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(RESEARCH ARTICLE)

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Synthesis of some triazole and triazoline derivatives by green chemistry and study of their molecular docking with a study of them against anticancer and antifungal

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Abstract

In our research, we prepared derivatives of the triazole ring and triazoline by click chemistry method, and we identified the prepared compounds by spectroscopic methods, then the molecular fusion of these compounds was studied to find out the most likely compound associated with colonic cancer. The compound S2 shows the highest association with the protein responsible for the malignant cells, then we studied the biological activity. The compound M116 against colonic cancer cell show good results as an inhibitor of the studied cancer cell.

Keywords: Cancer cell; Molecular fusion; Triazole ring; Synthesis

1. Introduction

Phthalimide is a substructure typically present in pharmacologically active substances, such as thalidomide and its analogs [1].[2] Phthalimide and its derivatives are expected to be n-type organic semiconductors [3] and light-emitting materials [4] in the fields of organic material chemistry and electronics. As a result, several articles often concentrate on these substances, particularly on their synthesis and properties.[5]

These compounds have many actions including antibacterial, antifungal, anti-HIV-1 actions, antitumor, analgesic, and anxiolytic. And due to these many activities the phthalimide (isoindoline-1, 3-dione) derivatives have drawn attention as they can be used as promising and effective drugs against many illnesses, including tumors, AIDS, multiple myeloma, diabetes, seizures, inflammation, pain, and bacterial infections.[6] Cu(I)-catalyzed azideealkyne cycloaddition (CuAAC) is the term used to describe click chemistry [7,8]. The 1,4-disubstituted 1,2,3-triazole that results from the reaction of an azide with a terminal alkyne is generated with high yield and excellent selectivity. CuAAC has been used in the efficient and common synthesis of 1,2,3 triazoles [9], several of which have interesting biomedical applications [10,11]. Triazoles are appealing pharmacophores that have the potential to intercalate, take part in hydrogen bonding, and in certain cases take the place of amides [12]. Although reactions in live systems are constrained by Cu(I)-associated toxicity [13], CuAAC has also been employed to produce triazole-based ligands [14] and for chemical conjugations, including labeling in biological systems.[15]

The 1,2,3-triazole group has a lengthy history as an important aromatic heterocycle system.First reported by Pechmann in 1888,[16] triazoles have evolved to become one of the most successful connective linkers[17] and functional heterocyclic cores in modern organic chemistry[18], thanks in large part to Huisgen's[19] pioneering work and subsequent discovery of the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click[20] reaction.[21] The weakly basic 1,2,3-triazole products [22] function as stable linkers that are resistant to metabolic degradation, but they can also

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associate effectively with biological targets and may function as pharmacophores,[23] sharing both topological and electronic properties of amides.[24] The 1-substituted-1,2,3-triazoles, which are found in a variety of medications and clinical candidates, are particularly important.[25,26]

An organized method for calculating the leading binding modes of a ligand and the structure of a three-dimensional protein is molecular docking. The ability to predict binding modes is essential for exposing important structural characteristics and interactions as well as for supplying information that may be used to create efficient inhibitors [27]. A ligand is a small molecule that can interact in one of several possible conformations with the binding sites of a protein.

The processes used for binding are known as binding modalities. Modern drug design frequently uses molecular docking to identify pharmacological information and consider receptor interactions. It is frequently used to assess the binding affinity, orientation, and activity of potential drug candidates with respect to a target protein. [28,29]

2. Material and Method

2.1. General

The chemicals utilized came from Acroc, TBCPL, B.D.H., and Sigma Aldrich. Stuart SMP30 melting point equipment was used to record melting points. The FT-IR spectra were captured using a Shimadzu FT-IR-8400S spectrophotometer. Tetramethylsilane TMS was employed as an internal standard, deuterated solvents (DMSO-d6) were utilized to prepare the sample, and 1H and 13C NMR spectra were obtained using a Varian Elemental INOVA 500MHZ spectrophotometer.

2.2. Synthesis of 2-(hex-5-yn-1-yl)isoindoline-1,3-dione a1

In a 100 mL round flask with two holes attached to condenser a 6-chlorohex-1-yne solvent (5mmol, 0.583gm) in dissolved (10ml) from the dry DMF with (6mmol, 1.11 gm) 1 compound in (15ml) of dry DMF, then the reaction was stirred for (16) hours at a temperature (80 ℃) and It was monitored by thin layer chromatography (TLC:(benzene:methanol)(4:1)(1:1) After the reaction was over, the mixture was cooled and then poured over ice groats, Then, the organic layer was separated from the aqueous layer using a separation funnel chloroform (3×15), the excess solvent was removed by distillation under rarefied pressure to be Obtaining a white precipitate after purification with absolute ethanol.[30] Physical properties.

2.3. General method for preparation of compounds azides (b1-b4)

Dissolve in a 250 ml round flask that has two holes and is attached to a 14.2 mmol condenser. After cooling in an ice bath to 0C, amine derivative [2-4] was added to 30 ml of a solution containing 10% hydrochloric acid (HCl), followed by the addition of 16.33 mmol of sodium nitrite. After dissolving ($NaNO_2$) in 5 milliliters of distilled water and stirring the mixture for 30 to 60 minutes at zero degrees Celsius, 20 milliliters of NaN_3 dissolved in 5 milliliters of water was added. Thereafter, layer chromatography was performed after the reaction mixture had been agitated for one to two hours. This iodine-doped thin film (TLC:(benzene:methanol)(4:1)(V:V)) was used to identify

The reaction's completion An organic separation funnel made of chloroform (3 x 15 ml) was used to separate the layer at the end of the reaction. The organic layer was then collected and cleaned with 15 ml of saturated sodium chloride solution (NaCl), followed by 3 x 15 ml of distilled water, dried with magnesium sulfate anhydrous ($MgSO_4$), filtered, and the solvent was extracted by distillation under rarefied pressure. Absolute ethanol was used to recrystallize it in order to produce a precipitate.[31]

2.4. General method for preparation of derivatives triazole (s1-s4)

The reaction mixture was ascended for 48–72 minutes in a 100 ml round flask with two holes connected to a condenser, solvent (2 mmol/4 mmol) from [a1] compound with (2 mmol) of one of the organic azides [b1–b4] in 20 ml of DMSO as a solvent in the presence of (0.2 mmol) sodium ascorbate and (0.1 mmol) of aqueous cupric sulfate as a catalyst. Thin layer chromatography (TLC) was used to clock and monitor the reaction: (benzene:methanol)(4:1)(V:V) The liquid is cooled and put onto ice or cold water when the reaction is finished, and the organic layer is removed using a separating funnel and chloroform (3×15ml). followed by anhydrous magnesium sulfate drying, filtering, distillation under rarefied pressure to remove excess solvent, and 100% ethanol recrystallization of the resultant material.[3

2.5. Molecular Docking

We investigated the molecular docking of triazole compounds [s1–s4] using the AutoDock 4.2 tool. We calculate the proportion of the chemicals' connection with colonic cancer-related proteins. ChemDraw Professional 15.0 was used to obtain the compounds in PDB format, and RSCB proteins (PDB: COD: 5lqf, 6lu7) were employed as solid particles to serve as the compounds' receptors. The acid residue Amino, open Babel 2 was treated by removing the water molecules and adding the polar hydrogen molecules.A PDB file with a population size of 300–50 and a Lamarckian Genetic molecular docking algorithm with a maximum of 2,500,000 energy ratings and a maximum of 27,000 generations was also created using the 3.1 program.

2.6. Studying the effectiveness of anti-cancer compounds in the colon

The compound [S2] is used at multiple concentrations (6.25, 12.5, 25, 50, 100 µg / ml) to show its effectiveness against colonic cancer cells (HCT116) , we used culture medium (Medium) to activate the cancer cells at room temperature. The method of culturing cells (1 x 104) cells/ml inside flat plates containing (96 holes) (96-Well-Flat-bottom-culture Plates) at a temperature of (37 °C) with (5%) of carbon dioxide , placing them in The incubator for (48) hours . After that time, the cells of the nanoparticles were treated at concentrations of (6.25, 12.5, 25, 50, 100) micrograms/ml for a period of (24) hours, then addition of (MTT) dye at a rate of 100 microliters per hole, and then we put them in The incubator for 4 hours. After that, isopropanol was added at a rate of 100 microliters to each hole using a micro-ELISA reader, and the optical effectiveness was measured at the wavelength of 450 nm.

3. Results and Discussion

3.1. Preparation of 2-(hex-5-yn-1-yl) isoindoline-1,3-dione (a1)

We prepared 2-(hex-5-yn-1-yl) isoindoline-1,3-dione (a1) by treatment of 6-chlorohex-1-yne with potassium 1,3-dioxoisoindolin-2-ide in DMF as shown in the following Figure (1)

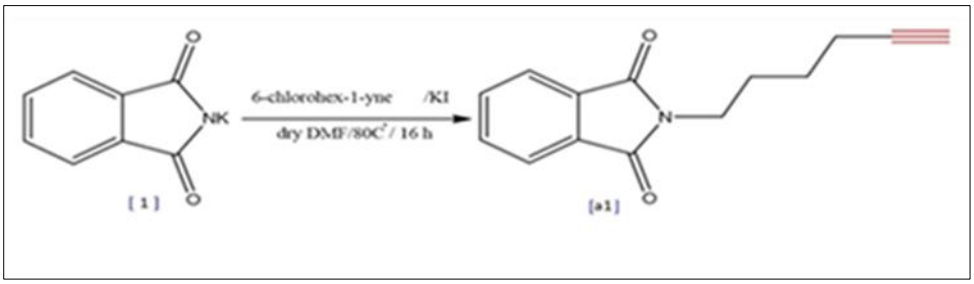
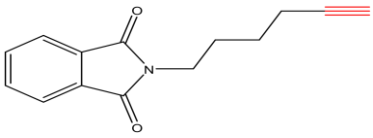


Figure 1 Preparation of 2-(hex-5-yn-1-yl) isoindoline-1,3-dione (a1)

Table 1 FTIR data (cm-1) for [a1]

no.	Co. structure	FT-IR cm-1		
		Alkyne	C=O Carbonyl	Other bands
a1		2110cm-1	1714cm-1	C=C Ar: 1439,1466 cm-1 Ar-H: 3061cm-1

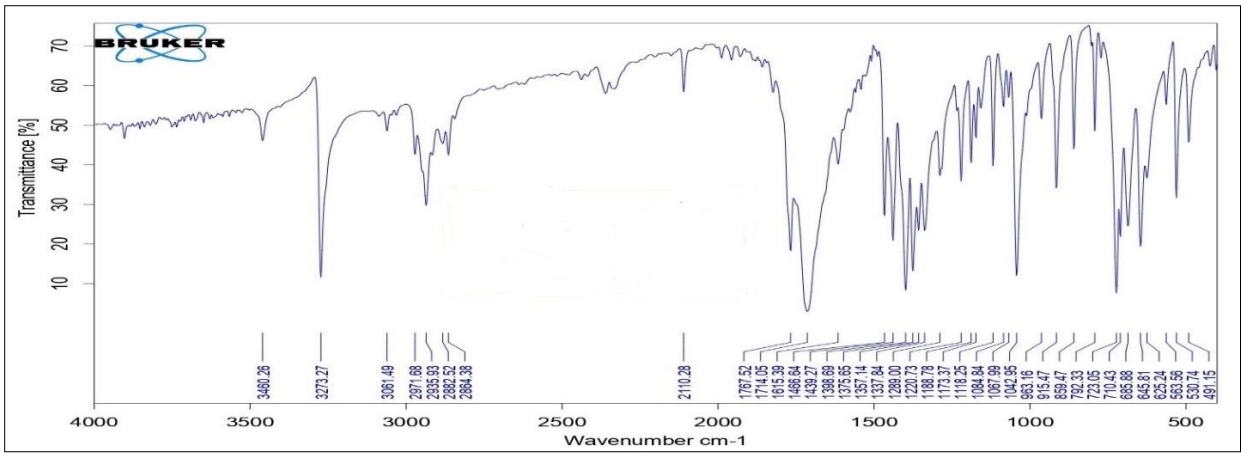


Figure 2 FTIR spectrum of compound a1

3.2. Synthesis of 1,4-diazidobenzene (b1)

The preparation of 1,4-diazidobenzene (b1) was made by treatment of benzene-1,4-diamine with NaN_3 in an HCl solution as shown in Figure (3)

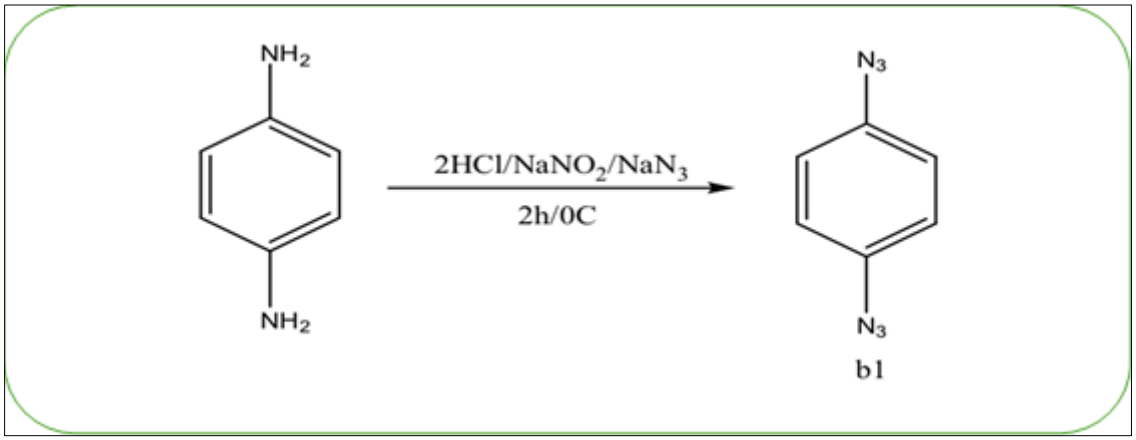
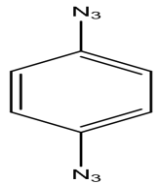


Figure 3 Preparation of 1,4-diazidobenzene (b1)

Table 2 FTIR (cm-1) of [b1]

no.	Co. structure	FT-IR spectral data, cm-1		
		N3	C=C Ar	Other bonds
b1		2110 cm-1	1504,1597cm-1	

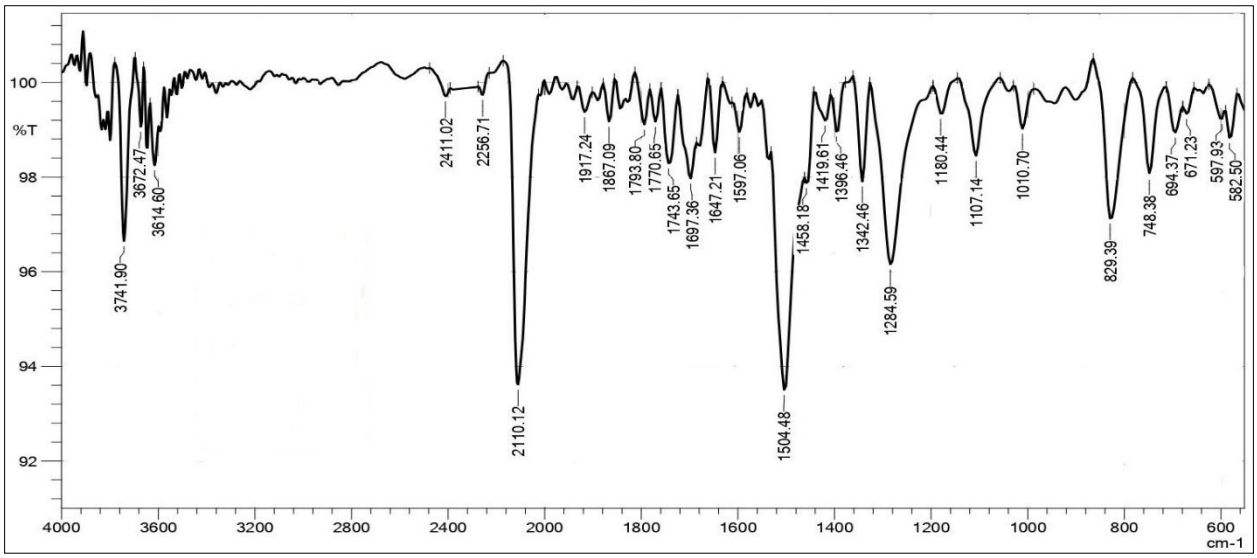


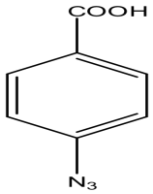
Figure 4 FTIR spectrum of compound b1

3.3. Synthesis of 4-azidobenzoic acid (b2)

Preparation Of 4-azidobenzoic acid (b2) was prepared by treatment 4-aminobenzoic acid with NaN_3 in an HCl solution as shown in Figure (5)

Figure 5 Preparation Of 4-azidobenzoic acid (b2)

Table 3 FTIR (cm-1) of [b2]

Comp. no.	Comp. structure	FT-IR spectral data, cm^{-1}		
		N_3	C=O	Other bands
b2		2106cm^{-1}	1681cm^{-1}	C=C Ar: 1504,1600cm^{-1} Ar-H: 3066cm^{-1} O-H : 2816cm^{-1}

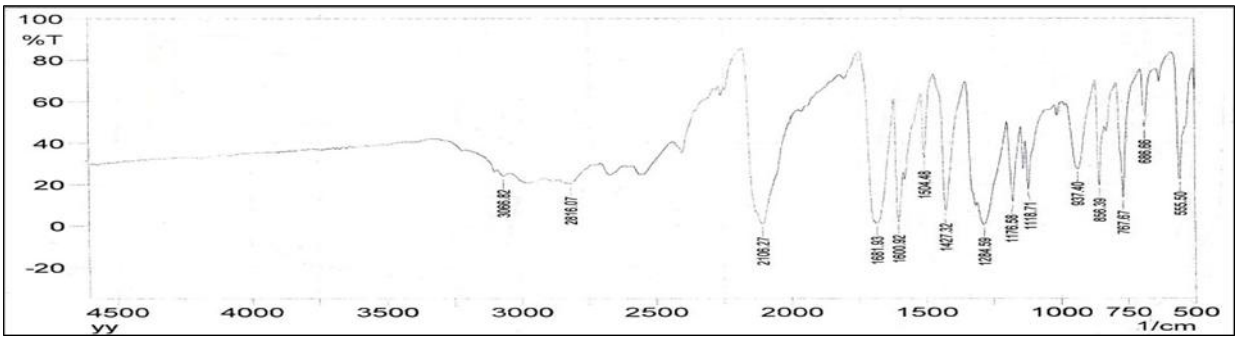


Figure 6 FTIR spectrum of compound b2

And the hydrogen nuclear magnetic resonance spectrum ^{1}HNMR showed a peak at (7.23-7.97ppm) due to the aromatic ring's protons and another peak at(12.99ppm) due to OH.

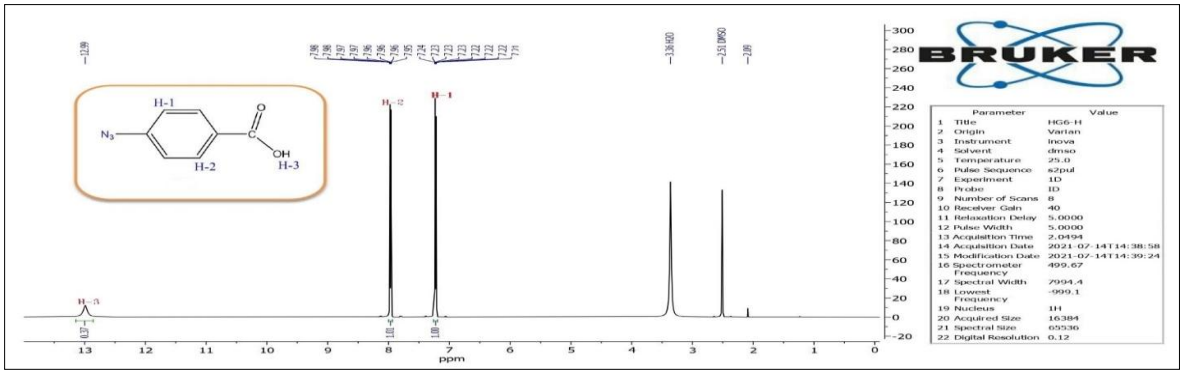


Figure 7 ^{1}HNMR spectrum of compound b2

Where the spectrum showed a signal at (119 ppm) belonging to the symmetrical aromatic carbon atoms (C-1), it also showed a signal at (127 ppm) belonging to the aromatic carbon atom adjacent to the carbonyl group, and the spectrum also showed a signal at (131 ppm) belonging to The two symmetrical aromatic carbon atoms (C-3), as the spectrum showed, its signal at (144 ppm) belongs to the aromatic carbon atom adjacent to the azide group, and the spectrum also showed a signal at (167 ppm) belonging to the carbon atom (C=O).

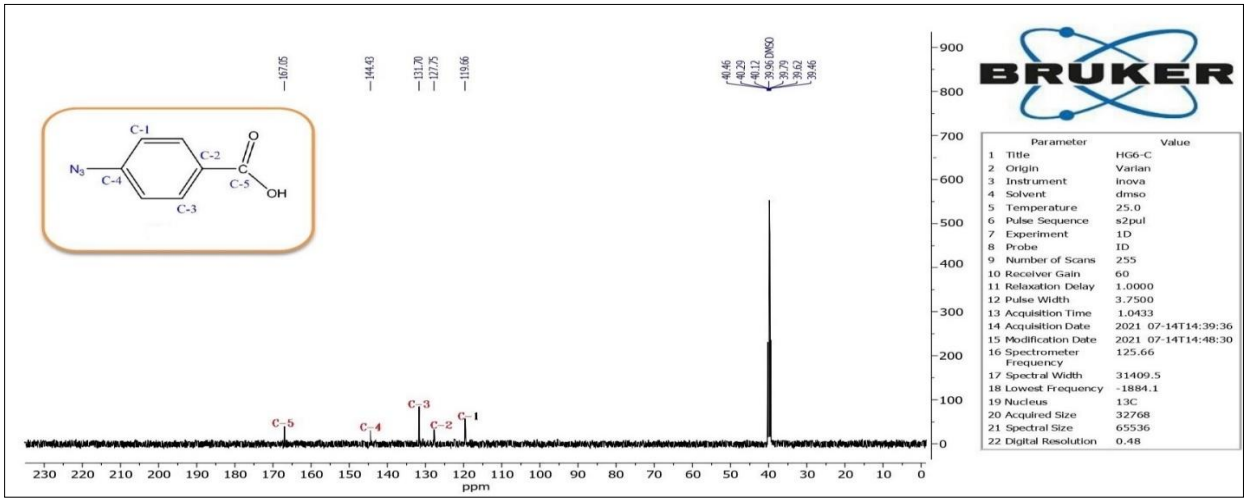


Figure 8 ^{13}CNMR spectrum of compound b2

3.4. Synthesis of 2,2'-((1,4-phenylenebis(1H-1,2,3-triazole-1,4-diyl))bis(butane-4,1-diyl))bis(isoindoline-1,3-dione) (S1)

The preparation of (S1) was made by treatment (a1) with (b1) in Sodium ascorbate and aqueous copper sulfate as catalysts solution in DMSO and this reaction is shown in the following Figure (9)

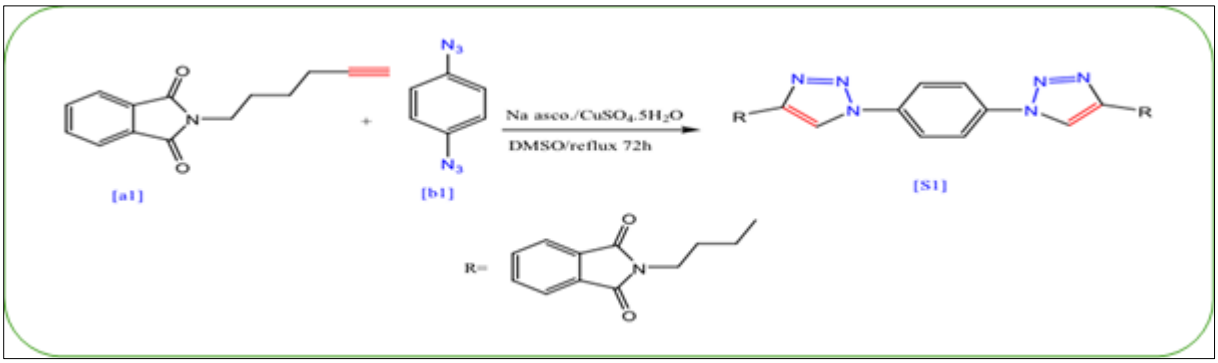
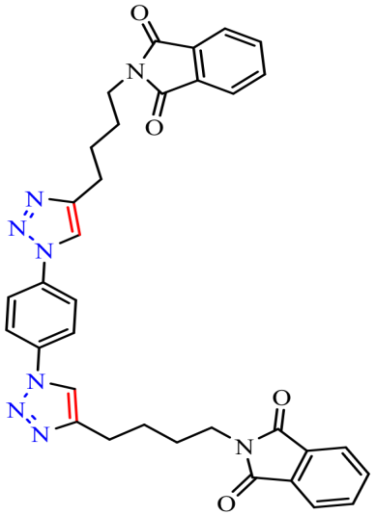


Figure 9 The preparation of (S1)

Table 4 FTIR (cm-1) of [S1]

Comp. no.	Comp. structure	FT-IR spectral data, cm^{-1}		
		C-H	C=O	Other bands
S1		3262cm^{-1}	1705cm^{-1}	C=C Ar: 1462 , 1519cm^{-1} Ar-H: 2862cm^{-1}

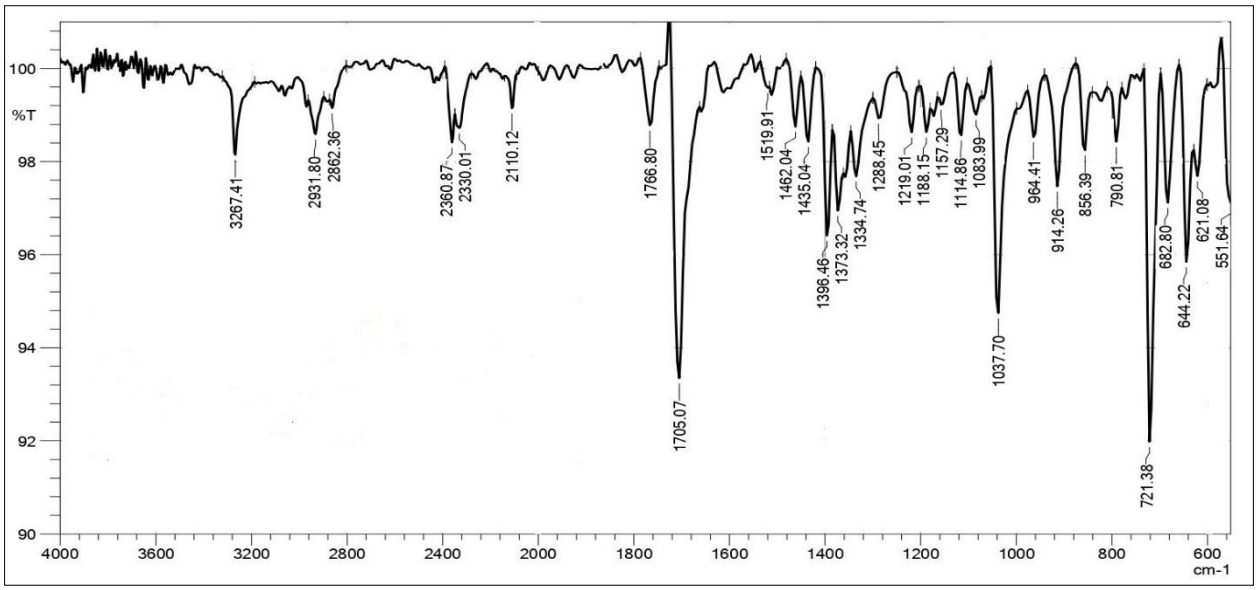


Figure 10 FTIR spectrum of compound S1

And the spectrum showed two adjacent signals at (1.43 and 1.66ppm) belonging to the protons of the aliphatic carbon atom (H-1, H-2). The spectrum also showed a signal at (2.73ppm) belonging to the proton of the carbon atom adjacent to the carbon atom of the double ring in the triazole ring. A signal appeared at (3.32ppm) belonging to the proton of the carbon atom adjacent to the nitrogen atom. The spectrum also showed a signal at (3.58ppm) belonging to the proton of the double-bonded carbon atom in the triazole ring. Multiple signals appeared at the range (7.83-7.86ppm) dating back to A proton of aromatic carbon atoms.

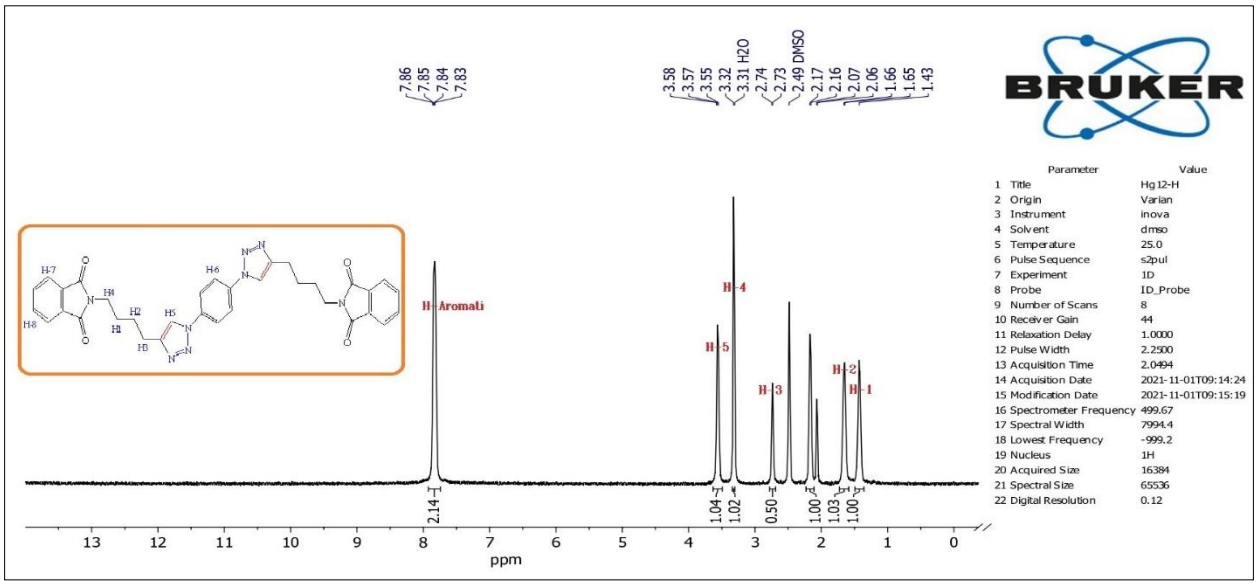


Figure 11 [1]HNMR spectrum of compound S1

3.5. Preparation of 4-(4-(4-(1,3-dioxoisoindolin-2-yl)butyl)-1H-1,2,3-triazol-1-yl)benzoic acid) (S2)

The Preparation of (S2) was prepared by treatment (a1) with (b2) in Sodium ascorbate and aqueous copper sulfate as catalysts solution in DMSO as shown in Figure (12)

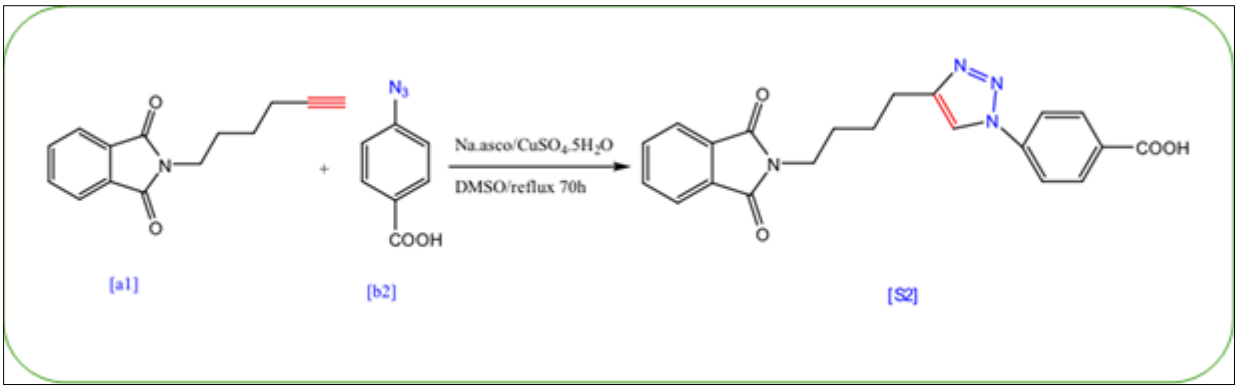


Figure 12 The Preparation of (S2)

Table 5 FTIR (cm-1) of [S2]

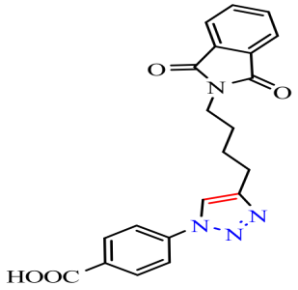
Symbole	Comp. structure	FT-IR spectral data, cm^{-1}		
		C-H	C=O	Other bands
S2		3086cm^{-1}	1708cm^{-1}	C=C Ar: 1516,1604cm^{-1} C=C 1685 cm^{-1} Ar-H: 2931cm^{-1}

Figure 13 FTIR spectrum of compound S2

The spectrum showed two signals at (1.69 and 2.73ppm) that belong to the protons of the aliphatic carbon atoms, and a signal at (2.89ppm) showed that it belongs to the proton of the carbon atom adjacent to the double bond in the triazole ring, and a signal at (3.62ppm) showed that it belongs to the proton of the carbon atom adjacent to the nitrogen atom, and the spectrum also showed a signal at (8.12ppm) belonging to the bonding proton of the double bonding carbon atom in the triol ring, and the spectrum showed multiple signals in the range (7.80, 8.68ppm) all of which belong to the protons of the aromatic ring, and the spectrum showed a signal at (13.22ppm) belongs to the (OH) group.

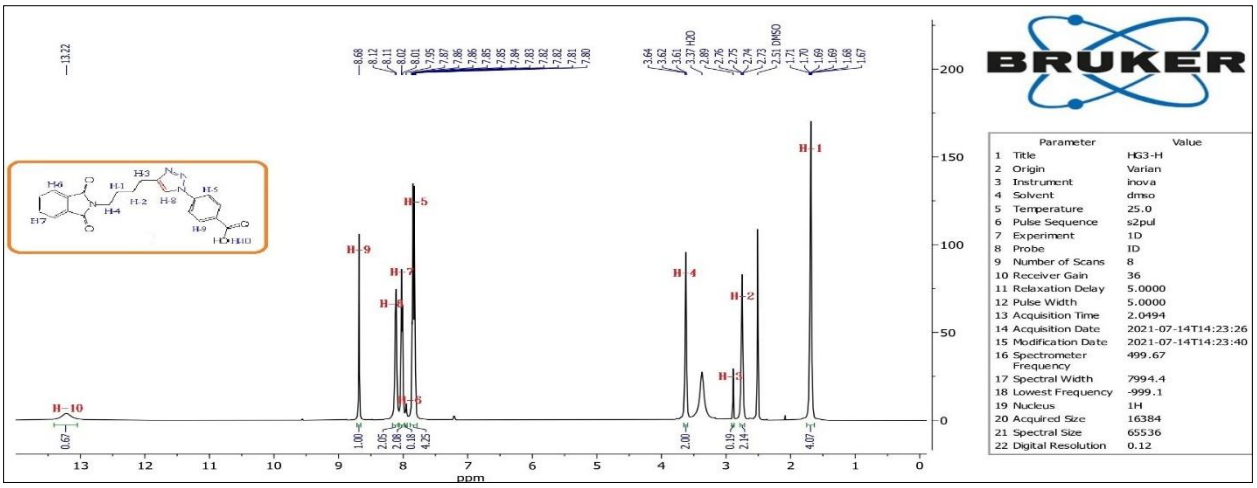


Figure 14 [1]HNMR spectrum of compound S2

And the spectrum showed two signals at (24.94, 26.43ppm) belonging to two aliphatic carbon atoms (C-1, C-2), and the spectrum showed a signal at (37.60ppm) belonging to a carbon atom adjacent to the double bond carbon atom in the triazole ring. (40.46ppm) belong to the carbon atom adjacent to the nitrogen atom, and the spectrum showed two signals at (119.94, 140.13ppm) belonging to the two carbon atoms of the double bond in the triazole ring, and the spectrum also showed several signals in the range (120.81-134.82ppm) belonging to the carbon atoms Aromatic, as shown by a sign at (168.44ppm) belonging to a carbon atom (C=O).

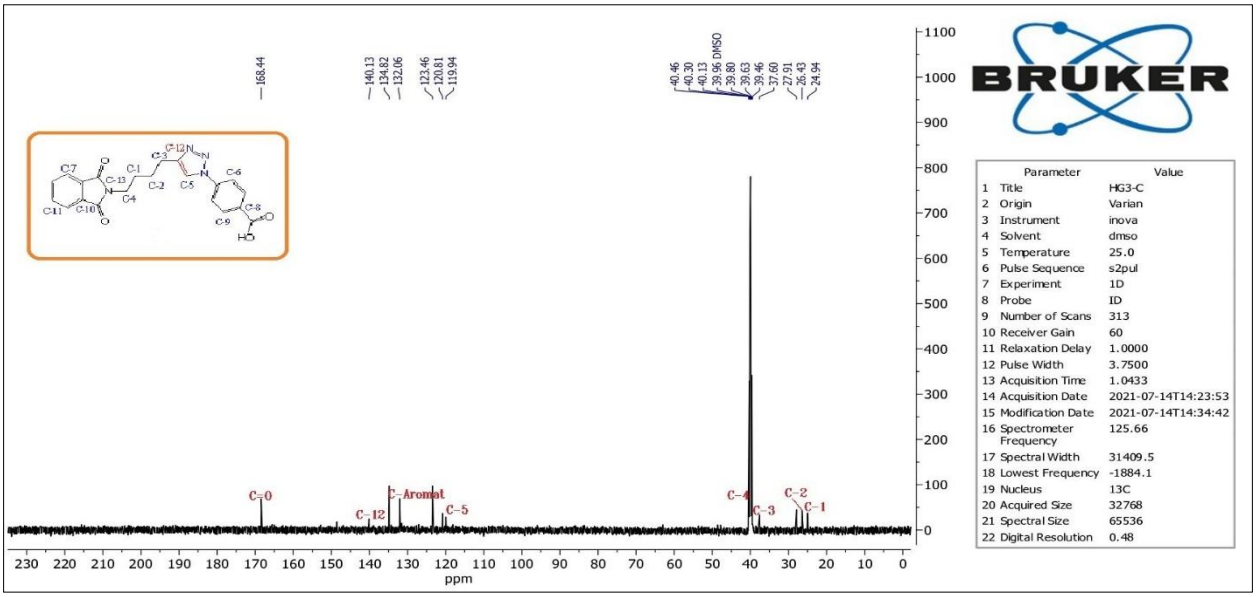


Figure 15 [13]CNMR spectrum of compound S2

3.6. Antifungal

The well diffusion method was adopted, by making three holes with a diameter of (6) mm using a sterile cork drill at equal distances from the center in the culture medium (P.D.A), followed by adding (10) microliters of the solutions of the compounds (S1, S2) to test their sensitivity at concentrations (250, 500, 1000) using a micropipette, leaving two dishes containing the sterile culture medium without adding the prepared compound solutions as a comparison factor (Control), then each dish was inoculated with the fungi Aspergillus flavus and Aspergillus terreus and Fusarium by placing a disk with a diameter of (5) mm in the center taken from the edge of a colony of the two fungi above at an age of (7) days, and the dishes were incubated at a temperature of (25) °C for (72) hours. The well diffusion method was adopted, by making three holes with a diameter of (6) mm using Sterile cork piercings were placed at equal distances from the center in the culture medium (P.D.A), followed by the addition of (10) microliters of solutions of the compounds (O2, O4, O5) to test their sensitivity at concentrations (250, 500, 1000) using a micropipette, leaving two dishes

containing the sterile culture medium without adding the prepared compound solutions as a comparison factor (Control), then each dish was inoculated with the fungi Aspergillus flavus and Aspergillus terreus and Fusarium by placing a disk with a diameter of (5) mm in the center taken from the edge of a colony of the two fungi above at the age of (7) days, and the dishes were incubated at a temperature of (25) °C for (72) hours

3.7. Docking Study

We used Autodock 4.2.6 program to study the molecular docking of two compounds toward the 5i5z protein of colon cancer, and the results of this study is shown in the table (6).

Table 6 molecular docking with a colon cancer protein 5i5z

Comp.No.	Lowest binding energy	Run
S1	-7.98	29
S2	-8.20	19

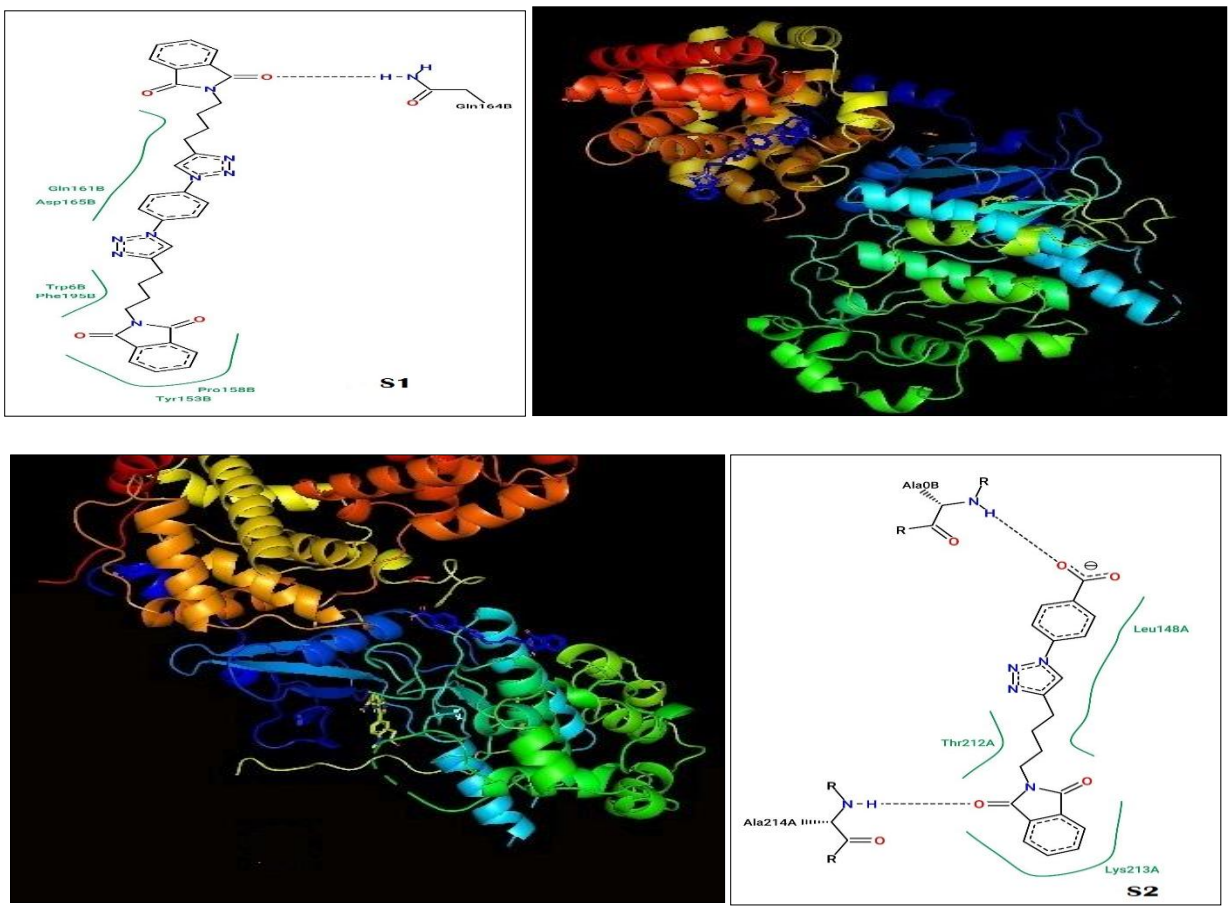


Figure 16 Docking Study

3.8. Biological effectiveness

Investigation was done on the compoundS [S2,S1] for anti-colon cancer properties using the HCT116 cell line, and the MTT methods were used for examining the biological effects of the substrate and the prepared extracellular derivatives against colon cancer.

The results were that (82.75%) is the percentage of inhibition of the compound [S2] , (67.05%) for cancer cells with time of 72 hours and concentration of. (100µg.ml-1)

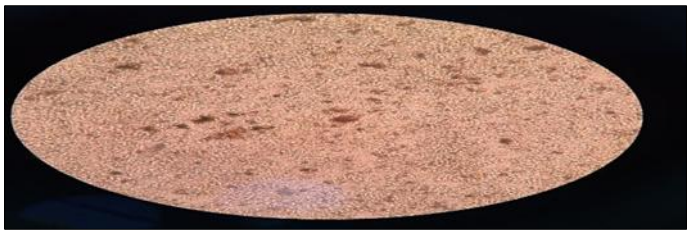


Figure 17 Demonstrates the effect of the compound [S2] on colon cancer

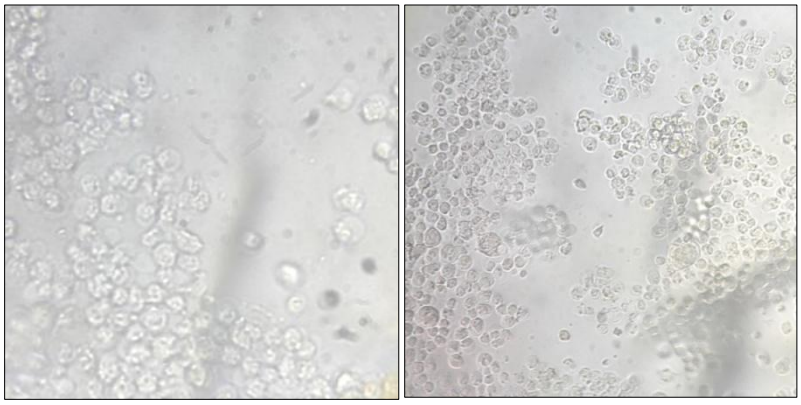


Figure 18 Demonstrates the effect of the compound [S1] on colon cancer

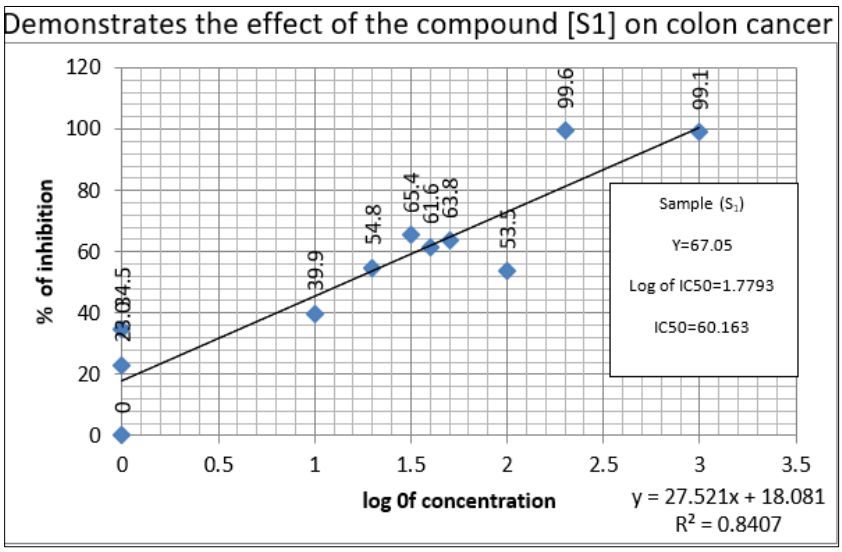


Figure 19 (3-100) IC50 of derivative (S_1)

3.8.1. Antioxidants

Table 7 demonstrates the reductive ability of the compound (S1) and the elimination of free radical

Sample name	Conc.	Abs.	%
S1	0.12 mg	0.4876	58.934
S2	0.25 mg	0.3655	69.558
b1	0.5 mg	0.3367	71.710
b2	1 mg	0.2987	74.887
	control	1.1898	

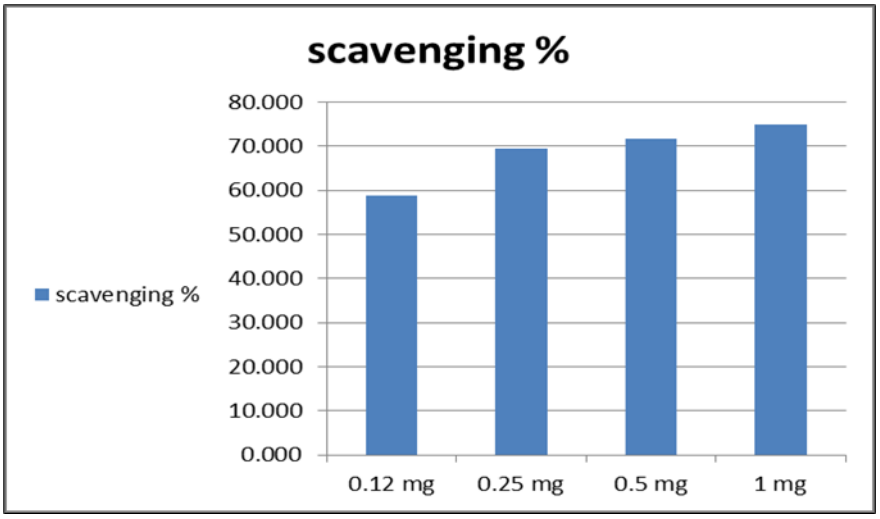


Figure 20 Demonstrates the effectiveness of eliminating free radicals of the compound

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed

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