Synthesis, characterization, anticancer activity, and molecular docking of novel maleimide–succinimide derivatives

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Background and objective
A wide range of maleimide heterobifunctional reagents are used for the preparation of targeted therapeutics. Succinimide derivatives are important compounds found in a variety of natural products that exhibit remarkable biological and pharmaceutical activity. The creation of new maleimide–succinimide derivatives will increase the importance and medicinal applications of these groups.
Materials and methods
The reaction of bismaleimide (**1–2**) with phenylhydrazide and 4-methylbenzohydrazide resulted in the formation of N'-[1-(4-[2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl] phenyl)-2,5-dioxopyrrolidin-3-yl] benzohydrazide (**3**), N'-[1-(4-[2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl] phenyl)-2,5-dioxopyrrolidin-3-yl]-4-methylbenzohydrazide (**4**), N'-[1-(4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-[1,1'-biphenyl]-4-yl)-2,5-dioxopyrrolidin-3-yl] benzohydrazide (**5**), and N'-[1-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-[1,1'- biphenyl]-4-yl)-2,5-dioxopyrrolidin-3-yl]-4-methylbenzohydrazide (**6**). The interaction of potential compounds with AKT1 and CDK2 proteins was performed using molecular docking to target the hydrogen bond and amino acid residues.
Results
The new compounds were characterized using Fourier-transform infrared spectroscopy, ^{1}H-NMR, ^{13}C-NMR spectroscopy, and mass spectrometry. The MTT assay was used to test cell viability against breast cancer cells (MCF-7). The cytotoxicity results revealed that compounds 3 and 5 were more toxic than compounds 4 and 6. Molecular docking of compounds that interacted with AKT1 and CDK2 showed affinity energy of –16.112 and –21.342 kcal/mol for compound 3, while –22.398 and –19.940 kcal/mol for compound 5. The root-mean-square deviation values for CDK2 and AKT1 were 2.27 and 1.61 for compound 3, respectively, and 1.93 and 1.90 for compound 5.
Conclusion
Toxicity and molecular docking studies revealed that compounds 3 and 5 could be developed as anticancer agents against breast cancer, indicating that further research is warranted.

Keywords:
bismaleimide, breast cancer, cell viability, docking studies, maleimide–succinimide derivatives

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Introduction

Maleimides are a kind of heterocyclic molecule that may be found in natural goods [1] and are employed in chemical and pharmaceutical chemistry. These uses are mostly based on two common maleimide reactions: (a) Michael addition with amines [2,3], alcohols [4], or thiols [5,6]; (b) addition of the cyclopentadiene [7] or furan [8,9] moiety to the Diels–Alder reaction. Michael donors (aliphatic or aromatic amines, amides, carbamates, or azides) interact with electron-deficient alkene molecules (Michael acceptors) such as α, β-unsaturated esters, vinyl ketones, vinyl sulfones, acrylamides, acrylonitrile, and vinylphosphonates [10,11]. Hence, bismaleimides are a class of compounds connected to two groups of maleimides by nitrogen atoms via a bonder [12,13]. Maleimides have been extensively studied in such reactions because, due to the presence of an activated double bond, they can be easily converted to substituted succinimides [14]. In addition, the compounds from the corresponding saturated model bis-succinimides were synthesized. Many medically significant medicines, such as phensuximide, ethosuximide, methsuximide, and andrimias, utilize the succinimide molecule as a precursor [15,16]. Some derivatives had interesting biological activities, such as analgesic [17], anticancer [18], antisplasmodic

[19], antibiotic [20,21], and muscle relaxant were among the biological actions of certain compounds [22]. We synthesized four new maleimide–succinimide derivatives and tested their toxicity against breast cancer (MCF-7) in this study. Thus, molecular docking studies of potential compounds using AKT1 and CDK2 proteins to target binding efficiency and amino acid residues were carried out.

Experimental

A Gallenkamp melting-point device was used to determine melting points. On a Bruker DRX 400 Advance spectrometer, proton and carbon NMR spectra were acquired at 400 and 100 MHz, respectively, using deuterated solvents and TMS as an internal standard. Chemical changes are measured in parts per million (ppm). An Fourier-transform infrared (FT-IR)-1600 Perkin-Elmer spectrophotometer (101 Mercury Dr, Champaign, IL, United States) was used to obtain IR spectra. Merck aluminum sheets of silica gel were used for thin-layer chromatography. Ultraviolet and I2 were used to seeing the thin-layer chromatography spots. Agilent Technologies used the EI technique to examine the mass spectrum at 70 eV. The molecular docking studies using AKT1 (PDB=5KCV) and CDK2 (PDB=4FX3) proteins were carried out based on the analysis procedure of reference [23,24].

Procedure for synthesis of phenyl-1,4-bismaleimide BMI (1–2)

Bismaleimides BMI (1–2) were made using procedures described in the literature [25,26]. To make bismaleamic acid, benzene-1,4-diamine or benzidine (0.02 mol) in 50 ml of acetone was combined with maleic anhydride (0.04 mol) in 40 ml of acetone.

About 0.02 mol bismaleamic acid dissolved in 25 ml of acetic anhydride was charged into a 100-ml round-bottom flask, then anhydrous sodium acetate (10–20% by weight) was added, and the mixture was refluxed in a water bath for 2–6 h, then cooled, and emptied into an ice bath while rapidly stirring. Bismaleimide was precipitated, filtered, dried, and recrystallized with ethanol.

Synthesis of maleimide–succinimide derivatives (3–6)

In acetonitrile (25 ml), a combination of bismaleimide BMI (**1–2**) (0.01 mol) and benzohydrazide or 4-methylbenzohydrazide (0.01 mol) was heated to reflux for 16–24 h under magnetic stirring. In ethanol, the white precipitate was filtered and recrystallized [27].

N'-[1-(4-[2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl]phenyl)-2,5-dioxopyrrolidin-3-yl]benzohydrazide (3)

A white substance was formed by reacting 0.01 mol phenyl-1,4-bismaleimide (BMI **1**) with 0.01 mol benzohydrazide in 25 ml of acetonitrile (65% yield), M.P.=220–222°C; FT-IR (KBr, cm^{-1}): 3400, 3377 (NH), 3099 (=CH Ar), 1776, 1718, 1656 (C=O), 1637 (C=C), 1517, and 1471 (C=C Ar); ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.19 (d, *J*=6.2 Hz, 1H, H_e), 7.84–7.20 (m, 11H, aromatic protons including CH=CH), 6.03 (q, *J*=7.3 Hz, 1H, H_d), 4.27 (dt, *J*=11.3, 5.4 Hz, 1H, H_c), 3.10 (dd, *J*=23.8, 11.3 Hz, 1H, H_a), and 2.83 (dd, *J*=23.8, 4.9 Hz, 1H, H_b); ^{13}C-NMR (100 MHz, DMSO-d6): δ=175.23 (C_1), 174.78 (C_4), 169.73 (C_6), 166.17 (C_5), [134.73, 132.78, 131.49, 128.35, 127.38, 127.17, 127.14 (C aromatic including CH=CH)], 57.69 (C_3), and 34.50 (C_2); MS *m/z* (%): 404.2 (M^+, 7), 283.1 (37), 121 (42), 105.1 (100), 77.1 (91), and 51.1 (65).

N'-[1-(4-[2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl]phenyl)-2,5-dioxopyrrolidin-3-yl]-4-methylbenzohydrazide (4)

Reaction of N,N′-(1,4-phenylene) dimaleimide (BMI **1**) (0.01 mol) with 4-methylbenzohydrazide (0.01 mol) in 25 ml of acetonitrile produced a white powder (75% yield), M.P.=240–242°C; FT-IR (KBr, cm^{-1}): 3475, 3338 (NH), 3095, 3078 (=CH Ar), 1780, 1720, 1639 (C=O), 1612 (C=C), 1517, and 1471 (C=C Ar); ^{1}H-NMR (400 MHz, DMSO-d6): 10.12 (d, *J*=6.2 Hz, 1H, H_e, 1), 7.75–7.20 (m, 10H, CH=CH including of aromatic protons), 5.99 (q, *J*=4 Hz, 1H, H_d), 4.27 (dt, *J*=11.2, 5.3 Hz, 1H, H_c), 3.09 (dd, *J*=23.8, 11.2 Hz, 1H, H_a), 2.84 (dd, *J*=23.8, 4.9 Hz, 1H, H_b), and 2.34 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d6): δ 175.27 (C_1), 174.81 (C_4), 169.73 (C_6), 166.15 (C_5), [141.47, 134.74, 131.95, 131.42, 131.28, 129.96, 128.88, 127.39, 127.20, 127.15 (C aromatic including CH=CH)], 57.75 (C_3), 34.51 (C_2), and 20.96 (CH_3); MS *m/z* (%): 418.2 (M^+, 13), 268.1 (15), 198.2 (17), 82.1 (35), 54 (100).

N'-[1-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-[1,1'-biphenyl]-4-yl)-2,5-dioxo pyrrolidin-3-yl] benzohydrazide (5)

Reaction of benzidine bismaleimide (BMI **2**) (0.01 mol) with benzohydrazide (0.01 mol) in 25 ml of acetonitrile yielded a white solid (65% yield), M. P.=270–272°C; FT-IR (KBr, cm^{-1}): 3300, 3221 (NH), 3051 (=CH Ar), 1782, 1712, 1649 (C=O), 1618 (C=C), 1575, and 1504 (C=C Ar); ^{1}H-NMR: δ 10.21 (d, *J*=6.2 Hz, 1H, H_e), 7.85–7.33 (m, 15H,

CH=CH including of aromatic protons), 6.03 (t, *J*=23.8, 11 Hz, 1H, H_d), 4.28 (dt, *J*=10.9, 5.5 Hz, 1H, H_c), 3.10 (dd, *J*=23.8, 11 Hz, 1H, H_a), and 2.84 (dd, *J*=23.8, 5 Hz, 1H, H_b); ^{13}C-NMR (100 MHz, DMSO-d6): 175.30 (C_1), 174.88 (C_4), 169.87 (C_6), 166.20 (C_5), [138.61, 134.74, 133.81, 131.52, 131.11, 128.37, 127.33, 127.22, 127.13 (C aromatic including CH=CH)], 57.67 (C_3), 34.5 (C_2); MS *m/z* (%): 480.2 (M^+, 6), 344.2 (27), 95 (30), 69.2 (45), 43.2 (100).

N'-[1-(4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-[1,1'-biphenyl]-4-yl)-2,5-dioxo-pyrrolidin-3-yl]-4-methylbenzohydrazide (6)

Reaction of benzidine bismaleimide (BMI **2**) (0.01 mol) with 4-methylbenzohydrazide (0.01 mol) in 25 ml of ethanol produced a white powder (70% yield), M. P.=254–256°C. FT-IR (KBr, cm^{-1}): 3469, 3217 (NH), 3041 (=CH Ar), 1782, 1714, 1647 (C=O), 1502, 1471 (C=C Ar); ^{1}H-NMR (400 MHz, DMSO-d6): δ 10.12 (d, *J*=8 Hz, 1H, H_e), 7.83–7.19 (m, 14H, aromatic protons including CH=CH), 5.99 (br.s, 1H, H_d), 4.27 (dt, *J*=11.2, 5.3 Hz, 1H, H_c), 3.09 (dd, *J*=23.8, 11.2 Hz, 1H, H_a), 2.84 (dd, *J*=23.8, 4.9 Hz, 1H, H_b), 2.34 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d6): δ175.55 (C_1), 175.10 (C_4), 170.07 (C_6), 166.38 (C_5), [141.67, 139.38, 134.92, 132.02, 130.18, 129.08, 127.53, 127.42, 126.76, 119.53 (C aromatic including CH=CH)], 57.95 (C_3), 34.73 (C_2), 21.61 (CH_3); MS *m/z* (%): 495.5 (M^++H, 10), 393.4 (8), 119.1 (100), 91.1 (69), 65.1 (39), 43.1 (32).

Cytotoxicity test

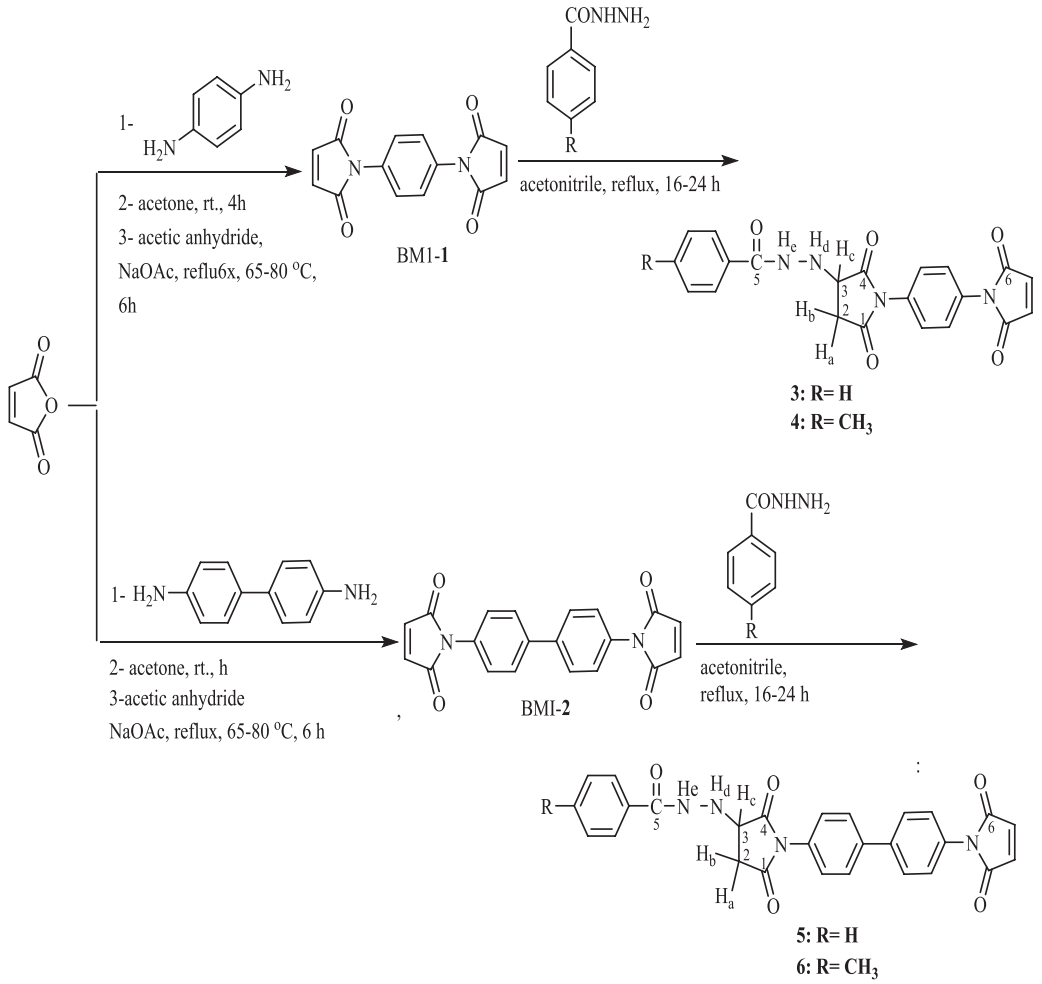
The MTT assay was performed on 96-well plates to determine cell viability. MCF-7 cells were seeded at a density of 1×10^4 cells per well. Cells were treated with 1000 μM of compounds after 24 h or when a confluent monolayer was achieved. Cell viability was determined after 72 h by adding 28 μl of a 2 mg/ml MTT solution (the cells were incubated for 2 h at 37°C). After removing the MTT solution, the crystals in the wells were incubated in 100 μl of DMSO (dimethyl sulfoxide) for 15 min and shaken at 37°C. The absorbency was measured using a microplate reader at 620 nm, and the assay was done in triplicate. The viability of the cells was calculated using the following equation [28]: Cell viability %={[A620 (control)–A620 (treated)]/A620 (control)}×100.

Results and discussion

The maleimide–succinimide derivatives (**3–6**) described here were made in two ways: the first uses diamines with maleic anhydride as building blocks, whereas the second uses benzohydrazide or 4-methylbenzohydrazide as well as bismaleimides. The approach produced bismaleimide (BMI) by reacting the required diamine with maleic anhydride in a solvent such as acetone, yielding bismaleamic acid without additional purification. Following that, in the presence of anhydrous sodium acetate, this intermediate was cyclized in acetic anhydride to give the bismaleimide BMI (**1–2**) [29]. Michael's addition to aromatic primary diamine resulted in the conversion of bismaleimide into maleimide–succinimide derivatives. BMI compounds (**1–2**) reacted with benzohydrazide or 4-methylbenzohydrazide in acetonitrile to afford a product (**3–6**) (Scheme 1).

The chemical structures of all the resulting maleimide–succinimide derivatives were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. The KBr disc was used to determine the properties of the IR-absorption bands (**3–6**). The IR spectrum was used to identify the functional groups of these compounds. The stretching bands corresponding to NH amide and NH groups were observed in the range 3469–3300 and 3377–3217 cm^{-1}, respectively. The absorption bands in the 1782–1676 cm^{-1} area are linked to symmetric C=O, whereas the bands in the 1720–1712 cm^{-1} area are attributed to asymmetric C&9552;O stretching. The bands at 1656–1639 cm^{-1} were due to C&9552;O amide. The two bands at 1637–1612 and 1575–1471 cm^{-1} were attributed to the C&9552;C in the maleimide cycle and C&9552;C aromatic stretching, respectively [30]. Maleimide–succinimide derivatives (**3–6**) were used to generate ^{1}H-NMR spectra. Signals at 2.5 and 3.3 ppm belong to the solvent DMSO-d6 and water, respectively. Because they are attached to carbon adjacent to the chiral center, the doublet of doublets peaks at around 2.84–2.83 and 3.10–3.09 ppm belongs to H_a and H_b protons, respectively. At 4.28–4.27 ppm, H_c was responsible for the triplet doublet. Quartet or triplet peaks at around 6.03–5.99 ppm were assigned to the proton of H_d. Doublet peaks at around 10.21–10.12 ppm were due to H_e. Aromatic protons were given the multiplet peak at roughly 7.85–7.19 ppm, which included the singlet peak for olefin protons corresponding to the maleimide ring [31]. The methyl group is responsible for the singlet at 2.34 ppm. The ^{13}C-NMR of the compounds **3–6** that showed signals at around 175.55–166.17 ppm was attributed to carbonyl groups. The signals of the carbon aromatic ring appeared in the range 141.67–119.32 ppm, including the carbon olefinic ring, and the aliphatic carbons are present in the range 57.95–20.95 ppm. The mass spectra of the **3–6** groups revealed the presence of a molecular ion (*m/z*): 404.2 (M^+), 418.2 (M^+), 480.2 (M^+), and 495 (M^++H). The mass spectra indicated that the structures were right. ^{1}H-NMR, ^{13}C-NMR, and MS spectroscopy were established in accordance with the proposed structure.

Scheme 1



Synthesis of maleimide–succinimide derivatives.

Cytotoxicity evaluation

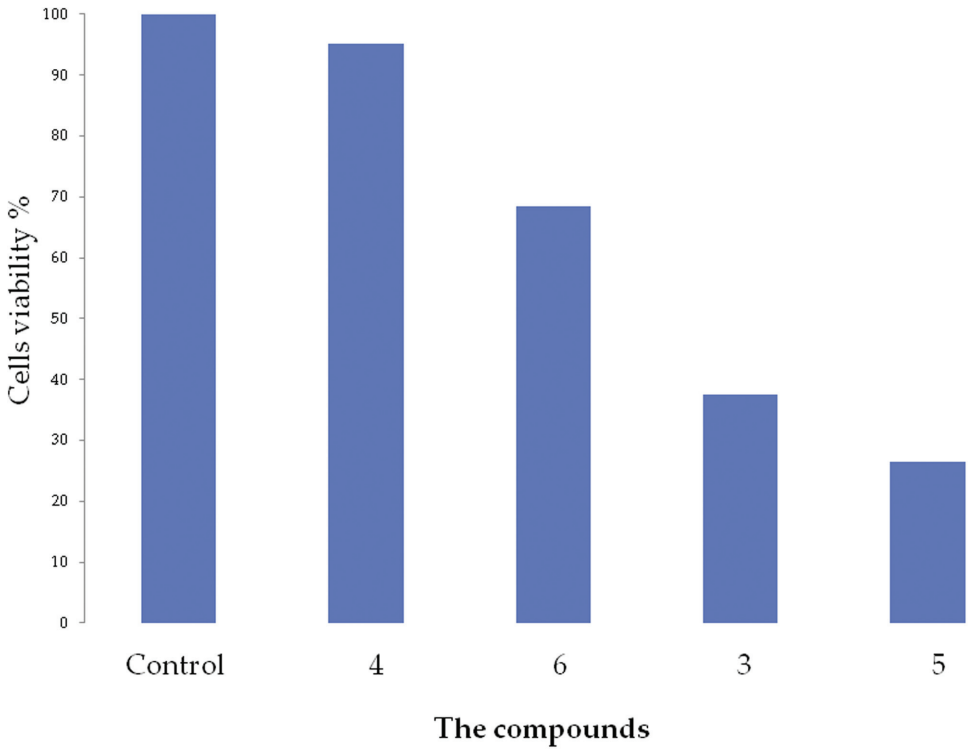
Many studies have shown that heterocyclic derivatives are an important class of compounds that could be used in the development of new anticancer agents [32,33]. Chemotherapy for breast cancer entails the use of drugs to specifically target and destroy cancer cells. Chemotherapy is frequently combined with other breast cancer treatments, such as surgery, radiation, or hormone therapy. Chemotherapy raises the risk of blood clots such as deep-vein thrombosis because breast cancer patients are predisposed to blood clots. As a result, developing new heterocyclic compounds with fewer side effects to combat breast cancer remains a challenge for researchers [34,35]. Some reports showed that maleimide derivatives and succinimide derivatives exhibited promising structures for developing new agents as anticancer agents with merit investigation [36–40].

For the first time, we synthesized new maleimide–succinimide derivatives and tested their toxicity against breast cancer (MCF-7) cells. Figure 1 shows that compound **5** had a higher killing ratio than the other compounds by ~26.4%, followed by compound **3** killing ratio of 37.6%, while compounds **4** and **6** were inactive. The methyl group distinguishes compound **3** from compound **6**, as does compound **5** from compound **4**. The methyl group is a donor group that may limit the ability of compounds **4** and **6** to inhibit the proliferation of MCF-7 cells.

Molecular docking

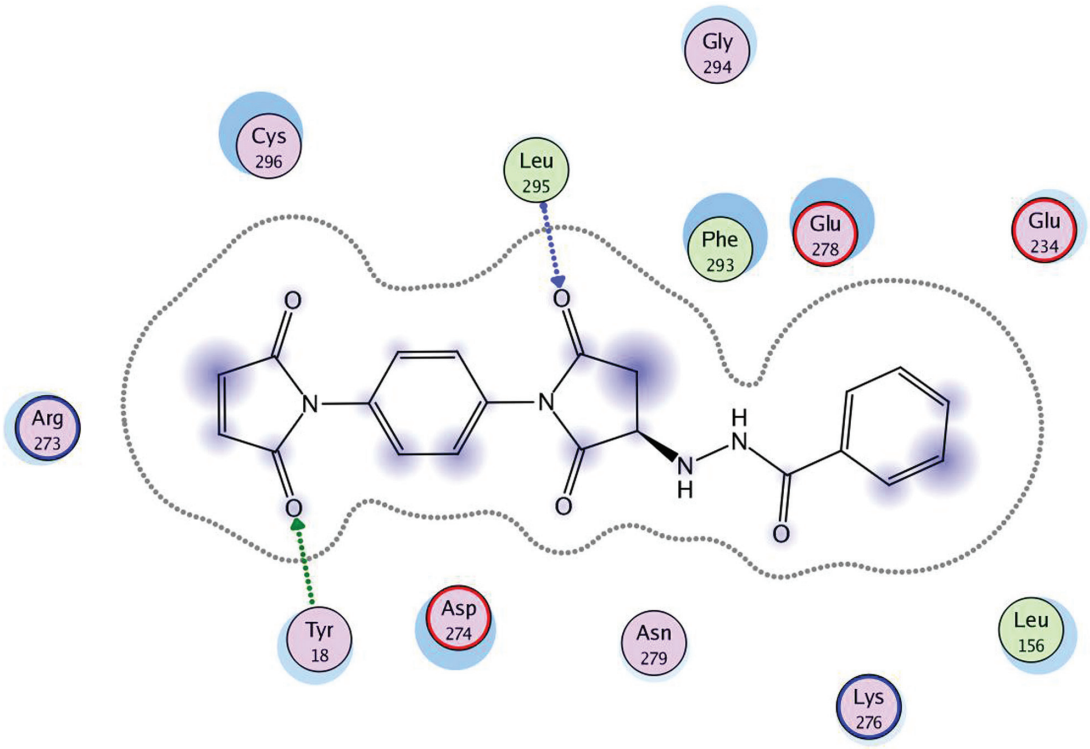
Docking analysis was used to determine how the target proteins' amino acid residues and hydrogen bonds interact with compounds 3 and 5. This method will aid in the identification of the compound as a protein inhibitor. AKT1 and CDK2 are important proteins for cancer cell proliferation and the cell cycle, and they were used in this study to determine the binding efficiency of compounds 3 and 5. Figures 2 and 3 show that the two-dimensional and three-dimensional compound 3 interacted with 5KCV. The affinity energy was −16.11 kcal/mol. The

Figure 1



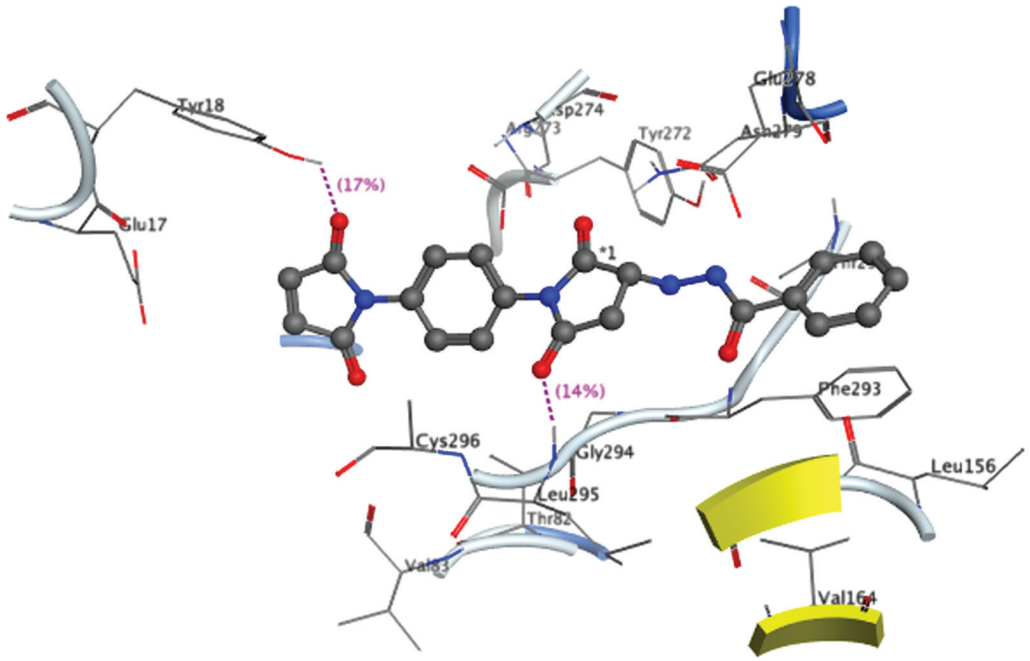
The toxicity test of compounds using MCF-7 cells for 48 h.

Figure 2



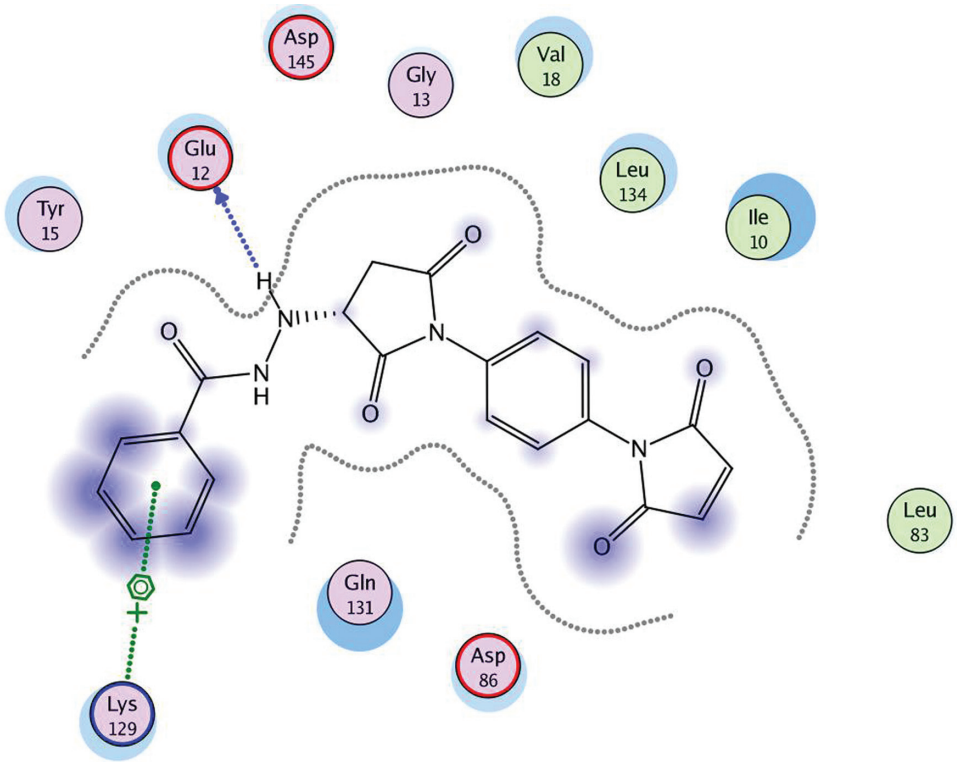
Two-dimensional compound **3** interaction with 5KVC.

Figure 3



Three-dimensional compound **3** interaction with 5KVC.

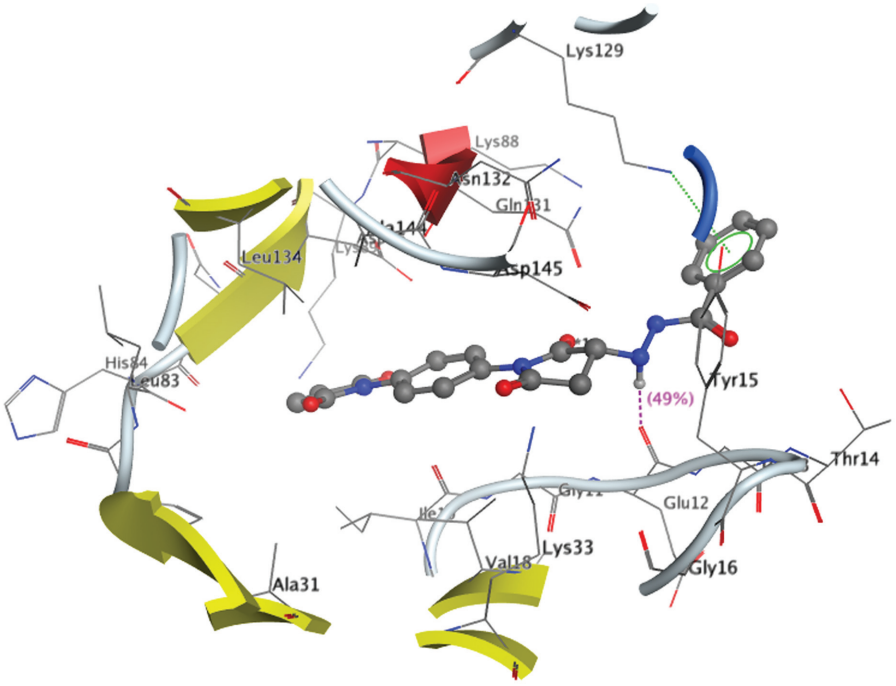
Figure 4



Two-dimensional compound **3** interaction with 4FX4.

number of hydrogen bonds were two, Leu295, distance value 2.07, and Tyr18, distance value 2.22. While in Figs 4 and 5, compound 3 interacted with 4FX3, the affinity energy was −22.39 kcal/mol, the number of hydrogen bonds was one, Glu12 distance value 1.8, and Tyr18 distance value 2.22, as shown in Table 1. Figures 6 and 7 show that the two-dimensional and three-dimensional compound 5 interacted with 5KCV.

Figure 5



Three-dimensional compound **3** interaction with 4FX3.

Table 1 Docking analysis of compounds 3 and 5 interaction with 5KCV and 4FX3, showed the affinity energy, root-mean-square deviation, amino acid residue, and H bonding

Compound (ligand)	Protein (receptor)	Affinity energy (kcal/mol)	RMSD	H bonding		
				Number of H bonding	Amino acid	H bonding distance (Å)
3	4FX3	−22.39	2.27	1	Glu12	1.80
	5KCV	−16.11	1.61	2	Leu295	2.07
					Tyr18	2.22
5	4FX3	−19.94	1.93	1	Lys129	2.54
	5KCV	−21.34	1.90	2	Glu278	1.85
					Gln79	2.57

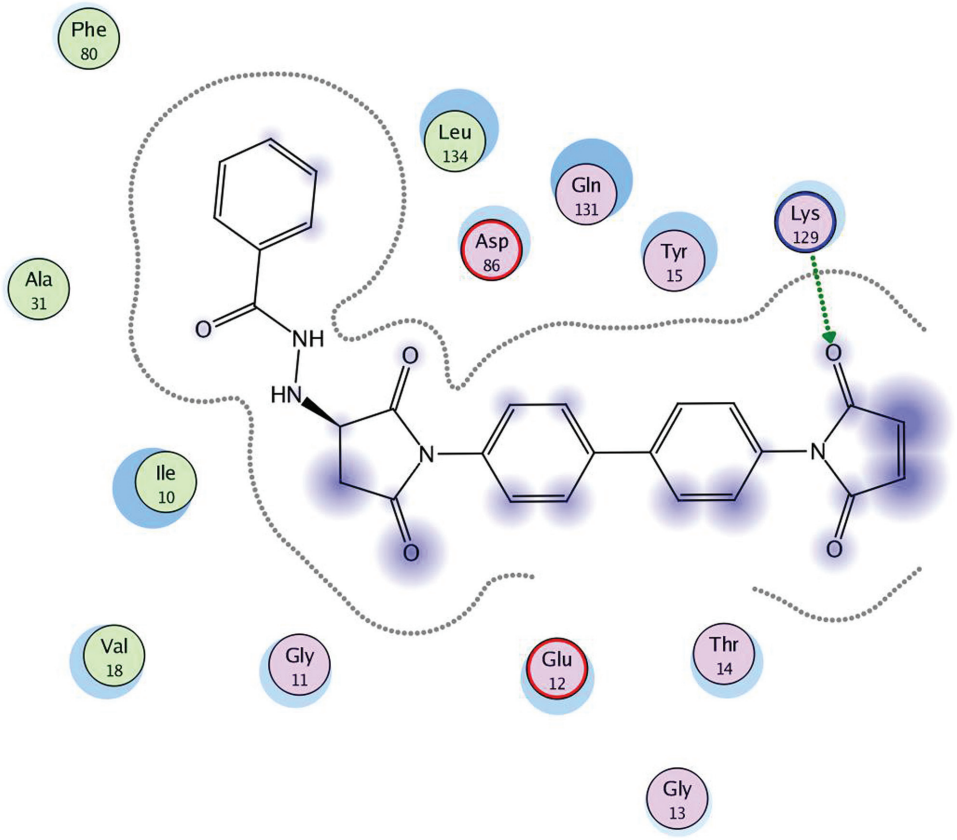
RMSD, root-mean-square deviation.

The affinity energy was −21.34 kcal/mol. The number of hydrogen bonds were two, Glu278, with a distance value of 1.85, and Gln79, with a distance value of 2.57. While in Figs 8 and 9, compound 5 interacted with 4FX3, the affinity energy was −19.94 kcal/mol, the number of hydrogen bonds was one, Lys129, distance value 2.54, as shown in Table 1. Furthermore, the average deviation between the corresponding atoms of two proteins is given by root-mean-square deviation (RMSD) values. Efficient algorithms have been developed to determine the best orientation of two structures with the least amount of RMSD. RMSD less than 2.0 clearly corresponds to good docking solutions. Docking solutions with RMSD between 2.0 and 3.0 deviate from the reference position while maintaining the desired orientation. Compound 3 with 4FX3=2.270, compound 5 with 4FX3=1.937, compound 3 with 5KCV=1.619, and compound 5 with 5KCV=1.900, as shown in Table 1. Compound 3 has a lower RMSD value than 5KCV, while compound 5 has two lower RMSD values than 4FX3 and 5KCV. Both compounds may be involved in the interaction of 4FX3 and 5KCV proteins.

Conclusion

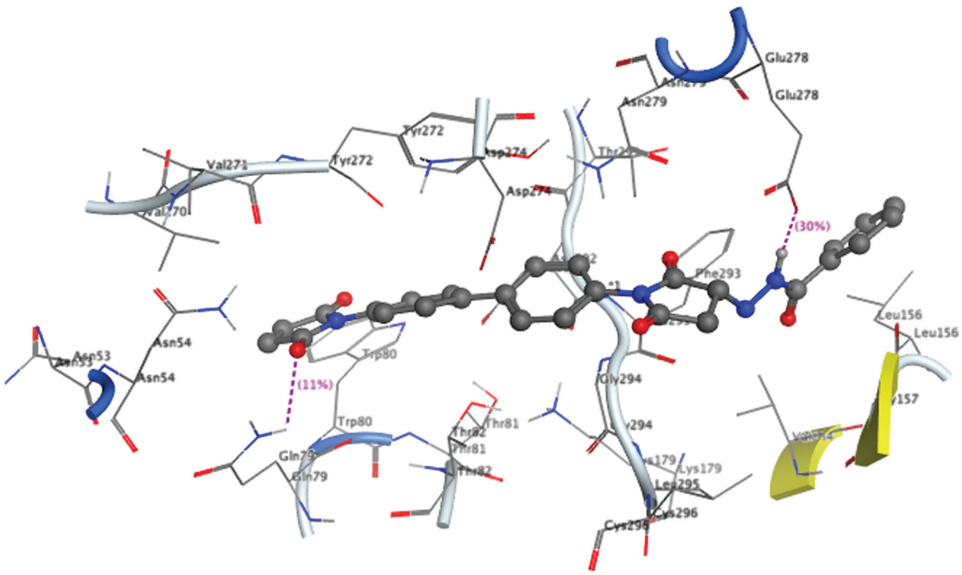
Four new maleimide–succinimide derivatives were synthesized and characterized using FT-IR spectroscopy, 1H-NMR, 13C-NMR spectroscopy, and mass spectrometry. The compounds were tested against breast cancer cells (MCF-7). The compounds N'-[1-(4- (2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl) phenyl)-2,5- dioxopyrrolidin-3-yl] benzohydrazide (**3**) and N'-[1-(4-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-

Figure 6



Two-dimensional compound **5** interaction with 5KVC.

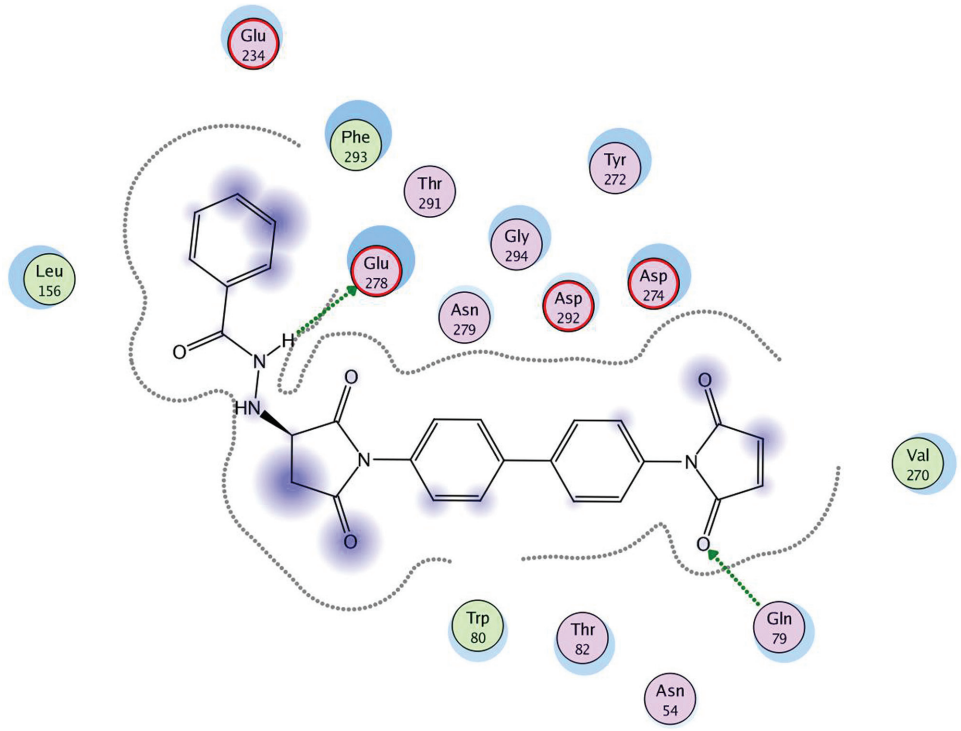
Figure 7



Three-dimensional compound **5** interaction with 5KVC.

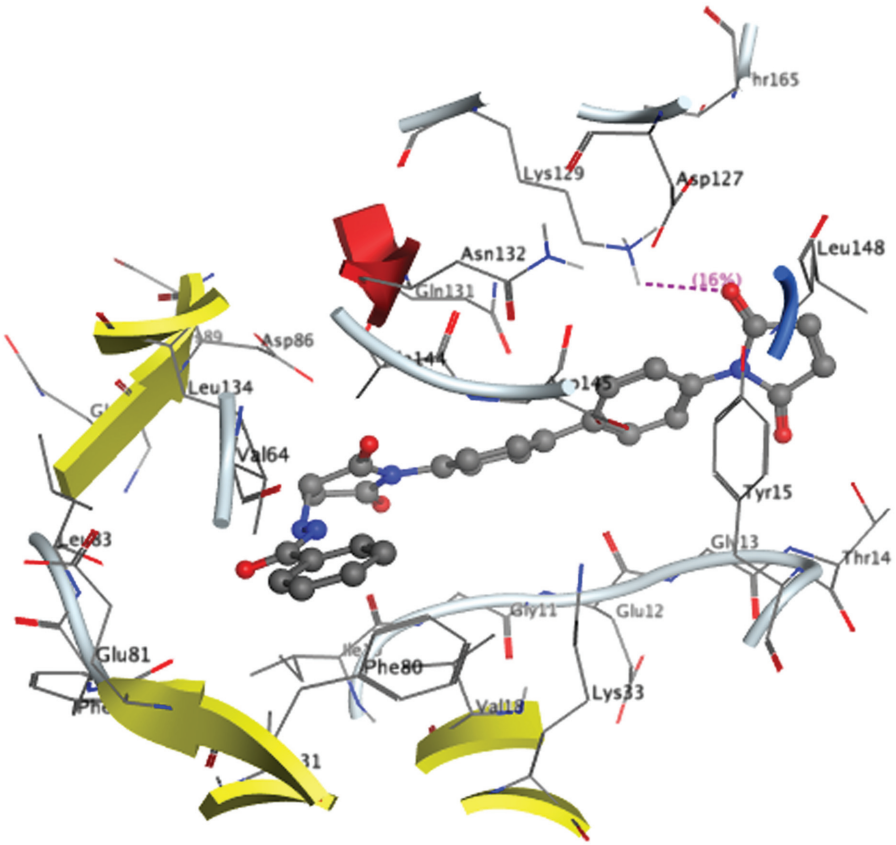
1-yl)-[1,1'-biphenyl]-4-yl)-2,5-dioxopyrro lidin-3-yl] benzohydrazide (**5**) were more toxic. Furthermore, molecular docking studies with the AKT1 and CDK2 proteins revealed the target amino acid residues and hydrogen bonds of both compounds. Compounds **3** and **5** will be investigated further in order to investigate and develop their anticancer activity against breast cancer.

Figure 8



Two-dimensional compound **5** interaction with 4FX4.

Figure 9



Three-dimensional compound **5** interaction with 4FX3.

Acknowledgements

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Nil.

Conflicts of interest

There are no conflicts of interest.

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