Anti-Cancer Activity, DFT and molecular docking study of new BisThiazolidine amide

Article *in* Results in Chemistry · October 2024

DOI: 10.1016/j.rechem.2024.101835

8 authors, including:

Ahmed A. Majed
University of Basrah

Kawkab Ali Hussein
University of Basrah

Dawood Abid
University of Basrah

Mohammed Aufy
University of Vienna

Results in Chemistry 12 (2024) 101835

Contents lists available at ScienceDirect

Results in Chemistry

journal homepage: www.sciencedirect.com/journal/results-in-chemistry

Anti-Cancer Activity, DFT and molecular docking study of new BisThiazolidine amide

Haider A. Omran [a,b], Ahmed A. Majed [a,*], Kawkab Hussein [a], Dawood S. Abid [a], Mostafa A. Abdel-Maksoud [c], Ahmed Elwahsh [d,e], Mohamed Aufy [f,*], Mohamed H. Kotob [f,g,*]

[a] *Department of Chemistry College of Education for Pure Sciences, Basrah University, Basrah, Iraq*
[b] *Ministry of Education, General Directorate of Education in Basra Governorate, Almdena Education Department, Iraq*
[c] *Botany and Microbiology department, College of Science, King Saud University, Saudi Arabia*
[d] *Central Radiology Institute, Kepler University Hospital GmbH, Linz, Austria*
[e] *Department of Molecular and Translational Medicine, Division of Biology and Genetics, University of Brescia, Brescia. Italy*
[f] *Department of Pharmaceutical Sciences, Division of Pharmacology and Toxicology, University of Vienna, Vienna, Austria*
[g] *Department of Pathology, Faculty of Veterinary Medicine, Assiut University, Assiut 71526, Egypt*

ARTICLE INFO

Keyword:
Bisthiazolidine Amide. Anticancer. Molecular Docking. DFT

ABSTRACT

In this study, a series of bis amide thiazolidine derivatives (Q1-Q6) were synthesized and their anticancer activity was evaluated against prostate (PC3) and breast (MCF7) cancer cells and normal cells line activity was evaluated against breast (MCF10), prostate (PNT1A) and living human cells (HUVEC) cancer cells. The thiazolidine rings were built from penicillamine and aromatic aldehydes (A1-A6), then converted to acetyl thiazolidines (B1-B6) using acetic anhydride, and finally linked with phenylene diamine to form the final compounds (Q1-Q6). Notably, compounds Q1 and Q3 displayed the highest activity against PC3, with IC50 values of 81 and 89 μg/ml, respectively. Docking simulations were performed for Q1, Q4, and Q5 against protein structures related to cancer (2FVD and 1SJ0). Additionally, DFT calculations were used to determine various molecular properties like HOMO/LUMO energies, band gap, and other descriptors, providing insights into the compounds' stability and reactivity.

Introduction

Cancer is a complex and fatal disease that affects a large number of organs in the body and spreads rapidly. This is the most harmful and common characteristic of all cancer diseases. Therefore, it represents a serious challenge to human health and well-being. Among the most common and harmful cancers are breast cancer and prostate cancer. Therefore, there is an urgent and necessarily need to discover and develop therapeutic organic compounds, develop medicines, and increase their effectiveness to get rid of the disease or stop its spread [1,2]. Chemistry contains a lot of wonderful and useful compounds in practical and scientific life, which are used to treat diseases and stop their spread, among those compounds, heterocyclic were considered first step of life begins in disease treatment [3,4]. Among those heterocyclic compounds of great importance, Thiazolidine has been described, which is a pentacyclic containing sulfur nitrogen in its composition, resulting from the condensation of carbonyl compounds with cysteine for its ability to release cysteine, and the biological activity properties of some substituted thiazolidine carboxylic acids have been studied and proven2- alkyl and aryl [5,6].

Thiazolidine derivatives have wide applications in medicinal and clinical chemistry, being effective as anticancer, anti-inflammatory [7], antioxidant, antimicrobial, anti-fungi, anti-HIV, and other important biological activities [8,9]. Thiazolidine-4-carboxylic acid is a condensation product of D-penicillamine or L-cysteine with formaldehyde [10]. It is an effective nitrile-restricting agent in the human body and may inhibit the endogenous formation of carcinogenic N-nitroso compounds [11]. Penicillamine has two types (D-penicillamine and L-penicillamine) with a carboxylic acid group which is biologically effective [12], which is similar in structure to the compound Alpha Cysteine, but with the two hydrogen atoms replaced by the m-CH2 group of the acid the amino L-cysteine. Among the two similar substances, L-penicillamine is toxic because it inhibits the action of pyridoxine, also known as vitamin B6 (22) [13]. Penicillamines were used as an anti-rheumatic drug, given to

---

* Corresponding authors.
E-mail addresses: eduppg.ahmed.majed@uobasrah.edu.iq (A.A. Majed), mohammed.aufy@univie.ac.at (M. Aufy), kotobm84@univie.ac.at (M.H. Kotob).

https://doi.org/10.1016/j.rechem.2024.101835
Received 26 August 2024; Accepted 30 September 2024

adults and children with rheumatoid arthritis, slowing it down and sometimes stopping the progression of the disease [14,15]. It is also used as a metal binder in cases of metal poisoning, and its goal is to remove lead, mercury, copper, or arsenic from the body. Penicillamine binds to these minerals and forms a chemical compound that the body can get rid of by excretion [16]. It has been demonstrated that density functional theory (DFT) is a workable approach for reasonably priced, highly accurate molecular property determination. Molecular docking is to use computational techniques to predict the structure of the ligand-receptor complex and led to drug discovery [17–19]. Finally, DFT, molecular docking and other computational studies of cyclic compounds including thiazolidine have been used to demonstrate the vast progress in understanding molecules as pharmaceutical compounds. Therefore, DFT has been widely used as a measure of the electronic structure, stability and interactions of these cyclic molecules [20,21], which gives a wonderful idea of the biological activity of these compounds and their potential use as drugs, the studies indicate the possibility of using different levels of DFT, such as B3LYP/6-311Gand B3LYP/6–311++G, to analyze different electronic properties as well as HOMO, LUMO and DG energies, electronegativity, ionization sites and other different factors, as well as knowing the electrostatic sites of MEPs binding and understanding receptor interactions [21–23]. Therefore, this technique provides a clear understanding of the chemical interaction, electronic and inductive properties of different thiazolidine derivatives and provides a clear study of target proteins and their biological activity [23–25]. New studies have also indicated the importance of molecular docking in the discovery of pharmaceutical compounds and determining similarity with other pharmaceutical compounds. For example, a study indicated the use of pkCSM and ADME and the drug movement of heterocyclic compounds [26–28]. Another study showed the use of thiazolidine derivatives as inhibitors of VEGFr using molecular docking and proving their effectiveness on living cells. Another study on the use of sulfonamide compounds containing heterocyclic compounds by molecular docking and DFT gave effectiveness in the biological factor, as well as the use of some dyes containing heterocyclic rings as pharmaceutical compounds. Therefore, this technology has made it possible to quickly screen and prepare heterocyclic compounds, including thiazolidine, improve biological activity, increase their effectiveness, and reduce the time in drug discovery. [29–33]. In this study, we will show and describe the synthesis, characterization and biological activity against cancer cells of some bis thiazolidine-4-carboxylic amide derivatives resulting from the reaction of D-penicillamine with benzaldehyde derivatives and the study of computational chemistry represented by molecular docking and DFT.

Materials and methods

Materials

Characterization of synthesized compounds included melting point determination, FTIR spectroscopy, and $^1H/^{13}C$ NMR analysis using a Bruker-400 MHz spectrometer with DMSO-d_6 and TMS as reference. Chemical shifts were reported relative to the solvent or decomposing peaks (δ: H,3.3and2.5 ppm),and coupling constants were expressed in Hz. The abbreviations for a signs used are as follows: s;(single), d; (double), t; (triple), m; (multiple) and dd; (double doubling).). Additionally, mass spectra were acquired using an Agilent 5975 quadrupole analyzer with EI technology (70 eV) to identify the molecular ions.

General method for preparing thiazolidine derivatives [A1, A2,A3, A4, A5, A6]

1.49 g (10 mmole) of D- penicillamine with (10mmole) of aromatic aldehyde derivatives in the presence ethyl alcohol (20 ml) and water (100 ml) in flask (250 ml) with continuous magnetic shaking at r. t for 8 h where a precipitate was observed. The result was filtered, and recrystallized with a mix of water and ethyl alcohol at a ratio of (3:1), and the reaction was followed up by using (TLC) thin layer chromatography using a solvent of (Ethanol: Chloroform) at a ratio of (1:9). Thiazolidine cycle (Fig. 1) has two kinds of diastereomers, they are difficult separated trans-(2S,4R) and cis-(2R,4R) because the presence of two atoms chiral, the isomers percentages (trans/ cis) were powerfully dependent on solvent [34–36].

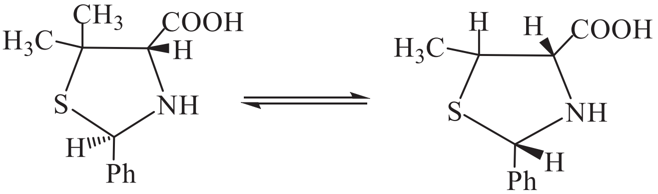


Fig. 1. Diastereoisomer of thiazolidine.

General method for preparation of 3-Actyl thiazolidine derivatives [B1, B2, B3, B4, B5, B6]

The 10 mmole of A1 to A6 compounds were dissolved in solution of (6 %)sodium carbonate (Na2CO3) (55 ml) in a 250 ml of flask, then the solution was cooled in 0° C an ice bath to and then (1.02 ml) was added to a mixture of acetic anhydride in drops over 5 min. The reaction was left on the magnetic stirrer for one h, after stopping a reaction the mix was acidified using a (10 %) hydrochloric acid and a brine solution (NaCl) was added to it for the purpose of equivalence, and the reaction was extracted by ethyl acetate (2 x 50 ml). The extracted organic layer was washed with water and dried using Anhydrous magnesium sulfate (Na2SO4) and the solvent was evaporated after that, it results a solid. The crystallization was done by a mixture of methanol with water in a ratio of (3:1) The reaction was followed up by using TLCtechnique using Solvent (ethyl acetate: Hexane) in a ratio of (7:3). [37,38].

3-Acetyl-2-(4-chlorophenyl)-5,5-dimethylthiazolidine-4-carboxylic acid (B1). Compound (B1): White, m.p: 203–205 ℃, Yield: 80 %. FT-IR (KBr): 3419 m (OH), 3080w (C-HAr), 2920w (C-Halph.), 1737 s (C = O). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm); show the two isomers (diastereoisomer). Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 83:17). Major: δ1.29 s, 1.57 s (6H, 2CH3), δ1.75 s (3H, CH3), δ4.51 s (1H, H4), δ6.42 s (1H, H2), δ7.42–7.77d (4H, J = 8 Hz, H-Ar), δ13.02 s(1H, OH). Minor: δ1.31 s, 1.58 s (6H, 2CH3), δ2.03 s (3H, CH3), δ4.69 s (1H, H4), δ6.16 s (1H, H2), δ12.99 s (1H, OH).

3-Acetyl-5,5-dimethyl-2-phenylthiazolidine-4-carboxylic acid (B2). Compound (B2): White, m.p:220–218 ℃,Yield: 74 %. FT-IR(KBr): 3431 m (OH), 3020w (C-HAr), 2964w (C-Halph.), 1734 s (C = O). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm); shown two isomers. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 93:7). Major: δ1.28 s, 1.57 s (6H, 2CH3), δ1.74 s (3H, CH3), δ4.51 s (1H, H4), δ6.41 s (1H, H2), δ7.2–7.7.7d, t (5H, J = 8 Hz, H-Ar), δ12.93 s (1H, OH). Minor: δ1.32 s, 1.56 s (6H, 2CH3), δ2.01 s (3H, CH3), δ4.68 s (1H, H4), δ6.2 s (1H, H2), δ12.93 s (1H, OH).

3-Acetyl-5,5-dimethyl-2-(3-nitrophenyl) thiazolidine-4-carboxylic acid (B3). Compound (B3): Yellow, m.p: 230–232 ℃,Yield: 65 %,. FT-IR (KBr): 3448 m (OH), 3061w (C-HAr), 2954w (C-Halph.), 1739 s (C = O) and 1336, 1508 (NO2). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): show two isomers. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 70: 30). Major: δ1.26 s, 1.58 s (6H,2CH3), δ1.77 s (3H, CH3), δ4.55 s (1H, H4), δ6.62 s (1H, H2), δ7.4–7. 8.2d, t, s (4H, J = 8 Hz, H-Ar), δ13.05 s (1H, OH). Minor: δ1.34 s, 1.61 s (6H, 2CH3), δ2.02 s (3H, CH3), δ4.74 s (1H, H4), δ6.36 s (1H, H2), δ13.05 s (1H, OH).

3-Acetyl-5,5-dimethyl-2-(3-nitrophenyl) thiazolidine-4-carboxylic acid (B4). Compound (B4): White, m.p:224–227 ℃,Yield: 83 %. FT-IR(KBr): 3446 m (OH), 3020w (C-HAr), 2964w (C-Halph.), 1734 s (C = O).

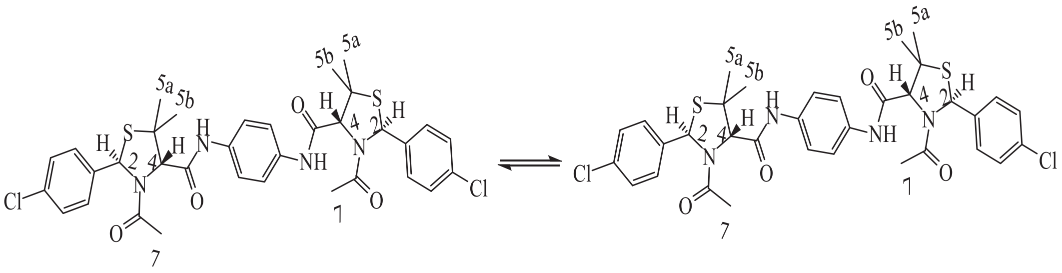


Fig. 2. Synthesis Diastereoisomer of bis amide thiazolidine derivatives.

^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): demonstration two isomers. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 83: 17). Major: δ1.4 s (CH3-Ar), 1.24 s, 1.55 s (6H, 2CH3), δ1.75 s (3H, CH3), δ4.51 s (1H, H4), δ6.52 s (1H, H2), δ7.3–7.7d (4H, J = 8 Hz, H-Ar), δ13.1 s (1H, OH). Minor: δ1.35 s, 1.61 s (6H, 2CH3), δ2.00 s (3H, CH3), δ4.74 s (1H, H4), δ6.16 s (1H, H2), δ13.1 s (1H, OH).

3-Acetyl-2-(4-methoxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic acid (B5). Compound (B5): Yellowish White, m.p:209–212 °C, Yield: 88 %. FT-IR(KBr): 3400 m (OH), 3028w (C-HAr), 2924w (C-Halph.), 1734 s (C = O) and 1197 (C-O). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): shown two diastomer. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 96: 4). Major: −δ1.27 s, 1.52 s (6H, 2CH3), δ1.74 s (3H, CH3), 3.77(OCH3) δ4.39 s (1H, H4), δ6.24 s (1H, H2), δ6. 7–8.1.2d (4H, J = 8 Hz, H-Ar), δ12.85 s (1H, OH). Minor: δ1.3 s, 1.54 s (6H, 2CH3), δ2s (3H, CH3), 3.78 s (OCH3), δ4.33 s (1H, H4), δ6.25 s (1H, H2), δ12.85 s (1H, OH).

3-acetyl-5,5-dimethyl-2-(4-nitrophenyl) thiazolidine-4-carboxylic acid (B6). Compound (B6): Yellow, m.p:224 dec, Yield: 88 %. °C. FT-IR (KBr): 3450 m (OH), 3080w (C-HAr), 2918w (C-Halph), 1730 s (C = O) and 1330, 1517 (NO2). ^{1}HNMR (400 MHz, DMSO-d_6, δ ppm): show two diastomers. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 85: 15). Major: δ1.26 s, 1.57 s (6H, 2CH3), δ1.73 s (3H, CH3), δ4.51 s (1H, H4), δ6.44 s (1H, H2), δ7.3–7.88 d (4H, J = 8 Hz, H-Ar), δ12.93 s (1H, OH). Minor: δ1.33 s, 1.53 s (6H, 2CH3), δ1.99 s (3H, CH3), δ4.67 s (1H, H4), δ6.18 s (1H, H2), δ12.93 s (1H, OH).

General synthesis of di amide thiazolidine compounds [Q1, Q2, Q3, Q4, Q5, and Q6]

Mix 4 mmole of [B1-6] compounds with 0.82 g (4 mmole) of N,N′-dicyclohexyl carbodiimide (DCC) and 0.54 g(HOBt) (4mmole) of 1-Hydroxybenzotriazole and (20 ml) of Dichloromethane as a solvent in acircular flask (100 ml) and left the solution with continuous magnetic at 0 Cfor (10) min., until the rection became clear, then (2 mmole) of a p-phenylene diamine was added to the reaction and left under continuous magnetic stirrer for (24) h at r. t, after which the formation of a precipitate was observed, and then the reaction was filtered to get rid of a precipitate, which is dicyclohexylurea (DCU). The filtrate solution was diluted with (20 ml) Dichloromethane. The mix was washed successively with a solution (5 %) Sodium bicarbonate, then with (10 %)citric acid, then with a solution sodiumchloride and finally with water. The reaction was dried by adding Anhydrous magnesium sulfate, then filtered and evaporated to make a precipitate recrystallized by a mixture of ethyl alcohol and water (1:1) The chemical reactor was carried out using (TLC) using a solvent (Formic acid, benzene, tetrahydrofuran) at a ratio of (2:6:2) [39,40].

N,N'-(1,4-phenylen) bis(3-acetyl-2-(4-chlorophenyl)-5,5-dimethylthiazolidine-4-carboxamide) (Q1). Compound (Q1) was described above: Yellow Crystals, m.p:187-188°C, Yield: 28 %. FT-IR(KBr):3327w (NH), 1737 s, 1658 m (C = O amide), 1627 m (NH bending). ^{1}HNMR spectra (400 MHz, DMSO-d_6,δ ppm); show the two isomers (Di stereoisomer) (Fig. 2). Trans (2S, 4R) major and Cis (2R,4R) minor(ratio 70:30).Major: δ1.44 s, 1.62 s (6H, 2CH3), δ1.7 s (3H, CH3), δ4.74 s (1H,H4), δ6.38 s (1H, H2),δ7.33d, 7.6d (8H,J = 8, H-Ar), 7.93d (4H, J = 8, H-Ar phenylene),δ10.55 s (1H, NH).Minor:δ1.47 s, 1.52 s(6H, 2CH3), δ2.1 s (3H, CH3),δ4.61 s (1H,H4),δ6.31 s (1H,H2), δ10.44 s (1H, NH).^{13}CNMR spectrum (100 MHz, DMSO-d_6, δ ppm); δ-23.06 (CH3), 31.23 (2CH3), 52.3(C5), 65.2 (C4), 72.12 (C2), 127.9, 128.3, 128.9, 132, 141.2, 150.85 (C-Ar), 168.32, 169.95 (C = O amide). Mass spectrum (EI, 70 ev); *m/z*:699($M^{\cdot+}$), Fragment: 43, 270, 374 and 91 peas peak.

N, N'-(1,4-phenylene) bis(3-acetyl-5,5-dimethyl-2-phenylthiazolidine-4-carboxamide) (Q2). Compound (Q2) is described: Yellow Crystals, m.p: 191–193 °C, Yield: 32 %. FT-IR(KBr): 3265w(NH), 1697 m, 1635 m (C = O amide), 1591 m (NH bending). ^{1}HNMR spectrum (400 MHz, DMSO-d_6, δppm); shown the two isomers (Di stereoisomer). Trans (2S, 4R) major and Cis (2R,4R) minor (ratio80:20). Major:δ1.47 s, 1.66 s (6H, 2CH3), δ1.79 s (3H, CH3),δ4.75 s (1H, H4),δ6.4 s (1H, H2), δ7.4d, 7.52 t,7.6d (10H,J = 8,4Hz, H-Ar),7.99d (4H, J = 8, H-Ar phenylene),δ10.59 s (1H, NH).Minor:δ1.4 s, 1.61 s (6H,2CH3), δ2.1 s (3H, CH3), δ4.61 s (1H, H4),δ6.12 s (1H, H2), δ10.56 s (1H, NH).^{13}CNMR spectra (100 MHz,DMSO-d_6,δppm); δ-25.1 (CH3), 31.4, 33.15 (2CH3), 52.5(C5), 64.6 (C4), 72.1 (C2), 127.4, 127.97, 128.1,128.87, 130.28, 131.7, 41.38 (C-Ar), 165.7, 168.3 (2C = O amide). Mass spectra (EI, 70 ev); *m/z*:630 ($M^{\cdot+}$), Fragment: 43, 207, 77, 285 and 109 peas peak.

N, N'-(1,4-phenylene) bis(3-acetyl-5,5-dimethyl-2-(3-nitrophenyl) thiazolidine-4-carboxamide) (Q3). Compound (Q3) has described Beige Crystals, m.p: 210–212 °C,Yield: 35 %. FT-IR(KBr): 3388 m(NH), 1710 m, 1662 m (C = O amide), 1600 m (NH bending). ^{1}HNMR spectrum (400 MHz, DMSO-d_6, δppm); show the two isomers (Di stereoisomer). Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 55:45).Major:δ1.47 s, 1.68 s (6H, 2CH3), δ2.13 s (3H, CH3),δ4.55 s (1H, H4),δ6.26 s (1H, H2), δ7.5d, 7.57 t, 8.12 s(8H, J = 8, H-Ar),7.93d (4H, J = 8, H-Ar phenylene),δ10.58 s (1H, NH).Minoer:δ1.4 s, 1.74 s (6H,2CH3),δ1.83 s(3H, CH3),δ4.78 s(1H,H4),δ6.59 s(1H,H2),δ10.45 s(1H,NH).^{13}CNMRspectra (100 MHz,DMSO-d_6,δppm);δ-22.4 (CH3), 30.44 (2CH3), 51(C5), 64.9 (C4), 73.3(C2),121, 125.97, 127, 127.9, 128.4, 128.4, 128.7, 141.2, 150.2 (C-Ar). Mass spectrum (EI, 70 ev); *m/z*:720($M^{\cdot+}$), Fragment: 43, 121, 153, and 270 peas peak.

N, N'-(1,4-phenylene) bis(3-acetyl-5,5-dimethyl-2-p-tolylthiazolidine-4-carboxamide) (Q4). Compound (Q4) was described: Yellow, m.p:187-190°C, Yield: 25 %. FT-IR(KBr): 3186w (NH),1715 s,1658 m (C = O amide), 1614 m (NH bending). ^{1}HNMR spectrum (400 MHz, DMSO-d_6, δ ppm);Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 65:35). Major: δ1.29 s (6H, CH3-Ar), 1.47 s, 1.61 s(6H, 2CH3), δ1.72 s (3H, CH3), δ4.76 s (1H, H4), δ6.38 s (1H, H2), δ7.35d, 7.46d (8H, J = 8, H-Ar), 7.93d(4H, J = 8, H-Ar phenylene), δ10.39 s (1H, NH). Minor: δ1.25 s (6H, CH3-Ar), 1.32 s, 1.69 s (6H, 2CH3),δ2.1 s (3H, CH3), δ4. 36 s (1H, H4), δ6.12 (1H, H2), δ10.39 s (1H, NH).^{13}CNMR spectra (100 MHz,DMSO-d_6, δppm); δ-14.45 (CH3-Ar), 25.1 (CH3), 31.43, 33.1 (2CH3), 52.5 (C5), 64.6 (C4), 72.03 (C2),127.4, 127.9, 128.1, 128.9, 130.2, 131.7, 141.4, 155 (C-Ar), 165.76, 168.3 (C = O amide). Mass spectra(EI, 70 ev); *m/z*: 658($M^{\cdot+}$), Fragment: 43, 109, 163, 316 and 276 peas peak.

N, N'-(1,4-phenylene) bis(3-acetyl-2-(4-methoxyphenyl)-5,5-dimethylthiazolidine-4-carboxamide) (Q5). Compound (Q5) is described above: Yellow Crystal, m.p:179-181ºC, Yield: 20 %. FT-IR(KBr):3170w (NH), 1701 s (C = O amide), 1606 m (NH bending), 1222(C-O). ^{1}HNMR spectrum (400 MHz,DMSO-d_6, δ ppm); shown the two isomers. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio 90:10).Major: δ1.42 s, 1.59 s (6H, 2CH3), δ1.72 s (3H, CH3),δ3.75 s (OCH3),δ4.62 s (1H, H4),δ6.56 s (1H, H2),δ7.46d, 7.6d, 8.33d (8H,J = 8, H-Ar),7.93d (4H, J = 8, H-Ar phenylene),δ10.55 s (1H, NH).Minor:δ1.25 s,1.53 s (6H, 2CH3), δ2.1 s (3H, CH3), 3.79 s (OCH3), δ4.78 s (1H, H4),δ6.38 s (1H, H2), δ10.45 s (1H,NH).^{13}CNMR spectra (100 MHz, DMSO-d_6, δppm); δ-23 (CH3), 31.2 (2CH3), 52.3(C5),62.7 (OCH3), 65.3 (C4), 72.1 (C2), 127.98, 128.3, 128.7, 132.2, 132.9, 141.6, 156.7 (C-Ar), 168.3, 169.9 (C = O). Mass spectrum (EI, 70 ev); *m/z*: 690(M$^{\cdot+}$), Fragment: 43, 89,135, 302 and 428 peas peak.

N, N'-(1,4-phenylene) bis(3-acetyl-5,5-dimethyl-2-(4-nitrophenyl) thiazolidine-4-carboxamide) (Q6). Compound (Q6) was described: Orange Crystals, m.p:199–201 dec. °C, Yield: 35 %. FT-IR(KBr): 3327w (NH), 1735 s (C = O amide), 1627 m (NH bending), 1350, 1560 m (NO2).^{1}HNMR spectra: (400 MHz, DMSO-d_6, δ ppm); shown the two isomers. Trans (2S, 4R) major and Cis (2R,4R) minor (ratio70:30). Major: δ1.45 s, 1.59 s (6H, 2CH3), δ1.7 s (3H, CH3),δ4.75 s (1H, H4), δ6.4 s (1H, H2), δ7.42d,7.78d, 8.79d (8H,J = 8, H-Ar), 7.88d (4H, J = 8, H-Ar phenylene),δ10.89 s (1H, NH).Minor:δ1.38 s, 1.61 s (6H, 2CH3), δ2.08 s (3H, CH3),δ4.62 s (1H, H4),δ6.12 s (1H, H2), δ10.44 s (1H, NH).^{13}CNMR spectrum (100 MHz,DMSO-d_6,δppm); δ-23.06 (CH3), 31.2 (2CH3), 52.3(C5), 65.3 (C4), 72.1 (C2), 127.9, 128.3,128.7, 132.2,132.9, 141.6, 149.6 (C-Ar). Mass spectrum (EI, 70 ev): *m/z*: 720 (M$^{\cdot+}$), Fragment: 43,134,332, 458 and 270 peas peak.

MTT assay study

The synthesis compounds(Q1-Q6) studied the orientation of two types of cancer cells, (PC3, MCF7) and.

two types of normal cells (MCF10, HUVEC and PNT1A) Acytotoxic effect of the prepared compound was evaluated against the following (cell lines) human cancer. All obtained from PC3 (human prostate cancer) and MCF7(human breast cancer) were bought from National Cells Banks in Iran (Pasteur Institute). The PC3 and MCF7 Cells were full-grown in (RPMI-1640) and medium with 10 % FBS(Gibco) complemented with antibiotics [100U/ml penicillin and 100 µg /ml streptomycin]. The Cell was maintained at 37 °C under air humidified contain (5 %) CO2 and was passaged using trypsin /EDTA (Gibco) and PBS solution (phosphate-buffered saline). Cell growth and cell viability were counted using an MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl-tetrazolium Bromide] (Sigma-Aldrich) assay in brief, the cell was digested by trypsin, adjusted to the density of (1.4 × 10^4 cells/well) and planted to 96 well plate filled with (200 µl) fresh intermediate per well for (24 h). The cells that formed a monolayer were treated with 600–6.5 µg /ml of the compounds (Q1-Q6) for 24 h at 37 °C in CO2 at the end of the treatment (24 h). In contrast, the monolayer cultures were left untouched in a novel plate, the supernatant was detached, and 100 µl/ well of MTT solutions (0.5 mg/ ml in PBS) were added. The plates were incubated at (37 °C) for an additional (4 h). MTT solutions (the supernatant of cells was detached, and dimethyl sulfoxide was added (100 µl per well). The Cell was incubated on a shaker at (37 °C) until the crystal was dissolved. The Cell viability was quantified by measuring absorbance at (570 nm) by an ELISA reader (Model wave xs2, BioTek/ USA). The concentration of compounds that caused (50 %) cell death IC50 were determined from the respective dose–response curve [41,42].

Table 1
The physical properties of prepared compounds.

Comp.	Molecular formula	M. wt g/ mol	Color	Time/ h	m.p (°C)	Yield (%)[a]
Q1	C34H36N4O4S2Cl2	699	yellow	24	187–188	28
Q2	C34H38N4O4S2	630	yellow	24	191–193	32
Q3	C34H36N6O8S2	720	Beige	21	210–212	35
Q4	C36H42N4O4S2	658	yellow	24	187–190	25
Q5	C36H42N4O2S2	690	yellow	24	179–181	20
Q6	C34H36N6O8S2	720	Orang	24	201–199	35

[a] Isolated pure derivative.

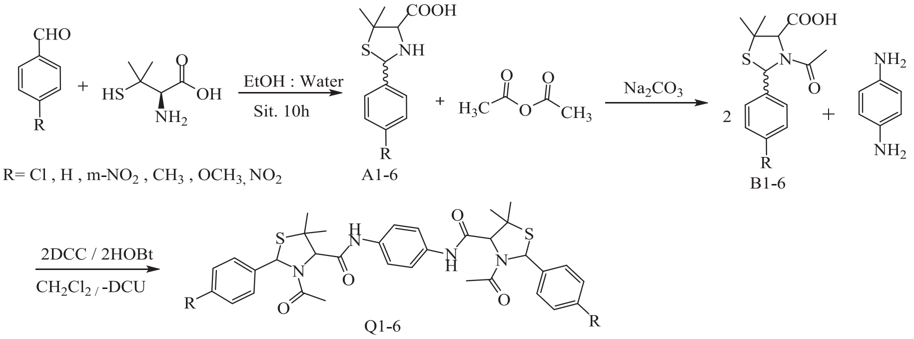
Result and Discussion

Synthesis of compound

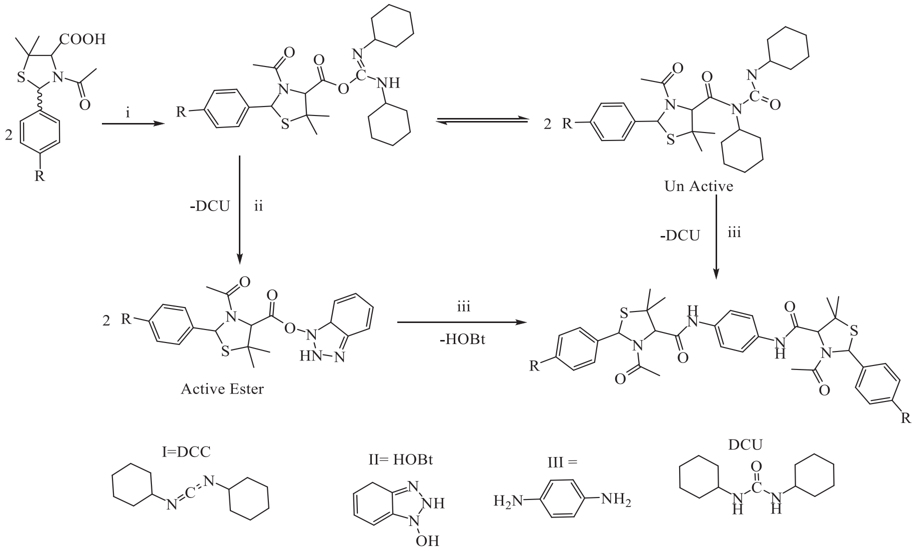
The study involved the synthesis of Bis thiazolidine amide derivatives(Q1-Q6) in three steps and from simple and available commercial materials Table 1. Firstly, the D-penicillamine reacts with benzaldehyde derivatives to form the ring thiazolidine-4-carboxylic acid (A1-A6) and yield well [34]. The thiazolidine ring product has a mixture of diastereomers, the C2 − (2R, 4R) −Cis and C2– (2S, 4R) Trans, which cannot be separated. An equilibrium due to desiccation occurs at C (2) between the two diastereomers. The (Cis/ Trans) ratio strongly depended on the nature of the solvent used; the dominant isomer in the DMSO-d_6 solvent was the Trans diastereomer. In CDCl3, the main isomer was the Cis isomer after complete equilibration. Second, the compounds (A1-A6) were reacted with acetic anhydride to the synthesis of 3-acetyl-5,5-dimethyl-2-Aryl thiazolidine-4-carboxylic acid (B1-B6) [35,36]. Finally, the synthesis bis amide thiazolidine derivatives as shown in diagrams (3.1) from the condensation of phenylenediamine with acetyl thiazolidine derivatives (B1-B6) in a ratio of (1:2) and the presence of DCC (N, N-dicyclohexyl carbodiamide) and HOBt (1-hydroxy benzotriazole) as catalysts. scheme 1.

This converts the inactive carboxyl group to the active ester group and gives the least isomer as a coupling reagent to give the corresponding amides. DCC is a low-cost coupling reagent compared to other reagents, but it has a major problem: the DCU is poorly soluble in most solvents and often difficult to remove altogether from the product. While the urea of Ethyl dimethyl aminopropyl carbodiimide (EDC) is soluble in acetic acid and Di-isopropyl urea is soluble in organic solvents, the two reagents outweigh the DCC by much price. The prepared amide thiazolidine derivatives showed medium yield products [36], as shown in the preparation mechanics of scheme 2:

The prepared compound was identified by FT-IR spectroscopy. The spectra of the compounds [Q1-Q6] were characterized by the appearance of a weak band at the range of 3100–3350 cm^{-1} due to the (NH) amid groups and the disappearance of the (OH) carboxylic acid band. We used proton nuclear magnetic resonance spectroscopy (^{1}HNMR) to confirm the validity of the prepared compounds using DMSO-d_6 as a solvent and TMSO as an internal reference. To the proton of the carboxyl group (OH) while that signal disappeared in the prepared amide compounds (Q1-Q6) and the appearance of the NH proton single at the range of (10.5–11.3 ppm) due to the protons of the amide (NH) group, and the increase in the aromatic ring singles in addition to the thiazolidine ring singles. Also, the ^{13}CNMR spectroscopy was used in the study amide thiazolidine was identified by the appearance of the thiazolidine ring singles (C5 = 50–55 ppm, C2, 4 = 65–75 ppm) and aromatic singles in the range of (115–156 ppm) as well the singles of the carbonyl group at the range (165–172 ppm), and also by using mass spectrometry, which proved the validity of the synthesized compounds by the appearance of the molecular ion peak (M$^{+\circ}$) in all the prepared compounds (Q1-Q6) [42–47].



Scheme 1. Synthesis of bis amide thiazolidine derivatives.



Scheme 2. Mechanism of bis amide thiazolidine derivatives.

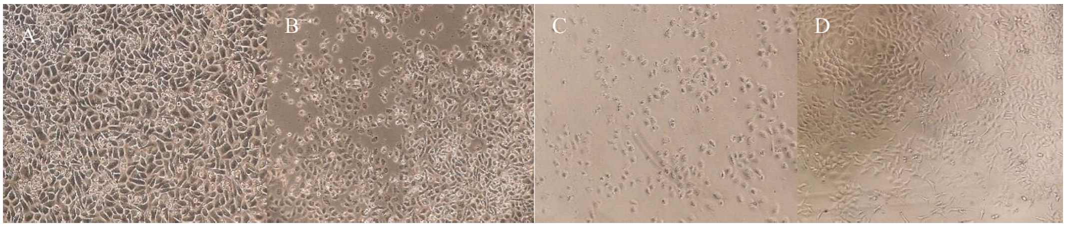


Fig. 3. Demonstrates the impact of the compound Q1 on PC3 cell morphology, (A) control PC3 cells, (B),(C) and (D) PC3 cells treated with compound Q1 in concentrations 25, 100, 200 μg/ml respectively and show the penetration of compound Q1 into cell membrane.

Biological activity

In vitro Anti-Cancer assay

The anti-cancer activity of the two series of new compounds was first tested for their in vitro cytotoxicity against two cell line human prostate cancer cells PC3 and breast cancer MCF7 and two cell line human cells HUVEC, HPNT1A and breast cell line MCF10 using the MTT assay at varying doses for 24 h, then cell viability was determined. Compounds (Q1, and Q3) showed strong growth inhibition properties toward PC3 as demonstrated in Fig. 3. At the same time, compounds (Q4 and Q5) exhibited moderate activity and low toxicity. In contrast, some of the compounds (Q1-Q6) were evaluated by in vitro cytotoxicity against cell line MCF7. It can be seen that compound Q1, has medium inhibition. On the other hand, compounds Q3 and Q6 did not show anticancer activity against MCF7 cell lines shown Table 2. Remarkably, compound Q1 showed the effect of dual inhibition during the activity of these compounds against two cell lines, MCF7and PC3. Another thing is that all the compounds generally showed anticancer activity different from each other on MCF7 and PC3 cell lines. The changes of the functional groups (methyl, chlorine, etc.) in the structures of Q1–Q6 did change the anticancer activities on the PC3 and MCF7 cell lines. Compounds Q1 and Q3 which contain groups Cl, NO2, and OCH3 showed good activity against PC3 with a good value of IC50, The most effective compounds (Q1, Q3, Q6) against normal living cells type MCF10 and HUVEC were compared and it was proven that the compounds have very weak effectiveness and only at high concentrations, which gives a clear vision of the possibility of using the compounds in the future against cancer cells as shown Table 2 [48,49]. With some experimental statistics for applying Bis thiazolidine amide anticancer drugs, these findings provide additional opportunities for drug research and development. Using an

Table 2
Cytotoxic activity of the tested products against the PC-3, MCF-7, MCF10, PNT1Aand HUVEC.

Compounds	PC3	MCF-7	MCF10 normal	HUVEC normal	PNT1A
	(Canser cells)IC50 μg/ml(normal cells)				
Q1	81.22 ± 0.99	297.6 ± 0.84	572 ± 0.95	374 ± 0.91	>400
Q2	148.25 ± 0.9	265.60 ± 0.96	–	–	–
Q3	89.72 ± 0.93	433.57 ± 0.78	≫500	345.3 ± 0.9	347 ± 0.96
Q4	148.35 ± 0.97	374.7 ± 0.9		–	–
Q5	207.64 ± 0.98	251.2 ± 0.99		–	–
Q6	112.79 ± 0.99	540.88 ± 0.97	602 ± 0.87	540.82 ± 0.92	–

optical microscope, the morphological variations of PC3 and MCF7 cells treated with the IC50 value of substances were noted in Fig. 3 of Q1. The compound-treated and control (untreated) cells have different cell surface morphologies. Due to the cytoplasmic condensation, the most noticeable morphological alterations in compounds treated cells include cell shrinkage and the formation of many cell surface protuberances at the plasma membrane, along with nuclear chromatin aggregation into dense masses beneath the nuclear membrane [50,51]. Recent attention has focused on the activities of thiazolidine rings, particularly those synthesized from cysteine and penicillamine. Previous research suggests that amide thiazolidine derivatives exhibit enhanced efficacy against bacteria, oxidation, and various cancer cells, with particular effectiveness against prostate cancer cells [52,53]. A recent study explored amide thiazolidine derivatives derived from isoniazid, demonstrating their high efficacy against prostate and liver cancer, albeit with reduced effectiveness against breast cancer. This finding opens the possibility of synthesizing a series of binary amide thiazolidine derivatives containing two thiazolidine rings and evaluating their effectiveness in comparison with previous studies [54]. Recent attention has focused on the activities of thiazolidine rings, particularly those synthesized from cysteine and penicillamine. Previous research suggests that amide thiazolidine derivatives exhibit enhanced efficacy against bacteria, oxidation, and various cancer cells, with particular effectiveness against prostate cancer cells. A recent study explored amide thiazolidine derivatives derived from isoniazid, demonstrating their high efficacy against prostate and liver cancer, albeit with reduced effectiveness against breast cancer. This finding opens the possibility of synthesizing a series of binary amide thiazolidine derivatives containing two thiazolidine rings and evaluating their effectiveness in comparison with previous studies.

Molecular docking studies

The proteins were chosen based on the levels of expression of numerous tumor-regulating genes, namely PC3 and MCF7, the most significant genes for prostate cancer and breast cancer that control apoptosis are 2FVD and 1SJ0 respectively. Examining ligand–protein interactions was the main objective of this investigation to determine how the highly active molecules Q1, Q4, and Q5 act on the receptor target. Two receptors, PDB (ID:2FVD) [44,45] for the PC3 cell line and PDB (ID:1SJ0) [55] for the MCF7,were provided for molecular docking (Fig. 4, Table 3). The geometry of the docked molecule was evaluated based on the binding energy values. For compound Q1, with a very good fit and affinity energy of −11.52 kcal/mol for the 2FVD receptor active site, compound Q1 displayed the best conformational docked pose, with different interactions with amino acid residues Lys89, Leu298, Glu8, Ala31, Gly11, Glu12, Thr14, Gly13, Ile10, Arg297, His84, Phe82, Leu134, Asp86, Ala144, Val18, Gln131, Asp145 and Asn132, and hydrogen bonds to Leu83, and Gln85. Compound Q4, primarily interacts with the receptor through interactions inside its active site with various amino acid residues, as demonstrated by docking calculations with the 2FVD receptor, with a good fit and affinity energy of −9.40 kcal/mol. These interactions include Thr14, Gly13, Asn132, Lys129, Asp86, Gln85, Lys89, His84, Val164, Glu162, Lys20, Val164, Glu162, Glu12, Gln131, Thr165, Lys88, Ile10, Glu8, and Phe82 and hydrogen-bond interactions with Asp86, Lys89 and Ile10.Compound Q5, which showed good binding mode to the lead compound with a high docking score value −12.14 kcal/mol with interactions are represented by residues, Ace160, Arg36, Glu162, Val163, Gln131, Asp145, Phe80, Val164, Thr14, Gly13, Lys129, Glu12, Gly11, Asp86, Gln85, Ile10, Leu134, Val64, Ala144, Ala31, and Val18, with hydrogen bonding Lys129, Glu12, Leu134 and Ile10. In contrast, compound Q1against PDB (ID: 1SJ0). The chemical nature of binding site residues suggested interactions between compound Q1 and, amino acid residues Leu387, Met388, Leu391, Leu346, Phe425, Ile424, Met421, Ala350, Cys530, and

Table 3
Parameters of the compounds that have the best protein conformation. **Refa = 45, and Refb = 46.**

Com	Cell line	Pdb	B. E (kcal/mol)	Ki uM	Length (A^{0})
Q1	PC3	2FVD	−11.52	3.61	2.10
Q4	PC3	2FVD	−9.40	127.71	1.95
Q5	PC3	2FVD	−12.14	1.26	2.30
Ref^{a}	PC3	2FVD	−7.85	1770	
Q1	MCF-7	1SJ0	−14.40	0.027	2.30
Ref^{b}	MCF-7	1SJ0	−13.33	0.168	

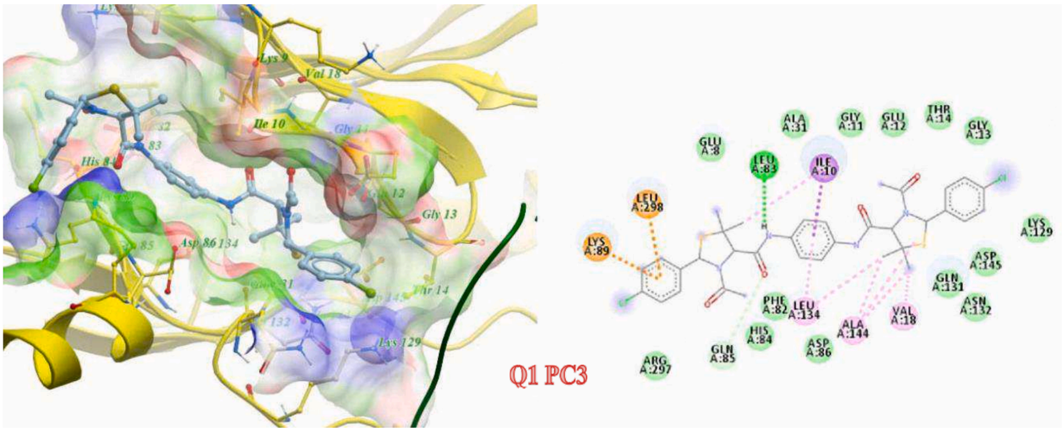


Fig. 4. 3D and 2D Docked Pose of compound Q1, showing interaction with amino acids residues in the binding site of Cyclin-Dependent Kinase 2 (Cdk2) (PDB:2FVD) and Human Estrogen Receptor Alpha (PDB:1Sj0).

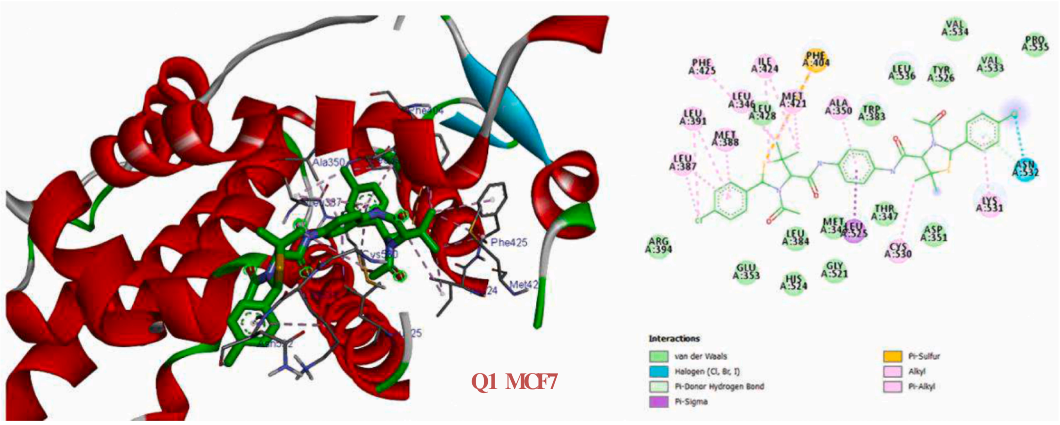


Fig. 5. Optimized structure of compounds prepared understudy.

Table 4
DFT calculated for the compounds synthesized.

Com	µ	HOMO	LUMO	ΔE	µ	η	S	ω	(χ)
	(Debye)	eV	eV	(eV)	(eV)	(eV)	(eV)	eV	
Q1	6.5529	−7.9927	−0.7140	7.2787	−4.3534	3.6393	0.2747	2.6037	4.3534
Q2	2.1224	−8.0175	−1.0237	6.9937	−4.5206	3.4968	0.2859	2.9220	4.5206
Q3	2.9002	−8.0725	−0.6405	7.4319	−4.3565	3.7159	0.2691	2.5537	4.3565
Q4	4.2860	−5.5092	−1.4054	4.1037	−3.4573	2.0518	0.4873	2.9127	3.4573
Q5	3.6178		−7.8077			−0.95816.8496–4.38293.42480.29192.8045			4.3829
Q6	9.4419		−8.2229			−0.63677.5862–4.42983.79310.26362.5867			4.4298

Dipole moment µ (Debye), chemical potential (µ), absolute hardness (η) softness (S), Electrophilicity (ω), Absolute electronegativity (χ).

Lys53, also in addition to hydrogen bonding interactions with Phe404 [56,57]. Diaminopyrimidines and antagonist inhibitors were used in this study as reference drugs that are used as a therapy for advanced prostate and breast cancer cell lines respectively [57–59]. Compared to Diaminopyrimidines and Antagonists, all compounds showed higher binding affinities than both references, it was found that compounds (Q1, Q3, and Q5) exhibited significant binding energy and lead molecules for good anticancer activity.

DFT study

The ground state geometries of the compounds were optimized at B3LYP/6-31G(d) level of theory (Fig. 5). Global reactivity descriptors include HOMO, LUMO, Energy gap (Eg), chemical hardness (η), electronegativity (X), chemical potential (µ), and global softness are presented in Table 4, From Table 3, the polarity of a molecule can be measured by its dipole moment (µ), which is organized as follows Q6>Q1>Q4>Q5>Q3>Q1.The dipole moment for compound Q6 is the most polar, probably based on the large sizes and electronegativity of their NO2 atoms which create more polar bonds. The HOMO-LUMO energy gap (ΔE) represents the final charge transfer interaction within the molecule. HOMO-LUMO low kinetic stability and strong chemical reactivity are characteristics of molecular structures with a small energy gap, as well as Q6 shows the highest band gap, due to showing more π conjugation as compared to the compounds molecules with a small energy gap are soft molecules consisting of a narrow energy band, according to the energy gap value, compound Q6 is more active than other compounds [53,60–63]. The greater the electronic chemical potential (absolute values), the less stable or reactive the compound, compound Q4 has greater chemical potential than other compounds. Electronegativity (ω) is unique because it evaluates the ability of an atom or collection of atoms to attract electrons the electronegativity (χ) is arranged as follows Q2>Q4>Q5>Q3>Q1>Q4. There is an energy gap of large for a hard molecule and small for a soft molecule. The calculated results of Q6 with a large energy gap and hard molecule. While chemical hardness (η) which order Q6 > Q3 > Q1 > Q2>Q5>Q4. In contrast, softness is the opposite of hardness. Softness (S) is a sign of polarization compound Q4 showed greater softness from all compounds, and the trend in softness values for compounds Q4>Q5>Q2>Q1>Q6>Q3. On the other hand, the electrophilicity (ω) is arranged as follows Q2 > Q4 > Q5 > Q1>Q6>Q3 [60–63].

Conclusion

Thiazolidine amide derivatives were obtained from the reaction of D-penicillamine and benzaldehyde derivatives easily and with very good yields to prepare ring thiazolidine −4-carboxylic acid, which reacts with acetic anhydride and then reacts with phenylenediamine to prepare amide thiazolidine compounds. We concluded from the results that all compounds have good biological activity against the type of PC3, and the others lose activity against the type of MCF7. Against the tumor cell lines PC3, compoundsQ1, Q4, and Q5, which were the most potent, demonstrated exceptional inhibitory action with IC50 81.22,148.35, and 207.64 µg/ml respectively. While Compound Q1 showed very good activity against the MCF-7 cell line with IC50 297.60 µg/ml. Molecular docking analysis that compounds Q1, Q4, and Q5 demonstrated very good binding energy with essential amino acid residues and revealed stability in the binding site and may efficiently inhibit 2FVD and 1SJ0. This compound may detect lead molecules as a drug candidate for cancer therapy. DFT analysis that compound Q6 has a high dipole moment (µ) and energy gap(ΔE). On the other hand, compound Q4 has greater chemical potential than other compounds. While the electronegativity (χ) is organized as follows Q2>Q4>Q5>Q3>Q1>Q4 and chemical hardness (η) which order Q6 > Q3 > Q1 > Q2>Q5>Q4. In contrast, compounds Q4 and Q2 showed greater softness and electrophilicity from all compounds.

CRediT authorship contribution statement

Haider A. Omran: Writing – original draft, Software, Methodology, Investigation, Conceptualization. **Ahmed A. Majed:** . **Kawkab Hussein:** Writing – original draft, Software, Methodology, Investigation. **Dawood S. Abid:** . **Mostafa A. Abdel-Maksoud:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Investigation, Funding acquisition. **Ahmed Elwahsh:** Writing – review & editing, Validation, Investigation, Data curation, Conceptualization. **Mohamed Aufy:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Mohamed H. Kotob:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgment

The authors extend their appreciation to the Researchers Supporting Project number (RSP2024R470) King Saud University, Riyadh, Saud Arabia. The authors were grateful to Chemistry Department, College of Education for Pure Sciences, Basrah university, Iraq, for providing basic facilities.

References

[1] M.S. Taghour, H. Elkady, W.M. Eldehna, N.M. El-Deeb, A.M. Kenawy, E.B. Elkaeed, A.A. Alsfouk, M.S. Alesawy, A.M. Metwaly, I.H. Eissa, Design and synthesis of thiazolidine-2,4-diones hybrids with 1,2-dihydroquinolones and 2-oxindoles as potential VEGFR-2 inhibitors: in-vitro anticancer evaluation and in-silico studies, J. Enzyme Inhib. Med. Chem. 37 (2022) 1903–1917, https://doi.org/10.1080/14756366.2022.2085693.

[2] A.A. Majed, D. AL-Duhaidahawi, H.A. Omran, S. Abbas, D.S. Abid, A.Y. Hmood, Synthesis, molecular docking of new amide thiazolidine derived from isoniazid and studying their biological activity against cancer cells, J. Biomol. Struct. Dyn. (2023) 1–12. 10.1080/07391102.2023.2276313.

[3] R.F. Costa, L.C. Turones, K.V.N. Cavalcante, I.A. Rosa Júnior, C.H. Xavier, L.P. Rosseto, H.B. Napolitano, P.F.d.S. Castro, M.L.F. Neto, G.M. Galvão, R. Menegatti, G.R. Pedrino, E.A. Costa,J.L.R. Martins, J.O. Fajemiroye, Heterocyclic Compounds: Pharmacology of Pyrazole Analogs From Rational Structural Considerations. Synthesis, molecular docking of new amide thiazolidine derived from isoniazid and studying their biological activity against cancer cells Front. Pharmacol. 12 (2021) 666725. 10.3389/fphar.2021.666725.

[4] A.C. Santana, R.C. Silva Filho, J.C.J.M.D.S. Menezes, D. Allonso, V.R. Campos, Nitrogen-Based Heterocyclic Compounds: A Promising Class of Antiviral Agents against Chikungunya Virus. Life, 11, (2021) 16. 10.3390/ life11010016.

[5] W. Lidia, R. Hanes, S. Rudy, R. Jan, H. Gerhard, Thiazolidine derivatives as source of free l- cysteine in rat tissue, Biochem. Pharmacol. 46 (1993) 1917–1928, https://doi.org/10.1016/0006- 2952(93)90632-7.

[6] B.O.F. Esra, S. Hande, A.T. Ebru, U.K. Reyhan, B. Kerem, A. Hulya, The cysteine releasing pattern of some antioxidant thiazolidine-4-carboxylic acids, Eur. J. Med. Chem. 114 (2016) 337–344, https://doi.org/10.1016/j.ejmech.2016.03.019.

[7] P. Yashshree, S. Ankita, S.K. Pramod, K. Nitin, Biological Activities of Thiazolidine-A Review, Curr. Pharm. Res. 1 (2011) 192–196.

[8] M. Guy, S. Gandhesiri, M. Roman, V.B. Ganga, B. Ashraf, Palladium-Mediated Cleavage of Proteins with Thiazolidine-Modified Backbone in Live Cells, Angew. Chem. 131 (2019) 13674–13683, https://doi.org/10.1002/ange.201906545.

[9] A. Majed, D.S. Abid, Synthesis, Characterization and Biological Activity and Anti-Oxidant Study of Some New Thiazolidine Derivatives Containing Oxadiazole, Ann. Rom. Soc. Cell Biol. 25 (2021) 11935–11945.

[10] M.A. Mohammed, D.S. Abid, S.G. Sayyah, Preparation, Characterization of some Thiazolidine Derived from Penicillamine and their Antioxidants Activity, Ann. Rom. Soc. Cell Biol. 25 (2021) 4653–4663.

[11] N. Frimayanti, V.S. Lee, S.M. Zain, et al., 2D, 3D-QSAR, and pharmacophore studies on thiazolidine-4-carboxylic acid derivatives as neuraminidase inhibitors in H3N2 influenza virus, Med. Chem. Res. 23 (2014) 1447–1453, https://doi.org/10.1007/s00044-013-0750-x.

[12] R. Munro, H.A. Capell, Penicillamine, Br. J. Rheumatol. 36 (1997) 104–109.

[13] M. Moussa, P.G. Athanasios, C.A. Mohamad, M. Yasmin, Update on cystine stones: current and futureconcepts in treatment, Intractable Rare Dis. Res. 9 (2020) 71–78, https://doi.org/10.5582/irdr.2020.03006.

[14] F. Razieh, K.M.S. Morteza, G. Ali, B. Hadi, Experimental and computational study of penicillamine drug and cysteine as water-soluble green corrosion inhibitors of mild steel, Prog. Org. Coat. 142 (2020) 105567, https://doi.org/10.1016/j.porgcoat.2020.105567.

[15] Y. Jianchao, T. Weijian, Y. Ruihan, C. Yu, W. Jing, W. Yihui, Y. Wan-Jian, Y. Ningyi, D. Jianning, Z. Wen-Hua, Defect mitigation using D-penicillamine for efficient methylammonium-free perovskite solar cells with high operational stability, Chem. Sci. 12 (2021) 2050–2059, https://doi.org/10.1039/D0SC06354A.

[16] T. Vajdi, W. Lee, T. Paravar, Penicillamine-associated cutis laxa and milia en plaque-case report and review of cutaneous changes associated with penicillamine, Dermatol. Online J. 22 (2016) 5, https://doi.org/10.5070/D3225030951.

[17] K. Karrouchi, S.A. Brandán, Y. Sert, H. El-marzouqi, S. Radi, M. Ferbinteanu, M. A. Faouzi, Y. Garcia, M. Ansar, Synthesis, X-ray structure, vibrational spectroscopy, DFT, biological evaluation and molecular docking studies of (E)-N'-(4-(dimethylamino)benzylidene)-5-methyl-1H-pyrazole-3-carbohydrazide, Journal of Molecular Structure 1219 (5) (2020) 128541, https://doi.org/10.1016/j.molstruc.2020.128541.

[18] T. Kaur, A. Madgulkar, M. Bhalekar, K. Asgaonkar, Molecular docking in formulation and development,Curr.DrugDiscov.Technol. 16(2019) 30–39. 10.2174/1570163815666180219112421.

[19] C.E. Theodore, A.M. Anusuya, G. Sivaiah, R. Jain, C.S.A. Kumar, S.B.B. Prasad, M. S. Raghu, F.A. Alharti, M.K. Prashanth, B. Jeon, Design, synthesis, molecular docking and biological evaluation of novel pyrazole derivatives bearing quinoxalinone moiety as multi-targeted anticancer agents, Journal of Molecular Structure 1288 (2023) 135765, https://doi.org/10.1016/j.molstruc.2023.135765.

[20] M. Gümüş, Ş. N. Babacan, Y. Demir, Y. Sert, İ. Koca, İ. Gülçin., Discovery of sulfadrug–pyrrole conjugates as carbonic anhydrase and acetylcholinesterase inhibitors., Arch. Pharm.(2022), 355;e2100242. Doi. Org/10.1002/ardp.202100242.

[21] Elkady, H., Mahdy, H. A., Taghour, M. S., Dahab, M. A., Elwan, A., Hagras, M., Hussein, M. H., Ibrahim, I. M., Husein, D. Z., Elkaeed, E. B., Alsfouk, A. A., Metwaly, A. M., & Eissa, I. H. New thiazolidine-2,4-diones as potential anticancer agents and apoptotic inducers targeting VEGFR-2 kinase: Design, synthesis, in silico and in vitro studies. Biochimica et Biophysica Acta (BBA) - General Subjects, (2024). 1868(6), 130599. 10.1016/J.BBAGEN.2024.130599. (10.1016/J.BBAGEN.2024.130599).

[22] N. Dege, H. Gökce, O.E. Doğan, G. Alpaslan, T. Ağar, S. Muthu, Y. Sert, Quantum computational, spectroscopic investigations on N-(2-((2-chloro-4,5-dicyanophenyl) amino)ethyl)-4 methylbenzenesulfonamide by DFT/TD-DFT with different solvents, molecular docking and drug-likeness researches, Colloids and Surfaces a: Physicochemical and Engineering Aspects 638 (2022) 128311, https://doi.org/10.1016/j.colsurfa.2022.128311.

[23] A.A. Balakit, S.Q. Makki, Y. Sert, F. Ucun, M.B. Alshammari, P. Thordarson, G. A. El-Hiti, Synthesis, spectrophotometric and DFT studies of new Triazole Schiff bases as selective naked-eye sensors for acetate anion, Supramolecular Chemistry 10 (1080/10610278) (2020) 1808217.

[24] Sameeh, M. Y., Khowdiary, M. M., Nassar, H. S., Abdelall, M. M., Amer, H. H., Hamed, A., & Elhenawy, A. A.. Thiazolidinedione Derivatives: In Silico, In Vitro, In Vivo, Antioxidant and Anti-DiabeticEvaluation.Molecules,(2022),27(3).. (10.3390/MOLECULES27030830).

[25] K. Veena, M.S. Roghu, K.Y. Kumar, K.A. Dahluous, A.A.A. Bahajjaj, G. Moni, B. Jeon, M.K. Prashonth, Development of penipanoid C-inspired 2-benzoyl-1-methyl-2,3-dihydroquinazolin-4(1H)-one derivatives as potential EGFR inhibitors: Synthesis, anticancer evaluation and molecular docking study, Journal of Molecular Structure 1258 (2022) 132674, https://doi.org/10.1016/j.molstruc.2022.132674.

[26] C.B.P. Kumar, M.S. Raghu, B.S. Prathibha, M.K. Prashanth, G. Kanthimathi, K. Y. Kumar, L. Parashuram, F.A. Alharthi, Discovery of a novel series of substituted quinolines acting as anticancer agents and selective EGFR blocker: Molecular docking study, Bioorganic and Medicinal Chemistry Letters 44 (2021) 128118, https://doi.org/10.1016/j.bmcl.2021.128118.

[27] Hashem, H. E., Ahmad, S., Kumer, A., & Bakri, Y. el. (2024). In silico and in vitro prediction of new synthesized N-heterocyclic compounds as anti-SARS-CoV-2. Scientific Reports. (2024), 14:1, 14(1), 1–18.. 10.1038/s41598-024-51443-7.

[28] K. Yogesh Kumar, C. B. Pradeep Kumar, K. N. N. Prasad, Byong-Hun Jeon, Ali Alsalme, M. K. Prashanth, Microwave-assisted N-alkylation of amines with alcohols catalyzed by MnCl2: Anticancer, docking, and DFT studies, Archiv der Pharmazie Volume 355, Issue 5 2100443(2022) 10.1002/ardp.202100443.

[29] Dhaybia Douche, Yusuf Sert, Silvia A. Brandán, Ameed Ahmed Kawther, Bayram Bilmez , Necmi Dege,Ahmed El Louzi , Khalid Bougrin, Khalid Karrouchi f , Banacer Himmi., 5-((1H-imidazol-1- yl)methyl)quinolin-8-ol as potential antiviral SARS-CoV-2 candidate: Synthesis, crystal structure, Hirshfeld surface analysis, DFT and molecular docking studies., Journal of Molecular Structure 1232 (2021) 130 0 05., 10.1016/j.molstruc.2021.130 0 05.

[30] A.A. Abdulridha, M.A. Albo, H. Allah, S.Q. Makki, Y. Sert, H.E. Salman, A. A. Balakit, Corrosion inhibition of carbon steel in 1 M H2SO4 using new Azo Schiff compound: Electrochemical, gravimetric, adsorption, surface and DFT studies, Journal of MolecularLiquids (2020), https://doi.org/10.1016/j.molliq.2020.113690.

[31] S. Khan, H. Ullah, M. Taha, F. Rahim, M. Sarfraz, R. Iqbal, N. Iqbal, R. Hussain, S. A. Ali Shah, K. Ayub, M.A. Albalawi, M.A. Abdelaziz, F.S. Alatawi, K.M. Khan, D. S. Synthesis, Molecular Docking and Biological Activity Evaluation of Thiazole-Sulfonamide Derivatives as Potent Alzheimer's Inhibitors, Molecules 28 (2) (2023), https://doi.org/10.3390/MOLECULES28020559/S1.

[32] M.K. Mahapatra, K. Bera, D.V. Singh, R. Kumar, M. Kumar, In silico modelling and molecular dynamics simulation studies of thiazolidine based PTP1B inhibitors, Journal of Biomolecular Structure and Dynamics 36 (5) (2018) 1195–1211, https://doi.org/10.1080/07391102.2017.1317026.

[33] Mahmood A. Albo Hay Allah, Asim A. Balakit, Hamida Idan Salman, Ali Ahmed Abdulridha & Yusuf Sert., New Heterocyclic Compound as Carbon Steel Corrosion Inhibitor in 1 M H_2SO_4, High Efficiency at Low Concentration: Experimental and Theoretical Studies., Journal of Adhesion Science and Technology, Volume 37, 2023 - Issue 3. 10.1080/01694243.2022.2034588.

[34] H.T. Nagasawa, D.G.W. Goon, F.N. Shirota, Epimerization at C-2 of 2-substituted thiazolidine-4-carboxylic acids, J. Heterocyclic Chem. 18 (1981) 1047–1051, https://doi.org/10.1002/jhet.5570180538.

[35] S. Thalamuthu, B. Annaraj, S. Vasudevan, S. Sengupta, M.A. Neelakantan, DNA binding, nuclease, and colon cancer cell inhibitory activity of a Cu(II) complex of a thiazolidine-4-carboxylic acid derivative, Coord. Chem. Rev. 66 (2013) 1805–1820, https://doi.org/10.1080/00958972.2013.791393S.

[36] S.E.M. Elisa, C. Dora, M. Dino, T.T.C. Nelia, P.D.V.M. Teresa, d-Penicillamine and l-cysteine derived thiazolidine catalysts: an efficient approach to both enantiomers of secondary alcohols, Tetrahedron 72 (2016) 5923–5927, https://doi.org/10.1016/j.tet.2016.08.036.

[37] X. Fernandez, E. Dunach, R. Fellous, L. Lizzani-Cuvelier, M. Loiseau, Thiazolidines and theiroxidation products as flavouring compounds, Flavour, Fragr. J. 17 (2002) 432–439, https://doi.org/10.1002/ffj.1121.

[38] M.A. Ahmed, A. S. Dawood, Synthesis of Some New 1,3,4- Oxadiazole Derivatives andThiazolidine Derived from Cysteine and Evaluation their Anticancer (MCF7) Activity, Biomed.Chem. Sci. 1 (2022) 83–87. 10.48112/bcs.v1i2.109.

[39] V. Gududuru, E. Hurh, T.J. Dalton, D.D. Miller, Discovery of 2-arylthiazolidine-4-carboxylic acid amides as a new class of cytotoxic agents for prostate cancer, J. Med. Chem. 48 (2005) 2584–2588, https://doi.org/10.1021/jm049208b.

[40] M..A.mohammed, D. S. Abid, S. G. Sayyah. Preparation,Characterization And Biological ActivityOf Some New Amides From Thiazolidine-4-carboxylic Acid. J. Kufa Chem. Sci. 2 (2023) 193–231. https://www.journal.uokufa.edu.iq/index.php/jkcs/article/view/1106.

[41] B.A.W. Francisco, S.G. Teresinha, P.R.D.G. Marina, B.P. Daniel, L.C.V. Leticia, M.D. O. Manoel, P. Claudia, M.D.B.F.A. Maria, A.D.C. Fabiane, G.L. Suely, P.R.D. Ivan, G.F.O. Marillia, Synthesis and cytotoxic activity of new acridine-thiazolidine derivatives, Bioorg MedChem. 20 (2012) 3533–3539, https://doi.org/10.1016/j.bmc.2012.04.007.

[42] K. Zainab, A.M.J. Adnan, A.K. Bushra, Synthesis, characterization and biological Activity of β-Lactam and Thiazolidinone Derivatives Based on Sulfonamide, Egypt. J. Chem. 6 (2022) 621–645, https://doi.org/10.21608/ejchem.2021.106965.4912.

[43] R.M. Jagtap, M.A. Rizvi, Y.B. Dangat, S.K. Pardeshi, Crystal structure, computational studies, and stereoselectivity in the synthesis of 2-aryl-thiazolidine-4-carboxylic acids via in situ imine intermediate, J. Sulphur Chem. 37 (2016) 401–425, https://doi.org/10.1080/17415993.2016.1156116.

[44] H.N. Ayat, A.S. Dawood, Preparation, Characterization and Biological Activity Study of some New Thiazolidine Derivatives, J. of Basra. Res. (sci.) 43 (2017) 10–29.

[45] W. Kitti, P. Apilak, Virapong, Facile synthesis of N-aroylurea analogs as potential antioxidants, Eur. J. Res. 31 (2009) 510–518.

[46] G. Isaac, W. J. M iranda, F. Dinesh, S. Aman, L. E. Richared, G. S. Jason, F. Cynthia, Y.Raghunandan, Synthesis and Evaluation of Thiazolidine Amide and N-Thiazolyl Amide Fluoroquinolone Derivatives, Arch. Pharm. 350 (2017) e201700029. 10.1002/ardp.201700029.

[47] M.A. Ahmed, A.S. Dawood, Synthesis, Characterization and Biological Activity Study of some New Thiazolidine Derivatives, Bas. J. Sci. 33 (2015) 101–117.

[48] H.E. Donia, H. Eman, E. Islam, S. Shou-Ping, C. Leng-Chiang, H. Yi-Jia, L. Hung-Yu, K.B. Adem, P.A. Gary, H. Mohammed, A.H. Ashraf, Novel thiazolidine derivatives as potent selective pro-apoptotic agents, Bioorg. Chem. 114 (2021) 105143, https://doi.org/10.1016/j.bioorg.2021.105143.

[49] D. Sharma, N. Sharma, S.V. Saini, V.K. Sharma, R.K. Thakur, P.C. Goyal, Sharma, Recent advances in synthetic strategies and SAR of thiazolidin-4-one containing molecules in cancer therapeutics, Cancer Metastasis Rev. 42 (2023) 847–889, https://doi.org/10.1007/s10555-023-10106-1.

[50] E.B. Elkaeed, H.A. Abd El Salam, A. Sabt, G.H. Al-Ansary, W.M. Eldehna, Recent Advancements in the Development of Anti-Breast Cancer Synthetic Small Molecules, Molecules 26 (2021) 7611, https://doi.org/10.3390/molecules26247611.

[51] J. P. Soni, Y. Yeole, Na. Shankaraiah, β-Carboline-based molecular hybrids as anticancer agents: a brief sketch RSC Med. Chem. 12 (2021) 730. 10.1039/d0md00422g.

[52] M.M.M. Hanafi, A. Afzan, H. Yaakob, R. Aziz, M.R. Sarmidi, J. Wolfender, J. M. Prieto, In Vitro Pro-apoptotic and Anti-migratory Effects of Ficus deltoidea L. Plant Extracts on the Human Prostate Cancer Cell Lines PC3, Front. Pharmacol. 8 (2017) 895, https://doi.org/10.3389/fphar.2017.00895.

[53] F. Peng, M. Liao, R. Qin, S. Zhu, C. Peng, L. Fu, Y. Chen, B. Han, Regulated cell death (RCD) in cancer: key pathways and targeted therapies, Signal Transduct Target Ther. 7 (2022) 286, https://doi.org/10.1038/s41392-022-01110-y.

[54] M. Kciuk, M. Malinowska, A. Gielecinska, R. Sundaraj, S. Mujwar, A. Zawisza and R.Kontek.,Synthesis, Computational, and Anticancer In Vitro Investigations of Aminobenzylnaphthols Derived from 2-Naphtol, Benzaldehydes, and α-Aminoacids via the Betti Reaction, Molecules, 28(2023) 7230. 10.3390/molecules28207230 .

[55] D. Darwati, A.N. Safitri, N. Ambardhani, T. Mayanti, N. Nurlelasari, D. Kurnia, Effectiveness and Anticancer Activity of a Novel Phenolic Compound from Garcinia porrecta Against the MCF-7 Breast Cancer Cell Line in vitro and in silico, Drug Des. Devel Ther. 15 (2021) 3523–3533, https://doi.org/10.2147/DDDT.S321824.

[56] K. Somandi, T.D. Seanego, T. Dlamini (née Molatsane), M. Maree, C.B. de Koning, J.Vanichtanankul, R. Rattanajak, T. Saeyang, Y. Yuthavong, S. Kamchonwongpaisan, A.L.Rousseau, Molecular Docking Studies, Synthesis and Biological Evaluation of SubstitutedPyrimidine-2,4-diamines as Inhibitors of Plasmodium falciparum Dihydrofolate Reductase, Chem.Med. Chem. 17 (2022) e202200418. 10.1002/cmdc.202200418.

[57] Y. Qi, Y. Li, Y. Fang, H. Gao, B. Qiang, S. Wang, H. Zhang, Design, Synthesis, Biological Evaluation, and Molecular Docking of 2,4-Diaminopyrimidine Derivatives Targeting Focal Adhesion Kinase as Tumor Radiotracers, Mol. Pharmaceutics 18 (2021) 1634–1642, https://doi.org/10.1021/acs.molpharmaceut.0c01088.

[58] S. Kim, J.Y. Wu, E.T. Birzin, K. Frisch, W. Chan, L. Pai, Y.T. Yang, R.T. Mosley, P.M. D. Fitzgerald, N. Sharma, J. Dahllund, A. Thorsell, F. DiNinno, S.P. Rohrer, J. M. Schaeffer, M.L. Hammond, Estrogen Receptor Ligands. II. Discovery of Benzoxathiins as Potent, Selective Estrogen Receptor α Modulators, J. Med. Chem. 47 (2004) 2171–2175, https://doi.org/10.1021/jm034243o.

[59] J.-I. Aihara, Reduced HOMO-LUMO Gap as an Index of Kinetic Stability for Polycyclic Aromatic Hydrocarbons, J. Phys. Chem. A,103 (1999) 7487–7495, https://doi.org/10.1021/jp990092i.

[60] L.H. Madkour, S.K. Elroby, inhibitive properties, thermodynamic, kinetics and quantum chemical calculations of polydentate Schiff base compounds as corrosion inhibitors for iron in acidic and alkaline media, Int. J. Ind. Chem. 6 (2015) 165–184, https://doi.org/10.1007/s40090-015-0039-7.

[61] M. Saracoglu, F. Kandemirli, M.A. Amin, C.D. Vurdu, M.S. Cavus, The Quantum Chemical Calculations of Some Thiazole Derivatives, in: 3rd International Conference on Computation for Science and Technology (ICCST-3), 2015, pp. 149–154.

[62] S. Kaya, C. Kaya, A new equation for calculation of chemical hardness of groups and molecules, Mol. Phys. 113 (2015) 1311–1319, https://doi.org/10.1080/00268976.2014.991771.

[63] V.K. Vishvakarma, N.S. Reetu, K. Kumari, R. Patel, P. Singh, A model to study the inhibition of nsP2B-nsP3 protease of dengue virus with imidazole, oxazole, triazole thiadiazole, and thiazolidine based scaffolds., Heliyon, 5(2019) e02124 10.1016/j.heliyon.2019.e02124.