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A facile one-pot green synthesis of novel 2-amino-4*H*-chromenes: antibacterial and antioxidant evaluation

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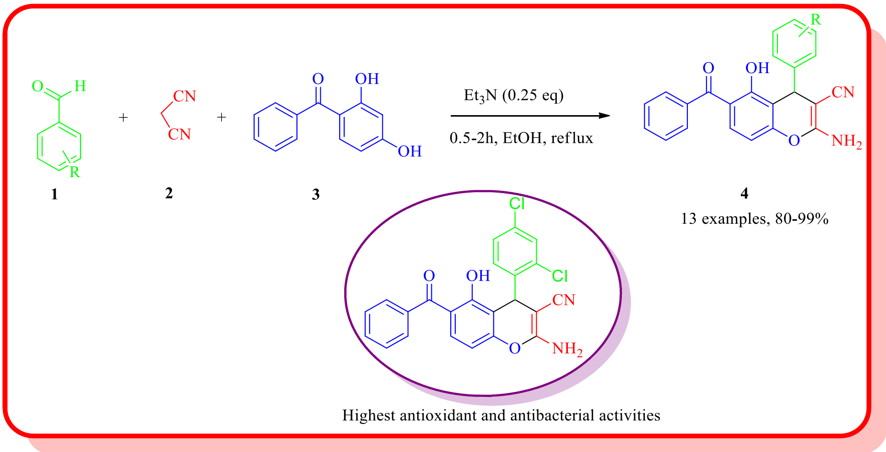
Abstract

Synthesis of novel derivatives of 2-amino-4*H*-chromene is reported via three-component reaction of 2,4-dihydroxybenzophenone, malononitrile, and aromatic aldehydes in the presence of catalytic amount of triethylamine in ethanol as a green solvent with high to excellent yields. The structure of the synthesized products was characterized by FTIR, ^{1}H, ^{13}C NMR spectroscopy, CHN analyses, and mass spectrometry. Simplicity of the procedure, green reaction conditions, short reaction time, and easy separation of the products make this an interesting alternative to other reported approaches. Also, their antibacterial and antioxidant activities were evaluated against *Staphylococcus aureus* as Gram-positive bacteria and *Escherichia coli* as Gram-negative bacteria through the minimum inhibitory concentration method, as well as the radical scavenger 2,2-diphenyl-1-picrylhydrazyl. Among these compounds, **4b** including halogen substituent and 2-amino-4*H*-pyran moiety showed the highest antioxidant and antibacterial activities.

Extended author information available on the last page of the article

Graphical abstract

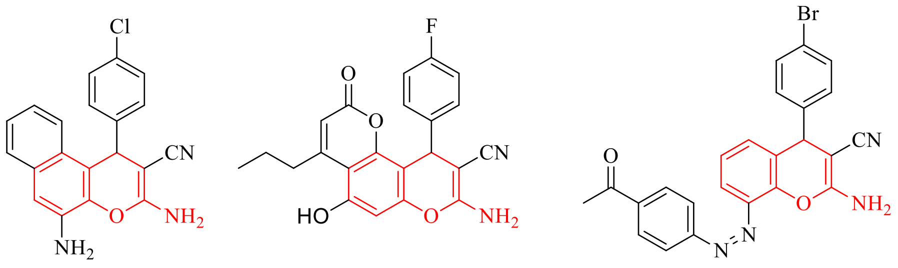


Keywords 2-Amino-4*H*-chromene · Three-component reaction · Antioxidant · Antibacterial · *OH*-acids · Minimum inhibitory concentration · Triethylamine

Introduction

Antimicrobial agents are important because they prevent bacteria from multiplying and growing. Antimicrobials are effective against a wide variety of infectious diseases caused by pathogens. In order to combat rising antimicrobial resistance, it is imperative to develop new and potentially beneficial antimicrobials that will be less toxic [1, 2]. The heterocyclic compounds possessing chromene moiety are widely used in many industries, containing pharmaceutics [3], cosmetics [4], biodegradable agrochemicals [5], and pigments [6]. 2-Amino-4*H*-chromenes as one of the most well-known chromene derivatives have attracted much attention for its medicinal and biological activities, such as antimalarial [7], anti-HIV [8], antifungal [9], antimicrobial [10], antitumor [11], antioxidant [12], antileishmanial [13], anti-inflammatory [14], hypotensive [15], and inhibitors properties [16]. As an example, compounds A [17], B [18], and C [19] exhibited antibacterial activities (Fig. 1). Additionally, they are widely used to treat neurodegenerative diseases by enhancing cognitive function such as, such as Parkinson, Alzheimer, schizophrenia, Down syndrome, myoclonus, and Huntington, as well as amyotrophic lateral sclerosis [20–24].

The importance of 2-amino-4*H*-chromene derivatives has resulted in the development of a variety of reactions to prepare them. One of the most important reactions in this context is the multicomponent condensation reaction of *OH*-Acids, aldehyde, and malononitrile. This transformation has been catalyzed with a variety of homogeneous or heterogeneous catalysts, such as, [Cu (bpdo)$_2$.2H$_2$O]$^{2+}$/montmorillonite [25], Basic ionic liquid [PEMIM][OH] [26], Ruthenia doped fluorapatite (RuO$_2$/



A B C

Fig. 1 Some biologically active compounds including 2-amino-4*H*-chromene moiety

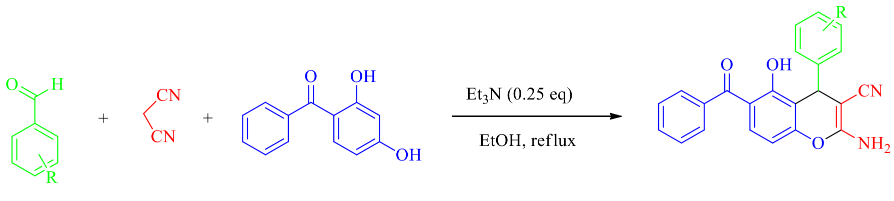
FAp) [27], Hyper-crosslinked microporous polyphenanthrene [28], Nano polypropylenimine dendrimer (DAB-PPI-G1) [29], $Ca(OH)_2$ [30], Tungstic acid functionalized mesoporous SBA-15 [31], Na_2CO_3 [32], CuO/ZnO@N-GQDs@l-proline hexagonal nanocomposite [33], *p*-Cymene Ru(II) complex [34], 4-(*N*,*N*-dimethylamino) pyridine (DMAP) [35], DABCO [36], Tetramethylguanidine [37], Diethylamine [38], Triethylamine [39], as well as Potassium phthalimide- N-oxyl (POPINO) [40]. Despite the fact that these procedures are suitable for synthesizing 4*H*-chromenes, many of them suffer from one or more drawbacks, such as long reaction times, difficult workups, the use of expensive catalysts, or the need for special equipment.

Multicomponent reactions (MCRs) can provide a cost-effective and time-saving method for constructing a wide range of chemicals including complex organic molecules, pharmaceuticals, and biologically active compounds. They have been extensively used in synthesizing natural products and other biologically active molecules since its discovery. In recent years, MCRs have gained significant popularity due to their various advantages, such as environmental friendliness, simplistic completion, mild conditions, and high efficiency [41].

The results of these findings encourage us to develop catalytically efficient, simple, fast, and green procedures for synthesizing heterocyclic compounds containing 2-amino-4*H*-chromene systems. Furthermore, as part of our research interest in the synthesis of potentially bioactive heterocyclic compounds [42–50], here we present the green protocol for synthesizing novel 2-amino-4*H*- chromene derivatives through a one-pot three-component condensation reaction of malononitrile, aromatic aldehydes, and 2,4-dihydroxybenzophenone in the presence of the catalytic amount of triethylamine (Scheme 1) and evaluation of their antioxidant and antibacterial activities.

Results and discussion

The optimal reaction conditions were determined by performing a three-component reaction with benzaldehyde (**1a**), malononitrile (**2**) with 2,4-dihydroxybenzophenone (**3**) in 10 mL ethanol with a catalyst. The optimal reaction conditions were investigated by performing a three-component reaction of the benzaldehyde



1a-m **2** **3** **4a-m**

1a: R=H
1b: R=2,4-diCl
1c: R=4-CHO
1d: R=4-CN
1e: R=4-Br
1f: R=4-Cl
1g; R=4-F
1h: R=3-NO_2
1i: R=3-Br
1j: R=3-Cl
1k: R=4-OMe
1l: R=2-Cl
1m:R=2-Me

Scheme 1 Preparation of 2-amino-4*H*-chromenes through a one-pot three-component condensation reaction

Table 1 The optimization of reaction conditions for the synthesis of compound **4a**

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield %[a,b]
1	–[c]	EtOH	reflux	240	trace
2	Piperidine (50)	EtOH	r.t	60	60
3	Et_3N (50)	EtOH	r.t	60	65
4	NaOH (50)	EtOH	r.t	60	42
5	KOH (50)	EtOH	r.t	60	45
6	K_2CO_3 (50)	EtOH	r.t	60	50
7	Et_3N (10)	EtOH	r.t	60	50
8	Et_3N (25)	EtOH	r.t	60	65
9	Et_3N (75)	EtOH	r.t	60	67
10	Et_3N (100)	EtOH	r.t	60	67
11	Et_3N (25)	MeOH	r.t	60	55
12	Et_3N (25)	H_2O	r.t	60	30
13	Et_3N (25)	EtOH:H_2O (1:1)	r.t	60	50
14	Et_3N (25)	CH_3CN	r.t	60	60
15	Et_3N (25)	THF	r.t	60	50
16	Et_3N (25)	$CHCl_3$	r.t	60	50
17	Et_3N (25)	Et_2O	r.t	60	40
18	Et_3N (25)	EtOH	40	60	74
19	Et_3N (25)	EtOH	60	60	83
20	**Et_3N (25)**	**EtOH**	Reflux	**60**	**90**

[a]Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and 2,4-dihydroxybenzophenone (1 mmol) in the presence of the catalyst in 10 mL solvent. [b]Isolated yields. [c]Free-catalyst condition

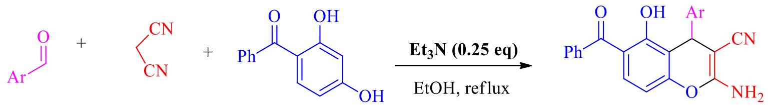
(**1a**), malononitrile (**2**) with 2,4-dihydroxybenzophenone (**3**) in the presence of a catalyst in 10 mL ethanol as a model reaction. As tabulated in Table 1, the reaction was examined in the presence of 0.5 equivalents of several bases such as piperidine, triethylamine, sodium hydroxide, potassium hydroxide, potassium carbonate, as well as a free-catalyst condition (entries 1–6). The results showed that Et_3N afforded to the desired product in higher yield than other bases (entry 3 compared to entries 2 and 4–6). Additionally, the reaction was tested with various amounts of Et_3N (entries 7–10) and a 25% proportion was determined as optimum (entry 8) and higher amounts of triethylamine did not improve the reaction yield. Following this, the model reaction was tested in various solvents, including MeOH, H_2O, EtOH, EtOH:H_2O, CH_3CN, THF, $CHCl_3$, and Et_2O demonstrating that EtOH is the optimal solvent for this reaction (entries 11–17). As a final step, the reaction was investigated at various temperatures (entries 18–20). Compared to entries 18 and 19, entry 20 yielded the highest yield when the reaction was carried out in refluxed ethanol.

Three-component reaction of aromatic aldehydes **1a–m**, malononitrile **2**, and 2,4-dihydroxybenzophenone **3** in refluxed ethanol and in the presence of Et_3N (25%) was carried out to determine the scope and limitations of this reaction. Table 2 shows good to excellent yields of the corresponding products (80–99%). According to the results, the reaction yields increased for aromatic aldehydes containing electron withdrawing substituents at the *para* position (entries 2–6 compared to entries 1 and 11). These aromatic aldehydes were more effective at obtaining the desired product with higher yield than aromatic aldehydes with electron withdrawing substituents at the *ortho* position (for example entry 6 compare to entry 12). It can be due to the result of steric hindrance of substituents at their *ortho* position of aromatic rings of the aldehydes.

The structure of all the synthesized 2-amino-4*H*-chromens was confirmed with IR, ^{1}H NMR, ^{13}C NMR, and mass spectrum. The FT-IR spectrum of **4f** displays two signals at 3334 cm^{-1} and 3199 cm^{-1} for NH_2 group, at 3059 cm^{-1} for the C_{sp2} –H group, at 2920 cm^{-1} for the C_{sp3} –H group, a sharp signal at 2205 cm^{-1} for the CN group, a strong absorption band at 1659 cm^{-1} for the carbonyl group, at 1603 cm^{-1} for the C=C group, and a sharp signal at 1254 cm^{-1} for the $C_{sp}{}^2$ –O group. The mass spectrum of this compound exhibits the two molecular ion peaks at $m/z = 404$ ($M^{+\cdot} + 2$) and $m/z = 402$ ($M^{+\cdot}$), and the base peak at $m/z = 291$ ($M^{+\cdot}$ -ClC_6H_4) agrees with the proposed structure.

The ^{1}H NMR spectrum of **4f** in DMSO-d_6 at 25 °C exhibits a singlet at about 4.76 ppm for the CH group of 4*H*-pyran moiety, a doublet at about 6.73 ppm (1H, $^3J_{HH} = 8.8$ Hz) for the aromatic CH proton, a broad signal at about 7.18 ppm for the exchangeable protons of NH_2 group, three doublets at about 7.22 (2H, $^3J_{HH} = 8.4$ Hz), 7.37 (2H, $^3J_{HH} = 8.4$ Hz), 7.49 (1H, $^3J_{HH} = 8.8$ Hz), a triplet signal at about 7.55 ppm (2H, $^3J_{HH} = 6.8$ Hz), a multiple signal at about 7.62–7.64 (3H) for the aromatic CH protons, and a broad signal at about 12.26 ppm for the exchangeable proton of OH group. The ^{13}C NMR spectrum of **4f** in DMSO-d_6 at 25 °C displays a signal at about 36.1 ppm for the CH group of 4*H*-pyran moiety, and signals at about 57.1, 160.8, 116.5 and 200.0 ppm for the quaternary carbons ($C^* = C$–N and $C = C^*$–N), CN group, and carbonyl group of ketone, respectively.

Table 2 Synthesis of 2-amino-4*H*-chromene derivatives **4a–m**



1a-m **2** **3** **4a-m**

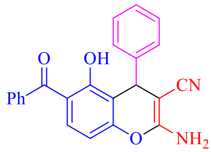
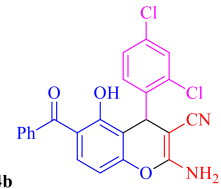
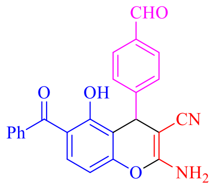
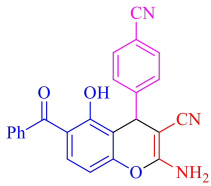
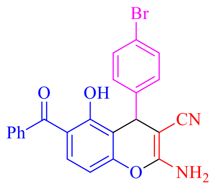
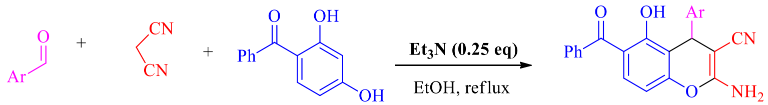
Entry	Ar	Time (min)	Yield (%)[a,b]	Mp °C	Structure
1	C_6H_5	60	90	276–278 (280–282)[c] [29]	 **4a**
2	2,4-diCl-C_6H_3	30	100	282–284	 **4b**
3	4-CHO-C_6H_4	30	98	218–220	 **4c**
4	4-CN-C_6H_4	30	96	254–255	 **4d**
5	4-Br-C_6H_4	30	95	254–256 (248–250)[c] [29]	 **4e**

Table 2 (continued)



1a-m **2** **3** **4a-m**

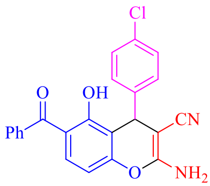
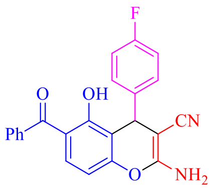
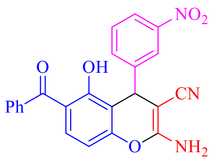
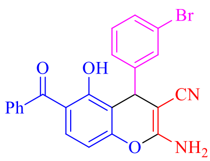
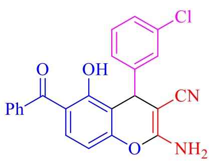
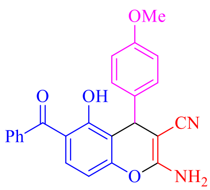
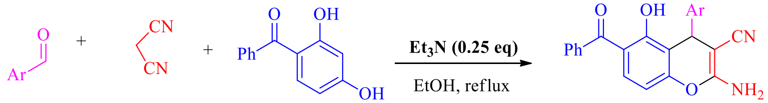
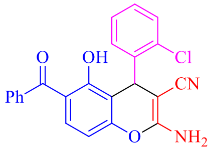
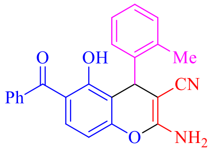
Entry	Ar	Time (min)	Yield (%)[a,b]	Mp °C	Structure
6	4-Cl-C_6H_4	30	94	235–236	 **4f**
7	4-F-C_6H_4	30	90	285–287	 **4g**
8	3-NO_2-C_6H_4	60	90	242–244	 **4h**
9	3-Br-C_6H_4	60	90	248–250	 **4i**
10	3-Cl-C_6H_4	60	90	235–236	 **4j**
11	4-OMe-C_6H_4	120	85	238–240 (232–233)[c] [29]	 **4k**

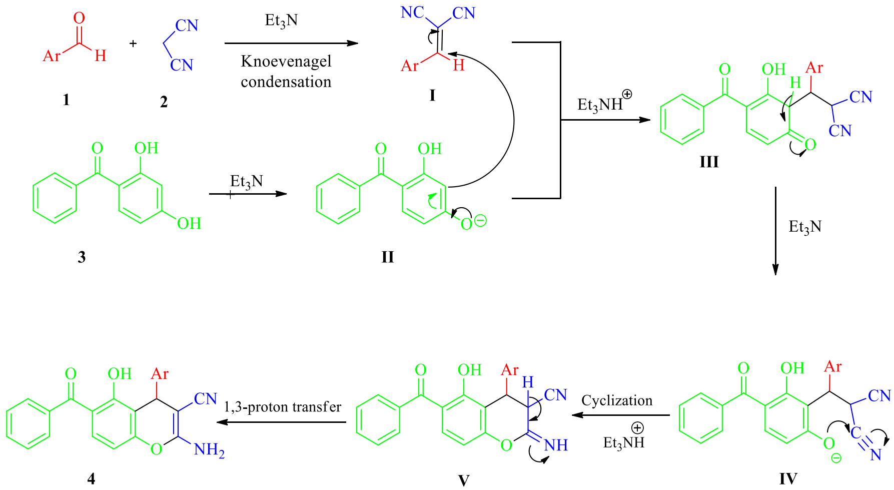
Table 2 (continued)



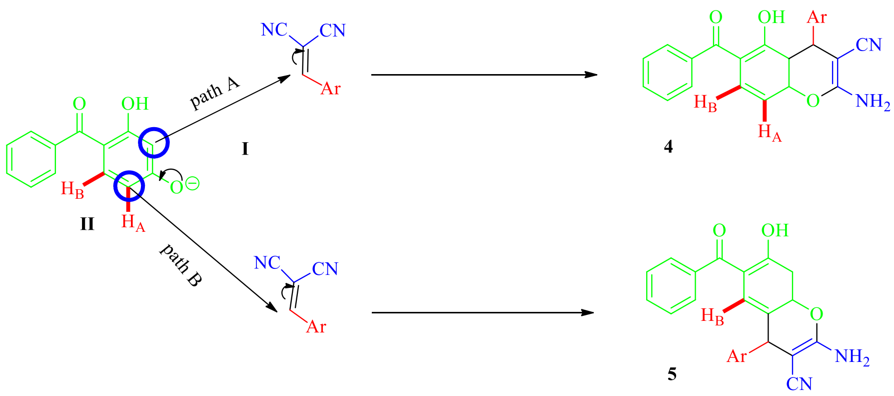
1a-m **2** **3** **4a-m**

Entry	Ar	Time (min)	Yield (%)[a,b]	Mp °C	Structure
12	2-Cl-C_6H_4	120	82	273–275	 **4l**
13	2-OMe-C_6H_4	120	80	255–257	 **4m**

[a]Reaction conditions: aromatic aldehydes (1 mmol), malononitrile (1 mmol), and 2,4-dihydroxybenzophenone (1 mmol) in the presence of the Et_3N (0.25 mmol), in 10 mL ethanol. [b]Isolated yields. [c]Reported melting point



Scheme 2 A proposed mechanism for preparing 2-amino-4*H*-chromenes **4a–m**



Scheme 3 Two possible positions for performing Michael addition

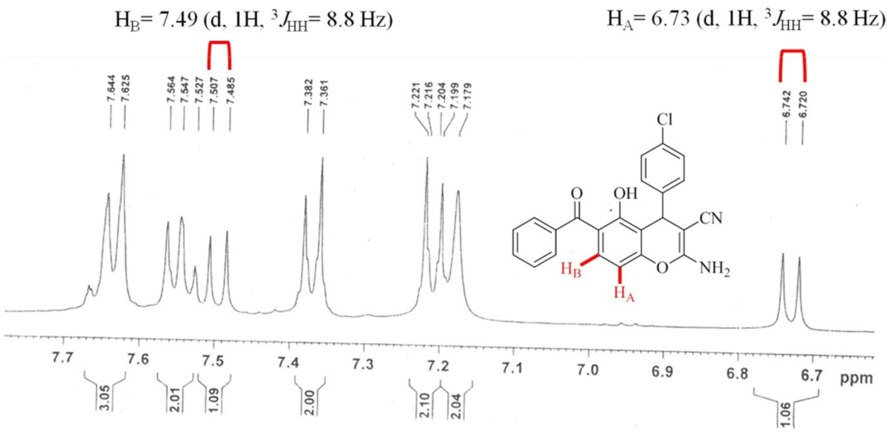


Fig. 2 The expanded ^{1}H NMR spectrum of compound **4f**

Also, the ^{13}C NMR spectrum of **4f** exhibited 14 signals with relevant chemical shifts for the aromatic carbons.

Scheme 2 illustrates a proposed mechanism for this reaction. Initially, *α,β*-unsaturated **I** is formed by the Knoevenagel condensation between aromatic aldehyde **1** and malononitrile **2** in the presence of triethylamine. In the basic condition, 2,4-dihydroxybenzophenone **3** loses its proton and is converted to the enolate ion **II** that performs Michael addition on C_β of compound **I** to obtain intermediate **III**. In the following, it carried out a cyclization reaction to afford compound **V** which lead to the corresponding product **4** through a 1,3-proton transfer.

As it can be seen in Scheme 3, there are two possible positions including path **A** and **B** for performing Michael's addition on C_β of compound **I** which could be led to products **4** and **5**, respectively.

Investigation of the ^{1}H NMR spectra of products **4a-m** showed that the splitting of H_B is appeared as a doublet signal which confirms the reaction has progressed only through path **A** and only product **4** was obtained. For example, expanded ^{1}H NMR spectrum of compound **4f** is shown in Fig. 2. Observing two doublet signals for H_A (6.73 ppm) and H_B (7.49 ppm) confirms that the reaction mechanism is performed only through path **A**.

Antioxidant activity

DPPH radical scavenging was used by Blois's method to assess the in vitro antioxidant activity of 2-amino-4*H*-chromenes **4a–m** and compound **3**. Antioxidants containing a high number of heteroatoms, π-electrons, and exchangeable hydrogen atoms are more effective to scavenge free radicals produced by DPPH. An absorption decrease at 517 nm wavelength could indicate the presence of antioxidants by changing the color of the DPPH test solution from dark purple to light yellow. Figure 3 shows that the synthesized compounds inhibited DPPH with potencies ranging from 71 to 95 percent, much better than ascorbic acid as a standard antioxidant (84%). Also, the IC_{50} values of the antioxidant activities of all tested samples were studied. Among these compounds, **4b** exhibited the highest free radical scavenging activity ($IC_{50} = 10.32 \pm 0.35$ μM), this could be due to the fact that it contains more heteroatoms with lone-pair electrons in its structure than other examined compounds and also includes exchangeable protons in NH_2 and OH groups. [51].

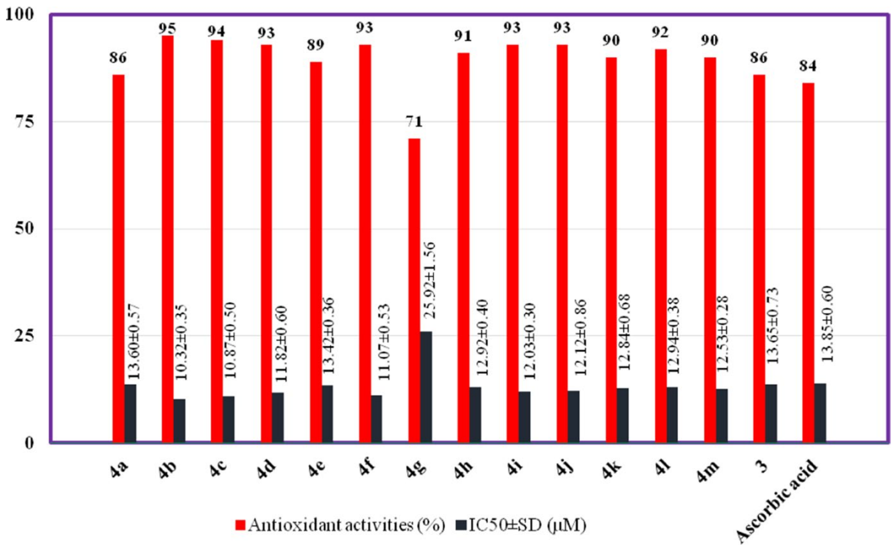


Fig. 3 Antioxidant activity of the synthesized compounds **3** and **4a–m**

Table 3 Antibacterial activity of the compounds **4a–m** using MIC values[a]

Entry	Sample	*Staphylococcus aureus* ATCC25923	*Escherichia coli* ATCC1399
1	**4a**	2.5	2.5
2	**4b**	0.625	1.25
3	**4c**	2.5	2.5
4	**4d**	1.25	2.5
5	**4e**	1.25	2.5
6	**4f**	1.25	2.5
7	**4 g**	0.625	1.25
8	**4 h**	1.25	2.5
9	**4i**	2.5	2.5
10	**4j**	1.25	2.5
11	**4 k**	2.5	2.5
12	**4 l**	1.25	2.5
13	**4 m**	2.5	2.5
14	**3**	> 2.5	2.5
15	Cefixim	0.01	0.02

[a]Minimum inhibitory concentration, values as mM

Antibacterial activity

The minimum inhibitory concentration (MIC) method was applied to investigate the antibacterial activity of compounds **3** and **4a–m** against *Staphylococcus aureus* (ATCC2592) as Gram-positive bacteria and Gram-negative bacteria *Escherichia coli* (ATCC1399), and was compared with Cefixim as a standard antibiotic. According to Table 3, the synthesized compounds **4a–m** are generally more effective than starting material (**3**) against all of the tested microorganisms. In addition, all of the examined samples showed higher antibacterial activity against Gram-positive bacteria than Gram-negative bacteria. Among these compounds, **4b** and **4 g** exhibited the highest activity against *S. aureus* as Gram-positive bacteria (MIC = 0.625 mM) and *E. coli* Gram-negative bacteria (MIC = 1.25 mM).

Conclusion

We have synthesized a novel series of 2-amino-4*H*-chromene derivatives by the three-component reaction between 2,4-dihydroxybenzophenone, malononitrile and a variety of aromatic aldehydes in the presence of triethylamine as catalyst in ethanol as a green solvent with high to excellent yields of the products. The structure of the synthesized products was characterized by FTIR, ^{1}H, ^{13}C NMR spectroscopy, CHN analyses, and mass spectrometry. In comparison to other reported procedures, this procedure is simple, eco-friendly, requires a short reaction time, and allows for easy separation of the products. The antibacterial and antioxidant activity of all of the products investigated against *Staphylococcus aureus* (a Gram-positive bacteria) and *Escherichia coli* (a Gram-negative bacteria) using the MIC method, as well as the radical scavenger DPPH. The results demonstrate that compound **4b** showed the highest antioxidant and antibacterial activities. We are investigating novel approaches to synthesize more complex structures that exhibit antimicrobial activities in continuation of our studies in heterocyclic chemistry.

Experimental

The following chemicals were purchased from the Merck Company (Germany): malononitrile, 2,4-dihydroxybenzophenone, triethylamine, aromatic aldehydes, and solvents. The structures of synthesized samples **4a–m** were confirmed using the following analyses. The melting point of the compounds **4a–m** was determined with Electrothermal IA9100 (Essex, UK). ^{1}HNMR and ^{13}CNMR spectra were recorded using DMSO-d_6 as solvent and TMS as an internal reference on a Bruker-400 Avance III spectrometer (Bruker, Germany). The FTIR spectra were recorded using a Bruker vector 22 spectrometer (Bruker, Karlsruhe, Germany). Mass spectra were measured out on Finnigan-MAT 8430 mass spectrometer operating in electron impact mode. The UV/Vis spectrophotometry was achieved by Anthos 2020 Microplate Reader (Anthos, Biochrom, UK).Elemental analyses were accomplished using a Heraeus CHN-O rapid analyzer (Germany). The GC report for compound **4b** was performed by a Agilent 7890A (USA).

General procedure for the synthesis of compounds 4a–m

A mixture of aromatic aldehydes **1a–m** (1.0 mmol), malononitrile **2** (1.0 mmol), and 2,4-dihydroxybenzophenone **3** (1.0 mmol) in the presence of 25% mole triethylamine was magnetically stirred in 10 ml of ethanol and agitated at the reflux condition for an appropriate time (Table 2). After completion of the reaction (followed by TLC), the mixture was allowed to cool to room temperature. The precipitated product was filtered and crystallized in ethanol to obtain the pure desired product **4a–m**.

2-Amino-6-benzoyl-4-phenyl-5-hydroxy-4H-chromene-3-carbonitrile (4a, $C_{23}H_{16}N_2O_3$)

Cream powder, m.p. 276–278 °C (Reported 280–282 °C [29],), yield: 90%; IR (KBr) (υ_{max}, cm^{-1}): 3501 (OH), 3422 and 3324 (NH_2), 3032 (C_{sp2} –H), 2922 (C $_{sp3}$–H), 2184 (CN), 1653 (C=O), 1603 (C=C), 1253(C $_{sp2}$–O). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ_H 4.75 (s, 1H, CH), 6.74 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.13 (s, 2H, NH_2), 7.19 (d, 2H, $^3J_{HH}$=7.2 Hz, $2CH_{Ar}$), 7.21 (t, 1H, $^3J_{HH}$=8.0 Hz, CH_{Ar}), 7.31 (t, 2H, $^3J_{HH}$=7.6 Hz, $2CH_{Ar}$), 7.50 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.55 (t, 2H, $^3J_{HH}$=8.4 Hz, $2CH_{Ar}$), 7.63–7.67 (m, 3H, $3CH_{Ar}$), 12.41 (s, 1H, OH).^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 36.6 (CH), 57.6 (C^*=C–N), 108.0 and 112.0 (Cq), 116.6 (CN), 120.5 (Cq), 127.2, 127.6, 128.9, 129.3, 132.6 133.9 and 137.6 (CH), 145.2, 154.3 and 160.0 (Cq), 160.7

(C=C*–N), 200.1 (C=O). MS: *m/z* (%) 368 ($M^{+\cdot}$, 15), 291 (M^+ –C_6H_4, 100), 213 [(M^+–($CH_3C_6H_4+C_6H_5$)), 57], 185 [(M^+–($C_6H_5+C_6H_5CO+H$), 5)], 105 ($C_6H_5CO^+$, 22), 77 ($C_6H_5^+$, 11); Anal. Calcd for $C_{23}H_{16}N_2O_3$ (368.12): C, 74.99; H, 4.38; N, 7.60, Found: C, 75.10; H, 4.37; N, 7.57.

2-Amino-6-benzoyl-4-(2,4-dichlorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4b, $C_{23}H_{14}Cl_2N_2O_3$)

Cream powder, m.p. 280–282 °C, yield: > 99%; IR (KBr) (υ_{max}, cm^{-1}): 3402 (OH), 3312 and 3201 (NH_2), 3083 (C_{sp2} –H), 2927 (C_{sp3}–H), 2198 (CN), 1659 (C=O), 1612 (C=C), 1259 (C_{sp2} –O). ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 5.23 (s, 1H, CH), 6.73 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.16 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.19 (s, 2H, NH_2), 7.36 (dd, 1H, $^3J_{HH}$=8.4 Hz,$^4J_{HH}$=2.4 Hz, CH_{Ar}), 7.52 (dd, 2H, $^3J_{HH}$=9.2 Hz, $^3J_{HH}$=8.0 Hz, $2CH_{Ar}$), 7.56–7.57 (m, 2H, $2CH_{Ar}$), 7.62–7.67(m, 3H, $3CH_{Ar}$), 12.38 (s, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 33.9 (CH), 55.6 (C*=C–N), 107.9 and 111.0 (Cq), 116.3 (CN), 119.8 and 128.3 (Cq), 128.9, 129.3 (CH), 132.3 (Cq), 132.4, 132.6 and 133.4 (CH), 134.3 (Cq), 137.4 (CH), 141.3 and 141.4 (Cq),154.5 and 159.9 (CH), 160.9 (C=C*–N), 200.0 (C=O). MS: *m/z* (%) 440 (M^+ +4, 3), 438 (M^+ +2, 7), 436 ($M^{+\cdot}$, 11), 403 (($M^{+\cdot}$+2)–Cl, 2)), 401 (M^+ -Cl, 7), 291 ($M^{+\cdot}$–$Cl_2C_6H_3$, 100), 213 [($M^{+\cdot}$–($Cl_2C_6H_3+C_6H_5+H$)), 60], 105 ($C_6H_5CO^+$, 13), 77 ($C_6H_5^+$, 15); Anal. Calcd for $C_{23}H_{14}Cl_2N_2O_3$ (436.04): C, 63.17; H, 3.23; N, 6.41, Found: C, 63.06; H, 3.22; N, 6.39.

2-Amino-6-benzoyl-4-(4-formylphenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4c, $C_{24}H_{16}N_2O_4$)

Cream powder, m.p. 218–220 °C, yield: 98%; IR (KBr) (υ_{max}, cm^{-1}): 3449 (OH), 3348 and 3206 (NH_2), 3064 (C_{sp2} –H), 2924 (C_{sp3}–H), 2850 (CO–H), 2195 (CN), 1692 and 1650 (C=O), 1605 (C=C), 1256 (C_{sp2} –O). ^1H NMR (400.1 MHz, DMSO-d_6): δ_H 4.86 (s, 1H, CH), 6.77 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.22 (s, 2H, NH_2), 7.41 (d, 2H $^3J_{HH}$=8.0 Hz, $2CH_{Ar}$), 7.52 (d, 2H, $^3J_{HH}$=8.8 Hz, $2CH_{Ar}$), 7.55 (d, 2H, $^3J_{HH}$=7.6 Hz, $2CH_{Ar}$), 7.62–7.65 (m, 2H, $2CH_{Ar}$), 7.87 (d, 2H, $^3J_{HH}$=8.4 Hz, $2CH_{Ar}$), 9.92 (s, 1H, CHO), 12.21 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 36.8 (CH), 56.7 (C*=C–N), 108.1 and 111.8 (Cq), 116.5 (CN), 120.2 (Cq), 128.5, 128.9, 129.3, 130.4, 132.7, 134.2 and 135.4 (CH), 137.5, 151.7, 154.1 and 159.6 (Cq), 160.7 (C=C*–N), 193.1 and 200.0 (C=O). MS: *m/z* (%) 396 ($M^{+\cdot}$, 24), 291 ($M^{+\cdot}$–$CHOC_6H_4$, 100), 291 ($M^{+\cdot}$–$CHOC_6H_4$, 100), 213 [($M^{+\cdot}$–($CHOC_6H_4+C_6H_5$), 46)], 185 [($M^{+\cdot}$–($CHOC_6H_4+C_6H_5CO+H$), 5)], 105 ($C_6H_5CO^+$, 10), 77 ($C_6H_5^+$, 12); Anal. Calcd for $C_{24}H_{16}N_2O_4$ (396.11): C, 72.72; H, 4.07; N, 7.07, Found: C, 72.80; H, 4.09; N, 7.05.

2-Amino-6-benzoyl-4-(4-cyanophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4d, $C_{24}H_{15}N_3O_3$)

Cream powder, m.p. 254–255 °C, yield: 96%; IR (KBr) (υ_{max}, cm^{-1}): 3545 (OH), 3451 and 3351 (NH_2), 3105 (C_{sp2} –H), 2922 (C_{sp3}–H), 2226 and 2197 (CN), 1650

(C=O), 1607 (C=C), 1256 (C $_{sp2}$ –O). ^{1}H NMR (400.1 MHz, DMSO-d$_6$): δ_H 4.87 (s, 1H, CH), 6.75 (d, 1H, $^3J_{HH}$=9.2 Hz, CH$_{Ar}$), 7.26 (s, 2H, NH$_2$), 7.39 (d, 2H, $^3J_{HH}$=8.4 Hz, 2CH$_{Ar}$), 7.50–7.56 (m, 3H, 3CH$_{Ar}$), 7.63–7.65 (m, 3H, 3CH$_{Ar}$), 7.79 (d, 2H, $^3J_{HH}$=7.6 Hz, 2CH$_{Ar}$), 12.30 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d$_6$): δ_C 38.8 (CH), 56.5 (C*=C–N), 108.1, 110.1 and 111.5 (Cq), 116.6 and 119.2 (CN), 120.1 (Cq), 128.8, 128.9, 129.3, 132.7 and 133.1 (CH), 134.2 (Cq), 137.5 and 150.5 (CH), 154.1 and 160.0 (Cq$_{Ar}$), 160.6 (C=C*–N), 199.9 (C=O). MS: *m/z* (%) 393 ($M^{+\cdot}$+23), 291 ($M^{+\cdot}$–CNC$_6$H$_{4,}$ 100), 213 [($M^{+\cdot}$–(CNC$_6$H$_4$+C$_6$H$_4$+H), 60], 185 [($M^{+\cdot}$–(CNC$_6$H$_4$+C$_6$H$_5$CO+H), 105 (C$_6$H$_5$CO$^+$, 15), 77 (C$_6$H$_5$$^+$, 16); Anal. Calcd for $C_{24}H_{15}N_3O_3$ (393.11): C, 73.27; H, 3.84; N, 10.68, Found: C, 73.36; H, 3.82; N, 10.70.

2-Amino-6-benzoyl-4-(4-bromorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4e, $C_{23}H_{15}BrN_2O_3$)

Orange powder, m.p. 254–256 °C (Reported 248–250 °C [29],), yield: 95%; IR (KBr) (υ_{max}, cm^{-1}): 3442 (OH), 3329 and 3251 (NH$_2$), 3054 (C $_{sp2}$ –H), 2921 (C $_{sp3}$–H), 2199 (CN), 1662 (C=O), 1607 (C=C), 1256 (C $_{sp2}$ –O). ^{1}H NMR (400.1 MHz, DMSO-d$_6$): δ_H 4.75 (s, 1H, CH), 6.74 (d, 1H, $^3J_{HH}$=9.2 Hz, CH$_{Ar}$), 7.15 (d, 2H, $^3J_{HH}$=8.0 Hz, 2CH$_{Ar}$), 7.19 (s, 2H, NH$_2$), 7.49–7.53 (m, 3H, 3CH$_{Ar}$), 7.56 (d, 2H $^3J_{HH}$=7.2 Hz, 2CH$_{Ar}$), 7.63–7.67 (m, 3H, 3CH$_{Ar}$), 12.40 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d$_6$): δ_C 36.2(CH), 57.0(C*=C–N), 108.1 and 112.2 (Cq), 116.5 (CN), 120.2 and 120.3(Cq), 128.9, 129.3,130.0, 131.8, 132.6, 134.0 and 137.5 (CH), 144.6, 154.1 and 159.9 (Cq), 160.7 (C=C*–N), 200.0 (C=O). MS: *m/z* (%) 448 ($M^{+\cdot}$+2, 14), 446 ($M^{+\cdot}$, 14), 367 ($M^{+\cdot}$ –Br, 5), 291 ($M^{+\cdot}$–BrC$_6$H4, 100), 213 [($M^{+\cdot}$–(BrC$_6$ H$_4$+C$_6$H$_5$), 64)], 185 [($M^{+\cdot}$–(BrC$_6$H$_4$+C$_6$H$_5$CO+H), 5)], 105 (C$_6$H$_5$CO$^+$, 17), 77 (C$_6$H$_5$$^+$, 19); Anal. Calcd for $C_{23}H_{15}BrN_2O_3$ (446.03): C, 61.76; H, 3.38; N, 6.26, Found: C, 61.57; H, 3.40; N, 6.28.

2-Amino-6-benzoyl-4-(4-chlorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4f, $C_{23}H_{15}ClN_2O_3$)

Yellow powder, m.p. 235–236 °C, yield: 94%; IR (KBr) (υ_{max}, cm^{-1}): 3433 (OH), 3334 and 3199 (NH$_2$), 3059 ($C_{sp}{}^2$ –H), 2920 ($C_{sp}{}^3$–H), 2205 (CN), 1659 (C=O), 1603 (C=C), 1254 ($C_{sp}{}^2$ –O). ^{1}H NMR (400.1 MHz, DMSO-d$_6$): δ_H 4.76 (s, 1H, CH), 6.73 (d, 1H, $^3J_{HH}$=8.8 Hz, CH$_{Ar}$), 7.18 (s, 2H, Exchangeable with D$_2$O, NH$_2$), 7.22 (d, 2H, $^3J_{HH}$=8.4 Hz, 2CH$_{Ar}$), 7.37 (d, 2H, $^3J_{HH}$=8.4 Hz, 2CH$_{Ar}$), 7.49 (d, 1H, $^3J_{HH}$=8.8 Hz, CH$_{Ar}$), 7.55 (t, 2H, $^3J_{HH}$=6.8 Hz, 2CH$_{Ar}$), 7.62–7.64 (m, 3H, 3CH$_{Ar}$), 12.26 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d$_6$): δ_C 36.1(CH), 57.1 (C*=C–N), 107.9 and 112.3 (Cq), 116.5 (CN), 120.3 (Cq) 128.9, 129.0, 129.3, 129.6, 131.7 and 132.6 (CH), 134.0 and 137.5 (Cq), 144.2 (CH), 154.1 and 159.9 (Cq), 160.8 (C=C*–N), 200.0 (C=O). MS: *m/z* (%) 404(($M^{+\cdot}$+2), 5), 402 ($M^{+\cdot}$, 17), 291 [($M^{+\cdot}$ -ClC$_6$H$_4$), 100], 213 [($M^{+\cdot}$–(ClC$_6$H$_4$+C$_6$H$_5$+H), 57], 185 [($M^{+\cdot}$–(ClC$_6$H$_4$+C$_6$H$_5$CO+H), 5], 105 (C$_6$H$_5$CO$^+$, 13), 77 (C$_6$H$_5$$^+$, 16); Anal. Calcd for $C_{23}H_{15}ClN_2O_3$ (402.08): C, 68.58; H, 3.75; N, 6.95, Found: C, 68.67; H, 3.74; N, 6.93.

2-Amino-6-benzoyl-4-(4-fluorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4 g, $C_23H_{15}FN_2O_3$)

Pink powder, m.p. 285–287 °C, yield: 90%; IR (KBr) (υ_{max}, cm^{-1}): 3442 (OH), 3327 and 3411 (NH_2), 3211 (C_{sp2} –H), 3061 (C_{sp3}–H), 2193 (CN), 1658 (C=O), 1608 (C=C), 1261 (C_{sp2} –O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 4.77 (s, 1H, CH), 6.74 (d, 1H, $^3J_{HH}$=9.2 Hz, CH_{Ar}), 7.13 (t, 2H, $^3J_{HH}$=8.8 Hz, $2CH_{Ar}$), 7.16 (s, 2H, NH_2), 7.20–7.24 (m, 2H, $2CH_{Ar}$), 7.49 (d, 1H $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.53–7.57 (m, 2H, $2CH_{Ar}$), 7.63–7.64 (d, 3H, $^3J_{HH}$=7.6 Hz, $3CH_{Ar}$), 12.42 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 36.0 (CH), 57.5 (C^*=C–N), 108.1 and 112.6 (Cq), 115.6 (d, $^2J_{CF}$=21.4 Hz) (CH), 116.5 (CN), 120.4 (Cq), 128.9, 129.3, 129.5 (d, $^3J_{CF}$=8.1 Hz), 132.6, 133.9 and 137.6 (CH), 141.4 (d, $^4J_{CF}$=2.7 Hz), 154.1 and 159.9 (Cq), 160.7 (C=C^*–N), 161.4 (d, $^1J_{CF}$=241.2 Hz) (Cq), 200.10 (C=O). MS: *m/z* (%) 386 ($M^{+\cdot}$, 38), 291 ($M^{+\cdot}$–FC_6H_4, 100), 213 [($M^{+\cdot}$–(FC_6H_4+C_6H_5), 69)], 185 [($M^{+\cdot}$–(FC_6H_4+C_6H_5CO+H), 5)], 105 ($C_6H_5CO^+$, 15), 77 ($C_6H_5^+$, 19); Anal. Calcd for $C_{23}H_{15}FN_2O_3$ (386.11): C, 71.50; H, 3.91; N, 7.25, Found: C, 71.49; H, 3.93; N, 7.22.

2-Amino-6-benzoyl-4-(3-nitrophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4 h, $C_{23}H_{15}N_3O_5$)

Brown powder, m.p. 242–244 °C, yield: 90%; IR (KBr) (υ_{max}, cm^{-1}): 3429 (OH), 3338 and 3207 (NH_2), 3061 (C_{sp2} –H), 2922 (C_{sp3}–H), 2195 (CN), 1645 (C=O), 1609 (C=C), 1530 and 1343 (NO_2), 1256 (C_{sp2} –O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 4.99 (s, 1H, CH), 6.78 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.29 (s, 2H, NH_2), 7.51–7.56 (m, 3H, $3CH_{Ar}$), 7.63–7.66 (m, 4H, $4CH_{Ar}$), 7.70 (d, 1H, $^3J_{HH}$=7.6 Hz, CH_{Ar}), 8.02 (s, 1H, CH_{Ar}),), 8.11 (d, 1H, $^3J_{HH}$=8.0 Hz, CH_{Ar}), 12.34 (s, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 36.4(CH), 56.6 (C^*=C–N), 108.2 and 111.6 (Cq), 116.8 (CN), 120.1 (Cq), 122.1, 122.4, 128.9, 129.4, 130.7 and 132.7 (CH), 134.3 (Cq), 134.6, 137.5 and 147.3 (CH), 148.2, 154.0 and 160.1 (Cq), 160.5 (C=C^*–N), 199.9 (C=O). MS: *m/z* (%) 413 ($M^{+\cdot}$+13), 291 ($M^{+\cdot}$–$NO_2C_6H_4$, 100), 213 [($M^{+\cdot}$–($NO_2C_6H_4$+C_6H_5+H), 37], 185 [($M^{+\cdot}$–($NO_2C_6H_4$+C_6H_5CO+H), 5)], 105 ($C_6H_5CO^+$, 6), 77 ($C_6H_5^+$, 7); Anal. Calcd for $C_{23}H_{15}N_3O_5$ (413.10): C, 66.83; H, 3.66; N, 10.16, Found: C, 66.75; H, 3.68; N, 10.18.

2-Amino-6-benzoyl-4-(3-bromorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4i, $C_{23}H_{15}BrN_2O_3$)

Yellow powder, m.p. 248–250 °C, yield: 90%; IR (KBr) (υ_{max}, cm^{-1}): 3439 (OH), 3340 and 3218 (NH_2), 3054 (C_{sp2} –H), 2918 (C_{sp3}–H), 2193 (CN), 1647 (C=O), 1606 (C=C), 1254 (C_{sp2}–O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 4.78 (s, 1H, CH), 6.75 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}),7.19 (d, 1H, $^3J_{HH}$=8 Hz, CH_{Ar}), 7.21 (s, 2H, NH_2), 7.29 (t, 1H, $^3J_{HH}$=7.6 Hz, CH_{Ar}), 7.35 (t, 1H, $^4J_{HH}$=1.6 Hz, CH_{Ar}), 7.43 (d, 1H, $^3J_{HH}$=7.6 Hz, CH_{Ar}), 7.51 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.53–7.57 (m, 2H, $2CH_{Ar}$), 7.63–7.67 (m, 3H, $3CH_{Ar}$), 12.37 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 36.3(CH), 57.0(C^*=C–N), 108.1, 112.0 (Cq), 116.6

(CN), 120.2 and 122.1 (Cq), 126.9, 128.9, 129.3 130.2 130.3, 131.3, 132.6, 134.1 and 137.5 (CH), 147.8, 154.1 and 160.0 (Cq), 160.6 (C=C*–N), 199.9 (C=O). MS: *m/z* (%) 448 ($M^{+\cdot}+2$, 2), 446 ($M^{+\cdot}$, 2), 367 ($M^{+\cdot}$–Br, 5), 307 [($M^{+\cdot}$–(Br+CN+NH_2+OH+H), 53], 291 ($M^{+\cdot}$–BrC_6H_4, 32), 261 [($M^{+\cdot}$–(BrC_6H_4 + CH+OH), 76)], 189 [($M^{+\cdot}$ -(BrC_6H_4+C_6H_4 –CN+H, 100)], 105 ($C_6H_4CO^+$, 6)، 77 (C_6H_5 $^+$, 7); Anal. Calcd for $C_{23}H_{15}BrN_2O_3$ (446.03): C, 61.76; H, 3.38; N, 6.26, Found: C, 61.55; H, 3.35; N, 6.28.

2-Amino-6-benzoyl-4-(3-chlorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4j, $C_{23}H_{15}ClN_2O_3$)

Orange powder, m.p. 231–233 °C, yield: 90%; IR (KBr) (υ_{max}, cm^{-1}): 3433 (OH), 3334 and 3199 (NH_2), 3059 (C $_{sp2}$ –H), 2920 (C $_{sp2}$–H), 2205 (CN), 1745 (C=O), 1659 (C=C), 1254 (C $_{sp2}$ –O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 4.79 (s, 1H, CH), 6.75 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.15 (d, 1H, $^3J_{HH}$=7.6 Hz, CH_{Ar}), 7.21 (s, 3H, NH_2 + CH_{Ar}), 7.28–7.31 (m, 1H), 7.36 (t, 1H, $^3J_{HH}$=7.6 Hz, CH_{Ar}), 7.51 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.55 (dd, 2H, $^3J_{HH}$=8.0 Hz, $^3J_{HH}$=8.0 Hz, $2CH_{Ar}$), 7.64–7.66 (m, 3H, $3CH_{Ar}$), 12.20 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 36.4 (CH), 57.0 (C*=C–N), 108.1 and 112.0 (Cq), 116.7 (CN), 120.3 and 126.5 (Cq), 127.2, 127.4, 128.9, 129.3, 131.0, 132.6 and 133.4 (CH), 134.1 (Cq), 137.6, and 147.6 (CH), 154.1 and 160.0 (Cq), 160.6 (C=C*–N), 199.9 (C=O). MS: *m/z* (%) 404 ($M^{+\cdot}+2$), 7), 402 ($M^{+\cdot}$, 21), 291 [($M^{+\cdot}$ -ClC_6H_4), 100], 213 [($M^{+\cdot}$–(ClC_6H_4+C_6H_5+H), 61], 185 [($M^{+\cdot}$–(ClC_6H_4+C_6H_5CO+H), 61)], 105 ($C_6H_5CO^+$, 12), 77 (C_6H_5 $^+$, 15)); Anal. Calcd for $C_{23}H_{15}ClN_2O_3$ (402.08): C, 68.58; H, 3.75; N, 6.95, Found: C, 68.49; H, 3.73; N, 6.97.

2-Amino-6-benzoyl-4-(4-methoxyphenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4 k, $C_{24}H_{18}N_2O_4$)

Cream powder, m.p. 238–240 °C (Reported 232–233 °C [29],), yield: 85%; IR (KBr) (υ_{max}, cm^{-1}): 3437 (OH), 3297 and 3331 (NH_2), 3065 (C $_{sp2}$ –H), 2925(C $_{sp^3}$–H), 2199 (CN), 1659 (C=O), 1606 (C=C). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 3.71 (s, 3H, OCH_3), 4.68 (s, 1H, CH_{Ar}), 6.73 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 6.87 (d, 2H $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.02 (s, 2H, NH_2), 7.10(d, 2H $^3J_{HH}$=8.4 Hz, CH_{Ar}),7.48 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.55 (t, 2H, $^3J_{HH}$=8.0 Hz, CH_{Ar}), 7.63–7.67 (m, 3H, CH_{Ar}), 12.43(s, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 35.8 (CH), 55.5 (C=C*–CN), 57.9 (OMe), 108.0 (Cq), 113.2 (CN), 116.3 and 120.5 (2Cq), 128.7,128.9, 129.3 and 132.6(4CH), 133.7 (Cq), 137.3 (CH), 137.6, 154.2 and 158.4(3Cq), 159.9 (CH), 160.8 (C=C*–NH_2), 200.1 (C=O). MS: *m/z* (%) 398 ($M^{+\cdot}+23$), 291 ($M^{+\cdot}$–$CH_3OC_6H_4$, 100), 213 [($M^{+\cdot}$–($CH_3OC_6H_4$+C_6H_4+H), 60], 185 [($M^{+\cdot}$–($CH_3OC_6H_4$+C_6H_5CO+H), 107 ($CH_3OC_6H_4^+$, 15), 77 ($C_6H_5^+$, 16)); Anal. Calcd for $C_{24}H_{18}N_2O_4$ (398.13): C, 72.35; H, 4.55; N, 7.03, Found: C, 72.26; H, 4.53; N, 7.06.

2-Amino-6-benzoyl-4-(2-chlorophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4 l, $C_{23}H_{15}ClN_2O_3$)

Yellow powder, m.p. 273–275 °C, yield: 82%; IR (KBr) (υ_{max}, cm^{-1}): 3423 (OH), 3317 and 3204 (NH_2), 3050 (C_{sp2}–H), 2925 (C_{sp3}–H), 2200 (CN), 1659 (C=O), 1612 (C=C), 1262 (C_{sp2}–O). ^{1}H NMR (400.1 MHz, DMSO-d_6) $\delta_{H:}$ 5.25 (s, 1H, CH), 6.74 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.12 (d, 1H, $^3J_{HH}$=7.6 Hz, CH_{Ar}), 7.13 (s, 2H, NH_2), 7.22–7.29 (m, 2H, $2CH_{Ar}$) 7.41 (dd, 1H, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.4 Hz, CH_{Ar}), 7.51 (d, 1H, $^3J_{HH}$=9.2 Hz, CH_{Ar}), 7.56 (d, 2H, $^3J_{HH}$=7.6 Hz, $2CH_{Ar}$), 7.62 -7.67 (m, 3H, $3CH_{Ar}$), 12.41 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 34.1 (CH), 56.2 (C^*=C–N), 107.9 and 111.5 (Cq), 116.2 (CN), 120.0 (Cq), 128.2, 128.9, 129.0, 129.3 and 129.9 (CH), 130.9 (Cq), 132.5 and 132.6 (CH), 134.2 (Cq), 137.5 and 142.2 (CH_{Ar}), 154.6 and 159.9 (Cq), 161.0 (C=C^*–N), 200.1 (C=O). MS: *m/z* (%) 404 (($M^{+\cdot}$+2), 3), 402 ($M^{+\cdot}$, 9), 291 [($M^{+\cdot}$–ClC_6H_4), 100], 213 [($M^{+\cdot}$–(ClC_6H_4+C_6H_5+H), 50], 185 [($M^{+\cdot}$–(ClC_6H_4+C_6H_5CO+H), 5)], 105 ($C_6H_5CO^+$, 54), 77 ($C_6H_5^+$, 33); Anal. Calcd for $C_{23}H_{15}ClN_2O_3$ (402.08): C, 68.58; H, 3.75; N, 6.95, Found: C, 68.69; H, 3.77; N, 6.93.

2-Amino-6-benzoyl-4-(2-methylophenyl)-5-hydroxy-4H-chromene-3-carbonitrile (4 m, $C_{24}H_{18}N_2O_3$)

Orange powder, m.p. 255–257 °C, yield: 80%; IR (KBr) (υ_{max}, cm^{-1}): 3409 (OH), 3315 and 3194 (NH_2), 3057 (C_{sp2}–H), 2927 (C_{sp3}–H), 2198 (CN), 1660 (C=O), 1613 (C=C), 1264 (C_{sp2}–O). ^{1}H NMR (400.1 MHz, DMSO-d_6): δ_H 2.52 (s, 3H, CH_3), 5.01 (s, 1H, CH), 6.74 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 6.86 (d, 1H $^3J_{HH}$=8.4 Hz, CH_{Ar}), 7.06 (s, 2H, NH_2), 7.09 (d, 1H $^3J_{HH}$=6.8 Hz, CH_{Ar}), 7.15 (d, 1H $^3J_{HH}$=6.8 Hz, CH_{Ar}), 7.49 (d, 1H, $^3J_{HH}$=8.8 Hz, CH_{Ar}), 7.52–7.56 (m, 2H, $2CH_{Ar}$), 7.62–7.65 (m, 3H, $3CH_{Ar}$), 12.42 (bs, 1H, OH). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ_C 19.5 (CH_3), 32.4 (CH), 57.6 (C^*=C–N), 107.9 and 113.3 (Cq), 116.1 (CN), 120.5 (Cq), 126.8, 127.0, 128.3, 128.9, 129.3, 130.4, 132.5, 133.8 and 135.1 (CH), 137.5, 144.1, 154.5, and 159.5 (Cq), 160.9 (C=C^*–N), 200.1 (C=O). MS: *m/z* (%) 382 ($M^{+\cdot}$, 30), 291 ($M^{+\cdot}$–$CH_3C_6H_{4,}$ 100), 291 (M^+ –$CH_3C_6H_{4,}$ 100), 213 [(M^+–(CH_3C_6 H_4+C_6H_5)), 57], 185 [($M^{+\cdot}$–($CH_3C_6H_4$+C_6H_5CO+H), 5)], 105($C_6H_5CO^+$, 21), 77 ($C_6H_5^+$, 11); Anal. Calcd for $C_{24}H_{18}N_2O_3$ (382.13): C, 75.38; H, 4.74; N, 7.33, Found: C, 75.49; H, 4.73; N, 7.31.

General procedure for evaluation of antioxidant activity

In a spectrophotometric study, the antioxidant activity of compounds **4a–m** was examined using the DPPH radical scavenging method [52]. First, triplicate samples of each compound were prepared in methanol solvent at five concentrations (200, 100, 50, 25, and 12.5 μM). Then, 100 μM DPPH methanolic solution was added (1:1 v/v) to each solution and shaken vigorously. The absorbance of solutions was measured at 517 nm after 1 h keeping them in the dark at room temperature. Assays were conducted in triplicate, and the percentage of inhibition was calculated as follows:

$\%\text{Inhibition} = \frac{(Ac-As)}{As} \times 100$where A_c is the absorbance value of the control sample (DPPH solution), and A_s is the absorbance value of the tested sample.

General procedure for evaluation of antibacterial activity

The MIC values of compounds **3** and **4a–m** were evaluated against *S. aureus* (ATCC2592) and *E. coli* (ATCC1399) according to the previously standard protocols documented by Clinical and Laboratory Standards Institute. [39] Firstly, suspensions of samples were prepared in lower concentration ranges from 2×10^{-3}–5 mM in DMSO and subsequently, 100 µL of diluted samples were poured into a 96-wells tray. To adjust turbidity, a half McFarland tube was used to prepare a suspension of freshly cultivated bacteria (18–20 h) in normal saline. After dilution with Müller Hinton Broth (1:100), 100 µL of this suspension was added to each well. Each well was tested with $0.5–1 \times 10^6$ CFU/mL of bacteria. In each well, the final concentration of test substance was halved by the addition of bacterial suspension (1×10^{-3}–2.5 mM). A minimum inhibitory concentration (MIC) was determined after 22 h of incubation at 37 °C.

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Data availability All spectra data (Copies of the ^{1}H NMR, ^{13}CNMR, MASS and FT-IR data spectra) are included in the supplementary information file.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest It is to specifically state that "No Competing interests are at stake and there is No Conflict of Interest" with other people or organizations that could inappropriately influence or bias the content of the paper.

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