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SYNTHESIS & PREDICTING THE POSSIBILITY OF 2, 5-DISUBSTITUTED-1, 3, 4-OXADIAZOLE DERIVATIVES AS GSK-3β INHIBITORS

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ABSTRACT

A new series of 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives were synthesized using appropriate methods & structures of the synthesized compounds were confirmed by IR,NMR & Mass spectral data.. These ligands were prefiltered for their drug likeness properties by Lipinski's rule of 5 and it was found that all the ligands satisfied the rule of 5 for oral bioavailability.The prefiltered ligands were subjected for docking studies using integrated web server called docking server to investigate the interactions between the target compounds and the amino acid residues of the Glycogen synthase kinase-3β. The docking studies were done using auto dock between computationally designed 2,5-disubstituted 1, 3, 4-oxadiazole derivatives and Glycogen synthase kinase-3beta (GSK-3β) protein. The Calculated free energy of binding and estimated inhibition constants (Ki) were remarkable when compared with the standard GSK-3β inhibitors. It is calculated by the Lamarckian Genetic Algorithm (LGA). These values & the proposed interactions suggested that the 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives are excellent inhibitors of GSK-3β.

INTRODUCTION: Recent developments indicate that the regeneration of beta cell function and mass in patients with diabetes is possible. A regenerative approach may represent an alternative treatment option relative to current diabetes therapies that fail to provide optimal glycemic control.

Specific and potent Glycogen Synthase Kinase-3beta inhibitors also alleviate the toxic effects of high concentrations of glucose and the saturated fatty acid palmitate on INS-1E cells. Furthermore, treatment of isolated rat islets with structurally diverse small molecule GSK3β inhibitors increases the rate of beta cell replication by 2–3-fold relative to controls.

Diabetes results from an inadequate supply of the body with insulin. In type 1 diabetes, beta cells are destroyed by an autoimmune attack [1-3].

Despite remarkable improvements in the management of diabetic patients over the last decades, new therapies are still needed to further improve metabolic control and thereby reduce the development of diabetic complications that are associated with significant rates of morbidity and mortality [4].

One of the most promising concepts for the treatment of diabetes is the development of therapies for the preservation and regeneration of beta cell mass and function.

Ongoing formation of new beta cells in patients with type 1 diabetes has been described even in patients with long disorder history. This suggests that beta cell regenerative treatments could be successful even in patients with longstanding type 1 diabetes, provided the autoimmune destruction of beta cells can be controlled [5-6]. Individuals with type 2 diabetes could also benefit from agents that preserve or expand beta cell mass, since several studies have demonstrated that the beta cell mass is significantly reduced in these patients [7-12].

Beta cell mass in humans and rodents is dynamically regulated in response to changes in insulin requirements [13]. A number of recent reports have demonstrated using rodent models of diabetes that pancreatic beta cell mass is responsive to pharmacologically active agents promoting beta cell expansion and/or protection. Several proteins exhibit beta cell regenerative activities in rodent models of diabetes, with long acting analogs of the incretin hormone GLP-1 being among the most promising candidates [14-18].

On the contrary, effective small molecule agents or chemically tractable candidate drug targets for systematic development of small molecule therapeutics are scarce. Studies with growth factors and genetic approaches have established the significance of certain intracellular pathways, including insulin signaling, Janus kinase/signal transducer and activator of transcription signaling, and G-protein-coupled receptor signaling for the regulation of beta cell mass [19].

In diabetes, beta cell loss and dysfunction are most likely resulting from synergistic effects of different factors negatively affecting beta cells for prolonged periods of time. For instance, chronic or recurrent exposure of beta cells to elevated levels of glucose and lipids (glucolipotoxicity) or to proinflammatory cytokines, such as interleukin-1β, tumor necrosis factor α, and interferon-γ, interferes with beta cell function and contributes to their destruction [20]. Using potent and specific small molecule GSK-3β inhibitors resulted in the inactivation of GSK-3β protein, leads to protection to beta cells against death induced by high concentrations of glucose and the saturated fatty acid palmitate.

In addition, small molecule GSK3 inhibitors robustly stimulate beta cell proliferation. These results suggest that GSK-3 plays a key role in the regulation of beta cell mass and is a target for beta cell regenerative therapies. Several 1, 3, 4-oxadiazole nucleus containing derivatives are known to inhibit Glycogen synthase kinase-3beta (GSK-3β).

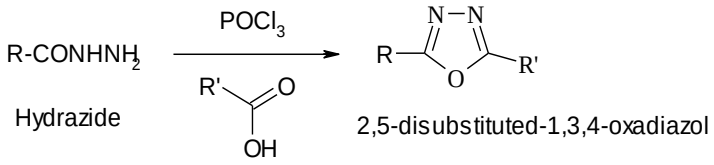
Taking these points in to account, some new 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives were synthesized by the appropriate methods. These ligands having different substitutions were designed computationally and targeted for Glycogen synthase kinase-3beta inhibitory activity based on molecular docking between ligands and GSK-3beta protein (PDB Code 3F7Z) using molecular docking server. The docked ligands were further synthesized using appropriate methods & identified by IR, NMR & Mass spectral data.

MATERIALS & METHODS:

Materials & Reagents for synthesis: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points of synthesized compounds were determined using open capillary tube and are uncorrected. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel (60GF-254) plates and visualized with UV light.IR spectra were recorded on Thermo Nicolet spectrophotometer by using KBr pellets. The ^{1}H-NMR was recorded on Bruker Avance II NMR 400 MHz instruments using DMSO as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm). The final compounds were synthesized as per the **Scheme 1**.

General procedure for Synthesis of 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives:(SS1-SS10) [21]: A mixture of corresponding hydrazide (0.01mole) and appropriate aromatic carboxylic acid 0.01mole in 50 ml ethanol containing phosphoryl chloride as a catalyst was refluxed for 4-5 h at 120^{o}C. The mixture was cooled and poured into crushed ice and made neutralize by 20% NaOH. The resulting solid was, filtered, and the separated product was purified by recrystallization from ethanol. The physico-chemical & spectral data of 2, 5-disubstituted-1, 3, 4-oxadiazoles (SS1-SS10) is depicted in **Table 1**.

Scheme-1



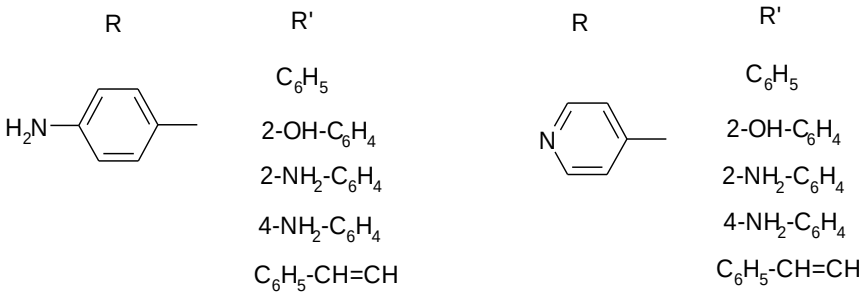
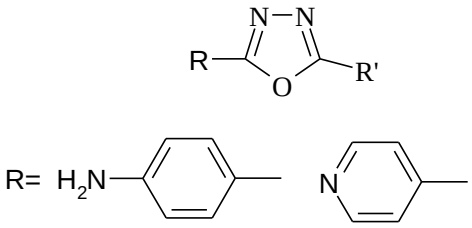


TABLE 1: PHYSICO-CHEMICAL DATA OF 2, 5-DISUBSTITUTED-1, 3, 4-OXADIAZOLES: (SS1-SS10)



Comp. No.	R^1	Appearance	Molecular Formula	Molecular Weight	M.P.(^{0}C)	Yield (%)
SS1	C_6H_5	Brown	$C_{14}H_{11}O_1N_3$	237	184-86	87
SS2	2-OH- C_6H_4	Yellowish brown	$C_{14}H_{11}O_2N_3$	253	216-18	52
SS3	C_6H_5-CH=CH	Yellowish	$C_{14}H_{13}O_1N_4$	264	210-12	53
SS4	2-NH_2- C_6H_4	Yellowish	$C_{14}H_{12}O_1N_4$	252	110-12	48
SS5	4-NH_2- C_6H_4	Yellowish	$C_{14}H_{12}O_1N_4$	252	240-42	57
SS6	C_6H_5	Yellowish white	$C_{13}H_9O_1N_3$	223	144-48	57
SS7	2-OH- C_6H_4	Brown	$C_{13}H_9O_2N_3$	239	142-44	70
SS8	C_6H_5-CH=CH	Blackish brown	$C_{15}H_{13}O_1N_4$	251	126-28	58
SS9	2-NH_2- C_6H_4	Yellowish	$C_{13}H_{10}O_1N_4$	238	220-26	49
SS10	4-NH_2- C_6H_4	Yellowish white	$C_{13}H_{10}O_1N_4$	238	190-94	71

Spectral data of 2, 5-disubstituted-1, 3, 4-oxadiazoles: (SS1-SS10)

1. **4-(5-phenyl-1, 3, 4-oxadiazol-2-yl)aniline(SS1):** FTIR(KBr)cm^{-1}: 1685.0,1655.9(C=N), 3005.9 (Aromatic C-H str), 3326.1, 3260.1(NH_2).1073.9(C-O-C); mass: m/z 237 (M^+).

2. **2-[5-(4-aminophenyl)-1,3,4-oxadiazol-2-yl]phenol (SS2):** FTIR(KBr)cm^{-1}: 16851635.5(C=N), 2922.2, 2961.5 (Aromatic C-H str), 3440.0(OH), 3253.3(NH_2),1059.8(C-O-C);mass: m/z 253 (M^+); ^{1}H-NMR (300 MHz,DMSO-d6)., 4.41- 4.53 (2H, d, NH_2), 10.17(1H,S,OH),7.56-7.82(8H, m, Aromatic protons).

3. **4-{5-[(*E*)-2-phenylethenyl]-1,3,4-oxadiazol-2-yl}aniline (SS3):** FTIR (KBr) cm^{-1}: 1611.56(C=N), 2938.56.0(Aromatic C-H str), 3421.05,3187.37(-NH_2 str), 1009.08(C-O-rfC) ;mass: m/z 264 (M^+); ^{1}H-NMR (300 MHz,DMSO-d6)., 4.03-4.11(2H,d,NH_2),6.29-6.34 (2H,d,CH) 7.28-7.85(9H, m, Aromatic protons).

4. **2-[5-(4-aminophenyl)-1, 3, 4-oxadiazol-2-yl] aniline(SS4):** FTIR(KBr)cm^{-1}: 1639.62 (C=N), 3025.21(Aromatic C-H str), 3437.96, 3199.81(NH_2), 1071.48(C-O-C); mass: m/z 252 (M^+).

5. **4, 4'-(1, 3, 4-oxadiazole-2,5-diyl)dianiline (SS5):** FTIR(KBr)cm^{-1}:1684.51(C=N), 3010.44 (Aromatic C-H str), 3329.47,3258.08(NH_2),973.52(C-O-C) ;mass: m/z 252 (M^+); ^{1}H-NMR (300 MHz,DMSO-d6)., 4.00,4.12,4.194.53(2H,d,NH_2), 7.62, 7.67, 7.83, 7.89, 7.96 (8H, m, Aromatic protons).

6. **4-(5-phenyl-1, 3, 4-oxadiazol-2-yl)pyridine (SS6):** FTIR(KBr)cm^{-1}:1691.22(C=N), 3014.98(Aromatic C-H str), 1073.9(C-O-C).;mass: m/z 223 (M^+).

7. **2-[5-(pyridin-4-yl)-1, 3, 4-oxadiazol-2-yl]phenol (SS7):** FTIR(KBr)cm^{-1}: 1613.47, 1545.68(C=N), 3048.86(Aromatic C-H str), 3443.30(-OH str), 1068.38(C-O-C); mass: m/z 239 (M^+).

8. **4-{5-[(*E*)-2-phenylethenyl]-1, 3, 4-oxadiazol-2-yl} pyridine (SS8):** FTIR(KBr)cm^{-1}: 1691.06(C=N), 2924.38(Aromatic C-H str), 1084.20(C-O-C); mass: m/z 251 (M^+); 1H NMR (300 MHz,DMSO-d6)., 6.29-6.34(2H d CH), 7.11, 7.45, 7.96, 8.53(9H, m, Aromatic protons).

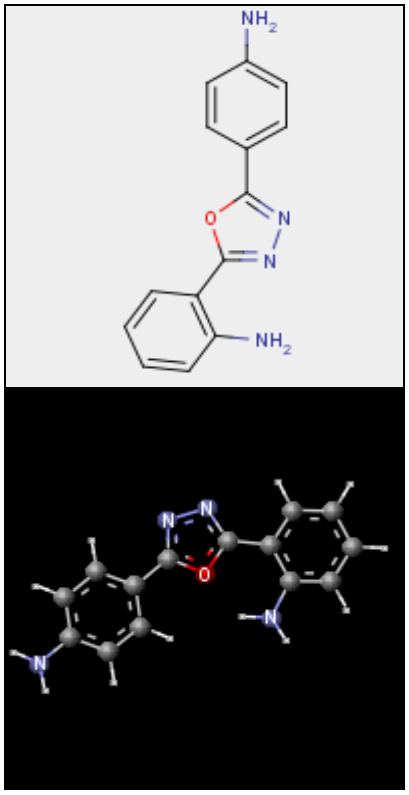
9. **2-[5-(pyridin-4-yl)-1, 3, 4-oxadiazol-2-yl]aniline (SS9):** FTIR(KBr)cm^{-1}: 1600.83(C=N), 2831.07 (Aromatic C-H str), 3258.08(NH_2),1084.98(C-O-C); mass: m/z 238 (M^+).

10. **4-[5-(pyridin-4-yl)-1, 3, 4-oxadiazol-2-yl]aniline (SS10):** FTIR(KBr)cm^{-1}: 1678.19(C=N), 3010.61 (Aromatic C-H str), 3335.86,(NH_2 str), 940.98(C-O-C); mass: m/z 238 (M^+).

The synthesized 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives were prefiltered for their drug-likeness properties using online version of molinspiration software which is based on the Lipinski's rule of 5 for checking the oral bioavailability of the drugs [22] & is shown in the **Table 2**.

Molecular docking studies:

Ligand Preparation: Docking calculations were carried out using DockingServer [23], The MMFF94 force field [24] was used for energy minimization of ligand molecule using molecular docking server Gasteiger partial charges were added to the ligand atoms. Non-polar hydrogen atoms were merged, and rotatable bonds were defined. **Figure 1** shows an example a 2, 5-disubstituted-1, 3, 4-oxadiazole derivative (SS4) in its 2D & 3D forms.



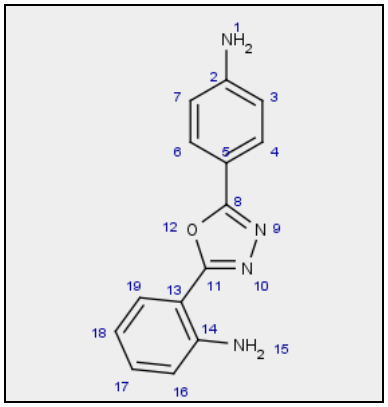


FIGURE 1: 2D & 3D STRUCTURE OF 2, 5-DISUBSTITUTED-1, 3, 4-OXADIAZOLE LIGAND

3F7Z Protein Preparation: Docking calculations were carried out on 2PRG protein model. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools [25] (Morris, Goodsell *et al*., 1998). Affinity (grid) maps of 20×20×20 Å grid points and 0.375 Å spacing were generated using the Autogrid program. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. **Figure 2** shows the x-ray co-crystal structure of the Glycogen synthase kinase-3beta protein.

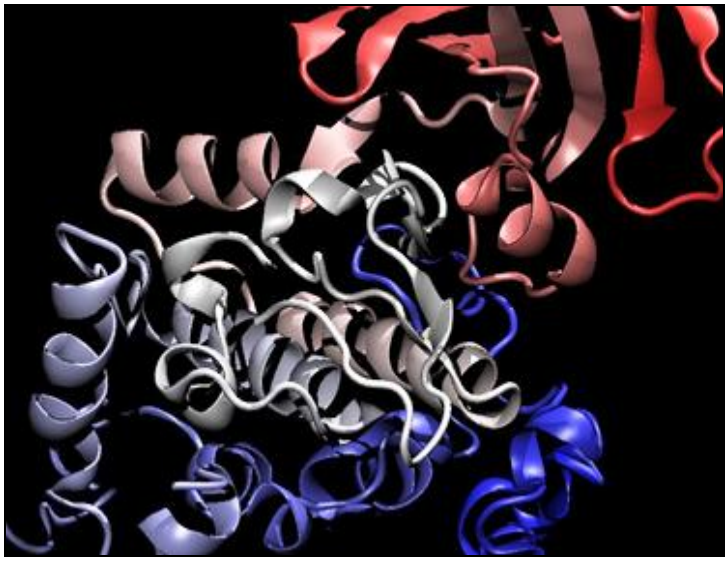
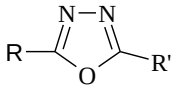
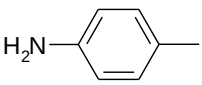
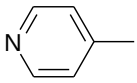


FIGURE 2: 3F7Z:X-RAY CO-CRYSTAL STRUCTURE OF GLYCOGEN SYNTHASE KINASE 3BETA FROM RCSB PROTEIN DATA BANK

Computational Methods: Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method [26]. Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

TABLE 2: PROPERTY PREDICTION OF THE SYNTHESIZED COMPOUNDS BY USING MOLINSPIRATION SOFTWARE



R=  , 

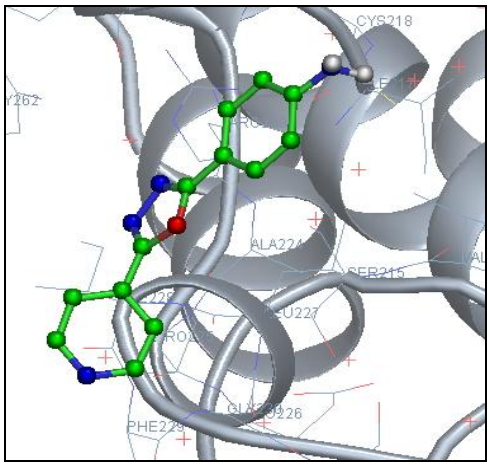
Compd. code	R^1	miLogP	TPSA	MW	nON	nOHNH	N violations	Nrotb	Molar refractivity (cm^3/mol)
SS1	C_6H_5	2.802	64.947	237.262	4	2	0	2	68.15 ± 0.3
SS2	2-OH- C_6H_4	2.535	85.175	253.261	5	3	0	2	70.03 ± 0.3
SS3	C_6H_5-CH=CH	2.815	64.947	263.3	4	2	0	3	80.95 ± 0.3
SS4	2-NH_2- C_6H_4	2.237	90.97	252.277	5	4	0	2	2.39 ± 0.3
SS5	4-NH_2- C_6H_4	1.878	90.97	252.277	5	4	0	2	72.39 ± 0.3
SS6	C_6H_5	2.437	51.816	223.235	4	0	0	2	62.01 ± 0.3
SS7	2-OH- C_6H_4	2.17	72.044	239.234	5	1	0	2	63.89 ± 0.3
SS8	C_6H_5-CH=CH	2.45	51.816	249.273	4	0	0	3	74.81 ± 0.3
SS9	2-NH_2- C_6H_4	1.872	77.839	238.25	5	2	0	2	66.24 ± 0.3
SS10	4-NH_2- C_6H_4	1.513	77.839	238.25	5	2	0	2	66.24 ± 0.3
Normal range		-0.4 to +5.6	<140	160 to 500	<10	<5	0	--	40 to 130

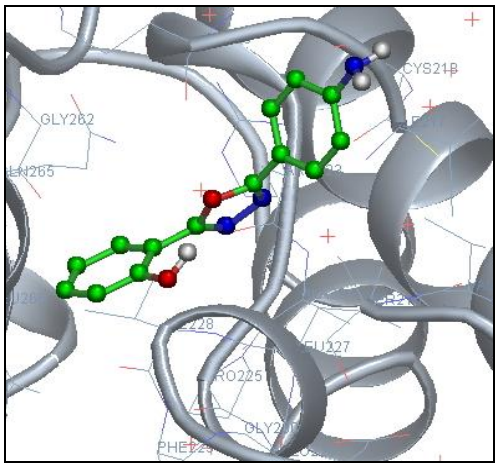
TABLE 3: ENERGY TABLE AND INTERACTIONS OF 2, 5-DISUBSTITUTED-1, 3, 4-OXADIAZOLES WITH 3F7Z

Comp. Code	R^1	Est. Inhibition Constant, Ki	Est. Free energy of binding (Kcal/mol)	vdW + Hbond + desolv Energy	Electrostatic Energy	Total Intermol. Energy	Interacting Surface
SS1	C_6H_5	0.69	-4.32	-5.23	+0.03	-5.20	550.711
SS2	2-OH- C_6H_4	1.00	-4.09	-5.06	+0.06	-5.00	540.054
SS3	C_6H_5-CH=CH	0.54	-4.46	-5.57	-0.07	-5.64	568.171
SS4	2-NH_2- C_6H_4	0.19	-5.06	-6.00	-0.15	-6.16	526.927
SS5	4-NH_2- C_6H_4	0.61	-4.38	-5.55	-0.01	-5.56	527.098
SS6	C_6H_5	1.03	-4.07	-4.64	-0.02	-4.66	508.802
SS7	2-OH- C_6H_4	0.73	-4.28	-4.56	-0.02	-4.58	483.925
SS8	C_6H_5-CH=CH	0.69	-4.31	-5.17	-0.03	-5.19	552.062
SS9	2-NH_2- C_6H_4	0.51	-4.49	-5.25	-0.01	-5.26	493.392
SS10	4-NH_2- C_6H_4	1.07	-4.06	-4.98	+0.04	-4.94	540.443
GSK3-beta inhibitor II		0.84	-4.20	-4.91	-0.11	-5.02	525.434
CHIR99021		0.20	-5.06	-6.40	-0.20	-6.60	720.07

TABLE 4: INTERACTION TABLE OF 4-[5-(2-AMINOPHENYL)-1, 3, 4-OXADIAZOL-2-YL]ANILINE (SS4)

Hydrogen bonds	Polar bonds	Other
N2-SER215	N2-ARG223	H8-VAL214
N3-SER215	N3-ARG223	N4-VAL214
------	------	H7-VAL214
------	------	C5-SER215
------	------	C8-ARG223





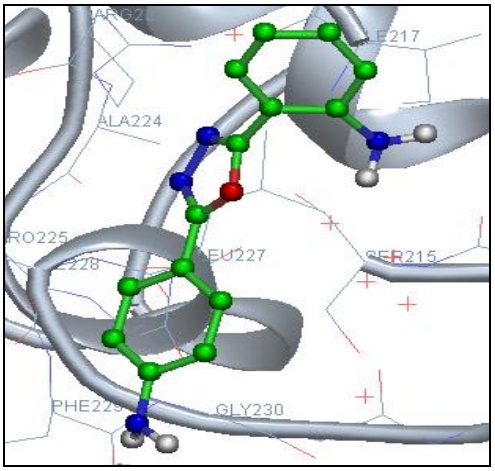


FIGURE 3: VISUALIZATION OF THE LOWEST ENERGY CONFORMATION OF COMPOUNDS (SS3, SS4 & SS9) to 3F7Z COMPLEX IS SHOWN IN ASTEXVIEWER™ (AN IN BUILT APPLICATION OF MOLECULAR DOCKING SERVER)

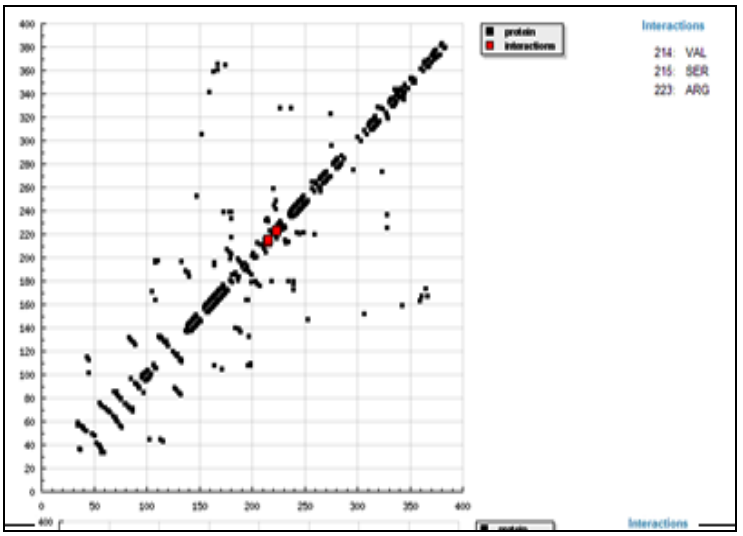


FIGURE 4: HB PLOT OF THE COMPOUND SS4 SHOWING INTERACTION WITH DIFFERENT AMINOACIDS OF THE PROTEIN [27, 28]

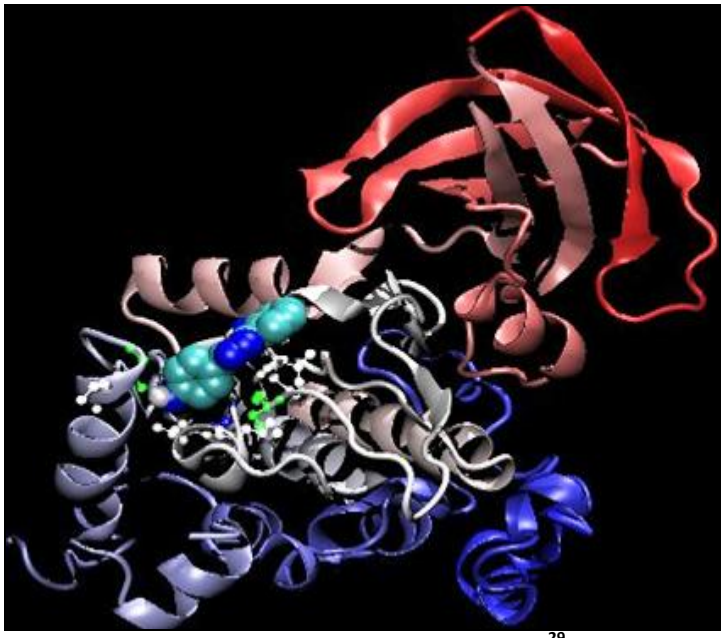


FIGURE 5: SS4 DOCKED WITH 3F7Z [29]

RESULTS & DISCUSSION: The synthetic route used to synthesize title compounds is outlined in Scheme 1. Various 2, 5-disubstituted-1,3,4-oxadiazoles (SS1-SS10) were prepared by treatment of corresponding hydrazides with various substituted aromatic carboxylic acid in the presence of phosphorous oxychloride. The structures of various synthesized compounds were assigned on the basis of their spectral studies. The physic-chemical data, FTIR, ^{1}H-NMR and Mass spectral data for all the synthesized compounds are reported in Table 1 & 2.The title compounds 2, 5-disubstituted-1, 3, 4-oxadiazoles (SS1-SS10) were obtained the reaction of corresponding hydrazides with different aromatic carboxylic acids in the presence of $POCl_3$. IR spectra of compounds showed characteristic peak of C=N at 1640.35 cm^{-1} , C-H (aromatic) at 3045.81 cm^{-1} , C=N at 1615.78 cm^{-1} ,O-H at 3440.15 cm^{-1} C-O-C at 1060.25 cm^{-1} . This is further supported by ^{1}H-NMR spectral data with δ value at 4.10(2H,d,NH_2), 6.30-7.78(8H,m.aromatic protons).

In the present study, we constructed a protein-ligands complex model with an X-ray crystal structure (PDB code 3F7Z; Figure 2) and the ligands were observed in crystal complex structures using MMFF94 simulation and by Gasteiger partial charges to gain better enrichment in virtual screening. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method (Solis and Wets, 1981). Initial position, orientation, and torsions of the ligand molecules were set randomly. Each docking experiment was derived from 10 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied. Interestingly, docking results reveal that all the compounds inside GSK3-β protein is outlined by different aminoacids and the hydrophobic pocket is comprised of VAL 214 & ILE 228.Small molecules are bound to human serum albumin by four binding modes; Hydrogen bonds, Van der vaals, electrostatic & hydrophobic interactions.

The result gives the total energy of four binding modes & is shown in **Table 3**. Calculated free energy of binding for compounds SS3, SS4 & SS9 in the inhibitor binding site (IBS) were -4.46, -5.06 and -4.49 kcal/mol respectively in the best pose (**Figure 3**). A comparison of different energies, interacting surfaces and frequencies of species etc. between compounds as well as GSK3-beta inhibitor II & CHIR99021 (known inhibitors) is listed in (Table 3).

The HB plot of the SS4-3F7Z complex shows the interaction of protein with the different aminoacid residues & is shown in **Figure 4**. The **Figure 5** Shows image of SS4 docked with 3f7z pdb code & software includes code developed by the Theoretical and Computational Biophysics Group in the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign. Ligand SS4 which has an amino group (-NH_2) at C14 & an amino group (-NH_2) at C2 is docked into IBS of 3F7Z outlined by SER 215, ARG 223, VAL 214.

In this position, 2 nitrogen atoms (N2 & N3) of oxadiazole ring appears hydrogen bonded with the SER 215 (bond length = 3.09 & 3.31 γ Å respectively). Polar interactions were made between the same 2 nitrogen atoms of oxadiazole ring & the ARG 223.The other interactions for compound SS4 comprised of VAL 214 (H8, N4, H7), SER215 (C5) & ARG 223 (C8). From our results, we presumed that compound SS4 is anchored in to inhibitory binding site by hydrogen bond between nitrogen atoms of oxadiazole & SER 215 while the confirmation stability is brought about by other weak interactions which involve H8, N4 & H7 bonded with VAL 214.

In the present study, we have made detailed analysis of compounds SS1-SS10 in the context of its inhibition of GSK-3beta activity. All the compounds screened in the present study have 1, 3, 4-oxadiazole ring having substitution at 2^{nd} & 5^{th} position. Compounds having such moiety most likely offer a wide range of bioactivities such as anti-inflammatory, antimycobacterial, anti-convulsant etc., activities. Recently, these compounds are found to possess anti-diabetic & anti-alzheimer activities. Hence 1,3,4-oxadiazole ring with substitutions at 2^{nd} & 5^{th} position seems to be important for imparting GSK-3beta inhibitory activity.

CONCLUSION: All the ligands have shown inhibition to GSK-3β, especially SS4 which contains activating substituents (-NH_2) on both ortho & para position of the aromatic ring attached to the 2^{nd} & 4^{th} position of 1, 3, 4-oxadiazole when compared with the standard GSK-3beta inhibitors. It is observed that the compounds have hydrogen & also other interactions which are important for the folding of proteins. This is important in keeping a protein alive and biologically active, because it allow to the protein to decrease in surface are and reduce the undesirable interactions with water. Therefore, it is evident that these 2, 5-disubstituted-1, 3, 4-oxadiazoles are good GSK-3beta inhibitors. These agents can be utilized to treat Type-I Diabetes mellitus & will play vital role as anti-diabetic agents.

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REFERENCES:

1. Gianani, R., and Eisenbarth, G. S.: The stages of type 1A diabetes. Immunol. Rev.2005; 204: 232-249.
2. Donath, M. Y., Ehses, J. A., Maedler, K., Schumann, D. M., Ellingsgaard, H., Eppler, E., and Reinecke, M.: Mechanisms of β-Cell Death in Type 2 Diabetes. Diabetes 2005; 54: Suppl. 2: 108-113.
3. Saltiel, A. R., and Kahn, C. R.: Insulin signalling and the regulation of glucose and lipid metabolism.Nature 2001; 414:799-806.
4. Steffes, M. W., Sibley, S., Jackson, M., and Thomas, W.: β-Cell Function and the Development of Diabetes-Related Complications in the Diabetes Control and Complications Trial. Diabetes Care 2003; 26: 832-836.
5. Atkinson, M. A.: Thirty Years of Investigating the Autoimmune Basis for Type 1 Diabetes: Why Can't We Prevent or Reverse This Disease? Diabetes 2005; 54: 1253-1263.
6. Meier, J. J., Bhushan, A., Butler, A. E., Rizza, R. A., and Butler, P. C.: Sustained beta-cell apoptosis in patients with long-standing type 1 diabetes: Indirect evidence for islet regeneration? Diabetologia 2005; 48:2221-2228.
7. Butler, A. E., Janson, J., Bonner-Weir, S., Ritzel, R., Rizza, R. A., and Butler, P. C.: β-Cell Deficit and Increased β-Cell Apoptosis in Humans with Type 2 Diabetes.Diabetes 2003; 52:102-110.
8. Clark, A., Wells, C. A., Buley, I. D., Cruickshank, J. K., Vanhegan, R. I., Matthews, D. R., Cooper, G. J., Holman, R. R., and Turner, R. C.: Islet amyloid, increased α-cells, reduced β-cells & exocrine fibrosis-quantitative changes in the pancreas in type-II diabetes. Diabetes Res.1988; 9: 151-159.
9. Deng, S., Vatamaniuk, M., Huang, X., Doliba, N., Lian, M. M., Frank, A., Velidedeoglu, E., Desai, N. M., Koeberlein, B., Wolf, B., Barker, C. F., Naji, A., Matschinsky, F. M., and Markmann, J. F. : Structural and Functional Abnormalities in the Islets Isolated From Type 2 Diabetic Subjects .Diabetes 2004;53:624-632.
10. Kloppel, G., Lohr, M., Habich, K., Oberholzer, M., and Heitz, P. U.: Islet Pathology and the Pathogenesis of Type 1 and Type 2 Diabetes mellitus Revisited. Surv. Synth. Pathol. Res.1985; 4: 110-125.
11. Sakuraba, H., Mizukami, H., Yagihashi, N., Wada, R., Hanyu, C., and Yagihashi, S.: Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese Type II diabetic patients. Diabetologia 2002; 45: 85-96.
12. Yoon, K. H., Ko, S. H., Cho, J. H., Lee, J. M., Ahn, Y. B., Song, K. H., Yoo, S. J., Kang, M. I., Cha, B. Y., Lee, K. W., Son, H. Y., Kang, S. K., Kim, H. S., Lee, I. K., and Bonner-Weir, S., : Selective β-Cell Loss and α-Cell Expansion in Patients with Type 2 Diabetes Mellitus in KoreaJ. Clin. Endocrinol. Metab. 2003; 88: 2300-2308.
13. Bernard-Kargar, C., and Ktorza, A.: Endocrine pancreas plasticity under physiological and pathological conditions. Diabetes 2001; 50: Suppl. 1: 30-35.
14. Arulmozhi, D. K., and Portha, B.,: GLP-1 based therapy for type 2 diabetes.Eur. J. Pharm. Sci. 2006; 28: 96-108.
15. Baggio, L. L., and Drucker, D. J.,: Therapeutic Approaches to Preserve Islet Mass in Type 2 Diabetes.Annu. Rev. Med. 2006; 57: 265-281.
16. Bouwens, L., and Rooman, I.: Regulation of pancreatic beta-cell mass. Physiol. Rev. 2005; 85:1255-1270.
17. Ogawa, N., List, J. F., Habener, J. F., and Maki, T.: Cure of Overt Diabetes in NOD Mice by Transient Treatment with Anti-Lymphocyte Serum and Exendin-4. Diabetes 2004; 53: 1700-1705.
18. Trucco, M., Regeneration of the pancreatic cell.J. Clin. Invest. 2005; 115: 5-12.
19. Vasavada, R. C., Gonzalez-Pertusa, J. A., Fujinaka, Y., Fiaschi-Taesch, N., Cozar-Castellano, I., and Garcia-Ocana, A.: Growth factors and beta cell replication. Int. J. Biochem. Cell Biol. 2006: 38: 931-950.
20. Prentki, M., and Nolan, C. J.: Islet β cell failure in type 2 diabetes.J. Clin. Invest. 2006;116: 1802-1812
21. Pattan SR, Rabara PA, Pattan JS, Bukitagar AA, Wakale VS, Musmade DS: Synthesis of some novel substituted 1, 3, 4-oxadiazole and pyrazole derivatives for antitubercular activity. Indian J Chem 2009; 43B:1453-56.
22. http://www.molinspiration.com/cgi-bin/ properties.
23. Bikadi, Z., Hazai, E.: Application of the PM6 semi-empirical method to modeling proteins enhances docking accuracy of AutoDock.J. Cheminf. 2009; 1: 15.

24. T. A. Halgren: Merck molecular force field. I. Basis, form, scope, parametrization, and performance of MMFF94. J of Computational Chemistry 1998; 17: 5-6: 490-519.
25. G. M. Morris, D. S. Goodsell, et al.: Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. J of Computational Chemistry 1998; 19: (14): 1639-62.
26. F. J. Solis and R. J. B.: Wets Minimization by Random Search Techniques. Mathematics of Operations Research 1981; 6: (1): 19-30.
27. Z. Bikadi, L. Demko and E. Hazai: Functional and structural characterization of a protein based on analysis of its hydrogen bonding network by hydrogen bonding plot Arch. Biochem. Biophys. 2007; 461: 225-234.
28. I. K. McDonald and J. M. Thornton: Satisfying Hydrogen Bonding Potential in Proteins. JMB 1994; 238: 777-93.
29. W. Humphrey, A. Dalke, and K. Schulten: VMD - Visual Molecular Dynamics. J. Mol. Graph. 1996; 14: 33-38.

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