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Synthesis, Characterization and Molecular Docking Study of New 1,3,4-Thiadiazole Derivatives

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Abstract

In this study, a series of 5-(5-{(Z)-[(4-R^1)methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2,3-triol (L_{1-3}), and 4-(5-{(Z)-[(4-R^1)methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2-diol (L_{4-6}) compounds were synthesized, where R^1 = 4-Nitro, 4-bromo, 4-chloro. The reaction between benzoic acid derivatives and hydrazinecarbothioamide in the basic medium gave the intended products with high yield and purity. The preparation of the compounds was confirmed by spectroscopic measurements in addition to physical properties. The biological properties of the prepared compounds were studied by molecular docking. The binding interaction between the new synthesized derivatives of 1,3,4-thiadiazole and the target, ADP-sugar pyrophosphatase, was studied. One of these 1,3,4-thiadiazole derivatives, 5-(5-{(Z)-[(4-nitrophenyl)methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2,3-triol (L_3) showed a high binding and coordination with its target. Molecular docking showed a docking score = −8.9 kcal/mol and MM-GBSA = −31.5 kcal/mol. The molecular docking estimation for the (L_3) compound exhibited that four hydrogen bonds were created with NUDT5 Gene.

Keywords: Breast cancer, Molecular docking, pyrophosphatase, Thiadiazol.

1. Introduction

Breast cancer stills one of the deadliest diseases affecting women in different countries of the world [1-3]. Recently, the focus has been on medicinal chemistry to develop new chemical compounds. Therefore, using these compounds makes it possible to target proteins and pathways associated with cancer to some extent. [4-6]. This creates a new path for more effective treatments. From these diverse molecular targets, ADP-sugar

pyrophosphatase (NUDT5) emerged as a key component that increases the spread of cancer cells through the metabolic process [7-9]. Hence, the NUDT5 Gene "ADP-sugar pyrophosphatase Protein" is an important and fundamental target in the drug development process [10].

The important and promising derivatives that have gained considerable interest from biological scientists for their wide and various biological activities are 1,3,4-thiadiazole derivatives as bioactive drugs (Figure 1), especially their anticancer properties. These compounds contain the 1,3,4-thiadiazole unit [11-13]. Moreover, these derivatives have shown a great capability to form stable bonds, including hydrogen bonds with proteins, affecting cancer cells [14-16]. Consequently, inhibiting critical biochemical paths within cancer cells. The 1,3,4-thiadiazole spin-offs may greatly contribute to the exploration of new pathways that could act as anti-breast cancer agents [17].

This work deals with the design and preparation of a group of compounds based on the 1,3,4-thiadiazole unit. They are groups (L_{1-3} and L_{4-6}). The synthesis process mainly involved providing a basic medium that acts as a catalyst, which enables the reaction of hydrazine carbothioamide with different derivatives of benzoic acid. From this standpoint, we have a group of promising compounds that contain different active groups [18-20]. Among these compounds, the compound (L_3) showed high biological potential and effectiveness as an anti-breast cancer compound. There are several studies that have addressed the use of molecular docking as a basic principle to determine the binding and interaction between novel synthetic compounds and the protein ADP-sugar pyrophosphatase (NUDT5) [21-25]. One of these synthetic compounds is 1,3,4-thiadiazole [26-28]. Docking investigations usually reveal the degree and strength of the binding and, thus, the stability of this binding. One of the most important factors of binding between compounds and their target is hydrogen bonds [29-30].

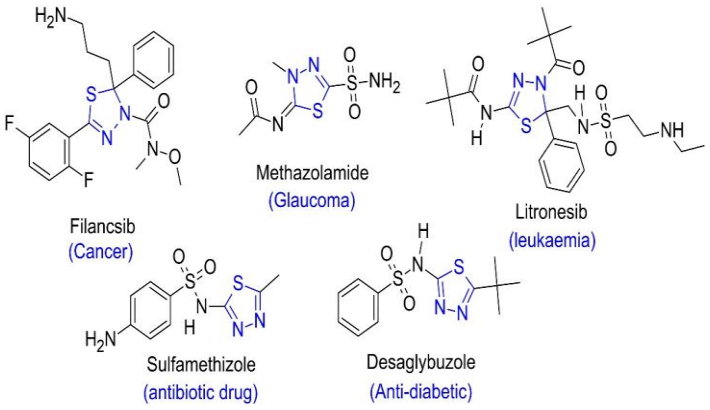


Figure 1: 1,3,4-thiadiazole drugs.

The aim of using synthetic chemistry in conjunction with the application of the

molecular docking concept in this work is to identify and characterize the potential of the prepared (L_{1-3} and L_{4-6}) compounds (1,3,4-thiadiazole unit) and several functional groups such as hydroxy groups as compounds with the potential to treat breast cancer. Also, their potential to target key enzymes such as NUDT5. This is done by detecting the strength and distance of the binding in addition to the potential biological interactions. This work can contribute to the knowledge regarding chemotherapeutics.

2. Experimental

2.1. Materials and method

All reactants and solvents used in the synthesis of the target compounds were provided by Sigma-Aldrich Co., Ltd and were used without further purification. Proton NMR spectra were measured using Burker 400MHz, and the solvent used was DMSO-d_6. ^{13}C NMR spectra were measured using (Burker 100.6 MHz). IR spectra were measured using Burker in the 4000-400 cm^{-1} range. Shimadzu GCMSQP 1000 EX was used to record and determine the mass spectra of the synthesized compounds.

2.2. General procedure for synthesizing 1,3,4-thiadiazole derivatives (L_{1-3} and L_{4-6}).

Step one involved the addition of benzoic acid derivatives (0.050 mol), hydrazinecarbothioamide (0.050 mol), and piperidine as a catalyst in (30 mL) dioxane as a solvent were mixed. The mixture was refluxed for 12h. TLC was used to monitor the reaction. After ending the reaction, the mixture was cooled to R.T. by adding (300 mL) of cold water. The precipitate was separated and recrystallized using ethanol to obtain the intermediate compounds shown in Scheme 1.

Step two involved the addition of intermediate compounds (0.050 mol), 30 mL of Con. H_2SO_4 and 30 mL of deionized water were mixed. Stirring was done using a stirrer at room temperature for15 hours. After the reaction time, the precipitate was washed with deionized water until the acid was removed. The (1,3,4-thiadiazol-2-NH_2) intermediate was obtained.

Moreover, the third step involved stepwise addition of a mixture of step 2 intermediate (0.05 mol) and an appropriately substituted benzaldehyde (0.05 mol) in (30 mL) MeOH and heated to reflux for 3 hours. TLC was employed to test the reaction. After ending the time of reaction, the mixture was

cooled to R.T., and (200 mL) of ice water was then added. The precipitate was isolated and recrystallized with MeOH to obtain the 1,3,4-thiadiazole derivatives (L_{1-3} and L_{4-6}) as shown in (Scheme 1)

2.3. 5-(5-{(Z)-[(4-bromophenyl) methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2,3-triol (L_1)

White precipitate, melting point = 222–224 °C, 80%; ^{1}H NMR (500 MHz, spectrum) δ, ppm: 9.44 (1H, azomethine proton, s), 9.00 (2H, hydroxyl, s), 8.97 (1H, hydroxyl, s), 8.35 (2H, s, Ar-H),8.22-7.32 (4H, dd, J = 7.8 and J = 1.6 Hz, arom-H). ^{13}C NMR (100.6 MHz): 169.92, 167.33, 159.25, 147.52, 145.43, 137.87, 135.01, 128.49, 123.53, 104.50. FTIR υ/cm^{-1}: 3447, 3422, 3019, 3010, 1613, 708. MS (ESI) m/z: 392 (60.8%).

2.4. 5-(5-{(Z)-[(4-chlorophenyl) methylidene]amino}-1,3,4-thiadiazol-2yl) benzene-1,2,3-triol (L_2)

White precipitate, melting point = 260–262 °C, 79%; ^{1}H NMR (500 MHz, spectrum) δ, ppm: 9.11 (1H, azomethine proton, s), 9.22 (2H, hydroxyl, s), 8.55 (1H, hydroxyl, s), 8.42 (2H, s, arom-H), 7.29-7.03 (4H, dd, J = 7.3 and J = 2.5 Hz, arom-H). ^{13}C NMR (100.6 MHz): 171.05, 166.30, 160.12, 145.50, 140.33, 135.18, 130.11, 125.35, 120.22, 101.40. FTIR υ/cm^{-1}: 3440, 3419, 3015, 3009, 1609, 830. MS (ESI) m/z: 347.7 (76.4%).

2.5. 5-(5-{(Z)-[(4-nitrophenyl) methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2,3-triol (L_3)

White precipitate, melting point = 325–327 °C, 80%; ^{1}H NMR (500 MHz, spectrum) δ, ppm: 9.85 (1H, azomethine proton, s), 9.22 (2H, hydroxyl, s), 8.65 (1H, hydroxyl, s), 8.41 (2H, s, arom-H),7.35-7.25 (4H, dd, J = 7.5 and J = 1.5 Hz, arom-H). ^{13}C NMR (100.6 MHz): 163.65, 161.62, 154.56, 143.21, 140.84, 136.52, 131.35, 126.65, 122.64, 100.95. FTIR υ/cm^{-1}: 3449, 3428, 3028, 3014, 1620, 1458, 1339. MS (ESI) m/z: 392 (60.8%). MS (ESI) m/z: 358 (70.0%).

2.6. 4-(5-{(Z)-[(4-bromophenyl) methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2-diol (L_4)

White precipitate, melting point = 201–203 °C, 77%; ^{1}H NMR (500 MHz, spectrum) δ, ppm: 10.00 (1H, azomethine

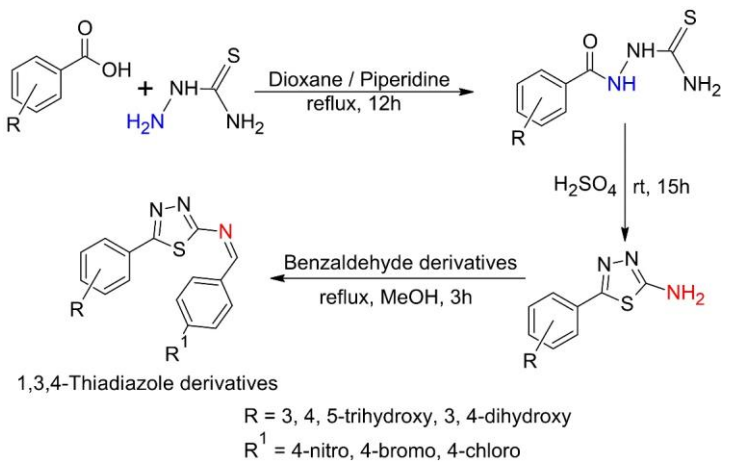
proton, s), 9.00 (1H, hydroxyl, s), 8.14 (1H, hydroxyl, s), 8.13 (1H, d, J = 7.6 Hz, arom-H), 8.09 (1H, s, arom-H), 8.05 (1H, d, J = 7.5 Hz, arom-H), 7.95-6.96 (4H, dd, J = 7.6 and J = 2.4 Hz, arom-H). ^{13}C NMR (100.6 MHz): 168.64, 167.07, 159.51, 145.70, 135.01, 133.70, 130.05, 128.75, 115.71, 104.50. FTIR υ/cm^{-1}: 3450, 3430, 3040, 3027, 1624, 709. MS (ESI) m/z: 376 (82.8%).

2.7. 4-(5-{(Z)-[(4-chlorophenyl) methylidene]amino}-1,3,4-thiadiazol-2-yl) benzene-1,2-diol (L_5)

White precipitate, melting point = 267–269 °C, 86%; ^{1}H NMR (500 MHz, spectrum) δ, ppm: 10.00 (1H, azomethine proton, s), 8.24 (1H, hydroxyl, s), 8.16 (1H, hydroxyl, s), 8.10 (1H, d, J = 7.6 Hz, arom-H), 8.09 (1H, s, arom-H), 8.02 (1H, d, J = 6.9 Hz, arom-H), 7.82-6.99 (4H, dd, J = 6.5 and J = 2.5 Hz, arom-H). ^{13}C NMR (100.6 MHz): 165.42, 163.10, 157.51, 148.65, 136.21, 132.21, 130.19, 127.35, 118.24, 105.43. FTIR υ/cm^{-1}: 3444, 3435, 3026, 3017, 1622, 830. MS (ESI) m/z: 331.7 (90.8%).

2.8. 4-(5-{(Z)-[(4-nitrophenyl) methylidene]amino}-1,3,4-thiadiazol-2-yl)benzene-1,2-diol (L_6)

White precipitate, melting point = 312–314 °C, 95%; ^{1}H NMR (500 MHz, spectrum) δ, ppm: 10.00 (1H, azomethine proton, s), 9.00 (1H, hydroxyl, s), 8.40 (1H, hydroxyl, s), 8.39 (1H, d, J = 7.5 Hz, arom-H), 8.22 (1H, s, arom-H), 8.16 (1H, d, J = 7.5 Hz, arom-H), 7.82-6.99 (4H, dd, J = 6.5 and J = 2.8 Hz, arom-H). ^{13}C NMR (100.6 MHz): 169.38, 165.11, 159.68, 149.94, 138.53, 134.09, 130.16, 124.98, 117.38, 108.65. FTIR υ/cm^{-1}: 3449, 3439, 3022, 3019, 1620, 1459, 1332. MS (ESI) m/z: 342 (91%).



Scheme 1: The reaction path of 1,3,4-thiadiazole derivatives (L_{1-3} and L_{4-6}).

2.9. Calculations Models

2.9.1. Ground-State predictions

The (L_{1-3} and L_{4-6}) in (Figure 2) were proposed with the appearance of breast cancer in women. The DFT was utilized in the present study through mcule.com. The

foundation group employed was 6-311G*, a hybrid functional function in the guise of the relations connection. Some physicochemical factors were estimated, including (ω), (η), (S), and (μ) [31-32].

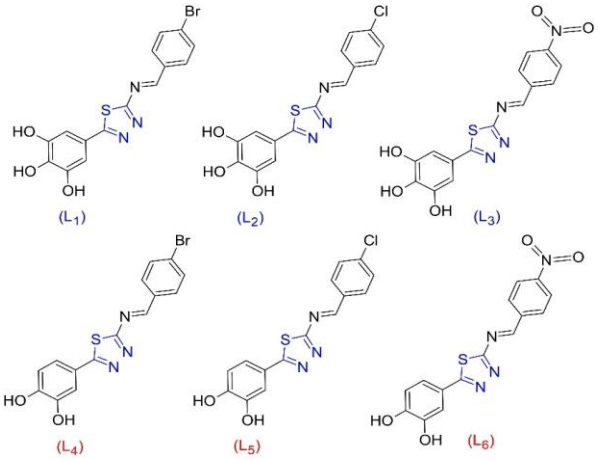


Figure 2: The structures of the calculated (L_{1-3} and L_{4-6})

2.9.2. Autodock calculations

Programs such as mcule.com and MGLtools were utilized in this investigation. DFT results through utilizing the (6-311G) foundation group suggested the structural development for the (L_{1-3} and L_{4-6}). A docking analysis was achieved on the studied (L_{1-3} and L_{4-6}) compounds as NUDT5 cancer cell inhibitors. Carefulness is provided to polar hydrogen atoms [33].

3. Results and discussion

3.1. Synthesis and characterization

The characterization by spectroscopic methods were confirmed the synthesis of the compounds. The FTIR spectral data showed the creation of the planned compounds. The synthesized (L_{1-3} and L_{4-6}) exhibited the receding of the stretching frequencies of the -NH_2, -COOH, and H-Aldehyde groups. Nevertheless, the unique absorption bands of -N=C-H (1609 - 1624 cm^{-1}) emerged for all compounds. The ^{1}H and ^{13}C NMR spectra of synthesized compounds gave a clear and accurate indication of the formation of compounds in their precise structural formula. As azomethine proton and phenolic -OH groups, the chemical shift value (s) at δ = 9.85-9.10 (ppm) because of one proton of the azomethine protons. However, the (δ, ppm) values fitting to the arom–OH protons are shown at δ = s, 9.22- 8.10 ppm. Moreover, Mass spectra clarified the formation of (L_{1-3} and L_{4-6}) compounds.

3.2. Total Electron Density map of the studies (L_{1-3} and L_{4-6})

The TED can be defined as the digit of electrons per m^2. (Figure 3) shows the numerous electronegative atoms, which are O, N, and S. These are represented in red, while the sites or groups with positive charges are represented in light gray. The chemical and physical features of the reactants are affected by the existence of charges. The (E^+) attack on (L_{1-3} and L_{4-6})

exhibited considerable effective areas, which can accept negative charge: (S and C atoms) [34].

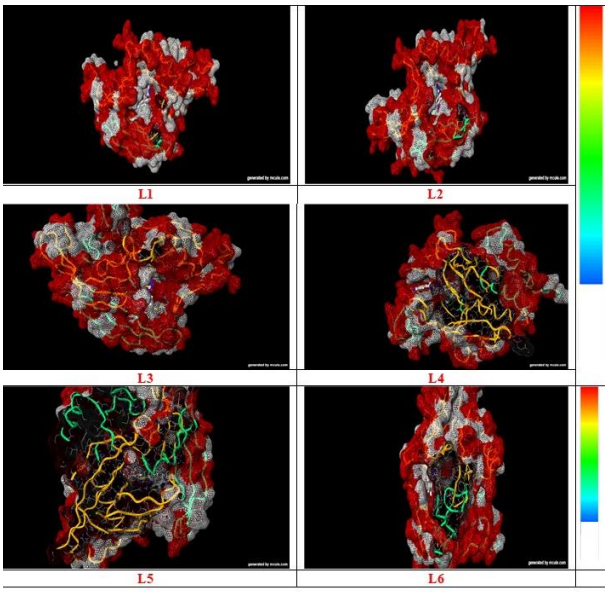


Figure 3: Total Electron Density of the calculated (L_{1-3} and L_{4-6})

3.3. Docking results

All 1,3,4-thiadiazole derivatives (L_{1-3} and L_{4-6}) were examined against breast cancer in women. The NUDIX has appeared as an essential category of hydrolytic enzymes due to the broad range of substrates. [35]. NUDT5 was found to serve as a regulator for hormone-conditional gene principles and expansion in breast cancer in women cells and has been involved in ADP-sugar pyrophosphatase metabolism [36]. NUDT5 regulators are investigated in this work to comprehend in any way NUDT5 holds a basic unit of heredity phrases and donates to the maturation of cancer cells. The present investigation exhibited that NUDT5 includes a function in ADP-sugar pyrophosphatase metabolism. Nonetheless, it cannot offer a relation to the elimination of terminated nucleotides. The binding of ligand-induced thermal stabilization of target NUDT5 is further improved by potent inhibitors. The organic compounds 1,3,4-thiadiazole derivatives (L_{1-3} and L_{4-6}) prepared in this study can inhibit nuclear ATP synthesis from PAR, which is progestin-dependent. Thus, potentially enabling subsequent chromatin remodeling, gene regulation, and cancer cell proliferation. Synthetic organic compounds with interesting physicochemical properties can act as inhibitors to enhance NUDT5 activity and metabolism studies. Using the protein data bank from mcule.com, it was found the crystal structure of ADP-sugar pyrophosphatase. The binding energy Eb and ligand efficiency LE are commonly used to determine the interaction of NUDT5 (5NQR) with inhibitors (synthesized organic compounds), and this determines the affinity of the sites of the substances to the protein binding energy (ADP-sugar pyrophosphatase) per atom of the ligand. Through the Eb values (kcal/mol), the study

showed the high ability of compounds L_3 and L_6 to inhibit NUDT5 as shown in Figure 4. The measurements showed that the receptor preferred binding site that extends from L1 to L10. As displayed in Table 1, the sequence of binding strengths of the prepared compounds with LDH-5 as the following:

$$L_3 > L_6 > L_1 > L_4 > L_2 > L_5$$

Table 1: The binding energy value and efficiency of the analyzed compounds.

Comp.	E_b	L_E	Best Local	RMS
L_1	-8.2	-0.21	1	8.64
L_2	-7.1	-0.19	4	24.11
L_3	-8.9	-0.29	1	31.33
L_4	-7.5	-0.21	4	6.44
L_5	-6.4	-0.19	7	6.92
L_6	-8.5	-0.29	6	13.17

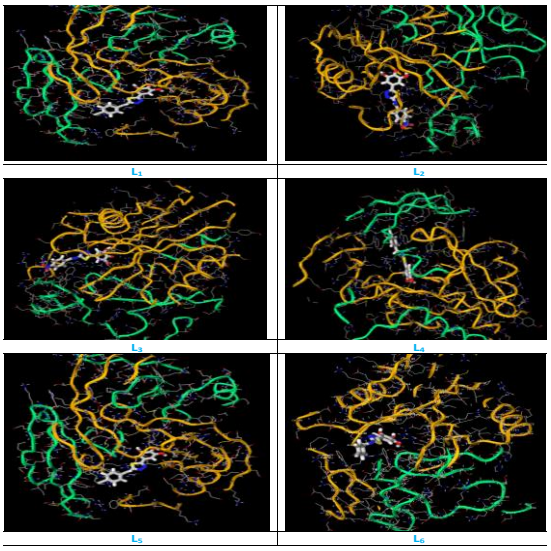


Figure 4: Interaction of compounds (L_{1-3} and L_{4-6}) with the receptor.

3.4. The molecules interaction

Determining the number and strength of hydrogen bonds is an essential factor in explaining the binding between the proposed organic pharmaceutical compounds and the target used. (Figure 5) shows the active regions that can form hydrogen bonds, whether they are acceptors or donors. The prepared compound L_3 can form 4 hydrogen bonds with the target receptor. There are certain regions in the synthesized compounds that are hydrophilic and other regions that are hydrophobic [37].

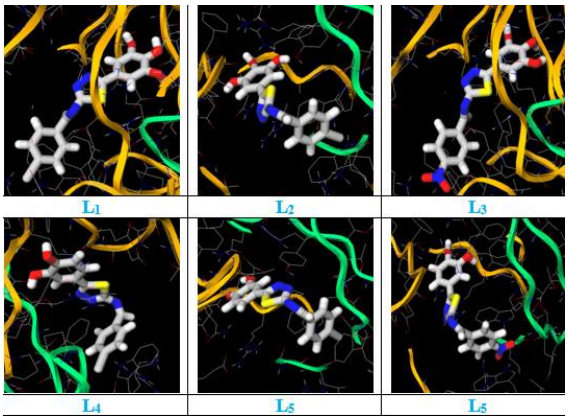


Figure 5: The donor/acceptor sites of hydrogen bond.

4. Conclusion

A straight and efficient preparation of six 1,3,4-thiadiazole compounds (L_{1-3} and L_{4-6}) from available starting materials with excellent yields was achieved. The new compounds (L_{1-3} and L_{4-6}) are offered as

breast anti-cancers in women. A complete theoretical simulation was performed on the synthesized compounds, which gave a clear picture of the efficiency of the prepared compounds to work as chemotherapeutics against cancer. The TED map showed that the electronic density in the compounds under study is centered on the sulfur, oxygen, and nitrogen atoms. The prepared compounds (L_3 and L_6) are highly effective as anti-breast cancer agents.

5. References

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