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Article

Synthesis, Antioxidant and Antimicrobial Evaluation of New Angular 6-Hydroxybenzo[*f*]chromene Anchored Derivatives

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Abstract: 2-Amino-6-hydroxy-4-phenyl-4*H*-benzo[*f*]chromene-3-carbonitrile (**1**) was synthesized *via* efficient cascade reaction of 2,7-dihydroxynaphathalene with benzylidene malononitrile. The precursor **1** was utilized to synthesize various angular 6-hydroxybenzo[*f*]chromene derivatives such as benzocoumarins, benzochromenothiazinthione and arylazobenzochromenes under different reactions conditions. Although many products showed promising activities, cyanodihydrocoumarin **4** manifests outstanding antioxidant and antimicrobial activities compared to the reference drugs.

Keywords: 6-Hydroxybenzo[*f*]chromene, antimicrobial, antioxidant, enaminonitrile

1. Introduction

Chromenes (Benzopyrans) are bicyclic heterocyclic compounds that result from condensation of a benzene ring with a 6-membered oxygenated pyran ring. These chromenes as well as their angular benzochromene derivatives are important motifs showing wide range of biological activities such as antioxidant,[1] antimicrobial,[2] hypolipidemic,[3] antiproliferative,[4] anticoagulant,[5] anticancer,[6] anti-rheumatic[7] and antitumor.[8-10] In addition to the known biological profile of benzo[*f*]chromene pharmacophore, it could be hopeful stand for lead organic molecules because of their angular skeleton.[11] Since hydroxyl group appears as the most common and optimal group in the modulation of lead molecules,[12] benzo[*f*]chromenes bearing hydroxyl group are expected to be core structure for compounds with biological interests.

On the other hand, enaminonitriles were confirmed to be a versatile precursor for diverse biologically active compounds either by the reaction with nucleophilic or electrophilic reagents.[13] Herein, we designed new angular benzo[*f*]chromene anchored derivatives with pendant hydroxyl group with the aim to be efficient antioxidant and antimicrobial agents.

2. Materials and Methods

2.1. Chemistry

2.1.1. General

All melting points are reported in degree Celsius (°C) (uncorrected) and were measured on a Gallenkamp apparatus. Ethanol was dried prior to use based upon the standard techniques.[14] The other chemicals were purchased from commercial suppliers and used without further purification. IR spectra were measured using the KBr disk technique on a Mattson 5000 and Thermo Scientific Nicolet iS10 FTIR Spectrometers at Mansoura University. ^{1}H NMR spectra were measured on Bruker AC 300 MHz (Cairo University), Bruker Avance III 400 MHz (Beni Suef University) and JEOL ECA II 500 MHz (Mansoura University) using tetramethylsilane (TMS) as an internal standard in DMSO-d_6 or $CDCl_3$ solvents. The signals' multiplicities are reported as follows: s = singlet, d = doublet, dd = doublet of doublets, m = multiplet. Exchangeable protons were detected through D_2O test. EI-Mass spectra were determined on Thermo Scientific DSQ II S GC/MS with FOCUS GC (70 ev) (Mansoura university). Elemental analyses (C, H and N) were executed at Cairo University. Biological screenings were performed at Mansoura University and the stock cultures of the tested organisms were obtained from the microbiological lab, Faculty of Medicine in Mansoura University.

2.1.2. Synthesis

2-Amino-6-hydroxy-4-phenyl-4*H*-benzo[*f*]chromene-3-carbonitrile (1)

A mixture of 2,7-dihydroxynaphthalene (480 mg, 3 mmol) and benzylidene malononitrile (462 mg, 3 mmol) in dry EtOH (30 mL) containing few drops of piperidine was refluxed for 2 hrs. After cooling, the formed precipitate was filtered off and recrystallized from dry EtOH affording compound **1** (800 mg, 85%); colorless crystals; m.p. = 150-152 °C; IR (KBr, ν/cm^{-1}): 3487 (OH), 3381 and 3329 (NH_2), 2189 (CN); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 3.43 (brs, 1H, OH), 4.99 (s, 1H, H-4), 6.91 (s, 2H, NH_2), 6.94-7.76 (m, 10H, ArH); EI-MS *m/z* (%): 314.1 [M^+] (15.9), 313.1 (1.9), 238.2 (16.1), 237.1 (100.0), 221.0 (3.7), 208.1 (3.2), 85.1 (20.4), 84.1 (41.5); Anal. calcd for $C_{20}H_{14}N_2O_2$ (314.34): C, 76.42; H, 4.49; N, 8.91%. Found: C, 76.31; H, 4.32; N, 8.99%.

6-Hydroxy-4-phenylbenzo[*f*]coumarin-3-carbonitrile (2)

A mixture of **1** (628 mg, 2 mmol) and iodine (564 mg, 2.22 mmol) in DMF (12 mL) containing H_2O (0.5 mL) was refluxed for 5 hrs. The reaction mixture was left to cool and quenched by pouring into saturated solution of sodium thiosulfate. The precipitate was filtered off, dried and recrystallized from dry EtOH to give product **2** (213 mg, 34%); yellowish green crystals; m.p. > 300 °C; IR (KBr, ν/cm^{-1}): 3401 (OH), 2224 (CN), 1721 (C=O), 1699 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 6.24-8.24 (m, 10H, ArH), 9.93 (s, 1H, OH); Anal. calcd for $C_{20}H_{11}NO_3$ (313.31): C, 76.67; H, 3.54; N, 4.47%. Found: C, 76.70; H, 3.58; N, 4.43%.

6-Hydroxy-4-phenyl-3,4-dihydrobenzo[*f*]coumarin-3-carbonitrile (4)

Procedure A: A solution of compound **1** (628 mg, 2 mmol) in formic acid (15 mL) was refluxed for 1 hr. After cooling the reaction mixture was poured over crushed ice. The formed precipitate was washed several times with cold water followed by hot water and recrystallized from dry EtOH to give the desired product (567 mg, 90%).

Procedure B: A cold solution of sodium nitrite (193 mg, 2.8 mmol) dissolved in water (5 mL) was added dropwisely to a cold solution of **1** (628 mg; 2 mmol) in conc. HCl (6 mL) with good stirring. The mixture was continued stirring overnight at room temperature. After the consumption of all starting material, the reaction mixture was poured onto cold water. The formed precipitate was filtered off, dried and recrystallized from dry EtOH to give compound **4** (265 mg, 42%); pale green crystals; m.p. = 299-301 °C; IR (KBr, ν/cm^{-1}): 3481 (OH) , 2267 (CN), 1756 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 5.32 (d, 1H, H-3, J = 6.30 Hz), 5.47 (d, 1H, H-4, J = 6.30 Hz), 7.03-7.92 (m, 10H, ArH), 9.99 (s, 1H, OH); Anal. calcd for $C_{20}H_{13}NO_3$ (315.33): C, 76.18; H, 4.16; N, 4.44%. Found: C, 76.23; H, 4.21; N, 4.40%.

6-Hydroxy-4-phenyl-3,4-dihydrobenzo[*f*]coumarin (7)

A mixture of compound **1** (628 mg, 2 mmol) in potassium hydroxide solution (40 mL, 40%) was refluxed for 2 hrs. Thereafter, the reaction mixture was poured over cold water followed by acidification with conc. HCl. The formed precipitate was filtered off, dried and purified *via* preparative chromatography using pet. ether: ethyl acetate (60:40) to give the compound **7** (470 mg, 81%); pale yellow crystals; m.p. = 80-82 °C; IR (KBr, ν/cm^{-1}): 3446 (OH), 1741 (lactonic C=O), 1631 (C=C); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) = 2.92 (dd, 1H, H-3, J = 1.50, 16.00 Hz), 3.45 (dd, 1H, H-4, J = 7.00, 16.00 Hz), 4.90 (d, 1H, H-3, J = 7.00 Hz), 6.99-7.85 (m, 10H, ArH), 9.89 (s, 1H, OH); Anal. calcd for $C_{19}H_{14}O_3$ (290.32): C, 78.61; H, 4.86%. Found: C, 78.45; H, 4.93%.

7-Hydroxy-4-imino-5-phenyl-5*H*-1,2-dihydro-4*H*-benzo[*f*]chromeno[2,3-*d*]-1,3-thiazine-2-thione (8)

A mixture of 2-amino-6-hydroxy-4-phenyl-4*H*-benzo[3,4-*f*]chromene-3-carbonitrile **(1)** (628 mg, 2 mmol), carbon disulfide (0.5 mL, 8.5 mmol) and potassium hydroxide pellets (140 mg, 2.5 mmol) were stirred in DMF (20 mL) at room temperature for 3 hrs. After completion of the reaction, it was poured over

cold water and neutralized by using few drops of conc. HCl. The precipitate was filtered off, dried and recrystallized from dry EtOH to afford the compound **8** (344 mg, 44%); yellow crystals; m.p. = 211-212 °C; IR (KBr, ν/cm^{-1}): 3423 (OH), 3272 (NH), 1661 (C=N); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 5.94 (s, 1H, H-5), 7.05-7.83 (m, 10H, ArH), 9.35-9.92 (m, 3H, 2NH, OH); Anal. calcd for $C_{21}H_{14}N_2O_2S_2$ (390.48): C, 64.60; H, 3.61; N, 7.17%. Found: C, 64.56; H, 3.65; N, 7.15%.

6-(Allyloxy)-2-amino-4-phenyl-4*H*-benzo[*f*]chromene-3-carbonitrile (9)

A mixture of compound **1** (628 mg, 2 mmol), allyl bromide (0.19 mL, 2.2 mmol) and anhydrous K_2CO_3 (1 g) in dry acetone (20 mL) was refluxed for 6 hrs. The mixture was left to cool then poured over cold water and neutralized by few drops of conc. HCl. The precipitate was filtered off, dried and recrystallized from dry EtOH to give the compound **9** (404 mg, 58%); yellowish green crystals; m.p. = 217-219 °C; IR (KBr, ν/cm^{-1}): 3458, 3342 (NH_2), 2188 (CN), 1660 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 4.40 (dd, 1H, $OCH_2CH=\underline{CH_{2a}}$, *J*= 5.10, *J* = 13.50 Hz), 4.58 (dd, 1H, $OCH_2CH=\underline{CH_{2b}}$, *J* = 5.10, *J* = 13.80 Hz), 5.25 (s, 1H, H-4), 5.33 (d, 2H, $O\underline{CH_2}CH=CH_2$, *J* = 1.80 Hz), 5.96 (m, 1H, $OCH_2\underline{CH}=CH_2$), 6.92 (s, 2H, NH_2), 7.02-7.82 (m, 10H, ArH); Anal. calcd for $C_{23}H_{18}N_2O_2$ (354.41): C, 77.95; H, 5.12; N, 7.90%. Found: C, 77.99; H, 5.18; N, 7.86%.

Synthesis of the compounds 10a,b

A cold solution of aryl diazonium chloride (2 mmol) [which previously prepared by mixing the appropriate aromatic amine (2 mmol), sodium nitrite (207 mg, 3 mmol) and conc. HCl (0.6 mL, 6 mmol) in 5 mL water] was added dropwisely to a cold solution (Temp. 0-5 °C) of **1** (628 mg, 2 mmol) in 10 mL pyridine with continuous stirring for 1-2 hrs. The formed precipitate was washed with water several times and then recrystallized from dry EtOH to afford the corresponding product.

2-Amino-6-hydroxy-4-phenyl-5-(phenyldiazenyl)-4*H*-benzo[*f*]chromene-3-carbonitrile (10a)

Yield: 712 mg, 85%; orange crystals; m.p. = 150-152 °C; IR (KBr, ν/cm^{-1}): 3250-3550 (br, OH, NH_2), 2187 (CN), 1653 (C=C); Anal. calcd for $C_{26}H_{18}N_4O_2$ (418.46): C, 74.63; H, 4.34; N, 13.39%. Found: C, 74.49; H, 4.50; N, 13.28%.

2-Amino-5-((4-chlorophenyl)diazenyl)-6-hydroxy-4-phenyl-4*H*-benzo[*f*]chromene-3-carbonitrile (10b)

Yield: 715 mg, 79%; scarlet orange crystals; m.p. = 264-266 °C; IR (KBr, ν/cm^{-1}): 3456, 3356 (NH_2), 2182 (CN), 1659 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.61 (s, 2H, NH_2), 6.36 (s, 1H, H-4), 6.80 (d, 1H, H-7, *J* = 9.60 Hz), 7.61 (d, 1H, H-9, *J* = 8.80 Hz), 7.68 (d, 1H, H-8, *J* = 9.60 Hz), 7.02-7.37 (m, 11H, ArH, OH); Anal. calcd for $C_{26}H_{17}ClN_4O_2$ (452.90): C, 68.95; H, 3.78; N, 12.37%. Found: C, 68.72; H, 3.89; N, 12.20%.

6-Hydroxy-4-phenyl-2-(1-pyrrol-1-yl)-4*H*-benzo[*f*]chromeno-3-carbonitrile (11)

A mixture of compound **1** (942 mg, 3 mmol), 2,5-dimethoxytetrahydrofuran (0.41 mL, 3.2 mmol) and water (0.5 mL) was refluxed in glacial acetic acid (20 mL) for 2 hrs. After that, it was poured over crushed ice and neutralized by using NaOH solution (0.1 N). The formed precipitate was filtered off, dried and recrystallized from a mixture of water : dimethylformamide mixture (1:2) to give the compound **11** (379 mg, 52%); gray powder; m.p. = 175-177 °C; IR (KBr, ν/cm^{-1}): 3444 (OH), 2209 (CN), 1656 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 5.46 (s, 1H, H-4), 6.39-7.89 (m, 14H, ArH), 9.98 (s, 1H, OH); Anal. calcd for $C_{24}H_{16}N_2O_2$ (364.40): C, 79.11; H, 4.43; N, 7.69%. Found: C, 79.05; H, 4.40; N, 7.65%.

2.2. Biological Evaluation

2.2.1. Antioxidant activity (ABTS)[15,16]

The antioxidant activity for 6-hydroxybenzo[*f*]chromene derivatives was evaluated using the ABTS method. The reaction mixture consisted of 2 mL of ABTS solution (60 μM) was added to MnO_2 (3 mL, 25 mg/mL) solution, all prepared in aqueous phosphate buffer solution (pH 7, 0.1 M). The mixture was shaken, centrifuged and filtered. The absorbance ($A_{control}$) of the resulting bluish green solution at 734 nm was adjusted to approximately ca. 0.5. Then, the absorbance was measured upon the addition of 50 μl of (2 mM) solution of the tested compounds in spectroscopic grade MeOH/phosphate buffer (1:1) (A_{tested}).The inhibition ratio was calculated using the following equation:

$$\text{Inhibition (\%)} = (A_{control}-A_{tested}) / A_{control} \times 100$$

L-Ascorbic acid (vitamin C) was used as standard antioxidant (positive control). Blank sample was run without ABTS and using MeOH/phosphate buffer (1:1) instead of the tested samples. Negative control sample was run with ABTS and MeOH/phosphate buffer (1:1) only instead of the tested samples.

2.2.2. Antimicrobial activity[17]

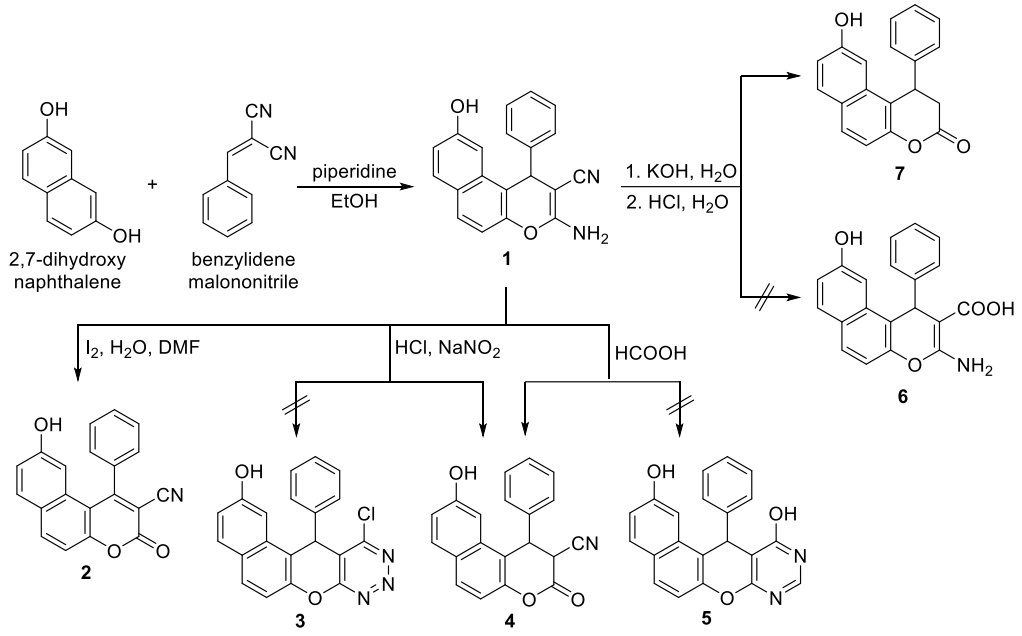
The antimicrobial activity of the 6-hydroxybenzo[*f*]chromene derivatives was estimated by filter paper disc method using inoculums containing 10^6 bacterial and fungal cells per mL to spread on nutrient agar. The sterilized filter paper discs (Whatman no.1, 6 mm in diameter) were saturated with the solution of the tested compounds in DMSO (0.01 g/mL) and another filter paper disc was saturated with DMSO to serve as control. The discs were placed on the surface of the agar plates seeded with the tested organisms. The plates were incubated at 28 °C for fungi and at 37 °C for bacteria. Diameters of the inhibition zone (mm) were measured after 18-24 hours.

3. Results and Discussion

3.1. Chemistry

The versatile precursor 2-amino-6-hydroxy-4-phenyl-4*H*-benzo[3,4-*f*] chromene-3-carbonitrile (**1**)

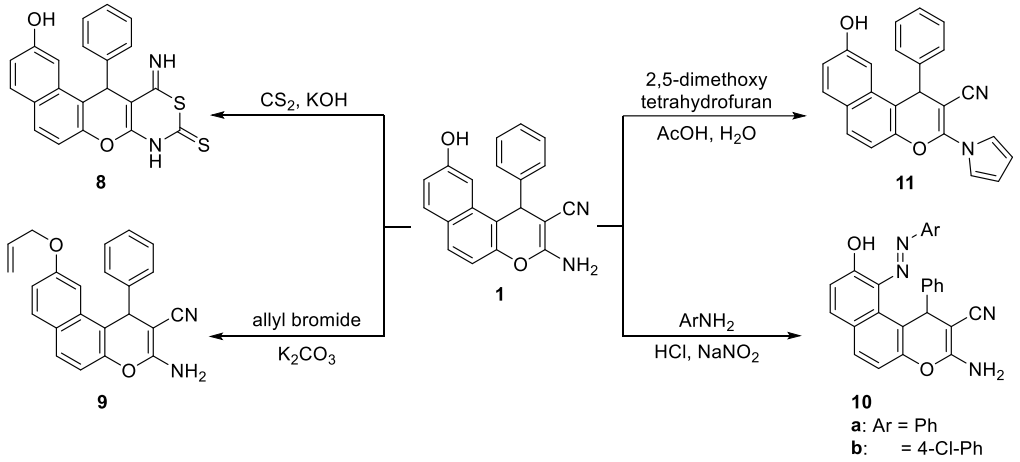
was achieved *via* Michael addition/cyclization tandem reaction between 2,7-dihydroxynaphthalene and benzylidene malononitrile in the presence of catalytic amount of piperidine as a high yielding protocol.[18] The reaction of the produced enaminonitrile **1** with iodine afforded the corresponding the benzo[*f*]coumarin **2**.[19] Under non-oxidative conditions, treatment of precursor **1** either with HCl/$NaNO_2$ in ice bath or refluxing with formic acid afforded the same product dihydrobenzo[*f*]coumarin **4** instead of the expected products chlorotriazine **3** or hydroxypyrimidine **5**, respectively (**Scheme 1**). The formation of coumarin **4** could be rationalized to the acid-catalyzed substitution of the amine functionality. This explanation was supported by refluxing precursor **1** in the presence of acidified ethanol which yielded the expected dihydrobenzo[*f*]coumarin **4**.



scheme 1

In an attempt to prepare *β*-aminocarboxylic acid **6**, the enaminonitrile **1** was allowed to be hydrolyzed in the presence of 40% KOH however the unexpected dihydrobenzo[*f*]coumarin **7** was obtained (**Scheme 1**). The plausible mechanistic pathway involved decarboxylation step followed by hydrolysis of enamine functionality to afford the corresponding dihydrobenzo[*f*]coumarin **7**. The structures of all products were elucidated based upon different analytical and spectral data. The infrared spectrum of compound **1** showed hydroxyl group absorption band at ν = 3487 cm^{-1} and the stretching bands at ν = 3381 and 3329 cm^{-1} which were attributed to the amino group in addition to cyano absorption band at ν = 2189 cm^{-1}. ^{1}H NMR spectrum showed a singlet at δ 4.99 ppm which was characteristic for H-4. Mass spectrum showed the molecular ion peak M^+ at *m/z* = 314 in addition to base peak appeared at m/z = 237 which related to [M^+-Ph]. The infrared spectrum of compound **2** revealed the disappearance of the amino group stretching band and appearance of two new characteristic bands at ν = 1721, 1699 cm^{-1} which related to the coumarin carbonyl and olefin groups, respectively. ^{1}H NMR spectrum supported the structure through the

disappearance of NH_2 and H-4 protons. The infrared spectrum of compound **4** revealed the appearance of a stretching band at ν = 1756 cm^{-1} which was attributable to coumarin carbonyl group. ^{1}H NMR spectrum showed two neighboring characteristic doublets at δ 5.32 and 5.47 ppm with vicinal coupling (*J* = 6.30 Hz) attributed to protons H-3 and H-4, respectively. The lower pK_a value of H-4 was evidenced through the disappearance of the corresponding ^{1}H-NMR signal after adding few drops of D_2O to the NMR tube. The infrared spectrum of compound **7** revealed the appearance of the $C{=}O_{(lactone)}$ band at ν = 1756 cm^{-1}. While the two doublets of doublets at δ 2.92 and 4.90 ppm in ^{1}H NMR spectrum of compound **7** were attributed to H-3 protons, the doublet of doublet at δ 3.45 ppm was attributed to H-4 proton.



Scheme 2

Additionally, enaminonitrile **1** was allowed to react with CS_2 in the presence of potassium hydroxide to yield the chromeno[*d*]thiazine derivative **8** through the cascade addition followed by cyclization. Treatment of the compound **1** with allyl bromide in the presence of anhydrous K_2CO_3 afforded the *O*-allylated product **9**. Moreover, coupling reaction of compound **1** with the diazonium salts of aniline or 4-chloroaniline afforded 5-arylazobenzochromene products **10**. Finally, the reaction of compound **1** with 2,5-dimethoxytetrahydrofuran in the presence of acetic acid and water afforded the uncommon pyrrolylbenzo[*f*]chromene **11** *via* Clauson-Kaas reaction (**Scheme 2**).[20] The infrared spectrum of compound **8** revealed the disappearance of CN absorption band, a new band assigned for C=N group appeared at *v* = 1661 cm^{-1}. ^{1}H NMR spectrum showed the characteristic H-5 proton as singlet at δ 5.94 ppm in addition to the exchangeable signals at δ 9.35 and 9.92 ppm assigned for NH and OH groups. The proton of H-5 in the case of compound **9** was detected in ^{1}H NMR spectrum as singlet at δ 5.96 ppm that attributable to H-5. The infrared spectrum and the elemental analysis were in a complete agreement with the proposed structure. While ^{1}H NMR spectrum of compound **10b** revealed the appearance of singlet signal at δ 4.61 ppm attributable to NH_2 group, H-5 proton appeared as singlet at δ 6.36 ppm. The thorough evaluation of the *J*-values for the aromatic proton doublets guided us to assign the azo coupling site of compounds **10a-b**. ^{1}H NMR spectrum of compound **11** showed two singlets at δ 5.46 and 9.98 ppm which were attributed to H-5

and OH group, respectively. The insertion of pyrrole heterocycle was supported by the detection of the protons H-3` and H-4` at δ 6.39 ppm in addition to protons H-2` and H-5` at δ 7.72 ppm.

3.2. Biological evaluation and structure activity relationships (SARs)

3.2.1. Antioxidant activity

The antioxidant activity of the prepared library was assessed by using ABTS method. The obtained results were collected in comparison with *L*-Ascorbic acid as reference drug (**Table 1**). As seen from **table 1**, cyanodihydrocoumarin **4** revealed excellent antioxidant activity in addition to enaminonitrile **1** with little bit lower activity. However the dihydrocoumarin **7** revealed very good antioxidant activity.

Table 1. Antioxidant activity of by ABTS scavenging assay

Compound	A[a]	Inhibition (%)
1	0.093	81.8
2	0.360	29.4
4	0.084	83.5
7	0.122	76.0
8	0.192	62.3
9	0.210	58.8
10a	0.237	53.5
10b	0.381	25.3
11	0.164	67.8
Control	0.510	0.0
LAA[b]	0.059	88.4

[a]A: Absorbance of the sample, [b]LAA: *L*-Ascorbic acid

The structure of cyanodihydrocoumarin **4** with three active antioxidant centers (OH, H-3 and H-4), which are good centers for trapping the oxidant species because of the high stability of the produced radicals, explained its superiority over other products. The loss of antioxidant active centers H-3 and H-4 as exemplified in cyanocoumarin **2**, demolished the antioxidant activity which highlight the role of H-3 and H-4 centers in the overall activity of cyanodihydrocoumarin **4**. This trend in the antioxidant activity was supported by the ease deuterium replacement of protons OH and H-4 during ^{1}H-NMR analysis in the presence of D_2O. Enaminonitrile **1** with two antioxidant active centers (OH, H-4) showed very good activity as well. The role of cyano group in compound **4** was highlighted by the decreased activity of dihydrocoumarin **7** which is cyano free product.

3.2.2. Antimicrobial activity

The synthesized compounds were screened for their antibacterial activity against *Erwinia carotovora* (gram -ve) and *Bacillus subtilis* (gram +ve) and against *Candida albicans* to evaluate their

antifungal activities. The activity was estimated by the disc diffusion method,[21,22] and the common antibiotic Streptomycin was used as reference drug. The activity index (%) was calculated from the following equation:

$$\% \text{ Activity Index} = \frac{\text{Diameter of the inhibition zone of the tested compound}}{\text{Diameter of the inhibition zone of the reference drug}} \text{ X } 100$$

From **table 2**, cyanodihydrocoumarin revealed a unique activity indexes against both of bacteria and fungi. In addition, the antimicrobial activity of product **4** surpasses that of the reference antibiotic Streptomycin. While compound **10b** appeared as excellent antifungal agent, it showed very good antibacterial activity. The activity of pyrrolylbenzo[*f*]chromene **11** was excellent against *B. subtilis*. Coming to the relation between the structure and activity, H-3 and H-4 in compound **4** play crucial role in the overall antimicrobial, and this was deduced by comparing its antimicrobial activity to that of cyanocoumarin **2**. Moreover, the role of cyano group as essential fragment for the unique antimicrobial effectiveness of cyanodihydrocoumarin **4** was suggested by comparison with dihydrocoumarin **7**. Finally, the conversion of amino group of precursor **1** into pyrrolyl substituent leaded to selective and excellent activity against *B. subtilis* in contrast to the other tested bacterial and fungal strains.

Table 2. Evaluation of Antimicrobial activity

Compound	*Erwinia carotovora*		*Bacillus subtilis*		*Candida albican*	
	D[a] (mm)	**AI[b] (%)**	**D[a] (mm)**	**AI[b] (%)**	**D[a] (mm)**	**AI[b] (%)**
1	9 (cidal)	60.0	10 (static)	66.6	9 (cidal)	56.2
2	NA[c]	NA[c]	NA[c]	NA[c]	9 (static)	56.2
4	16 (cidal)	106.6	15 (cidal)	100.0	17 (cidal)	106.2
7	10.5 (cidal)	70.0	10 (cidal)	66.6	11 (cidal)	68.7
8	10 (cidal)	66.6	9 (cidal)	60.0	8 (cidal)	50.0
9	9 (cidal)	60.0	7 (cidal)	46.6	7 (cidal)	43.7
10a	9 (cidal)	60.0	10 (cidal)	66.6	10 (cidal)	62.5
10b	12 (cidal)	80.0	12 (cidal)	80.0	16 (cidal)	100.0
11	NA[c]	NA[c]	14 (static)	93.3	7 (cidal)	43.7
Control (DMSO)	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
Streptomycin	15 (cidal)	100.0	15 (cidal)	100.0	16 (cidal)	100.0

[a]D: Diameter of inhibition zone, [b]AI: Activity index, [c]NA: No activity

4. Conclusions

Various 6-hydroxybenzo[*f*]chromene derivatives were synthesized from readily available enaminonitrile precursor **1**. Moreover, the synthesized products which were angular and bear hydroxyl group, were assessed for their antioxidant activity in addition to *in vitro* screening against different microbial strains. While many products have promising biological activity, the new cyanodihydrocoumarin

4 revealed excellent antioxidant and antimicrobial activities. Further work including fine tuning of the substituents around the nucleus of cyanodihydrocoumarin **4** in addition to molecular docking studies is currently underway.

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