Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

Design, Synthesis and Evaluation of 1, 3, 4-Oxadiazole Derivatives for Antidiabetic Activity

Mohini Patidar*, Mr. Nilesh Mandloi, Mr. Bhoopendra Patidar, Mr. Nitin Deshmukh, Mr. Aman Karma, Mr. Gourav Trivedi

Department of Pharmaceutical Chemistry, GRY Institute of Pharmacy, Borawan-451228

(Received: 07 January 2024 Revised: 12 February 2024 Accepted: 06 March 2024)

KEYWORDS

Anti-diabetics, 1,3,4 oxadiazole, *In-silico* study, Biological evaluation

ABSTRACT:

Introduction: Diabetes mellitus is a chronic metabolic disorder that leads to severe complications worldwide. 1,3,4-oxadiazole is one of the potent bioactive heterocyclic agent.

Objectives: The objective of the study is the *in-silico* prediction of physicochemical properties, molecular docking studies and synthesis of 1, 3, 4, oxadiazole derivatives as α-glucosidase enzyme inhibition for diabetes mellitus.

Methods: *In- silico* design of proposed derivatives were conducted by Molegro Virtual Docker software. The docking interaction of derivatives A4, A11, A12, and A15 has four hydrogen bonds with Arg 315, Thr310, Ser 241, Lys 156 amino acids, hydrophobic interaction with ASP242, hydrophobic interaction with Pro 312, Glu411 His280, and pi-pi stacking with Tyr 158 amino acids of receptor 3A4A. Compound A12 had the highest affinity for protein 3A4A and the highest binding energy, measuring -12.8327 kcal/mol with the highest affinity among the entire compound compared with the standard Metformin of -9.01594 kcal/mol.

Results: The synthesis of target compounds was performed by cyclization reaction using aromatic amines and carbon disulphide to get mannich bases. Yield of all compounds was in the range of 62.2-79.9 %. The anti-diabetic effects of all compounds were moderate to excellent. The acute toxicity study indicates that A12 and A15 when administered orally at the dose of 4000 mg/kg did not produce any sign of toxicity or death in treated animals. Our study reveals that oxadiazole pharmacophore are one of the important pharmacophores to develop antidiabetic potential compounds.

1. Introduction

The heterocyclic compounds have always been a fascinating part of a study in the field of chemistry. Nitrogen, oxygen & sulphur are some heteroatoms present in the rings replacing carbon.[1]1,3,4-oxadiazole derivatives among the family of heterocycles showed many promising pharmaceutical applications with a broad variety of biological activities such as medicament, analgesic, ulcerogenicity, apoptosis inducer, antimycobacterial, antifungal, antitumor, p-glycoprotein inhibitors, pesticides, 4-hydroxylase inhibitors, antiepileptic drug activity.[3]Extensive literature report reveals the anticancer, antioxidant, anti-hyperglycaemic, anti-tubercular properties of 1,3,4-oxadiazole scaffold.[2]Diabetes mellitus is a metabolic disorder with various etiologies. The disease is marked by chronic hyperglycaemia, which is associated with the disturbances of carbohydrate, protein and fat metabolism arising from defects in insulin secretion, action, or both. [4] Diabetes mellitus is caused either by deficiency of insulin secretion, damage of pancreatic β cell or insulin resistance related to non-use of insulin. [5] Diabetes is mainly categorized into two types, type-I diabetes and type-II diabetes.

Type-I diabetes- is known as insulin dependent diabetes and characterized by deficient production of insulin, requires daily administration of insulin.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

Type-II diabetes- commonly known as non-insulin dependent diabetes which causes due to the ineffective use of the insulin by the body. [6]

Symptoms

Frequent urination, Itchy skin, Intense hunger, Weight gain, unusual weight loss, Irritability, Blurred vision, Cuts and bruises don't heal properly or quickly, skin and/or yeast infections, Sexual dysfunction among men.[7]

Treatment

The major classes of antidiabetic medications include: Metformin, Phenoformin, Proguanil**,** Tolbutamide, Tolazamide, Glipizide, Miglitol**,** Repaglinide, Nateglinide, Miglitol, Piloglitazone, Linagliptin, Bromocriptine.[8]

Molecular Docking:

Molecular docking is a method to identify the architecture of compounds generated by two or more distinct molecules computationally. The objective of docking studies is to anticipate the desired three-dimensional structures. Docking is widely used to anticipate the alignment of small molecule therapeutic compounds concerning their protein targets in anticipating the small molecule's affinity and activity. Docking plays a critical role in rational drug design (Fig.1). Docking is the process of arranging molecules in the most advantageous arrangements for interaction with a receptor. [9]

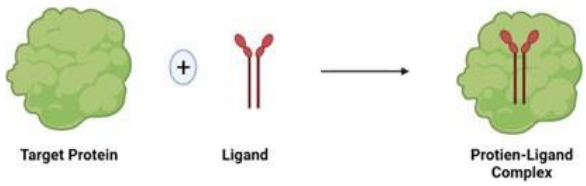


Fig 1: Molecular Docking

Protein Data Bank:

The Protein Data Bank was established at Brookhaven National Laboratory in 1971 as an archive for biological macromolecular crystal structures. Initial use of the PDB had been limited to a small group of experts involved in structural biology research. Today, depositors to the PDB have expertise in the techniques of X-ray crystal structure determination, NMR, cryo-electron microscopy and theoretical modelling. PDB users are a very diverse group of researchers in biology and chemistry, as well as educators and students of all levels. The tremendous influx of data, soon to be fuelled by the structural genomics initiative and the increased recognition of the value of these data toward understanding biological function, continually demand new ways to collect, organize and distribute the data.[10] Protein database containing experimentally determined three-dimensional structures of proteins, nucleic acids and other biological macromolecules.[11]

2. Objectives

The objective of the study is the *in-silico* prediction of physicochemical properties, molecular docking studies and synthesis of 1, 3, 4, oxadiazole derivatives as α-glucosidase enzyme inhibition for diabetes mellitus.

3. Methods

Chemistry

All reagents and solvents used in this work were of synthetic grade obtained from Oxford Laboratory and Lobachemie Pvt. Ltd. Melting points were determined by open tube capillary method and were uncorrectedof all synthesized compounds (˚C). Progress of the reactions was monitored by TLC on silica gel-G in solvent system hexane-ethyl acetate (1:1) and the spots were located under iodine vapours and UV light. IR spectrum was recorded on FTIR-1800 Shimadzu. 1HNMR and C^{13} NMR spectrums and Mass spectra were measured by IISER Bhopal.

Designing of compound:

Novel derivatives which consist of Oxadiazole is a five-membered heterocycle compound containing two carbon, two nitrogen, and one oxygen atom in the ring. Depending upon the position of the nitrogen atom, the oxadiazole ring may yield four different isomers. by Bukhari Asma et. al.[12] On the basis of reported literature review, 1,3,4-oxadiazole is the very important class in synthetic medicinal chemistry having different biological activities such as anti-inflammatory, analgesic, antimicrobial, anti-HIV, anticancer, anthelmintic, anticonvulsant, antiviral, hyperglycaemic, antitubercular [13] Gani Ramesh S. et. al. developing a novel class of antidiabetic agents. [14] On the basis of above facts we have designed a Pharmacophore **(Fig. 2)** consists carbon, nitrogen, and oxygen like nucleus and a substituted sulphur side chain. On the basis of reported structure activity relationship, 33 compounds were designed using ChemDraw ultra 8.0 as potential antidiabetic agents with different substitutions shown in **Table 1**

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

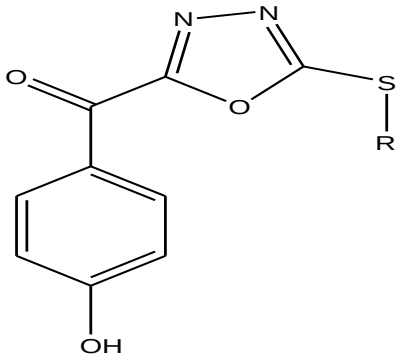


Fig 2 Designed Pharmacophore

Table 1: Designed 1,3,4-oxadiazole substituted analogues

S. No.	Compound ID	R
1	A1	$C_6H_5NH_2$
2	A2	$C_3H_7NO_2$
3	A3	C_5H_5N
4	A4	$C_9H_{11}NO_2$
5	A5	4- C_6H_6ClN
6	A6	2- C_6H_6ClN
7	A7	3- C6H6ClN
8	A8	$C_2H_8N_2$
9	A9	$C_8H_{11}N$
10	A10	$(CH_3)_2NH$
11	A11	$C_6H_{13}NO_2$
12	A12	$C_9H_{11}NO_3$
13	A13	$C_5H_{10}N_2O_3$
14	A14	$C_6H_6N_2O_2$
15	A15	2- $C_6H_6N_2O_2$
16	A16	$C_6H_8N_2$
17	A17	$C_7H_9NO_2S$
18	A18	$C_6H_8N_2O_2S$
19	A19	$C_7H_7NO_2$
20	A20	$C_{10}H_8$
21	A21	HOC_6H_4COOH
22	A22	$C_7H_5NO_3$
23	A23	$C_8H_8O_3$
24	A24	$C_8H_{10}OFN$
25	A25	$C_9H_{10}O_3$
26	A26	$C_6H_5NO_3$
27	A27	$C_{14}H_{14}O$
28	A28	$C_6H_7FN_2$
29	A29	$C_7H_6N_2$
30	A30	C_8H_9NO
31	A31	$(C_6H_5)_2CO$
32	A32	$C_6H_6NO_2$

Synthesis of compounds: On the basis of docking result, compounds A4, A11, A12, and A15 were synthesized using synthetic Scheme **(Fig 3)**

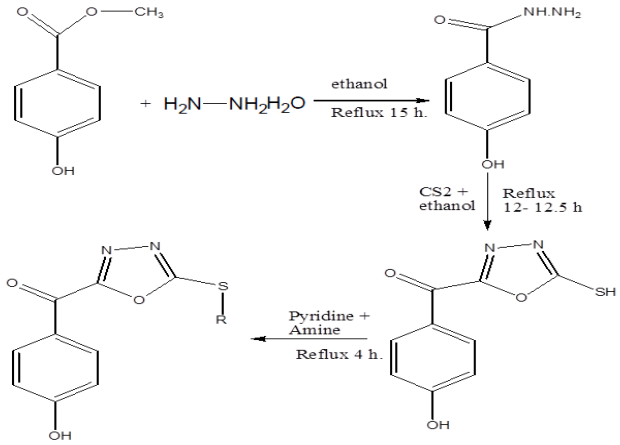


Fig.3: Scheme of Synthesis

Step-I: - General Procedure for the Synthesis of 4-hydroxybenzohydrazine- A mixture of (15.22ml, 0.1mole) Methyl 4-hydroxybenzoate and (6.41 ml, 0.2 mole) hydrazine hydrate were refluxed in 50ml ethanol for 15 hours. The resultant mixture was concentrated, cooled and poured into crushed ice. The solid mass thus separated out was dried and recrystallized from ethanol.

Step-II: - General Procedure for the Synthesis of 4-hydroxypheny1)(5-mercapto-1,3,4 oxadiazole-2-yl)methamone- A mixture of (1.52g, 0.01mole) of 4-hydroxybenzohydrazine, (0.56g, 0.01mole) of KOH and 10ml of CS2 (Carbon disulfide) were refluxed in 50ml of 95% ethanol for 12-12.5hours. The resultant mixture was concentrated and cooled to room temperature, acidified with dil. HCl. and the crude product was filtered and recrystallized from ethanol.

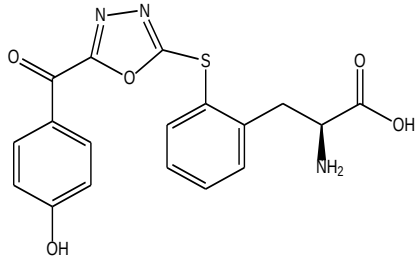
Step-III: -General Procedure for the Synthesis of (4-hydroxyphenyl)(5-(methylthio)-1,3,4, oxadiazole-2yl) methanone- A mixture of (0.97g, 0.005mol) of 4-hydroxypheny1)(5-mercapto-1,3,4 oxadiazole-2-yl)methamone and (0.005mol) of different Aromatic Amines were refluxed in 25ml of pyridine solution for 4 hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol.[15] The synthesized

Journal of Chemical Health Risks

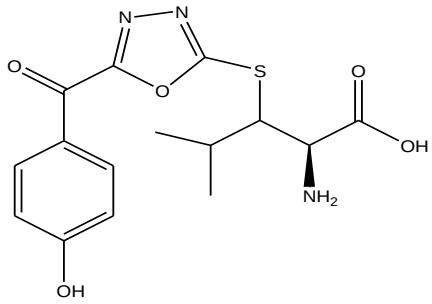
www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

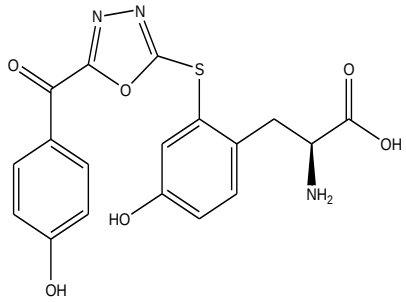
pharmaphores with chemical structure and their compound ID are shown in **Fig 4**



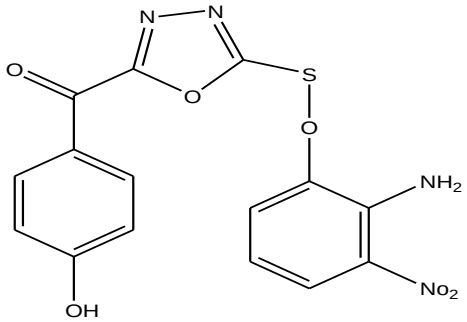
Compound ID: A4



Compound ID: A11



Compound ID: A12



Compound ID: A15

Fig.4: Structures of synthesized molecules having antidiabetics activity

4. Results

In - silico prediction of physicochemical properties:

- ***Lipinski rule of five:***

Table 2: Results of Lipinski rule of five

Discussion: According to Lipinski's rule, an orally active drug-like molecule shouldn't contain more than one violation of the following standards: Molecules with masses under 500 Dalton and high lipophilicity (defined as a Log P 5) Molar refractivity should be between 40 and 130, with less than five hydrogen bond donors and ten hydrogen bond acceptors. The compounds A4, A11, A12, and A15 were exhibited in the range of data, adhering to Lipinski's rule of five.

- ***Molinspiration Property:***

Table 3: Results of Molinspiration properties

Property	A4	A11	A12	A15
mi LogP	-0.54	-1.10	-1.05	0.42
TPSA	139.5	139.5	159.7	111.4
n Atoms	27	24	28	25
MW	385.40	351.38	401.40	846.33
n OH	8	8	9	7
n OHNH	4	4	5	3
n Violations	0	0	0	1
n Rotb	7	7	7	6
Volume	317.17	295.73	325.18	329.82

- ***Molinspiration Bioactivity:***

Table 4: Results of Molinspiration bioactivity

Property	A4	A11	A12	A15
GPCR ligand	0.03	-0.37	0.03	-0.23
Ion channel modulator	-0.28	-0.65	-0.29	-0.43
Kinase inhibitor	-0.16	-0.35	-0.16	-0.06
Nuclear receptor ligand	0.00	-0.30	0.03	-0.26
Protease inhibitor	0.28	0.08	0.26	-0.12
Enzyme inhibitor	0.29	-0.03	0.28	0.06

Comp. ID	Mass	H Bond Donor	H Bond Acceptors	LOG P	Molar Refractivity
A4	385.00	4	8	2.111	95.717
A11	351.00	4	8	1.534	85.931
A12	401.00	5	9	1.817	97.382
A15	374.00	3	9	2.582	89.831

Discussion: The bioactivity scores of the synthesised complexes were determined based on a variety of characteristics, including binding to nuclear and G protein-coupled receptor (GPCR) ligands, ion channel

Journal of Chemical Health Risks
www.jchr.org
JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

modulation, kinase and protease inhibition, and enzyme activity inhibition. By using Molinspiration software, all synthesised compounds (A4, A11, A12, and A15) displayed potential bioactivity scores for therapeutic targets.

- ***PreADMET study:***

Table 5: Results of ADME properties

Properties	A4	A11	A12	A15
BBB	0.048	0.067	0.038	0.056
Caco2	1.742	0.719	2.327	3.863
HIA	78.932	56.990	60.051	58.830
MDCK	4.253	56.990	0.272	0.500
P. Pro. Binding	68.189	34.190	67.799	92.119
Skin Permeability	-3.558	-3.808	-4.293	-3.665

- ***Molecular Docking Analysis:***

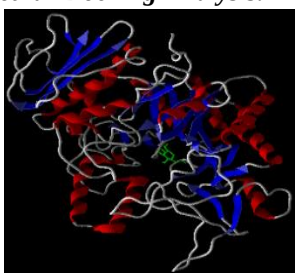
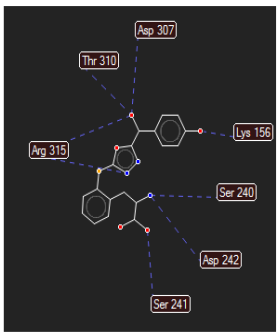
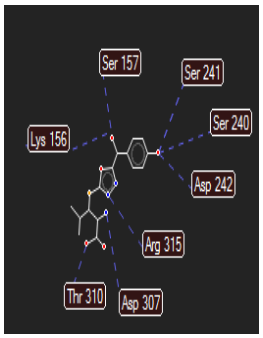


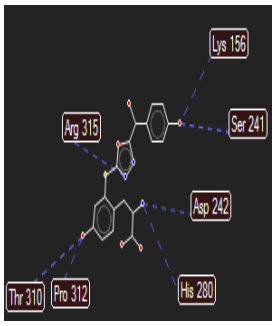
Fig 5: Target protein of diabetic receptor (3A4A)



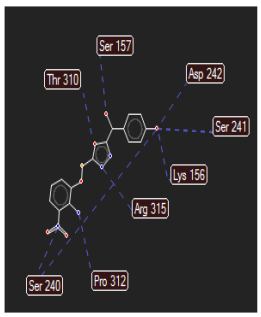
Compound ID: A4



Compound ID: A11



Compound ID: A12



Compound ID: A15

Fig 6: Hydrogen bond interaction of compound

Table 6: Results of docking analysis

Comp. ID	Mol Dock Score	H-bond interaction	Interaction
A4	-141.494	-8.70331	Thr310, Asp307, Arg315, Ser240, ASp242, Ser241
A11	-131.691	-12.4014	Ser157, Ser241, Ser240, Asp242, Arg315, Asp307, Thr310,
A12	-160.634	-12.8327	Lys156, Ser241, Asp242, His280, Pro312, Thr310, Arg315
A15	-142.342	-11.563	Ser157, Asp242, Ser241, Arg315, Pro312, Ser240
Standard	-97.4087	-9.01594	His112, Asp215, Tyr72, Asp69, Gln182

Discussion: Using Molegro Virtual Docker software, the molecular docking investigations examined the interaction patterns of pharmaphores (A4, A11, A12, and A15) with the active site of receptor PDB ID 3A4A. Derivatives A4, A11, A12, and A15 displayed bingeing energy with receptors ranging from -12.8327 to -8.70331 kcal/mol. Compound A12 had the highest affinity for PDB 3A4A and the highest binding energy, measuring -12.8327 kcal/mol. The chemicals interact with PDB ID 3A4A by a variety of mechanisms, including polar contacts, charged negative and positive interactions, hydrophobic interactions, pi-pi stacking, and hydrogen bonding are shown in table no.6. The best-fit compounds

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

A4, A11, A12, and A15 hydroxy groups and their carbonyl functions form four hydrogen bonds with Arg 315, Thr310, Ser 241, Lys 156 amino acids, hydrophobic interaction with ASP242, hydrophobic interaction with Pro 312, Glu411 His280, and pi-pi stacking with Tyr 158 amino acids of receptor 3A4A are shown in **Fig 6.**

Characterization:

Table 7: Physical Data of synthesised compound

Property	A4	A11	A12	A15
Molecular weight (g/mol)	385.39	351.38	401.39	374.76
Appearance	Light yellow	Pale yellow	White off	Pale yellow
Rf value	0.68	0.76	0.68	0.71
Melting point (°C)	269-283	285-290	270-290	110-120
Solubility	Ethanol, DMSO	Ethanol, DMSO	Ethanol, DCM	Ethanol, DCM
% yield	67 %	72 %	68 %	78 %

Structural Analysis of Compounds:

Compound A12: **λ Max. -** 222.00 nm.**IR: -**3400-3500 cm-1(OH stretching intermolecular H-bond), 2860-2980 (CH stretching),1600-1700 cm-1 (Cyclic Ester of C-O), 1720 cm-1 (Carboxylic acid COOH), 1400-1500 cm-1 (Ring Stretching), 1750 cm-1 (In plane bending of C-OH), 800-900 cm-1(C-O Stretching of primary alcohol).**H^1 NMR** -11.08 (OH of Carbonyl group), 6.570-7.640 (Aromatic Hydrogen), (C-OH Aromatic ring), 2.858-3.113 (Doublet of CH_2), 2.005 (Hydrogen of NH_2).**C^{13} NMR-** 186.23 (Carbonyl Carbon), 174.2488 (COOH), 156.72-162.88 (C-OH), 112.29-134.72 (Aromatic Carbon), 76.72-77.81($CDCl_3$), 57.65 (Carbon of Oxadiazole), 32.72 (Methylene Carbon) **MassSpectra**: -374.2 M^+

Compound A15: **λ Max. -**240.20 nm. **IR: -** 3400-3500 cm-1(OH stretching intermolecular H-bond), 2860-2980 (CH stretching), 1600-1700 cm-1 (Cyclic Ester of C-O), 1400-1500 cm-1 (Ring Stretching), 1750 cm-1 (In plane bending of C-OH), 800-900 cm-1 (C-O Stretching of primary alcohol), 700 cm-1 (Out of plane Bending Aromatic ring C-N bending). **H^1 NMR** -6.770-7.680 (Aromatic Hydrogen), (C-OH of Aromatic ring) 4.005 (Hydrogen of NH_2 group).**C^{13} NMR**-188.24 (Carbonyl Carbon), 162.34 (C-OH group), 144.93 (Carbon of C-O-S), 114.50-134.72 (Aromatic Carbon), 76.81-77.31 ($CDCl_3$), 67.65 (Carbon of Oxadiazole). **Mass Spectra**: -401.2M^+

Pharmacological Anti-diabetic activity:

The present study reveals that the treatment with A12 and A15 for 21 days shows a significant anti-diabetic effect on alloxan-induced diabetic rats. The acute toxicity study indicates that A12 and A15 when administered orally at the dose of 400 mg/kg did not produce any sign of toxicity or death in treated animals. This suggests that LD50 of both the compounds is a non-toxic and safe dose for further use in the study. Alloxan is a widely used chemical agent to induce diabetes in rats. It acts on pancreatic ß cells of Langerhans causing partial destruction and inducing diabetes mellitus through reduced insulin secretion.The intraperitoneal administration of alloxan at the dose of 120 mg/kg destroys pancreatic ß cells giving rise to glucose level in rats. The induction of diabetes was confirmed by fasting blood glucose level above 250 mg/kg on the third day of administration of alloxan intraperitoneally using glucose strips. A significant reduction in blood glucose level was observed in compounds treated rats when compared with the diabetic control group. The rats treated with alloxan shows a continuous rise in blood glucose level for 21 days. There are many drugs are used for the treatment of diabetes mellitus and were found to be a very effective alternative to present drugs which are having many side effects. So, considering this we attempted to evaluate the anti-diabetic potential of both the compounds in alloxan-induced diabetic rats. Both A12 and A15 on single as well as multi-dose administration were able to reduce the blood glucose level. The repeated administration of compounds for 21 days significantly reduces the blood glucose level when compared with the diabetic control group. In the present study, we found that A12 and A15 when administered to diabetic rats reduces blood glucose level when compared with the diabetic control group. The compounds might be produced their anti-diabetic activity by increasing the production or release of insulin from the pancreas or reducing insulin resistance.

It is well known that metformin produces hypoglycemia by decreasing the peripheral resistance to insulin and increasing glucose transporter activity in cells. In our study, both the compounds to reduce blood glucose levels which may be possible due to an increase in insulin release or due to an increase in peripheral glucose uptake. The compounds may be acting on some of the surviving pancreatic ß cells and increase the release of insulin responsible for anti-diabetic potential.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

In the oral glucose tolerance test blood, glucose level was estimated at the intervals of 0, 30, 60, 120, and 240 minutes. This test shows the glucose utilization by the body and is used to diagnose diabetes. The blood glucose level by administration of two different doses of A12 and A15 was found to be dose-dependent when compared to the diabetic control group. In lipid metabolism, alloxan produces hyperlipidemia in diabetic rats which may be due to an increase in the release of free fatty acids from stored fats.

Biochemical variations in Diabetes mellitus occur because of altered structure and function of the pancreas, enzyme activity, and resistance development to hormones. A high TC and TG are attributed to stopping cholesterol catabolism, lack of insulin, or adipose tissue releasing fatty acids by lipolysis. The rise in HDL-cholesterol levels used to wash out the excess cholesterol from the body is considerably reduced in DM. The improvement in HDL-cholesterol is complemented by an improved breakdown of VLDL and placing of TG in the central of HDL with cholesterol. This lipid normalizing action of A12 and A15 may be due to its actions on enzymes involved in lipid metabolism. This contributes to preventing the development of neuropathy, atherosclerosis, and cardiovascular complications associated with diabetes.

Our present study also reveals that the lipid profile i.e., triglyceride and total cholesterol were significantly decreased by A12 and A15 when compared to the diabetic control group. In contrast, the mean HDL level of compounds treated rats was significantly higher as compared to the diabetic control group. Thus, the treatment with A12 and A15 may act on stored fats which inhibits the release of free fatty acids and decreases the triglyceride and total cholesterol level. The compounds also increase HDL levels in diabetic rats after treatment for 21 days. In vitro studies have shown that alloxan is selectively toxic to the pancreatic ß cells, causing cell necrosis. The cytotoxic action of alloxan is mediated by reactive oxygen species, with a simultaneous massive increase in cytosolic calcium concentration, leading to a rapid destruction of ß cells. The metformin-treated group showed regeneration of ß cells. The comparable regeneration of ß cells was also shown by A12 and A15.

Table 8: Effect of Drugs on the serum lipid profiles in Alloxan-Diabetic rats after 21 days of treatment

Exp. Group	Treatment	Blood glucose concentration (mg/dl) (mean ± S.E.M.)		
		HDL mg/ dl	VLDL mg/dl	LDL mg/dl
1	Normal control	54.32± 1.1	24± 2.8	23.2± 1.8
2	Diabetic Control	38.26± 2.9	39.28± 2.3	36.68± 1.2
3	Metformin (150mg/kg)	42± 1.8	29.3± 2.5	24.25± 3.1
4	A12 (400mg/kg)	49.58± 0.4	39.8± 3.1	34.36± 2.5
5	A15 (400mg/kg)	49.32±0. 9	33.48±2. 2	27.20±3.2

Exp. Group	Treatment	Blood glucose concentration (mg/dl) (mean ± S.E.M.)	
		TG mg/dl	Total Cholesterol mg/dl
1	Normal control	71.75± 2.4	55.35± 2.2
2	Diabetic Control	128± 3.4	88.3± 4.2
3	Metformin (150mg/kg)	84± 2.7	59.35± 1.9
4	A12 (400mg/kg)	113± 3.1	75.30± 1.3
5	A15 (400mg/kg)	107± 2.8	72.85±2.1

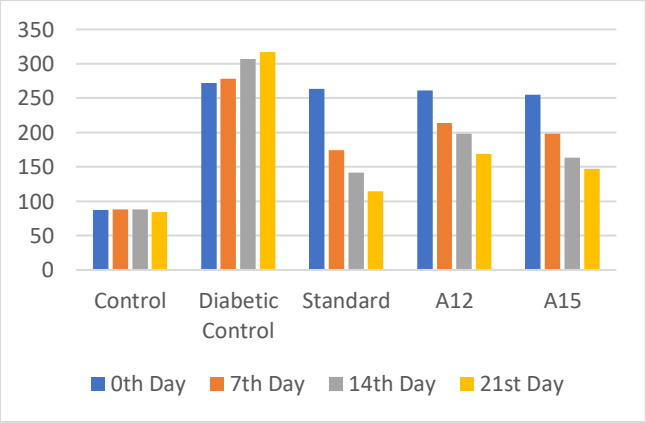


Fig.7: Effect of Drugs on the blood glucose levels in Alloxan induced diabetic rats (Multi dose treatment /sub-acute study)

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(2), 1942-1949 | ISSN:2251-6727

5. Discussion

In this study 1,3,4-oxadiazole derivativeswere synthesized and evaluated for their Antidiabetic potential. On the basis of physio-chemical, Molecular docking and in-slico prediction studies all of four derivatives **(A4, A11, A12, A15)** have been performed and synthesized. IR spectroscopy, NMR and Mass spectroscopy were performed for the characterization of the synthesized compound.The ligand-binding interactions of synthesized analogs with the protein. Docking studies of these compounds showed good interaction with the PDB ID- 3A4A and forces like hydrogen bond, polar, hydrophobic bond, and charged positive and charged negative interaction forces were found to be important in the compound binding to the receptors. Compound A12 displayed the maximum binding energy i.e., -12.8327 kcal/mol with the highest affinity among the entire compound compared with the standard Metformin of -9.01594 kcal/mol. Yield of all compounds was in the range of 62.2-79.9 %. The anti-diabetic effects of all compounds were moderate to excellent. The acute toxicity study indicates that A12 and A15 when administered orally at the dose of 4000 mg/kg did not produce any sign of toxicity or death in treated animals. Our study reveals that oxadiazole pharmacophore are one of the important pharmacophores to develop antidiabetic potential compounds. Further QSAR study requires to reveal essential structural requirement.

Refrences

1. Vaghani Hasit, 2021. 1, 3, 4-oxadiazole and its potency: a review. International Journal of Pharmaceutical Sciences and Research. 12(10),5292-5299. https://doi.org/10.13040/IJPSR.0975-8232.12(10).5292-9
2. Bhutani Rubina, 2019. Novel hybrids of benzothiazole-1,3,4-oxadiazole-4-thiazolidinone Synthesis, *in silico* ADME study, molecular docking and *in vivo* anti-diabetic assessment. Bioorganic Chemistry. 8(1),6–19. https://doi.org/10.1016/j.bioorg.2018.10.025
3. Hamada H Amer, 2018. Synthesis of some new 1,3,4-oxadiazole derivatives bearing sugars and α-aminophosphonate derived from 4-nitrophenol as anticancer agents. National Journal of Physiology, Pharmacy and Pharmacology. 8(9): 1275- 1286. DOI: 10.5455/njppp.2018.8.0416408052018
4. Semere Welday Kahssay, 2012. Design, Synthesis, Characterization and in vivo Antidiabetic Activity Evaluation of Some Chalcone Derivatives. Drug Design, Development and Therapy. 5(2), 3119- 3129.
5. Padhi santwana, 2020. Type II diabetes mellitus: a review on recent drug-based therapeutics. Journal of Biomedicine & Pharmacotherapy. 7(1), 1-23. https://doi.org/10.1016/j.biopha.2020.110708
6. Mukhopadhyay Nabarun, 2019. Antidiabetic Medicinal Plants: A Review. International Research Journal of Pharmacy. 10(2), 31- 37 DOI: 10.7897/2230-8407.100237.
7. Lal b. Suresh, 2016. Diabetes: causes, symptoms and treatments. Public health environment and social issues in India. 55- 67.
8. Tripathi K.D, 2013. Essential of medical pharmacology. Jaypee brothers medical publisher (P) Ltd. 7, 1-1002.
9. Raval Keval, 2022. Basics, types and applications of molecular docking: A review. IP International Journal of Comprehensive and Advanced Pharmacology. 7(1), 12-16.
10. Berman Helen M., 2002. The Protein Data Bank. International Union of Crystallography. 899-907.
11. Sussman Joel L., 1998. Protein Data Bank (PDB): Database of Three-Dimensional Structural Information of Biological Macromolecules. International Union of Crystallography. 54(1), 1078-1084.
12. Bukhari Asma, 2021. Novel oxadiazole derivatives as potent inhibitors of α-amylase and α-glucosidase enzymes: Synthesis, in vitro evaluation, and molecular docking studies. Iranian Journal of Basic Medical Sciences. 24: 1632-1642. doi:https://dx.doi.org/10.22038/IJBMS.2021.58429.12977
13. Singhai Anuj, 2018. Synthesis and Characterization of 1, 3, 4-Oxadiazole Derivatives. Journal of Drug Delivery and Therapeutics. 8(6-A), 25-27.
14. Gani Ramesh S., 2021. Synthesis of novel 5-(2,5-bis(2,2,2-trifluoroethoxy) phenyl)-1,3,4-oxadiazole-2-thiol derivatives as potential glucosidase inhibitors. Bioorganic Chemistry. 114(2), 1-11. https://doi. org/10.1016/j.bioorg.2021.105046.
15. Parikh Palak K., 2011. Synthesis And Biological Evaluation of 1,3,4-Oxadiazole Derivatives As Potential Antibacterial And Antifungal Agents. International Journal of Drug Development & Research. 3(2): 248- 255.