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Research paper

Synthesis, characterization, chemical and biological activities of 4-(4-methoxyphenethyl)-5- benzyl-2-hydroxy-*2H*-1,2,4-triazole-3*(4H)*-one phthalocyanine derivatives

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ABSTRACT

Different properties of phthalocyanine compounds can be measured both theoretically and experimentally. In this study, tetra substituted phthalocyanines (H2 **(2)** and Cu^{II} **(3)** were performed using 4-(4-(4-methoxyphenethyl)-3-benzyl-5-oxo-4,5-dihydro-1,2,4 triazol-1-yl)phthalonitrile **(1)**. The structures of all these original compounds synthesized were elucidated using distinctive of spectroscopic techniques.Theoretical comparison of the chemical and biological activities of phthalocyanine molecules and its copper metal complex has been made. Chemical activities were compared with Gaussian software program and biological activities were compared with molecular docking calculations. Used proteins for biological activity are the crystal structure of estrogen receptor protein (from the breast cancer), ID: 1A52, crystal structure of VEGFR kinase protein (from liver cancer), ID: 3WZE, crystal structure of MLK4 kinase (colon cancer) ID: 4UYA, and crystal structure of an allosteric Eya2 phosphatase inhibitor protein (from lung cancer), ID: 5ZMA. After, the interactions between molecules and proteins were determined using the Protein-Ligand Interaction Profiler (PLIP) server.

1. Introduction

The term phthalocyanine was first used by the scientist Professor Linstead in 1933 to describe the compound metallophthalocyanines, metal-free (dihydrogen) phthalocyanines, and organic compounds including phthalocyanine derivatives [1]. The first patent of compounds, known as phthalocyanines, is taken by Dandridge, Drescher, and Thomas in 1929. At the end of hard work, Professor Linstead and his colleagues illuminated the structures of metallo and metal-free phthalocyanines in 1934. The fundamental illumination of these structures was verified by Robertson using X-ray diffraction [2].

Phthalocyanines are synthetic analogs of porphyrin compounds such as hemoglobin, cobalamin and chlorophyll. These compounds play important role in the biological system [3]. Phthalocyanines have various properties such as planarity, thermal stability and photostability thanks to delocalized electrons in their structure [4]. They become a universal research subject by dint of high technological features since 1933. Phthalocyanines have outstanding properties such as the ability to connect>70 elements with coordinated covalent bonds in the center of the macrocyclic ring, permutableness substituents on peripheral or non-peripheral positions, aromatic structure, highly stable against external factors such as acid, alkali, heat and moisture [5,6]. Phthalocyanines are indispensable for chemistry and other basic sciences thanks to having wide applications [7,8]. Some of these applications are known as catalysts [9,10], PDT [11,12], electrochemical properties [13,14], solar cells [15], non-linear optics [16].

Triazoles, a member of the azoles class, are five-ring compounds including three nitrogen atoms. These compounds having the $C_2H_3N_3$ formula are one of the most known heterocyclic compounds [17]. They are used as starting substances for the synthesis of many compounds [18]. 1,2,4-Triazoles are the biologically active heterocyclic organic compound. 1,2,4-Triazole and derivatives have many biological activities such as environmental [19], industrial [20], agricultural [21], antimicrobial [22], anti-inflammatory [23], anti-viral [24], anti-fungal [25], anti-bacterial [26], anti-tubercular [27], anticancer [28], antioxidant [29] and anticonvulsant [30].

Theoretical calculations have become quite common in recent studies. Parameters derived from theoretical calculations are a procedure that provides significant benefits in explaining many properties of molecules [31–34]. However, with the calculations made, the potential

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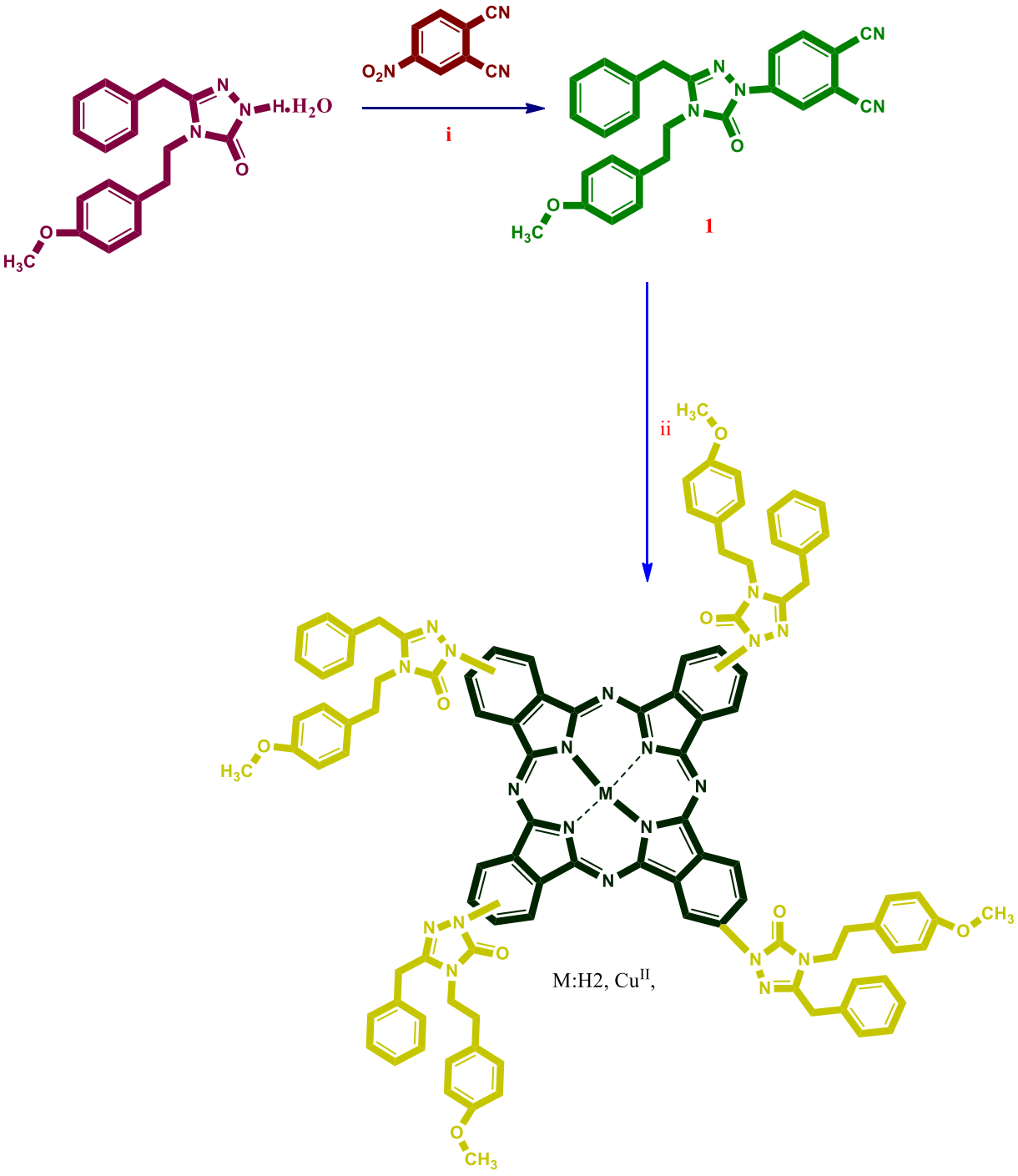

Scheme 1. The synthesis route of compound phthalonitrile **(1)** and phthalocyanines **(2,3)** (M = H_2, Cu(II)). Reaction terms: i: N_2, K_2CO_3, dehydrated dimethylformamide, 60 °C. ii; dehydrated *n*-amyl alcohol, anhydrous of $CuCl_2$, DBU, reflux temperature.

of the molecules to be used as drugs can be examined. In short, theoretical calculations allow us to have a lot of information about molecules without doing any experimental work.

In our research, we synthesized and characterized H2 **(2)** and Cu^{II} **(3)** phthalocyanines containing 1,2,4 triazole groups (Scheme 1) [35]. The structures of all original compounds synthesized were elucidated using distinctive of spectroscopic techniques. Theoretical measurements of phthalocyanines have also become very important recently. Therefore, in the second part of the research, the phthalocyanine molecule and its copper metal complex were commented on the activities of the molecules with the gaussian package program and the molecular docking calculations. The interactions between molecules and proteins were determined using the Protein-Ligand Interaction Profiler (*PLIP) server.

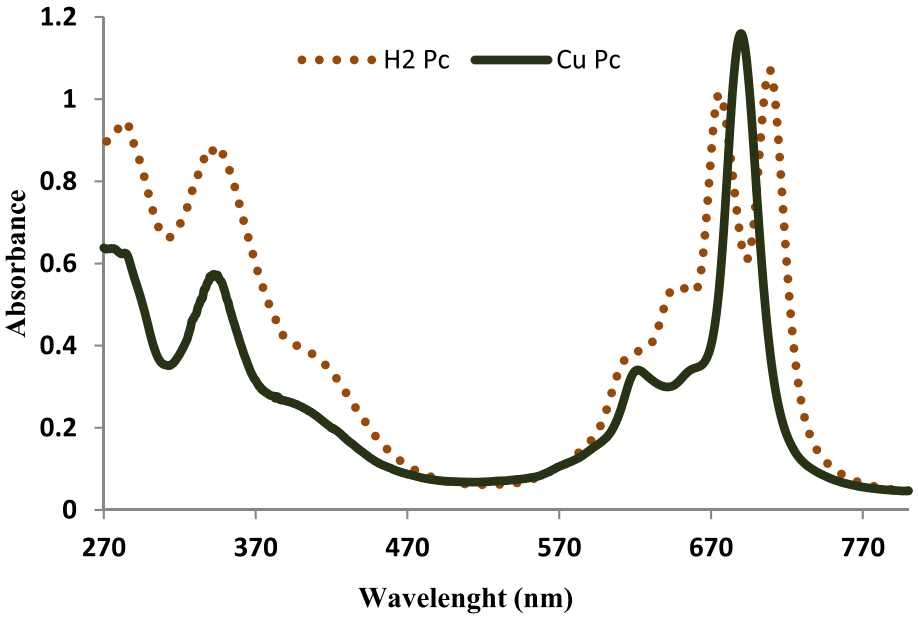

Fig. 1. UV–vis electronic absorption spectra of peripheral substituted H2Pc (**2**) and CuPc **(3)** at different concentrations in DMF.

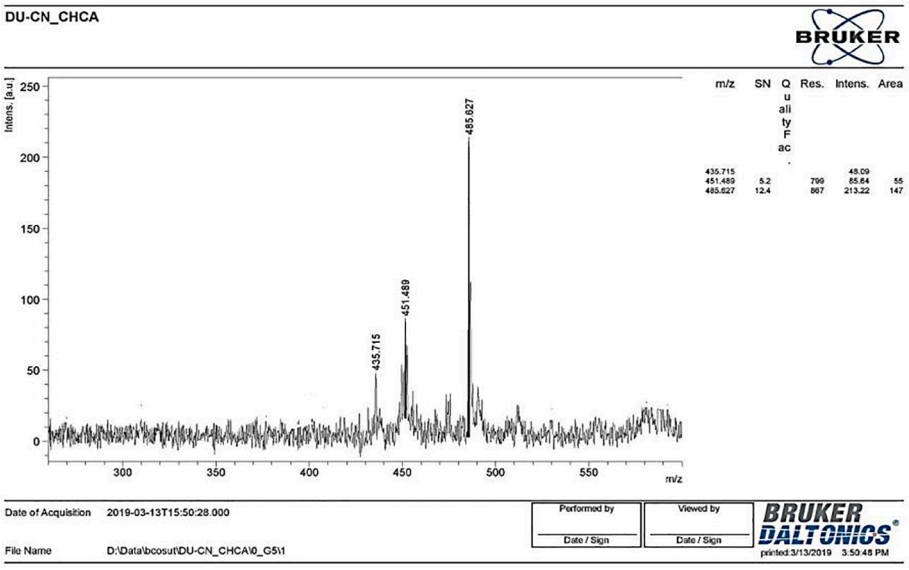

Fig. 2. The mass spectra of phthalonitrile derivative (**1**).

2. Experimental

2.1. Synthesis

2.1.1. 4-(4-(4-methoxyphenethyl)-3-benzyl-5-oxo-4,5-dihydro-1,2,4 triazol-1yl)phthalonitrile (1)

4-(4-methoxyphenethyl)-5-benzyl-2*H*-1,2,4-triazole3 (4*H*)-one [35] (1.8 g, 5.49 mmol) and (1 g, 3.16 mmol) was solubilized in 15 mL of dehydrated N,*N*-dimethylethylamine under a nitrogen atmosphere and K_2CO_3 (2.27 g, 16.47 mmol) was added to this mixture. Reaction content was stirred for 138 h at 60 °C. Next, the reaction mixture was cooled about at 25 °C. The reaction content was poured into crushed ice. The brown solid product was filtrated and dried. The crude product was purified using column chromatography via aluminum oxide as column material and $CHCl_3$ as an eluent.

2.1.2. 4-(4-(4-methoxyphenethyl)-3-benzyl-5-oxo-4,5-dihydro-1,2,4 triazol-1-yl)phthalonitrile (1)

Yield: 0.85 g (36 %). M.p.: 149–151 °C. FT-IR (ATR), ν/cm^{-1}: 3082–3006 ν C—H (Ar), 2958–2849 ν C—H (Alp), 2232 ν C≡N, 1717 ν -C=O,

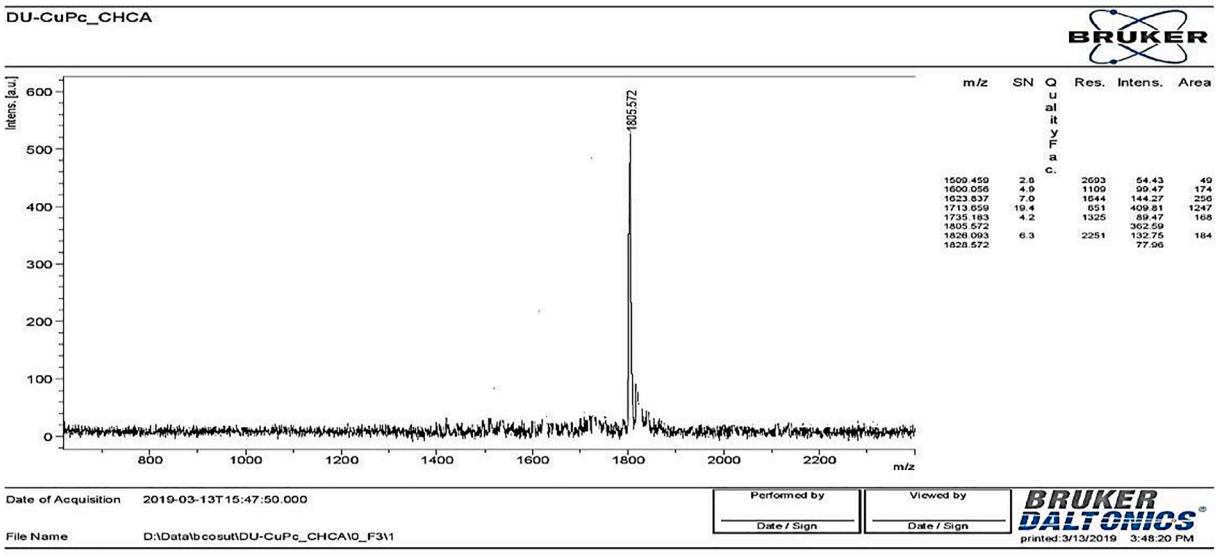

Fig. 3. The mass spectra of peripheral substituted H_2Pc (**2**).

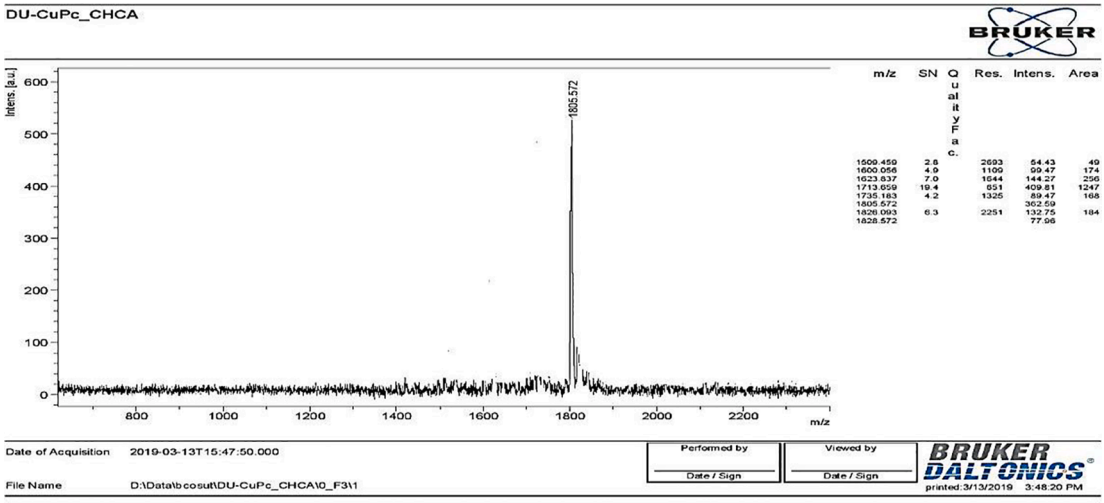

Fig. 4. The mass spectra of peripheral substituted CuPc (**3**).

1666, 1579, 1495, 1397, 1302, 1176, 1091, 1030, 990, 870, 627, 555. ^{1}H NMR ($CDCl_3$), (δ:ppm): 2.51 (s, 2H, CH_2) 2.63–2.59 (t, 2H, CH_2), 3.72 (s, 3H, OCH_3), 2.91–2.88 (t, 2H, CH_2), 6.88–6.83 (m, 2H, Ar-H), 7.03–6.95 (dd, 2H, Ar-H), 7.43–7.27 (m, 4H, Ar-H), 8.51 (m, 1H, Ar-H), 8.36–8.34 (m, 2H, Ar-H), 8.23–8.21 (d, 1H, Ar-H).^{13}C NMR ($CDCl_3$), (δ:ppm): 31.54, 33.13, 47.61, 55.50, 110.01, 110.30, 114.50, 116.37, 116.45, 121.69, 121.82, 126.98, 127.79, 129.29, 129.35, 129.80, 130.35, 134.57, 134.72, 135.20, 135.97, 138.68, 141.55, 149.41, 152.19, 158.60. MALDI-TOF-MS, (*m/z*): Calcd.: 435.49 for $C_{26}H_{21}N_5O_2$; Found: 435.71 $[M]^+$.

2.1.3. Synthesis of phthalocyanine (2)

Under a nitrogen atmosphere (0.1 g, 0.22 mmol) compound (**1**) was solubilized with 10 mL of dehydrated *n*-amyl alcohol and 15 drops of DBU was added to the mixture. The reaction content was heated at 140 °C for 20 h. The reaction mixture which cooling to about 25 °C was rarefied with 20 mL of ethanol and stirred about for 2 h. The green-colored substance was leached, washed with hot ethanol, methanol and diethyl ether in order and dried in vacuo. Eventually, it was dissolved in a small amount of chloroform and purified on basic alumina using chloroform: ethyl alcohol (100:5) solvent system. The extracts were evaporated by dryness and dried in vacuo.

2.1.4. Synthesis of phthalocyanine (3)

Under a nitrogen atmosphere, (0.1 g, 0.22 mmol) compound (**1**) was solubilized with 10 mL of 140 °C dehydrated *n*-amyl alcohol. Anhydrous, metal salt (15 mg, 0.11 mmol) $CuCl_2$ and 5 drops of DBU were added. The reaction content was heated at 140 °C for 20 h. The reaction

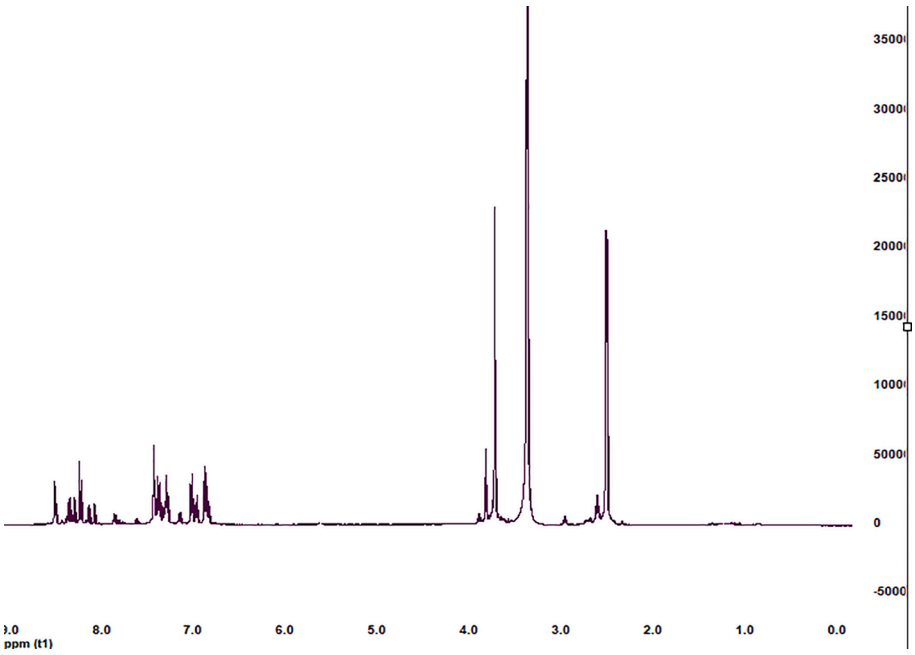

Fig. 5. ^{1}H NMR spectra of phthalonitrile derivative (**1**) in $CDCl_3$.

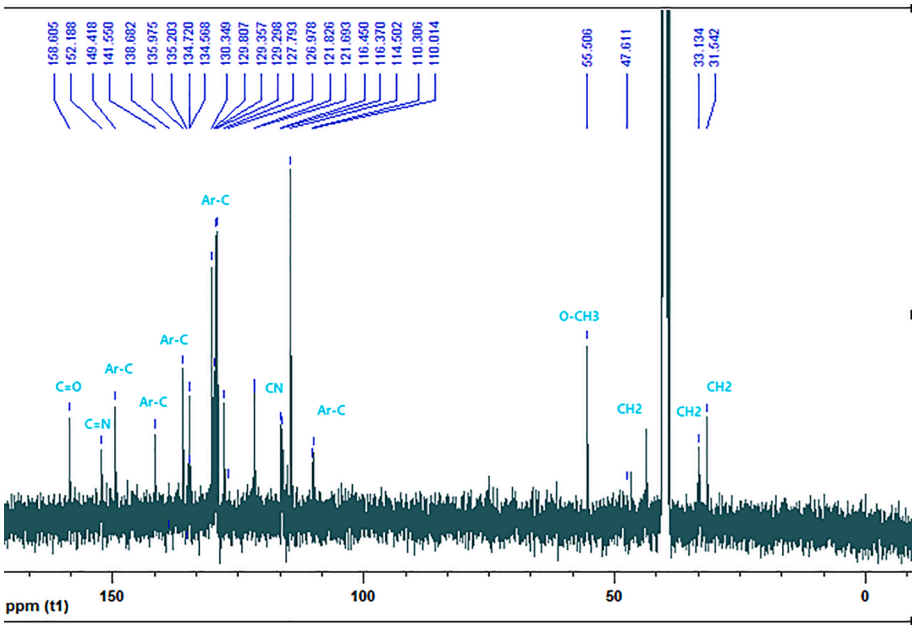

Fig. 6. ^{13}C NMR spectra of phthalonitrile derivative (**1**) in $CDCl_3$.

content which cooling to about at 25 °C was rarefied by 20 mL of ethanol and stirred under about at 25 °C for 2 h. The green-colored substance was leached, washed with hot ethanol, methanol and diethyl ether in order and dried in vacuo. Finally, It was dissolved in a small amount of chloroform and purified on basic alumina using a $CHCl_3$:C_2H_5OH (100:1) solvent system. The extracts were evaporated by dryness and then dried in vacuo.

2.1.5. 2(3), 9(10), 16(17), 23(24)-Tetrakis[4-(4-methoxyphenethyl)-5-benzyl-2H-1,2,4-triazol-3 (4H)-one] phthalocyaninato (2)

Yield: 0.030 g (30 %). M.p.: >300 °C. FT-IR (ATR), ν/cm^{-1}: 3289 ν N—H, 3059–3025 ν C—H (Ar), 2958–2850 ν C—H (Alp), 1706 ν C—O, 1651, 1611, 1582, 1512, 1494, 1461, 1319, 1115, 1013, 890, 747, 653. ^{1}H NMR ($CDCl_3$), (δ:ppm): 1.23 (s, 8H, CH_2), 2.29–2.26 (t, 8H, CH_2) 2.66 (s, 2H, NH), 3.36 (s, 12H, OCH_3), 3.71–3.70 (m, 8H, CH_2), 7.02–6.87 (m,

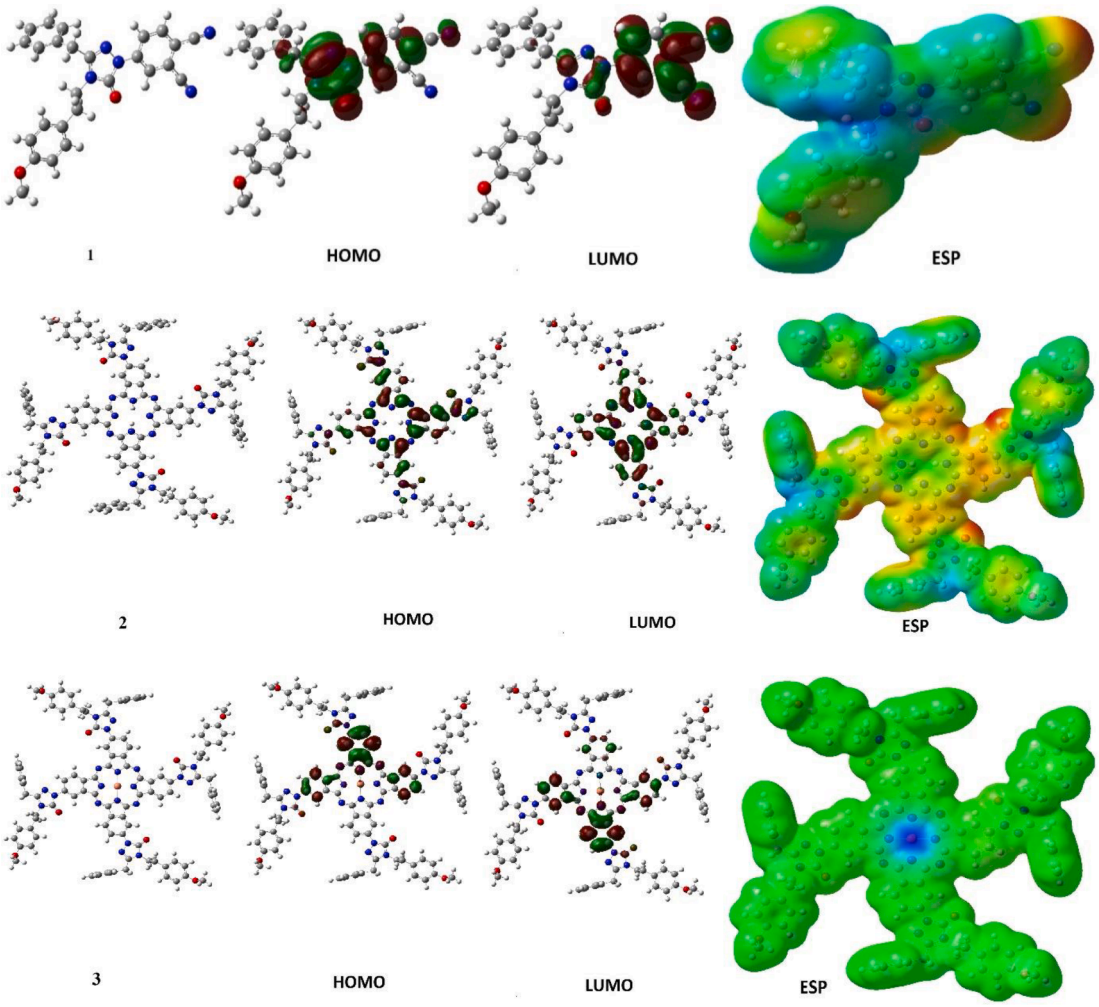

Fig. 7. Representations of HOMO, LUMO, ESP, and optimized structures of molecules.

Table 1
The calculated quantum chemical parameters of molecules.

	E_{HOMO}	E_{LUMO}	I	A	ΔE	η	σ	χ	Pİ	ω	ε	dipol	Energy
B3LYP/6–31++g(d,p) LEVEL													
1	−6.1833	−2.1187	6.1833	2.1187	4.0646	2.0323	0.4921	4.1510	−4.1510	4.2392	0.2359	14.307	−38826.5590
2	−4.5623	−2.4569	4.5623	2.4569	2.1054	1.0527	0.9500	3.5096	−3.5096	5.8505	0.1709	2.012	−155340.8385
3	−5.2309	−2.9808	5.2309	2.9808	2.2501	1.1251	0.8888	4.1058	−4.1058	7.4919	0.1335	2.687	−199946.8986
HF/6–31 g LEVEL													
1	−8.6514	1.5045	8.6514	−1.5045	10.1559	5.0780	0.1969	3.5734	−3.5734	1.2573	0.7953	12.309	−38580.3818
2	−5.3283	0.4925	5.3283	−0.4925	5.8208	2.9104	0.3436	2.4179	−2.4179	1.0044	0.9957	9.232	−154351.4860
3	−6.6209	1.1949	6.6209	−1.1949	7.8157	3.9079	0.2559	2.7130	−2.7130	0.9417	1.0619	7.438	−198919.2465
M062X/6–31 g LEVEL													
1	−7.5784	−1.1745	7.5784	1.1745	6.4040	3.2020	0.3123	4.3764	−4.3764	2.9908	0.3344	14.157	−38811.2005
2	−5.4186	−2.0444	5.4186	2.0444	3.3742	1.6871	0.5927	3.7315	−3.7315	4.1266	0.2423	3.634	−155279.9574
3	−5.3808	−1.9064	5.3808	1.9064	3.4744	1.7372	0.5756	3.6436	−3.6436	3.8211	0.2617	3.566	−199884.3797

Table 2
E total energy values of molecules against proteins.

	Breast cancer	Liver cancer	Colon cancer	Lung cancer
Molecule 1	−346.37	−291.78	−327.61	−291.85
Molecule 2	−612.53	−573.29	−665.76	−514.86
Molecule 3	−611.89	−551.36	−614.76	−517.59

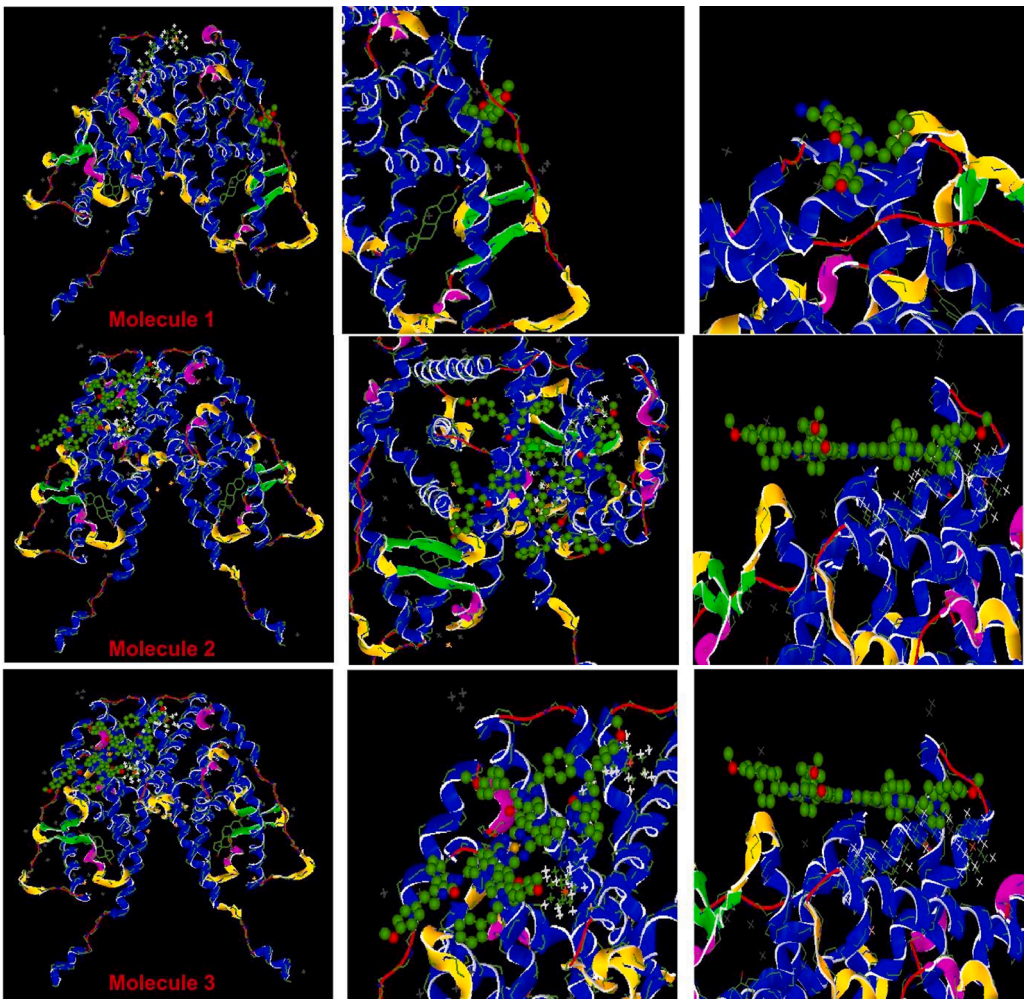

Fig. 8. Demonstration interplays of afzelin with α-Gly enzyme.

22H, Ar-H), 7.82–7.48 (m, 22H, Ar-H), 8.37 (s, 4H, Ar-H). UV–vis (DMF): λ^{max}, nm (log ε): 710 (4.97), 684 (4.99), 640 (5.29), 621 (5.41), 341 (5. 25), 286 (5.03). MALDI-TOF-MS, (*m/z*): Calcd.: 1743.92 for $C_{104}H_{86}N_{20}O_8$; Found: 1743.06 $[M]^+$.

2.1.6. 2(3), 9(10), 16(17), 23(24)-Tetrakis[4-(4-methoxyphenethyl)-5-benzyl-2H-1,2,4-triazol-3 (4H)-one] phthalocyaninato copper(II) (3)

Yield 0.025 g (24 %). Mp: >300 °C. FT-IR (ATR), ν/cm^{-1}: 3056, 2956–2849 $\nu_{C-H\ (Alp)}$, 1705 $\nu_{C=O}$, 1612, 1581, 1494, 1409, 1462, 1361, 1302, 1176, 1095, 933, 891, 615. UV–vis (DMF): λ^{max}, nm (log ε): 691 (4.93), 629 (5.49), 346 (5.25), 285 (5.20). MALDI-TOF-MS, (*m/z*): Calcd.: 1805.45 for $C_{104}H_{84}CuN_{20}O_8$; Found: 1805.57 $[M]^+$.

2.2. Theoretical methods

Theoretical calculations were made to compare both the chemical and biological activity of phthalocyanine molecules and their copper metal complex. Theoretical studies carried out in recent years have been quite advanced and have made great progress with technology. This has been the reason for the programs studied to give faster results. The programs used in this study were GaussView 5.0.8 [36], ChemDraw Professional 15.1 [37], and Gaussian09 AS64L-G09RevD.01 [38] package programs. Many quantum chemical parameters of phthalocyanine molecule and their its copper metal complex were calculated with the help of these programs. Calculations of Chemical activity values of phthalocyanine molecules and its copper metal complex in the Hartree–Fock (HF) method [39,40], Becke, three-parameter, Lee-Yang-Parr (B3LYP) [41,42], and M06-2X [43] with 6-31G basis set were made using the method. The chemical and biological activities of the molecules were compared using the numerical value of these parameters. Many parameters such as E_{HOMO} (Highest Occupied Molecular Orbital), E_{LUMO} (Lowest Unoccupied Molecular Orbital), ΔE (HOMO-LUMO) energy range, chemical hardness (η), chemical potential (μ), nucleophilicity (ε), electronegativity (χ), electrophilicity (ω), spherical softness (σ) and proton affinity (PA) have been calculated. With the help of these parameters, their chemical properties were compared and important comments were made about their chemical activities.

Except for DFT calculations, the process of comparing the activities of molecules against cancer proteins is done using the HEX 8.0 software [44] program to compare the activities of molecules against biological materials. Some important parameters in the HEX 8.0.0 program for the interactions of molecules and proteins are as follows; correlation type

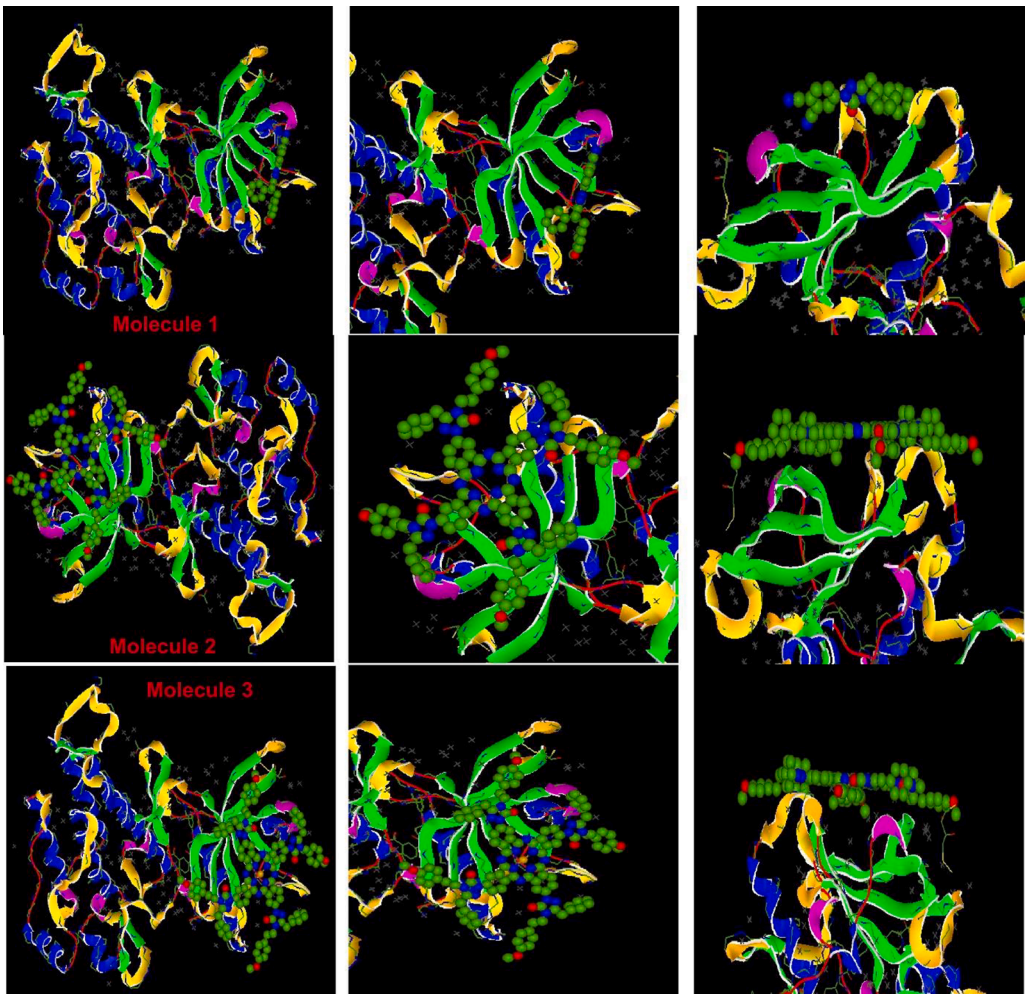

Fig. 9. Demonstration interplays of molecules with liver cancer.

(shape only), FFT mode (3D), grid size (0.6), acceptor spacing (180), ligand spacing (180)twist-spacing (360), and distance spacing (40) [45–47]. In addition, the Protein-Ligand Interaction Profiler (PLIP) server was used to examine the interaction between protein and molecules (1–3) [48].

3. Results and discussion

3.1. Synthesis and characterization

Phthalonitrile (**1**) was synthesized through a base-catalyzed reaction of 3,4-dicyanonitrobenzene with 4-(4-methoxyphenethyl)-5-benzyl-2*H*-1,2,4-triazol-3(4*H*)-one in dehydrated N,*N*-dimethylethylamine at 60 °C under a nitrogen atmosphere. Phthalonitrile derivative **1** was made pure by column chromatography on aluminum oxide using $CHCl_3$ solvent. The dihydrogen *Pc* (**2**) was produced by cyclotetramerization of phthalonitrile derivate (**1**) without any metal salt. The metallophthalocyanine compound (**3**) was produced by cyclotetramerization of phthalonitrile derivate (**1**) in the presence of relevant copper salt. The synthetic pathway of all compounds (**1**–**3**) is given in Scheme 1. The synthesized phthalocyanine compounds (**2,3**) were made pure by aluminum oxide using a suitable solvent system. The structures of novel compounds were characterized by some spectroscopic techniques. For example, Fouirer Transform Infrared, Proton Nuclear Magnetic Resonance, Carbon-13-Nuclear Magnetik Resonance, Ultraviolet–visible and Mass Spectrometry.

The FT-IR spectra of 4-(4-methoxyphenethyl)-5-benzyl-2*H*-1,2,4-triazol-3(4*H*)-one showed a vibrational peak at 3289 cm^{-1} ν_{NH}. In addition, compound **1** was openly confirmed by the appearance of the stretching vibrations of -C≡N groups at 2232 cm^{-1}. The formation of compound **2** was approved by the appearance of the stretching vibration of the N—H group at 3289 cm^{-1}. The IR spectra of compounds **2,3** resemble each similar, it was observed that the C≡N peak at 2238 cm^{-1} which belongs to the starting compound (**1**) disappeared in the IR spectra of compound 2 and 3.

The molecular ion peaks of original compounds (**1**–**3**) were spied out at 435.48 for **1** as $[M]^+$ (indicated in Fig. 2), 1743.06 for **2** as $[M]^+$ (indicated in Fig. 3), 1805.57 for **3** as $[M]^+$ (indicated in Fig. 4).

The UV–vis spectra of the novel phthalocyanine derivates (**2,3**) were recorded in DMF given in Fig. 1. UV–vis spectra of phthalocyanines in the solution include two main bands B band and the Q band. Characteristic absorption of the B band is observed as broadband at about 350

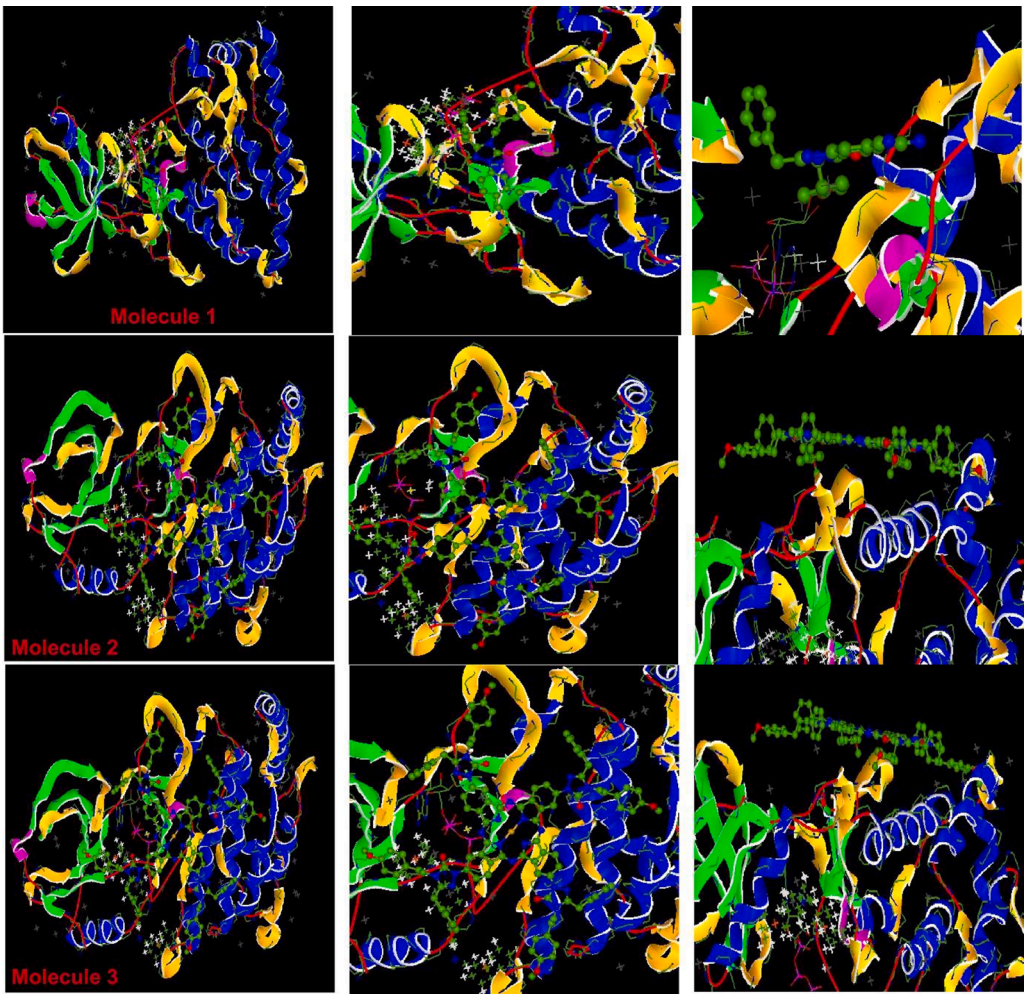

Fig. 10. Demonstration interplays of molecules with colon cancer.

nm. The second band is observed around 650–700 nm and is called the Q band [49]. The Q band of the synthesized phthalocyanine **2** was exhibited as splitted, phthalocyanine (**3**) was exhibited as a single sharp band which is an originated Q band of shape showed difference according to the symmetry of the molecule. The Q bands of these phthalocyanines were recorded in the range of 681–724 nm in DMF. The B bands of these complexes (**2,3**) were obtained at around 330 nm in this solvent.

In the ^{1}H NMR spectra of phthalocyanine derivate **1** aromatic protons were exhibited between 6.88 and 8.23 ppm. In the ^{1}H NMR spectra of phthalocyanine derivate **2** the typical aromatic protons were between 7.02 and 8.37 ppm (indicated in Fig. 5). The methyl protons were also observed in the range of 2.51 ppm and 3.88 ppm. In the ^{13}C NMR spectra of compound **1** the typical resonances belonging to the C≡N were observed in 116.37 and 116.45 (indicated in Fig. 6).

3.2. Theoretical comparison of the chemical and biological activities

Theoretical calculations are one of the fast and economical methods of comparing molecular activities. Among the theoretical methods, DFT and molecular docking calculations are of great importance [50]. The gaussian software program is used in DFT calculations. In the calculations made with this program, many quantum chemical parameters of the molecules are calculated. The numerical values of these parameters allow us to comment on the activity of the phthalocyanine molecule and its copper metal complex. Among the many calculated quantum chemical parameters, the most well-known parameters are HOMO and LUMO. Lowest Unoccupied Molecular Orbitals briefly LUMO, and Highest Occupied Molecular Orbitals briefly HOMO are parameters used to describe the activities of molecules [51].

The numerical value of the HOMO parameter of the molecules shows the electron donating abilities of the molecules. For this reason, the ability of molecules to donate electrons is higher than other molecules, indicating that the molecule has higher activity [51]. On the other hand, the numerical value of the LUMO parameter of the molecules shows the electron accepting abilities of the molecules. Therefore, the electron accepting ability of molecules shows that they are more active than other molecules [52]. The numerical value of the HOMO and LUMO parameters of the molecules are important parameters in explaining the activities of the molecules. However, the ΔE (E_{HOMO}-E_{LUMO}) parameter of the molecules is another important parameter in explaining the activity [51]. The molecule with the smallest numerical value of this

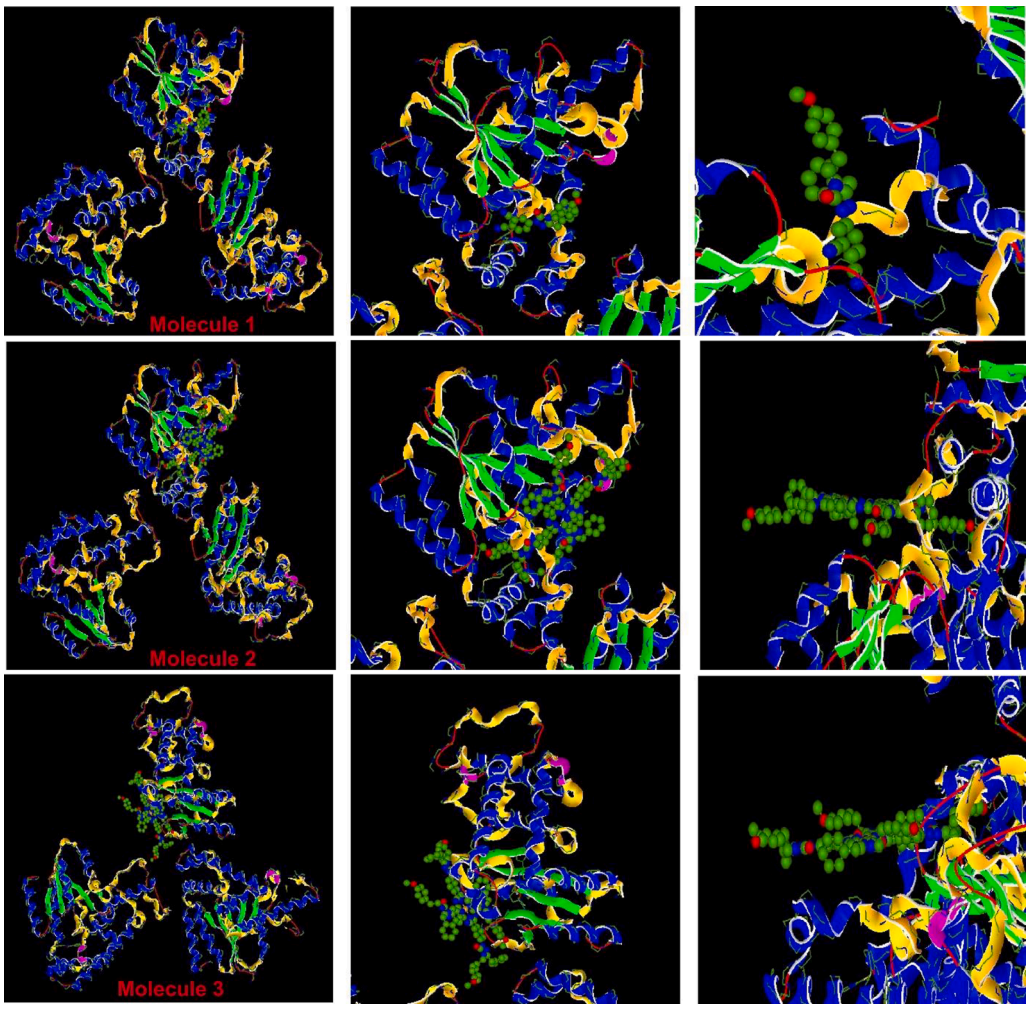

Fig. 11. Demonstration interplays of molecules with lung cancer.

parameter has higher activity than other molecules. The low numerical value of this parameter indicates that it is easier for electrons to pass between HOMO and LUMO orbitals [52]. The fact that this transition is easier indicates that the activities of the molecules are high.

Another important calculated quantum chemical parameter is electronegativity, which shows the strength of atoms in the molecule to attract bond electrons. If this value is high, the atoms attract more bond electrons [52]. In this case, it makes intermolecular electron transfer difficult. Therefore, it causes the chemical activities of the molecules to be low. Although many quantum chemical parameters are calculated, these few parameters are used more than others to explain the activities of molecules [52]. The visuals of some calculated parameters are given in Fig. 7. All calculated parameters are given in Table 1.

It is possible to explain the chemical activities of molecules using many parameters. however, molecular docking calculations are performed to compare its activity against biological materials. Molecular docking calculations are made with the HEX 8.0 software program. Many cancer proteins are used in this program. These cancer proteins are the crystal structure of estrogen receptor protein (from the breast cancer) ID: 1A52 [53], the crystal structure of VEGFR kinase protein (from liver cancer) ID: 3WZE [54], crystal structure of MLK4 kinase (colon cancer) ID: 4UYA [55], and crystal structure of an allosteric Eya2 phosphatase inhibitor protein (from lung cancer) ID: 5ZMA [56].

Something affects the biological activities of molecules against proteins. The first of these is the chemical interactions that occur between molecules and proteins. As these chemical interactions increased, it was observed that the biological activities of the molecules increased. These chemical interaction sites that occur are predicted to be active sites of molecules and proteins [57]. These chemical interactions are hydrogen bonds, polar and hydrophobic interplays, π-π and halogen [46,50,51]. As a result of molecular docking calculations, the interplays of all molecules with cancer proteins and their results are given in Table 2 and Figs. 8-11.

The most important parameter obtained from molecular docking calculations to compare the biological activities of molecules is the E total energy value. It is known that the molecule with the most negative numerical value of this parameter has higher biological activity than other molecules. In this respect, it is known that the most important factor affecting the numerical value of this parameter is the chemical. In the molecular docking calculations, it was found that the molecule with

Table 3
Hydrophobic Interactions of proteins and molecule 2.

Index	Residue	AA	Distance	Ligand atom	Protein atom
Breast cancer-molecule 2					
1	396B	MET	3.61	4884	3178
2	437B	MET	3.88	4797	3573
3	441B	GLN	2.69	4897	3612
4	470A	GLU	3.04	4928	1568
5	493B	ALA	2.58	4899	4115
6	495B	LEU	3.49	4852	4129
7	495B	LEU	3.22	4896	4128
8	499B	GLN	2.89	4909	4166
9	499B	GLN	3.79	4907	4165
Liver cancer-molecule 2					
1	831A	ARG	3.30	3225	174
2	832A	ASP	3.88	3228	191
3	836A	LEU	3.53	3123	241
4	838A	LYS	3.02	3243	254
5	872A	GLU	2.24	3145	563
colon cancer proteins-molecule 2					
1	181A	PRO	1.84	2557	432
2	235A	HIS	3.67	2668	765
3	236A	VAL	3.55	2671	779
4	238A	VAL	2.78	2656	795
5	246A	ARG	3.34	2549	871
6	249A	LEU	3.91	2721	903
7	249A	LEU	2.61	2650	904
8	254A	GLU	2.59	2722	952
9	273A	GLU	3.65	2632	1133
10	282A	ASN	3.14	2678	1201
11	395A	LEU	3.13	2734	2076
aaa12	395A	LEU	2.74	2731	2078
13	396A	GLU	3.87	2734	2084
14	399A	THR	3.38	2736	2105
15	407A	THR	2.90	2661	2123
Lung cancer proteins-molecule 2					
1	277A	GLU	2.79	7218	2502
2	282A	PHE	3.41	7328	2544
3	282A	PHE	2.74	7405	2549
4	286A	LEU	3.86	7325	2587
5	290A	PHE	3.19	7401	2617
6	309A	GLU	3.56	7330	2796
7	504A	VAL	3.32	7229	4437

In table: ALA: Alanine, ARG: Arginine, ASN: Asparagine, ASP: Aspartate, GLN: Glutamine, GLU: Glutamic acid, HIS: Histidine, LEU: Leucine, LYS: Lysine, PHE: Phenylalanine; PRO: Proline, THR: Threonine, VAL: Valine.

the most negative E total energy value was molecule 2. It is known that the metal complexes formed in general have higher activity than the metal-free states [57]. But in these molecules, when the copper metal complex is placed in the center of the molecule, the overall electron density of the molecule appears to decrease [45]. When the DFT calculations made are examined in detail, it is seen that the electron density of the center of molecule 2 is high in the ESP representation of molecule 2 [46]. This causes molecule 2 to form more and stronger interactions.

The Protein-Ligand Interaction Profiler (PLIP) server analysis was performed in order to examine the interplays of the studied molecules with cancer proteins in more detail. Since the activity of molecule 2 is higher than the other molecules, the chemical interplays that cause this activity have been investigated in more detail. The interplays obtained in this analysis are given in Tables 3 and 4 and the visual forms of the interplays obtained are given in Figs. 12-15.

As a result of the DFT calculations, it is seen that as a result of the

Table 4
Hydrogen Bonds of proteins and molecule 2.

Index	Residue	AA	Distance H-A	Distance D-A	Donor angel	Protein donor?	Side chain	Donor Atom	Acceptor Atom
Breast cancer-molecule 2									
1	477A	ARG	3.67	4.06	105.50	√	√	1648 [N3]	4829 [O2]
2	503B	ARG	3.05	3.62	117.49	√	√	4226 [Ng +]	4832 [O2]
Liver cancer-molecule 2									
1	871A	LYS	2.24	3.06	135.14	√	√	554 [N3 +]	3180 [Nar]
Colon cancer-molecule 2									
1	239A	ASN	2.72	3.65	154.90	√	√	805 [Nam]	2614 [O2]
2	273A	GLU	2.87	3.23	104.28	√	√	1136 [O3]	2605 [Nar]
Lung cancer-molecule 2									
1	284A	SER	3.37	3.94	120.56			2569 [O3]	7276 [Nar]
2	293A	ARG	3.06	3.76	128.35			2642 [N3]	7276 [Nar]
3	293A	ARG	2.51	3.33	139.06			2643 [Npl]	7276 [Nar]
4	309A	GLU	3.54	4.01	110.79			2792 [Nam]	7412 [O2]

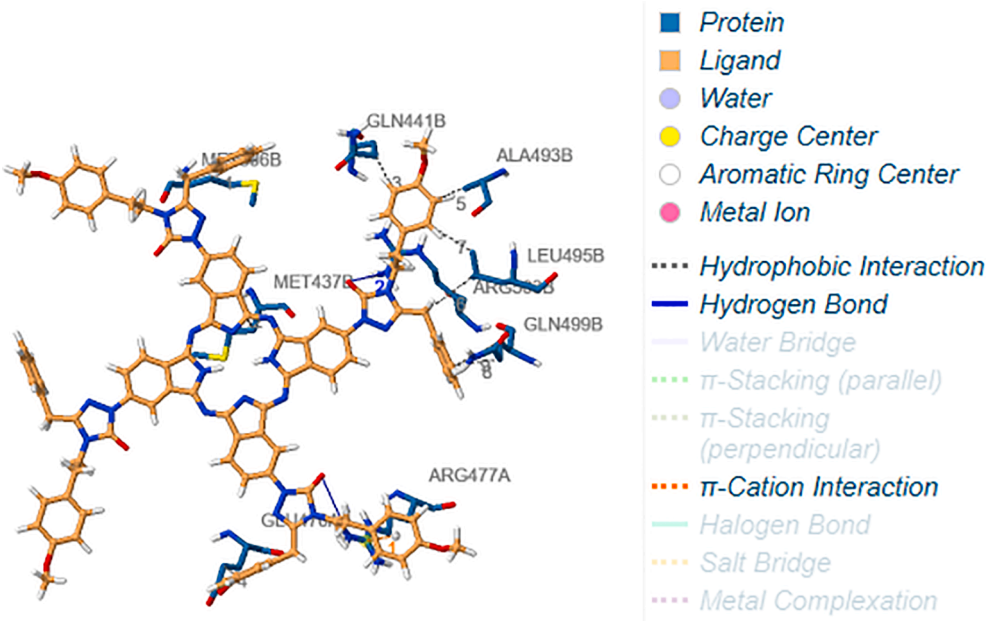

Fig. 12. Demonstration of interplays between molecule 2 and breast cancer protein.

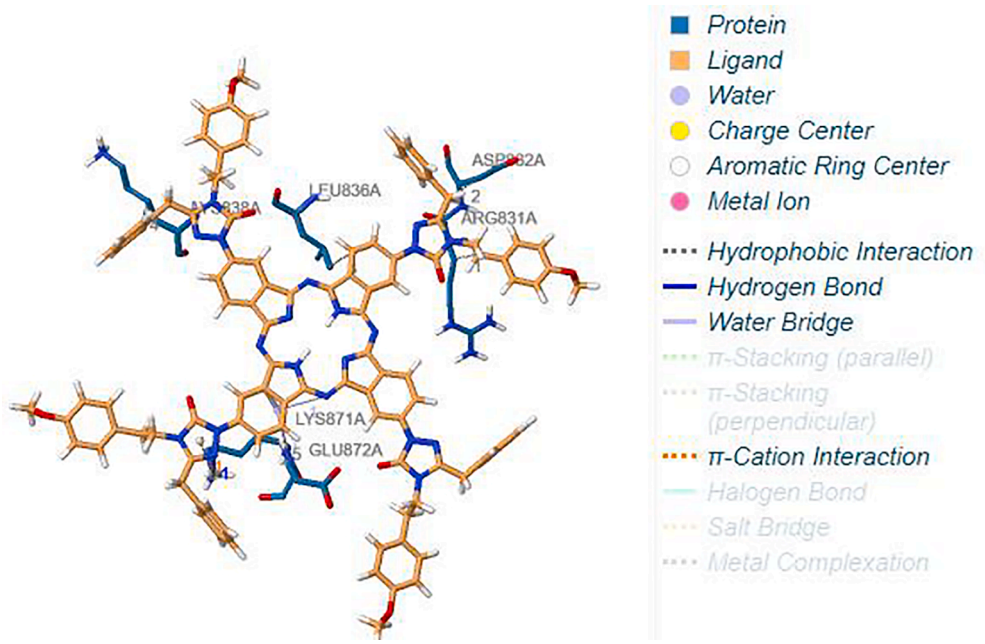

Fig. 13. Demonstration of interplays between molecule 2 and liver cancer protein.

calculations of the thermodynamic parameters of the ligand molecule and its metal complexes, Sum of eletronic and thermal energies (E), Sum of eletronic and thermal enthalpies (H), and Sum of eletronic and thermal free energies (G) values of the ligand molecule and its metal complexes with metal ions are calculated (given in Table 5-7). The Gibbs free energies value gives information about the self-forming feature of the metal complex formed. The metal complex with the most negative numerical value of this parameter is expected to form more easily than other metal complexes. Since Cu-complex has more negative value than other metal complexes, it is expected to form more easily.

4. Conclusions

One out of every-five people are diagnosed with cancer. According to researches, cancer will be a bigger problem for low and middle developed countries. Therefore, studies in this area maybe promising. Theoretical calculations are one of the fast and economical methods of comparing molecular activities. Many cancer proteins are used in molecular docking calculations such as ID: IA52, ID: 3WYA, ID: 5ZMA. This study describes the synthesis, characterization and theoretical studies of novel 1,2,4-triazole carrying peripheral H2 **(2)** and Cu^{II} **(3)** phthalocyanine compounds. The obtained compounds were characterized by Fouirer Transform Infrared, Proton Nuclear Magnetic Resonance, Carbon-13-Nuclear Magnetik Resonance, Ultraviolet–visible and Mass Spectrometry methods. We studied the interactions between molecules and proteins. As a result of theoretical calculations, many quantum chemical and biological parameters were found. The numerical value of these parameters shows that; According to the results found in B3lyp

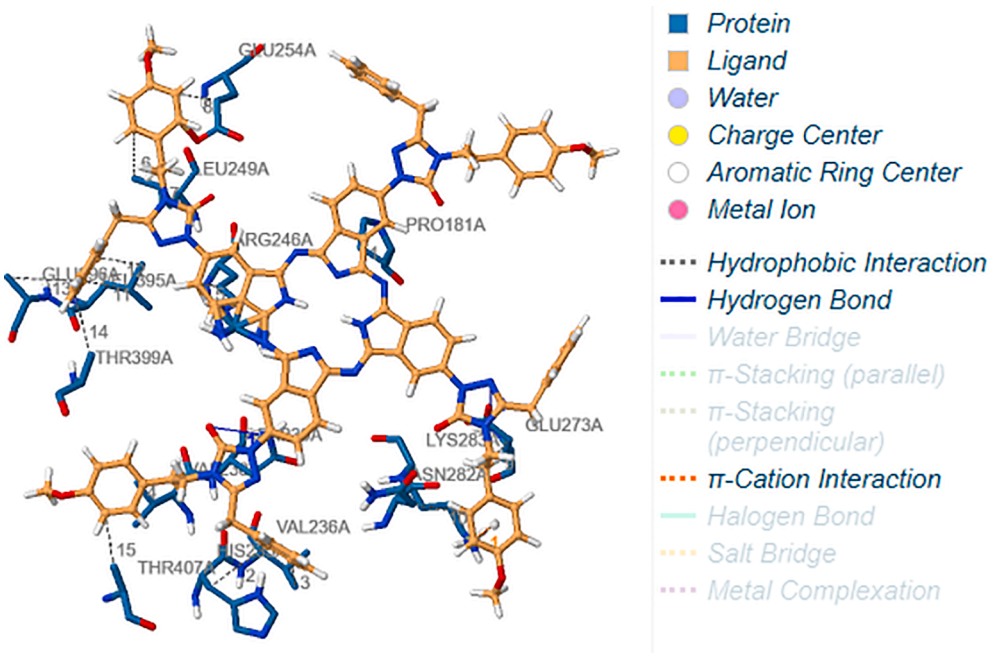

Fig. 14. Demonstration of interplays between molecule 2 and colon cancer protein.

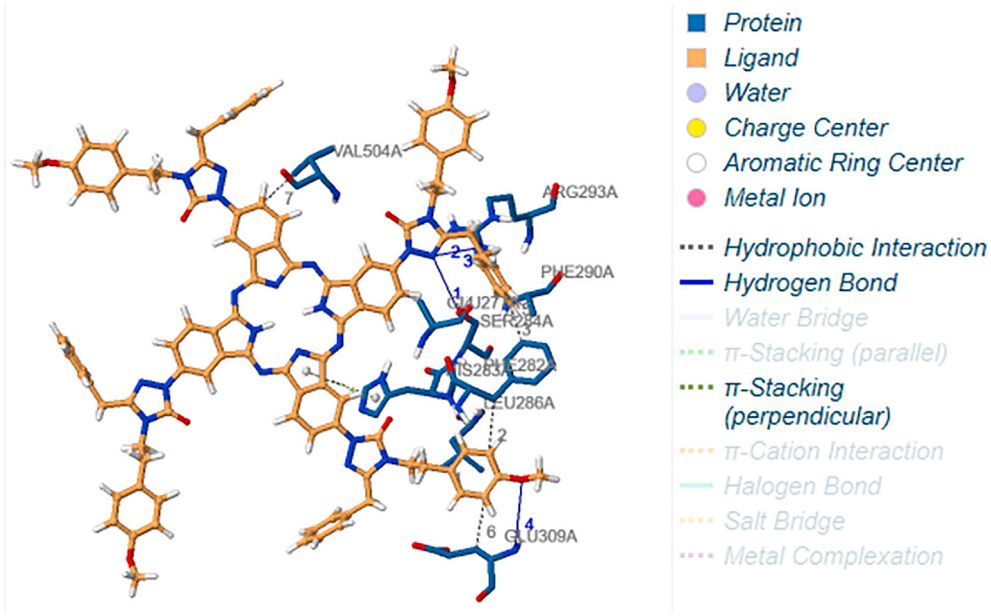

Fig. 15. Demonstration of interplays between molecule 2 and lung cancer protein.

Table 5
Value of thermodynamic parameters of metal complexes (a.u.).

	E	H	G
Ligand	−1417.79175	−1417.70110	−1417.70205
Cu-complex	−7309.82235	−7309.82140	−7310.12004
Co-complex	−7052.29395	−7052.29300	−7052.59077
Ni-complex	−7177.57869	−7177.57774	−7177.87057
Mg-complex	−5870.61477	−5870.61383	−5870.90636
Zn-complex	−7448.46366	−7448.46271	−7448.75708
Mn-complex	−7280.00980	−7280.00886	−7280.3053

Table 6
Value of thermodynamic parameters of metal ions (a.u.).

	E	H	G
Cu metal ion	−1637.7881	−1637.7871	−1637.8060
Co metal ion	−1380.2656	−1380.2646	−1380.2834
Ni metal ion	−1505.6405	−1505.6396	−1505.6577
Mg metal ion	−198.8102	−198.8093	−198.8262
Zn metal ion	−1776.6107	−1776.6097	−1776.6280
Mn metal ion	−1608.0032	−1608.0022	−1608.0287

Table 7
Value of thermodynamic parameters of metal complexes (a.u.).

	ΔE	ΔH	ΔG
Cu metal ion	−0.87	−1.23	−1.51
Co metal ion	−0.86	−1.22	−1.50
Ni metal ion	−0.77	−1.13	−1.40
Mg metal ion	−0.64	−1.00	−1.27
Zn metal ion	−0.69	−1.05	−1.32
Mn metal ion	−0.84	−1.20	−1.47

with −4.5623 and HF with −5.3283, it was seen that the HOMO value of molecule 2 was the most positive. On the other hand, the numerical value of the LUMO parameter of molecule 2 was found to be 0.4925 in HF and −2.0444 in M062X, the molecule with the highest chemical activity. On the other hand, molecular docking calculations of molecules showed that molecule 2 had the highest activity against various cancer proteins.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ica.2022.121113.

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