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Computational Docking Analysis of Some Novel Compounds Targeting Monoamine Oxidase B and Dopamine D_2 Receptor: A Potential Therapeutic Strategy for Parkinson's Disease

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ABSTRACT

Parkinson's disease, a neurodegenerative disorder could be the reason for the most prevalent cause of death at second place. Therefore it is an urgent need for novel, effective and safe medicines for the treatment of latter. As a promising function of computer-aided drug design (CADD); Structure based virtual screening (SBVS) is being heavily applied in processes of drug discovery and development. The utilization of molecular docking, as a helping tool for SVBS is providing essential data about the poses and the occurring interactions between ligands and target molecules. This work represents a brief discussion of the role of MAOs and dopamine receptor(D_2R) in the treatment of Parkinson's disease. Based on the published Research articles, Pharmacophoric features for the inhibition of Mono amino oxidase B enzyme and as Dopamine agonist are designed. And also this includes the structures of the compounds together with the utilized docking software in the PDB codes of the crystal targets applied in each study is provided. The developed workflow successfully identified Pyrazolidine could aid in developing novel drug candidates as MAO B inhibitors and as Dopamine(D_2R) agonist for the treatment of Parkinson's Disease.

KEY WORDS: Parkinson's Disease, MAO B, Dopamine D_2, Pharmacophoric features, Molecular docking, Pyrazolidine

INTRODUCTION

Parkinson's disease(PD) is a prevalent and complicated neurological condition that causes early noticeable death of dopaminergic neurons in the substantia nigra pars compacta (SNpc).[1] Death of dopaminergic neurons leads to the reduced dopamine concentration in the brain. Insufficient dopamine concentration, results in reduced inhibition of striatal neurons, which regulate the balance of body motions.[2] Developing an appropriate treatment strategy for this severe neurodegenerative illness continues to be a crucial aspect of medicinal chemistry research. These days, an innovative approach that suggests using a single therapeutic molecule to target several pathobiological components is becoming more and more popular. Even though big pharmaceutical companies still mostly use the single-target approach for drug discovery, the limits of this approach for complicated disorders are becoming more widely acknowledged. There are two fundamental ways of treating Parkinson's disease, either by replacing dopamine or mimicking its effect. PD are associated with elevated levels of Mono amino Oxidase B(MAO B) enzyme in the brain.[3] Mitochondrial flavoenzyme (MAO B) which is present in outer membrane involves in the oxidative deamination of dopamine in the striatum. Inhibition of the flavoenzyme (MAO B) in the brain slows down the depletion of dopamine level in the brain. This also helps in the neuroprotective effect by decreasing the production of dopamine byproducts.[4]

Dopamine D2 agonists are another class of promising Anti-Parkinsonism agents.[5] Dopamine receptor(DR) targeting drugs act in different ways such as agonists in PD by activating the receptor (or) partial agonists used in treating bipolar disorders (or) addiction.[6-8] . About 65 drugs have been approved by the US Food and Drug Administration (FDA). Out of this 60 drugs, target D2R such as Levodopa, Apomorphine for PD, Amoxapine, Aripiprazole and Haloperidol for depression, Psychosis (or) Schizophrenia[9-11].At initial stage these drugs are very effective and overtime the efficacy decreases. Particularly Levodopa is problematic in chronic settings due to treatment induced dyskinesia and other Levodopa-induced motor symptoms such as postural abnormalities and speech impairments and also non-motor side effects such as Nausea, depression, insomnia and gambling addiction.

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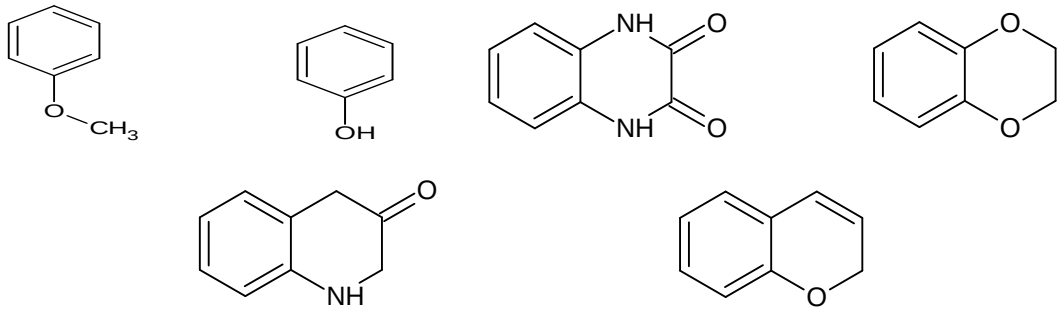
Pharmacophore identification

A Pharmacophore is defined as a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule biological activity. Pharmacophore modelling correlates the biological activity with the spatial arrangement of various features in the set of active analogues. The pharmacophore features in the ligand conformation used for hypothesis generation include Hydrogen bond acceptor (A), Hydrogen bond donor (D), Hydrophobic group (H), Positively ionizable (P), Negatively Ionizable (N) and aromatic rings (R) defined by a set of chemical structural patterns. The Pharmacophore of active ligands that contain identical sets of features with similar spatial arrangements are grouped together to give rise to a common pharmacophore hypothesis. These features were identified as the best model for designing ligands to produce the required actions on the targets.[12]

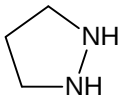
Construction of Virtual Scaffold Library

New lead molecules were designed based on the knowledge of binding interaction of ligand with both the targets and also the common pharmacophoric features necessary for biological activity of a molecule. The chemical features like Hydrogen bond acceptor (HBA), Hydrogen bond donor (HBD) and aromatic ring features were used to screen database.

HBA



HBD



LINKER

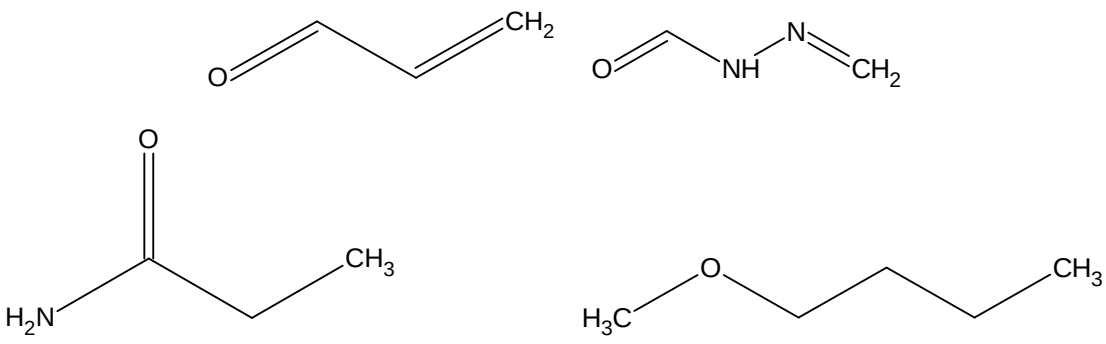


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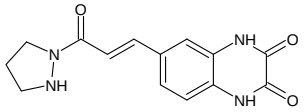
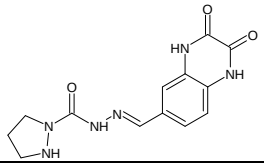
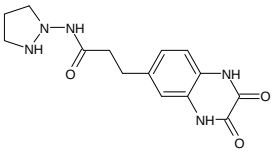
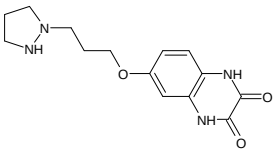
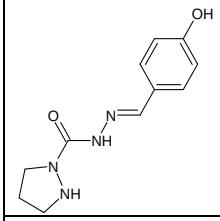
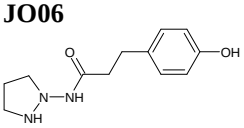
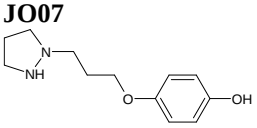
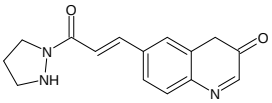
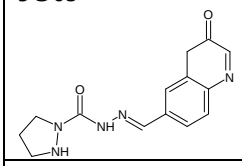
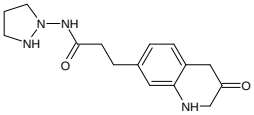
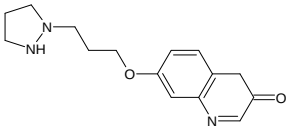
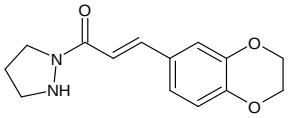
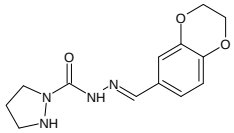
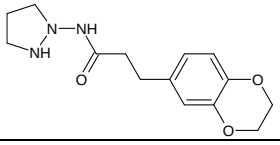
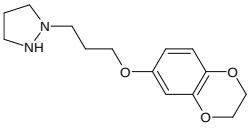
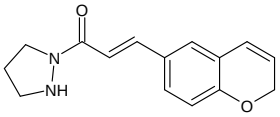
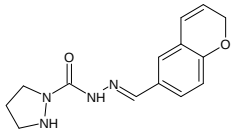
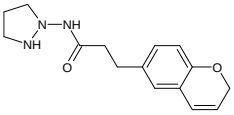
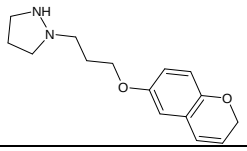
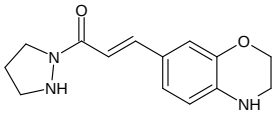
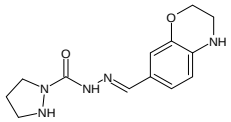
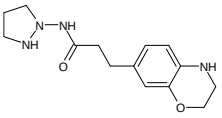
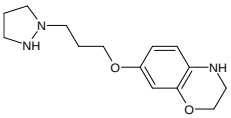
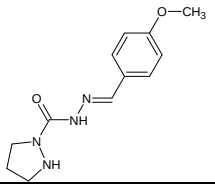
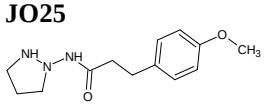
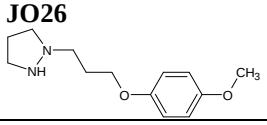
Table 1:2D Structures of the designed molecules

JO01 	**JO02** 	**JO03** 	**JO04** 
JO05 	**JO06** 	**JO07** 	**JO08** 
JO09 	**JO10** 	**JO11** 	**JO12** 
JO13 	**JO14** 	**JO15** 	**JO16** 
JO17 	**JO18** 	**JO19** 	**JO20** 
JO21 	**JO22** 	**JO23** 	**JO24** 
JO25 	**JO26** 		

Molecular docking studies

For molecular docking simulations using AutoDock 4.2, ligand structures were generated in ChemSketch, converted to 3D structures in ChemUltra3D, and energy-minimized. The prepared ligands were then used as input for AutoDock 4.2. To validate the docking protocol, co-crystallized ligands were docked into the inhibitor-binding cavity of human MAO-B and Dopamine D2 receptor, and the docked poses were compared to the crystal structure poses using RMSD values (2.00 and 2.86 Å, respectively). The Lamarckian genetic algorithm was employed for docking, using a standard procedure with a rigid protein and flexible ligand. A grid box with a spacing of 0.375 Å was used, and default settings were applied for other parameters. Finally, the best-docked poses were analyzed for hydrogen bonding interactions using Biovia Discovery Studio Visualizer.

Calculation of physicochemical parameters

The percentage absorption (%ABS) of the compounds was estimated using the method described by Zhao et al., which employs the following equation: %ABS = 109 - (0.345 × TPSA), where TPSA represents the topological polar surface area. Additionally, molecular properties such as TPSA, miLogP, number of rotatable bonds, and adherence to Lipinski's "Rule-of-Five" were calculated using the Molinspiration online toolkit.

RESULTS AND DISCUSSION

Based on the Pharmocophoric features about 26 ligands were designed and 2D structures are sketched using ChemSketch Online software.

Table 2: Results obtained after docking of Compounds with MAO B

LIGAND CODE	BINDING ENERGY kcal/mol	PREDICTED INHIBITION CONSTANT,Ki (µm)	H BOND INTERACTIONS
JO01	-10.33	26.66	THR426 ILE14 SER15
JO02	-7.40	3.74	CYS172 ILE198
JO03	-7.61	2.66	ILE198 CYS172 LYS296 SER59 GLY58
JO04			
JO05	-7.67	2.39	TYR435
JO06	-6.83	9.85	LEU171 ILE199
JO07	-5.17	162.52	TYR435 CYS172 LYS296 TYR60
JO08	-7.12	6.00	TYR60 GLY434 GLY58
JO09	-9.62	88.35	ALA35 SER15 ARG42
JO10	-10.06	42.31	ILE198 GLN206
JO11	5.13	19.80	TYR60
JO12	-5.65 kcal/mol	71.60	171.299 A
JO13	-6.52	51.23	LEU171
JO14	-8.18	7.12	TYR435
JO15	-6.4	19.31	GLY40 TYR60
JO16	-6.53	8.53	TYR435
JO17	-7.48	3.31	MET436
JO18	-5.47	18.15	GLY40
JO19	-5.41	4.35	ALA35 SER15 ARG42
JO20	-7.35	58.42	ALA376 ALA122

JO21	-8.21	62.11	ASP114 SER197
JO22	-5.11	25.63	SER193 TYR435
JO23	-7.14	6.23	CYS118 SER197
JO24	-8.30	9.11	ASP114
JO25	-6.51	17.03	CYS118 SER197
JO26	-5.75	60.69	HIS393

Table 3: Results obtained after docking of Compounds with D_2R

LIGAND CODE	BINDING ENERGY kcal/mol	PREDICTED INHIBITION CONSTANT,Ki (µm)	H BOND INTERACTIONS
JO01	-6.89	8.97	ASP114 SER197
JO02	-7.01	7.28	TRP413 ASP114
JO03	-6.14	31.42	ASP114
JO04	-5.33	123.78	ASP114 TYR416
JO05	-6.08	34.82	TYR209
JO06	-5.79	56.56	SER409 VAL91 TRP413 THR412
JO07	-5.55	85.64	ALA376 ALA122
JO08	-7.24	4.95	SER197
JO09	-8.08	1.20	SER197 TYR416
JO10	-5.96	42.51	ASP114 HIS393
JO11	-6.40	20.20	THR412
JO12	-6.26	25.90	ASP114 CYS118 SER197
JO13	-5.52	90.34	SER193 SER197
JO14	-6.07	35.40	TYR416
JO15	-6.38	21.23	SER197
JO16	-9.43	121.66	SER197
JO17	-7.50	3.18	SER193
JO18	-7.03	7.08	ASP114 CYS118 SER197
JO19	-6.54	16.15	ASP114
JO20	-9.62	89.51	ASP114 THR119
JO21	-8.02	1.33	TYR416 SER197 CYS118
JO22	-7.02	7.12	TYR416 ASP114 SER197

JO23	-7.26	4.79	SER197 TYR416
JO24	-6.48	17.73	SER197
JO25	-5.62	75.43	ASP114
JO26	-6.45	18.57	ALA379

Table 4: Physicochemical parameters for good oral bioavailability

LIGAND CODE	%ABS	TPSA	MW	LogP	HBA	HBD	n-ROTB	LIPINSKI'S VIOLATION
JO01	75.16	98.06	286.29	-0.32	7	3	2	0
JO02	69.35	114.92	294.31	-1.48	9	4	1	0
JO03	71.01	110.09	303.32	-0.59	8	4	4	0
JO04	77.87	90.22	290.32	-0.04	7	3	5	0
JO05	82.45	76.95	234.26	1.37	6	3	2	0
JO06	86.71	64.59	235.29	1.16	5	3	4	0
JO07	93.56	44.73	222.29	1.71	4	2	5	0
JO08	87.68	61.77	269.30	0.98	5	1	2	0
JO09	78.71	87.77	286.31	2.79	1	3	2	0
JO10	83.53	73.80	286.33	0.69	6	2	4	0
JO11	90.39	53.93	273.34	1.24	5	1	5	0
JO12	91.47	50.80	260.29	1.42	5	1	2	0
JO13	83.05	75.19	276.30	1.53	7	2	2	0
JO14	87.32	62.83	277.32	1.32	6	2	4	0
JO15	94.17	42.97	264.32	1.67	5	1	5	0
JO16	90.50	53.60	259.31	1.61	5	2	2	0
JO17	86.24	65.96	272.31	2.22	6	2	2	0
JO18	90.50	53.60	273.34	2.01	5	2	4	0
JO19	97.36	33.73	260.34	2.56	4	1	5	0
JO20	90.50	53.60	259.31	1.61	5	2	2	0
JO21	82.09	77.99	275.31	1.53	7	3	2	0
JO22	90.50	53.60	259.31	1.61	5	2	2	0
JO23	93.21	45.76	263.34	1.67	5	2	5	0
JO24	86.24	65.96	248.29	1.91	6	2	3	0
JO25	90.50	53.60	249.31	1.69	5	2	5	0
JO26	97.36	33.73	236.31	2.24	4	1	6	0

CONCLUSION

In conclusion, these computational studies not only shed a light on understanding the dual mechanism of MAO-B inhibition as well as agonistic activity of Dopamine D_2 receptor, but also provides information regarding the pharmacophoric features of the both(MAO B and D_2R) and computational method to identify and design novel Anti parkinsonism drug candidates. This study also reveals about the potency of Pyrazolidine as Anti parkinsonism agents.

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CONFLICTS OF INTEREST

The author declares there is no conflict of interest.

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Conflict of Interest Statement: All authors have nothing else to disclose.