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Structure based virtual screening, molecular docking studies and modification of hydantoin nucleus analogues as anticonvulsants

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Neurological disorders such as epilepsy remain a major concern to public health even though considerable therapy efforts aimed for developing effective medicine. The goal of the research is to design, development and identification of potential molecules by analysis and prediction of its interaction pattern with target along its pharmacokinetic parameters. In the present study we have screened and retrieved the Human voltage gated sodium channel target protein entries for epilepsy available in RCSBPDB database and the commercially available drugs as a ligand (such as Phenytoin, Ethotoin, Mephenytoin, fosphenytoin). The drugs have been docked to the above said receptor and the bio affinities values of the docked drugs Phenytoin (−6.50 kcal/mol), Mephenytoin (−6.52 kcal/mol) and Ethotoin (−6.40 kcal / mol) have been calculated using the NOVODOCKER docking module of Inventus v1.1 software. Depending on the bioaffinities values of the drugs several modifications have been carried out on the functional groups to improve the binding scores of the drugs. After screening through HitsGen; hits molecules the analogues of drug molecule were prepared using ChemDraw. Docking studies have been performed and further analysed by pharmacokinetic screening through pharmacopredicta which works through six assays namely CACO, efflux, BBB, FD_p,VDSS and finally top 20 modified analogues those being satisfied through all the screening results, have been found to be better than the conventional drugs available and can be taken up for synthesis and *in vivo* studies.

Keywords: Epilepsy, drug targets, molecular docking, Novodocker, HitsGen, ChemDraw

Epilepsy is a chronic brain function disorders characterized by unpredictable and periodic seizures also impairs consciousness, and possesses high risk owing to long - term therapy[1]. Existing antiepileptic drugs areonly effective in 65% of people affected with seizure disorders and undesirable side - effects are associated in more than 50% of people after receiving them so the on-going research in epileptic disease for improved anticonvulsant drugs needed for better antiepileptic therapies[2]. Approximately 10 million people are suffering from epilepsy and if those remains untreated even after availability of antiepileptic treatment, about 2-3 lakh patients died[3]. At present the majority of antiepileptic drugs available in the market to treat various types of seizures also aiming to reduce seizure frequency but they are not considered as safe, the undesirable side effects of drugs render therapy difficult so there is high demand for new agents with more selectivity and less toxicity in this area[4,5]. In this study hydantoin nucleus containg drug like phenytoin is taken as a reference drug. Phenytoin is an effective drug but it also causes various side effects and toxicity due to having narrow therapeutic index, high degree of serum protein binding, non - linear elimination pharmacokinetics and also individual variations in metabolism[6]. The main objective of the present study for finding rationality in the search of antiepileptic agents through two approaches they are design and screening. This will give help in quantitative estimation of anticonvulsant agent in terms of potency previously to the pharmacological screening; identification of best candidates from thousands of compounds. With the help of computational chemistry speed of drug discovery process increases and designing methods also varies for identification of novel compounds. Computational study gives idea about insight of drug - receptor interaction, bio affinity scores and pharmacokinetic parameters of compounds which are more important data for therapeutics in betterment of agents[7,8].

Results and Discussion

The protein structure 4JPZ was selected, downloaded from RCSBPDB[9] and subjected in INVENTUS v1.1 software for identification and

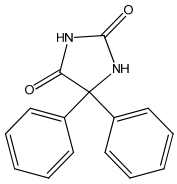
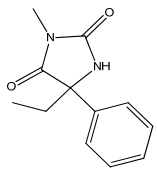
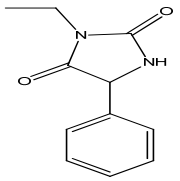
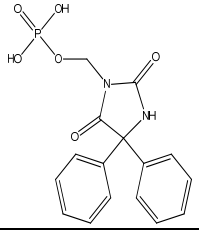
visualization of 3 - dimensional structure. After that the energy minimization process was performed through EnergyOpt module by Inventus software after giving the parameters steepest descent (SD) and conjugate gradient (CG) algorithm information required for optimizing the energy. Results of energy minimization were given as follows: Energy minimized from initial energy (8.345E + 05 kcal/mol) to final energy (−2.245E + 03 kcal/mol); towards negative means stability of protein increases. Then the pocket /cavity1 was selected through PocketDetector module by Inventus software (Figure 1). Cavity (active site) residues were as follows; LEU 3, GLU 5, ASP 6, ASP 7, PHE 8, GLU 9, MET 10, PHE 11, TYR 12, GLU 13, TRP 15, GLU 16, ASP 19, ALA 22, GLN 24, PHE 34, LEU 38, LEU 42, HIS 66, CYS 67, LEU 68, ILE 70, LEU 71, PHE 72, THR 75, LEU 88, GLN 91, MET 92, GLU 93, GLU 94, ARG 95, PHE 96, MET 97, ALA 98, SER 99, ASN 100, PRO 101, TYR 106. The commercially approved drugs were taken like Phenytoin, Ethotoin, Mephenytoin, fosphenytoin because these all contains hydantoin moiety in their chemical structure (drawn *via* Chem Draw) and the comparison of new analogues would be better by taking all of the above drugs. Calculation of physicochemical properties was done through Inventus software (Table I). All results followed the Lipinski rule for CNS agents which were discussed as follows; Lipinski's Rule for CNS drugs: CNS penetration is likely if: Molecular weight ≤ 400, Log p ≤ 5 (1.5 - 2.7), Hydrogen bond donor ≤ 3, and Hydrogen bond acceptor ≤ 7 (Ref 10).

Docking studies

Docking studies of the reference compounds were performed using NovoDocker module by Inventus

Figure 1 — Representation of target cavity prediction from Pocket Detector Module

Table I — Representation of physicochemical properties for reference drugs

S. No.	Compd	Chemical structure	Log P	Molecular weight(g/mol)	H-bond donors	H-bond acceptors
1	Phenytoin		1.77	252.27	2	4
2	Mephenytoin		1.47	218.25	1	4
3	Ethotoin		1.58	204.23	1	4
4	Fosphenytoin		1.89	362.27	3	8

software; thus scoring in terms of bio affinities were calculated. Results concluded that all the drugs shown good drug- receptor interaction pattern except fosphenytoin (Table II). During phenytoin (now selected only reference) drug - receptor interaction various residues (Figure 2) were involved; those residues have been mentioned below:

Active site residues: GLU 5, PHE 8, GLU9, TYR 12, TRP 15, GLU 16, GLN 24, CYS 67, LEU 71, MET 92, ARG 95, PHE 96, ALA 98, SER 99, ASN 100.

Hydrophobic Interaction: GLU 9, TYR 12, ARG 95, SER 99.

Electrostatic Interaction: GLU 5, GLU 9, TYR 12, ARG 95, PHE 96**,** SER 99.

Calculation of ADME (Structure Based) properties prediction

Calculation of blood brain barrier permeability; an important parameter of CNS agents was performed *via* using PharmoPredicta module by Inventus software (Table III). All drugs followed the range of BBB penetration prediction (except fosphenytoin) as well as also passed other parameters like Caco- permeability, Human absorption, FDp,Volume of distribution at Steady State, Protein Binding, *etc*.

Hits compounds were screened through HitsGen module by Inventus software. Screening of compound libraries for selected protein target with physicochemical properties was performed. With the help of screened compounds and structure - activity relationship detail of hydantoin nucleus; structures of the different analogues were drawn by using Chem Draw. Calculation of physicochemical properties was done through Inventus software. All analogues followed the Lipinski rule for CNS agents. Here 29 analogues passed BBB penetration prediction. After according to docking scores, BBB penetration prediction, and calculation of other parameters like Caco- permeability, Human absorption, FDp,Volume of distribution at Steady State, 22 analogues were selected for further work. All the drugs followed the limits of ADME (structure based) parameters given below.

ADME (Structure Based)

Human absorption, FDp (%) results are classified as:

(i) Low (0%-33% absorbed)
(ii) Medium (34%-66% absorbed)
(iii) High (67%-100% absorbed)
(iv) Caco-2 permeability (A→B or apical to basolateral), P eff at *p*H 7.4 (cm/s)

Table II — Representation of bioaffinity scores for reference drugs

S. No.	Compd	BioAff (Kcal / mol)
1	Phenytoin	-6.50
2	Mephenytoin	-6.52
3	Ethotoin	-6.40
4	Fosphenytoin	No docking

Table III — Representation of BBB permeability prediction for reference drugs

S. No.	Compd	BBB penetration	BBB confidence
1	Phenytoin	1	High
2	Mephenytoin	1	High
3	Ethotoin	1	High
4	Fosphenytoin	0	High

(0 if no penetration, 1 if penetration)

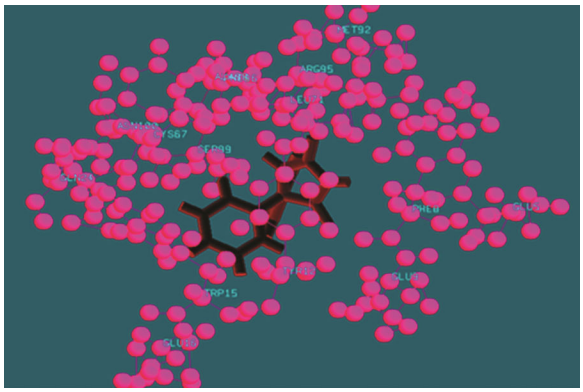


Figure 2 — Docking result of best pose for phenytoin with receptor *via* Novodocker tool

(v) Caco-2 permeability (B→A or basolateral to apical) at *p*H 7.4 (cm/s)
(vi) Efflux at *p*H 7.4 (0 if ≤ 5.3, 1 if > 5.3)
(vii) Blood Brain Barrier permeability (0 if no penetration, 1 if penetration)
(ix) Protein Binding (0 if ≤ 85%, 1 if > 85%)
(x) Volume of Distribution at Steady State, VDSS (lit.)
(xi) Prediction Confidence (high, medium, low)

Final analogues which passed prediction of BBB penetration and also shown the good drug – receptor interaction were given below:

22 analogues were selected has been given as below with their physicochemical properties calculation, bioaffinity score calculation, pharmacokinetic calculation (structure only) along with their chemical structures (Table IV, Table V, Table VI). All analogues followed the Lipinski rule for CNS agents.Finally 20 analogues were selected according to docking scores, pharmacokinetic parameters (structure only) which were as follows: Analogue no. 39, 41, 42, 46, 48, 49, 51, 52, 53, 54, 55, 58, 59,

Table IV — Representation of physicochemical properties for analogues

Analogue No.	Log P	Molecular weight	H-bond donors	H-bond acceptors
Analogue 39	1.57	255.27	2	5
Analogue 40	1.41	241.25	3	5
Analogue 41	1.71	255.27	2	5
Analogue 42	1.29	259.30	3	5
Analogue 46	2.69	268.31	2	4
Analogue 48	1.69	244.29	2	4
Analogue 49	1.26	258.27	2	5
Analogue 50	1.30	230.26	2	4
Analogue 51	2.06	269.30	2	5
Analogue 52	2.06	269.30	2	5
Analogue 53	1.57	255.27	2	5
Analogue 54	2.29	273.33	2	5
Analogue 55	1.88	269.30	2	5
Analogue 58	1.62	257.29	2	5
Analogue 59	1.94	267.28	2	5
Analogue 60	1.54	243.26	2	5
Analogue 61	1.54	243.26	2	5
Analogue 62	1.88	269.30	2	5
Analogue 63	2.60	272.32	2	4
Analogue 64	1.89	248.30	2	4
Analogue 65	1.20	229.23	3	5
Analogue 67	1.16	244.25	2	5
Reference (Phenytoin)	1.77	252.27	2	4

60, 61, 62, 63, 64, 65 and 67 were having good interaction with receptor when docked into the receptor protein for checking drug - receptor interaction. (Table VII). The binding mode of top 20 compounds with receptor has been shown in (Figure 3). Further residues involved in drug receptor interaction were studied and found that the analogues were having similar binding residues interaction as reference drug phenytoin. The docking energies of the ligands were negative which shows the stable binding interaction between the receptor and the ligands.

Materials and Methods

Target screening and identification: Selection, identification and visualization of protein

The epilepsy target having three-dimensional structures were screened and identified through various biological databases; in which the protein 4JPZ of voltage-gated sodium channel was retrieved from RCSB PDB for the *Homo sapiens*. The protein structure was subjected in INVENTUS v1.1 software for identification and visualization of 3 - dimensional structure in PDB format. For the present study various biological databases were used like RCSB PDB (Protein Data Bank), UniProt[11], PubChem[12], Drug Bank[13], Therapeutic target database (TTD)[14], PubMed[15], ChemDraw[16] and Pasilla online converter[17].

Energy optimization of the protein

It comprises the energy minimization process. The INVENTUS v 1.1 software uses the values of steepest descent (SD) and conjugate gradient (CG) for minimizing the energy of protein molecule.

Pocket (binding cavity) detection

The active site prediction is done through the pocket detector in INVENTUS v 1.1 software which gives active sites according to ranking order.

Screening (HitsGen)

HitsGen is used to screen multimillion compound libraries embedded with Physico-chemical properties for selected protein target in Inventus. Libraries are divided as per target classes, diseases and its nature. Also enable us to screen hits using structure based high throughput screening for protein target and later on can proceed ahead with docking studies.

Docking Studies (NovoDocker)

NOVODOCKER module predicts the binding of receptor and ligand efficiently and gives scoring results in terms of bioaffinity thus from this, the lowest energy (scores) conformations were regarded as the best binding conformations.

Bioaffinity calculation (BioAff)

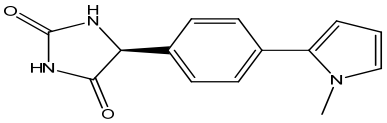
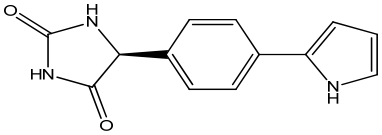
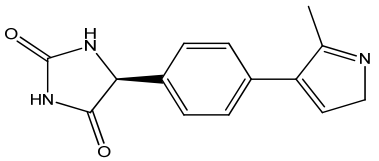
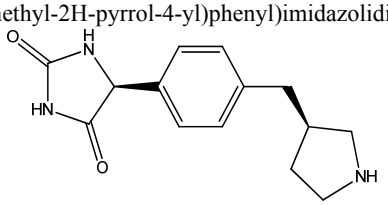
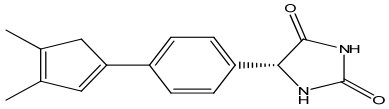
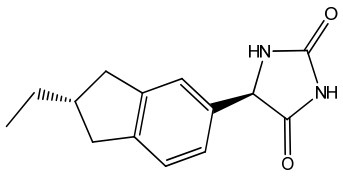
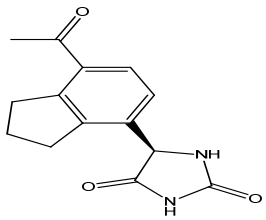
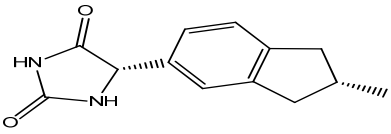
It employs for predicting binding affinity of protein-ligand complex in Kcal/mol, value towards the negative makes the complex/pose more stable.

Pharmacokinetic and ADME characteristic prediction (PharmacoPredicta)

PharmacoPredicta is a comprehensive predictive ADME software system developed and validated to predict relevant pharmacokinetic and ADME characteristics of selected Hits/Lead molecules before proceeding ahead with cell line and animal studies.

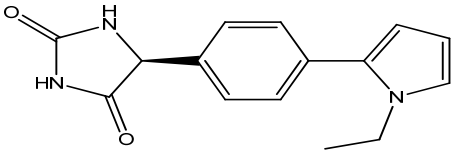
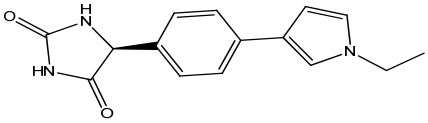
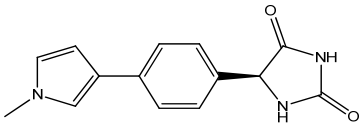
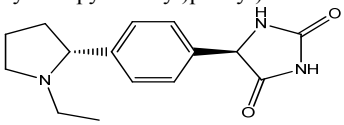
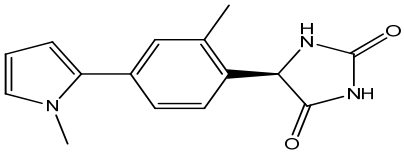
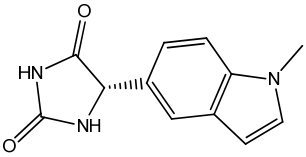
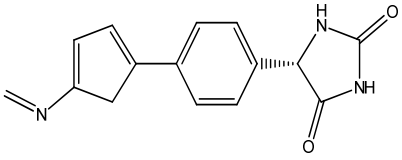
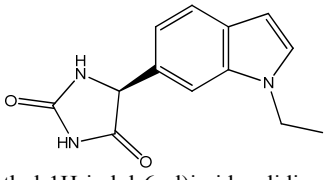
Historically, inappropriate pharmacokinetic (PK) properties have been a major reason for the failure of compounds in the later stages of drug development. This fact was largely due to an inability to identify and rectify poor pharmacokinetic characteristics present in many lead series accepted for lead optimization. With the adoption of high throughput screening, combinatorial chemistry, and parallel synthesis in drug discovery, the need for early information on the absorption, metabolism, distribution and elimination (ADME) of a compound has become increasingly important in the lead selection and optimization process.

Table V — Representation of chemical structures, BBB penetration prediction with bioaffinity scores of analogues

S. No.	Chemical structure	BBB penetration	BioAff (Kcal/mol)
Analogue 39	 (S)-5-(4-(1-methyl-1H-pyrrol-2-yl)phenyl)imidazolidine-2,4-dione	1	-6.67
Analogue 40	 (S)-5-(4-(1H-pyrrol-2-yl)phenyl)imidazolidine-2,4-dione	1	-5.12
Analogue 41	 (S)-5-(4-(5-methyl-2H-pyrrol-4-yl)phenyl)imidazolidine-2,4-dione	1	-6.53
Analogue 42	 (S)-5-(4-((R)-pyrrolidin-3-ylmethyl)phenyl)imidazolidine-2,4-dione	1	-6.53
Analogue 46	 (R)-5-(4-(3,4-dimethylcyclopenta-1,3-dien-1-yl)phenyl)imidazolidine-2,4-dione	1	6.52
Analogue 48	 (R)-5-((S)-2-ethyl-2,3-dihydro-1H-inden-5-yl)imidazolidine-2,4-dione	1	-6.81
Analogue 49	 (R)-5-(7-acetyl-2,3-dihydro-1H-inden-4-yl)imidazolidine-2,4-dione	1	-6.54
Analogue 50	 (S)-5-((S)-2-methyl-2,3-dihydro-1H-inden-5-yl)imidazolidine-2,4-dione	1	-5.08

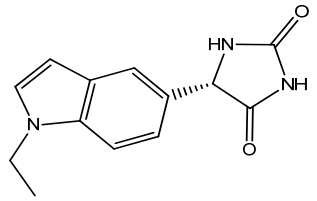
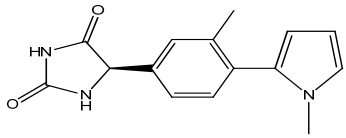
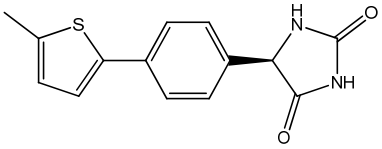
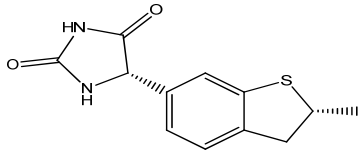
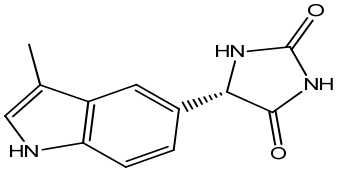
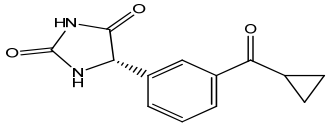
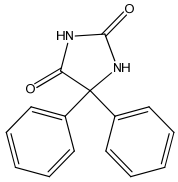
(*Contd*.)

Table V — Representation of chemical structures, BBB penetration prediction with bioaffinity scores of analogues (*Contd*.)

S. No.	Chemical structure	BBB penetration	BioAff (Kcal/mol)
Analogue 51	 (S)-5-(4-(1-ethyl-1H-pyrrol-2-yl)phenyl)imidazolidine-2,4-dione	1	-8.47
Analogue 52	 (S)-5-(4-(1-ethyl-1H-pyrrol-3-yl)phenyl)imidazolidine-2,4-dione	1	-8.02
Analogue 53	 (S)-5-(4-(1-methyl-1H-pyrrol-3-yl)phenyl)imidazolidine-2,4-dione	1	-6.85
Analogue 54	 (R)-5-(4-((R)-1-ethylpyrrolidin-2-yl)phenyl)imidazolidine-2,4-dione	1	-7.81
Analogue 55	 (R)-5-(2-methyl-4-(1-methyl-1H-pyrrol-2-yl)phenyl)imidazolidine-2,4-dione	1	-8.44
Analogue 58	 (S)-5-(1-methyl-1H-indol-5-yl)imidazolidine-2,4-dione	1	-6.51
Analogue 59	 (S)-5-(4-(4-(methyleneamino)cyclopenta-1,3-dien-1-yl)phenyl)imidazolidine-2,4-dione	1	-6.51
Analogue 60	 (S)-5-(1-ethyl-1H-indol-6-yl)imidazolidine-2,4-dione	1	-6.54

(*Contd*.)

Table V — Representation of chemical structures, BBB penetration prediction with bioaffinity scores of analogues (*Contd*.)

S. No.	Chemical structure	BBB penetration	BioAff (Kcal/mol)
Analogue 61	 (S)-5-(1-ethyl-1H-indol-5-yl)imidazolidine-2,4-dione	1	-6.53
Analogue 62	 (R)-5-(3-methyl-4-(1-methyl-1H-pyrrol-2-yl)phenyl)imidazolidine-2,4-dione	1	-7.70
Analogue 63	 (R)-5-(4-(5-methylthiophen-2-yl)phenyl)imidazolidine-2,4-dione	1	-5.51
Analogue 64	 (S)-5-((R)-2-methyl-2,3-dihydrobenzo[b]thiophen-6-yl)imidazolidine-2,4-dione	1	-6.54
Analogue 65	 (S)-5-(3-methyl-1H-indol-5-yl)imidazolidine-2,4-dione	1	-6.54
Analogue 67	 (S)-5-(3-(cyclopropanecarbonyl)phenyl) imidazolidine-2,4-dione	1	-6.49
Reference (Phenytoin)	 5,5-diphenylimidazolidine-2,4-dione	1	-6.50

(0 if no penetration, 1 if penetration**)**

Table VI — Representation of ADME (structure only) prediction for analogues

Analogue No.	Caco -2 (a→b) permeability (cm/s)-confidence	Caco-2 (b→a) Permeability (cm/s)-confidence	Efflux-confidence	FDp(%)-confidence	Probind (%)-confidence	VDSS (Lit.)-confidence
39	1.65E-05 Medium	3.77E-05 High	1 High	High High	0 High	10 High
40	6.30E-06 Medium	3.40E-05 High	1 High	High High	0 High	1 High
41	1.56E-05 Medium	4.56E-05 High	1 High	High High	0 High	1 High
42	6.38E-06 Medium	1.74E-05 High	1 High	High High	0 High	10 High
46	2.62E-05 Medium	4.50E-05 High	1 High	High Medium	1 High	10 High
48	3.32E-05 High	4.93E-05 High	1 High	High High	0 High	10 High
49	1.42E-05 High	4.53E-05 High	1 High	High High	0 High	1 Medium
50	3.33E-05 High	4.96E-05 High	1 High	High High	0 High	1 High
51	1.50E-05 Medium	3.24E-05 High	1 High	High High	0 High	10 High
52	1.54E-05 Medium	3.28E-05 High	1 High	High High	0 High	10 High
53	1.72E-05 Medium	3.61E-05 High	1 High	High High	0 High	10 High
54	1.67E-05 Medium	3.26E-05 High	1 High	High medium	0 High	10 High
55	1.58E-05 Medium	3.75E-05 High	1 High	High High	0 High	10 High
58	1.94E-05 Medium	3.47E-05 High	1 High	High High	0 High	10 High
59	1.15E-05 Medium	4.30E-05 High	1 High	High Medium	0 High	1 High
60	1.92E-05 Medium	3.49E-05 High	1 High	High High	0 High	10 High
61	1.94E-05 Medium	3.54E-05 High	1 High	High High	0 High	10 High
62	1.73E-05 Medium	3.82E-05 High	1 High	High High	0 High	10 High

(*Contd.*)

Table VI — Representation of ADME (structure only) prediction for analogues (*Contd*.)

Analogue No.	Caco -2 (a→b) permeability (cm/s)-confidence	Caco-2 (b→a) Permeability (cm/s)-confidence	Efflux-confidence	FDp(%)-confidence	Probind (%)-confidence	VDSS (Lit.)-confidence
63	2.11E-05 High	4.90E-05 High	1 High	High Medium	1 High	10 High
64	2.76E-05 High	4.93E-05 High	1 High	High medium	0 High	1 High
65	8.35E-06 Medium	3.49E-05 High	1 High	High Medium	0 High	1 High
67	1.32E-05 High	4.32E-05 High	1 High	High medium	0 High	1 Medium
Ref. Phenytoin	2.53E-05 High	5.73E-05 High	0 High	High High	1 High	10 High

Table VII — Representation of residues involved in drug- receptor interaction

Analogue No.	Active site residues	Hydrophobic Interaction	Electrostatic Interaction
39	GLU 5, PHE 8, GLU9, TYR 12, GLU 13, TRP 15, GLU 16, ARG 95, PHE 96, ALA 98, SER 99	GLU 9, TYR 12, GLU 16, ARG 95, SER 99	GLU 5, GLU 9, TYR 12, ARG 95, SER 99
41	GLU 5, PHE 8, GLU9, TYR 12, TRP 15, GLU 16, ASP 19, ALA 22, GLN 24, CYS 67, ARG 95, PHE 96, SER 99, ASN 100	GLU 5, PHE 8, GLU9, TYR 12, ALA 22, GLN 24	PHE 8, GLU 9, TYR 12, ALA 22, GLN 24, ARG 95, SER 99
42	GLU9, PHE 11, TYR 12, TRP 15, GLU 16, ALA 22, GLN 24, CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	TYR 12, GLN 24, ARG 95, PHE 96, SER 99	TYR 12, ALA 22, GLN 24, CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100
46	GLU 5, GLU9, TYR 12, GLN 24, CYS 67, LEU 71, ARG 95, PHE 96, SER 99, ASN 100	GLU 5, GLU9, TYR 12, GLN 24, PHE 96, SER 99	GLU 5, GLU9, TYR 12, ARG 95, SER 99, ASN 100
48	GLU 5, PHE 8, GLU9, TYR 12,GLU 13, TRP 15, GLU 16 ARG 95, PHE 96,ALA 98, SER 99, ASN 100	GLU 5, GLU9, TYR 12, GLN 24, PHE 96, SER 99	GLU 5, GLU9, TYR 12, ARG 95, SER 99, ASN 100
49	GLU 5, GLU9, PHE 11, TYR 12,TRP 15, GLN 24, CYS 67, LEU 71, ARG 95, PHE 96,ALA 98, SER 99, ASN 100	GLU9, TYR 12, ARG 95, SER 99	GLU9, TYR 12, GLN 24, CYS 67, ARG 95, PHE 96, ALA 98, SER 9
51	GLU 5, PHE 8, GLU 9, TYR 12,GLU 13, TRP 15,GLU 16, MET 92, ARG 95, PHE 96, ALA 98, SER 99	GLU9, TYR 12, GLU 13, GLU 16, ARG 95	GLU 5, GLU9, TYR 12, GLU 13,GLU 16, ARG 95, PHE 96, SER 99
52	GLU 5, PHE 8, GLU 9, TYR 12, TRP 15,GLU 16, ASP 19, ALA 22,GLN 24,CYS 67, ARG 95, PHE 96, SER 99, ASN 100	GLU 5, TYR 12, TRP 15, GLN 24,SER 99, ASN 100	GLU9, TYR 12, TRP 15, ALA 22,GLN 24, CYS 67, ARG 95, PHE 96, SER 99, ASN 100

(*Contd*.)

Table VII — Representation of residues involved in drug- receptor interaction (*Contd*.)

Analogue No.	Active site residues	Hydrophobic Interaction	Electrostatic Interaction
53	GLU 5, PHE 8, GLU9, TYR 12, TRP 15,GLU 16, ASP 19, ALA 22,GLN 24,CYS 67, ARG 95, PHE 96, SER 99, ASN 100	TYR 12, TRP 15, GLU 16, ALA 22,GLN 24,SER 99,	GLU 5, GLU9, TYR 12, GLU 16, ALA 22, GLN 24, ARG 95, SER 9
54	GLU 5, GLU9, TYR 12, TRP 15, GLU 16, GLN 24, GLU 94, ARG 95, PHE 96, ALA 98, SER 99	GLU9, ARG 95, SER 99	GLU9, TYR 12, GLU 16, ARG 95, PHE 96, ALA 98, SER 99
55	GLU 5, PHE 8, GLU9, TYR 12, GLN 24,CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	TYR 12, GLN 24, ARG 95, PHE 96, SER 99, ASN 100	GLU 5, GLU9, TYR 12, GLN 24, CYS 67, ARG 95, SER 99, ASN 100
58	GLU 5, TYR 12, TRP 15, ALA 22, GLN 24,CYS 67, LEU 71, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	TYR 12, GLN 24, PHE 96, SER 99, ASN 100	TYR 12, GLN 24, ARG 95, PHE 96, SER 99, ASN 100
59	GLU 5, GLU 9, TYR 12, GLU 13, TRP 15,GLU 16, ALA 22, GLN 24,CYS 67, MET 92, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	TYR 12, GLU 16, ARG 95, PHE 96, SER 99	GLU 9, TYR 12, GLU 13, GLU 16, ARG 95, PHE 96, SER 99
60	PHE 8, GLU 9, PHE 11, TYR 12,TRP 15,ALA 22,GLN 24,CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	TYR 12, GLN 24, ARG 95, SER 99	TYR 12, GLN 24, CYS 67, ARG 95, ALA 98, SER 99, ASN 100
61	GLU 5, PHE 8, GLU 9, TYR 12,TRP 15, GLN 24,CYS 67, LEU 71, MET 92, ARG 95, PHE 96, SER 99, ASN 100	GLU 5, GLU 9, TYR 12, GLN 24, CYS 67, PHE 96, SER 99	GLU 5, TYR 12, TRP 15, GLN 24, CYS 67, ARG 95, SER 99, ASN 100
62	GLU 5, PHE 8, GLU 9, TYR 12, TRP 15, GLU 16, ASP 19, PRO 20, ALA 22, GLN 24,CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	GLU 9, TYR 12, GLU 16, GLN 24, ARG 95	GLU 9, TYR 12, TRP 15, GLU 16, ASP 19, ALA 22, GLN 24, ARG 95, SER 99, ASN 100
63	GLU 5, GLU 9, TYR 12, TRP 15, GLU 16, ASP 19, ALA 22, GLN 24, ARG 95, SER 99, ASN 100	GLU 5, GLU 9, GLU 16, GLN 24	GLU 9, TYR 12, GLU 16, ALA 22, GLN 24, ARG 95, SER 99
64	GLU 5, GLU 9, PHE 11, TYR 12, TRP 15, ALA 22, GLN 24, CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	ARG 95, SER 99	GLU 5,TYR 12, GLN 24, CYS 67, ARG 95, SER 99
65	GLU 5, PHE 8, GLU 9, TYR 12, GLN 24, CYS 67, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	GLU 5, TYR 12, ARG 95, SER 99	GLU 5,PHE 8, GLU 9, TYR 12, GLN 24, ARG 95, SER 99, ASN 100

(*Contd*.)

Table VII — Representation of residues involved in drug- receptor interaction (*Contd*.)

Analogue No.	Active site residues	Hydrophobic Interaction	Electrostatic Interaction
67	GLU 5, PHE 8, GLU 9, TYR 12, GLN 24, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	GLU 9, TYR 12, ARG 95, SER 99	GLU 9, TYR 12, ARG 95, ALA 98, SER 99
Ref. phenytoin	GLU 5, PHE 8, GLU9, TYR 12, TRP 15, GLU 16, GLN 24, CYS 67, LEU 71, MET 92, ARG 95, PHE 96, ALA 98, SER 99, ASN 100	GLU 9, TYR 12, ARG 95, SER 99	GLU 5, GLU 9, TYR 12, ARG 95, PHE 96, SER 99

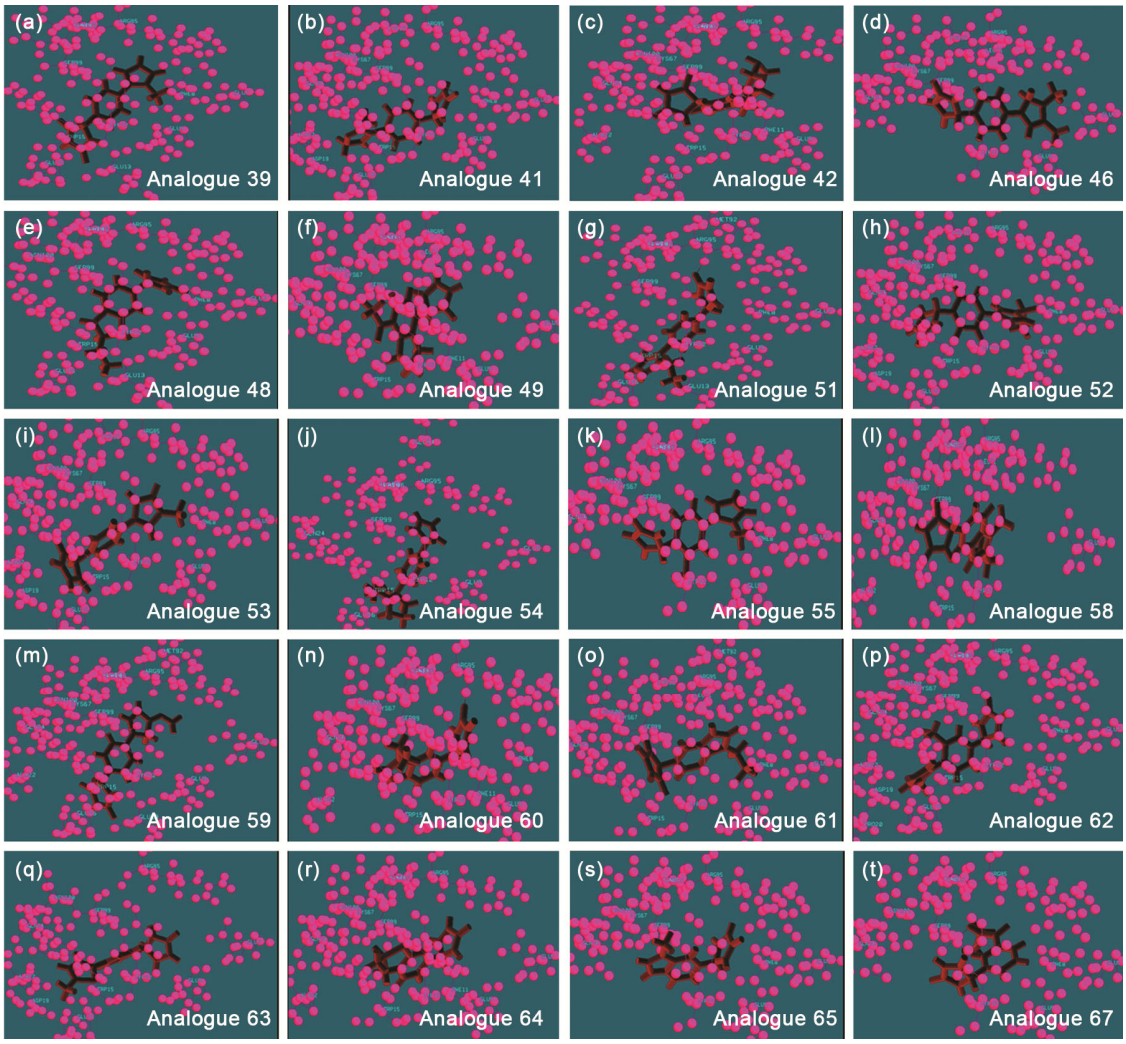


Figure 3 — Representation of binding modes of final 20 compounds with receptor

Following predictions based on chemical structure could be calculated:

Caco-2 (B→A), Caco-2(A→B) permeability, absorption (FDp) classification level, efflux, blood brain barrier permeability, protein binding and volume of distribution. A prediction confidence metric is provided for each of these[18-20].

Conclusion

A systematic computational medicinal chemistry approach helps in research for treatment of various diseases. As an alternative to animal experiments, *in vitro* and *in silico* screening methods has been

introduced to assist in the development of CNS active drugs. The aim of this study is to understand drug- receptor interaction patternandpharmacokinetic parameters of hydantoin nucleus analogues. Calculated or measured physicochemical properties may give first indications on the BBB permeability of a compound. Here again, specific molecular properties can be identified that favour BBB permeability. One of the major consequences of inadequate pharmacokinetics of both developmental and marketed drugs is failure in advanced development and/or market withdrawal. The balance between optimization of the physiochemical and pharmacokinetic properties to make the best in properties is critical for designing new drugs likely to penetrate the blood brain barrier and affect relevant biological systems. The modified analogues were docked with target protein shown good scores of bio affinity revealed that modified analogues can be further studied for synthesis and *in vivo*. From this we can conclude that some of the modified analogues were better than the commercial drugs available in the market. In future research work analogues can be used further in clinical trials to test it effectiveness and for social benefit thus reducing the time and cost in drug discovery process.

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