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Exploring in silico drug design and pharmacokinetics study for identification of potent antidepressant agents

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ABSTRACT

In furtherance to our previous study, in silico drug design and pharmacokinetics study were employed on some arylpiperazine derivatives as inhibitors of serotonin transporter (SERT) for identification of potential antidepressant agents. A simulated molecular docking study carried out showed that the binding affinity between the receptor (PDB: 4m48) and the ligands range from -8.1 to -10.35kcal/mol with prominent hydrogen bonding and hydrophobic interactions. Some selected ligands displayed good binding affinity range from -9.55 to -10.35kcal/mol and remarkable biochemical interactions were revealed at the active site of the protein target compared to an FDA approved drug (Brexpiprazole) with a lower binding affinity (-9.5kcal/mol). More so, compound 15 shows an exceptional non-bonding interactions with five (5) hydrogen bonds to important amino acid residues (TYR124, ASP46, PHE319, SER421 and ASP475) at a shorter bond length (2.939Å) compared to Brexpiprazole with only one hydrogen bond to the amino acid residue (ASP401) at a longer bond length (3.754Å). Similarly, the predicted ADMET profiles revealed that all the selected compounds possessed good pharmacokinetics properties. Likewise, the computed drug-like properties of the selected compounds portends good pharmacological profiles/ bioavailability tendency as drug candidates. The BOILED-Egg graphics shows that all the selected compounds would be absorbed by the human gastrointestinal system and penetrate to the brain. Furthermore, the calculated physicochemical parameters of all the newly designed compounds having smaller molecular weights when compared with template compound with higher molecular weight satisfied the perquisites of drug-like compounds, an indication that the designed compounds would be orally bioavailable. Also, toxicity profiles of the designed compounds showed that none of the compounds portends carcinogenicity or skin sensitization toxicities. In consequence, all the selected and the designed compounds could be developed and optimized as potential antidepressant agents. However, further experimental studies and in vivo investigations are suggested to evaluate the mode of the actions and other pharmacological effects on these compounds.

1. Introduction

Depression is a multifarious and severe psychiatric disorder characterized by excessive and extensive anxiety, feelings of sadness, unruly emotions, hopeless altitude, insomnia and loss of interest that affects millions of people across the world with a considerable number of morbidity and mortality rates [1][2]. Apart from major implications of depression which include a remarkable reduction in quality of life, loss of job and expensive cost of treatments, a great occurrence of suicidal attempts in depressed patients suggested that mental disorder associated with depression would be the second leading cause of death globally in the nearest future [3][2]. Serotonin transporter (SERT) is the major target of therapeutic for antidepressant agents/drugs in which inhibitors of the serotonin transporter (SERT) are considered as the standard treatment/medication for

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depression [4]. Serotonin transporter (SERT) is a member of monoamine transporters that plays a significant role in the termination of serotonergic neurotransmission by transporting serotonin from the synaptic cleft into the presynaptic neuron [2]. The reuptake of serotonin into the presynaptic terminal is controlled by the concentration of synaptic serotonin, thus, any agent or drug that can inhibit or block the transportation of serotonin into the presynaptic terminal are considered as potential antidepressant agents [1][5]. There are many antidepressant agents (drugs) as inhibitors of serotonin transporter (SERT) in the markets e.g. Brexpiprazole, Fluoxetine, Nefazodone e.tc but with varying degree of side effects which includes liver failure, constipation and unresolved mechanisms of action of some of these antidepressant agents/ antipsychotic drugs are still worrisome [3][6]. Similarly, the in vivo or experimental testing for drug candidates including antidepressant agents/ antipsychotic drugs are very expensive, time-consuming and labor-intensive adventures [3]. In recent times, cheminformatics study and computer-aided drug design (CADD) are some of the important modern approaches employing by many pharmaceutical industries in drug discovery, design and development processes [7][8]. Therefore, in an effort to consolidate findings from our previous study[1], molecular docking analysis, pharmacokinetics study/ bioavailability and bioactivity predictions and structure-based drug design approaches were employed as fast and inexpensive techniques to examine binding interactions, investigate pharmacokinetic properties/ bioavailability and bioactivity parameters and design of new compounds to search for novel inhibitors with better biochemical interactions and excellent pharmacological properties as potential antidepressants agents

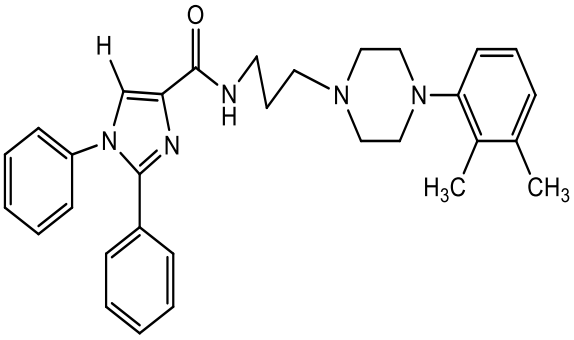
2. Materials and methods

2.1 Experimental dataset and Ligands Preparation

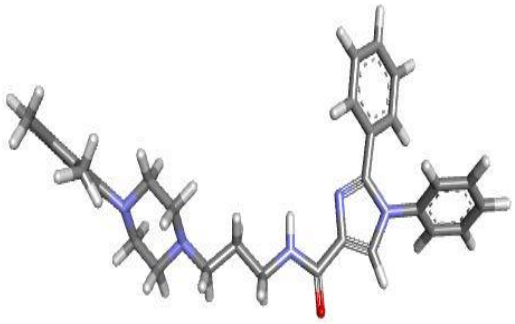
As part of the ongoing investigations from our previous study[1], two-dimensional structures arylpiperazine derivatives (Supplementary Table SR1) of the experimental dataset used were sketched using Chemdraw software ultra-version 12.0 and thereafter converted to 3D structures with the aid of Spartan 14 software[3].The obtained 3D structures were subsequently optimized geometrically using Density Functional Theory (DFT) approach with Spartan 14 software package from Wavefunction Inc, thereafter, the optimized compounds (ligands) were saved in pdb file format as prepared ligands for molecular docking simulations study[9].

2.2 Retrieval of receptor and preparation protocol

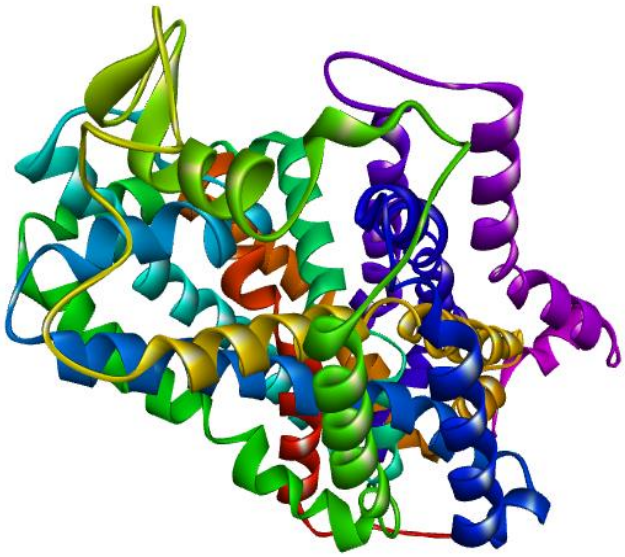
The preparation protocol for the receptor was followed by downloading 3D structure of the protein complex (PDB: 4m48) from Protein Databank (http://www.rcsb.org/pdb). The downloaded 3D structure of the protein complex was prepared by protonation (addition of hydrogen) and elimination of all bound ligands, water molecule and other heteroatoms using the Discovery Studio Visualizer 2016 version and thereafter saved in pdb file format as a refined/ prepared receptor [3] [10]. Figure 1 depicts (a) 2D structure of compound 30 (b) 3D structured the prepared ligand 30 and (c) 3D structure of a prepared receptor (PDB: 4m48).



a. 2D structure of ligand 30



b. 3D structure of the prepared ligand 30



c. 3D structures of the prepared receptor

Figure 1. (a) 2D structure of compound 30 (b) 3D structured the prepared ligand 30 and (c) 3D structure of the prepared receptor.

2.3 Molecular docking simulation

Molecular docking study was conducted to compute the scoring function and investigate protein-ligand interactions in predicting the binding affinity and

biochemical activity of the ligand, [11]. To estimate the binding affinity, AutoDock Vina 4.2 of PyRx software was used while visualization of protein-ligand interactions by non-bonding and hydrophobic interactions was explored by using Discovery Studio Visualizer software 2016 version [9].

Table 1. Molecular docking simulation results of some selected ligands with highest binding affinity

S/N	Binding affinity (kcal/mol)	RMSD value	Number of Hydrogen bonds	Hydrogen bond length (Å)	Hydrogen bonding and amino acid residues	Hydrophobic interactions and amino acid residues of	Electrostatics interactions amino acid residues
6	-9.55	1.771	3	2.122, 3.488, 3.675	PHE319,ASP475, ASP475	PRO386,PRO386, VAL120, TRP51,TRP51, TYR124,PHE468, PHE471,PHE471, HIS472, VAL120	ASP46, ASP475
7	-10.1	1.828	1	3.679	ARG476	VAL120, PHE43, PHE325, TYR542, LEU538, VAL120, ALA479, ALA117, ALA479, ARG476	ASP46
15	-9.65	1.795	5	2.939	TYR124, ASP46, PHE319, SER421, ASP475	PHE43, TYR124, VAL120, TYR124, PRO386	ASP46
30	-10.35	0.457	0	0	0	VAL120, PHE43, PHE325 ARG476, LEU538, VAL120, ALA479, ALA479	ASP46
Brexpiprazole	-9.5	1.816	1	3.754	ASP401	PHE320,PHE320, PHE320, ALA319, ARG30, VAL33, ALA319, ARG30, ALA319, LEU400	ARG30, ARG30

2.4 ADMET/ pharmacokinetics analysis and bioavailability/ drug-like predictions

The important pharmacokinetic properties such as absorption, distribution, metabolism, excretion and toxicity (ADMET)s and bioavailability indicators e.g. Lipinski's rule of five (RO5) before a compound could be assumed and optimized as a drug molecule were carefully investigated [12]. The online software such as SwissADME (http://www.swissadme.ch/index.php) [13], pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) [14], Molinspiration(https://www.molinspiration.com/cgi-bin/properties) [15] and admetSAR 2.0 (http://lmmd.ecust.edu.cn/admetsar2)[16] were used to compute the important pharmacokinetic properties, predict bioavailability and bioactivity indicators.

2.5 Structure-based drug design of novel arylpiperazine derivatives

Structure-based drug design technique was adopted to design new compounds of arylpiperazine derivatives with better biochemical interaction between the protein target and the designed compounds (ligands) by selecting the compound with serial number 4 (Supplementary Table SR1) as the lead compound. Compound 4 was selected as the lead compound because from our previous study, it has remarkable attributes such that it has better inhibitory activity, fell within the applicability domain, low standard residual value, good bioavailability properties

by not violating Lipinski's rule of five (RO5) for a drug-like compound [17] and also from the present findings, the lead compound not only has superior binding affinity but also displayed better molecular interaction with the protein target.

3. Results and discussion

3.1 Molecular docking analysis and virtual screening

A molecular docking simulation and virtual screening investigations were carried out to determine and evaluate ligands efficiency (binding affinity) towards the receptor (protein target) and visualize/ elucidate molecular interactions between the receptors and ligands to identify types of amino acids responsible for the biochemical interactions at the active site of the protein target. The computed binding energy scores resulting from the docked complexes range from -8.1 to -10.35 kcal/mol with RMSD values for the majority of the complexes (over 80%) estimated to be less than 2.0Å (Supplementary Table SR1). This suggests that the ligands were successfully docked to the active site of the receptor and the performance of Docking Algorithms used for this study is very reliable because a docking complex with RMSD value less than 2Å is considered as a successful and correct docking prediction[18][19]. The results of docked complexes with its binding energy, types of interactions and the amino acid residues responsible for the biochemical interactions at the active site of the protein target for some selected compounds (ligands) are reported in Table 1.

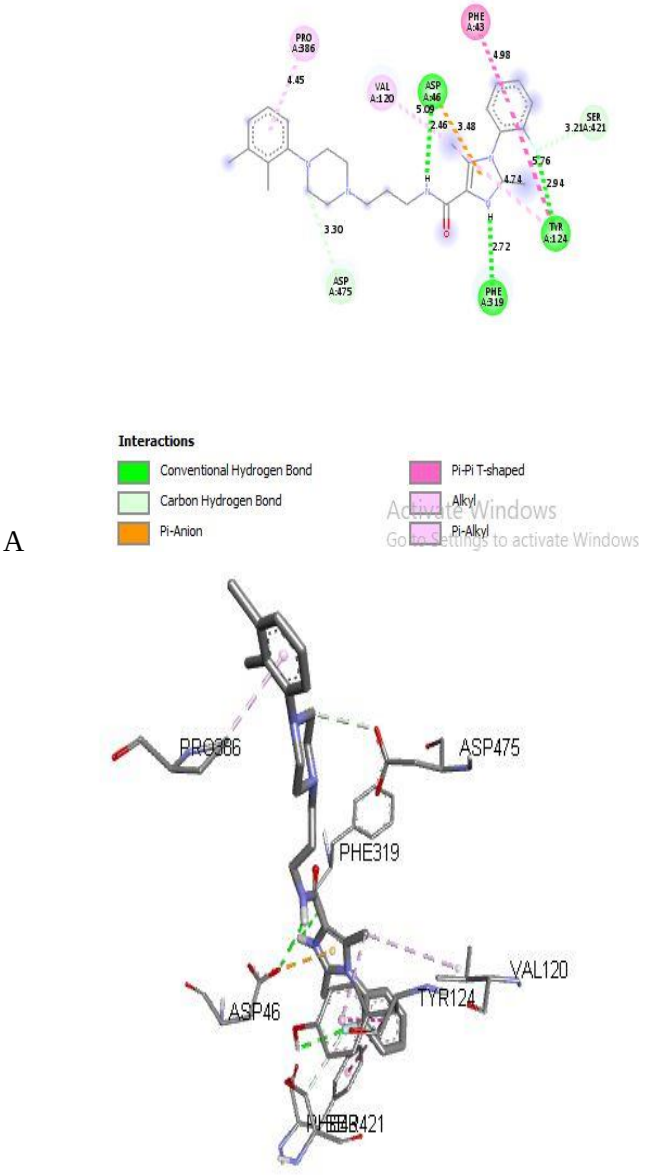
All the selected compounds revealed the good binding affinity and better molecular interaction at the active site of the protein evidenced from their binding affinity scores and the RMSD values. The binding affinity scores of the selected compounds (-9.55 to -10.35kcal/mol) were found to be better compared to an FDA approved drug (Brexpiprazole) with binding affinity of -9.5kcal/mol.

Also, by using Discovery studio visualizer to elucidate the molecular interactions and amino acid residues that are responsible for hydrogen bonding, hydrophobic and other interactions by the selected compounds at the active site of the protein target (Table 1), compound 15 shows a remarkable non-bonding interaction by forming five (5) hydrogen bonds with important amino acid residues (TYR124, ASP46, PHE319, SER421 and ASP475) at a relatively shorter bond length (2.939Å) compared to Brexpiprazole (approved drug) that forms only one hydrogen bond with the amino acid residue (ASP401) at a longer bond length (3.754Å).

The important amino acid residues involving hydrophobic and electrostatic interactions by the compound 15 are PHE43, TYR124, VAL120, TYR124, PRO386 and ASP46 respectively. Figure 2 represents 2D and 3D interactions of compound (ligand) 15 while Figure 3 shows docking pose and receptor surfaces of hydrogen bonds of ligand 15.

3.2 ADMET property predictions and Physicochemical parameters evaluation of some selected compounds

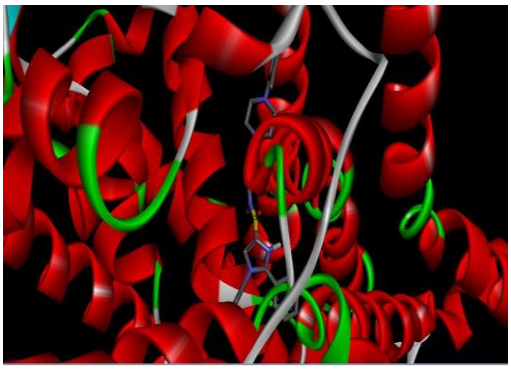
ADMET (Absorption, distribution, metabolism, excretion and toxicity) property predictions and physicochemical parameters evaluation were investigated on some selected compounds. The computed physicochemical parameters of the selected compounds are presented in Table 2 while the predicted ADMET properties are tabulated in Table 3. The obtained values for physicochemical parameters analysis (Table 2) of all the selected compounds showed to be within the suitable ranges for oral bioavailability as drug candidates. That is, all the selected compounds including the approved drug (Brexpiprazole) obeyed Lipinski's rule of five[17].



A

B

Figure 2. (A) 2D and (B) 3D interactions between the receptor and ligand 15



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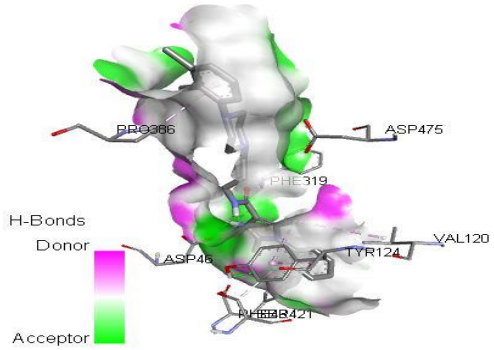


B

Figure 3. (A) Docking pose and (B) Receptor surfaces of hydrogen bonds of ligand 15

Also, the Topological polar surface area (TPSA) scores of all the selected compounds were found to be within the acceptable range (<130Å^2), this implies that these compounds possessed a good physiochemical attribute generally considered in clinical trials that accounts for good transport properties of a drug candidate [12].

Similarly, the predicted ADMET properties (Table 3) of all the selected compounds revealed to possessed a good absorption, distribution, metabolism excretion and toxicity profiles. A drug candidate is considered to be poorly absorbed if the predicted human intestinal absorption parameter is less than 30%[14].

Luckily enough, the predicted human intestinal absorption parameter for all the selected compounds is greater than 30% (87.392 - 92.339%), this means, all the selected compounds including the approved drug would be readily absorbed via human intestinal absorption. Similarly, Caco2 permeability parameter is generally used as in vitro indicator to predict absorption of orally administered drugs and a compound or drug candidate is assumed to be high Caco2 permeability if the predicted value is greater than 0.9[14]. Compound 6 was found to exhibit a remarkable absorption profile with a superior percentage human intestinal absorption parameter (87.392%), excellent Caco2 permeability (1.214), better water solubility attribute (-3.199) and skin permeability (-2.735) compared to other selected compounds. More so, the BBB and CNS permeability parameters (> 0.3 and > -2.0 respectively) of the compound 6 proved that this compound would readily permeate or cross the blood-brain-barrier and penetrate to the central nervous system[14] when compared to the FDA approved drug (Brexpiprazole). For drug metabolism in humans, the influence of cytochrome P450 enzymes showed that all the selected compounds are inhibitors of CYP2C19, CYP2C9, CYP2D6 and CYP3A4 but non- inhibitors of CYP1A2 cytochrome P450 enzymes. Likewise, the toxicity profiles of the selected compounds revealed that none of the selected compounds portend skin sensitization toxicity property but may possess some hepatotoxicity and human ether-a-go-go-related gene toxicity including Brexpiprazole (FDA approved).

3.3 Bioactivity, bioavailability and medicinal chemistry profiles of some selected compounds

Bioactivity, bioavailability (drug-likeness) and medicinal Chemistry profiles of some selected compounds were evaluated via the online-based software[15][13]. The predicted bioactivity scores, drug-likeness (bioavailability) parameters and medicinal Chemistry properties for the selected compounds are reported in Table 4. A predicted bioactive score of a value greater than 0.00, between -0.5 and 0.00 and a value less than -0.5 is considered as more active (bioactive), moderately active and non-active respectively for a drug candidate/ compound [20]. Interestingly, the predicted bioactive score for the G protein-coupled receptor (GPCR) ligand for all the selected compounds including an FDA approved drug (Brexpiprazole) is greater than zero (Table 4), this implies that these compounds would be more active as drug candidates. Similarly, the predicted bioavailability parameters (Table 4) which account for drug efficacy, safety, or metabolism by using Lipinski's rule of five (RO5) revealed that all the selected compounds including the FDA approved drug (Brexpiprazole) obeyed Lipinski's rule of five (RO5). Because of this, the selected compounds portend good pharmacological profiles (drug-like properties) and could be orally bioavailable as drug candidates[17][1].

Likewise, human intestinal absorption (HIA), the brain access (penetration) and medicinal attributes for all the selected compounds and the FDA approved drug (Brexpiprazole) were illustrated by the BOILED Egg graphics (Figure 4) while oral bioavailability radar charts for compounds 4 and 6 were depicted by Figure 5 with the aid of Swiss ADME online tool. The white region of the graphics (Figure 4) indicates a section of the highest probability of being absorbed by the human gastrointestinal system while the yellow (yolk) portion represents the area of the highest chance to the brain access (penetration)[1]. The BOILED Egg graphics unveils that all the selected compounds including the FDA approved drug (Brexpiprazole) situated within the yellow (yolk) portion. This implies that the selected

compounds would be highly absorbed by the human gastrointestinal system and penetrate the brain [21][22]. The oral bioavailability radar charts (Figure 5) for the selected compounds 4 and 6 reveal that these compounds possessed good physiochemical properties required for an orally bioavailable drug candidate [12].

Table 2. Physicochemical parameters of some selected compounds including Brexpiprazole (FDA approved drug)

S/N	Molecular Formula	Molecular weight g/mol	No of Rotatable bonds	No of H-bond acceptors	No of H-bond donors	Total polar surface area	logP	WLOGP	Lipinski violations
4	C25H29Cl2N5O	486.44	7	5	1	53.4	4.738	3.98	0
6	C27H33Cl2N5O	514.49	9	5	1	53.4	5.3821	4.62	1
15	C25H28Cl2FN5O	504.43	7	5	1	53.4	4.8771	4.54	1
19	C27H34ClN5O2	496.04	8	6	1	62.63	4.4017	3.64	0
30	C31H35N5O	493.64	8	5	1	53.4	5.0982	4.34	0
Brexpiprazole	C25H27N3O2S	433.57	7	5	1	76.81	4.724	3.96	0

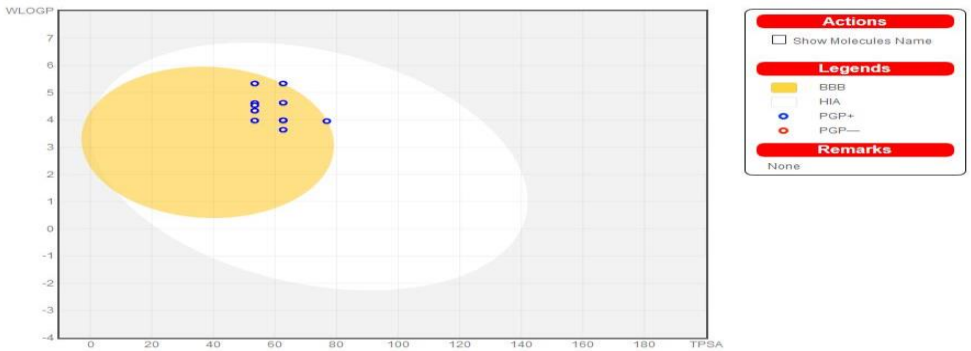


Figure 4. BOILED-Egg graphics of the all the studied compounds including the standard drug

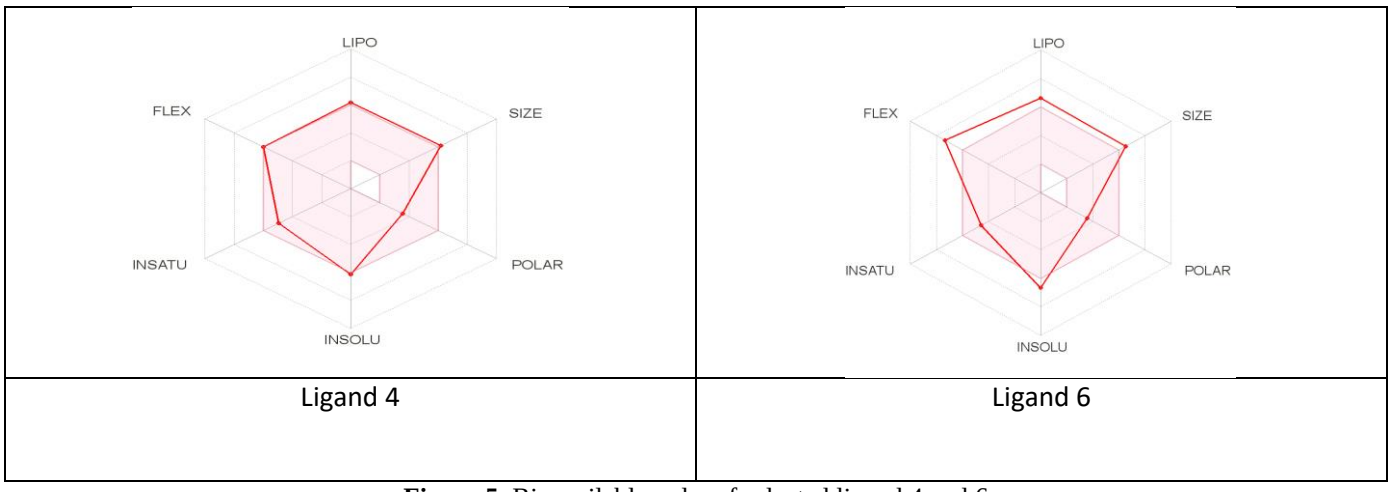


Figure 5. Bioavailable radar of selected ligand 4 and 6

Table 3. ADMET/pharmacokinetics properties of selected ligands with highest binding affinity

			Selected compounds				**Approved drug**
Properties	Parameters	Measurement/unit	4	6	15	30	Brexpiprazole
Absorption	Water solubility	(log mol/L)	-3.127	-3.199	-3.129	-3.052	-4.389
	Caco2 permeability	(log Papp in 10-6 cm/s)	0.907	1.214	1.12	0.89	0.947
	Intestinal absorption (human)	(% Absorbed)	89.382	87.392	88.568	92.339	89.608
	Skin Permeability	(log Kp)	-2.736	-2.735	-2.736	-2.735	-2.769
	P-glycoprotein I inhibitor	(Yes/No)	Yes	Yes	Yes	Yes	Yes
Distribution	VDss (human)	(log L/kg)	0.91	0.84	0.871	0.375	1.107
	BBB permeability	(log BB)	0.203	0.347	0.08	0.296	0.199
	CNS permeability	(log PS)	-2.06	-2.076	-2.081	-1.969	-1.092
Metabolism	CYP1A2 inhibitor	(Yes/No)	No	No	No	No	Yes
	CYP2C19 inhibitor	(Yes/No)	Yes	Yes	Yes	Yes	No
	CYP2C9 inhibitor	(Yes/No)	Yes	Yes	Yes	Yes	No
	CYP2D6 inhibitor	(Yes/No)	Yes	Yes	Yes	Yes	Yes
	CYP3A4 inhibitor	(Yes/No)	Yes	Yes	Yes	Yes	Yes
Excretion	Total Clearance	(log ml/min/kg)	0.588	0.79	0.517	0.506	1.171
	Renal OCT2 substrate	(Yes/No)	Yes	Yes	Yes	Yes	No
Toxicity	AMES toxicity	(Yes/No)	No	Yes	No	Yes	Yes
	hERG II inhibitor	(Yes/No)	Yes	Yes	Yes	Yes	Yes
	Hepatotoxicity	(Yes/No)	Yes	Yes	Yes	Yes	Yes
	Skin Sensitization	(Yes/No)	No	No	No	No	No

Table 4. Bioactivity and drug-like predictions and medicinal chemistry profiles of some selected ligands

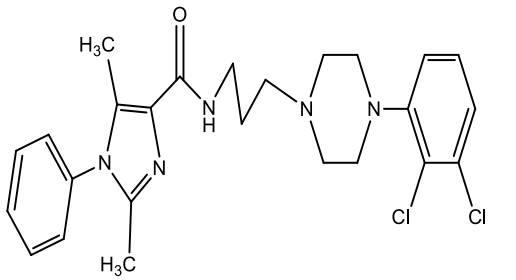
		Selected compounds				Referenced drug
Properties Predicted	Computed parameters	4	6	15	30	Brexpiprazole
Bioactivity score	GPCR ligand	0.35	0.4	0.32	0.32	0.17
	Ion channel modulator	-0.04	-0.01	-0.18	0.08	-0.04
	Kinase inhibitor	-0.06	-0.07	-0.04	0.16	0.27
	Nuclear receptor ligand	-0.4	-0.24	-0.39	-0.18	0.02
	Protease inhibitor	-0.24	-0.22	-0.24	-0.05	-0.1
	Enzyme inhibitor	-0.12	-0.07	-0.16	0.09	0.05
Drug-likeness	Lipinski violations	0	1	1	0	0
	VEBER violations	0	0	0	0	0
	Bioavailability Score	0.55	0.55	0.55	0.55	0.55
Lipophilicity (Log Po/w)	iLOGP	4.18	5.14	4.17	4.42	4.14
	XLOGP3	5.33	6.12	5.43	5.66	4.67
	MLOGP	3.46	3.85	3.82	3.75	3.45
Medicinal chemistry	PAINS alerts	0	0	0	0	0
	Synthetic accessibility	3.57	3.93	3.58	3.96	3.17
	Lead likeness	3	3	3	3	2

Moreover, the computed PAINS alerts (pan assay interference), synthetic accessibility and Lead likeness for medicinal Chemistry profiles (Table 4) for the selected compounds including the FDA approved drug (Brexpiprazole) indicate no PAINS alerts (PAINS alert= 0) and the synthetic accessibility (SA) scores is between 1 and 4 (synthetic accessibility 1-4 implies easy to synthesize) for all the selected compounds. This asserts that all the selected compounds would not only yield false positive biological assays (promiscuous compounds) but also would be very easy to synthesize in the laboratory for drug optimization [13] [12].

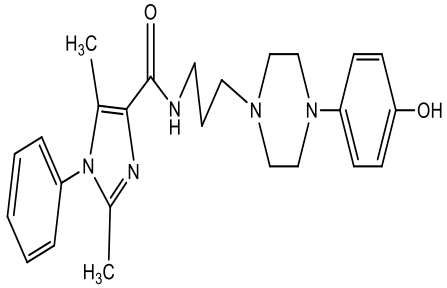
3.5 Structure-based drug design of new arylpiperazine derivatives

Structure-based drug design (SBDD) mechanism was employed to design new arylpiperazine derivatives as inhibitors of serotonin transporter (SERT) by selecting the compound with serial number 4 as the template compound (Supplementary Table SR1) from the dataset

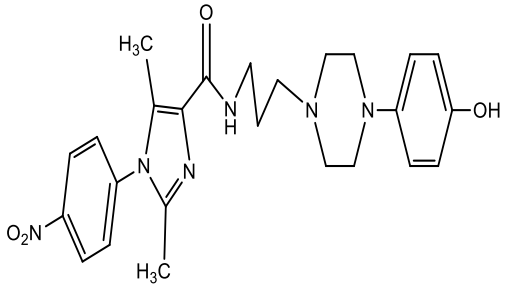
used in our previous and present studies. The quality attributes for the choice of compound 4 as the template compound are; it situated within the applicability domain, better inhibitory activity and binding affinity, a remarkable physicochemical/ drug-like properties and it satisfied criteria stipulated by Lipinski's rule of five (RO5) for oral bioavailable drug candidates[1][17]. The design was carried out by introducing some new active substituents/pharmacophores into the structure of the template compound. The template compound and the 3 newly designed arylpiperazine derivatives are shown in Figure 6.



Template compound



4a



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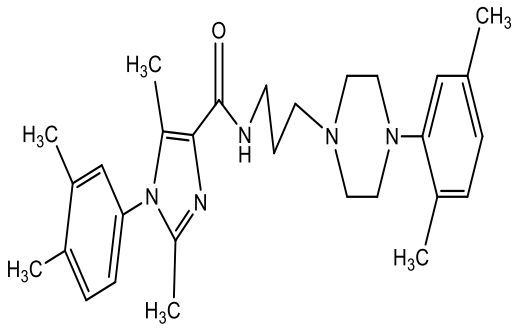


4c

Figure 6. 2D structures of template compound and the new designed compounds (4a,4b and 4c*)*

3.6 Molecular docking simulation, pharmacokinetic evaluations and bioavailability/ drug-like predictions of the designed compounds

The designed compounds were investigated via simulated molecular docking analysis to determine the types of molecular interactions and the amino acid residues responsible for the interactions at the binding site of the receptor. Also, the pharmacokinetic profiles and the bioavailability/ drug-like properties of the newly designed compounds were evaluated accordingly using online web tools[13][14]. The results of the molecular docking simulation after a careful visualization via Discovery studio visualizer software showed that these ligands (designed compounds) were firmly bounded through Hydrogen bonding and hydrophobic interactions to the active site of the protein target through its amino acids residues. Table 5 unveils the binding affinity, types of interactions and the amino acid residues between the protein target (receptor) and the ligands (designed compounds). From the table, the binding affinity of the designed compounds ranges from -9.6-10.6 kcal/mol but that of the template compound and the FDA approved drug were found to be -9.1kcal/mol and -9.5kcal/mol respectively, lower values compared to the designed compounds. More so, there are remarkable biochemical interactions observed in the ligands most especially ligand 4c (compound 4c) with the receptor (PDB: 4m48) which could be due to higher binding affinity and types of non-bonding interactions in the complex. Compound 4c displayed to be firmly bounded with the receptor by forming four (4) Hydrogen bonds and ten (10) hydrophobic interactions with the protein target at the highest binding affinity of -10.6kcal/mol compared to the template compound with the formation of only two (2) hydrogen bonds and six (6) hydrophobic interactions at the binding affinity of -9.1kcal/mol. The binding affinity of receptor-ligand interaction has been demonstrated to be influenced by the number of hydrogen bonding and distance in a protein-ligand complex formation[23]. Figure 7A shows 2D and 3D interactions of ligand 4a while Figure 7B displays receptor surfaces of hydrogen bonds and hydrophobic interactions of ligand 4a.

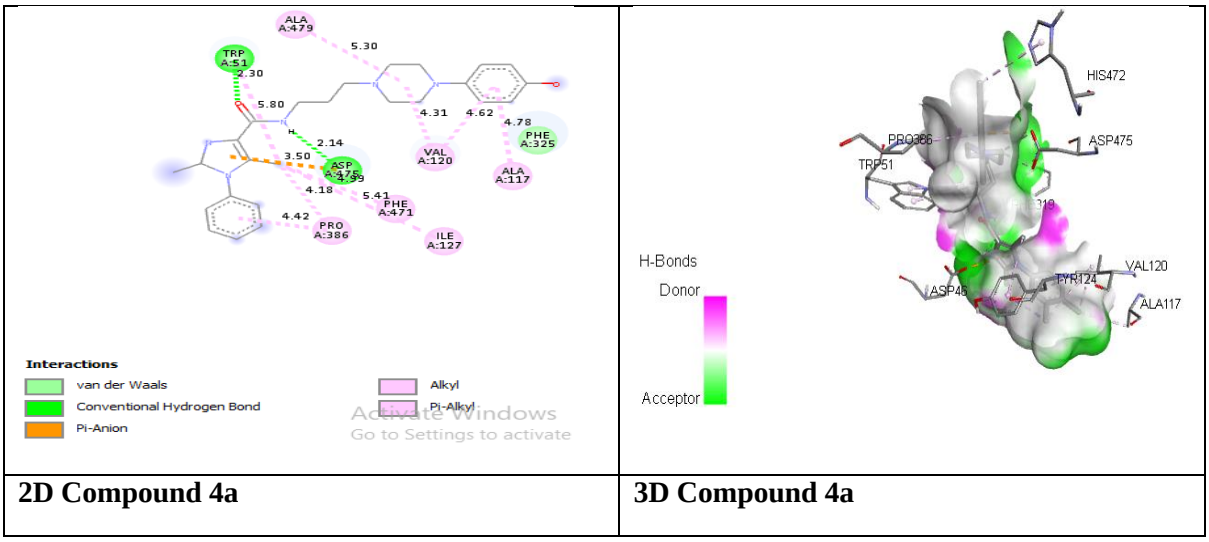
Figure 7B. Receptor surfaces of hydrogen bonds and hydrophobic interactions of ligand 4a

Similarly, to examine bioavailability/ drug-like attributes and pharmacokinetics profiles of the designed compounds, some important physicochemical parameters and ADMET property predictions were carefully evaluated. Supplementary Tables SR2 and SR3 revealed the predicted physicochemical parameters and ADMET/pharmacokinetics properties of the designed compounds respectively. The drug-likeness attributes of a compound give information about the possibility of that compound to become a potential drug candidate[12]. Luckily enough, the predicted physicochemical parameters of all the designed compounds with smaller

molecular weight when compared with template compound (higher molecular weight) satisfied the perquisites of drug-likeness and also obeyed Lipinski's rule of five (RO5)[17]. This suggests that the designed compounds would be orally bioavailable and more pharmacological active as drug candidates[1]. Likewise, the predicted ADMET properties (Supplementary Tables SR3) disclosed that all the designed compounds would be readily absorbed by human intestinal absorption with the percentage of absorption of the designed compound 4c (92.03%) greater than that of FDA approved drug (89.608%). Furthermore, toxicity profiles of the compounds indicate that none of the designed compounds including the Brexpiprazole (FDA approved drug) portends carcinogenicity or skin sensitization toxicities.

Table 5. Amino acid residues of hydrogen bonding and other interactions between the receptor (PDB: 4M48) and hypothetical designed compounds

S/N	Binding affinity (kcal/mol)	No of Hydrogen bonding formed	No of Hydrophobic interactions displayed	Amino acid residues of Hydrogen bonding	Amino acid residues of Hydrophobic interactions	Amino acid residues of Electrostatics interactions
Template	-9.1	2	6	PHE319, PHE319	VAL120,GLU384, GLY385,ARG52, PRO386, TYR124, PRO386	ASP46
4a	-9.7	2	10	TRP51, ASP475	VAL120, ALA479, ILE127, PRO386, TRP51, TRP51, PHE471, ALA117, VAL120, PRO386	ASP475
4b	-9.6	3	3	PHE319,ASP475,ASP475	ASP46,ASP475	ASP46
4b	-10.6	4	10	PHE319,PHE319,ASP475,ASP475	VAL120,TYR124 ALA117,VAL120, VAL120,TRP51,TRP51,TYR124,HIS472, PRO386	ASP46,ASP475
Brexpiprazole (FDAapproveddrug)	-9.5	1	10	ASP401	PHE320,PHE320,PHE320, ALA319,ARG30,VAL33,ALA319,ARG30,ALA319, LEU400	ARG30,ARG30



2D Compound 4a | **3D Compound 4a**

Figure 7A. 2D and 3D interactions between the receptor and designed compound 4a

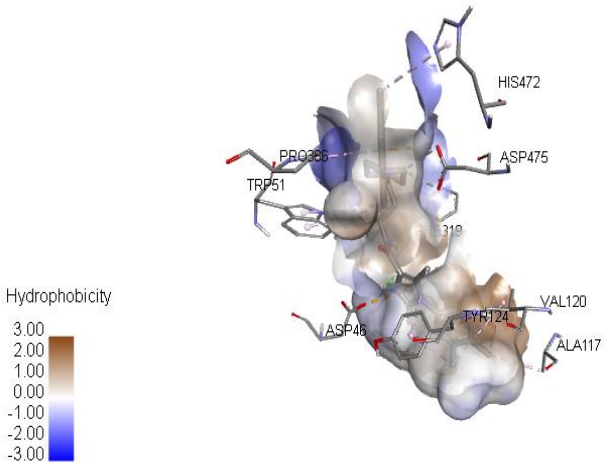


Figure 7B. Receptor surfaces of hydrogen bonds and hydrophobic interactions of ligand 4a

4. Conclusion

Molecular docking simulation, ADMET/ pharmacokinetics evaluations, bioavailability/ bioactivity predictions and structure-based drug design were performed on some arylpiperazine derivatives as inhibitors of serotonin transporter (SERT) in dicoverying potential antidepressant agents. A simulated molecular docking analysis showed that the binding affinity between the receptor (PDB: 4m48) and the ligands range from -8.1 to -10.35kcal/mol with prominent interactions that involved hydrogen bonding, hydrophobic and electrostatic interactions. Some ligands with a remarkable binding affinity were selected including an FDA approved drug (Brexpiprazole) as a positive control to elucidate the biochemical interactions and types of amino acid residues associated with the observed interactions at the active site of the protein target. Interestingly, all the selected compounds displayed excellent binding affinity and prominent molecular interactions at the active site of the protein evidenced by their higher binding affinity and lower RMSD values. The binding affinity of the selected compounds range from -9.55 to -10.35kcal/mol which were found to be better compared to an FDA approved drug (Brexpiprazole) with a lower binding affinity of -9.5kcal/mol. More so, with the aid of Discovery visualizer, compound 15 shows an outstanding non-bonding interaction by forming five (5) hydrogen bonds with important amino acid residues (TYR124, ASP46, PHE319, SER421 and ASP475) at a shorter bond length (2.939Å) compared to Brexpiprazole that forms only one hydrogen bond with the amino acid residue (ASP401) at a longer bond length (3.754Å). The important amino acid residues involving hydrophobic and electrostatic interactions by the compound 15 are PHE43, TYR124, VAL120, TYR124, PRO386 and ASP46 respectively. Similarly, the predicted ADMET properties revealed that all the selected compounds possessed good absorption, distribution, metabolism and excretion profiles and none of the selected compounds portend skin sensitization toxicity. The computed drug-like properties of the selected compounds portend good pharmacological profiles and could be orally bioavailable as drug candidates. The BOILED-Egg graphics shows that all the selected compounds could be absorbed by the human gastrointestinal system and could easily penetrate into the brain. Furthermore, the predicted physicochemical parameters of all the newly designed compounds of smaller molecular weights when compared with template compound of higher molecular weight satisfied the perquisites of drug-likeness, which means they would be orally bioavailable and more pharmacological active as drug candidates. Also, toxicity profiles of the newly designed compounds showed that none of the designed compounds portends carcinogenicity or skin sensitization toxicities. In consequence, all the selected and the newly designed compounds could be developed and optimized as potential antidepressant agents in the pharmaceutical industries. However, further experimental studies and in vivo assessments or clinical investigations are suggested to evaluate the mode of the actions and other pharmacological effects of these compounds.

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