Research Article

One-Pot Synthesis of Novel Furochromone and Oxazocine Derivatives as Promising Antitumor Agents with Their Molecular Docking Studies

Rita M. Borik ⓘD

Chemistry Department, Faculty of Science (Female Section), Jazan University, Jazan 82621, Saudi Arabia

Correspondence should be addressed to Rita M. Borik; retag6066@hotmail.com

One-pot efficient synthesis of novel chromone derivatives **4a–h** and that of **5a–h** were described in a simple method via four-component reaction between furochromone carbaldehyde, amine, isocyanate derivatives, and benzoic acid derivatives or nicotinic acid, respectively. Also, oxazocine derivatives **7a**, **b** were prepared via reaction of visnagine carbaldehyde, ethyl acetoacetate and isocyanate derivatives **2a**, **b**. The obtained derivatives of novel furochromone and oxazocine derivatives were evaluated as promising antitumor agents against panel of two human cell lines, hepatocellular carcinoma (HEPG2) and breast carcinoma (MCF7). The antitumor results suggested that furochromone derivatives **5a–h** have activity against MCF7 in comparison with doxorubicin as the standard drug. Furthermore, the molecular docking studies of these novel derivatives of furochromone and oxazocine showed good agreement with the biological results when their binding pattern and affinity towards the active site of EGFR was investigate.

1. Introduction

Cancer is uncontrolled growth of abnormal cells, one of the most widespread serious diseases and its growth and metastasis depends on angiogenesis [1–4]. So, targeting of angiogenesis is a great goal for inhibition of tumor growth, invasion, and metastasis [5, 6].

Treatment of cancer using cytotoxic drugs (antineoplastics that preventing replication of cells) has many side effects [7, 8] although they are toxic to cancer cells. However, they all tend to work by interfering with some aspect of how the cells divide and multiply. For example, some work by affecting the cells' genetic "makeup" (material which controls specific cell characteristics) and others work by blocking cells from using nutrients needed to divide and multiply. The choice of cytotoxic drugs depends on the type and stage of cancer [9]. Survey and research to get safe novel drugs with less side effects are still in continuation [10, 11].

In point of this view, heterocyclic organic compounds play an important and vital role in synthesis and preparation of novel pharmacological compounds that may have a good manner in treatment of various types of tumors [12] and the human immunodeficiency virus (HIV) [13]. Our initial studies focused on the chromone and its derivatives which are important class of heterocyclic compounds. These heterocyclic compounds show a variety of pharmacological properties [14]. The tricycle-heterocyclic compounds especially dibenzooxazocine and furochromone or visnagine derivatives are used for the treatment of pain and/or inflammation [15], and also they have efficient activity against tumor cells [16–18].

Imidazole derivatives are an important class of heterocyclic compounds [19, 20] that exhibiting biological and pharmacological properties [21–23]. Also, oxazocine heterocyclic compounds are active compounds against CNS disorders and are used for the treatment of pain and/or inflammation [24].

So, according to this survey and in continuation of our heterocyclic synthesis of novel active compounds against some carcinoma cell lines [25], we aim to synthesize novel

derivatives of furochromone and oxazocine as promising antitumor agents towards hepatic and breast cell lines (HEPG2 and MFC7) as well as the normal cell line (human normal melanocyte, HFB4) using the MTT colorimetric test [26–29] depending on their molecular docking studies via one-pot reaction of three or four components of carbaldehyde, amine, isocyanate, and benzoic acid derivatives.

2. Experimental

All chemicals were provided by Fluka or Aldrich companies and were used without additional purification. Elemental microanalyses were carried out at Microanalytical Unit, Central Services Laboratory, National Research Centre, Dokki, Giza, Egypt, using Vario Elementar and were found within ± 0.4% of the theoretical values. All melting points were uncorrected and were taken in open capillary tubes using electrothermal apparatus 9100. FT-IR spectra were recorded with a Perkin-Elmer Frontier. Routine NMR spectra were recorded at room temperature on a Bruker Avance TM 400 (or 300) spectrometer as solutions in dimethyl sulfoxide (DMSO-d_6) or chloroform (CDCl$_3$). All chemical shifts are quoted in δ relative to the trace resonance of protonated dimethyl sulfoxide ($\delta 2.50$ ppm), DMSO ($\delta 39.51$ ppm) or CDCl$_3$ ($\delta 7.28$ ppm), ($\delta 77.28$ ppm), and external 85% aqueous H$_3$PO$_4$ ($\delta 0.0$ ppm). The mass spectra were measured with a GC Finnigan MAT SSQ-7000 mass spectrometer. The reactions were followed, the purity of the compounds was checked using TLC on silica gel-precoated aluminum sheets (Type 60, F 254, Merck, Darmstadt, Germany), and the spots were detected by exposure to UV lamp at $\lambda_{254\ nm}$. The chemical names given for the prepared compounds are according to the IUPAC system. The reported yields are based upon pure materials isolated by column chromatography. Solvents were dried/purified according to conventional procedures.

2.1. General Procedure for the Preparation of Compounds 4a–h and 5a–h.

The desired compounds were synthesized utilizing a 25 ml round bottom flask. Mixture A, aniline/or benzyl amine (1.1 mmol), was added to furochromone carbaldehyde 1 (1.1 mmol) in methanol (20.0 ml); then the mixture A was stirred for 15–30 min at room temperature. Mixture B, benzoic acid/or p-amino benzoic acid/or p-nitro benzoic acid/or nicotinic acid, respectively, (1.1 mmol) and phenyl isocyanate/or cyclohexyl isocyanate, respectively, (1.1 mmol) in methanol were stirred for 5 minutes. Then, Mixture B was poured on Mixture A. Finally, the resultant mixture was stirred at room temperature for 23–68 h, and solid K$_2$CO$_3$ (0.38 mmol) was added and refluxed for 76–100 h. After the reaction was completed, the crude material was concentrated and redissolved in dichloromethane. The resulting organic solution was then washed with 1 M HCl (aq). This was followed by adding a saturated aqueous solution of NaHCO$_3$ (aq) combined with brine. The resulting organic layer was collected, dried by MgSO$_4$, and then concentrated in vacuum at 40°C for 8 h to afford the crude material. The crude material was purified by ethanol to give the desired products 4a–h.

2.1.1. N-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl) (Phenylimino) Methyl)-N-phenyl Benzamide (4a).

Product 4a was separated as orange crystals, yield 59%. m.p. 210–212°C. IR (KBr, cm^{-1}) 1674, 1656 (2C=O), 1623 (C=N). ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 3.99$, 4.00 (s, 6H, 2OCH$_3$); 6.22, 6.60 (dd, 2H, $J = 2.01$ Hz, furan ring), 7.10 (s, 1H, H$_7$), 7.00–7.31 (m, 15H, CH arom) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ176.2 (CO), 173.7 (CO), 164.0 (CN), 155.8, 152.9, 150.1, 147.0, 146.5, 146.1, 134.1, 133.5, 132.1, 130.0, 128.9, 128.0, 127.6, 127.1, 123.1 124,0, 122.1, 121.6 (aromatic C-H), 118.2, 111.3, 106.3, 55.0 (OCH$_3$), 54.5 (OCH$_3$) ppm. MS (m/z): M$^+$ 543 (31%), 542 (17%), 541(55%). Anal. for C$_{33}$H$_{24}$N$_2$O$_6$ (544.55): Calcd. C, 72.78; H, 4.44; N, 5.14. Found C, 72.21; H, 4.02; N, 4.82.

2.1.2. N-(Cyclohexylimino) (4,9-Dimethoxy-5-oxo-5H-furo [3,2-g]chromen-6-yl)methyl)-N-phenyl Benzamide (4b).

Product 4b was separated as brown solid, yield: 52%, m.p. 182°C. IR (KBr, cm^{-1}) 1674, 1646 (2C=O), 1621(C=N). ^{1}H-NMR (500 MHz, DMSO-d_6): $\delta = 1.25$–1.64 (m, 10H, 5CH$_2$ cyclohexane); 3.10 (dd, H, CH-N cyclohexane); 3.88 (s, 6H, 2OCH$_3$); 6.64, 6.56 (dd, 2H, $J=2.0$ Hz 1, furan ring); 7.21–7.10 (m 10H, CH armo.); 8.00 (s, 1H, H$_7$). MS (m/z): M$^+$ 550.6, m/e: 549 (13%), 548 (36%), 547 (64%). Anal. for C$_{33}$H$_{30}$N$_2$O$_6$ (550.21): Calcd: C, 71.99; H, 5.49; N, 5.09, Found: C, 71.42; H, 5.02; N, 4.64.

2.1.3. 4-Amino-N-((4,9-dimethoxy-5-oxo-5H-furo [3,2-g] Chromen-6-yl) (Phenylimino) Methyl)-N-phenyl Benzamide (4c).

Product 4c was separated as yellow solid, yield: 55%. m.p. 177°C. IR (KBr, cm^{-1}) 1622 (C=N), 1686, 1645 (2CO) and 3347 (NH$_2$). ^{1}H-NMR (500 MHz, DMSO-d_6): $\delta = 3.89$ (s, 6H, 2OCH$_3$); 6.92–6.24 (m, 14H, arom.), 6.73, 6.36 (dd, 2H, $J=2.01$ Hz, furan ring); 7.89 (s, 1H, H$_7$) and 8.82 (s, 2H, NH$_2$, exchangeable D$_2$O). ^{13}C NMR (100 MHz, DMSO-d_6): δ, 177.6 (CO), 174.1 (CO), 164.1 (CN), 156.1, 155.3, 153.8, 151,1, 147.5, 147.0, 146.3, 134.0, 133,2, 132.4, 129.0, 128.7, 127.6, 124.8, 124.3 123.1, 122.3, 121.6 (aromatic C-H), 113.0, 112,1, 56.6 (OCH$_3$), 56.3 (OCH$_3$). MS (m/z): M$^+$: 558 (9%), 557 (35%), 556 (43%). Anal. for C$_{33}$H$_{25}$N$_3$O$_6$ (559.57): Calcd: C, 70.83; H, 4.50; N, 7.51, Found: C, 70.43; H, 4.24; N, 7.24.

2.1.4. 4-Amino-N-(cyclohexylimino) (4,9-Dimethoxy-5-oxo-5H-furo [3,2-g] Chromen-6-yl) Methyl)-N-phenylbenzamide (4d).

Product 4d was separated as brown solid, yield: 56%. m.p. 196°C, IR (KBr, cm^{-1}) 1623 (C=N), 1699, 1653 (2C=O) and 3345 (NH$_2$). ^{1}H-NMR (500 MHz, DMSO-d_6): δ1.58–1.24 (m, 10H, 5CH$_2$ cyclohexane); 3.02 (dd, H, CH-N cyclohexane); 4.01, 4.03 (s, 6H, 2OCH$_3$); 6.67, 6.33 (dd, 2H, $J=2.00$ Hz, furan ring); 6.54–6.20 (m, 9H, arom.); 8.10 (s, 1H, H$_7$) and 8.79 (s, 2H, NH$_2$ exchangeable with D$_2$O). MS (m/z): M$^+$: 565 (11%), 564 (48%), 563 (76%). Anal. for

$C_{33}H_{31}N_3O_6$ (565.62) Calcd: C, 70.07; H, 5.52; N, 7.43, Found: C, 69.78; H, 5.12; N, 7.01.

2.1.5. N-((4,9-Dimethoxy-5-oxo-5H-furo [3,2-g] Chromen-6-yl) (Phenylimino) Methyl)-4-nitro-N-phenylbenzamide (4e).

Product **4e** was separated as yellow solid, yield: 66%. m.p. 214°C. IR (KBr, cm^{-1}) 1621 (C=N),1672, 1642 (2C=O). ^{1}H-NMR (500 MHz, DMSO-d$_6$): 3.76, 3.77 (ss, 6H, 2OCH$_3$), 6.54–7.20 (m, 14H, arom); 7.28, 6.56 (dd, 2H, J=2.01 Hz, furan ring); 7.54 (s, 1H, H$_7$). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 177.3 (CO), 174.0 (CO), 164.1 (CN), 156.1, 155.0, 153.7, 151.0, 147.1, 147.0, 146.0, 134.2, 133.1, 132.3, 129.0, 128.7, 127.6, 124.4, 123.3, 122.5, 121.7 (aromatic C-H), 113.1, 112.2, 106.1, 56.1 (OCH$_3$), 54.6 (OCH$_3$) MS (m/z): M$^+$: 589.15 (76.0%), 588 (32%), 587 (45). Anal. for $C_{33}H_{23}N_3O_8$ (589.55) Calcd C, 67.23; H, 3.93; N, 7.13, Found: C, 66.77; H, 3.41; N, 5.85.

2.1.6. N-((Cyclohexylimino) (4,9-Dimethoxy-5-oxo-5H-furo [3,2-g] Chromen-6-yl) Methyl)-4-nitro-N-phenylbenzamide (4f).

Product **4f** was separated as brown solid, yield: 64%. m.p. 146°C, IR (KBr, cm^{-1}) 1618 (C=N), 1677, 1641 (2C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 1.44–1.12 (m, 10H, 5CH$_2$ cyclohexane); 3.02 (dd, H, CH-N cyclohexane), 3.76, 3.77 (s, 6H, 2OCH$_3$), 7.11, 6.42 (dd, 2H, J=2.01 Hz, furan ring); 7.00–6.98 (m, 9H, CH arm.); 7.56 (s, 1H, H$_7$). MS (m/z): M$^+$: 595.2 (14%), 593 (36%), 592 (83%), Anal. for $C_{33}H_{29}N_3O_8$ (595.6). Calcd C, 66.55; H, 4.91; N, 7.06, Found: C, 66.01; H, 4.33; N, 6.84.

2.1.7. N-((4,9-Dimethoxy-5-oxo-5H-furo [3,2-g] Chromen-6-yl) (Phenylimino) Methyl)-N-phenyl Nicotinamide (4g).

Product **4g** was separated as brown solid, yield: 64%. m.p. 176°C, IR (KBr, cm^{-1}) 1620 (C=N), 1664, 1634 (2C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 3.99, 3.86 (s, 6H, 2OCH$_3$), 7.54–7.00 (m, 14H, arom); 7.12, 6.33 (dd, 2H, J=2.01 Hz, furan ring); 7.74 (s, 1H, H$_7$). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 177.4 (CO), 174.1 (CO), 164.1 (CN), 156.1, 153.7, 151.0, 150.8, 149.0, 147.4, 146.2, 134.2, 133.1, 132.2, 129.0, 128.8, 127.6, 124.6, 124.3, 121.7 (aromatic C-H), 113.1, 112.3, 112.1, 106.1, 56.5 (OCH$_3$), 56.3 (OCH$_3$), MS (m/z): M$^+$: 545 (9%), 544 (58%), 543 (60%). Anal. for $C_{32}H_{23}N_3O_6$ (545.54) Calcd C, 70.45; H, 4.25; N, 7.70, found: C, 70.00; H, 3.87; N, 7.24.

2.1.8. N-(Cyclohexylimino) (4,9-Dimethoxy-5-oxo-5H-furo [3,2-g] Chromen-6-yl) Methyl)-N-phenylnicotinamide (4h).

Product **4h** was separated as brown solid, yield: 62%. m.p. 211°C, IR (KBr, cm^{-1}) 1623 (C=N), 1672, 1642 (2C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 1.41–1.22 (m, 10H, 5CH$_2$ cyclohexane); 3.11 (dd, H, CH-N cyclohexane), 3.96, 3.78 (ss, 6H, 2OCH$_3$), 7.54–6.20 (m, 9H, arom.); 7.54, 6.44 (dd, 2H, J=2.01 Hz, furan ring); 7.23–7.10 (m 9H, CH arm.); 7.34 (s, 1H, H$_7$). MS (m/z): M$^+$: 551.21 (67.0%), 550 (35.2%), 549 (7.5%). Anal. for $C_{32}H_{29}N_3O_6$ (551.59) C, 69.68; H, 5.30; N, 7.62, Found: C, 69.31; H, 4.80; N, 7.02.

2.1.9. 4,9-Dimethoxy-6-(1,4,5-Triphenyl-1H-imidazol-2-yl)-5H-furo [3,2-g] Chromen-5-One (5a).

Product **5a** was separated as brown solid, yield: 63%. m.p. 214°C. IR (KBr, cm^{-1}) 1646 (C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 3.97 (s, 6H, 2OCH$_3$); 6.78, 6.52 (dd, 2H, J=2.01 Hz, furan ring); 7.00 (s, 1H, H$_7$) and 7.31–7.11 (m, 15H, CH arom.). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 174.7 (CO), 158.6, 152.7, 149.8, 147.5, 146.0, 136.9, 137.1 133.1, 132.1, 129.7, 129.2, 128.6, 127.3, 124.6, 123.1, 122.5 (aromatic C-H), 118.3, 113,0, 106.1, 55.8 (OCH$_3$), 54.8(OCH$_3$). MS (m/z): M$^+$: 539 (10%), 462 (38%), 401 (67%), 387 (73%), 311 (62%), 245 (66%). Anal. for $C_{34}H_{24}N_2O_5$ (540.56) C, 75.54; H, 4.48; N, 5.18, Found: C, 75.01; H, 4.11; N, 4.66.

2.1.10. 6-(1-Cyclohexyl-4,5-diphenyl-1H-imidazol-2-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one (5b).

Product **5b** was separated as brown solid, yield: 62%. m.p. 215°C, IR (KBr, cm^{-1}) 1638 (C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 1.25–1.34 (m, 10H, 5CH$_2$ cyclohexane); 3.00 (dd, H, CH-N cyclohexane); 3.89 (s, 6H, 2OCH$_3$); 6.76, 6.44 (dd, 2H, J=2.01 Hz, furan ring); 7.22–7.90 (m, 10 H, CH arom.); 7.99 (s, 1H, H$_7$). MS (m/z): M$^+$: 546 (78%), 545 (39%), 544 (79%). Anal. for $C_{34}H_{30}N_2O_5$ (546.61) C, 74.71; H, 5.53; N, 5.12, Found: C, 74.22; H, 5.32; N, 4.88.

2.1.11. 6-(5-(4-Aminophenyl)-1,4-diphenyl-1H-imidazol-2-yl)-4,9-dimethoxy-5H-furo[3,2-g] Chromen-5-One (5c).

Product **5c** was separated as brown solid, yield: 64%. m.p. 186°C, IR (KBr, cm^{-1}) 1645 (C=O) and 3346 (NH$_2$). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 3.98 (s, 6H, 2OCH$_3$); 6.78, 6.11 (dd, 2H, J=2.01 Hz, furan ring); 7.48 (s, 1H, H$_7$); 7.21–7.00 (m, 14H, CH arom.) and 9.01 (s, 2H, NH$_2$ exchangeable with D$_2$O). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 175.0 (CO), 158.9, 153.3, 150.7, 148.0, 147.1, 145.8, 139.0, 137.1, 136.8, 132.7, 131.7, 129.2, 129.0, 128.9, 128.0, 127.1, 124.5, 123.0, 122.7, 122.1 (aromatic C-H), 118.0, 116.3, 112.7, 111.6, 105.8, 56.1 (OCH$_3$), 56.0(OCH$_3$). MS (m/z): M$^+$: 555 (49%), 554 (55%), 553 (67%). Anal. for: $C_{34}H_{25}N_3O_5$ (555.58) C, 73.50; H, 4.54; N, 7.56, found: C, 73.00; H, 4.12; N, 7.22.

2.1.12. 6-(5-(4-Aminophenyl)-1-cyclohexyl-4-phenyl-1H-imidazol-2-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one (5d).

Product **5d** was separated as yellow solid, yield: 63%. m.p. 192°CIR (KBr, cm^{-1}) 1648 (C=O) and 3346 (NH$_2$). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 1.55–1.24 (m, 10H, 5CH$_2$ cyclohexane); 3.11 (dd, H, CH-N cyclohexane); 3.89 (s, 6H, 2OCH$_3$); 6.67, 6.51 (dd, 2H, J=2.01 Hz, furan ring); 7.23–7.10 (m, 9H, CH arom.); 8.11 (s, 1H, H$_7$) and 8.87 (s, 2H, NH$_2$ exchangeable with D$_2$O. MS (m/z): M$^+$: 561 (20%), 560 (57%), 559 (51%). Anal. for $C_{34}H_{31}N_3O_5$ (561.63), C, 72.71; H, 5.56; N, 7.48, Found: C, 72.71; H, 5.56; N, 7.48.

2.1.13. 4,9-Dimethoxy-6-(5-(4-nitrophenyl)-1,4-diphenyl-1H-imidazol-2-yl)-5H-furo[3,2-]chromen-5-one (5e).

Product **5e** was separated as yellow solid, yield: 61%. m.p. 222°C, IR (KBr, cm^{-1}) 1643 (C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ,

3.97 (s, 6H, 2OCH$_3$); 6.78, 6.52 (dd, 2H, J=2.01 Hz, furan ring); 7.00 (s, 1H, H$_7$) and 7.31–7.11 (m, 14H, CH arom.). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 175.5 (CO), 158.9, 153.7, 151.0, 147.6, 150.1, 145,8, 140.7, 137.8, 137.1, 132.8, 132.2, 129.8, 129.2, 129.0, 128.5, 127.7, 124.6, 123.1, 122.7, 121.5, 118.4, 113.1, 112,0, 105.2 (aromatic C-H), 56.6 (OCH$_3$), 56.4 (OCH$_3$). MS (m/z): M$^+$: 585 (41%), 584 (66%), 583 (62%), Anal. for C$_{34}$H$_{23}$N$_3$O$_7$ (585.56), C, 69.74; H, 3.96; N, 7.18, Found: C, 69.21; H, 3.64; N, 6.84.

2.1.14. 6-(1-Cyclohexyl-5-(4-nitrophenyl)-4-phenyl-1H-imidazol-2-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one (5f).

Product **5f** was separated as brown solid, yield: 73%. m.p. 186°C, IR (KBr, cm^{-1}) 1635 (C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 1.55–1.34 (m, 10H, 5CH$_2$ cyclohexane); 3.11 (dd, H, CH-N cyclohexane); 3.88 (s, 6H, 2OCH$_3$); 6.60, 6.52 (dd, 2H, J=2.01 Hz, furan ring); 7.23–7.07 (m 9H, CH arom). 8.01 (s, 1H, H$_7$). MS (m/z): M$^+$: 591.2 (22%), 590 (45%), 589 (48%). Anal. for C$_{34}$H$_{29}$N$_3$O$_7$ (591.61), C, 69.03; H, 4.94; N, 7.10, found: C, 68.76; H, 4.23; N, 6.76.

2.1.15. 4,9-Dimethoxy-6-(1,4-diphenyl-5-(pyridin-4-yl)-1H-imidazol-2-yl)-5H-furo[3,2-g]chromen-5-one (5g).

Product **5g** was separated as orange solid, yield: 64%. m.p. 196°C, IR (KBr, cm^{-1}) 1647 (C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 3.97 (s, 6H, 2OCH$_3$); 6.78, 6.52 (dd, 2H, J=2.01 Hz, furan ring); 7.00 (s, 1H, H$_7$) and 7.31–7.11 (m, 14H, CH arom.). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 175.2 (CO), 159.7, 153.0, 150.9, 148.2, 147.6, 145.7, 139.1, 137.3, 136.6, 132.7, 131.8, 129.6, 129.3, 129.2, 128.3, 127.2 124.2, 123.4, 122.5, 122.0 (aromatic C-H), 118.2 116.4, 112.4, 111.1, 105.7, 56.1 (OCH$_3$), 56.0 (OCH$_3$). MS (m/z): M$^+$: 540 (12%), 464 (44%), 387 (74%), 311 (52%), 245 (73%). Anal. for C$_{33}$H$_{23}$N$_3$O$_5$ (541.55), C, 73.19; H, 4.28; N, 7.76, Found: C, 73.12; H, 4.24; N, 7.70.

2.1.16. 6-(1-Cyclohexyl-4-phenyl-5-(pyridin-4-yl)-1H-imidazol-2-yl)-4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one (5h).

Product **5h** was separated as brown solid, yield: 73%. m.p. 201°C, IR (KBr, cm^{-1}) 1644 (C=O). ^{1}H-NMR (100 MHz, DMSO-d$_6$): δ, 1.44–1.21 (m, 10H, 5CH$_2$ cyclohexane); 3.00 (dd, H, CH-N cyclohexane); 3.88 (s, 6H, 2OCH3); 6.64, 6.56 (dd, 2H, J=2.01 Hz, furan ring); 7.28–7.10 (m, 9H), 7.56 (s, 1H, H$_7$). MS (m/z): M$^+$: 547 (9%), 546 (56%), 545 (64%). Anal. for C$_{33}$H$_{29}$N$_3$O$_5$ (547.6), C, 72.38; H, 5.34; N, 7.67, Found: C, 72.01; H, 4.82; N, 7.03.

2.2. General Procedure for the Preparation of (7a, b).

A solution of ethyl acetoacetate (1 mmol) and 7-hydroxy-5-methoxy-4-oxo-4H-chromene-6 carbaldehyde **6** (1 mmol) in dichloromethane (3 ml) was stirred, and then phenyl isocyanate/or cyclohexyl isocyanate (1 mmol) was added to the mixture. The reaction mixture was stirred for 24–36 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 2:1), the solvent was removed under vacuum, and the solid residue was washed with ether and the products **4a, b** were obtained and recrystallized from ethanol.

2.2.1. 5-Acetyl-7-methoxy-10-methyl-3-phenylchromeno[6,7-g][1,3]oxazocine-2,4,8 (3H)-trione (7a).

Product **7a** was separated as beige solid, yield: 55%. m.p. 215°C, IR (KBr, cm^{-1}): 1775, 1770, 1658, 1587 (4C=O). ^{1}HNMR (100 MHz, DMSO-d$_6$): δ, 2.01 (s, 3H, CH$_3$); 2.47 (s, 3H, COCH$_3$), 4.06 (s, 3H, OCH$_3$); 6.74 (s, 1H, CH$_{12}$); 7.87 (d, 1H, CH=C) and 7.31–7.11 (m, 6H, CH arom.). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 198.0 (CO), 181.2 (CO), 164.8 (CO), 164.1 (CO), 160.3, 157.5, 157.2, 152.6, 148.6, 134.3, 133.0, 129.2, 123.3, 121.6 (aromatic C-H), 114.2, 110.4, 108.1, 103.2, 55.2 (OCH$_3$), 25.4 (COCH$_3$), 20.1 (CH$_3$),. MS (m/z): M$^+$: 419.10 (66.0%), 418 (43.1%), 417 (54.2%). Anal. for C$_{23}$H$_{17}$NO$_7$ (419.38), Calcd C, 65.87; H, 4.09; N, 3.34 found: C, 65.66; H,, 4.01; N, 3.31.

2.2.2. 5-Acetyl-3-cyclohexyl-7-methoxy-10-methylchromeno[6,7-g][1,3]oxazocine-2,4,8 (3H)-trione (7b).

Product **7b** was separated as yellow solid, yield: 60%. m.p. 181°C, IR (KBr, cm^{-1}): 1759, 1720 1658 and 1639 (4C=O). ^{1}HNMR (100 MHz, DMSO-d$_6$): δ, 1.01–2.26 (10H, m, 5CH$_2$ of cyclohexyl); 2.46 (s, 3H, CH$_3$); 2.47 (s, 3H, COCH$_3$) 3.32 (H, s, CH–N of cyclohexyl); 4.06 (s, 3H, OCH$_3$) 6.03 (s, 1H, CH$_{12}$) and 8.23 (d, 1H, CH=C). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ, 198.1 (CO), 182.0 (CO), 164.8 (CO), 164.1 (CO), 159.8, 157.5, 157.2, 155.2, 146.5, 133.8 (aromatic C-H), 111.1, 110.6, 108.0, 103.0, 55.9 (OCH$_3$), 30.8 (COCH$_3$), 28.1, 25.7, 23.0 (CH$_2$), 21.0 (CH$_3$). MS (m/z): M$^+$: 425.11 (33.0%), 424 (65.1%), 423 (45.5%). Anal. for C$_{23}$H$_{23}$NO$_7$ (425.43), Calcd C, 64.93; H, 5.45; N, 3.29, Found C, 64.23; H, 5.15; N, 3.21.

2.3. Determination of Anticancer Activities

2.3.1. Cell Lines.

For anticancer activity screening of the newly synthesized compounds, liver HepG2 and breast MCF-7 cell lines as well as the normal cell line (human normal melanocyte, HFB4) were obtained from National Cancer Institute, Cairo University. The cells were maintained in Dulbecco's modified Eagle's medium (DMEM) enhanced with 10% warm inactivated fetal calf serum (GIBCO), penicillin (100 U/ml), and streptomycin (100 μg/ml) at 37°C in humidified air containing 5% CO$_2$. Cells at a concentration of 0.50×10^6 were grown in a 25 cm^2 flask in 5 ml of culture medium.

2.3.2. Cell Viability

(1) Fast Screening.

Cells were seeded in 96 wells plates. The newly synthesized compounds were applied on the two cell lines to test their anticancer activity. The compounds were tested in two distinct concentrations (0.05 μg/ml and 5 μg/ml). The two working solutions were prepared using the complete medium. Three technical replicates were carried out for each concentration. The treated cells were

incubated for 48 h at 37°C and 5% CO_2. Afterwards, cell viability was determined by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). The comparison was performed between the treated cells to the positive control (reference drugs) and the negative control (DMEM). The tests were performed in biological replicates.

(2) IC$_{50}$ Determination. Cells were seeded in 96-well plates. The synthesized compounds that showed a significant reduction in the cell viability were chosen for further analysis. Each compound was tested on the two cell lines in 4 different concentrations (5, 12.5, 25, and 50 μg/ml). The working solutions were prepared using the complete medium. Three technical replicates were performed for each concentration. The treated cells were incubated for 48 h at 37°C and 5% CO_2. The viability of the cells was determined using MTT test. IC$_{50}$ (50% inhibitory concentration) values were calculated with a four-parameter logistic function and presented in a mean. The test was performed in biological replicates.

2.3.3. MTT Assay. The cells were washed with 50 μL of PBS and then the PBS was discarded [30]. Afterwards, 50 μL of MTT working solution was applied to each well and the cells were incubated for 15–30 min at 37°C and 5% CO_2. The cells were examined microscopically for formazan (black precipitate) development. The supernatant was discarded from each well and the formazan was dissolved using DMSO. The absorbance of the developed color was measured using an automated plate reader at 570 nm with a background wavelength of 670 nm. The results were presented in percentage to the values obtained from untreated cells (negative control).

2.4. Molecular Docking Studies. Promising biological evaluation of new furochromone and oxazocine derivatives **4a–h**, **5a–h,** and **7a**, **b** encourages us to study their interaction mechanism into the active site of EGFR (PDB ID: 5CAV) by molecular docking technique [31] using MOE 2008.10 program.

2.4.1. Preparation of Receptor. Binding sites were generated from co-crystallized ligand within crystal protein (PDB codes: 5CAV). Water molecules were removed from the complex. Then, the crystallographic disorders and protein energy was minimized by applying CHARMM and MMFF94 force fields. By applying fixed atom constraint, the rigid binding site of protein structure was obtained. The protein essential amino acids are defined and prepared for docking process. 2D structures of tested compounds were drawn using Chem. Bio. Draw Ultra14. 3D structures were protonated, and energy was minimized by applying 0.05 RMSD kcal/mol. CHARMM force field. Then, the minimized structures were prepared for docking using prepared ligand protocol [32].

2.4.2. Molecular Docking Process. Docking process was carried out using CDOCKER protocol, by employing CHARMM-based molecular dynamics (MD) scheme to dock ligands into a receptor binding site. The receptor was held rigid while the ligands were allowed to be flexible during the refinement, where each molecule was allowed to produce seven different interaction poses with the protein and then docking scores (CDOCKER interaction energy) of the best-fitted poses with the active site at (EGFR, PDB codes: 5CAV).

We use all the mentioned processes to predict the proposed binding mode affinity, preferred orientation of each docking pose, and binding free energy (ΔG) of the tested compounds with EGFR. The calculated interaction energies for the tested compounds were in complete agreement with experimental results which showed that our compounds are potent inhibitors against EGFR.
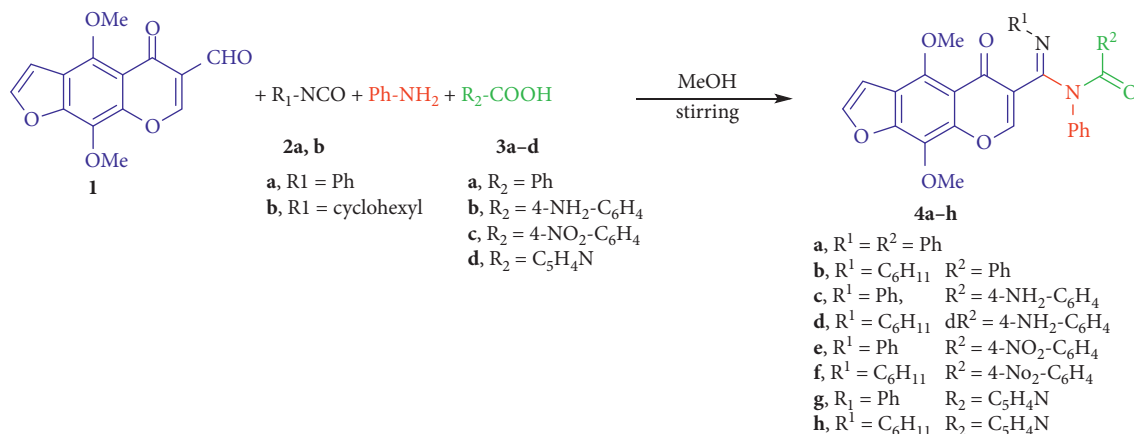
3. Results and Discussion

3.1. Chemistry. Highly substituted chromone derivatives **4a–h** and **5a–h** were synthesized *via* a one-pot, four-component reaction of aniline, furochromone carbaldehyde **1**, acid derivatives **3a–d**, namely, benzoic acid/or 4-amino-, 4-nitrobenzoic acid/or nicotinic acid, and phenyl isocyanate/or cyclohexyl isocyanate (Scheme 1). The structures of **4a–h** were elucidated from their elemental and spectroscopic analyses (IR, ^{1}H NMR, and ^{13}C NMR) together with mass spectra which prove the structures via getting molecular ion peaks at appropriate *m/z* values. ^{1}H NMR spectra of **4a** as example revealed characteristic doublet peaks for furan ring protons at $\delta = 6.22$, 6.60 ppm, while aromatic protons appeared at 7.00–7.31 ppm as multiples. ^{13}C NMR spectrum of **4a** showed 26 distinct resonances characteristic for carbon atoms 55.0 (OCH$_3$), 54.5 (OCH$_3$), 176.2 (CO), and 173.7 (CO) ppm. IR spectra of **4a–h** showed disappearance of the aldehydic group.

The mechanism of the formation of compounds **4a–h** is depicted in Scheme 2. Intermediate (A) in situ is formed between acid and isocyanate. Also, nucleophilic attack of amine toward the most active site of aldehydic carbon afforded the amine intermediate (B). Intermediate (A) attacks intermediate (B) to form oxadiazine ring (D) over expulsion of carbon dioxide molecule with rearrangement to afford the desired products **4a–h** (Scheme 2).

In the same manner, furochromone carbaldehyde **1** reacted in one-pot reaction at room temperature in methanol with beneylamine together with isocyanate derivatives **2a**, **b** with benzoic acid derivatives **3a–d** to give imidazole derivatives of furochromone **5a–h** in a good yield (Scheme 3). The structures of the novel compounds are elucidated via elemental and spectroscopic analysis (*cf.* Experimental). IR spectra showed disappearance of the aldehydic group. The ^{13}C NMR spectrum of **5a** showed 21 distinct resonances characteristic for carbon atoms.

The mechanism of formation of compounds **5a–h** is cited in Scheme 4, and it revealed similarity with formation mechanism of compounds **4a–h** with cyclization of

2a, b
a, R1 = Ph
b, R1 = cyclohexyl

3a–d
a, R_2 = Ph
b, R_2 = 4-NH_2-C_6H_4
c, R_2 = 4-NO_2-C_6H_4
d, R_2 = C_5H_4N

4a–h
a, $R^1 = R^2$ = Ph
b, $R^1 = C_6H_{11}$ R^2 = Ph
c, R^1 = Ph, R^2 = 4-NH_2-C_6H_4
d, $R^1 = C_6H_{11}$ dR^2 = 4-NH_2-C_6H_4
e, R^1 = Ph R^2 = 4-NO_2-C_6H_4
f, $R^1 = C_6H_{11}$ R^2 = 4-No_2-C_6H_4
g, R_1 = Ph R_2 = C_5H_4N
h, $R^1 = C_6H_{11}$ R_2 = C_5H_4N

SCHEME 1: Synthesis of compounds **4a–h**.

intermediate due to expulsion of water and carbon dioxide molecules to give the final products (Scheme 4).

Synthesis of new derivatives of oxazocine **7a, b** at one-pot three-component reaction is studied. Visnagine carbaldehyde **6**, ethyl acetoacetate, and isocyanate derivatives **2a, b** under mild conditions to afford derivatives **7a, b** in a good yield (Scheme 5). The structures of new compounds **7a, b** were confirmed based on analytical and spectral data. IR spectra showed disappearance of the characteristic band of (CHO) group and it exhibited 4C=O groups. ^{1}HNMR (DMSO-d_6) spectra of compounds (**7a, b**) showed a doublet around $\delta7.87$, 8.23 ppm, respectively, for CH=C group. ^{13}C-NMR for compound **7a** as example was showed 21 signals characteristic for carbon atoms 198.0 (CO), 181.2 (CO), 164.8 (C0), 164.1 (CO) 55.2 (OCH$_3$), 25.4 (COCH$_3$), and 20.1 (CH$_3$).

3.2. Antitumor Activity.

It has been proved that chromones have various kinds of biological activities, including antitumor, antimicrobial, antiviral, anti-inflammatory, antioxidant, and so on. Cytotoxicity refers to cell death, cell lysis, and the inhibition on cell proliferation induced by some substances. *In vitro*, most of chromones's cytotoxicity against tumor cells has been tested to confirm their antitumor activity. Cell toxicity is generally evaluated using the MTT (microculture tetrazolium) or SRB (sulforhodamine B) assay. Chromones demonstrate cell toxicity against a quantity of cell lines from a great variety of tumors, including cervical epithelioid carcinoma, breast adenocarcinoma [33], hepatoma carcinoma, lung cancer, leukemia cancer, and colon cancer [34, 35].

3.2.1. Cell Viability

(1) Fast Screening. Quick screening was performed to determine the newly synthesized derivatives which demonstrated a significant reduction in the cell viabilities against the two cell lines: hepatocellular carcinoma (HepG2) and breast carcinoma (MCF7). The impact of the newly derivatives on the breast carcinoma cell line

(MCF7) after 48 hrs, as an example, is illustrated in (Figure 1).

Most of the compounds exhibited a distinct reduction in the cell viability of at least one of the two cell lines. Therefore, all the compounds were further analyzed to determine their IC$_{50}$ values.
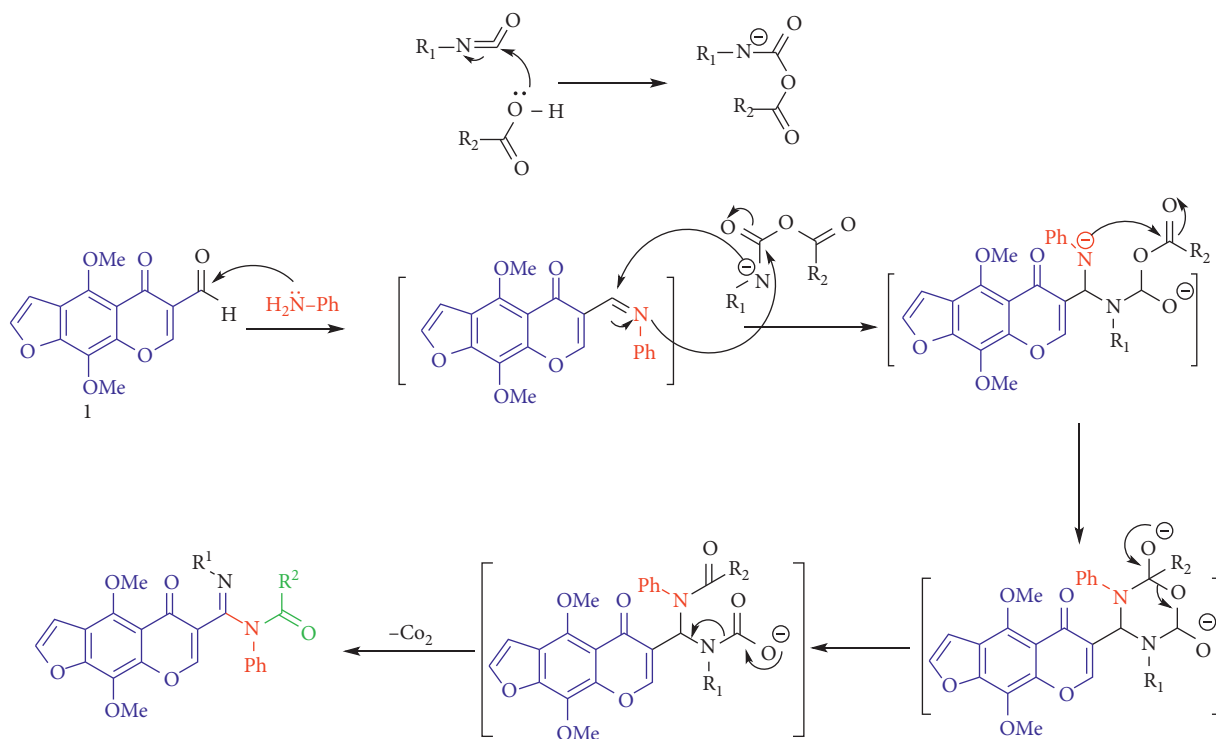
(2) IC$_{50}$ Determination. The data calculated as the concentration of the tested samples needed to inhibit half of the cancer cells population IC$_{50}$ values were calculated for each compound separately and, mean values ± SD are presented Table 1.

The results stated in Table 1 reveal that many compounds showed good antiproliferative activity against breast cancer cell line (MCF7) with no toxicity on normal cell line. According to National Cancer Institute guidelines, the compound with an IC$_{50}$ value < 30 μg/mL is active [36]. Therefore, as almost all compounds showed inhibition of cell growth, all the compounds were further analyzed to determine their IC$_{50}$. MTT test for the investigated compounds showed that most of them expressed the IC$_{50}$ ranging from 18 to 64 μg/ml compared with the standard drugs in used range of concentration, and they have low toxicity on the normal cell line (Table 1). From the all tested derivatives on these two cancer cell lines, compound **5a–h** had the lowest IC$_{50}$ ranging from 18–26 μg/ml against breast carcinoma cell line (MCF7) (Figure 2).
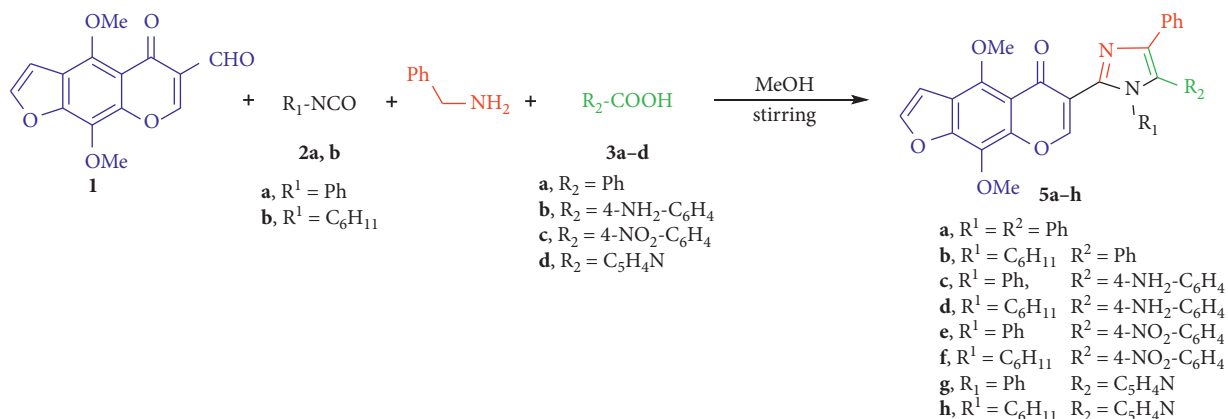
The abovementioned results showed that different cell lines varied greatly in their response against different synthesized compounds. This correlates well with previously reported results [37, 38], where this can be attributed to the inherent different cells in their specific membrane structure and organization.
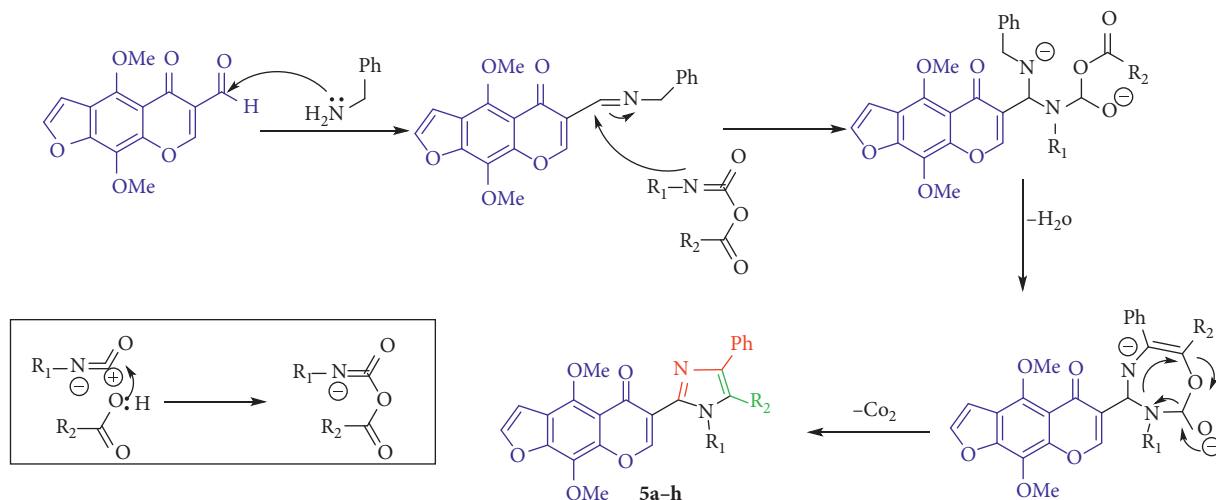
3.3. Molecular Docking Studies

3.3.1. Reference Ligand and Docking in EGFR Domain.

The binding mode of 4ZQ exhibits an energy binding of −24.81, for RMSD (1.67). 4ZQ formed a hydrogen bond with H-bond with (Lys 745) at bond distance 3.13°A, (Met 793) at bond distance of 2.95°A and (Thr 854) at 2.79°A. Docking
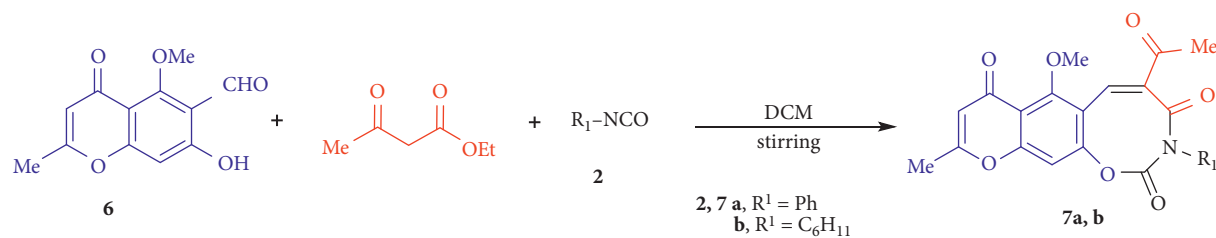
SCHEME 2: Proposed mechanism for formation of compounds **4a–h**.

2a, b

a, R^1 = Ph
b, R^1 = C_6H_{11}

3a–d

a, R_2 = Ph
b, R_2 = 4-NH_2-C_6H_4
c, R_2 = 4-NO_2-C_6H_4
d, R_2 = C_5H_4N

5a–h

a, R^1 = R^2 = Ph
b, R^1 = C_6H_{11} R^2 = Ph
c, R^1 = Ph, R^2 = 4-NH_2-C_6H_4
d, R^1 = C_6H_{11} R^2 = 4-NH_2-C_6H_4
e, R^1 = Ph R^2 = 4-NO_2-C_6H_4
f, R^1 = C_6H_{11} R^2 = 4-NO_2-C_6H_4
g, R_1 = Ph R_2 = C_5H_4N
h, R^1 = C_6H_{11} R_2 = C_5H_4N

SCHEME 3: Synthesis of compounds **5a–h**.

SCHEME 4: Proposed mechanism for formation of compounds **5a–h**.

SCHEME 5: Synthesis of compounds 7a, b.
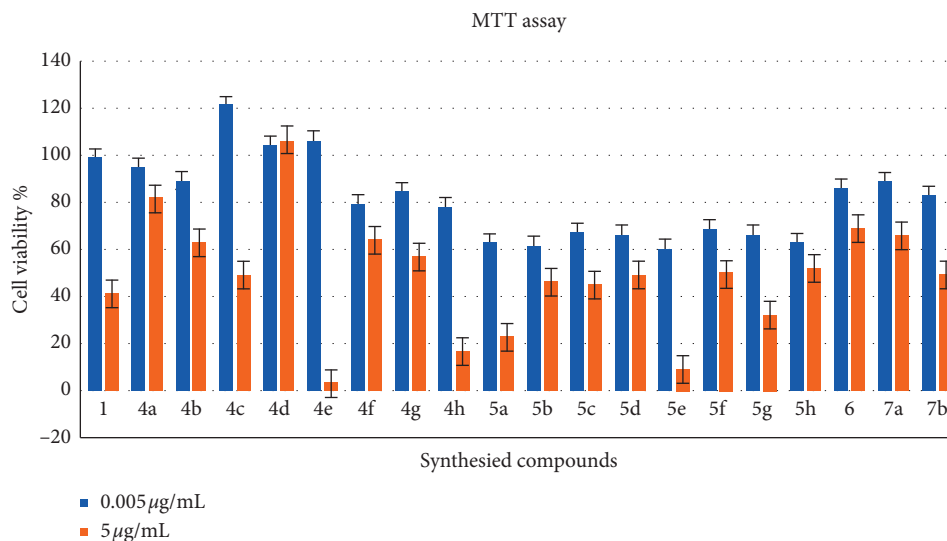
FIGURE 1: Breast carcinoma cell line (MCF7) cell viability after 48 h treatment with the synthesized derivatives.

TABLE 1: The antiproliferative potency of the newly prepared derivatives toward hepatic and breast cancer cell lines.

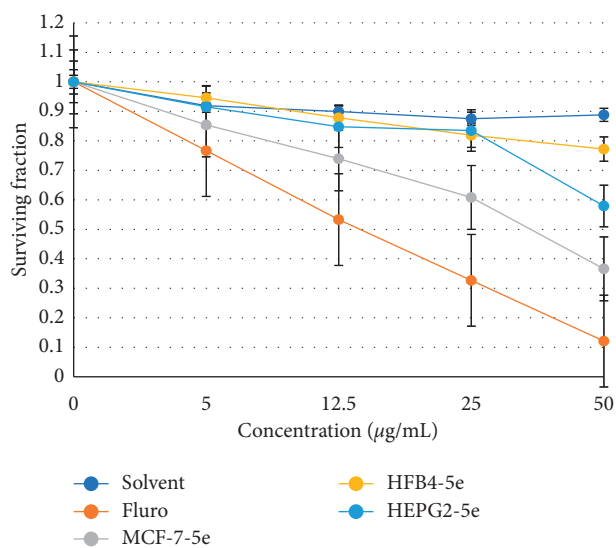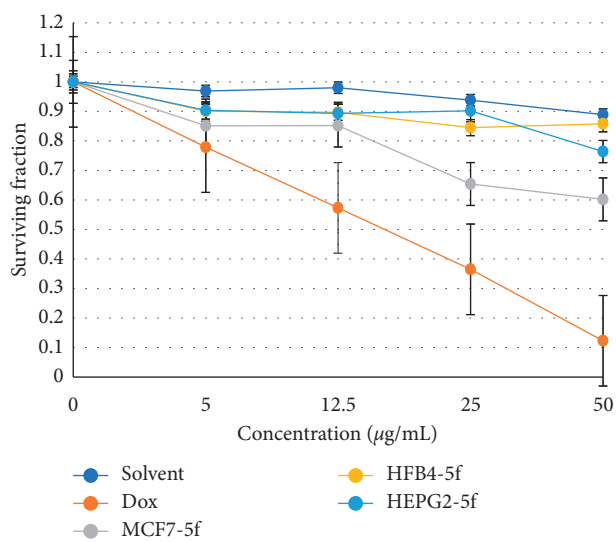| Compound	Cell lines	
	MCF-7 IC$_{50}$ ± SD (μg/mL)	HEPG-2 IC$_{50}$ ± SD (μg/mL)
Solvent (DMSO)	76 ± 0.66	77 ± 0.53
1	53 ± 0.35	44 ± 5.43
4a	43 ± 0.20	35 ± 0.12
4b	37 ± 1.17	43 ± 2.90
4c	55 ± 0.58	51 ± 0.37
4d	45 ± 1.04	49 ± 1.10
4e	41 ± 11.28	33 ± 2.10
4f	50 ± 2.79	64 ± 3.10
4g	52 ± 1.52	45 ± 0.47
4h	43 ± 1.15	55 ± 1.33
5a	23 ± 1.03	47 ± 2.80
5b	20 ± 1.44	33 ± 2.33
5c	19 ± 1.22	43 ± 1.57
5d	25 ± 2.67	32 ± 1.67
5e	18 ± 1.73	54 ± 1.27
5f	24 ± 0.10	45 ± 0.09
5g	26 ± 3.23	56 ± 2.59
5h	19 ± 1.19	41 ± 1.39
6	44 ± 1.86	56 ± 1.79
7a	34 ± 1.34	45 ± 1.64
7b	33 ± 2.79	39 ± 0.47
5 fluorouracil	13 ± 0.56	
Doxorubicin		14 ± 1.07
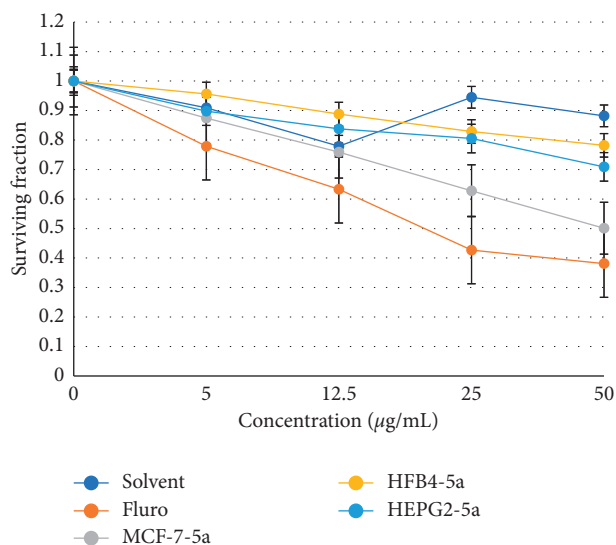
(a)
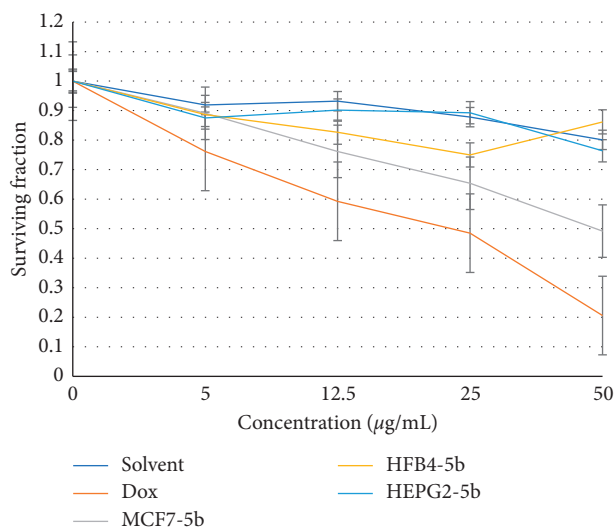
(b)
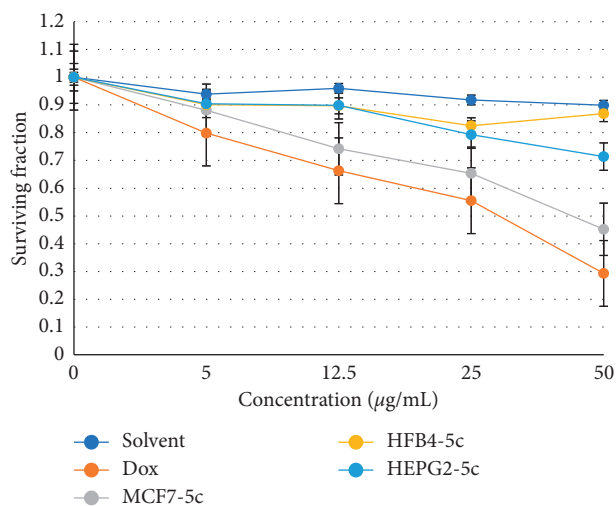
(c)
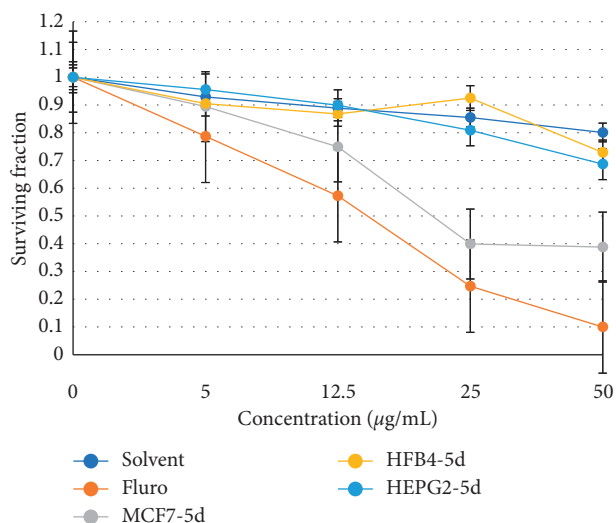
(d)

(e)

(f)

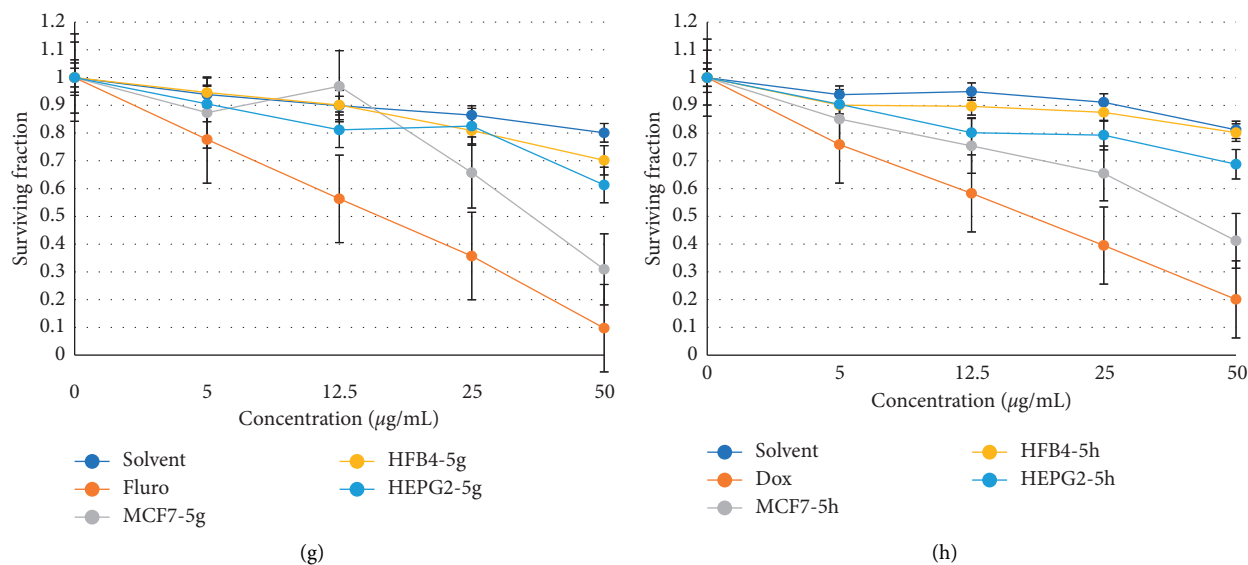FIGURE 2: Continued.

(g)

(h)

Figure 2: Dose-dependent response of two cell lines cells treated with the derivatives **5a–h** determined by MTT assay (48 h).

Table 2: Docking results of the newly synthesized compounds **4a–h**, **5a-h**, and **7a**, **b** docked with EGFR protein (PDB ID: 5CAV) active site.

Compd. no	Binding energy score $(kJ \, mol^{-1})$	Bonds number H.B. B. length	Pi	Amino acid residues	Ligand atom
4ZQ	−24.81	3 3.13,2.95,2.79	0	Lys 745, Met 793, Thr854	O of OCH_3, N of pyrimidine ring, N of pyridine ring
4a	−26.17	1 3.15	1	Lys 745, Phe723	O of OCH_3, benzene ring
4b	−20.69	1 2.94	1	Phe723	O of OCH_3, benzene ring
4c	−24.55	2 3.71, 2.67	2	Phe723	O of OCH_3, benzene ring
4d	−24.76	1 2.79	1	Lys 745, Phe723	O of OCH_3, benzene ring
4e	−23.22	2 3.00, 2.78	2	Lys 745, Phe723	O of OCH_3, CO, benzene ring
4f	−19.01	1 3.04	2	Lys 745, Phe723	O of OCH_3, benzo furan moiety
4g	−25.05	2 3.41,2.98	1	Lys745,Cys797, Phe723	O of OCH_3, N of pyridine ring
4h	−25.47	2 3.11,2.72	2	Lys 745, Phe723	O of OCH_3, CO, benzene furan moiety
5a	−29.31	1 2.62	1	Lys 745, Phe723	CO, imidazole ring
5b	−25.47	2 2.98,2.74	1	Lys 745, Phe723	O of OCH_3, CO, Benzene ring
5c	−30.07	1 2.59	1	Lys 745, Phe723	CO, imidazole ring
5d	−26.66	1 2.61	1	Lys 745, Phe723	CO, imidazole ring
5e	−26.11	1 3.43	2	Lys 745, Phe723	O of OCH_3, benzo furan moiety

TABLE 2: Continued.

| Compd. no | Binding energy score (kJ mol^{-1}) | Bonds number | | Amino acid residues | Ligand atom |
		H.B. B. length	Pi		
5f	−29.15	1 3.73	2	Lys 745, Phe723	O of OCH$_3$, benzo furan moiety
5g	−27.29	1 2.63	0	Cys797	CO
5h	−25.15	2 3.01,2.69	1	Lys745, Phe723	O of OCH$_3$, CO, benzene ring
7a	−18.48	1 2.59		Lys745	CO
7b	−17.16	1 2.63		Met 793	CO

(a)
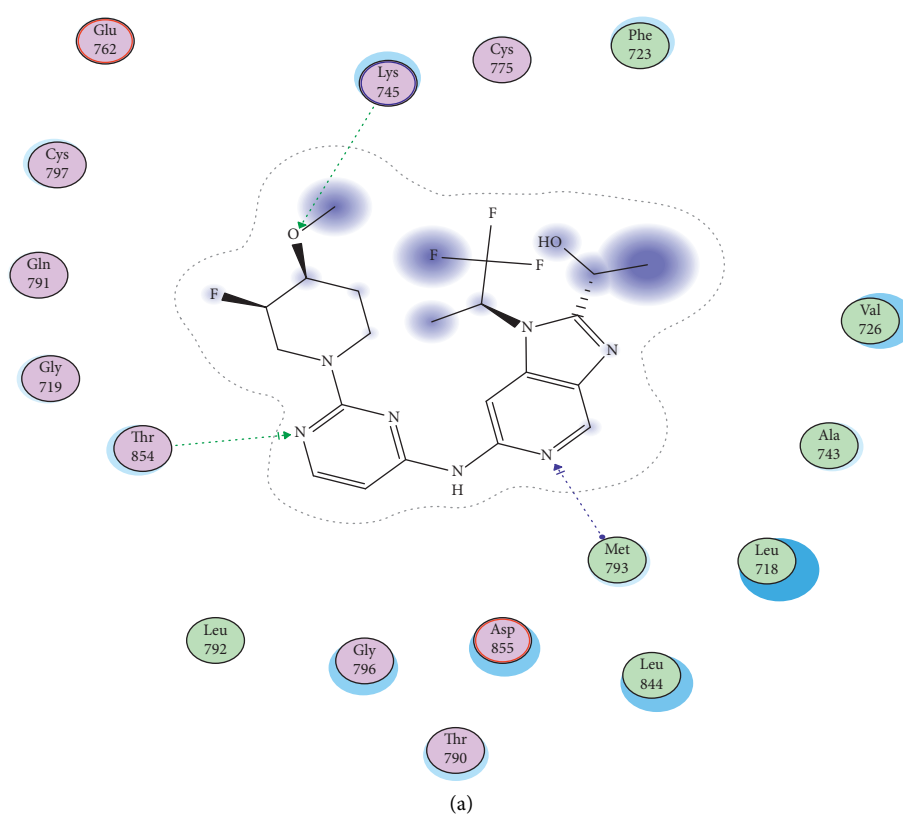
FIGURE 3: Continued.

(b)
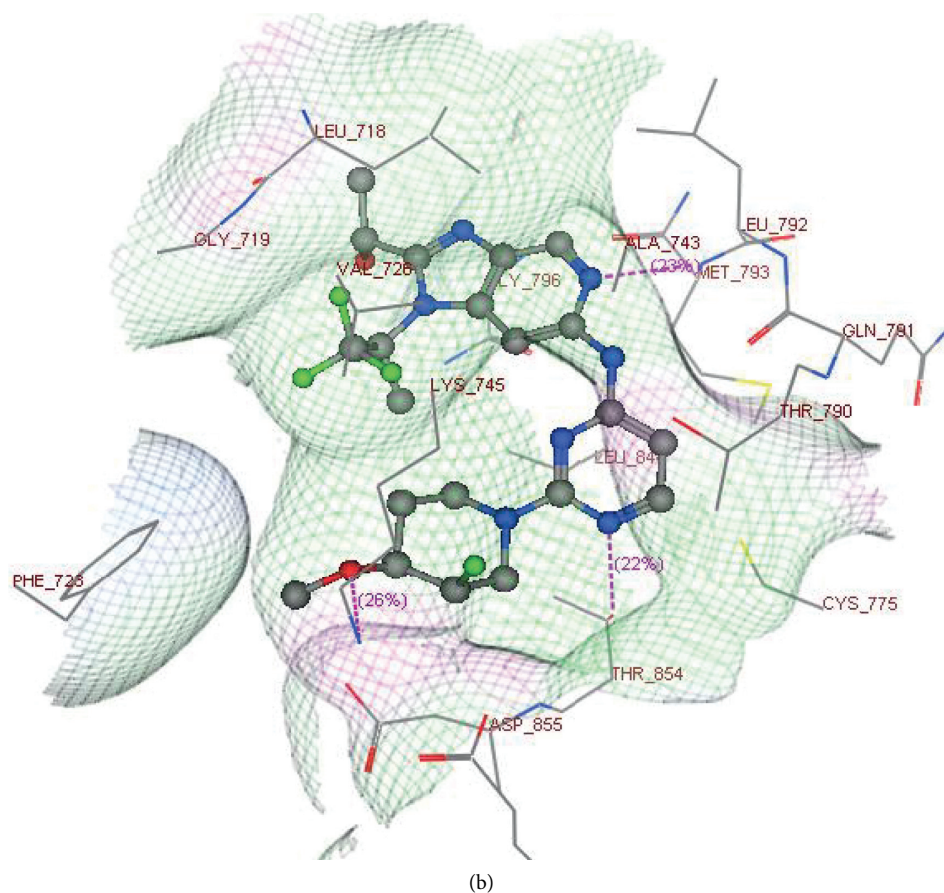
FIGURE 3: (a) The 2D depiction of the docked conformation of co-crystallized ligand (4ZQ) in the EGFR protein (PDB ID: 5CAV) binding site. (b) The 3D depiction of the docked conformation of co-crystallized ligand (4ZQ) in the EGFR protein (PDB ID: 5CAV) binding site.
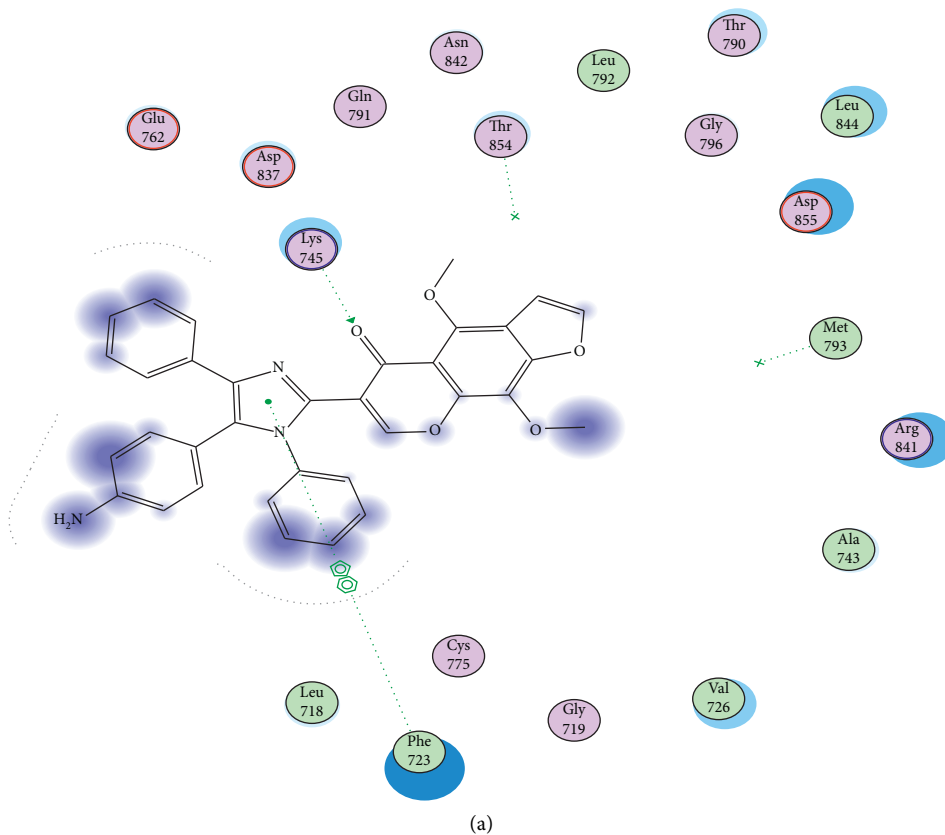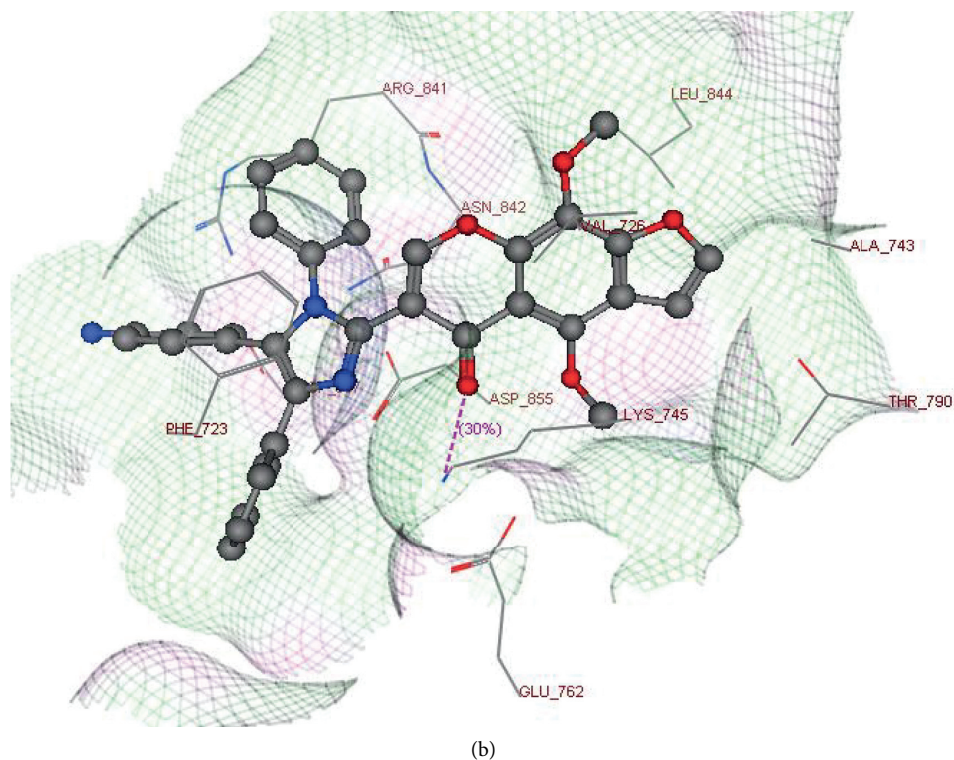

(a)

FIGURE 4: Continued.

(b)

Figure 4: (a) The 2D depiction of the docked conformation of **5c** in the EGFR protein (PDB ID: 5CAV) binding site. (b) The 3D depiction of the docked conformation of **5c** in the EGFR protein (PDB ID: 5CAV) binding site.
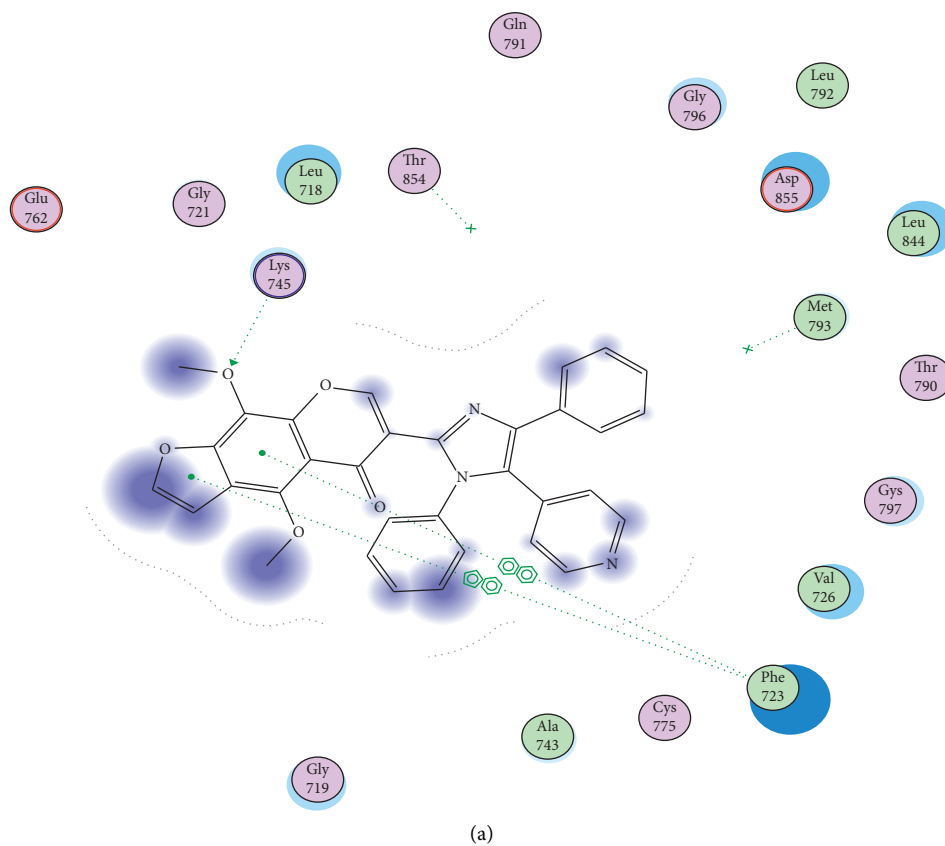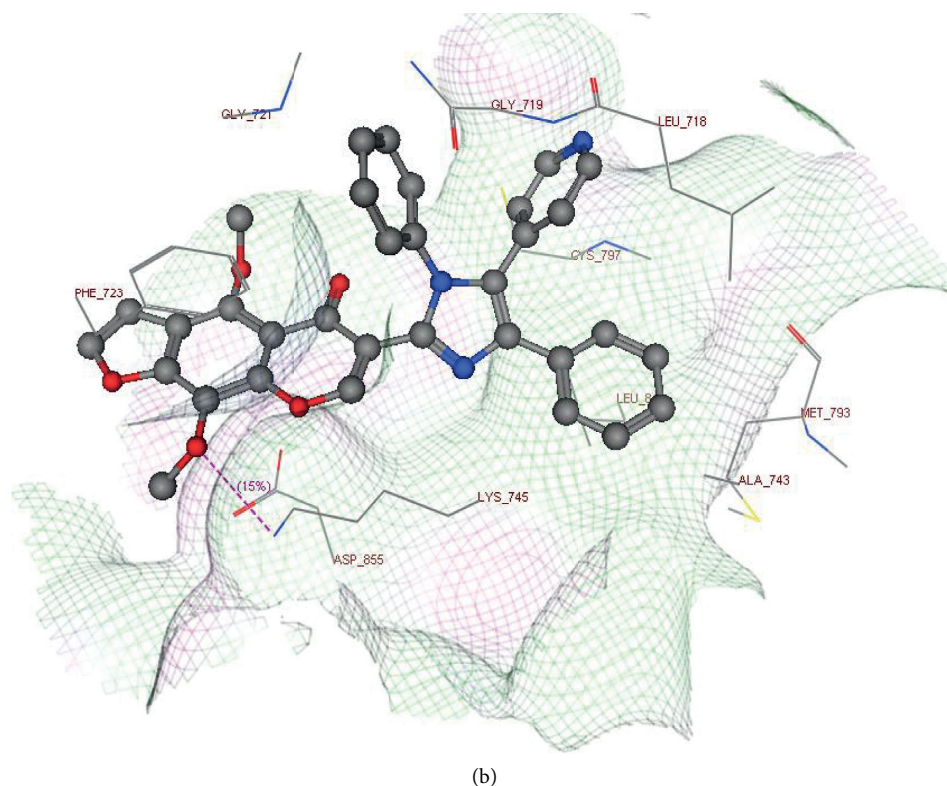

(a)

Figure 5: Continued.

(b)

FIGURE 5: (a) The 2D depiction of the docked conformation of **5e** in the EGFR protein (PDB ID: 5CAV) binding site. (b) The 3D depiction of the docked conformation of **5e** in the EGFR protein (PDB ID: 5CAV) binding site.

results of the newly synthesized compounds **4a–h**, **5a–h,** and **7a**, **b** which docked with EGFR protein (PDB ID: 5CAV) active site (Table 2).

The results revealed that compounds **5a–h** showed better docking score ranging from −30.07 to −25.15 kJ/mol, compared to the co-crystallized ligand (4QZ) of −24.81 kJ/mol and root-mean-square deviation value of 1.67 (Table 2). Also, compounds **5a–h** showed good binding interaction to the protein active site *via* formation of hydrogen bonds with the same amino acid residue (Lys 745) as the co-crystalline ligand (Table 2). The results of anticancer activity and docking studies for compounds **5c** and **5e** were compatible. Compounds **5c** and **5e** showed potent anticancer activity against MCF-7 cell line (IC$_{50}$ value 19 and 18 μg/ml) compared to reference drug 5-fluorouracil (IC$_{50}$ 13 μg/ml), and also exhibited better docking score (−30.07 and −26.11 kJ/mol) and good binding interaction *via* formation of one hydrogen bond with amino acid residue Lys 745 (2.59 Å and 3.43 Å) and Pi interaction with amino acid residue Phe 723 compared to co-crystallized ligand of docking score −24.81 kJ/mol and three hydrogen bonds with Lys 745, Met 793, and Thr 854 (Figures 3–5).

4. Conclusion

The newly synthesized furochromone and oxazocine derivatives seemed to be preferred for pharmaceutical studies. The results obtained from the synthesized compounds showed reasonable medical indices especially potent activities and, besides this, their lower possible side effects due to

no or weak action on normal cell lines. Compounds **5a–h** exhibited good antiproliferative potency against breast cancer cell line with week or no effect on normal cell lines. Their activities exceeded the tested standard drugs themselves. These findings may be used to design more effective and less harmful derivatives as potential anticancer agents.

The binding mode of the newly synthesized compounds **4a–h**, **5a–h,** and **7a**, **b** was assessed by docking with the active site of EGFR protein (PDB ID: 5CAV). Our results exhibited that compounds **5c** and **5e** demonstrated better binding energy (−30.07 and −26.11 kJ/mol) and good fitting inside the active site of the protein molecular surface in comparison with the co-crystallized ligand, which agrees well with the biological results. In this way, they may be viewed as great inhibitors of EGFR protein and consequently have a high anticancer activity.

Data Availability

The data supporting the findings of the study are already given within the article.

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] P. Carmeliet and R. K. Jain, "Angiogenesis in cancer and other diseases," *Nature*, vol. 407, no. 6801, pp. 249–257, 2000.

[2] N. Nishida, H. Yano, T. Nishida, T. Kamura, and M. Kojiro, "Angiogenesis in cancer," *Vascular Health and Risk Management*, vol. 2, no. 3, pp. 213–219, 2006.

[3] Y. Yang, M. Sun, L. Wang, and B. Jiao, "HIFs, angiogenesis, and cancer," *Journal of Cellular Biochemistry*, vol. 114, no. 5, pp. 967–974, 2013.

[4] Y. Zhao and A. A. Adjei, "Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor," *The Oncologist*, vol. 20, no. 6, pp. 660–673, 2015.

[5] L. Ellis, H. Hammers, and R. Pili, "Targeting tumor angiogenesis with histone deacetylase inhibitors," *Cancer Letters*, vol. 280, no. 2, pp. 145–153, 2009.

[6] Z. Wang, C. Dabrosin, X. Yin et al., "Broad targeting of angiogenesis for cancer prevention and therapy," *Seminars in Cancer Biology*, vol. 35, pp. S224–S243, 2015.

[7] K. J. M. Schimmel, D. J. Richel, R. B. A. van den Brink, and H.-J. Guchelaar, "Cardiotoxicity of cytotoxic drugs," *Cancer Treatment Reviews*, vol. 30, no. 2, pp. 181–191, 2004.

[8] R. V. J. Chari, "Targeted cancer therapy: conferring specificity to cytotoxic drugs," *Accounts of Chemical Research*, vol. 41, no. 1, pp. 98–107, 2008.

[9] C. Han, J. P. Braybrooke, G. Deplanque et al., "Comparison of prognostic factors in patients in phase I trials of cytotoxic drugs vs new noncytotoxic agents," *British Journal of Cancer*, vol. 89, no. 7, pp. 1166–1171, 2003.

[10] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2016," *CA: A Cancer Journal for Clinicians*, vol. 66, no. 1, pp. 7–30, 2016.

[11] A. D. Ricart and A. W. Tolcher, "Technology insight: cytotoxic drug immunoconjugates for cancer therapy," *Nature Clinical Practice Oncology*, vol. 4, no. 4, pp. 245–255, 2007.

[12] D. Rajiv, S. Suman, S. K. Sonwane, and S. K. Srivastava, "Pharmacological significance of synthetic heterocycles scaffold: a review," *Advances in Biological Research*, vol. 5, no. 3, pp. 120–144, 2011.

[13] M. El-Hussieny, N. F. El-Sayed, E. F. Ewies, N. M. Ibrahim, M. R. H. Mahran, and M. A. Fouad, "Synthesis, molecular docking and biological evaluation of 2-(thiophen-2-yl)-1H-indoles as potent HIV-1 non-nucleoside reverse transcriptase inhibitors," *Bioorganic Chemistry*, vol. 95, Article ID 103521, 2020.

[14] M. B. Teimouri, F. Zolfaghari, and S. Naderi, "Furochromone-isatin conjugates via an uncatalyzed diastereoselective [4 + 1] cycloaddition/tautomerization/Friedel-Crafts hydroxyalkylation domino reaction," *Tetrahedron*, vol. 73, no. 3, pp. 262–271, 2017.

[15] E. A. Elhefny, S. M. Abu-Bakr, N. M. Fawzy, A. Nasef, and M. S. Aly, "An efficient method for synthesis of 4,9-dimethoxy-5H-furo[3,2-g]chromen-5-one derivatives via multicomponent reactions with expected anticancer activities," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 32, pp. 85–94, 2015.

[16] K. M. Amin, Y. M. Syam, M. M. Anwar, H. I. Ali, T. M. Abdel-Ghani, and A. M. Serry, "Synthesis and molecular docking studies of new furochromone derivatives as p38α MAPK inhibitors targeting human breast cancer MCF-7 cells," *Bioorganic & Medicinal Chemistry*, vol. 25, no. 8, pp. 2423–2436, 2017.

[17] O. M. Abdelhafez, H. I. Ali, K. M. Amin, M. M. Abdalla, and E. Y. Ahmed, "Design, synthesis and anticancer activity of furochromone and benzofuran derivatives targeting VEGFR-2 tyrosine kinase," *RSC Advances*, vol. 5, no. 32, pp. 25312–25324, 2015.

[18] S. Demir, C. Ö.mi, M. Ceylan-Ünlüsoy, M. Ö.lüso, and O. Bozdağ-Dündar, "Novel Furochromone derivatives: synthesis and anticancer activity studies," *Journal of Heterocyclic Chemistry*, vol. 56, no. 4, pp. 1341–1351, 2019.

[19] M. V. Dubovis, G. F. Rudakov, A. S. Kulagin et al., "A new method of synthesis of substituted 1-(1H-imidazole-4-yl)-1H-1,2,3-triazoles and their fungicidal activity," *Tetrahedron*, vol. 74, no. 6, pp. 672–683, 2018.

[20] R. Takashima, K. Tsunekawa, M. Shinozaki, and Y. Suzuki, "Selective synthesis of 1,4,5-trisubstituted imidazoles from α-imino ketones prepared by N-heterocyclic-carbene-catalyzed aroylation," *Tetrahedron*, vol. 74, no. 18, pp. 2261–2267, 2018.

[21] A. H. Mageed, B. W. Skelton, A. N. Sobolev, and M. V. Baker, "Exploring structural and conformational behaviour of cyclophanes incorporating imidazole-2-thiones," *Tetrahedron*, vol. 74, no. 24, pp. 2956–2966, 2018.

[22] M. Adib, F. Peytam, M. Rahmanian-Jazi, H. R. Bijanzadeh, and M. Amanlou, "A new synthetic strategy towards 2,4,5-trisubstituted 1H-imidazoles and highly substituted pyrrolo[1,2-c]imidazoles by use of α-azidochalcones via Michael addition-cyclization followed by Wittig reaction," *Tetrahedron*, vol. 73, no. 48, pp. 6696–6705, 2017.

[23] L. You and C. Chen, "Rapid access to the core skeleton of the [3 + 2]-type dimeric pyrrole-imidazole alkaloids by triplet ketone-mediated C-H functionalization," *Tetrahedron*, vol. 74, no. 8, pp. 769–772, 2018.

[24] X. Ouyang, Z. Chen, L. Liu, C. Dominguez, and A. S. Kiselyov, "Novel and highly efficient synthesis of substituted dibenz[b,g]1,5-oxazocines, a direct comparison of the solution versus solid-phase approach," *Tetrahedron*, vol. 56, no. 16, pp. 2369–2377, 2000.

[25] R. Borik, N. Fawzy, S. Abu-Bakr, and M. Aly, "Design, synthesis, anticancer evaluation and docking studies of novel heterocyclic derivatives obtained via reactions involving curcumin," *Molecules*, vol. 23, no. 6, p. 1398, 2018.

[26] G. Van Goietsenoven, J. Hutton, J. P. Becker et al., "Targeting of eEF1A with Amaryllidaceae isocarbostyrils as a strategy to combat melanomas," *The FASEB Journal*, vol. 24, no. 11, pp. 4575–4584, 2010.

[27] L. Ingrassia, F. Lefranc, J. Dewelle et al., "Structure–Activity relationship analysis of novel derivatives of narciclasine (anAmaryllidaceaeIsocarbostyril derivative) as potential anticancer agents," *Journal of Medicinal Chemistry*, vol. 52, no. 4, pp. 1100–1114, 2009.

[28] F. Lefranc, T. Mijatovic, Y. Kondo et al., "Targeting the α 1 subunit of the sodium pump to combat glioblastoma cells," *Neurosurgery*, vol. 62, no. 1, pp. 211–222, 2008.

[29] F. Branle, F. Lefranc, I. Camby et al., "Evaluation of the efficiency of chemotherapy in in vivo orthotopic models of human glioma cells with and without 1p19q deletions and in C6 rat orthotopic allografts serving for the evaluation of surgery combined with chemotherapy," *Cancer*, vol. 95, no. 3, pp. 641–655, 2002.

[30] D. Sladowski, S. J. Steer, R. H. Clothier, and M. Balls, "An improved MIT assay," *Journal of Immunological Methods*, vol. 157, no. 1-2, pp. 203–207, 1993.

[31] H.-J. Bohm, "The development of a simple empirical scoring function to estimate the binding constant for a protein-ligand complex of known three-dimensional structure," *Journal of Computer-Aided Molecular Design*, vol. 8, no. 3, pp. 243–256, 1994.

[32] W. J. Allen, T. E. Balius, S. Mukherjee et al., "Dock 6: impact of new features and current docking performance," *Journal of Computational Chemistry*, vol. 36, no. 15, pp. 1132–1156, 2015.

[33] P. Klausmeyer, Q. Zhou, D. A. Scudiero et al., "Cytotoxic and HIF-1α inhibitory compounds from Crossosoma bigelovii," *Journal of Natural Products*, vol. 72, no. 5, pp. 805–812, 2009.

[34] W. J. Andrioli, R. Conti, M. J. Araújo et al., "Mycoleptones A-C and polyketides from the endophyte mycoleptodiscus indicus," *Journal of Natural Products*, vol. 77, no. 1, pp. 70–78, 2014.

[35] Y.-d. Duan, Y.-y. Jiang, F.-x. Guo et al., "The antitumor activity of naturally occurring chromones: a review," *Fitoterapia*, vol. 135, pp. 114–129, 2019.

[36] K. Hostettmann, P. M. Dey, and J. B. Harborne, "Methods in plant biochemistry," in *Assays for Bioactivity*, K. Hostettmann, Ed., Academic Press, London, UK, 1991.

[37] E. A. Elsayed, M. A. Sharaf-Eldin, and M. Wadaan, "In vitro evaluation of cytotoxic activities of essential oil from moringa oleifera seeds on HeLa, HepG2, MCF-7, CACO-2 and L929 cell lines," *Asian Pacific Journal of Cancer Prevention*, vol. 16, no. 11, pp. 4671–4675, 2015.

[38] E. A. Elsayed, M. Farooq, D. Dailin et al., "*In vitro* and *in vivo* biological screening of kefiran polysaccharide produced by Lactobacillus kefiranofaciens," *Biomedical Research*, vol. 28, no. 2, pp. 594–600, 2017.