Journal of Applied Pharmaceutical Science Vol. 10(12), pp 035-043, December, 2020
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2020.101205
ISSN 2231-3354

Synthesis and cytotoxic evaluation of novel chromenes and chromene(2,3-d)pyrimidines

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ARTICLE INFO

Received on: 18/08/2020
Accepted on: 16/10/2020
Available online: 05/12/2020

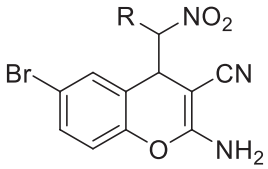
Key words:
Tetrahydrochromenes, chromene(2,3-*d*)pyrimidines, chromenotriazolopyrimidine, pyrimidines, triazolopyrimidine, cytotoxic activity.

ABSTRACT

The synthesis of novel compounds starting from 2-amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **2** has been studied. Diarylidene cyclohexanone reacts with malononitrile to afford compound **2**. Compound **2** reacts with benzoyl chloride to afford compound **3**. *N*-(8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-3-cyano-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)benzamide **3** reacts with acetic anhydride to afford compound **4**. Compound **2** reacts with acetic anhydride to afford 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-*d*]pyrimidin-4-one **5**. Chromene derivative **2** reacts with formic acid to give compound **6**. Compounds **4–6** react with phosphorus oxychloride to give compounds **7a–c**. Chromeno[2,3-*d*]pyrimidine derivatives **7a–c** react with hydrazine hydrate to afford compounds **8a–c**. Chromeno[2,3-*d*]pyrimidine derivatives **8a,b** react with xylose and glucose to give compounds **9a–d**. Chromeno[2,3-*d*]pyrimidine derivatives **9a–d** react with acetic anhydride to give compounds **10a–d**. Screening of most of the synthesized compounds against A-549, CaCo-2, and HT-29 cell lines were done. 2-Amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **2** gives high cytotoxic activity against A-549 and HT-29 cancer cell lines as compared to doxorubicin as the reference drug.

INTRODUCTION

Chromenes have recently gained the attention of many researchers due to their various applications. Chromene derivatives have shown different remarkable biological activities against various targets. 4-Substituted-4*H*-chromenes have shown significant anticancer activity (Aridoss *et al*., 2012). Also, 4-substituted-4*H*-chromenes have anticoagulant activity (Bonsignore *et al*., 1993) and are used as regulators of the potassium cation channel (Jin *et al*., 2004). 2-Amino-6-bromo-4-(nitromethyl)-4*H*-chromene-3-carbonitrile (**Ia**) and 2-amino-6-bromo-4-(1-nitroethyl)-4*H*-chromene-3-carbonitrile (**Ib**) have afforded good cytotoxic activity with IC_{50}<4 µg/ml and they have activity four times more than the standard drug Etoposide (Zonouzi *et al*., 2013).



I a,b
a, R=H
b, R=CH3

In addition, 4*H*-chromene derivatives have shown spasmolytic, diuretic, anticoagulant, and antianaphylactic activities (Ghorbani-Vaghei *et al*., 2011). 4*H*-Chromene derivatives bind to the Bcl-2 protein and initiate apoptosis in cancer cells. The Bcl-2 protein improves neoplastic cell proliferation by preventing normal cell turnover. Increasing Bcl-2 gene expressions are present in many types of human cancers and can result in cancer cell resistance to chemotherapy and radiotherapy. Therefore, Bcl-2 protein-binding compounds are promising compounds as anticancer agents (Ghorbani-Vaghei *et al*., 2011).

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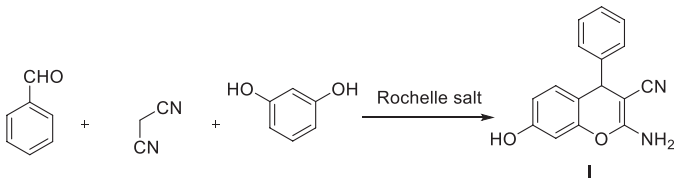
Aminochromene derivatives have also shown antihypertensive and anti-ischemic behavior (Ghorbani-Vaghei *et al*., 2011).

Chromenes are also used as food additives, cosmetic agents, and potent biodegradable agrochemical (Subbareddy *et al*., 2017). They are used as antifungal, anti-HIV, antimalarial, antibacterial, antioxidant, and anti-influenza virus agents (Subbareddy *et al*., 2017). The chromene derivative MX58151 has been used in the treatment of drug-resistant cancers (Fig. 1) (Subbareddy *et al*., 2017). In addition, chromene derivative EPC2407 is used in phase I/II clinical trials as a vascular disrupting anti-tumoral drug for the treatment of advanced solid tumors (Fig. 1) (Subbareddy *et al*., 2017). Chromene derivative HA14-1 is used as an inhibitor of acute myeloid leukemia. Ethyl 2-amino-4-(1*H*-indol-3-yl)-4*H*-chromene-3-carboxylate **II** is used as an anti-human immunodeficiency virus reverse transcriptase (anti-HIV-1 RT) (Fig. 1) (Subbareddy *et al*., 2017). *N*-(4-Chlorophenyl)-8-methoxy-2-methyl-4-(2-methyl-1*H*-indol-3-yl)-4*H*-chromene-3-carboxamide **III** has high antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*. Compound **III** has a minimum inhibitory concentration in the range of 9.3–18.7 mg/ml (Subbareddy *et al*., 2017).

The pyranopyrimidines have also shown various pharmacological activities, e.g., antibacterial activity, antifungal activity, antigenotoxic activity, antiplatelet activity, antithrombotic activity, and analgesic and anti-inflammatory activity (Chaker *et al*., 2017).

All the aforementioned biological activities and our previous work (El-Gazzar *et al*., 2008; Fayed and Yousif, 2019; Fayed *et al*., 2019a, 2019b; Nemr *et al*., 2019; Soliman *et al*., 2014; Yousif *et al*., 2017; 2018, Yousif *et al*., 2019,; 2019a; 2019b; 2019c; 2020; 2021) directed us to prepare novel chromene derivatives and measure the cytotoxic activity of the prepared compounds.

4-*H*-Chromene derivative **(I)** has been synthesized from aromatic aldehyde, malononitrile, and phenol derivatives in a one-pot three-component reaction (El-Maghraby *et al*., 2014).



I

Experimental section

The apparatus used was as in a previously reported study (Yousif *et al*., 2019b). Compound **1** (diarylidene cyclohexanone) was prepared according to previously known literature (Kumar *et al*., 2011).

2-Amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 2

A mixture of diarylidene cyclohexanone (0.01 mmol.), malononitrile (0.01), and 5-ml triethylamine in 50 ml absolute ethanol was refluxed for 8 hours. Then, the reaction mixture was cooled and filtered. The precipitate was crystalized from ethanol. Yield: 95%; m.p. 244–246°C; IR (KBr) cm^{-1}, ν: 2,215 (CN), 3,210 (NH_2); ^{1}H NMR (DMSO) δ/ppm: 1.74 (t, 2H, *J* =7.1 Hz, CH_2), 2.04 (t, 2H, *J* =7.1 Hz, CH_2), 2.10 (m, 2H, CH_2), 2.46 (brs, 2H, NH_2), 3.91 (s, 1H, CHAr), 5.23 (s, 1H, CH=), 7.27–7.51 (m, 8 H, Ar). ^{13}C NMR (DMSO) δ/ppm: 22.19, 26.97, 27.06 ($3CH_2$), 39.38 (CH), 115.8, 119.8, 120.6, 127.3, 128.5, 129.24, 129.27, 129.7, 129.9, 130.9, 131.4, 131.5 (12 aromatic C=), 132.8 (CN), 133.3, 135.2, 135.4 (3 C=), 141.27 (=C-O), 160.6 (=CNH_2). MS (*m/z*): 409.3 (M+, 23%). Anal. calcd. for $C_{30}H_{22}Cl_2N_2O_2$: C, 70.18; H, 4.32; N, 5.46; Found: C, 70.43; H, 4.50; N, 5.67.

N-(8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-3-cyano-5,6,7,8-tetrahydro-4*H*-chromen-2-yl)benzamide 3

A mixture of compound **2** (0.01 mol) and benzoyl chloride (0.01 mol) in 50-ml pyridine was refluxed for 4 hours. The reaction mixture was cooled and filtered. The precipitate crystalized from ethanol. Yield: 50%; m.p. 184°C–186°C; IR (KBr) cm^{-1}, ν: 1,660 (C=O), 2,215 (CN), 3,210 (NH); ^{1}H NMR (DMSO) δ/ppm: 1.51 (t, 2H, *J* =7.1 Hz, CH_2), 1.84 (t, 2H, *J* =7.1 Hz, CH_2), 1.93 (m, 2H, CH_2), 2.34 (brs, 1H, NH), 4.10 (s, 1H, CHAr), 4.41 (s, 1H, CH=), 7.12–7.40 (m, 13H, Ar). ^{13}C NMR (DMSO) δ/ppm: 21.0, 24.92, 26.02 ($3CH_2$), 40.20 (CH), 110.10, 116.20, 118.1,118.4, 118.40, 124.80, 125.3, 126.1, 126.48, 127.8, 128.15, 129.57, 129.60, 129.91, 130.30, 130.9, 131.32, 131.40 (18 aromatic C=), 131.6 (CN), 132.1, 133.2, 134.1 (3 aromatic C=), 141.27 (=C-O), 160.6 (=CNH), 165.23 (C=O). MS (*m/z*): 513.4 (M+, 17%). Anal. calcd. for $C_{30}H_{22}Cl_2N_2O_2$: C, 70.18; H, 4.32; N, 5.46; Found: C, 70.43; H, 4.50; N, 5,67.

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-d]pyrimidin-4-one 4

A mixture of compound **3** (0.01) and 30-ml acetic anhydride was refluxed for 12 hours. The reaction mixture was cooled and filtered. The precipitated filtered crystallized from ethanol. Yield: 56%; m.p. 270–272°C; IR (KBr) cm^{-1}, ν: 1,675 (C=O), 1,620 (C=N); ^{1}H NMR (DMSO) δ/ppm: 1.21 (t, 2H, *J*=7.1 Hz, CH2), 1.64 (t, 2H, *J* =7.1 Hz, CH2), 1.73 (m, 2H, CH2), 2.51 (brs, 1H, NH), 4.10 (s, 1H, CHAr), 4.73 (s, 1H, CH=), 7.21–7.35 (m, 13H, Ar). MS (*m/z*): 513.4 (M+, 29%). Anal. calcd. for $C_{30}H_{22}Cl_2N_2O_2$: C, 70.18; H, 4.32; N, 5.46; Found: C, 70.20; H, 4.42; N, 5.49.

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-d]pyrimidin-4-one 5

A mixture of compound **2** (0.01 mol) and 30-ml acetic anhydride was refluxed for 10 hours. The reaction mixture was cooled and filtered. The precipitate crystalized from ethanol. Yield: 55%; m.p. 260°C–262°C; IR (KBr) cm^{-1}, ν: 1,655 (C=O), 1,630 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.32 (t, 2H, *J* =7.1 Hz, CH_2), 1.51 (t, 2H, *J* =7.1 Hz, CH_2), 1.62 (m, 2H, CH_2), 1.70 (s, 3H, CH_3), 2.91 (brs, 1H, NH), 3.80 (s,1H, CHAr), 4.91 (s, 1H, CH=), 7.32–7.45 (m, 8H, Ar); MS (*m/z*): 451.3 (M^+, 31%). Anal. calcd. for $C_{25}H_{20}Cl_2N_2O_2$: C, 66.53; H, 4.47; N, 6.21; Found: C, 66.63; H, 4.50; N, 6.29.

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-d]pyrimidin-4-one 6

A mixture of compound **2** (0.01 mol) and 30-ml formic acid was refluxed for 10 hours. The reaction mixture was cooled

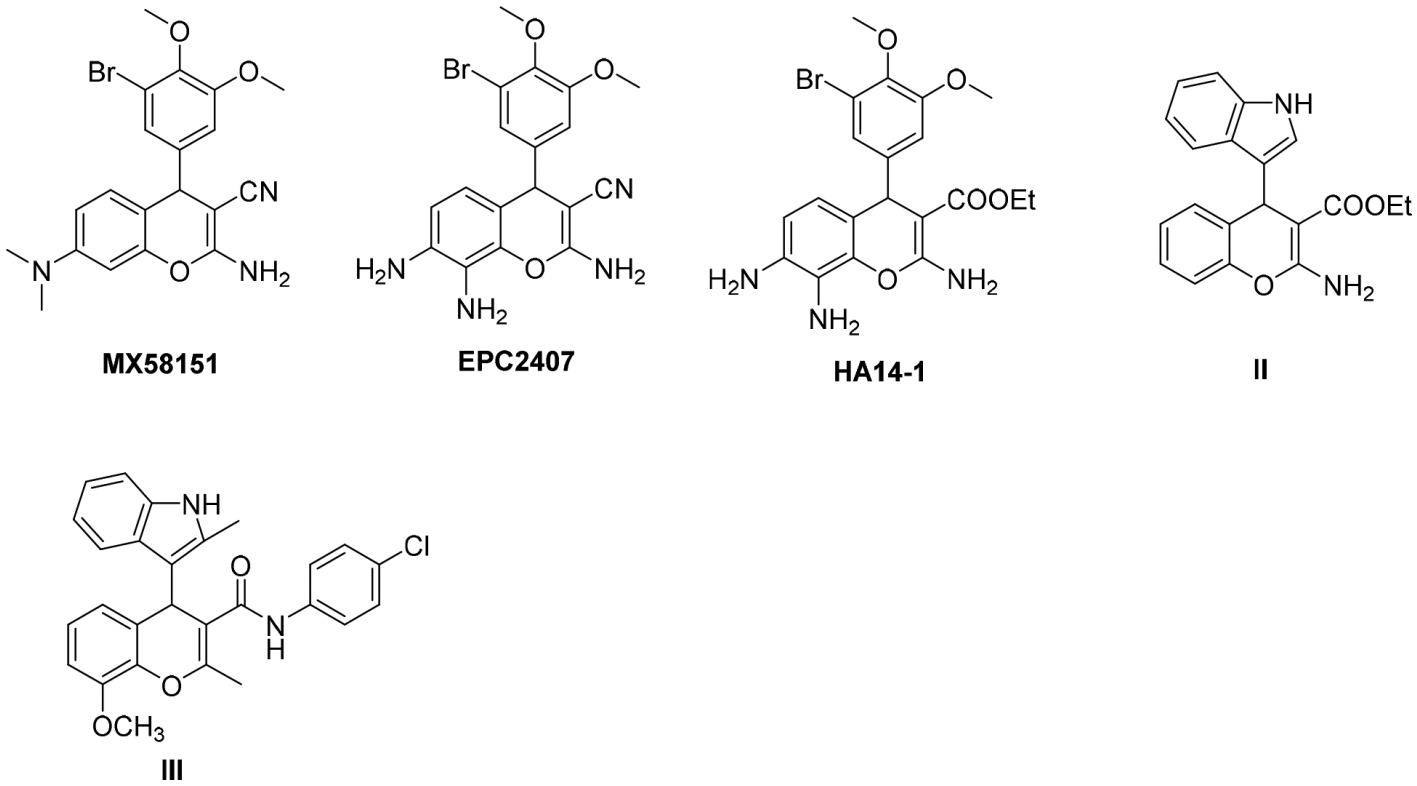


Figure 1. Chemical structures of biological active chromenes.

and filtered. The precipitate crystalized from ethanol. Yield: 60%; m.p. 224°C–226°C; IR (KBr) cm^{-1}, ν: 1,675 (C=O), 1,615 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.41 (t, 2H, *J* =7.1 Hz, CH_2), 1.62 (t, 2H, *J* =7.1 Hz, CH_2), 1.75 (m, 2H, CH_2), 3.81(s, 1H, CHAr), 4.42 (brs, 1H, NH), 5.23 (s, 1H, CH=), 7.13–7.25 (m, 8H, Ar), 8.43 (s, 1H, NCH); ^{13}C NMR (DMSO) δ/ppm: 23.6, 23.9, 25.9 (3 CH_2), 32.4 (CHAr), 124.0, 124.9 (2 C=), 126.1, 126.8, 126.9, 127.4, 127.9, 128.3, 129.4, 130.1, 135.1, 137.2, 138.3, 139.8 (12 Ar C), 140.1, 146.9, 147.9, 148.2(4 C=)150.4 (C=N), 162.3 (C=O). MS (*m/z*): 437.3 (M^+, 41%). Anal. calcd. for $C_{24}H_{18}Cl_2N_2O_2$: C, 65.92; H, 4.15; N, 6.41; Found: C, 66.03; H, 4.20; N, 6.49.

General procedure for the preparation of compounds 7a–c

A mixture of compounds **4–6** (0.01 mol), 30-ml phosphorus oxychloride, and 2 g phosphorous pentachloride was refluxed for 6 hours. Then, the reaction mixture was cooled and filtered. The precipitate was filtered and crystalized from ethanol to give compound **7a–c**.

4-chloro-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine 7a

Yield: 50%; m.p. 100°C–102°C; IR (KBr) cm^{-1}, ν: 1,635 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.34 (t, 2H, *J* =7.1 Hz, CH_2), 1.71 (t, 2H, *J* =7.1 Hz, CH_2), 1.78 (m, 2H, CH_2), 4.20 (brs, 1H, NH), 3.95 (s, 1H, CHAr), 5.12 (s, 1H, CH=), 7.21–7.35 (m, 13H, Ar). MS (*m/z*): 531.8 (M^+, 17%). Anal. calcd. for $C_{30}H_{21}Cl_3N_2O$: C, 67.75; H, 3.98; N, 5.27; Found: C, 67.80; H, 4.01; N, 5.31.

4-chloro-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine 7b

Yield: 55%; m.p. 140°C–142°C; IR (KBr) cm^{-1}, ν: 1,615 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.16 (t, 2H, *J* =7.1 Hz, CH_2), 1.45 (t, 2H, *J* =7.1 Hz, CH_2), 1.73 (m, 2H, CH_2), 1.70 (s, 3H, CH_3), 4.01 (s, 1H, CHAr), 5.81 (brs, 1H, NH), 5.31 (s, 1H, CH=), 7.21–7.35 (m, 8H, Ar); MS (*m/z*): 469.7 (M^+, 31%). Anal. calcd. for $C_{25}H_{19}Cl_3N_2O$: C, 63.92; H, 4.08; N, 5.96; Found: C, 64.02; H, 4.15; N, 6.02.

4-chloro-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine 7c

Yield: 60%; m.p. 120°C–122°C; IR (KBr) cm^{-1}, ν: 1,628 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.20 (t, 2H, *J* =7.1 Hz, CH2), 1.71 (t, 2H, *J* =7.1 Hz, CH2), 1.95 (m, 2H, CH_2), 3.82 (brs, 1H, NH), 4.21 (s, 1H, CHAr), 5.43 (s, 1H, CH=), 7.21–7.45 (m, 8H, Ar), 8.19 (s, 1H, NCH); ^{13}C NMR (DMSO) δ/ppm: 23.4, 23.6, 24.1 (3 CH_2), 35.2 (CHAr), 123.0, 125.1 (2 C=), 127.2, 127.3, 127.4, 127.9, 128.1, 128.3, 129.9, 131.2, 134.3, 136.1, 137.1, 140.8, 145.6 (13 Ar C), 147.0, 147.1, 147.9, 148.2 (4 C=), 151.4 (C=N). MS (*m/z*): 455.7 (M^+, 35%). Anal. calcd. for $C_{24}H_{17}Cl_3N_2O$: C, 63.25; H, 3.76; N, 6.15; Found: C, 63.30; H, 3.85; N, 6.21.

General procedure for the preparation of compounds 8a–c

A mixture of compounds **7a–c** (0.01 mol), 1-ml hydrazine hydrate in 30-ml dioxane was refluxed for 4 hours.

Then, the reaction mixture evaporated under reduced pressure. The residue was crystallized from ethanol to give compounds **8a–c**.

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-4-hydrazinyl-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine 8a

Yield: 60%; m.p. 224°C–226°C; IR (KBr) cm^{-1}, ν: 1,610 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.20 (t, 2H, *J* =7.1 Hz, CH_2), 1.51 (t, 2H, *J* =7.1 Hz, CH_2), 1.78 (m, 2H, CH_2), 5.10 (brs, 3H, NH,NH_2), 3.71 (s, 1H, CHAr), 5.53 (s, 1H, CH=), 7.17–7.35 (m, 13H, Ar). MS (*m/z*): 527.4 (M^+, 20%). Anal. calcd. for $C_{30}H_{24}Cl_2N_4O$: C, 68.32; H, 4.59; N, 10.62; Found: C, 68.42; H, 4.69; N, 10.74.

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-4-hydrazinyl-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine 8b

Yield: 55%; m.p. 170°C–172°C; IR (KBr) cm^{-1}, ν: 1,615 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.23 (t, 2H, *J* =7.1 Hz, CH_2), 1.35 (t, 2H, *J* =7.1 Hz, CH_2), 1.53 (m, 2H, CH_2), 1.80 (s, 3H, CH_3), 4.30 (s, 1H, CHAr), 5.84 (s, 1H, CH=), 7.10–7.43 (m, 8H, Ar), 8.51 (brs, 3H, NH, NH2); MS (*m/z*): 465.3(M^+, 38%). Anal. calcd. for $C_{25}H_{22}Cl_2N_4O$: C, 64.52; H, 4.77; N, 12.04; Found: C, 64.61; H, 4.87; N, 12.21.

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-4-hydrazinyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine 8c

Yield: 60%; m.p. 164°C–166°C; IR (KBr) cm^{-1}, ν: 1,627 (C=N); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.31 (t, 2H, *J* =7.1 Hz, CH_2), 1.54 (t, 2H, *J* =7.1 Hz, CH_2), 1.78 (m, 2H, CH_2), 4.10 (s, 1H, CHAr), 4.32 (brs, 3H, NH, NH_2), 5.81 (s, 1H, CH=), 7.12–7.41 (m, 8H, Ar), 7.81 (s, 1H, NCH); ^{13}C NMR (DMSO) δ/ppm: 22.1, 23.4, 25.2 (3 CH_2), 36.1 (CHAr), 124.1, 126.2 (2 C=), 127.5, 127.7, 127.8, 128.0, 128.2, 128.5, 128.9, 131.9, 134.1, 136.2, 137.2, 141.5, 146.4 (13 Ar C), 147.3, 147.7, 147.9, 148.1 (4 C=), 152.4 (C=N). MS (*m/z*): 451.3 (M^+, 29%). Anal. calcd. for $C_{24}H_{20}Cl_2N_4O$: C, 63.87; H, 4.47; N, 12.41; Found: C, 63.95; H, 4.56; N, 12.59.

General procedure for the preparation of compounds 9a–d

A mixture of compounds **8a,b** (0.01 mol), 40-ml ethanol, 5-ml distilled water, 1-ml acetic acid, and glucose or xylose (0.01 mol) was refluxed for 6 hours. The reaction mixture evaporated under reduced pressure. The residue crystallized from ethanol to give compounds **9a–d**.

5-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidin-4-yl) hydrazono)pentane-1,2,3,4-tetraol 9a

Yield: 60%; m.p. 170°C–172°C; IR (KBr) cm^{-1}, ν: 1,624 (C=N), 3,210 (NH), 3,345 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.06 (t, 2H, *J*=7.1 Hz, CH_2), 1.23 (brs, 4H, 4OH), 2.62 (t, 2H, *J*=7.1 Hz, CH_2), 2.91 (m, 2H, CH_2), 3.06 (d, 1H, *J*=7.0 Hz CHO), 3.40 (q, 1H, *J* =7.0 Hz, CHO), 3.52 (t, 1H, *J* =7.0 Hz, CHO), 3.90 (s, 1H, CHAr), 4.18 (d, 2H, *J* =7.0 Hz, CH_2OH), 4.48 (brs, 1H, NH), 6.14 (s, 1H, CH=), 7.17 (d, 1H, J=6.2 Hz, NCH=), 7.25–7.34 (m, 13H, Ar). Anal. calcd. for $C_{35}H_{32}Cl_2N_4O_5$: C, 63.74; H, 4.89; N, 8.49; Found: C, 63.90; H, 4.97; N, 8.70.

6-(2-(9-(2-Chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidin-4-yl) hydrazono)hexane-1,2,3,4,5-pentaol 9b

Yield: 65%; m.p. 130°C–132°C; IR (KBr) cm^{-1}, ν: 1,635 (C=N), 3,140 (NH), 3,310 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.02 (t, 2H, *J*=7.1 Hz, CH_2), 1.13 (brs, 5H, 5OH), 2.82 (t, 2H, *J*=7.1 Hz, CH_2), 2.84 (m, 2H, CH_2), 3.02 (d, 1H, *J*=7.0 Hz, CHO), 3.33 (q, 1H, *J* =7.0 Hz, CHO), 3.49 (t, 1H, *J* =7.0 Hz, CHO,), 3.49 (t, 1H, *J* =7.0 Hz, CHO), 3.82 (s, 1H, CHAr), 4.20 (d, 2H, *J* =7.0 Hz, CH_2OH), 4.50 (brs, 1H, NH), 6.10 (s, 1H, CH=), 7.20 (d, 1H, *J*=6.2 Hz, NCH=), 7.30–7.36 (m, 13H, Ar). Anal. calcd. for $C_{36}H_{34}Cl_2N_4O_6$: C, 62.70; H, 4.97; N, 8.12; Found: C, 62.89; H, 5.10; N, 8.21.

5-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidin-4-yl) hydrazono)pentane-1,2,3,4-tetraol 9c

Yield: 70%; m.p. 220°C–222°C; IR (KBr) cm^{-1}, ν: 1,642 (C=N), 3,240 (NH), 3,325 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.12 (t, 2H, *J*=7.1 Hz, CH_2), 1.54 (brs, 4H, 4OH), 2.21 (s, 3H, CH_3), 2.31 (t, 2H, *J*=7.1 Hz, CH_2), 2.51 (m, 2H, CH_2), 3.12 (t, 1H, *J*=7.0 Hz, CHO), 3.40 (t, 1H, *J* =7.0 Hz, CHO), 3.52 (q, 1H, *J* =7.0 Hz, CHO), 3.82 (s, 1H, CHAr), 4.18 (d, 2H, *J* =7.0 Hz, CH_2OH), 4.78 (brs, 1H, NH), 6.14 (s, 1H, CH=), 7.17 (d, 1H, J=6.2 Hz, NCH=), 7.25–7.34 (m, 8H, Ar). ^{13}C NMR (DMSO) δ/ppm: 21.2, 22.1, 24.2 (3 CH_2), 37.1 (CHAr), 38.1 (CH_3), 70.1, 71.3, 73.2 (3 CHOH), 75.1 (CH_2OH), 123.1, 124.2 (2 C=), 126.5, 127.1, 127.5, 128.1, 128.5, 128.7, 128.9, 130.9, 131.1, 134.2, 136.2, 140.5, 145.4 (13 Ar C), 146.3, 146.7, 147.1, 148.2 (4 C=), 152.3, 155.2 (2 C=N). Anal. calcd. for $C_{30}H_{29}Cl_2N_4O_5$: C, 60.41; H, 4.90; N, 9.39; Found: C, 60.47; H, 5.10; N, 9.50.

6-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidin-4-yl) hydrazono)hexane-1,2,3,4,5-pentaol 9d

Yield: 75%; m.p. 194°C–196°C; IR (KBr) cm^{-1}, ν: 1,617 (C=N), 3,140 (NH), 3,442 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.02 (t, 2H, *J*=7.1 Hz, CH_2), 1.64 (brs, 5H, 5 OH), 2.31 (s, 3H, CH_3), 2.40 (t, 2H, *J*=7.1 Hz, CH_2), 2.57 (m, 2H, CH_2), 3.02 (t, 1H, *J*=7.0 Hz, CHO), 3.30 (t, 2H, *J* =7.0 Hz, 2CHO), 3.68 (q, 1H, *J* =7.0 Hz, CHO), 4.12 (s, 1H, CHAr), 4.22 (d, 2H, *J* =7.0 Hz, CH_2OH), 4.61 (brs, 1H, NH), 6.01 (s, 1H, CH=), 7.09 (d, 1H, *J*=6.2 Hz, NCH=), 7.16–7.49 (m, 8H, Ar). Anal. calcd. for $C_{31}H_{32}Cl_2N_4O_6$: C, 59.34; H, 5.14; N, 8.93; Found: C, 59.45; H, 5.20; N, 9.05.

General procedure for the preparation of compounds 10a–d

A mixture of compounds **9a–d** (0.01 mol) and 10-ml acetic anhydride was refluxed for 20 hours. Then, the reaction mixture was poured into water and the solid formed filtered, dried, and crystallized from ethanol to give compounds **10a–d**.

1-(2-Acetyl-8-(2-chlorobenzylidene)-12-(2-chlorophenyl)-5-phenyl-2,3,8,10,11,12-hexahydro-9*H*-chromeno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-yl)butane-1,2,3,4-tetrayl tetraacetate 10a

Yield: 60%; m.p. 130°C–132°C; IR (KBr) cm^{-1}, ν: 1,644 (C=N), 1,744 (C=O); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.12, 1.68 (2s, 12H, $4CH_3$), 2.01 (s, 9H, $3CH_3CO$), 2.23 (t, 2H, *J*=7.1 Hz, CH2), 2.35 (t, 2H, *J*=7.1 Hz, CH_2), 2.58 (m, 2H, CH_2), 4.28 (s, 1 H, CHAr), 4.97, 5.08, 5.14 (3 d, 3H, *J*=7 Hz, 3CHO), 5.27 (s, 1H, CH=), 5.95 (d, 1H, *J*=7 Hz, CHN), 6.10 (m, 1H, CHO), 7.19–7.47 (m, 13H, Ar). Anal. calcd. for $C_{45}H_{42}Cl_2N_4O_{10}$: C, 62.14; H, 4.87; N, 6.44; Found: C, 62.30; H, 4.96; N, 6.60.

1-(2-Acetyl-8-(2-chlorobenzylidene)-12-(2-chlorophenyl)-5-phenyl-2,3,8,10,11,12-hexahydro-9*H*-chromeno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-yl)pentane-1,2,3,4,5-pentayl pentaacetate 10b

Yield: 65%; m.p. 105°C–107°C; IR (KBr) cm^{-1}, ν: 1,631 (C=N), 1,734 (C=O); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.41, 1.72 (2s, 12H, $4CH_3CO$), 2.12 (s, 9H, $2CH_3CO$), 2.31 (t, 2H, *J*=7.1 Hz, CH_2), 2.41 (t, 2H, *J*=7.1 Hz, CH2), 2.49 (m, 2H, CH_2), 4.31 (s, 1 H, CHAr), 4.51, 5.19, 5.20 (3 d, 4H, *J*=7 Hz, 4CHO), 5.29 (m, 1H, CHOAc), 5.31 (d, 2H, CH_2OAc), 5.35 (s, 1H, CH=), 5.83 (d, 1H, *J*=7 Hz, CHN), 7.19–7.47 (m, 13H, Ar). Anal. calcd. for $C_{48}H_{46}Cl_2N_4O_{12}$: C, 61.21; H, 4.92; N, 5.95; Found: C, 61.36; H, 5.0; N, 6.10.

1-(2-Acetyl-8-(2-chlorobenzylidene)-12-(2-chlorophenyl)-5-methyl-2,3,8,10,11,12-hexahydro-9*H*-chromeno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-yl)butane-1,2,3,4-tetrayl tetraacetate 10c

Yield: 70%; m.p. 152°C–154°C; IR (KBr) cm^{-1}, ν: 1,614 (C=N), 1,746 (C=O); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.22, 1.35 (2s, 12H, $4CH_3CO$), 2.01 (s, 3H, CH_3CO), 2.10 (s, 3H, CH_3C=N), 2.13 (t, 2H, *J*=7.1 Hz, CH_2), 2.23 (t, 2H, *J*=7.1 Hz, CH_2), 2.41 (m, 2H, CH_2), 4.14 (s, 1 H, CHAr), 4.86, 5.13 (2 d, 3H, *J*=7 Hz, 2CHO), 5.19 (s, 1H, CH=), 5.81 (d, 1H, *J*=7 Hz, CHN), 6.10 (m, 1H, CHO), 7.13–7.32 (m, 8H, Ar). ^{13}C NMR (DMSO) δ/ppm: 20.1, 21.4, 25.7 (3 CH_2), 36.7 (CHAr), 38.2, 38.3, 38.6, 39.3, 39.7, 50.9 (6 CH_3), 60.1, 60.9, 73.6 (3 CHOAc), 74.3 (CH_2OH), 121.1, 122.4 (2 C=), 124.8, 126.2, 126.7, 127.2, 127.7, 128.2, 128.1, 130.1, 130.9, 134.7, 135.1, 139.4, 145.9 (13 Ar C), 146.1, 146.4, 147.3, 148.1 (4 C=), 151.3, 154.1 (2 C=N), 161.2 (C=O). Anal. calcd. for $C_{40}H_{40}Cl_2N_4O_{10}$: C, 59.48; H, 4.99; N, 6.94; Found: C, 59.60; H, 5.10; N, 7.16.

1-(2-Acetyl-8-(2-chlorobenzylidene)-12-(2-chlorophenyl)-5-methyl-2,3,8,10,11,12-hexahydro-9*H*-chromeno[3,2-e][1,2,4]triazolo[4,3-c]pyrimidin-3-yl)pentane-1,2,3,4,5-pentayl pentaacetate 10d

Yield: 75%; m.p. 120°C–122°C; IR (KBr) cm^{-1}, ν: 1,632 (C=N), 1,748 (C=O); ^{1}H NMR ($CDCl_3$) δ/ppm: 1.11, 1.28 (2s, 12H, $4CH_3CO$), 2.05 (s, 3H, $2CH_3CO$), 2.12 (s, 3H, CH_3C=N), 2.14 (t, 2H, *J*=7.1 Hz, CH2), 2.35 (t, 2H, *J*=7.1 Hz, CH_2), 2.48 (m, 2H, CH_2), 4.30 (s, 1 H, CHAr), 4.39 (d, 2H, CH_2OAc), 4.86, 5.13, 5.24 (3 d, 3H, *J*=7 Hz, 2CHO), 5.28 (s, 1H, CH=), 5.62 (d, 1H, *J*=7 Hz, CHN), 6.10 (m, 1H, CHOAc), 7.24–7.46 (m, 8H, Ar). Anal. calcd. for $C_{43}H_{44}Cl_2N_4O_{12}$: C, 58.71; H, 5.04; N, 6.37; Found: C, 58.90; H, 5.19; N, 6.50.

Cytotoxic activity

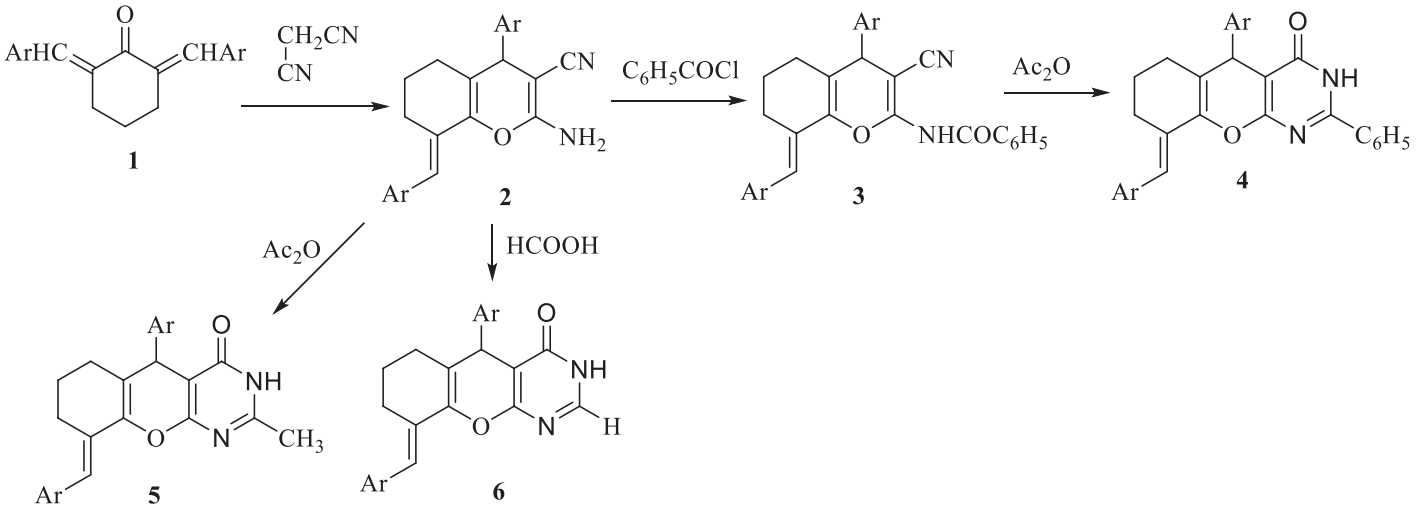
The cytotoxic activity was carried out based on a previously reported procedure (Yousif *et al*., 2019c).

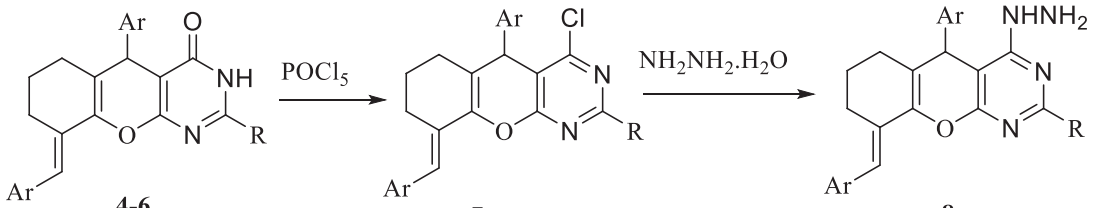
RESULTS AND DISCUSSION

Diarylidene cyclohexanone **1** reacts with malononitrile in triethylamine to produce 2-Amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **2**. Compound **2** has been previously reported (Wang *et al*., 2004a; Jin *et al*., 2005; Wang *et al*., 2004b; Kumar *et al*., 2011). The method of preparation of compound **2** was a modified method, by using triethylamine as a weak base instead of sodium methoxide in a solvent-free reaction. The proposed structure is in agreement with spectral data. The IR of compound **2** shows the absorption band for CN group and NH_2 group and shows the disappearance of carbonyl group absorption band. Mass spectroscopy for compound **2** shows a molecular ion peak at *m/z* 409.

2-amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 2 reacts with benzoyl chloride to afford *N*-(8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-3-cyano-5,6,7,8-tetrahydro-4*H*-chromen-2-yl) benzamide **3**. Compound **3** is heated under reflux in acetic anhydride to give 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-*d*] pyrimidin-4-one **4**. Also, 2-amino-8-(2-chlorobenzylidene)-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **2** is heated under reflux in acetic anhydride to give 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-*d*]pyrimidin-4-one **5**. Compound **2** reacts with formic acid to afford 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-3,5,6,7,8,9-hexahydro-4*H*-chromeno[2,3-*d*]pyrimidin-4-one **6**. The spectral data of compounds **3–6** are compatible with the proposed structure. The IR spectrum of compound **3** shows the absorption band for carbonyl group. The ^{13}C NMR of compound **3** shows a characteristic signal for carbonyl group at δ 165.23 ppm. The IR of compound **4** shows the disappearance of the absorption band for cyano group (CN). The mass spectrum for compound **4** shows a molecular ion peak at *m/z* 513. The IR spectrum of compounds **5,6** shows the disappearance of the absorption band of cyano functional group. The mass spectrum of compound **5** shows a molecular ion peak at *m/z* 451. The ^{13}C NMR of compound **6** shows a signal at δ 162.3 ppm characteristic for carbonyl group.

Chlorination of compounds **4–6** using phosphorous pentachloride and phosphorus oxychloride affords 4-chloro-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidine **7a**, 4-chloro-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidine **7b**, and 4-chloro-9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine **7c** respectively. Also, compounds **7a–c** react with hydrazine hydrate to give

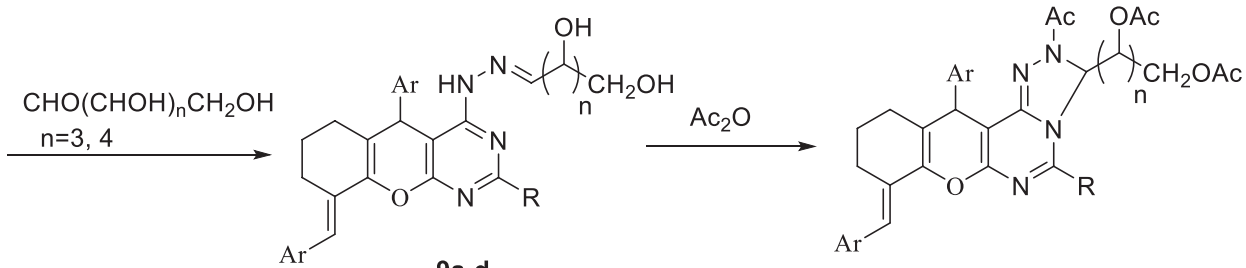




4-6
4, R=C_6H_5
5, R=CH_3
6, R=H

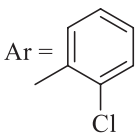
7a-c
a, R=C_6H_5
b, R=CH_3
c, R=H

8a-c
a, R=C_6H_5
b, R=CH_3
c, R=H



9a-d
a, R=C_6H_5, n=3
b, R=C_6H_5, n=4
c, R=CH_3, n=3
d, R=CH_3, n=4

10a-d
a, R=C_6H_5, n=3
b, R=C_6H_5, n=4
c, R=CH_3, n=3
d, R=CH_3, n=4



Scheme 1

9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-4-hydrazinyl-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidine **8a**, 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-4-hydrazinyl-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidine **8b**, and 9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-4-hydrazinyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-d]pyrimidine **8c**, respectively. The structures of compounds **7a–c** and **8a–c** were elucidated from ^{1}H NMR, IR, and mass spectral data. The IR of compounds **7a–c** shows the disappearance of the absorption band of carbonyl function group. The ^{13}C NMR of compound **7c** shows the disappearance of signal for carbonyl group. Also, the IR of compounds **8a–c** shows the appearance of the absorption band of NH, NH_2 groups. The mass spectrum of compound **8a** shows a molecular ion peak at *m/z* 527.

Compounds **8a–b** react with xylose and glucose to afford 5-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidin-4-yl)hydrazono) pentane-1,2,3,4-tetraol **9a**, 6-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-phenyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidin-4-yl)hydrazono) hexane-1,2,3,4,5-pentaol **9b**, 5-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidin-4-yl)hydrazono) pentane-1,2,3,4-tetraol **9c**, and 6-(2-(9-(2-chlorobenzylidene)-5-(2-chlorophenyl)-2-methyl-6,7,8,9-tetrahydro-5*H*-chromeno[2,3-*d*]pyrimidin-4-yl)hydrazono)hexane-1,2,3,4,5-pentaol **9d**, respectively. In addition, compounds **9a–d** were acetylated using acetic anhydride to afford acetylated sugar derivatives **10a–d**. The spectral data of compounds **9a–d** and **10a–d** are compatible with the proposed structure. The IR spectrum of compounds **9a–d** shows the absorption band for hydroxyl group. Also, the IR of compounds **10a–d** shows the absorption band for carbonyl group and disappearance of absorption band for hydroxyl group, indicating acetylation of hydroxyl groups of compounds **9a–d**. The ^{13}C NMR of compound **10c** shows a signal at δ 161.2 ppm indicating carbonyl function group.

Cytotoxic activity

The cytotoxic activity of the new synthesized compounds was carried out against three different cancer cell lines, namely adenocarcinomic human alveolar basal epithelial cells A-549, human epithelial colorectal adenocarcinoma cells CaCo-2, and human colorectal adenocarcinoma cell line HT-29, using (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (Yousif *et al*., 2019c). The results are presented in Table 1 as cytotoxic activity of the synthesized compounds at 100 μM on the three cell lines. The results show that compounds **9b**,**d** and **10b**,**d** have moderate cytotoxic activity toward A-549 cell lines when compared to doxorubicin as the reference drug. Compounds **3–6**, **7b**, and **8a–b** have a weak cytotoxic activity toward A-549 cell lines. Compound **2** has high cytotoxic activity toward CaCo-2 cell lines when compared to doxorubicin as the reference drug. Compounds **5**, **6**, **9b**, and **10b** have a weak cytotoxic activity toward CaCo-2 cell lines. Compound **2** shows high cytotoxic activity toward HT-29 cell lines. Compounds **3**, **5**, **6**, **7a–b**, **8a–b**, **9b**,**d**, and **10b**,**d** show a weak cytotoxic activity toward HT-29 cell lines.

Table 1. Percentage cytotoxicity of compounds on human tumor cancer cell lines at 100 μM.

Compound	A-549	CaCo-2	HT-29
2	–	88.3 ±1.3	76.4 ± 1.6
3	16.6 ± 4.6	–	33.1 ± 4.1
4	17.3 ± 10.6	0	0
5	27.4 ± 6.9	0.7 ± 0.9	2.0 ± 1.4
6	37.4 ± 8.8	24.6 ±4.1	20.4 ± 2.9
7a	–	–	5.1 ± 3.8
7b	21.0 ± 2.5	0	3.3 ± 1.7
8a	10.2 ± 6.5	–	10.3 ± 8.1
8b	25.3 ± 1.5	0	9.9 ± 3.5
9b	45.9 ± 5.7	7.5 ± 2.2	0.5 ± 0.9
9d	47.8 ± 0.3	–	32.9 ± 6.6
10b	44.8 ± 10.1	7.0 ± 4.2	8.7 ± 11.8
10d	52.5 ± 21	0	3.0 ± 2.2
Doxorubicin	100	100	100

$p \leq 0.01$, $n = 3$.
*Results are shown as average percentage cytotoxicity ± standard deviation.

From the aforementioned biological activity, we can deduce the structural activity relationship. The presence of the amino group at position 2 and the cyano group at position 3 in compound **2** increases the cytotoxic activity toward CaCo-2 and HT-29 cell lines. The presence of the hydrazine group linked to glucose in compounds **9b**,**d** makes the cytotoxic activity moderate toward A-540 cell lines. The presence of the triazolo ring linked to acetylated glucose in compound **10b**,**d** makes the cytotoxic activity moderate toward A-549 cell lines. The disappearance of the amino group in compound **3** and the presence of the pyrimidine ring linked to chromene afford a weak cytotoxic activity toward A-549 cell lines. The presence of the pyrimidine ring linked to chromene and chlorine atom at position 4 in compound **7b** makes cytotoxic activity weak toward A-549 cell lines. Also, the presence of the pyrimidine ring linked to chromene and hydrazine function group at position 4 in compound **8a,b** makes the cytotoxic activity weak toward A-549 cell lines. The presence of the pyrimidine ring linked to chromene in compounds **5**,**6** makes the cytotoxic activity toward CaCo-2 cell lines weak. Also, the presence of the pyrimidine ring linked to the chromene and hyrazino function group and linked to glucose in compound **9b** makes cytotoxic activity weak towards CaCo-2 cell lines. In addition, the presence of the pyrimidine ring and triazolo ring linked to chromene and acetylated glucose in compound **10b** makes the cytotoxic activity weak toward CaCo-2 cell lines.

CONCLUSION

Novel compounds derived from chromene have been synthesized and structurally elucidated using mass spectroscopy, infrared, and nuclear magnetic resonance spectroscopy. Screening of most of the synthesized compounds against A-549, CaCo-2, and HT-29 cell lines has been made.

ACKNOWLEDGMENTS

The authors acknowledge the National Research Centre for providing the chemicals needed for this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

The authors received funding for this paper from National Research centre internal project number 12010104.

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How to cite this article:
Yousif MNM, El-Gazzar AR, Fayed AA, El-Manawaty MA, Yousif NM. Synthesis and cytotoxic evaluation of novel chromenes and chromene(2,3-d)pyrimidines. J Appl Pharm Sci, 2020; 10(12):035–043.