Synthesis and antimicrobial activities of 2-substituted 12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines, 3-ethoxycarbonyl-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*] pyrimidine-2-one and ethyl 2-formylamino- and 2-acetylamino-4*H*-chromene-3-carboxylates

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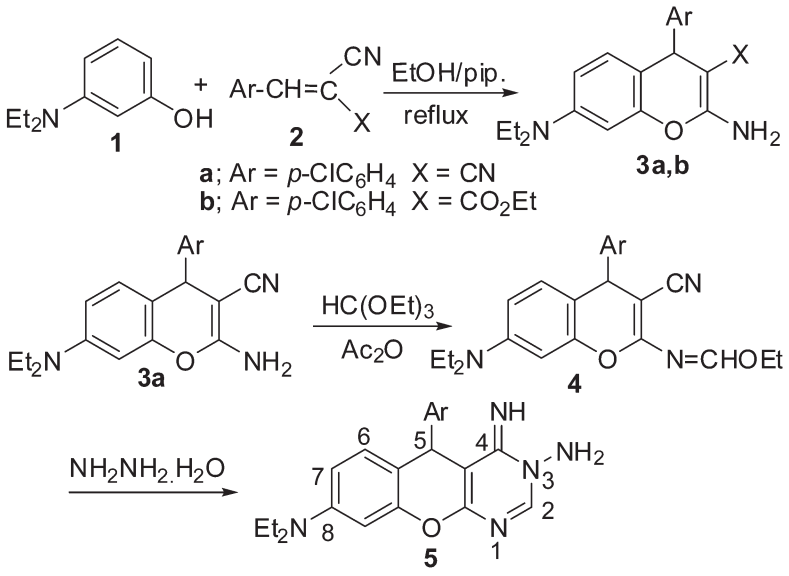
Preparation of 2-substituted 9-(diethylamino)-12-(4-chlorophenyl)-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines is reported. Furthermore, 3-benzylideneamino-5-(4-chlorophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5*H*-chromeno[2,3-*d*]pyrimidine, 3-ethoxycarbonyl-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2-one, ethyl 2-formylamino- and 2-acetylamino-4*H*-chromene-3-carboxylates were prepared. Structures of these compounds were established on the basis of IR, UV, ^{1}H NMR, ^{13}C NMR and MS data. The new compounds were evaluated for antimicrobial activities.

Keywords: 4*H*-chromene, chromeno[2,3-*d*]pyrimidine, triazolo[1,5-*c*]pyrimidine, antimicrobial activities

4*H*-Chromenes and fused 4*H*-chromenes nuclei are often found in biologically active molecules and are widely used as antileishmanial,[1–5] antitumour,[6,7] antiproliferative and antitubulin,[8] antiarrhythmic,[9] hypolipidaemic,[10,11] and antidepressant agents,[12] as well as for the treatment of Alzheimer's disease and schizophrenia.[13,14] In addition they function as inhibitors of influenza virus sialidases.[15,16] They also exhibit anti-inflammatory,[17–24] DNA stand-breaking, mutagenic,[25] antiviral,[26] anticoagulant [27–31] and analgesic activities[32–38] and also act as sex pheromone homologues.[39] The present study is a part of our research programme[40–52] directed towards the synthesis of novel 4*H*-chromene and fused 4*H*-chromene derivatives using *β*-enaminonitriles and *β*-enaminocarboxylic esters and their use as building blocks in the synthesis of novel fused chromenes; with the aim of evaluating their antimicrobial activities. Treatment of 3-(diethylamino)phenol **1** with *α*-cyano-*p*-chlorocinnamonitrile **2a** in ethanolic piperidine afforded 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carbonitrile **3a**,[53] while treatment of **1** with ethyl *α*-cyano-*p*-chlorocinnamate **2b** under the same conditions gave ethyl 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carboxylate **3b**[53] (Scheme 1). Treatment of **3a** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding 2-ethoxymethyleneamino-4*H*-chromene-3-carbonitrile **4**[53] (Scheme 1). Hydrazinolysis of **4** in ethanol at room temperature afforded 3-amino-5-(4-chlorophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5*H*-chromeno [2,3-*d*]pyrimidine **5**[53] (Scheme 1).

The imino compound **5** proved to be a useful intermediate for the synthesis of a variety of 2-substituted 12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives. Thus, treatment of **5** with either formic acid, methyl formate or triethyl orthoformate in dry benzene at reflux provided the tetracycle **6a**. In a similar manner, acylation of **5** with acetyl chloride or acetic anhydride gave the 2-methyltriazolopyrimidine **6b**, whilst condensation with ethyl cyanoacetate and with diethyl oxalate afforded **6c** and **6d** respectively. Aroylation of **5** with benzoyl chloride in refluxing benzene proceeded readily to give the 2-phenyl derivative **6e** (Scheme 2).



Scheme 1

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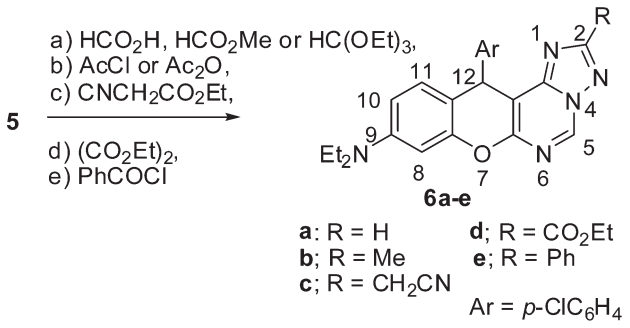


Scheme 2

Structures **6a–e** were established on the basis of spectral data and in conjunction with our previous work.[41–47] The IR spectra showed the absence of NH_2 and NH absorptions and the presence of a CN band at υ 2260 cm^{-1} for **6c** and a CO band at υ 1747 cm^{-1} for **6d**. The ^1H and ^{13}C NMR spectra of **6a** showed signals at δ 8.20 (s, 1H. H-2) and 154.34 (C-2). Characteristic resonances were observed at δ 2.41 (s, 3H, CH_3) and 14.21 (CH_3) for **6b** and at δ 3.30 (s, 2H, CH_2) and 25.81 (CH_2) for **6c.** In compound **6d** the ester group gave ^1H signals at 4.55 (q, 2H, CH_2, J = 7.1 Hz) and 1.48 (t, 3H, CH_3, J = 7.1 Hz) with the corresponding signals in the ^{13}C spectrum at 62.73 and 14.23 ppm respectively.

Condensation of **5** with benzaldehyde afforded the open chain product 3-(benzylideneamino)-chromeno[2,3-*d*]pyrimidine derivative **7**[47] (Scheme 3). Cyclisation of **7** in 1,4-dioxane-piperdine solution under reflux[47] afforded the cycloaddition product **6e**, which can also be obtained as described above from the aroylation of **5** with benzoyl chloride (m.p. and mixed m.p.) (Scheme 3). Structure **7** was established on the basis of its IR spectrum, which showed the absence of NH_2 bands and the presence of an NH absorption at υ 3349 cm^{-1}. The ^1H and ^{13}C NMR spectra of **7** showed signals at δ 8.97 (s, 1H, N=CH) and 154.56 ppm (N=CH).

Interaction of **5** with ethyl chloroformate in dry benzene at reflux afforded a 1:2 adduct, 3-ethoxycarbonyltriazolopyrimidine-2-one **11** instead of the 1:1 adduct, triazolopyrimidine-2-one **10** (Scheme 4).

The formation of **11** is assumed to proceed *via* interaction of **5** with one mole of ethyl chloroformate with elimination of HCl to yield the intermediate **9**, which then cyclised to the non-isolable compound **10** *via* elimination of EtOH. Intermediate **10** is reacted with another mole of ethyl chloroformate with elimination of HCl to give **11**. Alternatively, interaction of **5** with two moles of ethyl chloroformate with elimination of HCl yields the intermediate bis-(ethoxycarbonyl) derivative **8**, which then cyclises to **11** with elimination of ethanol (Scheme 4).

The structure of **11** was established on the basis of its IR spectrum, which showed the absence of NH_2 and NH bands and the presence of two CO groups at υ 1759 and 1736 cm^{-1}. The ^1H and ^{13}C NMR spectra of **11** revealed the presence of signals at 4.48 (q, 2H, CH_2, J = 7.5 Hz), 1.40 (t, 3H, CH_3, J = 7.5 Hz) and 155.49 (CO) and 154.90 ppm (CO ester).

Treatment of **3b** with triethyl orthoformate in acetic anhydride at reflux afforded a mixture of the 2-formylamino derivative **12**, together with the 2-acetylamino compound **13**, rather than the imidate[54] **16** (Scheme 5). The 2-acetyl derivative **13** was separated from the filtrate of the reaction mixture.

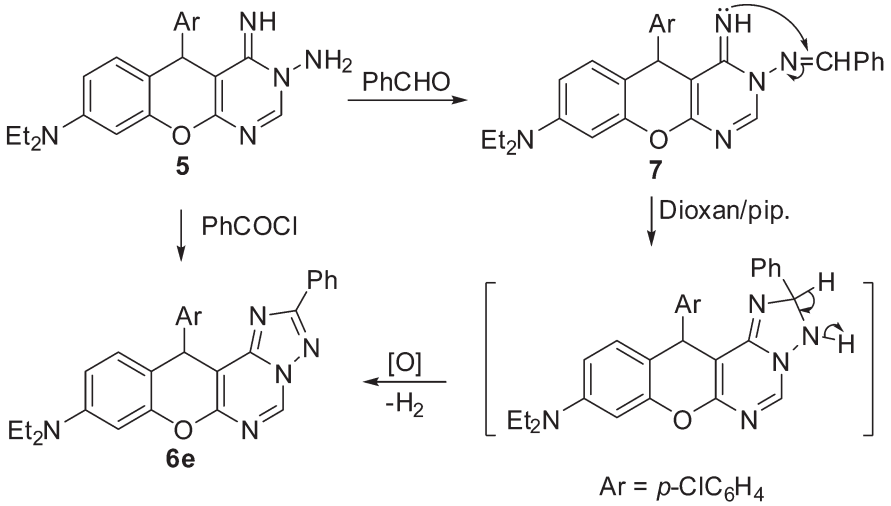
The structure of **12** was established on the basis of its IR spectrum which showed two NH bands at υ 3251 and 3217 as well as C=O absorptions at υ 1700 and 1677 cm^{-1}. The ^1H NMR spectrum of **12** revealed the presence of signals for the formamido group at δ 10.85 (d, 1H, CHO, J = 10 Hz), 9.14 (d, 1H, NH, J = 10 Hz), whilst the ^{13}C NMR spectrum showed two carbonyl signals at δ 168.09 (CO ester) and 159.80 ppm (CO). The ^{13}C NMR - DEPT spectrum at 45°, 90° and 135° of **12** (Figure 1) provided additional evidence in support of the proposed structure.

Hydrazinolysis of **12** in ethanol at room temperature gave the addition product **14**, from which formic acid hydrazide was eliminated to gave the *β*-enaminoester[55] **3b** (m.p. and mixed m.p.) rather than the pyrimidine-4-one derivative **15**[54] (Scheme 5).

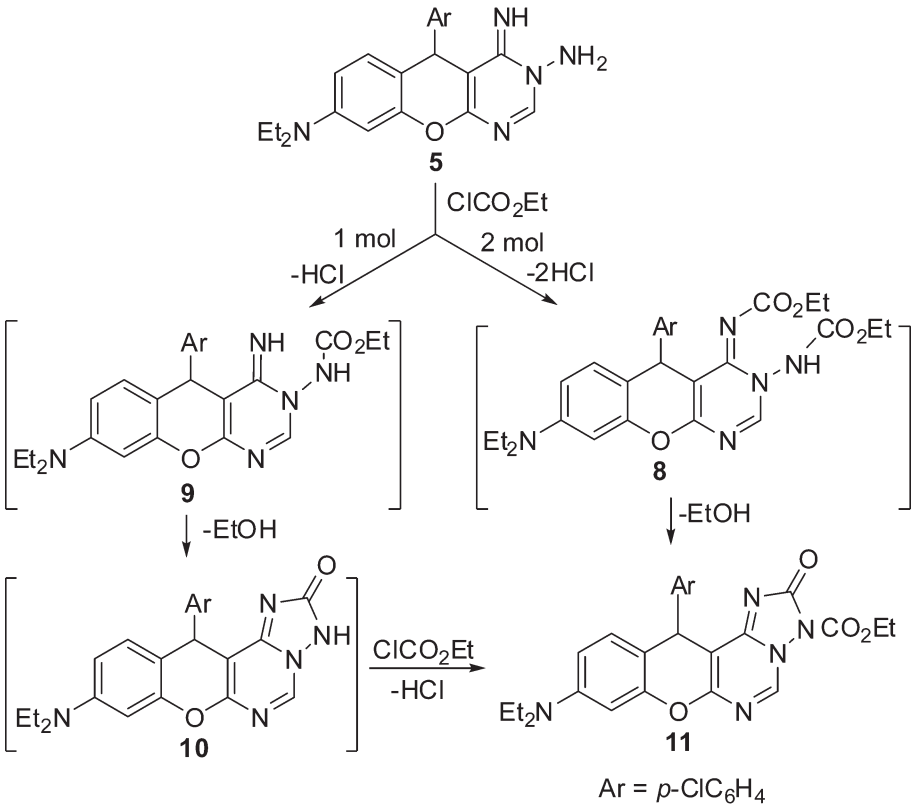
The formation of **12** from **3b** can be rationalised through the initial product **17** of the addition of H_2O to ethoxymethyleneamino group (–N=CHOEt) of the non-isolable intermediate **16**, from which elimination of ethanol affords **12** (Scheme 5).

Antibacterial activities

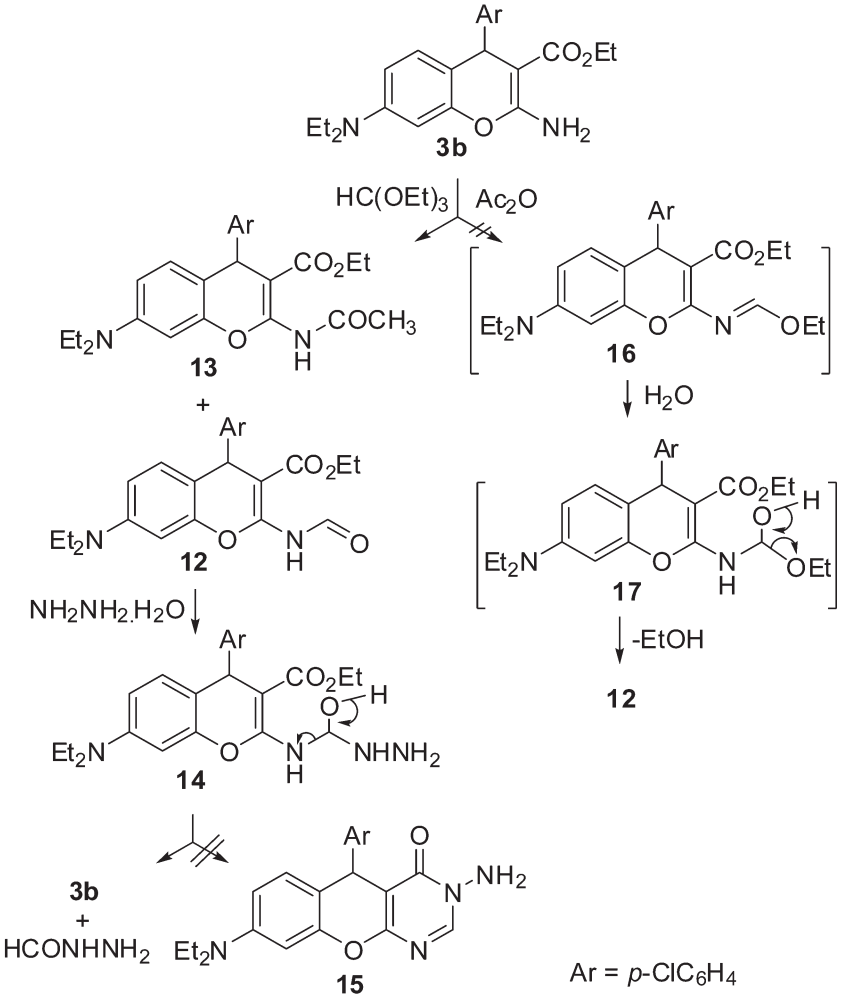
The newly synthesised compounds **6a–e, 7** and **11–13** were tested *in vitro* for their antimicrobial activities[56,57] by the agar diffusion method using Mueller–Hinton agar medium for bacteria and Sabouraud's agar medium for fungi. The microorganisms tested were obtained from the culture collection at



Scheme 3



Scheme 4



Scheme 5

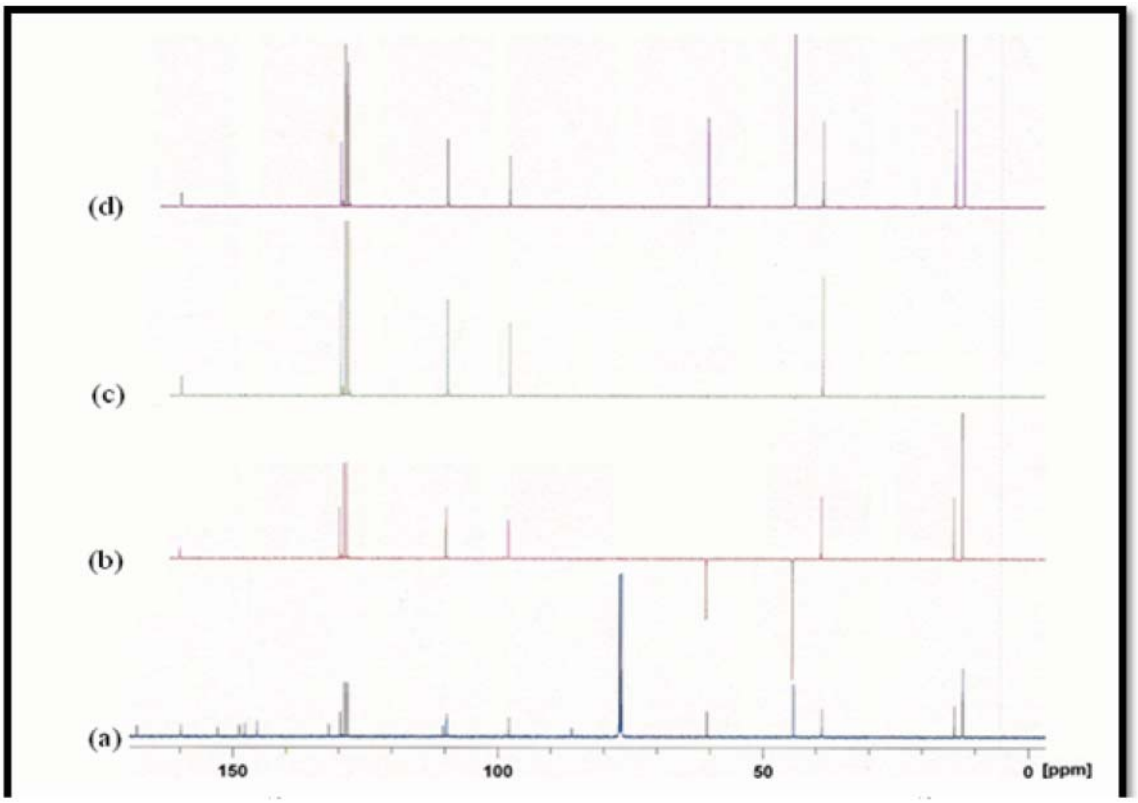


Fig. 1 (a) Standard ^{13}C NMR decoupled spectrum of compound **12**. (b) ^{13}C NMR/DEPT 135° CH and CH_3 up, CH_2 down. (c) ^{13}C NMR/DEPT 90° CH only up. (d) ^{13}CMR/DEPT 45° CH, CH_2 and CH_3 up.

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^{-1} as a reference compound and two fungi (*Candida albicans* ATCC 10231 and *Saccharomyces cervesia* ATCC 9080) using Mycostatine 25 μg mL^{-1} 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).

The screening results indicate that compounds **11** and **13** did not show any antimicrobial activity against all the tested bacteria and fungi. Compound **6d** showed activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*, while compounds **6a,b,e** showed activity against *Staphylococcus epidermidis* and compound **7** showed activity against *Bacillus subtilis*. Compounds **6c** and **12** showed high activity against all tested microorganisms at a concentration of 25 μg mL^{-1}. The preliminary *in vitro* antimicrobial activity has demonstrated that the 4*H*-chromene with a 2-formylamino group in combination with the cyano group in the 3-position was more active than the 4*H*-chromene with the 2-acetylamino group and the chromeno[2,3-*d*]pyrimidine, whilst 2-cyanomethyl-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **6c** was

Table 1 Antibacterial screening of the synthetic compounds

Cpd	*Bordetella bronchiseptica* (-ve)	*E. coli* (-ve)	*Bacillus pumilus* (+ve)	*Bacillus subtilis* (+ve)	*Staph. aureus* (+ve)	*Staph. epidermidis* (+ve)	*Candida albicans*	*Saccharomyces cerevisa*
6a	NA	NA	NA	NA	NA	12	NA	NA
6b	NA	NA	NA	NA	NA	16	NA	NA
6c	24	18	28	28	27	25	15	21
6d	NA	NA	NA	NA	15	18	NA	NA
6e	NA	NA	NA	NA	NA	13	NA	NA
7	NA	NA	NA	14	NA	NA	NA	NA
11	NA	NA	NA	NA	NA	NA	NA	NA
12	**22**	**17**	**23**	**14**	**20**	**20**	**13**	**18**
13	NA	NA	NA	NA	NA	NA	NA	NA
Ampicillin	24	25	20	25	26	25	–	–
Mycostatine (25 μg mL^{-1})	–	–	–	–	–	–	22	24

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

found to be more active than other members of the 12*H*-chromeno[3,2-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine series.

Experimental

Melting points were determined with a Stuart Scientific Co. Ltd apparatus. UV spectra were measured on a Shimadzu UV-160 1PC UV-Vis 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 polarisation transfer (DEPT), with this technique, the signals from CH and CH_3 carbons were positive (up) whilst signals from CH_2 environments are negative (down). Mass spectra 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.

*2-Amino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carbonitrile* **(3a)**: Prepared according to the literature procedure.[53]

*Ethyl 2-amino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carboxylate* **(3b)**: Prepared according to the literature procedure.[53]

*4-(4-Chlorophenyl)-7-(diethylamino)-2-ethoxymethyleneamino-4*H*-chromene-3-carbonitrile* **(4)**: Prepared according to the literature procedure.[53]

*3-Amino-5-(4-chlorophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5*H*-chromeno[2,3-*d*]-pyrimidine* **(5)**: Prepared according to the literature procedure.[53]

*12-(4-Chlorophenyl)-9-(diethylamino)-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* **(6a)**

*Method **A**:* A solution of **5** (0.01 mmol) and triethyl orthoformate (0.01 mmol) in dry benzene was refluxed for 6 h to give **6a** as colourless crystals which was collected by filtration and recrystallised from benzene; m.p. 215–216 °C, 79%; IR (KBr) υ (cm^{-1}): 3082, 2971, 2930 (CH stretching), 1630 (C=N); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 9.15 (s, 1H, H-5), 8.20 (s, 1H, H-2), 7.50–6.25 (m, 7H, aromatic), 5.45 (s, 1H, H-2), 3.41 (q, 4H, $2CH_2$, *J* = 7.0 Hz), 1.05 (t, 6H, $2CH_3$, *J* = 7.0 Hz); ^{13}C NMR (125 MHz) (DMSO-d_6) δ: 156.24 (C-6a), 154.34 (C-2), 152.51 (C-9), 150.65 (C-7a), 147.98 (C-12b), 138.75 (C-5), 132.25 (C-11), 109.30 (C-11a), 107.89 (C-12a), 102.90 (C-10), 98.71 (C-8), 44.47 (CH_2), 38.91 (C-12), 12.11 (CH_3), 143.23, 129.71, 129.40, 128.42 (aromatic); MS *m/z* (%): 407 [M$^+$+2] (21), 405 [M]$^+$ (65.5), 294 (100), 269 (98.5), 250 (49), 197 (75), 150 (69), 113 (18.5), 56 (31); Anal. Calcd for $C_{22}H_{20}ClN_5O$: C, 65.10; H, 4.97; N, 17.25. Found: C, 65.25; H, 5.12; N, 17.38%.

*Method **B**:* A solution of **5** (0.01 mmol) and methyl formate (0.01 mmol) in dry benzene was refluxed for 3 h to give **6a** (m.p. and mixed m.p.) yield (81%).

*Method **C**:* A solution of **5** (0.01 mmol) and formic acid (0.01 mmol) in dry benzene was refluxed for 3 h to give **6a** (m.p. and mixed m.p.) yield (63%).

*12-(4-Chlorophenyl)-9-(diethylamino)-2-methyl-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* **(6b)**

*Method **A**:* A solution of **5** (0.01 mmol) and acetyl chloride (0.01 mmol) in dry benzene was refluxed for 6 h to give **6b** as colourless crystals which was collected by filtration and recrystallised from benzene; m.p. 216–217 °C, 81%; IR (KBr) υ (cm^{-1}): 3039, 2979, 2887 (CH stretching), 1631 (C=N); ^{1}H NMR (500 MHz) (DMSO-d_6) δ: 9.28 (s, 1H, H-5) 7.96–6.40 (m,7H, aromatic), 5.67 (s, 1H, H-12), 3.45 (q, 4H, $2CH_2$, *J* = 7.5 Hz), 2.41 (s, 3H, CH_3), 1.17 (t, 6H, $2CH_3$, *J* = 7.5 Hz); ^{13}C NMR (125 MHz) (DMSO-d_6) δ: 166.28 (C-6a), 155.20 (C-2), 153.10 (C-9), 152.45 (C-7a), 150.33 (C-12b), 132.30 (C-5), 129.34 (C-11), 128.23 (C-11a), 118.20 (C-12a), 105.50 (C-10), 101.30 (C-8), 44.47 (CH_2), 39.13 (C-12), 14.21 (CH_3), 12.11 (CH_3), 139.20, 129.88, 128.99, 128.58, (aromatic); MS *m/z* (%): 421 [M$^+$ +2], (23), 419 [M]$^+$, (61), 308 (100), 263 (23), 188 (20), 111 (12), 98 (14); Anal. Calcd for $C_{23}H_{22}ClN_5O$: C, 65.79; H, 5.28; N, 16.68. Found: C, 65.65; H, 5.17; N, 16.55%.

*Method **B**:* A solution of **5** (0.01 mmol) and acetic anhydride (0.01 mmol) was refluxed for 6 h to give **6b** (m.p. and mixed m.p.) yield (79%).

*12-(4-Chlorophenyl)-2-cyanomethyl-9-(diethylamino)-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* (**6c**): A solution of **5** (0.01 mmol) and ethyl cyanoacetate (0.01 mmol) in dry ethanol was refluxed for 6 h to give **6c** as colourless crystals which was collected by filtration and recrystallised from benzene; m.p. 210–211 °C, 76%; IR (KBr) υ (cm^{-1}): 3069, 2973, 2917, 2899, (CH stretching), 2260 (CN), 1626 (C=N); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 8.60 (s, 1H, H-5) 7.27–6.32 (m, 7H, aromatic), 4.94 (s, 1H, H-12), 3.30 (s, 2H, CH_2), 3.25 (q, 4H, $2CH_2$, *J* = 7.5 Hz), 1.08 (t, 6H, $2CH_3$, *J* = 7.5 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 167.31 (C-6a), 159.87 (C-9), 153.25 (C-7a), 150.74 (C-2), 148.89 (C-12b), 140.70 (C-5), 130.08 (C-11), 116.78 (CN), 109.86 (C-11a), 106.43 (C-12a), 99.04 (C-10), 97.31 (C-8), 44.48 (CH_2), 39.14 (C-12), 25.81 (CH_2), 12.44 (CH_3), 148.45, 134.35, 129.57, 128.96 (aromatic); MS *m/z* (%): 446 [M$^+$ +2], (17), 444 [M]$^+$, (40), 333 (100), 242 (28), 188 (6), 111 (6), 88 (2); Anal. Calcd for $C_{24}H_{21}ClN_6O$: C, 64.79; H, 4.76; N, 18. 89. Found: C, 64.68; H, 4.64; N, 18.78%.

*Ethyl 12-(4-chlorophenyl)-9-(diethylamino)-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2-carboxylate* (**6d**): A solution of **5** (0.01 mmol) and ethyl cyanoacetate (0.01 mmol) in dry ethanol was refluxed for 6 h to give **6c** as colourless crystals which was collected by filtration and recrystallised from benzene; m.p. 230–231 °C, 82%; IR (KBr) υ (cm^{-1}): 3088, 2970, 2901, 2927, 2891 (CH stretching), 1747 (CO), 1627 (C=N); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 9.16 (s, 1H, H-5) 7.35–6.51 (m, 7H, aromatic), 5.72 (s, 1H, H-12), 4.55 (q, 2H, CH_2, *J* = 7.1 Hz), 3.39 (q, 4H, $2CH_2$, *J* = 7.05 Hz), 1.48 (t, 3H, CH_3, *J* = 7.1 Hz) 1.21 (t, 6H, $2CH_3$, *J* = 7.05 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 160.01 (C-6a), 158.51 (CO), 155.02 (C-2), 153.66 (C-9), 151.19 (C-7a), 148.29 (C-12b), 138.91 (C-5), 129.85 (C-11), 110.19 (C-11a), 108.16 (C-12a), 104.50 (C-10), 99.24 (C-8), 62.73 (CH_2 ester), 44.58 (CH_2), 38.86 (C-12), 14.23 (CH_3 ester), 12.49 (CH_3), 142.83, 132.88, 129.77, 129.58 (aromatic); MS *m/z* (%): 479 [M$^+$ +2], (26.5), 477 [M]$^+$, (69), 465 (31), 463 (100), 352 (1), 308 (1), 294 (19), 238 (2), 195 (13), 138 (7), 75 (5); Anal. Calcd for $C_{25}H_{24}ClN_5O_3$: C, 62.82; H, 5.06; N, 14.65. Found: C, 62.70; H, 5.00; N, 14.55%.

*12-(4-Chlorophenyl)-9-(diethylamino)-2-phenyl-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine* (**6e**)

*Method **A**:* A solution of **5** (0.01 mmol) and benzoyl chloride (0.01 mmol) in dry benzene was refluxed for 6 h to give **6e** as colourless crystals which was collected by filtration and recrystallised from benzene; m.p. 220–221 °C, 78%; IR (KBr) υ (cm^{-1}): 3057, 3030, 2977 (CH stretching), 1627 (C=N); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 9.01 (s, 1H, H-5) 8.19–6.40 (m,12H, aromatic), 5.61 (s, 1H, H-12), 3.31 (q, 4H, $2CH_2$, *J* = 7.0 Hz), 1.13 (t, 6H, $2CH_3$, *J* = 7.0 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 166.97 (C-6a), 154.40 (C-2), 153.74 (C-9), 151.38 (C-7a), 148.25 (C-12b), 138.23 (C-5), 130.82 (C-11), 129.97 (C-12a), 109.48 (C-11a), 108.33 (C-12a), 103.13 (C-10), 99.13 (C-8), 44.51 (CH_2), 39.14 (C-12), 12.54 (CH_3), 143.27, 132.66, 130.01,129.86, 128.74, 128.58, 128.35, 127.78 (aromatic); MS *m/z* (%):483 [M$^+$+2], (21), 481 [M]$^+$, (62.15), 370 (100), 294 (0.57), 241(5.27), 181 (4.89), 140 (10.46), 103 (33.51), 77 (36.62); Anal. Calcd for $C_{28}H_{24}ClN_5O$: C, 69.78; H, 5.02; N, 14. 53. Found: C, 69.81; H, 5.06; N, 14.57%.

*Method **B**:* Compound **7** (0.01 mmol) was heated under reflux in 1,4-dioxane (20 mL) and piperidine (0.5 mL) for 3 h to give **6e** (m.p. and mixed m.p.) yield (68%).

*3-Benzylideneamino-5-(4-chlorophenyl)-8-(diethylamino)-4-imino-3,4-dihydro-5*H*-chromeno[2,3-*d*]pyrimidine* (**7**): A mixture of **5** (0.01 mmol), benzaldehyde (0.01 mmol), ethanol (20 mL) and piperidine (0.5 mL) was refluxed for 2 h. The solid product, which formed, was collected by filtration and recrystallised from ethanol give **7** as yellow crystals; m.p. 197–198 °C; 87%; IR (KBr) υ (cm^{-1}): 3349 (NH), 3058, 2970, 2932, 2891 (CH stretching), 1636 (C=N); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 9.94 (bs, 1H, NH), 8.97 (s, 1H, N=CH) 8.55–6.33 (m,12H, aromatic), 5.67 (s, 1H, H-4), 3.34 (q, 4H, $2CH_2$, *J* = 7.5 Hz), 1.07 (t, 6H, $2CH_3$, *J* = 7.5 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 164.85 (C-4), 158.65 (C-2), 156.87 (C-10a), 154.56 (N=CH), 150.44 (C-9a), 148.44 (C-8), 129.90 (C-6), 110.34 (C-5a), 109.91 (C-7), 99.92 (C-9), 98.63 (C-4a), 44.43 (CH_2), 38.70 (C-5), 12.49 (CH_3), 143.92, 138.14, 133.86, 132.89, 129.79, 129.27, 128.64, 128.77, 127.83 (aromatic); MS *m/z* (%): 485 [M$^+$ +2], (4), 483 [M]$^+$, (15), 381 [M$^+$ +2], (30.5), 379 [M]$^+$, (100), 268 (7), 242 (2), 182 (12), 150 (9), 104 (21.5), 76 (16); Anal. Calcd for $C_{28}H_{26}ClN_5O$: C, 69.48; H, 5.41; N, 14.47. Found: C, 69.35; H, 5.31; N, 14.37%.

*3-Ethoxycarbonyl-12-(4-chlorophenyl)-9-(diethylamino)-2,3-dihydro-12*H*-chromeno[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-2-one* (**11**): A solution of **5** (0.01 mmol) and ethyl chloroformate (0.01 mmol) in dry benzene was refluxed for 2 h to give **11** as colourless crystals which was collected by filtration and recrystallised from benzene; m.p. 213–214 °C, 79%; IR (KBr) υ (cm^{-1}): 3120, 2973, 2928 (CH stretching), 1759, 1736 CO, 1684 (C=N); ^{1}H NMR (500 MHz)

($CDCl_3$) δ: 9.24 (s, 1H, H-5), 7.20–6.40 (m, 7H, aromatic), 5.26 (s, 1H, H-12), 4.48 (q, 2H, CH_2, *J* = 7.5 Hz), 3.28 (q, 4H, $2CH_2$, *J* = 7.5 Hz), 1.40 (t, 3H, CH_3, *J* = 7.5 Hz), 1.11 (t, 6H, $2CH_3$, *J* = 7.5 Hz); ^{13}C NMR (125 MHz) (DMSO-d_6) δ: 158.17 (C-6b), 155.49 (CO), 154.90 (CO ester), 150.67 (C-6a), 149.76 (C-7a), 148.37 (C-9), 142.43 (C-5), 129.95 (C-11), 110.08 (C-11a), 107.84 (C-10), 101.16 (C-8), 99.04 (C-12a), 65.60 (CH_2 ester), 44.50 (CH_2), 38.44 (C-12), 14.23 (CH_3 ester), 12.48 (CH_3), 138.83, 132.97, 129.77, 128.74 (aromatic); MS *m/z* (%): 495 [M^++2], (30.24), 493 [M]$^+$, (100), 480 (35), 478 (96), 452 (1), 450 (3), 408 (17), 406 (43), 380 (6), 378 (14), 266 (43), 238 (20), 182 (15), 100 (5), 68 (5); Anal. Calcd for $C_{25}H_{24}ClN_5O_4$: C, 60.79; H, 4.90; N, 14.18. Found: C, 60.80; H, 4.95; N, 14.20%.

Reaction of **3b** *with triethyl orthoformate*: A mixture of *β*-enaminoester **3b** (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 separated solid was recrystallised from benzene to give **12** and the compound **13** was separated from the filtrate of the reaction and recrystallised from ethanol. The physical and spectra data of the compounds **12** and **13** are as follows.

*Ethyl 4-(4-chlorophenyl)-7-(diethylamino)-2-formylamino-4*H*-chromene-3-carboxylate* **(12)**: Colourless needles; m.p. 175–176 °C; 35%; IR (KBr) υ (cm^{-1}): 3251, 3217 (NH), 3087, 3038, 3022, 2972, 2926, (CH stretching), 1700, 1677 (CO); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 10.85 (d, 1H, CH, *J* = 10.0 Hz), 9.14 (d, 1H, NH, *J* = 10.0 Hz), 7.19–6.22 (m,7H, aromatic), 4.79 (s, 1H, H-4), 4.03 (q, 2H, CH_2, *J* = 7.5 Hz), 3.24 (q, 4H, $2CH_2$, *J* = 7.1 Hz), 1.09 (t, 3H, CH_3, *J* = 7.5 Hz),1.07 (t, 6H, $2CH_3$, *J* = 7.1 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 168.09 (CO ester), 159.80 (CO), 152.89 (C-2), 148. 89 (C-8a), 147.83 (C-7), 129.82 (C-5), 110.37 (C-4a), 109.72 (C-6), 98.01 (C-8), 86.19 (C-3), 60.64 (CH_2 ester), 44.40 (CH_2), 39.00 (C-4), 14.07 (CH_3 ester) 12.49 (CH_3) 145.57, 132.02, 129.02, 128.48 (aromatic); ^{13} C NMR - DEPT spectrum at 135° CH, CH_3 [positive (up)], CH_2 (negative), revealed the following signals at δ 159.80 (CHO ↑), 129.82 (C-5 ↑), 129.02 (CH ↑ aromatic), 128.48 (CH ↑ aromatic), 109.74 (C-6 ↑), 98.01 (C-8 ↑), 60.62 (CH_2 ester ↓), 44.40 (CH_2 ↓), 39.00 (C-4 ↑), 14.07 (CH_3 ester ↑), 12.49 (CH_3 ↑). In the DEPT spectrum at 90° only CH signals are positive (up), and showed δ 159.80 (CHO formyl ↑), 129.82 (C-5 ↑), 129.02 (CH ↑ aromatic), 128.48 (CH ↑ aromatic), 109.74 (C-6 ↑), 98.01 (C-8 ↑), 39.00 (C-4 ↑). In the DEPT spectrum at 45° (CH, CH_2 and CH_3 positive) revealed signals at δ 159.80 (CHO formyl ↑), 129.82 (C-5 ↑), 129.02 (CH ↑ aromatic), 128.48 (CH ↑ aromatic), 109.74 (C-6 ↑), 98.01 (C-8 ↑), 60.62 (CH_2 ester ↑), 44.40 (CH_2 ↑), 39.00 (C-4 ↑), 14.07 (CH_3 ester ↑), 12.49 (CH_3 ↑); MS *m/z* (%): 430 [M^++2] (9), 428 [M]$^+$, (31.5), 317 (17), 289 (97), 243 (100), 199 (19), 138 (35.5), 77 (56); Anal. Calcd for $C_{23}H_{25}ClN_2O_4$: C, 64.41; H, 5.88; N, 6.53. Found: C, 64.30; H, 5.90; N, 6.55%.

*Ethyl 2-acetylamino-4-(4-chlorophenyl)-7-(diethylamino)-4*H*-chromene-3-carboxylate* **(13)**: Yellow needles, m.p. 170–171 °C; 83%; IR (KBr) υ (cm^{-1}): 3300, 3217 (NH), 3088, 3021, 2972, 2927, (CH stretching), 1698, 1677 (CO); ^{1}H NMR (500 MHz) ($CDCl_3$) δ: 11.02 (bs, 1H, NH), 7.20–6.21 (m,7H, aromatic), 4.79 (s, 1H, H-4), 4.04 (q, 2H, CH_2, *J* =7.5 Hz), 3.25 (q, 4H, $2CH_2$, *J* = 7.1 Hz), 1.60 (s, 3H, $COCH_3$), 1.09 (t, 3H, CH_3, *J* =7.5 Hz),1.08 (t, 6H, $2CH_3$, *J* = 7.1 Hz); ^{13}C NMR (125 MHz) ($CDCl_3$) δ: 168.09 (CO ester), 159.80 (CO), 153.15 (C-2), 148. 89 (C-8a), 147.83 (C-7), 129.82 (C-5), 110.38 (C-4a), 109.72 (C-6), 98.02 (C-8), 86.50 (C-3), 60.73 (CH_2 ester), 44.40 (CH_2), 39.00 (C-4), 29.71 (CH_3 acetyl),14.06 (CH_3 ester), 12.49 (CH_3) 145.57, 132.02, 129.01, 128.48 (aromatic) ; MS *m/z* (%): 444 [M^++2], (13), 442 [M]$^+$, (32.5), 331 (58.), 289 (100), 243 (56), 199 (16), 150 (19), 115 (13), 77 (20). Anal. Calcd for $C_{24}H_{27}ClN_2O_4$: C, 65.08; H, 6.14; N, 6.32. Found: C, 65.15; H, 6.20; N, 6.45%.

Reaction of 12 with hydrazine derivatives: A mixture of **12** (0.01 mmol), hydrazine hydrate (0.01 mmol) in EtOH was stirring at room temperature or reflux for 1 h to give *β*-enaminoester **(3b)** (m.p. and mixed m.p.) yield (81%).

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