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Designing and comparison of docking analysis of quinazolinedione sulphonamide derivatives with AMPA and GABA

Parul [1], Shweta Sharma [1], Ajeet [1,*], Hina Chadha [2], Babita Aggarwal [3]

[1]Department of Pharmaceutical Chemistry and Drug Design, Vishveshwarya Group of Institutions, Greater Noida-II, 203207, Uttar Pradesh, India
[2]Department of Pharmacology, Vishveshwarya Group of Institutions, Greater Noida-II, 203207, Uttar Pradesh, India
[3]Department of Pharmacognosy, Vishveshwarya Group of Institutions, Greater Noida-II, 203207, Uttar Pradesh, India
*corresponding author e-mail address: ***ajeet_pharma111@rediffmail.com***

ABSTRACT

Epilepsy is getting common now a day but it is a serious brain disorder. It is universal, with any age, sex, geographical, social class or racial boundaries. Few of the most important mechanisms for handling it are via AMPA and GABA receptors. In same context while studying the treatment of epilepsy we found the significant effects of the derivatives of the quinazolinedione sulphonamide, this promotes us to study this moiety by the means of *in-silico* resources with antiepileptic/anticonvulsant effects. Results revealed that the major interacting amino acids for anticonvulsant action mediated via AMPA and GABA could be Ser277, Arg149, Tyr256 and GLn284. It was also found that between AMPA & GABA, possibly AMPA could results in better prospects for designed molecules against epilepsy.

Keywords: *Docking; Protein-receptor interaction; Epilepsy; sulphonamide.*

1. INTRODUCTION

Epilepsy is a class of neurological disorders characterized by epileptic seizures [1, 2]. Epileptic seizures are the episodes that can vary from small and nearly undetectable to long periods. These seizures sometimes can result in physical injuries like occasionally broken bones. The cause is unknown of most cases of epilepsy [3]. Some cases are the result of brain injury, stroke, brain tumors, infections of the brain and birth defects, through a process known as epileptogenesis[3-4].

Epileptic seizures can result due to excessive and abnormal nerve cell action in the cortex of the brain[5]. Seizures are controllable by medication in approximate 70% of cases. [6] Even inexpensive options are often available. Not all cases of epilepsy are carried lifelong, and many people improve to the point that treatment is no longer needed [3].

The ionotropic glutamate receptors (iGluRs) are a class of ion channels which are broadly divided into three subtypes N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors [7].

The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor) is a non-NMDA (N-methyl-D-aspartate) type ionotropic glutamate receptors (iGluRs). These channels are permeable for Na^+, K^+ and Ca^{2+} synaptic transmission. Over stimulation of these receptors causes an uncontrolled Ca^{2+}-influx into the cells resulting in excitotoxicity and possible cell death. Other several disorders are (at least in part linked to over-activity of iGluRs) epilepsy, chronic pain and neuropathology ensuing from cerebral ischemia to cardiac arrest. There are too many antagonists exists for various sites of these receptors which shown to have anticonvulsant, neuroprotective or antinociceptive effects in a range of animal models. AMPA receptors are found in many parts of the brain and are the most commonly found receptor in the nervous system[7]. There are few types of subunits for AMPA receptors, known as GluR1 (GRIA1), GluR2 (GRIA2), GluR3 (GRIA3), and GluR4 (GRIA4), which combine to form tetramers. Each AMPA receptor has four sites where an agonist can bind, one for each subunit [7].

The GABA (gamma-aminobutyric acid) receptors inhibit the mature vertebrate central nervous system. They respond to the neurotransmitter gamma –aminobutyric acid[8]. GABA receptors are classified in to two categories: GABA'A' receptors which are the ligand - gated ion channels and GABA'B'receptors which are G protein coupled receptors[8].

$GABA_A$ receptors are also known as ionotropic receptors. Due to direct activation of anion channel, Bicuculline and Picrotoxin blocked the fast response of neurons to GABA-this channel is termed as $GABA_A$ receptor[9-10]. These are a members of family of Cys-loop-gated ion channels[11]. Whereas $GABA_B$ receptors are also known as metabotropic transmembrane receptors[12] They are found in the central as well as autonomic region of the peripheral nervous system. Their function is to stimulate the opening of the K^+ channels due to which neurons become closed to the equilibrium potential of K^+ and reduces the frequency of action potential and also of neurotransmitter release.

The quinazolinedione sulfonamides are a class of competitive AMPA receptor antagonists. It displaying nanomolar affinities and providing examples- albeit of lower affinity with oral activity in animal models for antiepileptic effects. Quinazoline-2,4-diones with a sulfonamide group attached at N(3) ring atom constitute a novel class of competitive AMPA receptor antagonists. AMPA receptors have been associated to a variety of neurodegenerative and psychiatric diseases such as ischemic brain damage, schizophrenia and epilepsy. Excessive stimulation of the

glutamatergic system often plays a role in triggering seizures associated with epilepsy [13].

The use of *in-silico* methods (computational methods) in drug design has grown significantly in popularity over the past few years. This *in-silico* structure-based design is rapidly becoming the lead identification method for many drug discovery processes.[13] Drug design is also known as rational drug design or rational design. It is the inventive process of finding new medications on the basis of the knowledge of a biological target.[14] The drug is commonly known as an organic small molecule which stimulates/inhibits the function of a biomolecule like a protein, which in turn results in therapeutic benefits to the patient. It involves design of small molecules that are complementary in shape & charge to biomolecular target. These are the two major types of drug design.The first one is ligand-based drug designand the second, structure-based drug design[15].

Structure-based *in-silico* methods fall into two main categories–virtual screening and *de-novo* design. The most well-known tools are AutoDock, AutoDock Vina and DOCK3 and so on[13], out of which we have used AutoDock Vina in this manuscript.

2. EXPERIMENTAL SECTION

2.1. Data and database. For carrying out this study, Protein Data Bank's (PDB) website was used as biological and chemical data sources.

Proteins were downloaded from Protein Data Bank as PDB files. They are the glutamate receptor 2 (GluR2)- AMPA receptor and ATU2422 - GABA receptor.

2.2. Structure designing, structure optimization – Tools. The 2D structure construction, energy minimization and geometry optimization of the novel derivatives were carried out by using ChemDraw Ultra 7.0 and Chem3D Pro 7.0 (CambridgeSoft Corporation, 100 CambridgePark Drive, Cambridge MA, 02140 USA) on an Intel(R) Core(TM)2 Duo Central Processing Unit T6670 @ 2.20 GHz and 4.00 GB of RAM, running the Windows 7 Home Basic, 64-bit compatible operating system.[16] The energy minimization was carried out to minimum RMS Gradient of 0.100, with step interval of 2.0 Fs and frame interval of 10 Fs.

2.3. Screening and evaluation of novel Quinazolinedione Sulfonamide derivatives as anticonvulsant agent – Docking. Docking has been performed with AutoDock Vina docking software.[17] It is virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets. It enables medicinal chemists to run virtual screening form any platform and helps users in every steps of this process- from data preparation to job submission and analysis of the results.

For screening process, all the novel molecules has been docked with all the 6 different proteins/binding sites of previously well-known anticonvulsant agents.

2.4. Docking analysis. Now, the docked poses of the novel molecules are analysed for the binding energy, number of hydrogen bonds and binding pattern such as element, type of bond, atom number and residue at binding site.

3. RESULTS SECTION

Pharmacophore used for designing novel derivatives is shown in Figure 1.

3.1. Novel Designed molecules. All the novel designed molecules are shown in Table 1.

3.2. Docking based screening of novel molecules. Now, the novel molecules have been kept for the virtual docking based screening. The results of docking based screening are shown in Table 2 & 3 and docked images are given in Fig. 2 & 3.

3.3. Docking analysis. On docking of the Quinazolinedione sulfonamide derivatives with the well known receptors recognized for the antiepileptic action, we found some very interesting points. Firstly, we docked the ligand **PS1** with GluR2 for its inhibition, then, it results with the 2 hydrogen bonds with binding affinity of -7.2 Kcal/mol. The residue to which they bind is Ser217. While when we docked the ligand **PS1** with Atu2422 for its inhibition, then, it results with 3 hydrogen bonds with binding affinity of -6.5 Kcal/mol with residues Lys266, Thr253 and Asn271.

In the same way, when ligands PS2, PS3, PS4, PS5, PS6, PS7, PS8, PS9 and PS10 have been docked with the GluR2 receptor individually, then the protein-ligand interactions affinity was found to be -7.2,-7.1,-7.4,-7.2,-7.3,-7.3,-7.3,-7.3,-7.2 respectively while when docked with ATU2422 receptors, then theprotein-ligand interactions affinity was found to be -6.6,-6.5,-6.2,-6.1,-6.5,-6.4,-6.8,-6.4,-6.4 respectively.

Numbers of hydrogen bonds and other binding details have been shown previously in Tables 2 and 3.

In this study major interacting residues found are-

1. Ser277, Arg149 and Tyr256 when docked with AMPA receptor
2. GLn284 when docked with GABA receptor.

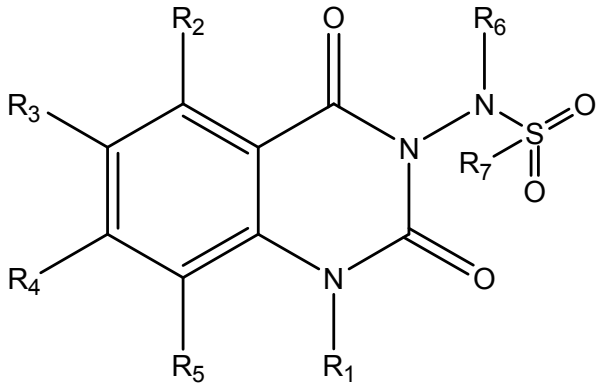


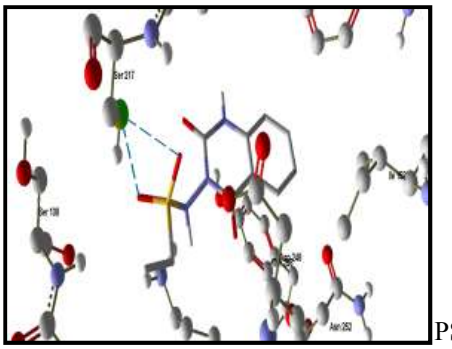
Fig.**1.** Pharmacophore.

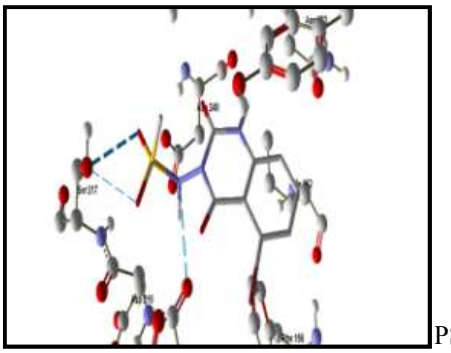
Table 1. Novel designed derivatives as anticonvulsant agent

Compound code	R
PS1	R7-C_2H_5
PS2	R2-Br R7-CH_3
PS3	R2-Cl R7-C_2H_5
PS4	R3-Br R7-CH_3
PS5	R3-Br R7-C_2H_5
PS6	R5-Br R7-CH_3
PS7	R5-Br R7-C_2H_5
PS8	R4-Br R7-CH_3 R1-CH_3
PS9	R4-Cl R7-C_2H_5 R1-CH_3
PS10	R4-Br R7-C_2H_5 R1-CH_3

Table 2. Docking results of novel desinged Quinazolinedione Sulfonamide derivatives with AMPA receptor.

Ligand (Comp. no.)	Recep.	Affinity Kcal/mol	H-bonds	H- Binding Ligand				H- Binding Receptor		
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
PS1	GluR2	-7.2	2	O	17	Acceptor	Ser217	O	1687	Both
				O	16	Acceptor	Ser217	O	1687	Both
PS2	GluR2	-7.2	3	O	18	Acceptor	Ser217	O	1687	Both
				O	17	Acceptor	Ser217	O	1687	Both
				N	14	Donor	Leu215	O	1669	Acceptor
PS3	GluR2	-7.1	4	O	17	Acceptor	Arg149	N	1145	Donor
				O	18	Acceptor	Arg149	N	1145	Donor
				O	118	Acceptor	Arg149	N	1144	Donor
				O	10	Acceptor	Arg149	N	1144	Donor
PS4	GluR2	-7.4	6	O	11	Acceptor	Tyr256	O	4014	Both
				O	18	Acceptor	Lys251	N	3957	Donor
				N	6	Donor	Asp248	O	3930	Acceptor
				N	14	Donor	Asn241	O	1661	Acceptor
				O	10	Acceptor	Ser217	O	1687	Both
				O	17	Acceptor	Ser217	O	1687	Both
PS5	GluR2	-7.2	3	O	17	Acceptor	Ser217	O	1687	Both
				O	18	Acceptor	Ser217	O	1687	Both
				N	14	Donor	Leu215	O	1669	Acceptor
PS6	GluR2	-7.3	3	O	18	Acceptor	Ser217	O	1687	Both
				O	17	Acceptor	Ser217	O	1687	Both
				N	8	Acceptor	Tyr256	O	4014	Both
PS7	GluR2	-7.3	1	N	8	Acceptor	Tyr256	O	4014	Both
PS8	GluR2	-7.3	3	O	17	Acceptor	Ser108	N	2841	Donor
				O	18	Acceptor	Ser217	O	1687	Both
				N	6	Acceptor	Tyr256	O	4014	Both
PS9	GluR2	-73	3	O	18	Acceptor	Ser217	O	1687	Both
				O	17	Acceptor	Ser217	O	1687	Both
				N	6	Acceptor	Tyr256	O	4014	Both
PS10	GluR2	-7.2	3	O	18	Acceptor	Ser217	O	1687	Both
				O	17	Acceptor	Ser217	O	1687	Both
				N	6	Acceptor	Tyr256	O	4014	Both


PS1


PS2

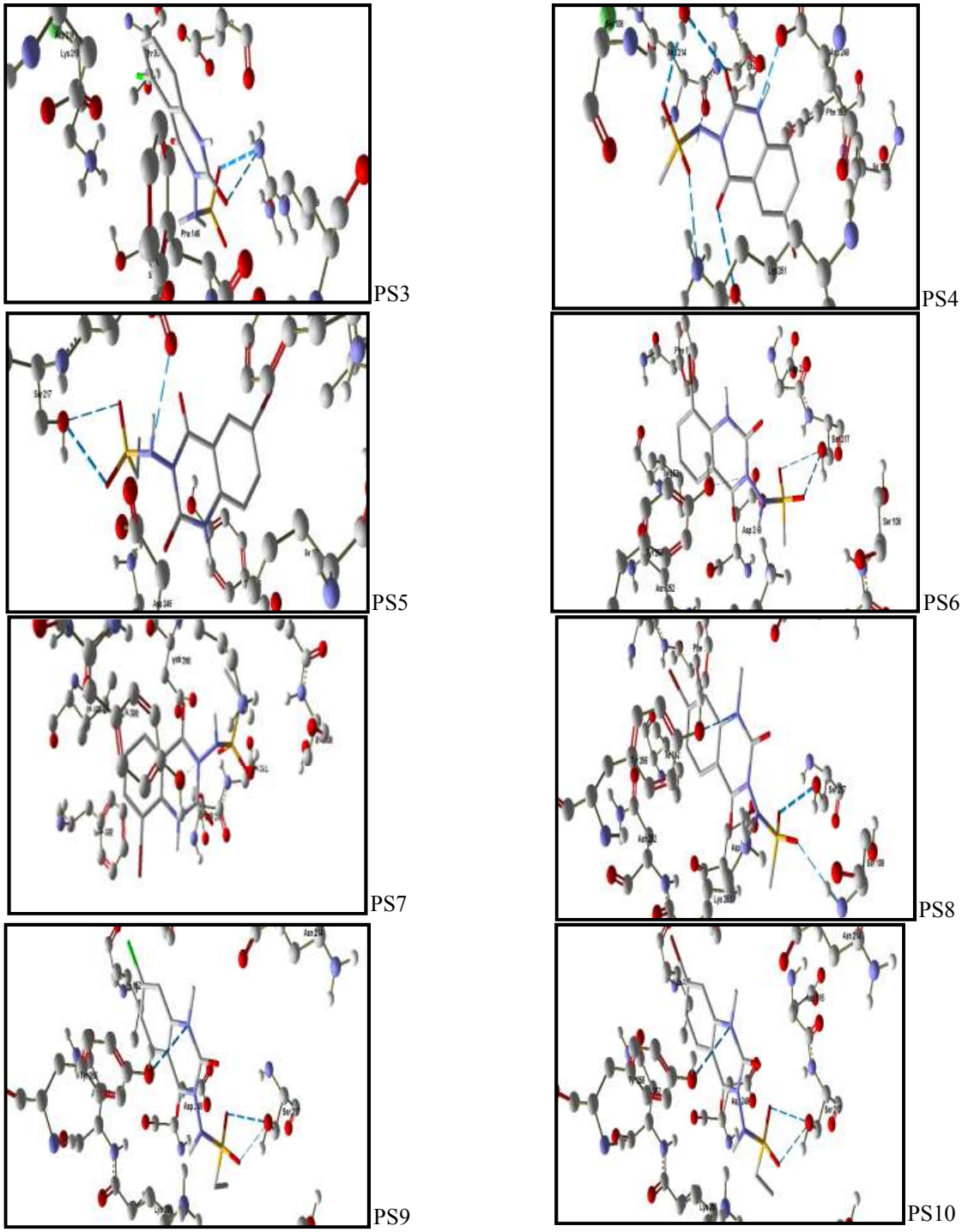
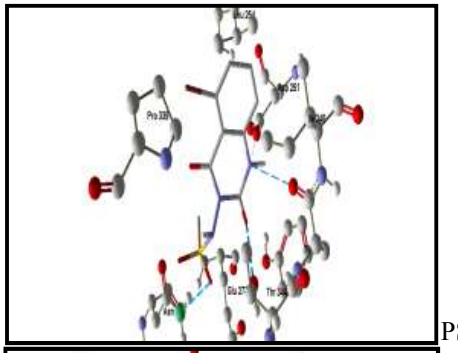


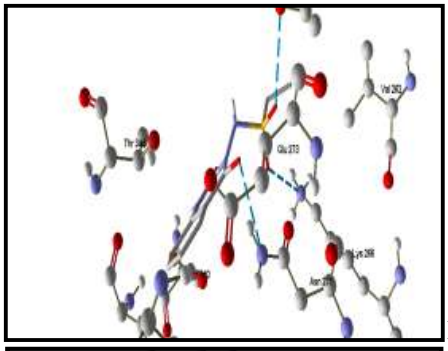
Figure 2. Docked images of Quinazolidinedione sulfonamide derivatives PS1-PS10 with AMPA receptor.

Table 3. Docking results of novel designed Quinazolinedione Sulfonamide derivatives with GABA receptor.

Ligand (Comp. no.)	Recept.	Affinity Kcal/mol	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At. ID.	Type	Res.	Elem.	At.ID.	Type
PS1	Atu2422	-6.5	3	O	16	Acceptor	Lys266	N	1955	Donor
				O	17	Acceptor	Thr253	O	1840	Both
				O	11	Acceptor	Asn271	N	1988	Donor
PS2	Atu2422	-6.6	4	N	6	Donor	Asp251	O	1827	Acceptor
				N	6	Donor	Tyr345	O	2540	Acceptor
				O	10	Acceptor	Thr344	O	2535	Both
				O	18	Acceptor	Asn271	N	1988	Donor
PS3	Atu2422	-6.5	4	O	11	Acceptor	Gln284	N	2093	Donor
				O	18	Acceptor	Gln284	N	2093	Donor
				N	14	Donor	Tyr280	O	2066	Both
				N	6	Donor	Asp32	O	215	Acceptor
PS4	Atu2422	-6.2	4	O	17	Acceptor	Asn34	N	235	Donor
				O	11	Acceptor	Asn34	N	235	Donor

				O	10	Acceptor	Ile46	N	309	Donor
				N	14	Donor	Ile44	O	295	Acceptor
PS5	Atu2422	-6.1	3	O	11	Acceptor	Gln284	N	2093	Donor
				O	18	Acceptor	Gln284	N	2093	Donor
				N	16	Donor	Asp32	O	215	Acceptor
PS6	Atu2422	-6.5	4	N	6	Donor	Asp251	O	1827	Acceptor
				N	6	Donor	Tyr345	O	2540	Acceptor
				O	10	Acceptor	Thr344	O	2535	Both
				O	17	Acceptor	Asn271	N	1988	Donor
PS7	Atu2422	-6.4	4	N	6	Donor	Asp251	O	1827	Acceptor
				N	6	Donor	Tyr345	O	2540	Acceptor
				O	10	Acceptor	Thr345	O	2535	Both
				O	17	Acceptor	Asn271	N	1988	Donor
PS8	Atu2422	-6.8	3	O	17	Acceptor	Gln284	N	2093	Donor
				O	10	Acceptor	Gln284	N	2093	Donor
				O	18	Acceptor	Tyr280	O	2066	Both
PS9	Atu2422	-6.4	3	O	17	Acceptor	Gln284	N	2093	Donor
				O	10	Acceptor	Gln284	N	2093	Donor
				O	18	Acceptor	Tyr280	O	2066	Both
PS10	Atu2422	-6.4	3	O	17	Acceptor	Gln284	N	2093	Donor
				O	10	Acceptor	Gln284	N	2093	Donor
				O	18	Acceptor	Tyr280	O	2066	Both


PS1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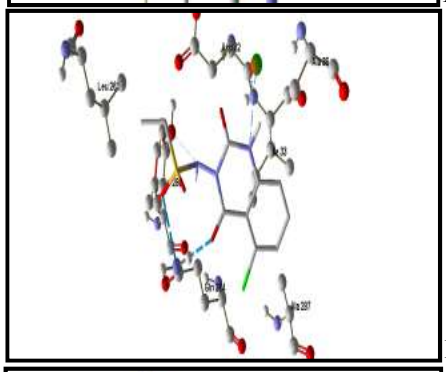
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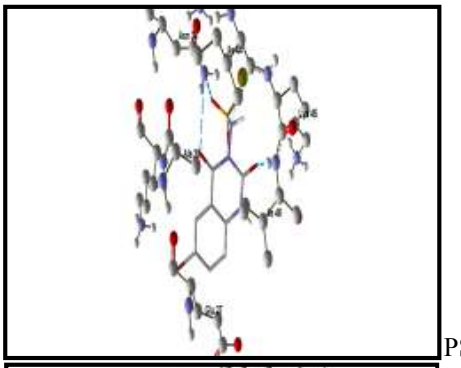
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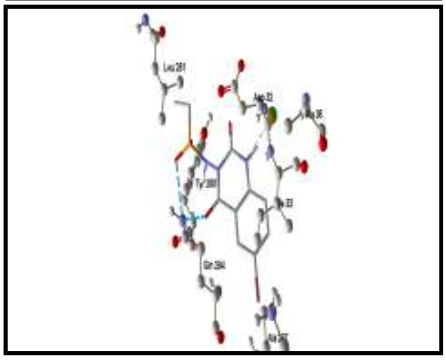
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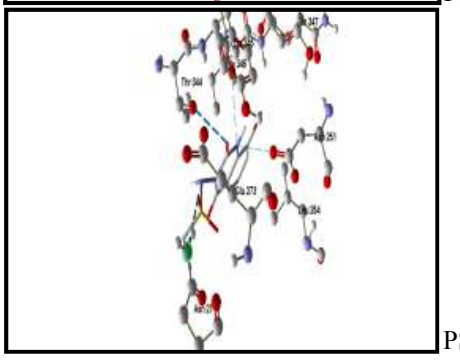
PS6

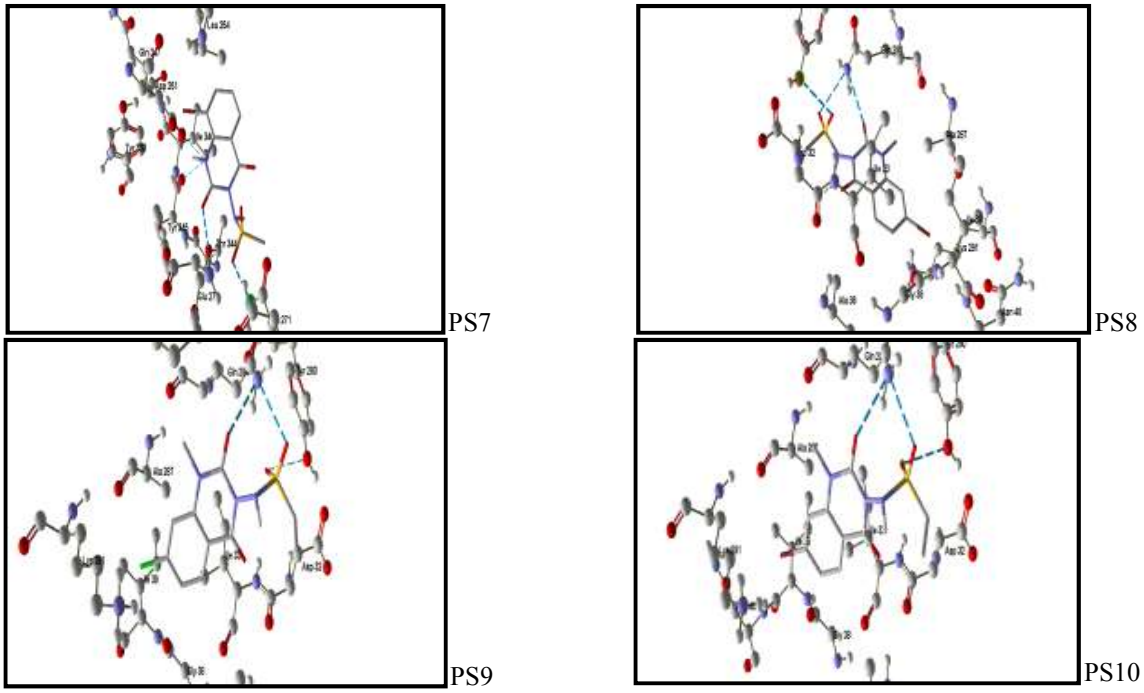

Figure 3. Docked images of Quinazolinedione Sulphonamide derivatives PS1-PS10 with GABA Receptor.

4. CONCLUSIONS

Structure based drug designing is significantly based on the protein-ligand interaction. A series of Quinazolinedione sulfonamide derivatives were designed and docked with their previously well known receptors for anticonvulsant activity. After analysis of docking results, as already discussed in previous sections of this manuscript, it may conclude that the designed compounds may have anti-convulsant activity with possible mechanism of action mediated through AMPA and GABA.

Further, it may also concluded after comparison of results of AMPA & GABA that possibly AMPA could results with better prospects for designed molecules against epilepsy.

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