Original Article

Automated Drug Design And Discovery By Application Of AI/ML

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Abstract

Artificial intelligence (AI) is this era playing an important role almost in all areas including drug design and discovery process. Numerous applications of artificial intelligence (AI) including virtual screening, lead identification, lead optimization and pre-clinical analysis have been used in the past. In this study, we are focused on automated design and discovery of lead molecule using AI by first creating a combinatorial library of drug molecules and then identification and optimization of lead molecule by integrating combinatorial library with various software like Molsoft , Molinspiration, Toxim etc..

Keywords: Isatin, Schiff base, Cancer cell-lines, CAAD, automated drug discovery.

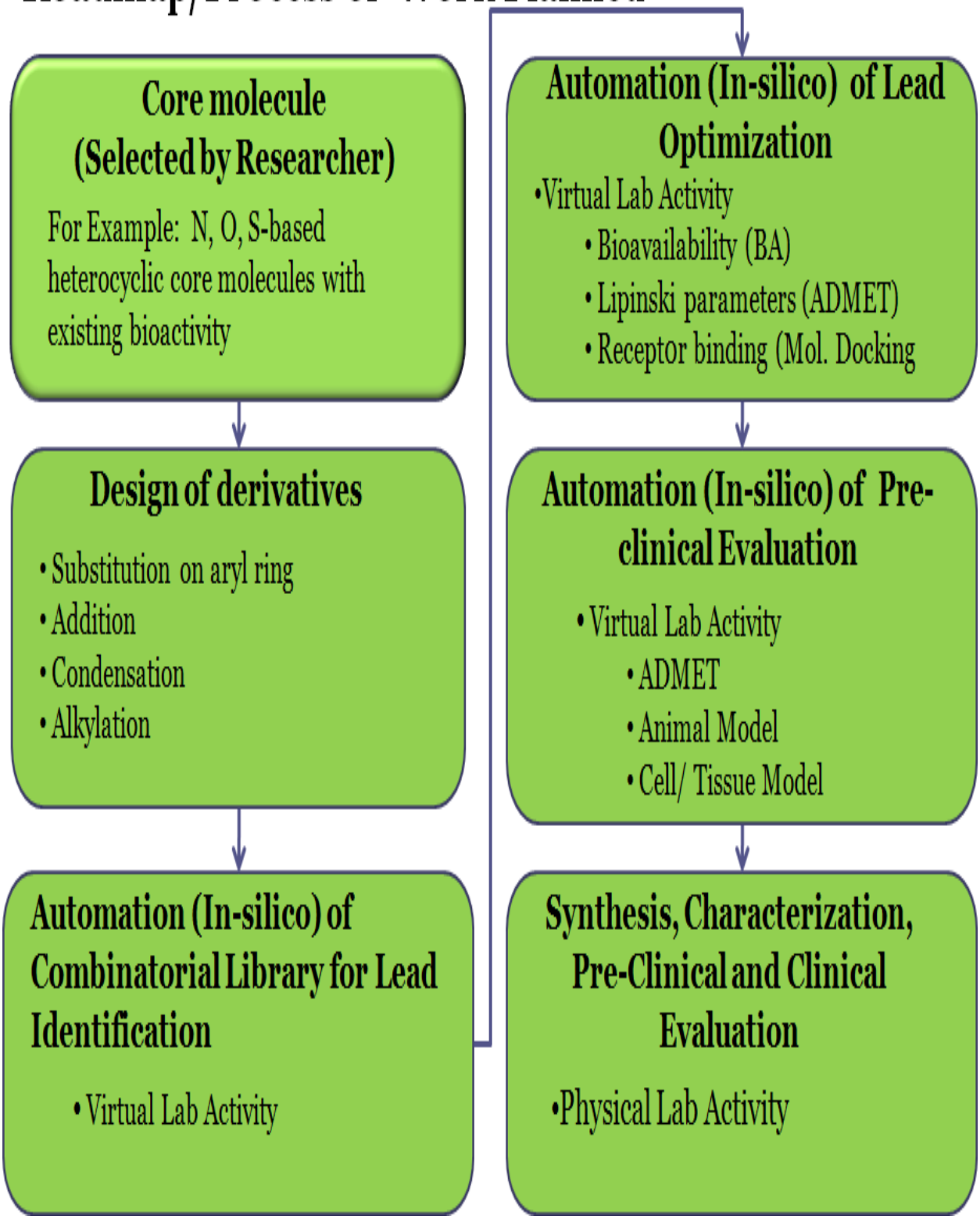
1. Introduction

The main challenge in drug design and discovery today is to discover new drugs faster and cheaper considering our experience with COVID where quick discovery of vaccine was required in cheaper price to lessen the burden on world economy in covering vast population of the World. The future mantra in drug discovery should be quicker, cheaper and accuracy by using high end computing, less physical lab work replaced with virtual labs in identification and validation of Target, identification and optimization of Lead and preclinical/clinical human MODEL covering all the metabolic pathways using Automation and AI-based models. Automation and AI-based models need to be used in the drug discovery pipeline for the identification and validation of target, identification and optimization of lead, and for pre- clinical/clinical by using animal and human models having various metabolic pathways, for the rapid discovery and development of the drugs [1][2].

The scope of the work includes automation for the identification and validation of the Targets, automation of the identification of Lead and automated generation of combinatorial library of the derivatives of core molecule identified by the researcher as potential pharmacophoric moieties. All the derivatives of the molecule are generated using SMILES of core molecule and SMILES of various substituents, other moieties for alkylation, condensation, addition etc. The SMILES of the created derivatives are stored in MYSQL database and evaluated for their physiochemical properties, bio- dynamicity and toxicity. SMILES are fetched one by one from the database and properties of the derivatives are calculated using various available softwares/tools (Molsoft, Molinspiration, Autodoc, TOXIM etc). Moreover, Algorithms for machine learning and deep learning are used to optimise the Lead using various parameters/rules (like Lipinski's rule). Automated pre-clinical analysis . All the derivatives in the database are processed for the ADMET analysis, pre-clinical models [3][4].

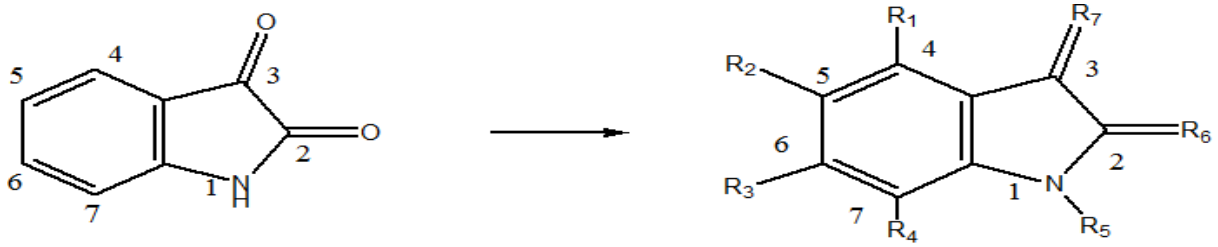
For implementation and testing of automated drug design and discovery pipeline, Isatin isconsidered as a core molecule to design a derivative. Derivatives of Isatin have a broad spectrum of bioactivities and are utilised as starting materials in the production of a variety of Hétérocyclic substances. Past research on isatin derivatives has revealed that they have a number of additional biodynamic characteristics, including anticancer, effects that are anti-bacterial, anti-fungal, anti-HIV, anticonvulsant, antiviral, and anti-inflammatory. Epilepsy, TB, and bulimia are among the illnesses that are treated using medications that include the isatin skeleton. There is more room to develop and investigate Isatin derivatives for novel therapeutic targets when taking into account isatin's and its derivatives' biological characteristics [5][6].

Roadmap/Process of Work Planned



Design of Derivatives for Lead Identification for a Particular Target

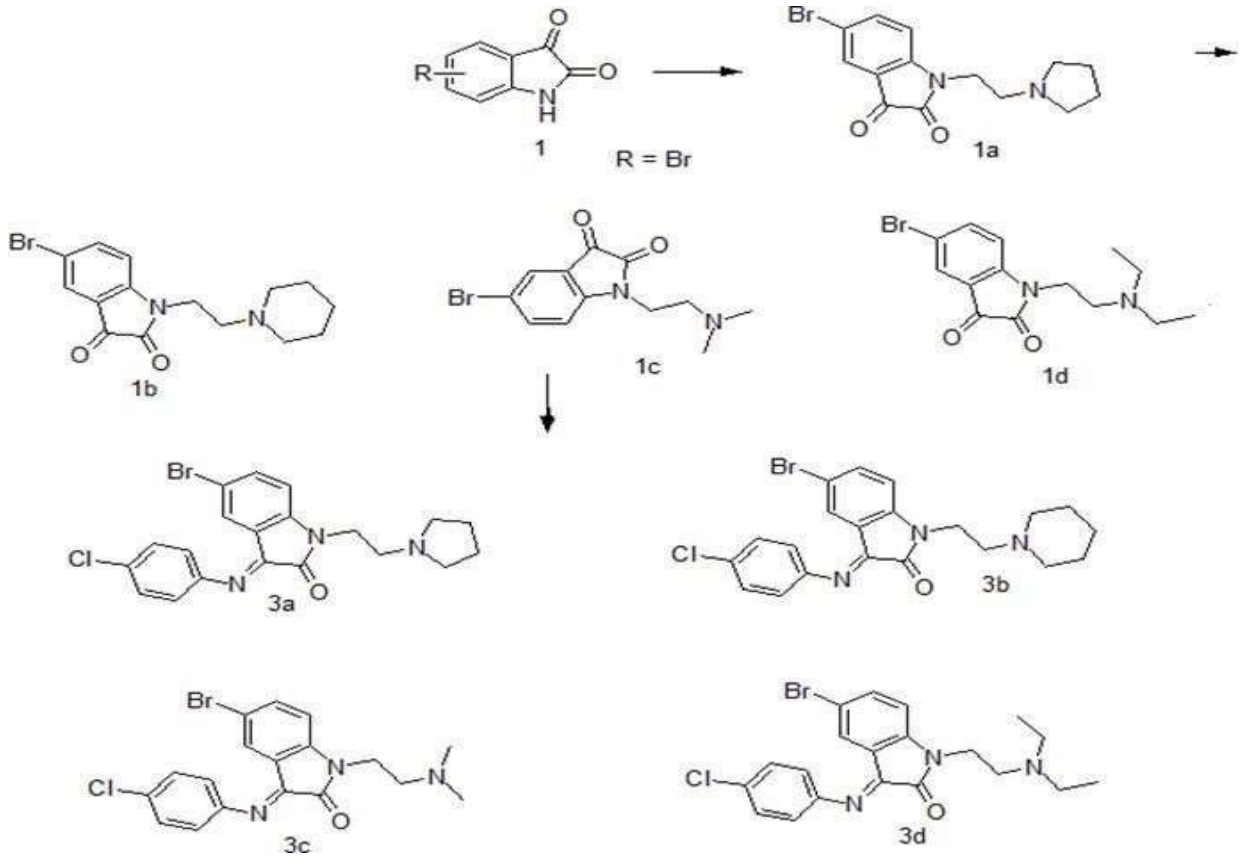
The structure of the core molecule provides various positions for substitution, addition, condensation tocreate new derivatives. For example, the substitution at 4, 5, 6, 7 positions of benzene ring of isatin [7][8][9].

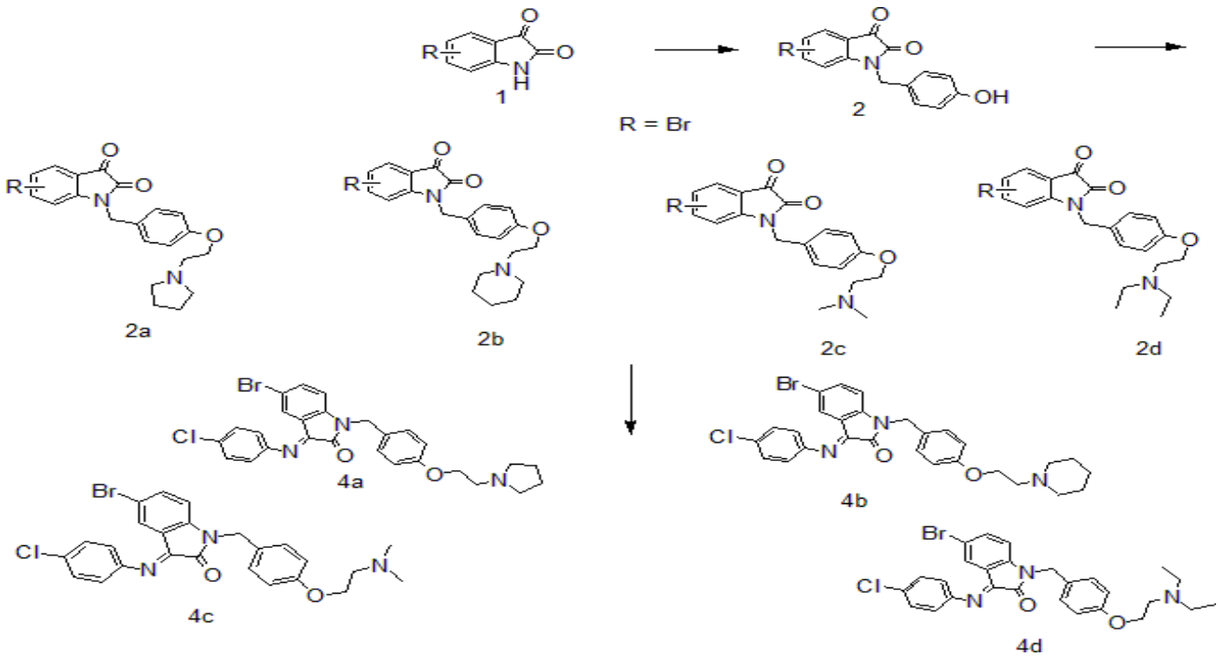


R1, R2, R3, R4= -F, -Cl, -Br, -I, -OH, -NO2, -CH3, -OCH3, -H etc.
R5 = Alkyl, Aryl, N-based heterocyclic, S-based heterocyclic, O-based heterocyclic moities
R6, R7 = imine, hydrazones etc.

provides scope for creating many analogues of isatin by mono, di, tri- substitution with various functional group such as halo, nitro, methyl, methoxy, hydroxy etc. The Ring of the pyrrole in position N-1 of isatin provides the flexibility to create potential derivatives by alkylation using alkyl, aryl, acyl, amino group, nitrogen-based heterocylic, sulfure-based hetercyclic, oxygen-based heyerocyclic moieties etc. Further, the keto positions at 2, of pyrrole ring can be used to create new isatin derivatives [10][11].

The Isatin derivatives in 2 series: series-1 (1a-d), series-2 (2a-d), series-3 (3a-d) and series-4 (4a-d) were designed using combinatorial library as per following schemes [12][13][14].





In order to obtain better derivatives of isatin, computational investigations will be performed for all the designed compounds for predicting molecular employing Molsoft and Molinspiration software, attributes based on ratings for drug similarity, bioactivity, and Lipinski's rule of five [15][16].

The affiliated organization working on development of software tool to integrate molsoft, molinsipiration, molecular docking and other AI-based models to vet the various parameters and to store in the database for all derivatives SMILES created by combinatorial Library [17][18].

The five-point rule of Lipinski serves as a criterion for Along with the prediction of drug-like attributes, a proposed compound's oral activity is indicated. Only molecules that meet the followingcriteria are considered orally active: (a) molecular weight 500 da, logP 5, the number of hydrogen bonds acceptors (10), the number of hydrogen bonds donors (5.40), and the logP value of 5.An major factor in determining medication permeability is hydrogen bonding. In addition to Blood- brain barrier (BBB) penetration, intestinal absorption, bioavailability, permeability of human intestinal epithelial adenocarcinoma (Caco-2) cells, and PSA (molecular polar surface area) have all been shown to be excellent descriptors characterising drug absorption and transportation properties. Derivatives PSA and logP are regarded as two crucial variables for predicting a drug'soral bioavailability.the TPS linked with drug transport capabilities across membranes, BBB prediction, and intestinal passage.With TPSA/PSA ratios between 160 and 60, molecules show strong intestine absorption and BBB penetration [19][20].

Bioactivity against protease inhibitor, enzyme inhibitor, and nuclear receptor ligand, and GPCR (G- protein coupled receptor) ligand receptors will be evaluated for each of the proposed derivatives. The Molinspiration toolset will be used to investigate the bioactivity against the ligands. By using a numerical assignment, the bioactivity ratings of all the proposed derivatives will be displayed. A higher score indicates that a molecule is more likely to be active.

The designed compounds will have their drug-likeness model score predicted using the Molsoft toolkit, which uses the chemical fingerprints of marketed drugs from the WDI (World drug index) as a training set (5K positives) and 10K carefully chosen non-drug compounds (10K negatives) [21][22].

Automated generation of derivatives and their computational analysis of series-1

The software component was developed to create combinatorial library of the derivatives using potentialpharmacophoric moieties to create SMILES of derivatives and storing in the database.

S. No.	SMILES	Name
1	N1C(CCC1)CN1C(C(C2=CC(=CC=C12)Br)=O)=O	N-((2-pyrrolidyl)methyl) 5-bromo indole-2,3-dione
2	N1(CCCCC1)CCN1C(C(C2=CC(=CC=C12)Br)=O) =O	N-((2-pyrrolidyl) ethyl) 5-bromo indole- 2,3-dione
3	CN(CCN1C(C(C2=CC(=CC=C12)Br)=O)=O)C	N-(2-(piperidyl) ethyl) 5-bromo indole-2,3-dione
4	C(C)N(CCN1C(C(C2=CC(=CC=C12)Br)=O)=O)C C	N-(2-(dimethyl amino)ethyl) 5-bromo indole-2,3-dione

This section contains tabulated values for physicochemical properties and bioactivity score for all thecompoundsof Series-1 [23][24].

Compound	BBB	n violations	LogP	logS	%ABS	Volume Å^3	PSA Å^2	n Atoms	NROTB	n ON Accept-ors	n OHNH Donors	Formula Weight
1a	5.2	0.0	2.1	-2.9	94.4	244.6	42.3	19	3	4	0	323.2
1b	5.2	0.0	2.6	-3.3	94.4	261.4	42.3	20	3	4	0	337.2
1c	5.1	0.0	1.7	-2.5	94.4	221.4	42.3	17	3	4	0	297.2
1d	52	0.0	2.5	-2.9	94.4	255.0	42.3	19	5	4	0	325.2

Table 1: Physiochemical properties of the compounds (1a-1d) of Series-1

Compound	Bioactivity Scores						Drug likeliness
	GPCRL	ICM	KI	NRL	PI	EI	
1a	-0.11	-0.58	-0.22	-1	-0.2	-0.01	0.98
1b	-0.07	-0.56	-0.21	-0.95	-0.21	-0.01	1.11
1c	-0.34	-0.71	-0.38	-1.37	-0.52	-0.13	0.7
1d	-0.2	-0.66	-0.3	-1.09	-0.37	-0.09	0.63

Table 2:Bioactivity Ratings and a compound's likelihood of being a medication (1a-1d) of Series-1

Automated generation of derivatives and their computational analysis of series-2

This section contains tabulated values for physicochemical properties for all the compounds ofSeries-2.

S. No.	SMILES	Name
1	ClC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN 1CCCC1)=O	3-(4-chloro phenylimino)N-(2-(pyrrolidyl) ethyl) 5-bromo indole-2-one
2	ClC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CC N1 CCCCC1)=O	3-(4-chloro phenylimino)N-(2-(piperidyl) ethyl) 5-bromo indole-2-one
3	ClC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12) Br)CCN(C)C)=O	3-(4-chloro phenylimino)N-(2-(dimethyl-amino)ethyl) 5-bromo indole-2-one
4	ClC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CC N(C C)CC)=O	N-(2-(dimethyl amino)ethyl) 5-bromo indole-2,3-dione3-(4- chloro phenylimino)N-(2-(diethyl-amino) ethyl) 5- bromo indole-2-one
5	BrC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CC N1 CCCC1)=O	3-(4-bromo phenylimino) N-(2-(pyrrolidyl) ethyl)5-bromo indole-2-one
6	BrC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN CCCCC1)= O	3-(4-bromo phenylimino) N-(2-(piperidyl) ethyl)5-bromo indole-2-one
7	BrC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)C CN1 CCCCC1)=O	3-(4-bromo phenylimino) N-(2-(dimethyl-amino) ethyl) 5-bromo indole-2- one
8	BrC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CC N(C C)CC)=O	3-(4-bromo phenylimino) N-(2-(diethyl-amino) ethyl)5- bromo indole-2-one

9	COC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN1 CCCC1)=O	3-(4-methoxy phenylimino) N-(2-(pyrrolidyl) ethyl) 5-bromo indole-2-one
10	COC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN1 CCCCC1)=O	3-(4-methoxy phenylimino) N-(2- (piperidyl) ethyl)5-bromo indole-2-one
11	COC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN(C)C)=O	3-(4-methoxy phenylimino)N-(2- (dimethyl-amino)ethyl) 5-bromo indole-2-one
12	COC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN(CC)CC)=O	3-(4-methoxyphenylimino) N-(2-(diethyl-amino)ethyl) 5-bromo indole-2-one
13	OC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN1C CCC1)=O	3-(4-hydroxy phenylimino) N-(2- (pyrrolidyl) ethyl)5-bromo indole-2-one
14	OC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN1C CCCC1)=O	3-(4-hydroxy phenylimino) N-(2-(piperidyl)ethyl) 5-bromo indole-2-one
15	OC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN(C) C)=O	3-(4-hydroxy phenylimino) N-(2-(dimethyl- amino) ethyl) 5- bromo indole- 2-one
16	OC1=CC=C(C=C1)N=C1C(N(C2=CC=C(C=C12)Br)CCN(C C)CC)=O	3-(4-hydroxyphenylimino) N-(2-(diethyl-amino)ethyl) 5-bromo indole-2-one

Compound	BBB	n violations	LogP	logS	%ABS	Volume Å^3	PSA Å^2	n Atoms	NROTB	n ON Accept-ors	n OHNH Donors	Formula Weight (Da)
3a	5.5	0	3.2	-3.5	93.4	352	45.2	27	5	5	0	430.4
3b	5.5	0	3.7	-3.8	93.4	368.8	45.2	28	5	5	0	444.4
3c	5.5	0	2.8	-3.4	93.4	328.8	45.2	25	5	5	0	404.3
3d	5.5	0	3.6	-3.7	93.4	362.4	45.2	27	7	5	0	432.4
4a	5.5		1.0	5.3	-4.3	96.0	338.2	37.6	26.0	4.0	4.0	0.0	477.2
4b	5.4		1.0	5.8	-4.8	96.0	355.0	37.6	27.0	4.0	4.0	0.0	491.2
4c	5.5		0.0	4.9	-4.2	96.0	314.9	37.6	24.0	4.0	4.0	0.0	451.2
4d	5.5		1.0	5.7	-4.6	96.0	348.5	37.6	26.0	6.0	4.0	0.0	479.2
5a	5.3		0.0	4.6	-3.9	92.8	345.8	46.8	27.0	5.0	5.0	0.0	428.3

5b	5.3	1.0	5.1	-4.2	92.8	362.6	46.8	28.0	5.0	5.0	0.0	442.4
5c	5.3	0.0	4.2	-3.7	92.8	322.6	46.8	25.0	5.0	5.0	0.0	402.3
5d	5.3	0.0	4.9	-4.1	92.8	356.2	46.8	27.0	7.0	5.0	0.0	430.4
6a	5.0	0.0	4.0	-3.5	89.0	328.3	57.8	26.0	4.0	5.0	1.0	414.3
6b	5.0	0.0	4.6	-3.6	89.0	345.1	57.8	27.0	4.0	5.0	1.0	428.3
6c	5.0	0.0	3.6	-3.4	89.0	305.1	57.8	24.0	4.0	5.0	1.0	388.3
6d	5.0	0.0	4.4	-3.5	89.0	338.7	57.8	26.0	6.0	5.0	1.0	416.3

Table 3: Physiochemical properties of the compounds of Series-2

Bioactivity against G-protein coupled receptor) ligand, ion channel modulator, nuclear receptor ligand, protease inhibitor, and enzyme inhibitor receptors was examined for all the proposed compounds of Series-2. Scores for drug-likeness were also examined.All of the receptors were subject to moderate to considerable bioactivity from the drugs (3a–3d). The compounds demonstrated considerable bioactivity against GPCRL in the range of -0.16 to -0.1, with the greatest value of -0.1 being displayed by compounds 3a and 3b. Bioactivity against ICM ranged from -0.38 to -0.32 whereas that against KI was in the neighbourhood of -0.6. The bioactivity was between -0.36 to -0.29 against NRL. Compound 3a had a respectable result of -0.15 for the bioactivity against PI, which was measured in the range of -0.26 to -
0.15. Compounds 3a and 3b had the highest bioactivity against EI, with values ranging from -0.28 to - 0.23[25].

Compound	**Bioactivity Scores**						**Drug likeliness**
	GPCRL	**ICM**	**KI**	**NRL**	**PI**	**EI**	
3a	-0.1	-0.33	-0.59	-0.26	-0.15	-0.23	0.85
3b	-0.1	-0.32	-0.6	-0.29	-0.19	-0.23	0.96
3c	-0.16	-0.38	-0.65	-0.36	-0.26	-0.28	0.56
3d	-0.15	-0.38	-0.65	-0.32	-0.26	-0.27	0.48
4a	-0.11	-0.84	-0.29	-0.99	-0.68	-0.39	0.75
4b	-0.11	-0.81	-0.32	-0.99	-0.71	-0.38	0.86
4c	-0.19	-0.95	-0.33	-1.16	-0.87	-0.46	0.45
4d	-0.18	-0.9	-0.35	-1.06	-0.81	-0.44	0.37

5a	-0.15	-0.88	-0.32	-0.97	-0.72	-0.42	0.89
5b	-0.15	-0.85	-0.34	-0.97	-0.74	-0.41	1
5c	-0.23	-0.98	-0.35	-1.13	-0.89	-0.49	0.4
5d	-0.21	-0.93	-0.38	-1.04	-0.83	-0.47	0.39
6a	-0.07	-0.8	-0.25	-0.86	-0.67	-0.34	0.94
6b	-0.07	-0.78	-0.28	-0.86	-0.7	-0.33	1.04
6c	-0.15	-0.91	-0.28	-1.02	-0.86	-0.4	0.69
6d	-0.14	-0.86	-0.32	-0.93	-0.8	-0.39	0.61

Table 4: Bioactivity Scores and drug likeliness of the compounds of Series-2

The following graphs for compounds (3a-3d) displayed the medication likeness rating. The drug-likeness score of the compounds (3a-3d) were found in the range of 0.56-0.96. The compound 3b showed the good drug likeness value 0.96.

Result and Discussion

Computational analysis for compounds of Series-1 and Series-2

After analyzing all the physiochemical properties, bioactivity and drug likeness score,allthe

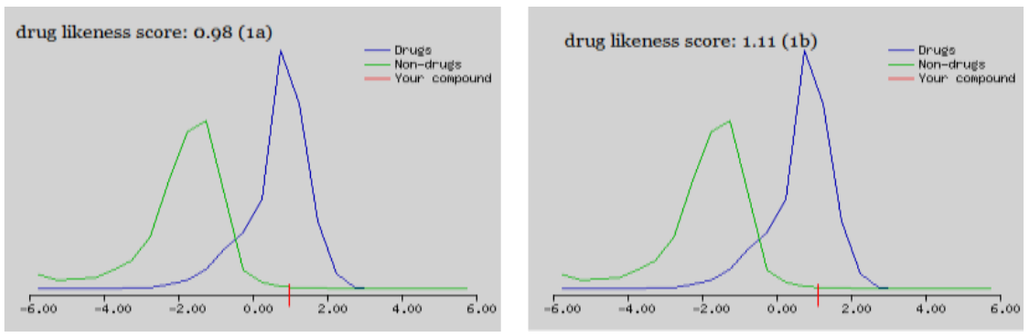


Figure 1: Drug likeliness score graph for compounds 1a and 1b

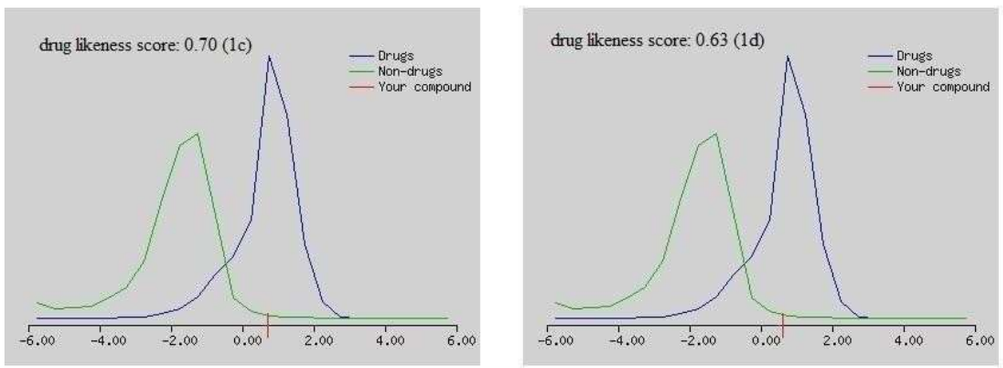


Figure 2: Drug likeliness score graph for compounds 1c and 1d

All of the compounds from Series-1 were taken into consideration for the synthesis and biological assessment after examining

all of the physiocochemical characteristics, bioactivity, and drug similarityscore.

Computational analysis for compounds of Series-2

The compounds (3a-3d) have several donors of hydrogen bonds (five) and approvers (10). All of thecompounds have molecular weights between 404 and 444, and the log P value is between 2.8 and
3.7. Lipinski's rule of five is supported by the physicochemical parameters, suggesting excellent oralpotency for all the substances.

The compounds (4a–4d) include several donors of hydrogen bonds (5), and approvers (10), and acceptors (10). All of the compounds had molecular weights between 451 and 491 and a log P value between 4.9 and 5.8.

The compounds (5a-5d) include several donors of hydrogen bonds (5), and approvers (10), and acceptors (10). The molecular weights of all the compounds are between 402 and 442, and the log P value is between 4.2 and 5.1.
The compounds (6a-6d) contain several donors of hydrogen bonds (5), acceptors (10), and approvers.All of the compounds have molecular weights between 388 and 428, and the value of log P is between 3.6 and 4.6.

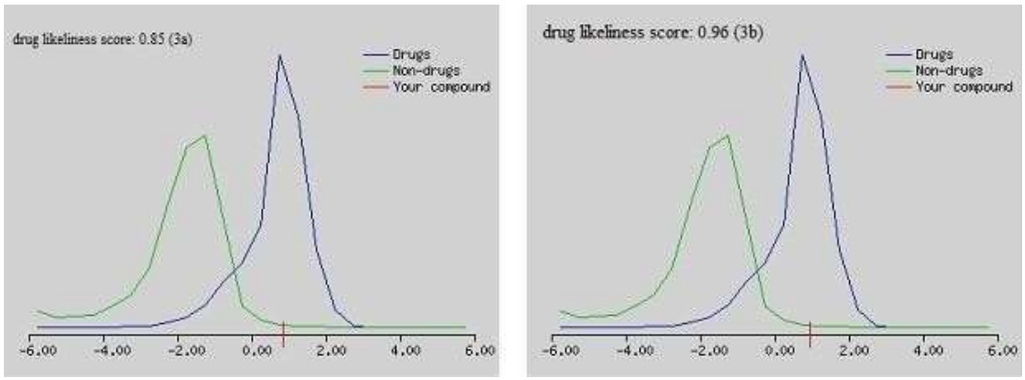


Figure 3: Drug likeliness score graph for compounds 3a and 3b

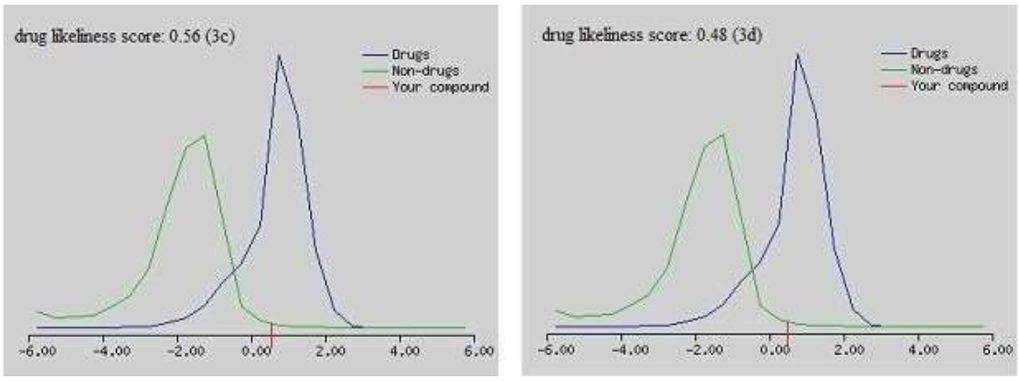


Figure 4: Drug likeliness score graph for compounds 3c and 3d

The drug likeness score for compounds (4a–4d) was displayed in the graphs below. The compounds (4a-4d) were found to have drug-likeness scores between 0.37 and 0.86. Compound 4b had a favourable drug likeness value of 0.86.

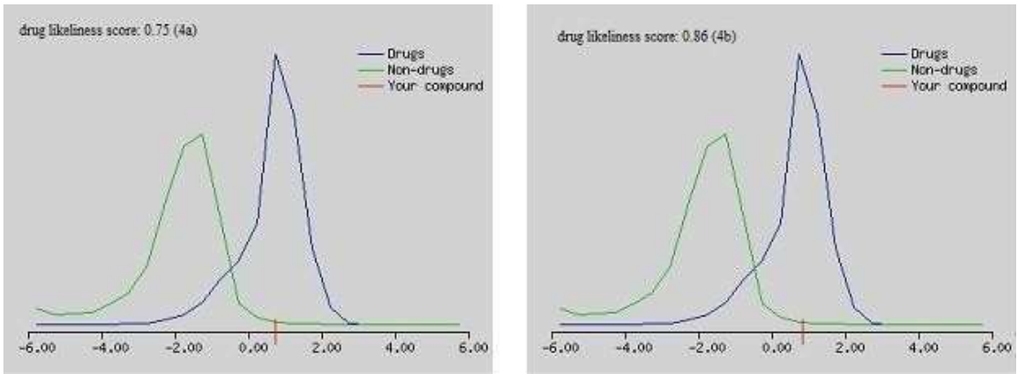


Figure 5: Drug likeliness score graph for compounds 4a and 4b

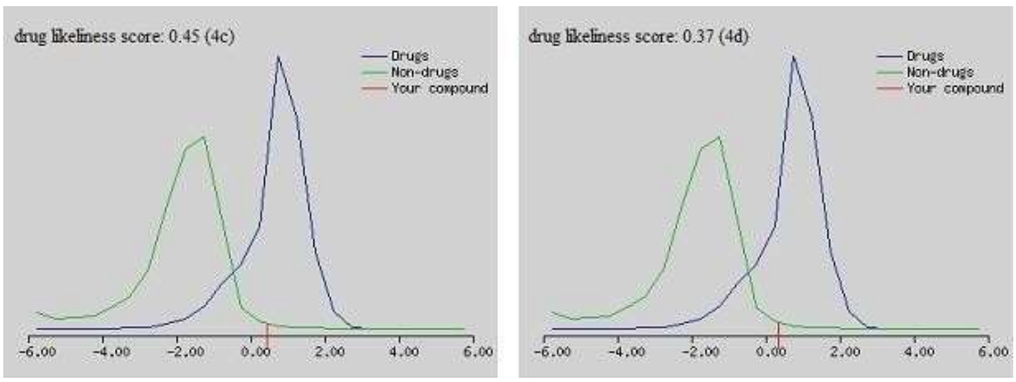


Figure 6: Drug likeliness score graph for compounds 4c and 4d

The drug likeness score for compounds (5a-5d) was displayed in the graphs below. The compounds (5a-5d) were found to have drug-likeness scores between 0.39 and 1.00. Compound 5b had a favourable drug likeness value of 1.00.

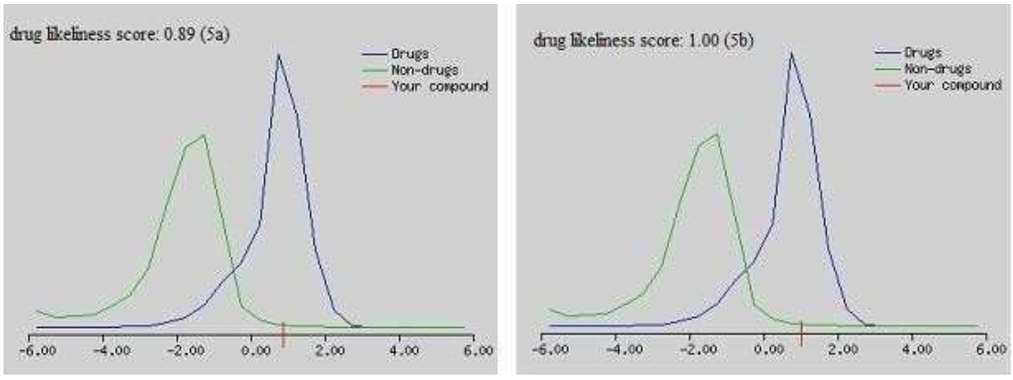


Figure 7: Drug likeliness score graph for compounds 5a and 5b

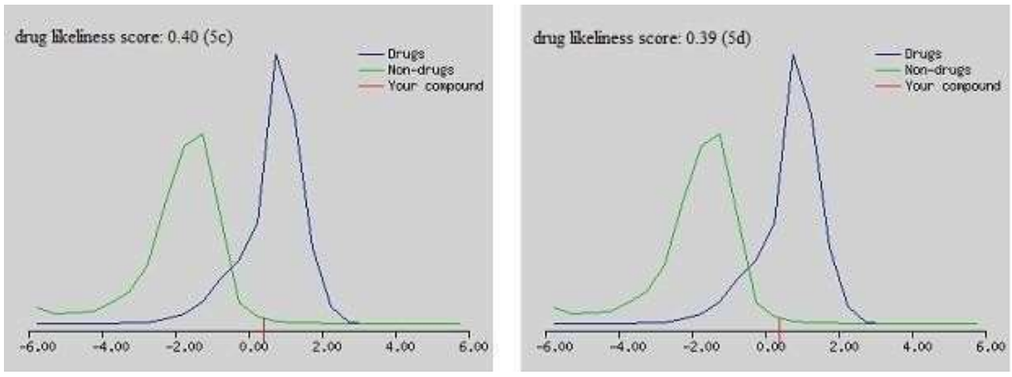


Figure 8: Drug likeliness score graph for compounds 5c and 5d

The drug likeness score for compounds (6a–6d) was displayed in the graphs below. The compounds (6a-6d) were found to have drug-likeness scores between 0.61 and 1.04. Compound 6b had a favourable drug likeness value of 1.04.

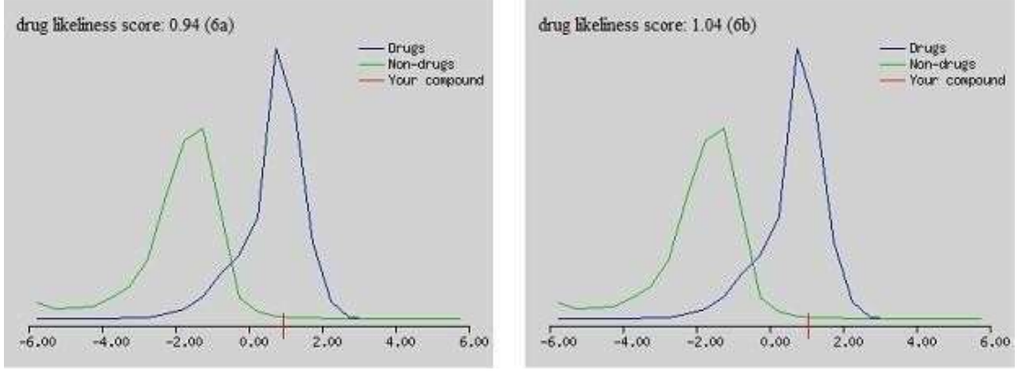


Figure 9: Drug likeliness score graph for compounds 6a and 6b

For the purpose of making the final decision on which isatin derivatives to proceed with the synthesis of and test in vitro, results for physiochemical parameters, bioactivity scores, and drug resemblance were examined. Finally, the compounds (3a-3d) can be chosen and synthesised infurther detail. The remainders of Series-2 compounds (4a-4d, 5a-5d, and 6a-6d) may be eliminated.

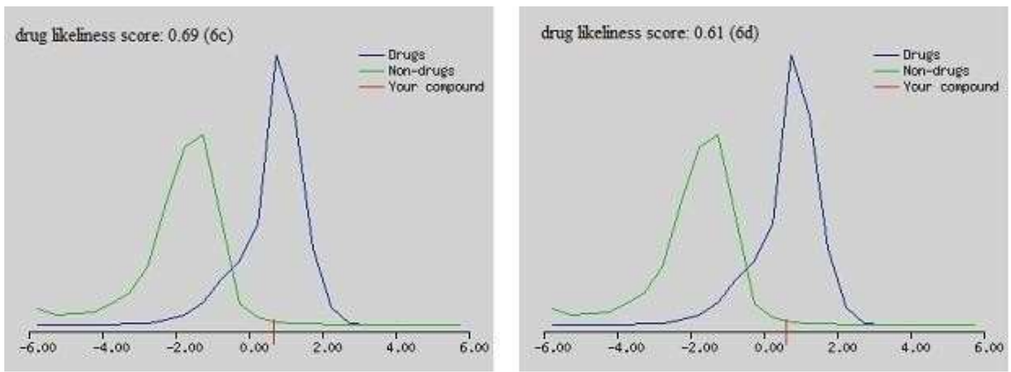


Figure 10: Drug likeliness score graph for compounds 6c and 6d

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