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In silico Study of Pyrano [2,3-C] Pyrazoles Derivatives as Selective Serotonin Reuptake Inhibitiors

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ABSTRACT

We planned to design a potent Selective serotonin reuptake inhibitor(SSRI) using insilico techniques which may be used as Anti-depressant activity.. In this current study we have chosen Pyrano[2,3-c] pyrazoles as the parent moiety along with several derivatives. These will acts as ligand molecules for computational protocols. The crystalline structure of Selective serotonin reuptake inhibitor was downloaded from protein database and the pdb code was 4MM8. This will act as target for computational studies. Virtual screening library of derivatives determining by Pyrx software. Molecular docking of potent derivatives were carried using autodock software X:Y:Z (50:26:40). Molinspiration's online property calculator and Protox II's structural property calculator were used to quantify certain insilico properties, as well as acute oral toxicity. Derivatization of the parent moiety in the molecule is needed to increase its biological potential. The research discovered the best molecule with potent antidepressant action. The ligand molecule was found to be both safe and effective against selective serotonin reuptake inhibitors. The LD50 was estimated to be 100 mg/kg. Other in-silico properties were calculated as well.

KEY WORDS: ANTI-DEPRESSANT, SELECTIVE SEROTONIN REUPTAKE INHIBITOR, PYRX SOFTWARE, AUTODOCK SOFTWARE.

INTRODUCTION

Since the previous year's prevalence of 5%, depression has been a leading cause of disability and mortality worldwide (Wang al., 2020). It has a negative impact on one's quality of life, functional capacity, and is often linked to anxiety (Wyman, L et al., 2012). Reduced vitality, lack of appetite, and motivational symptoms of anergia and fatigue explain depression, which is a complex psychiatric illness with affective, cognitive, and physical symptoms. (Sampogna, G 2020). It has a rather heterogeneous and pleiotropic pathophysiology (Li, Y et al., 2020).

Antidepressant side effects include metabolic, cardiovascular, and sleep disturbances, as well as severe abnormal activity. (Kochanowska, A. J et al., 2008)). The rising prevalence of depression and its traditional side effects on the use of anti-depressant drugs is having an impact on our society. Today, there is a pressing need to create a new lead molecule or moiety that is more tolerable and effective against depression. (Bhat, Z 2011).

Heterocyclic compounds are primarily found in nature and play an ancient role in the life cycle. Heterocyclic compounds have a wide range of properties that apply to medicinal chemistry (Pozharskii A f 1997). In the last

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two to three decades, there has been a lot of study on heterocyclic chemistry (Jug K 2001).

In recent years, the synthesis and application of heterocyclic compounds with medium-sized rings have become well-known In recent years, there has been a lot of research into fused heterocyclic compounds and their pharmacological significance. The pyranopyrazole heterocyclic ring has gotten more coverage. Pyranopyrazoles are composed of a fused five-membered pyrazole ring and a six-membered pyran ring (Elnagdi Mh & Sadek. Ku 1987). The pyranopyrazole nucleus demonstrates that it can be used to make a variety of biologically important compounds. There are a few rules to follow there are maximum four possible isomer formation such as pyranopyrazole-pyrano[2,3-c] pyrazole, pyrano[4,3-c]pyrazole as well as pyrano[3,2-c] pyrazole and pyrano[3,4-c]-pyrazole.

Objective: In the Present research Project we are done with screen binding efficiency of pyrano[2,3-c] pyrazoles derivative with Selective serotonin reuptake inhibitor receptor [SSRI] also structural and biological properties of ligand will be predicted.

MATERIAL AND METHODS

3.1 Softwares: Chemsketch software used for drawing tool of the ligand compounds (Chemsketch 2014). The convert .mol file to .pdb format by the help of Avogadro software (Avogadro 2010). Autodock 4.0 were used for preliminary docking program for semi-flexible protein and ligand compound docking studies. Chemical properties was determine by using the Molinspiration Online property calculator. Crystalline structure Target compound Serotonin Reuptake Inhibitor was downloaded from protein database and the pdb code was [PDB: 4MM8]. This will act as target for computational studies. Pyrx software was used for virtual screening of library of derivatives. Discovery studio 3.5 was used for molecular interaction and visualization.

3.2 Ligand Structure Preparation: Chemsketch programme was used to draw the ligand structure, and the clean structure tool was used to clean it up. The structure was saved as a.mol file in the ligand working folder after it was drawn. Avogadro software was used to evaluate the.mol code, and an optimization tool was used to optimise the structure. Save the structure until it has been configured.

3.3 Receptor Compound Preparation: With the aid of an online database, the anti-inflammatory behaviour of Crystal structure was downloaded in.pdb format, and the structure was corrected using Autodock v4.0 software. By dispersing the charges around the receptor, the formation of energy was reduced. Remove the water molecules that were bound to the receptor and replace them with hydrogen molecules.

3.4 Receptor-Ligand Compound Docking: The Auto dock v4.0 programme was used to distinguish binding poses based on the presence of binding energies and the inverse relationship between energy and stability, with the conformation with the highest binding energy being the least stable. The default parameters in the software programme have been implemented in a similar manner to the protocol adopted by, The scoring energy was set as co-ordinates such as X = 50, Y = 26 and Z = 40 with 0.375 angstroms grid points with linear spacing using the Lamarckian Genetic Algorithm (LGA) , which included default atomic salvation parameters 126 (x, y, and z) the ratio of grid box (60:60:60). Ensure that the active site of the receptor is surrounded by the 3D grid box center during the grid box preparation.

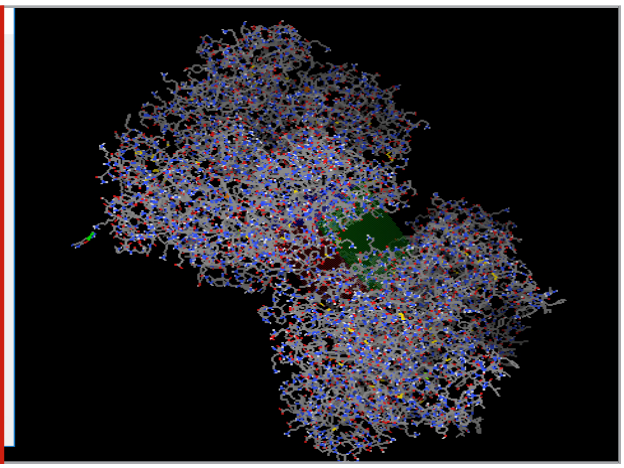
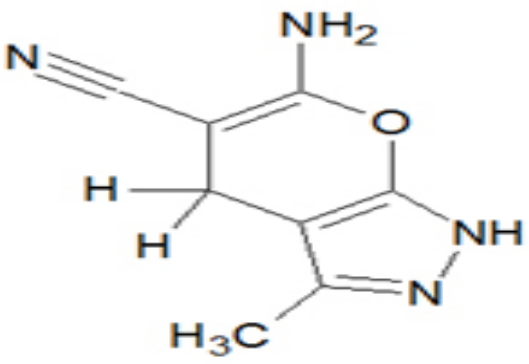


Figure 1: (a) ligand Structure



3.5 Calculator for chemical properties: Molinspiration's online property calculator was used to calculate the ligand property [14]. The ligand is a substance that binds to a The structure was created with the help of an inbuilt tool and several properties. Property classification was divided into two categories: structural property and bioactivity. The Protox II web server was used to predict acute oral toxicity[17,18].

RESULTS AND DISCUSSION

Figure 1 shows how the structure of the ligand and receptor compounds is analysed and drawn using insilico methods. Using Autodock v4.0 software, a grid box for a compound like X:Y:Z (50:26:40) was developed, as shown in fig.2.

The docking study result in Fig 3 suggested that the ligand was adequately bound in the grid box's middle. TRP114; TYR149; ILE152; PRO155; LEU162; ASN397; PHE320; ASP401; LEU400; TRP114; TYR149; ILE152; PRO155; LEU162;

Figure 2: (b): Receptor structure; (c): Grid box of compound IUPAC:- (6-amino-3-methyl-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile)

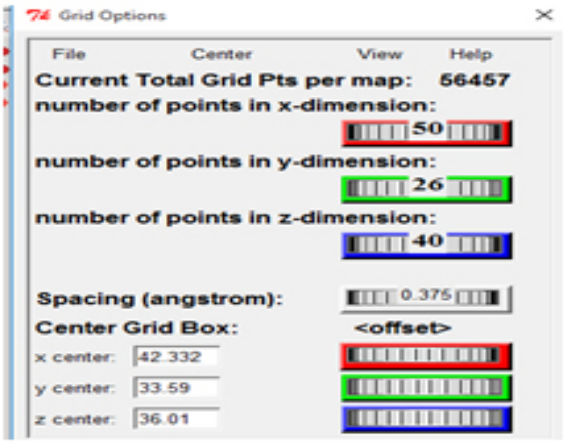
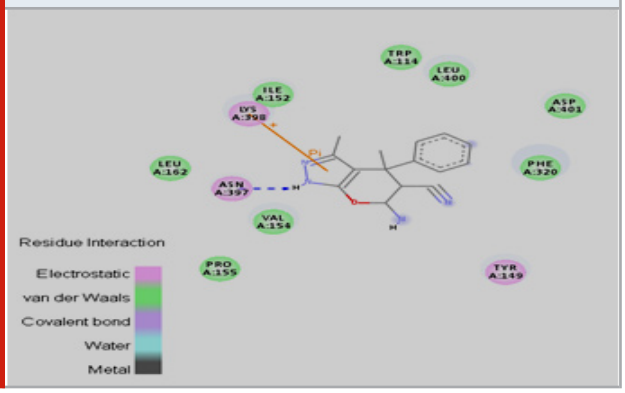


Figure 4: Molecular interactions of Compound



The root mean square deviation (RMSD) value was found to be 11.75 and the mean binding energy to determine the best conformation was found to be -7.5. The compound's

Figure 3: Ligand Docking with receptor

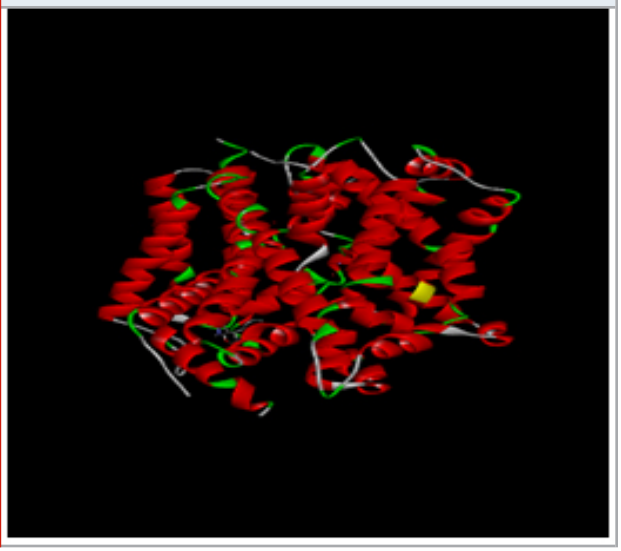


Table 1. Binding Affinity result of Molecule

Sr.no.	Affinity of compound (Kcal/mol)	Distance from rmsd l.b.	Best mode rmsd u.b.
1	-7.5	0.000	0.000
2	-7.3	8.829	11.715
3	-7.2	10.768	12.553
4	-7.1	11.575	13.957
5	-7.1	12.590	15.132
6	-7.0	11.291	13.878
7	-6.9	9.467	11.839

free energy was discovered to be -1345.90 Kcal/mo1. Table 1 shows the structural property and expected bioactivity of the molinspiration online property calculator results.

A number of related studies on depression were reported. Studies by Pal et. al., Ransing et. al., Gaidhane et. al. and Quazi et. al. were reviewed.

Table 2. The Molinspiration online property calculator

Sr.number	Structural Property of compound		Predicated Bioactivity of compound	
	Property	Value of compound	Sites	Binding Efficiency compound
1	miLog P	0.23	GPCR Ligand	-1.29
2	TPSA	87.73	Ion linked Channel Modulator	-0.92
3	Number of atoms	13	Kinase Inhibitor sites	-1.32
4	Molecular Weight	178.19	Nuclear Receptar Ligand molecule	-2.01
5	Number of ON	5	Protease Inhibitor site	-1.46
6	Number of OHNH	3	Enzyme Inhibitor site	-1.01
7	Volume	158.18		

CONCLUSION

Pyrano[2,3-c] was discovered in the analysis. 6-amino-3-methyl-1,4-dihydropyrano[2,3-c] is the IUPAC name for pyrazole. pyrazole-5-carbonitrile, a molecule with antidepressant properties. Though the ligand compound was more safe and efficient for Selective Serotonin Reuptake Inhibitor, the results revealed that (SSRI). The calculated LD50 was 100 mg/kg, and all other physicochemical properties were within acceptable limits.

In Silico Study gave Physicochemical properties and predicted bioactivity of molecule which will elaborated for further studies.

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Disclosure of conflict of Interest: The authors declare that there are no conflicts of interest.

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