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Original article

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

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ABSTRACT

Condensation of 3-*N*,*N*-diethylaminophenol (**1**) with α-cyanocinnamonitriles (**2a**–**c**) and ethyl α-cyanocinnamates (**2d**–**f**) provided compounds **3a**–**f** and **4a**–**c**. 12*H*-Chromeno[2,3-*d*]pyrimidine derivatives **6**, **11**–**13** and **16** were obtained by treatment of 4*H*-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.

1. Introduction

4*H*-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 anesthetic [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 anesthetic [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 homologes [22].

The present study is a part of our research program [1c,23–34] directed toward the synthesis of novel 4*H*-chromene and coumarin compounds using β-enaminonitriles and β-enaminocarboxylic esters and their use as building blocks in the synthesis of novel fused chromenes and evaluation of their antimicrobial and antitumor activities.

2. Chemistry

Treatment of 3-*N*,*N*-diethylaminophenol (**1**) with various substituted α-cyanocinnamonitriles (**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)-4*H*-chromene-3-carboxylate (**3d**–**f**) and 4-(4-halophenyl)-7-(diethylamino)-coumarin-3-carbonitrile (**4a**–**c**) (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 [33], 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 [33] (Scheme 2).

NMR spectra of **3a**–**f** showed characteristic signals for 4*H*-chromene: singlets at δ 4.51–4.75 ppm in the ^{1}H NMR and

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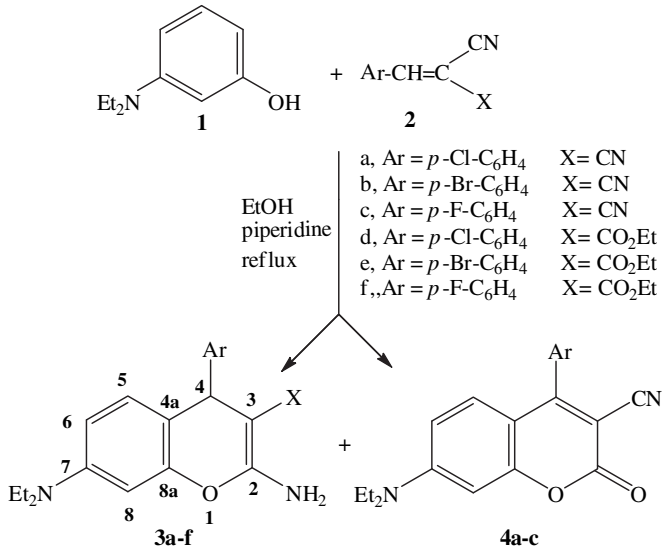
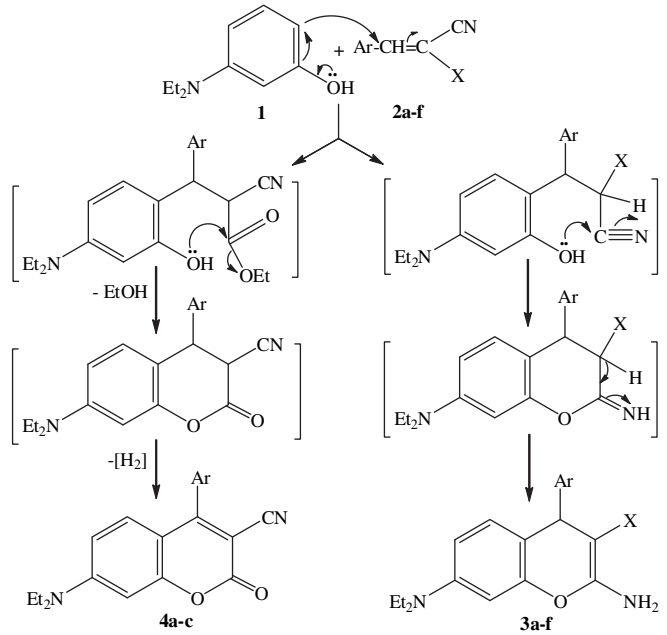


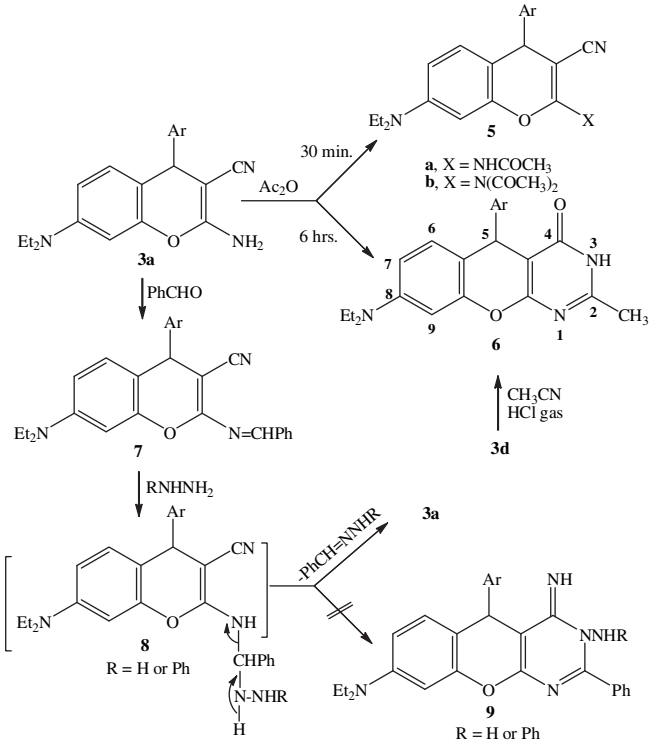
Scheme 1. Synthesis of 2-amino-4-(4-halophenyl)-7-(diethylamino)-4H-chromene derivatives (**3a-f**) and 4-(4-halophenyl)-7-(diethylamino)-coumarin-3-carbonitrile derivatives (**4a-c**).

38.91–39.81 ppm in the ^{13}C NMR. The IR spectra showed NH_2 stretch at υ 3471-3401, 3334-3304 and 3216-3196 cm^{-1}; CN stretch at υ 2194-2191 cm^{-1} for **3a**–**c**; CO stretch at υ 1675–1676 cm^{-1} for **3d**–**f**. The UV spectra of **3a**–**f** revealed a weak shoulder characteristic for 4*H*-chromene [23–25,27,35] at λ_{max} (CH_3COCH_3) 396–430 nm (log ϵ 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 4*H*, while the IR spectra showed the absence of NH_2 and the appearance of the CN stretch at υ 2193–2221 cm^{-1} and CO stretch at υ 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)-4*H*-chromene-3-carbonitrile (**3a**) with acetic anhydride for 30 min afforded the *N*,*N*-diacetylamino derivative 2-diacetylamino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carbonitrile (**5b**), while



Scheme 2. Mechanism formation of compounds (**3a-f**) and (**4a-c**).



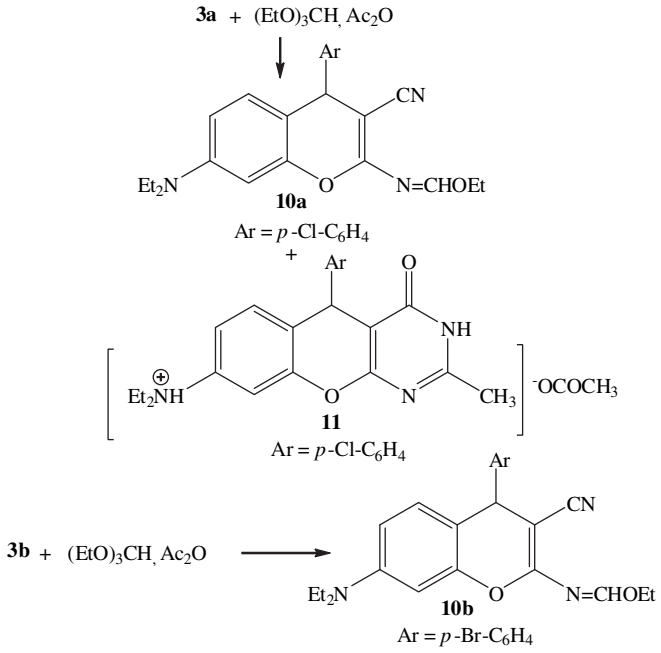
Scheme 3. Synthetic protocol of the compounds (**5b-7**).

heating of **3a** with acetic anhydride for 6 h afforded 5-(4-chlorophenyl)-8-(diethylamino)-2-methyl-3,4-dihydro-5*H*-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)-4*H*-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)-4*H*-chromene-3-carboxylate (**3d**) and acetonitrile in the presence of HCl gas [36] (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 [1c,23–34].

Condensation of 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carbonitrile (**3a**) with benzaldehyde in ethanol and piperidine under reflux gave the corresponding 2-benzylideneamino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carbonitrile (**7**) (Scheme 3). Structure of **7** was confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR and MS data [31].

When 2-benzylideneamino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-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 β-enaminonitrile (**3a**) [31,37] instead of the pyrimidine derivative (**9**) (Scheme 3).

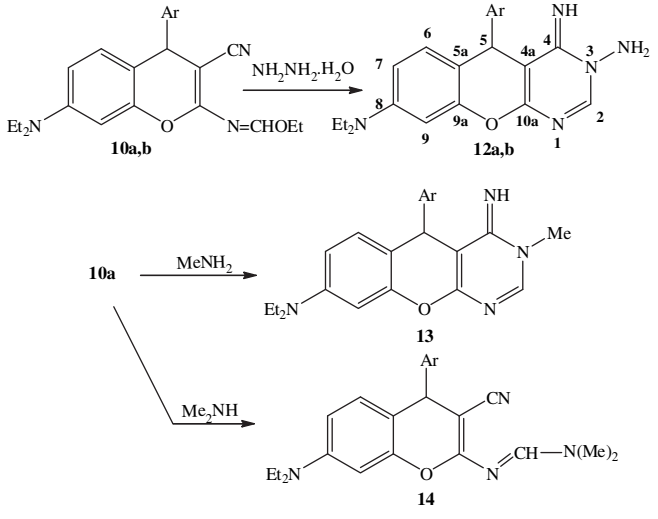
Treatment of **3a** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding 4-(4-chlorophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4*H*-chromene-3-carbonitrile (**10a**) together with the quaternary ammonium salt 5-(4-chlorophenyl)-*N*,*N*-diethyl-2-methyl-4-oxo-4,5-dihydro-3*H*-chromeno-[2,3-*d*]pyrimidin-8-aminium 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-4*H*-chromene-3-carbonitrile (**10b**) (Scheme 4). Structures of **10** and **11** were established on the basis of IR, ^{1}H NMR, ^{13}C NMR and MS data [1c,23–34].



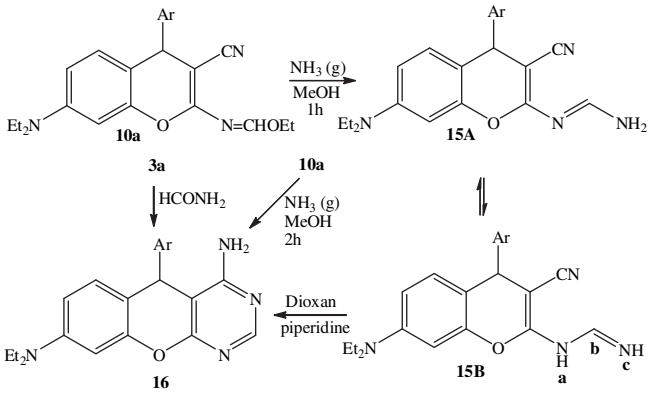
Scheme 4. Formation of 2-ethoxymethyleneamino-4H-chromene derivatives (**10a,b**) and ammonium salt (**11**).

Hydrazinolysis of **10a**,**b** in ethanol at room temperature afforded the aminoimino derivatives 3-amino-5-(4-chloro/bromophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5*H*-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_3 gas in methanol at room temperature for 1h yielded the open chain product (*E*) *N*′-(4-(4-chlorophenyl)-3-cyano-7-(diethylamino)-4*H*-chromen-2-yl)formimidamide (**15A**) which is in equilibrium with its tautomer *N*-(4-(4-chlorophenyl)-3-cyano-7-(diethylamino)-4*H*-chromen-2-yl)formimidamide (**15B**) (Scheme 6). Similar ammonolysis of **10a** for 2 h afforded the cyclic addition product 4-amino-5-(4-chlorophenyl)-8-(diethylamino)-5*H*-



Scheme 5. Synthesis of 5H-chromeno[2,3-d]pyrimidine derivatives (**12a,b & 13**) and 2-dimethylaminomethyleneamino-4H-chromene derivative (**14**).



Scheme 6. Synthetic protocol of the compounds (**15**) and (**16**).

chromeno[2,3-*d*]pyrimidine (**16**). Structure of **16** was supported by its independent synthesis from **3a** and formamide [26,29] and also by cyclization of **15** in dioxan and piperdine under reflux [31] (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 υ 2196 and NH stretch or NH_2 stretch at υ 3370 & 3163 cm^{-1}. The ^1H NMR spectrum for **15** showed signals at δ 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 δ 160.20 ppm (C-2) and 154.64 ppm (N=CH). In compound **16**, IR showed the presence of NH_2 stretches at υ 3467, 3317 cm^{-1}. The ^1H NMR spectrum for **16** showed signals at δ 8.20 ppm (s, 1H, H-2) and 4.87 ppm (bs, 2H, NH_2), while the ^{13}C NMR showed signals at δ 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 [38,39] 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 2 g-negative (*Bordetella bronchiseptica* ATCC 4617 and *Escherichia coli* ATCC 14169) and 4 g-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 cervesia* 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).

4. Cytotoxicity assays

Compounds **3a**–**e** were evaluated for their human tumor cell growth inhibitory activity against two cell lines: MCF-7 (breast

Table 1
Antibacterial screening data for some of the synthetic compounds.

Compounds (25 μg/ml)	*Bo. bronchiseptica* (−ve)	*E. coli* (−ve)	*Ba. pumilus* (+ve)	*Ba. subtilis* (+ve)	*St. aureus* (+ve)	*St. epidermidis* (+ve)	*Ca. albicans*	*Sa. cerevisa*
3a	NA	NA	NA	NA	14	15	NA	NA
3b	NA	NA	NA	NA	NA	NA	NA	NA
3c	NA	NA	NA	NA	NA	NA	NA	NA
3d	NA	NA	NA	NA	NA	NA	NA	NA
3e	NA	NA	NA	NA	NA	NA	NA	NA
3f	NA	NA	NA	NA	14	14	NA	NA
4a	NA	NA	NA	NA	NA	NA	NA	NA
4b	NA	NA	NA	NA	NA	NA	NA	NA
4c	NA	NA	NA	NA	13	14	NA	NA
5b	NA	NA	NA	NA	NA	NA	NA	NA
7	NA	NA	NA	NA	NA	NA	NA	NA
10a	NA	NA	NA	NA	NA	NA	NA	NA
10b	NA	NA	NA	NA	NA	NA	NA	NA
11	NA	NA	NA	NA	NA	NA	NA	NA
12a	22	17	27	17	26	24	16	24
12b	21	16	25	15	24	22	15	22
13	20	21	25	21	24	25	14	20
14	NA	NA	NA	NA	NA	NA	NA	NA
15	NA	NA	NA	NA	NA	NA	NA	NA
16	21	20	25	21	25	24	15	20
Ampicillin	24	25	20	25	26	25	–	–
Mycostatine	–	–	–	–	–	–	22	24

NA = not active Diameter of the hole = 10 mm.

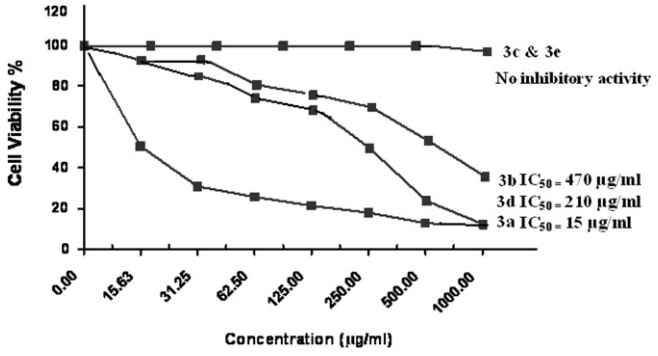


Fig. 1. Evaluation of cytotoxicity against MCF-7 cell line.

adenocarcinoma) and HCT (lung carcinoma). The measurement of cell growth and viability were determined as described in the literature [40].

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 Figs. 1 and 2.

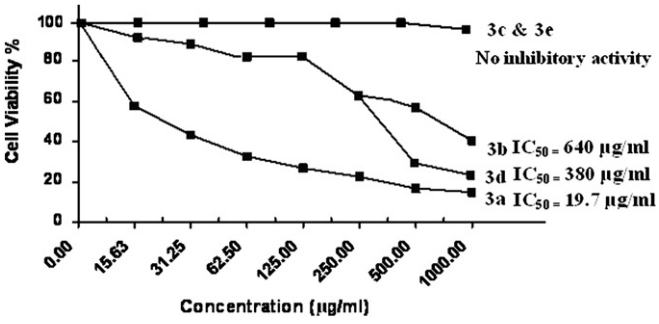


Fig. 2. Evaluation of cytotoxicity against HCT cell line.

5. Result and discussion

The 4*H*-chromene and coumarin derivatives were chosen for study because it is known that 4*H*-chromene and coumarin derivatives are an important families of active compounds with a wide range of pharmacological properties [1,41,42]. Twenty-one compounds of both 4*H*-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 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 Figs. 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-4*H*-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 4*H*-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 4*H*-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 4*H*-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 4*H*-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 4*H*-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 1 PC 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-cyanocinnamonitriles (**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 $C_{20}H_{20}ClN_3O$: 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 (NH_2), 2970, 2929, 2886, 2868 (CH), 2194 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36–6.18 (m, 7H, aromatic), 4.79 (bs, 2H, NH_2), 4.75 (s, 1H, H-4), 3.17 (q, J = 7.0 Hz, 4H, $2CH_2$), 1.00 (t, J = 7.0 Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 39.81 (C-4), 12.50 (CH_3) 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 $C_{20}H_{20}BrN_3O$: 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 (NH_2), 2971, 2909, 2886, 2868 (CH), 2193 (CN); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.11–6.16 (m, 7H, aromatic), 4.55 (s, 1H, H-4), 4.49 (bs, 2H, NH_2), 3.23 (q, J = 7.5 Hz, 4H, $2CH_2$), 1.07 (t, J = 7.5 Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.82 (C-2), 159.34 (C-8a), 149.55 (C-7), 129.48 (C-5), 120.16 (CN), 115.41 (C-4a), 109.14 (C-6), 98.16 (C-8), 61.14 (C-3), 44.41 (CH_2), 39.56 (C-4), 12.50 (CH_3), 160.87, 141.17, 129.92, 115.58(aromatic); *m*/*z* (%) 337 (M^+, 21.10), 242 (100), 207 (32.20), 170 (7.35), 133 (10.50), 75 (12.30); Anal. Calcd for $C_{20}H_{20}FN_3O$: 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**).* Colorless needles from ethanol; m.p. 143–144 °C; 45%; IR (cm^{-1}) in KBr: 3410, 3308, 3200 (NH_2), 2969, 2926, 2902 (CH), 1676 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.12–6.17 (m, 9H, aromatic and NH_2), 4.72 (s, 1H, H-4), 3.95 (q, J = 5.9 Hz, 2H, CH_2), 3.21 (q, J = 7.0 Hz, 4H, $2CH_2$), 1.10 (t, J = 7.0 Hz, 6H, $2CH_3$), 1.02 (t, J = 5.9 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2 ester) 44.40 (CH_2), 39.07 (C-4), 14.36 (CH_3 ester), 12.55 (CH_3), 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 $C_{22}H_{25}ClN_2O_3$: 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**).* Colorless needles from ethanol; m.p. 145–146 °C; 42%; IR (cm^{-1}) in KBr: 3401, 3304, 3216 (NH_2), 2974, 2925, 2892, 2874 (CH), 1676 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.34–6.28 (m, 9H, aromatic and NH_2), 4.81 (s, 1H, H-4), 4.07 (q, J = 7.5 Hz, 2H, CH_2), 3.32 (q, J = 7.5 Hz, 4H, $2CH_2$), 1.17 (t, J = 7.5 Hz, 6H, $2CH_3$), 1.13 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 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_2 ester), 44.40 (CH_2), 39.14 (C-4), 14.35 (CH_3 ester), 12.54 (CH_3), 147.53, 131.08, 129.42, 119.36 (aromatic); MS *m*/*z* (%): 446 (M^+ +2, 9.24), 444 (M^+, 8.00), 289 (100), 243 (61.18), 199 (19.11), 151 (11.01), 76 (10.39); Anal. Calcd for $C_{22}H_{25}BrN_2O_3$: 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**).* Colorless needles from ethanol; m.p. 135–136 °C; 40%; IR (cm^{-1}) in KBr: 3409, 3306, 3205 (NH_2), 2977, 2928, 2903, 2874 (CH), 1675 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.19–6.18 (m, 9H, aromatic and NH_2), 4.74 (s, 1H, H-4), 3.99 (q, J = 7.5 Hz, 2H, CH_2), 3.23 (q, J = 7.5 Hz, 4H, $2CH_2$), 1.08 (t, J = 7.5 Hz, 6H, $2CH_3$), 1.05 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 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_2 ester), 44.40 (CH_2), 38.91 (C-4), 14.32 (CH_3 ester), 12.54 (CH_3), 160.47, 144.60, 128.97, 114.77 (aromatic); MS *m*/*z* (%): 384 (M^+, 7.10), 367 (30.00), 271 (32.00), 227 (8.00), 207 (100), 177 (6.20), 133 (10.50), 75 (18.30), Anal. Calcd for $C_{22}H_{25}FN_2O_3$: 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^{-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 $C_{20}H_{17}ClN_2O_2$: 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 $C_{20}H_{17}BrN_2O_2$: 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-Fluoromophenyl)-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), 128.89 (C-5), 116.26 (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), 162.85, 153.20, 130.80, 115.31(aromatic); *m/z* % 336 (M^+, 39.33), 321 (100), 293 (26.10), 199 (3.15), 170 (7.80), 133 (8.50), 75 (5.60); Anal. Calcd for $C_{20}H_{17}FN_2O_2$: C, 71.42; H, 5.09; N, 8.33. Found: C, 71.33; H, 5.04; N, 8.28.

*7.1.2. 2-Diacetylamino-4-(4-chlorophenyl)-7-(diethylamino)-4H-chromene-3-carbonitrile (**5b**)*

A solution of **3a** (0.01 mmol) in Ac_2O (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); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48–6.36 (m, 7H, aromatic), 5.13 (s, 1H, H-4), 3.40 (q, J = 7.0 Hz, 4H, $2CH_2$), 2.44 (s, 6H, $2COCH_3$), 1.05 (t, J = 7.0 Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 40.38 (C-4), 24.00 (CH_3), 12.22 (CH_3), 142.13, 132.25, 129.67, 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 $C_{24}H_{24}ClN_3O_3$: 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 Ac_2O (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 colorless crystals; m.p. 238–239 °C; 75%; IR (cm^{-1}) in KBr: 3300 (NH), 2966, 2929, 2868 (CH), 1647 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2), 2.34(s, 3H, CH_3), 1.08(t, J = 7.0 Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 37.67 (C-5), 21.23 (CH_3), 12.49 (CH_3), 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 $C_{22}H_{22}ClN_3O_2$: C, 66.75; H, 5.60; N, 10.61. Found: C, 66.64; H, 5.55; N, 10.56.

7.1.3.2. Method (b). 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-Benzylideneamino-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, 3034, 2969, 2927, 2891 (CH), 2207 (CN), 1638 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) 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, $2CH_2$), 1.09 (t, J = 7.0 Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 42.35 (C-4), 12.58 (CH_3), 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 $C_{27}H_{24}ClN_3O$: 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 Ac_2O (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); ^{1}H NMR (500 MHz, $CDCl_3$) 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, CH_2), 3.34 (q, J = 7.2 Hz, 4H, $2CH_2$), 1.40 (t, J = 7.2 Hz, 3H, CH_3), 1.83 (t, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2 ethoxy), 44.42 (CH_2), 41.68 (C-4), 13.96 (CH_3 ethoxy), 12.54 (CH_3), 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 $C_{23}H_{24}ClN_3O_2$: 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, $CDCl_3$) 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, CH_2), 3.34 (q, $J = 7.0$ Hz, 4H, $2CH_2$), 1.40 (t, $J = 7.2$ Hz, 3H, CH_3), 1.83 (t, $J = 7.0$ Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 159.43 (C-2), 157.69 (N=CH), 150.01 (C-8a), 148.14 (C-7), 129.94 (C-5), 118.45 (CN), 109.37 (C-4a), 107.38 (C-6), 98.25 (C-8), 80.76 (C-3), 64.09 (CH_2 ethoxy), 44.41 (CH_2), 41.75 (C-4), 13.95 (CH_3 ethoxy), 12.54 (CH_3), 143.45, 131.89, 131.68, 121.19 (aromatic); MS *m/z* (%): 455 (M^+ +2, 30.46), 453 (M^+, 27.52), 298 (100), 242 (38.41), 198 (21.59), 151 (8.33), 74 (3.07); Anal. Calcd for $C_{23}H_{24}BrN_3O_2$: 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, 1663 (CO); ^1H NMR (500 MHz, $CDCl_3$) 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, CH_2), 2.37 (s, 3H, CH_3), 1.21 (t, $J = 7.0$ Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 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 $C_{24}H_{26}ClN_3O_4$: 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**).* Colorless 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); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.00 (s, 1H, H-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, $CDCl_3$) δ: 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), 108.94 (C-7), 98.97 (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 $C_{21}H_{22}ClN_5O$: 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**).* Colorless 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); ^1H NMR (500 MHz, $CDCl_3$) δ: 8.05 (s, 1H, H-2), 7.29–6.35 (m,7H, aromatic), 6.09 (br,1H, NH), 4.84 (brs, 2H, NH_2), 4.80 (s, 1H, H-5), 3.31 (q, $J = 6.2$ Hz, 4H, $2CH_2$), 1.14(t, $J = 6.2$ Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 39.82 (C-5), 12.52 (CH_3), 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 $C_{21}H_{22}BrN_5O$: 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 crystallized from ethanol to give **13** as colorless 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, $CDCl_3$) 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, CH_3), 3.22 (q, $J = 7.5$ Hz, 4H, $2CH_2$), 1.06 (t, $J = 7.5$ Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (CH_2), 39.52 (C-5), 35.12 (CH_3), 12.49 (CH_3), 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 $C_{22}H_{23}ClN_4O$: 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 crystallized from ethanol to give **14** as colorless 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, $CDCl_3$) 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, 4H, $2CH_2$), 3.14, 3,12 (s, 6H, $2CH_3$), 1.18 (t, $J = 7.5$ Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 160.32 (C-2), 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 (CH_3), 34.76 (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), 253 (14.45), 204 (12.06), 150 (1.51), 127 (6.33), 74 (1.34); Anal. Calcd for $C_{22}H_{25}ClN_4O$: 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 crystallized from ethanol to give **15** as colorless 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); ^1H NMR (500 MHz, $CDCl_3$) δ: 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, $J = 7.5$ Hz, 4H, $2CH_2$), 1.07 (t, $J = 7.5$ Hz, 6H, $2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 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 $C_{21}H_{21}ClN_4O$: C, 66.22; H, 5.56; N, 14.71. 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 2h, then the mixture was left overnight. The solid product was collected and crystallized from benzene to give **16** as colorless 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, $CDCl_3$) δ: 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, $CDCl_3$) δ: 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 $C_{21}H_{21}ClN_4O$: 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).

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