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AN EFFICIENT ROUTE FOR SYNTHESIS AND REACTIONS OF SELENO[2, 3-*c*]COUMARIN

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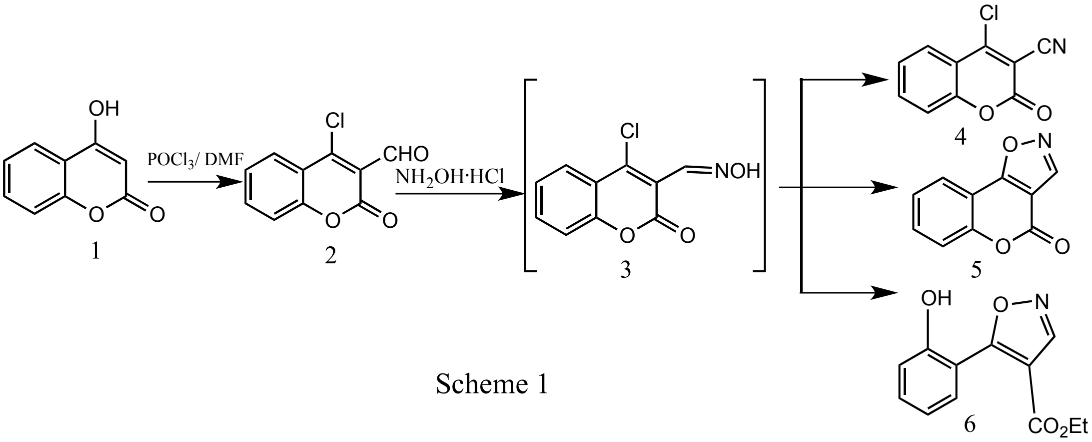
Abstract — Synthesis of new selenium-containing coumarin moiety *via* the reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbonitrile with selenium and sodium borohydride gave 3-cyano-4-coumarinselenol which reacted with different halo-acids, such as chloroacetonitrile, ethyl chloroacetate and chloroacetamide to give the corresponding 3-amino-4-oxo-4*H*-seleno[3,2-*c*]chromene derivatives. Hydrazonolysis of the obtained new ethyl 3-amino-4-oxo-4*H*-seleno[3,2-*c*]-hyphen chromene-2-carboxylate afforded the corresponding hydrazino compound. The hydrazino compound was used as a versatile precursor for synthesis of new other heterocyclic compounds containing selenocoumarin moiety. The newly synthesized compounds were characterized using the spectroscopic tools (IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy) as well as microanalysis.

INTRODUCTION

Coumarins natural and synthetic have been found to exhibit a variety of pharmacological activities like anti-HIV,[1] anticoagulant,[2] antibacterial,[3] antioxidant,[4] and anti-inflammatory.[5] Among the diverse biological activities of coumarin the most intriguing bioactivity is the effect against breast cancer. [6-9] On the other hand, in last years, many kinds of selenophene derivatives have been increased remarkably in organic synthesis due to their chemical properties and biological activities.[10-18] For example a series of selenophene derivativies are reported as potent inhibitors CHK1 kinase.[19] Therefore, many medicinal preparations have been produced on the basis of organic derivatives of selenophene. In continuation of our program on selenium containing heterocyclic systems,[14-18] here in this paper we discuss the synthesis of selenophene based on coumarin moiety to discover new useful compounds for the treatment of many diseases and act as antioxidant and anti-inflammatory agents with significant analgesic effect.

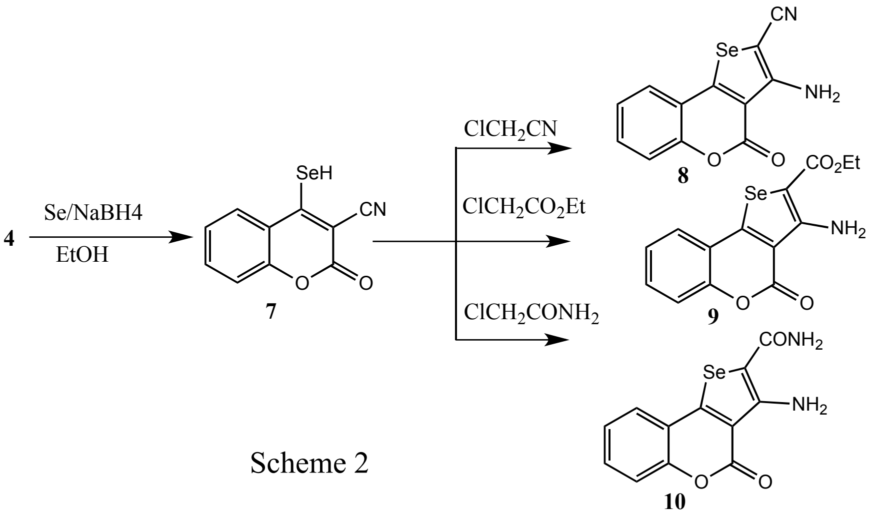
RESULTS AND DISCUSSION

To achieve our target compounds, we started from compound, 4-hydroxycoumarin (**1**), which undergoes Vilsmeier formylation onto 4-chloro-3-formylcoumarin (**2**). Compound **2** showed different reactivity depending on the reaction conditions. Its reaction with hydroxylamine gives a variety of products which described before in the last our paper.[20] The obtained products were 4-chloro-3-cyanocoumarin (**4**); 4*H*-coumarino[3,4-*d*]isoxazol-4-one (**5**); ethyl 5-(2-hydroxyphenyl)isoxazole-4-formate (**6**) via the intermediate compound (**3**) (**Scheme 1**).



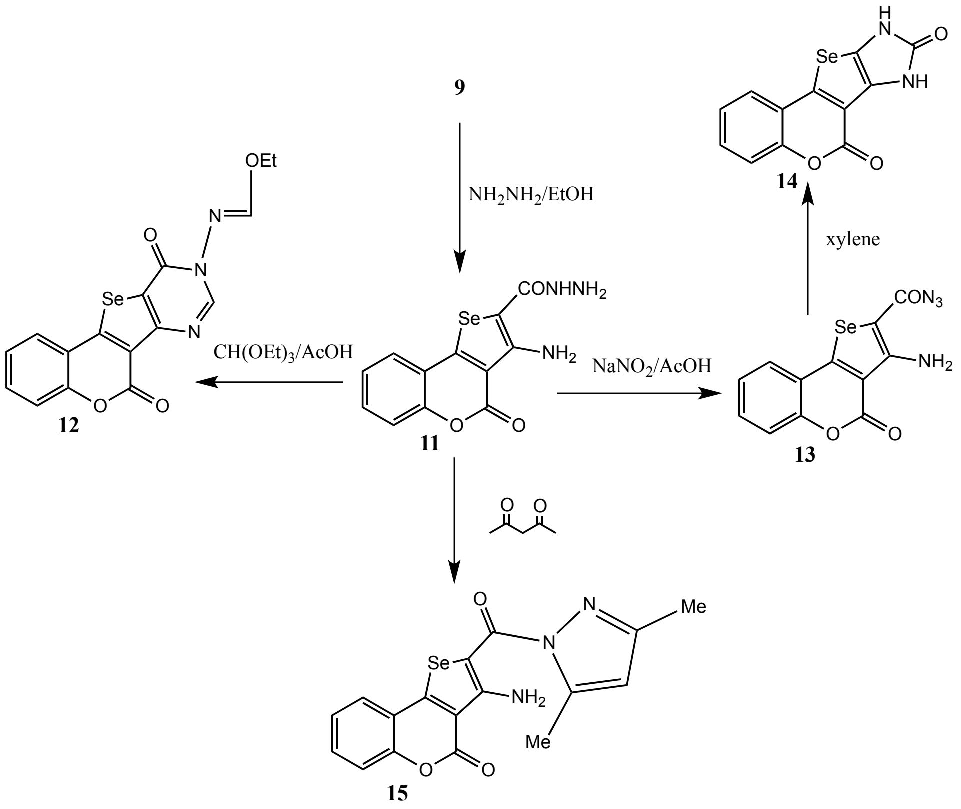
Scheme 1

Those compounds were separated in good yields by preparative TLC. Chlorocyanocoumarin **4** was used as a versatile precursor for synthesis of new 3-cyano-4-coumarinselenol (**7**) by refluxing with selenium metal and sodium borohydride in ethanol. Compound **7** was characterized by ^{1}H NMR spectrum which showed singlet peak at (δ, ppm): 14.02 due to (-SeH). Compound **7** reacted with different halo-acids such as chloroacetonitrile or ethyl chloroacetate or chloroacetamide in DMF and excess of NaOH underwent Thorpe-Ziegler cyclization to afford the corresponding compounds selenochromene carbonitrile (**8**), selenochromenecarboxylate (**9**) and selenochromenecarboximide (**10**) derivatives (**Scheme 2**). All the newly synthesized compounds **2-10** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy as well as microanalysis.



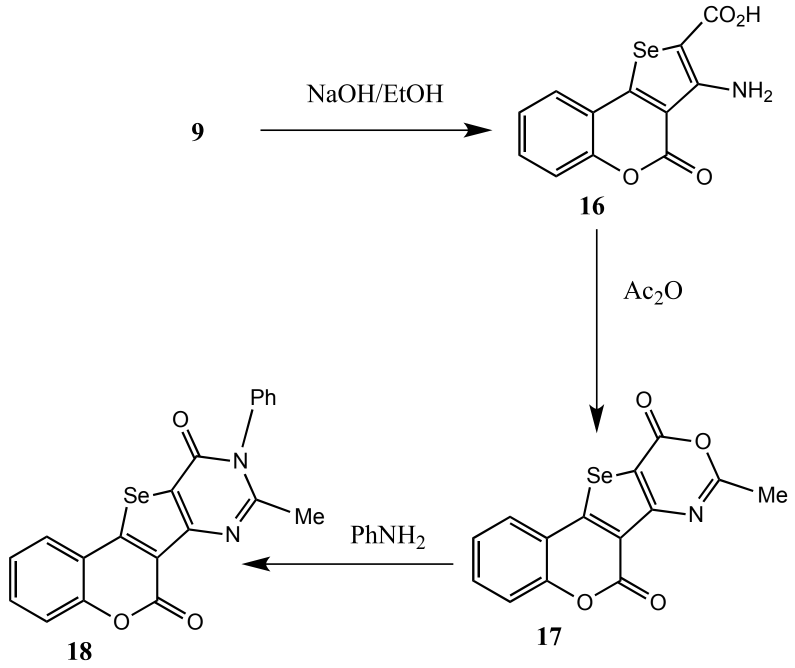
Scheme 2

Selenochromenecarboxylate **9** was used as a key in the synthesis of different new heterocyclic system based on coumarin. The reactivity of the ester group in **9** was tested *via* its hydrazonolysis with hydrazine hydrate which, afforded the corresponding selenochromenecarbohydrazide (**11**). Compound **11** would be served as precursor of other heterocyclic compounds as follows: compound **11** was reacted with triethyl orthoformate in ethanol in the presence of catalytic drops of acetic acid to give chromenoselenopyrimidine (**12**). Also, compound **11** reacted with sodium nitrite solution in acetic acid to give the corresponding carbonylazide derivative (**13**) which underwent Curtius rearrangement upon boiling in dry xylene giving chromenoselenoimidazole derivative (**14**). On the other hand condensation of carbohydrazide **11** with acetylacetone in ethanol afforded pyrazolylselenochromen derivative (**15**) (**Scheme 3**).



Scheme 3

Finally, the reaction of selenochromenecarboxylate **9** with alcoholic sodium hydroxide under reflux afforded 3-amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carboxylic acid (**16**) which reacted with acetic anhydride under reflux to give 8-methyl-6,10-dihydro-chromeno[3',4':4,5]seleno[3,2-*d*][1,3]-oxazine-6,10-dione (**17**). Refluxing of compound **17** with aniline gave 8-methyl-6,10-dihydro-7(6*H*)-chromeno[3',4':4,5]seleno[3,2-*d*]pyrimidine-6,10-dione (**18**) (**Scheme 4).**



Scheme 4

Chemical structures of all products obtained **11-18** were confirmed by IR and NMR spectroscopy, mass spectrometry and elemental microanalysis.

EXPERIMENTAL

General Methods. The melting points were determined by using the Kofler melting point apparatus, and were uncorrected. IR (KBr, cm^{-1}) spectra were recorded on a Pye-Unicam SP3–100 instrument at Taif University. ^{1}H NMR spectra were obtained on a Varian (400 MHz) EM 390 USA instrument at King Abdel-Aziz University. ^{13}C NMR spectra were recorded on a JNM-LA spectrometer (100 MHz) at King Abdel-Aziz University, Saudi Arabia. For both ^{1}H and ^{13}C NMR, DMSO-d_6 or (CDCL$_3$) was used. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q). Mass spectra were recorded on ISQ Thermo Scientific GC-MS. GC column TG-SQC, Trace GC ultra at Taif University KSA for compounds **2-6**. Purity of the compounds was checked by thin layer chromatography (TLC) using silica gel plates.

Note: Compounds **7-18** were determined by using EI-MS on JEOL-JMS-AX 500 at Cairo National Research Center Cairo, Egypt.

4-Chloro-3-coumarincarbaldehyde (2). Compound **2** was prepared as previously describe by Sabitae *et al.* with a little modification.[20-21] The pale yellow solid was collected by filtration and recrystallized from acetone to give 10.5 g (84%) of **2**; mp 133-135 °C (lit. 130 °C).[20] ^{1}H NMR (DMSO-d_6) δ, ppm: 10.39 (1H, s, CH=O), 8.16–7.28 (4H, m, Ar-H); IR ν 1720 (C=O-pyrone), 1663 (CHO) cm^{-1}. EI-MS *m/z*: 208 (M$^+$, 11), 182 (31), 180 (100), 154 (31), 152 (91), 124 (20), 101 (11), 89 (80), 63 (37), 62 (31), 61 (14); EI-HRMS: *m/z* 207.9909 (calculated for $C_{10}H_5ClO_3$ 207.9927)

3-Cyano-4-chlorocoumarin (4), 4*H*-chromeno[3,4-*d*]isoxazol-4-one (5), ethyl 5-(2-hydroxyphenyl)-isoxazole-4-carboxylate (6): were prepared as previously described.[20]

Compound **4** as yellow crystal mp 198-200 °C (Lit, 199-200 °C).[22]

4*H*-Chromeno[3,4-*d*]isoxazol-4-one (5), mp 222-224 °C; ^{1}H NMR (DMSO-d_6) δ, ppm: 10.21 (1H, s, CH-isoxazole), 8.03–7.41 (4H, m, Ar-H); ^{13}C NMR δ, ppm: 165.50, 155.04, 154.90, 152.80, 133.36, 125.29, 124.07, 117.67, 110.24, 107.83. IR ν 1761 (C=O-pyrone), 1608 (C=N) cm^{-1}. EI-MS *m/z*: 187 (M$^+$, 100), 159 (33), 131 (11), 119(4), 103 (54), 76 (26). EI-HRMS: *m/z* 187.0268 (calculated for $C_{10}H_5NO_3$: 187.0269)

Ethyl 5-(2-hydroxyphenyl)isoxazole-4-formate (6), mp 218-220 °C; ^{1}H NMR ($CDCl_3$) δ, ppm: 9.02 (1H, s, CH-isoxazole), 8.12–7.01 (4H, m, Ar-H), 4.37 (2H, q, *J*= 6.80 Hz, CH$_2$); 1.36 (3H, t, *J*= 6.80 Hz, CH$_3$).^{13}C NMR δ, ppm: 175.80, 163.49, 160.60, 155.68, 134.01, 125.66, 122.80, 118.68, 116.20.93.54, 60.29, 13.72.IR ν 1669 (C=O…H-bond), 1601 (C=N) cm^{-1}. EI-MS *m/z* 233 (M$^+$, 33), 187 (100), 159 (41), 131 (12), 119 (4), 103 (35), 76 (8); EI-HRMS: *m/z* 233.0684 (calculated for $C_{12}H_{11}NO_4$: 233.0688).

3-Cyano-4-coumarinselenol (7).

A mixture of compound **4** (2.05 g, 0.01 mol), selenium powder (1g, 0.12 mol) and $NaBH_4$ (1.2 g, 0.031 mol) were refluxed in 50 mL of EtOH for 3 h, and then the reaction mixture cooled and poured onto 50 mL crushed ice/HCl. The precipitated compound was collected, dried and recrystallized from EtOH as orange precipitate in 85% yield, mp 218-220 °C. IR: 2223 (CN), 1719 (C=O chromene) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ, ppm: 14.02 (s, 1H, SeH), 7.20–7.80 (4H, m, Ar-H). ^{13}C NMR δ, ppm: 160.1, 155.4, 128.3, 127.8, 126.8, 125.4, 119.9, 104.8, 100.4, 115.3. Mass: *m/z*: 251 [M$^+$ + 1, 27%]. Anal. Calcd for $C_{10}H_5NO_2Se$ (250.11): C, 48.02; H, 2.01; N, 5.60%. Found: C, 47.99; H, 2.00; N, 5.55%.

3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carbonitrile (8), Ethyl 3-amino-4-oxo-4*H*-seleno[3,2-*c*]-chromene-2-carboxylate (9), 3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carboximide (10)

General procedure:

A mixture of seleno compound (**7**) (2.51 g, 0.01 mol) and halo compounds (chloroacetonitrile or ethyl chloroacetate or chloroacetamide) (0.012 mol) was dissolved in DMF (30 mL) containing aq. KOH (10%, 5 mL). The reaction mixture was stirred for 1 h, after that another KOH solution (5 mL) was added and stirred for another 1 h. The precipitate product that formed was collected, dried and recrystallized from EtOH affording compounds **8-10** respectively.

3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carbonitrile (8), as a yellow crystal in 85% yield, mp 275–277 °C; IR: 3460, 3350 (NH_2), 1725 (C=O chromene), 2217 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): δ, ppm: 6.90 (2H, s, NH_2), 7.20–7.80 (4H, m, Ar-H).). ^{13}C NMR δ, ppm: 175.1, 160.1, 155.4, 128.3, 127.8, 126.8, 125.4, 119.9, 139.1, 131.5, 113.9, 75.3. Mass: *m/z*: 289 [M^+, 20%]. Anal. Calcd for $C_{12}H_6N_2O_2Se$ (289.15): C, 49.85; H, 2.09; N, 9.69%. Found: C, 49.68; H, 2.00; N, 9.54%.

Ethyl 3-amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carboxylate (9), as a yellow crystal in 88% yield, mp 200–202 °C; IR: 3470, 3367 (NH_2), 1725 (C=O chromene), 1695 (C=O ester) cm^{-1}. ^1H NMR ($CDCl_3$): δ, ppm: 1.35–1.40 (3H, J = 7.0 Hz, t, CH_3), 4.30–4.50 (2H, J = 6.0 Hz, q, CH_2), 7.19 (2H, s, NH_2), 7.20–7.80 (4H, m, Ar-H). ^{13}C NMR δ, ppm: 166.9, 165.4, 160.1, 155.4, 139.7, 131.5, 128.3, 127.8, 126.8, 125.4, 119.9, 95.6, 63.1, 14.8. Mass: *m/z*: 337 [M^+ + 1, 100%]. Anal. Calcd for $C_{14}H_{11}NO_4Se$ (336.20): C, 50.01; H, 3.30; N, 4.17%. Found: C, 49.88; H, 3.25; N, 4.01%.

3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carboximide (10), as an orange crystal in 80% yield, mp 280–282 °C; IR: 3500, 3460, 3350, 3250 (2NH_2), 1725 (C=O chromene), 1660 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6): δ, ppm: 7.19 (2H, s, NH_2), 5.90 (2H, s, NH_2); 7.20–7.80 (4H, m, Ar-H). ^{13}C NMR δ, ppm: 168.3, 164.3, 160.1, 155.4, 139.0, 131.0, 128.3, 127.8, 126.8, 125.4, 119.9, 97.5. Mass: *m/z*: 307 [M^+, 20%]. Anal. Calcd for $C_{12}H_8N_2O_3Se$ (307.16): C, 46.92; H, 2.63; N, 9.12%. Found: C, 46.76; H, 2.55; N, 9.00%.

3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carbohydrazide (11).

A mixture of compound (**9**) (3.36 g, 0.01 mol) and hydrazine hydrate (3 mL, 0.06 mol) was refluxed for 1 h then absolute EtOH (20 mL) was added. The reaction mixture was refluxed for additional 2 h. The precipitated product which formed was dried and recrystallized from EtOH to give pale yellow crystals in 66% yield, mp 270–272 °C. IR: 3450, 3350, 3180 (NH, NH_2), 1725 (C=O chromene), 1650 (CONH) cm^{-1}. ^1H NMR (DMSO-d_6): δ, ppm: 4.45 (2H, s, NH_2), 6.90 (2H, s, NH_2), 7.20–7.50 (4H, m, Ar-H), 8.85 (1H, s, NH). ^{13}C NMR δ, ppm: 166.5, 164.3, 160.1, 155.4, 139.0, 131.0, 128.3, 127.8, 126.8, 125.4, 119.9, 97.5. Mass: *m/z* 322 [M^+, 30%]. Anal. Calcd for $C_{12}H_9N_3O_3Se$ (322.18): C, 44.74; H, 2.82; N, 13.04%. Found: C, 44.58; H, 2.77; N, 13.00%.

(*E*)-Ethyl *N*-(6,10-dioxo-6*H*-chromeno[3',4':4,5]seleno[3,2-*d*]pyrimidin-9(10*H*)-yl)formimidate (12).

A mixture of compound (**11**) (3.22 g, 0.01 mol) and triethyl orthoformate (8 mL, 0.027 mol) was refluxed in presence of glacial acetic acid (3 mL) for 3 h. The precipitate product which formed on hot was filtered off, dried and recrystallized from DMF/EtOH mixture giving pale yellow crystals in 55% yield, mp > 300 °C. IR: 1720 (C=O chromene), 1660 (C=O pyrimidine) cm^{-1}. ^1H NMR (DMSO-d_6): δ, ppm: 1.25–1.40 (3H, t, CH_3, J=7 Hz), 4.30–4.40 (2H, q, CH_2, J=7.1 Hz); 7.60–8.50 (6H, m, Ar-H + CH-pyrimidine+ CH=N). ^{13}C NMR δ, ppm: 168.0, 163.5, 160.1, 157.4, 150.8, 149.5, 139.6, 131.01, 128.3, 127.8, 126.8, 125.4, 119.9, 115.05, 63.4, 15.3. Mass: *m/z* 388 [M$^+$, 25%]. Anal. Calcd for $C_{16}H_{11}N_3O_4Se$ (388.24): C, 49.50; H, 2.86; N, 10.82%. Found: C, 49.45; H, 2.77; N, 10.59%.

3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carbonylazide (13).

To a stirred solution of compound (**11**) (3.22 g, 0.01 mol) in glacial acetic acid (15 mL) sodium nitrite solution (4.5 g, 0.07 mol) was added dropwise at 0-5 °C for 15 min, a brown precipitate was formed and then filtered off, washed with water, dried and used without recrystallization for the following step, in 47% yield, mp 145–147 °C. IR: 3450, 3350 (NH_2), 2100 (N3), 1725 (C=O chromene), 1660 (C=O azide) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ, ppm: 7.19 (2H, s, NH_2), 7.25–7.60 (4H, m, Ar-H). ^{13}C NMR δ, ppm: 189.5, 172.0, 160.1, 155.4, 139.3, 131.6, 128.3, 127.8, 126.8, 125.4, 119.9, 107.01. Mass: *m/z* 333[M$^+$, 30%]. Anal. Calcd for $C_{12}H_6N_4O_3Se$ (333.16): C, 43.26; H, 1.82; N, 16.82%. Found: C, 43.10; H, 1.76; N, 16.78%.

7,9-Dihydro-6*H*,8*H*-chromeno[3',4':4,5]seleno[2,3-*d*]imidazole-6,8-dione (14).

A mixture of **13** (1 g, 0.003 mol) in dry xylene (10 mL) was refluxed for 2 h. The solid product which formed on hot was filtered off, washed three times by xylene, dried and recrystallized from xylene as dark green crystals in 50% yield, mp > 300 °C. IR: 3450, 3350 (2NH), 1725 (C=O chromene), 1645 (C=O imidazole) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ, ppm: 5.90 (2H, s, 2NH); 7.20–7.75 (4H, m, Ar-H). ^{13}C NMR δ, ppm: 160.1, 155.4, 151.01, 139.5, 131.08, 128.3, 127.8, 126.8, 125.4, 119.9, 118.68, 99.5. Mass: *m/z* 305 [M$^+$, 50%]. Anal. Calcd for $C_{12}H_6O_3N_2Se$ (305.15): C, 47.23; H, 1.98; N, 9.18%. Found: C, 47.11; H, 1.80; N, 9.11%.

3-Amino-2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4*H*-seleno[3,2-*c*]chromen-4-one (15).

A mixture of carbohydrazide (**11**) (3.22 g, 0.01 mol) and acetylacetone (1.2 mL, 0.013 mol) was refluxed in EtOH (10 mL) for 3 h. The precipitate product was filtered off and recrystallized from EtOH as yellow crystals in 60% yield, mp 250–252 °C. IR: 3350, 3250 (NH_2), 1720 (C=O chromene), 1690 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ, ppm: 2.30–2.45 (6H, 2s, $2CH_3$), 6.90 (2H, s, $2NH_2$), 5.50 (1H, s, CH-pyrazole), 7.20–7.50 (4H, m, Ar-H). ^{13}C NMR δ, ppm: 188.8, 170.2, 164.0, 161.9, 160.1, 152.3, 155.4, 143.2, 131.7, 128.3, 127.8, 126.8, 125.4, 119.9, 105.5, 13.7, 13.2. Mass: *m/z* 386 [M$^+$, 45%]. Anal. Calcd for $C_{17}H_{13}N_3O_3Se$ (386.26): C, 52.86; H, 3.39; N, 10.88%. Found: C, 52.66; H, 3.29; N, 10.78%.

3-Amino-4-oxo-4*H*-seleno[3,2-*c*]chromene-2-carboxylic acid (16).

A suspension of ester compound (**9**) (3.36 g, 0.01 mol) in 10% ethanolic sodium hydroxide (40 mL) was heated under reflux for 3 h, and then allowed to cool. The reaction mixture was diluted with 50 mL of water, filtered, and then acidified with dilute acetic acid. The precipitate was filtered off and recrystallized from dioxane to give orange crystals, yield 68%; mp 245–247 ºC. IR: 3420, 3300 (NH_2), 1720 (C=O chromene), 1640 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d*6*): δ, ppm: 10.55 (1H, s, COOH); 7.20-7.75 (6H, m, H-Ar + NH_2). ^{13}C NMR δ, ppm: 168.0, 164.4, 160.1, 155.4, 139.1, 131.8, 128.3, 127.8, 126.8, 125.4, 119.9, 93.5. Mass:

m/z 309 [M$^+$ +1, 35%]. Anal. Calcd for $C_{12}H_7NO_4Se$ (308.15): C, 46.77; H, 2.29; N, 4.55%. Found: C, 46.55; H, 2.15; N, 4.44%.

8-Methyl-6,10-dihydrochromeno[3',4':4,5]seleno[3,2-*d*][1,3]oxazine-6,10-dione (17).

Compound **16** (3.08 g, 0.01 mol) in acetic anhydride (25 mL) was heated under reflux for 3 h, and allowed to cool at room temperature. The crystalline product was collected, dried in air, and applied in the next reaction without recrystallization, yield 35%; mp 265–267 ºC. IR: 1720 (C=O chromene), 1640 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ, ppm: 7.20–7.55 (4H, m, H-Ar); 1.95 (3H, s, CH_3). ^{13}C NMR δ, ppm: 175.1, 164.0, 161.8, 160.1, 140.0, 134.2, 155.4, 128.3, 127.8, 126.8, 125.4, 119.9, 112.6, 16.3. Mass: *m/z* 333 [M$^+$ +1, 15%]. Anal. Calcd for $C_{14}H_7NO_4Se$ (332.17): C, 50.62; H, 2.12; N, 4.22%. Found: C, 50.33; H, 2.11; N, 4.10%.

8-Methyl-6,10 dihydro-7(6*H*)-chromeno[3',4':4,5]seleno[3,2-*d*]primidine-6,10-dione (18)

A mixture of compound **17** (3.32 g, 0.01 mol) and aniline (1 mL) in glacial acetic acid (10 mL) was heated under reflux for 3 h. The reaction mixture was cooled and diluted with water. The solid precipitate was collected and recrystallized from an EtOH/DMF mixture to give pale yellow crystals, yield 35%; mp 235–237 ºC. IR: 1720 (C=O chromene), 1660 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ, ppm: 7.20-7.95 (9H, m, H Ar); 2.10 (3H, s, CH_3). ^{13}C NMR δ, ppm: 168.1, 164.5, 160.1, 157.9, 140.1, 133.4, 155.4, 128.3, 127.8, 126.8, 125.4 (2-Ar), 119.9, 115.4, 25.8. Mass: *m/z* 408 [M$^+$ +1, 65%]. Anal. Calcd for $C_{20}H_{12}N_2O_3Se$ (407.28): C 58.98; H 2.97; N 6.88% . Found: C 58.88; H 2.78; N 6.77%.

REFERENCES

1. T. Ma, L. Liu, H. Xue, L. Li, C. Han, L. Wang, Z. Chen, and G. Liu, *J. Med. Chem.*, 2008, **51**, 1432.
2. A. G. Kidane, H. Salacinski, A. Tiwari, K. R. Bruckdorfer, and A. M. Seifalian, *Biomacromolecules*, 2004, **5**, 798.
3. G. Appendino, E. Mercalli, N. Fuzzati, L. Arnoldi, M. Stavri, S. Gibbons, and A. Ballero Maxia, *J. Nat. Prod.*, 2004, **67**, 2108.
4. C. A. Kontogiorgis and D. L. Hadjipavlou-Latina, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 611.
5. K. C. Fylaktakidou, D. J. Hadjipavlou-Latina, K. E. Litinas, and D. N. Nicolaides, *Curr. Pharm. Des.*, 2004, **10**, 3813.
6. (a) M. A. Musa and J. S. Cooperwood, *Curr. Med. Chem.*, 2008, **15**, 2664; (b) N. Peter, L. Philipp, and B. Andreas, *J. Med. Chem.*, 2002, **45**, 4310; (c) G. Le Bras, C. Radanyi, J.-F. Peyrat, J.-D. Brion, M. Alami, V. Marsaud, B. Stella, and J.-M. Renoir, *J. Med. Chem.*, 2007, **50**, 6189.
7. H. Brady, S. Desai, L. M. Gayo-Fung, S. Khammungkhune, J. A. McKie, E. O'Leary, L. Pascasio, M. K. Sutherland, D. W. Anderson, S. S. Bhagwat, and B. Stein, *Cancer Res.*, 2002, **62**, 1439.
8. J. A. Burlison, L. Neckers, A. B. Smith, A. Maxwell, and B. S. Blagg, *J. Am. Chem. Soc.*, 2006, **128**,

15529.

9. S. J. Stanway, A. Purohit, L. W. Woo, S. Sufi, D. Vigushin, R. Ward, R. H. Wilson, F. Z. Stanczyk, N. Dobbs, E. Kulinskaya, M. Elliott, B. V. Potter, M. J. Reed, and R. C. Coombes, *Clin. Cancer Res.*, 2006, **12**, 1585.
10. V. P. Litvinov and V. D. Dyachenko, *Russ. Chem. Rev.*, 1997, **66**, 923.
11. P. K. Atanassov, A. Linden, and H. Heimgartner, *Heterocycles*, 2003, **61**, 569.
12. F. T. Burling and B. M. Goldstein, *J. Am. Chem. Soc.*, 1992, **114**, 2313.
13. K. Burger, M. Gold, H. Neuhauser, M. Rudolph, and E. Hoess, *Synthesis*, 1992, 1145.
14. Sh. H. Abdel-Hafez, Sh. A. Abdel-Mohsen, and Y.A. El-Ossaily, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2006, **181**, 2297.
15. Sh. H. Abdel-Hafez, *Eur. J. Med. Chem.*, 2008, **43**, 1971.
16. Sh. H. Abdel-Hafez and M. A. Hussein, *Arch. Pharm*, 2008, **341**, 240.
17. Sh. H. Abdel-Hafez, L. M. Break, and A. M. Alsaadi, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2013, **188**, 1281.
18. L. M. Break, M. A. Mohamed, and Sh. H. Abdel-Hafez, *Orient. J. Chem.*, 2014, **30**, 1639.
19. P. C. Hong, L. J. Chen, T. Y. Lai, H.Y. Yang, S. J. Chiang, Y. Y. Lu, P. K. Tsai, H. Y. Hsu, W.Y. Wei, and C. B. Liao, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5068.
20. A. Elkhateeb, A. S. Alshehri, Gilbert Kirsch, and Sh. H. Abdel-Hafez, *Orient. J. Chem.*, 2016 (in press).
21. A. Sabatie, D. Vegh, and L. Floch, *ARKIVOC*, 2001, **vi**, 122.
22. J. Andrieux, J. P. Battioni, M. Giraud, and D. Molho, *Bull. Soc. Chim. Fr.*, 1973, **6**, 2093.