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A FACILE SYNTHESIS OF NOVEL HETEROCYCLIC COMPOUNDS WITH ANTICIPATED ANTIBACTERIAL ACTIVITIES BASED ON COUMARIN MOIETY

Asmaa Kamal Mourad,* Fathia Korany Mohamed, and Ahmed Yousef Soliman

Department of Chemistry, Faculty of Science, Fayoum University, 63514 Fayoum, Egypt; E-mail: akk00@fayoum.edu.eg

Abstract – A novel series of coumarin derivatives has been disclosed by allowing 2-aminonicotinonitrile derivative **1** to undergo alkylation, diazotization, and condensation reactions. Moreover, different reagents, such as thiourea, phenyl isothiocyanate, carbon disulfide, ethylenediamine, and hydroxylamine hydrochloride, have been exploited to synthesize more coumarin derivatives, aiming to increase the synthetic potential of coumarin and study the antibacterial activities of the newly synthesized compounds.

INTRODUCTION

Coumarins (2*H*-1-benzopyran-2-one) comprise an enormous array of phenolic compounds found in plants and are made of fused benzene and α-pyrone rings. Coumarins owe their name to 'Coumarou' which is the colloquial name of Tonka bean (*Dipteryx odorata*), from which coumarin was separated in 1820.[1] Both natural and synthetic coumarins possess a broad range of biological activities.[2-5] Naturally occurring coumarins have been used in medicine as an anticoagulant, cosmetic products like perfumes as an enhancing agent, and in rubber as a neutralizer.[6,7] Coumarins exhibit significant pharmacological properties such as antibacterial,[8-10] antifungal,[11,12] antioxidant,[13,14] anticancer,[15-17] anti-HIV,[18] anticoagulant,[19] antiarthritic,[20,21] anti-inflammatory,[22,23] anti-HCV,[24] and antiviral.[25] Coumarin derivatives are also used as additives in optical brighteners,[26] dispersed fluorescent and laser dyes.[27-29]

Various coumarin derivatives can be utilized as efficient scaffolds for constructing valuable heterocyclic ring systems. As a part of our ongoing endeavor to synthesize novel heterocyclic rings through simple and straightforward convenient routes,[30-32] we have explored the use of coumarin derivative **1** to construct some new polyfunctional fused pyridine, thiazine, and imidazolinyl derivatives.

RESULTS AND DISCUSSION

In a continuation of our earlier investigation of 3-pyridylcoumarin derivative **1** reactivity towards *C*-nucleophiles,[32] we have succeeded in constructing various heterocyclic rings bearing different valuable function groups fused to the pyridine moiety in compound **1** through simple and direct reactions.

The synthetic strategy for building up pyrrole nucleus fused to pyridine moiety in compound **1** based on its alkylation with α-haloacetic acid derivatives (chloroacetonitrile and ethyl bromoacetate), then cyclization of the alkylation product in basic medium. The alkylation was achieved in dry acetone containing anhydrous potassium carbonate. As compound **1** contains both amino and hydroxyl groups and they are both susceptible to alkylation under the proposed conditions, this might result in a mixture of products. Actually no alkylation noticed on hydroxyl group and the *N*-alkylation products **2** and **3** were the sole products obtained. The IR spectrum of compound **2** showed the appearance of nitrile absorption band at 2215 cm^{-1} and the presence of hydroxyl group indicated from the absorption band at 3569 cm^{-1}. Furthermore, the IR spectrum of compound **3** showed the disappearance of nitrile absorption band and the presence of hydroxyl group indicated from the absorption band at 3556 cm^{-1}. Also, it showed the appearance of new peak at 1742 cm^{-1} characteristic for the ester carbonyl group. The ^1H NMR data of later compound displayed a triplet-quartet pattern for the ethoxy group at 1.31 and 4.31 ppm, and displayed broad band at 5.37 ppm confirmed that no alkylation takes place on hydroxyl group. The mass spectrum exhibited a molecular ion peak at *m/z* = 471 in accordance with the molecular formula $C_{26}H_{21}N_3O_6$.

A convenient approach for the synthesis of polyfunctional fused pyridine was achieved by refluxing compound **1** with diethyl malonate in glacial acetic acid in the presence of excess ammonium acetate to furnish ethyl 4-amino-5-(4-hydroxy-3-methoxyphenyl)-2-oxo-7-(2-oxo-2*H*-chromen-3-yl)-1,2-dihydro-1,8-naphthyridine-3-carboxylate **4**, its IR spectrum showed the disappearance of nitrile absorption band and the presence of carbonyl (cyclic amide) indicated from the absorption band at 1676 cm^{-1}, and carbonyl of ester at 1736 cm^{-1}. The ^1H NMR data displayed a triplet-quartet pattern for the ethoxy group at 1.34 and 4.36 ppm, furthermore two resonances at 5.37 and 10.21 ppm, confirming the existence of two exchangeable protons (OH and NH). The mass spectrum exhibited a molecular ion peak at *m/z* = 500 in accordance with (M+1). Additionally, for the synthesis of more fused polyfunctional pyridine, compound **1** was heated with ethyl cyanoacetate and excess of ammonium acetate in glacial acetic acid to afford compound **5** instead of **5a**, which might be formed *via* the hydrolysis of the cyano group followed by its decarboxylation due to the presence of acetic acid. Examination of the reaction product spectra excluded structure **5a**. In the IR spectrum no absorption bands were observed in the region corresponding to nitrile group, also it showed a strong absorption band at 1671 cm^{-1} corresponding to amide carbonyl group. The ^1H NMR spectrum of the compound showed a singlet peak at 5.25 ppm due to resonance of 3-*H* of 2-pyridone nucleus. The mass spectrum of compound **5** revealed an ion peak at *m/z* = 429 equivalent to (M+2).

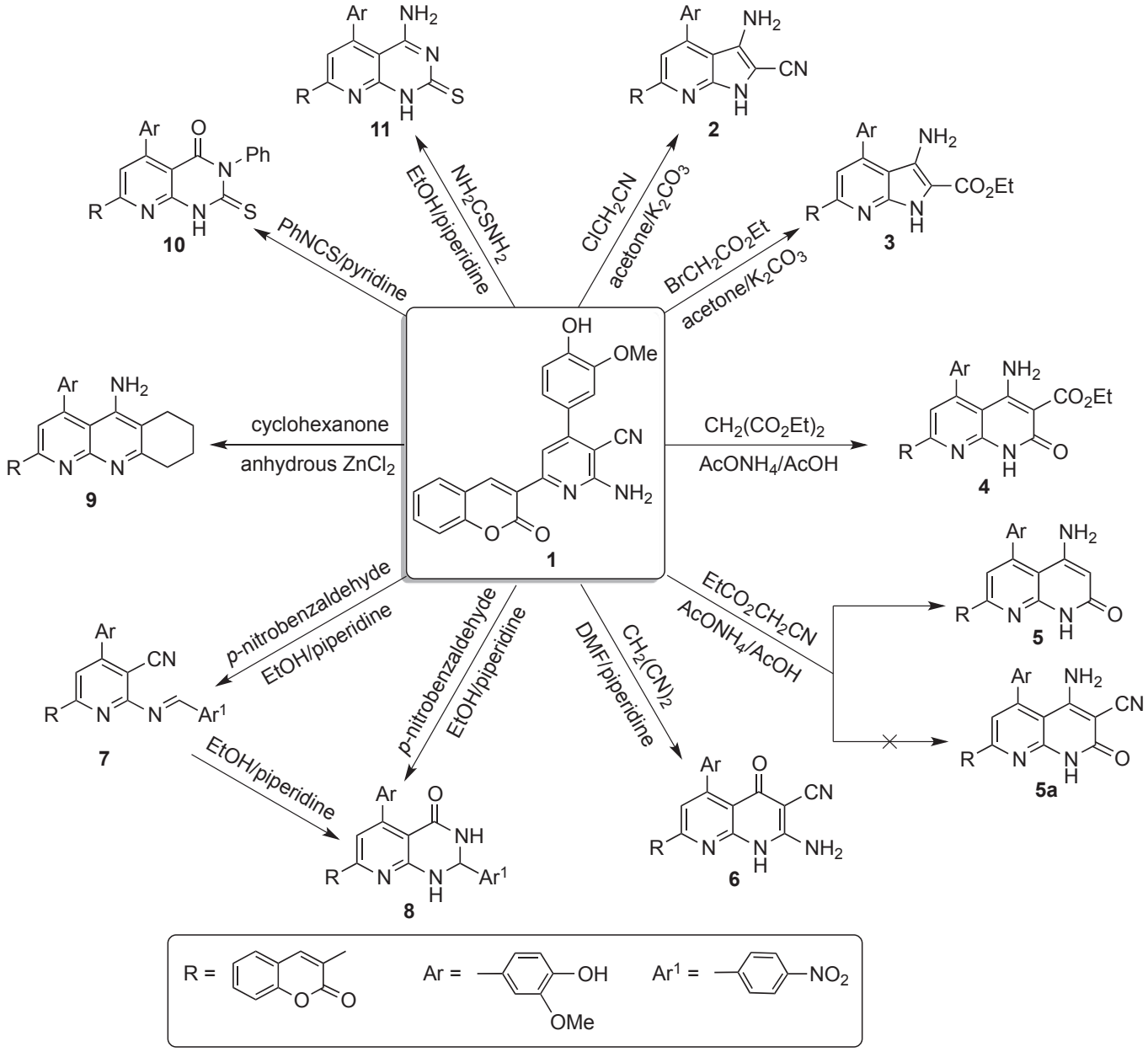
A new synthetic approach for 2-amino-5-(4-hydroxy-3-methoxyphenyl)-4-oxo-7-(2-oxo-2*H*-chromen-3-yl)-1,4-dihydro-1,8-naphthyridine-3-carbonitrile **6** was achieved through the interaction between compound **1** and malononitrile. The IR spectrum showed a strong absorption band at 1666 cm^{-1} corresponds to new carbonyl group. Also exhibited absorption bands at 3488, 3386, 3337 and 3191 cm^{-1} correspond to stretching vibration of OH, NH_2 and NH. The ^1H NMR spectrum of the compound revealed a marked change in the chemical shifts from the starting material. Moreover, the mass spectrum exhibited a molecular ion peak at *m/z* = 452 equivalent to molecular formula $C_{25}H_{16}N_4O_5$.

Fusion of compound **1** with *p*-nitrobenzaldehyde and few drops of piperidine for 1.5 h afforded compound **8** instead of compound **7**. However, Schiff's base **7** was accessible by the reflux of **1** with *p*-nitrobenzaldehyde in ethanol containing few drops of piperidine for 4 h. The IR spectrum of Schiff's base **7** showed an absorption band at 2221 cm^{-1} due to nitrile group while its ^1H NMR spectrum showed a singlet peak at 8.73 ppm due to (N=C*H*). On the other hand, The IR spectrum of compound **8** showed the disappearance of nitrile absorption band and the presence of new carbonyl (cyclic amide) indicated from absorption band at 1651 cm^{-1}. Moreover, the IR spectrum of pyrimidinone **8** revealed strong absorption bands at 3434, 3377, and 3316 cm^{-1} due to OH and 2NH. The ^1H NMR spectrum of the compound **8** showed a singlet peak at 6.12 ppm due to (NHC*H*NH) and 9.45 ppm due to (N*H*CO). The mass spectrum exhibited a molecular ion peak at *m/z* = 534 equivalent to (M-2). Finally, the structure of pyrimidinone **8** was confirmed chemically; through its synthesis from the corresponding Schiff's base **7** *via* its fusion for 1 h in the presence of few drops of piperidine as a catalyst.

Furthermore, fused pyridine derivative **9** was accessible by the condensation between compound **1** and cyclohexanone in the presence of anhydrous zinc chloride as a Lewis acid. This reaction represents an important way for preparation of Tacrine analogues.[33] IR showed no absorption band for nitrile group. Further assistance for the proposed structure is gained from the mass spectrum which revealed a molecular ion peak at *m/z* = 463 equivalent to (M-2).

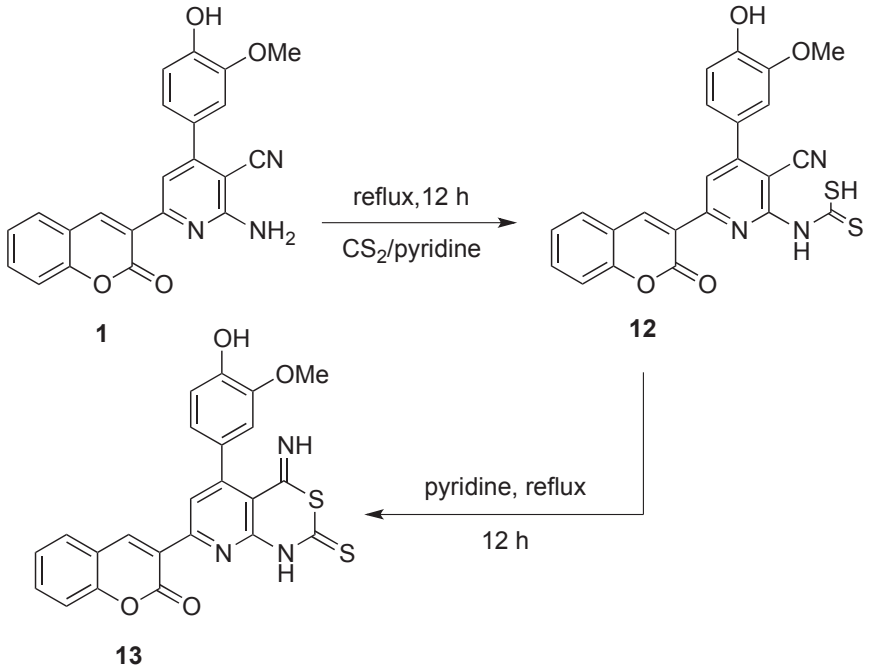
An additional synthetic pathway for more fused pyrimidines was accomplished through the interaction between compound **1** and phenyl isothiocyanate. The reaction was conducted in pyridine under reflux temperature to give the pyrimidinethione **10**. IR spectrum showed three absorption bands at 3532, 3413 and 3361 cm^{-1} corresponding to OH and NH functions, no absorption bands were observed in the region corresponding to the cyano group, it also showed absorption bands at 1673 and 1376 cm^{-1} corresponding to amide carbonyl and C=S respectively. The mass spectroscopy was in satisfactory agreement with the proposed structure, it showed a molecular ion peak at *m/z* = 520 equivalent to (M-1). In continuation of our trials to synthesize more fused pyrimidinethiones, compound **1** and thiourea was heated together under dry condition until fusion, followed by heating in methanol for few hours to afford compound **11**. The IR spectrum displayed the absorption frequencies of OH, NH_2 and NH groups at 3570, 3466, 3367 and 3189

cm^{-1} respectively. The mass spectrum revealed a molecular ion peak at *m/z* = 445 equivalent to (M+1).



Scheme 1

Also, compound **1** could be used for building up fused thiazine ring through its reaction with carbon disulfide in refluxing pyridine. At first the reaction was conducted for 12 h followed by finishing the reaction and examination of the reaction product through the spectra obtained. From the IR spectrum an absorption band at 2209 cm^{-1} suggesting that it still contains the nitrile group, therefore no cyclization was achieved. We wished to get the cyclic compound **13**; hence the isolable intermediate **12** was further refluxed in dry pyridine for additional 12 h.



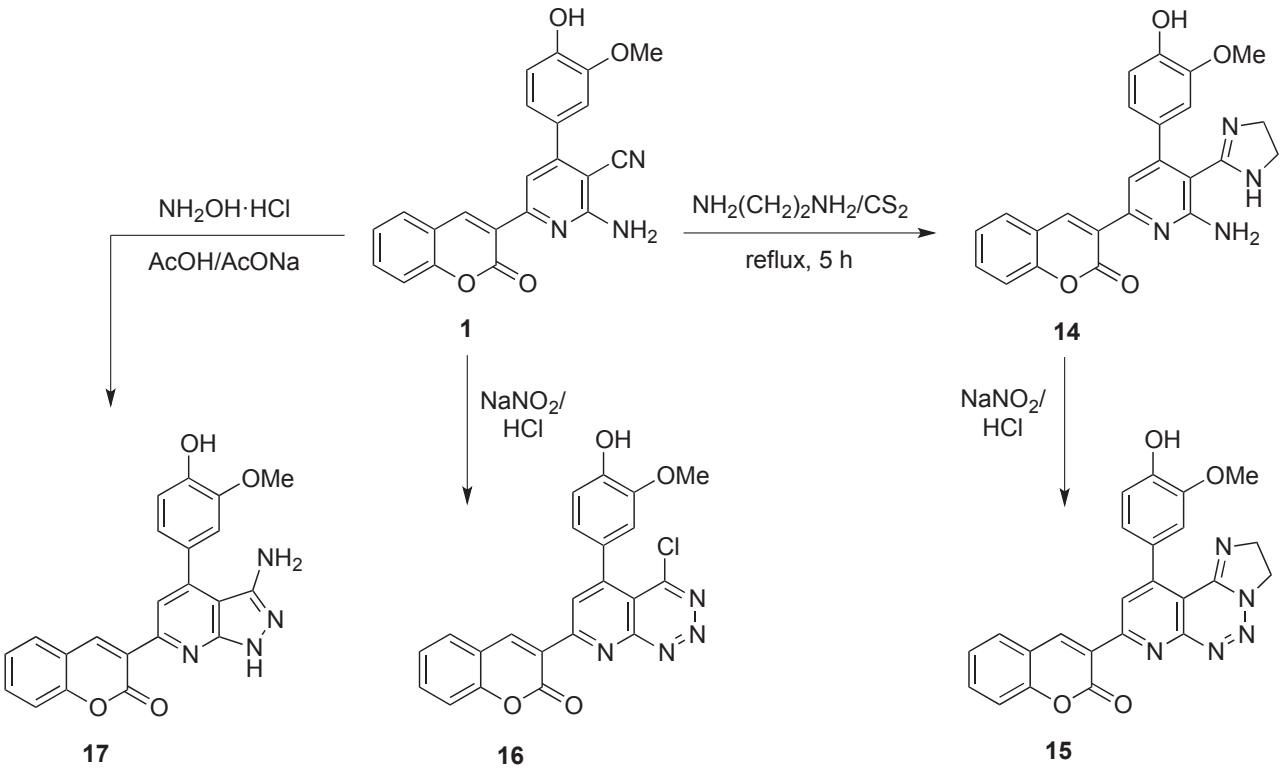
1 **12** **13**

Scheme 2

Previous work has demonstrated the straight conversion of cyano function of *o*-aminonitrile into the corresponding 4,5-dihydro-1*H*-imidazol-2-yl group through the reaction of aminonitrile and ethylenediamine in the presence of carbon disulfide or phosphorus pentasulfide.[30,34] Accordingly, 3-(6-amino-5-(4,5-dihydro-1*H*-imidazol-2-yl)-4-(4-hydroxy-3-methoxyphenyl)pyridin-2-yl)-2*H*-chromen-2-one **14** could be obtained *via* refluxing compound **1** with ethylenediamine in the presence of a catalytic amount of carbon disulfide. Structure confirmation of the reaction product was gained from spectroscopic data and microanalysis, IR showed no absorption for nitrile group, another piece of evidence provided from the ^{1}H NMR spectrum which showed a triplet at 1.58 ppm integrating for two protons (C*H*$_2$N=C of imidazoline), a multiplet at 3.49 ppm (2H, C*H*$_2$ of imidazoline). Further assistance for the proposed structure was gained from the mass spectrum which showed a molecular ion peak at *m/z* = 426 equivalent to (M-2). The imidazolinyl derivative **14** could be used for the synthesis of the subsequent triazine derivative **15**.[35] Thus diazotization of compound **14** with sodium nitrite in acetic acid-HCl mixture afforded compound **15**. IR spectrum of **15** showed no absorption bands in the region 3100-3400 and hence no NH_2 or NH functions. Additionally from the ^{1}H NMR spectrum it was obvious that the resonance due to the NH and NH_2 function in the starting material had disappeared. The mass spectrum revealed a molecular ion peak at *m/z* = 439 in accordance with the molecular formula $C_{24}H_{17}N_5O_4$. While diazotization of compound **1** under ordinary condition afforded 3-(4-chloro-5-(4-hydroxy-3-methoxyphenyl)pyrido[2,3-*d*][1,2,3]-triazine-7-yl)-2*H*-chromen-2-one **16**. The IR spectrum of the compound **16** is devoid from absorption bands of amino and cyano groups. The mass spectrum showed the molecular ion peak at *m/z* = 433

equivalent to (M+1).

It was reported that 2-aminonicotinonitrile derivatives react with equimolar amount of hydroxylamine hydrochloride in glacial acetic acid to provide pyrazolopyridine derivative.[36] Thus, compound 3-(3-amino-4-(4-hydroxy-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-2*H*-chromen-2-one **17** was obtained *via* the reflux of compound **1** with hydroxylamine hydrochloride in glacial acetic acid containing a catalytic amount of anhydrous sodium acetate for 5 h. The IR spectrum of compound **17** was devoid from absorption band of the cyano group. Also, it showed three absorption bands for NH_2 and NH functions at, 3364, 3276, 3218 cm^{-1}. Another evidence for the proposed structure of compound **17** was gained from ^1H NMR spectrum which revealed D_2O exchangeable resonances at 7.66 and 9.32 ppm which are slightly broad attributable to NH_2 and NH, respectively. Also the mass spectrum displayed a peak at *m/z* = 399 in accordance with (M-1).



Scheme 3

ANTIMICROBIAL ASSAY

Coumarin containing antibiotics such as novobiocin, clorobiocin, and coumermycin A_1 have been of great interest due to its strong inhibition effect of bacterial DNA gyrase and topoisomerase.[37]

Moreover, coumarin (2*H*-1-benzopyran-2-one) revealed potent antibacterial activity against both bacterial strains used here and this probably attributed to its lipophilic nature and planar molecular structure.[38]

The antibacterial activity of compounds under investigation was assessed against *Streptococci* as a representative example of Gram-positive bacteria and *Escherichia coli* as a representative example of Gram-negative bacteria. Antibiotic ampicillin was utilized as a control criterion for *in vitro* antibacterial activity. Antibacterial activity was expressed as inhibition diameter zones in millimeters (mm) of newly synthesized compounds against the pathological strains as following in Table.

Table. *In vitro* antibacterial activity of compounds under investigation

Entry	Compound	Gram (+ve) bacteria		Gram (–ve) bacteria	
		Streptococci		*Escherichia coli*	
		I.Z.±S.D.*	% Activity index	I.Z.±S.D.*	% Activity index
1	**2**	NA[a)]	-	NA	-
2	**3**	4±0.29	17.4	7±0.50	29.2
3	**4**	8±0.50	34.8	14±0.29	58.3
4	**5**	NA	-	NA	-
5	**6**	NA	-	11±0.58	45.8
6	**8**	6±0.29	26.1	4±0.5	16.7
7	**9**	18±0.29	78.3	NA	-
8	**10**	20±0.76	87.0	9±0.29	37.5
9	**11**	17±0.29	73.9	6±0.76	25.5
10	**12**	NA	-	22±0.29	91.7
11	**13**	NA	-	12±0.29	50.5
12	**14**	NA	-	NA	-
13	**15**	3±0.29	13.0	NA	-
14	**16**	NA	-	NA	-
15	**17**	19±0.76	82.6	16±0.87	66.7
16	**Ampicillin**	23	100	24	100

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

Compounds under investigation showed variation in their antibacterial activities (Table). Compounds **2**, **5**, **14**, and **16** exhibited no biological activity against the tested Gram-positive and Gram-negative bacteria (Table; entries 1, 4, 12, 14, respectively). In the same context, compounds **6**, **12**, and **13** were biologically inactive against Gram-positive bacteria only (Table; entries 5, 10, 11, respectively) whilst compounds **9** and

15 showed no activity only against Gram-negative bacteria (Table; entries 7 and 13, respectively). Moreover, compounds **9-11** and **17** showed strong biological activity against Gram-positive bacteria, namely *Streptococci*, however their activities against Gram-negative bacteria, namely *Escherichia coli*, varied from no activity to moderate activity (Table; entries 7-9, 15, respectively). Finally, compound **12** revealed an execllent antibacterial activity against Gram-negative bacteria (Table; entry 10).

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

Structure-activity relationship studies (SAR) inferred that the substituents type and nature at 3-position of coumarin are significantly varying the antibacterial activity. Introducing the electron withdrawing esteric group in compounds **3** and **4** inhibited the bacterial growth in both Gram-positive and Gram-negative bacteria (Table; entries 2 and 3).

Also, SAR studies disclosed that coumarinyl pyridopyrimidine conjugates **8**, **10**, and **11** were biologically active against both Gram-negative and -positive bacterial strains but it was obvious that thion group at 2-position of pyrimidine moiety is playing a pivotal role in augmenting the biological activity (Table; entries 6, 8, and 9). Moreover, in comparison to the other coumarinyl pyridopyrimidine conjugates, compound **10** exhibited better results due to the presence of the carbonyl group at 4-position along with thion group at 2-position of pyrimidine ring (Table; entry 8).

Cyclization of compound **12** to construct a new thiazine ring in compound **13** decreased the antimicrobial activity remarkably. The presence of the electron withdrawing thiol group in compound **12** was indispensable to possess robust activity against *E. coli* (Table; entries 10 and 11).

Similarly, the amino substituent in the pyrazolyl ring of compound **17** was needed to have a strong inhibitory activity against both Gram-positive and Gram-negative bacteria (Table; entry 15).

CONCLUSION

In conclusion, we prepared a series of new coumarin derivatives utilizing nicotinonitrile derivatives. The *N*-alkylation of nicotinonitrile derivative **1** with α-haloacetic acid derivatives followed by subsequent cyclization gave rise to a new pyrrole nucleus fused to pyridine moiety in compound **1**. Moreover, reactions with phenyl isothiocyanate or thiourea led to construction of new pyrimidinethiones bearing various function groups, while an extra substituted pyrimidine ring was accessible by the reaction with aromatic aldehydes. In addition, heterocyclic compounds bearing coumarin moiety bind to imidazole, triazine, and pyrazole rings were successfully synthesized *via* straightforward simple reactions. On screening the synthesized compounds for antimicrobial activity, many compounds showed strong activities against Gram-positive bacteria (Table; entries 7-9, 15) while compound **12** revealed an excellent activity against Gram-negative bacteria (Table; entry 10). All the new compounds were 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).

3-Amino-4-(4-hydroxy-3-methoxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonitrile (2).

A mixture of compound **1** (3.85 g, 10 mmol), chloroacetonitrile (1.50 mL, 20 mmol) and anhydrous K_2CO_3 (1.37 g, 10 mmol) in dry acetone was refluxed with stirring for 10 h. The reaction mixture was cooled down and poured over crushed ice, the formed precipitate was filtered off, washed with water, dried, washed with hot EtOH, and crystallized from dioxane as reddish brown crystals in 78% yield: mp > 360 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.85 (s, 3H, OCH_3), 5.37 (s, 1H, O*H*), 7.03-7.88 (m, 8H, ArH), 8.69 (s, 1H, coumarin4-H), 9.10 (s, 2H, NH_2), 10.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.38, 104.98, 109.14, 110.22, 112.80, 113.56, 115.34, 118.80, 119.98, 120.89, 124.50, 128.35, 128.80, 128.90, 129.50, 132.82, 140.20, 143.85, 147.50, 149.94, 154.10, 154.29, 159.81, 160.53; IR (KBr) *υ*: 3569, 3450, 3378, 3212, 3110, 3056, 2918, 2215, 1712, 1625 cm^{-1}; MS (70 eV) *m/z* (%): 424 (M$^+$, 27.03), 45 (100). Anal. Calcd for $C_{24}H_{16}N_4O_4$: C: 67.92, H: 3.80, N: 13.20. Found: C: 67.81, H: 3.67, N: 13.32.

Ethyl 3-amino-4-(4-hydroxy-3-methoxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)-1*H*-pyrrolo[2,3-*b*]-pyridine-2-carboxylate (3).

A mixture of compound **1** (3.85 g, 10 mmol), ethyl bromoacetate (2.21 mL, 20 mmol) and anhydrous K_2CO_3 (1.37 g, 10 mmol) in dry acetone was refluxed with stirring for 10 h. The reaction mixture was left overnight then poured over crushed ice. The formed precipitate was filtered off, washed with water, dried, washed with hot EtOH, and crystallized from dioxane as reddish brown crystals in 70% yield: mp 268-270 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.31 (t, J = 6.2 Hz, 3H, CH_3CH$_2$), 3.85 (s, 3H, OCH_3), 4.31 (q, J = 6.2 Hz, 2H, CH$_2$CH_3), 5.37 (s, 1H, O*H*), 7.03-7.88 (m, 8H, ArH), 8.69 (s, 1H, coumarin 4-H), 9.10 (s, 2H, NH_2), 10.12 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 14.89, 56.38, 61.50, 103.22, 104.58, 111.01, 112.48, 115.33, 118.77, 119.90, 120.87, 124.45, 128.81, 128.90, 129.50, 129.77, 132.80, 140.55,

143.85, 147.55, 149.90, 154.11, 155.45, 160.43, 160.68, 166.79 ; IR (KBr) *v*: 3556, 3465, 3417, 3220, 3209, 3065, 2920, 1742, 1722, 1653 cm^{-1}; MS (70 eV) *m/z* (%): 471 (M^+, 9.92), 45 (100). Anal. Calcd for $C_{26}H_{21}N_3O_6$: C: 66.24, H: 4.49, N: 8.91. Found: C: 66.35, H: 3.38, N: 8.78.

Ethyl 4-amino-5-(4-hydroxy-3-methoxyphenyl)-2-oxo-7-(2-oxo-2*H*-chromen-3-yl)-1,2-dihydro-1,8-naphthyridine-3-carboxylate (4).

A mixture of compound **1** (3.85 g, 10 mmol), diethyl malonate (1.52 mL, 10 mmol), ammonium acetate (6 g, 80 mmol) and glacial AcOH (1.2 mL) was heated under reflux for 2 h then cooled and poured over crushed ice. The formed solid was collected by filtration and crystallized from aqueous EtOH as yellow crystals in 85% yield: mp 198-200 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.34 (t, *J* = 6.4 Hz, 3H, C*H*$_3$CH$_2$), 2.12 (s, 2H, N*H*$_2$), 3.84 (s, 3H, OC*H*$_3$), 4.36 (q, *J* = 6.4 Hz, 2H, C*H*$_2$CH$_3$), 5.37 (s, 1H, O*H*), 6.87-7.85 (m, 7H, ArH), 7.86 (s, 1H, pyridine H-5), 8.69 (s, 1H, coumarin 4-H), 10.21 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 14.89, 56.40, 61.50, 91.60, 108.79, 110.24, 112.59, 115.33, 118.50, 119.98, 120.89, 124.45, 128.80, 128.90, 129.50, 132.80, 145.74, 143.87, 147.65, 149.91, 151.80, 154.09, 155.94, 158.42, 160.53, 163.75, 169.70; IR (KBr) *v*: 3504, 3437, 3384, 3256, 3193, 3095, 2978, 1736, 1715, 1676 cm^{-1}; MS (70 eV) *m/z* (%): 500 (1.23) (M^++H), 63 (100). Anal. Calcd for $C_{27}H_{21}N_3O_7$: C: 64.93, H: 4.24, N: 8.41. Found: C: 64.77, H: 4.38, N: 8.76.

4-Amino-5-(4-hydroxy-3-methoxyphenyl)-7-(2-oxo-2*H*-chromen-3-yl)-1,8-naphthyridin-2(1*H*)-one (5).

A mixture of compound **1** (3.85 g, 10 mmol), ethyl cyanoacetate (1.06 mL, 10 mmol), ammonium acetate (6 g, 80 mmol), and glacial AcOH (1.2 mL) was heated under reflux for 2 h then cooled and poured over crushed ice. The formed solid was collected by filtration and recrystallized from EtOH as yellow crystals in 71% yield: mp 258-260 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.12 (s, 2H, N*H*$_2$), 3.83 (s, 3H, OC*H*$_3$), 5.25 (s, 1H, pyridinone C-3), 5.33 (s, 1H, OH), 6.89-7.85 (m, 8H, ArH), 8.69 (s, 1H, coumarin 4-H), 10.45 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.38, 101.30, 109.40, 111.07, 110.22, 115.35, 118.74, 119.96, 120.89, 124.43, 128.81, 128.89, 129.50, 132.81, 143.80, 143.78, 147.55, 149.90, 151.37, 154.13, 154.66, 156.31, 160.50, 161.25; IR (KBr) *v*: 3455, 3364, 3226, 3183, 3026, 2884, 1721, 1671 cm^{-1}; MS (70 eV) *m/z* (%): 429 (0.53) (M^++2H), 63 (100). Anal. Calcd for $C_{24}H_{17}N_3O_5$: C: 67.44, H: 4.01, N: 9.83. Found: C: 67.57, H: 4.18, N: 9.76.

2-Amino-5-(4-hydroxy-3-methoxyphenyl)-4-oxo-7-(2-oxo-2*H*-chromen-3-yl)-1,4-dihydro-1,8-naphthyridine-3-carbonitrile (6).

To a mixture of compound **1** (3.85 g, 10 mmol) and malononitrile (0.66 g, 10 mmol) in DMF, a few drops of piperidine was added and the resulting mixture was refluxed for 12 h, the mixture was allowed to cool down to room temperature, poured over crushed ice acidified with HCl, the formed precipitate was collected by filtration, dried, and recrystallized from toluene as dark red crystals in 75% yield: mp 318-320 ºC; ^{1}H NMR

(DMSO-d_6, 300 MHz, ppm) δ: 3.88 (s, 3H, OCH_3), 5.26 (s, 1H, N*H*), 5.66 (s, 1H, O*H*), 6.89-7.85 (m, 8H, ArH), 8.68 (s, 1H, coumarin 4-H), 10.44 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.38, 76.86, 107.86, 111.03, 114.55, 115.35, 118.68, 119.96, 120.89, 121.70, 124.45, 128.81, 128.89, 129.51, 132.80, 143.78, 147.50, 149.93, 153.11, 154.12, 154.57, 157.43, 160.53, 168.32, 173.68; IR (KBr) *v*: 3488, 3386, 3337, 3191, 3091, 2984, 2193, 1715, 1666 cm^{-1}; MS (70 eV) *m/z* (%): 452 (M^+, 3.51), 451 (4.77), 63 (100). Anal. Calcd for $C_{25}H_{16}N_4O_5$: C: 66.37, H: 3.56, N: 12.38. Found: C: 66.42, H: 3.48, N: 12.26.

4-(4-Hydroxy-3-methoxyphenyl)-2-(4-nitrobenzylideneamino)-6-(2-oxo-2*H*-chromen-3-yl)-nicotinonitrile (7).

A mixture of compound **1** (3.85 g, 10 mmol) and *p*-nitrobenzaldehyde (1.51 g, 10 mmol) was refluxed in EtOH containing few drops of piperidine for 4 h. The mixture was allowed to cool down to room temperature, poured over crushed ice acidified with HCl, the formed precipitate was collected by filtration, dried, and recrystallized from EtOH as yellow crystals in 79%: mp 200-202 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.84 (s, 3H, OCH_3), 5.66 (s, 1H, O*H*), 6.89-7.85 (m, 12H, ArH), 8.68 (s, 1H, coumarin 4-H), 8.73 (s, 1H, N=C*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.34, 107.97, 111.30, 111.65, 114.71, 115.35, 118.80, 119.98, 120.90, 124.60, 124.60, 124.60, 128.80, 128.90, 129.53, 131.49, 131.49, 132.81, 139.97, 143.83, 147.63, 149.91, 149.57, 151.75, 151.90, 154.11, 157.01, 160.23, 160.55; IR (KBr) *v*: 3434, 3052, 2946, 2221, 1714, 1590 cm^{-1}; MS (70 eV) *m/z* (%): 518 (16.21) (M^+-2H), 124 (100). Anal. Calcd for $C_{29}H_{18}N_4O_6$: C: 67.18, H: 3.50, N: 10.81. Found: C: 67.05, H: 3.38, N: 10.66.

5-(4-Hydroxy-3-methoxyphenyl)-2-(4-nitrophenyl)-7-(2-oxo-2*H*-chromen-3-yl)-2,3-dihydropyrido-[2,3-*d*]pyrimidin-4(1*H*)-one (8).

Method A. A mixture of compound **1** (3.85 g, 10 mmol) triturated with EtOH, *p*-nitrobenzaldehyde (1.51 g, 10 mmol), and few drops of piperidine was fused in oil bath for 1.5 h and the reaction mixture was left to cool then the resulting solid was dissolved in EtOH. The resulting solution was diluted with crushed ice acidified with HCl then the formed precipitate was collected by filtration, dried, and recrystallized from EtOH as yellow crystals in 68% yield: mp 314-316 ºC.

Method B. A mixture of compound **7** (2.59 g, 5 mmol) triturated with EtOH and few drops of piperidine was fused in oil bath for 1 h then left to cool down and the resulting solid was dissolved in EtOH. The obtained solution was diluted with crushed ice acidified with HCl, the formed precipitate was collected by filtration, dried, and recrystallized from EtOH as yellow crystals in 88% yield: mp 314-316 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.84 (s, 3H, OCH_3), 5.29 (s, 1H, N*H*CH), 5.66 (s, 1H, OH), 6.12 (s, 1H, NHC*H*NH), 6.89-7.85 (m, 12H, ArH), 8.68 (s, 1H, coumarin 4-H), 9.45 (s, 1H, N*H*CO); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.61, 62.59, 108.30, 111.12, 114.47, 115.35, 118.80, 120.22, 120.95, 124.22, 124.22, 124.56, 127.14, 127.14, 128.79, 128.90, 129.51, 132.80, 143.77, 146.42, 147.62, 147.55, 147.72, 149.90, 153.98, 154.09, 155.98, 160.08, 160.51; IR (KBr) *v*: 3434, 3377, 3316, 3052, 2946, 1714,

1651 cm^{-1}; MS (70 eV) *m/z* (%): 534 (4.01) (M^+-2H), 124 (100). Anal. Calcd for $C_{29}H_{20}N_4O_7$: C: 64.92, H: 3.76, N: 10.44. Found: C: 64.75, H: 3.58, N: 10.36.

3-(5-Amino-4-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydrobenzo[*b*][1,8]naphthyridin-2-yl)-2*H*-chromen-2-one (9).

A mixture of compound **1** (3.85 g, 10 mmol), cyclohexanone (5 mL) and anhydrous zinc chloride (1 g, 5 mmol) was refluxed under dry conditions for 10 h, the reaction mixture was left to cool, triturated with EtOH, diluted with water. The formed precipitate was collected by filtration, dried, and recrystallized from EtOH as dark brown crystals in 74%: mp 240 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.79 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.76 (m, 2H, cyclohexan C-4), 3.12 (m, 2H, cyclohexan C-2), 3.84 (s, 3H, OCH_3), 5.36 (s, 1H, phenyl O*H*), 6.27 (s, 2H, NH_2), 6.89-7.88 (m, 8H, ArH), 8.68 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 23.49, 24.47, 29.10, 32.12, 56.38, 109.38, 112.40, 114.92, 115.46, 118.78, 120.12, 122.03, 122.65, 124.56, 126.98, 129.50, 130.07, 132.80, 143.48, 145.51, 147.66, 149.32, 154.10, 154.14, 157.27, 160.15, 160.50, 162.21; IR (KBr) *v*: 3536, 3472, 3404, 3052, 2917, 1727, 1620 cm^{-1}; MS (70 eV) *m/z* (%): 463 (12.12) (M^+-2H), 62 (100). Anal. Calcd for $C_{28}H_{23}N_3O_4$: C: 72.24, H: 4.98, N: 9.03. Found: C: 72.35, H: 4.73, N: 9.26.

5-(4-Hydroxy-3-methoxyphenyl)-7-(2-oxo-2*H*-chromen-3-yl)-3-phenyl-2-thioxo-2,3-dihydropyrido-[2,3-*d*]pyrimidin-4(1*H*)-one (10).

A mixture of compound **1** (3.85 g, 10 mmol) and phenyl isothiocyanate (1.2 mL, 10 mmol) in pyridine (10 mL) was refluxed for 12 h then cooled down. The reaction mixture was diluted with EtOH, the formed precipitate was collected by filtration, dried, and recrystallized from EtOH as dark brown crystals in 72%: mp > 360 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.84 (s, 3H, OCH_3), 5.66 (s, 1H, O*H*), 6.89-7.85 (m, 13H, ArH), 8.68 (s, 1H, coumarin 4-H), 10.58 (s, 1H, N*H*CS); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.37, 106.85, 107.31, 111.25, 115.33, 118.81, 119.98, 120.95, 124.45, 128.79, 128.89, 129.01, 129.51, 129.58, 129.58, 130.79, 130.79, 132.80, 137.22, 143.83, 147.50, 148.53, 149.91, 154.11, 154.21, 155.37, 160.53, 161.88, 171.48; IR (KBr) *v*: 3532, 3413, 3361, 3052, 2917, 1724, 1673 1376 cm^{-1}; MS (70 eV) *m/z* (%): 520 (26.4) (M^+-H), 131 (100). Anal. Calcd for $C_{29}H_{19}N_3O_5S$: C: 66.78, H: 3.67, N: 8.06, S: 6.15. Found: C: 66.75, H: 3.73, N: 10.56, S: 6.21.

3-(4-Amino-5-(4-hydroxy-3-methoxyphenyl)-2-thioxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-7-yl)-2*H*-chromen-2-one (11).

A mixture of compound **1** (3.85 g, 10 mmol) and thiourea (0.91 g, 12 mmol) was fused under dry conditions in oil bath for 0.5 h, the fused mixture was dissolved in EtOH (10 mL) and the resulting solution was refluxed for 3 h. After cooling, the precipitate formed was collected by filtration and the filtrate further worked up by diluting with cold water to give additional amount of the product which was washed with water, dried, and recrystallized from EtOH to furnish the product as yellow crystals in 63%: mp 218-220

ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.83 (s, 3H, OC*H*$_3$), 5.36 (s, 1H, O*H*), 6.27 (s, 2H, N*H*$_2$), 6.89-7.85 (m, 8H, ArH), 8.68 (s, 1H, coumarin 4-H), 10.58 (s, 1H, N*H*CS); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 56.38, 101.73, 111.32, 111.36, 115.35, 118.79, 120.34, 120.95, 124.65, 128.80, 128.90, 129.50, 132.81, 143.30, 143.80, 147.55, 149.89, 152.60, 154.13, 157.08, 160.51, 175.09, 178.06; IR (KBr) *v*: 3570, 3466, 3388, 3367, 3189, 3032, 2928, 1717, 1609 cm^{-1}; MS (70 eV) *m/z* (%): 445 (4.52) (M^++H), 45 (100). Anal. Calcd for $C_{23}H_{16}N_4O_4S$; C: 62.15, H: 3.63, N: 12.61, S: 7.21. Found: C: 62.04, H: 3.71, N: 12.56, S: 7.06.

3-Cyano-4-(4-hydroxy-3-methoxyphenyl)-6-(2-oxo-2*H*-chromen-3-yl)pyridin-2-ylcarbamodithioic acid (12).

Carbon disulfide (2 mL, excess) was dropped to a solution of compound **1** (1.92 g, 5 mmol) in absolute pyridine (15 mL) and the mixture was heated carefully under reflux in water bath for 12 h. During the reflux time fresh carbon disulfide was added two times, the reaction mixture was cooled, poured over crushed ice acidified with HCl, the formed precipitate was collected by filtration, washed several times with water, dried, and recrystallized from butanol as yellow crystals in 66% yield: mp 259-260 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 2.5 (s, 1H, SH), 3.70 (s, 3H, OC*H*$_3$), 5.65 (s, 1H, O*H*), 6.85-7.82 (m, 7H, ArH), 7.82 (s, 1H, PyrH), 8.81 (s, 1H, coumarin 4-H), 9.32 (s, 1H, N*H*); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 56.29, 104.53, 110.36, 111.22, 115.35, 115.50, 118.87, 120.35, 120.97, 124.45, 128.81, 128.90, 129.51, 132.80, 143.83, 147.50, 149.90, 152.87, 154.12, 155.33, 160.55, 162.10; IR (KBr) *v*: 3570, 3209, 3090, 2932, 2209, 1709, 1458 cm^{-1}; MS (70 eV) *m/z* (%): 458 (16.07) (M^+-3H), 44 (100). Anal. Calcd for $C_{23}H_{15}N_3O_4S_2$; C: 59.86, H: 3.28, N: 9.10, S: 13.90. Found: C: 59.74, H: 3.11, N: 9.19, S: 13.75.

3-(5-(4-Hydroxy-3-methoxyphenyl)-4-imino-2-thioxo-2,4-dihydro-1*H*-pyrido[2,3-*d*][1,3]thiazin-7-yl)-2*H*-chromen-2-one (13).

A solution of compound **12** (2.35 g, 5 mmol) in absolute pyridine was refluxed in water bath for 12 h, the reaction mixture was cooled, poured over crushed ice acidified with HCl, the formed precipitate was collected by filtration, washed several times with water, dried, and recrystallized from toluene as yellow crystals in 54% yield: mp > 360 ºC; ^{1}H NMR (DMSO-*d*$_6$, 300 MHz, ppm) δ: 3.80 (s, 3H, OC*H*$_3$), 5.45 (s, 1H, O*H*), 5.89 (s, 1H, C=N*H*), 6.85-7.82 (m, 7H, ArH), 7.78 (s, 1H, PyrH), 8.80 (s, 1H, coumarin 4-H), 9.09 (s, 1H, N*H*); ^{13}C NMR (DMSO-*d*$_6$, 100 MHz, ppm) δ: 56.38, 111.25, 114.27, 115.33, 118.84, 120.51, 120.35, 120.96, 124.54, 128.80, 128.90, 129.50, 132.80, 143.83, 146.08, 147.50, 149.91, 152.77, 154.10, 156.57, 159.08, 160.52, 178.88; IR (KBr) *v*: 3556, 3365, 3248, 3065, 2946, 1715, 1457 cm^{-1}; MS (70 eV) *m/z* (%): 461 (M^+, 13.21), 44 (100). Anal. Calcd for $C_{23}H_{15}N_3O_4S_2$; C: 59.86, H: 3.28, N: 9.10, S: 13.90. Found: C: 59.74, H: 3.11, N: 9.19, S: 13.75.

3-(6-Amino-5-(4,5-dihydro-1*H*-imidazol-2-yl)-4-(4-hydroxy-3-methoxyphenyl)pyridin-2-yl)-2*H*-chromen-2-one (14).

To a mixture of compound **1** (1.92 g, 5 mmol) and ethylenediamine (7.5 mL), carbon disulfide (0.7 mL) was added drowsily, the reaction mixture was heated under reflux for 5 h, excess of ethylenediamine was evaporated under reduced pressure, the resulting resin was dissolved in EtOH and diluted with cold water, the formed precipitate was filtered off, washed with water, and recrystallized from petroleum ether 60-80 as yellow crystals in 51% yield: mp 148-150 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.58 (t, J = 3.59 Hz, 2H, CH_2N=C), 3.49 (m, 2H, CH_2NH), 3.86 (s, 3H, OCH_3), 5.56 (s, 1H, OH), 6.32 (s, 1H, NH), 6.82-7.95 (m, 8H, ArH), 8.88 (s, 1H, coumarin 4-H), 10.32 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 45.01, 56.38, 57.48, 108.99, 111.30, 115.35, 118.75, 119.03, 120.41, 120.97, 124.43, 128.81, 128.89, 129.51, 132.81, 143.48, 143.80, 147.53, 149.90, 154.11, 154.33, 159.29, 160.50, 166.20; IR (KBr) v: 3556, 3457, 3223, 3149, 3059, 2985, 1723 cm^{-1}; MS (70 eV) *m/z* (%): 426 (0.02) (M$^+$-2H), 247 (100). Anal. Calcd for $C_{24}H_{20}N_4O_4$: C: 67.28, H: 4.71, N: 13.08. Found: C: 67.04, H: 4.53, N: 13.19.

3-(10-(4-Hydroxy-3-methoxyphenyl)-2,3-dihydroimidazo[1,2-*c*]pyrido[3,2-*e*][1,2,3]triazin-8-yl)-2*H*-chromen-2-one (15).

To a cold solution of **14** (2.14 g, 5 mmol) in conc. HCl (10 mL) and AcOH (10 mL), a solution of sodium nitrite (2 g) in water (10 mL) was added within 30 min. After completion of the addition the ice bath was removed and stirring was continued for 2 h, the solid product was filtered off, washed with water, dried, and recrystallized from EtOH as brown crystals in 54% yield: mp > 360 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.68 (t, J = 7.1 Hz, 2H, CH_2N=C), 3.89 (s, 3H, OCH_3), 4.09 (m, 2H, CH_2N), 5.52 (s, 1H, OH), 6.80-7.97 (m, 8H, ArH), 8.89 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 54.12, 56.32, 59.07, 111.32, 111.57, 114.37, 115.35, 118.75, 120.43, 120.97, 124.50, 128.81, 128.90, 129.50, 132.80, 139.25, 143.80, 147.50, 149.91, 154.12, 155.29, 160.52, 160.71, 163.31; IR (KBr) v: 3524, 3085, 2936, 1721 cm^{-1}; MS (70 eV) *m/z* (%): 439 (M$^+$, 22.2), 247 (100). Anal. Calcd for $C_{24}H_{17}N_5O_4$: C: 65.60, H: 3.90, N: 15.94. Found: C: 65.75, H: 3.79, N: 15.79.

3-(4-Chloro-5-(4-hydroxy-3-methoxyphenyl)pyrido[2,3-*d*][1,2,3]triazin-7-yl)-2*H*-chromen-2-one (16).

To a cold solution of compound **1** (0.54 g, 14 mmol) in conc. HCl (2 mL), a solution of sodium nitrite (0.15 g, 2 mmol) in 5 mL water was added with stirring in ice bath (at 5 ºC). After the completion of sodium nitrite solution addition, the product was separated, collected by filtration, and recrystallized from EtOH as dark brown crystals in 60% yield: mp > 360 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.80 (s, 3H, OCH_3), 5.43 (s, 1H, OH), 6.80-7.95 (m, 8H, ArH), 8.88 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.38, 112.40, 113.85, 115.46, 118.80, 120.50, 122.03, 123.23, 124.45, 126.98, 129.51, 130.07, 132.80, 139.04, 145.51, 147.66, 149.32, 154.11, 158.80, 159.18, 160.53, 162.19, 162.19; IR (KBr) v: 3542,

3040, 2951, 1715 cm^{-1}; MS (70 eV) *m/z* (%): 433 (0.73) (M^++H), 63 (100). Anal. Calcd for $C_{22}H_{13}N_4O_4Cl$: C: 61.05, H: 3.03, Cl: 8.19, N: 12.94. Found: C: 61.21, H: 3.29, Cl: 8.32, N: 12.78.

3-(3-Amino-4-(4-hydroxy-3-methoxyphenyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-2*H*-chromen-2-one (17).

A mixture of **1** (1.92 g, 5 mmol) and hydroxylamine hydrochloride (0.3 g, 5 mmol) in glacial AcOH (30 mL) containing anhydrous sodium acetate (1 g) was refluxed for 5 h, the reaction mixture was left over night at room temperature and then poured over crushed ice, the solid precipitate was filtered off, washed with water, dried, and recrystallized from EtOH as dark brown crystals in 69% yield: mp > 360 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.86 (s, 3H, OCH_3), 5.35 (s, 1H, O*H*), 6.80-7.95 (m, 8H, ArH), 7.66 (s, 2H, NH_2), 8.87 (s, 1H, coumarin 4-H), 9.32 (s, 1H, N*H*); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 56.29, 100.41, 111.25, 112.32, 115.33, 118.78, 120.43, 120.98, 124.50, 128.79, 128.90, 129.50, 132.81, 133.38, 143.81, 147.52, 148.00, 149.91, 154.10, 157.91, 160.50, 160.61; IR (KBr) *v*: 3556, 3364, 3276, 3218, 3053, 2946, 1718 cm^{-1}; MS (70 eV) *m/z* (%): 399 (18.95) (M^+-H), 44 (100). Anal. Calcd for $C_{22}H_{16}N_4O_4$: C: 66.00, H: 4.03, N: 13.99. Found: C: 66.25, H: 4.15, N: 13.82.

ANTIMICROBIAL ACTIVITY ASSAY

The antimicrobial activity of tested compounds was assessed against *Streptococci* bacteria as an example of Gram-positive bacterial strains and *Escherichia coli* bacteria as an example of Gram-negative bacterial strains by disc diffusion technique employing sterile Whatman-No.5 filter paper discs (11 mm diameter). The compounds under investigation were dissolved in ethanol. Filter paper discs (11 mm) were loaded with 10 mg/mL of the tested material (50 μL) then complete dryness was accomplished by leaving the discs with care under hot air.

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 then 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 outgrowth was recorded. The plates were done in triplicate and the average inhibition zone diameters were measured in millimeters and used as criterion for the antimicrobial activity. The inhibitory action of the compounds under investigation 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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