Studying The Effects Of Some Oxadiazole Derivatives On Transaminases Activities in Serum and Tissue Homogenate of Hepatocellular Cancer Patients

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Abstract

This study conducted to evaluate the effect of some oxadiazole derivatives 1-(4-ethoxy benzylidene amino)-4-(2-n- butyl thio-1,3,4-oxadiazole-5yl) benzene[I] and 1-(4-pentoxy benzylidene amino)-4-(2-n- butyl thio-1,3,4-oxadiazole-5yl) benzene[II], on the activities of alanine transaminase (ALT) and aspartate transaminase (AST) in serum and tissue's homogenate of hepatocellular cancer patients (HCC).

The results revealed that compound I and compound II showed activation effect on ALT enzyme in serum of HCC patients, while they were competitive inhibitors on ALT enzyme in the tissue's homogenate of the same patients with Vmax values (105.26)U/L and (102.04)U/L respectively, and Km values (38.76 and 100)mmol/L and (38.46 and 105.26)mmol/L for compounds I and II for uninhibited and inhibited enzyme respectively.

The effect of compound I on SAST enzyme was found to be noncompetitive inhibitor with Vmax values (142.86 and 105.26)U/L for uninhibited and inhibited enzyme and Km value (33.33)mmol/L, while it showed activitory effect on the same enzyme in tissue's homogenate of HCC patients.

Compound II was found to be competitive inhibitor on SAST enzyme with Vmax value (121.95)U/L and Km values (66.67 and 125)mmol/L for uninhibited and inhibited enzyme, and it was noncompetitive inhibitor on AST in tissue's homogenate of HCC patients with Vmax values (138.9 and 105.26)U/L for uninhibited and inhibited enzyme and Km value (33.9)mmol/L.

In conclusion oxadiazole derivatives I and II showed inhibitory and activatory effects on ALP and AST enzymes in serum and tissue's homogenate of HCC patients.

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Key words; transaminases enzymes , hepatocellular cancer, liver cancer oxadiazole derivatives , alanine transaminase (ALT) ,aspartate transaminase (AST)

Introduction

Cancer is a genetic disease resulting in the abnormal proliferation of a clone of cells. Carcinogenesis is recognized as multistep process in which a series genetic alterations within a cell and through processes of promotion and progressing leads to malignancy. [1]

Liver cancer (hepatocellular cancer HCC) is one of the most common malignancies worldwide. There is extensive evidence that chronic infection with hepatitis B and hepatitis C virus plays a role in the etiology of HCC. [2]

The presenting symptoms relate to the effects of hepatomegaly and ascites includes pain, anorexia, weight loss, malaise, occasionally abnormal mass and rarely jaundice. Associated paraneoplastic syndromes and laboratory tests include abnormal hepatic enzymes present in approximately 75% of symptomatic cases of HCC. [3]

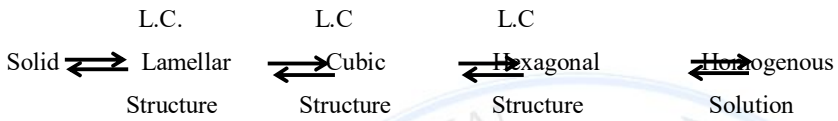
Transaminases or aminotranseferases enzymes are catalyze the transamination reactions which are very important in amino acid metabolism which include serum glutamate oxaloacetate transaminase (AST) and serum glutamate pyruvate transaminase (ALT). Both enzymes are useful as diagnostic enzymes in liver function test. [4]

Oxadiazole compounds have been of special interest mainly due to large number of uses in divers area i.e. drug synthesis, scintillation material and the dye stuffs industry. [5]

Many of 1,3,4-oxadiazole derivatives have been reported to possess diverse biological activities, a number of them used as antibiotics which are commerically used in medicine[6].

The oxadiazole derivatives under investigation are among liquid crystal compounds which is a state of order between crystals and liquid. Liquid crystals possess properties that are not found in liquids and solids, they can be classified into two main categorries, thermotropic liquid crystals and lyotropic liquid crystals. Thermotropic liquid crystal occurs when raising the temperature of a solid and/or lowering the temperature of a liquid. The

lyotropic liquid crystal is a type of liquid crystal results from changes in concetration of solution, when the concentration increase, a transition from a non-ordered to an ordered solution can take plase, and it have many phases result by changing the solusion concentration. [7] [8]



In 1970s, researches showed that liquid crystals have been detected in diseases. Once the knowledge of the role of liquid crystals in diseases is expanded, it should be able to treat certain diseases by simple chemical methods. Diseases evidently alter the liquid crystalline structures in cells, tissues, and organelles. Many biochemical studies related to disease have ignored the fact that the reaction is taking place in a liquid crystalline environment and not only in water. Once the functioning of liquid crystals as solvents for biological reactions was accepted, and some important steps forward was made in understanding certain diseases. [9]

The aim of the present study is to evaluate the effect of 1,3,5-oxadiazole derivatives on the activities of AST and ALT in serum and tissue's homogenate of HCC patients and to determine the type of inhibition of these compounds.

Patients and methods

Patients

Ten patients, their ages ranged from (45-71)year, suffering from HCC were included in this study. The ten patients were admitted for treatment at Baghdad Teaching Hospital, they were selected according to the investigation of histopathologist. The surgical operation was carried out under the supervision of surgeons.

Preparation of Blood Samples

Five milliliters of venous blood were drawn from the patient by vein puncture just before surgery, left to clot, and then centrifuged at 4000 r.p.m. for 10 min. Serum was separated and stored at -20˚C until time of analysis.

Collection of Specimens

The tumor tissue was surgically removed from the patient. The specimen was immediately kept in normal saline solution and stored at -20˚C until the time of homogenizing process.

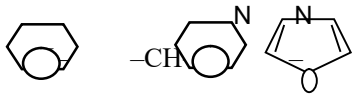
Homogenization of Tumor Tissues

The frozen tissue was sliced finely scalped in petridish standing on ice, and then homogenized with three fold volumes of phosphate buffer pH 7.4 by the homogenizer.

The homogenate was filtered through nylon gauze to eliminate fiber connective tissues. The filtrate was centrifuged at 4000 r.p.m for 30 min at 4˚C in order to precipitate the remaining intact cells and the intact nucleus. The supernatant and precipitate fraction were separated and frozen at -20˚C until use. The supernatant was used to evaluated the enzyme activity.

Preparation of oxadiazole derivatives 1-(4-alkoxy benzylidene amino)-4-(2-n butyl thio-1,3,4-oxadiazole-5yl) benzene

The principle of preparation of these compounds started by the reaction of p-amino benzoic acid with acidic ethanol to get the ethyl-4-amino benzoate, which was refluxed with hydrazine hydrate for two hours in 95% ethanol to get the corresponding hydrazide. The next step is getting the 1,3,4-oxadiazole ring by closing the ring with carbon disulfide. Two shiff bases [I] and [II] were prepared by adding 4-x-benzaldehyde to 2-n butyl thio-5-(4-amino phenyl)-1,3,4-oxadiazole in precens of glacial acetic acid with reflux for 3 hours. The synthesized compoumds were purified by recrystallization with absolute ethanol and characterized by IR, NMR, CHN and hot stage microscope. [10]



where X= $-OC_2H_5$[I] ,

X= $-OC_5H_{11}$[II]

These oxadiazole derivatives were evaluated for their effects on the reaction catalyzed by ALT and AST enzymes in sera and tissues' homogenate of HCC patients.

Determination of ALT and AST activities

Colorimetric method for determination of ALT and AST activities in serum and tissue's homogenate of patients with HCC was utilized by a ready kit form Randox[11], England as follows:

L-alanine + α-ketoglutarate ⟶ pyruvate + L-glutamate

L-aspartate + α-ketoglutarate ⟶ oxaloacetate + L-glutamate

Preparation of different concentrations of compounds I and II were made from a stock solution 10^{-2} M, five different dilutions 10^{-3} M, 10^{-4} M,10^{-5} M,10^{-6} M and 10^{-7} M from compounds I and II were prepared by dilution with absolute ethanol.

Determination of Km and Vmax for ALT and AST

The activities of ALT and AST were performed using different concentrations of substrate.

Determination of percentage inhibition

The percentage of inhibition or activation was determinde by using different concentrations of compounds I and II, while the concentration of substrate [S] was fixed. The activity of the enzymes without addition of any compound was considered to be 100% and all the results were relative to it.

The inhibitor concentration that gives the highest percentage of inhibition was used throughout the study to obtain the type of inhibition.

Determination of the type of inhibition

Fixed concentrations of compounds I and II were used by utilizing the same concentrations of substrate without using both compounds were performed. The effect of absolute ethanol, which used as diluents, was determined by adding a quantity equivalent to the sample and all steps completed as in the method of determination of ALT and AST activities. It's inhibition effect was determined and substrated from the results before determining the inhibition or activation of the compounds.

Result and Discussion

The Michaels-Menten plot for ALT activity in the serum and tissue's homogenate of HCC patients are shown in figure (1) and figure (2) respectively. The value for V max was equal to 19.25 U/L and Km value was calculated to be 44.0 mmol/L for ALT in serum of HCC patients, while the V max was 83.2 U/L and Km value was 31.5 mmol/L for ALT in tissue homogenate of HCC patients.

The effect of compound I on serum ALT activity in HCC patients is shown in table (1). Compound I was found to be an activator for ALT in the serum of the patients. The percentage of activation did not show correlation with changing of the concentration of the compound.

Table (2) showed the percentage of inhibition of compound I on ALT activity in tissue homogenate of HCC patients. The percentage of inhibition was increased with increasing of compound concentration.

Figure (3) showed the type of inhibition of compound I on ALT activity in tissue's homogenate of HCC patients using Lineweaver-Burk plot. It was found to be a competitive inhibitor with Vmax value (105.26)U/L and Km values (38.67 and 100) mmol/L for the uninhibited and the inhibited enzyme respectively.

Table (3) showed the results of the percentage of activation of compound II on serum of HCC patients. This compound showed activating effect on SALT activity in two concentrations (10^{-5} and 10^{-7}) and it doesn't show any effect in other concentrations.

Table (4) showed the inhibition percentage of compound II on ALT activity in tissue homogenate of HCC patients. The percentage of inhibition was found to be in narrow range varied from (13.70-26.64)% which wasn't proportional to the concentration of the compound.

Figure (4) showed the type of inhibition of compound II on ALT activity in tissue's homogenate of HCC patients using Lineweaver-Burk plot. It was found to be a competitive inhibitor with Vmax value (102.04)U/L and Km values (38.46 and 105.26)mmol/L for the uninhibited and the inhibited enzyme respectively.

Figures (5) and (6) showed Michaels-Menten plots for AST activity in serum and tissue's homogenate of HCC patients. The values for Vmax were 92 U/L and 110 U/L and the values for Km were 36 mmol/L and 25 mmol/L respectively.

Compound I was found to be an inhibitor for SAST activity in HCC patients. The percentage of inhibition is shown in table (5), and it did not show concentration depend.

Figure (7) showed the type of inhibition of compound I on SAST activity in serum of HCC patients using Lineweaver-Burk plot. It was found to be noncompetitive inhibitor with Vmax values (142.86 and 105.26) U/L for uninhibited and inhibited enzyme respectively, and Km value (33.33)mmol/L.

Table (6) showed the activation effect of compound I on AST activity in tissue's homogenate in HCC patients. The percentage of activation did not show concentration depend.

Table (7) showed the percentage of inhibition of compound II on SAST in HCC patients. The percentage of inhibition was not proportional to the concentrations. The type of inhibition is shown in figure (8) using Lineweaver-Burk plot. It was found to be competitive

inhibitor with Vmax value (121.95)U/L and Km values (66.67 and 125)mmol/L for uninhibited and inhibited enzyme respectively.

Table (8) showed the inhibitory effect of compound II on AST in tissue homogenate of HCC patients which was found to be not correlated with concentrations of compound. The inhibitory effect of compound II was shown in figure (9) using Lineweaver-Burk plot compound II was found to be noncompetitive inhibitor with Vmax values (138.9 and 105.26)U/L for uninhibited and inhibited enzyme respectively, and Km value is (33.9)mmol/L.

A study was conducted on the type of inhibition using different substrates for ALT activity showed that when L-alanine used as substrate, aminooxyacetic acid was found to act as competitive inhibitor, however, when 2-oxoglutarate was used as substrate aminooxyacetic acid showed uncompetitive inhibition, the authors suggested that the enzyme is structurally unaltered, but it has significantly higher affinity for the substrate L-alanine and provide evidence for the subtle changes in the enzyme complex formation.[12]

A study conducted to evaluate the inhibitory effect of some organic derivatives of oxadiazole and thaiadiazole compounds on the activity of AST in serum of HCC patients were found to range from 14% to 70% and the type of inhibition was found as that some derivatives of oxadiazole were noncompetitive inhibitors and others were uncompetitive inhibitors. [13]

Some cobate containing compounds were found to be competitive and noncompetitive inhibitors on elevated serum liver enzymes, the inhibitory effect was explained by the blockage of active sites of these enzymes. [14]

A study conducted to evaluate the effect on organic anion transporters (OATs) using novobiocin, from the study it was concluded that novobiocin inhibited (OAT) mediated uptake in a competitive manner. However the study conducted to evaluate the effect of (OATs) were not mediated through a change in transporter protein abundance on the plasma

membrane. Taken togather, the conclude that novobiocin seems to interact with the substrate-binding sites of OATs from both the intercellular and the extracellular sides, and this interaction interferes with substrate-binding site(s) on respective carriers leading to an apparent reduction in carriers available for the substrates. [15]

A study conducted *in vitro* study, have demonstrated a competitive inhibition for adenosine triphosphate from HCC patients which lead the authors to use antagonist of Dasatinib as specific inhibitor which may be an attractive treatment for patients with HCC.[16]

Many studies stated that polyphynolic compounds exert different inhibitory effect on the activity of many enzymes in the rate serum, human serum and human serum albumin solutions. They explained these actions by the high affinity for the binding site of these enzymes to the phenol derivatives. [17] [18]

Since these oxadiazole derivatives 1-(4-ethoxy benzylidene amino)-4-(2-n butyl thio-1,3,4-oxadiazole-5yl) benzene[I] and 1-(4-pentoxy benzylidene amino)-4-(2-n butyl thio-1,3,4-oxadiazole-5yl) benzene[II] were synthesized and no data in literatures concerning their effects on activity of enzymes ALT and AST, however the activation and inhibition effect of them could be explain due to the facts:

1. The variable activitory effect of compounds I and II on ALT and AST in HCC patients could be due to different isoenzymes of them which differ in their effective rates towered these synthesized derivatives, also to the difference in the affinity of such compounds to the active sit of the enzyme, which exert a change in the stereostructure of the active site in the presence of these compounds, or such derivatives showed sito-toxic effect on the enzymes from HCC and other gastric and lung cancer.[19]

2.The inhibitory effect of these compounds for both enzymes ALT and AST could be due to molecular interaction between the atoms N,O and S of oxadiazole moiety with active sites of amino acids $-NH_2$, –OH and –COOH, then the competition of the compounds with the

substrate changes the rate of formation of the enzyme-substrate complex [ES] and their dissociation to products[20].

3. These oxadiazole derivatives act as inhibitors and activators, this effect showed not proportionate with the increase of their concentrations. It is well known that these organic molecules show liquid crystalline properties. Liquid crystallinity arise as a result of temperature variations (heating or cooling), thus the term "thermotropic liquid crystals" is used. Liquid crystals may also result from the change in concentration of solutions this kind called "lyotropic liquid crystals". These almost include in their structure two parts, one polar and the other nonpolar (i.e. surfactant derivativeds).[21] These synthesized oxadiazole compounds in this study have lyotropic liquid crystals proparties thus when the concentration was increased a transition from non ordered solution to an ordered solution can take place and the compound pass through many lyotropic phases; lamellar structure, cubic structure and hexagonal structure lyotropic liquid crystal (figure 10); which have differant molecules order, then the rate of the comounds inhibition or activation effects were changed may be according to the change of their solutions concentrations and the phase of the lyotropic liquid crystals they have at those concentrations which may change the modulation of the affinity of the enzymes towards their substrate by changing the sterostructure of the active site.

Conclusion

From the results of the present study a conclusion could be drawn that oxadiazole derivatives namely 1-(4-ethoxy benzylidene amino)-4-(2-n butyl thio-1,3,4-oxadiazole-5yl) benzene[I] and 1-(4-pentoxy benzylidene amino)-4-(2-n butyl thio-1,3,4-oxadiazole-5yl) benzene[II] showed 1.Different activation effects on the activity of ALT and AST enzymes in the sera and tissues' homogenate of HCC patients due to the effective rate of isoenzymes towards these compounds and their affinity towards the active site of each isoenzyme. 2.Inhibition effects on the activity of ALT and AST enzymes in the sera and tissues' homogenate of HCC patients due to the interaction between N, O and S atoms in oxadiazole

moiety and with active sites of amino acids $-NH_2$, –OH and –COOH. 3. These effects showed not proportionate with the increase of their concentrations due to the lyotropic liquid crystal nature of the compounds under investigation.

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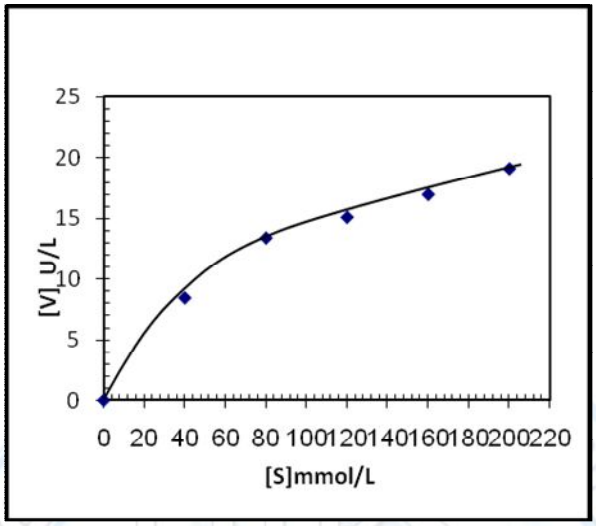

Figure 1. Michaelis-Menten plot for serum ALT of liver cancer patients

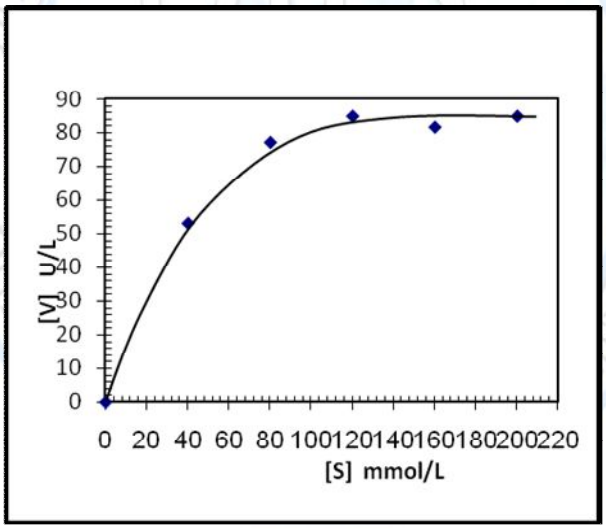

Figure 2. Michaelis-Menten plot for tissue homogenate ALT of liver cancer patients

Concentration of compound I	% Activation
Zero	100
10^{-7}	Zero
10^{-6}	14.48
10^{-5}	4.71
10^{-4}	2.82

Table 1. The Activation percentage of oxadiazole derivative I on SALT activity of HCC patients after ignored the solvent inhibition

Concentration of compound I	% inhibition
Zero	100
10^{-7}	13.01
10^{-6}	13.67
10^{-5}	28.45
10^{-4}	46.74

Table 2. The inhibition percentage of oxadiazole derivative I on tissue homogenate ALT activity of HCC patients after ignored the solvent inhibition

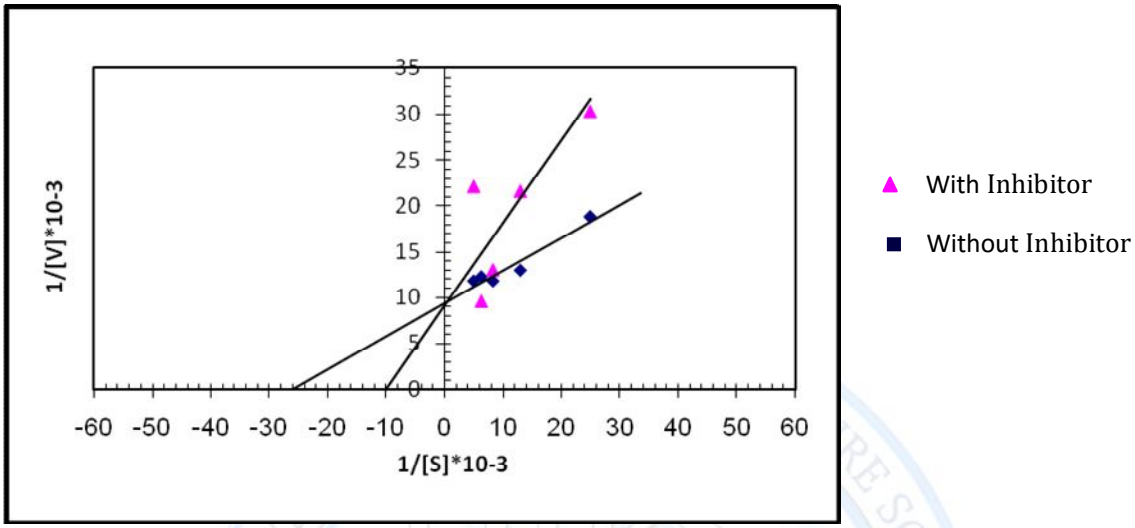

Figure 3• Lineweaver-Burk plot for compound I effect on for tissue homogenate ALT activity of HCC patient

Concentration of compound II	% Activation
Zero	100
10^{-7}	25
10^{-6}	zero
10^{-5}	8.002
10^{-4}	zero

Table 3. The Activation percentage of oxadiazole derivative II on SALT activity of HCC patients after ignored the solvent inhibition

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Concentration of compound II	% inhibition
Zero	100
10^{-7}	22.23
10^{-6}	24.45
10^{-5}	13.7
10^{-4}	26.64

Table 4. The inhibition percentage of oxadiazole derivative II on tissue homogenate ALT activity of HCC patients after ignored the solvent inhibition

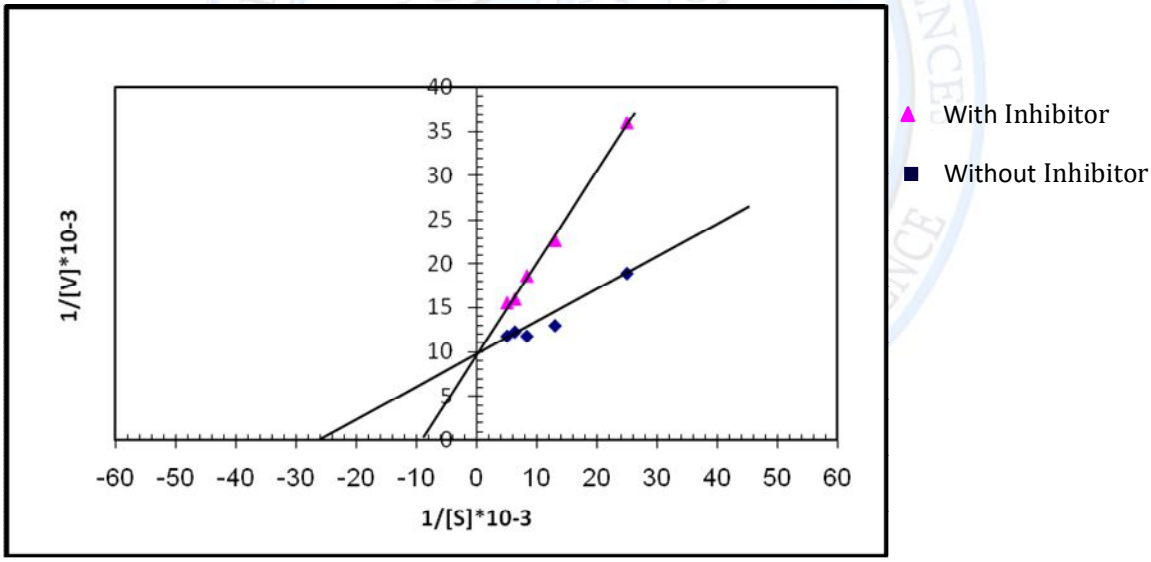

Figure 4• Lineweaver-Burk plot for compound II effect on for tissue homogenate ALT activity of HCC patients

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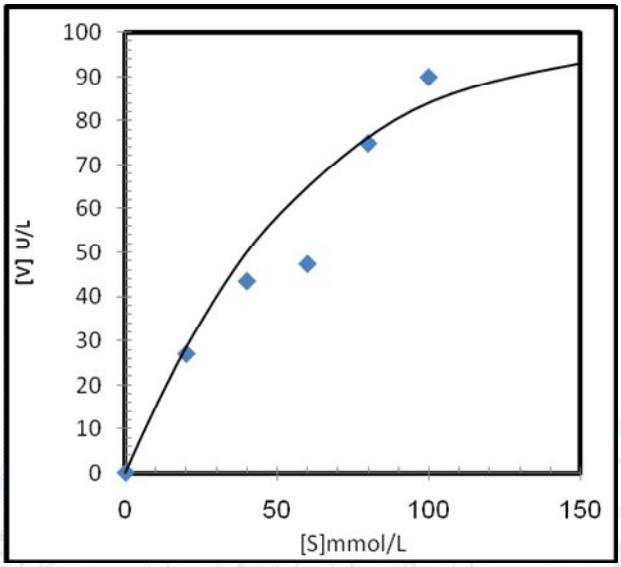

Figure 5. Michaels-Menten plot for serum AST of liver cancer patients

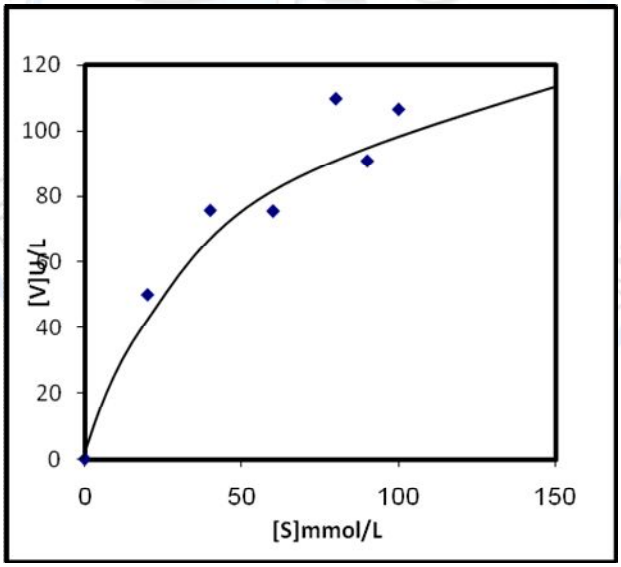

Figure 6. Michaels-Menten plot for tissue homogenate AST of liver cancer patients

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Concentration of compound I [M]	% Inhibition
Zero	100
10^{-7}	69.44
10^{-6}	63.44
10^{-5}	66.3
10^{-4}	58.67

Table 5. The inhibition percentage of oxadiazole derivative I on SAST activity of HCC patients after ignored the solvent inhibition

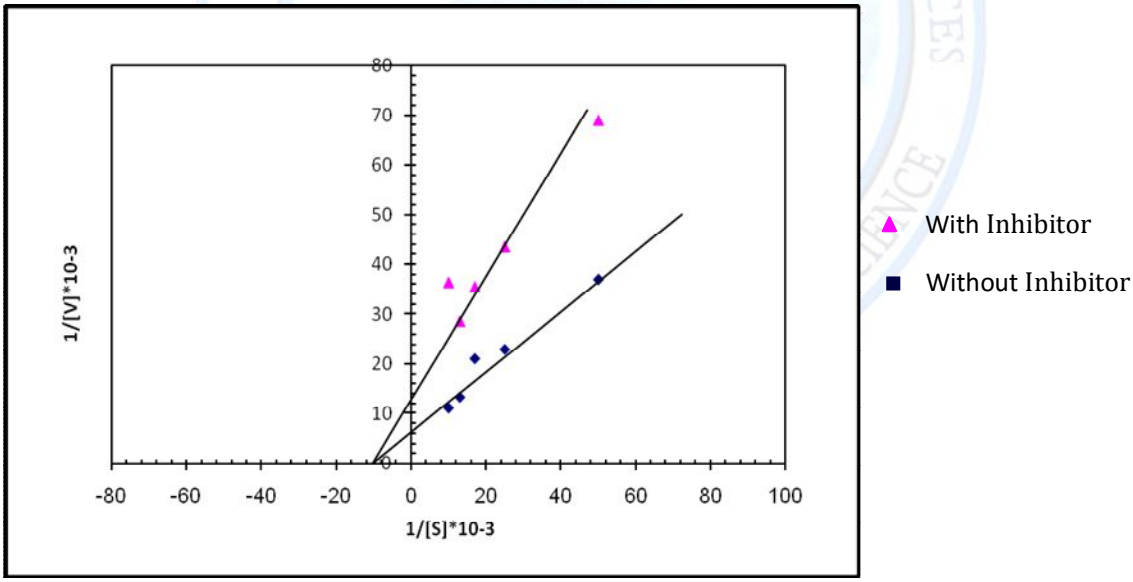

Figure 7• Lineweaver-Burk plot for compound I effect on for SAST activity of HCC patients

Concentration of compound I[M]	% Activation
Zero	100
10^{-7}	6.5
10^{-6}	Zero
10^{-5}	11.24
10^{-4}	2.0

Table 6. The Activation percentage of oxadiazole derivative I on tissue's homogenate AST activity of HCC patients after ignored the solvent inhibition

Concentration of compound I [M]	% Inhibition
Zero	100
10^{-7}	63.22
10^{-6}	61.67
10^{-5}	60.0
10^{-4}	65.0

Table 7. The Inhibition percentage of oxadiazole derivative II on SAST activity of HCC patients after ignored the solvent inhibition

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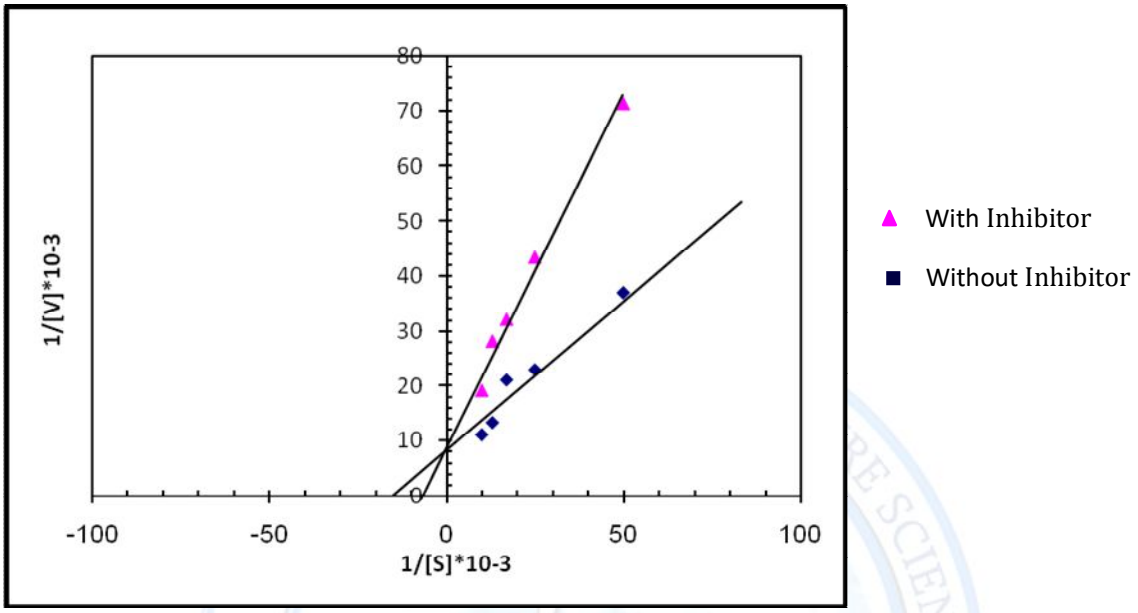

Figure 8• Lineweaver-Burk plot for compound II effect on for SAST activity of HCC patients

Concentration of compound I [M]	% Inhibition
Zero	100
10^{-7}	63.22
10^{-6}	61.67
10^{-5}	60.0
10^{-4}	65.0

Table 8. The Inhibition percentage of oxadiazole derivative II on tissue's homogenate AST activity of HCC patients after ignored the solvent inhibition

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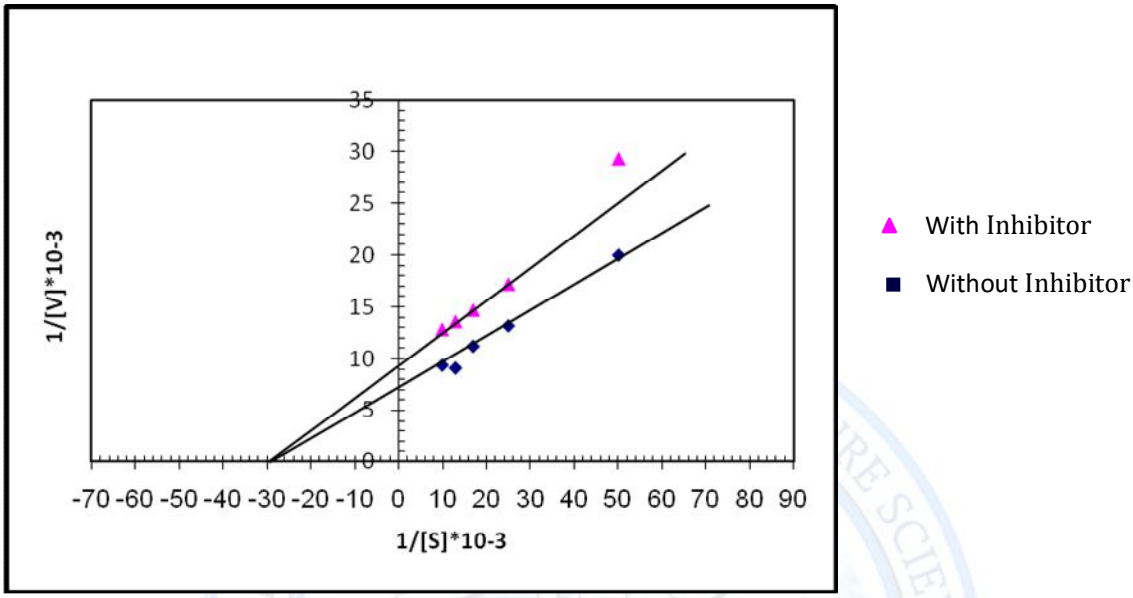
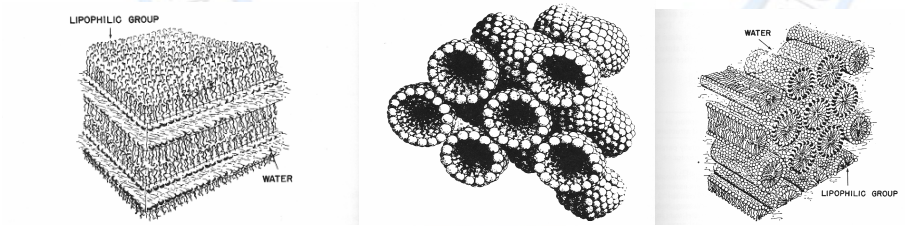


Figure 9• Lineweaver-Burk plot for compound II effect on for tissue's homogenate AST activity of HCC patients



Lamellar Cubic Hexagonal

Figure 10• Types of Lyotropic Liquid Crystals

Studying The Effects Of Some Oxadiazole Derivatives On Transaminases Activities in Serum and Tissue Homogenate of Hepatocellular Cancer Patients

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دراسة تأثيرات بعض مشتقات الاوكساديازول على انزيمات الترانس أمينيز في مصل ونسيج مرضى مصابين بسرطان الكبد

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تم في هذا البحث دراسة تأثير بعض مشتقات الاوكساديازل 1-(4-ايثوكسي بنزلدن أمينو)-4-(2-ن-بيوتيل ثايو-4,3,1-اوكساديازول -5-يل) بنزين [I] و1-(4-بنتوكسي بنزلدن أمينو)-4-(2-ن-بيوتيل ثايو-4,3,1-اوكساديازول -5-يل) بنزين [II], على فعالية انزيمي الالنين ترانس أمينيز ALT وأسبارتيت ترانس أمينيز AST في مصل ومجانس نسيج مرضى سرطان الكبد.

وقد أشارت النتائج بان المركب I والمركب II أظهرا تأثيرا منشطا على انزيمALT في أمصال مرضى سرطان الكبد, في حين أظهرا تثبيطا تنافسيا على أنزيم ALT في مجانس نسيج نفس المرضى وكانت قيم Vmax U/L(105.26) وU/L(102.04) وقيم Km mmol/L(100, 38.76) و mmol/L(105.26 ,38.46) للانزيم غير المثبط والمثبط للمركبين Iو II بالتعاقب.

وقد وجد تأثير المركب I على انزيم SAST فكان مثبط لاتنافسي مع قيم Vmax U/L(105.26, 142.86) للانزيم غير المثبط والمثبط بالتعاقب وقيمة Km mmol/L(33.33) في حين أظهر تأثيرا منشطا على نفس الانزيم في مجانس مرضى سرطان الكبد.

وقد وجد ان المركب II كان مثبطا تنافسيا على أنزيم SAST مع قيمة Vmax U/L(121.95) وقيم Km mmol/L(125, 66.67) للانزيم غير المثبط والمثبط بالتعاقب, في حين أظهر نفسه تثبيطا لاتنافسيا على أنزيم AST في مجانس نسيج سرطان الكبد مع قيم Vmax U/L(105.26, 138.9) للانزيم غير المثبط والمثبط بالتعاقب, وقيمة Km mmol/L(33.9).

نستنتج من ذلك ان مشتقي الاوكساديازول I وII أظهروا تأثيرات مختلفة مثبطة ومنشطة على انزيمي ALT وAST في مصل ومجانس نسيج مرضى سرطان الكبد.

الكلمات المفتاحية: انزيمات الترانس امينيز , سرطان الكبد ,مشتقات الاوكساديازول , الانلين ترانس امينيز , الاسبارتيت ترانز امينيز