Original Article

Synthesis, Characterization, and Molecular Docking of New Tetrazole Derivatives as Promising Anticancer Agents

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Abstract

This work included the synthesis of azo dye [F1] by the reaction of dapsone's diazonium salt with salicylaldehyde at (0-5) 0C, synthesis of Schiff base [F2-F4] through the reaction of the substituted aromatic amine with aldehyde group in azo compound [F1] in ethanol, synthesis of tetrazole derivatives [F5-F7] by reaction of Schiff base with sodium azide in THF, and characterization of the synthesized compounds by using spectroscopic techniques FT-IR, 1H-NMR using DMSO-d6 as a solvent, SEM, in addition, melting point. This work also included a study of anticancer activity for some prepared compounds [F3, F7]. Besides, Molecular docking of the prepared compounds with the cancer proteins has also been studied using the Auto Dock v4.2 program in an attempt to find out the inhibitory potential of the compounds and the places of these compounds with the active site of the protein and compare them with the practical results obtained.

Keywords: Anticancer, Dapsone Reaction, Diazotisation, Tetrazole.

Introduction

Azo compounds are a family of chemical compounds that is getting a lot of interest in scientific circles. They are brightly colored and have long been used as dyes and paints [1]. Furthermore, their excellent thermal and optical properties have been extensively studied in applications such as visual recording medium, toner, and ink-jet printing [2]. As a result, much research on the synthesis and spectrum characteristics of various azo has been published. In addition, the azo compounds have been described as an anti-diabetic anti-neoplastic antibacterial [3], and anticancer agent [4]. Add to it that azo compounds are known to impede DNA, RNA, carcinogenesis, and protein production [5]. The azomethine group (-HC=N-) is present in Schiff bases. Hugo Schiff originally described them in 1864 as condensation products of ketones or aldehydes with primary amines. Schiff base formation is usually catalyzed by acids, bases, or heat [6].

Schiff bases are employed as intermediates in amino acid synthesis or ligands to create metal complexes with various structures [7, 8]. Aromatic aldehydes, particularly those with a sound conjugation system, produce persistent Schiff bases, while aliphatic aldehydes are unstable and polymerize quickly [9]. Schiff base ligands with hydrazone moiety have gotten a lot of interest recently because of their ease of synthesis, which leads to varied various structures and beneficial functions, particularly biological ones [10].

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Access this article online

Quick Response Code:

Website: www.pnrjournal.com

DOI: 10.47750/pnr.2022.13.03.079

How to cite this article: Yuosra Khalaf Alasadi, Fawzi Hameed Jumaa, Adil Hussein Dalaf, Safa Mahmood Shawkat, Mohammed Ghanam Mukhlif, Synthesis, Characterization, and Molecular Docking of New Tetrazole Derivatives as Promising Anticancer Agents, J PHARM NEGATIVE RESULTS 2022;13:513-522.

By creating drug carrier systems, hydrazones and their related compounds have been shown to enhance the selectivity of certain anticancer drugs [11, 12]. The tetrazole motif is a common synthetic scaffold used in medicine, and biochemistry [13]. It may be found in explosives, photography [14], polymers, gas generators, and agrochemicals [15]. In 1885, the first tetrazole synthesis was published [16]. The growing significance of 1,5-disubstituted tetrazoles in many applications, such as bioactive agents and medicines [17], has prompted more efficient synthesis techniques. Various techniques for the synthesis of disubstituted tetrazoles from amides have recently been devised. It is made by reacting Schiff's bases derivatives with sodium azide, which is one of the most contemporary ways of making it [18], along with the use of microwaves [19] and ultra-sonic in modern procedures [20]. Chlorinating agents make imidoyl chlorides, which are combined with an azide source to make disubstituted tetrazoles [21]. Flow seems to be a suitable reaction format for synthesizing tetrazoles from nitriles and an azide source [22].

Cancer is one of the most frightening illnesses in people and animals and is one of the leading causes of death worldwide [23]. As a result, new anticancer medication molecules must be discovered, developed, and improved to effectively inhibit proliferative pathways and cell clonal growth, it is critical to build new structural heterocyclic moieties to develop prospective anticancer agents with interesting biological uses [24]. Cancer is a significant global public health issue. Chemotherapy is one of the most frequently utilized treatments for breast cancer. This treatment is often associated with adverse side effects, ranging from nausea to bone marrow failure and the development of multidrug resistance [25].

Experimental

MATERIAL

All the used chemicals in this work were purchased from Fluka, Aldrich, and BDH companies, and were used without further purifications.

DEVICES USED

The melting points were measured using Electrothermal Melting Apparatus 9300. The reactions were tracked, and purity was tested using TLC. The CHNS analysis was carried out on an Elementar vario El III CHNS analyzer. The FT-IR spectra were captured using a Shimadzu FT-IR 8400S spectrophotometer with a scale of (400-4000) cm-1 by KBr disc. DMSO-d6 as solvents were used to capture 1H-NMR spectra on Varian instruments running at 400 MHZ. SEM measurement was carried out using a type Quanta 200 FEG, FEI Corporate device at Osman Gazi Pasha University-Turkey. TE SCAN/ Belsorp Mini II/ Czech Republic (Kashan University/ Iran) Scanning Electron Microscope was used.

SYNTHESIS OF AZO DYE [F1] [34]

Azo dye was prepared in two main steps:

Step 1/ Preparation of diazonium salt: 0.01 mol, 1.841 gm of dapsone dissolved in 30 ml, 37% HCl at a temperature of (0-5) 0C with continuous stirring, then add a solution of sodium nitrite 0.01 mol, 0.69 gm.

Step 2/ Coupling reaction: 0.01 mol, 1.22 ml of salicylaldehyde dissolved in 30 ml of the pyridine and cooled to (0-5) 0C in the ice bath. This solution is then slowly added to the cooled diazonium salt solution to yield an azo compound. Physical properties are given in table (1).

[F1] 5,5'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-hydroxybenzaldehyde). Orange, Yield 82%, mp 253–254°C. IR spectrum, ν, cm–1: 3392 (OH), 3093 (CH Arom.), 1730 (C=O), 1587, 1487 (C=C), 1433 (N=N), 1344 (S=O), 1191 (C-N), 1066 (C-N). 1H NMR spectrum, δ, ppm: 10.39 s (2H, 2OH); 9.04 s (2H, 2HC=O); 7.25-8.24 m (14H, aromatic benzene). Found, %: C, 60.27; H, 3.12; N, 10.54; S, 5.97. C26H18N4O6S. Calculated, %: C, 60.69; H, 3.53; N, 10.89; S, 6.23.

SYNTHESIS OF SCHIFF BASES [F2-F4] [35]

A solution of 0.001 mol, 0.514 gm of azo dye [F1] in 25 ml of absolute ethanol was added to 0.002 mol of different aromatic amines in 20 ml absolute ethanol and four drops of glacial acetic acid then the mixture was refluxed for (7-9) hours. The mixture was cooled to room temperature, filtered, dry and rec-crystallized in THF. Physical properties are given in table (1).

[F2] 4,4'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-((Z)-((4-nitrophenyl)imino) methyl)phenol). Light orange, Yield 74%, mp 248–250°C. IR spectrum, ν, cm–1: 3442 (OH), 3091 (CH Arom.), 1654 (C=N), 1479, 1578 (C=C), 1427 (N=N), 1377 (S=O), 1155 (C-N), 1070 (N-N). 1H NMR spectrum, δ, ppm: 10.38 s (2H, 2OH); 8.74 s (2H, 2HC=N); 7.18-8.23 m (22H, aromatic benzene). Found, %: C, 60.05; H, 2.98; N, 14.67; S, 3.86. C38H26N8O8S. Calculated, %: C, 60.47; H, 3.47; N, 14.85; S, 4.25.

[F3] 4,4'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-((Z)-((4-aminophenyl)imino) methyl)phenol). Light yellow, Yield 81%, mp 213–215°C IR spectrum, ν, cm–1: 3465 (OH), 3056 (CH Arom.), 1652 (C=N), 1497, 1581 (C=C), 1425 (N=N), 1381 (S=O), 1159 (C-N), 1065 (N-N). 1H NMR spectrum, δ, ppm: 10.39 s (2H, 2OH); 8.74 s (2H, 2HC=N); 7.17-8.25 m (22H, aromatic benzene); 3.36 s (2H, 2NH2). Found, %: C, 65.18; H, 3.94; N, 15.78; S, 4.27. C38H30N8O4S. Calculated, %: C, 65.69; H, 4.35; N, 16.13; S, 4.62.

[F4] 4,4'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-((Z)-((4-bromophenyl)imino) methyl)phenol). Light yellow, Yield 78%, mp 224–226°C. IR spectrum, ν, cm–1: 3459 (OH), 3056 (CH Arom.), 1654 (C=N), 1475, 1594 (C=C), 1429 (N=N), 1381 (S=O), 1169 (C-N), 1078 (N-N). 1H NMR spectrum, δ, ppm: 10.38 s (2H, 2OH); 8.73 s (2H, 2HC=N); 6.95-8.32 m (22H, aromatic benzene). Found,

%: C, 55.17; H, 2.76; N, 9.86; S, 3.68. C38H26Br2N6O4S. Calculated, %: C, 55.49; H, 3.19; N, 10.22; S, 3.90.

SYNTHESIS OF TETRAZOLE [F5-F7] [36]

In 25 ml of tetrahydrofuran (THF), Schiff bases prepared [F2-F4] 0.002 mol are combined with 0.004 mol, 0.26 gm of sodium azide and refluxed for (7-8) hours. The residue was extracted and ethanol was used to re-crystallize it. Physical properties are given in table (1).

[F5] 4,4'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-(1-(4-nitrophenyl)-4,5-dihydro-1H-tetrazol-5-yl)phenol). Light yellow, Yield 86%, mp 262–263°C. IR spectrum, ν, cm–1: 3431 (OH), 3200 (NH), 3028 (CH Arom.), 1480, 1575 (C=C), 1430 (N=N), 1379 (S=O), 1171 (C-N), 1083 (N-N). 1H NMR spectrum, δ, ppm: 10.15 s (2H, 2OH); 7.2-8.48 m (22H, aromatic benzene); 6.39 s (2H, 2CH tetrazole); 2.90 s (2H, 2NH tetrazole). Found, %: C, 54.28; H, 3.36; N, 23.32; S, 3.81. C38H28N14O8S. Calculated, %: C, 54.28; H, 3.36; N, 23.32; S, 3.81.

[F6] 4,4'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-(1-(4-aminophenyl)-4,5-dihydro-1H-tetrazol-5-yl)phenol). Yellow, Yield 82%, mp 276–278°C. IR spectrum, ν, cm–1: 3485 (OH), 3186 (NH), 3075 (CH Arom.), 1486, 1593 (C=C), 1421 (N=N), 1385 (S=O), 1166 (C-N), 1052 (N-N). 1H NMR spectrum, δ, ppm: 10.25 s (2H, 2OH); 7.23-8.95 m (22H, aromatic benzene); 6.58 s (2H, 2CH tetrazole); 4.06 s (2H, 2NH2); 3.10 s (2H, 2NH tetrazole). Found, %: C, 58.13; H, 3.74; N, 24.85; S, 3.63. C38H32N14O4S. Calculated, %: C, 58.45; H, 4.13; N, 25.11; S, 4.11.

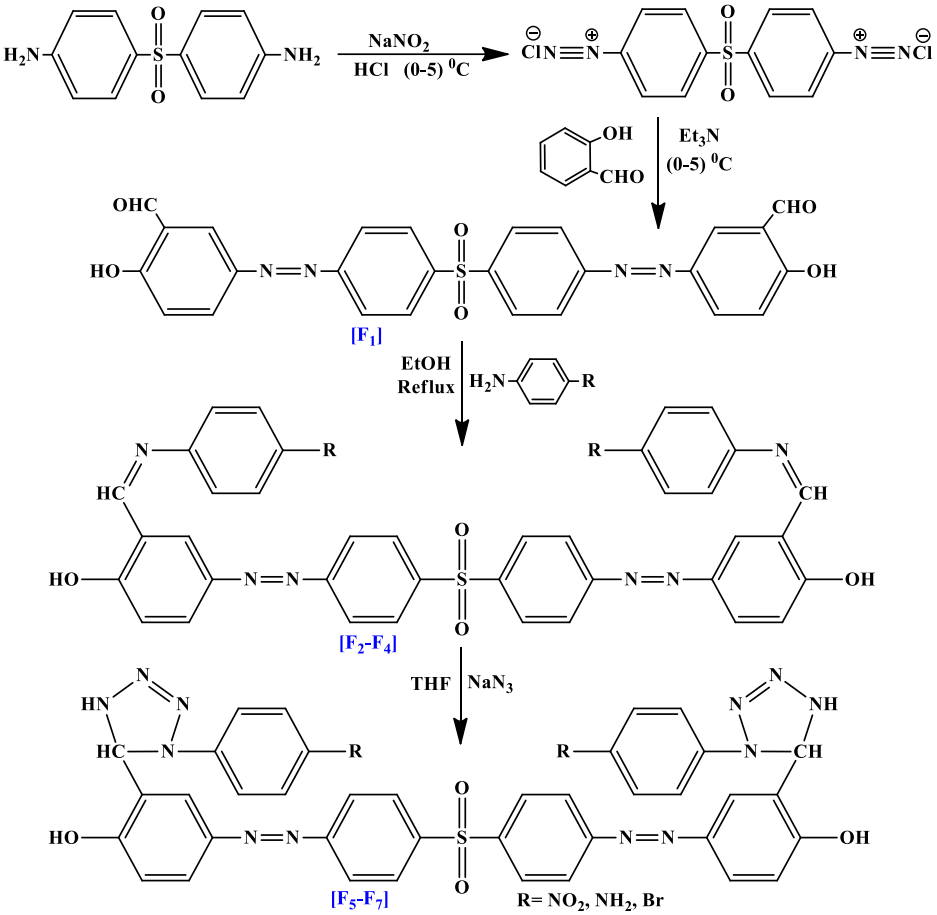
[F7] 4,4'-((sulfonylbis(4,1-phenylene))bis(diazene-2,1-diyl))bis(2-(1-(4-bromophenyl)-4,5-dihydro-1H-tetrazol-5-yl)phenol). Yellow, Yield 74%, mp 201–202°C. IR spectrum, ν, cm–1: 3427 (OH), 3159 (NH), 3035 (CH Arom.), 1481, 1579 (C=C), 1431 (N=N), 1386 (S=O), 1163 (C-N), 1087 (N-N). 1H NMR spectrum, δ, ppm: 10.13 s (2H, 2OH); 6.60-8.47 m (22H, aromatic benzene); 6.30 s (2H, 2CH tetrazole); 2.91 s (2H, 2NH tetrazole). Found, %: C, 49.81; H, 2.97; N, 18.17; S, 3.19. C38H28Br2N12O4S. Calculated, %: C, 50.23; H, 3.11; N, 18.50; S, 3.53.

METHOD OF ANTICANCER ACTIVITY ASSAY USING MTT [37]

MTT [4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide] was done to measure the anticancer activity of the [F3, F7] on cancer cells. The [F3, F7] were dissolved in DMSO, and the stock solutions were diluted to the required concentrations. MCF-7 Breast cancer cells were used to examine the anti-tumor activity of the compounds. Cancer cells were plated in a 96-well plate. Following 24 hours incubation period, the [F3, F7] were added at concentrations of 0.1µM, 1 µM, 10µM, 100µM, 200µM, and 400 µM. DMSO was used as a negative control. After 48hr of treatment, an MTT test was performed. Briefly, the medium was removed from the 96-well plate, and 100µL of fresh medium was added to each well. 10 µL of the previously prepared 12 mM MTT (SERVA) stock solution was added to each well. Cells were incubated at 37 °C for 4 hours, then 100 µL of 0.01 M SDS-HCl solution was added to each well. After an additional 4 hours of incubation, the samples were mixed with a pipette, and then the absorbance was measured at 570 nm. Experiments were repeated three times for statistical evaluation.

Results and discussion

In this research, many compounds were prepared, including azo [F1], Schiff bases [F2-F4], and tetrazole [F5-F7] as in the scheme (1) and characterized by FT-IR, 1H-NMR Spectra, and SEM.



Scheme 1: Route of prepared compounds [F1-F7]

IR SPECTRA

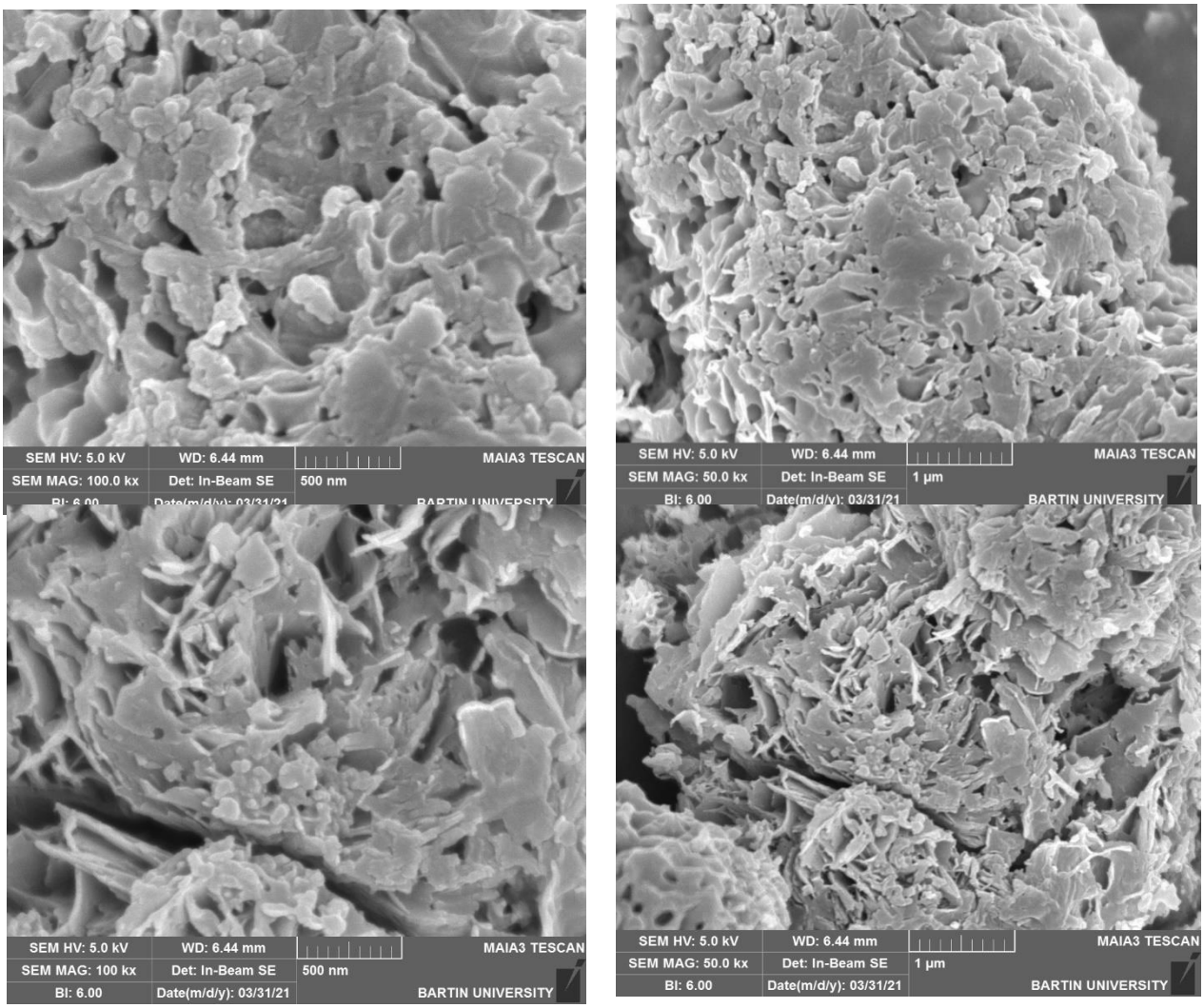
The FT-IR spectrum of [F1] revealed the appearance of a distinct band at (1433) cm-1 attributed to the azo group (N=N) as well as (C=O) aldehyde group that appeared at (1730) cm-1 [26] in addition to the rest of the effective groups. The spectra of the prepared Schiff bases [F2-F4] revealed the appearance of a distinct band in the range (1652-1654) cm-1 attributed to the azomethine group (C=N) after the disappearance of the aldehyde carbonyl bands [27], as well as the presence of (N=N) group that appeared in the range (1425-1429) cm-1 in addition to the rest of the listed active groups. The spectra of the prepared tetrazole [F5-F7] revealed the disappearance of a band for the azomethine group (C=N) and the appearance of bands in the range (3159-3200) cm-1 attributed to the (NH) group of tetrazole ring [28], in addition to the rest of the active groups mentioned in the experimental part.

H-NMR

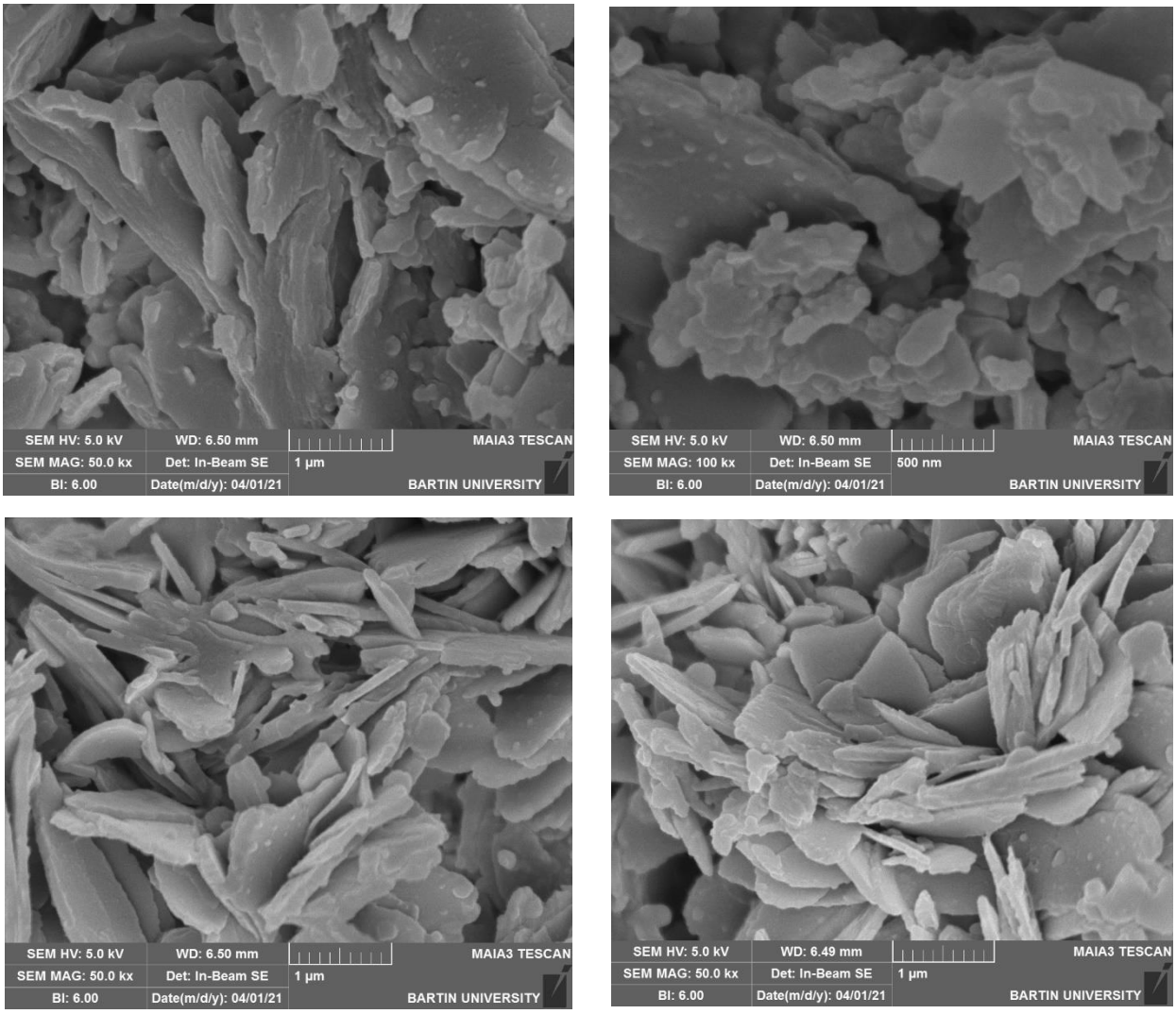
The H-NMR spectrum of [F1] showed a singlet at 10.39ppm attributed to (OH) groups, and appeared as a singlet at 9.04ppm attributed to the proton of the aldehyde group, the multiplet in the rang 7.25-8.24ppm attributed to protons of aromatic benzene. The spectrum of [F2] showed a singlet at 10.38ppm attributed to (OH) groups and appeared as a singlet at 8.74ppm attributed to the proton of the azomethine group, the multiplet in the rang 7.18-8.23ppm attributed to protons of phenyl rings, the spectrum of [F3] showed a singlet at 10.39ppm attributed to (OH) groups and appeared as a singlet at 8.74ppm attributed to the proton of the azomethine group, the multiplet in the rang 7.17-8.25ppm attributed to protons of phenyl rings and protons of amine groups, the spectrum of [F4] showed a singlet at 10.38ppm attributed to (OH) groups and appeared as a singlet at 8.73ppm attributed to the proton of the azomethine group, the multiplet in the rang 6.95-8.32ppm attributed to protons of phenyl rings. The spectrum of [F5] showed a singlet at 10.15ppm attributed to (OH) groups and appeared as a multiplet in the rang 7.20-8.48ppm attributed to protons of phenyl rings and protons of NH tetrazole groups and appeared as a singlet at 6.39ppm attributed to the proton of CH tetrazole group, the spectrum of [F6] showed a singlet at 10.25ppm attributed to (OH) groups and appeared as a multiplet in the rang 7.23-8.95ppm attributed to protons of phenyl rings and protons of NH tetrazole groups and appeared as a singlet at 6.58ppm attributed to the proton of CH tetrazole group, the spectrum of [F7] showed a singlet at 10.13ppm attributed to (OH) groups and appeared as a multiplet in the rang 6.60-8.95ppm attributed to protons of phenyl rings and protons of NH tetrazole groups and appeared as a singlet at 6.30ppm attributed to the proton of CH tetrazole group.

SEM for [F5, F7]

When conducting SEM analysis of some prepared compounds, such as the [F5] compound, where the crystal structure of this compound appeared in the form of rock structures measuring (500µm), but when zoomed in to (1µm), the nanostructure appears in the form of rocky deposits in figure (1). While compound [F7] appeared, where the crystal structure of this compound appeared in the form of rock blocks measuring (500µm), when zoomed in to (1µm), the nanostructure appears in the form of lamellar structures in figure (2).



(Fig. 1): SEM of compound [F5]



(Fig. 2): SEM of compound [F7].

Anticancer for [F3] and [F7]

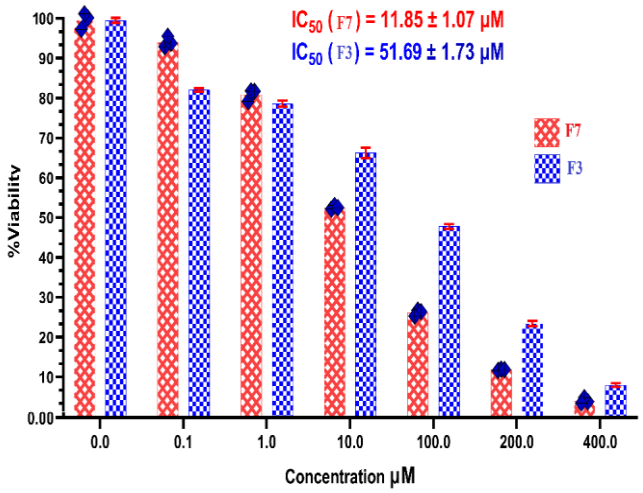
Two compounds were initially tested for the activity to inhibit the growth of cells against human breast cell lines (MCF-7), using cis-platin as the positive control. The effects of the four complexes on the development of MCF-7 were studied and recorded after 24 h, and the calculated IC50 values are listed in Tables (1, 2) with figure (3). The compounds [F3, F7] had IC50 values of 11.85 ± 1.07 mM and 51.69 ± 1.73 mM, respectively, and they were less active than cisplatin (4.45 ± 0.04 mM). Our findings are comparable to and, in some cases, much better than activities reported for azo compounds. The results showed the growth inhibition of cancer cell lines depending on the concentration of the two compounds. Compound [F7] displayed the highest inhibitory effect on cell proliferation. This is because the compound [F7] has two tetrazole rings in structure, which will enhance the cytotoxic activity [F7]. This is consistent with the literature that species with tetrazole heterocyclic compounds are more active [29-31].

Table 1: Cell viability (%) of compounds [F3, F7] against MCF-7 cell line

Concentration (µM)	Cell viability (%)	
	F_3	F_7
0.000	100.0	100.0
0.100	90.87	94.52
1.000	87.09	81.30
10.00	73.47	52.93
100.0	53.06	26.45
200.0	26.13	12.100
400.0	9.10	4.280

Table 2: IC50 values of [F3, F7] against MCF-7 cell line compared with cis-platin

Compound	IC_{50} value (μM)
F_3	51.69± 1.73
F_7	11.58 ± 1.07
Cis-platin	4.45 ± 0.04



(Fig. 3): MCF-7 cell viability after treatment of compounds F3 and F7 at different concentrations (□M). P value = 0.005 in each case.

MOLECULAR DOCKING SIMULATIONS STUDIES OF PREPARED COMPOUNDS [F1-F7]

Molecular docking is used to demonstrate how the compounds synthesized in this study are associated with the active site of the proteins and to demonstrate the critical amino acids in the process of binding inhibitors within the proteins after deleting the water and other molecules within the crystalline structure, to rationalize the binding site interactions of inhibitor molecular docking studies were carried out against cancer under investigation. The RCSB Protein Data Bank was used to obtain the most settled crystal structure of cancer under consideration (PDB). Prepared compounds were discovered to attach near the active site pocket's entry. The prepared compounds [F1-F7] have formed an association of different types with the cancer proteins under study, which gives an indication of their effectiveness within these limits and that the variation in the rates of inhibition may be the difference in concentration, or that these prepared compounds may affect in another way the work of the cancer cell. It is noted that through studying the free energy for the bonding and the root mean square deviation (RMSD) between the ligand and the protein in the compounds [F1-F7], they are both theoretically and practically converging about the inhibition of a divisive activity with the appearance of variations [32, 33], Table (3), figure (4).

The compound [F1] gave a certain number of bonds, namely: Four hydrogen bonds: The first and second bonds link the electron pair of the oxygen atom of the phenol group with the amino acid residues THR1004 and the A chain of DNA located in the active site. For the protein, the third hydrogen bond is between the electron pair of the oxygen atom of the sulfide group with the amino acid residue ARG1045 located in the active site of the protein, the fourth hydrogen bond is between the electron pair of the oxygen atom of the aldehyde carbonyl group with the amino acid residue LYS1018 Located in the active site of the protein, there is also a pi-pi bond linking the A chain of DNA with the aromatic ring electrons, and a pi-cation bond linking the aromatic ring electrons with the amino acid residue ARG1045 It is located in the active site of the protein.

The compound [F2] gave a certain number of bonds, namely: Seven hydrogen bonds: the first, second, third, and fourth bonds link the electron pair of the sulfide group oxygen atom with the amino acid residue LYS1338 and the amino acid residues of the two C chains, G, located in the active site of the protein, and the fifth, sixth and seventh hydrogen bonds are linked between the electron double of the nitro-oxygen atom with the amino acid residues THR1160, GLY1154 and the DNA residues of the C chain of DNA. Two pi-sulfur bonds link the aromatic ring electrons with the histidine residue GLU1307 and the G-chain of DNA located in the active site of the protein, and two pi- bonds pi the electrons of the aromatic ring bind to the C-strand of DNA, which is located in the active site of the protein.

The compound [F3] gave a certain number of bonds, namely: Five hydrogen bonds: the first, second, and third bonds link the electron pair of the nitrogen atom of the azo group with the amino acid residues LYS1018, ARG1045, and the DNA residues of the G chain. It is located in the active site of the protein, and the fourth hydrogen bond is between the electron pair of the oxygen atom of the sulfide group and the DNA residues of the G chain of the DNA located in the active site of the protein, and two Donor-Donor bonds link Between the two hydrogen atoms of the amino group with the amino acid residue THR1004 and the A chain of the DNA located in the active site of the protein. Compound [F4 and F7] did not show molecular docking simulations picture, and only the binding energy and RMSD appeared.

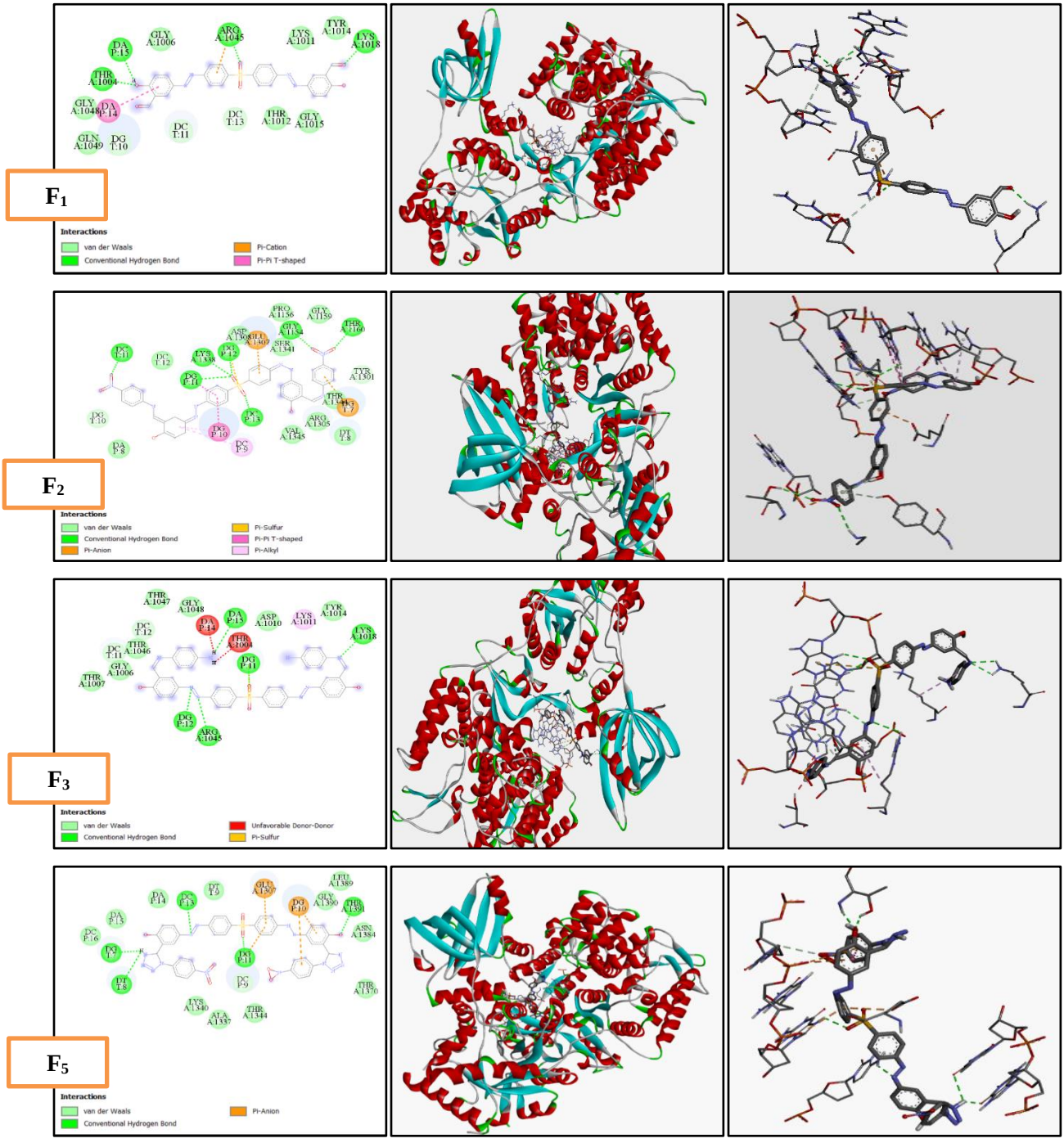
The compound [F5] gave a certain number of bonds: Five hydrogen bonds: The first bond links the electron pair of the oxygen atom of the phenol group with the amino acid residue THR1391 located in the active site of the protein. The second hydrogen bonds between the electron pair of the oxygen atom of the sulfide group and the residues of the DNA of the G chain of the DNA located in the active site of the protein, while the third hydrogen bond links the electron pair of the azo group nitrogen with the residues of the DNA of the C chain The DNA located in the active site of the protein, and the fourth and fifth hydrogen bonds link the two hydrogen atoms of the five ring with the DNA residues of the T, G chain of the DNA located in the active site of the protein. In four pi-Anion bonds, the electrons of the aromatic ring are attached to the amino acid residue GLU1307 and the residues

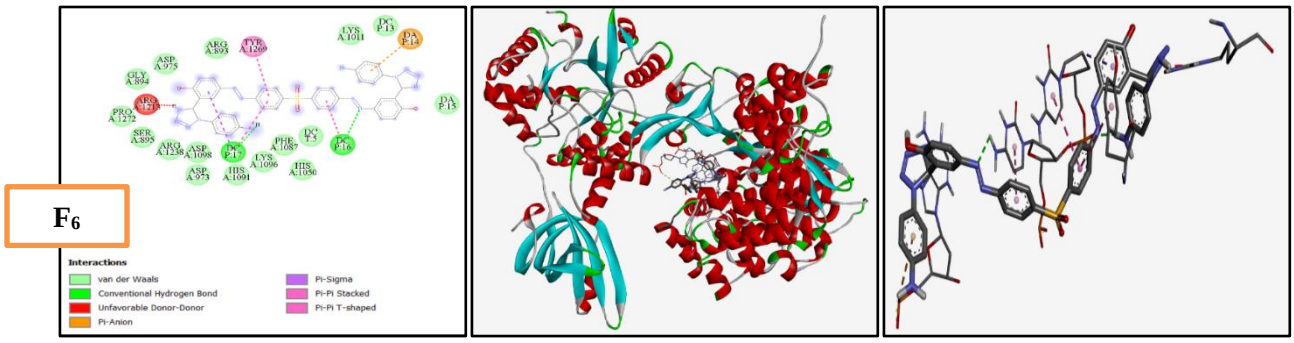
of the DNA of the G chain located in the protein's active site.

The compound [F6] gave a certain number of bonds, namely: two hydrogen bonds: the first bond connects the electron pair of the nitrogen atom of the azo group with the remains of the DNA of the C chain located in the active site of the protein, while the hydrogen bonds the second is that it binds between the hydrogen atom of the amine group and the DNA residues of the C-chain DNA located in the active site of the protein. And four pi-pi-staked bonds. The aromatic ring electrons are linked to the amino acid residue TUR1269 and the C-chain DNA residues located in the protein's active site. The pi-anion bond is by the ring electrons. Aromatic with the residues of the DNA of the A chain located in the protein's active site, and its pi-pi sigma bond. The electrons of the aromatic ring bind with the residues of the DNA of the C chain located in the protein's active site.

Table 3: Binding Energy kcal/mol and Reference RMSD A for [F1-F7]

Comp.	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Binding	-	-	-	-	-	-	-
energy	11.0	11.6	11.3	11.1	11.7	11.5	11.8
RMSD	0.23	0.22	0.32	0.12	0.41	0.52	0.32





(Fig. 4): Molecular docking simulations for prepared compounds [F1, F2, F3, F5, F6].

Conclusions

Through spectroscopic and physical measurements, the prepared compounds' accuracy and validity were found. These compounds are stable at laboratory temperature and did not disintegrate or change color. The compounds [F3, F7] had IC50 values of 11.85 ± 1.07 mM and 51.69 ± 1.73 mM, respectively, and they were less active than cisplatin (4.45 ± 0.04 mM). The results showed the growth inhibition of cancer cell lines depending on the concentration of the two compounds. Compound [F7] displayed the highest inhibitory effect on cell proliferation. This is because the compound [F7] has two tetrazole rings in structure, which will enhance the cytotoxic activity [F7]. The molecular docking of compounds [F1-F7] with the proteins of cancer under study has been studied on the active side of these proteins to explain the ability of these molecules to inhibit and know the type of interference between them and the protein of cancer.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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