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Title: Synthesis of 4H-chromene, coumarin, 12H-chromeno[2,3-d]pyrimidine derivatives and some of their antimicrobial and cytotoxicity activities

Authors: Nermien M. Sabry, Hany M. Mohamed, Essam Shawky A.E.H. Khattab, Shymaa S. Motlaq, Ahmed M. El-Agrody

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Condensation of 3-N,N-diethylaminophenol (1) with various substituted α-cyanocinnamionitriles (2a-c) in ethanolic piperidine afforded 3a-c, while condensation of 3-N,N-diethylaminophenol (1) with ethyl α-cyanocinnamate (2d-f) in ethanolic piperidine afforded in addition to ethyl 2-amino-4-(4-halophenyl)-7-(diethylamino)-4H-chromene-3-carboxylate (3d-f), the 4-(4-halophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (4a-c).
Synthesis of $4H$-chromene, coumarin, $12H$-chromeno[2,3-$d$]pyrimidine derivatives and some of their antimicrobial and cytotoxicity activities

Nermien M. Sabry b, Hany M. Mohamed c, Essam Shawky A.E.H. Khattab a, Shymaa S. Motlaq b and Ahmed M. El-Agrody a*

a Chemistry Department, Faculty of Science, King Khalid University, 9004, Abha, Saudi Arabia
b Chemistry Department, Girls College of Education, King Khalid University Abha, Saudi Arabia
c Chemistry Department, Faculty of Medicine (Boys Branch), Jazan University, Jazan, Saudi Arabia

Condensation of 3-$N,N$-diethylaminophenol (1) with $\alpha$-cyanocinnamionitriles (2a-c) and ethyl $\alpha$-cyanocinnamates (2d-f) provided compounds 3a-f and 4a-c. $12H$-Chromeno[2,3-$d$]pyrimidine derivatives 6, 11-13 and 16 were obtained by treatment of $4H$-chromene compounds (3) with different electrophiles followed by nucleophilic reagents. Structures of these compounds were established on the basis of IR, UV, $^1$H NMR, $^{13}$C NMR and MS data. Some of the new compounds were evaluated for antimicrobial and cytotoxicity activities.

Keywords: $\alpha$-Cyanocinnamionitriles, Ethyl $\alpha$-cyanocinnamates, 3-$N,N$-Diethylaminophenol

1. Introduction

$4H$-Chromene and its derivatives are biologically interesting compounds known for their antimicrobial and antifungal [1], antioxidant [2], antileishmanial [3], antitumor [4], hypotensive [5], antiproliferation [6], local anaesthetic [7], antiallergenic [8,9], central nervous system (CNS) activities and effects [10], as well as treatment of Alzheimer’s disease [11] and Schizophrenia disorder [12]. Fused chromene ring systems have platelet antiaggregating, local anaesthetic [13-15] and antihistaminic activities [16]. They also exhibit antidepressant effects [17], inhibitory effect on influenza virus sialidases [18,19], DNA breaking activities and mutagenicity [20], antiviral activities [21] and act as sex pheromone homologues [22].

The present study is a part of our research program [23-35] directed towards the synthesis of novel $4H$-chromene and coumarin compounds using $\beta$-enaminonitriles and $\beta$-enaminocarboxylic esters and their use as building blocks in the synthesis of novel fused chromenes and evalutation of their antimicrobial and antitumor activities.

* Corresponding author. Tel.: +966 530175825
E-mail addresses: elagrody_am@yahoo.com
2. Chemistry

Treatment of 3-N,N-diethylaminophenol (1) with various substituted α-cyanocinnamionitriles (2a-c) in ethanol and piperidine afforded 3a-c, while treatment of 3-N,N-diethylaminophenol (1) with ethyl α-cyanocinnamate (2d-f) in ethanol and piperidine afforded ethyl 2-amino-4-(4-halophenyl)-7-(diethylamino)-4H-chromene-3-carboxylate (3d-f) and 4-(4-halophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (4a-c) (Scheme 1).

Scheme 1

The formation of 3 indicates that the phenolate anion (C-6) of 1 attack at the β-carbon of 2 to yield an acyclic Michael adduct [34], which underwent cyclization as shown in Scheme 2. The formation of 4 indicates that the phenolate anion (C-6) of 1 attack at the β-carbon of 2 to yield an acyclic Michael adduct which underwent cyclization via the elimination of ethanol and aromatization [34] (Scheme 2).
NMR spectra of 3a-f showed characteristic signals for 4H-chromene: singlets at δ 4.51-4.75 ppm in the $^1$H NMR and 38.91-39.81 ppm in the $^{13}$C NMR. The IR spectra showed NH$_2$ stretch at $\nu$ 3471-3401, 3334-3304 and 3216-3196 cm$^{-1}$; CN stretch at $\nu$ 2194-2191 cm$^{-1}$ for 3a-c; CO stretch at $\nu$ 1675-1676 cm$^{-1}$ for 3d-f. The UV spectra of 3a-f revealed a weak shoulder characteristic for 4H-chromene [23-25, 28, 36] at $\lambda_{max}$ (CH$_3$COCH$_3$) 396-430 nm (log $\varepsilon$ 1.47-3.54). The structure of 4 was established in the same way. $^1$H NMR and $^{13}$C NMR spectra showed the absence of 4H, while the IR spectra showed the absence of NH$_2$ and the appearance of the CN stretch at $\nu$ 2193-2221 cm$^{-1}$ and CO stretch at $\nu$ 1725-
1726 cm\(^{-1}\) for 4a-c. The mass spectra of compounds 3a-f and 4a-c gave additional
evidences for the proposed structures.

Treatment of 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-
carbonitrile (3a) with acetic anhydride for 30 min. afforded the N,N-diacetylamino
derivative 2-diacetylamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-
carbonitrile (5b), while heating of 3a with acetic anhydride for 6 h afforded 5-(4-
chlorophenyl)-8-(diethylamino)-2-methyl-3,4-dihydro-5H-chromeno[2,3-d]pyrimidin-4-
one (6) (Scheme 3). Attempts to obtain the N-acetyl derivative were unsuccessful: 2-
acetylamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (5a) was not
formed. Structure of 6 was also supported by an independent synthesis of the same
compound from ethyl 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-
carboxylate (3d) and acetonitrile in the presence of HCl gas [37] (m.p. and mixed m.p.)
(Scheme 3). Structures of 5b and 6 were established by spectral data and in conjunction
with our previous work [23-35].

Condensation of 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-
carbonitrile (3a) with benzaldehyde in ethanol and piperidine under reflux gave the
corresponding 2-benzylideneamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-
carbonitrile (7) (Scheme 3). Structure of 7 was confirmed on the basis of IR, UV, \(^1\)H NMR,
\(^{13}\)C NMR and MS data [32].

When 2-benzylideneamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-
carbonitrile (7) was treated with hydrazine hydrate or phenyl hydrazine in ethanol at room
temperature or under reflux, the addition product 8 was formed (R= H or Ph, respectively).
From the intermediate 8, benzaldehyde hydrazone or benzaldehyde phenylhydrazone were
eliminated to give \(\beta\)-enaminonitrile (3a) [32,38] instead of the pyrimidine derivative (9)
(Scheme 3).
Treatment of 3a with triethyl orthoformate in acetic anhydride at reflux gave the corresponding 4-(4-chlorophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4H-chromene-3-carbonitrile (10a) together with the quaternary aminium salt 5-(4-chlorophenyl)-N,N-diethyl-2-methyl-4-oxo-4,5-dihydro-3H-chromeno[2,3-d]pyrimidin-8-aminium acetate (11), which can be separated from the reaction (See experimental part).
The same treatment with 3b afforded 4-(4-bromophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4H-chromene-3-carbonitrile (10b) (Scheme 4). Structures of 10 and 11 were established on the basis of IR, UV, $^1$H NMR, $^{13}$C NMR and MS data [23-35].

Hydrazinolysis of 10a,b in ethanol at room temperature afforded the aminomino derivatives 3-amino-5-(4-chloro/bromophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5H-chromeno-[2,3-d]pyrimidine (12a,b) (Scheme 5). Reaction of 10a with methylamine in ethanol at room temperature yielded the chromeno[2,3-d]pyrimidine derivative 13, while reaction with dimethylamine in ethanol at room temperature yielded the open chain product 14 (Scheme 5).
Treatment of 10a with NH\textsubscript{3} gas in methanol at room temperature for 1h yielded the open chain product (E) \(N'-(4-(4-chlorophenyl)-3-cyano-7-(diethylamino)-4H\text{-chromen-2-yl})\text{formimidamide (15A)}\) which is in equilibrium with its tautomer \(N-(4-(4-chlorophenyl)-3-cyano-7-(diethylamino)-4H\text{-chromen-2-yl})\text{formimidamide (15B)}\) (Scheme 6). Similar ammonolysis of 10a for 2h afforded the cyclic addition product 4-amino-5-(4-chlorophenyl)-8-(diethylamino)-5H-chromeno[2,3-d]pyrimidine (16). Structure of 16 was supported by its independent synthesis from 3a and formamide [26,30] and also by cyclization of 15 in dioxan and piperidine under reflux [32] (m.p. and mixed m.p.) (Scheme 6).
The structure of 15 was supported by IR spectroscopy, which showed the presence of a CN stretch at $\nu$ 2196 and NH stretch or NH$_2$ stretch at $\nu$ 3370 & 3163 cm$^{-1}$. The $^1$H NMR spectrum for 15 showed signals at $\delta$ 8.83 ppm [d, $J = 10.0$ Hz, 1H, NH(a)], 8.39, 8.38 ppm [dd, $J = 10.0$ Hz, 1H, CH(b)] and 5.76 ppm [d, $J = 10.0$ Hz, 1H, NH(c)], while the $^{13}$C NMR spectrum showed signals at $\delta$ 160.20 ppm (C-2) and 154.64 ppm (N=CH). In compound 16, IR showed the presence of NH$_2$ stretches at $\nu$ 3467, 3317 cm$^{-1}$. The $^1$H NMR spectrum for 16 showed signals at $\delta$ 8.20 ppm (s, 1H, H-2) and 4.87 ppm (bs, 2H, NH$_2$), while the $^{13}$C NMR showed signals at $\delta$ 162.62 ppm (C-4) and 157.26 ppm (C-2). A compound that contains one chlorine atom will have an M+2 peak approximately one-third the intensity of the molecular ion peak because of the presence of a molecular ion containing the $^{37}$Cl isotope, thereby the mass spectrum of 15 showed m/z (%) peaks at 382 (M$^+$+2, 21.38) and 380 (M$^+$, 57.35) with the base peak at 269 (100), while the mass spectrum of 16 showed m/z (%) peaks at 382 (M$^+$+2, 17.75) and 380 (M$^+$, 50.76) with the base peak at 269 (100).
3. Antibacterial activities

Compounds 3a-f, 4a-c, 5b, 7, 10a,b, 11, 12a,b and 13-16 were tested in vitro for their antimicrobial activities [39,40] by agar diffusion method using Mueller–Hinton agar medium for bacteria and Sabouraud’s agar medium for fungi. The tested microorganisms were obtained from the culture collection at the Microbiology laboratory, National Organization for Drug Control and Research (NODCAR). The assayed collection included two gram-negative (Bordetella bronchiseptica ATCC 4617 and Escherichia coli ATCC 14169) and four gram-positive (Bacillus pumilus ATCC 14884, Bacillus subtilis ATCC 6633, Staphylococcus aureus ATCC 29737 and Staphylococcus epidermidis ATCC 12228) pathogenic bacteria using ampicillin 25 µg/ml as a reference compound and two fungi (Candida albicans ATCC 10231 and Saccharomyces cerevisiae ATCC 9080) using mycostatine 25 µg/ml as a reference compound. The inhibition zone diameters were read and rounded up to the nearest whole number (mm) for analysis. The inhibitory effects of the synthetic compounds against these organisms are given in (Table 1).

**Table 1**: Antibacterial screening data for some of the synthetic compounds

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<th>Compounds (25 µg/ml)</th>
<th>Bo. bronchiseptica (+ve)</th>
<th>E. coli (+ve)</th>
<th>Ba. pumilus (+ve)</th>
<th>Ba. subtilis (+ve)</th>
<th>St. aureus (+ve)</th>
<th>St. epidermidis (+ve)</th>
<th>Ca. albicans</th>
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NA = not active

Diameter of the hole = 10 mm
4. Cytotoxicity assays

Compounds 3a-e were evaluated for their human tumor cell growth inhibitory activity against two cell lines: MCF-7 (breast adenocarcinoma) and HCT (lung carcinoma). The measurement of cell growth and viability were determined as described in the literature [41].

Cytotoxicity evaluation using viability assays were performed by a Regional Center for Mycology & Biotechnology (RCMP), Al-Azhar University. The inhibitory activity of the synthetic compounds 3a-e against two different human tumor cell lines MCF-7 (breast adenocarcinoma) and HCT (lung carcinoma) are given in figures 1 and 2.

Fig. 1. Evaluation of cytotoxicity against MCF-7 cell line
5. Result and discussion

The 4H-chromene and coumarin derivatives were chosen for study because it is known that 4H-chromene and coumarin derivatives are an important families of active compounds with a wide range of pharmacological properties [1,42,43]. Twenty one compounds of both 4H-chromene and coumarin derivatives were prepared. Structures of the synthesized compounds were elucidated on the basis of IR, $^1$H NMR, $^{13}$C NMR and MS data. Compounds 3a-f, 4a-c, 5b, 7, 10a,b, 11, 12a,b and 13-16 were screened in vitro for their antibacterial and antifungal activity against various gram-negative, gram-positive bacteria and fungal strains using the agar diffusion method. The investigation of antibacterial and antifungal screening data revealed that some of the compounds tested have demonstrated congruent activity against all tested microorganisms as compared with the standards ampicillin and mycostatine. Compounds 3b-e, 4a,b, 5b, 7, 10a,b, 11, 14 and 15 did not show any antimicrobial activity against all the tested bacteria and fungi. Compounds 3a,f and 4c showed activity against Staphylococcus aureus and Staphylococcus epidermidis, while compounds 12a,b, 13 and 16 showed high activity against all tested microorganisms at a concentration of 25 µg/ml. These data indicate that the activity is considerably affected.

![Graph showing cell viability vs concentration](image)

**Fig. 2. Evaluation of cytotoxicity against HCT cell line**
by the presence of the pyrimidine moiety in the structure, and not of the chromene or coumarin moieties.

Compounds 3a-e were tested against two different human tumor cell lines MCF-7 (breast adenocarcinoma) and HCT (lung carcinoma) and the cytotoxicity evaluation using viability assays and the inhibitory activities are given in Figures 1 and 2. IC$_{50}$ values were in the low concentration in microgram range. Compound 3a had the most prominent activity against the human breast tumor cells (MCF-7) (IC$_{50}$ = 15 µg/ml) and human lung cancer cells (HCT) (IC$_{50}$ = 19.7 µg/ml).

The structure activity relationship (SAR) of 4-aryl-4H-chromenes demonstrates that substitution of the chlorine atom at the 4-position of the phenyl ring and the cyano group at the 3-position in the 4H-chromene generally increased the activity profile. The type and position of the halogen atom at the phenyl ring and the cyano or ester group attached to the 4H-chromene seemed to have a variable influence on the cytotoxic activity against various cell lines.

6. Conclusion

In this paper we report the synthesis of some 4H-chromene, coumarin and chromeno-[2,3-d]pyrimidine derivatives and the antimicrobial & antitumor evaluation of some of the novel compounds. The preliminary in vitro antimicrobial data demonstrated that the chromeno[2,3-d]pyrimidine derivatives are more active than 4H-chromene and coumarin derivatives.

Compound 3a has the most potent activity against the human breast tumor cells (MCF-7) and human lung cancer cells (HCT). This potency could be attributed to the presence of the chloro atom in the 4-position of the phenyl ring in combination with the cyano group in the 3-position in 4H-chromene.

7. Experimental

7.1. Chemistry
Melting points were determined with a Stuart Scientific Co. Ltd apparatus. UV spectra were measured on a Shimadzu UV-160 1PC UV-visible spectrophotometer. IR spectra were determined as KBr pellets on a Jasco FT/IR 460 plus spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded using a Bruker AV 500 MHz spectrometer. $^{13}$C NMR spectra were obtained using distortionless enhancement by polarization transfer (DEPT), with this technique, the signals of CH & CH$_3$ carbon atoms appears normal (up) and the signal of carbon atoms in CH$_2$ environments appears negative (down). The MS were measured on a Shimadzu GC/MS-QP5050A spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 microanalyser in the Faculty of Science Cairo University.

7.1.1. Reaction of 3-N,N-diethylaminophenol (1) with 2a-f:

7.1.1.1. General procedure:

A solution of 3-N,N-diethylaminophenol (1) (0.01 mmol) in EtOH (30 ml) was treated with α-cyanocinnamitonitriles (2a-c) or ethyl α-cyanocinnamates (2d-f) (0.01 mmol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation occurred (reaction times: 60 min. for 2a-c; 120 min. for 2d-f. The solid product which formed was collected by filtration and crystallized from ethanol for compounds 3a-f. Compounds 4a-c where separated from the filtrate of the reaction and crystallized from benzene. The physical and spectral data of compounds 3a-f and 4a-c are as follows:

7.1.1.2. 2-Amino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (3a): Yellow needles from ethanol; m.p. 152-153 °C; 81%; IR (cm$^{-1}$) in KBr: 3471, 3334, 3196 (NH$_2$), 2972, 2932, 2870 (CH), 2192 (CN); $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.17-6.15 (m, 7H, aromatic), 4.57 (bs, 2H, NH$_2$), 4.51(s, 1H, H-4), 3.21 (q, $J = 7.0$ Hz, 4H, 2CH$_2$), 1.05 (t, $J = 7.0$ Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 159.58 (C-2), 149.57 (C-8a), 147.95 (C-7), 129.88 (C-5), 120.25 (CN), 109.13 (C-4a), 108.39 (C-6), 98.19 (C-8), 60.50 (C-3), 44.42 (CH$_2$), 39.74 (C-4), 12.52 (CH$_3$) 143.98, 132.69, 129.33, 129.07 (aromatic); MS m/z (%): 355 (M$^+$+2, 0.94), 353 (M$^+$, 2.80), 242 (3.27), 198 (23.89), 170 (2.80), 125 (2.03), 111 (34.45), 74 (100); Anal. Calcd for C$_{20}$H$_{19}$ClN$_3$O: C, 67.89; H, 5.70; N, 11.88. Found: C, 67.97; H, 5.79; N, 11.81.
7.1.1.3. 2-Amino-4-(4-bromophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (3b): Red needles from ethanol; m.p. 150-151 °C; 80%; IR (cm⁻¹) in KBr: 3430, 3329, 3196 (NH₂), 2970, 2929, 2886, 2868 (CH), 2194 (CN); ¹H NMR (500 MHz, CDCl₃) δ: 7.36-6.18 (m, 7H, aromatic), 4.79 (bs, 2H, NH₂), 4.75 (s, 1H, H-4), 3.17 (q, J = 7.0 Hz, 4H, 2CH₂), 1.00 (t, J = 7.0 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 159.69 (C-2), 149.57 (C-8a), 147.95 (C-7), 129.69 (C-5), 120.36 (CN), 109.13 (C-4a), 108.31 (C-6), 98.20 (C-8), 60.17 (C-3), 44.42 (CH₂), 39.81 (C-4), 12.50 (CH₃) 144.53, 131.76, 129.86, 120.81 (aromatic); MS m/z (%): 399 (M⁺ +2, 35.82), 397 (M⁺, 31.37), 383 (100), 381 (87.67), 229 (7.03), 189 (91.94), 162 (24.08), 112 (8.99), 74 (10.06); Anal. Calcd for C₂₀H₂₀BrN₃O: C, 60.31; H, 5.06; N, 10.55. Found: C, 60.32; H, 5.16; N, 10.46.

7.1.1.4. 2-Amino-4-(4-fluorophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (3c): Red needles from ethanol; m.p. 165-166 °C; 82%; IR (cm⁻¹) in KBr: 3470, 3302, 3203 (NH₂), 2971, 2909, 2886, 2868 (CH), 2193 (CN); ¹H NMR (500 MHz, CDCl₃) δ: 7.11-6.16 (m, 7H, aromatic), 4.55 (s, 1H, H-4), 4.49 (bs, 2H, NH₂), 3.23 (q, J = 7.5 Hz, 4H, 2CH₂), 1.07 (t, J = 7.5 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 162.82 (C-2), 149.55 (C-7), 129.48 (C-5), 120.16 (CN), 115.41 (C-4a), 98.16 (C-8), 61.14 (C-3), 44.41 (CH₂), 39.56 (C-4), 12.50 (CH₃) 160.87, 141.17, 129.92, 115.58 (aromatic); m/z (%) 337 (M⁺ +2, 35.82), 397 (M⁺, 31.37), 383 (100), 381 (87.67), 229 (7.03), 189 (91.94), 162 (24.08), 112 (8.99), 74 (10.06); Anal. Calcd for C₂₀H₂₀FN₃O: C, 71.20; H, 5.97; N, 12.45. Found: C, 71.42; H, 6.11; N, 12.63.

7.1.1.5. Ethyl 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-carboxylate (3d): Colourless needles from ethanol; m.p. 143-144 °C; 45%; IR (cm⁻¹) in KBr: 3410, 3308, 3200 (NH₂), 2969, 2926, 2902 (CH), 1676 (CO); ¹H NMR (500 MHz, CDCl₃) δ: 7.12-6.17 (m, 9H, aromatic and NH₂), 4.72 (s, 1H, H-4), 3.95 (q, J = 5.9 Hz, 2H, CH₂), 3.21 (q, J = 7.0 Hz, 2CH₂), 1.10 (t, J = 7.0 Hz, 6H, 2CH₃), 1.02 (t, J = 5.9 Hz, 3H, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 169.54 (CO), 160.51 (C-2), 149.65 (C-8a), 147.52 (C-7), 129.77 (C-5), 112.15 (C-4a), 108.81 (C-6), 98.25 (C-8), 78.97 (C-3), 59.37 (CH₂ ester) 44.40 (CH₂), 39.07 (C-4), 14.36 (CH₃ ester), 12.55 (CH₃), 147.39, 131.25, 129.00, 128.14 (aromatic); MS m/z (%): 402 (M⁺ +2, 5.67), 400 (M⁺, 12.02), 289 (100), 243
(76.61), 199 (9.64), 151 (16.59), 111 (6.81), 76 (5.39); Anal. Calcd for C\textsubscript{22}H\textsubscript{25}ClN\textsubscript{2}O\textsubscript{3}: C, 65.91; H, 6.29; N, 6.99. Found: C, 66.09; H, 6.46; N, 6.95.

7.1.1.6. Ethyl 2-amino-4-(4-bromophenyl)-7-(diethylamino)-4H-chromene-3-carboxylate (3e):
Colourless needles from ethanol; m.p. 145-146 °C; 42%; IR (cm\textsuperscript{-1}) in KBr: 3401, 3304, 3216 (NH\textsubscript{2}), 2974, 2925, 2892, 2874 (CH), 1676 (CO); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 7.34-6.28 (m, 9H, aromatic and NH\textsubscript{2}), 4.81 (s, 1H, H-4), 4.07 (q, \(J = 7.5\) Hz, 2H, CH\textsubscript{2}), 3.32 (q, \(J = 7.5\) Hz, 4H, 2CH\textsubscript{2}), 1.17 (t, \(J = 7.5\) Hz, 6H, 2CH\textsubscript{3}), 1.13 (t, \(J = 7.5\) Hz, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 169.51 (CO), 160.49 (C-2), 149.64 (C-8a), 147.89 (C-7), 129.76 (C-5), 112.04 (C-8), 108.81 (C-4a), 98.25 (C-6), 78.90 (C-3), 59.38 (CH\textsubscript{2} ester), 44.40 (CH\textsubscript{2}), 39.14 (C-4), 14.35 (CH\textsubscript{3} ester), 12.54 (CH\textsubscript{3}), 147.53, 131.08, 129.42, 119.36 (aromatic); MS m/z (%): 446 (M\textsuperscript{+} +2, 9.24), 444 (M\textsuperscript{+}, 8.00), 289 (100), 243 (61.18), 199 (19.11), 151 (11.01), 76 (10.39); Anal. Calcd for C\textsubscript{22}H\textsubscript{25}BrN\textsubscript{2}O\textsubscript{3}: C, 59.33; H, 5.66; N, 6.29. Found: C, 60.64; H, 6.04; N, 6.23.

7.1.1.7. Ethyl 2-amino-4-(4-fluorophenyl)-7-(diethylamino)-4H-chromene-3-carboxylate (3f):
Colourless needles from ethanol; m.p. 135-136 °C; 40%; IR (cm\textsuperscript{-1}) in KBr: 3409, 3306, 3205 (NH\textsubscript{2}), 2977, 2928, 2903, 2874 (CH), 1675 (CO); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 7.19-6.18 (m, 9H, aromatic and NH\textsubscript{2}), 4.74 (s, 1H, H-4), 3.99 (q, \(J = 7.5\) Hz, 2H, CH\textsubscript{2}), 3.23 (q, \(J = 7.5\) Hz, 4H, 2CH\textsubscript{2}), 1.08 (t, \(J = 7.5\) Hz, 6H, 2CH\textsubscript{3}), 1.05 (t, \(J = 7.5\) Hz, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\): 169.57 (CO), 162.08 (C-2), 149.68 (C-8a), 147.53 (C-7), 129.76 (C-5), 112.62 (C-8), 108.88 (C-4a), 98.35 (C-6), 79.34 (C-3), 59.28 (CH\textsubscript{2} ester), 44.40 (CH\textsubscript{2}), 38.91 (C-4), 14.32 (CH\textsubscript{3} ester), 12.54 (CH\textsubscript{3}), 160.47, 144.60, 128.97, 114.77 (aromatic); MS m/z (%): 446 (M\textsuperscript{+} +2, 9.24), 444 (M\textsuperscript{+}, 8.00), 289 (100), 243 (61.18), 199 (19.11), 151 (11.01), 76 (10.39); Anal. Calcd for C\textsubscript{22}H\textsubscript{25}FN\textsubscript{2}O\textsubscript{3}: C, 68.73; H, 6.55; N, 7.29. Found: C, 68.71; H, 6.62; N, 7.33.

7.1.1.8. 4-(4-Chlorophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (4a): Yellow needles from benzene; m.p. 175-176 °C; 35%; IR (cm\textsuperscript{-1}) in KBr: 3085, 2977, 2931, (CH),
2221 (CN), 1725 (CO); $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.48-6.45 (m, 7H, aromatic), 3.40 (q, J = 7.5 Hz, 4H, 2CH$_2$), 1.17 (t, J = 7.5 Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 161.79 (C-4), 158.79 (CO), 157.24 (C-8a), 153.19 (C-7), 129.99 (C-5), 115.17 (CN), 110.07 (C-4a), 107.21 (C-6), 97.49 (C-8), 92.26 (C-3), 45.26 (CH$_2$), 12.43 (CH$_3$) 136.77, 131.26, 129.27, 128.34 (aromatic); MS m/z (%): 354 (M$^+$ +2, 11.24), 352 (M$^+$, 37.36), 339 (32.60), 337 (100), 311 (10.42), 309 (33.01), 198 (4.34), 151 (20.89), 69 (86.45), 55 (95.37); Anal. Calcd for C$_{20}$H$_{17}$ClN$_2$O$_2$: C, 68.09; H, 4.86; N, 7.94. Found: C, 68.02; H, 4.91; N, 8.00.

7.1.1.9. 4-(4-Bromophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (4b): Orange needles from benzene; m.p. 187-188 °C; 34%; IR (cm$^{-1}$) in KBr: 3080, 2977, 2931, (CH), 2222 (CN), 1726 (CO); $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.71-6.54 (m, 7H, aromatic), 3.49 (q, J = 7.5 Hz, 4H, 2CH$_2$), 1.27 (t, J = 7.5 Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 161.78 (C-4), 158.17 (CO), 157.24 (C-8a), 153.19 (C-7), 129.99 (C-5), 115.15 (CN), 110.06 (C-4a), 107.13 (C-6), 97.49 (C-8), 92.20 (C-3), 45.26 (CH$_2$), 12.43 (CH$_3$), 132.22, 131.73, 130.16, 125.06 (aromatic); MS m/z (%): 398 (M$^+$ +2, 46.39), 396 (M$^+$, 43.33), 383 (100), 381 (96.34), 227 (1.00), 189 (66.89), 151 (13.34), 75 (10.14); Anal. Calcd for C$_{20}$H$_{17}$BrN$_2$O$_2$: C, 60.47; H, 4.31; N, 7.05. Found: C, 59.72; H, 5.44; N, 6.29.

7.1.1.10. 4-(4-Fluoromphenyl)-7-(diethylamino)-coumarin-3-carbonitrile (4c): Orange needles from benzene; m.p. 208-209 °C; 36%; IR (cm$^{-1}$) in KBr: 3060, 2979, 2934, (CH), 2217 (CN), 1725 (CO); $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.48-6.53 (m, 7H, aromatic), 3.49 (q, J = 5.0 Hz, 4H, 2CH$_2$), 1.25 (t, J = 5.0 Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 164.85 (C-4), 162.02 (CO), 158.90 (C-8a), 157.12 (C-7), 129.99 (C-5), 115.06 (CN), 110.34 (C-4a), 107.35 (C-6), 97.43 (C-8), 92.23 (C-3), 45.25 (CH$_2$), 12.42 (CH$_3$), 132.22, 131.73, 130.16, 125.06 (aromatic); MS m/z (%): 398 (M$^+$ +2, 46.39), 396 (M$^+$, 43.33), 383 (100), 381 (96.34), 227 (1.00), 189 (66.89), 151 (13.34), 75 (10.14); Anal. Calcd for C$_{20}$H$_{17}$FN$_2$O$_2$: C, 71.42; H, 5.09; N, 5.65. Found: C, 71.33; H, 5.04; N, 5.51.

7.1.2 2-Diacetylamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (5b):
A solution of 3a (0.01 mmol) in Ac₂O (20 ml) was heated under reflux for 30 min. The solid product that formed was filtered, washed with cooled EtOH, dried and crystallized from ethanol to give 5b as pale yellow crystals; m.p. 137-138 °C; 75%; IR (cm⁻¹) in KBr: 3065, 2964, 2924, 2894 (CH), 2224 (CN), 1742 (CO); ¹H NMR (500 MHz, CDCl₃): δ: 7.48-6.36 (m, 7H, aromatic), 5.13 (s, 1H, H-4), 3.40 (q, J = 7.0 Hz, 2CH₂), 2.44 (s, 6H, 2COCH₃), 1.05 (t, J = 7.0 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃): δ: 170.51 (CO), 152.13 (C-2), 149.28 (C-8a), 147.86 (C-7), 129.88 (C-5), 115 (CN), 110.07 (C-4a), 108.18 (C-6), 97.92 (C-8), 92.18 (C-3), 43.64 (CH₂), 40.38 (C-4), 24.00 (CH₃), 12.22 (CH₃), 142.13, 132.25, 128.73 (aromatic); m/z (%): 439 (M⁺ +2, 0.32), 437 (M⁺, 1.10), 356 (3.67), 354 (14.33), 316 (39.69), 314 (100), 290 (16.75), 288 (49.80), 176 (13.28), 151 (89.89), 89 (18.51), 54 (42.87); Anal. Calcd for C₂₄H₂₄ClN₃O₃: C, 65.82; H, 5.52; N, 9.60. Found: C, 65.61; H, 5.34; N, 9.41.

7.1.3. 5-(4-Chlorophenyl)-8-(diethylamino)-2-methyl-3,4-dihydro-5H-chromeno-[2,3-d]-pyrimidin-4-one (6):

7.1.3.1. Method (a):

A solution of 3a (0.01 mmol) in Ac₂O (20 ml) was heated under reflux for 15 min., 30 min. or 6h. The solid product was filtered, washed with cooled EtOH, dried and crystallized from ethanol to give 6 as colourless crystals; m.p. 238-239 °C; 75%; IR (cm⁻¹) in KBr: 3300 (NH), 2966, 2929, 2868 (CH), 1647 (CO); ¹H NMR (500 MHz, CDCl₃): δ: 13.00 (br, 1H, NH) 7.23-6.31(m, 7H, aromatic), 5.02 (s, 1H, H-4), 3.24 (q, J = 7.0 Hz, 2H, CH₂), 2.34(s, 3H, CH₃), 1.08(t, J = 7.0 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃): δ: 165.35 (C-2), 162.59 (C-10a), 157.98 (C-4), 150.59 (C-9a), 147.29 (C-8), 130.01(C-6), 109.26 (C-5a), 109.03 (C-7), 100.87 (C-9), 99.13 (C-4a), 44.49 (CH₂), 37.67 (C-5), 21.23 (CH₃), 12.49 (CH₃), 144.43, 132.11, 129.63, 128.30 (aromatic); MS m/z (%): 397 (M⁺ +2, 32.88), 395 (M⁺, 100), 282 (24.41), 380 (79.84), 270 (35.08), 240 (94.75), 198 (26.08), 150 (25.26), 114 (24.01), 74 (11.91); Anal. Calcd for C₂₂H₂₄ClN₃O₂: C, 66.75; H, 5.60; N, 10.61. Found: C, 66.64; H, 5.55; N, 10.56.
A stream of dry HCl gas was passed through a solution of 3d (0.01 mmol) in MeCN (30 ml) for 4-6 h. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution to give 6 with a yield of (62 %) (m.p. and mixed m.p. 238-239 °C).

7.1.4. 2-Benzylimideneamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (7):
A mixture of 3a (0.01 mmol), benzaldehyde (0.01 mmol), ethanol (20 ml) and piperidine (0.5 ml) was refluxed for 2 h. The solid product, was collected by filtration and crystallized from ethanol give 7 as yellow crystals; m.p. 185-186 °C; 85%; IR (cm⁻¹) in KBr: 3083, 3061, 2969, 2927, 2891 (CH), 2207 (CN), 1638 (C=N); ¹H NMR (500 MHz, CDCl₃) δ: 8.92 (s, 1H, N=CH), 7.94-6.30 (m,12H, aromatic), 4.75 (s, 1H, H-4), 3.27 (q, J = 7.0 Hz, 4H, 2CH₂), 1.09 (t, J = 7.0 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 162.21(C-2), 158.23 (N=CH), 150.01 ( C-8a), 148.30 (C-7), 130.23 (C-5), 117.96 (CN), 109.53 (C-4a), 107.29 (C-6), 98.38 (C-8), 88.16 (C-3), 44.47 (CH₂), 42.35 (C-4), 12.58 (CH₃), 142.54, 134. 98, 133.24, 133.18, 129.96, 129.69, 129.05, 128.96 (aromatic); MS m/z (%): 443 (M⁺ +2, 21.64), 441 (M⁺, 61.98), 243 (32.65), 198 (27.49), 148 (25.89), 104 (68.23), 88 (100). Anal. Calcd for C₂₇H₂₄ClN₃O: C, 73.38; H, 5.47; N, 9.51. Found: C, 73.41; H, 5.34; N, 8.91.

7.1.5. Reaction of 7 with hydrazine derivatives:
A mixture of 7 (0.01 mmol), hydrazine hydrate or phenyl hydrazine (0.01 mmol) in EtOH was stirring at room temperature or reflux for 2 h to give 3a (m.p. and mixed m.p. 152-153 °C) yield (80%).

7.1.6. Reaction of 3a,b with triethyl orthoformate:
7.1.6.1. General procedure:
A mixture of β-enaminonitrile 3a (0.01 mmol), triethyl orthoformate (0.01 mmol) and Ac₂O (30 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the resulting solid was crystallized from benzene to give 10a, while the remaining solid was
crystallized from ethanol to give 11. The same treatment with 3b afforded 10b which was crystallized from benzene. The physical and spectra data of the compounds are as follows:

7.1.6.2. 4-(4-Chlorophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4H-chromene-3-carbonitrile (10a): Pale yellow crystals from benzene; m.p. 144-145 °C; 61%; IR (cm⁻¹) in KBr: 2967, 2925, 2868 (CH), 2203 (CN), 1644 (C=N); ¹H NMR (500 MHz, CDCl₃) δ: 8.43 (s, 1H, N=CH), 7.31-6.31 (m,7H, aromatic), 4.75 (s, 1H, H-4), 4.44 (q, J = 7.2 Hz, 2H, CH₂); ¹³C NMR (125 MHz, CDCl₃) δ: 159.44 (C-2), 157.68 (N=CH), 150.01 (C-8a), 148.14 (C-7), 129.93 (C-5), 118.47 (CN), 109.14 (C-4a), 107.47 (C-6), 98.27 (C-8), 80.87 (C-3), 64.08 (CH₂ ethoxy), 44.42 (CH₂), 41.68 (C-4), 13.96 (CH₃ ethoxy), 12.54 (CH₃), 142.97, 133.01, 129.59, 128.64 (aromatic); MS m/z (%): 411 (M⁺ +2, 17.18), 409 (M⁺, 40.29), 298 (100), 270 (18.86), 242 (52.75), 169 (13.86), 113 (15.08), 75 (12.16); Anal. Calcd for C₂₃H₂₄ClN₃O₂: C, 67.39; H, 5.90; N, 10.25. Found: C, 67.47; H, 6.01; N, 10.32.

7.1.6.3. 4-(4-Bromophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4H-chromene-3-carbonitrile (10b): Pale red crystals from benzene; m.p. 143-144 °C; 83%; IR (cm⁻¹) in KBr: 2966, 2925, 2868 (CH), 2204 (CN), 1644 (C=N); ¹H NMR (500 MHz, CDCl₃) δ: 8.43 (s, 1H, N=CH), 7.47-6.30 (m,7H, aromatic), 4.74 (s, 1H, H-4), 4.44 (q, J = 7.2 Hz, 2H, CH₂); ¹³C NMR (125 MHz, CDCl₃) δ: 159.43 (C-2), 157.69 (N=CH), 150.01 (C-8a), 148.14 (C-7), 129.94 (C-5), 118.45 (CN), 109.14 (C-4a), 107.38 (C-6), 98.25 (C-8), 80.76 (C-3), 64.09 (CH₂ ethoxy), 44.41 (CH₂), 41.75 (C-4), 13.95 (CH₃ ethoxy), 12.54 (CH₃), 143.45, 131.89, 131.68, 121.19 (aromatic); MS m/z (%): 455 (M⁺ +2, 17.18), 409 (M⁺, 40.29), 298 (100), 242 (38.41), 198 (21.59), 151 (8.33), 74 (3.07); Anal. Calcd for C₂₃H₂₄BrN₃O₂: C, 60.80; H, 5.32; N, 9.25. Found: C, 60.93; H, 5.42; N, 9.34.

7.1.7. 5-(4-Chlorophenyl)-N,N-diethyl-2-methyl-4-oxo-4,5-dihydro-3H-chromeno[2,3-d]-pyrimidin-8-aminium acetate (11): Pale red crystals; m.p. 234-235 °C; 35%; IR (cm⁻¹) in KBr: 3389 (NH), 2972, 2934, 2871 (CH), 1652 (CO); ¹H NMR (500 MHz, CDCl₃) δ: 13.37 (br, 1H, NH), 7.38-6.41 (m,7H, aromatic), 5.08 (s, 1H, H-4), 3.33 (q, J = 7.0 Hz, 2H, CH₂),
2.37 (s, 3H, CH$_3$), 1.21 (t, J = 7.0 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 165.53 (C-2), 162.62 (C-10a), 158.11 (C-4), 150.60 (C-9a), 147.89 (C-8), 130.03 (C-6), 109.47 (C-5a), 104.30 (C-7), 99.16 (C-4a), 97.11 (C-9), 44.69 (CH$_2$), 39.07 (C-5), 21.17 (CH$_3$), 12.60 (CH$_3$), 144.47, 132.24, 129.67, 128.35 (aromatic); MS m/z (%): 457 (M$^+$+2, 0.89), 455 (M$^+$, 2.70), 284 (100), 270 (13.68), 240 (25.00), 198 (10.15), 143 (3.29), 111 (9.73), 77 (32.91); Anal. Calcd for C$_{24}$H$_{26}$ClN$_3$O$_4$: C, 63.22; H, 5.75; N, 9.22. Found: C, 63.30; H, 5.82; N, 9.33.

7.1.8. Reaction of 10 with hydrazine hydrate:

7.1.8.1. General procedure:
A solution of (10a,b) (0.01 nmol) and hydrazine hydrate (99%, 5 ml) in EtOH (50 ml) was stirred at room temperature for 1h. The solid product, was collected by filtration and crystallized from benzene to give 12a,b. The physical and spectra data of the compounds 12a,b are as follows:

7.1.8.2. 3-Amino-5-(4-chlorophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5H-chromeno-[2,3-d]pyrimidine (12a): Colourless needles; m.p. 178-179 °C; 81%; IR (cm$^{-1}$) in KBr: 3322, 3315, 3300, 3266 (NH$_2$ and NH), 3060, 2969, 2880 (CH), 1636 (C=N); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.00 (s, 1H, C-2), 7.19-6.26 (m, 7H, aromatic), 6.00 (br, 1H, NH), 4.71 (brs, 2H, NH$_2$), 4.67 (s, 1H, H-5), 3.22 (q, J = 7.5 Hz, 4H, 2CH$_2$), 1.05 (t, J = 7.5 Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 158.62 (C-4), 157.06 (C-10a), 150.46 (C-9a), 149.55 (C-8), 143.09 (C-2), 129.62 (C-6), 109.17 (C-5a), 108.97 (C-4a), 98.03 (C-9), 44.43 (CH$_2$), 39.85 (C-5), 12.51 (CH$_3$), 147.88, 132.93, 129.46, 128.87 (aromatic); MS m/z (%): 397 (M$^+$+2, 5.65), 395 (M$^+$, 13.16), 381 (37.05), 379 (100), 354 (4.80), 352 (14.81), 242 (19.70), 197 (32.49), 151 (21.09), 113 (9.06), 74 (5.57). Anal. Calcd for C$_{21}$H$_{22}$ClN$_5$O: C, 63.71; H, 5.60; N, 17.69. Found: C, 63.59; H, 5.48; N, 17.58.

7.1.8.3. 3-Amino-5-(4-bromophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5H-chromeno-[2,3-d]pyrimidine (12b): Colourless needles; m.p. 175-176 °C; 80%; IR (cm$^{-1}$) in KBr: 3345, 3315, 3299, 3266 (NH$_2$ and NH), 3061, 2970, 2927, 2890 (CH), 1636 (C=N); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.05 (s, 1H, C-2), 7.29-6.35 (m, 7H, aromatic), 6.09 (br, 1H,
NH), 4.84 (brs, 2H, NH₂), 4.80 (s, 1H, H-5), 3.31 (q, J = 6.2 Hz, 2H, 2CH₂), 1.14(t, J = 6.2 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 158.62 (C-4), 157.06 (C-10a), 150.48 (C-9a), 149.56 (C-8), 143.10 (C-2), 129.86 (C-6), 109.17 (C-5a), 108.95 (C-7), 99.26 (C-4a), 98.97 (C-9), 44.42 (CH₂), 39.82 (C-5), 12.52 (CH₃), 147.88, 132.90, 129.86, 128.87 (aromatic); MS m/z (%): 439 (M⁺, 3.34), 423 (4.48), 398 ((M⁺ +2, 10.10), 396 ((M⁺, 10.46), 242 (100), 198 (40.13), 157 (11.49), 114 (14.53), 76 (9.97). Anal. Calcd for C₂₁H₂₂BrN₇O: C, 57.28; H, 5.04; N, 15.90. Found: C, 57.15; H, 5.06; N, 15.82.

7.1.9. 5-(4-Chlorophenyl)-8-(diethylamino)-4-imino-3-methyl-3,4-dihydro-5H-chromeno-[2,3-d]pyrimidine (13):
A mixture of 10a (0.01 mmol) and methylamine (0.01 mmol) in ethanol was stirred at room temperature for 1h. The solid product was collected and crystallised from ethanol to give 13 as colourless needles, m.p. 160-161 °C; 83%; IR (cm⁻¹) in KBr: 3334 (NH), 2971, 2930, 2880 (CH), 1638 (C=N); ¹H NMR (500 MHz, CDCl₃) δ: 7.71 (s, 1H, H-2), 7.17-6.27 (m,8H, aromatic and NH), 4.73 (s, 1H, H-5), 3.33 (s, 3H, CH₃), 3.22 (q, J = 7.5 Hz, 4H, 2CH₂), 1.06 (t, J = 7.5 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 158.32 (C-4), 157.51(C-10a), 150.01 (C-9a), 149.59 (C-2), 147.88 (C-8), 129.65 (C-6), 109.28 (C-5a), 108.94 (C-7), 99.01 (C-9), 98.30 (C-4a), 44.42 (CH₂), 39.52 (C-5), 35.12 (CH₃), 12.49 (CH₃), 143.22, 132. 83, 129.19, 128.84 (aromatic); MS m/z (%): 396 (M⁺ +2, 17.42), 394 (M⁺, 44.42) 379(100), 242 (26.25), 198 (42.89), 141 (26.15), 113 (10.43), 77 (6.96). Anal. Calcd for C₂₂H₂₃ClN₄O: C, 66.91; H, 5.87; N, 14.19. Found: C, 67.02; H, 6.03; N, 14.21.

7.1.10. 2-Dimethylaminomethyleneamino-4-(4-Chlorophenyl)-8-(diethylamino)-4H-chromene-3-carbonitrile (14):
A mixture of 10a (0.01 mmol) and dimethylamine (0.01 mmol) in ethanol was stirred at room temperature for 1h. The solid product was collected and crystallised from ethanol to give 14 as colourless needles, m.p. 159-160 °C; 81%; IR (cm⁻¹) in KBr: 2974, 2910, 2895, 2875 (CH), 2193 (CN), 1670 (C=N); ¹H NMR (500 MHz, CDCl₃) δ: 8.24 (s, 1H, N=CH), 7.28-6.31 (m,7H, aromatic), 4.72 (s, 1H, H-4), 3.35 (q, J = 7.5 Hz, 2H, CH₂), 3.14, 3.12 (3, 6H, 2CH₃), 1.18 (t, J = 7.5 Hz, 6H, 2CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 160.32 (C-4), 153.91 (N=CH), 150.45 (C-8a), 147.97 (C-7), 129.84 (C-5), 120.64 (CN), 108.88 (C-4a),
108.58 (C-6), 98.30 (C-8), 74.07 (C-3), 44.38 (CH$_2$), 41.80 (CH$_3$), 40.87 (C-4), 12.54 (CH$_3$), 144.09, 132.53, 129.49, 128.96 (aromatic); MS m/z (%): 410 (M$^+$ +2, 11.84), 408 (M$^+$, 32.06), 297 (100), 235 (14.45), 250 (12.06), 150 (1.51), 127 (6.33), 74 (1.34); Anal. Calcd for C$_{22}$H$_{25}$ClN$_4$O: C, 67.55; H, 6.16; N, 13.70. Found: C, 67.60; H, 6.24; N, 13.83.

7.1.11. (E) N’-(4-(4-chlorophenyl)-3-cyano-7-(diethylamino)-4H-chromen-2-yl)formimidamide (15):
A mixture of 10a (0.01 mmol) and NH$_3$ gas in methanol was stirred for 1 h, then the mixture was left overnight. The solid product was collected and crystallised from ethanol to give 15 as colourless needles; m.p. 170-171 °C; 80%; IR (cm$^{-1}$) in KBr: 3370, 3164 (NH$_2$), 2975, 2933, 2880 (CH), 2196 (CN), 1677 (C=N); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.83 [d, $J$ = 10 Hz, 1H, NH(a)], 8.39, 8.38 [dd, $J$ = 10 Hz, 1H, CH(b)], 7.29-6.18 (m, 7H, aromatic), 5.76 [d, $J$ = 10 Hz, 1H, NH(c)], 4.58 (s, 1H, H-4), 3.24 (q, $J$ = 5.0 Hz, 4H, 2CH$_2$), 1.07 (t, $J$ = 5.0 Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 160.20 (C-2), 154.64 (N=CH), 150.09 (C-8a), 148.06 (C-7), 129.77 (C-5), 120.91 (CN), 109.10 (C-4a), 106.22 (C-6), 98.24 (C-8), 74.59 (C-3), 44.39 (CH$_2$), 41.58 (C-4), 12.55 (CH$_3$), 143.68, 132.77, 129.54, 128.85 (aromatic); MS m/z (%): 382 (M$^+$+2, 21.38), 380 (M$^+$, 57.35), 269 (100), 242 (8.26), 225 (13.91), 198 (16.50), 149 (4.72), 95 (11.67), 69 (20.88); Anal. Calcd for C$_{21}$H$_{21}$ClN$_4$O: C, 66.13; H, 5.44; N, 14.65. Found: C, 66.13; H, 5.44; N, 14.65.

7.1.12. 4-Amino-5-(4-chlorophenyl)-8-(diethylamino)-5H-chromeno[2,3-d]pyrimidine (16):
7.1.12.1. Method (a):
A mixture of 10a (0.01 mmol) and NH$_3$ gas in methanol was stirred for 2 h, then the mixture was left overnight. The solid product was collected and crystallised from benzene to give 16 as colourless needles; m.p. 240-241 °C; 81%; IR (cm$^{-1}$) in KBr: 3467, 3317, 3148 (NH$_2$), 2972, 2931, 2895 (CH), 1649 (C=N); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.20 (s, 1H, H-2), 7.21-6.25 (m, 7H, aromatic), 4.87 (bs, 2H, NH$_2$), 4.79 (s, 1H, H-5), 3.22 (q, $J$ = 7.5 Hz, 4H, 2CH$_2$), 1.04 (t, $J$ = 7.5 Hz, 6H, 2CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 163.20 (C-10a), 162.62 (C-4), 157.26 (C-2), 149.85 (C-8), 148.03 (C-9a), 129.65 (C-6), 108.90 (C-5a), 108.65 (C-7), 99.24 (C-4a), 96.46 (C-9), 44.43 (CH$_2$), 39.10 (C-5), 12.49 (CH$_3$),
142.81, 133.34, 129.61, 128.95 (aromatic); MS m/z (%): 382 (M$^+$+2, 17.75), 380 (M$^+$, 50.76), 369 (100), 242 (13.02), 225 (15.84), 198 (25.26), 168 (6.88), 112 (5.70), 94 (5.176), 68 (5.72); Anal. Calcd for C$_{21}$H$_{21}$ClN$_4$O: C, 66.22; H, 5.56; N, 14.71. Found: C, 66.33; H, 5.61; N, 14.83.

7.1.12.2. Method (b):
A mixture of 3a (0.01 mmol) and formamide (0.01 mmol) was stirred at reflux for 3 h. The solvent was removed under vacuum. The solid obtained was recrystallized from benzene to give 16 with a (61%) yield (m.p. and mixed m.p. 240-241 °C).

7.1.12.3. Method (c):
Compound 15 (0.01 mmol) was heated under reflux in dioxan (20 ml) and piperidine (0.5 ml) for 3 h to give 16 with a (58%) yield (m.p. and mixed m.p. 240-241 °C).

References


In this paper we report the synthesis of $4H$-chromene, coumarin and chromeno[2,3-$d$]-pyrimidine derivatives and examine the antimicrobial & antitumor activity of some of this novel series. The preliminary *in vitro* antimicrobial activity has demonstrated that the chromeno[2,3-$d$]pyrimidine derivatives are more active than $4H$-chromene and coumarin derivatives.

Compound 3a had the most prominent activity against the human breast tumor cells (MCF-7) and human lung cancer cells (HCT). This neoplastic cells growth inhibition could be attributed to the presence of the chloro atom in the 4-position of the phenyl ring in combination with the cyano group in the 3-position in $4H$-chromene.