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Synthesis, identification of some new 1,2,4-triazole derivatives from 6-amino-1,3-dimethyluracil and evaluation of their molecular docking, Anti-oxidant and experimental

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***Abstract*---**The present work includes synthesis of new series of heterocyclic derivatives containing 6-amino-1,3-dimethyl uracil moiety linked to 1,2,4-triazole [6-8 and 10]. The first way includes reaction of 6-amino-1,3-dimethyluracil with ethyl chloroacetate with K2CO3 as catalyst in DMF as solvent to gives ester derivative [1]. Then, compound [1] was converted into (semicarbazide, thiosemicarbazide, phenylsemicarbazide and hydrazide derivatives) as a result of the compound [1] reaction with (semicarbazide, thiosemicarbazide, and phenylsemicarbazide and hydrazine hydrate) corresponding compound [2-5] respectively. Then, Cyclization of compound [2-5] in alkaline media (4N-NaOH) to give 1,2,4-triazole derivatives compounds [6-8] respectively. While, Compound [5] cyclization by reaction with CS2 in alkaline media (20% KOH) to give compound [9] that reacted directly with hydrazine hydrate to gives 1,3,4-triazole derivative [10]. The synthesized compounds were identified by spectral methods their [FTIR and some of them by 1HNMR, 13C-NMR] and measurements some of its physical properties and some specific testes. All the compounds were screened for in vitro antioxidant studies by 2,2-diphenyl-1-picrylhydrazyl (DPPH) and phosphomolybdenum methods. Among the synthesized bioactive molecules [1-10] exhibited promising antioxidant activity compared with the standard drug Ascorbic acid. Furthermore, in order to support the biological results of the compounds, molecular docking studies were performed against

Aromatase enzyme for compounds which revealed that the compounds [1-8,10] compared with the standard drug Exemestane.

***Keywords*---**6-amino-1,3-dimethyluracil, 1, 2, 4-triazole derivatives, anti-oxidant, molecular docking, ethyl chloroacetat.

Introduction

Heterocyclic compounds are necessary for human survival. Synthetic heterocyclic compounds have a significant impact on pharmaceuticals, chemotherapeutic agents, dyestuffs, photo graphics, co-polymers, and other products [1]. Furthermore, these materials are primary constituents of both organic synthetic materials and natural products [2].Nitrogen-rich heterocyclic compounds based on imidazoles [3], pyrazoles [4], triazoles [5], tetrazoles [6], oxadiazole [6,7] and tetrazines [8] have received a lot of attention in the evolution of new energetic compounds in recent years. Because of their increased nitrogen content, high density, and high enthalpy of formation, triazole frameworks have typically been chosen as possible building blocks for the structure of nitrogen-rich heterocyclic compounds [(9).] 6-aminouracil is a common subunit in many complex molecules, and its derivatives are of great interest in organic chemistry as a primary starting material and as a privileged scaffold. Many chemists are interested in this molecule because it can act as both a nucleophile and an electrophile. The most significant nucleophilic activity is observed at position 3. This compound is easily synthesized into fused annulated compounds with other materials and polycyclic compounds with biological targets such as pyrido-, pyrrolo-, and pyrimido-pyrimidines [10-11]. These derivatives have demonstrated a remarkable range of pharmacological and biological activities, including antimicrobial [11] activity, antibacterial activity [12], anti-influenza avius activity [13], anti-neuroinflammatory activity [14], antioxidant activity [15], anticancer activity [16], and anti-HIV activity [17].

Materials and Methods

Chemicals used in this research are supplied from BDH, Fluka, Merck and Sigma Aldrich companies and used without further purification. In addition to melting points were uncorrected and registered by Electro thermal melting point apparatus. FTIR spectra of the synthesized compounds in the (4000-600) cm^{-1} spectral range were recorded on SHIMAZU FTIR-8400 Fourier transform Infrared spectrophotometer using KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on BRUKER 400MHz in Iraq, instrument using TMS as internal reference and DMSO-d_6 as a solvent. Spectrophotometers were recorded by Shimadzu 1900i, Japan, Technical institute of Adiwaniyah, Al-Forat Alawsat university.

Synthesis of 6-amino ethylacetate-1,3-dimethyl pyrimidine-6-yl.[1][(18)]

6-amino-1,3-dimethyluracil (0.7 g ,0.0045 mol.) and K_2CO_3 (0.6 g , 0.0045 mol.) were dissolved in dimethylformamide (6 mL.) in a round bottom flask (50 mL.) supplied with a magnetic stirring bar. Then ethyl chloroacetat was added (0.5 mL.; 0.0045 mol.). The solution was stirred, and the temperature was gradually increased to (75-85) °C for 16 hours. The reaction mixture was poured into ice

water and filtered after the reaction was completed. Washed with water then recrystallized from ethanol. Some of the physical properties of compound [1] and FTIR spectral data are listed in table-1.

Synthesis of 1,3-Dimethyl-6-(amino aceto) semicarbazide [2]; thiosemicarbazide [3]; phenylsemicarbazide[4] pyrimidine 2,4-dione-6-yl.[19]

A compound [1] (0.5 g; 0.002 mol.) is dissolved in (8 mL.) ethanol and drops of DMF with (0.002 mol.) of each (semicarbazide, thiosemicarbazide, and phenylsemicarbazide) respectively and stirred for some minutes. Then added to the reaction mixture (0.17 g; 0.002 mol.) of sodium acetate and refluxed for (18-20) hours. After cooling the reaction mixture and pouring it into ice-cold water, the precipitate is filtered and recrystallized with a suitable solvent. Some of the physical properties of compound [2-4] and FTIR spectral data are listed in table-1.

Synthesis of 1,3-dimethyl-6-(amino aceto hydrazine) pyrimidine-2,4-dione-6-yl.[5][20]

Compound [1] (0.5 g; 0.002 mol.) was dissolved in (8 mL) ethanol as a solvent; excess of hydrazine hydrate was added to the reaction mixture and refluxed for 8 hours. After cooled and pouring the reaction mixture into ice, the product was filtered, washed with water, and recrystallized by ethanol-water. Some of the physical properties of compound [5] and FTIR spectral data are listed in table-1.

Synthesis of 1,3-dimethyl-6-(5-hydroxy-4H-1,2,4-triazol-3-yl [6] ; 5-mercapto-4H-1,2,4-triazol-3-yl [7] and 5-hydroxy-4-phenyl-1,2,4-triazol-3-yl) [8] methylamino] pyrmidine-2,4-dione-6-yl.[21]

The compound [2-4] was reflexed with 4N. aqueous NaOH solution (15–20 mL.) for (10-12) hours. The reaction of the mixture has cooled to room temperature, poured into ice-cold water. After neutralization with (1:3) hydrochloric acid, the formed precipitate was filtered, and recrystallized with suitable solvent. Some of the physical properties of compound [6-8] and FTIR spectral data are listed in table-2.

Synthesis of 1,3-dimethyl-6-[aminoaceto dithiocarbazide] pyrmidine-2,4-dione-6-yl.[9][22]

To a stirred ethanolic solution of (0.12 g; 0.0022 mol.) KOH in ethanol absolute (15 mL.), hydrazide derivative [5] (0.5 g; 0.0022 mol.), and carbon disulfide (0.13 mL.; 0.0022 mol.) slowly added to the reaction mixture and stirred overnight. The filtered product was washed with (15 mL.) of ether and dried. The salt [9] was obtained in almost quantitative yield and employed in the next step without further purification. Then recrystallization by ether. Some of the physical properties of compound [9] and FTIR spectral data are listed in table-2.

Synthesis of 1,3-dimethyl-6-(5-mercapto-4-amino-1,2,4-triazole-3-yl-methylamino) pyrmidine-2,4-dione-6-yl.[10][22]

The potassium salt [9] (0.4 g; 0.0011mol.) suspension in excess hydrazine hydrate (4mL.) was refluxed until the evolution of Hydrogen Sulfide was ceased. During reflux the color of the reaction mixture changed to yellow. After cooling, the reaction mixture was acidified with 10% HCl to yield a yellow precipitate. The precipitate was recrystallized from ethanol to give crystals. Some of the physical properties of compound [10] and FTIR spectral data are listed in table-2.

Table 1
Physical properties and FTIR spectral data cm-1 of the synthesized compounds [1-5]

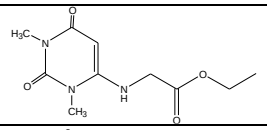
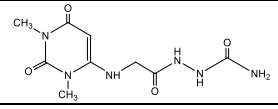
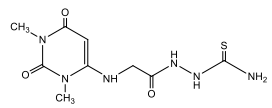
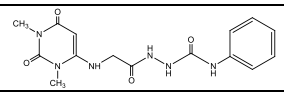
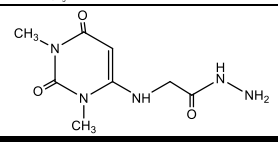
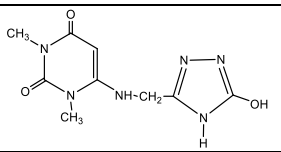
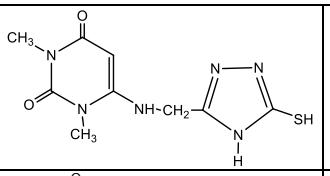
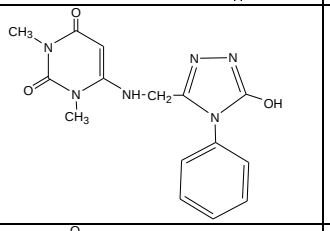
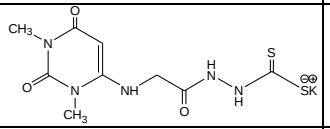
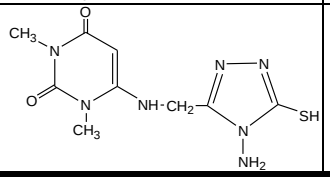
Com. No.	Physical properties				Major FTIR Absorptions cm-1				
	Compound Structure	m.p °C	Yield %	Color	νN-H	νC-H Aliph	νC=O Amide	νC=C	Other bands
1		338-339	65	Orange	3159	2997 2921	1654	1620	ν(C=O)ester 1693 ν(C-O-C) 1234
2		>360	78	White	3298	2977	1639	1620	ν(NH_2) Asym. 3434 Sym. 3309
3		347-348	80	Off white	3284	2983	1639	1620	ν(NH_2) Asym. 3431 Sym. 3317 ν(C=S) 1413
4		344-345	85	Orange	3288	2958	1654	1620	ν(C-H) Arom. 3037
5		347-348	90	White	3292	2968	1670 1656	1614	ν(NH_2) Asym. 3396 Sym. 3353

Table 2
Physical properties and FTIR spectral data cm-1 of the synthesized compounds [6-10]

Com. No.	Physical properties				Major FTIR Absorptions cm-1				
	Compound Structure	m.p °C	Yield %	Color	νN-H	νC-H Aliph	νC=O Amide	νC=C	Other bands
6		340-341	85	Grey	3288	2956 2923	1652	1620	ν(O-H) 3404 ν(C=N) 1620

7		339-340	90	Light gray	3288	2954	1654	1622	ν(C=N) 1622
8		>360	80	White	3288	2977	1681	1620	ν(O-H) 3429 ν(C=N) 1639 ν(C-H)Arom 3070
9		341-342	95	White	3288	2956	1652	1620	ν(C=S) 1413
10		249-250	85	Yellow	3247	2977	1652	1620	ν(NH_2) Asym. 3404 Sym. 3330 ν(C=N) 1620

Antioxidant activity (DPPH radical scavenging assay)[24,25]

The antioxidant activity of compounds (1-10) was determined using the stable DPPH free radical and a standard procedure. The synthesized compounds (1-10) were mixed with methanol solution (up to 2mL) containing 0.0002 g/mL of DPPH radical and prepared at three different concentrations (50, 100, 150) µM in DMSO. Using a spectrophotometer, the absorbance of the reaction mixture was measured at 517 nm after 30 minutes of incubation at room temperature. At the same concentrations of the tested compounds, ascorbic acid was used as a control. The percentage inhibitions of compounds (1-10) and ascorbic acid were calculated using the following formula: DPPH inhibition effect (%) = ((Ac-As)/Ac) *100 Were Ac=Absorbance reading of the control; As=Absorbance reading of the sample.

Total antioxidant capacity [26]

The phosphomolybdenum method was used to assess the total antioxidant capacity of the synthesized compounds. A different concentration of an aliquot compound solution (50, 100, 150 µg/mL.) was combined with (1 mL.) of reagent (0.6 M) sulfuric acid, (28 mM) sodium phosphate, and (4 mM) ammonium molybdate). All test tubes containing the reaction solution for the compounds being tested were sealed and incubated at 95°C for 90 minutes. The tubes were then cooled to room temperature, and the absorbance of each tube was measured against a blank using a spectrophotometer at 695 nm. Total antioxidant activity is measured in gram equivalents of ascorbic acid. Ascorbic acid concentrations of 10, 20, 30, 50, 70, 90, 120, 180, and 200 g/mL with DW were used to plot the calibration curve.

In silico studies
Ligand preparation[27]

Molecular docking studies were carried out using the Small Drug Discovery Suites package (Schrodinger 2020-3, LLC). The twodimensional structures of the synthesized compounds were sketched and then converted to threedimensional structures using the LigPrep module in Maestro 12.5. To prepare ligands for docking, they were adjusted to physiological pH and energy minimization was performed using the OPLS2005 force field. The Epik option was used to keep the ligand in the suitable protonation state.

Protein processing and binding site identification

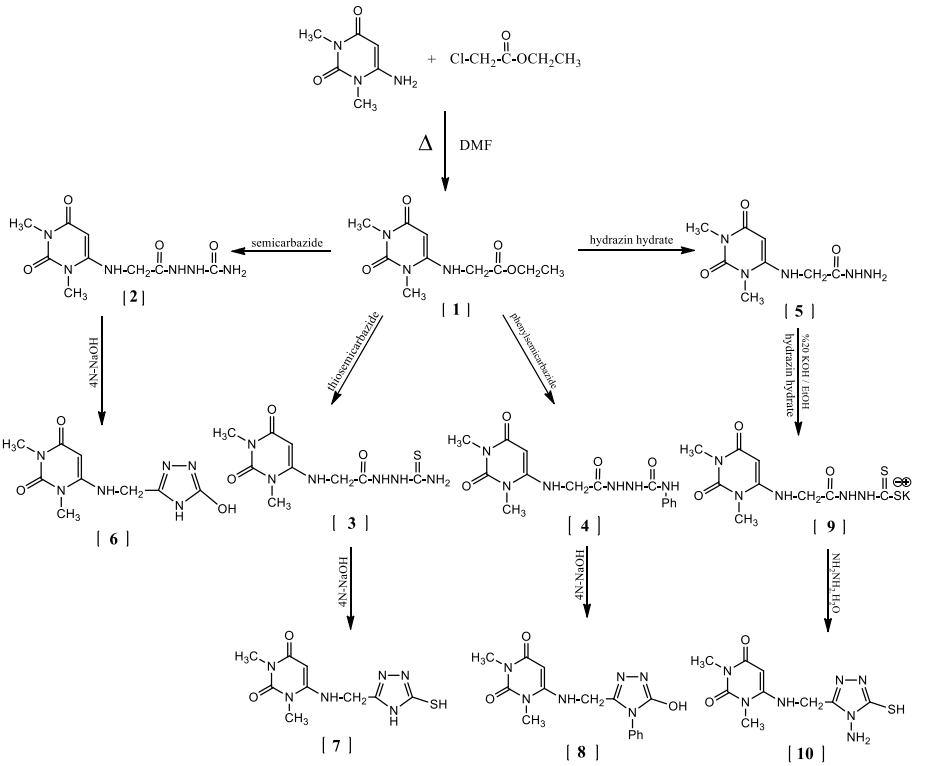
The aromatase enzyme's 3D crystal structure was obtained from the RCSB Protein Data Bank (PDB ID: 3S7S). The protein preparation wizard in Maestro 12.5 was used to repair and prepare the 3D crystal structure. First and foremost, all water molecules were removed from the crystal structure. Bond orders and charges were assigned, and then all missing hydrogen atoms were added to the protein structure. Propka software was used to ionize amino acids by adjusting physiological pH. Finally, using the OPLC force field, a restrained minimization step was performed. This minimized structure was the best for molecular docking. Following protein preparation, topranked potential protein binding sites were identified to determine the most suitable binding site of proteins using the maestro 12.5 glide grid tool.

Molecular docking studies

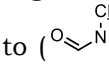
Ligand docking was used to predict the best poses and binding energies of ligands at binding sites identified by the glide grid tool on the receptor. To begin, all ligands were docked on receptors in Maestro 12.5 using the Glide docking module. Using the receptor grid generation platform, a grid box was generated around the selected co-crystallized ligand at the binding site. Then, using Maestro 12.5, rigid receptor docking simulations were run. Finally, using the maestro 12.5 work space visualizer, poses were visualized and results were analyzed.

Results and Discussion

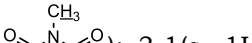
The synthetic series for preparation of new amino substituted traizole as in schemes-1

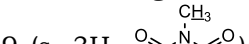
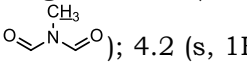
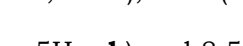


Scheme 1. preparation of new amino substituted traizole.

Compound [1] was prepared by the reaction of 6-amino-1,3-dimethyluracil, ethyl chloroacetate with K_2CO_3 in DMF as solvent. The FTIR spectrum[28] indicated the presence of a ν(N-H) at (3159 cm^{-1}); ν(C-H) Aliph at (2997 cm^{-1}); ν(C=O) ester at (1693 cm^{-1}), ν(C=O) amide at (1654 cm^{-1}) and ν(C=C) at (1620 cm^{-1}) were appeared, shown listed in table-1. ^{1}HNMR spectrum[29] showed triplet signal at δ= (1.3) ppm due to (-CH2-C**H₃**) protons, singlet signal at δ=(2.51) ppm due to (-N-C**H₂**-) , singlet signal at δ= (3.15) ppm due to (-N**H**), singlet signal at δ=(3.27) ppm due to (-N-C**H**$_3$), singlet signal at δ= (3.29) ppm due to (), quartate signal at δ= (3.4) ppm due to (-OC**H₂**), singlet signal at δ= (3.55) ppm due to (-C**H₂**-) protons and singlet signal at δ= (4.2) ppm due to (=C-**H**) all signal shown in listed table-3. ^{13}C-NMR spectrum data [27] of this compound [1] were shown listed in table-4.

Compound [1] was converted to semicarbazide [2], thiosemicarbazide [3], phenylsemicarbazide [4] and hydrazide derivatives [5] by the reaction with (semicarbazide, thiosemicarbazide, phenylsemicarbazide and hydrazine hydrate) respectively (scheme 1). FTIR spectral data showed absorption at (3434-3396) cm^{-1} asym. for ν-NH_2, sym. for ν-NH_2 at (3353-3309) cm^{-1} respectively of compound [2-3,5], (3298-3284) cm^{-1} for ν-NH, absorption bands of νC-H Aliph. at (2983-2958) cm^{-1}, absorption bands at (1670-1639) cm^{-1} for νC=O, absorption bands for νC=C at (1620-1614) cm^{-1} respectively of compound (2-5). The compound 3 have νC=S at (1413 cm^{-1}) and compound [4] have νC-H aromatic at (3037 cm^{-1}). While the ^{1}H-NMR spectra data in DMSO-d6 solvent of compound [4] show in table-3

the signal in 3.15 of (s, 1H, N**H**); 3.15 (s, 3H, N-C**H₃**); 3.27 (s, 3H, ); 3.36 (S, 1H, N**H**-ph); 3.51 (s, 2H, N-C**H₂**-); 4.2 (s, 1H, =C-**H**); 6.81-7.31 (m, 5H, -**ph**) and 7.51(s, 1H, N**H**-N**H**). ^{13}C-NMR spectrum data of this compound [4] were listed in table-4. ^{1}H-NMR spectra data of compound (5) all signal show in table-3 that contain of signal in 3.07 (s, 2H, -C**H₂**-); 3.15 (s, 1H, -N-**H**); 3.27 (s, 3H, N-C**H₃**); 3.29 (s, 3H, ); 3.1(s, 1H, N**H**); 4.2 (s, 1H, =C-**H**); 4.6 (s, 2H, N**H₂**) and 6.8(s, 1H, N**H**-NH_2). ^{13}C-NMR spectrum data of this compound [5] were listed in table-4

Treatment of compounds [2-4] with (4N. NaOH) solution afford intramolecular cyclization to give the hydroxytriazole [6], thiohydroxytriazole [7] phenylhydroxytriazole [8] were identified from FTIR spectra shows result in table-2. All the spectrum data showed the presence of absorption ofν-NH (3288) cm^{-1}, absorption bands of νC-H Aliph at (2977-2923) cm^{-1}, absorption bands of νC=O of at (1681-1652) cm^{-1}, absorption bands at νC=C group about (1622-1620) cm^{-1} and absorption bands of imine groups νC=N group at (1639-1620) cm^{-1} of compound [6-8]. The compound [6, 8] have ν-OH group at (3429-3404) cm^{-1} and the compound [8] have νC-H aromatic at (3070 cm^{-1}). While the ^{1}H-NMR spectra data in DMSO-d_6 solvent of compound [6-8] show in table-3 the signal in 2.51 (s, 2H, -C**H₂**-); 3.15 (s, 1H, N**H**); 3.27 (s, 3H, N-C**H₃**); 3.29 (s, 3H, ); 4.2 (s, 1H, =C-**H**); 7.51 (S, 1H,NH-triazole); 8.89(s, 1H,-OH). While the compound [7] show signal in 2.9 (s, 2H, -C**H₂**-); 3.15 (s, 1H, -N-**H**); 3.27 (s, 3H, N-C**H₃**); 3.29 (s, 3H, ); 4.2 (s, 1H, =C-**H**); 7.58 (s, 2H, S**H**); 8.9 (S, 1H, N**H**-triazole) and the compound [8] show signal in 2.5 (s, 2H, -C**H₂**-); 3.15 (s, 1H, -N-**H**); 3.27 (s, 3H, N-C**H₃**); 3.36 (s, 3H, ); 4.2 (s, 1H, =C-**H**); 7.5-7.8 (m, 5H, **ph**) and 8.5 (s, 2H, O**H**). all data of ^{13}C-NMR spectrum of this compound [6-7] were listed in table-4.

To preparation of compound [10] by reaction of hydrazide [5] with CS_2 in ethanolic KOH gave the dithiocarbazate salt [9] in excellent yield, which, was then cyclized by refluxing with 98% hydrazine hydrate to give a very good yield of triazole derivative [10]. FTIR spectrum showed absorptions at (3404 cm^{-1}) asym. and(3330cm^{-1}) Sym. for –NH_2 group , (3247 cm^{-1}) for N-H group, (1652 cm^{-1}) for C=O and (1620 cm^{-1}) for νC=N group and C=C onerlap with C=N. ^{1}HNMR spectrum showed singlet signal at δ= (2.51) ppm of (-C**H₂**-); singlet signal at δ= (3.15) ppm of (-N**H**); singlet signal at δ= (3.28) ppm of (-NC**H₃**); singlet signal at δ= (3.29) ppm of (); singlet signal at δ= (4.6) ppm of (-N**H₂**) and singlet signal at δ= (7.51) ppm of (-S**H**) protons as shown in table-3. ^{13}C-NMR spectrum data of this compound [10] were listed in table4.

Table 3
^{1}H-NMR spectral data (δ ppm) for compound [1,4-8 and 10]

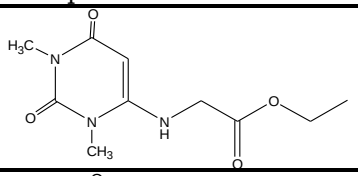
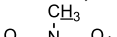
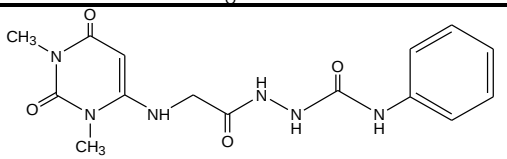
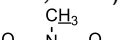
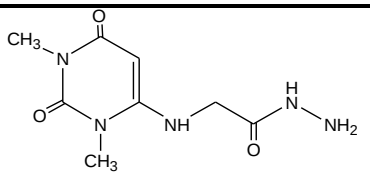
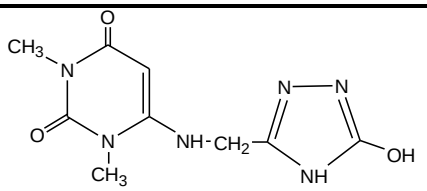
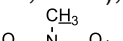
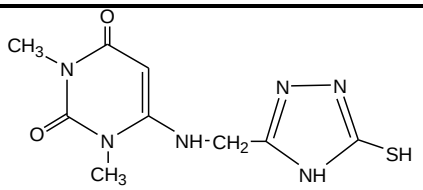
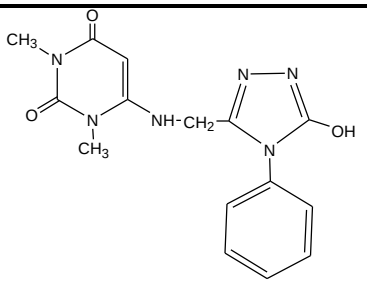
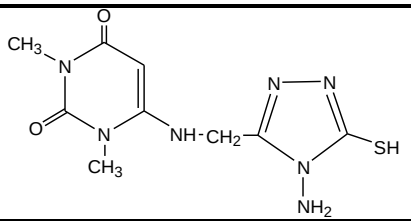
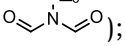
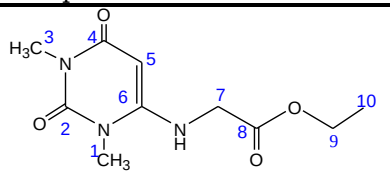
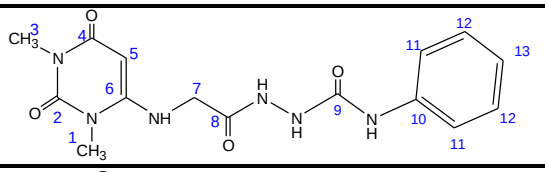
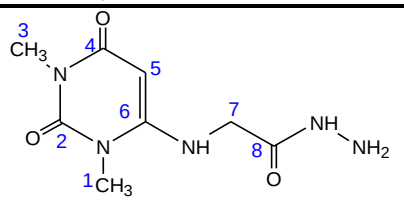
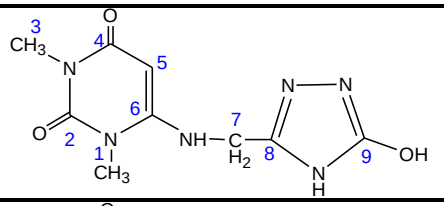
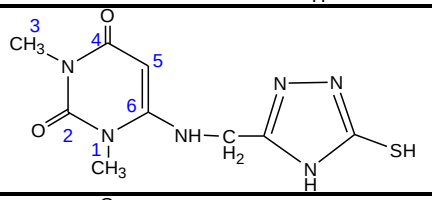
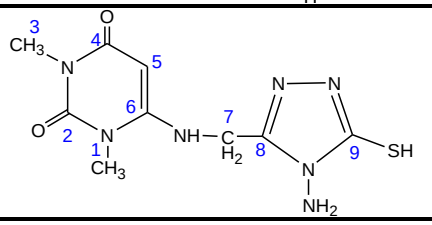
No.	Compound structure	^{1}H-NMR spectral data ($^{\delta}$ppm)
1		1.3 (t, 3H, -CH_3); 2.51 (s, 2H, N-CH_2-); 3.15 (s, 1H, NH); 3.27 (s, 3H, N-CH_3); 3.29 (s, 3H, ); 3.4 (q, 2H, -OCH_2); 4.2 (s, 1H, =CH).
4		3.15 (s, 1H, -NH); 3.27 (s, 3H, N-CH_3); 3.27 (s, 3H, ); 3.36(S, 1H, NH-ph); 3.51 (s, 2H, N-CH_2-); 4.2 (s, 1H, =CH); 6.81-7.31 (m, 5H, -ph); 7.51(s, 1H, NH-NH).
5		3.07(s, 2H, N-CH_2-); 3.15 (s, 1H, -NH); 3.27 (s, 3H, N-CH_3); 3.29 (s, 3H,); 3.1(s, 1H, -NH); 4.2 (s, 1H, =CH); 4.6 (s, 2H, -NH_2); 6.8(s, 1H, NH-NH_2).
6		2.51 (s, 2H, N-CH_2-); 3.15 (s, 1H, -NH); 3.27 (s, 3H, N-CH_3); 3.29 (s, 3H, ); 4.2 (s, 1H, =CH); 7.51 (S, 1H, NH-triazole); 8.89(s, 1H,-OH).
7		2.9 (s, 2H, N-CH_2-); 3.15 (s, 1H, -NH); 3.27 (s, 3H, N-CH_3); 3.29 (s, 3H,); 4.2 (s, 1H, =CH); 7.58 (s, 2H, -SH); 8.9 (S, 1H, NH-triazole).
8		2.5 (s, 2H, N-CH_2-); 3.15 (s, 1H, -NH); 3.27 (s, 3H, N-CH_3); 3.36 (s, 3H,); 4.2 (s, 1H, =CH); 7.5-7.8 (m, 5H, -ph); 8.5 (s, 2H, -OH).
10		2.51 (s, 2H, N-CH_2-); 3.15 (s, 1H, -NH); 3.28 (s, 3H, N-CH_3); 3.29 (s, 3H, ); 4.2 (s, 1H, =CH); 4.6 (S, 2H, -NH_2); 7.51 (s, 2H, -SH).

Table 4
^{13}C-NMR spectral data (δ ppm) for compound [1,4-7 and 10]

No.	Compound structure	^{13}C-NMR spectral data ($^{\delta}$ppm)
1		19.35 (C_{10}); 28.36(C_1); 30.26 (C_3); 85.24 (C_7); 85.82 (C_9); 98.5 (C_5); 150.19(C_6); 163.82(C_2, C_4); 173.34(C_8).
4		28.35(C_1); 30.25 (C_3); 85.24 (C_7); 98.5 (C_5); 117.3(C_{13}); 120.83(C_{12}); 125.15 (C_{11}); 128.75(C_{10}); 150.91(C_6); 161.51(C_9); 163.82(C_2, C_4); 165.53(C_8);
5		27.51(C_1); 29.75 (C_3); 75.33 (C_7); 98.5 (C_5); 152.07(C_6); 155.35 (C_4); 161.89 (C_2); 167.45(C_8).
6		28.36(C_1); 30.25 (C_3); 85.26 (C_7); 98.5 (C_5); 150.98(C_6); 152.42 (C_8); 156.23 (C_9); 163.73 (C_2, C_4).
7		28.35(C_1); 30.26 (C_3); 85.26 (C_7); 98.5 (C_5); 150.88(C_6); 154.11 (C_8); 157.21(C_9); 163.71 (C_4); 164.91 (C_2).
10		28.35(C_1); 30.29 (C_3); 85.25 (C_7); 98.5 (C_5); 150.91(C_6); 151.41 (C_8); 154.13(C_9); 163.83 (C_4); 164.91 (C_2).

Antioxidant activity

Antioxidant compounds have a high free radical scavenging capacity. Antioxidants help to delay or prevent the oxidation of easily oxidable substances in living bodies. Antioxidant compounds shield macromolecules and cells from free radical molecules. As a result, finding antioxidants has become increasingly important in recent years. Because they are less expensive and more effective, synthetic antioxidants are now more widely used than natural antioxidants. [25]

DPPH scavenging activity

The compounds that prepared (1-10) showed similar or slight less activity to the standard (ascorbic acid). It was estimated by (2,2- diphenyl-1-picrylhydrazyl) assay method at different concentrations (50 ,100 and 150 µg/ml). The result depending on the reaction of distinguish by change its deep violet color (DPPH) or color disappearing is stoichiometric with respect to number of electrons captured. The results in these prepared concentrations show that the definite effectiveness decreases as the concentration decreases. It was found that the best result was compound (10) at a concentration of (150 µg/ml) by comparing it with the rest of the results, showing the higher antioxidant activity. Figure 1 represented the DPPH scavenging activity of the newly synthesized compound (1-10).

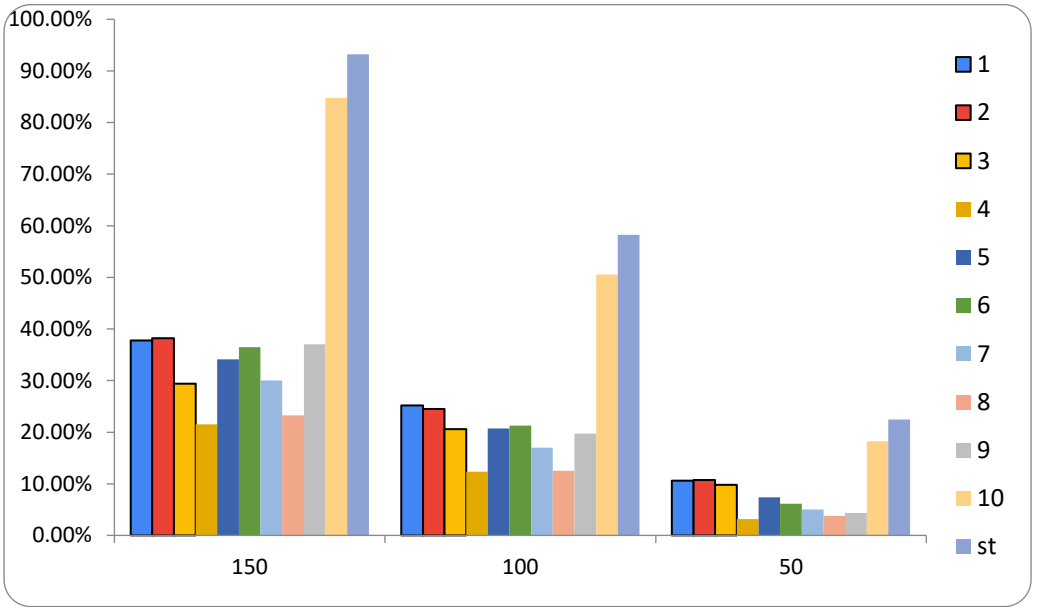
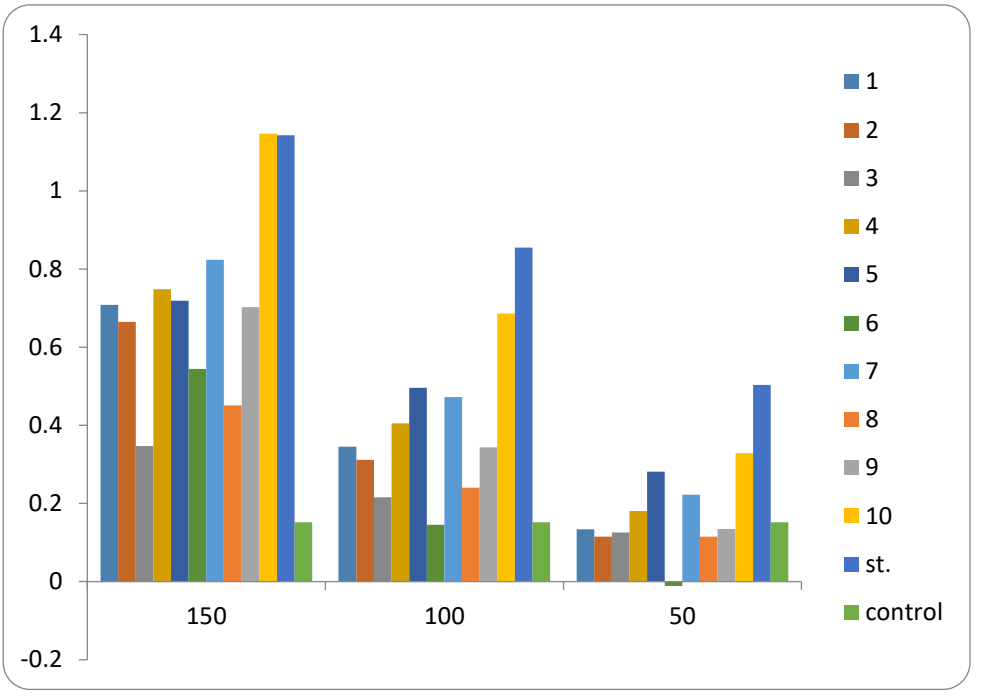


Figure 1. DPPH scavenging activity of the newly synthesized compound(1-10)

Total antioxidant capacity

The total antioxidant capacity of all synthesized compounds (1-10) was evaluated using the phosphomolybdenum method, which is based on the reduction of colorless 70 Molybdenum(VI) to blue Molybdenum(V) using the synthesized compounds and subsequent formation of a green phosphate - Mo(V) complex in acidic pH. The antioxidant activity of the compounds was compared to that of standard ascorbic acid. Compounds (1-10) have a weak antioxidant capacity against reduced Mo(VI) to Mo(V) among the newly synthesized uracil derivatives, as shown in figure (2).



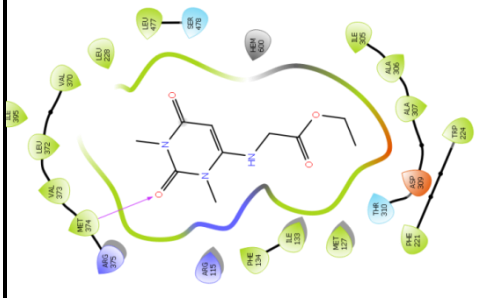
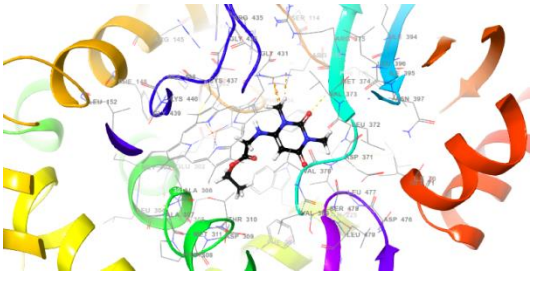
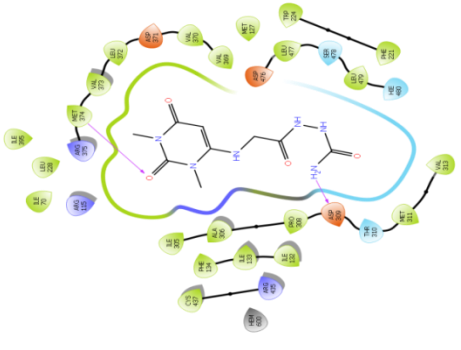
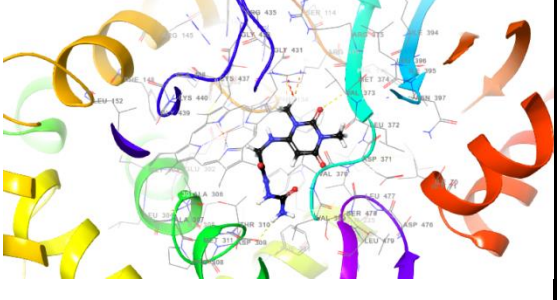
Docking studies

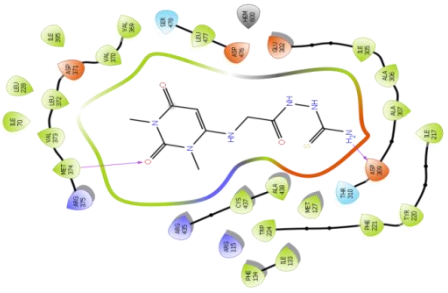
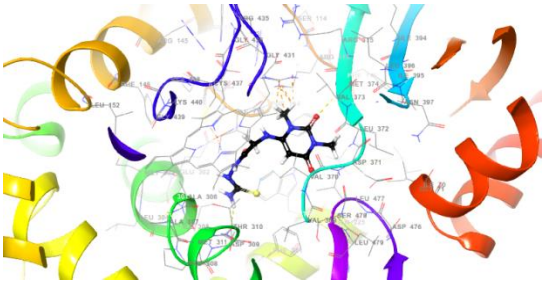
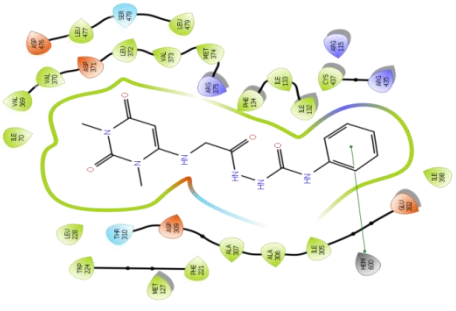
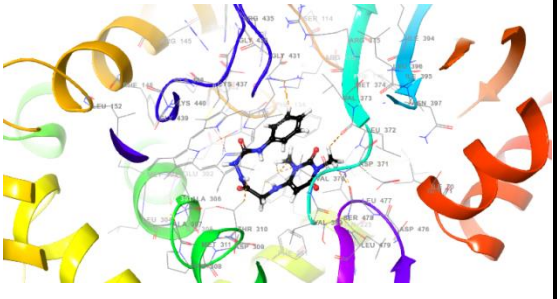
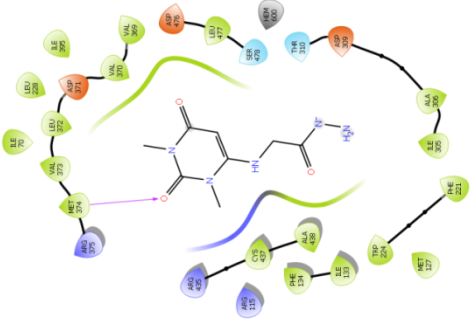
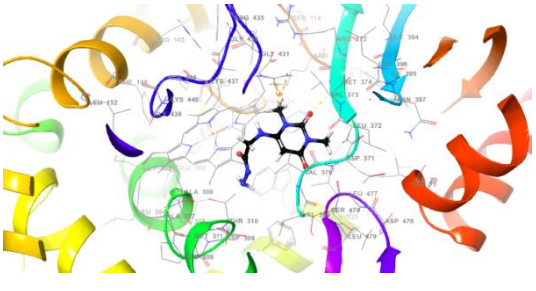
In an attempt to rationalize the antioxidant activity for the synthesized compounds (1-8,10). Docking analysis was carried out with selective pharmacological targets such as aromatase enzymatic protein of breast cancer which is involved in the pathogenesis and induction of cancer. The crystal structure of aromatase (PDB id: 3S7S) was retrieved from the Protein Data Bank and it has complexes with the reference drug Exemestane (EXM). Docking studies showed in table-5, The binding modes of compounds (1-8,10) indicated that they fitted more stably into the aromatase binding pocket by interacting with key residues MET374, ASP309, HEM600, TRP224 and mimicked the binding mode of the reference drug Exemestane. Compound (2) in table-5 has shown dock score (-5.535kcal/mol.) comparable to the standard (-3.657 kcal/mol.) Show highest dock score compared to co-crystalline. Consequence, these interactions support the observed decrease in aromatase activity. As a side effect, the current study shows that the synthesized compounds could be one of the next generation chemotherapy drugs that can be used effectively in the treatment of breast cancer and other related disorders. Figure-2 shows the 3S7S enzyme structure (Exemestane).

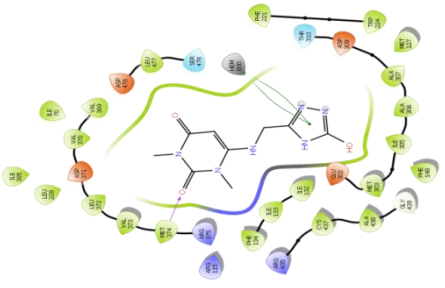
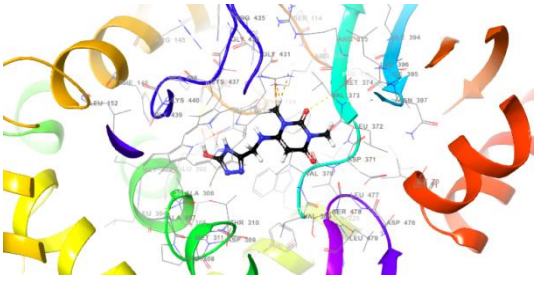
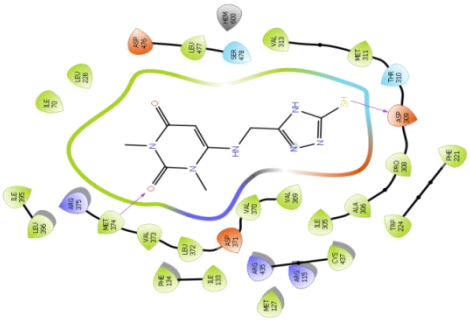
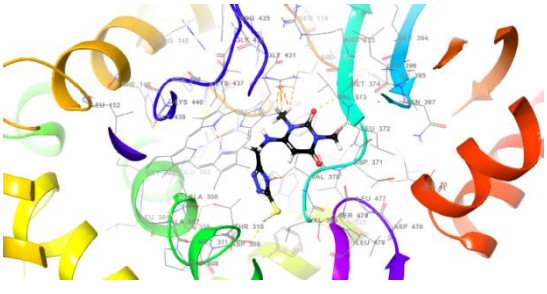
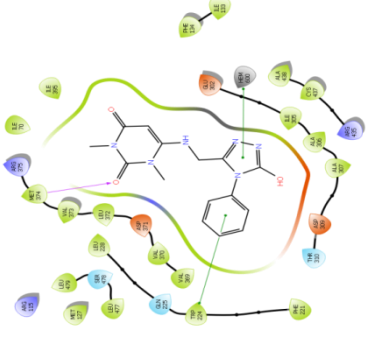
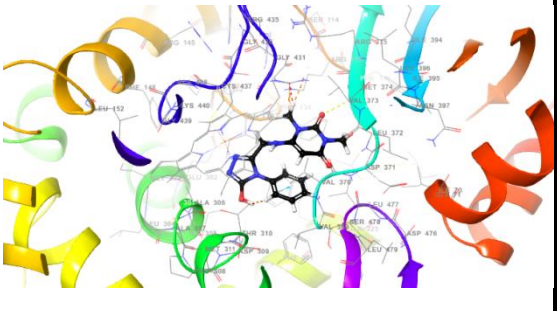
Table 5
Showing consequences of molecular docking of compound (1-8,10)

Compounds	Types of residues	Types of interaction	Docking score	Glide Energy
1	MET 374	Hydrogen bonding	-5.198	-41.045

2	MET 374 , ASP 309	Hydrogen bonding	-5.535	-46.135
3	MET 374	Hydrogen bonding	-5.248	-44.866
4	HEM 600	Hydrogen bonding	-5.089	-39.71
5	MET 374	Hydrogen bonding	-4.527	-37.55
6	MET 374	Hydrogen bonding	-5.347	-46.051
7	MET 374 , ASP 309	Hydrogen bonding	-5.252	-42.391
8	MET 374	Hydrogen bonding Hydrophobic	-4.888	-45.161
10		Hydrogen bonding	-5.25	-47.489
Standard	MET 374	Hydrogen bonding	-3.657	-18.206

Com. NO.	Molecular interaction of compound M(1-10) against aromatase enzyme	
1		
2		

3		
4		
5		

6		
7		
8		

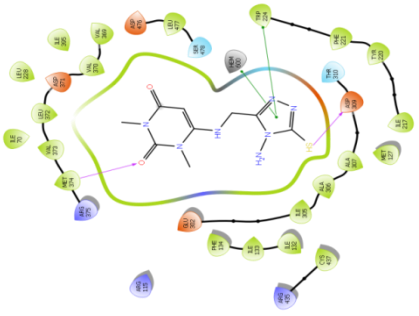
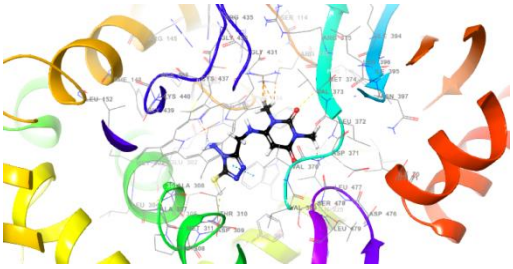
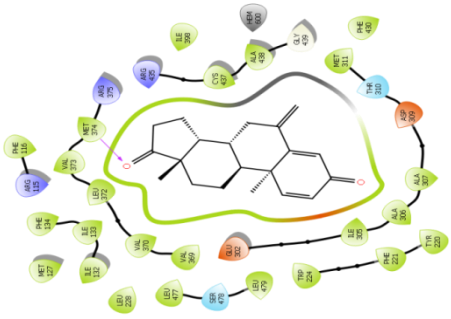
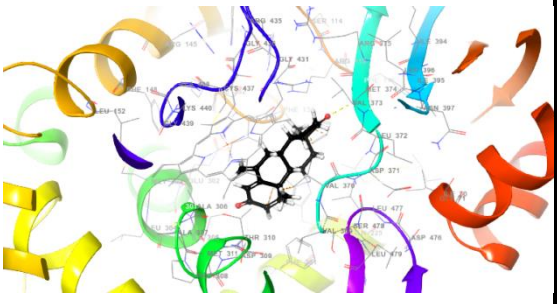
10		
St		

Figure 2. View docking Molecular of compounds (1-8,10) and standard

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