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# Synthesis and Biological Evaluation of Novel Quinazoline, Chromene and Chromeno[2,3-d]pyrimidine Derivatives

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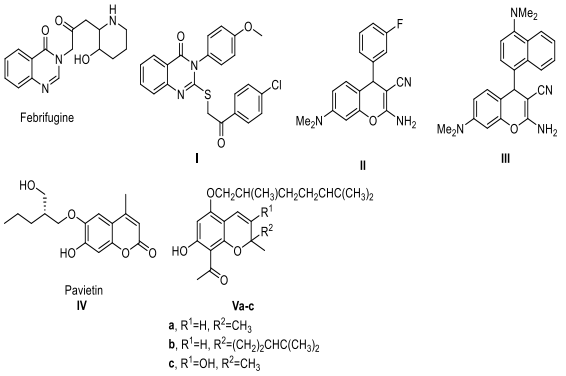
**Abstract**

2-(2-Chlorobenzylidene)cyclohexan-1-one reacts with various organic reagents. It reacts with guanidine and aminoguanidine to give the quinazoline derivatives 1a,b. 2-(2-Chlorobenzylidene)cyclohexan-1-one reacts with urea and malononitrile to afford chromene derivatives 2 and 3 respectively. Chromene derivative 3 reacts with formic acid and acetic acid to give chromeno[2,3-d]pyrimidine derivatives 4a and b respectively. Also, chromene derivative 3 reacts with acetic acid in presence of sulphuric acid to afford the chromene derivative 5. Chromene derivative 5 reacts with benzoyl chloride to afford corresponding benzoyl derivative 6. Chromene derivative 3 reacts with triethyl orthoformate to afford chromene derivative 7 which reacts with hydrazine hydrate to afford chromeno[2,3-d]pyrimidine derivative 8. The Quinazoline derivative 1b reacts with ribose and glucose to produce quinazoline derivatives 9a,b which were acetylated using acetic anhydride to give quinazoline derivatives 10a and b respectively. Some of the prepared compounds are screened for anticancer activity against doxorubicin as reference drug.

Keywords Quinazoline, Chromene , Chromeno[2,3-d]pyrimidine, anticancer activity, antibacterial activity

## Introduction

Quinazoline derivatives have gained the attention of many researchers due to their biological activity.[1,2] They have antimicrobial, antimalarial, antioxidant, anti-inflammatory, anticonvulsant, antihypertensive, antidiabetic, and antitumor activities [3]. Also, quinazoline derivatives present in many plants, microorganisms and animals such as febrifugine which has antimalarial activity. Febrifugine is extracted from Chinese plant aseru (Dichroa febrifuga Lour) [3]. Quinazoline derivative **I** has antitumor activity [3, 4]. Also, chromene derivatives have variety of biological activities. It has anticancer, anticonvulsant, antimicrobial, anticholinesterase, antituberculosis, and antidiabetic activities [5]. Chromene derivatives **II** and **III** have potent anticancer activity with $IC_{50}$ less than 1µM and 7.4 µM respectively [5-7]. Pavietin **IV**, a natural product isolated from leaves of Aesculus pavia, has potent antifungal activity against Guignardia aesculi at three concentrations 50, 100 and 200 µM [8,9]. Chromene derivatives **Va-c** which are isolated from fruits of Melicope semecarpifolia have anti-inflammatory activity with $IC_{50}$ between 7-31 µg/mL [8,10]. Chromene derivative tecarfarin has antithrombotic effect as it reduces the level of Vitamin K-dependant coagulation factors (factors II, VII, IX, X) and prolongs prothrombin time. In addition, chromene[2,3-d]pyrimidines have different biological activities. Chromene[2,3-d]pyrimidines have high antibacterial and antifungal activity [11]. Also, chromene[2,3-d]pyrimidines have anticancer, and antioxidant activities [12]. Chromeno[2,3-d]pyrimidines have potent redox properties in the conversion of some alcohols to aldehydes and ketones [13]. All the above mentioned information directed us to synthesize of novel quinazoline, chromene and chromeno[2,3-d]pyrimidine derivatives.

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**Experimental**

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). $^1$H NMR was determined on a Jeol-Ex-400 NMR spectrometer (Jeol, Tokyo, Japan) and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal standard. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA). Microanalyses were operated using Mario El Mentar apparatus and satisfactory results were within the accepted range (±0.30 of the calculated values). Follow up the reactions and checking the purity of the compounds was made by TLC on silica gel-protected aluminium sheets (Type 60 F254, Merck). Mass spectra, and elemental analysis were done in Microanalytical Centre in Faculty of Science, Cairo University. $^1$H &$^{13}$C NMR, IR spectra, and antimicrobial activity were done in National Research Centre, Cairo, Egypt. All used chemicals were of reagent grade and were used as supplied directly unless otherwise stated**.**

*General procedure for preparation of compounds **1a,b***

A mixture of 2-(2-chlorobenzylidene)cyclohexan-1-one (0.01 mole), guanidine sulphate or aminoguanidine (0.01 mole) is refluxed with 50 mL methanol and 1.5 gm sodium metal. The volatile material was refluxed for 6 hours. Then, the reaction mixture was evaporated under reduced pressure. The residue was crystallized from acetic acid / water to give compounds **1a,b** respectively**.**

*4-(2-Chlorophenyl)-1,2,5,6,7,8-hexahydroquinazolin-2-amine **1a***

Yield: 65%; m.p. 145-147 °C; IR (KBr) cm$^{-1}$, ν: 3350 ($NH_2$), 3220 (NH); $^1$H NMR (DMSO) δ/ppm: 0.08 t (2H, J =7.1 Hz, $CH_2$), 0.87 t (2H, J =7.1 Hz, $CH_2$), 1.29 m (2H, $CH_2$), 1.43 m (2H, $CH_2$), 3.47 brs (3H, NH, $NH_2$), 4.61 s (1H, CH), 7.20-7.60 m (4 H, Ar). $^{13}$C NMR (DMSO) δ/ppm: 22.18, 26.17, 27.02, 29.30 ($4CH_2$), 80.48 (CHN), 110.7, 118.8, 120.5, 125.3, 127.3, 128.34, 129.32, 130.7, 132.7 (9 C=). MS (m/z): 261.7 ($M^+$, 33%). Anal. Calcd. for $C_{14}H_{16}ClN_3$: C, 64.24; H, 6.16; N, 16.05; Found: C, 64.31; H, 6.19; N, 16.13**.**

*4-(2-Chlorophenyl)-2-hydrazinyl-1,2,5,6,7,8-hexahydroquinazoline **1b***

Yield: 70 %; m.p. 120-122 °C; IR (KBr) cm$^{-1}$, ν: 3340 ($NH_2$), 3310 (NH), 3250 (NH); $^1$H NMR (DMSO) δ/ppm: 0.05 t (2H, J =7.1 Hz, $CH_2$), 0.80 t (2H, J =7.1 Hz, $CH_2$), 1.19 m (2H, $CH_2$), 1.53 m (2H, $CH_2$), 3.25 brs (4H, 2NH, $NH_2$), 4.50 s (1H, CH), 7.10-7.80 m (4 H, Ar). $^{13}$C NMR (DMSO) δ/ppm: 22.32, 39.91, 40.08, 40.24 ($4CH_2$), 90.02.38 (CHN), 120.09, 127.54, 129.82, 130.09, 131.31, 132.5, 135.49, 140.91, 143.24 (9 C=). MS (m/z): 276.7 ($M^+$, 41%). Anal. Calcd. for $C_{14}H_{17}ClN_4$: C, 60.76; H, 6.19; N, 20.24; Found: C, 60.81; H, 6.23; N, 20.29**.**

*4-(2-Chlorophenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one **2***

A mixture of 2-(2-chlorobenzylidene)cyclohexan-1-one (0.01 mole), and urea (0.01 mole) are refluxed in 20 mL methanol and 20 mL concentrated hydrochloric acid. The volatile materials were refluxed for 6 hours. Then, the volatile materials were evaporated under reduced pressure. The formed solid was crystallized from ethanol to give compound **2.**

Yield: 65%; m.p. 115-117 °C; IR (KBr) cm$^{-1}$, ν: 3350 (NH), 1653 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.04 t (2H, J =7.1 Hz, $CH_2$), 1.30 t (2H, J =7.1 Hz, $CH_2$), 1.50 m (2H, $CH_2$), 1.60 m (2H, $CH_2$), 1.80 brs (2H, NH), 3.75 s (1H, CH), 7.25-7.50 m (4 H, Ar). $^{13}$C NMR (DMSO) δ/ppm: 21.18, 22.17, 25.16, 25.90 ($4CH_2$), 39.38 (CHN), 116.8, 119.7, 121.5, 126.1, 127.2, 128.24, 129.31, 129.72 (8 C=), 150.27 (C=O). MS (m/z): 262,7 ($M^+$, 35%). Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66; Found: C, 64.09; H, 5.81; N, 10.72**.**

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

Compound **3** was prepared according to previously reported procedure [13]. Reported and measured melting point of compound **3** is 272-274 °C**.**

General procedure for the preparation of compounds **4a,b**

A mixture of compound **3** (0.01mole) and 20 mL of formic acid or acetic anhydride are refluxed for 6 hours. Then, the reaction mixture is evaporated under reduced pressure. The formed solid is crystallized from ethanol to give compounds **4a,b** respectively**.**

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

Yield: 60%; m.p. 225-227 °C; IR (KBr) cm$^{-1}$, ν: 3405 (NH), 1670 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.02 t (2H, J =7.1 Hz, $CH_2$), 1.30 t (2H, J =7.1 Hz, $CH_2$), 1.50 m (2H, $CH_2$), 1.60 m (2H, $CH_2$), 2.03 s (1H, CH), 2.30 brs (1H, NH), 7.30-7.50 m (4H, Ar), 7.80 s (1 H, CH=). $^{13}$C NMR (DMSO) δ/ppm: 20.19, 22.97, 25.02, 26.30 ($4CH_2$), 39.43 (CH), 126.7, 127.3, 128.9, 129.5, 129.9, 130.2, 132.14, 135.14, 135.9, 135.7, 138.2 (11 C=), 162.1 (C=O). MS (m/z): 314.7 ($M^+$, 42%). Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90; Found: C, 65.04; H, 4.89; N, 9.03**.**

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

Yield: 65%; m.p. 230-232 °C; IR (KBr) cm$^{-1}$, ν: 3360 (NH), 1658 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.05 t (2H, J =7.1 Hz, $CH_2$), 1.26 t (2H, J =7.1 Hz, $CH_2$), 1.42 m (2H, $CH_2$), 1.73 m (2H, $CH_2$), 2.03 s (1H,

CH), 2.27 s (3H, $CH_3$), 3.20 brs (1H, NH), 7.20-7.50 m (4H, Ar). $^{13}$C NMR (DMSO) δ/ppm: 21.18, 22.17, 26.14, 27.10 ($4CH_2$), 29.3 ($CH_3$), 115.1, 119.2, 121.3, 126.1, 127.3, 127.80, 129.10, 129.7, 129.9, 130.7, 131.2 (11 aromatic C=), 158.8 (C=O). MS (m/z): 328.8 ($M^+$, 23%). Anal. Calcd. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21; N, 8.52; Found: C, 65.81; H, 5.29; N, 8.60**.**

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

A mixture of compound **3** (0.01 mole), 20 mL acetic acid and 20mL concentrated sulphuric acid is refluxed for 3 hours. Then, the reaction mixture is poured into water and filtered. The formed precipitate is crystallized from ethanol to give compound **5.**

Yield: 80%; m.p. 110-112 °C; IR (KBr) $cm^{-1}$, ν: 3355 ($NH_2$), 3210 (OH), 1722 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.02 t (2H, J =7.1 Hz, $CH_2$), 1.10 t (2H, J =7.1 Hz, $CH_2$), 1.50 m (2H, $CH_2$), 1.80 m (2H, $CH_2$), 1.90 brs (3H, $NH_2$,OH), 2.10 s (1H, CHAr), 7.10-7.60 m (4 H, Ar). $^{13}$C NMR (DMSO) δ/ppm: 23.19, 24.91, 26.02, 27.10 ($4CH_2$), 29.18 (CH), 115.2, 119.2, 120.1, 126.3, 127.1, 127.24, 129.27, 129.7, 144.8, 150.1 (10 C=), 165.3 (C=O). MS (m/z): 305.7 ($M^+$, 41%). Anal. Calcd. for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58; Found: C, 62.91; H, 5.30; N, 4.63**.**

*2-Benzamido-4-(2-chlorophenyl)-5,6,7,8-tetrahydro-4H-chromene-3-carboxylic acid **6***

A mixture of compound **5** (0.01 mole), benzoyl chloride (0.01 mole) is refluxed in 20 mL pyridine for 10 hours. Then, the reaction mixture is poured into cold diluted hydrochloric acid. The formed solid is filtered and crystalized from ethanol to give compound **6.**

Yield: 70%; m.p. 95-97 °C; IR (KBr) $cm^{-1}$, ν: 3310 (OH), 3480 (NH), 1657 (C=O), 1715 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.73 t (2H, J =7.1 Hz, $CH_2$), 1.09 t (2H, J =7.1 Hz, $CH_2$), 1.20 m (2H, $CH_2$), 1.45 m (2H, $CH_2$), 2.21 s (1H, CHAr), 3.53 brs (2H, NH, OH), 7.15-7.46 m (9 H, Ar). $^{13}$C NMR (DMSO) δ/ppm: 21.19, 23.17, 24.06, 24.51 ($4CH_2$), 27.18 (CH), 114.8, 114.8, 120.6, 122.4, 122.6, 123.14, 124.27, 125.1, 126.3, 126.5, 127.1, 128.5, 128.7, 129.1 (14 aromatic C=), 141.2, 145.5 (2CHO), 163.2, 175.1 (2 C=O). MS (m/z): 409.8 ($M^+$, 53%). Anal. Calcd. for $C_{23}H_{20}ClNO_4$: C, 67.40; H, 4.92; N, 3.42; Found: C, 67.49; H, 4.97; N, 3.49**.**

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

A mixture of compound **3** (0.01 mole), and 10 mL triethylorthoformate are refluxed for 6 hours. The formed solid is filtered and crystalized from ethanol to give compound **7.**

Yield: 50 %; m.p. 145-147 °C; IR (KBr) $cm^{-1}$, ν: 2212 (CN); $^1$H NMR (DMSO) δ/ppm: 1.25 t (2H, J =7.1 Hz, $CH_2$), 1.28 t (2H, J =7.1 Hz, $CH_2$), 1.51 m (2H, $CH_2$), 1.80 m (2H, $CH_2$), 2.34 s (1H, CHAr), 2.44 t (3H, J=8 Hz, $CH_3$), 3.34 m (2H, $CH_2$), 7.10-7.60 m (4H, Ar), 8.58 s (1 H, CH=). $^{13}$C NMR (DMSO) δ/ppm: 15.2 ($CH_3$), 21.11, 22.47, 23.10, 24.12 ($4CH_2$), 37.18 (CH), 61.7 ($CH_2$), 64.1, 110.3 (2C=), 117.1, 119.4, 120.1, 121.3, 127.5, 128.14 (6 aromatic C=), 130.1 (CN), 145.2, 150.3 (2 OC=), 153.1 (CH=N). MS (m/z): 342.8 ($M^+$, 44%). Anal. Calcd. for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17; Found: C, 66.62; H, 6.09; N, 8.19**.**

*5-(2-Chlorophenyl)-4-imino-6,7,8,9-tetrahydro-4H-chromeno[2,3-d]pyrimidin-3(5H)-amine **8***

Compound **7** (0.01 mole) is dissolved in 50 mL benzene in an ice bath. Then, 2 mL hydrazine hydrate were added gradually and the volatile materials are left under room temperature for 10 hours with stirring. Then, the reaction mixture is evaporated at reduced pressure. The formed solid is crystallized from diluted ethanol to give compound **8.**

Yield: 55%; m.p. 165-167 °C; IR (KBr) $cm^{-1}$, ν: 3348 ($NH_2$), 3310 (NH); $^1$H NMR (DMSO) δ/ppm: 1.23 t (2H, J =7.1 Hz, $CH_2$), 1.51 t (2H, J =7.1 Hz, $CH_2$), 1.61 m (2H, $CH_2$), 1.86 m (2H, $CH_2$), 2.12 s (1H, CHAr), 3.56 brs (3H, NH, $NH_2$), 7.13-7.42 m (3 H, Ar), 8.30 s (1H, CH=). $^{13}$C NMR (DMSO) δ/ppm: 21.21, 22.17, 23.16, 25.10, 27.30 ($4CH_2$, CH), 90.1, 110.2 (2C=), 115.1, 119.2, 120.3, 121.4, 122.6, 123.14 (6 aromatic C=), 144.1, 153.2 (2 OC=), 153.6, 156.1 (2 C=N). MS (m/z): 328.8 ($M^+$, 35%). Anal. Calcd. for $C_{17}H_{17}ClN_4O$: C, 62.10; H, 5.21; N, 17.04; Found: C, 62.19; H, 5.26; N, 12.09**.**

**General method for preparation of compounds 9a,b**

A mixture of compound **1b** (0.01 mole) and ribose or glucose (0.01 mole) is refluxed in 40 mL ethanol, 5 mL water, and 1 mL acetic acid for 6 hours. Then, the volatile materials are evaporated under reduced pressure. The formed solid is crystallized from ethanol to give compounds **9a,b** respectively.

*5-(2-(4-(2-Chlorophenyl)-1,2,5,6,7,8-hexahydroquinazolin-2-yl)hydrazono)pentane-1,2,3,4-tetraol **9a***

Yield: 90%; m.p. 135-137 °C; IR (KBr) $cm^{-1}$, ν: 3420 (NH), 3335 (OH); $^1$H NMR (DMSO) δ/ppm: 1.20 t (2H, J =7.1 Hz, $CH_2$), 1.51 t (2H, J =7.1 Hz, $CH_2$), 1.55 brs (4H, OH), 1.80 m (2H, $CH_2$), 2.25 m (2H, $CH_2$), 3.25 t (H, J=7 Hz, CHOH), 3.50 t (1 H, J= 7 Hz, CHOH), 3.60 m (1H, CHOH), 3.80 brs (2H, 2NH), 3.90 d (2H, J=7 Hz, $CH_2$OH), 5.60 s (1H, CHN), 7.17-7.50 m (4 H, Ar), 7.80 d (1H, J=6.2 Hz, CH=). $^{13}$C NMR (DMSO) δ/ppm: 21.29, 23.17, 25.10, 25.41 ($4CH_2$), 54.18, 55.12, 60.3, 65.2 (4COH), 101.2 (CH), 110.2 (C=), 119.1, 120.2, 125.1, 127.2, 128.14, 129.13 (6 aromatic C=), 151.1, 155.6 (2 C=N), 156.2 (=CN). Anal. Calcd. for $C_{19}H_{25}ClN_4O_4$: C, 55.81; H, 6.16; N, 13.70; Found: C, 55.89; H, 6.19; N, 13.78**.**

*6-(2-(4-(2-Chlorophenyl)-1,2,5,6,7,8-hexahydroquinazolin-2-yl)hydrazono)hexane-1,2,3,4,5-pentaol* ***9b***

Yield: 70 %; m.p. 135-137 °C; IR (KBr) $cm^{-1}$, ν: 3340 (NH), 3240 (OH); $^1$H NMR (DMSO) δ/ppm: 0.10 t (2H, J =7.1 Hz, $CH_2$), 0.70 t (2H, J =7.1 Hz, $CH_2$), 0.80 brs (5H, 5OH), 1.00 m (2H, $CH_2$), 1.45 m (2H, $CH_2$), 1.70 brs (2H, 2NH), 2.40 t (3H, J=7 Hz, 3CHOH), 3.21 m (1H, CHOH), 3.90 d (1H, J=7 Hz, $CH_2$OH), 4.40 s (1H, CHN), 7.25-7.40 m (4 H, Ar), 7.50 d (1H, J=6.2 Hz, CH=). Anal. Calcd. for $C_{20}H_{27}ClN_4O_5$: C, 54.73; H, 6.20; N, 12.77; Found: C, 54.79; H, 6.28; N, 12.81**.**

**General method for preparation of compounds 10a,b**

Compounds **9a,b** (0.01 mole) are refluxed with acetic anhydride (0.01 mole) for 20 hours. Then, the volatile materials are evaporated under reduced pressure. The formed solid is washed with water and crystallized from dilute ethanol to give compounds **10a,b** respectively.

*5-(2-(4-(2-Chlorophenyl)-1,2,5,6,7,8-hexahydroquinazolin-2-yl)hydrazono)pentane-1,2,3,4-tetrayl tetraacetate* ***10a***

Yield: 70 %; m.p. 110-112 °C; IR (KBr) $cm^{-1}$, ν: 3380 (NH), 3280 (OH), 1745 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.80 t (2H, J =7.1 Hz, $CH_2$), 1.10 s (12H, 4$CH_3$), 1.25 t (2H, J =7.1 Hz, $CH_2$), 1.50 m (2H, $CH_2$), 1.60 m (2H, $CH_2$), 3.50 s (1H, CHN), 3.70 t (2H, J=7.0 Hz, 2CHOAc), 4.1 m (1H, CHOAc), 4.40 d (2H, J=6.2 Hz, $CH_2$OAc), 7.20-7.40 m (4 H, Ar), 7.8 d (1 H, J=6.2 Hz, CH=), 9.4 brs (2H, 2NH). $^{13}$C NMR (DMSO) δ/ppm: 22.18, 23.17, 24.13, 25.2 (4$CH_2$), 26.1, 26.3, 26.5, 27.1 (4 $CH_3$), 61.2, 62.4, 63.2, 63.9 (4 CO), 100.18, 101.3 (CHN, C=), 115.3, 121.6, 122.3, 123.1, 123.2, 129.27 (6 aromatic C=), 140.1, 145.3 (2 C=N), 151.2 (NC=), 175.2 (C=O). Anal. Calcd. for $C_{27}H_{33}ClN_4O_8$: C, 56.20; H, 5.76; N, 9.71; Found: C, 56.20; H, 5.81; N, 9.80**.**

*6-(2-(4-(2-Chlorophenyl)-1,2,5,6,7,8-hexahydroquinazolin-2-yl)hydrazono)-3-hydroxyhexane-1,2,4,5-tetrayl tetraacetate* ***10b***

Yield: 65%; m.p. 110-112 °C; IR (KBr) $cm^{-1}$, ν: 3340 (NH), 3280 (OH), 1740 (C=O); $^1$H NMR (DMSO) δ/ppm: 0.80 t (2H, J =7.1 Hz, $CH_2$), 1.02 s (15 H, 5$CH_3$), 1.25 t (2H, J =7.1 Hz, $CH_2$), 1.50 m (2H, $CH_2$), 1.60 m (2H, $CH_2$), 1.80 brs (2H, 2NH), 3.91 d (2H, $CH_2$OAc), 4.40 s (1H, CHN), 4.50 t (3H, J=7.0 Hz, 3 CHOAc), 5.00 m (1H, CHOAc), 7.10-7.40 m (4 H, Ar), 7.5 d (1H, J=6.2 Hz, CH=). Anal. Calcd. for $C_{28}H_{35}ClN_4O_9$: C, 55.40; H, 5.81; N, 9.23; Found: C, 55.49; H5.89; N, 9.23.

**Results and Discussion**

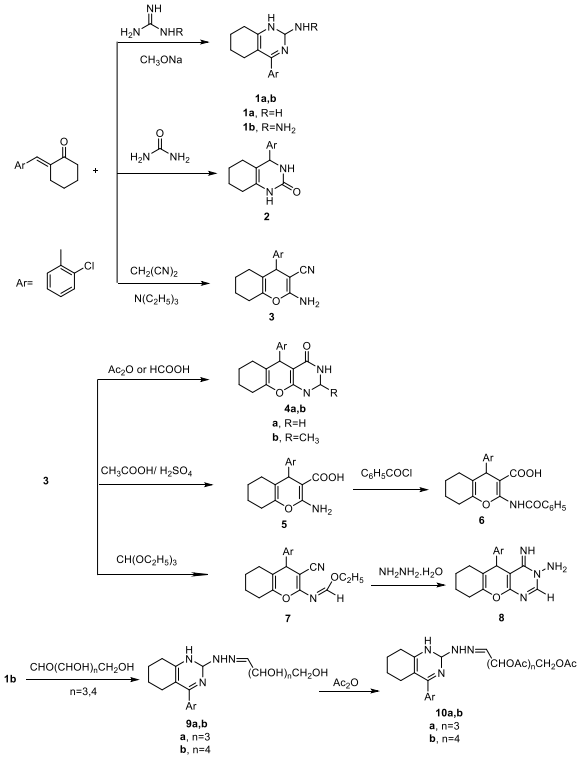
3.1 Chemistry

2-(2-Chlorobenzylidene)cyclohexan-1-one reacts with guanidine and aminoguanidine to afford hexahydroquinazoline derivatives **1a** and **b** respectively. Also, 2-(2-chlorobenzylidene)cyclohexan-1-one reacts with urea and malononitrile to afford hexahydroquinazolin-2(1H)-one **2** and tetrahydro-4H-chromene **3** respectively. Spectral data ($^1$H NMR, mass, IR) are in agreement with the proposed structures (cf. experimental). The IR spectrum of compound **1a** shows the expected absorption bands of the amino groups at 3350 and 3220 $cm^{-1}$. The IR of compound **2** shows the absorption band of the amide functional group at 1653 $cm^{-1}$. The $^1$H NMR of compound **1** shows a characteristic signal at δ 4.61 ppm for CHN. The $^{13}$C NMR of compound **2** shows signal at δ 150.2 ppm corresponding to carbonyl group**.**

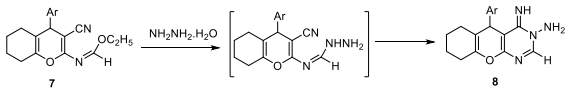
Tetrahydro-4H-chromene derivative **3** reacts with formic acid and acetic anhydride to afford hexahydro-4H-chromeno[2,3-d]pyrimidin-4-one derivatives **4a** and **4b** respectively. Also, tetrahydro-4H-chromene **3** reacts with acetic acid in sulphuric acid to afford tetrahydro-4H-chromene derivative **5** which reacts with benzoyl chloride to give compound **6**. The structures of compounds **4a-f**, **5** and **6** are elucidated from $^1$H NMR, IR, and mass spectral data. The IR spectra of compounds **4a,b** show absorption band for the amide functional group. Also, the IR spectrum of compound **5** shows absorption band for hydroxyl functional group. The IR spectra of compounds **4a,b**, **5** and **6** show disappearance of absorption band of cyano group. The $^{13}$C NMR of compound **4a** shows signal at δ 162.1 ppm corresponding to the carbonyl function group. The $^{13}$C NMR of compound **5** shows signal at δ 165.3 corresponding to carbonyl group**.**

Tetrahydro-4H-chromene **3** reacts with trietyl orthoformate to afford chromene derivative **7** which reacts with hydrazine hydrate to produce tetrahydro-4H-chromeno[2,3-d]pyrimidin-3(5H)-amine **8**. Hexahydroquinazoline derivative **1b** reacts with ribose and glucose to produce hexahydroquinazoline derivatives **9a** and **9b** which were acetylated using acetic anhydride to give hexahydroquinazoline derivatives **10a** and **10b** respectively. The spectral data of compounds **7**, **8**, **9a,b** and **10a,b** are compatible with the proposed structures. The mechanism of intramolecular cyclization of compound **8** is illustrated in scheme 2. The IR spectrum of compound **7** shows disappearance of the absorption band for the amino group. The $^1$H NMR of compound 7 shows a characteristic signal at δ 8.58 ppm corresponding to CH=N. The $^{13}$C NMR of compound 7 shows a characteristic signal at δ 153.1 corresponding to CH=N. The IR of compound **8** shows disappearance of absorption band of cyano group and shows absorption band for amino group. The $^1$H NMR of compound **8** shows a characteristic signal at δ 8.30 ppm corresponding to CH=N. The IR

spectra of compounds **9a** and **9b** show the absorption band for the hydroxyl group. The $^1$H NMR of compound **9a** shows a characteristic signal at δ 7.80 ppm corresponding to CH=N. The IR spectra of compounds **10a,b** show appearance of the absorption band of the carbonyl group and disappearance of the absorption band of the hydroxyl group. The $^1$H NMR of compound **10a** shows a characteristic signal at δ 1.10 ppm corresponding to the methyl group. The $^{13}$C NMR of compound **10a** shows a characteristic signal at δ 175.2 ppm corresponding to C=O**.**



Scheme 1



Scheme 2

3.2 Biological activity

Antimicrobial screening of the new prepared compounds were evaluated against Gram-positive bacteria (S. aureus), Gram-negative bacteria (E. coli, K. pneumoniae, Pseudomonas aeruginosa) and two fungal strains (Candida albicans and Candida glabrata) (Table 1). Activities of the tested compounds were evaluated by agar diffusion method. The MIC (minimum inhibitory concentration) of the most active compounds showed MICs ranged between 20-30 mg/disk. The activity is tested at concentration of 50 mg/disk. The minimum inhibitory concentrations (MIC) for compounds with high activity are presented in table 2. In accordance with results obtained in the primary screening, compounds **1a**, **2a,b**, **4a**, **5**, **6**, and **9a,b** show high activity towards E. Coli. Compounds **1b**, and **8** show moderate activity towards E. Coli. Compounds **1a,b**, **2a,b**, **5**, **6**, **9a,b** show high activity towards Klebsiella pneumoniae. Compound **8** has moderate activity towards Klebsiella pneumoniae. All tested compounds show high activity towards Staphylococcus aureus and Pseudomonas aeruginosa. Compound **1a** shows high activity towards Candida albicans. Compound **2b** has moderate activity towards Candida albicans. Compounds **1b**, **2a**, **4a**, **5**, **6**, **8**, and **9a,b** have slight activity towards Candida albicans. Compound **1a** has high activity towards Candida glabrata. Compound **2b** has moderate activity towards Candida glabrata. Compounds **1b**, **2a**, **4a**, **5**, **6**, **8**, and **6a,b** have slight activity towards Candida glabrata**.**

Table 1: Inhibition zone in mm as a criterion of antibacterial and antifungal activities of the newly synthesized compounds

| Comp. No. | Gram +ve bacteria | Gram –ve bacteria | | | Fungi | |
|---|---|---|---|---|---|---|
| | Staphylococcus Aureus | E. Coli | Klebsiella pneumoniae | Pseudomonas aeruginosa | Candida Albicans | Candida glabrata |
| 1a | **21** | **19** | **20** | **20** | **16** | **16** |
| 1b | **17** | **15** | **16** | **16** | **6** | **7** |
| 2a | **23** | **20** | **20** | **23** | **8** | **6** |
| 2b | **23** | **22** | **21** | **23** | **12** | **12** |
| 4a | **19** | **16** | **16** | **18** | **6** | **7** |
| 5 | **17** | **17** | **16** | **16** | **9** | **10** |
| 6 | **20** | **17** | **19** | **21** | **6** | **7** |
| 8 | **19** | **15** | **15** | **18** | **7** | **8** |
| 9a | **22** | **21** | **20** | **22** | **8** | **7** |
| 9b | **22** | **19** | **20** | **21** | **7** | **8** |
| Nystatin | - | - | - | - | **20** | **20** |
| Nalidixic acid | **25** | **25** | **25** | **25** | - | - |

Inhibition zone, 6-10 mm slight activity, 11-15 mm moderate activity, more than 15mm high activity

Table 2: MIC in mg/ml of novel synthesized compounds

| Comp. No. | Gram +ve bacteria | Gram –ve bacteria | | | Fungi | |
|---|---|---|---|---|---|---|
| | *Staphylococcus Aureus* | *E. Coli* | *Klebsiela pneumonia* | *Pseudomonas Aerognosa* | *Candida Albicans* | *Candida gabrata* |
| 1a | **30** | **30** | **30** | **30** | **30** | **30** |
| 1b | **30** | **30** | **30** | **30** | **30** | **30** |
| 2a | **30** | **30** | **30** | **30** | **30** | **30** |
| 2b | **30** | **30** | **30** | **30** | **30** | **30** |
| 4a | **20** | **20** | **20** | **20** | **40** | **40** |
| 5 | **40** | **20** | **20** | **40** | **40** | **40** |
| 6 | **30** | **30** | **30** | **30** | **30** | **30** |
| 8 | **30** | **30** | **30** | **30** | **50** | **50** |
| 9a | **30** | **30** | **30** | **30** | **30** | **30** |
| 9b | **30** | **30** | **30** | **30** | **30** | **30** |

The newly synthesized compounds were evaluated for their in vitro anticancer activity against human colon cancer (HT-29), liver cancer (HepG-2) and breast adenocarcinoma (MCF-7) cell lines by MTT assay [15]. Compound **9a** has equal potency as doxorubicin against HT-29 cell lines. Compound **2b** has more potent activity than doxorubicin against HT-29 cell lines. Compounds **1a,b**, **2a**, **4a**, **5**, **6**, **8**, **9b** have lower potency towards doxorubicin against HT-29 cell lines. Compound **2b** has nearly the same potency as doxorubicin against HePG2 cell lines. Compounds **1a,b**, **2a**, **4a**, **5**, **6**, **8**, **9a,b** have lower potency towards doxorubicin against HePG2 cell lines. Compounds **2b**, and **9a** are more potent towards doxorubicin against MCF-7 cell lines. Compounds **1a,b**, **2a**, **4a**, **5**, **6**, **8**, **9b** have lower potency towards doxorubicin against MCF-7 cell lines**.**

Table 3: Inhibition of the growth of human colon cancer (HT-29), liver cancer (HepG-2), breast adenocarcinoma (MCF-7) by synthesized compounds

| Comp. No. | $IC_{50}$ (µmol $L^{-1}$)[a] | | |
|---|---|---|---|
| | HT-29 | HePG2 | MCF-7 |
| 1a | **1.78 ± 0.16** | **1.64 ± 0.09** | **1.54 ± 0.12** |
| 1b | **2.78 ± 0.14** | **2.51 ± 0.17** | **2.74 ± 0.21** |
| 2a | **2.14 ± 0.15** | **2.28 ± 0.26** | **2.04 ± 0.11** |
| 2b | **0.28 ± 0.16** | **0.38 ± 0.10** | **0.12 ± 0.08** |
| 4a | **3.48 ± 0.16** | **4.70 ± 0.80** | **4.06 ± 0.12** |
| 5 | **3.66 ± 0.37** | **3.50 ± 0.31** | **3.64 ± 0.23** |
| 6 | **1.50 ± 0.09** | **1.46 ± 0.12** | **1.78 ± 0.15** |
| 8 | **4.08 ± 0.31** | **5.30 ± 0.62** | **5.52 ± 0.55** |
| 9a | **0.32 ± 0.03** | **0.43 ± 0.12** | **0.08 ± 0.04** |
| 9b | **1.16 ± 0.06** | **1.97 ± 0.10** | **1.78 ± 0.12** |
| Doxorubicin | **0.32 ± 0.03** | **0.36 ± 0.02** | **0.14 ± 0.01** |

[a] $IC_{50}$= 50 % inhibitory concentration. Results are shown as mean ± SEM, n=3

**Conflicts of interest**

There are no conflicts to declare.

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