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# Synthesis of Novel Acetylinc Derivative of Metformin as a DPP-4 Inhibitors and Study its Effects on Sera of Rabbits with induced Diabetes

Firas Shawki Abdul Razzak * Zeinab M. Al-Rubaei ** Yusra Abdul-Ghafoor Mohammed*
*Chemistry Department, College of Education for pure science/ Tikrit University
**Chemistry Department, College of Education, (Ibn-Al-Haitham) for pure Science/Baghdad University

**Abstract:**

The study aimed to prepare novel derivative of metformin similar to the work of the enzyme inhibitors DPP-4 and so the need for new inhibitors may be a side effect with less addition to linking types of drugs have a stronger effect on patients with diabetes and to study the impact of this derivative inside the living cell has been prepared derived through interaction metformin with propargyl chloride. It was to make sure the chemical structure by using analytical and spectral methods (FT-IR, $^{1}$H-NMR, and $^{13}$C-NMR), and the results confirming the obtained structures, then purified by column chromatography by using silica gel as stationary phase and methanol as a mobile phase. The study is derived on the impact of rabbits where they were taking the 40 rabbits with similar weights and were divided into four groups (10 rabbits per group) weredivided as follows, the first group G1 obtained as a control group, which did not gave any things. The second group G2 has injected by aloxane a concentration of 120 mg / kg using syringes medical capacity of 3 ml to inject rabbits in the vein ear and after two hours of injection they were given glucose solution of 10%, the confirmed they injured rabbits diabetes by measuring blood sugar to 10 rabbits have been selected randomly and then it was taken two sets of this group, the third group G3 were given a drug sitagliptin with concentration of 10 mg / kg, and the fourth group G4, were given the prepared derivative with concentration of 8 mg / kg for 3 days and pulled blood samples after the last dose on the third day. Serum used in determination of lipid profile,DPP-4 activity,alanine transaminase(ALT),Aspartate transaminase(AST) and insulin. Results of statistical analysis showed a significant decrease in the level of FBG and DPP-4 activity of the prepared derivative, and also showed a decrease in the level of cholesterol, triglyceride, LDL and VLDL, while results showed increase in HDL level in G4 comparing to G1.

**Keywords** : Diabetes Mellitus , Dipeptidylpeptidase -4 , metformin .

## Introduction

Diabetes is a major global disease that around 382 million people of the world's population have diabetes mellitus in 2013 and by 2035, this will rise to 592 million[1]. Therapies targeting the incretin system are important for management of type 2 diabetes. Two principal incretin hormones—glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP)—are rapidly released after meals. Both hormones augment glucose dependent insulin secretion; and GLP-1, but not GIP, also suppresses glucagon secretion, delays gastric emptying, and decreases food intake. GLP-1 and GIP are inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4)[2]. Incretin-based therapies consist of two drug classes: GLP-1 receptor agonists, which have biological activity similar to GLP-1, but are resistant to DPP-4; and DPP-4 inhibitors, which prevent enzymatic inactivation of endogenous GLP-1 and GIP[3].

The dipeptidyl peptidase (DPP)-4 inhibitors are a new class of anti hyperglycaemic agents which were developed for the treatment of type 2 diabetes by rational drug design, based on an understanding of the underlying mechanism of action and knowledge of the structure of the target enzyme[4]. As a therapeutic class, the DPP-4 inhibitors comprise a diverse group of compounds, which can be broadly divided into those that mimic the dipeptide structure of DPP-4 substrates and those which are non-peptido mimetic compounds such as sitagliptin (β-amino acid based)[5]. The DPP-4 enzyme has two binding pockets/sites (S1, and S2). The S1 pocket consists of catalytic triad (Ser630, Asn710 and His740) and the S2 pocket involves key interactions with Glu205 and Glu206 dyad and Arg125. Later is a larger cavity surrounded by residues of Val207, Ser209, Arg358 and Phe357 which makes S2 extensive subsite[6]

## Materials and Methods

### 1-Organic part:

### Preparation of metformin derivative[7]

In a round bottomed flask(5gm, 0.03 mole) metformin and (1.2 gm, 0.03 mole)sodium hydroxide in (150 mL) methanol were added, stirred for 10 minutes, then 2.1 mL of propargyl chloride in 21 mL methanol was added to

the mixture drop wise, refluxed for 24 hours. The solvent evaporated under reduced pressure to result (6.2 gm, 93.32%). The resulting purified by a column chromatography length of 70 cm and diameter of 2.5 cm, packing by silica gel (35-70) as a stationary phase and methanol as a mobile phase, the spot was followed by TLC.

**2-Biochemistry part**

In this study, 40 rabbits has been obtained and divided in to four groups, (G1) control group, (G2) rabbits with diabetic induced by 120mg/Kg alloxane, (G3) rabbits with diabetic that adminstrated 10mg/Kg sitagliptin drug for 3 days and (G4) rabbits with diabetic that adminstrated 8mg/Kg of the prepared derivative for 3 days. Ten milliliters of fasting blood were collected from all subjects. The serum obtained used in determination of Dipeptidyl peptidase-4(DPP-4) by ELISA, (US Biological Kit/ USA), depending on the competitive with antibodies of DPP-4 on wells of the plate and antibodies at horseradish peroxidase to linked with the DPP-4 antigen in blood serum[8], fasting blood glucose(FBG)[9], Insulin by determined TOSOH instrument with special kit[10], alanine transaminase(ALT), Aspartate transaminase(AST)[11,12] and lipid profile(total cholesterol (Ch)[13], triglyceride(TG)[14],high density lipoprotein(HDL)[15],determined according to the standard procedures of the biochemistry laboratory of the hospital.and (VLDL-Ch),(LDL) concentrations were described by the following equations.[16]

:

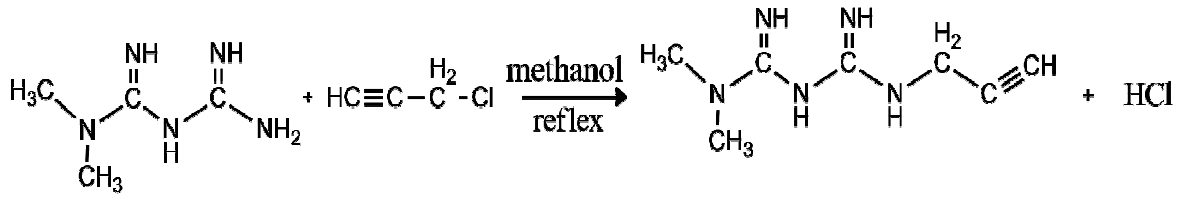
**VLDL-CH(mg/dL) = Triglyceride / 5**

**LDL-Ch(mg/dL) = Total cholesterol-(HDL-Ch + VLDL-Ch)**

**Results and Discussion:**

**1-Organic part:**

The synthesis of acetylinc derivative of metformen has been obtained by the reflux of metformine with propargyl chloride in methanol according to the reaction below:




The derivative was purified by a column chromatography(silica gel as stationary phase and methanol as a mobile phase) and follow up by TLC. The characterization of the acetylinc derivative was accomplished by measuring spectral data, FT-IR which showed the presence of the absorbance band at 3178 $cm^{-1}$ for H acetylinic, and at 2191 $cm^{-1}$ for acetylinc group, while the results of $^{1}$HNMR and $^{13}$C-NMR showed by the following table:

**Table(1): $^{1}$HNMR and $^{13}$CNMR of metformin derivative**

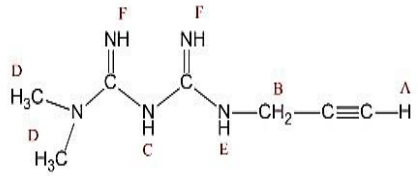
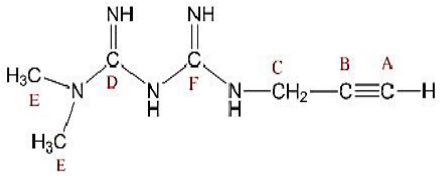
| $^{1}$HNMR | | $^{13}$CNMR | |
|---|---|---|---|
|  | |  | |
| **A** | **66.10 – 73.20** | **A** | **2.65 – 2.70** |
| **B** | **80.10 – 82.01** | **B** | **3.20 – 3.66** |
| **C** | **33.30 – 36.09** | **C** | **5.00 – 5.02** |
| **D** | **160.01 – 166.09** | **D** | **2.83 – 2.97** |
| **E** | **37.80 – 38.60** | **E** | **4.70 – 4.74** |
| **F** | **172.16 – 173.01** | **F** | **5.00 – 5.02** |

Figure (1,2 and 3) showsFTIR, $^{1}$H-NMR and $^{13}$CNMR spectrum for the metformin derivative respectively.

**2-Biochemistry part**

The results of DPP-4 at table (2), and figure(4) showed significant decrease in the concentration of enzyme inG3and G4 compared with the G2, and the values were 55.32± 26.96, 31.64±12.65 and 137.65±30.90 Pg/mL respectively.Significant decrease found in G3 compared with G4, , Results also showed a significant decrease in the FBG level in G3 and G4 compared with the G2, and the values were 150.70± 11.96, 124.30± 25.88 and 214.90± 27.67 mg/ dl respectively, which means that the effect of the prepared derivative record the strongest inhibitory effect than sitagliptin , Results showed a significant decrease in the insulin level in of G3 and G4 compared with the G2, and the values were 9.48±1.48, 8.67±1.70 and 13.07±1.67 µU/mL respectively. The DPP-4 inhibition with sitagliptin improved the expression of GLP-1 and GLP-1R in pancreas. Since, GLP-1R stimulate the adenylyl cyclase pathway, and increase the insulin synthesis in langerhans islet[17][18], so sitagliptin can restore damaged pancreas[19]. The change in all hormones with respect to expression and blood glucose level indicate that sitagliptin may cause the regulation of hyperglycemia in type-2 diabetes[20].

All these results confirm the novel ability of the prepared derivative in treating the hyperglycemic, and its results similar to the results of sitagliptin which mean that may be have similar properties.

Figure(5) show the proposed designing model of the combination between the prepared derivative and the active site of DPP-4.

The results of table(3), and figure(6) shows inhibitory effect in G3 and G4 comparing with the injury group G2 in the liver enzymes AST and ALT, and the values were 52.500± 8.50, 50.700±12.18 and 76.700± 16.36 U/L for AST, 43.100± 8.87, 44.600±12.20 and 77.700±15.46 U/L for ALT respectively.

Table (4), and figure(7) illustrates the comparing between the divided groups on lipid profile, data that indicate a significant decreases in the levels of cholesterol and triglyceride in G3 and G4 comparing with G2, and the values were 144.08±18.78, 152.34±25.11 and 255.25±18.28 mg/dL for Ch, 154.70±30.38, 158.08±52.11 and 299.92±28.73 for TG respectively. Furthermore, table (4) showed a significant increased in HDL-Ch in G3 and G4 comparing with G2, and the values were 31.20±3.61, 33.50±4.62 and 27.80±2.29 mg\dL respectively, and a significant decreases in LDL-Ch and VLDL-Ch between G3 and G4 comparing with G2, and the values were 84.64±19.10, 88.05±20.22 and 136.66±20.8 mg/dL for LDL-Ch, and 30.94±6.07, 31.60±10.06 and 61.98±5.82 mg/dL respectively.

The level of free fatty acids in blood serum increase because of the low levels of glucose in diabetic patients,so the free fatty acids are catabolized In liver to result acetyl CoA, the excess of acetyl CoA is convert to cholesterol, triglyceride and ketone bodies and other lipoproteins like LDL and VLDL. The abnormally high

concentration of serum lipoprotein in the diabetic patients may also be due to the increase in the mobilization of free fatty acids from the peripheral fat depots by glucagon in the absence of insulin [21].

Tables (5,6,7 and 8) shows Correlations between biochemical parameters for G1, G2, G3 and G4 respectively.

## Conclusions

Adding acetylinic terminal to metformin gives good results in lowering level of sugar. The prepared derivative reduce the concentration of DPP-4 more than sitagliptin at the same dose. The glucose level reduced to normal value when the rabbits with diabetic treated with the prepared derivative. The level of insulin back to the normal level when rabbits treated with the prepared derivative. Cholesterol, triglyceride and LDL-Ch beck to the normal value when treated with the prepared derivative.

## References

**1.** International Diabetes Federation Diabetes Atlas, 6th ed., (2013), The Global Burden: 29-50.
**2.** Nauck MA., (2009) Unraveling the science of incretin biology., Am. J. Med., 122: S3–10.
**3.** Drucker DJ, Nauck MA. , (2006), The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes., Lancet, 368: 1696–705.
**4.** Deacon C.F., (2011), Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review, Diabetes, Obesity and Metabolism,13: 7–18.
**5.**Vincent S., Reed J., Bergman A. et al., (2007) Metabolism and excretion of the dipeptidyl peptidase 4 inhibitor [14C]sitagliptin in humans., Drug Metab. Dispos., 35: 533–538.
**6**. Bhumika D. and Manjunath D., (2014), Recent approaches to medicinal chemistry and therapeutic potential of dipeptidyl peptidase-4 (DPP-4) inhibitors, Journal of Medicinal Chemistry,74:574-605
**7.**A. Sharba, R. Al-Bayati, N. Rezki and M. Aouad, (2005), Synthesis of Thiadiazoles and 1,2,4-Triazoles Derived from Cyclopropane Dicarboxylic Acid, Molecules, 10(9), 1153-1160
**8.**Dipeptidyl peptidase IV (DPP4) BioAssay™ ELISA Kit (Rabbit), United State Biological. P. O. Box 261.
**9.** Trinder P (1969). Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6: 24-25.
**10.** TOSOH Bioscience AIA-PACK Test Cups - IRI (Insulin) Kit, Inc., South San Francisco.
**11.** Approved recommendations, (1986), on IFCC methods for the Measurement of Catalytic Concentration of Enzyme.Part 2: IFCC Method for Aspartate Aminotransferase (EC 2.6.1.1), J. Clin. Chem. Clin. Biochem., 24:497-510.
**12.** Approved recommendations, (1986), on IFCC methods for the Measurement of Catalytic Concentration of Enzyme.Part 3: IFCC Method for Alanine Aminotransferase (EC 2.6.1.2). J. Clin. Chem. Clin. Biochem., 24:481-510.
**13.** Richmond W. Proceeding, (1974), The development of an Enzymatic technique for the assay at cholesterol in biological fluids. Clin, Sci, Mol, Med., 46(1):6-7.
**14.** Fossati P.,Prencipe L.,(1982), Measurement of serum triglyceride calorimetrically with an enzyme that produce $H_2O_2$, Clin. Chem., 28(10):2077-2088.
**15.** Buristein M.;Osbar A.,Laki K.,&Jensen JS., (1970) ,Rapid method for the isolation of lipoproteins from human serum by precipitation poly anions. Lipid Res.,11:583-595.
**16.** Friedewald WT., Levy RL., & Fredickson DS., (1972), Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of ultracentrifuge. Clin. Chem., 18:499-502
**17.** Bhumika D.Patel , Manjunath D . Ghate, (2014) **,**Recent approaches to medicinal chemistry and therapeutic potential of dipeptidyl peptidase-4 (DPP-4) inhibitors, Europ. J. Med. Chem., 74 574-605.
**18.** Varga T, Somogyi A, Barna G, Wichmann B, Nagy G, Racz K, Selmeci L,Firneisz G., (2012), Higher serum DPP-4 enzyme activity and decreased lymphocyte CD26 expression in type 2 diabetes. Pathol Oncol Res.,17(4):925-930.
**19.** Watanabe T, Nishimura K, Hosaka YZ, Shimosato T, Yonekura S, Suzuki D, et al., (2014), Histological analysis of glucagon-like peptide-1 receptor expression in chicken pancreas. Cell Tissue Res, 351(1):55–61.
**20.** Sezin Karabulut , Zeynep Mine Coskun , Sema Bolkent, (2015), Immunohistochemical, apoptotic and biochemical changes by dipeptidyl peptidase-4 inhibitor-sitagliptin in type-2 diabetic rats. Pharmacological Reports, 67: 846–853.
**21.** Hauwa'u Yakubu Bako, Ja'afaru Sani Mohammad, (2014), Lipid Profile of alloxane-nduced diabetic wistar rats treated with methanolic extract of adansonia digitata fruit pulp: 1597-6343.

**Table (2): Mean ± SD of DPP-4, Glucose and Insulin for G1, G2,G3 and G4**

| Parameters | Group | N | Mean ±SD |
|---|---|---|---|
| DPP-4 pg/ mL | G1 | 10 | $29.55^{a}$± 8.33 |
| | G2 | 10 | $137.65^{c}$± 30.90 |
| | G3 | 10 | $55.32^{b}$± 26.96 |
| | G4 | 10 | $31.64^{a}$± 12.65 |
| Glucose mg/ dl | G1 | 10 | $106.50^{a}$± 19.173 |
| | G2 | 10 | $214.90^{b}$± 27.67 |
| | G3 | 10 | $150.70^{a}$± 11.96 |
| | G4 | 10 | $124.30^{a}$± 25.88 |
| Insulin µU/mL | G1 | 10 | $6.03^{a}$± 1.75 |
| | G2 | 10 | $13.07^{c}$± 1.67 |
| | G3 | 10 | $9.48^{b}$± 1.48 |
| | G4 | 10 | $8.67^{b}$± 1.70 |

**letters vertically means that there is significant difference between the groups, P≤0.05**

**Table (3): Mean ± SD of AST and ALT for G1, G2,G3 and G4**

| Parameters | Group | N | Mean ±SD |
|---|---|---|---|
| AST U/L | G1 | 10 | $28.000^{a}$± 9.23 |
| | G2 | 10 | $76.700^{c}$± 16.36 |
| | G3 | 10 | $52.500^{b}$± 8.50 |
| | G4 | 10 | $50.700^{b}$± 12.18 |
| ALT U/L | G1 | 10 | $27.300^{a}$± 11.28 |
| | G2 | 10 | $77.700^{c}$± 15.46 |
| | G3 | 10 | $43.100^{b}$± 8.87 |
| | G4 | 10 | $44.600^{b}$± 12.20 |

**Difference letters vertically means that there is significant difference between the groups, P≤0.05**

**Table (4): Mean ± SD of Ch, TG, HDL, LDL-CH, and VLDL-Ch for G1, G2,G3 and G4**

| Parameters | Group | N | Mean ±SD |
|---|---|---|---|
| Cholesterol(Ch) mg\dL | G1 | 10 | 131.26[a]+ 14.08 |
| | G2 | 10 | 255.25[c] ± 18.28 |
| | G3 | 10 | 144.08[ab]± 18.78 |
| | G4 | 10 | 152.34[b]± 25.11 |
| Triglyceride(TG) mg\dL | G1 | 10 | 116.89[a]± 25.87 |
| | G2 | 10 | 299.92[c]± 28.73 |
| | G3 | 10 | 154.70[b]± 30.38 |
| | G4 | 10 | 158.08[b]± 52.11 |
| HDL- Ch mg\dL | G1 | 10 | 41.60[c] ± 3.77 |
| | G2 | 10 | 27.80[a]+ 2.29 |
| | G3 | 10 | 31.20[b] ± 3.61 |
| | G4 | 10 | 33.50[b]± 4.62 |
| LDL- Ch mg\dL | G1 | 10 | 71.18[a]± 14.41 |
| | G2 | 10 | 136.66[b]+ 20.84 |
| | G3 | 10 | 84.64[a]± 19.10 |
| | G4 | 10 | 88.05[a]± 20.22 |
| VLDL- Ch mg\dL | G1 | 10 | 23.37[a]± 5.18 |
| | G2 | 10 | 61.98[c] ± 5.82 |
| | G3 | 10 | 30.94[b]+ 6.07 |
| | G4 | 10 | 31.60[b]+ 10.06 |

**Difference letters vertically means that there is significant difference between the groups, P≤0.05**

**Table (5): Correlations between biochemical parameters for G1**

| | DDP-4 Pg/mL | ALT U/L | AST U/L | Ch. mg/dL | HDL mg/dL | TG mg/dL | LDL mg/dL | VLDL mg/dL | Glu. mg/dL |
|---|---|---|---|---|---|---|---|---|---|
| **ALT U/L** | -0.491 | | | | | | | | |
| **AST U/L** | -0.125 | 0.020 | | | | | | | |
| **Ch. mg/dL** | -0.073 | -0.339 | -0.121 | | | | | | |
| **HDL mg/dL** | 0.024 | 0.092 | -0.529 | -0.273 | | | | | |
| **TG mg/dL** | -0.434 | 0.013 | 0.079 | -0.141 | -0.137- | | | | |
| **LDL mg/dL** | -0.128 | -0.341 | 0.222 | 0.828** | -0.635* | -0.231 | | | |
| **VLDL mg/dL** | -0.710* | 0.360 | -0.025 | -0.518 | 0.137 | 0.605 | -0.389 | | |
| **Glu. mg/dL** | 0.492 | -0.189 | 0.376 | 0.234 | -0.293 | -0.305 | 0.289 | -0.659* | |
| **Insulin µU/mL** | -0.038 | 0.516 | 0.145 | 0.296 | -0.448 | -0.318 | 0.373 | -0.382 | 0.401 |

*. Correlation is significant at the 0.05 level (2-tailed)

**. Correlation is significant at the 0.01 level (2-tailed)

**Table (6): Correlations between biochemical parameters for G2**

| | DDP-4 Pg/mL | ALT U/L | AST U/L | Ch. mg/dL | HDL mg/dL | TG mg/dL | LDL mg/dL | VLDL mg/dL | Glu. mg/dL |
|---|---|---|---|---|---|---|---|---|---|
| **ALT U/L** | -0.491 | | | | | | | | |
| **AST U/L** | -0.125 | 0.020 | | | | | | | |
| **Ch. mg/dL** | -0.073 | -0.339 | -0.121 | | | | | | |
| **HDL mg/dL** | 0.024 | 0.092 | -0.529 | -0.273 | | | | | |
| **TG mg/dL** | -0.434 | 0.013 | 0.079 | -0.141 | -0.137- | | | | |
| **LDL mg/dL** | -0.128 | -0.341 | 0.222 | 0.828** | -0.635* | -0.231 | | | |
| **VLDLmg/dL** | -0.710* | 0.360 | -0.025 | -0.518 | 0.137 | 0.605 | -0.389 | | |
| **Glu. mg/dL** | 0.492 | -0.189 | 0.376 | 0.234 | -0.293 | -0.305 | 0.289 | -0.659* | |
| **Insulin µU/mL** | -0.038 | 0.516 | 0.145 | 0.296 | -0.448 | -0.318 | 0.373 | -0.382 | 0.401 |

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

**Table (7): Correlations between biochemical parameters for G3**

| | DDP-4 Pg/mL | ALT U/L | ASTU/L | Ch. mg/dL | HDL mg/dL | TG mg/dL | LDL mg/dL | VLDL mg/dL | Glu. mg/dL |
|---|---|---|---|---|---|---|---|---|---|
| **ALT U/L** | 0.228 | | | | | | | | |
| **AST U/L** | 0.703* | -0.094 | | | | | | | |
| **Ch. mg/dL** | -0.607 | 0.085 | 0.495 | | | | | | |
| **HDL mg/dL** | 0.822** | -0.264 | -0.792** | -0.698* | | | | | |
| **TG mg/dL** | 0.346 | 0.551 | -0.186 | 0.089 | 0.016 | | | | |
| **LDL mg/dL** | -0.657* | -0.163 | 0.414 | 0.857** | -0.548 | -0.012 | | | |
| **VLDL mg/dL** | 0.114 | 0.515 | -0.156 | -0.199 | -0.118 | 0.294 | -0.513 | | |
| **Glu. mg/dL** | 0.554 | 0.055 | -0.693* | -0.548 | 0.644* | -0.223- | -0.345 | -0.078 | |
| **Insulin µU/mL** | 0.037 | -0.088 | -0.113 | -0.524 | 0.201 | -0.429 | -0.188 | -0.138 | 0.711* |

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

**Table (8): Correlations between biochemical parameters for G4**

| | DDP-4 Pg/mL | ALT U/L | AST U/L | Ch. mg/dL | HDL mg/dL | TG mg/Dl | LDL mg/dL | VLDL mg/dL | Glu mg/dL |
|---|---|---|---|---|---|---|---|---|---|
| **ALT U/L** | 0.045 | | | | | | | | |
| **AST U/L** | -0.439 | 0.629 | | | | | | | |
| **Ch. mg/dL** | 0.018 | -0.339 | -0.340 | | | | | | |
| **HDL mg/dL** | 0.126 | -0.522 | -0.589 | 0.361 | | | | | |
| **TG mg/dL** | 0.176 | 0.142 | 0.364 | 0.448 | -0.147 | | | | |
| **LDL mg/dL** | -0.158 | -0.400 | -0.474 | 0.900** | 0.359 | 0.044 | | | |
| **VLDLmg/dL** | 0.176 | 0.143 | 0.364 | 0.447 | -0.148 | 1.000** | 0.043 | | |
| **Glu. mg/dL** | -0.126 | 0.627 | 0.165 | 0.342 | -0.106 | 0.222 | 0.341 | 0.223 | |
| **Insulin µU/mL** | 0.354 | -0.221 | -0.279 | 0.439 | 0.451 | 0.548 | 0.173 | 0.548 | 0.106 |

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed)

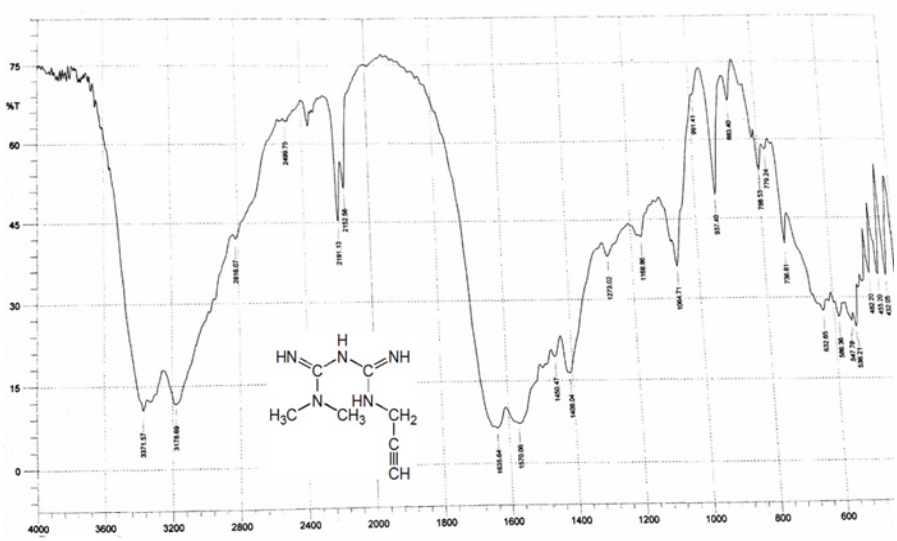
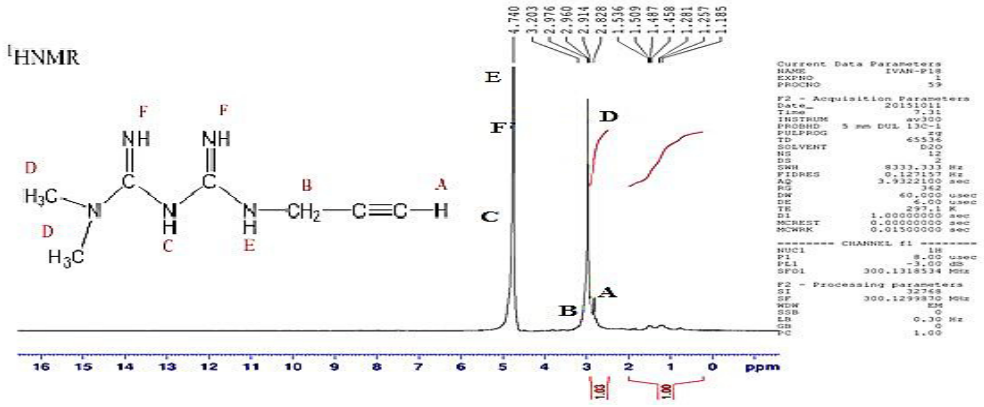



**Figure (1) Shown FTIR spectrum for metformin derivative**




**Figure(2)Shown Spectrum [1]HNMR for metformin derivative**

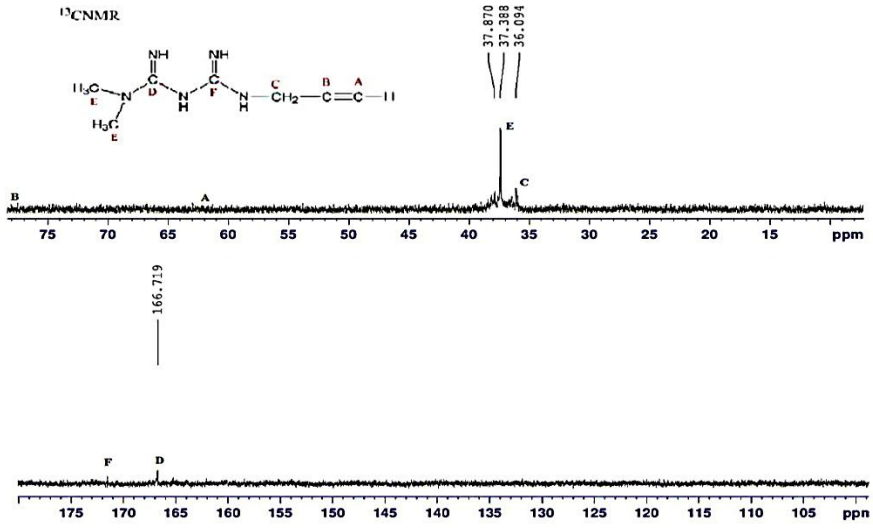



**Figure (3) Shown spectrum[13]CNMR for metformin derivative**

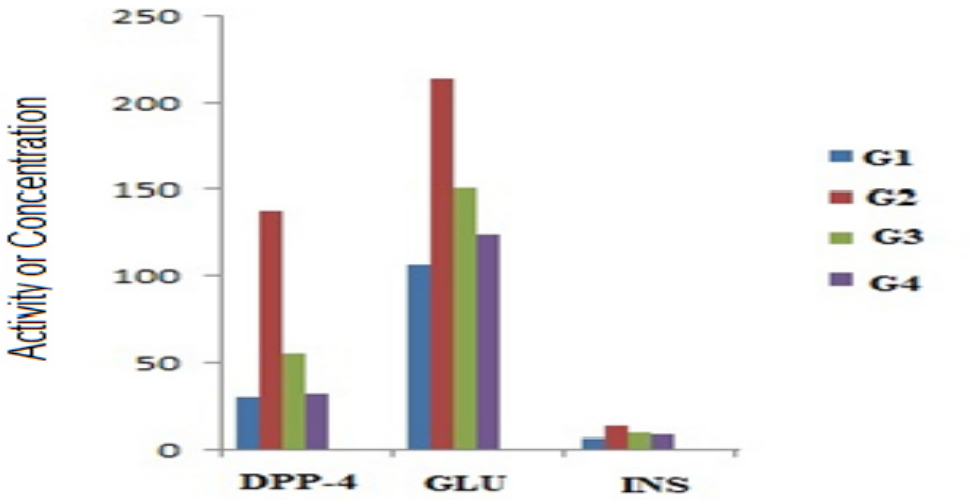
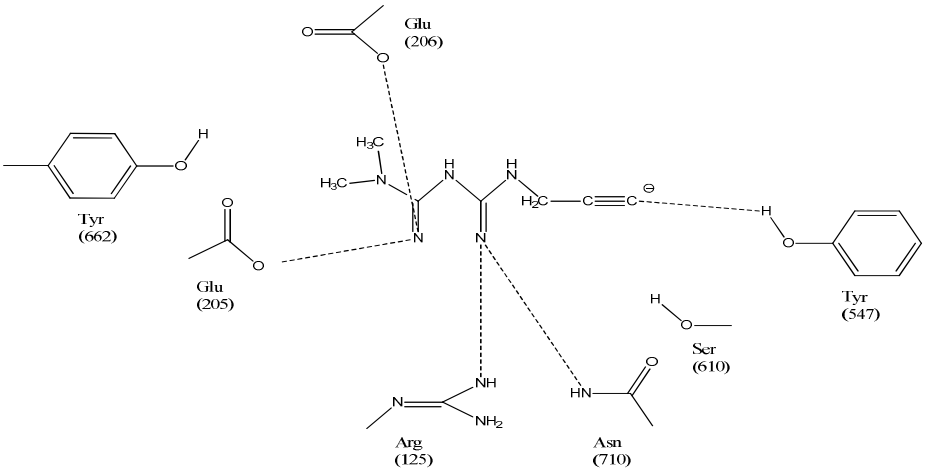
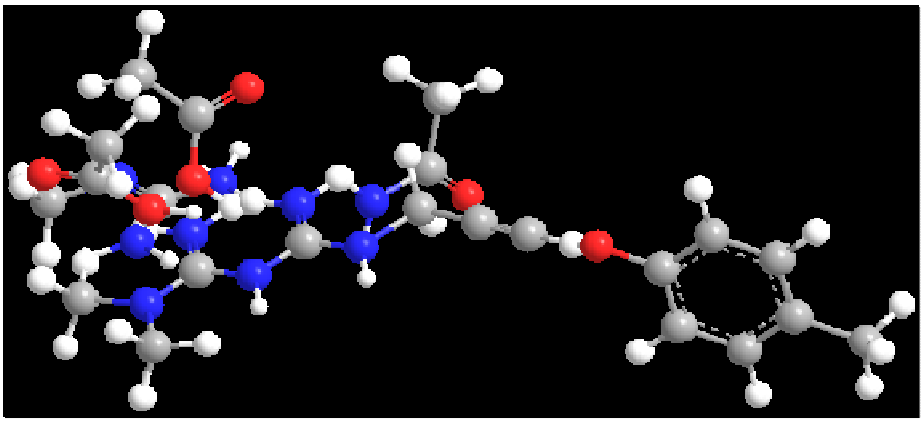



**Figure (4): Difference between the groups at DPP-4, Glucose and Insulin**



**Figure(5) The proposed interaction between the prepared derivative and the active site of DPP-4**

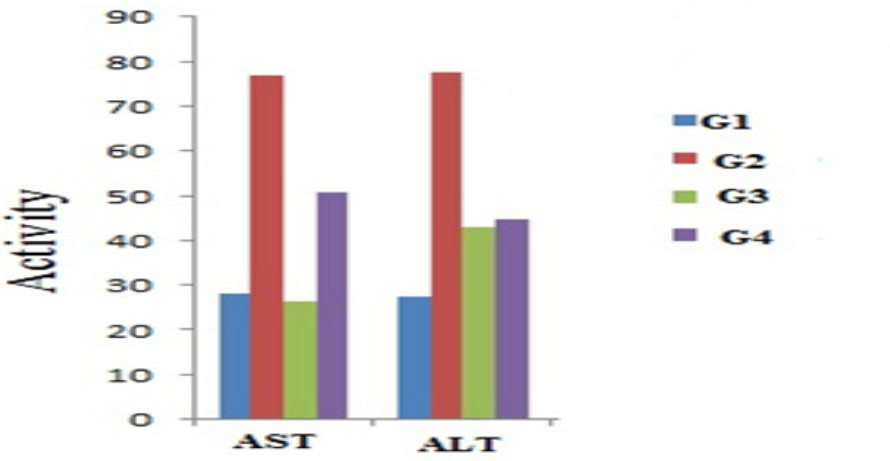



**Figure (6): Difference between the groups at AST and ALT**

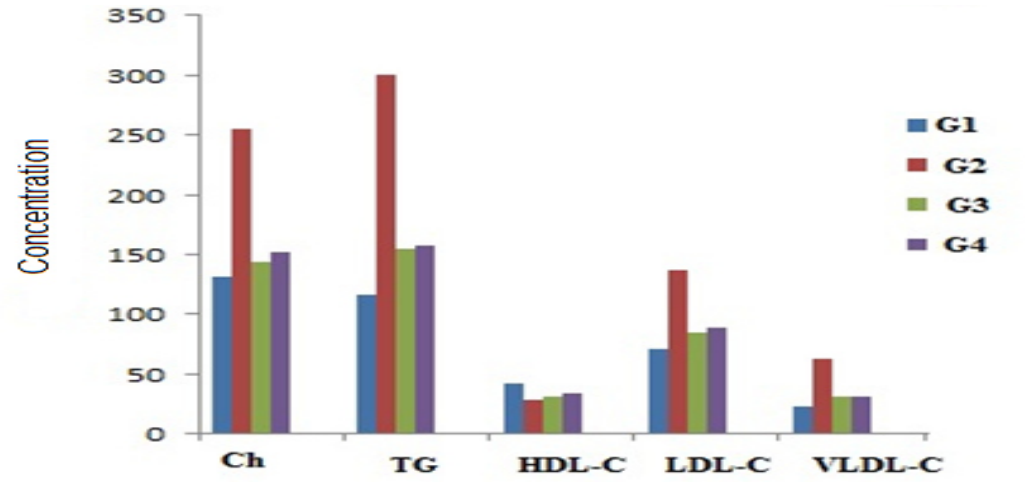



**Figure (7): Difference between the groups at Ch., HDL-Ch., TG, LDL-Ch. and VLDL-Ch**