

SYNTHESIS OF HYDROXYQUINOLINE DERIVATIVES, AMINO-HYDROXYCHROMENE, AMINOCOUMARIN AND THEIR ANTI-BACTERIAL ACTIVITIES

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Abstract- Some new diaminochromenes (**3a-f**, **7a-c**, and **10**), 7-amino-4-aryl-coumarins (**8a,b**), 7-hydroxy-4-aryl-1,2-dihydroquinolines (**9a-c**) and 2-amino-7-hydroxy-4-(4-chlorophenyl)-4*H*-chromenes (**16a-d**) were synthesized *via* Michael addition of different substituted aminonaphthol (**1**), aminophenol (**6**), resorcinol derivatives (**15a-d**), chloronaphthol (**17**) and 4-hydroxycoumarin (**19**) with α -cyanocinnamitriles (**2a-c**) and ethyl α -cyanocinnamate (**2d-f**). 2-Acetylamino-7-amino-4-(4-chlorophenyl)-4*H*-chromene-2-carbonitrile (**14**) was obtained as a unique product *via* hydrazinolysis of ethoxymethyleneamino derivative (**13**). The formation of coumarins (**8a,b**) and quinolines (**9a-c**) were anomalous case. Structures of the titled compounds cited in this article were elucidated by spectrometric data (IR, ¹H NMR, ¹³C NMR (APT) and EMS). All of the newly synthesized compounds were evaluated for antimicrobial activities, where **16b** and **16c** exhibited activity against *staphylococcus aureus* (ATCC 25923).

INTRODUCTION

Naturally occurring coumarins have exhibited several biomedical applications including platelet aggregation, cytotoxic activity, enzyme inhibition, antiviral, antibacterial, antifungal activities, etc.¹⁻¹⁰ Coumarin and chromene derivatives are widely found in plants belonging to the families, Belliferae, Rutaceae, and Compositae.¹ New derivatives of coumarins have been isolated from plants with an ever-increasing variety of uses.¹¹⁻²⁰

More recently, specific studies looking at the effects of coumarins as a cytochrome P-450 inhibitor, which is a carcinogen metabolizing enzyme.^{21,22} The ability of some coumarins to inhibit acetylcholinesterase

and monoamine oxidase may decrease the β -amyloid depositions, which indicate that these compounds may have some therapeutic values to treat the Alzheimer's disease.²³ Acting as selective dopamine antagonists, chromen-2-ones have been synthesized to reduce the negative effects of schizophrenia.²⁴ Coumarins have also been found to have beneficial effects on lymphedema and malaria.²⁵⁻²⁶ In addition, there is evidence that coumarins prevent or slow tumor growth, by acting as antioxidants and inhibiting superoxide and nitric oxide production.^{19,27-29} Based on the biological importance of several coumarins; new coumarins, chromenes, and other benzo- and naphopyrans have been synthesized.³⁰⁻³³ Coumarins and their derivatives may also possess valuable optical properties, especially the 3-heterarylcoumarins.³⁴⁻³⁶ By binding coumarins to biological effectors molecules, the path of the molecule through a biological system may be traced.³⁷ In addition, the removal of a coumarin unit through photolysis has been used to selectively release compounds in living systems.³⁸ In this paper, we report the synthesis of fused chromenes and coumarins which involves the addition of a variety of phenols and naphthols to substituted α -cyanocinnamionitriles and ethyl α -cyanocinnamates.

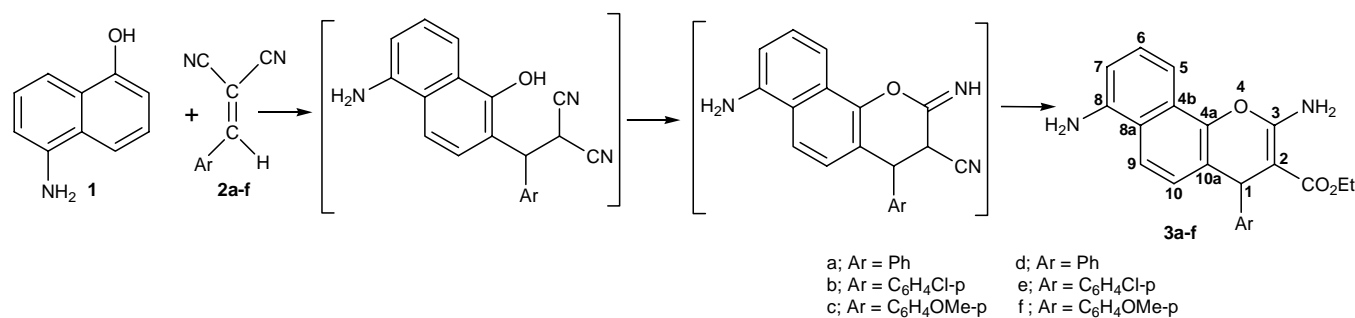
RESULTS AND DISCUSSION

Our compounds (**3a-f**) (yield 72-84%) were produced through condensation of 5-amino-1-naphthol (**1**) with substituted α -cyanocinnamionitriles (**2a-c**) and ethyl α -cyanocinnamates (**2d-f**) in ethanolic piperidine (Scheme 1). The formation of **3a-f** indicated that the naphtholate anion attacked at the carbon adjacent to the aryl ring of **2** to yield the products.

Compounds (**3a-f**) were isolated as stable gray or red solids and their structures were confirmed with the aid of spectroscopic data. In the IR spectra, the sharp absorptions at 3463-3167 cm^{-1} indicated the presence of amino functionality. The absorptions at 2201-2186 cm^{-1} were assigned to ν (CN) vibration for compounds (**3a-c**), while at 1667-1677 cm^{-1} were assigned to the ν (C=O) vibration of the chelated carbonyl group for compounds (**3d-f**). In the ^1H NMR spectra (Table 1), characteristic signals for *H*-1 appeared as singlets at δ 5.00-4.77 ppm. In the ^{13}C NMR spectra (Table 2), we assigned the signals on the basis of the observed chemical shifts using an attached proton test (APT) and by comparison with the known and standard chemical shifts for 1*H*-chromenes.^{39,40}

As opposed to the anticipated formation of the 8-amino-3-ethoxymethyleneamino-1-(4-methoxyphenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (**4**), the reaction of **3c** with neat triethyl orthoformate produced the 3-amino-8-ethoxymethyleneamino-1-(4-methoxyphenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (**5**), in which the triethyl orthoformate attacked the amino group substituted at C-8 instead of the amino group present at C-3.^{3,4,39-41} We believe that formation of **5** from **3c** may be due to the steric hindrance between two amino groups and nucleophilic power. Structure (**5**) was also supported by ^1H NMR spectrum, in which the hydrogens attached to C-8N disappeared, while the ^{13}C NMR spectrum showed the resonance

of C-2 at δ 56.6 ppm rather than at δ 77.9 ppm for compound (**4**). Structure (**5**) was also further confirmed *via* a reaction of **5** with hydrazine hydrate in ethanol or benzene with stirring at room temperature. An addition product formed, which on elimination of ethyl formate hydrazone gave the enamionitrile (**3c**) (Scheme 2).^{4,43}



Scheme 1

Table-1: Selected ¹H NMR Chemical Shifts (ppm) of 1*H*-Chromene Derivatives in DMSO-*d*₆

	H-1	NH ₂ -3	H-5	H-7	NH ₂ -8	H-9	H-10
3a	4.83	7.08	7.44	6.71	5.77	7.74	6.93
3b	4.88	7.11	7.42	6.70	5.77	7.74	6.90
3c	4.77	7.00	7.42	6.70	5.77	7.71	6.87
3d	4.98	7.75	7.21- 7.72	6.70	5.75	7.21- 7.72	7.11
3e	5.00	7.78	7.14- 7.73	6.72	5.76	7.14- 7.73	7.10
3f	4.91	7.69	7.06- 7.74	6.68	5.74	7.06- 7.74	6.76

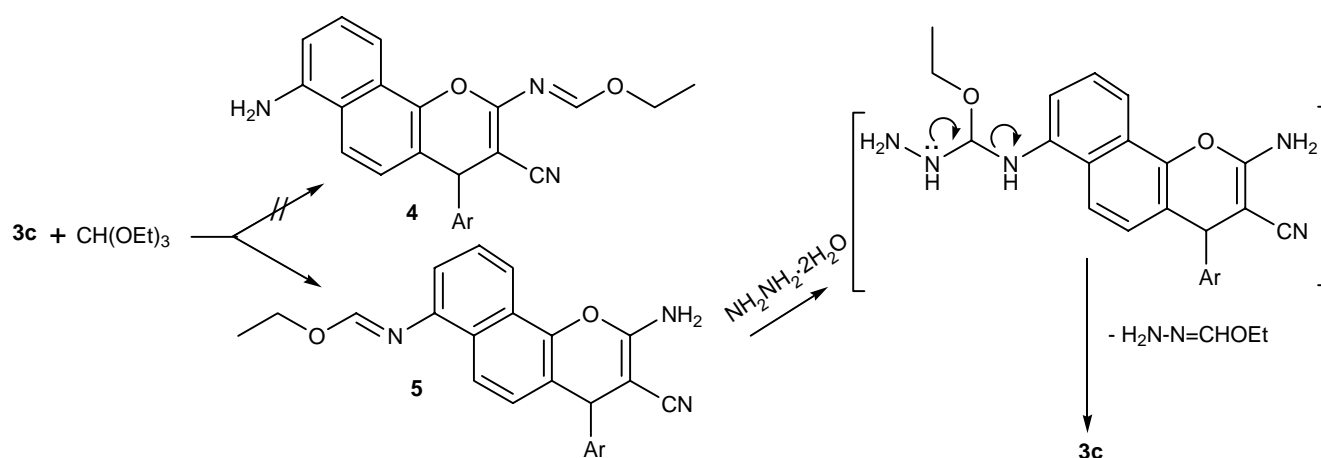
Condensation of 3-aminophenol (**6**) with α -cyanocinnamitriles (**2a-c**) in ethanolic piperidine resulted in 1:1 adducts (**7a-c**) (yield 77-90%) . Interaction of **6** with ethyl α -cyanocinnamates (**2d,e**) afforded the coumarin derivatives (**8a,b**) (yield 37-42%) in the ratio of 1:1 together with the quinoline derivatives (**9a,b**) (yield 38-41%) in the ratio of 1:1, while reaction of **6** with **2f** gave the 46% of chromene derivative (**10**) and 37% of quinoline derivative (**9c**) in the ratio of 1:1. Compounds (8a, b; 9a, b; 9c and 10) were purified by using silica gel flash chromatography. The formation of **7a-c** and **10** indicated that the

phenolate anion (C-6) attacked at the β -carbon of **2a-c,f** to yield an acyclic Michael adduct which underwent cyclization (Schemes 3, 4).

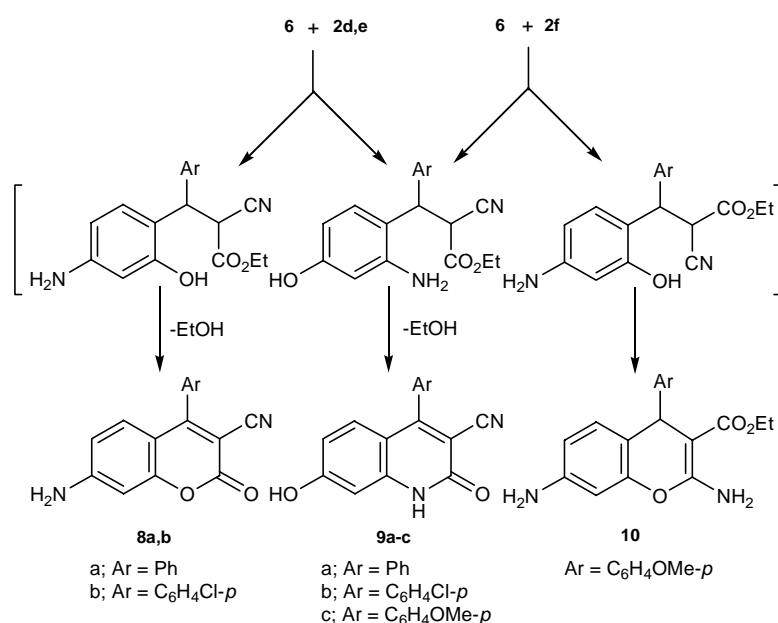
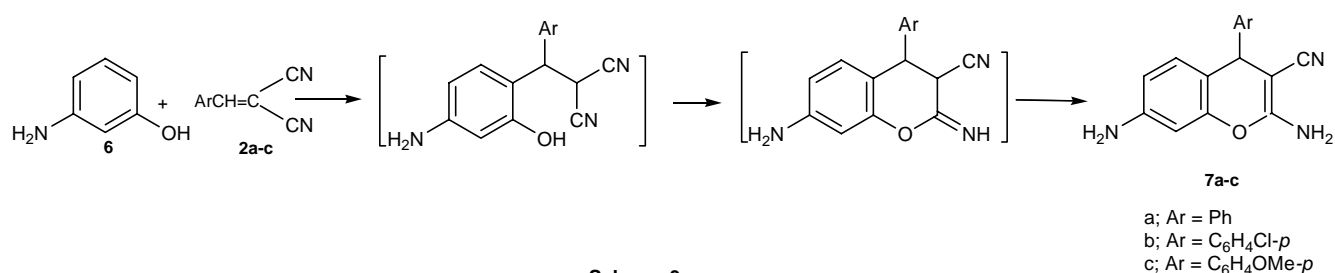
Table 2: Selected ^{13}C NMR Shifts (ppm) of 1*H*-Chromene Derivatives

3	C-1	C-2	C-3	C-4a	C-4b	C-8	C-8a	C-10a
a	40.3	55.6	159.7	145.2	123.4	144.2	121.4	120.0
b	40.2	55.9	160.4	144.9	124.1	144.8	122.2	120.6
c	40.1	56.5	160.2	144.9	124.1	142.8	122.0	120.7
d	40.1	76.5	161.1	148.0	124.2	143.1	122.0	120.1
e	40.3	76.5	161.4	147.5	124.6	143.5	122.5	120.3
f	39.2	76.7	160.9	144.8	124.1	142.9	121.9	120.8

The formation of **8a,b** indicated that the phenolate anion (C-6) attacked at β -carbon of **2d,e** to yield an acyclic Michael adduct which underwent cyclization followed by elimination of EtOH to gives **8a,b**. The formation of **9a-c** indicated that phenolate anion (C-4) attacked at β -carbon of **2d-f** to yield an acyclic Michael adduct which underwent cyclization to give **9a-c**, with elimination of EtOH and aromatization (Scheme 4).



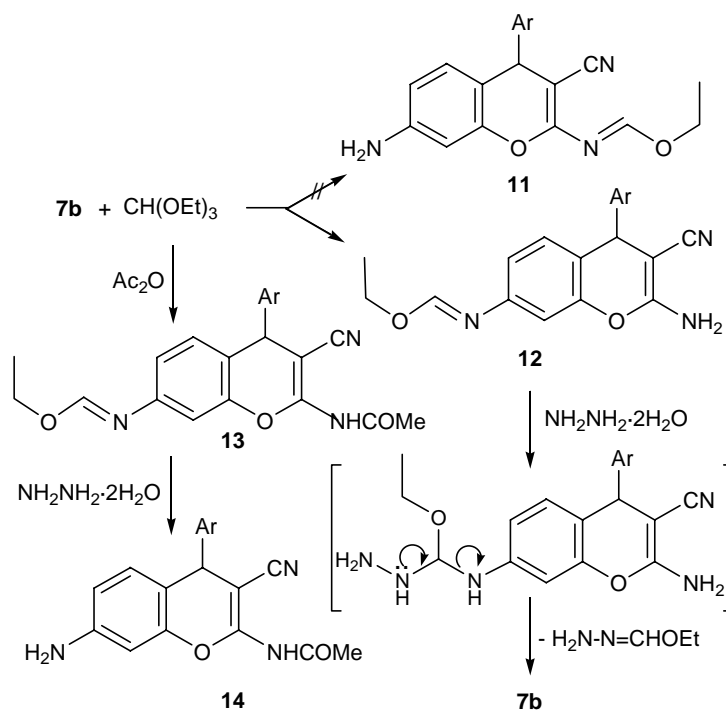
Scheme 2



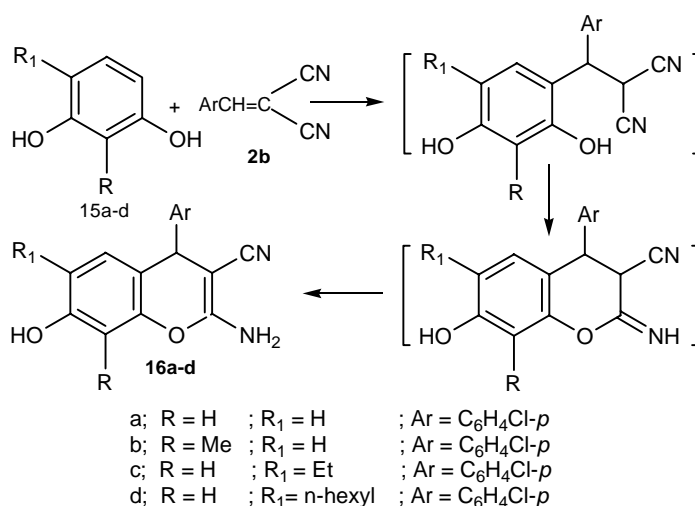
Again, in contrast to the anticipated formation of the 7-amino-2-ethoxymethyleneamino-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**11**), the reaction of **7b** with neat triethyl orthoformate without acetic anhydride had the triethyl orthoformate attacked the amino group substituted at C-7 instead of the amino group present at C-22 to afford (**12**) similarly to compound (**3c**).³⁹⁻⁴¹ Compound (**12**) was supported by ¹H NMR spectrum, in which the C-3/NH₂ disappeared, while the ¹³C NMR spectrum showed C-3 at δ 55.6 ppm, instead of at δ 77.9 ppm for the expected compound. The reaction of **12** with hydrazine hydrate in ethanol or benzene with stirring at room temperature produced an addition product, from which elimination of ethyl formate hydrazone returned to the enaminonitrile (**7b**) instead of the cycloaddition product, as in the case of **3c**.^{42,43}

The reaction of **7b** with triethyl orthoformate in acetic anhydride afforded the 2-acetylamino-7-ethoxymethyleneamino-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**13**), hydrazinolysis of the later afforded the 2-acetylamino-7-amino-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**14**). This reaction

provided a selective acetylation of **7b**, in which the C-3/NH₂ can be acetylated and the proper amino group substituted at C-7 remained free (Scheme 5).



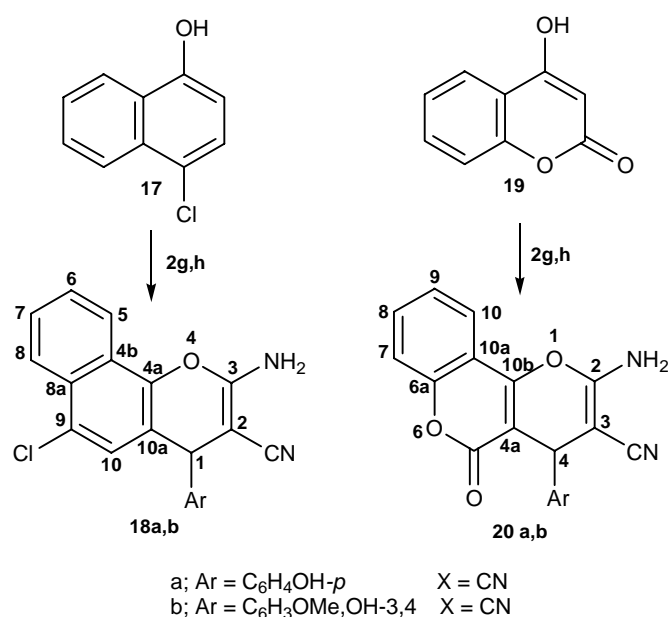
Scheme 5



Scheme 6

Compounds (**16a-d**) were synthesized through condensation of resorcinol (**15a**) or resorcinol derivatives (**15b-d**) with α -cyanocinnamitrile (**2b**) (Scheme 6). Condensation of 4-chloro-1-naphthol (**17**) and 4-hydroxycoumarin (**19**) with substituted α -cyanocinnamitriles (**2g,h**) in ethanolic piperidine gave 1:1 adducts (**18a,b**, **20a,b**) (yield 74-85%) as shown in Scheme 7. The formation of **16a-d**, **18a,b**, **20a,b** indicated that the phenolate and naphtholate anion attacked at the β -carbon of **2** to yield an acyclic Michael adduct which underwent intramolecular cyclization (Schemes 6, 7).

The reaction of **16a** with triethyl orthoformate in acetic anhydride resulted in the 7-acetoxy-2-ethoxymethyleneamino-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**21**) with acetylation of the hydroxy group at position 7, hydrazinolysis of the later in ethanol at room temperature under stirring yielded the 3-amino-10-(4-chlorophenyl)-4-imino-3,10-dihydro-4*H*-9-oxa-1,3-diazaanthracen-7-ol (**22**) with the deacetylation of the acetoxy group at position 7. Interaction of **16b** with triethyl orthoformate in acetic anhydride afforded the 7-acetoxy-2-amino-8-methyl-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**23**) as the only isolable product, while reaction of **16b** with neat triethyl orthoformate produced the 2-ethoxymethyleneamino-7-hydroxy-8-methyl-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**24**). The reaction of **23** with hydrazine hydrate returned to **16b**, while **24** with hydrazine hydrate gave 3-amino-8-methyl-10-(4-chlorophenyl)-4-imino-3,10-dihydro-4*H*-9-oxa-1,3-diazaanthracen-7-ol (**25**). The reaction of **16c,d** with triethyl orthoformate in acetic anhydride afforded the 7-hydroxy-2-acetylamino-6-ethyl/n-hexyl-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (**26a,b**) as the only isolable products (Scheme 8).

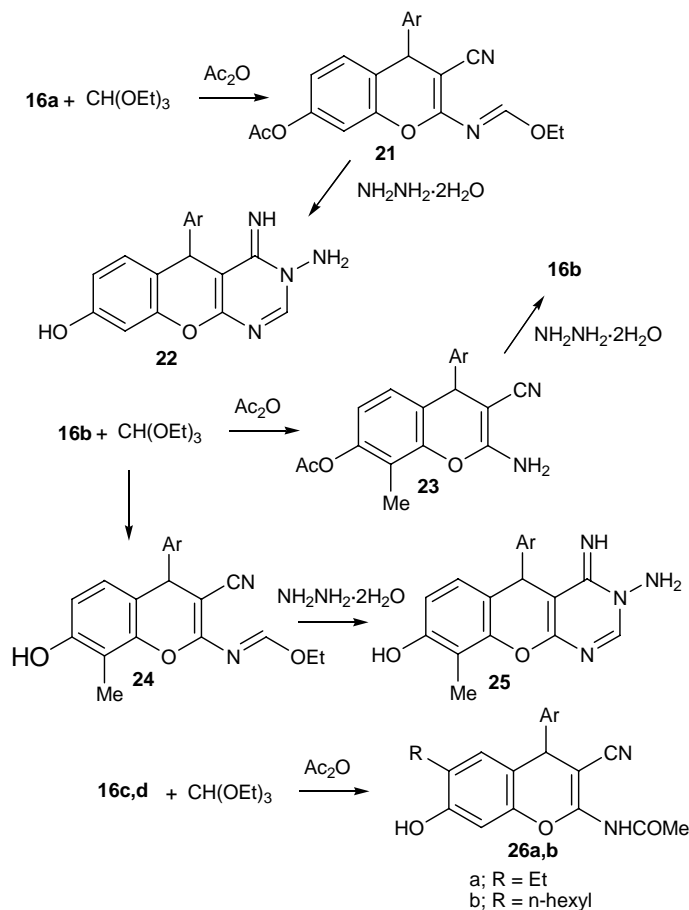


Scheme 7

Here, we presented a facile method for the synthesis of chromene, coumarin and quinoline derivatives containing a proper amino or hydroxy group, which might be the key intermediate for the preparation of new dyes containing fused chromenes, coumarins and quinolines.

All of the newly synthesized compounds were tested for antibacterial activity against *Streptococcus pyogenes* (ATCC 19615), *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 19433), *Escherichia coli* (ATCC 25933), and *Pseudomonas aeruginosa* (ATCC 27853) at the concentration of 25

$\mu\text{g/mL}$, 50 $\mu\text{g/mL}$ and 100 $\mu\text{g/mL}$ by using disc agar diffusion method. We found that only compounds (**16b**) and (**16c**) exhibited antibacterial activity against *Staph. aureus* at all of the above-mentioned concentrations. The diameters of zones of inhibition of compounds (**16b**) and (**16c**) at the concentration of 25 $\mu\text{g/ml}$ were measured 15 mm and 12 mm, respectively.



Scheme 8

EXPERIMENTAL

Melting points were measured in open capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz respectively, on a Varian Gemini 200 spectrometer, in DMSO-d_6 , with chemical shifts being calculated from the solvent signals. NH, NH_2 and OH groups were verified by adding D_2O to the solvent and observing which peaks were no longer present. ^{13}C NMR spectra were obtained by using an attached proton test (APT). MS spectra were reported on Hewlett Packard 5989 B Mass Spectrometer. IR spectra were recorded on Bomem MB-Series FT-IR spectrophotometer (KBr pellet).

General Procedure for the synthesis of 3a-f; 7a-c; 8a,b; 9a-c; 10; 16a-d; 18a,b and 20a,b:

A solution of phenolic compounds (**1**, **6**, **15a-d**, **17**) or 4-hydroxycoumarin (**19**) (10 mmol) in ethanol (75 ml) was treated with substituted α -cyanocinnamionitriles (**2a-c,g,h**) (10 mmol) or ethyl α -cyanocinnamates (**2d-f**) (10 mmol) and piperidine (0.2 g, 2 mmol). The reaction mixture was heated with

stirring until complete precipitation (reaction time: approx. 15 min for **2a-c,g,h**; 120 min for **2d-f**). The solid product, which formed, was collected by filtration and recrystallized from a suitable solvent to give **3a-f**; **7a-c**; **8a,b**; **9a-c**; **10**; **16a-d**; **18g,h** and **20g,h**.

3,8-Diamino-1-phenyl-1*H*-benzo[*h*]chromene-2-carbonitrile (3a):

Gray crystals from ethanol/benzene; mp 267-268 °C; yield 83 %; ¹H NMR (200 MHz) δ 7.74 (d, aromatic, J = 8.6 Hz, 1H), 7.44 (d, aromatic, J = 7.8 Hz, 1H), 7.34-7.16 (m, aromatic, 6H), 7.08 (br s, NH₂-3, 2H), 6.93 (d, aromatic, J = 8.6 Hz, 1H), 6.71 (d, aromatic, J = 7.4, 1.2 Hz, 1H), 5.77 (br s, NH₂-8, 2H), 4.83 (s, 1H, H-1); ¹³C NMR (50 MHz) δ 159.7 (C-3), 145.2 (C-4a), 144.2 (C-8), 123.4 (C-4b), 121.4 (C-8a), 120.0 (C-10a), 55.6 (C-2), 40.3 (C-1), 116.8 (CN), 142.3, 128.0, 126.9, 126.8, 126.2, 122.7, 118.0, 107.8, 107.4 (aromatic); IR cm⁻¹ (KBr) 3428, 3401, 3338, 3299, 3179 (2 NH₂), 2201 (CN); MS m/z (%): 313 (M⁺, 36), 276 (14), 236 (100), 208 (3), 181 (4), 149 (3), 118 (7), 97 (10), 57 (24); Anal. Calcd for C₂₀H₁₅N₃O: C, 76.66; H, 4.82; N, 13.41. Found: C, 76.78; H, 4.89; N, 13.57.

3,8-Diamino-1-(4-chlorophenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (3b):

Gray crystals from ethanol/benzene; mp 235-236 °C; yield 75 %; ¹H NMR (200 MHz) δ 7.74 (d, aromatic, J = 7.4 Hz, 1H), 7.42 (d, aromatic, J = 7.8 Hz, 1H), 7.36-7.23 (m, aromatic, 5H), 7.11 (br s, NH₂-3, 2H), 6.90 (d, aromatic, J = 9.0 Hz, 1H), 6.70 (d, aromatic, J = 5.6 Hz, 1H), 5.77 (br s, NH₂-8, 2H), 4.88 (s, 1H, H-1); ¹³C NMR (50 MHz) δ 160.4 (C-3), 144.9 (C-4a), 144.8 (C-8), 124.1 (C-4b), 122.2 (C-8a), 120.6 (C-10a), 55.9 (C-2), 40.2 (C-1), 117.0 (CN), 143.0, 131.5, 129.6, 128.7, 127.6, 123.3, 118.8, 108.6, 108.2 (aromatic); IR cm⁻¹ (KBr) 3463, 3445, 3415, 3342, 3287 (2 NH₂), 2187 (CN); MS m/z (%): 349 (M⁺+2, 9), 347 (M⁺, 25), 276 (36), 236 (100), 208 (3), 181 (4), 101 (3), 77 (4); Anal. Calcd for C₂₀H₁₄N₃OCl: C, 69.07; H, 4.06; N, 12.08. Found: C, 69.01; H, 4.07; N, 12.01.

3,8-Diamino-1-(4-methoxyphenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (3c):

Grey crystals from ethanol/benzene; mp 209-210 °C; yield 84 %; ¹H NMR (200 MHz) δ 7.71 (d, aromatic, J = 8.6 Hz, 1H), 7.42 (d, aromatic, J = 7.4 Hz, 1H), 7.30-7.11 (m, aromatic, 5H), 7.00 (br s, NH₂-3, 2H), 6.87 (d, aromatic, J = 8.2 Hz, 1H), 6.70 (d, aromatic, J = 7.0 Hz, 1H), 5.77 (br s, NH₂-8, 2H), 4.77 (s, 1H, H-1), 3.70 (s, 3H, MeO); ¹³C NMR (50 MHz) δ 160.2 (C-3), 144.9 (C-4a), 142.8 (C-8), 124.1 (C-4b), 122.0 (C-8a), 120.7 (C-10a), 56.5 (C-2), 40.1 (C-1), 117.8 (CN), 158.1, 138.0, 128.7, 127.5, 123.5, 118.6, 114.0, 108.4, 108.1 (aromatic); IR cm⁻¹ (KBr) 3421, 3378, 3330, 3202 (2 NH₂), 2186 (CN); MS m/z (%): 343 (M⁺, 23), 276 (100), 236 (46), 220 (4), 184 (4), 164 (4), 130 (4), 101 (2), 77 (3).

Ethyl 3,8-Diamino-1-phenyl-1*H*-benzo[*h*]chromene-2-carboxylate (3d):

Gray crystals from ethanol/benzene; mp 203-204 °C; yield 75 %; ¹H NMR (200 MHz) δ 7.75 (br s, NH₂-3, 2H), 7.72-7.21 (m, aromatic, 8H), 7.11 (d, aromatic, J = 8.6 Hz, 1H), 6.70 (d, aromatic, J = 7.0 Hz, 1H), 5.75 (br s, NH₂-8, 2H), 4.98 (s, 1H, H-1), 3.98 (q, CH₂, 2H, J = 7.0 Hz), 1.07 (t, 3H, J = 7.0 Hz);

^{13}C NMR (50 MHz) δ 168.7 (CO), 161.1 (C-3), 148.0 (C-4a), 143.1 (C-8), 124.2 (C-4b), 122.0 (C-8a), 120.1 (C-10a), 76.5(C-2), 40.1(C-1), 144.9, 128.2, 127.3, 126.0, 123.8, 118.5, 108.2, 108.1 (aromatic), 58.6 (CH₂), 14.3 (Me); IR cm⁻¹ (KBr) 3433, 3397, 3354, 3281 (2 NH₂), 1677 (CO); MS m/z (%): 360 (M⁺, 28), 283 (100), 237 (40), 209 (6), 181 (5), 143 (5), 118 (6), 105 (3), 77 (5); Anal. Calcd for C₂₂H₂₀N₂O₃: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.19; H, 5.51; N, 7.81.

Ethyl 3,8-Diamino-1-(4-chlorophenyl)-1*H*-benzo[*h*]chromene-2-carboxylate (3e):

Red crystals from ethanol; mp 185-186 °C; yield 72 %; ^1H NMR (200 MHz) δ 7.78 (br s, NH₂-3, 2H), 7.73-7.14 (m, aromatic, 7H), 7.10 (d, aromatic, J = 8.6 Hz, 1H), 6.72 (d, aromatic, J = 8.0 Hz, 1H), 5.76 (br s, NH₂-8, 2H), 5.00 (s, 1H, H-1), 4.00 (q, CH₂, J = 7.0 Hz, 2H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz) δ 168.7 (CO), 161.4 (C-3), 147.5 (C-4a), 143.5 (C-8), 124.6 (C-4b), 122.5 (C-8a), 120.3 (C-10a), 76.5(C-2), 40.3(C-1), 145.3, 130.9, 129.6, 128.5, 127.8, 124.1, 119.1, 108.8, 108.6 (aromatic), 56.1 (CH₂), 14.7 (Me); IR cm⁻¹ (KBr) 3463, 3420, 3397, 3323, 3251 (2 NH₂), 1668 (CO); MS m/z (%): 396 (M⁺+ 2, 9), 394 (M⁺, 27), 283 (100), 237 (36), 209 (6), 181 (5), 154 (4), 118 (5), 101 (3), 77 (3); Anal. Calcd for C₂₂H₁₉N₂O₃Cl: C, 66.92; H, 4.85; N, 7.09. Found: C, 67.03; H, 4.91; N, 7.14.

Ethyl 3,8-Diamino-1-(4-methoxyphenyl)-1*H*-benzo[*h*]chromene-2-carboxylate (3f):

Red crystals from ethanol; mp 192-193 °C; yield 75 %; ^1H NMR (200 MHz) δ 7.69 (br s, NH₂-3, 2H), 7.74-7.06 (m, aromatic, 7H), 6.76 (d, aromatic, J = 8.6 Hz, 1H), 6.68 (d, aromatic, J = 6.7 Hz, 1H), 5.74 (br s, NH₂-8, 2H), 4.91 (s, 1H, H-1), 3.98 (q, CH₂, J = 7.0 Hz, 2H), 3.64 (s, MeO, 3H), 1.09 (t, Me, 3H, J = 7.0 Hz); ^{13}C NMR (50 MHz) δ 168.4 (CO), 160.9 (C-3), 144.8 (C-4a), 142.9 (C-8), 124.1 (C-4b), 121.9 (C-8a), 120.8 (C-10a), 76.7(C-2), 39.2(C-1), 157.5, 140.2, 128.2, 127.3, 123.9, 118.4, 113.5, 108.8, 108.1 (aromatic), 58.6 (CH₂), 54.9 (MeO), 14.32 (Me); IR cm⁻¹ (KBr) 3463, 3366, 3342, 3257 (2 NH₂), 1667 (CO); MS m/z (%): 390 (M⁺, 32), 361 (10), 317 (18), 283 (100), 237 (37), 209 (6), 181 (5), 172 (7), 123 (3), 109 (2), 77 (3); Anal. Calcd for C₂₃H₂₂N₂O₄: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.75; H, 5.70; N, 7.15.

2,7-Diamino-4-phenyl-4*H*-chromene-3-carbonitrile (7a):

Pale yellow crystals from ethanol; mp 236-237 °C; yield 81%; ^1H NMR (200 MHz) δ 7.33-7.14 (m, aromatic, 5H), 6.80 (br s, NH₂-2, 2H), 6.64 (d, aromatic, J = 8.2 Hz, 1H), 6.29 (dd, aromatic, J = 8.2, 2.4 Hz, 1H), 6.24 (d, aromatic, J = 1.8 Hz, 1H), 5.24 (br s, NH₂-7, 2H), 4.53 (s, 1H, H-4); ^{13}C NMR (50 MHz) δ 160.4 (C-2), 148.9 (C-8a), 148.8 (C-7), 129.4 (C-5), 120.2 (C-4a), 111.2 (C-6), 100.0 (C-8), 56.5 (C-3), 40.1 (C-4), 110.2 (CN), 146.8, 128.5, 127.4, 126.5 (aromatic); IR cm⁻¹ (KBr) 3429, 3353, 3305, 3163 (2 NH₂), 2198 (CN); MS m/z (%): 263 (M⁺, 13), 226 (42), 186 (100), 170 (3), 104 (3), 106 (3), 58 (7); Anal. Calcd for C₁₆H₁₃N₃O: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.10; H, 4.99; N, 15.97.

2,7-Diamino-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (7b):

Pale yellow crystals from ethanol; mp 226-227 °C; yield 77 %; ¹H NMR (200 MHz) δ 7.34 and 7.17 (2 d, aromatic, J = 8.2 Hz, 4H), 6.83 (br s, NH₂-2, 2H), 6.60 (d, aromatic, J = 8.2 Hz, 1H), 6.27 (dd, aromatic, J = 8.2, 2.4 Hz, 1H), 6.21 (d, aromatic, J = 2.0 Hz, 1H), 5.25 (br s, NH₂-7, 2H), 4.56 (s, 1H, H-4); ¹³C NMR (50 MHz) δ 160.4 (C-2), 155.6 (C-8a), 148.9 (C-7), 129.4 (C-5), 120.7 (C-4a), 111.2 (C-6), 99.9 (C-8), 56.0 (C-3), 39.4 (C-4), 109.5 (CN), 145.7, 131.1, 129.2, 128.5 (aromatic); IR cm⁻¹ (KBr) 3443, 3367, 3317, 3240, 3221 (2 NH₂), 2190 (CN); MS m/z (%): 299 (M⁺ + 2, 3), 297 (M⁺, 10), 226 (37), 186 (100), 170 (3), 131 (3), 114 (1), 58 (6); Anal. Calcd for C₁₆H₁₂N₃OCl: C, 64.54; H, 4.06; N, 14.11. Found: C, 64.72; H, 4.12; N, 14.19.

2,7-Diamino-4-(4-methoxyphenyl)-4H-chromene-3-carbonitrile (7c):

Pale yellow crystals from ethanol; mp 218-219 °C; yield 90 %; ¹H NMR (200 MHz) δ 7.05, 6.84 (d, aromatic, J = 8.6 Hz, 4H), 6.73 (br s, NH₂-2, 2H), 6.59 (d, aromatic, J = 8.2 Hz, 1H), 6.25 (dd, aromatic, J = 8.2, 2.4 Hz, 1H), 6.19 (d, aromatic, J = 2.0 Hz, 1H), 5.21 (br s, NH₂-7, 2H), 4.46 (s, 1H, H-4), 3.70 (s, 3H, MeO); ¹³C NMR (50 MHz) δ 160.3 (C-2), 148.9 (C-8a), 148.7 (C-7), 129.5 (C-5), 121.0 (C-4a), 111.2 (C-6), 100.0 (C-8), 56.8 (C-3), 39.3 (C-4), 110.5 (CN), 158.0, 138.9, 128.4, 113.9 (aromatic), 55.0 (MeO); IR cm⁻¹ (KBr) 3444, 3372, 3311, 3226, 3226 (2 NH₂), 2958, 2897, 2837, (CH aliphatic), 2188 (CN); MS m/z (%): 293 (M⁺, 23), 226 (56), 186 (100), 170 (5), 141 (3), 114 (4), 77 (4); Anal. Calcd for C₁₇H₁₅N₃O₂: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.50; H, 5.14; N, 14.22.

7-Amino-4-phenylcoumarin-3-carbonitrile (8a):

Yellow crystals from ethanol/benzene; mp 285-286 °C; yield 42 %; ¹H NMR (200 MHz) δ 7.60-7.49 (m, aromatic, 5H), 7.03 (br s, NH₂-7, 2H), 6.90 (d, aromatic, J = 8.6 Hz, 1H), 6.58 (dd, aromatic, J = 8.2, 2.4 Hz, 1H), 6.50 (d, aromatic, J = 1.6 Hz, 1H); ¹³C NMR (50 MHz) δ 163.1 (CO), 156.8 (C-4), 156.6 (C-8a), 152.0 (C-7), 128.3 (C-5), 115.7 (C-4a), 112.9 (C-6), 98.3 (C-8), 97.7 (C-3), 107.3 (CN), 132.9, 130.3, 130.2, 128.7 (aromatic); IR cm⁻¹ (KBr) 3457, 3366, 3250 (NH₂), 2217 (CN), 1693 (CO); MS m/z (%): 262 (M⁺, 100), 234 (57), 205 (41), 178 (7), 151 (10), 117 (6), 103 (10), 76 (16), 44 (9); Anal. Calcd for C₁₆H₁₀N₂O₂: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.15; H, 3.83; N, 10.74.

7-Amino-4-(4-chlorophenyl)coumarin-3-carbonitrile (8b):

Yellow crystals from ethanol/benzene; mp 335-336 °C; yield 37 %; ¹H NMR (200 MHz) δ 7.67, 7.52 (2d, aromatic, J = 8.6 Hz, 4H), 7.07 (br s, NH₂-7, 2H), 6.90 (d, aromatic, J = 9.0 Hz, 1H), 6.58 (dd, aromatic, J = 8.6, 2.4 Hz, 1H), 6.49 (d, aromatic, J = 1.8 Hz, 1H); ¹³C NMR (50 MHz) δ 161.8 (CO), 158.3 (C-4), 156.8 (C-8a), 156.7 (C-7), 128.9 (C-5), 115.6 (C-4a), 113.0 (C-6), 98.3 (C-8), 91.0 (C-3), 107.2 (CN), 135.1, 131.8, 130.3, 130.2 (aromatic); IR cm⁻¹ (KBr) 3457, 3359, 3251 (NH₂), 2220 (CN), 1699 (CO); MS m/z (%): 298 (M⁺ + 2, 34), 296 (M⁺, 100), 268 (57), 205 (58), 177 (13), 151 (11), 117 (9), 89 (13), 44 (20); Anal. Calcd for C₁₆H₉N₂O₂Cl: C, 64.77; H, 3.06; N, 9.44. Found: C, 64.82; H, 3.11; N, 9.53.

7-Hydroxy-4-phenyl-2-oxo-1,2-dihydroquinoline-3-carbonitrile (9a):

Yellow crystals from ethanol/benzene; mp > 360 °C; yield 38 %; ¹H NMR (200 MHz) δ 12.31 (s, OH, 1H), 10.84 (br s, NH, 1H), 7.60-7.47 (m, aromatic, 5H), 7.00 (d, aromatic, J = 9.0 Hz, 1H), 6.75 (dd, aromatic, J = 8.2, 2.4 Hz, 1H), 6.65 (d, aromatic, J = 2.4 Hz, 1H); ¹³C NMR (50 MHz) δ 162.8 (CO), 160.0 (C-4), 159.2 (C-7), 142.3 (C-8a), 128.5 (C-5), 116.0 (C-4a), 113.6 (C-6), 100.2 (C-8), 97.7 (C-3), 111.4 (CN), 134.2, 130.0, 129.6, 128.7 (aromatic); IR cm⁻¹ (KBr) 3461, 3372 (NH), 3245 (OH), 2221 (CN), 1693 (CO); MS m/z (%): 262 (M⁺, 100), 234 (35), 205 (12), 178 (5), 151 (8), 131 (4), 89 (9), 76 (15), 51 (4); Anal. Calcd for C₁₆H₁₀N₂O₂: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.40; H, 3.91; N, 10.60.

7-Hydroxy-4-(4-chlorophenyl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile (9b):

Pale yellow crystals from acetic acid; mp > 360 °C; yield 41 %; ¹H NMR (200 MHz) δ 12.30 (s, OH, 1H), 10.90 (br s, NH, 1H), 7.58 (2d, aromatic, J = 7.8 Hz, 4H), 7.00 (d, aromatic, J = 7.8 Hz, 1H), 6.79- 6.70 (m, aromatic, 2H); ¹³C NMR (50 MHz) δ 162.8 (CO), 160.3 (C-4), 159.8 (C-7), 142.3 (C-8a), 128.5 (C-5), 115.8 (C-4a), 113.7 (C-6), 100.2 (C-8), 98.3 (C-3), 111.2 (CN), 135.1, 130.5, 130.3, 129.9 (aromatic); IR cm⁻¹ (KBr) 3463, 3368, (NH), 3241 (OH), 2225 (CN), 1693 (CO); MS m/z (%): 296 (M⁺, 100), 298 (M⁺ + 2, 34), 268 (10), 233 (51), 205 (6), 177 (10), 151 (7), 116 (7), 89 (10), 75 (16), 44 (41); Anal. Calcd for C₁₆H₉N₂O₂Cl: C, 64.77; H, 3.06; N, 9.44. Found: C, 64.79; H, 3.06; N, 9.43.

7-Hydroxy-4-(4-methoxyphenyl)-2-oxo-1,2-dihydroquinoline-3-carbonitrile (9c):

Yellow crystals from dioxane; mp 355-356 °C; yield 37 %; ¹H NMR (200 MHz) δ 12.30 (s, OH, 1H), 10.83 (br s, NH, 1H), 7.39 (2d, aromatic, J = 8.6 Hz, 4H), 7.10 (d, aromatic, J = 8.6 Hz, 1H), 6.75-6.70 (dd aromatic, J = 10.2, 2.2 Hz, 1H), 6.65 (d, aromatic, J = 2.2 Hz, 1H); ¹³C NMR (50 MHz) δ 163.1 (CO), 162.9 (C-4), 159.8 (C-7), 142.4 (C-8a), 126.2 (C-5), 116.4 (C-4a), 113.7 (C-6), 100.4 (C-8), 97.8 (C-3), 111.5 (CN), 156.8, 130.1, 129.5, 124.9 (aromatic), 56.3 (MeO); IR cm⁻¹ (KBr) 3480, 3370 (NH), 3246 (OH), 2971, 2946, 2849 (CH aliphatic), 2225 (CN), 1699 (CO); MS m/z (%): 292 (M⁺, 100), 264 (25), 249 (15), 221 (12), 192 (6), 146 (5), 121 (6), 97 (6), 57 (14); Anal. Calcd for C₁₇H₁₂N₂O₃: C, 69.86; H, 4.14; N, 9.58. Found: C, 70.01; H, 4.21; N, 9.70.

Ethyl 2,7-Diamino-4-(4-methoxyphenyl)-4H-chromene-3-carboxylate (10):

Colorless crystals from ethanol; mp 175-176 °C; yield 46 %; ¹H NMR (200 MHz) δ 7.52 (br s, NH₂-2, 2H), 7.03, 6.75 (2d, aromatic, J = 8.6 Hz, 4H), 6.76 (d, aromatic, J = 8.2 Hz, 1H), 6.28 (dd, aromatic, J = 7.2, 2.0 Hz, 1H), 6.14 (d, aromatic, J = 2.4 Hz, 1H), 5.14 (br s, NH₂-7, 2H), 4.65 (s, 1H, H-4), 3.94 (q, CH₂, J = 7.0 Hz, 2H), 3.65 (s, MeO, 3H), 1.06 (t, Me, J = 7.0 Hz, 3H); ¹³C NMR (50 MHz) δ 168.6 (CO), 161.2 (C-2), 149.2 (C-8a), 148.2 (C-7), 129.4 (C-5), 113.8 (C-4a), 111.0 (C-6), 100.1 (C-8), 77.2 (C-3), 38.2 (C-4), 157.2, 141.4, 127.9, 113.4 (aromatic), 58.5 (CH₂), 54.9 (MeO), 14.3 (Me); IR cm⁻¹ (KBr) 3417, 3372, 3325, 3224 (2 NH₂), 2983, 2959, 2899, 2831 (CH aliphatic), 1665 (CO); MS m/z (%): 340 (M⁺, 11), 293 (9), 273 (55), 233 (100), 187 (65), 159 (6), 131 (6), 104 (5), 58 (9), 43 (12); Anal.

Calcd for C₁₉H₂₀N₂O₄: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.06; H, 5.94; N, 8.22.

2-Amino-7-hydroxy-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (16a):

Colorless crystals from ethanol; mp 230-231 °C (Literature⁴⁴ mp 178 °C); yield 85 %; ¹H NMR (200 MHz) δ 9.8 (br, OH, 1H), 7.36, 7.18 (2d, aromatic, J = 8.6 Hz, 4H), 6.91 (br s, NH₂-2, 2H), 6.77 (d, aromatic, J = 8.6 Hz, 1H), 6.49, 6.45 (dd, aromatic, J = 8.2, 2.2 Hz, 1H), 6.39 (d, aromatic, J = 2.4 Hz, 1H), 4.65 (s, 1H, H-4); ¹³C NMR (50 MHz) δ 160.3 (C-2), 157.4 (C-8a), 148.8 (C-7), 129.8 (C-5), 120.5 (C-4a), 112.5 (C-6), 102.2 (C-8), 55.8 (C-3), 39.3 (C-4), 113.0 (CN), 145.3, 131.2, 129.8, 129.3 (aromatic); IR cm⁻¹ (KBr) 3400, 3336, 3214 (OH, NH₂), 2186 (CN); MS m/z (%):300 (M⁺+ 2, 4), 298 (M⁺, 11), 187 (100), 144 (1), 131 (2), 89 (2), 75 (3), 43 (5); Anal. Calcd for C₁₆H₁₁N₂O₂Cl: C, 64.33; H, 3.71; N, 9.38. Found: C, 64.44; H, 3.78; N, 9.46.

2-Amino-7-hydroxy-8-methyl-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (16b) :

Beige needles from ethanol; mp 220-221 °C ; yield 89 %; ¹H NMR (200 MHz) δ 9.62 (br, OH, 1H), 7.33, 7.16 (2d, aromatic, J = 7.8 Hz, 4H), 6.93 (br s, NH₂-2, 2H), 6.63 (d, aromatic, J = 8.2 Hz, 1H), 6.54 (d, aromatic, J = 8.2 Hz, 1H), 4.64 (s, 1H, H-4), 2.09 (s, Me, 3H); ¹³C NMR (50 MHz) δ 160.6 (C-2), 155.1 (C-8a), 147.3 (C-7), 129.3 (C-5), 120.8 (C-4a), 111.4 (C- 6), 111.2 (C-8), 55.9 (C-3), 39.5 (C-4), 113.5 (CN), 145.6, 131.3, 128.6, 126.1 (aromatic), 8.5 (Me); IR cm⁻¹ (KBr) 3458, 3380, 3322, 3213 (OH, NH₂), 2196 (CN); MS m/z (%):314 (M⁺+ 2, 3), 312 (M⁺, 10), 201 (100), 156 (1), 128 (3), 103 (2), 75 (4), 51 (1); Anal. Calcd for C₁₇H₁₃N₂O₂Cl: C, 65.29; H, 4.19; N, 8.96. Found: C, 65.21; H, 4.15; N, 8.99.

2-Amino-6-ethyl-7-hydroxy-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (16c):

Colorless crystals from ethanol; mp 215-216 °C ; yield 92 %; ¹H NMR (200 MHz) δ 9.37 (br, OH, 1H), 7.35, 7.19 (2d, aromatic, J = 7.0 Hz, 4H), 6.78 (br s, NH₂-2, 2H), 6.65 (s, aromatic, 1H), 6.47 (s, aromatic, 1H), 4.63 (s, 1H, H-4), 2.41 (q, CH₂, J = 7.4 Hz, 2H), 1.02 (t, Me, J = 7.4 Hz, 3H); ¹³C NMR (50 MHz) δ 160.3 (C-2), 154.7 (C-8a), 146.7 (C-7), 129.2 (C-5), 127.2 (C-4a), 120.6 (C- 6), 101.8 (C-8), 55.9 (C-3), 39.4 (C-4), 112.7 (CN), 145.4, 131.1, 128.7, 128.5, (aromatic), 22.2 (CH₂) 14.1 (Me); IR cm⁻¹ (KBr) 3419, 3333, 3221 (OH, NH₂), 2966, 2935, 2874 (CH aliphatic), 2180 (CN); MS m/z (%):328 (M⁺+ 2, 3), 326 (M⁺, 9), 215 (100) 171 (3), 115 (3), 89 (2), 69 (4), 51 (1); Anal. Calcd for C₁₈H₁₅N₂O₂Cl: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.23; H, 4.70; N, 8.63.

2-Amino-6-(n-hexyl)-7-hydroxy-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (16d):

Colorless crystals from ethanol; mp 195-196 °C; yield 89 %; ¹H NMR (200 MHz) δ 9.60 (br, OH, 1H), 7.26 (2d, aromatic, J = 7.0 Hz, 4H), 6.86 (br s, NH₂-2, 2H), 6.61 (s, aromatic, 1H), 6.47 (s, aromatic, 1H), 4.63 (s, 1H, H-4), 2.30 (t, CH₂, 2H, J = 7.2 Hz), 1.36-1.14 (m, 4 CH₂, 8H), 0.78 (t, Me, J = 4.6 Hz, 3H); ¹³C NMR (50 MHz) δ 160.3 (C-2), 154.7 (C-8a), 146.7 (C-7), 129.6 (C-5), 125.6 (C-4a), 120.6 (C-6), 101.8 (C-8), 55.9 (C-3), 39.4 (C-4), 112.5 (CN), 145.4, 131.2, 129.2, 128.5 (aromatic), 31.0 (CH₂), 29.1 (CH₂), 28.9 (CH₂), 28.3 (CH₂), 22.1 (CH₂) 13.8 (Me); IR cm⁻¹ (KBr) 3468, 3334, 3215 (OH, NH₂), 2966,

2923, 2875, 2850 (CH aliphatic), 2198 (CN); MS m/z (%): 382 (M⁺, 7), 384 (M⁺+ 2, 3), 271 (100), 200 (12), 171 (3), 128 (1), 89 (1), 69 (6), 43(9); Anal. Calcd for C₂₂H₂₃N₂O₂Cl: C, 69.01; H, 6.05; N, 7.32. Found: C, 68.94; H, 6.04; N, 7.30.

3-Amino-9-chloro-1-(4-hydroxyphenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (18a):

Pale yellow crystals from ethanol; mp 241-242 °C; yield 81 %; ¹H NMR (200 MHz) δ 9.37 (br, OH, 1H), 8.19 (2d, aromatic, J = 7.4 Hz, 4H), 7.74 (d, aromatic, J = 7.8 Hz, 1H), 7.25 (s, aromatic, 1H), 7.15 (br s, NH₂-3, 2H), 7.07-6.68 (m, aromatic, 3H), 4.78 (s, 1H, H-1); ¹³C NMR (50 MHz) δ 159.8 (C-3), 141.9 (C-4a), 129.2 (C-8a), 128.3 (C-6), 127.8 (C-10), 126.1 (C-7), 125.5 (C-4b), 124.0 (C-9), 123.9 (C-8), 121.5 (C-5), 120.4 (C-10a), 56.6 (C-2), 39.9 (C-1), 119.2 (CN), 156.5, 135.7, 128.8, 115.6 (aromatic); IR cm⁻¹ (KBr) 3427, 3384, 3348 (OH, NH₂), 2196 (CN); MS m/z (%): 348 (M⁺, 24), 350 (M⁺+ 2, 8), 255 (100), 200 (2), 128 (2), 100 (3), 65 (2), 43 (2); Anal. Calcd for C₂₀H₁₃ClN₂O₂: C, 68.87; H, 3.76; N, 8.03. Found: C, 68.96; H, 3.79; N, 8.12.

3-Amino-9-chloro-1-(4-hydroxy-3-methoxyphenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (18b):

Colorless needles from ethanol; mp 248-249 °C; yield 84 %; ¹H NMR (200 MHz) δ 8.94 (s, OH, 1H), 8.32-8.27 (m, aromatic, 6H), 7.31 (s, aromatic, 1H), 7.16 (br s, NH₂-3, 2H), 6.88 (d, aromatic, J = 2.0, 1H), 4.78 (s, 1H, H-1), 3.72 (s, MeO, 3H); ¹³C NMR (50 MHz) δ 159.8 (C-3), 141.8 (C-4a), 129.2 (C-8a), 128.2 (C-6), 127.6 (C-10), 126.0 (C-7), 125.4 (C-4b), 124.0 (C-9), 123.8 (C-8), 121.5 (C-5), 120.4 (C-10a), 56.4 (C-2), 40.2 (C-1), 119.1 (CN), 147.6, 141.8, 136.2, 120.2, 115.0, 111.9 (aromatic); IR cm⁻¹ (KBr) 3474, 3323, 3251, 3202 (OH, NH₂), 2983, 2928, 2837 (CH aliphatic), 2199 (CN); MS m/z (%): 380 (M⁺+ 2, 8), 378 (M⁺, 23), 255 (100), 220 (4), 193, (10), 164 (5), 124 (6), 94 (2), 75 (1), 43 (2); Anal. Calcd for C₂₁H₁₅N₂O₃Cl: C, 66.58; H, 3.99; N, 7.40. Found: C, 66.65; H, 4.10; N, 7.48.

2-Amino-3-cyano-4-(4-hydroxyphenyl)-4*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (20a):

Colorless crystals from dioxane; mp 265-266 °C; yield 85 %; ¹H NMR (200 MHz) δ 9.34 (s, OH, 1H), 7.87, 7.65 (2d, aromatic, J = 8.2 Hz, 4H), 7.56 to 7.41 (m, aromatic, 2H), 7.32 (br s, NH₂-2, 2H), 7.05, 7.02 (dd aromatic, J = 8.2, 1.6 Hz, 1H), 6.68 (dd aromatic, J = 8.2, 1.6 Hz, 1H), 4.32 (s, 1H, H-4); ¹³C NMR (50 MHz) δ 159.6 (CO), 158.0 (C-2), 156.6 (C-10b), 152.1 (C-6a), 128.8 (C-8), 124.6 (C-10), 122.4 (C-9), 119.5 (C-10a), 116.5 (C-7), 104.5 (C-4a), 58.6 (C-3), 36.3 (C-4), 113.0 (CN), 153.0, 133.8, 132.7, 115.3 (aromatic); IR cm⁻¹ (KBr) 3514, 3417, 3295, 3186 (OH, NH₂), 2197 (CN), 1708 (CO); MS m/z (%): 332 (M⁺, 39), 265 (44), 239 (100), 211 (5), 184 (4), 145 (5), 121 (43), 92 (12), 66 (19), 55 (1); Anal. Calcd for C₁₉H₁₂N₂O₄: C, 68.67; H, 3.64; N, 8.43. Found: C, 68.82; H, 3.74; N, 8.40.

2-Amino-3-cyano-4-(4-hydroxy-3-methoxyphenyl)-4*H*,5*H*-pyrano[3,2-*c*]benzopyran-5-one (20b):

Colorless crystals from dioxane; mp 252-253 °C; yield 74 %; ¹H NMR (200 MHz) δ 8.92 (s, OH, 1H), 7.89-7.41 (m, aromatic, 4H), 7.32 (br s, NH₂-2, 2H), 6.81-6.75 (m, aromatic, 3H), 4.35 (s, 1H, H-4) 3.72 (s, MeO, 3H); ¹³C NMR (50 MHz) δ 159.6 (CO), 158.0 (C-2), 153.0 (C-10b), 152.1 (C-6a), 132.8 (C-8),

124.6 (C-10), 122.4 (C-9), 119.4 (C-10a), 116.5 (C-7), 104.3 (C-4a), 58.4 (C-3), 36.5 (C-4), 113.0 (CN), 147.3, 145.8, 134.3, 119.9, 115.5, 112.1 (aromatic), 55.7 (Me); IR cm^{-1} (KBr) 3417, 3299, 3251, 3190 (OH, NH_2), 2191 (CN), 1711 (CO); MS m/z (%): 362 (M^+ , 40), 331 (23), 295 (23), 279 (19), 239 (100), 161 (5), 121 (43), 92 (12), 66 (18), 51 (6); Anal. Calcd for $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_5$: C, 66.30; H, 3.89; N, 7.73. Found: C, 66.31; H, 3.94; N, 7.77.

General Procedure for the synthesis of 5; 12; 13; 21; 23; 24 and 26a,b:

Method (a):

A mixture of **3c**, **7b**, **16b** (10 mmol) and triethyl orthoformate (4.99 g, 30 mmol) was refluxed for 3 h. The solid product that formed on cooling was collected and crystallized from a suitable solvent to give **5**, **12** and **24**.

Method (b):

A mixture of **7b**, **16a-d** (10 mmol), triethyl orthoformate (4.99 g, 30 mmol) and acetic anhydride (20 mL) was refluxed for 3 h. The solid product that formed on cooling was collected and crystallized from a suitable solvent to give **13**, **21**, **23** and **26a,b**.

3-Amino-8-ethoxymethyleneamino-1-(4-methoxyphenyl)-1H-benzo[h]chromene-2-carbonitrile (5):

Pale gray crystals from benzene; mp 195-196 °C; yield 73 %; ^1H NMR (200 MHz) δ 8.06 (s, $\text{N}=\text{CH}$, 1H), 7.98 (br s, NH_2 -3, 2H), 7.76 (d, aromatic, $J = 9.4$ Hz, 1H), 7.55-7.03 (m, aromatic, 7H), 6.85 (d, aromatic, $J = 8.2$ Hz, 1H), 4.82 (s, 1H, H-1), 4.34 (q, CH_2 , $J = 7.0$ Hz, 2H), 3.69 (s, 3H, MeO), 1.33 (t, Me, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz) δ 160.1 (C-3), 155.9 ($\text{N}=\text{CH}$), 144.4 (C-4a), 142.7 (C-8), 128.0 (C-4b), 123.5 (C-8a), 120.6 (C-10a), 56.6 (C-2), 40.2 (C-1), 118.5 (CN), 158.2, 137.9, 128.7, 128.3, 127.0, 125.7, 119.6, 116.8 (C-), 115.4, 114.0 (aromatic), 62.3 (CH_2), 55.0 (MeO), 14.1 (Me); IR cm^{-1} (KBr) 3405, 3326, 3205 (NH_2), 2191 (CN), 1664 (C=N); MS m/z (%): 399 (M^+ , 38), 370 (4), 292 (100), 264 (16), 236 (5), 208 (2), 164 (3), 151 (1), 77 (2); Anal. Calcd for $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_3$: C, 72.16 H, 5.30; N, 10.52. Found: C, 72.35; H, 5.22; N, 10.60.

2-Amino-7-ethoxymethyleneamino-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (12):

Pale yellow crystals from benzene; mp 135-136 °C; yield 81 %; ^1H NMR (200 MHz) δ 7.96 (s, $\text{N}=\text{CH}$, 1H), 7.37, 7.21 (2d, aromatic, $J = 8.6$ Hz, 4H), 6.98 (br s, NH_2 -2, 2H), 6.92 (d, aromatic, $J = 8.2$ Hz, 1H), 6.71 (dd, aromatic, $J = 7.8, 2.0$ Hz, 1H), 6.64 (d, aromatic, $J = 2.0$ Hz, 1H), 4.76 (s, 1H, H-4), 4.19 (q, CH_2 , $J = 7.0$ Hz, 2H), 1.21 (t, Me, $J = 7.0$ Hz, 3H); ^{13}C NMR (50 MHz) δ 160.3 (C-2), 156.7 ($\text{N}=\text{CH}$), 148.5 (C-8a), 147.9 (C-7), 129.6 (C-5), 120.4 (C-4a), 118.4 (C-6), 108.5 (C-8), 55.6 (C-3), 39.5 (C-4), 118.5 (CN), 144.9, 131.4, 129.3, 128.6 (aromatic), 62.1 (CH_2), 14.0 (Me); IR cm^{-1} (KBr) 3360, 3318, 3161 (NH_2), 2977, 2934, 2892, 2861 (CH aliphatic), 2196 (CN); MS m/z (%): 355 ($\text{M}^+ + 2$, 1), 353 (M^+ , 4), 297 (11), 268 (5), 242 (36), 214 (5), 186 (100), 170 (4), 114 (5), 89 (4), 75 (2); Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_2\text{Cl}$: C, 64.50 H, 4.56; N, 11.88. Found: C, 64.56; H, 4.57; N, 11.92.

2-Ethoxymethyleneamino-7-hydroxy-8-methyl-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile**(24):**

Pale yellow crystals from benzene; mp 212-213 °C; yield 82 %; ¹H NMR (200 MHz) δ 9.66 (br, OH, 1H), 8.62 (s, N=CH, 1H), 7.32 (2d, aromatic, J = 8.2 Hz, 4H), 6.62 (d, aromatic, J = 8.6 Hz, 1H), 6.56 (d, aromatic, J = 8.6 Hz, 1H), 4.92 (s, 1H, H-4), 4.33 (q, CH₂, J = 7.0 Hz 2H), 2.07 (s, Me, 3H), 1.31 (t, Me, J = 7.0 Hz, 3H); ¹³C NMR (50 MHz) δ 161.1, (N=CH), 160.6 (C-2), 157.6 (C-8a), 155.3 (C-7), 126.3 (C-5), 131.9 (C-4a), 112.1 (C-6), 111.7 (C-8), 79.6 (C-3), 41.0 (C-4), 118.1 (CN), 147.2, 143.8, 129.7, 128.8 (aromatic), 63.9 (CH₂), 13.8 (Me), 8.4 (Me); IR cm⁻¹ (KBr) 3365 (OH), 2983, 2928 (CH aliphatic), 2213 (CN); MS m/z (%): 370 (M⁺+ 2, 5), 368 (M⁺, 15), 257 (100), 229 (16), 201 (72), 165 (2), 128 (4), 103 (3), 77 (5), 43 (6); Anal. Calcd for C₂₀H₁₇N₂O₃Cl: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.24; H, 4.69; N, 7.69.

2-Acetylamino-7-ethoxymethyleneamino-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (13):

Colorless crystals from benzene; mp 194-195 °C; yield 67 %; ¹H NMR (200 MHz) δ 10.09 (br s, NH, 1H), 8.67 (s, N=CH, 1H), 7.67 (s, aromatic, 1H), 7.34 (2d, aromatic, J = 8.6 Hz, 4H), 7.10 (d, aromatic, J = 8.2 Hz, 1H), 6.89 (d, aromatic, J = 8.2 Hz, 1H), 5.00 (s, 1H, H-4), 4.32 (q, CH₂, J = 7.0 Hz, 2H), 2.02 (s, COMe, 3H), 1.30 (t, Me, J = 7.0, Hz, 3H); ¹³C NMR (50 MHz) δ 168.6 (CO), 161.9 (N=CH), 157.8 (C-2), 148.2 (C-8a), 143.2 (C-7), 129.9 (C-5), 117.9 (C-4a), 116.0 (C-6), 106.6 (C-8), 56.5 (C-3), 40.3 (C-1), 115.7 (CN), 139.42, 132.0, 129.4, 128.8 (aromatic), 63.9 (CH₂), 24.0 (COMe), 13.8 (Me); IR cm⁻¹ (KBr) 3330, 3287 (NH), 2984, 2958, 2892, (CH aliphatic), 2208 (CN), 1702 (CO); MS m/z (%): 395 (M⁺, 14), 397 (M⁺+ 2, 5), 284 (100), 256 (12), 228 (33), 186 (40), 158 (6), 114 (3), 103 (1), 75 (2); Anal. Calcd for C₂₁H₁₈N₃O₃Cl: C, 63.72; H, 4.58; N, 10.62. Found: C, 63.71; H, 4.62; N, 10.66.

7-Acetoxy-2-ethoxymethyleneamino-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (21):

Colorless crystals from benzene; mp 145-146 °C; yield 81 %; ¹H NMR (200 MHz) δ 8.34 (s, N=CH, 1H), 7.36-7.06 (m, aromatic, 7H), 4.81 (s, 1H, H-4), 4.34 (q, CH₂, J = 7.2 Hz, 2H), 2.27 (s, COMe, 3H), 1.35 (t, Me, J = 7.2 Hz 3H); ¹³C NMR (50 MHz) δ 168.9 (CO), 159.6 (N=CH), 157.1 (C-2), 156.6 (C-8a), 150.3 (C-7), 130.2 (C-5), 129.0 (C-4a), 118.8 (C-6), 110.2 (C-8), 80.6 (C-3), 41.9 (C-4), 117.6 (CN), 141.0, 133.5, 129.5, 129.1 (aromatic), 64.3 (CH₂), 21.0 (Me), 13.8 (Me); IR cm⁻¹ (KBr) 2966, 2953 (CH aliphatic), 2212 (CN), 1726 (CO); MS m/z (%): 398 (M⁺+ 2, 7), 396 (M⁺, 21), 285 (87), 243 (100), 215 (18), 187 (1), 158 (7), 114 (3), 103 (2), 69 (2), 43 (3); Anal. Calcd for C₂₁H₁₇N₂O₄Cl: C, 63.56; H, 4.32; N, 7.06. Found: C, 63.50; H, 4.31; N, 7.00.

7-Acetoxy-2-Amino-8-methyl-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (23):

Colorless crystals from ethanol; mp 200-201 °C ; yield 76 %; ¹H NMR (200 MHz) δ 7.38, 7.23 (2d, aromatic, J = 8.2 Hz, 4H), 7.08 (br s, NH₂-2, 2H), 6.90 (d, aromatic, J = 8.4 Hz, 1H), 6.70 (d, aromatic, J = 8.4 Hz, 1H), 4.80 (s, 1H, H-4), 2.28 (s, MeCO, 3H), 2.06 (s, Me, 3H); ¹³C NMR (50 MHz) δ 168.8

(CO), 160.4 (C-2), 148.3 (C-8a), 146.9 (C-7), 129.3 (C-5), 120.4 (C-4a), 120.2 (C-6), 118.2 (C-8), 55.3 (C-3), 39.8 (C-4), 118.3 (CN), 144.7, 131.5, 128.7, 126.4 (aromatic), 20.4 (Me) 8.9 (Me); IR cm^{-1} (KBr) 3411, 3332, 3220, 3213 (NH₂), 2971, 2934 (CH aliphatic), 2195 (CN), 1748 (CO); MS m/z (%): 354 (M⁺, 11), 356 (M⁺+ 2, 4), 243 (38), 201 (100), 172 (1), 128 (2), 101 (1), 77 (2), 43 (3); Anal. Calcd for C₁₉H₁₅N₂O₃Cl: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.20; H, 4.21; N, 7.85.

2-Acetylamino-7-hydroxy-6-ethyl/n-hexyl-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (26a,b):
26a:

Colorless crystals from benzene; mp 160-161 °C; yield 67 %; ¹H NMR (200 MHz) δ 11.09 (br, OH, 1H), 8.64 (br s, NH, 1H), 7.77-7.01 (m, aromatic, 6H), 5.09 (s, 1H, H-4), 2.38 (q, CH₂, J = 7.4 Hz, 2H), 2.36 (s, MeCO, 3H), 1.00 (t, Me, J = 7.4 Hz, 3H); ¹³C NMR (50 MHz) δ 169.0 (CO), 163.0 (C-2), 148.0 (C-8a), 146.1 (C-7), 129.7 (C-5), 132.2 (C-4a), 119.6 (C-6), 111.1 (C-8), 56.5 (C-3), 40.3 (C-4), 116.8 (CN), 142.4, 133.5, 129.6, 129.1 (aromatic), 22.2 (CH₂), 20.5 (Me), 14.1 (Me); IR cm^{-1} (KBr) 3315, 3180 (OH, NH), 2971, 2934, 2964, 2873 (CH aliphatic), 2209 (CN), 1728 (CO); MS m/z (%): 370 (M⁺+ 2, 0), 368 (M⁺, 1), 243 (100), 215 (96), 165 (3), 115 (3), 89 (2), 69 (14); Anal. Calcd for C₂₀H₁₇N₂O₃Cl: C, 65.13; H, 4.65; N, 7.60. Found: C, 65.15; H, 4.67; N, 7.62.

26b: Colorless crystals from ethanol; mp 150-151 °C; yield 57 %; ¹H NMR (200 MHz) δ 11.10 (br, OH, 1H), 8.73 (br, NH, 1H), 7.75, 7.59 (2d, aromatic, J = 8.4 Hz, 4H), 7.02 (s, aromatic, 1H), 6.96 (s, aromatic, 1H), 5.08 (s, 1H, H-4), 2.50 (t, CH₂, 2H, J = 6.6 Hz), 2.37 (s, MeCO, 3H), 1.50-1.10 (m, 4 CH₂, 8H), 0.81 (t, Me, J = 4.3 Hz, 3H); IR cm^{-1} (KBr) 3329 (NH), 2954, 2926, 2855 (CH aliphatic), 2192 (CN), 1708 (CO); MS m/z (%): 426 (M⁺+ 2, 1), 424 (M⁺, 3), 381 (49), 298 (98), 171 (100), 240 (6), 200 (15), 139 (2), 89 (1), 69 (18), 43 (91); Anal. Calcd for C₂₄H₂₅N₂O₃Cl: C, 67.84; H, 5.93; N, 6.59. Found: C, 67.90; H, 5.99; N, 6.67.

Reaction of 5 and 12 with hydrazine hydrate:

A solution of **5** or **12** (10 mmol) and hydrazine hydrate (0.84 g, 12 mmol) in 30 mL of ethanol or benzene was stirred at rt for 1 h to give **3c** as pale gray crystals; mp 209-210 °C; yield 83% and **7b** as pale yellow crystals; mp 226-227 °C; yield 82 % (mp and mixed mp).

2-Acetylamino-7-amino-4-(4-chlorophenyl)-4H-chromene-3-carbonitrile (14):

A mixture of **13** (3.95 g, 10 mmol) and hydrazine hydrate (0.84 g, 12 mmol) in ethanol (30 mL) was stirred at room temperature for 1 h. The solid product that formed on cooling was collected and crystallized from (SOLVENT) to give **14** as colorless crystals; mp 210-211 °C; yield 81 %; ¹H NMR (200 MHz) δ 10.05 (br s, NH, 1H), 7.58 (s, aromatic, 1H), 7.36, 7.19 (2d, aromatic, J = 8.6 Hz, 4H), 7.08-7.03 (dd, aromatic, J = 8.2, 1.8 Hz, 1H), 6.98 (br s, NH₂-7, 2H), 6.90 (d, aromatic, J = 8.2 Hz, 1H), 4.72 (s, 1H, H-4), 2.02 (s, COMe, 3H); ¹³C NMR (50 MHz) δ 168.6 (CO), 160.3 (C-2), 148.2 (C-8a), 145.0 (C-7), 129.9 (C-5), 120.4 (C-4a), 115.3 (C-6), 106.1 (C-8), 55.6 (C-3), 39.5 (C-1), 117.1 (CN), 139.2, 131.4,

129.3, 128.6 (aromatic), 24.0 (COMe); IR cm^{-1} (KBr) 3384, 3330, 3202 (NH_2 , NH), 2928 (CH aliphatic), 2194 (CN), 1687 (CO); MS m/z (%): 341 ($\text{M}^+ + 2$, 4), 339 (M^+ , 13), 295 (12), 268 (10), 228 (100), 186 (39), 158 (4), 141 (3), 114 (3), 66 (5), 43 (32); Anal. Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}_2\text{Cl}$: C, 63.63; H, 4.15; N, 12.37. Found: C, 63.85; H, 4.24; N, 12.51.

3-Amino-10-(4-chlorophenyl)-4-imino-3,10-dihydro-4H-9-oxa-1,3-diazaanthracen-7-ol (22):

A solution of **21** (3.96 g, 10 mmol) and hydrazine hydrate (0.84 g, 12 mmol) in 30 mL of ethanol or benzene was stirred at room temperature for 1 h to give **22** as colorless needles; mp 225-226 °C; yield 91 %; ^1H NMR (200 MHz) δ 9.72 (br, OH, 1H), 8.05 (s, 1H, H-2), 7.34- 6.50 (m, aromatic, 7H), 6.62 (br, NH, 1H), 5.63 (br s, NH_2 , 2H), 5.09 (s, 1H, H-10); ^{13}C NMR (50 MHz) δ 157.2 (C-4), 156.0 (C-8), 154.9 (C-9a), 150.6 (C-2), 149.6 (C-7), 131.1 (C-5), 114.0 (C-10), 112.6 (C-6), 102.8 (C-8), 98.3 (C-4a), 38.1 (C-10), 144.5, 131.1, 129.4, 128.4 (aromatic); IR cm^{-1} (KBr) 3349, 3298, 3221, 3182 (OH, NH, NH_2), 1660 (C=N); MS m/z (%): 342 ($\text{M}^+ + 2$, 7), 340 (M^+ , 20), 324 (78), 297 (17), 214 (100), 187 (42), 162 (4), 131 (3), 89 (4), 58 (11); Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_4\text{O}_2\text{Cl}$: C, 59.92; H, 3.85; N, 16.44. Found: C, 59.90; H, 3.83; N, 16.42.

Reaction of 23 with hydrazine hydrate:

A solution of **23** (3.54 g, 10 mmol) and hydrazine hydrate (0.84 g, 12 mmol) in 30 mL of ethanol or benzene (30 mL) was stirred at rt for 1 h to give **16b** as beige needles; mp 220-221 °C (mp and mixed mp); yield 83 %.

3-Amino-10-(4-chlorophenyl)-4-imino-8-methyl-3,10-dihydro-4H-9-oxa-1,3-diazaanthracen-7-ol (25):

A solution of **24** (3.68 g, 10 mmol) and hydrazine hydrate (0.84 g, 12 mmol) in ethanol or benzene (30 mL) was stirred at room temperature for 1 h to give **25** as pale yellow crystals; mp 283-284 °C; yield 88 %; ^1H NMR (200 MHz) δ 9.92 (s, OH, 1H), 9.10 (br s, NH, 1H), 8.72 (s, 1H, H-2), 7.35- 6.69 (m, aromatic, 6H), 6.66 (br, NH_2 , 2H), 5.57 (s, 1H, H-10), 2.15 (s, Me, 3H); ^{13}C NMR (50 MHz) δ 160.5 (C-4), 160.4 (C-2), 156.0 (C-8a), 155.6 (C-9a), 147.1 (C-7), 128.3 (C-5), 125.9 (C-6), 113.0 (C-8), 112.0 (C-10a), 98.0 (C-4a), 36.8 (C-10), 142.3, 131.9, 129.3, 128.7 (aromatic), 8.4 (Me); IR cm^{-1} (KBr) 3439-2980 (br, OH, NH, NH_2), 1647 (C=N); MS m/z (%): 356 ($\text{M}^+ + 2$, 9), 354 (M^+ , 27), 338 (100), 228 (85), 169 (12), 128 (5), 77 (6), 43 (5); Anal. Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_4\text{O}_2\text{Cl}$: C, 60.94; H, 4.26; N, 15.79. Found: C, 60.99; H, 4.35; N, 15.72.

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