H*)-one derivative **7** due to hydrolysis of cyano group in acidic medium followed by its decarboxylation, the IR spectrum of the product was devoid from absorption band of the cyano group, the absorption band at 1681 cm^{-1} is in consistence with the amide group. The ^1H NMR data displayed two singlet peaks at 5.79 and 5.86 (each integrating for one proton) characteristic for protons at C5 and C3 of pyridinone ring. More confirmation for the proposed structure obtained from MS that showed an ion at 305 consistent with the proposed structure.



Scheme 1



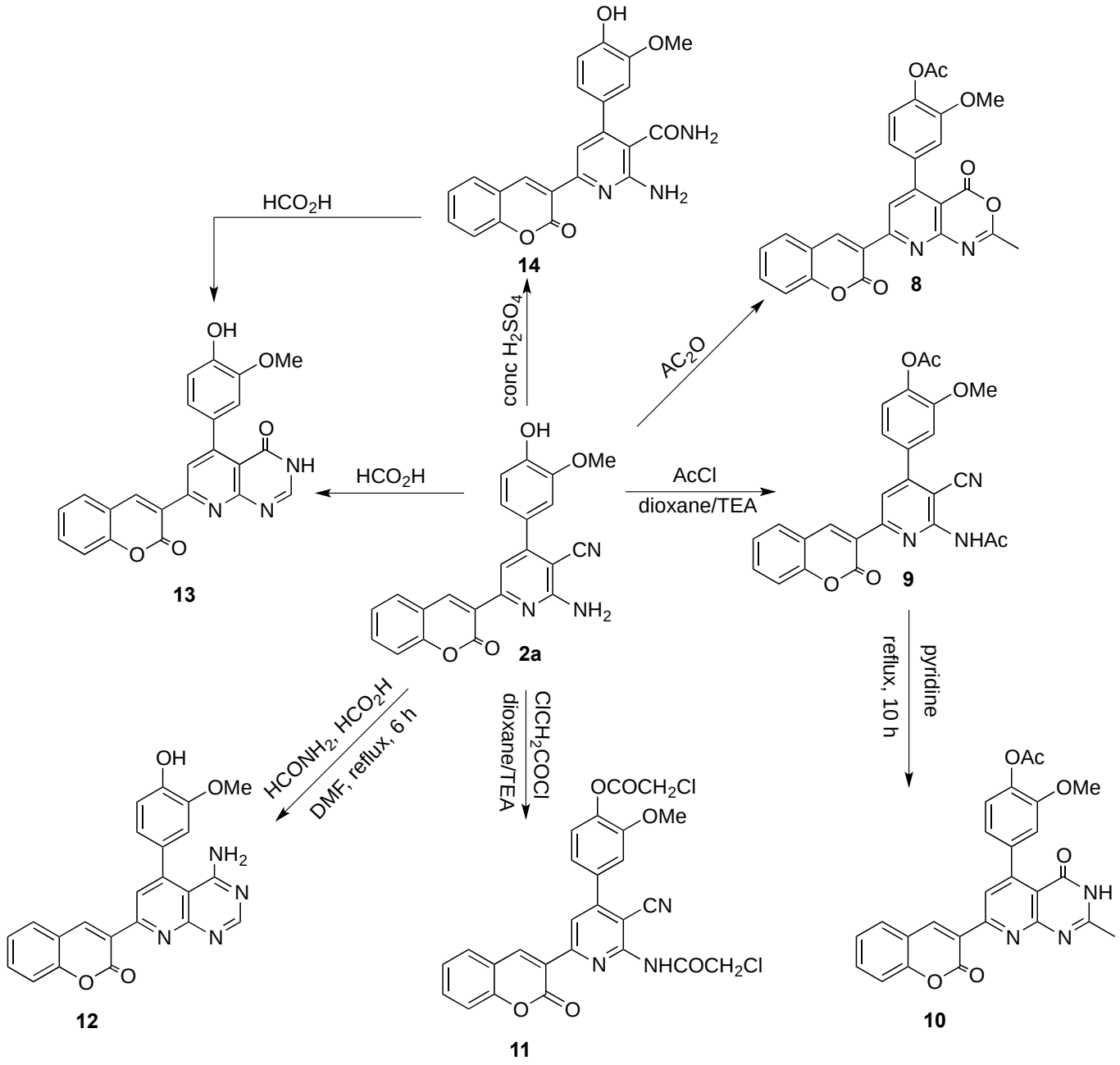
Scheme 2

An approach to fused oxazinone heterocyclic system was achieved by cyclocondensation of compound **2a** and acetic anhydride. Thus refluxing compound **2a** in acetic anhydride for 5 h afforded compound **8** (Scheme 3). The IR spectrum of the oxazinone **8** showed absorption bands at 1763 and 1736 cm^{-1} due to carbonyl of oxazinone and ester respectively. In the ^1H NMR spectrum there were three resonances at 2.32, 2.59 and 3.87 ppm all are singlet and each integrating for three protons which suggesting the presence of three methyl group. While acetylation of compound **2a** with acetyl chloride in dry dioxane in presence of triethylamine gave *N*-acetyl derivative **9**, the IR spectrum exhibited strong absorption bands at 1754 and 1687 cm^{-1} due to ester carbonyl group and amide carbonyl group respectively, and it also showed a peak characteristic for nitrile group at 2198 cm^{-1}. An approach to fused pyrimidine heterocyclic systems was achieved by refluxing acetylation product **9** in pyridine for 10 h to give 3,4-dihydropyrido[2,3-*d*]pyrimidin-4-one derivative **10**, which formed as result of nitrile-amide conversion; an amide-imidol toutomerism of the acetyl group followed by loss of water molecule (Scheme 3). IR spectrum showed the disappearance of nitrile absorption band and the presence of carbonyls of cyclic amide and ester indicated from the absorption bands at 1660 and 1736 cm^{-1} respectively. Another piece of evidence obtained from ^1H NMR spectrum which showed three resonances at 2.28, 2.57 and 3.85 ppm, all are singlet and each integrating for three protons which suggesting the presence of three methyl group.

Chloroacetylation was achieved by refluxing compound **2a** with chloroacetyl chloride in dry dioxane in presence of triethylamine and afforded compound **11** (Scheme 3). The IR spectrum of **11** exhibited a strong absorption bands at 1752 and 1646 cm^{-1} due to ester and amide carbonyl groups respectively, it showed a peak characteristic for nitrile group at 2199 cm^{-1}, and also it showed peak characteristic for NH group at 3205 cm^{-1}. ^1H NMR data displayed two singlet peaks at 4.27 and 4.39 ppm (each one integrating for two protons) suggesting two methylene groups of $NHCOCH_2Cl$ and $OCOCH_2Cl$. Also its mass spectrum showed the molecular ion peak at 539.

A facile synthesis for construction of more fused pyrimidine heterocyclic systems, was achieved by the reaction between the compound **2a** and formamide in refluxing DMF furnishing 3-(4-amino-5-(4-hydroxy-3-methoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl)-2*H*-chromen-2-one **12** (Scheme 3). The IR spectrum of compound **12** is devoid from absorption band for the cyano group. It also showed two bands for NH_2 group at 3256 and 3147 cm^{-1}. Another evidence for the proposed structure of compound **12** was gained from ^1H NMR data which revealed a resonance at 8.34 ppm, a singlet peak characteristic for the protons at C2 of pyrimidine. On the other hand, cyclocondensation of compound **2a** with hot formic acid led to the formation of the 5-(4-hydroxy-3-methoxyphenyl)-7-(2-oxo-2*H*-chromen-3-yl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one **13** (Scheme 3). The proof of pyrimidinone **13** was assisted from spectroscopic data such as IR which showed the disappearance of nitrile absorption band

and the presence of carbonyl (cyclic amide) indicated from the absorption band at 1696 cm^{-1}. The ^1H NMR spectrum of the compound showed a singlet peak at 8.36 ppm due to resonance of C2 of pyrimidinone ring, furthermore two resonances at 5.37 and 10.45 ppm confirming the existence of two exchangeable protons (OH and NH). The mass spectrum of compound **13** revealed an ion peak at 409 (M-4). Finally, the structure of that compound was confirmed chemically, it was also prepared *via* the hydrolysis of the cyano group in compound **2a** into amide group using sulphuric acid followed by reaction of the product **14** with formic acid (Scheme 3).



Scheme 3

ANTIMICROBIAL ACTIVITIES

The antimicrobial activity of each compound under investigation was evaluated against *Basillus subtilis* and *Streptococci* as example of Gram-positive bacteria and *Klebsiella pneumoniae* and *Escherichia coli* as example of Gram-negative bacteria. Ampicillin was used as control standard for *in vitro* antibacterial activity. Antimicrobial activity was expressed as inhibition diameter zones in millimeters (mm) of synthesized compounds against the pathologial strains as following in Table.

Table. *In vitro* antimicrobial activity of the synthesized compounds

Entry	Compound	Gram (+ve) bacteria				Gram (–ve) bacteria			
		Basillus subtilis		*Streptococci*		*Klebsiella pneumoniae*		*Escherichia coli*	
		I.Z.*	% Activity index	I.Z.	% Activity index	I.Z.	% Activity index	I.Z.	% Activity index
1	**1a**	NA[a)]	-	7	30.4	NA	-	NA	-
2	**1b**	NA	-	NA	-	NA	-	4	16.7
3	**1c**	8	32.0	NA	-	NA	-	19	79.2
4	**1d**	19	76.0	16	69.6	20	8.0	18	75.0
5	**1e**	NA	-	2	8.7	NA	-	NA	-
6	**2a**	NA	-	18	78.3	23	92.0	20	83.3
7	**2b**	NA	-	NA	-	NA	-	NA	-
8	**2c**	NA	-	NA	-	NA	-	NA	-
9	**3**	NA	-	21	91.3	23	92.0	20	83.3
10	**4b**	NA	-	NA	-	4	16.0	NA	-
11	**5**	10	40.0	17	73.9	19	76.0	NA	-
12	**6**	NA	-	NA	-	2	8.0	NA	-
13	**8**	3	12.0	NA	-	NA	-	NA	-
14	**11**	2	8.0	NA	-	NA	-	NA	-
15	**13**	NA	-	2	8.7	4	16	NA	-
16	**14**	4	16.0	NA	-	NA	-	NA	-
17	**Ampicillin**	25	100	23	100	25	100	24	100

***** I.Z. Inhibition diameter zones expressed in millimeters (mm).
[a)] NA: No antimicrobial activity detected.

The tested compounds showed variation in their antibacterial activities (Table). Among the starting compounds **1a-e**, only compound **1d** showed strong activity against both Gram-positive and

Gram-negative bacteria (Table; entry 4). Contrarily, compounds **2b** and **2c** were biologically inactive against Gram-positive and Gram-negative bacteria (Table; entries 7, 8, respectively). Moreover, compounds **2a** and **3** exhibited an excellent effect against Gram-positive and Gram-negative bacteria except for *Basillus subtilis* bacteria (Table; entries 6, 9).

CONCLUSION

In conclusion, we prepared a series of chalcones bearing coumarin moiety. Reaction of the chalcones with malononitrile, cyanoacetamide, ethyl cyanoacetate and thiosemicarbazide led to construction of pyridine, pyran, and pyridinone with various function groups, respectively. On screening the synthesized compounds for antimicrobial activity, the compound **2a** showed an excellent activity against Gram-positive and Gram-negative bacteria (Table; entry 6). Consequently, the compound has been used for synthesis of more fused heterocyclic compounds bearing coumarin moiety and most of the synthesized compounds have been screened for antimicrobial activity. All the new compounds are well characterized using; elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, and ESI-Mass spectrum.

EXPERIMENTAL

Melting points were determined by an electrothermal melting point apparatus and are uncorrected. The reaction times were determined using the thin-layer chromatography (TLC) technique which was performed with fluorescent silica gel plates HF245 (Merck) and plates were viewed with iodine. Silica gel (230-400 mesh) was used for flash chromatography separations. Elemental analysis were carried out by Micro analytical Unit, (Faculty of Science, Cairo University), IR (KBr) spectra were recorded on a Pye-Unicam infrared spectrophotometer SP 2000 (Faculty of Science, Fayoum University), The mass spectra were run by a Shimadzu-GC-MS-GP 1000 EX using the direct inlet system and nuclear magnetic resonance spectra were recorded on Varian Mercury 300 MHz spectrometer using TMS as internal standard; chemical shifts are recorded in δ units (National Centre Researcher).

Synthesis of 3-(3-arylacryloyl)-2*H*-chromen-2-one (1a-e).

General procedure: A mixture of 3-acetylcoumarin (20 mmol), appropriate aryl and heteroaryl-aldehydes (20 mmol) namely (vanillin, furfural, piperonal, 3-formylchromone and 2-hydroxynaphthaldehyde) and piperidine (0.2 mL) in absolute EtOH (25 mL) was refluxed for 5-8 h, as monitored by TLC. After cooling the solid formed was filtered off and recrystallized from a suitable solvent to afford the pure product.

3-(2′-Amino-3′-cyano-4′-arylpyrid-6′-yl)coumarin derivatives (2a-c).

General procedure:

Method A. A mixture of compounds **1a-c** (10 mmol), malononitrile (0.66 g, 10 mmol) and excess of

ammonium acetate (3 g, 40 mmol) was refluxed in absolute EtOH for 3 h, as monitored by TLC. The reaction mixture was left to cool, poured over crushed ice, the precipitated products were filtered off, washed with water, dried and crystallized from the proper solvent to afford the pure product.

Method B. A mixture of 3-acetylcoumarin (10 mmol), appropriate aryl-and heteroaryl-aldehydes (10 mmol) namely (vanillin, furfural, piperonal), malononitrile (0.66 g, 10 mmol) and excess of ammonium acetate (3 g, 40 mmol) was refluxed in hot EtOH for 3 h. The reaction mixture was left to cool, poured over crushed ice, the precipitated products were filtered off, washed with water, dried and crystallized from the proper solvent.

(2a): crystallized from EtOH as yellow crystals in 85% yield: mp 210 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.72 (s, 3H, OC*H*$_3$), 5.62 (s, 1H, O*H*), 7.19 (s, 2H, N*H*$_2$), 6.90-7.84 (m, 7H, ArH), 7.85 (s, 1H, PyrH), 8.80 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 56.38, 98.28, 110.88, 114.31, 115.08, 116.37, 117.30, 119.74, 121.10, 124.22, 128.65, 128.75, 129.13, 130.05, 143.85, 146.55, 148.35, 154.11, 154.75, 155.88, 160.45, 162.80; IR (KBr) ν: 3546, 3347, 3221, 3043, 2920, 2210, 1724 cm^{-1}; MS (70 eV) *m/z* (%): 385 (M$^+$, 20.8), 51 (100). Anal. Calcd for $C_{22}H_{15}N_3O_4$: C: 68.57, H: 3.92, N: 10.90. Found C: 68.33, H: 3.81, N: 10.74.

(2b): crystallized from EtOH as brown crystals in 76% yield: mp 238-240 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 7.22 (s, 2H, N*H*$_2$), 6.95-7.96 (m, 7H, ArH), 7.85 (s, 1H, PyrH), 8.80 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 94.37, 106.89, 108.73, 113.66, 115.89, 117.32, 119.98, 124.25, 128.45, 129.15, 130.54, 144.78, 145.04, 143.80, 149.75, 153.18, 155.98, 160.30, 161.08; IR (KBr) *v*: 3352, 3218, 3053, 2208, 1722 cm^{-1}; MS (70 eV) *m/z* (%): 329 (M$^+$, 10.5), 51 (100). Anal. Calcd for $C_{19}H_{11}N_3O_3$: C: 69.30, H: 3.37, N: 12.76. Found C: 69.69, H: 3.19, N: 12.35.

(2c): crystallized from EtOH as yellow crystals in 76% yield: mp 227-229 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 6.15 (s, 2H, OC*H*$_2$O); 7.14 (s, 2H, N*H*$_2$), 6.70-7.44 (m, 7H, ArH), 7.85 (s, 1H, PyrH), 8.80 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 98.22, 103.21, 108.80, 110.85, 114.40, 116.37, 117.30, 119.75, 121.25, 124.23, 128.65, 129.13, 130.05, 130.52, 143.83, 147.73, 149.51, 154.11, 154.73, 155.87, 160.43, 162.82; IR (KBr) *v*: 3350, 3204, 3069, 2910 , 2206, 1719 cm^{-1}; MS (70 eV) *m/z* (%): 383 (M$^+$, 25.3), 202 (100). Anal. Calcd for $C_{22}H_{13}N_3O_4$: C: 68.93, H: 3.42, N: 10.96. Found C: 68.66, H: 3.29, N: 10.55.

3-(2′-Amino-4′-arylpyrid-6′-yl)coumarin derivatives (3). A mixture of compound **1c** (3.20 g, 10 mmol), malononitrile (0.66 g, 10 mmol) and excess of ammonium acetate (3 g, 40 mmol) was refluxed in EtOH for 8 h. The reaction mixture was left to cool, the formed precipitate was filtered, washed with EtOH, dried and crystallized from EtOH as yellow crystals in 55% yield: mp 258-260 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 6.12 (s, 2H, OC*H*$_2$O), 6.85 (s, 1H, pyridine H-5), 6.96 (s, 1H, pyridine H-3), 6.98-7.84 (m, 7H, ArH), 7.75 (s, 2H, N*H*$_2$), 8.66 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ:

103.22, 108.86, 110.87, 115.75, 117.50, 118.23, 119.98, 121.17, 122.45, 128.43, 129.12, 131.29, 130.42, 143.85, 148.04, 149.55, 153.63, 154.11, 155.93, 159.77, 160.45; IR (KBr) *v*: 3240, 3179, 3052, 2935, 1713, 1614 cm^{-1}; MS (70 eV) *m/z* (%): 357 (6.50) (M^+-H), 202 (100). Anal. Calcd for $C_{21}H_{14}N_2O_4$: C: 70.39, H: 3.94, N: 7.82. Found C: 70.03, H: 3.67, N: 7.75.

3-(2′-Amino-3′-cyano-4′-arylpyran-6′-yl)coumarin derivatives (4a,b).

General procedure: a mixture of compounds **1a,b** (10 mmol), malononitrile (0.66 g, 10 mmol) and piperidine (0.2 mL) was fused in oil bath for 0.5 h then refluxed in absolute EtOH for 1 h. The reaction mixture was left to cool, poured over crushed ice acidified with HCl. The precipitated products were filtered off, washed with water, dried, and crystallized from the proper solvent to afford the pure product.

3-(2′-Amino-3′-cyano-4′-(4-hydroxy-3-methoxyphenyl)pyran-6′-yl)coumarin (4a): crystallized from toluene as red crystals in 78% yield: mp 268-270 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.72 (s, 3H, OCH_3), 3.94 (d, *J* = 6.2 Hz, 1H, pyran 4H), 4.61 (d, *J* = 6.4 Hz, 1H, pyran 5H), 5.62 (s, 1H, O*H*), 6.1-7.9 (m, 7H, Ar-H), 8.50 (s, 2H, NH_2), 8.68 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 34.10, 56.38, 62.64, 112.47, 113.00, 115.66, 117.32, 119.75, 120.25, 122.45, 124.20, 127.21, 127.74, 129.13, 130.03, 132.35, 132.41, 147.37, 147.43, 153.18, 156.09, 162.79; IR (KBr) *v*: 3546, 3342, 3225, 3043, 2920, 2212, 1722 cm^{-1}; MS (70 eV) *m/z* (%): 388 (M^+, 25.20), 51 (100). Anal. Calcd for $C_{22}H_{16}N_2O_5$: C: 68.04, H: 4.15, N: 7.21. Found C: 68.46, H: 4.29, N: 7.35.

3-(2′-Amino-3′-cyano-4′-(fur-2-yl)pyran-6′-yl)coumarin (4b): crystallized from EtOH as yellow crystals in 83% yield: mp 300-302 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.94 (d, *J* = 6.2 Hz, 1H, pyran 4H), 4.61 (d, *J* = 6.2 Hz, 1H, pyran 5H), 6.1-7.9 (m, 7H, Ar-H), 8.50 (s, 2H, NH_2), 8.68 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 40.76, 68.72, 110.96, 113.15, 117.30, 119.75, 120.82, 122.45, 124.23, 127.74, 129.12, 130.23, 130.93, 131.17, 140.76, 149.90, 152.81, 154.10, 162.79; IR (KBr) *v*: 3340, 3227, 3055, 2210, 1721 cm^{-1}; MS (70 eV) *m/z* (%): 331 (26.61) (M^+-H), 40 (100). Anal. Calcd for $C_{19}H_{12}N_2O_4$: C: 68.67, H: 4.64, N: 8.43. Found C: 68.46, H: 4.39, N: 8.35.

5-(Fur-2-yl-)-3-(2-oxo-2*H*-chromen-3-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (5). A mixture of **1b** (2.66 g, 10 mmol) and thiosemicarbazide (0.91 g, 10 mmol) was refluxed in absolute EtOH containing drops of piperidine for 10 h. The reaction mixture was left to cool, then poured over crushed ice acidified with conc. HCl, filtered, washed with water, dried and crystallized from toluene as brown crystals in 77% yield, mp 188-190 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.32 (d, *J* = 5 Hz, 2H, CH_2 of pyrazole), 3.78 (t, *J* = 4.7 Hz, 1H, CH of pyrazole), 6.44-7.86 (m, 7H, Ar H), 8.65 (s, 1H, coumarin 4-H), 11.15 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 34.65, 69.91, 94.02, 110.72, 110.96, 117.32, 119.98, 122.83, 124.25, 129.15, 130.22, 140.74, 149.38, 154.12, 160.17, 161.45, 177.81; IR (KBr) *v*: 3438, 3249, 3068, 2936, 1724, 1614, 1252 cm^{-1}; MS (70 eV) *m/z* (%): 340 (1.13) (M^++H), 239 (100). Anal. Calcd for $C_{17}H_{13}N_3O_3S$: C: 60.17, H: 3.86, N: 12.38, S: 9.45. Found C: 60.29, H: 3.57, N:

12.14, S: 9.65.

4-(Fur-2-yl)-2-oxo-6-(2-oxo-2*H*-chromen-3-yl)-1,2-dihydropyridine-3-carbonitrile (6). A mixture of **1b** (2.66 g, 10 mmol) and cyanoacetamide (0.84 g, 10 mmol) with drops of piperidine was fused in oil bath for about 1 h, then refluxed in absolute EtOH for 3 h. The reaction mixture was left to cool, then poured over crushed ice acidified with conc. HCl, filtered, washed with water, dried, and crystallized from Et_2O as brown crystals in 73% yield: mp 168-170 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.97(s, 1H, pyridine H-5), 6.88-8.22 (m, 7H, ArH), 8.67 (s, 1H, coumarin 4-H), 11.85 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 94.25, 111.21, 112.60, 117.32, 119.18, 119.75, 122.52, 123.26, 124.22, 126.50, 129.12, 130.05, 130.13, 141.37, 144.04, 153.19, 154.74, 162.75, 164.17; IR (KBr) *v*: 3127, 3094, 2945, 2221, 1719, 1684 cm^{-1}; MS (70 eV) *m/z* (%): 328 (17.09) (M^+-2H), 63 (100). Anal. Calcd for $C_{19}H_{10}N_2O_4$: C: 69.09, H: 3.05, N: 8.48. Found C: 69.29, H: 3.37, N: 8.24.

4-(Fur-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)pyridin-2(1*H*)-one (7). A mixture of compound **1b** (2.66 g, 10 mmol), ethyl cyanoacetate (1.13 g, 10 mmol), excess of ammonium acetate (3 g, 40 mmol) in absolute EtOH was refluxed for 6 h. The reaction mixture was left to cool then pored over crushed ice, the formed precipitate was filtered, washed several times with water and crystallized from EtOH as yellow crystals in 67% yield: mp 255-257 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 5.79 (s, 1H, pyridine H-5), 5.86 (s, 1H, pyridine H-3), 6.84-8.14 (m, 7H, ArH), 8.68 (s, 1H, coumarin 4-H), 11.78 (s, H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 108.57, 112.60, 116.36, 117.30, 118.44, 119.75, 122.16, 122.52, 124.24, 129.13, 130.13, 130.21, 144.04, 144.14, 154.11, 154.60, 164.13, 164.79; IR (KBr) *v*: 3210, 3048, 2982, 1716, 1681 cm^{-1}; MS (70 eV) *m/z* (%): 305 (M^+, 18.76), 43 (100). Anal. Calcd for $C_{18}H_{11}NO_4$: C: 70.82, H: 3.63, N: 4.59. Found C: 70.53, H: 3.47, N: 7.75.

2-Methoxy-4-(2-methyl-4-oxo-7-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyrido[2,3-*d*][1,3]oxazin-5-yl)phenyl acetate (8). A solution of compound **2a** (3.85 g, 10 mmol) in acetic anhydride (10 mL) was heated under reflux for 5 h, the reaction mixture was cooled and poured over crushed ice, the formed precipitate was filtered off, washed with water dried and crystallized from EtOH as red crystals in 79% yield: mp 230-231 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.32 (s, 3H, CH_3), 2.59 (s, 3H, OCOCH_3), 3.87 (s, 3H, OCH_3), 7.05-7.85 (m, 8H, ArH), 8.69 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 20.59, 21.95, 21.95, 112.03, 113.97, 117.51, 117.93, 119.73, 124.22, 128.65, 129.11, 130.23, 138.98, 141.57, 143.85, 153.17, 158.21, 159.38, 160.32, 162.35, 163.78; IR (KBr) *v*: 3032, 2920, 1763, 1736, 1700, 1605 cm^{-1}; MS (70 eV) *m/z* (%): 458 (30.80) (M^+-12), 77 (100). Anal. Calcd for $C_{26}H_{18}N_2O_7$: C: 66.38, H: 3.86, N: 5.95. Found C: 66.03, H: 3.67, N: 5.75.

4-(2-Acetamido-3-cyano-6-(2-oxo-2*H*-chromen-3-yl)pyridin-4-yl)-2-methoxyphenyl acetate (9). A mixture of compound **2a** (3.85 g, 10 mmol), acetyl chloride (0.466 mL, 20 mmol) and TEA (2.78 mL, 20 mmol) in dioxane (20 mL) was heated under reflux for 4 h, the reaction mixture was cooled and poured

over crushed ice, the precipitate formed was filtered off, washed with water, dried, and crystallized from EtOH as red crystals in 82% yield: mp 188-190 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 2.29 (s, 3H, OCOC*H*$_3$), 3.75 (s, 3H, OCOC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 7.21-7.86 (m, 8H, ArH), 8.48 (s, 1H, coumarin 4-H), 10.48 (s, 1H, N*H*); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 20.89, 23.80, 56.31, 106.06, 111.02, 114.94, 115.31, 117.31, 119.97, 120.87, 121.35, 124.25, 128.43, 129.13, 130.22, 137.25, 142.85, 143.89, 149.92, 152.87, 154.08, 154.46, 160.32, 160.43, 168.18, 169.07; IR (KBr) *v*: 3275, 3033, 2925, 2198, 1754, 1687, 1633 cm^{-1}; MS (70 eV) *m/z* (%): 469 (M$^+$, 22.45), 77 (100). Anal. Calcd for $C_{26}H_{19}N_3O_6$: C: 66.52, H: 4.08, N: 8.95. Found C: 66.33, H: 3.87, N: 8.79.

2-Methoxy-4-(2-methyl-4-oxo-7-(2-oxo-2*H*-chromen-3-yl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-5-yl)-phenyl acetate (10). A solution of compound **9** (2.34 g, 5 mmol) in pyridine (10 mL) was heated under reflux for 10 h, cooled, then poured over crushed ice acidified with HCl, the solid obtained was filtered, washed several times with water, dried, and firstly washed several times with hot toluene and crystallized from EtOH as brown crystals in 84% yield: mp > 360 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 2.28 (s, 3H, C*H*$_3$), 2.57 (s, 3H, OCOC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 7.05-7.85 (m, 8H, ArH), 8.69 (s, 1H, coumarin 4-H), 10.40 (s, 1H, N*H*); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 20.73, 20.89, 56.40, 111.98, 114.94, 117.34, 119.76, 120.87, 121.10, 121.35, 124.23, 128.65, 129.13, 130.26, 137.25, 142.85, 143.86, 146.14, 149.92, 154.11, 156.79, 157.22, 159.40, 160.45, 163.24, 169.98; IR (KBr) *v*: 3229, 3057, 2967, 2922, 1736, 1660, 1646, 1596 cm^{-1}; MS (70 eV) *m/z* (%): 469 (M$^+$, 0.71), 63 (100). Anal. Calcd for $C_{26}H_{19}N_3O_6$: C: 66.52, H: 4.08, N: 8.95. Found C: 66.33, H: 3.87, N: 8.79.

4-(2-(2-Chloroacetamido)-3-cyano-6-(2-oxo-2*H*-chromen-3-yl)pyridin-4-yl)-2-methoxyphenyl 2-chloroacetate (11). A mixture of compound **2a** (3.85 g, 10 mmol), chloroacetyl chloride (1.59 mL, 20 mmol) and TEA (2.78 mL, 20 mmol) in dioxane (30 mL) was heated under reflux for 4 h, the reaction mixture was cooled and poured over crushed ice, the formed precipitate was filtered off, washed with water, dried, and crystallized from EtOH as reddish brown crystals in 82% yield; mp > 360 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.83 (s, 3H, OC*H*$_3$), 4.27 (s, 2H, NHCOC*H*$_2$Cl), 4.39 (s, 2H, OCOC*H*$_2$Cl), 7.24-7.94 (m, 8H, ArH), 8.69 (s, 1H, coumarin 4-H), 10.40 (s, 1H, N*H*); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 40.77, 41.74, 56.38, 105.96, 111.01, 114.76, 115.30, 117.30, 119.77, 120.61, 120.81, 124.24, 128.43, 129.12, 130.23, 136.70, 143.04, 143.85, 149.61, 152.99, 154.10, 154.29, 160.43, 160.66, 167.22, 168.73; IR (KBr) *v*: 3205, 3066, 2929, 2199, 1752, 1712, 1646, 1574 cm^{-1}; MS (70 eV) *m/z* (%): 538 (M$^+$, 1.95), 56 (100). Anal. Calcd for $C_{26}H_{17}N_3O_6Cl_2$: C: 58.01, H: 3.18, Cl: 13.17, N: 7.81. Found C: 58.23, H: 3.27, Cl: 13.28, N: 7.79.

3-(4-Amino-5-(4-hydroxy-3-methoxyphenyl)pyrido[2,3-*d*]pyrimidin-7-yl)-2*H*-chromen-2-one (12). A mixture of compound **2a** (3.85 g,10 mmol), formamide (10 mL), DMF (5 mL) and formic acid (2 mL) was heated under reflux for 4 h, cooled, poured over crushed ice acidified with conc. HCl, the formed

precipitate was filtered off, washed several times with water, dried and crystallized from EtOH as dark red crystals in 79% yield, mp > 360 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.85 (s, 3H, OC*H*$_3$), 5.36 (s, 1H, O*H*), 7.14-7.86 (m, 8H, ArH), 8.34 (s, 1H, CH of pyrimidine), 8.68 (s, 1H, coumarin 4-H), 7.65 (s, 2H, N*H*$_2$); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 56.34, 105.55, 112.40, 115.46, 117.32, 118.54, 119.97, 122.03, 124.23, 126.98, 129.15, 130.03, 130.07, 144.80, 145.51, 147.66, 149.32, 154.09, 156.86, 157.48, 160.42, 161.18, 164.52; IR (KBr) *v*: 3256, 3147, 3068, 2947, 1736, 1715, 1616 cm^{-1}; MS (70 eV) *m/z* (%): 412 (M$^+$, 11.45), 63 (100). Anal. Calcd for $C_{23}H_{16}N_4O_4$: C: 66.99, H: 3.91, N: 13.59. Found C: 66.39, H: 3.99, N: 13.65.

5-(4-Hydroxy-3-methoxyphenyl)-7-(2-oxo-2*H*-chromen-3-yl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (13).

Method A: a mixture of compound **2a** (3.85 g, 10 mmol) and formic acid was refluxed overnight, cooled, poured over crushed ice. The formed precipitate was collected by filtration, dried, and crystallized from EtOH as red precipitate in 67% yield.

Method B: a mixture of compound **14** (2.0 g, 5 mmol) and formic acid was refluxed for 8 h, cooled, poured over crushed ice. The formed precipitate was collected by filtration, dried, and crystallized from EtOH as red precipitate in 86% yield; mp > 360 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.86 (s, 3H, OC*H*$_3$), 5.37 (s, 1H, O*H*), 7.05-7.87 (m, 8H, ArH), 8.36 (s, 1H, CH of pyrimidine), 8.69 (s, 1H, coumarin 4-H), 10.45 (s, 1H, N*H*); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 56.40, 110.97, 110.97, 115.07, 117.33, 119.98, 121.12, 121.21, 124.23, 128.73, 128.62, 129.13, 130.05, 143.83, 145.23, 146.55, 148.32, 150.64, 153.18, 158.23, 159.21, 160.45, 162.92; IR (KBr) *v*: 3308, 3068, 2897, 1731, 1696, 1644 cm^{-1}; MS (70 eV) *m/z* (%): 409 (60.0) (M$^+$-4), 64 (100). Anal. Calcd for $C_{23}H_{15}N_3O_5$; C: 66.83, H: 3.66, N: 10.16. Found C: 66.39, H: 3.57, N: 10.25.

2-Amino-4-(4-hydroxy-3-methoxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)nicotinamide (14).

Concentrated sulphuric acid (30 mL) was cooled to 20 ºC and compound **2a** (3.85 g, 10 mmol) was added with stirring so that the temperature did not rise above 30 ºC, the addition of **2a** took 0.5 h the solution was stirred at room temperature for 4 h, the sulphuric acid solution was then poured with stirring into a mixture of 200 mL of water and ice, the solution left overnight in the refrigerator. The product was precipitated, collected by filtration, washed several times with water, dried, and crystallized from EtOH/ MeCN mixture as a brown crystals in 63% yield: mp > 360 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.85 (s, 3H, OC*H*$_3$), 5.36 (s, 1H, O*H*), 7.05-7.87 (m, 8H, ArH), 8.69 (s, 1H, coumarin 4-H), 7.50 (s, 2H, N*H*$_2$), 10.58 (s, 2H, N*H*$_2$CO); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 106.41, 111.88, 117.32, 119.77, 124.23, 127.73, 129.15, 130.24, 137.51, 147.29, 154.10, 154.49, 161.79, 160.43, 168.07; IR (KBr) *v*: 3539, 3425, 3360, 3246, 3171, 3066, 2933, 1724, 1660, 1592 cm^{-1}; MS (70 eV) *m/z* (%): 403 (M$^+$, 7.35), 63 (100). Anal. Calcd for $C_{22}H_{17}N_3O_5$; C: 65.50, H: 4.25, N: 10.42. Found C: 65.38, H: 4.57, N: 10.31.

ANTIMICROBIAL ACTIVITY ASSAY

The antimicrobial activity of each compound under investigation was evaluated against two Gram-positive bacterial strains (*Basillus subtilis* and *Streptococci*) and two Gram-negative bacterial strains (*Klebsiella pneumoniae* and *Escherichia coli*) by disc diffusion method utilizing sterile whatman-No5 filter paper discs (11 mm diameter). Each compound was dissolved in ethanol. Filter paper discs (11 mm) were loaded with 10 mg/mL of the tested material (50 µL) then left with care under hot air to complete dryness.

Test plates were prepared by pouring 10 mL Muller-Hinton agar medium seeded with the test organism. The discs were deposited on the surface of agar plates. The discs were incubated at 5 ºC for 1 h to permit good diffusion. All the plates were then incubated for 24 h at 37 ºC.

After incubation, the microorganism's growth was recorded. The plates were done in triplicate and the average inhibition zone diameters were calculated in millimeters and used as criterion for the antimicrobial activity. The inhibitory action of the tested compound is proportional to the size of the clear zone observed. Solvent disc control was included in every experiment as negative control. Ampicillin (standard drug) was also screened for antibacterial activity under similar conditions, for comparison.

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