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MOLECULAR DOCKING STUDIES ON OXADIAZOLE DERIVATIVE AS BETA SECREATASE INHIBITOR

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ABSTRACT

Objective: In the present study a novel series of 1,3,4 oxadiazole derivatives were docked against the *β-secretase*. 2,5 disubstituted 1,3,4 oxadiazole derivatives were modified an used for docking studies. Methods: The three dimensional structure of the protein was obtained from PDB and its active sites were predicted. The structure of all the compounds were drawn using chemdraw software version 8.o the docking studies were done using Schrodinger software against the enzyme *β-secretase*. Totally 48 compounds were docked based on glide score. Results: compounds 1AmS and 1AcS were identified as the most active compounds against *β-secretase*. In this docking study the oxadiazole analogues were showing good binding energy with glide score ranging from -5.3 to -1.3. The amino acid residues namely Ser36, Gly 230, Tyr 71,Asp 228, Try 198 in the *secretase* domain active site form hydrogen bond with ligand. Conclusion: The compounds 1AmS and 1AcS showed better interaction with *β-secretase* than the other drug molecules.

KEYWORDS: oxadiazole derivative, molecular docking Schrodinger software, ligand binding energy, *protein kinase G enzyme β-secretase.*

INTRODUCTION

Alzheimer's disease (AD) is a multifactorial neurodegenerative condition[1] characterized by severe loss of cholinergic neurons from the nucleus basalis.[2] The three main stages of symptoms: mild, moderate, and severe, each characterized by an increasing severity of cognitive impairment. Thus, in the mild, early stage, symptoms include namely memory loss and problems with concentration. In the moderate, middle stage, which represents the longest stage, symptoms may include trouble remembering events, difficulty engaging in successful problem-solving thought and action, impulsive behavior, shortened attention span, language difficulties, and potential restlessness and/or agitation. In the severe, late stage, patients cannot communicate and are completely reliant on others for their care. AD is inexorably progressive and fatal within 5 to 10 years Recently, a new earlier stage of AD has been proposed and has been designated the prodormal period of AD. This transition stage of AD is also referred to as mild cognitive impairment (MCI) where the symptoms include evidence of episodic memory loss, delayed recall, decrease in executive abilities, and behavior issues most notably depression, ay, and sleep disturbances.[3] Interesting, with regard to depression, studies have indicated a 20-25% of AD patients suffer from a major depressive episode and another 20-30% of patients experience symptoms of minor depression.[4]

The neuronal destruction is associated with the extracellular accumulation of insoluble forms of amyloid- (A) in plaques, mostly fragment, intracellular aggregation of the microtubule protein tau in neurofibrillary tangles, neuronal cell death, and synaptic dysfunction.[5] The A42 40 peptide is derived from the amyloid- protein precursor (APP) via sequential cleavage by the beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) and by the gamma-site aspartyl protease-secretase.[6] The A*β* oligomers interact with neurons and glial cells leading to the dysfunction of APP metabolism and futher production of A*β* peptide .BACE 1is an aspartic acid protease important in the formation of myelin sheath in peripheral nerve cells. The transmembrane protein contains 2 active sites aspartate residues in its extracellular protein domain and may function as dimer. *B-secreatase* cuts APP at the position outside the cell and gamma secretase which cut APP at position inside the cell. BACE1 inhibitors potentially inhibits BACE1 activity in brain resulting of compound A*β*-peptide in the cerebrospinal fluid of AD particles.[7] The dominant technique for the identification of new lead compound in drug discovery is the physical screening of large libraries of chemical against the

biological target. Another approach is to computational screen large libraries of chemical compound that complement target of known structure. in recent decade reseach has indicated that the oxadiazole constitute structural framework with broad spectrum biological activity such as antinflamatory analgesic, antimicrobial , anti -convulsant, anti -proliferative, anti-mycobacterial anti-protozoal, anti-diabetic, anti-helmintic, hypoglycemic, anti-allergy enzyme inhibitors, insecticidal, anticancer, antidepressant, antineoplastic, cns depressant and pesticidal property .1,3,4 oxadiazole is a very good bioisoterase of amide and ester functional group and is reported to contribute substantially to pharmacological activity by participating in hydrogen bonding interaction with various respects oxadiazole is very weak base due to the inductive effect of the extra heteroatom. The replacement of two –CH= group in furan by 2 pyridine type nitrogen(-N=) reduces the aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene literature survey reveal that the oxadiazole undergoes number of reaction such as electrophilic nucleophilic substitution thermal and photochemical.and so attempt has made to inhibit beta secretase by using substituted oxadiazole.[8]

MATERIALS AND METHODS

Schrodinger software version was used for the docking studies. For the determination of protein–Ligand binding affinities and scoring function GLIDE 4.0 (Grid Based Ligand Docking with Energies).[9,10,11]

Ligand preparation

Ligands build in the database need to be prepared by which we would get ligands of very high quality. LigPrep is a utility of the Schrodinger software suit that combines tools for generating 3D structures from1D (Smiles) and 2D (SDF) representation, searching for tautomers and steric isomers, and performing geometry minimization of the ligands. Molecular Mechanics Force Fields OPLS 2005 was used with default settings.

Protein/enzyme Preparation

The protein selection is carried out from the RCSB PDB (protein data bank). Protein data bank is resource for studying biological macromolecules. It contains information about experimentally determined structures of proteins, nucleic acids and complex assemblies. Also providing a variety of tools and resources users can performs simple and advance searches base on annotations, relating to sequences, structures and function. The PDB code for the selected target *β-secretase* was 3BRA. Further Evaluated by its Resolution value, R Free, R value and Ramachandran plot.

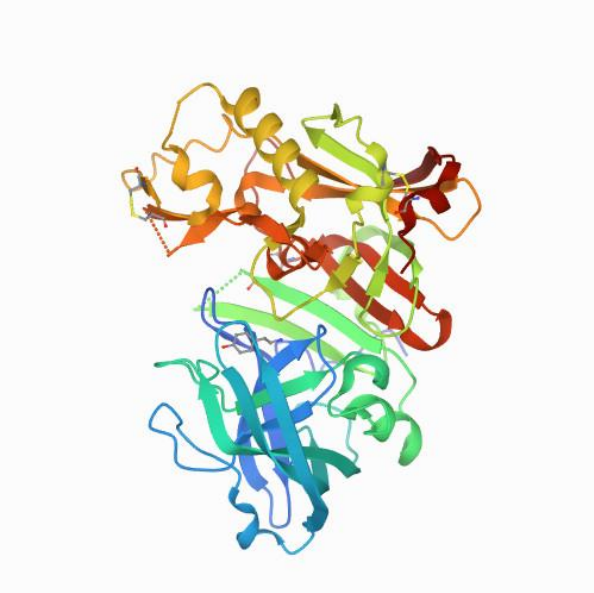


Fig 1: *β- secretase* (PDB ID: 3BRA.

a. Ligand receptor docking and predicting activity

Molecular docking in Silico experiments were performed with GLIDE (an application tool of Maestro 9.9) v5 HTVS, SP, XP docking program (Schrodinger Inc. using a Dell Precision workstation T3400 running in an Intel Core2 Duo Processor, 4 GB RAM, 250 GB hard disk, and NvidiaQuadro FX 4500 graphics card.

b. Selecting the Docking Precision

There are three choices of docking precision, given under Precision in the Docking section

- **HTVS** (**high-throughput virtual screening**)—High-throughput virtual screening (HTVS) docking is intended for the rapid screening of very large numbers of ligands. HTVS has much more restricted conformational sampling than SP docking, and cannot be used with score-in-place.
- **SP (standard precision**)—Standard-precision (SP) docking is appropriate for screening ligands of unknown quality in large numbers.
- **XP** (**extra precision**). Extra-precision (XP) docking and scoring is a more powerful and discriminating procedure, which takes longer to run than SP. XP is designed to be used on ligand poses that have a high score using SP docking. We recommend that you run your database through SP docking first, then take the top 10% to 30% of your final poses and dock them using XP,

c. Scoring methods

Scoring functions can be divided in empirical scoring functions, scoring functions derived from force fields, and knowledge-based scoring functions. Scoring functions derived from force fields handle the ligand binding prediction with the use of potential energies (non-bonded interaction terms) and sometimes in combination with solvations and entropy contributions. Knowledge-based scoring functions are based on atom pair potentials derived from structural databases. Forces

and potentials are collected from known protein-ligand complexes to get a score for their binding affinities

RESULTS AND DISCUSSION

β-Secretase

Resolution of β-secretase (3BRA) selected was 2.3 A˚ and the R value and r free value was found to be (0.264, 0.222). The target protein was prepared and viewed through the Ramachandran plot which shows clearly for all the essential amino acids to be in the favourable region (Red colour), some in slightly favourable region (yellow) and none in unfavourable region (White).

Table 2: Residue Interaction patterns for the Screened 1,3,4-oxadiazoles compounds against β –Secretase.

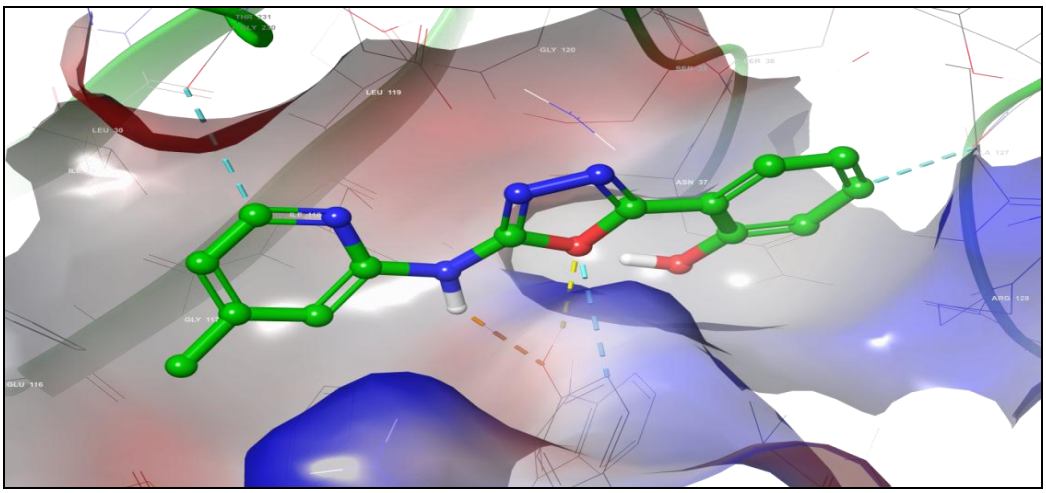
ID	Important Interactions of Native Ligands with Amino Acids of Binding Site of β-secretase				
	Hydrogen Bonding	**Hydrophobic**	**Positive Ionizable**	**Negative Ionizable**	**Polar**
1AS	Asp32, Trp76	Trp76,Ile118,Tyr71, Val69	Arg231, Arg128	Asp32, Asp228	Ser35, Ser36, Asn37, Thr237
1AnS	Asp32, Tyr71	Phe108, Ile110,Trp115,Leu30, Ile118,Trp76,Trp71, Val69,Ile126,Tyr198	Arg235, Lys107, Arg128	Asp32, Asp228	Ser35, Thr231, Thr232
1AmS	Asp32	Ile110,Phe108,Leu30, Trp115,Ile118,Tyr198, Ile226	Arg235	Asp32, Asp228	Ser35, Thr231, Tht232
1AcS	Asp32, Tyr329	Ile226,Val332,Tyr198, Tyr71,Phe108,Trp115, Ile118,Leu30	Arg235, Lys224	Asp32, Asp228	Ser35. Thr231, Thr329
1IS	Asp32	Phe108,Ile118,Ala39, Trp76,Tyr71,Val69	Arg128, Arg235	Asp32, Asp228	Ser35, Ser36, Asn37, Thr231
2FP	Asp32, Asp228	Tyr71,Phe108,Ile110, Trp115,Ile118,Leu30	Lys107	Asp32, Asp228	Gln73, Thr231
2DP	Asp32, Lys107	Phe108,Trp115,Leu30, Ile118,Ile226,Ile126, Tyr71,Tyr198,Val332	Lys107	Asp32, Asp228	Ser35, Thr231,Thr232, Gln73
2AP	Asp228, Phe108	Ile110,Phe108,Leu30, Trp115,Ile118,Tyr71, Ile226,Tyr198	Arg235	Asp228	Ser35, Thr231
2AnP	Asp32	Tyr71,Phe108,Trp115, Ile118,Leu30,Tyr198	Lys107, Arg235	Asp32, Asp223	Ser35, Thr231, Thr329
2AmP	Phe108, Asp228	Phe108,Ile110,Trp115, Leu30,Ile18,Tyr71	Lys107	Asp32, Asp228	Ser35, Thr231
2AcP	Asp32, Asp228, Lys107	Ile110,Phe108,Ile118, Tyr171	Lys107	Asp32, Asp228	Ser35, Phr231
2IP	Asp32, Asp228, Lys107	Ile110,Phe108,Tyr71, Ile118	Lys107	Asp32, Asp228	Ser35,Gln12,Thr231
3FN	Asp32	Trp115,Phe108,Leu30, Ile118,Pyr71,Val69, Trp76	Arg128	Asp32	Ser35, Asn37
3DN	Asp32	Phe108,Ile110,Trp115, Leu30,Ile118,Ile226, Val332,Tyr71,Tyr198	Arg235, Lys224, Lys107	Asp32, Asp228	Ser35, Thr231,Thr329
3AN	Phe108	Phe108,Ile110,Trp115, Leu30,Ile118,Tyr71	Lys107	Asp32, Asp238	Gln73, Thr231
3AnN	Asp32	Phe108,Ile110,Trp115, Trp76,Ile118,Leu30, Tyr71,Val69,Ile126	Arg128, Lys107	Asp228, Asp32	Ser35, Asn37, Gln73

3AmN	Phe108	Phe108,Ile110,Trp115, Leu30,Ile118	Lys107	Asp32, Asp228	Thr231
3AcN	Asp32	Tyr71,Tyr198,Ile226, Leu30,Ile118,Trp115, Phe108	Lys107	Asp32, Asp228	Ser35, Thr231, Gln73
3IN	Asp32	Phe108,Tyr71,Leu30, Ile118,Ile226,Tyr198	Lys107	Asp32, Asp228	Ser35, Gln73,Thr231
4FA	Asp32	Tyr71,Ile110,Phe108, Trp115,Ile118,Trp76, Ile118,Tyr198,Ile226, Val332	Lys107	Asp32, Asp228	Ser35, Thr231
4DA	Asp32	Phe108,Ile110,Trp115, Ile118,Leu30,Val232, Ile226,Tyr98,Tyr71	Lys107, Lys224, Arg235	Asp32, Asp238	Ser35, Thr231, Thr329
4PA	Tyr71	Tyr71,Ile110,Phe108, Trp115,Ile118,Tyr198, Ile226,Val332	Arg235, Lys107	Asp32, Asp228	Ser35, Thr232, Thr231, Thr329
4AA	Asp32	Tyr71,Tyr198,Ile110, Phe108,Trp115,Ile118, Leu30	Lys107	Asp32, Asp228	Ser35, Thr231
4AnA	Asp32	Phe108,Trp115,Ile118, Leu30,Ala127,Ile126, Tyr198,Tyr77,Val69	Arg128, Lys107	Asp32, Asp228	Ser35, Ser36, Gln73, Thr231
4AmA	Asp32	Ile118,Trp115,Phe108, Leu30,Tyr71,Ala127, Ile126,Tyr198	Arg128	Asp32, Asp228	Ser35, Ser36, Asn37
4AcA	Asp32	Phe108,Trp118,Ile118, Leu30,Trp71,Val69, Ala127,Ile126,Tyr198	Arg128	Asp32	Ser35,Asp36, Asn37
4IA	Asp32	Ile110,Phe108,Trp115, Ile118,Tyr71,Tyr198, Leu30,Ile226	Lys104	Asp32, Asp228	Ser35, Thr231
5FC	-	Phe108,Trp115,Ile110, Ile118,Leu30,Tyr71, Tyr198	Lys107	Asp32, Asp228	Ser35, Gln73
5DC	Asp32, Tyr71	Phe108,Ile110,Trp115, Leu30,Ile118,Tyr71, Val332,Ile226,Tyr198	Lys107, Lys224	Asp32, Asp228	Ser35, Thr231,Thr329
5AC	Asp32	Phe108,Tyr71,Leu30, Ile226,Ile118, Tyr198	Lys107	Asp32, Asp228	Ser35, Thr231
5AnC	Tyr71	Ile110,Ile118,Phe108, Trp115,Tyr71,Tyr198, Leu30,Ile226,Val332	Arg235, Lys228	Asp32, Asp228	Ser35, Asn233 Gln73, Thr231,Thr232, Thr329
5AmC	-	Ile110,Phe108,Trp115, Leu30,Ile118,Tyr71, Tyr198,Trp76	Arg235, Lys224	Asp32, Asp228	Ser35, Thr231, Thr329
5AcC	Tyr71	Val332,Tyr198,Ile226, Tyr71,Ile118,Leu30, Trp115,Phe108,Ile110	Lys224, Arg228	Asp32, Asp228	Ser35, Thr329, Thr231
5IC	Asp32	Ile118,Leu30,Tyr198, Ile226,Val332	Arg235	Asp32, Asp228	Ser35, Thr231, Thr232,Asn233
6FB	Asp32	Phe108,Ile110.Trp115, Ile118,Leu30,Tyr98,	Lys107	Asp32, Asp228,	Ser35, Gln23,

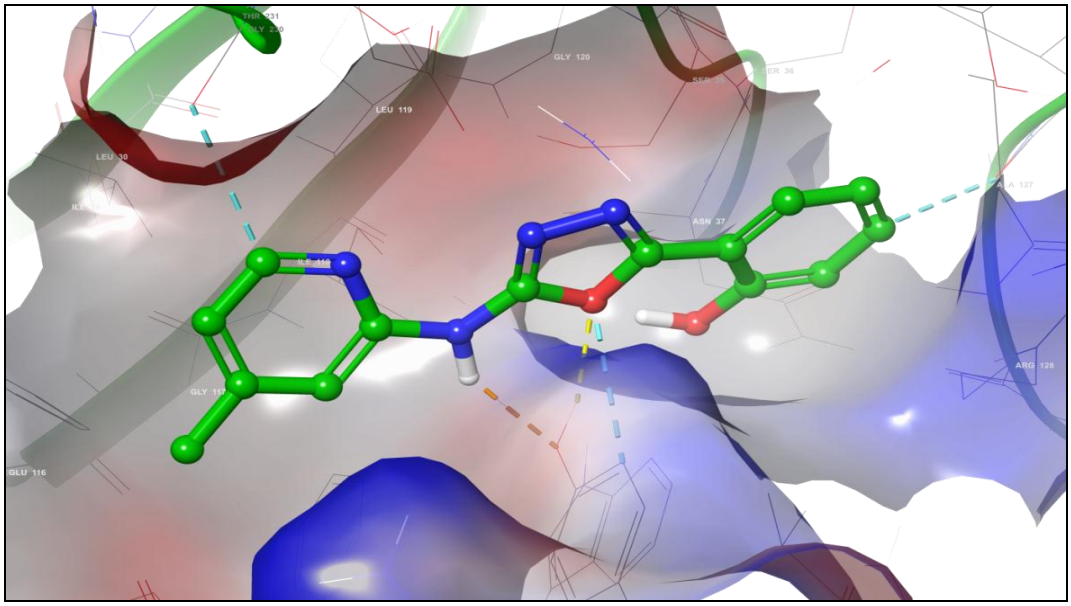
		Tyr71		Asp106	Thr231
6AB	Asp32	Tyr71,Tyr198,Phe108, Ile110,Trp115,Ile118, Leu30	Lys107	Asp32, Asp106, Asp228.	Ser35, Thr231, Gln73

Table 2:Docking Score for the Screened 1,3,4-oxadiazoles against *β-secretase*.

ID	Dock score[a]	Lipophilic EvdW[b]	H Bond[c]	Electro[d]	Site map[e]	Low MW[f]	Expos Penal[g]	Rot Penal[h]
1AS	-3.11	-2.08	-1.04	-0.45	0	-0.5	0.22	0.37
1AnS	-4.46	-2.58	-1.59	-0.38	0	-0.29	0.11	0.25
1AmS	-4.69	-2.57	-1.72	-0.26	0	-0.5	0	0.32
1AcS	-4.44	-2.99	-0.74	-0.51	0	-0.5	0	0.28
1IS	-3.12	-2.13	-2.85	-0.6	0	-0.5	0.04	0.34
2FP	-3.12	-2.15	-0.8	-0.3	0	-0.5	0.38	0.46
2DP	0.92	-2.24	-1	-0.58	0	-0.5	0	0.27
2AP	-2.49	-1.35	-0.77	-0.49	-0.37	-0.5	-0.23	0.38
2AnP	-3.06	-2.31	-1	-0.28	0	-0.3	-0.77	0.25
2AmP	-3.31	-2.25	-0.83	-0.29	0	-0.5	0.2	0.32
2AcP	-4.43	-2.43	-1.57	-0.48	0	-0.5	0.27	0.28
2IP	-3.82	-2.65	-0.7	-0.31	0	-0.5	0	0.34
3FN	-3.65	-2.38	-0.93	-0.19	0	-0.5	0	0.51
3DN	-2.36	-1.9	-0.35	-0.2	0	-0.5	0	0.51
3AN	-2.08	-1.34	-0.49	-0.29	-0.35	-0.5	-0.07	0.42
3AmN	-2.01	-2.39	-0.7	-0.61	0	-0.5	0	0.35
3IN	-3.49	-2.05	-0.35	-0.42	0	-0.5	0	0.38
4FA	-2.34	-2.14	-0.35	-0.13	0	-0.5	0.31	0.46
4DA	-1.94	-3	-0.35	-0.46	0	-0.4	0	0.3
4PA	-2.44	-2.6	-0.69	-0.59	0	-0.2	1.3	0.33
4AA	-2.28	-1.7	-0.54	-0.27	-0.29	-0.5	0.33	0.4
4AmA	-2.75	-1.96	-2.33	-0.67	0	-0.49	0.59	0.35
5DC	-2.9	-2.29	-0.19	-0.29	0	-0.48	0	0.34
6FB	-3.66	-2.94	-0.35	-0.22	0	-0.5	0	0.35
6AB	-1.84	-1.1	-0.35	-0.48	0	-0.5	0	0.28
6IB	-3.18	-1.66	-0.58	-0.34	0	-0.49	0	0.26

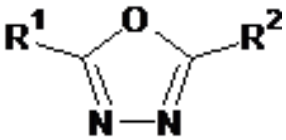


Compound 1AcS showing 2D ligand Interaction of compound 1AcS with Beta Secretase receptor and Compound 1AcS been docked with the beta secretase receptor



Compound 1AmS showing 2D ligand Interaction of compound 1AmS with Beta Secretase receptor and Compound1AmS been docked with the beta secretase receptor

GENERAL STRUCTURE



Compound code	R1	R2
1IS	N-5methyl 1,2-oxazole-3amine	2-hydroxyl phenyl
1IN		3-pyridyl
1IA		2-chlorobenzyl
IIC		2-phenyl ethenyl
1IP		4-aminophenyl
1IB		3,4 dimethoxy phenyl
2AcS	4Chloro 2 aminopyridine	2-hydroxyl phenyl
2AcN		3-pyridyl
2AcA		2-chlorobenzyl
2AcC		2-phenyl ethenyl
2AcP		4-aminophenyl
2AcB		3,4 dimethoxyl phenyl
3AmS	4-amino-2aminopyridine	2-hydroxyl phenyl
3AmN		3-pyridyl
3AmA		2-chlorobenzyl
3AmC		2-phenyl ethenyl
3AmP		4-aminophenyl
3AmB		3,4 dimethoxy phenyl
4AnS	1,5-Dimethyl-4-(amino)-2-phenyl-1,2 dihydro-3H-pyrazol-3-one	2-hydroxyl phenyl
4AnN		3-pyridyl
4AnA		2-chlorobenzyl
4AnC		2-phenyl ethenyl
4AnP		4-aminophenyl
4AnB		3,4 dimethoxy phenyl
5DS	N,N Dimethyl 1,4 diamine	2-hydroxyl phenyl
5DN		3-pyridyl
5DA		2-chlorobenzyl
5DC		2-phenyl ethenyl

5DP		4-aminophenyl
5DB		3,4 dimethoxy phenyl
6FS	Furfural amine	2-hydroxyl phenyl
6FN		3-pyridyl
6FA		2-chlorobenzyl
6FC		2-phenyl ethenyl
8FP		4-aminophenyl
6FB		3,4 dimethoxy phenyl
7AS	1-aminotriazole	2-hydroxyl phenyl
7AN		3-pyridyl
7AA		2-chlorobenzyl
7AC		2-phenyl ethenyl
7AP		4-aminophenyl
7AB		3,4 dimethoxy phenyl
8BS	p-amino diazobenzene	2-hydroxyl phenyl
8BN		3-pyridyl
8BA		2-chlorobenzyl
8BC		2-phenyl ethenyl
8BP		4-aminophenyl
8BB		3,4 dimethoxy phenyl

CONCLUSION

In the present study novel disubstituted 1,3,4-Oxadiazoles were designed through database. Among the screened 48 compounds in 1,3,4-Oxadiazoles compounds namely 1AcS and 1Am were found to be potent. The major interactions formed by ligands with the receptor β-secretase may be categorized as hydrogen bond, hydrophobic bond, π-π stacking and electrostatic interactions. **2,5 disubstituted 1,3,4 Oxadiazoles formed Hydrogen Bonding with amino acids namely** Asp32, Tyr 32, Asp228, Lys107, Phe108, Tyr 71 and Trp 76. **Hydrophobic** interactions found in 1,3,4 Oxadiazoles were with amino acids Phe108, Ile110,Trp115, Leu30, Ile118,Trp76,Trp71, Val69,Ile126 and Tyr198. **Polar** bonds in 1,3,4 oxadiazoles were found in were formed with Arg128, Arg 235, Lys 107 and Lys 224.**Positive Ionisable** bonds in 1,3,4 Oxadiazoles were formed withAsp106, Asp 32 and Asp 228. **Negative Ionisable** interactions in 1,3,4 Oxadiazoles were found with Ser35,Thr232, Thr231 and Thr329

The future study is planned for synthesis of identified compounds followed by in vitro and in vivo studies.

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AUTHORS CONTRIBUTIONS: All the experimental work has been carried by the first author, second author has supervised them.

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