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Synthesis, Investigation, Theoretical Study And Effect Of Some New Triazole Derivatives On Creatinine Ring On The Activity Of Some Transferase Enzymes.

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ABSTRACT

This report describes the synthesis of triazole derivatives on creatinine ring, The Synthetic route started from reaction creatinine chloroacetylchloride with thiourea to give compound(1), then compound (1) react with benzaldehyde and *m*- nitrobenzaldehyde respectively to give compounds (2-3) compounds, then compounds (2-3) react with α- chloroethylacetate to give compounds (4-5). Hydrazide derivatives were synthesized by the reaction compounds (4-5) with hydrazine hydrate to give compounds (6-7). The compounds (6-7) reacts with benzonitrile and acetonitrile respectively to give compounds (8-9) The synthesized compounds were characterized by FT-IR, ^{1}HNMR, and ^{13}CNMR spectroscopy. Also, we worked theoretical study involving calculated the spectra, total energy, dipole moment etc.. This triazole derivatives were designed to show the effects of it on the activities of GOT and GPT enzymes in sera. This compounds demonstrated activation effects on GOT and GPT activities. These effects increased with increasing the concentration of the compounds. The causes of the increases in the enzymes activities are discussed.

Keywords: triazole, GOT, GPT, sera, dipole moment, total energy.

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INTRODUCTION

Triazole heterocyclic compounds have been paid unique consideration because of their potential applications as medicinal agents and agrochemicals, triazole ring is an essential five-membered heterocycle with three nitrogen molecules. This kind of novel structure enriches triazole derivatives to readily bind with a lot of enzymes and receptors in biological system and show various types of biological activities. Triazole ring can be utilized as important linker to combine unique pharmacophore parts to produce bifunctional medicate particles, giving a helpful and effective pathway to create different bioactive and useful atoms. The triazole ring is likewise a critical isostere of imidazole, oxazole, pyrazole, thiazole, and amide moiety. Furthermore in designing different types of new drug molecule. An extensive number of triazole-based derivatives have been broadly prepared and examined for their biological activities, which is one of the most important areas in the researches and developments of new drugs. Especially, triazole derivatives as antifungal drugs have been playing a very important part in clinical treatment, and have been the primary decision drugs for the treatment of fungous infection. More triazole derivatives, with strong pharmacological activity, low toxicity, less unfavorable impacts, less multi-sedate protections, high bioavailability, great pharmacokinetics property and drug-targeting, diversity of drug administration, broad spectrum, and better curative effect., have been frequently becoming clinical drugs for the treatment of various kinds of diseases[1- 4].

EXPERIMENTAL

Materials and physical measurements

All starting materials and solvents were purchased from Sigma-Aldrich and Fluka and used without further purification. Melting points were measured on Gallen Kamp capillary melting point apparatus and were uncorrected, FT-IR measurements were recorded on Shimadzu model FTIR-8400S. ^{1}HNMR, and ^{13}CNMR spectra were obtained with Bruker spectrophotometer model ultra-shield at 400 MHz in D_2O solution with the TMS as internal standard. Note: in some ^{1}HNMR and ^{13}CNMR spectra, the peaks at δ 4.66 and 39.65 ppm are for the solvent (H_2O-D_2) respectively.

Synthesis of the organic compounds

Synthesis of compound (1) [5]

Literature procedure was used with modifications. In 100 mL R.B.F (0.02 mole) of compound (1) and (0.02 mole) of thiourea were dissolved in 1,4-dioxane (20mL) and the blend were refluxed for 18 hours. The obtained product was filtered, and recrystallized from ethanol. The physical properties of synthesized compound (1) is given in Table 1.

Synthesis of compounds (2-3) [6]

To 20 mL of hot ethanol, (0.005 mole) of benzaldehyde/*m*-nitrobenzaldehyde and (0.0025 mole) of compound (1) were dissolved. To this mixture 1.0 mL of glacial acetic acid was added. The reaction mixture was then refluxed on a water bath in a 250 mL R.B.F for 12 hours. Completion of the reaction was monitored by TLC. The mixture was allowed to stand for 24 hours at room temperature. The product was collected and recrystallized with ethanol. The Physical properties of synthesized compounds (2-3) are given in Table1

Synthesis of compounds (4-5) [7]

Compounds (2-3) respectively (0.01mole) were dissolved in absolute ethanol (20 mL), then NaOH (1M, 10 mL) was added at (0°C). α-chloroethylacetate (0.01) was added to the mixture. This mixture was stirred at room temperature overnight. The precipitate was filtered and then dried. The product was collected and recrystallized with ethanol. The Physical properties of synthesized compounds (4-5) are given in Table1.

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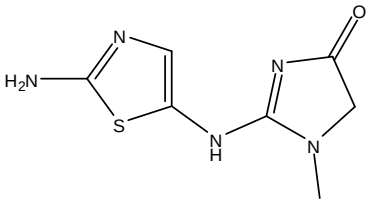
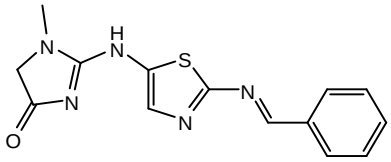
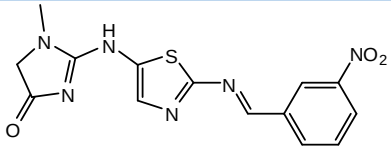
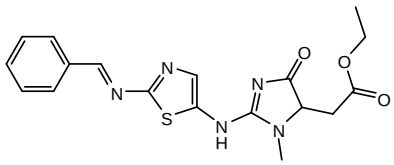
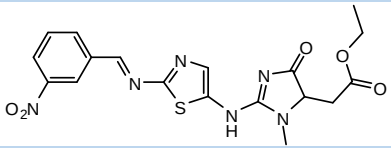
Synthesis of compounds (6-7) [8]

Generally, a solution of compounds (4-5) (0.01mole), hydrazine hydrate (0.01 mole,85%) in absolute ethanol(50mL) were prepared. The reaction mixture was refluxed for 24hr. The obtained product was filtered, and recrystallized from ethanol. The physical properties of synthesized compounds (6-7) are given in Table 1.

Synthesis of compounds (8-9) [9]

A mixture of (0.01 mole) of compounds (6-7), benzonitrile and acetonitrile respectively (0.01) mole in presence of DMF as a solvent were refluxed for 17 hrs. The separated precipitate was cooled, filtered and purified by dissolved in DMF and reprecipitate from acetone. The physical properties of synthesized compounds (8-9) are given in Table 1.

No. of compd.	Structure and name of compounds	Chemical formula	Color	Molecular weight	M. P. ˚C Dec.	Yield%
1	 2-(2-aminothiazol-5-ylamino)-1-methyl-1H-imidazol-4(5H)-one	$C_7H_9N_5OS$	Brown	211.24	212-215	85.00
2	 2-(2-(benzylideneamino)thiazol-5-ylamino)-1-methyl-1H-imidazol-4(5H)-one	$C_{14}H_{13}N_5OS$	Yellow	299.35	235-237	82.00
3	 1-methyl-2-(2-(3-nitrobenzylideneamino)thiazol-5-ylamino)-1H-imidazol-4(5H)-one	$C_{14}H_{12}N_6O_3S$	Yellow	344.35	222-224	86.00
4	 ethyl 2-(2-(2-(benzylideneamino)thiazol-5-ylamino)-1-methyl-4-oxo-4,5-dihydro-1H-imidazol-5-yl)acetate	$C_{18}H_{19}N_5O_3S$	Yellow	385.44	168-170	98.00
5		$C_{18}H_{18}N_6O_5S$	Pale Yellow	430.44	175-177	94.00

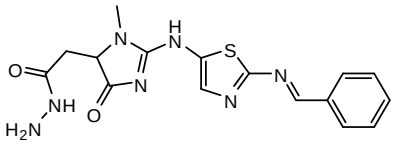
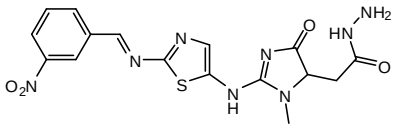
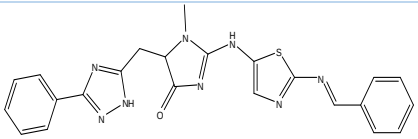
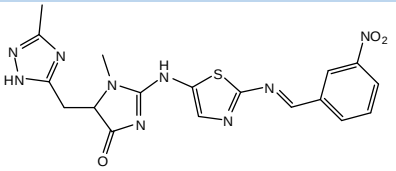
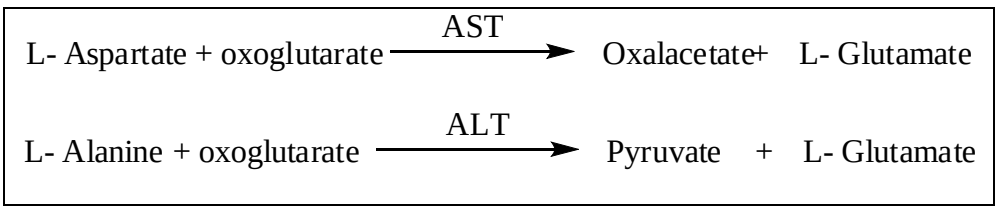
	ethyl 2-(1-methyl-2-(2-(3-nitrobenzylideneamino)thiazol-5-ylamino)-4-oxo-4,5-dihydro-1H-imidazol-5-yl)acetate					
6	 2-(2-(2-(benzylideneamino)thiazol-5-ylamino)-1-methyl-4-oxo-4,5-dihydro-1H-imidazol-5-yl)acetohydrazide	$C_{16}H_{17}N_7O_2S$	White	371.42	185-187	70.00
7	 2-(1-methyl-2-(2-(3-nitrobenzylideneamino)thiazol-5-ylamino)-4-oxo-4,5-dihydro-1H-imidazol-5-yl)acetohydrazide	$C_{16}H_{16}N_8O_4S$	White	416.41	193-195	72.00
8	 2-(2-(benzylideneamino)thiazol-5-ylamino)-1-methyl-5-((3-phenyl-1H-1,2,4-triazol-5-yl)methyl)-1H-imidazol-4(5H)-one	$C_{23}H_{20}N_8OS$	White	456.52	216-219	92.00
9	 1-methyl-5-((3-methyl-1H-1,2,4-triazol-5-yl)methyl)-2-(2-(3-nitrobenzylideneamino)thiazol-5-ylamino)-1H-imidazol-4(5H)-one	$C_{18}H_{17}N_9O_3S$	White	439.45	207-209	85.00

Table1: The physical properties of synthesized compounds (1- 9)

Materials and methods of biological activity section

Effect of compounds (8-9) on GOT, and GPT activities

Colorimetric determination of GOT or GPT activity according to the following reactions:



The pyruvate or oxaloacetate formed was measured in its derived from 2,4- dinitrophenylhydrazine, which was absorbed at wave length 546 nm (SYRBIO kit).

A stock solution (0.01 M) of compounds (8-9)

A stock solution (0.01 M) of compounds (8-9) were prepared by dissolving it in distilled water, and the following concentrations (10^{-2}, 10^{-3}, 10^{-4}, 10^{-5} M) were prepared by diluting with distilled water . The enzymes GOT, and GPT activities were measured in human serum by using the same methods of these enzymes with replace 100 µl of buffer with 100 µl of compounds (8-9).The activation percentage was calculated by comparing the activity with and without compounds (8-9) and under the same conditions, according to the equation:

% Activation =100× The activity in the presence of activator/The activity in the absence of activator – 100

The activation constant (K_i) was calculated according to the following equation:

$$V_{max} + A = V_{max} - A/ (1+ [A]/ K_i)$$

Where A is activation constant.

+A is with activator
-A is without activator
[A] is activator concentration

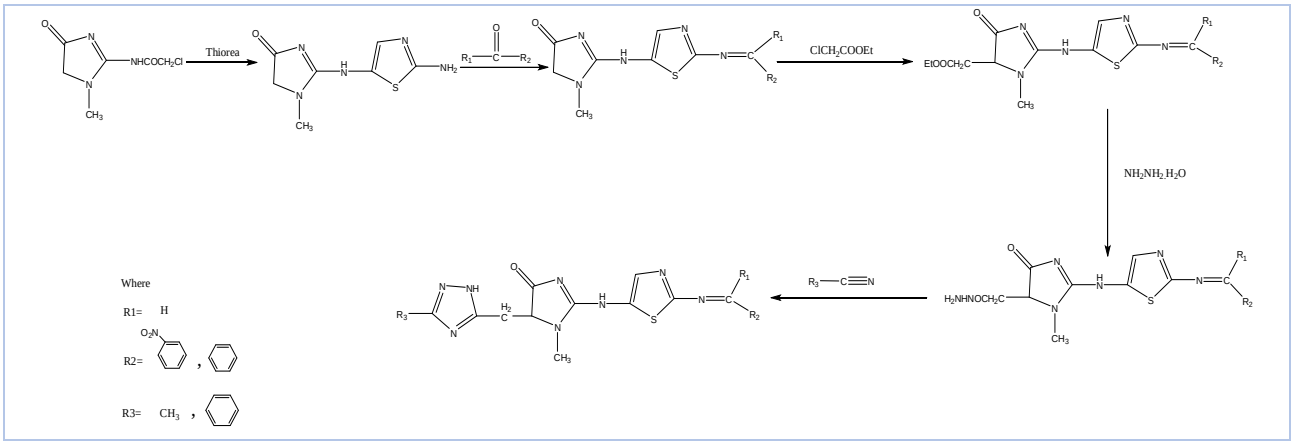
A constant concentration of compounds (8-9) (10^{-2} M)

A constant concentration of compound (8-9) (10^{-2} M) were used with different substrate concentrations of (40, 80, 120, 160, 200) mmol/L for GOT and GPT to study the type of activation. Buffers were used to prepared different substrates concentrations of these enzymes, GOT, GPT (phosphate buffer pH = 7.40, 100 mmol/L). The enzymes velocity was determined with and without compounds (8-9), by using the Linweaver and Burke equation and plotting 1/v against 1/[s] were evaluated values; Ki, apparent V_{max} (V_{mapp}), apparent Km (K_{mapp}), type of inhibition or activation [10] .

RESULT AND DISCUSSION

Synthesis

Scheme 1 included synthesis creatinine derivatives. The characterization data of all compounds 1–9 are given in the experimental section. All the newly synthesized compounds gave satisfactory analysis for the proposed structures, which were confirmed on the basis of, FTIR, ^{1}HNMR, and ^{13}CNMR data.



Schem1: The chemical steps for the synthesis of compounds (1-9)

FT-IR spectra

The FTIR spectrum of compound (1) revealed a medium stretching vibration band at (1633cm^{-1}) and (Asy.= 3473 , Sy.= 3415) that corresponds to olefinic (C=C) and (NH_2)groups respectively (see Table 2), (NH_2) group in compound (2-3) which are disappeared The FT-IR spectrum of compounds (1-3) are listed in Table 2 [11].

Comp. No.	C=N Shiffbase	ν C-H aliphatic	ν C=C Olefinic	ν =CH	ν NH_2	ν N-H
1	-----	2952	1633	3091	Asy.= 3473 Sy.= 3415	3249
2	1627	2958	1656	3100	------	3281
3	1625	2975	1650	3149	------	3259

Table 2: FT-IR Spectral data of synthesized compounds (1-3) in cm^{-1}

The FTIR spectra of compounds (4-5) have important characteristic stretching vibration bands that corresponds to (C=O) ester band. Show Table 3.

Comp. No.	ν C-H Aromatic	ν C=O Ester	ν C=C Aromatic	ν C=O Cycl. amide	ν N-H
4	3041	1747	1643	1697	3249
5	3029	1747	1670	1697	3253

Table 3: FT-IR Spectral data of synthesized compounds (4-5) in cm^{-1}

The FTIR spectra of compounds (6-7) have important characteristic stretching vibration bands that corresponds to (C=O) ester band which are disappeared and stretching vibration bands that corresponds to (C=O) amide band which are appeared Table 4.

Comp. No.	ν C-H Aromatic	ν C-H Aliphatic	ν C=O Amide	ν NH_2	ν N-H
6	3020	2902	1666	Asy.= 3353 Sy.=3413	3303
7	3083	2804	1668	Asy.= 3400 Sy.=3411	3284

Table 4: FT-IR Spectral data of synthesized compounds (6-7) in cm^{-1}

The FTIR spectra of compounds (8-9)

The FTIR spectra of compounds have important characteristic stretching vibration bands that corresponds to (NH) of triazole ring band which are appeared, also stretching vibration bands that corresponds to (NH_2) and (C=O) amide band which are disappeared. Show Table 5 [11].

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Comp. No.	ν C-H Aliphatic	ν C=O Amide	ν NH_2	ν C=N (Triazole ring)	ν N-H (Triazole ring)
8	2933	-----	-----	1608	3352
9	2952	-----	-----	1620	3305

Table 5: FT-IR Spectral data of synthesized compounds (8-9) in cm^{-1}

^{1}HNMR and ^{13}CNMR Spectra

The ^{1}HNMR and ^{13}CNMR spectra of compounds (1,8 and 9) are listed in Table 6 and Table 7 respectively and show in figures(1-6) respectively [12].

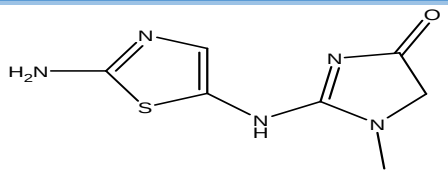
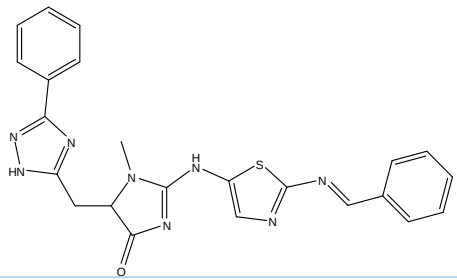
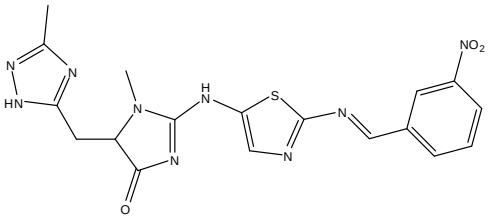
Comp. No.	Compound structure	^{1}HNMR data of (δ-H) in ppm
1		Singlet 2H of $–NH_2$ group (4.10); Singlet 1H of =CH (4.74); Singlet 1H of -NH (2.95); Singlet 3H of N-CH_3 (2.91); Singlet 2H of CH_2-CO (2.71).
8		Singlet 1H of -NH in triazole ring (8.35); Singlet 2H of -CH_2 group (1.11); Singlet 1H of –CO-CH (2.74); Singlet 3H of -N-CH_3 (2.91); Singlet 1H of -NH (3.81); Singlet 1H of -CH= (4.36); Singlet 1H of -N=CH (3.12); multiplet 6H of aromatic ring (6.24-8.05).
9		Singlet 3H of $–CH_3$ group (1.77); Singlet 1H of -NH in triazole ring (8.30); Singlet 2H of -CH_2 group (2.66); Singlet 1H of –CO-CH (2.71); Singlet 3H of -N-CH_3 (2.85); Singlet 1H of -NH (3.90); Singlet 1H of -CH= (4.34); Singlet 1H of -N=CH (2.89); multiplet 3H of aromatic ring (6.21-7.78).

Table (6) ^{1}HNMR data of compounds (1,8 and 9) in ppm

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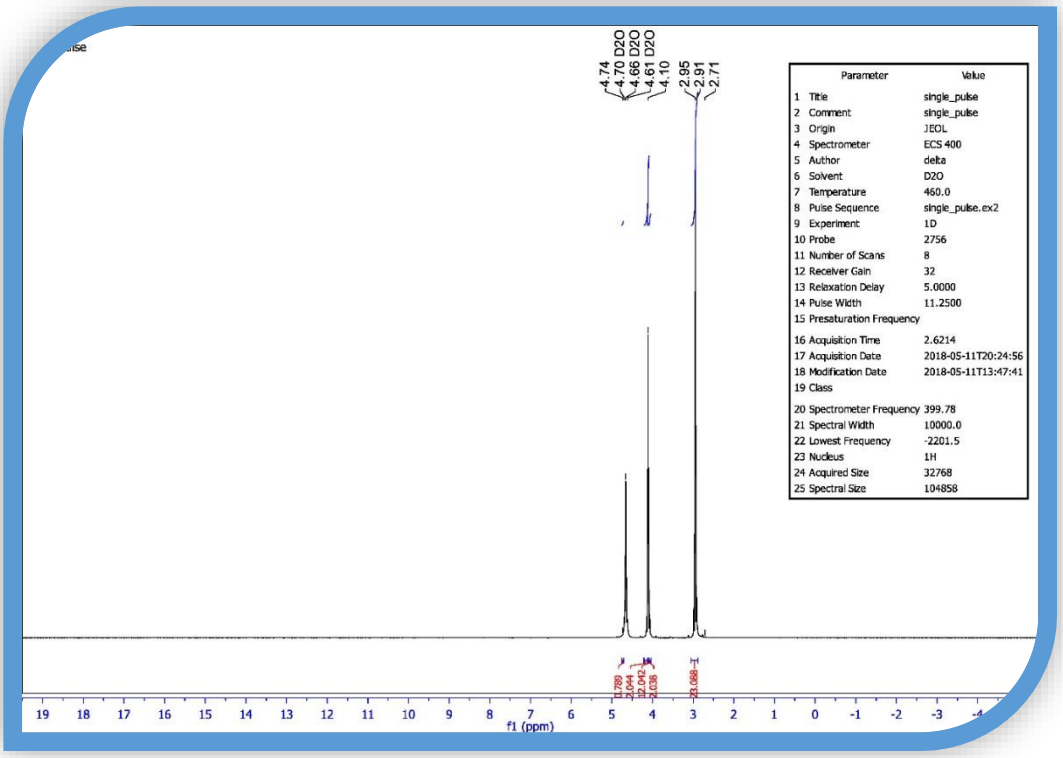

Figure.1: ^{1}HNMR spectrum of compound(1)

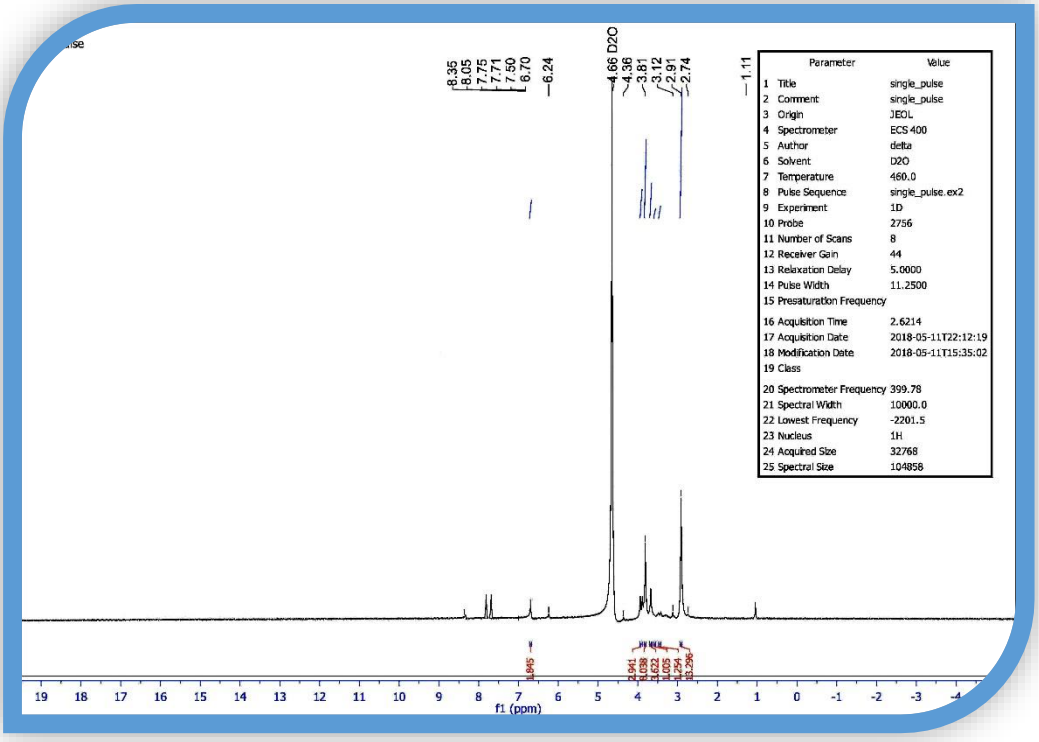

Figure. 2: ^{1}HNMR spectrum of compound (8)

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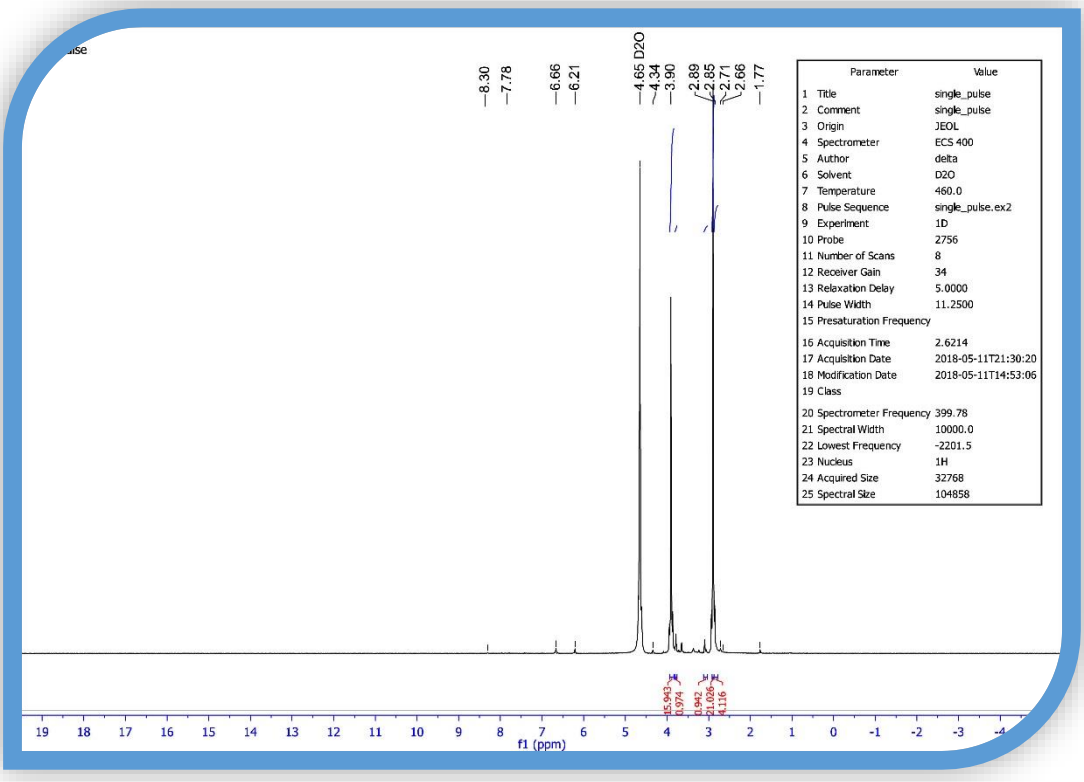
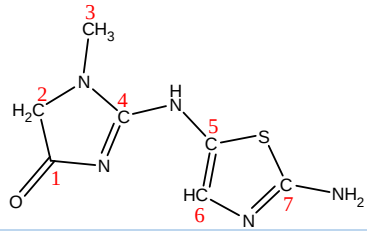
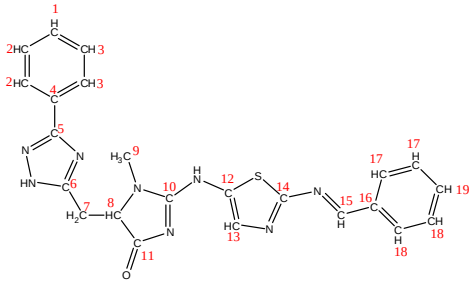


Figure. 3: ^{1}HNMR spectrum of compound(9)

Comp. No.	Compounds structure	^{13}CNMR data of (δ-H) in ppm
1		C1= 173.01; C2=37.06; C3= 54.16; C4= 157.17; C5=130.14; C6=131.42; C7= 160.10.
8		C1= 124.93; C2= 125.32; C3= 125.65 C4= 126.83; C5= 151.22; C6= 151.48 C7= 40.19; C8= 56.48; C9= 37.53; C10= 153.13; C11= 179.81; C12= 129.31 C14= 153.46; C15= 168.83; C16= 31.21 C17= 135.24; C18= 130.02; C19=130.55;

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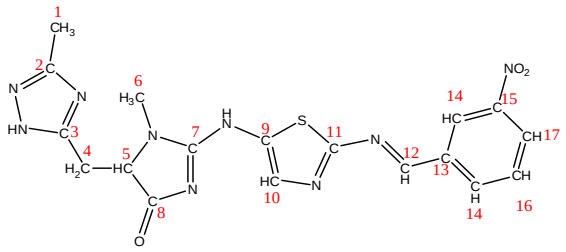
9		C1= 29.11; C2= 152.26; C3= 154.41 C4= 40.44; C5= 54.13; C6= 34.22 C7=151.53; C8= 174.02; C9= 123.23 C10= 130.87; C11= 152.26; C12= 162.51 C13= 131.54; C14= 123.50; C15=148.91; C16= 123.93; C17= 124.43.

Table (7) ^{13}CNMR data of compounds (1,8 and 9) in ppm

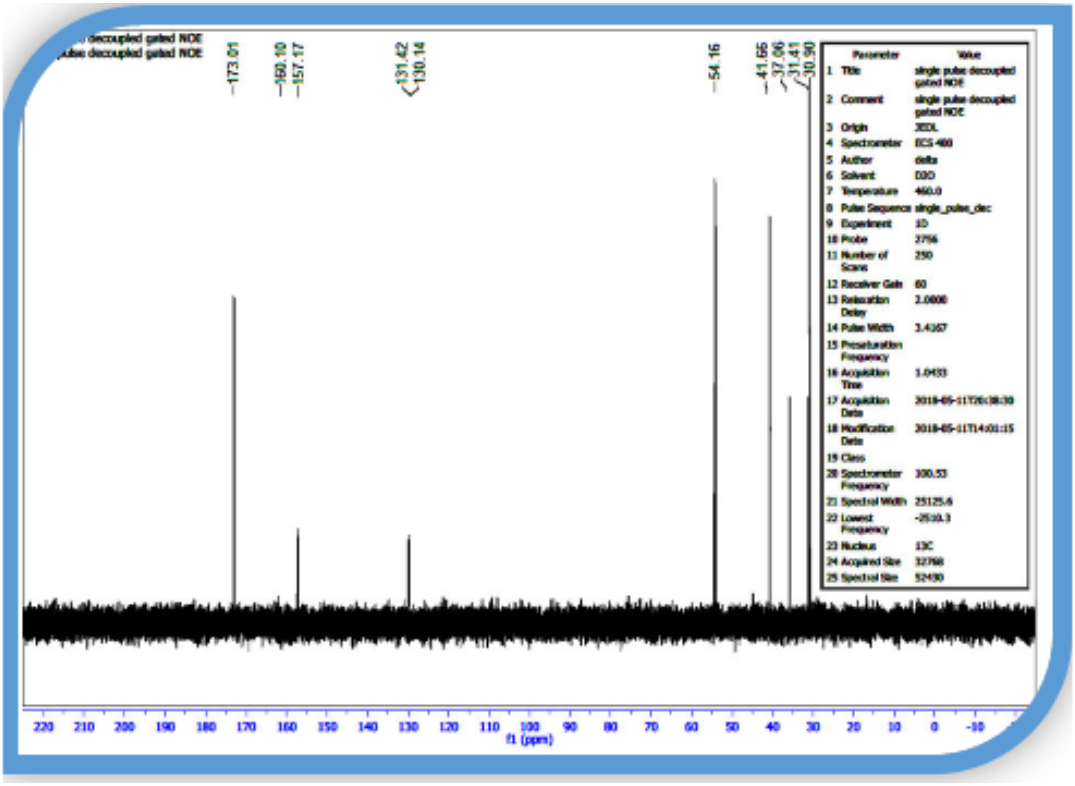


Figure.4: ^{13}CNMR spectrum of compound (1)

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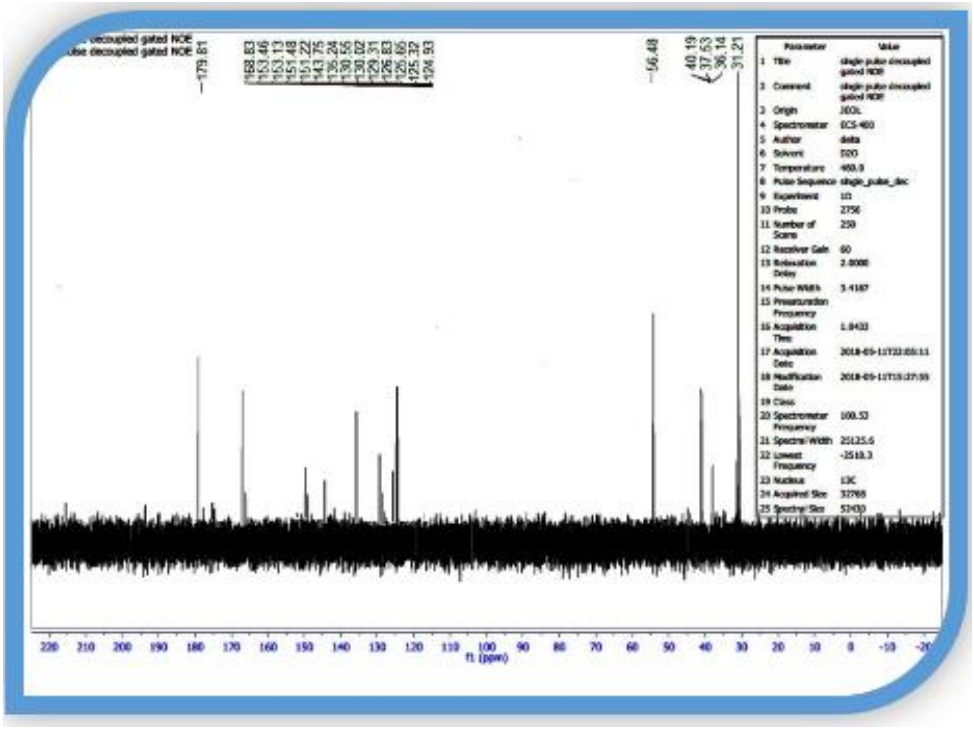

Figure. 5: ^{13}CNMR spectrum of compound (8)

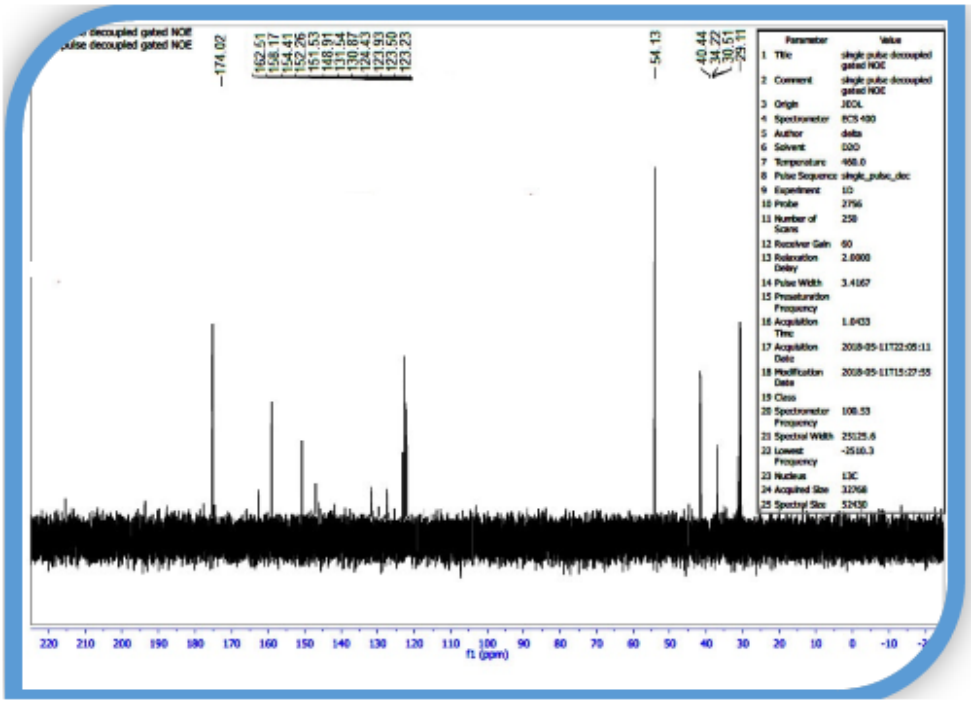

Figure. 6: ^{13}CNMR spectrum of compound (9)

Biological activity of transferase enzymes (GOT and GPT).

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This research addresses investigation of the effects of compounds (8-9) of GOT and GPT enzymes. The biochemical tests revealed that this compounds caused stimulation effects on GOT and GPT enzymes activities. Table (8) is listed below shows the effect of different concentration of compounds (8-9) on the activity of GOT and GPT enzymes in human serum. This research addresses investigation of the effects of compounds (8-9) of GOT and GPT enzymes. The biochemical tests revealed that this compounds caused activatory effects on GOT and GPT enzymes activities. The normal value of the GOT and GPT enzyme activities were (12 and 14 U/L) respectively. The relationship between compounds (8-9) concentrations versus and the activity of enzymes were shown in Figures (7-8). These results observed that any increase in compound concentrations caused increase in percentage of activation of enzymes.

Concentration (M)	GOT activity (U/L)	Activation (%)	GPT activity (U/L)	Activation (%)
Sample				
0	12	0.000	14	0.000
Compound (8)				
10^{-2}	82	583.333	80	471.428
10^{-3}	39	225.000	44	214.285
10^{-4}	18	50.000	25	78.571
10^{-5}	14	16.666	19	35.714
Compound (9)				
10^{-2}	88	633.333	91	550.000
10^{-3}	47	291.666	64	357.142
10^{-4}	22	83.333	27	92.857
10^{-5}	17	41.666	20	42.857

Table 8: The effect of different concentration of compounds (8-9) on the activity of GOT and GPT enzymes in human serum.

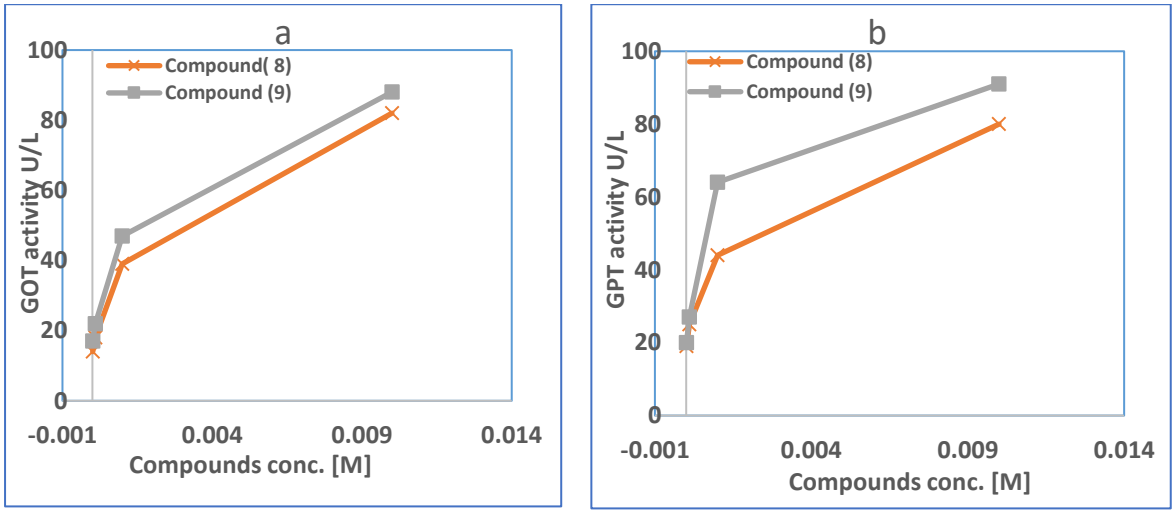

Figure. 7: (a) The relationship between concentration of compounds (8-9) and GOT enzyme activity. (b) The relationship between concentration of compounds (8-9) and GPT enzyme activity.

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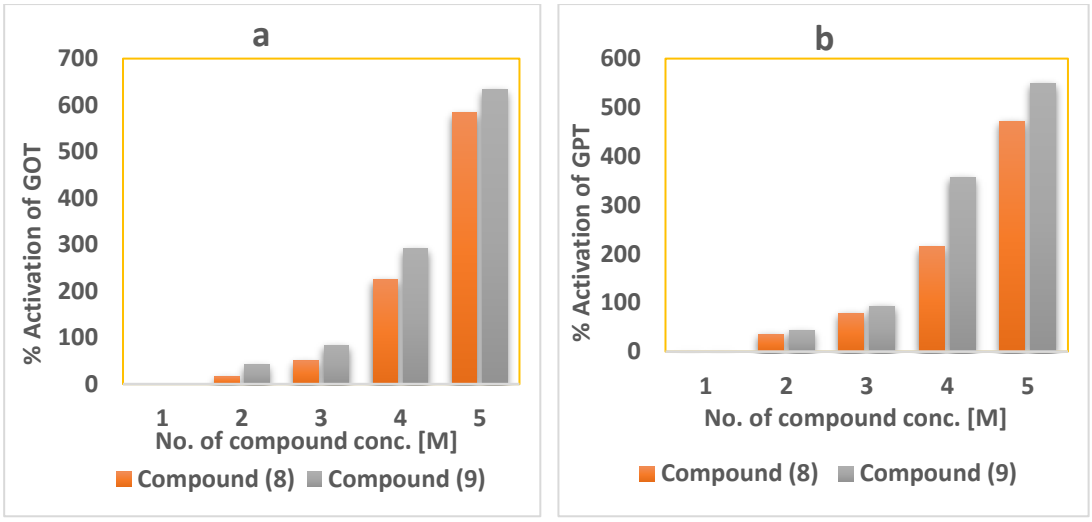

Figure.8: (a) The percentage of activation GOT enzyme and compounds (8-9) concentration. (b) The percentage of activation GPT enzyme and compounds (8-9) concentration.

Competitive, noncompetitive and uncompetitive inhibition can be easily distinguished with the use of double reciprocal plot of the Lineweaver–Burk plot. Two sets of rate determination in which enzyme concentration was held constant, were carried out. In the first experiment the velocity of uninhibited enzyme was established, in the second experimental constant amount of inhibitor is included in each enzyme assay. Varieties of substances have the ability to reduce or eliminate the catalytic activity of specific enzyme [13].

Table 9 and Figure (9) showed that the type of enzyme activation using Lineweaver–Burk plot for compounds (8-9) on serum GOT and GPT activity. The Vmax and Km values determined with 10^{-2} M of compounds (8-9) and without it. Vmax without compounds (8-9) were greater than Vmax in the precence compounds (8-9). A liquate 10^{-2} M of compounds (8-9) were noncompetitive activation for enzymes activity. Noncompetitive activation changed the Vmax of the enzyme but not the Km. By using Lineweaver– Burk equation, the Ki values of enzyme for compound which was studied in different concentrations.

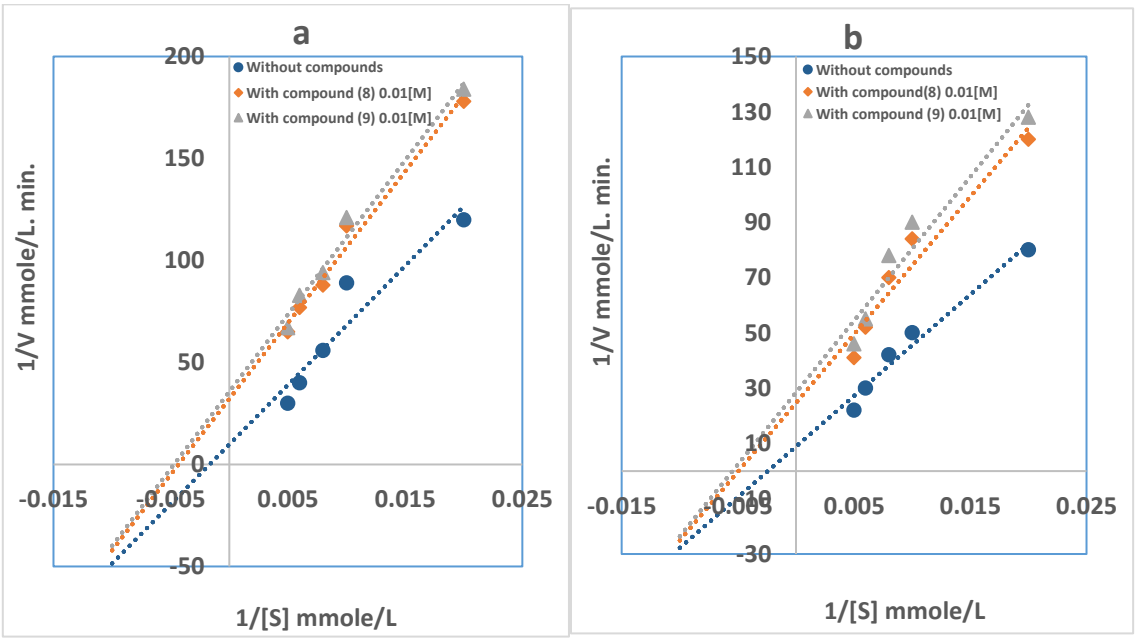

Figure. 9: Lineweaver-Burk plots for compounds (8-9) effects on (a) GOT, (b) GPT.

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Enzymes	K_m (mmole/L)	V_{max} (mmole/ L). min.	K_i (mmole/L)	Type of effect
GOT				
Without compounds	200	0.101		------
Compound (8)	200	0.031	0.0044	Noncompetitive
Compound (9)	200	0.028	0.0038	Noncompetitive
GPT				
Without compounds	192	0.112		-------
Compound (8)	192	0.040	0.0055	Noncompetitive
Compound (9)	192	0.035	0.0045	Noncompetitive

Table 9: The kinetic properties of GOT and GPT with compounds (8-9)

The enzymes play important role in amino acid metabolism and in urea and tricarboxylic acid cycles. We suggested that compounds (8-9) have (N– and O=) groups by which, it activities the active sides of amino acids of GOT and GPT enzymes by increasing affinity of active sides of enzymes to react with the substrates.

4.5. Optimize geometry of compound (8).

The Optimize geometry of atoms for the compound (8) calculating by using semi-empirical (PM3) method was depicted in figure 10

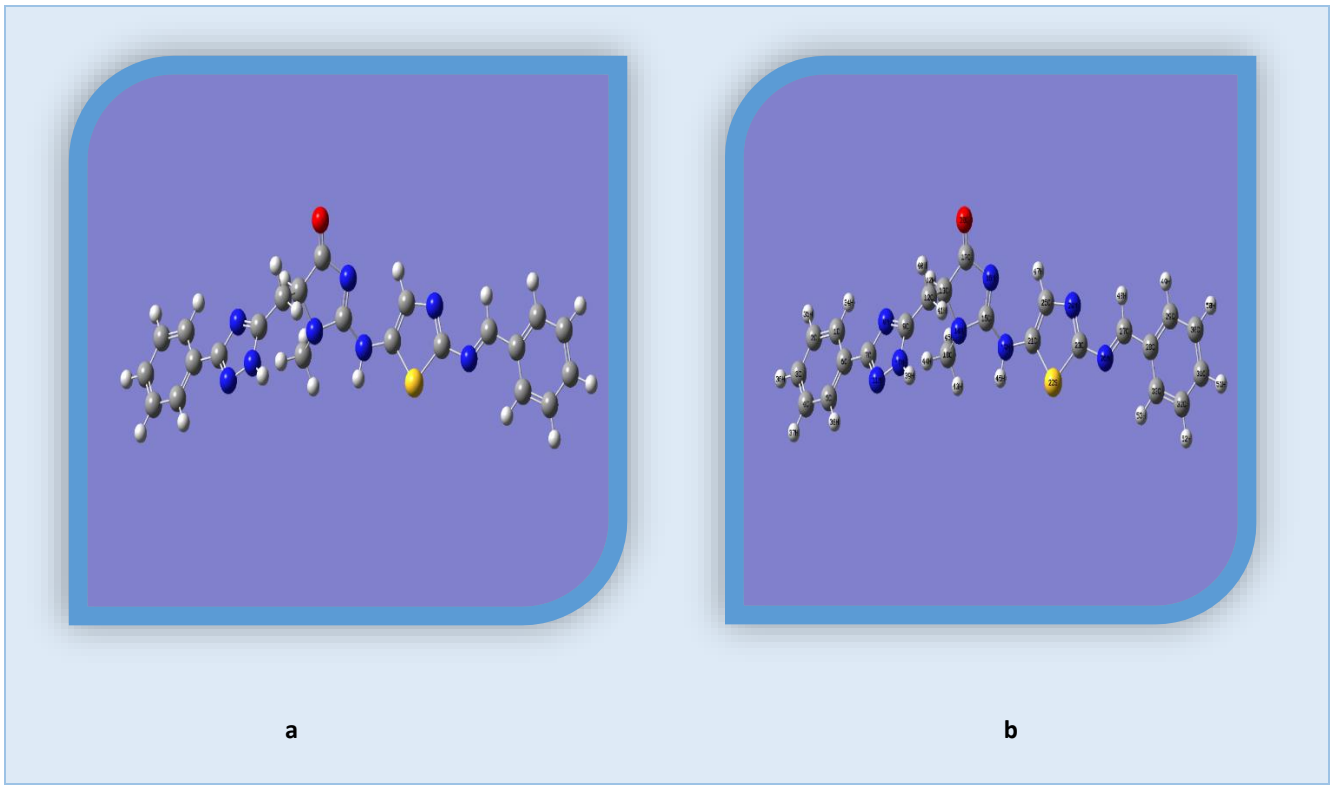


Figure 10. a) The Optimize geometry, b) The numbering Optimize geometry for compound (8)

The result of the calculated optimized structural parameters for compound (8) such as bonds length and bonds angle (A°) were calculating by using semi-empirical (PM3) method. Table 10 and 11 respectively revealed that the results of this work were in good agreement with experimental data.

Atoms	Actual	Optimal
N(26)-Lp	0.6001	0.6000
N(24)-Lp	0.6018	0.6000
N(16)-Lp	0.6006	0.6000
N(11)-Lp	0.6001	0.6000
N(8)-Lp	0.5997	0.6000
C(33)-H(53)	1.1017	1.1000
C(32)-H(52)	1.1022	1.1000
C(27)-H(48)	1.1011	1.1000
C(25)-H(47)	1.0976	1.1000
N(19)-H(46)	1.0504	1.0500
C(18)-H(45)	1.1134	1.1130
C(18)-H(44)	1.1131	1.1130
C(15)-N(16)	1.3305	1.2600
N(14)-C(15)	1.3810	1.4620
N(10)-N(11)	1.3622	1.4260
C(9)-N(10)	1.3381	1.4620
C(4)-C(5)	1.3964	1.4200
C(3)-C(4)	1.3963	1.4200
C(2)-C(3)	1.3961	1.4200
C(1)-C(2)	1.3957	1.4200

Table 10. The calculated bonds length for compound (8)

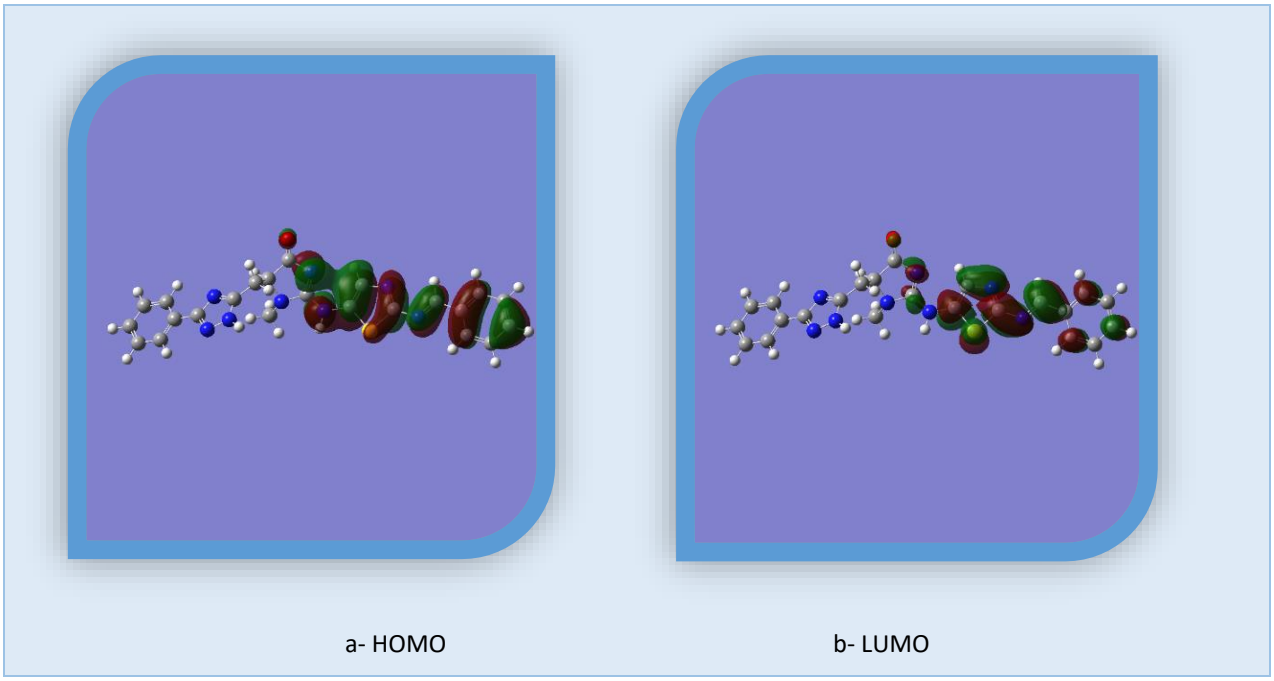
Atoms	Actual	Optimal
H(52)-C(32)-C(33)	119.9647	120.0000
H(52)-C(32)-C(31)	119.8356	120.0000
C(33)-C(32)-C(31)	120.1996	--------
C(32)-C(31)-C(30)	119.7304	--------
C(31)-C(30)-C(29)	120.0986	--------
C(30)-C(29)-C(28)	120.7485	--------
Lp-N(26)-C(27)	119.3656	122.5000
Lp-N(26)-C(23)	118.4185	122.5000
C(27)-N(26)-C(23)	122.2047	115.0000
H(47)-C(25)-N(24)	119.0732	116.5000
N(24)-C(25)-C(21)	115.9450	123.5000
Lp-N(24)-C(25)	124.2271	122.5000
Lp-N(24)-C(23)	124.0951	122.5000
C(4)-C(3)-C(2)	119.6991	--------

H(35)-C(2)-C(3)	119.9474	120.0000
H(35)-C(2)-C(1)	120.0022	120.0000
C(3)-C(2)-C(1)	120.0485	--------
C(6)-C(1)-C(2)	120.7887	--------

Table 11. The calculated bonds angle for compound (8)

Property	PM_3 method
Point group	C_1
Symmetry	A
E_{tot} (kcal/mole)	-110852.7056
E_b (kcal/mole)	-5845.4107
ΔH^o_f (kcal/mole)	157.0582
E_{HOMO} (a.u.)	-0.3317
E_{LOMO} (a.u.)	-0.0524
$\Delta E_{HOMO-LUMO}$(a.u.)	0.2793
μ (debye)	4.0454

Table 12. Some energies and physical properties for compound (8)



a- HOMO b- LUMO

Figure 11. The calculated a- HOMO, b- LUMO for the compound (8)

The following figures 12 electron distribution governs the electrostatic potential of the molecules. The electrostatic potential (E.P) describes the interaction of energy of the molecular system with a positive point

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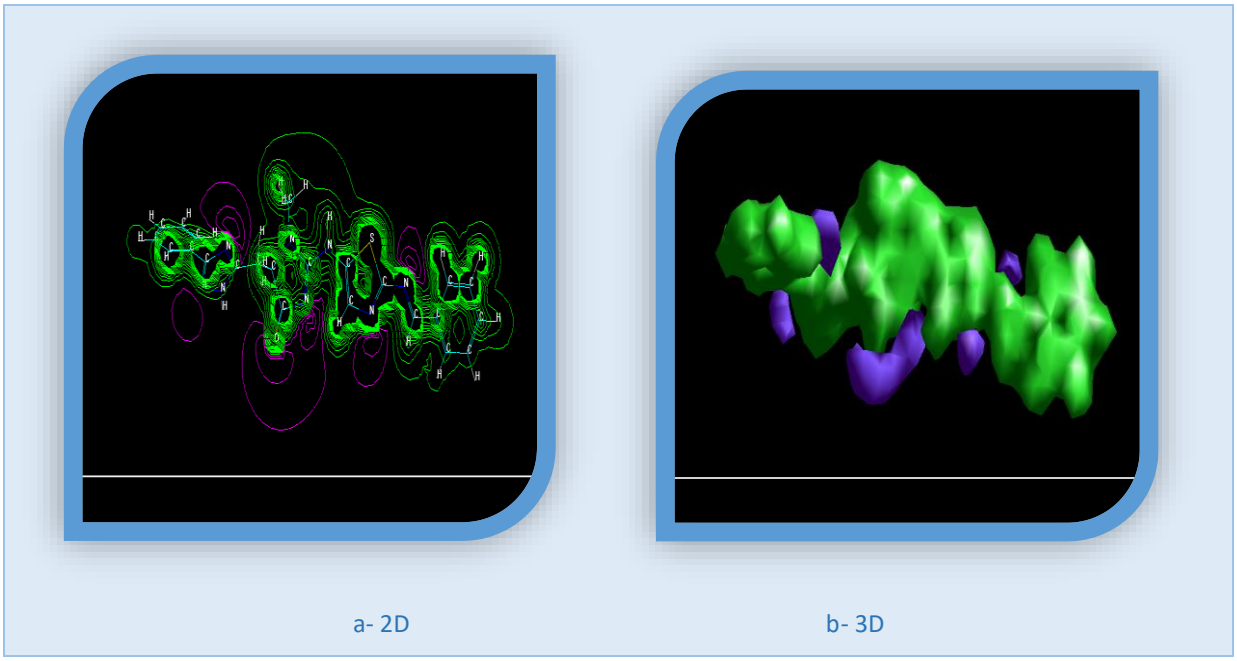
charge. The E.P is useful for finding sites of reaction in a molecule ; positively charged species tends to attack a molecule where the electrostatic potential is strongly negative.[14,15]



a- 2D b- 3D

Figure 12. The calculated electrostatic potential a- 2D , b- 3D for compound (8)

Partial atomic charge of compound (8)

The calculated partial atomic charge using the PM_3 method for individual atoms were illustrated in figure 13 The PM3 method give more reasonable value, showing that the O, N, S atoms have negative partial charge and positive in C atoms, figure 13 Since the O, N, S atom have more electronegativity than C atom.

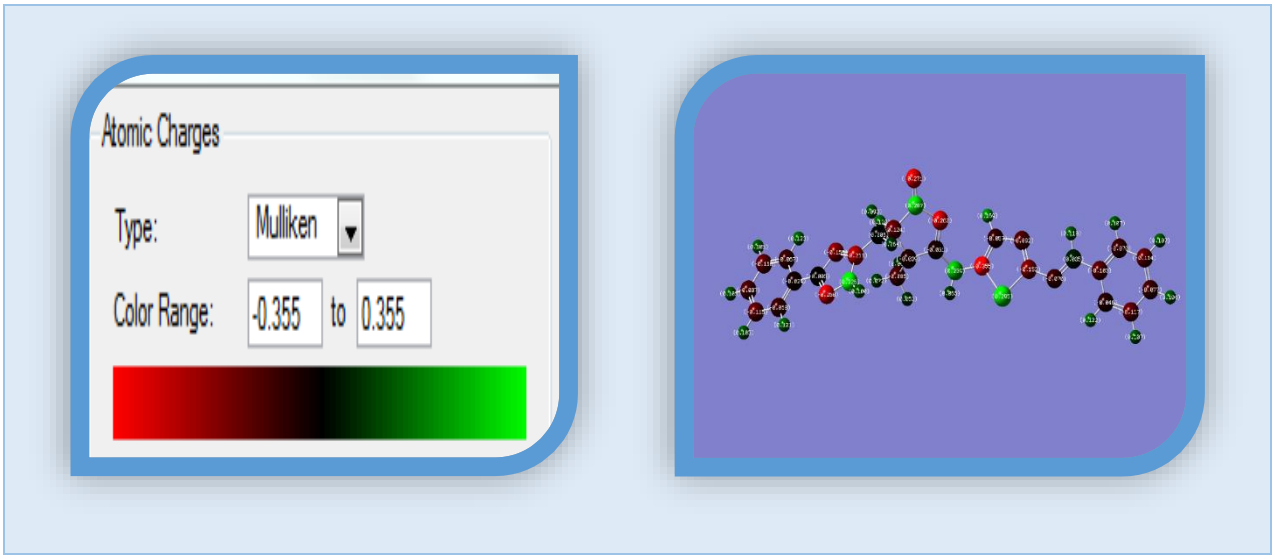


Figure 13. The partial atomic charges for compound (8)

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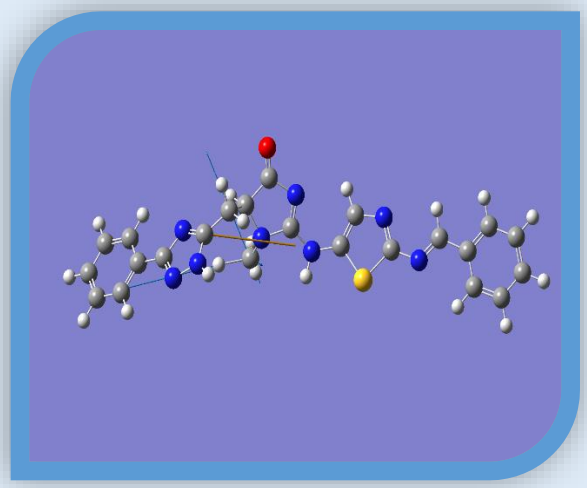
The vibrational spectra of compound (8)

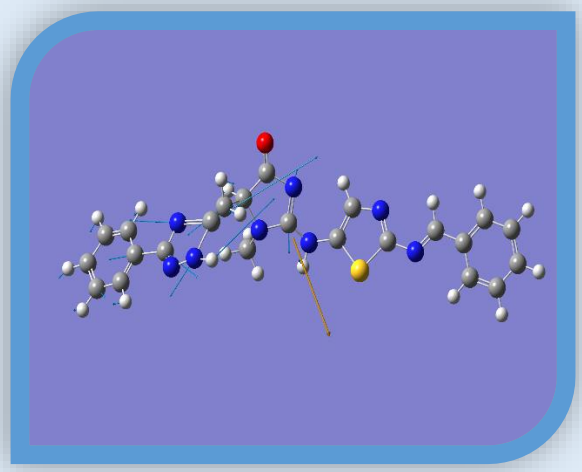
Compound (8) belongs to (C_1) point group and symmetry (A), The Table are shown below revealed that the theoretical data of this work were in good agreement with experimental data, calculating by using semi-empirical method (PM3).

Description	Theoretical		Experimental
	Frequency cm^{-1}	Intensity Km/mole	Frequency
NH str.(Triazole ring)	3350	15.55	3352
C=N str.	1610	12.31	1608
C-H str. (aromat.)	3071	36.76	3072
C-H str. (aliph.)	2934	7.53	2933

Table 13. PM_3 vibration frequencies and IR absorption intensities for compound (8)



C-H (aliphatic) stretching vibration 2934 cm^{-1}



C=N stretching vibration 1611 cm^{-1}

Figure 14. Some Modes of vibration frequencies compound (8)

The NMR spectra of compound (8)

The Tables are shown below revealed that the theoretical data were in good agreement with experimental data, calculating by using DFT and B_3LYP methods (3-21G).

Description	Chemical shift ppm	
	Experimental	Theoretical
C2	125.32	125.19
C4	126.82	127.22
C11	179.81	178.55
C18	130.02	129.88

Table 14. DFT and B3LYP (3-21 G) ^{13}CNMR for compound (8)

Description	Chemical shift ppm	
	Experimental	Theoretical
1H of $-CH_2$ group	1.11	1.08
1H of =CH	4.36	4.85
3H of -N-CH_3	2.91	3.01
1H of -NH in triazole ring	8.35	8.44

Table 15. DFT and B3LYP (3-21 G) ^{1}HNMR for compound (8)

CONCLUSION

Creatinine derivatives were synthesized and structually characterized by using spectroscopic techniques. The Synthetic route started from reaction creatinine chloroacetylchloride with thiourea to give compound(1), then compound (1) converted to compounds (2-3) by the reaction it with benzaldehyde and *m*-nitrobenzaldehyde respectively to give compounds (2-3). Esterification of compounds (2-3) with α-chloroethylacetate to give compounds (4-5). Hydrazide derivatives were synthesized by the reaction compounds (4-5) with hydrazine hydrate to give compounds (6-7). The compounds (6-7) reacts with benzonitrile and acetonitrile respectively to give compounds (8-9). The biochemical studies revealed that the creatinine derivatives caused activatory effects on GOT and GPT enzymes activities. Finally, we we worked theoretical study For the purpose of comparison with the experimental results.

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