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In-silico Designing and Docking of Novel N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine Carboamide as Anticonvulsant Agent

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Abstract A series of N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine carboamide were designed and carried with *in-silico* methods keeping in view the structural requirement of pharmacophore as potent anticonvulsant agents. These agents were then screened on the basis of docking procedures and further docking analysis of novel agents has been performed. The docking analysis reveals that compounds IPSR2, IPSR3, IPSR6 and IPSR9 perfectly docked with the T-type calcium channel with the highest bonding affinity range (-7 Kcal/mol to -7.5 Kcal/mol) and hydrogen bonds (5 to 7). Compounds IPSR4, IPSR5, IPSR7 and IPSR8 are found to dock with Na-channel with the bonding affinity range (-7.5 Kcal/mol to -8.3 Kcal/mol) and hydrogen bond (4 to 6). IPSR10 is found to dock with Glutamate receptor with significant bonding affinity and hydrogen bonds.

Keywords: *hydrazine carboamide derivatives, anticonvulsant agent, In-silico, docking, AutoDock Vina*

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1. Introduction

Epilepsy is one of the most common disorders of the brain, affecting more than 50 million individuals worldwide Epilepsy is a chronic and often progressive disorder characterized by the periodic and unpredictable occurrence of epileptic seizures that are caused by abnormal discharge of cerebral neurons. Resistance to antiepileptic drugs (AEDs) and the side effects associated with the current AEDs are the most serious problems in the current treatment pattern of epilepsy [1-9]. So, there is a need to design anticonvulsants for the development of more effective and safer AEDs.

Hydrazones possessing an azomethine -NHN=CH- proton constitute an important class of compounds for new drug development. In the past decade, hydrazones have been designed as potential anticonvulsants that were structurally dissimilar from very common anticonvulsants containing the dicarboximide function (CONRCO), which may contribute to toxic side effects [10].

2. Materials and Method

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 voltage gated sodium channel, GABA(A) alpha-1, GABA (A) delta, Glutamate, Na/H exchanger and T-type calcium channel.

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. 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 N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine Carboamide Derivatives as Anticonvulsant Agent - Docking

Docking has been performed with AutoDock Vina docking software [11]. 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 and Discussion

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

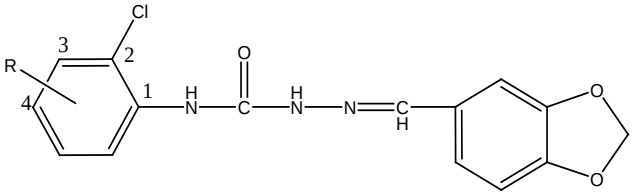

Figure 1. Pharmacophore

3.1. Novel Designed Molecules of N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine Carboamide Moiety as Anticonvulsants

All the novel designed molecules are shown in Table 1.

Table 1. Novel designed derivatives as anticonvulsant agent

Compound code	R
IPSR2	4Cl-
IPSR3	4Br-
IPSR4	4F-
IPSR5	3, 4-dichloro
IPSR6	$4CH_3$-
IPSR7	$4C_2H_5$-
IPSR8	$4OCH_3$-
IPSR9	$4OC_2H_5$-
IPSR10	$4NO_2$-

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.

Table 2. Docking results of novel N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine carboamide derivatives

Ligand	Receptor	Affinity (Kcal/mol)	H-bonds	H- Binding Ligand			H- Binding Receptor			
				Elem.	At.No.	Type	Res.	Elem.	At.No.	Type
IPSR2	GABA(A) alpha-1	-6.6	4	N	06	Donor	SER	O	137	Both
				N	03	Acceptor	SER	O	137	Both
				O	02	Acceptor	SER	O	137	Both
				O	02	Acceptor	SER	N	132	Donor
	GABA (A) delta	-6.1	0	-	-	-	-	-	-	-
	Glutamate	-7.8	3	N	03	Donor	ASP	O	794	Acceptor
				N	06	Donor	ASP	O	794	Acceptor
				O	02	Acceptor	ALA	N	674	Donor
	Na/H exchanger	-5.8	0	-	-	-	-	-	-	-
	Na channel	-7.8	2	N	06	Donor	GLU	O	629	Acceptor
				N	03	Donor	GLU	O	629	Acceptor
	T- type calcium	-7.4	5	N	00	Acceptor	ASN	O	347	Acceptor
				N	03	Donor	ASN	O	347	Acceptor
				N	06	Acceptor	ASN	O	347	Acceptor
				N	03	Donor	ASN	O	350	Acceptor
				O	02	Acceptor	ARG	N	982	Donor
IPSR3	GABA(A) alpha-1	-6.3	3	O	02	Acceptor	SER	O	137	Both
				N	03	Acceptor	SER	O	137	Both
				N	06	Donor	SER	O	137	Both
	GABA (A) delta	-6	0	-	-	-	-	-	-	-
	Glutamate	-7.4	5	O	02	Acceptor	SER	O	815	Both
				N	06	Donor	SER	O	815	Acceptor
				O	02	Acceptor	SER	N	810	Donor
				N	03	Donor	ALA	O	677	Acceptor
				N	00	Donor	ALA	O	677	Acceptor
	Na/H exchanger	-5.8	3	N	00	Donor	GLU	O	99	Acceptor
				N	03	Acceptor	GLU	0	99	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
	Na channel	-8	2	N	06	Donor	GLU	O	1615	Acceptor
				N	03	Donor	GLU	O	1615	Acceptor

	T- type calcium	-7.3	7	N	06	Acceptor	SER	O	1851	Acceptor
				N	03	Acceptor	SER	O	1851	Acceptor
				N	03	Donor	LEU	O	1843	Acceptor
				N	03	Donor	LEU	O	1863	Acceptor
				N	00	Donor	LEU	O	1843	Acceptor
				N	06	Donor	LEU	O	1863	Acceptor
				O	02	Acceptor	GLN	N	1868	Donor
IPSR4	GABA(A) alpha-1	-6.2	3	O	02	Acceptor	SER	O	137	Both
				N	06	Donor	SER	O	137	Both
				O	16	Acceptor	SER	N	132	Donor
	GABA (A) delta	-6.3	0	-	-	-	-	-	-	-
	Glutamate	-8.1	3	N	06	Acceptor	ASP	O	794	Acceptor
				N	03	Donor	ASP	O	794	Acceptor
				O	02	Acceptor	ALA	N	674	Donor
	Na/H exchanger	-5.7	3	N	00	Acceptor	GLU	O	99	Acceptor
				N	03	Donor	GLU	O	99	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
	Na channel	-8.2	4	N	00	Donor	GLU	O	1615	Acceptor
				N	03	Donor	GLU	O	1615	Acceptor
				N	06	Donor	GLU	O	1615	Acceptor
				O	02	Acceptor	TRP	N	1417	Donor
	T- type calcium	-7.2	1	O	02	Acceptor	ARG	N	1007	Acceptor
IPSR5	GABA(A) alpha-1	-6.4	3	O	02	Acceptor	SER	O	137	Both
				N	06	Donor	SER	O	137	Both
				O	16	Acceptor	SER	N	132	Donor
	GABA (A) delta	-6	0	-	-	-	-	-	-	-
	Glutamate	-8.1	3	N	06	Donor	ASP	O	794	Acceptor
				N	03	Acceptor	ASP	O	794	Acceptor
				O	02	Acceptor	ALA	N	674	Donor
	Na/H exchanger	-5.8	3	N	00	Donor	GLU	O	99	Acceptor
				N	03	Acceptor	GLU	O	99	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
	Na channel	-8.3	4	N	06	Donor	GLU	O	1615	Acceptor
				N	03	Donor	GLU	O	1615	Acceptor
				O	02	Acceptor	GLY	N	1688	Donor
				O	02	Acceptor	TRP	N	1417	Donor
	T- type calcium	-7.8	3	N	03	Acceptor	GLN	O	355	Acceptor
				N	06	Donor	GLN	O	355	Acceptor
				N	00	Donor	ASN	O	347	Acceptor
IPSR6	GABA(A) alpha-1	-6.5	3	N	06	Donor	SER	O	134	Both
				N	03	Acceptor	SER	O	134	Acceptor
				O	02	Acceptor	SER	O	134	Both
	GABA (A) delta	-6	2	N	06	Donor	PHE	O	338	Acceptor
				O	02	Acceptor	VAL	N	346	Donor
	Glutamate	-7.9	3	N	03	Acceptor	ASP	O	794	Acceptor
				N	06	Donor	ASP	O	794	Acceptor
				O	02	Acceptor	ALA	N	674	Donor
	Na/H exchanger	-5.8	3	N	00	Donor	GLU	O	99	Acceptor
				N	03	Acceptor	GLU	O	99	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
	Na channel	-7.2	6	N	03	Donor	ASP	O	1361	Acceptor
				N	03	Acceptor	ASP	O	1360	Acceptor
				N	03	Donor	ILE	O	1341	Acceptor
				N	00	Donor	ASP	O	1360	Acceptor
				N	00	Acceptor	ASN	O	1349	Acceptor
				N	06	Acceptor	ILE	O	1341	Acceptor

	T- type calcium	-7.5	5	N	00	Donor	ASN	O	347	Acceptor
				N	03	Donor	ASN	O	347	Acceptor
				N	06	Donor	ASN	O	347	Acceptor
				O	02	Acceptor	ARG	N	982	Donor
				N	03	Donor	ASN	O	350	Acceptor
IPSR7	GABA(A) alpha-1	-6.1	3	N	03	Donor	TRP	O	266	Acceptor
				N	06	Donor	TRP	O	266	Acceptor
				O	16	Acceptor	SER	O	134	Both
	GABA (A) delta	-6.4	0	-	-	-	-	-	-	-
	Glutamate	-8.6	3	N	06	Donor	ASP	O	661	Acceptor
				N	03	Donor	ASP	O	661	Acceptor
				O	02	Acceptor	ALA	N	674	Donor
	Na/H exchanger	-5.9	3	N	06	Donor	LEU	O	68	Acceptor
				N	03	Donor	LEU	O	68	Acceptor
				N	00	Donor	GLU	O	99	Acceptor
	Na channel	-7.5	6	N	03	Donor	LYS	O	515	Acceptor
				N	06	Donor	LYS	O	515	Acceptor
				N	03	Donor	ALA	O	540	Acceptor
				N	06	Donor	ALA	O	540	Acceptor
				N	06	Donor	GLU	0	628	Acceptor
				O	02	Acceptor	LYS	N	520	Donor
	T- type calcium	-7.3	5	N	00	Donor	ASN	O	350	Acceptor
				N	03	Donor	ASN	O	350	Acceptor
				N	00	Donor	ASN	O	347	Acceptor
				N	03	Donor	ASN	O	347	Acceptor
				O	02	Acceptor	ARG	N	982	Donor
IPSR8	GABA(A) alpha-1	-5.9	3	N	06	Donor	TRP	O	266	Acceptor
				N	03	Donor	TRP	O	266	Acceptor
				O	16	Acceptor	SRN	O	137	Both
	GABA (A) delta	-6.4	1	O	16	Acceptor	TRP	N	288	Donor
	Glutamate	-7.7	4	N	03	Donor	LEU	0	701	Acceptor
				N	06	Donor	LEU	0	701	Acceptor
				N	00	Donor	SER	0	815	Both
				O	16	Acceptor	THR	O	712	Both
	Na/H exchanger	-5.6	5	N	06	Donor	LEU	O	68	Acceptor
				N	03	Donor	LEU	O	68	Acceptor
				N	06	Donor	ALA	O	63	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
				N	00	Donor	GLU	O	99	Acceptor
	Na channel	-7.6	4	N	00	Donor	GLU	O	1615	Acceptor
				N	03	Donor	GLU	O	1615	Acceptor
				N	06	Donor	GLU	O	1615	Acceptor
				O	02	Acceptor	TRP	N	1417	Donor
	T- type calcium	-7.4	5	O	24	Acceptor	THR	O	1532	Both
				O	24	Acceptor	THR	N	1527	Donor
				N	00	Donor	MET	O	1721	Acceptor
				N	03	Donor	PRO	O	1904	Acceptor
				O	16	Acceptor	ASN	N	1683	Donor
IPSR9	GABA(A) alpha-1	-6.6	5	N	06	Donor	SER	O	137	Both
				N	03	Donor	SER	O	137	Both
				O	02	Acceptor	SER	O	137	Both
				O	02	Acceptor	SER	N	132	Donor
				O	24	Acceptor	SER	O	151	Both

	GABA (A) delta	-6.2	2	N	03	Donor	ALA	O	367	Acceptor
				N	00	Donor	ALA	O	367	Acceptor
	Glutamate	-7.4	5	O	02	Acceptor	SER	O	815	Both
				N	06	Donor	SER	O	815	Both
				N	03	Donor	ALA	O	677	Acceptor
				N	00	Donor	ALA	O	677	Acceptor
				O	02	Acceptor	SER	N	810	Donor
	Na/H exchanger	-5.5	3	N	00	Donor	GLU	O	99	Acceptor
				N	03	Donor	GLU	O	99	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
	Na channel	-8	2	N	03	Donor	GLU	O	1615	Acceptor
				N	06	Donor	GLU	O	1615	Acceptor
	T- type calcium	-7	7	N	03	Donor	LEU	O	1863	Acceptor
				N	06	Donor	LEU	O	1863	Acceptor
				N	03	Donor	SER	O	1851	Acceptor
				N	06	Donor	SER	O	1851	Acceptor
				N	03	Donor	LEU	O	1843	Acceptor
				N	00	Donor	LEU	O	1843	Acceptor
				O	02	Acceptor	GLN	N	1868	Donor
IPSR10	GABA(A) alpha-1	-6.8	7	O	25	Acceptor	SER	O	151	Both
				N	24	Acceptor	SER	O	151	Both
				O	26	Acceptor	SER	O	151	Both
				N	06	Donor	SER	O	137	Both
				O	02	Acceptor	SER	O	137	Both
				O	02	Acceptor	SER	N	132	Donor
				O	26	Acceptor	ASN	N	175	Donor
	GABA (A) delta	-6.2	2	N	00	Donor	ALA	O	367	Acceptor
				N	03	Donor	ALA	O	367	Acceptor
	Glutamate	-7.8	6	N	06	Donor	SER	O	815	Both
				O	02	Acceptor	SER	O	815	Both
				O	02	Acceptor	SER	O	810	Donor
				N	03	Donor	ALA	O	677	Acceptor
				N	00	Donor	ALA	O	677	Acceptor
				O	26	Acceptor	ASP	N	791	Donor
	Na/H exchanger	-5.7	4	N	00	Donor	GLU	O	99	Acceptor
				N	03	Donor	GLU	O	99	Acceptor
				N	03	Donor	GLY	O	95	Acceptor
				N	06	Donor	GLY	O	95	Acceptor
	Na channel	-8.1	2	N	03	Donor	GLU	O	1615	Acceptor
				N	06	Donor	GLU	O	1615	Acceptor
	T- type calcium	-7.6	3	O	25	Acceptor	LEU	N	604	Donor
				O	25	Acceptor	GLY	N	600	Donor
				N	00	Donor	ASP	O	672	Acceptor

3.3. Docking Analysis

On docking of the novel N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine carboamide derivatives with the well known receptors recognized for the antiepileptic action, we found some very interesting points. Firstly, we docked the ligand **IPSR2** with GABA(A)alpha-1for its inhibition, then, it results with the 4 hydrogen bonds with binding affinity of -6.6 Kcal/mol. The residue to which they bind is SER. In the same way ligand IPSR2 has been docked with voltage gated sodium channel with number of hydrogen bonds of 2 and the affinity of -7.8 Kcal/mol with residue GLU.

In the same way, ligands IPSR3, IPSR4, IPSR5, IPSR6, IPSR7, IPSR8 and IPSR9 have been docked with all the receptors individually in order to find the most appropriate binding. All the results have been shown previously in Table 2.

4. Conclusion

Structure based drug designing is significantly based on the protein-ligand interaction. A series of N'-(Substituted 2-Chlorophenyl)-2-(1, 3-benzodioxo-5-carbylidene) Hydrazine carboamide derivatives were designed and docked with their previously well known receptors for anticonvulsant activity. They were analyzed under docked conditions and this analysis reveals that compounds **IPSR2, IPSR3, IPSR6** and **IPSR9** perfectly docked with the **T-type calcium channel** with the highest bonding affinity range (**-7 Kcal/mol to -7.5 Kcal/mol**) and hydrogen bonds (**5 to 7**). Compounds **IPSR4, IPSR5, IPSR7** and **IPSR8** are

found to dock with Na channel with the bonding affinity range **(-7.5 Kcal/mol to -8.3 Kcal/mol)** and hydrogen bond **(4 to 6)**. IPSR10 is found to dock with Glutamate receptor with significant bonding affinity and hydrogen bonds. Finally, we could conclude that these compounds could be further synthesize and may proceed for the in-vitro and in-vivo procedures for developing a highly improved anticonvulsant agents.

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