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Designing and Screening of Substituted Oxadiazeno Indole Derivatives for Anti-Depressant Activity by *In-Silico and Docking* Studies

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Abstract

Isatins and its analogues are the most variable substrates used for the synthesis of number of heterocyclic compounds. These derivatives possess different biological activities like anti-depressants[1,] anti-convulsant[2], sedative -hypnotic[3], anti –histamines[5], anti-cancer[6], anti-inflammatory[7,] antimicrobial, antioxidant[9] and anti-bacterial[10]. So, for the past few decades these derivatives are received much attention. Because of these therapeutic uses, docking studies are performed with a new series of substituted oxadiazeno indole derivatives using target as selective serotonin reuptake transporter as protein(PDB:6DZW) *In silico* studies like molinspiration, Swiss ADME are also performed.Among all the compounds, substitution with chlorine, bromine and iodine shows good activity to treat depression. So, based on these docking studies and *In silico* results we planned to synthesize the compounds which shows good activity

Keywords

Isatin, substituted oxadiazeno indole derivatives, selective serotonin reuptake transporter as protein (PDB:6DZW).

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INTRODUCTION:

Depression is a mood disorder characterized by a persistently low mood and a feeling of sadness and lot of interest. Generally, it is a life-threatening disorder affected by hundreds of people in millions all over the world. This impact is more in females compared to males and some of people are affected by bipolar disorder equally in males and females.

According to National Institute of Mental health, USA Depressive disorder is an illness induces body, mood, the way of eating, sleeping and the way of over-thinking. Depression occurs due to deficiency of noradrenaline and Serotonin. So majority of drugs acts by affecting the neurotransmitters in brain, this leads to action of mechanism that is capable of increasing concentration in brain.

Mechanism involved to treat depression are

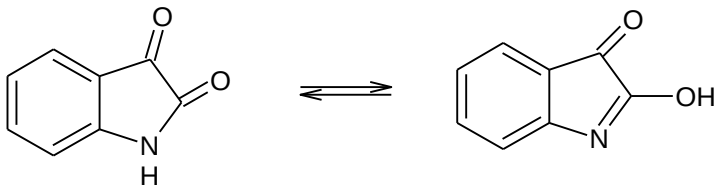
- Monoamine uptake inhibitors which acts by inhibiting the reuptake of selectively serotonin and noradrenaline or non-selectively by binding to the selective serotonin transporter thus results in increasing in the levels of monoamines

- MAO inhibitors act by inhibiting the MAO enzyme in both forms of MAO -A and MAO- B so as to increase in the cystolic stores of 5-HT and Noradrenaline in nerve terminals
- alpha -2- adrenoreceptor antagonists can directly increases 5-HT release.

In the last decades, indole derivatives receive more attention due to wide range of applications. Presence of simple indole nucleus possess biological activities like antimicrobial, antiviral, antitubercular, anticancer, anti inflammatory, antidiabetic, anticonvulsant, antioxidant and antidepressant activities. Indole is a heterocyclic compound fused with six membered aromatic ring having pyrrole ring with N in the centre.

In research indoles are used as a material for the synthesis of biologically active structures because of various activities.

Indoles are generally electrophilic in nature. So Nucleophilic addition reactions occurs at 3rd position and this 3rd position of indole is highly active than 2nd position because 2nd position undergoes keto-enol tautomerism.

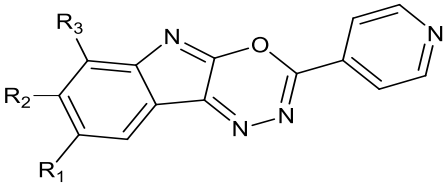


Indoles and 5-HT are structurally similar, so we are expecting the drugs having indole derivatives possess CNS activity like Anticonvulsants, Antidepressants etc

So we are going for the *In-silico* studies like molinspiration, Pre ADMET and Swiss ADME for newly synthesized compounds containing indole as a main moiety in order to know the activity of drugs acting on CNS. Now-a-days In-*silico* studies and molecular docking becomes an important component in drug discovery because of more benefits like

- Low cost implications
- Easy to use
- Reduces time
- Prediction of molecular properties and bioactivity based on structure
- Reduction of usage of animals
- Hit identification
- Lead optimisation

The series of designed compounds are evaluated for *In silico* and docking studies



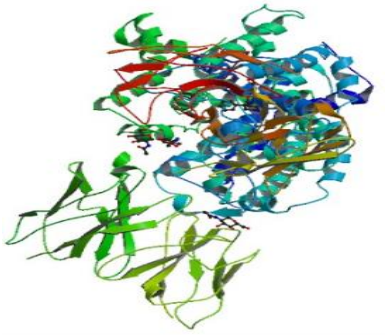
S.NO	COMPOUND	R_1	R_2	R_3
1.	1a	H	H	H
2.	1b	CH_3	H	H
3.	1c	I	H	H
4.	1d	F	H	H
5.	1e	H	H	Cl
6.	1f	NO_2	H	CL
7.	1g	Cl	Cl	H
8.	1h	Br	H	H
9.	1i	Br	H	H
10.	1j	NO_2	H	H

COMPUTATIONAL MOLECULAR BINDING STUDIES:

Molecular docking:

Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode(s) of a ligand with a protein of known three-dimensional structure.

PDB (protein data bank), RCSB PDB is a resource powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.



PDB ID:6DZW

Preparation of target and ligand:

The target protein structures were downloaded from RCSB PDB and Saved as a pdb file.The structure of ligand molecules were drawn using Chemdraw version 12.0.Convert in to a 3D conformation using Biochem 3D and minimize energy.Save it as a PDB file.Then the target and receptor were docked using PATCHDOCK a free online software. Finally, results were visualized in Chymera.

A) **Software for virtual screening:**

The software used for molecular docking was **PATCH DOCK**. It is an online free software available for docking. The results are given as best pose binding energy scores. The prepared ligands and target molecules were docked, and the results are given in the table.

***IN SILICO* METHODS**

The tools used in the analysis of the compounds were SwissADME and molinspiration. The molinspiration was used to generate bioactivity scores (GPCR ligand, ion channel inhibitor, kinase inhibitor, nuclear receptor ligand, protease inhibitor, enzyme inhibitor) of the series of compounds and Swiss ADME was used to study various parameters like physicochemical properties, lipophilicity, pharmacokinetic parameters, obeyance of Lipinski rule, bioactivity score and leadlikeness.

i) Physicochemical parameters: The parameters of the molecules which effect the nature of the compound. Ex: No: rotatable bonds, H-bond donors or acceptors, molecular weight etc.
ii) Lipophilicity: From the various values of LogP, MlogP value is considered.
iii) Pharmacokinetic parameters: the parameters like gastro-intestinal absorption, blood brain barrier penetrability and P-glycoprotein substrate or inhibitor.
iv) Lipinski rule
v) Bioavailability score
vi) Leadlikeness

RESULTS AND DISCUSSION:

MOLINSPIRATION:

To calculate molecular properties like miLogp, HBD, HBA, TPSA, MV and MW

S.no	Compound	Total polar Surface area	No.of atoms	M.Wt	nON	nOHNH	No.ofviolations	No.of rotatable bonds	Volume
1.	1a	58.88	19	250.26	5	1	1	1	214.23
2.	1b	58.88	20	268.25	5	1	1	1	227.88
3.	1c	58.88	20	284.71	5	1	1	1	227.8
4.	1d	58.88	20	329.16	5	1	1	1	232.29
5.	1e	58.88	20	376.16	5	1	1	1	238.68
6.	1f	58.88	20	264.29	5	1	1	1	230.4
7.	1g	104.7	22	295.26	8	1	2	2	237.25
8.	1h	64.71	21	317.13	8	0	1	1	235.6
9.	1i	110.5	23	327.69	5	0	2	2	245.25
10.	1j	110.5	23	327.14	8	0	2	2	249.6

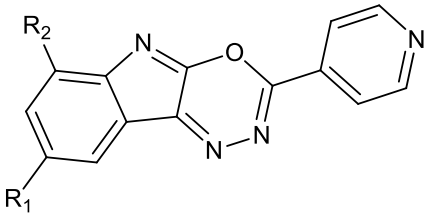
PREDICTION OF BIOACTIVITY:

S.no	Compound	MI bioactivity score	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Proteaseinhibitor	Enzyme inhibitor
1.	1a	2018.03	-0.35	-0.35	-0.34	-0.5	-0.29	0.02
2.	1b	2018.03	-0.25	-0.34	-0.23	-0.43	-0.23	0.05
3.	1c	2018.03	-0.30	-0.42	-0.39	-0.64	0.38	0.11
4.	1d	2018.03	-0.44	-0.44	-0.37	-0.64	-0.40	-0.07
5.	1e	2018.03	-0.28	-0.34	-0.29	-0.42	-0.34	-0.05
6.	1f	2018.03	-0.34	-0.43	-0.34	-0.49	-0.29	-0.04
7.	1g	2018.03	-0.39	-0.37	-0.36	-0.47	-0.30	-0.10
8.	1h	2018.03	0.09	0.07	-0.21	-0.30	0.30	0.02
9.	1i	2018.03	-0.24	-0.11	-0.14	-0.37	-0.43	-0.09
10.	1j	2018.03	-0.29	0.18	-0.09	-0.50	-0.40	-0.09

SWISS ADME:

Compounds	Physicochemical properties				Lipophilicity	Pharmacokinetics			Lipinski rule	BA score	Leadlikeness
	n-rotb	H-acceptor	H-donor	TPSA(Å)	mlogP	GI	BBB	P-gp			
1a	1	4	1	81.62	1.88	High	No	No	Yes	0.55	Yes
1b	1	5	1	58.87	1.95	High	Yes	No	Yes	0.55	Yes
1c	1	4	1	58.87	2.11	High	Yes	No	Yes	0.55	Yes
1d	1	4	1	58.87	2.40	High	Yes	No	Yes	0.55	Yes
1e	1	4	1	58.87	2.22	High	Yes	No	Yes	0.55	No
1f	1	4	1	58.87	2.29	High	Yes	No	Yes	0.55	Yes
1g	2	6	1	104.69	1.45	High	No	No	Yes	0.55	Yes
1h	1	5	0	64.70	2.36	High	Yes	Yes	Yes	0.55	Yes
1i	2	7	0	110.52	2.00	High	No	No	Yes	0.55	Yes
1j	2	7	0	110.52	1.86	High	No	No	Yes	0.55	No

MOLECULAR DOCKING STUDIES:



s.no	Receptor	compound	Score	Area	ACE
1.	6DZW	**1a**	3592	480.70	-272.68
2.	6DZW	1b	3640	454.10	-323.10
3.	6DZW	1c	3932	491.20	-256.29
4.	6DZW	1d	3606	374.30	-145.67
5.	6DZW	1e	3830	469.59	-259.34
6.	6DZW	1f	3814	473.60	-166.61
7.	6DZW	1g	3906	449.90	-212.68
8.	6DZW	1h	3788	495.60	-249.41
9.	6DZW	1i	3664	482.10	-237.38
10.	6DZW	1j	3539	446.3	-215.15

CONCLUSION:

The designed compounds were evaluated by docking using patch dock software and *in silico* studies (Molinspiration, Swiss ADME). From the docking studies, we noticed that the compound with chloro, bromo and iodo substitutions shows good activity by the interaction of ligand with protein. The score which is having the highest negative score represents

the least energy required to bind the target. Based on *in silico* results designate that all the compounds should be used as potential lead for the designing and synthesizing of more potent Anti depressants. From the swiss ADME software we concluded that all the designed compounds obey Lipinskii rule of five with no violations which shows leadlikeness.

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