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ONLINE COMPUTATIONAL TOOLS FOR THE PREDICTION OF TOXICITY, DRUGLIKENESS, RECEPTOR INHIBITION AND LIGAND BASED PHARMACOPHORE DETECTION OF NOVEL 2-(2-OXO-DIHYDRO-2H-INDOL-2-YLIDENE) HYDRAZINE CARBOXMIDE SCHIFF BASES

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ABSTRACT

Drug discovery and development is complicated and time-consuming process. Recently, a trend towards the use of Insilico chemistry and molecular modelling for computer-aided drug design has gained significant importance. Insilico drug design skills are used in nanotechnology, molecular biology, biochemistry etc. The main benefit of the Insilico drug design is cost effective in research and development of drugs. There are wide ranges of software that are used in Insilico drug design, Grid computing, window based general PBPK/PD modelling software, PKUDDS for structure-based drug design, Molinspiration, PHARMAGIST, Chemaxon, Data warrior, O-Series, O Chem, JAVA, Perl and Python. The present study was focused to evaluate the series of building blocks with 2-(3-oxo-dihydro-2H-indol-2-ylidene) hydrazinecarboxmide Schiff bases moiety as a target molecule for anti-convulsant activity. The hypothetically developed 2-(2-oxo-dihydro-2H-indol-2-ylidene) hydrazinecarboxmide Schiff bases targets are ensured of their reliability on in silico drug designing model. The designed molecules were subjected to a preliminary study of physicochemical properties by screening their violation to Lipinski rule of five if any, predicted for their profile study by using Cheminformatics software viz. Molinspiration, O-Series, O-Chem, PharmaGist, chemaxon and data warrior. The results obtained from these tools shows all the compounds (1s-14s) follows Lipinski rule of five, bioactive scores predict were that all the compounds were moderately active towards enzyme targets (except 10s which is active) and kinase receptor (except 3s, 9s, 11s which are active). Data Warrior which was involved in toxicity predictions showed no mutagenic (except 3s), Tumorigenic (except 3s), irritant (except 3s, 6s, 7s, 8s, 11s) and reproductive effects. The designed molecules which were studied for inhibition against cytochrome p450 and its 5 subtypes model results showed that all the compounds are inhibitors of all subtypes except compounds 3s, 8s, 11s (inhibitors of CYP2D6) 3s, 8s (inhibitors of CYP2C19) 3S (inhibitors of CYP2C9) 3S-8S, 11S (inhibitors of CYP1A2) was observed for designed molecules. The pharmacophore mapping studies for anticonvulsant activity in comparison with the standard phenytoin exbhiting best pairwise alignments with a score ranging from (6.01837 for the1s, 2s, 14s & 6.3238 for 3s, 5s & 4.52 for 6s, 7s, 8s, 13s and 4.53 for 4s, 10s, 11s & 4.84 for 9s) .9.05026 for 12 with good activity. Thus, designed Schiff base derivatives might serve as the best drug lead for the existence of minimizing pathogen anti convulsant activity.

KEY WORDS

Insilico, Molinspiration, Data Warrior, O-Chem, Pharma Gist.

INTRODUCTION

*Insilico*is a term that means "computer aided". The phrase was coined in 1989 as an analogy to the Latin phrases *in vivo*, *in vitro*, and *in situ*. So *Insilico*drug design means rational design by which drugs are designed/discovered by using computational methods. According to Kubinyi [1], most of the drugs in the past were discovered by coincidence or trial and error method, or in other words, serendipity played an important role in finding new drugs. Current trend in drug discovery is shifted from discovery to design, which needs understanding the biochemistry of the disease, pathways, identifying disease causative proteins and then designing compounds that are capable of modulating the role of these proteins. This has become common practice in biopharmaceutical industries. Both experimental and computational methods play significant roles in the drug discovery and development and most of the times run complementing each other [2]. The main aim of computer aided drug design (CADD) is to bring the best chemical entities to experimental testing by reducing costs and late stage attrition [3]. CADD involves:

a. Computer based methods to make more efficient drug discovery and development process.

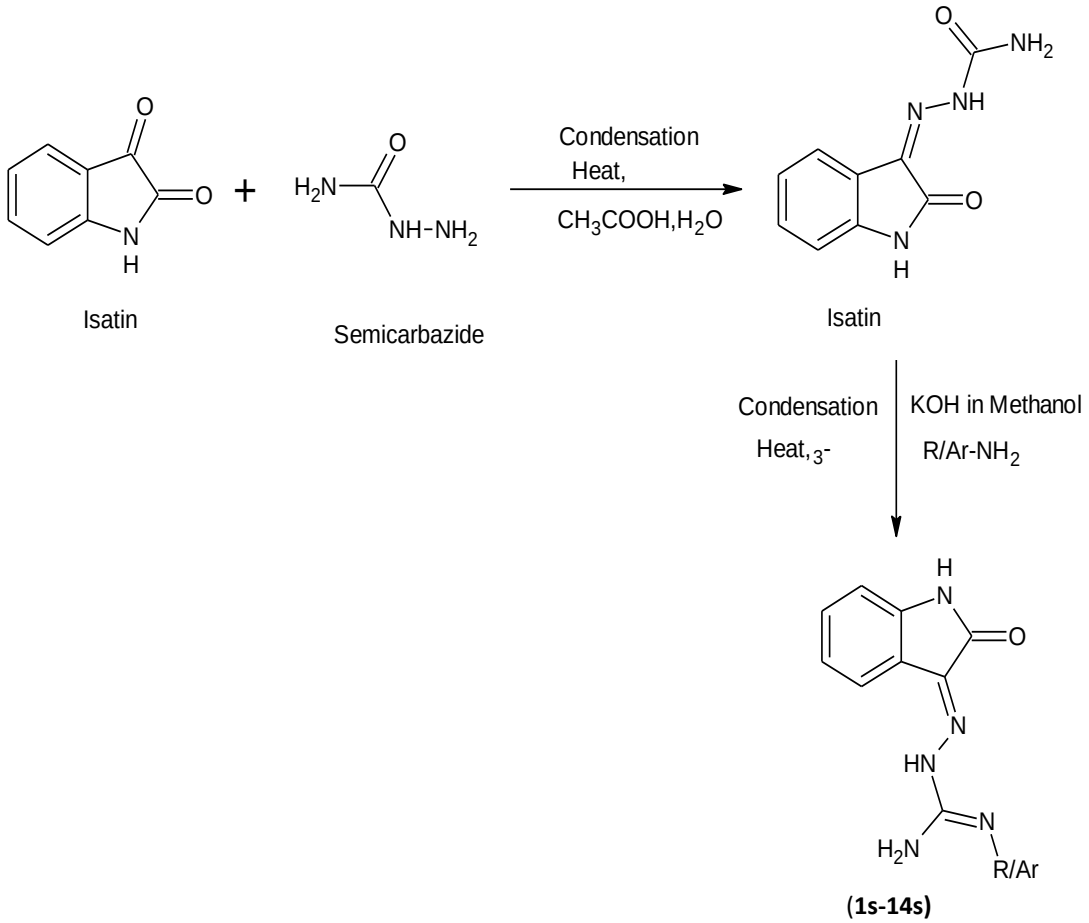
b. Building up chemical and biological information databases about ligands and targets/proteins to identify and optimize novel drugs. c. Devising *Insilico*filters to calculate drug likeness or pharmacokinetic properties for the chemical compounds prior to screening to enable early detection of the compounds which are more likely to fail in clinical stages and further to enhance detection of promising entities. *Insilico* methods have been of great importance in target identification and in prediction of novel drugs. There are different techniques used in *Insilico* drug design visualization, homology, molecular dynamic, energy minimization molecular docking and QSAR etc. *Insilico* drug design can take part considerably in all stages of drug development from the preclinical discovery stage to late stage clinical development. Its research in drug development helps in the selection of only a potent lead molecule and may decrease failures in last stage of clinical trials, thereby a major decrease in cost can be achieved.

Epilepsy is characterized by recurrent impulsive seizures of cerebral origin, donating with episodes of sensory, motor or autonomic phenomenon with or without loss of awareness. Epilepsy is a variety of disorders reflecting underlying brain dysfunction that may result from many diverse reasons [4]. Glutamate and γ-amino butyric acid (GABA) are two important excitatory and inhibitory neurotransmitters in epilepsy [5]. It has different symptoms such as staring, muscle stiffness (tonic movements), muscle spasms (clonic movements), and impaired consciousness [6]. The cellular and neurocircuit base of epilepsy is not well understood [7]. Treatment of epilepsy was improved by several third generation of anticonvulsant drugs during the past decades. But, resistance to antiepileptic drugs and intolerability in 2030% of the patients led to the fact that currently available antiepileptic drugs (AEDs) are symptomatically ineffective in 25-35% patients. However, there are serious demands for developing new drugs or strategies for epilepsy treatment [8, 9]. Therefore, search and investigation for new antiepileptic drugs (AED) with better efficacy and lesser side effects remains an essential goal. Isatin and its derivatives have different biological effects, including anti-inflammatory, antibacterial, antifungal, antiviral, antituberculosis, anticancer, anti-HIV and anticonvulsant [10-15]. During initial screening of isatin products, they have shown good activity in the maximum electroshock seizure (MES) test [16, 17]. In the semicarbazone analogues of isatin it has been proposed a binding site hypothesis for these compounds eliciting anticonvulsant activity.

General procedure:

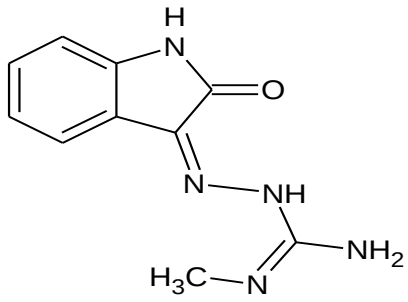
Synthesis of (2z)-2-(2-oxo-dihydro-2H-indol-2-ylidene) hydrazinecarboxmide Schiff bases [18-19]:

Isatin 3 Semicarbazone were prepared by condensation of 0.01 moles of Isatin with 0.02 moles of Semicarbazide HCl in presence glacial acetic acid and hot water. The reaction mixture was refluxed for 4hr. The reaction mixture was cooled; precipitate was filtered, dried, recrystallized from methanol and confirmed by thin layer chromatography and melting point. (2z)-2-(3-oxo-dihydro-2H-indol-2-ylidene) hydrazine carboxmide Schiff bases synthesis was preceded by condensation of equimoles (0.001moles) of step 1 with various aliphatic & aromatic amines in methanol and few drops of 40% KOH. The reaction mixture was refluxed for 4hr, cooled, the product formed was filtered, dried and recrystallized from methanol. The progress and the purity of the reaction was confirmed by thin layer chromatography and melting point. The procedure was illustrated under **Scheme 1**

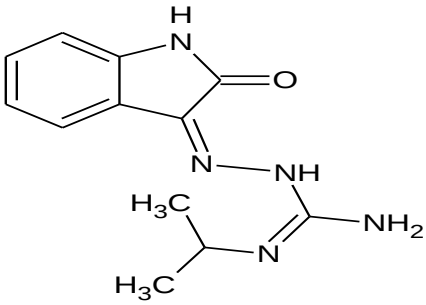


Scheme

1S



2S



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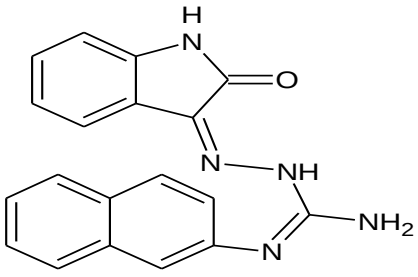
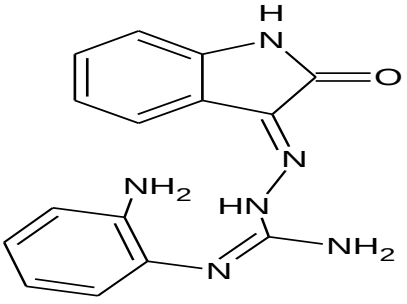
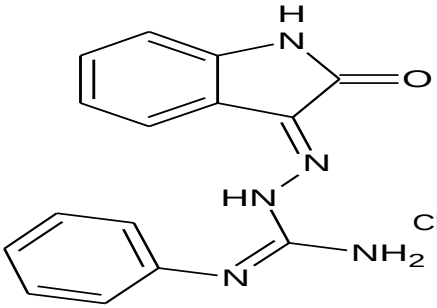


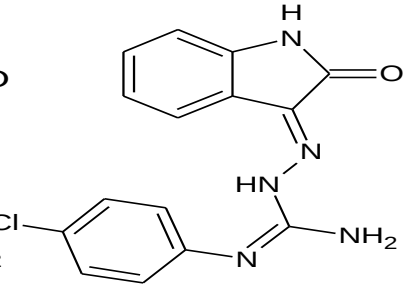
4S



5S



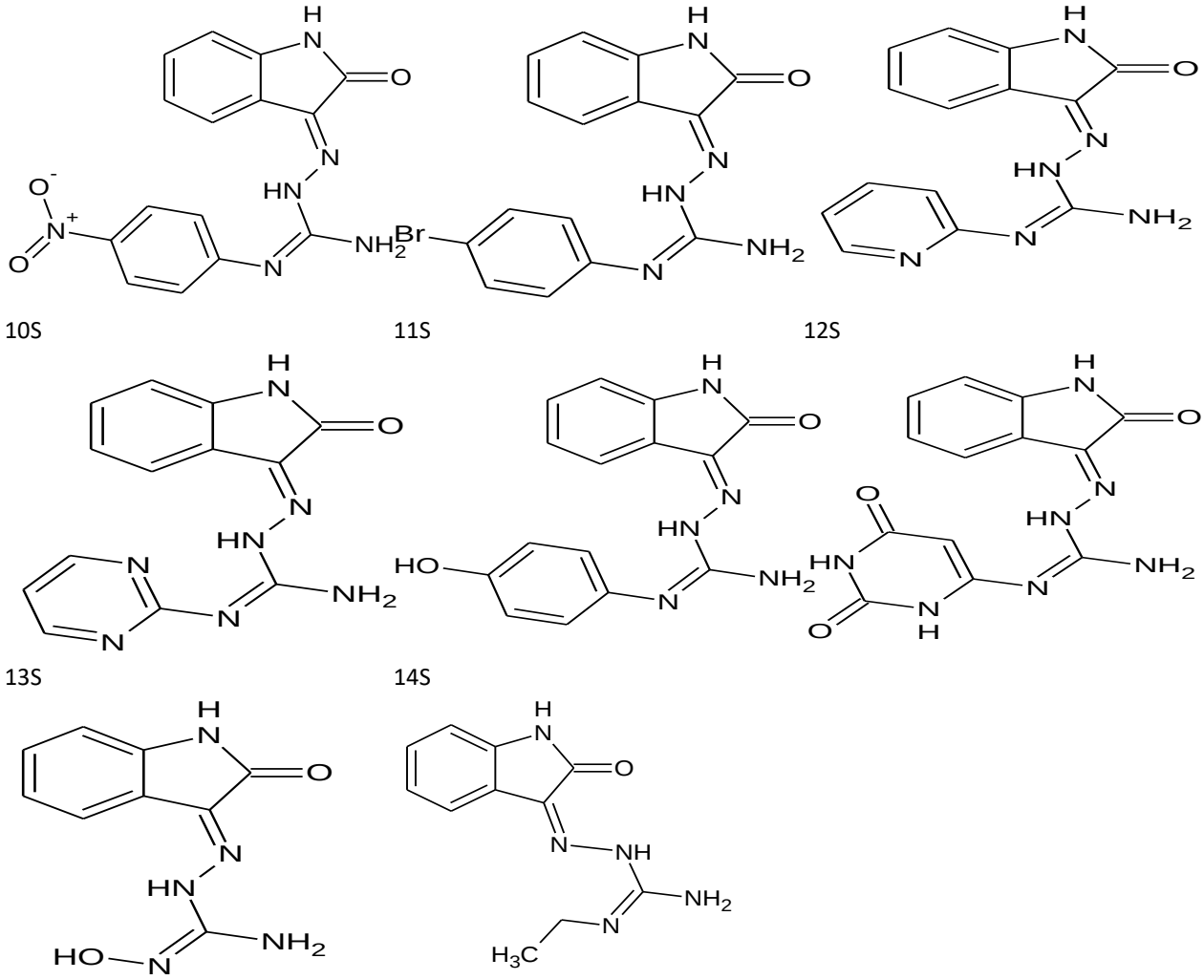
6S



7S

8S

9S



***INSILICO* METHODS:**

The designed structured were evaluated by Insilico methods i.e computational software's such as

Molinspiration[20]: (http://www.molinspiration.com) Molinspiration offers broad range of Cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomer's, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches.

O-CHEM [21]: (https://ochem.eu/home/show.do**)** The Online Chemical Modeling Environment (OCHEM) a unique and a web-based platform which supports all the steps required to create a predictive model: one such model developed was cytochrome P450 with 5 subtypes. The compounds were evaluated to assess their inhibition on the subtypes of cytochrome P450.

Open source program OSIRIS Property Explorer [22]: It is an offline software downloaded from Open source program OSIRIS Property used to predict the fragment-based drug-likeness of title to assess the occurrence frequency of each fragment in the individual structure. The program estimated the risks of side effects, such as mutagenic, tumorigenic, irritant and reproductive effects, as well as drug-relevant properties including clog, Logs (solubility), MW and drug likeness. The in-silico drug-relevant properties obtained by OSIRIS Property Explorer given in Table 7.

Pharma Gist [23]:

(http://bioinfo3d.cs.tau.ac.il/PharmaGist): Predicting molecular interactions is a major goal in rational drug design. Pharmacophore, which is the spatial arrangement of features that is essential for a molecule to interact with a specific target receptor, is important

for achieving this goal. Pharma Gist is a freely available web server for pharmacophore detection.

RESULTS AND DISCUSSION:

Three Cheminformatics programs were used to evaluate the various parameters of designed drugs such as drug likeness of compounds, toxicity predictions, to assess the inhibition of the derivatives against 5 subtypes of cytochrome P450.

In silico drug-likeness and toxicity predictions:

Open source program OSIRIS Property Explorer was used to predict the fragment-based drug-likeness of title compounds to assess the occurrence frequency of each fragment in the individual structure. The program estimated the risks of side effects, such as mutagenic, tumorigenic, irritant and reproductive effects, as well as drug-relevant properties including clog, Logs (solubility), MW and drug likeness. The in-silico drug-relevant properties obtained by OSIRIS Property Explorer given in Table 1.

Table 1: Osiris Calculations of Compounds.

Compound	Toxicity Risks				Molecular properties calculation				
	MUT	TUMO	IRRI	REP	MW	CLP	H-A	DL	H-D
1s	none	none	None	Low	217.231	-0.1131	6	4.5714	3
2s	none	none	none	Low	245.285	0.6525	6	4.5328	3
3s	low	high	low	Low	329.362	2.3954	6	4.3809	3
4s	none	none	none	Low	294.317	0.5237	7	4.3809	4
5s	none	none	none	Low	279.302	1.201	6	4.3809	3
6s	none	none	low	Low	313.747	1.807	6	4.4154	3
7s	none	none	low	Low	324.299	0.4403	9	-0.72911	3
8s	none	none	low	Low	358.198	1.9262	6	2.5909	3
9s	none	none	none	Low	280.29	0.5515	7	4.3809	3
10s	none	none	none	Low	281.278	0.0073	8	4.3809	3
11s	none	none	low	Low	295.301	0.8553	7	4.3708	4
12s	none	none	none	Low	313.276	-0.6084	10	3.6287	5
13s	none	none	none	Low	219.203	0.3819	7	4.278	4
14s	none	none	none	Low	231.258	0.2932	6	4.5236	3

MUT: Mutagenic; TUMO: Tumorogenic; IRRI: Irritant; REP: Reproductive Effective; CLP: ClogP; Log s: Solubility mol/lit; DL: Drug-Likeness; DS: Drug-Score. MW: Molecular weight; H-A: Proton acceptor; H-D: Proton donor.

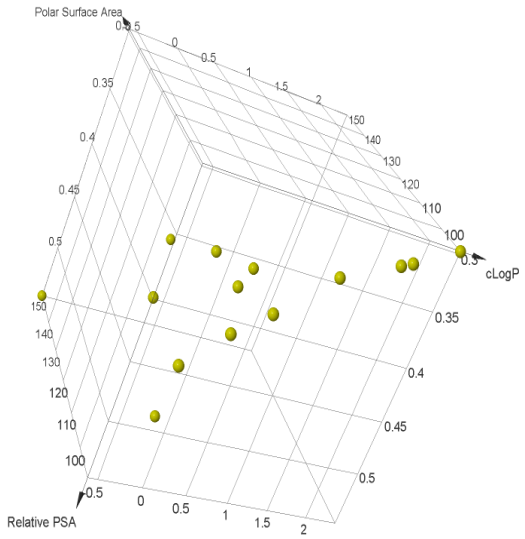


Fig-1: 3D GRID view of C log P, MUT, TUM

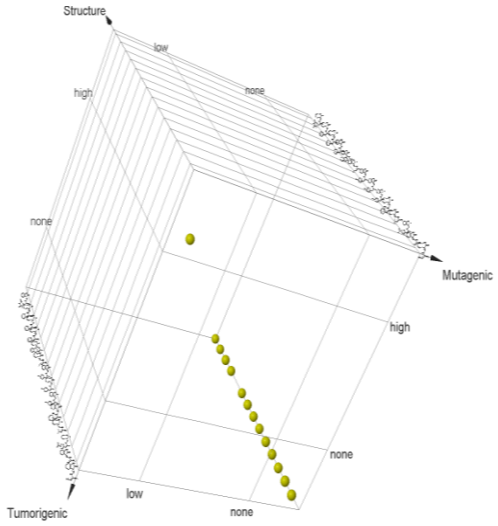


Fig-2: 3D GRID view of Structure, Relative PSA, PSA

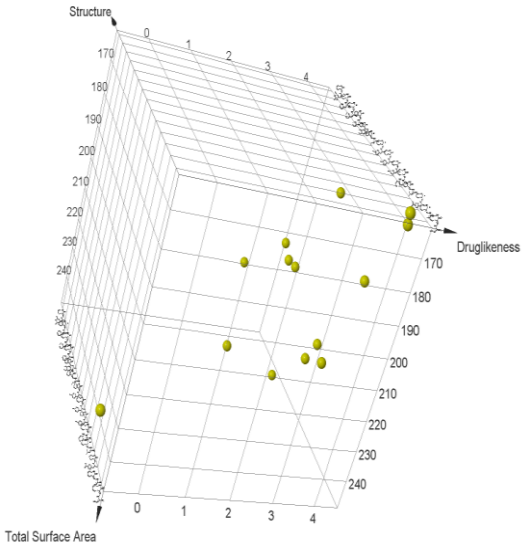


Fig-3: 3D GRID view of Structure, DL, TSA

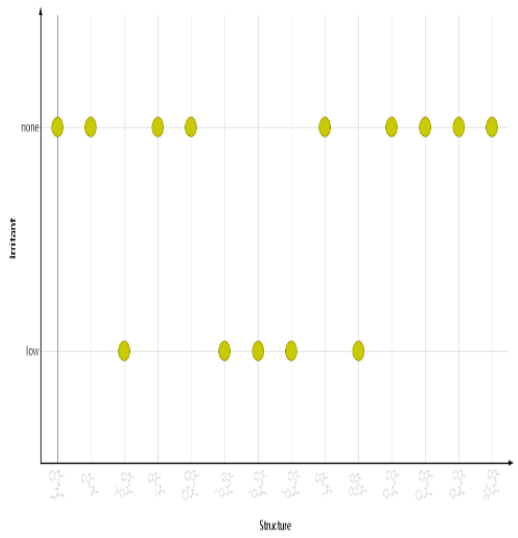


Fig-4: 2D GRID view of Structure & Irritant

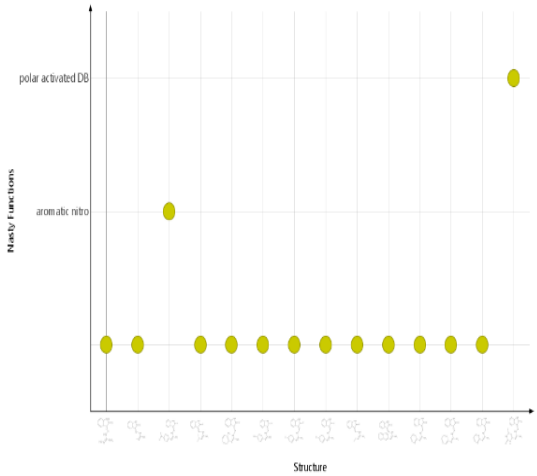


Fig-5: 2D GRID view of Structure & Irritant

Molinspiration Cheminformatics was used for calculating important drug like properties like logP, Polar surface area, Number of hydrogen bond donors, Number of hydrogen bond acceptors, Number of rotatable bonds, Volume, Number of violations from rule of five. It was also used to predict bioactive scores against important drug targets like GPCR ligand, Kinase inhibitors, Ion channel modulators, nuclear receptors, Protease inhibitors, Enzyme inhibitors.

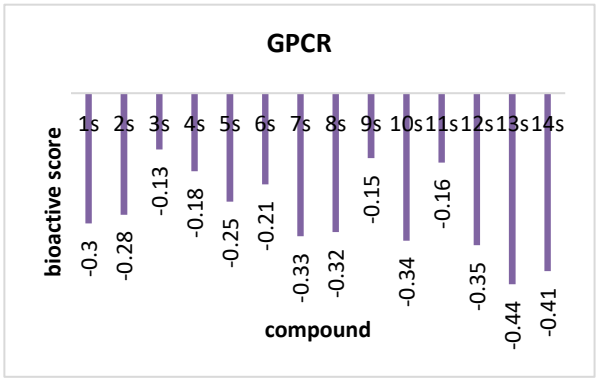
Table 6: drug –likeness properties

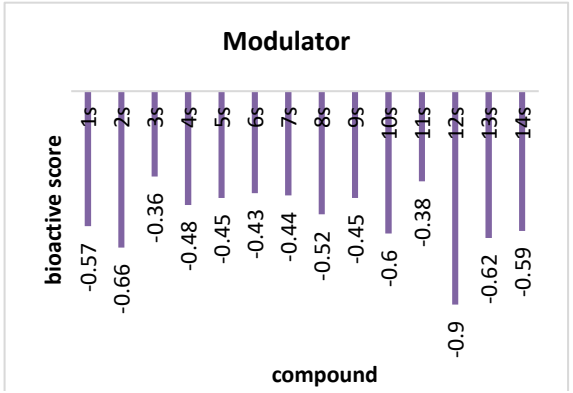
COMPOUND	Mi LOGP	TPSA	n atmos	MW	n ON	n OH NH	n violations	n rotb	Volume
1s	0.62	95.64	16	217.23	6	4	0	2	191.36
2s	1.29	95.64	18	245.29	6	4	0	3	224.74
3s	3.50	95.64	25	329.36	6	4	0	3	290.20
4s	1.75	121.66	22	294.32	7	6	1	3	257.50
5s	2.32	95.64	21	279.30	6	4	0	3	246.21
6s	3.00	95.64	22	313.75	6	4	0	3	259.74
7s	2.28	141.46	24	324.30	9	4	0	4	269.54
8s	3.13	95.64	22	358.20	6	4	0	3	264.09
9s	1.42	108.53	21	280.29	7	4	0	3	242.05
10s	0.50	121.42	21	281.28	8	4	0	3	237.90
11s	1.84	115.87	22	295.30	7	5	0	3	254.23
12s	-0.17	161.36	23	313.28	10	6	1	3	254.15
13s	0.30	115.87	16	219.20	7	5	0	2	182.82
14s	1.00	95.64	17	231.26	6	4	0	3	208.16

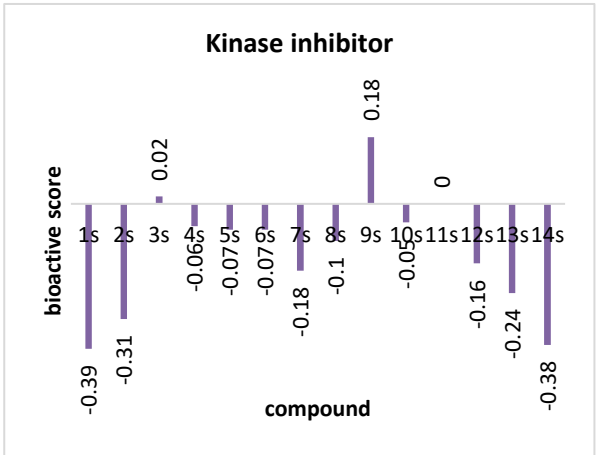
Table 7: Bioactive scores.

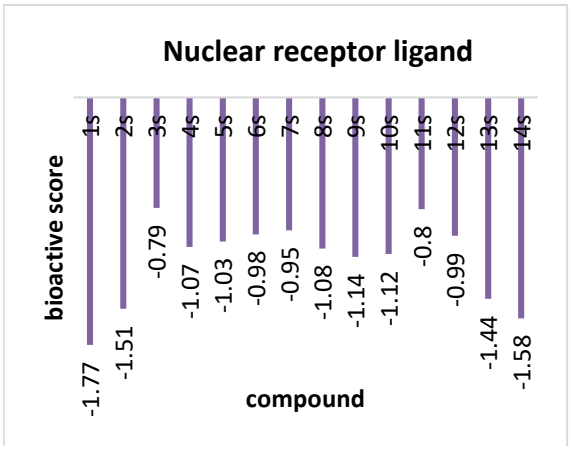
Compound	IUPAC	GPCR	Modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1s	(2z)-N1-methyl (-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.30	-0.57	-0.39	-1.77	-0.72	-0.12
2s	(2z)-N1, N1-DImethyl (-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene) hydrazine-1- carboximidamide	-0.28	-0.66	-0.31	-1.51	-0.61	-0.07
3s	(2z)-N1-(naphthalene-2-yl) -2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.13	-0.36	0.02	-0.79	-0.38	-0.11
4s	(2z)-N1-(4-aminophenyl) -2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.18	-0.48	-0.06	-1.07	-0.56	-0.06
5s	(2z)- 2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) N1-phenylhydrazinecarboximidamide	-0.25	-0.45	-0.07	-1.03	-0.60	-0.17
6s	(2z)-N^1-(4-chloro phenyl-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.21	-0.43	-0.07	-0.98	-0.59	-0.21
7s	(2z)-N^1-(4-nitro phenyl)-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.33	-0.44	-0.18	-0.95	-0.59	-0.26
8s	(2z)-N^1-(4-bromo phenyl)-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.32	-0.52	-0.10	-1.08	-0.67	-0.25
9s	(2z)-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene)-N1-pyridin-3-yl) hydrazine carboximidamide	-0.15	-0.45	0.18	-1.14	-0.34	-0.04
10s	(2z)-$N^{1-(}$pyrimidin-4yl)-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.34	-0.60	-0.05	-1.12	-0.74	0.19
11s	(2z)-N^1-(4-hydroxyphenyl)- 2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene)-hydrazine carboximidamide	-0.16	-0.38	0.00	-0.80	-0.52	-0.11
12s	(2z)-N^1-(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.35	-0.90	-0.16	-0.99	-0.60	-0.06
13s	(2z)-N^{1-}hydroxy2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.44	-0.62	-0.24	-1.44	-0.67	-0.11
14s	(2z)-N^1-ethyl (-2-(3-oxo-1,3-dihydro-2H-indol-2-ylidene) hydrazine carboximidamide	-0.41	-0.59	-0.38	-1.58	-0.64	-0.10

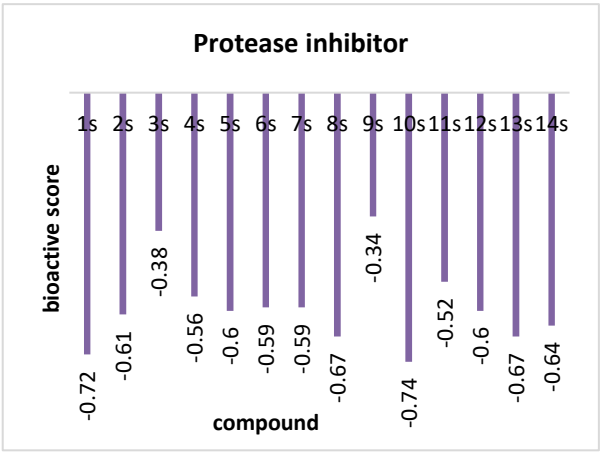
Table 8: Graphical representation of bio active score

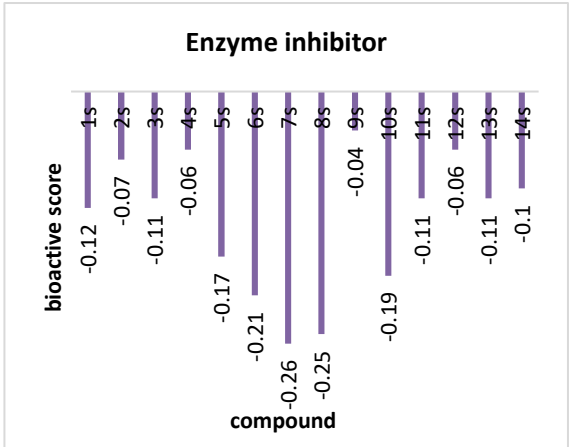












The Online Chemical Modeling Environment (OCHEM) a unique and a web-based platform which supports all the steps required to create a predictive model: one such model developed was cytochrome P450 with 5 subtypes. The compounds were evaluated to assess their inhibition on the subtypes of cytochrome P450.

Table 9: Online Chemical Modelling

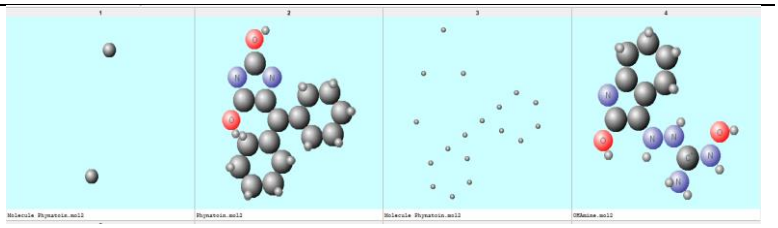
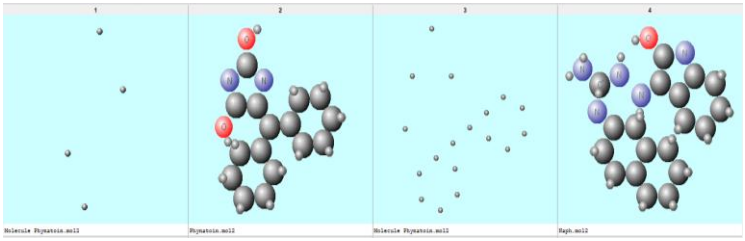
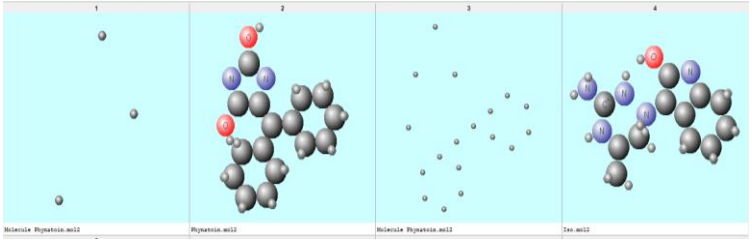
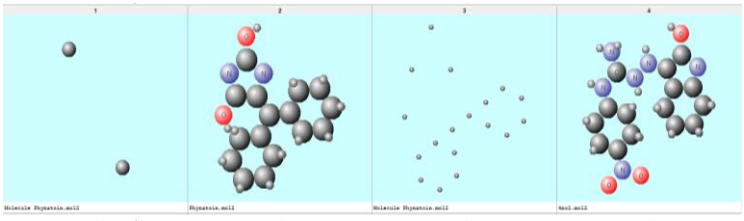
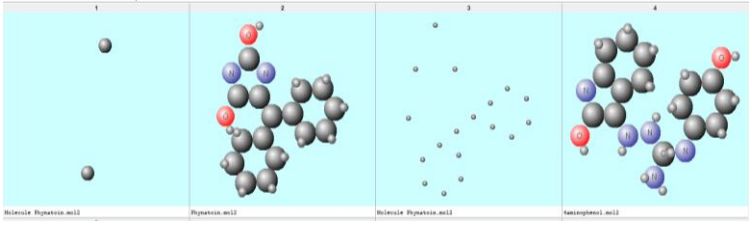
Compound	AMES	CYP3A4	CYP2D6	CYP2C19	CYP2C9	CYP1A2	MELTING POINT	PYROLSIS POINT (CELSIUS)
1S	Active	-	-	-	-	-	210°C	230
2S	Active	-	-	-	-	-	240°C	210
3S	Active	-	+	+	+	+	250°C	260
4S	Active	-	-	-	-	+	240°C	240
5S	Active	-	-	-	-	+	240°C	250

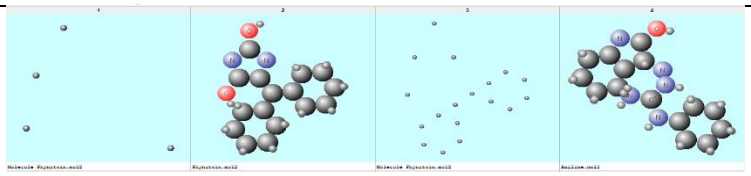
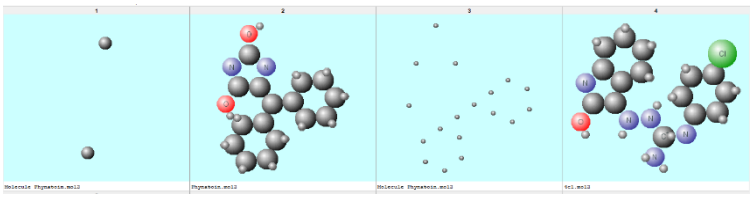
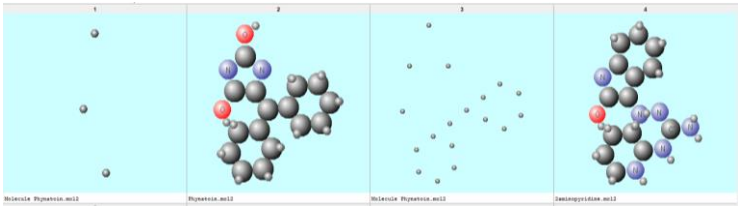
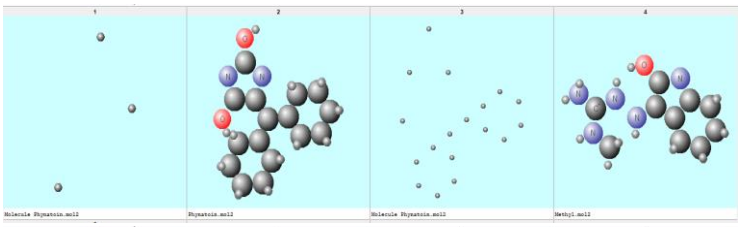
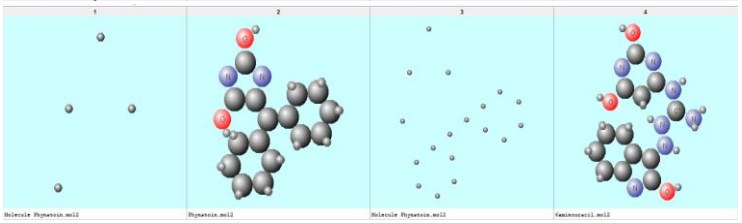
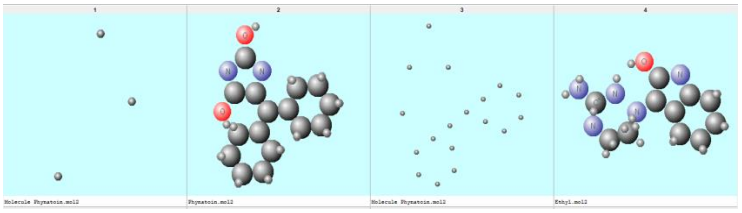
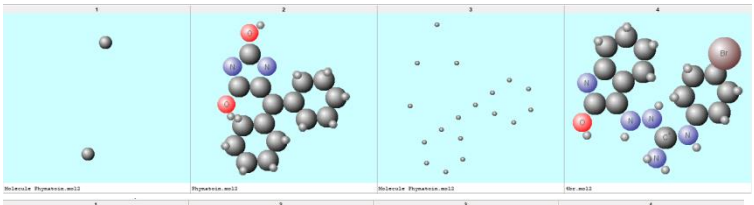
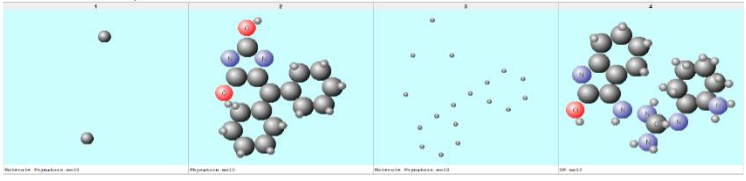
6S	Active	-	-	-	-	+	260°C	270
7S	Active	-	-	-	-	+	260°C	270
8S	Active	-	+	+	-	+	260°C	260
9S	Active	-	-	-	-	-	250°C	260
10S	Active	-	-	-	-	-	260°C	250
11S	Inactive	-	+	-	-	+	260°C	280
12S	Active	-	-	-	-	-	290°C	290
13S	Active	-	-	-	-	-	240°C	240
14S	Active	-	-	-	-	-	230°C	220

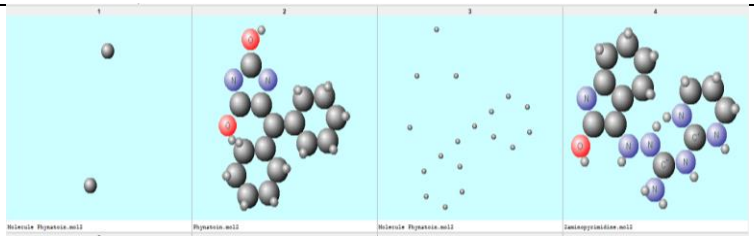
+ Inhibitor, - Non inhibitor

PHARMA GIST: The performance of Pharma Gist for virtual screening was successfully evaluated on a commonly used data set of G-Protein coupled receptor alpha 1A. Additionally, a large-scale evaluation using the DUD (directory of useful decoys) data set was performed.

Table: 10 Best pairwise pharmacophore maps for input molecules

BEST PAIRWISE MOLECULES	SCORE	MOLECULES
Std, (13s)	4.52921	
Std, (3s)	6.32358	
Std, (2s)	6.01837	
Std, (7s)	4.52896	
Std, (11s)	4.53	

BEST PAIRWISE MOLECULES	SCORE	MOLECULES
Std, (5s)	6.32198	
Std, 4Chloroaniline(6s)	4.52909	
Std, (9s)	4.84	
Std, (1s)	6.01837	
Std, (12s)	9.05026	
Std, (14s)	6.01837	
Std, (8s)	4.52909	
Std, (4s)	4.53	

BEST PAIRWISE MOLECULES	SCORE	MOLECULES
Std, (10s)	4.53	

DISSCUSION:

Molinspiration: lipophilicity is a major determining factor in a compound's absorption, distribution in the body, penetration across vital membranes and biological barriers, metabolism and excretion (ADME properties). According to 'Lipinski's Rule of 5' (developed at Pfizer) the logP of a compound intended for oral administration should be <5. Based on the above concept Log P values of isatin schiff bases (1s-14s) derivatives were found to be in the range of (0.32 to 3.5 except 12s). From the results summarized in table–6all compounds obey Lipinski rule of five.

The results of the present study demonstrated that the designed compounds are biologically active molecules and will produce the physiological actions by interacting with GPCR ligands, nuclear receptor ligands and inhibit protease, kinase enzymes. The predicted bioactivity scores of screened compounds are summarized in Table 7. Bioactive scores of various compounds larger is the bioactivity score, higher is the probability of the active compound.

Data warrior: Drug likeness, a qualitative concept used in drug design for how "drug like" a substance is with respect to bioavailability usually given a score based on Lipinski rule of five concept.as per this the higher the value the more likely a compound acts as a drug. Compound (expect **7s**) in table-1 with high score is more liable to have good ADME properties. Data Warrior which was involved in toxicity predictions showed no mutagenic, Tumorigenic, irritant and reproductive effects.

O-CHEM: The designed molecules which were studied for inhibition against **cytochrome p450** and its 5 subtypes model results showed that all the compounds are inhibitors of all subtypes except compounds **3s, 8s, 11s** (inhibitors of CYP2D6) **3s, 8s** (inhibitors of CYP2C19) **3S** (inhibitors of CYP2C9) **3S-8S, 11S** (inhibitors of CYP1A2) was observed for designed molecules.

Pharma Gist: The pharmacophore mapping studies for anticonvulsant activity in comparison with the standard phenytoin exbhiting best pairwise alignments with a score ranging from (6.01837 for **the1s, 2s, 14s** & 6.3238 for **3s**, **5s** & 4.52 for **6s, 7s, 8s, 13s &** 4.53 for **4s, 10s, 11s** & 4.84 for **9s**). 9.05026 for **12s** with good pharmacophore activity.

CONCLUSION:

An in silico study of the hypothetically developed (2z)-2-(2-oxo-dihydro-2H-indol-2-ylidene) hydrazine carboxmide Schiff base derivatives were carried out by using web-based computational techniques like molinspiration (for physiochemical property prediction), O-SERIES (for toxicity prediction), O-Chem (for inhibitory activity) & Pharma Gist (for pharmacophore detection). These results are indicative of a possible chemical stability and the less toxicity risk irrespective of all the parameters which come under *Insilico*tool in order to evaluate the developed molecules as a possible drug candidate for its anti-convulsant action. Based on this fact, the molecules those show best drug-likeness (molecular property bioactivity score) show the best compatibility with the Lipinski's rule of five. Hence according to the present study, it can be suggested that the study of these 14(2z)-2-(2-oxo-dihydro-2H-indol-2-ylidene) hydrazine carboxmide Schiff base molecules could be the first step in the development of a novel agent which can act as a better anti-convulsant drug.

AUTHOR CONTRIBUTION STATEMENT

R. Satyavani - Who is fully contributed to preparing this whole manuscript write up, followed by plagiarism check if any and to check the grammar by using the grammarly online software. Moreover, she is the one who done the molecular property, prediction by using online software K.N.VChenchu Lakshmi - With her guidance, the author moved further to complete this work and also he guided for how to write the manuscript and finally the proofreading of this manuscript was done by her.

CONFLICT OF INTEREST

Conflict of interest declared none.

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