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DOCKING ANALYSIS AND SYNTHESIS SOME NEW 1-(4-ETHYL-PHENYL)-2-(5,5-DISUBSTITUTED-4-HYDRO-[1,3,4]OXADIAZOLE-2-YL)-ETHANONE AS IMPENDING ANTI-DIABETIC AGENTS

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ABSTRACT

A new series of 2-[5-substituted phenyl-5-alkyl-4-hydro-[1,3,4] Oxadiazole-2-yl]-1-(4-ethyl-phenyl)-ethanone derivatives were synthesize by the esterification reaction of 4-(4-Ethyl-phenyl)-4-oxo-butyric acid with H_2SO_4 and ethanol. Followed by hydrazine hydrate to give substituted hydrazides and then hydrazone with substituted ketons, which were cyclise with chloramines-T to give the 2-[5-substituted phenyl-5-alkyl-4-hydro-[1,3,4]-Oxadiazole-2-yl]-1-(4-ethyl-phenyl)-ethanone derivatives. All these compounds were evaluated for *in-silico* anti-diabetic activity (docking on Glycogen Phosphorylase B protein) and also screened *in-vivo* anti-diabetic activity by alloxan induce diabeties mellitus model. All compounds were characterized by FT-IR, ^{13}CNMR, ^{1}HNMR and elemental analysis (CHNO). The titled compound exhibited good binding property with molecular target. Some of the compounds have shown good anti-diabetic activity and few have shown moderate anti-diabetic activity as compared to the standard drug.

KEYWORDS: 1,3,4-Oxadiazole, Docking, Anti-diabetic Activity.

INTRODUCTION

Diabetes mellitus (DM) is metabolic disorder which is produce due to the abnormal metabolism of carbohydrate, proteins and fats.[1] In Diabetic condition blood glucose level of patient have been increased, Diabetes Mellitus mainly in to: Type 1 (IDDM) & Type 2

(NIDDM). On the etiology basis type 1 diabeties is present in patients who have lower or no endogenous insulin secretory capacity and therefore patient requires insulin therapy for their survival. The two main forms of clinical type 1 diabetes are type 1a (about 90% of type 1 cases in Europe) which is thought to be due to immunological destruction of pancreatic β-cells resulting in insulin deficiency; and type 1b (idiopathic, about 10% of type 1 diabetes), in which there is no evidence of autoimmunity. It is caused by insulin deficiency, often combined with insulin resistance.[2] Type II is prevalent in 90% of the patients where insulin resistance and abnormal carbohydrate metabolism are considered to be the causative factors.[3] In patients with this condition, insulin levels are 2-4 folds higher than in nondiabetics.[4,5]

It is one of life threatening disorder occurs worldwide and its occurrence is increasing quickly in most of the countries.[6] Recent survey showed the roughly estimated data 30 million cases in 1985 to 177 million in 2000. Based on the current trends > 360 million individuals will have diabetes by the year 2030.[7]

The synthetic drugs which are available for the treatment of diabeties have large toxicity such as liver, kidney and recently shown that synthalin (a first antidiabetic agent) is selectively toxic to the α-cells of the islets of Langerhans. These facts allowed us to search novel anti-diabetic compounds with greater efficacy and fewer side effect.[8,9]

Oxadiazole, a heterocyclic nucleus has attracted a wide attention of the chemist in a search for a new therapeutic molecule. Out of its four possible isomers 1,3,4-oxadiazole is widely exploited for various application.[10,11]

1,3,4-Oxadiazoles compounds are not intermediates, it is very effective organic compounds in their own right. It has become an important construction motif for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum[12,13] such as antiedema, anti-inflammatory activity,[14,15,16,17] analgesic, antimicrobial,[18,19] anti-tubercular,[20] anticonvulsant,[21] anti-tumour activity[22] and antioxidant activities.[23,24,25]

The aim of the present study was to synthesize new 1,3,4-Oxadiazole derivatives from 4-(4-ethyl-phenyl)-4-oxo-butyric acid Hydrazones and evaluate their anti-diabetic activities.

Experimental Protocol

Chemistry

All the chemicals and solvents were purchased form Merck (India), S. D. Fine, Spectrochem (India) and used without further purification. The purity of synthesize compounds were ascertained by thin layer chromatography on silica gel G (coated to a thickness of about 0.3 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader) in benzene and ethyl acetate (3:1) solvent system. Elemental Melting points were determined by using open capillary melting point apparatus and are uncorrected. FT-IR spectra (KBr) were recorded on a Perkin-Elmer Spectrometer BX-II spectrophotometer. Proton 1H-NMR spectra and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker 300 MHz High Resolution NMR spectrometer. Chemical shifts were reported in ppm (d) and signals were described as singlet (s), doublet (d), triplet (t), and multiplet (m).The mass spectra were recorded on a Waters Micro-Mass ZQ 2000 mass spectrophotometer. Elemental analysis was carried out on Vario-EL III CHNO Elemental analyzer and the values were found within 0.4% of the theoretical values.

Synthesis

Synthesis of 4-(4-ethyl-phenyl)-4-oxo-butyric acid (3)

The compound *p*-substituted aroyl propanoic acid (3) were synthesized by the mixing of ethyl-phenyl (1) (50 ml), succinic anhydride 10.0 g (0.1M) and aluminium chloride 13.3 g (0.1M) was added as once and stirred on magnetic stirrer at room temperature for 48 hrs. After completion the reaction dilute HCl (2% v/v, 50 ml) was added. Excess solvent was removed by stem distillation and the hot solution was poured in to a beaker containing cold water (200 ml), solid mass was separated out and then filtered it, wash with cold water dried and crystallized with methanol.

Synthesis of 4-(4-Ethyl-phenyl)-4-oxo-butyric acid methyl ester (4)

4-(4-Ethyl-phenyl)-4-oxo-butyric acid methyl ester (4) were synthesized by the reaction of 4-(4-Ethyl-phenyl)-4-oxo-butyric acid 3 20.6 g (0.10 M) with methanol under reflux for 6 hours in presence of con. H_2SO_4 (3 ml). The excess solvent was removed under vacuum and the residue was filtered under suction, washed with water, and dried in air.

Synthesis of 4-(4-Ethyl-phenyl)-4-oxo-butyric acid hydrazide (5)

An equimolar quantity of 4-(4-Ethyl-phenyl)-4-oxo-butyric acid methyl ester (4) 22.0 g (0.1 M) and hydrazine hydrates 4 ml (0.1 M) 99% moisture in methanol (150 ml) refluxed for 8

hours. The excess solvent was removed under vacuum and the residue was filtered under suction, washed with water, and dried in air.

Synthesis of Substituted Hydrazone (6a-h)

A solution of R- 4-(4-Ethyl-phenyl)-4-oxo-butyric acid hydrazide (5) 0.22 g (0.001 M) in glacial acetic acid (20 ml), aromatic ketone (0.001 M) was added and refluxed for 45 minute and cooled. The solid product obtained on pouring onto cursed ice (100 g), filtered it and dried in air.[26]

Synthesis of substituted Oxadiazole derivatives (7a-h)

Substituted hydrazone (6a-h) (0.01 mole) was dissolved in ethanol (80 ml) and chloramine T (0.01 mole) was added to it. The solution was refluxed for 8 hrs, sodium chloride which separated out during the course of reaction was filtered off. Excess ethanol was completely removed by distillation and a solid mass separated out was crystallised in ethanol and chloroform (2:2).

Characterization of the synthesized compounds

1-(4-Ethyl-phenyl)-2-(5-ethyl-5-phenyl-4-hydro-[1,3,4]oxadiazole-2-yl)-ethanone (7a)

Brown colored flakes, m. p. 63-65 ^{0}C, R_f 0.56, yield 87.95 %, IR (KBr, cm-1, υ): 3434.83(-NH-); 3019.13(-CH-); 1655.02(-C=O); 1385.04(-N=C); 1215.52(-O-), ^{1}HNMR($CDCl_3$, 400 MHz): δ 6.936-8.499 (m, 9H, Ar-H), 0.850-3.916 (m, 12H, Ali-H), 4.807 (s, 1H, NH); ^{13}C-NMR($CDCl_3$- d_1) 77.0, 50.98, 76.39, 76.81, 126.51, 126.90, 127.38, 127.99, 128.34, 128.57, 128.89, 129.90, 129.62, 129.91, 130.78,131.96, 133.55, 133.77, 134.45, 139.30, 139.95, *Anal.* Calcd. for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; O, 9.39. Found: C, 76.23; H, 6.91; N, 8.89; O, 10.68, m. f. $C_{20}H_{22}N_2O_2$.

1-(4-Ethyl-phenyl)-2-(5-hydroxy-phenyl-methyl)-5-phenyl-4-hydro-[1,3,4]oxadiazole-2-yl)-ethanone (7b)

Brown colored flakes, m. p. 60-62 ^{0}C, R_f 0.31, yield 80.00 %, IR (KBr, cm-1, υ): 3404.94(-NH-); 3021.07(-CH-); 1670.79(-C=O); 1319.98(-N=C); 1330.33(O-H); 1215.25(-O-), ^{1}HNMR($CDCl_3$ 400 MHz), δ 6.912-8.527 (m, 14H, Ar-H), 1.064-4.133 (m, 8H, Ali-H), 5.956 (s, 1H, Ali-OH), 4.827 (s, 1H, NH), ^{13}C-NMR($CDCl_3$- d_1) 77.0, 21.63, 50.78, 76.39, 76.81, 126.51, 126.98, 127.38, 127.94, 128.34, 128.49, 128.86, 129.30, 129.52, 129.81, 131.76, 132.34, 133.14, 133.69, 134.09, 135.12, 139.07, 139.55, 143.55, 145.81, *Anal.* Calcd.

For $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 7.0; O, 11.99. Found: C, 74.34; H, 6.89; N, 7.56; O, 13.34, m. f. $C_{25}H_{24}N_2O_3$

2-(5-benzoyl-5-phenyl-4-hydro-[1,3,4]oxadiazole-2-yl)-1-(4-ethyl-phenyl)-ethanone (7c)

Brownish yellow colored flakes, m. p. 58-60 ^{0}C, R_f 0.44, yield 95.3 %, IR (KBr, cm-1, υ): 3435.33(-NH-); 3019.56(-CH-); 1668.53(-C=O); 1385.11(-N=C); 1215.44(-O-), ^{13}C-NMR($CDCl_3$- d_1) 77.0, 49.98, 75.79, 76.89, 126.01, 126.78, 127.38, 127.69, 128.24, 128.76, 129.50, 129.91, 130.38,131.86, 132.34, 133.14, 134.69, 135.09, 138.12, 139.97, 139.55, *Anal.* Calcd. For $C_{26}H_{26}N_2O_3$: C, 73.90; H, 5.45; N, 6.76; O, 11.58. Found: C, 75.71; H, 5.86; N, 6.79; O, 11.64, m. f. $C_{26}H_{26}N_2O_3$

2-[5-(4-chloro-phenyl)-5-methyl-4-hydro-[1,3,4]oxadiazole-2-yl)-1-(4-ethyl-phenyl)-ethanone (7d)

Brownish yellow colored flakes, m. p. 80-82 ^{0}C, R_f 0.48, yield 82.86 %, IR (KBr, cm-1, υ): 3403.09(-NH-); 3020.98(-CH-); 1662.6(-C=O); 1337.51(-N=C); 1161.01(-O-); 1093.74(-C-Cl) ^{13}C-NMR($CDCl_3$- d_1) 77.0, 49.78, 75.39, 76.89, 126.31, 126.88, 127.48, 127.99, 128.54, 128.96, 129.50, 130.91, 132.38,133.86, 134.34, 135.14, 136.69, 137.09, 139.12, 140.32, *Anal.* calcd. For $C_{21}H_{27}ClN_2O_2$: C, 67.28; H, 7.26; N, 7.47; O, 8.54. Found: C, 61.23; H, 2.95; N, 7.90; O, 12.99, m. f. $C_{21}H_{27}ClN_2O_2$

1-(4-Ethyl-phenyl)-2-[5-(4-fluoro-phenyl)-5-methyl-4-hydro-[1,3,4]oxadiazole-2-yl)-ethanone (7e)

Light brown colored flakes, m. p. 59-61 ^{0}C, R_f 0.37, yield 88.95 %, IR (KBr, cm-1, υ): 3403.84(-NH-); 3021.58(-CH-); 1699.61(-C=O); 1311.91(-N=C); 1188.31(-O-); 1202.74(-C-F), ^{13}C-NMR($CDCl_3$- d_1) 77.0, 46.78, 76.39, 76.89, 125.01, 126.18, 127.08, 127.79, 128.24, 128.76, 129.50, 129.91, 130.38, 131.86, 131.94, 134.64, 135.69, 138.09, 138.12, 139.57, *Anal.* Calcd. For $C_{19}H_{19}FN_2O_2$: C, 69.92; H, 5.87; N, 8.58; O, 9.80. Found: C, 66.97; H, 8.14; N, 8.98; O, 9.01, m. f. $C_{19}H_{19}FN_2O_2$

1-(4-Ethyl-phenyl)-2-(5-methyl-5-phenyl-4-hydro-[1,3,4]oxadiazole-2-yl)- ethanone (7f)

Palish yellow colored flakes, m. p. 58-60 ^{0}C, R_f 0.45, yield 97.72 %, IR (KBr, cm-1, υ): 3434.36(-NH-); 3021.01(-CH-); 1656.27(-C=O); 1390.04(-N=C); 1279.35(-O-), ^{13}C-NMR($CDCl_3$- d_1) 77.0, 21.65, 76.37, 76.80, 126.57, 127.95, 128.24, 128.85, 129.30, 129.81, 130.07, 133.16, 133.67, 134.08, 135.09, 139.11, 139.39, 143.58, 194.80, 199.17, *Anal.*

Calcd. For $C_{19}H_{20}N_2O_2$: C, 74.0; H, 6.54; N, 9.08; O, 10.38. Found: C, 52.33; H, 3.26; N, 3.91 O, 14.79, m. f. $C_{19}H_{20}N_2O_2$

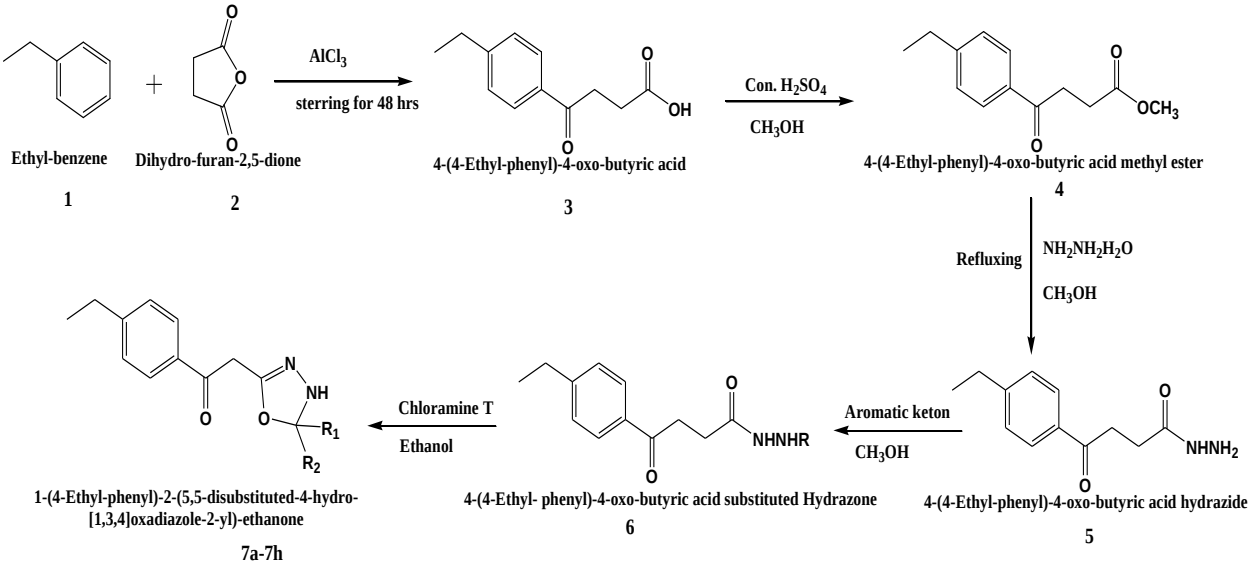
2-[5-(4-Amino-phenyl)-5-methyl-4-hydro-[1,3,4]oxadiazole-2-yl)- 1-(4-ethyl-phenyl)-ethanone (7g)

Yellowish brown colored flakes, m. p. 55-57 ^{0}C, R_f 0.47, yield 92.87 %, IR (KBr, cm-1, υ): 3479.09(-NH-); 3290.09 (NH_2); 3110.90(-CH-); 1677.26(-C=O); 1312.11(-N=C); 1122.51(-O-); ^{13}C-NMR($CDCl_3$- d_1) 77.0, 55.65, 66.37, 76.80, 126.57, 127.95, 128.24, 128.85, 130.30, 131.81, 132.07, 134.16, 135.67, 138.08, 140.09, 142.11, 144.39, 145.58, 196.80, 199.97, *Anal.* Calcd. For $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99; O, 9.89. Found: C, 71.00; H, 6.16; N, 13.56; O, 6.87, m. f. $C_{19}H_{21}N_3O_2$

2-[5-(4-Bromo-phenyl)-5-methyl-4-hydro-[1,3,4]oxadiazole-2-yl)- 1-(4-ethyl-phenyl)-ethanone (7h)

Brown colored flakes, m. p. 57-59 ^{0}C, R_f 0.56, yield 90.00 %, IR (KBr, cm-1, υ): 3358.77(-NH-); 3021.73(-CH-); 1674.99(-C=O); 1392.14(-N=C); 1215.52(-O-); 1163.95(-C-Br), ^{13}C-NMR($CDCl_3$- d_1) 77.0, 21.65, 71337, 76.40, 126.07, 127.75, 128.04, 128.85, 129.30, 130.81, 131.07, 133.16, 135.67, 136.08, 141.09, 144.11, 147.39, 149.58, 198.80, 199.17, *Anal.* Calcd. For $C_{20}H_{23}BrN_2O_2$: C, 59.56; H, 5.75; N, 6.95; O, 7.93. Found: C, 59.96; H, 6.58; N, 5.46; O, 7.13, m. f. $C_{20}H_{23}BrN_2O_2$

Synthetic Scheme1



Comp.	7a	7b	7c	7d	7e	7f	7g	7h
R1	-C2H5,	-C6H5,	-C6H5,	-CH3,	-CH3,	-CH3,	-CH3,	-CH3,
R2	-C6H5,	-CHOHC6H5,	-COC6H5,	-C6H5Cl,	-C6H5F,	-C6H5,	-C6H5NH2,	-C6H5Br

Molecular Docking

Database and tools

For carrying out the study, National Center for Biotechnology Information's (NCBI.) website and Protein Data Bank's (PDB) website were used as biological and receptor sources. For designing and optimizing the geometry of the derivatives, Chemdraw Ultra 7.0[27] was used. For docking studies of derivatives, AutoDock Vina[28] molecular docking software has been employed and for descriptor calculations PaDEL software has been used.[29]

Molecule designing and optimization

The chemical structures of the hybrid derivatives were drawn using ChemDraw Ultra 7.0 and energy minimization of derivatives was achieved with Chem3D Pro of ChemOffice suit for taking energy of each molecule up to its lowest energy state (highest stability). 3D structure of Glycogen Phosphorylase B Complex protein (PDB id: **1H5U**) was retrieved from PubChem compound database at NCBI.

Docking studies

The docking analysis of derivatives with Glycogen Phosphorylase B Complex protein (PDB id: **1H5U**) was carried out by AutoDock Vina. The incorporation of various algorithms makes it a very good tool, as docking search algorithm is based on evolutionary algorithm. It is an iterative optimization technique inspired by Darwinian evolution theory. Evolutionary algorithm consists of population of individuals, which is exposed to random variation by means of variation operators, like mutation and recombination.

To identify the potential anti-diabetic activity of a lead compound among all synthesized 1,3,4-Oxadiazole docking calculation were performed using EXHZ version 1.4 and Auto Dock Vina 4.0 on fedora Linux WS 3.0 in to the 3D structure of the catalytic site of Glycogen Phosphorylase B Complex protein (PDB id: **1H5U**). The conversion of available ligand to 3D format carried out for the identification and visualization of possible binding site and the distribution of surrounding residue in the active site. As a result, 3 active sites have been predicted; it also gives residue in active site and centre of active with X, Y, Z, coordination of all the active site. Out of which, one active site has been selected (centre of active site 27.394, 0.178, 41.138), which is present closer to the ligand selected (7a-h) from the chosen receptor. Parameters have been chosen for docking of ligand with the chosen receptor (PDB id **1H5U**). Grid center as: 23.357, 19.489, 18.247 (XYZ coordinates), npts 110, 110, 110 (number of

grid point in xyz), spacing 0.982 (spacing Å), (<0, AD4 distance-dep.diel;>0) and LGA algorithm (Lamarckian genetic algorithm).

Protein-Ligand Docking has been carried out using pdb id **1H5U** as a receptor with bound ligand (7a-h) and obtained results were evaluated in the term of binding energy.

Anti-diabetic evaluation

Mail albino mice weighing between 20-25 g were use for acute type of diabetic condition. They were housed under standard laboratory condition maintained 25 ^{0}C temp and humidity at 45-60% for one week before anti-diabetic activity was carried out by using alloxan induced diabetes animal models. Food and water were withdrawn prior to the experiment. All the result was statistically analyzed.

RESULT ANT DISCUSSION

The present studies reported eight new substituted 1,3,4-oxadiazole and their structure were established on the basis of spectral studies and elemental analysis. Auto Dock Vina molecular docking software has been used for descriptor calculation. Biological activity of all compounds were performed by using alloxan induced diabetes animal models in which Mail albino mice were use for acute type of diabetic condition.

Binding site analysis

The experimental analysis of binding site shows that Arg 310, Arg 242, Asp 227, Arg 193, Trp 67, Thr 240, Gln 71, Tyr 791, Asn 560, Lys574, Asn284 and Phe285 could be the catalytic site residue present in the structure of Glycogen Phosphorylase B Complex protein.

Docking studies of derivatives 7a-h with Glycogen Phosphorylase B complex protein

The protein-ligand interaction affinities were given by AutoDock Vina for best pose of novel derivatives. The best pose ligand-protein interaction affinity of all 8 designed molecules was found to be as -8.8 Kcal/mol, -8 Kcal/mol, -10.2 Kcal/mol, -8.8 Kcal/mol, -8.5 Kcal/mol, -8.8 Kcal/mol, -8.1 Kcal/mol and -8.3 Kcal/mol with 2, 4, 3, 3, 2, 2, 2 and 2 hydrogen bonds respectively. Here, negative values for interaction energy would reflect the positive docking approach. Number of hydrogen bonds and other binding details are given in table 2 and docking images are given in Fig. 1.

Table 1. Docking results of derivatives (7a-h) and glibenclamide

LIGAND	RECEPTOR	Affinity (Kcal/mol)	H- bonds	H- Binding Ligand			H- Binding R		
				Element	Atom No.	Type	Residue	Element	A
7a	GLYCOGEN PHOSPHORYLASE-B	-8.8	2	O	09	Acceptor	Arg 310	N	
				O	09	Acceptor	Arg 242	N	
7b		-8	4	O	20	Both	Arg 310	N	
				O	20	Both	Arg 242	N	
				N	01	Donor	Asp 227	O	
				O	24	Acceptor	Arg 193	N	
7c		-10.2	3	O	24	Acceptor	Trp 67	N	
				O	24	Acceptor	Thr 240	O	
				O	09	Acceptor	Arg 310	N	
7d		-8.8	3	N	03	Donor	Gln 71	O	
				N	04	Donor	Gln 71	O	
				O	10	Acceptor	Thr 240	O	
7e		-8.5	2	N	03	Donor	Tyr 791	O	
				N	03	Donor	Asn 560	O	
7f		-8.8	2	O	10	Acceptor	Arg 310	N	
				O	10	Acceptor	Arg 242	N	
7g		-8.1	2	N	03	Donor	Tyr 791	O	
				N	14	Donor	Tyr 791	O	
7h		-8.3	2	O	05	Acceptor	Thr 240	O	
				O	10	Acceptor	Arg 193	N	
Glibencl-amide		-5	3	O	19	Acceptor	Lys574	N	
				O	10	Acceptor	Asn284	N	
				N	26	Donor	Phe285	O	

On docking analysis, Glibenclamide has been found to be weakly docked with the protein Glycogen Phosphorylase B Complex, the protein binding with Glycogen Phosphorylase B Complex have been observe in order to study its inhibitory activity. When it is docked with the protein PDB ID **1H5U** it forms 3 hydrogen bonds with binding affinity of -5 Kcal/mol. On residue study, the amino acid Lys547, Asn284 and Phe285 were found to be significant. On the account of ligand here oxygen and nitrogen both atoms are significant in the binding. The type of binding found with donor bonds, whereas the significant element in receptor binding is oxygen.

From these eight synthesis compound were selected best on the basis of least mean binding energy among the all synthesize compounds 7c, was found in a best conformation with least mean binding energy -10.2.

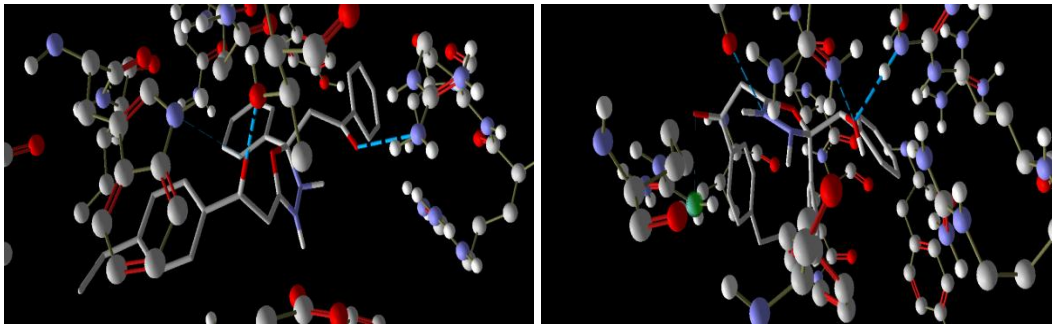


Fig.1 1H5U receptor with atom interaction with individual best eight compounds

Anti-diabetic results

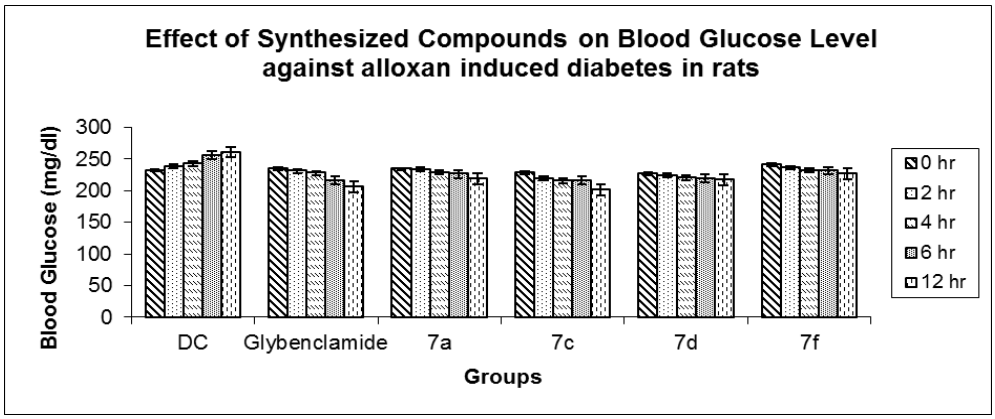
It was observed that the test agents decrease the alloxan induce diabetes. Moreover the effect of the test drugs 7c and 7d were found to be comparable to that of glibenclamide as standard drug. The test drug could decrease the blood glucose level of the chronic diabetes in alloxan model.

Table no. 1.1 Hypoglycemic activity of compounds 7a-h (One day study)

Groups	0 hrs	2 hrs	4 hrs	6 hrs	12 hrs
Diabetic Control (DC)	232.3 ±2.77	238.6 ±2.81	242.4 ±2.81	256 ±2.89	261 ±2.93
Glibenclamide (Std)	235 ±2.77	231.2 ±2.77*	227.6 ±2.73**	216.4 ±2.65**	206.5 ±2.61**
7a	234 ±2.77	233.6 ±2.77	229 ±2.73*	226 ±2.73**	219 ±2.69**
7c	228.1 ±2.73	219.4 ±2.69*	216 ±2.65**	216.2 ±2.65**	201.3 ±2.65**
7d	226.4 ±2.73	224.1 ±2.69*	220.5 ±2.69**	219 ±2.69**	217.1 ±2.65**
7f	241.2 ±2.81	236.3 ±2.77	232.3 ±2.77	231.6 ±2.77**	226.1 ±2.73**

Test compound = 36 mg/kg; orally, reference standard glibenclamide = 30 mg/kg; orally

The result are expressed as mean ± sem. The data is analyzed using one way analysis of variance (ANOVA) followed by dunnett test (n=6), ** p<0.01, *p<0.05, ns-non significant



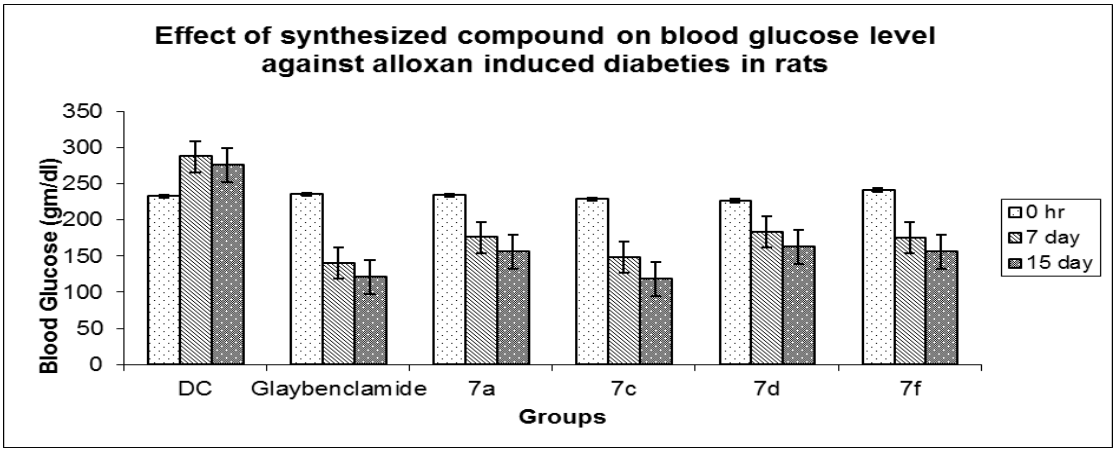
Graph 1.

Table no. 1.2 Hypoglycemic activity of compounds 7a-h (fifteen day study)

Groups	0 hrs	7th day	15th day
Diabetic Control (DC)	232.3 ±2.77	287.6 ±3.06	276.2 ±3.02
Glibenclamide (Std)	235 ±2.77	140.5 ±2.16**	120.4 ±2.02**
7a	234 ±2.77	175.6 ±2.40**	156.4 ±2.24**
7c	228.1 ±2.73	147.8 ±2.32**	118.4 ±2.20**
7d	226.4 ±2.73	183.5 ±2.44**	162.6 ±2.32**
7f	241.2 ±2.81	175.5 ±2.440**	155.6 ±2.24**

Test compound = 36 mg/kg; orally, reference standard glibenclamide = 30 mg/kg; orally

The result are expressed as mean ± sem. The data is analyzed using one way analysis of variance (ANOVA) followed by dunnett test (n=6), ** p<0.01, *p<0.05, ns-non significant



Graph 2.

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REFERENCES

1. Pulipaka S, Challa SR, Pingili RB, Competative Antidiabetic Activity of methanolic extract of Operculina turpethum stem and root against healthy and streptozotocin induced diabetic rat. International Current Pharmaceutical Journal., 2012; 1(9): 272-278.
2. Prajapati BK, Sen DJ, (2013) Design, Synthesis and oral Glucose Tolerance Screening of Some 5-Substituted benzylidene-3-[2-(2-methyl-1H-benzimidazole-1-yl)-2-oxoethyl]-1,3-thiazolidine-2,4-dione Derivatives on Rats. American J of Advanced Drug Delivery, ISSN-2321-547X.
3. Nikaljea APG, Choudharia S, Uneb H, Design, Synthesis and hypoglycaemic Activity of novel 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-substituted acetamide derivatives. European Journal of Experimental Biology., 2012; 2(4): 1302-1314.
4. Defronzo RA, Ferrannini E, Simonson DC, Metabolism., 1989; 38: 387-395.
5. Kandadi MR, Rajanna PK, Unnikrishnan MK, Boddu SP, Yinan Hau, Ji Li, Du M, Ren J, Sreejayan N, 2-(3,4-dihydro-2H-pyrrolium-1-yl)-3-oxoindan-1-olate (DHPO), A Novel Synthetic Small Molecule that Alleviates Insulin Resistance and Lipid Abnormalities. Biochem Pharmacol., 2010; 79(4): 623-631.
6. Robbins. Pathologic Basis of Disease, 6th Ed. Philadelphia: Harcourt (India) Pvt Lt., 2000; 913-914.
7. Harisons, Principles of internal medicine. 17th edition, 2007; 2275-77.
8. Kini D, Ghate M, Synthesis and hypoglycaemic activity of 3-[5'-Methyl-2'-aryl-3'-(thiazol-2''-yl amino) thiazolidin-4'-one] coumarin derivatives. E J of Chem., 2011; 8(1): 386-390.
9. Paul R, Popli SP, Dhar ML, Studies in possible Oral Hypoglycemic Agents: Part I-Synthesis of some Hydantoins, Hydantonic Esters and Related compound. J. Sci. Indust. Res., 1959; 18C: 21-24.
10. Bachwanin M, Sharma V, Kumar R, Biological activities of 1,3,4-oxadiazole: A Review. Int researct journal of pharmacy., 2011; 2(12): 1.

11. Nagarj, Chaluvaraju KC, Niranjan MS, Kiran S, 1,3,4-oxadiazole: A Potent Drug Candidate with Various Pharmacological Activities. Int J pharm pharm sci., 2011; 3(3): 9-16.
12. Boström, J., Hogner, A., Llinàs, A., Wellner, E., Plowright, AT., (2012) Oxadiazoles in Medicinal Chemistry. J. Med. Chem., 2012; *55*: 1817–1830.
13. Oliveira CS, Lira BF, Barbosa-Filho JM, Lorenzo JGF, Athayde-Filho PF, Synthetic approaches and Pharmacological Activity of 1,3,4-oxadiazoles: A review of the literature from 2000-2012 Molecules., 2012; 17: 10192-10231.
14. Kamble RR, Sudha BS, Synthesis and Pharmacological screening of 5-methyl-3-[p-(6'-aryl-2'-thioxo-1',2',5',6'-tetrahydro-pyrimidin-4'-yl)-phenyl]-3H-2-oxo-D4-1,3,4-oxadiazoles. Indian J Pharm Sci, 2006; 6: 249–253.
15. Narayana B, Vijayraj KK, Ashalatha BV, Kumari NS, Synthesis of some new 2-(6-methoxy-2-napthyl)-5-Aryl-1,3,4-oxadiazoles as possible Non-steroidal Anti-inflammatory and Analgesic Agents. Arch der Pharm., 2005; 338: 373-377.
16. Hussain A, Ahuja P, Sarafroz, Synthesis and Biological evaluation of β-aroylpropionic acid based 1,3,4-oxadiazole. Indian J Pharm Sci., 2009; 71(1): 62-66.
17. Omar FA, Mahfouz NM, Rahman MA, Design, Synthesis and anti-inflammatory Activity of 1,3,4-oxadiazole derivatives. Eur J Med Chem., 1996; 31: 819-825.
18. Ingole PS, Mohane SR, Berad BN, Synthesis and Antimicrobial activity of 2-alkyl/aryl-5-(pyrid-4-yl)-1,3,4-oxadiazole. Asian J Chem., 2007; 19: 2683-2686.
19. Karthikeyan MS, Prasad DJ, Mahalinga M, Holla BS, Kumari NS, Antimicrobial studies of 2,4,-dichloro-5-fluorophenyl containing oxadiazoles. Eur J Med Chem., 2008; 43: 25-31.
20. Somani RR, Shirodkar PY, Synthesis, Antibacterial and Anti tubercular Evaluation of some 1,3,4-Oxadiazole Analogues. Asian J Chem., 2008; 20: 6189-6194.
21. Zarghi A, Tabatabai SA, Faizi M, Ahadian A, Navabi P, Zanganeh V, Shafiee A, Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxphenyl)-1,3,4-oxadiazoles. Bioorg Med Chem Lett., 2005; 15: 1863-1865.
22. Holla BS, Poojary KN, Bhat KS, Ashok M, Poojary B, Synthesis and anticancer activity studies on some 2-chloro-1,4-bis-(5-substituted-1,3,4-oxadiazol-2-ylmethyleneoxy) phenylene derivatives. Indian J Chem., 2005; 44B: 1669-1673.
23. Padmavathi V, Reddy SN, Mahes K, Synthesis, Antimicrobial and Antioxidant Activities of Sulfone linked bis Heterocycles-pyrazolyl Oxadiazoles and Pyrazolyl Thiadiazole. Chem Pharm Bull (Tokyo)., 2009; 57: 1376-1380.

24. Padmavathi V, Reddy SN, Reddy GD, Padmaja A, Synthesis and bioassay of aminosulfonyl-1,3,4-oxadiazoles and their interconversion to 1,3,4-thiadiazoles. Eur J Med Chem., 2010; 45: 4246-4251.
25. Rajasekaran S, Rao GK, Pai DPN, Vedavathi J, Microwave assisted synthesis of some 5-pyridyl-2-[(N-substituted phenyl) thioacetamido]-1,3,4-oxadiazoles as antibacterial and antioxidant agents J Chem Pharm Res., 2010; 2: 101-106.
26. Raj V, Kumar P, Kumar A,(2014) Design and Synthesis of 4-(4-ethyl-phenyl)-4-oxo-butyric acid (3-oxo-1,3-diphenyl-propylidene)/[1-(4-chloro-phenyl)-ethylidene]-hydrazide as potential anticonvulsant agent, Med. Chem. Res., DIO 10.1007/s00044-014-1154-2.
27. Mills N, ChemDraw Ultra 10.0., J Am Chem Soc., 2006; 128(41): 13649–13650.
28. Trott O, Olson AJ, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading. J Comput Chem., 2010; 31: 455-461.
29. Yap, CW, PaDEL-descriptor: An open source software to calculate molecular descriptors and fingerprints, J Comput Chem., 2011; 32(7): 1466-1474.
30. Anna Pratima GN, Choudharia S, Uneb H, Design, Synthesis and Hypoglycaemic Activity of Novel 2-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl)-2-methoxyphenoxy)-N-substituted acetamide derivatives. E J of Exp. Bio., 2012; 2(4): 1302-1314.