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A comprehensive synthesis and antimicrobial evaluation of some fused heterocycles based on coumarin moiety

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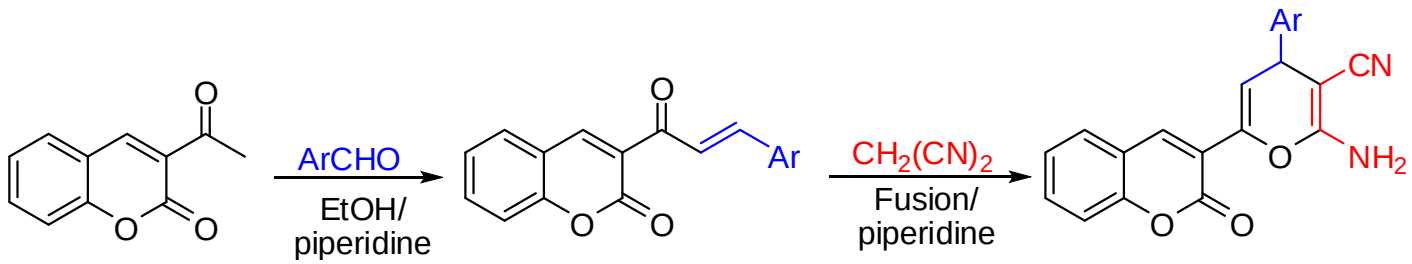
Abstract

Chalcones and coumarins represent significant naturally occurring plant constituents which exhibit a wide array of pharmacological and biological activities. Herein, synthesis of coumarin-chalcone hybrid derivatives was achieved in a good yield *via* Claisen-Schmidt aldolic condensation reaction employing 3-acetylcoumarin as a precursor. The reaction of the new chalcones with malononitrile gave rise to a new substituted pyran ring attached to a coumarin moiety. Subsequently, various *C*-nucleophiles were allowed to react with 3-(4*H*-pyran-2-yl)coumarin derivative **2a** in order to construct novel fused and attached heterocyclic rings bearing different valuable function groups through simple and straightforward reactions. Finally, the antimicrobial activity of the synthesized compounds was evaluated against both Gram-positive and Gram-negative bacteria using Amoxicillin as a standard drug.



Keywords: 3-Acetylcoumarin, chalcones, pyrimidine, pyridine, thiazolidinone

Introduction

Simple coumarins and analogues, also known as benzopyranones, have drawn attention for decades due to their biological activities.[1-5]

The name coumarin was coined from *Coumarouna odorata Aube* which is the Caribbean name of the Tonka bean, from which coumarin was isolated for the first time 200 years ago.[6]

Natural and synthetic coumarins exhibit numerous biological activities such as antibacterial,[7,8] anti-HIV,[9,10] anti-tubercular,[11] antitumoral,[12,13] antioxidant,[14] and anticancer.[15,16] Furthermore, they have shown to be valuable as anticoagulant,[17] cytotoxic,[18] anti-inflammatory,[19] antipyretic,[20] antiviral,[21] antileishmanial,[22] and antifungal.[23,24] Additionally, they have enzyme inhibition effects of crucial importance.[25] Moreover, many coumarins have been used as additives in foods, perfumes, cosmetics, pharmaceuticals,[26] dispersed fluorescent, and laser dyes.[27-29]

In the same context, chalcones are of utmost importance as essential scaffolds for constructing divers rang of different-sized heterocyclic systems of high-biological pertinent.[30]

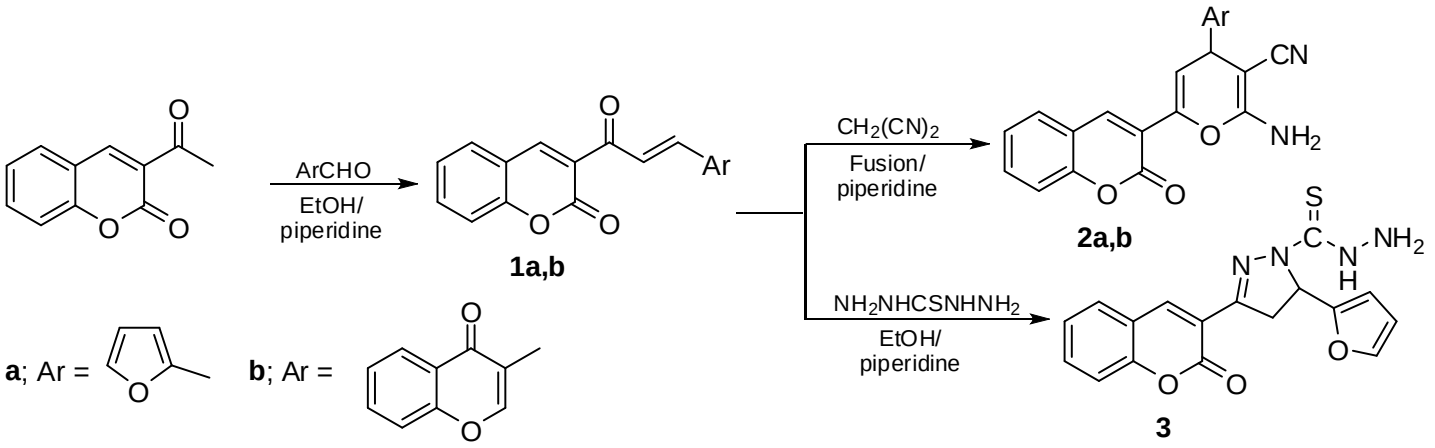
As a part of our continuing attempts to synthesize valuable heterocyclic building blocks, 3-acetylcoumarin was exploited as a precursor to construct new chalcones bearing coumarin moiety.[31] Subsequently, simple and straightforward reactions were used to synthesize novel coumarin derivatives aiming to promote their synthetic potential and investigate the associated biological activities.

Results and Discussion

In 2010, Ajani and co-worker reported the formation of chalcone **1a** exploiting microwave irradiation.[32] However, chalcones **1a,b** were synthesized according to reported procedure.[33] Subsequently, chalcones **1a,b** were used as precursors to prepare 3-(2'-amino-3'-cyano-4'-arylpyran-6'-yl)coumarin derivatives **2a,b**.[31]

As the product of the reaction between chalcone and malononitrile depends on the reaction conditions,[34] fusion of chalcones **1a,b** with malononitrile in the presence of catalytic amount of piperidine furnished 3-(2'-amino-3'-cyano-4'-arylpyran-6'-yl)coumarin derivatives **2a,b** (Scheme 1).[31] The IR spectrum of compound **2a** showed a strong absorption bands for NH_2 at 3340, 3227 cm^{-1} and for nitrile at 2210 cm^{-1} while for **2b** strong absorption bands for NH_2 group at 3356, 3196 cm^{-1} and for nitrile at 2193 cm^{-1} were observed.

Also, refluxing a mixture of chalcone **1a** with *N*-aminothiosemicarbazide and catalytic amount of piperidine in absolute ethanol afforded 5-(furan-2-yl)-3-(2-oxo-2*H*-chromen-3-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**3**) (Scheme 1).[35] The spectral data of compound **3** provided sufficient information about its structure. IR spectrum revealed strong absorption bands at 3398, 3352 cm^{-1} characteristic for NH_2 group, 3218 cm^{-1} for NH group, 1608 cm^{-1} for C=N, and a strong absorption band at 1276 cm^{-1} due to C=S in addition to the appearance of the molecular ion peak at *m/z* = 354.



Scheme 1. Synthesis of compounds **2a,b** and **3**.

Moreover, acetylation of compound **2a** with acetyl chloride in dry dioxane and few drops of triethylamine yielded *N*-acetyl derivative **4** (Scheme 2). IR spectrum of the product was devoid from the absorption band of the amino group but exhibited strong absorption bands at 3223 cm^{-1} due to NH group, at 2212 cm^{-1} characteristic for nitrile group, and a strong absorption bands at 1688 cm^{-1} in correspondence with amide carbonyl. Moreover, ^{1}H NMR data displayed a singlet peak at δ 2.51 ppm integrating for three protons which suggesting the presence of a methyl group that was also detected at 25.91 ppm in ^{13}C NMR. Additionally, mass spectrum of compound **4** revealed ion peak at *m/z* = 374 equivalent to molecular formula $C_{21}H_{14}N_2O_5$.

Likewise, chloroacetylation of the amino group was observed by refluxing compound **2a** with chloroacetyl chloride in dry dioxane containing triethylamine (Scheme 2). The structure of 2-chloro-*N*-(3-cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-yl)acetamide (**5**) was asserted on the basis of its spectroscopic data as IR spectrum showed strong absorption bands at 3234, 1683 cm^{-1} due to NH group and amide carbonyl group, respectively. However, ^{1}H NMR spectrum exhibited a singlet peak at 3.44 ppm integrating for two protons of methylene which its carbon appeared in ^{13}C NMR at chemical shift equal to 40.41 ppm. Finally, mass spectrum showed the molecular ion peak of compound **5** at *m/z* = 408.

A new approach to a fused pyrimidine heterocyclic system was achieved *via* condensation-addition protocol between compound **2a** and formamide in refluxing dimethyl formamide to furnish 3-(4-amino-5-(furan-2-yl)-5*H*-pyrano[2,3-*d*] pyrimidin-7-yl)-2*H*-chromen-2-one (**6**) (Scheme 2). Formation of compound **6** was proved by spectral data. IR spectrum of compound **6** was devoid from the absorption band characteristic for the cyano group. Also, it exhibited two absorption bands at 3244, 3134 cm^{-1} attributed to NH_2 group and a band at 1620 cm^{-1} for C=N group. Another piece of evidence was obtained from ^{1}H NMR spectrum which revealed a singlet signal at 8.40 ppm characteristic for the proton at C2 of pyrimidine and D_2O exchangeable slightly broad signal at 7.78 ppm corresponding to NH_2 group. The mass spectrum was in adequate agreement with the proposed structure, it revealed a molecular ion peak at *m/z* = 359 in accordance with the molecular weight of $C_{20}H_{13}N_3O_4$.

Moreover, compound **2a** underwent cyclocondensation reaction with formic acid to form 5-(furan-2-yl)-7-(2-oxo-2*H*-chromen-3-yl)-3*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-one (**7**) (Scheme 2). IR spectrum of this compound showed the disappearance of nitrile absorption band and the appearance of two new strong absorption bands at 3360, 1689 cm^{-1} in correspondence with NH group and cyclic amide carbonyl group, respectively. Also, a signal at wavenumber 1607 cm^{-1} was observed for C=N. ^{1}H NMR spectrum of compound **7** showed a singlet peak at 8.07 ppm due to the resonance of the proton at C2 in the pyrimidinone ring, on the other hand a

resonant frequency was recorded at 7.37 ppm proving the existence of NH group. Furthermore, ^{13}C NMR spectrum showed a new signal at 159.75 ppm due to carbonyl carbon in pyrimidinone ring.

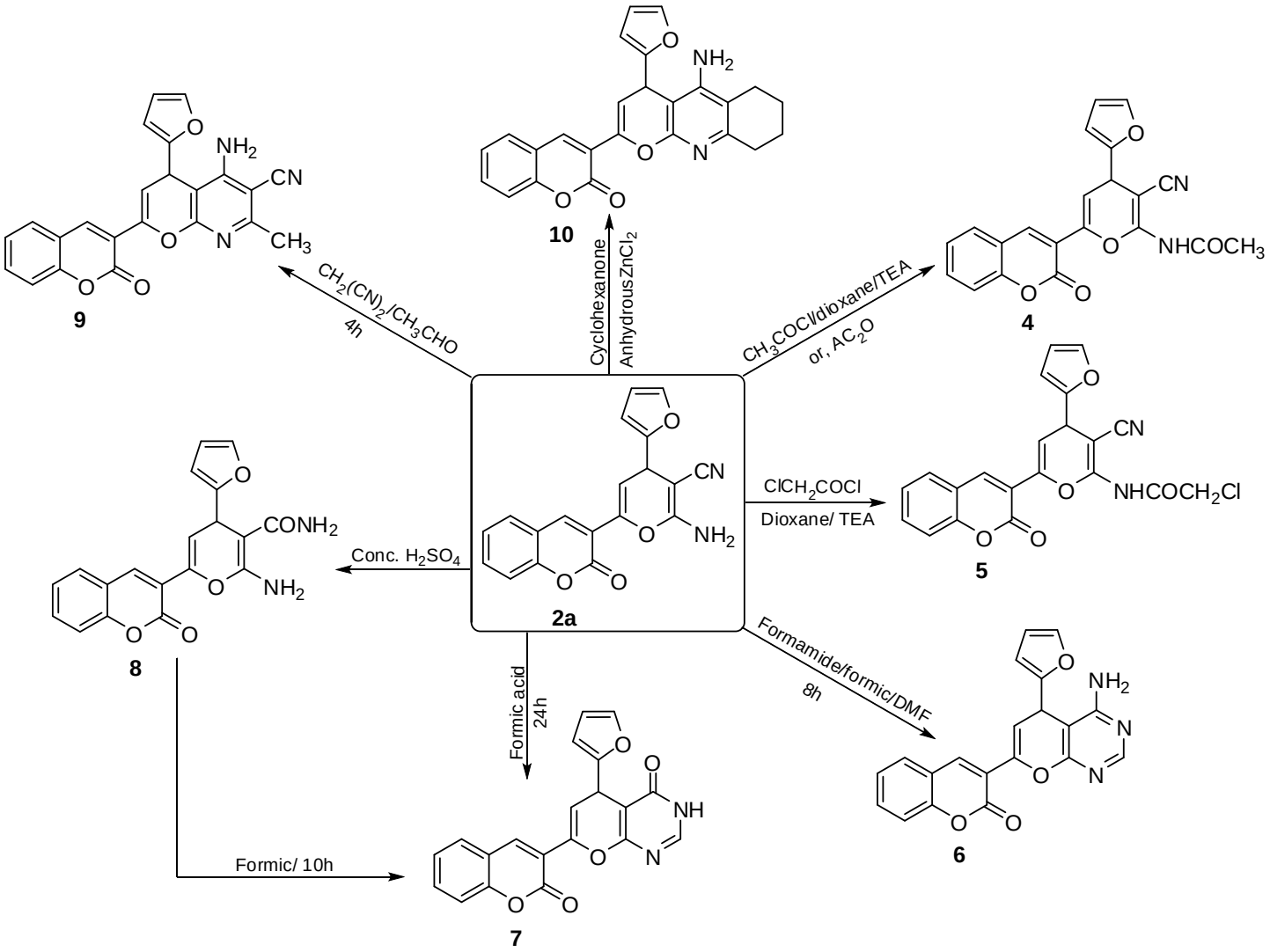
Interestingly, the structure of compound **7** was also confirmed chemically *via* exploring an alternative synthetic route of preparation, it included the hydrolysis of the cyano group in compound **2a** into amide group utilizing sulfuric acid to yield 2-amino-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carboxamide (**8**) followed by the exposure of the later compound **8** to formic acid for 10 h (Scheme 2). The formation of compound **8** was confirmed by its IR spectrum which showed the disappearance of the characteristic nitrile absorption band and the appearance of four absorption bands at 3457, 3385, 3267, 3228 cm^{-1} corresponding to two NH_2 groups, also a strong band at 1649 cm^{-1} was reveled due to amide carbonyl group. The mass spectrum of compound **8** disclosed an ion peak at *m/z* = 350, equivalent to [M^+].

Additionally, aminopyridine derivative **9** was accessible by the cyclocondensation reaction between compound **2a**, acetaldehyde, and malononitrile (Scheme 2). The proof of aminopyridine derivative **9** formation was acquired from spectroscopic data such as IR which showed strong absorption bands for NH_2 group at 3340, 3213 cm^{-1}, aliphatic-CH at 2950 cm^{-1}, and cyano group at 2208 cm^{-1}. Moreover, a singlet peak integrating for three protons was recorded in ^{1}H NMR at 2.51 ppm which suggesting the presence of new methyl group. The methyl group was also observed in ^{13}C NMR at 24.26 ppm while the mass spectrum showed a molecular ion peak at *m/z* = 397 equivalent to molecular formula $C_{23}H_{15}N_3O_4$.

Likewise, condensation between compound **2a** and cyclohexanone in the presence of Lewis acid such as anhydrous zinc chloride furnished pyranoquinoline derivative **10** (Scheme 2). The product was asserted by the analytical and spectroscopic data as IR was devoid from cyano group absorption band but exhibited strong absorption bands for amino group at 3410, 3332 cm^{-1}, aliphatic-CH at 2923 cm^{-1}, and C=N group at 1616 cm^{-1}.

An additional pathway for the synthesis of more fused aminopyridine rings was achieved through the reaction between concentrated phosphoric acid and compound **2a** in acetic anhydride to afford 5-amino-4-(furan-2-yl)-2-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyrano[2,3-*b*]pyridine-7-ylacetate (**11**) (Scheme 3). IR spectrum of the later compound disclosed the absence of cyano group absorption frequency and the appearance of strong absorption bands at 3431, 3238 cm^{-1} characteristic for NH_2 group, 2938 cm^{-1} for aliphatic-CH, 1667 for ester carbonyl group, and 1604 cm^{-1} for C=N group absorption. Furthermore, mass spectrum revealed a molecular ion peak at *m/z* = 416 in accordance with the molecular formula $C_{23}H_{16}N_2O_6$.

A new synthetic approach for the substituted pyridine derivative 7-amino-4-(furan-2-yl)-5-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (**12**) was achieved through the interaction between compound **2a** and malononitrile in dimethyl formamide containing few drops of piperidine at reflux temperature (Scheme 3). Compound **12** was confirmed by IR spectrum that revealed a strong absorption at 1659 cm^{-1} for a new carbonyl group along with the ordinary δ-lactone carbonyl group at 1726 cm^{-1}. Also, bands at 3429, 3372 cm^{-1}, 3225 cm^{-1}, and 2212 cm^{-1} in correspondence with NH_2, NH, and CN stretching frequencies were observed. Mass spectrum indicated a molecular ion peak at *m/z* = 399.

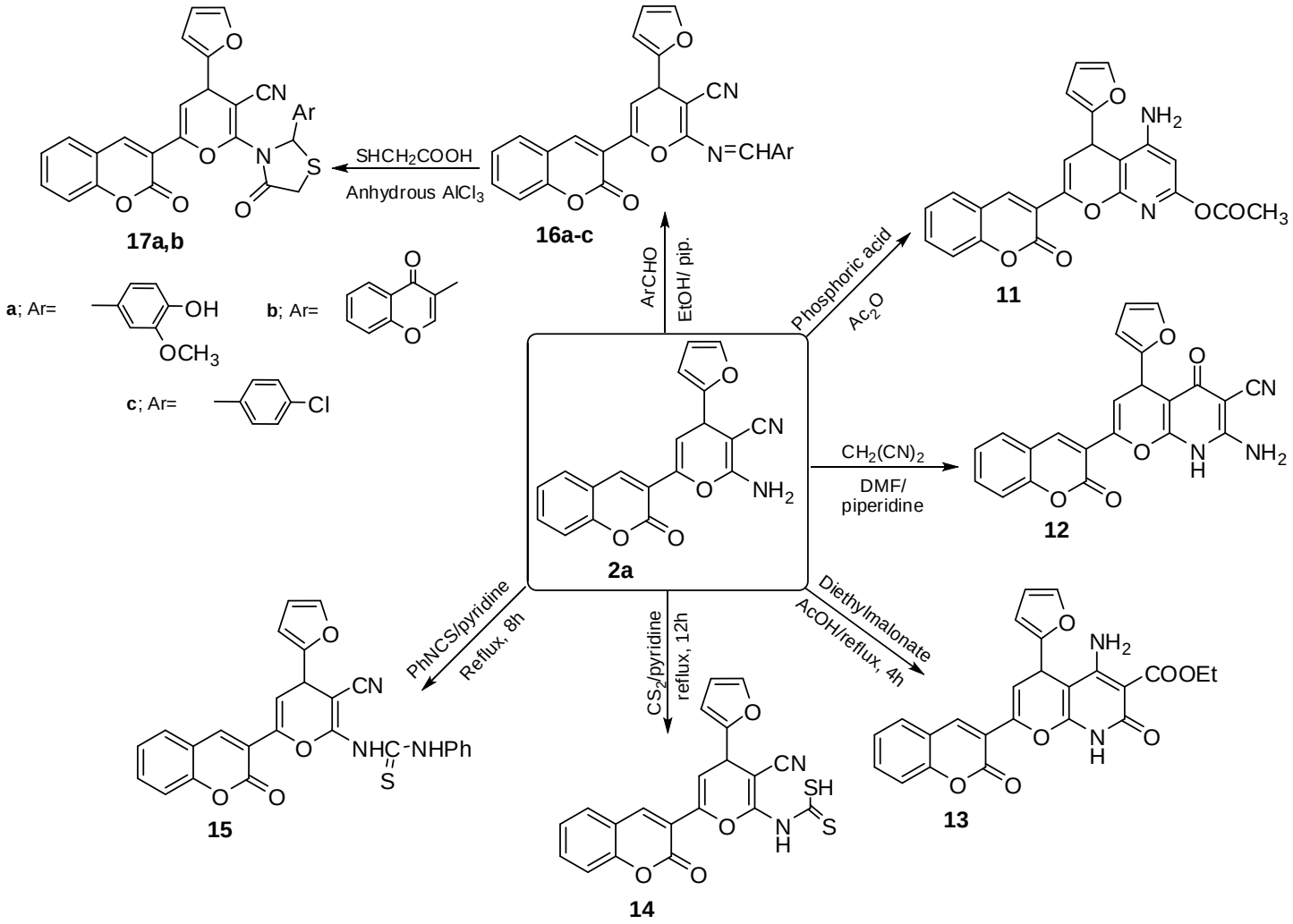


Scheme 2. Reactions of compound **2a**.

Additionally, ethyl 5-amino-4-(furan-2-yl)-7-oxo-2-(2-oxo-2*H*-chromen-3-yl)-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine-6-carboxylate (**13**) was yielded *via* the reaction of compound **2a** with diethylmalonate in glacial acetic acid (Scheme 3). The structure was confirmed by IR spectrum that revealed no absorption for nitrile group but exhibited strong absorption bands at 3145 cm^{-1} for NH group, 1688 cm^{-1} for ester carbonyl group, and at 1668 for amide carbonyl group. Also, 3-cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-yl carbamodithioic acid (**14**) was accessible through the reaction of compound **2a** with carbon disulfide in absolute pyridine (Scheme 3). An evidence for the formation of compound **14** was obtained from IR spectrum which was devoid from the characteristic absorption band of amino group but exhibited strong absorption bands for NH group at 3361 cm^{-1}, SH group at 2352 cm^{-1}, and C=S group at 1256 cm^{-1}. ^1H NMR spectrum exhibited singlet signals for NH at 7.30 ppm and at 2.34 ppm for SH. The interaction between compound **2a** and phenyl isothiocyanate in pyridine under reflux temperature submitted 1-(3-cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-yl)-3-phenylthiourea (**15**) (Scheme 3). The product structure confirmation was acquired from spectroscopic data and microanalysis, IR showed no absorption for NH_2 group but new absorption bands at 3329 cm^{-1} corresponding to NH group and 1230 cm^{-1} corresponding to C=S group were recorded. Mass spectrum of **15** displayed a peak at *m/z* = 467 in accordance with $[M^+]$. Fusion of **2a** with

aromatic aldehydes (namely; vanillin, formylchromone, or *p*-chlorobenzaldehyde) gave rise to Schiff's bases **16a-c** (Scheme 3). IR spectrum of compound **16a** was devoid from stretching vibrations of amino group, it also showed the appearance of new bands at 3466 and 1608 cm^{-1} characteristic for OH group and C=N bond, respectively. Moreover, ^{1}H NMR spectrum exhibited singlet signals at 8.92 ppm for N=CH, 4.11 ppm for OH, and at 3.93 ppm corresponding to CH_3 which was also observed in ^{13}C NMR at 57.97 ppm. Likewise, IR spectrum of **16b** was devoid from stretching vibrations of amino group but revealed an absorption band at 1617 cm^{-1} characteristic for C=N bond however **16c** exhibited the absorption frequency of C=N bond at 1606 cm^{-1}.

Interestingly, Schiff's bases **16a,b** underwent a [3+2] cycloaddition reaction with thioglycolic acid in presence of catalytic amount of anhydrous aluminum chloride to give an access to new attached substituted thiazolidinone ring **17a,b** (Scheme 3). Spectroscopic data and microanalysis asserted the structure as IR spectrum of **17a** showed the appearance of a new C=O group absorption band at 1683 cm^{-1} whereas ^{1}H NMR spectrum exhibited singlet at 4.36 ppm integrating for two protons ($COCH_2S$ of thiazolidinone). As well, IR spectrum of **17b** showed the C=O group absorption band at 1683cm^{-1} however ^{1}H NMR spectrum revealed a singlet peak at 4.35 ppm due to resonance of thiazolidinone two protons at C5.



Scheme 3. Reactions of compound **2a**.

Antimicrobial assay. Antibiotics bearing coumarin moiety have attracted a great attention owing to their potent inhibitory effect of bacterial DNA gyrase and topoisomerase.[36]

In addition, coumarin (2*H*-1-benzopyran-2-one) exhibited robust antibacterial activity against plentiful Gram-positive and Gram-negative bacteria and this mainly attributed to its planar molecular structure and lipophilicity.[37] The antimicrobial activity of compounds under investigation was evaluated against *Bacillus subtilis*, *Staphylococcus aureus*, and *Staphylococcus enteritis* as representative examples of Gram-positive bacteria and *Escherichia coli* as a representative example of Gram-negative bacteria. Antibiotic Amoxicillin was utilized as a control criterion for *in vitro* antibacterial activity. Antimicrobial activity of newly-synthesized compounds against several pathological strains was expressed as inhibition diameter zones in millimeters (mm) as following in Table.

Table 1. *In vitro* antimicrobial activity of compounds under investigation

Entry	Compound	Gram (+Ve) bacteria						Gram (-Ve) bacteria	
		Bacillus subtilis		*Staphylococcus aureus*		*Staphylococcus enteritis*		*Escherichia coli*	
		I.Z.±S.D.*	% Activity index	I.Z.±S.D.*	% Activity index	I.Z.±S.D.*	% Activity index	I.Z.±S.D.*	% Activity index
1	2a	NA[a]	-	8±0.29	47.1	3.5±0.29	46.7	NA	-
2	3	NA	-	9±0.12	52.9	4.5±0.50	60.0	NA	-
3	4	3.5±0.12	46.7	NA	-	NA	-	3.5±0.29	50.0
4	5	NA	-	4.5±0.29	26.5	NA	-	3.5±0.15	50.0
5	6	5±0.25	66.7	5.5±0.50	32.4	NA	-	4±0.36	57.1
6	7	NA	-	4.5±0.29	26.5	NA	-	NA	-
7	8	4.5±0.12	60.0	10±0.29	58.8	4.5±0.29	60.0	4±0.29	57.1
8	9	5±0.29	66.7	5±0.15	29.4	5±0.25	66.7	5±0.58	71.4
9	10	4±0.15	53.3	11±0.36	64.7	3.5±0.12	46.7	4±0.20	57.1
10	11	3.5±0.50	46.7	8.5±0.12	50.0	4±0.12	53.3	NA	-
11	12	5±0.58	66.7	3.5±0.12	20.6	5±0.20	66.7	4±0.25	57.1
12	13	3.5±0.50	46.7	NA	-	5.5±0.58	73.3	NA	-
13	14	4±0.20	53.3	3±0.20	17.6	5±0.29	66.7	3±0.12	42.9
14	15	3±0.12	40	4±0.29	23.5	5±0.29	66.7	NA	-
15	16a	NA	-	8±0.25	47.1	NA	-	4.5±0.29	64.3
16	16b	NA	-	4.5±0.12	26.5	6.5±0.50	86.7	4.5±0.29	64.3
17	17a	6±0.25	80	18±0.87	105.9	7±0.76	93.3	5±0.87	71.4
18	17b	3.5±0.50	46.7	NA	-	5±0.29	66.7	3.5±0.15	50.0
19	*Amoxicillin*	7.5	100	17	100	7.5	100	7	100

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

The investigated compounds showed variation in their antibacterial activities (Table). Compounds **8-10**, **12**, and **14** were active against all examined pathogens (Table; entries 7-9, 11, and 13, respectively). Interestingly, among all the investigated compounds, only **17a** revealed the highest activity against all bacterial strains used in this test (Table; entry 17). Compounds **2**, **3**, **5**, **7**, **16a,b** exhibited no biological activity against *Bacillus subtilis* (Table; entries 1, 2, 4, 6, 15, and 16, respectively) while compounds **4**, **13**, and **17b** were biologically inactive against *Staphylococcus aureus* (Table; entries 3, 12, and 18, respectively). In addition, compounds **4**-**7** and **16a** exhibited no inhibition effect with *Staphylococcus enteritis* (Table; entries 3-6 and 15, respectively. In the same context, all the tested compounds were biologically active against Gram-negative bacteria, namely *Escherichia coli*, and their activities varied from moderate to good activity except compounds **2**, **3**, **7**, **11**, **13** and **15** (Table; entries 1, 2, 6, 10, 12 and 14, respectively) however compound **9** showed the exact activity of the promising compound **17a**.

Conclusions

In conclusion, coumarin–chalcone hybrid compounds were used to synthesize new valuable heterocycles aiming to increase their synthetic potential. Moreover, coumarin derivative **2a** was used as a valuable scaffold to construct various fused and attached heterocyclic rings *via* simple and straightforward reactions. Finally, on the screening of newly-synthesized compounds for their antimicrobial activity against selected microbial strains, compound **17a** showed an excellent activity against both Gram-positive and Gram-negative bacteria (Table, entry 17). All the new synthesized compounds were well characterized using; elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, and ESI-Mass spectrum.

Experimental Section

General. 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 HF_{245} (Merck) and plates were viewed with iodine. Silica gel (230-400 mesh) was used for flash chromatography separations. The Microanalytical Center of Cairo University performed the microanalyses. 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. Nuclear magnetic resonance spectra were recorded on Varian Mercury 300 MHz spectrometer using TMS as internal standard at National Research Center. Chemical shifts (δ) and coupling constants (*J*) were recorded in ppm and Hertz units respectively.

General procedure of chalcones derivatives (1a-b).[33] A mixture of 3-acetyl coumarin (0.001 mol), appropriate aryl or heteroarylaldehyde (0.001 mol) namely (furfural, 3-formyl chromone) and piperidine (0.1 mL) in absolute ethanol (20 mL) was refluxed for 4-8 h and monitored by TLC. After cooling down, the solid formed was filtered off and recrystallized from suitable solvent as pure product.

3-(3-(Furan-2-yl)acryloyl)-2*H*-chromen-2-one (1a).[32] Recrystallized from ethanol as brown crystals in 82% yield, Mp 135-137 °C, IR (KBr): 3045 (Ar-CH), 1723, 1682 cm^{-1} (δ-lactone and ketone CO). Anal. calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 72.06; H, 3.57.

3-(3-(4-Oxo-4*H*-chromen-3-yl)acryloyl)-2*H*-chromen-2-one (1b).[31] Recrystallized from ethanol as pale yellow crystals in 52% yield, Mp 104 °C, IR (KBr): 3034 (Ar-CH), 1734, 1673 cm^{-1} (δ-lactone and ketone CO). Anal. Calcd for $C_{21}H_{12}O_5$: C, 73.25; H, 3.51. Found: C, 73.04; H, 3.42.

3-(2'-Amino-3'-cyano-4'-arylpyran-6'-yl)coumarin derivatives (2a-b). General procedure. A mixture of **1a-b** (0.01 mol), malononitrile (0.66 g, 0.01 mol), and piperidine (0.2 mL) was fused in oil bath for 30 minutes then refluxed in absolute ethanol for one hour. The reaction mixture left to cool, poured over crushed ice, and acidified with HCl. The precipitated product was filtered off, washed with water, dried, and recrystallized from the proper solvent to afford the pure product.

2-Amino-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (2a).[31] Recrystallized from ethanol as yellow crystals in 83% yield, Mp 300-302 °C, IR (KBr): 3340, 3227 (NH_2), 3055 (Ar-CH), 2210 (CN), 1721 cm^{-1} (δ-lactone CO). Anal. Calcd for $C_{19}H_{12}N_2O_4$: C: 68.67, H: 4.64, N: 8.43. Found C: 65.46, H: 4.39, N: 8.35.

2-Amino-6-(2-oxo-2*H*-chromen-3-yl)-4-(4-oxo-4*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (2b). Recrystallized from ethanol as yellow crystals in 78% yield, Mp 260 °C, IR (KBr): 3356, 3196 (NH_2), 2193 (CN), 1714 cm^{-1} (δ-lactone CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.46 (s, 1H, pyran-H), 4.32 (s, 1H, pyran-H), 6.9-7.20 (m, 8H, Ar-H), 7.9 (s, 1H, coumarin 4-H), 8.21 (s, 1H, chromenyl 2-H), 10.2 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 33.03, 56.91, 113.35, 117.32, 118.28, 120.45, 122.37, 122.82, 124.19, 169.53, 125.15, 125.54, 125.72, 126.34, 127.05, 127.74, 128.87, 132.25, 133.79, 148.23, 153.54, 154.22, 159.13, 160.81. Anal. Calcd for $C_{24}H_{14}N_2O_5$: C, 70.24; H, 3.44; N, 6.83. Found: C, 71.33; H, 2.95; N, 7.21. MS (70 eV) *m/z* (%): 411 (28.78) (M^++1), 410 (M^+, 2.35), 385 (9.32), 370 (5.8), 226 (100).

5-(Furan-2-yl)-3-(2-oxo-2*H*-chromen-3-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothiohydrazide (3). A mixture of **1a** (2.66 g, 0.01 mol) and *N*-aminothiosemicarbazide (1.06 g, 0.01 mol) in absolute ethanol containing drops of piperidine was refluxed for 10 h, left to cool, then poured over crushed ice and acidified with HCl. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol as brown crystals in 52% yield, Mp 150 °C, IR (KBr): 3398, 3352 (NH_2), 3218 (NH), 1726 (δ-lactone CO), 1608 (C=N), 1276 cm^{-1} (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.98 (s, 2H, NH_2), 3.30 (d, *J* 5.0 Hz, 2H, pyrazole-CH_2), 4.12 (t, *J* 4.7 Hz, 1H, pyrazole-CH), 6.38-6.64 (m, 2H, furanyl-H), 6.89 (s, 1H, NH), 7.24-7.38 (m, 3H, 2ArH+furanyl-H), 7.41-7.54 (m, 2H, ArH), 8.35 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ; 34.55, 69.63, 93.58, 110.85, 111.25, 117.34, 119.03, 121.97, 124.54, 128.37, 132.85, 140.87, 150.24, 153.91, 160.84, 163.01, 172.32. Anal. Calcd for $C_{17}H_{14}N_4O_3S$: C, 57.62; H, 3.98; N, 15.81; S, 9.05. Found: C, 57.58; H, 3.94; N, 15.76; S, 8.95. MS (70 eV) *m/z* (%): 355 (4.87) (M^++H), 354.38 (2.07) (M^+), 280.28 (2.37), 240.28 (22.89), 73 (100).

***N*-(3-Cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-yl)acetamide (4). Method A.** A mixture of compound **2a** (3.32 g, 0.01 mol), acetyl chloride (0.233 mL, 0.01 mol), and TEA (1.39 mL, 0.01 mol) in dioxane (20 mL) was heated under reflux for 4 h, cooled, then poured over crushed ice. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

Method B. A mixture of compound **2a** (3.32 g, 0.01 mol) in acetic anhydride was refluxed for 5 h, cooled then poured over crushed ice. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol as yellow crystals in 57% yield, Mp 189 °C, IR (KBr): 3223 (NH), 3068 (Ar-CH), 2935 (aliphatic-CH), 2212 (CN), 1725 (δ-lactone CO), 1688 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.51 (s, 3H, CH_3), 3.45 (d, *J* 6.8 Hz, 1H, pyran-H), 3.66 (d, *J* 6.2 Hz, 1H, pyran-H), 6.45 (m, 2H, furanyl-H), 6.47 (s, 1H, NH), 6.93-7.32 (m, 3H, 2ArH+furanyl-H), 7.29-7.65 (m, 2H, Ar-H), 8.38 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ; 25.91, 40.50, 56.50, 107.33, 113.65, 116.75, 119.05, 120.22, 122.24, 125.50, 127.44, 129.63, 133.50, 144.49, 146.50, 149.07, 159.05, 160.87, 171.76. Anal. Calcd for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48. Found: C, 67.21; H, 3.68; N, 7.39. MS (70 eV) *m/z* (%): 374 (6.28) (M^+), 348 (4.08), 281 (5.34), 266 (100).

2-Chloro-*N*-(3-cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-yl)acetamide (5). Chloroacetyl chloride (0.795 mL, 0.01 mol) and TEA (1.39 mL, 0.01 mol) were added to a solution of **2a** (3.32 g, 0.01 mol) in dioxane (30 mL). The reaction mixture was heated under reflux for 4 h, cooled, then poured over crushed ice. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol as brown

crystals in 68% yield, Mp 156-158 °C, IR (KBr): 3234 (NH), 2939 (aliphatic-CH), 2213 (CN), 1726 (δ-lactone CO), 1683 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.44 (s, 2H, CH_2), 3.62 (d, *J* 7.4 Hz, 1H, pyran-H), 4.02 (d, *J* 5.3 Hz, 1H, pyran-H), 6.65-6.78 (m, 2H, furanyl-H), 6.94 (s, 1H, NH), 7.47-7.60 (m, 3H, 2Ar-H+furanyl-H), 8.57 (dd, *J* 7.7, 1.4 Hz, 2H, Ar-H), 8.64 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ; 40.28, 40.41, 65.24, 113.45, 115.47, 116.76, 119.09, 122.10, 127.43, 129.73, 130.65, 131.85, 143.69, 149.43, 154.17, 158.56, 161.51, 169.43. Anal. Calcd for $C_{21}H_{13}N_2O_5Cl$: C, 61.7; H, 3.21; N, 6.85. Found: C, 61.09; H, 2.17; N, 6.81. MS (70 eV) *m/z* (%): 408 (0.22) (M^+), 406 (0.22) (M-2H), 65 (100).

3-(4-Amino-5-(furan-2-yl)- 5*H*-pyrano[2,3-*d*]pyrimidin-7-yl)-2*H*-chromen-2-one (6). A mixture of compound **2a** (3.32 g, 0.01 mol), formamide (10 mL), DMF (5 mL), and formic acid (2 mL) was refluxed for 8 h. The reaction mixture left to cool and poured over crushed ice acidified with conc. HCl. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol as yellow crystals in 58% yield, Mp 230 °C, IR (KBr): 3244, 3134 (NH_2), 3067 (Ar-CH), 1724 (δ-lactone CO), 1620 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.08 (d, *J* 6.2 Hz, 1H, pyran-H), 6.18-6.28 (m, 1H, furanyl-H), 6.51 (d, *J* 6.2 Hz, 1H, pyran-H), 6.76 (dd, *J* 11.0, 4.4 Hz, 1H, furanyl-H), 7.16-7.25 (m, 2H, Ar-H), 7.26 (dd, *J* 7.5, 1.4 Hz, 1H, furanyl-H), 7.43-7.53 (m, 1H, Ar-H), 7.59 (dd, *J* 4.3, 3.6 Hz, 1H, Ar-H), 7.78 (s, 2H, NH_2), 7.91 (s, 1H, pyrimidine-H), 8.40 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ; 40.42, 109.86, 119.06, 120.14, 122.22, 125.4, 129.40, 131.58, 135.90, 140.40, 145.29, 156.16, 161.89, 162.80. Anal. Calcd for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.69. Found: C, 66.2; H, 3.59; N, 11.73. MS (70 eV) *m/z* (%): 359 (0.08) (M^+), 355 (1.87), 207 (100).

5-(Furan-2-yl)-7-(2-oxo-2*H*-chromen-3-yl)-3*H*-pyrano[2,3-*d*]pyrimidin-4(5*H*)-one (7). Method A: A mixture of compound **2a** (3.32 g, 0.01 mol) and formic acid was refluxed for 24 h, cooled, then poured over crushed ice. The formed precipitate was collected by filtration, dried, and recrystallized from ethanol as brown crystals.

Method B: A mixture of compound **8** (3.5 g, 0.01 mol) and formic acid was refluxed for 10 h, cooled then the formed precipitate was collected by filtration, dried, and recrystallized from ethanol as brown crystals in 70% yield, Mp 220 ^{o}C, IR (KBr): 3360 (NH), 3067 (Ar-CH), 1724 (δ-lactone CO), 1689 (amide CO), 1607 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.62 (d, *J* 6.2 Hz, 1H, pyran-H), 6.17-6.24 (m, 2H, furanyl-H), 6.90 (d, *J* 6.2 Hz, 1H, pyran-H), 7.22 (dd, *J* 7.5, 1.4 Hz, 1H, furanyl-H), 7.37 (s, 1H, NH), 7.41-7.73 (m, 4H, Ar-H), 7.91 (s, 1H, pyrimidine-H), 8.07 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 162.53, 159.75, 154.27, 149.18, 144.73, 140.42, 133.35, 131.06, 129.75, 127.77, 125.45, 122.76, 120.77, 119.35, 117.03, 110.89, 96.33, 40.44. Anal. Calcd for $C_{20}H_{12}N_2O_5$: C, 66.67; H, 3.36; N, 7.77. Found: C, 66.61; H, 3.4; N, 7.5. MS (70 eV) *m/z* (%): 356 (M-4H) (0.01), 332 (0.11), 264 (2.50), 224 (100).

2-Amino-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carboxamide (8). To compound **2a** (3.32 g, 0.01 mol), concentrated sulfuric acid (30 mL) cooled to 20 °C was added with continues stirring within 0.5 h. The temperature was kept below 30 °C and the solution was stirred at room temperature for additional 4 h then poured with stirring into 200 mL ice-cold water and left overnight in the refrigerator. The precipitated product was collected by filtration, washed with water, dried, and recrystallized from ethanol as brown crystals in 78% yield, Mp 120 °C, IR (KBr): 3457, 3385, 3267, 3228 ($2NH_2$), 1705 (δ-lactone CO), 1649 cm^{-1} (amide CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.21 (d, *J* 6.4 Hz, pyran-H), 4.62 (d, *J* 6.1 Hz, pyran-H), 6.09-6.10 (m, 2H, furanyl-H), 7.19 (dd, *J* 7.3, 1.6 Hz, furanyl-H), 7.20 (m, 2H, ArH), 7.43 (s, 2H, NH_2CO), 7.56-7.78 (m, 2H, ArH), 8.38 (s, 1H, coumarin 4-H), 10.47 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 41.50, 88.29, 111.93, 117.39, 119.20, 121.76, 122.35, 125.42, 128.10, 128.85, 130.16, 132.08, 134.15, 142.83, 150.29, 154.69, 156.53, 163.92, 172.16. Anal. Calcd for $C_{19}H_{14}N_2O_5$: C, 65.14; H, 4.03; N, 8.00. Found: C, 66; H, 4.05; N, 7.96. MS (70 eV) *m/z* (%): 353 (100) (M+3H), 350 (2.44) (M^+), 306 (6.16).

5-amino-4-(furan-2-yl)-7-methyl-2-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyrano[2,3-b]pyridine-6-carbonitrile (9). To a suspension of compound **2a** (3.32 g, 0.01 mol) in absolute ethanol and drops of piperidine, a solution of

acetaldehyde (0.56 mL, 0.01 mol) and malononitrile (1.32 g, 0.02 mol) in absolute ethanol (20 mL) was added. The reaction mixture was refluxed for 4 h and left to cool down to room temperature. The formed solid product was filtered off and recrystallized from ethanol as yellow crystals in 70% yield, Mp 262 °C, IR (KBr): 3340, 3213 (NH_2), 2950 (aliphatic-CH), 2208 (CN), 1727 cm^{-1} (δ-lactone CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.51 (s, 3H, CH_3), 4.49 (d, *J* 10.1 Hz, 1H, pyran-H), 6.40 (t, *J* 7.4 Hz, 1H, furanyl-H), 6.50 (d, *J* 6.2 Hz, 1H, pyran-H), 6.81 (dd, *J* 7.4, 1.6 Hz, 1H, furanyl-H), 6.91 (s, 2H, NH_2), 7.20 (d, *J* 7.5 Hz, 2H, Ar-H), 7.36 (dd, *J* 7.4, 1.5 Hz, 1H, furanyl-H), 7.41-7.68 (m, 2H, Ar-H), 8.01 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 24.26, 39.56, 88.74, 98.42, 111.46, 116.61, 118.48, 119.20, 120.70, 122.59, 125.52, 128.97, 129.68, 132.53, 136.78, 140.87, 146.24, 154.28, 156.29, 159.61, 162.85, 164.74. Anal. Calcd for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10.57. Found: C, 69.48; H, 3.73; N, 10.49. MS (70 eV) *m/z* (%): 397 (2) (M^+), 356 (5.10), 207 (100).

3-(5-Amino-4-(furan-2-yl)-6,7,8,9-tetrahydro-4*H*-pyrano[2,3-*b*]quinolin-2-yl)-2*H*-chromen-2-one (10). A mixture of compound **2a** (3.32 g, 0.01 mol), cyclohexanone (5 mL), and anhydrous zinc chloride (1.0 g) was refluxed under dry condition for 10 h. The reaction mixture was left to cool, dissolved in ethanol, and diluted with water. The formed precipitate was collected by filtration dried and recrystallized from ethanol as brown crystals in 70% yield, Mp 240 °C, IR (KBr): 3410, 3332 (NH_2), 3043 (Ar-CH), 2923 (aliphatic-CH), 2213 (CN), 1732 (δ-lactone CO), 1616 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.75 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.87 (m, 2H, cyclohexan C-4), 3.11 (m, 2H, cyclohexan C-2), 4.97 (d, *J* 6.2 Hz, 1H, pyran-H), 6.25-6.29 (m, 2H, furanyl-H), 6.35 (s, 2H, NH_2), 6.42 (d, *J* 6.2 Hz, 1H, pyran-H), 7.12 (dd, *J* 6.7, 2.3 Hz, 1H, furanyl-H), 7.45-7.78 (m, 4H, ArH), 8.11 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 22.97, 25.50, 29.85, 32.62, 37.43, 105.40, 110.83, 115.63, 117.63, 119.19, 120.33, 121.86, 125.74, 129.15, 130.34, 131.09, 132.73, 137.29, 140.64, 147.68, 150.57, 151.38, 154.54, 156.30, 161.73. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.77; H, 4.82; N, 6.85. MS (70 eV) *m/z* (%): 411 (0.48) (M-H), 291 (49.68), 265 (100).

5-Amino-4-(furan-2-yl)-2-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyrano[2,3-*b*]pyridine-7-yl acetate (11). To a solution of compound **2a** (3.32 g, 0.01 mol) in acetic anhydride (15 mL), concentrated phosphoric acid (30 mL) was added and the reaction mixture was heated under reflux for 10 h then poured into crushed iced-water and neutralized by solid sodium carbonate till pH = 7. The formed solid product was collected by filtration and recrystallized from acetic acid as brown crystals in 63% yield, Mp 140 °C, IR (KBr): 3431, 3238 (NH_2), 3090 (Ar-CH), 2938 (aliphatic-CH), 1711 (δ-lactone CO), 1667 cm^{-1} (ester CO), 1604 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.54 (s, 3H, CH_3), 4.87 (d, *J* 6.2 Hz, 1H, pyran-H), 5.32 (s, 1H, pyridine-H), 6.20-6.31 (m, 2H , furanyl-H), 6.45 (d, *J* 6.1 Hz, 1H, pyran-H), 7.15 (m, 2H, ArH), 7.20 (dd, *J* 6.8, 1.6 Hz, furanyl-H), 7.46-7.68 (m, 2H, ArH), 8.12 (s, 1H, coumarin 4-H), 8.98 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 21.30, 39.84, 98.92, 102.73, 112.56, 117.03, 118.65, 120.88, 121.78, 125.51, 129.15, 129.37, 130.68, 132.11, 135.95, 140.07, 145.46, 150.64, 153.27, 155.16, 156.31, 161.36, 172.14. Anal. Calcd for $C_{23}H_{16}N_2O_6$: C, 66.34; H, 3.87; N, 6.73. Found: C, 66.52; H, 3.93; N: 6.68. MS (70 eV) *m/z* (%): 418 (1.29) (M+2H), 416 (1.25) (M^+), 400 (4.12), 341 (8.82).

7-Amino-4-(furan-2-yl)-5-oxo-2-(2-oxo-2*H*-chromen-3-yl)-5,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine-6-carbonitrile (12). A mixture of **2a** (3.32 g, 0.01 mol) and malononitrile (1.32 g, 0.02 mol) in (20 mL) DMF and few drops of piperidine was reflux for 10 h then cooled and poured into ice-cold water. The precipitated solid was filtered off and recrystallized from ethanol as yellow crystals in 74% yield, Mp 320 °C, IR (KBr): 3429, 3372 (NH_2), 3225 (NH), 2212 (CN), 1726 (δ-lactone CO), 1659 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.50 (s, 1H, NH), 3.55 (d, *J* 6.2 Hz, 1H, pyran-H), 6.22-6.35 (m, 2H, furanyl-H), 6.79 (s, 2H, NH_2), 6.85 (d, *J* 8.0 Hz, 1H, pyridine-H), 7.41 (dd, *J* 7.0, 2.2 Hz, 1H, furanyl-H), 7.85-7.42 (m, 4H, Ar-H), 8.01 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 40.41, 54.99, 97.80, 111.22, 115.75, 118.77, 120.53, 122.25, 125.07, 128.57, 130.21, 131.38, 133.14, 140.96, 147.93, 151.79, 154.34, 161.91, 167.40, 169.20. Anal. Calcd for $C_{22}H_{13}N_3O_5$: C,

66.17; H, 3.28; N, 10.52. Found: C, 66.02; H, 3.13; N, 9.87. MS (70 eV) *m/z* (%): 399 (1.2) (M^+), 396 (100) (M-3H), 357 (2.38).

Ethyl 5-amino-4-(furan-2-yl)-7-oxo-2-(2-oxo-2*H*-chromen-3-yl)-7,8-dihydro-4*H*-pyrano[2,3-*b*]pyridine-6-carboxylate (13). A mixture of compound **2a** (3.32 g, 0.01 mol) and diethylmalonate (1.52 mL, 0.01 mol) in glacial acetic acid was refluxed for 4 h then cooled and poured over iced-water. The precipitated solid was filtered off, dried, and recrystallized from ethanol as yellow crystals in 68% yield, Mp 200 °C, IR (KBr): 3257, 3215 (NH_2), 3145 (NH), 3093 (Ar-CH), 1731 (δ-lactone CO), 1688 cm^{-1} (ester CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 1.35 (t, *J* 6.0 Hz, 3H, CH_3), 2.38 (s, 2H, NH_2), 4.26 (d, *J* 6.2 Hz, 1H, pyran-H), 4.35 (q, *J* 6.2 Hz, 2H, CH_2), 6.26-6.29 (m, 2H, furanyl-H), 6.65 (d, *J* 6.2 Hz, 1H, pyran-H), 7.22-7.29 (m, 3H, 2Ar-H+furanyl-H), 7.54-7.74 (m, 2H, ArH), 7.95 (s, 1H, coumarin 4-H), 9.89 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 14.39, 37.15, 62.44, 80.63, 104.11, 111.58, 117.68, 118.35, 120.71, 121.87, 125.14, 127.09, 128.19, 130.35, 131.24, 133.61, 141.59, 145.65, 147.72, 148.06, 155.32, 162.48, 163.15, 166.68. Anal. Calcd for $C_{24}H_{18}N_2O_7$: C, 64.57; H, 4.06; N, 6.28. Found: C, 64.51; H, 3.97; N: 6.11. MS (70 eV) *m/z* (%): 373 (0.12), 291 (7.93), 107 (100).

3-Cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-ylcarbamodithioic acid (14). To a solution of compound **2a** (3.32 g, 0.01 mol) in absolute pyridine (15 mL), carbon disulfide (2 mL, excess) was dropped and the reaction mixture was heated carefully under reflux on water bath for 12 h. During refluxing time, fresh carbon disulfide was added two times. The reaction mixture was cooled and poured over crushed ice acidified with conc. HCl. The formed precipitate was collected by filtration, washed several times with water, dried, and recrystallized from ethanol as brown crystals in 63% yield, Mp 260 °C, IR (KBr): 3361 (NH), 2352 (SH), 2213 (CN), 1715 (δ-lactone CO), 1256 cm^{-1} (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 2.34 (s, 1H, SH), 3.52 (d, *J* 6.2 Hz, 1H, pyran-H), 3.94 (d, *J* 6.2 Hz, 1H, pyran-H), 6.28-6.29 (m, 2H, furanyl-H), 7.10 (d, *J* 7.5 Hz, 1H, furanyl-H), 7.20-7.24 (m, 2H, Ar-H), 7.30 (s, 1H, NH), 7.44-7.53 (m, 2H, Ar-H), 8.01 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 40.45, 73.28, 110.76, 113.68, 116.78, 120.74, 121.81, 121.87, 125.29, 127.34, 129.68, 130.88, 132.27, 132.54, 140.39, 142.83, 149.32, 154.26, 163.20. Anal. Calcd for $C_{20}H_{12}N_2O_4S_2$: C, 58.81; H, 2.96; N, 6.86; S, 15.70. Found: C, 58.88; H, 3.05; N, 6.92; S, 15.66. MS (70 eV) *m/z* (%): 405 (0.01) (M-3H), 265 (18.99), 266 (100).

1-(3-Cyano-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-2-yl)-3-phenylthiourea (15). A mixture of compound **2a** (3.32 g, 0.01 mol) and phenyl isothiocyanate (1.2 mL, 0.01 mol) in 20 mL pyridine was refluxed for 8 h. After cooling down, the reaction mixture was poured into iced-water acidified with conc. HCl. The precipitated solid was collected by filtration, dried, and recrystallized from ethanol as brown crystals in 70% yield, Mp 250 °C, IR (KBr): 3329 (NH), 2926 (aliphatic-CH), 2208 (CN), 1714 (δ-lactone CO), 1230 cm^{-1} (C=S). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.20 (d, *J* 6.2 Hz, 1H, pyran-H), 5.98 (d, *J* 6.2 Hz, 1H, pyran-H), 6.26 (m, 2H, furanyl-H), 7.17-7.22 (m, 2H, ArH), 7.26 (m, 1H, furanyl-H), 7.31-7.63 (7H, ArH), 8.01 (s, 1H, coumarin H-4), 9.13 (s, 1H, NH), 10.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 41.39, 76.45, 110.72, 112.35, 117.58, 119.49, 120.46, 121.33, 122.76, 123.86, 125.13, 127.69, 128.19, 129.80, 130.68, 131.13, 132.70, 138.28, 141.67, 148.89, 155.11, 156.32, 160.73, 177.92. Anal. Calcd for $C_{26}H_{17}N_3O_4S$: C, 66.80; H, 3.67; N, 8.99; S, 6.86. Found: C, 66.71; H, 3.62; N, 8.93; S, 6.80. MS (70 eV) *m/z* (%): 467 (M^+) (4.87), 396 (100), 39 (7.79).

4-(Furan-2-yl)-2-(aryl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (16a-c). A mixture of **2a** (3.32 g, 0.01 mol), appropriate aromatic aldehyde; namely (vanilline, formylchromone, and *p*-chlorobenzaldhyde), and few drops of piperidine was refluxed in (25mL) ethanol for 12 h. After cooling, the separated solid was filtered off and crystalized from the proper solvent as pure product.

4-(Furan-2-yl)-2-(4-hydroxy-3-methoxybenzylideneamino)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (16a). Crystallized from ethanol as yellow crystals in 65% yield, Mp 207 °C, IR (KBr): 3466 (OH), 3057 (Ar-CH), 2932 (aliphatic-CH), 2215 (CN), 1707 (δ-lactone CO), 1608 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm)

δ: 3.91 (d, *J* 6.2 Hz, 1H, pyran-H), 3.93 (s, 3H, OCH_3), 4.11 (s, 1H, OH), 6.17-6.24 (m, 2H, furanyl-H), 6.39 (d, *J* 6.1 Hz, 1H, pyran-H), 6.76 (dd, *J* 3.4, 1.9 Hz, 1H, furanyl-H), 6.85 (d, *J* 7.5 Hz, 1H, Ar-H), 7.20-7.28 (m, 2H, Ar-H), 7.48 (dd, *J* 7.5, 1.5 Hz, 1H, Ar-H), 7.63 (d, *J* 1.6 Hz, 1H, Ar-H), 7.75 (d, *J* 8.2 Hz, 1H, Ar-H), 8.00 (s, 1H, coumarin 4-H), 8.51 (dd, *J* 7.4, 1.5 Hz, 1H, Ar-H), 8.92 (s, 1H, C*H*=N); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 40.60, 57.97, 60.11, 109.97, 110.29, 111.19, 113.80, 119.36, 120.41, 120.74, 122.39, 124.03, 125.76, 126.68, 127.21, 130.96, 131.35, 132.62, 133.26, 141.17, 146.64, 149.77, 150.17, 153.65, 158.93, 164.15, 167.13. Anal. Calcd for $C_{27}H_{18}N_2O_6$: C, 69.52; H, 3.89; N, 6.01. Found: C, 69.57; H, 3.92; N, 6.08. MS (70 eV) *m/z* (%): 466.44 (0.01) (M^+), 342.32 (0.16), 104.11 (22.36), 73 (100).

4-(Furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-2-((4-oxo-4*a*,8*a*-dihydro-4*H*-chromen-3-yl)methyleneamino)-4*H*-pyran-3-carbonitrile (16b). Crystallized from ethanol as brown crystals in 74% yield, Mp 194 °C, IR (KBr): 2972 (aliphatic-CH), 2201 (CN), 1720 (δ-lactone CO), 1617 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.96 (d, *J* 6.2 Hz, 1H, pyran-H), 5.86 (d, *J* 6.2 Hz, 1H, pyran-H), 6.01-6.31 (m, 2H, furanyl-H), 6.90 (d, *J* 7.6 Hz, 1H, Ar-H), 7.06 (dd, *J* 7.4, 1.5 Hz, 1H, furanyl-H), 6.92-7.38 (m, 2H, Ar-H), 7.55 (dd, *J* 7.3, 1.4 Hz, 1H, Ar-H), 7.75 (dd, *J* 7.3, 1.4 Hz, 1H, Ar-H), 8.17 (dd, *J* 7.4, 1.3 Hz, 1H, Ar-H), 7.85-8.07 (m, 2H, Ar-H), 8.44 (s, 1H, coumarin 4-H), 8.65 (s, 1H, C*H*=N), 8.98 (s, 1H, chromenyl 2-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 40.77, 57.84, 110.52, 110.75, 117.14, 117.35, 120.68, 120.82, 121.45, 125.40, 125.53, 125.91, 126.01, 126.56, 127.73, 129.56, 131.30, 132.25, 132.67, 134.21, 140.56, 149.30, 150.98, 154.13, 155.80, 161.65, 162.66, 163.65, 169.70. Anal. Calcd for $C_{29}H_{16}N_2O_6$: C, 71.31; H, 3.30; N, 5.74. Found: C, 71.22; H, 3.27; N, 5.71. MS (70 eV) *m/z* (%): 488.45 (0.06) (M^+), 252.24 (1.40), 77 (4.76), 73 (100).

2-(4-Chlorobenzylideneamino)-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (16c). Crystallized from ethanol as yellow crystals in 68% yield, Mp 187 °C, IR (KBr): 2211 (CN), 1726 (δ-lactone CO), 1606 cm^{-1} (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 4.89 (d, *J* 6.0 Hz, 1H, pyran-H), 5.96-6.01 (m, 2H, furanyl-H), 6.85 (d, *J* 6.2 Hz, 1H, pyran-H), 6.95 (d, *J* 4.6 Hz, 1H, Ar-H), 7.07-7.30 (m, 2H, Ar-H), 7.57 (dd, *J* 7.5, 1.4 Hz, 1H, furanyl-H), 7.61 (d, *J* 9.1 Hz, 2H, Ar-H), 7.78 (dd, *J* 7.1, 3.6 Hz, 1H, Ar-H), 7.82-7.94 (m, 1H, Ar-H), 8.47 (s, 1H, coumarin 4-H), 8.84 (d, *J* 7.3 Hz, 1H, Ar-H), 8.88 (s, 1H, C*H*=N); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 48.42, 61.25, 108.30, 110.30, 112.55, 116.50, 119.49, 120.95, 123.01, 125.08, 126.72, 128.67, 129.63, 130.67, 131.77, 132.91, 134.25, 138.50, 144.09, 149.39, 153.64, 158.26, 159.23, 161.54. Anal. Calcd for $C_{26}H_{15}ClN_2O_4$: C, 68.65; H, 3.32; N, 6.16. Found: C, 68.7; H, 3.30; N, 6.20. MS (70 eV) *m/z* (%): 454 (M^+, 23), 331 (39), 76 (100).

2-(3-Chloro-2-(aryl)-4-methyleneazetidin-1-yl)-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (17a,b). To a mixture of compound **16a,b** (0.01 mol) and triethylamine (0.42 mL, 0.03 mol) in (20 mL) dry dioxane, chloroacetylchloride (0.32 mL, 0.04 mol) was added drop-wisely with continues stirring for 30 minutes, then stirring was continued for 3 h. After cooling down, the separated solid was filtered off, dried, and crystalized from the proper solvent as pure product.

2-(2-Aryl-4-oxothiazolidin-3-yl)-4-(furan-2-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (17a,b). A mixture of compound **16** (0.01 mol), thioglycolic acid (0.165 g, 0.015 mol), anhydrous aluminum chloride (0.5 g) in dry DMF (20 mL), and few drops of piperidine was refluxed for 24 h. The reaction mixture was poured over crushed ice and the precipitated solid was filtered off, dried, and crystallized from the proper solvent as pure product.

4-(Furan-2-yl)-2-(2-(4-hydroxy-3-methoxyphenyl)-4-oxothiazolidin-3-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (17a). Crystallized from acetic acid as yellow crystals in 64% yield, Mp 206 °C, IR (KBr): 3351 (OH), 2925 (aliphatic CH), 2211 (CN), 1726 (δ-lactone CO), 1683 cm^{-1} (CO). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.64 (s, 1H, OH), 3.74 (d, *J* 6.2 Hz, 2H, pyran-H), 3.76 (s, 3H, OCH_3), 4.16 (d, *J* 6.2 Hz, 1H, pyran-H), 4.36 (s, 2H, thiazolidin-CH_2), 6.19-6.34 (m, 2H, furanyl-H), 6.75-6.80 (m, 4H, Ar-H), 6.91 (s, 1H, thiazolidin-CH), 7.20

(d, *J* 6.9 Hz, 1H, furanyl-H), 7.40-7.53 (m, 4H, Ar-H), 7.63 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 35.49, 41.33, 57.70, 65.33, 75.65, 110.78, 111.18, 112.56, 113.88, 117.24, 119.38, 120.49, 121.72, 122.11, 125.00, 126.49, 129.25, 130.70, 132.67, 133.34, 135.16, 140.22, 145.43, 146.51, 148.39, 150.86, 156.27, 160.87, 172.18. Anal. Calcd for $C_{29}H_{20}N_2O_7S$: C, 64.44; H, 3.74; N, 5.18. Found: C, 64.40; H, 3.52; N, 4.92. MS (70 eV) *m/z* (%): 540 (M^+, 16.01), 417 (8.17), 391 (3.21), 73 (100).

4-(Furan-2-yl)-2-(4-oxo-2-(4-oxo-4*H*-chromen-3-yl)thiazolidin-3-yl)-6-(2-oxo-2*H*-chromen-3-yl)-4*H*-pyran-3-carbonitrile (17b). Crystallization from methanol as brown crystals in 70% yield, Mp 186 °C, IR (KBr): 2945 (aliphatic CH), 2215 (CN), 1726 (δ-lactone CO), 1683 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz, ppm) δ: 3.55 (d, *J* 6.2 Hz, 1H, pyran-H), 4.35 (s, 2H, thiazolidin-CH_2), 4.83 (d, *J* 6.2 Hz, 1H, pyran-H), 5.32 (s, 1H, thiazolidin-CH), 6.21-6.28 (m, 2H, furanyl-H), 6.76-6.88 (m, 1H, Ar-H), 7.04 (dd, *J* 7.5, 1.4 Hz, 1H, Ar-H), 7.15-7.17 (m, 2H, Ar-H), 7.19 (d, *J* 5.3 Hz, 1H, furanyl-H), 7.28-7.44 (m, 2H, Ar-H), 7.47 (dd, *J* 7.4, 1.4 Hz, 1H, Ar-H), 7.66 (s, 1H, chromenyl 2-H), 7.82 (dd, *J* 7.2, 1.2 Hz, 1H, Ar-H), 7.95 (s, 1H, coumarin 4-H); ^{13}C NMR (DMSO-d_6, 100 MHz, ppm) δ: 34.19, 41.29, 56.15, 72.58, 110.30, 113.41, 115.62, 117.65, 118.83, 120.43, 120.67, 121.89, 124.76, 125.47, 125.88, 126.34, 128.69, 129.37, 130.40, 132.32, 133.68, 135.61, 140.11, 144.58, 150.03, 154.21, 155.74, 158.47, 160.91, 172.81, 174.12. Anal. Calcd for $C_{31}H_{18}N_2O_7S$: C, 66.19; H, 3.23; N, 4.98. Found: C, 66.13; H, 3.18; N, 4.94. MS (70 eV) *m/z* (%): 562 (M^+, 1.03), 536 (2.3), 291 (6.8), 73 (100).

Antimicrobial activity assay. The antimicrobial activity of compounds under investigation was recorded against selected microbial strains, by disc diffusion technique employing sterile Whatman-No.5 filter paper discs (11 mm diameter).[38] The tested compounds 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 reached 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 °C for 1 h to permit good diffusion. All the plates were then incubated for 24 h at 37 °C.

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. Amoxicillin (standard drug) was also screened for antibacterial activity under similar conditions, for comparison.

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