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Unveiling novel inhibitors of dopamine transporter via in silico drug design, molecular docking, and bioavailability predictions as potential antischizophrenic agents

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Abstract

Background: The inhibition of dopamine transporter is known to play a significant role in the treatment of schizophrenia-related and other mental disorders. In a continuing from our previous study, computational drug design approach, molecular docking simulation, and pharmacokinetics study were explored for the identification of novel inhibitors dopamine transporter as potential Antischizophrenic agents. Consequently, thirteen (13) new inhibitors of dopamine transporter were designed by selecting the molecule with serial number 39 from our previous study as the template molecule because it exhibits good pharmacological attributes.

Results: Molecular docking simulation results revealed excellent molecular interactions between the protein target (PDB: 4m48) and the ligands (designed inhibitors) with major interactions that involved hydrogen bonding and hydrophobic interactions. Also, some of the designed inhibitors displayed a superior binding affinity range from -10.0 to -10.7 kcal/mol compared to the referenced drug (Lumateperone) with a binding affinity of -9.7 kcal/mol. Computed physicochemical parameters showed that none of the designed inhibitors including the referenced drug violate Lipinski's rule of five indicating that all the designed inhibitors would be orally bioavailable as potential drug candidates. Similarly, the ADMET/pharmacokinetics evaluations of some designed inhibitors revealed that they possessed good absorption, distribution, metabolism and excretion properties and none of the inhibitors is neither carcinogens nor toxic toward human ether-a-go-go related gene (hERG I) inhibitor or skin sensitization. Likewise, the BOILED-Egg graphics unveils that all the designed inhibitors demonstrate a high probability to be absorbed by the human gastrointestinal tract and could permeate into the brain. Besides, the predicted bioactive parameters suggested that all the selected inhibitors would be active as drug candidates. Furthermore, the synthetic accessibility scores for all the selected inhibitors and referenced drug lied within the easy zone (i.e., between 1–4) with their computed values range from 2.55 to 3.92, this implies that all the selected inhibitors would be very easy to synthesize in the laboratory.

Conclusions: Hence, all the designed inhibitors having shown excellent pharmacokinetics properties and good bioavailabilities attributes with remarkable biochemical interactions could be developed and optimized as novel Antischizophrenic agents after the conclusion of other experimental investigations.

Keywords: ADMET, Inhibitor, Dopamine, Receptor, Disorder, Schizophrenia

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Background

Dopamine transporter (DAT) is a member of monoamine transporters that regulates dopamine (DA) neurotransmission, and it is also involved in various physiological functions and certain mental disorders [1]. DAT is a building block membrane protein functioning to remove dopamine from the synaptic cleft and accumulates it in surrounding cells, thus ending the signal of the neurotransmitter. Excessive neurotransmission of dopamine is a clinical condition termed by disordered thought commonly known as schizophrenia [2, 3]. Schizophrenia is a chronic neuropsychiatric disorder with reduced cognitive flexibility as a major symptom, other positive or residual symptoms may include hallucinations, delusions, anti-social behaviors suspiciousness, incoherent speech, strange, and dangerous altitudes [2]. Mental disorders associated with immoderate neurotransmission of dopamine levels by implicating DAT as well as dysfunction of dopamine (DA) neurotransmission are important contributing factors in the pathophysiology of neuropsychiatric disorders such as depression, bipolar disorder, Parkinson's disease, and attention deficit hyperactivity disorder (ADHD) [3]. The inhibition of DAT blocks the reuptake of dopamine from extracellular space into the synapse thereby raising the quantity of dopamine availability which in turns improves the possibility of dopamine receptor activation; however, the inhibition by most of the DAT inhibitors is limited with associated adverse side effects [4, 5]. Generally, drugs targeting the dopamine transporter (DAT) are majorly used to improve cognitive abilities as therapeutic agents for schizophrenia-related cognitive impairments and other neuropsychiatric disorders [6]. Many antipsychotics also known as neuroleptics medications such as Lumateperone, Modafinil, Chlorpromazine, Cariprazine, Risperidon are available as a class of compounds with a strong affinity for various subtypes of dopamine receptors for the treatment of schizophrenic patients to decrease excess levels of dopamine thereby lessen the positive symptoms of the disorder but none of the beneficial effects for any of the medication strategies were considered to be of clinically significant [2, 7]. Also, the mechanism of actions of many of these drugs remained unresolved [6]. Therefore, the need to design new inhibitors of DAT having more therapeutic potential with lower or no side effects as antischizophrenic agents is calling for global attention.

In a continuous effort to our previous study [2], computer-aided structure-based drug design, virtual screening, and in silico pharmacokinetics predictions were procured for the present study as a time saving and cost-effective approaches for the identification of novel inhibitors of DAT with better therapeutic potential for the treatment of schizophrenia-related

cognitive impairments and other neuropsychiatric disorders. This method stems from the fact that the structure-based drug design approach has been widely applied in the analysis of molecular recognition through binding affinities, molecular interactions, induced conformational changes, and toxicity filters for the design and identification of novel compounds containing important physicochemical properties due to efficient structural adjustment/modification in the design of new molecules [8].

Methods

Computational drug design approach

In a continuation from our previous work [2], computational drug design technique was employed to design and identify novel inhibitors of dopamine transporter (DAT) of better therapeutic properties that could serve as potential antipsychotic agents for schizophrenia-related mental disorders. Template compound was selected from the previous work for the design of new inhibitors of DAT. Chemdraw software ultra-version 12.0 was used to sketch the 2D molecular structures of the hypothetical designed inhibitors while Spartan 14 software was employed for the geometric optimization after converting the 2D structures to three-dimensional (3D) structures. Each molecule was initially optimized with the molecular mechanics via MMFF (molecular mechanics force field) and subsequently re-optimized by density functional theory (DFT) using the B₃LYP/ 6-31G* basis set with the aid of Spartan 14 Version 1.1.0 software. The optimized molecules were then saved in pdb file format via Spartan 14 software as prepared ligands for molecular docking study. The prepared ligands were docked with the prepared structure of dopamine transporter (target protein) using PyRx software via AutoDock Vina 4.2 version software. The docking results were visualized and analyzed with the aid of Discovery Studio Visualizer software 2020 version [9, 10]. Molecular docking, ADMET/pharmacokinetics predictions, and bioactive evaluation were further performed on the new designed compounds (inhibitors of dopamine transporter). The 2D chemical structures of template molecule and some designed inhibitors are shown in Fig. 1.

Selection of template molecule and design of new inhibitors of dopamine transporter

The molecule with serial number 39 as contained in Supplementary Table SD1 of the dataset used in our previous study [2] was selected as the template molecule to design hypothetical inhibitors of DAT using structure-based drug design (SBDD) approach. The template molecule was selected owing to its superior quality assurance features such that it fell within the

Fig. 1 2D structure of template molecule and some designed inhibitors (39b, 39c, and 39g)

applicability domain with low standard residual value, it has relatively better inhibitory activity and good binding affinity and above all, and it possesses remarkable drug-like property because it fulfilled Lipinski's rule of five (RO5) for a pharmacologically active compound [11].

Preparation of the target protein and ligands

The dopamine transporter protein (DTP) is responsible in maintaining dopamine levels via the reuptake of dopamine in neuronal cells. Dopamine is generated in the presynaptic neuron and moved to the synaptic cleft, where it can bind to dopamine receptors on the postsynaptic neuron. DAT disallows dopamine accumulation by removing unbound dopamine molecules from the synaptic cleft [12]. Three-dimensional structure of the protein (PDB code: 4M48) retrieved from Protein Data Bank site (<http://www.rcsb.org/pdb>) was prepared by adding hydrogen atoms (protonation) and removing all bound ligands and other heteroatoms by using the Discovery Studio Visualizer 2016 version [2]

and subsequently saved in pdb file format for molecular docking simulation processes. Similarly, designed inhibitors (ligands) were prepared by transforming 2D molecular structures to 3D structures for energy minimization (optimization) using Spartan 14 software at DFT [13]. The optimized 3D structures of the designed inhibitors were then saved in pdb file format as prepared ligands. Figure 2a and b represent 3D structures of the prepared receptor and a ligand (designed compound 39g) respectively.

Molecular docking analysis and virtual screening

Molecular docking simulation was performed to estimate the binding affinity (scoring function), and visualize and evaluate receptor-ligand interactions in order to examine the binding mode and activity of the ligand. PyRx software via AutoDock Vina 4.2 version and Discovery Studio Visualizer software 2020 version were used to generate the scoring functions (binding affinities) and visualize protein-ligand interactions

Fig. 2 **a** 3D structure of the prepared protein target (PDB: 4m48) and **b** 3D structure of a prepared ligand 39g

involving non-bonding polar and hydrophobic interactions [13].

ADMET/pharmacokinetics predictions and bioactive evaluation

Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties and other pharmacokinetics parameters are critical attributes and stages for any compound to pass through prior to be optimized and developed as drug candidates which must be carefully investigated [14]. In the present study, SwissADME (<http://www.swissadme.ch/index.php>), admetSAR 2.0 (<http://lmmd.ecust.edu.cn/admet-sar2>), pkCSM (<http://biosig.unimelb.edu.au/pkcsm/prediction>), and Molinspiration (<https://www.molinspiration.com/cgi-bin/properties>) were procured as online web tools/software to predict the ADMET/pharmacokinetics properties, profile the physicochemical parameters [15–17], and compute the bioactive scores of the designed inhibitors [18].

Results

Tables and figures are shown in this section.

Discussion

Computational drug design of new inhibitors of dopamine transporter

Pharmacophore is a molecular framework or a structural feature in a molecule that is recognized at the receptor site which is responsible for the pharmacological or biological activity of a molecule [19]. Structural modification of a template molecule using most important pharmacophores by incorporating or removing H-bond

donor or H-bond acceptor or hydrophobic substituents was applied in the computational drug design of the new inhibitors that could improve its molecular interactions with the biological target [19]. 2D structures of the newly designed 13 molecules (inhibitors of dopamine transporter) were reported in Supplementary Table DS2. The impact of activating groups ($-\text{NH}_2$, $-\text{OH}$, $-\text{OCH}_3$, $-\text{COOH}$, and $-\text{CH}_3$) in the designed compounds were significantly felt compare to the deactivating substituents ($-\text{NO}_2$, $-\text{CF}_3$, $-\text{F}$, and Cl) evidenced from the obtained result of binding affinity or biochemical interactions between the receptor and the designed compounds (Supplementary Table DS2). The electron-donating property of the pharmacophores using activating groups could account for an increase in electron density thereby led to improve the reactivity of the compound via the molecular interactions with the biological target in contrast to the deactivating substituents which decrease the reactivity by withdrawing electron density from a compound as observed in the designed compounds [20].

Molecular docking investigation of the new inhibitors of dopamine transporter

A molecular docking simulation study of the designed inhibitors was investigated on the receptor (PDB code: 4m48) to determine the types of amino acid residues responsible for the biochemical interaction at the binding site. The computed binding affinities for all the designed compounds ranges from -9.5 to -10.7 kcal/mol while the binding affinity of a referenced drug (Lumateperone) was calculated to be -9.7 kcal/mol (Supplementary Table DS2). This implies that almost all the designed compounds showed remarkable biochemical interactions

at the binding site of the protein target. Using the Discovery Studio Visualizer software, some of the designed compounds were visualized to examine the type of molecular interactions and amino acid residues responsible for the observed biochemical interactions at the binding site of the receptor. The result of molecular docking simulation for some designed compounds and a referenced drug (Lumateperone) is presented in Table 1. From the result (Table 1), the binding affinity for all the selected compounds range from -10.00 to -10.70 kcal/mol compared to Lumateperone (Referenced drug) with the binding energy of -9.70 kcal/mol. More so, the observed number of amino acid residues associated with hydrogen bonding and hydrophobic interactions were conspicuously higher in all the selected compounds with shorter hydrogen bond length (less than 3.0 Å) compared to Lumateperone with only one amino acid residue Phenylalanine (PHE319) linked to hydrogen bonding at a higher bond length of 3.52 Å.

Similarly, all the selected compounds revealed good biochemical interactions with the target protein by forming strong hydrogen bonding with a unique amino acid residue Arginine (ARG52) at different bond lengths. Compound 39g and 39m were discovered to possess the highest binding affinity (-10.70 and -10.6 kcal/mol respectively) with superior hydrophobic interactions at the binding site of the receptor in addition to amino acid residue Arginine (ARG52) connected to hydrogen bonding of shorter bond lengths and electrostatic interactions with amino acid residue Aspartic acid (ASP475). The outstanding biochemical interactions and higher binding affinity could be linked to the observed structural differences in the compounds (39g and 39m) due to electrophilic aromatic substitution (activating substituents $-\text{CH}_3$) at para-positions in the two compounds

(Supplementary Table DS2). Figure 3a and b show 2D and 3D interactions of the compounds 39g and 39m between the receptor while Fig. 3c depicts the docking pose of compound 39g showing hydrogen bonding and hydrophobic interactions with the protein target.

ADMET /Pharmacokinetics properties and drug-likeness predictions of the designed inhibitors of dopamine transporter

In some cases, the best-docked compounds are often considered as potential drug candidates based on their binding affinity; however, it is more important to evaluate some critical pharmacokinetic parameters or ADME T properties (absorption, distribution, metabolism, excretion, and toxicity) as most significant attributes by using appropriate steps in drug design, development, and discovery adventures [21, 22]. For these reasons, physicochemical parameters of all the designed compounds (Table 2) and ADMET properties of some selected compounds (Table 3) were carefully investigated by utilizing some online web-based software [15–17] and the obtained results were compared with a referenced drug (Lumateperone). The predicted physicochemical parameters which play a very important role in a molecule efficacy, safety, or metabolism were evaluated for all the designed compounds using Lipinski's rule of five (RO5) as reported in Table 2; the result showed that none of the designed compounds including the referenced drug (Lumateperone) violates Lipinski's rule of five (RO5). This suggests that all the designed inhibitors possessed good attributes of drug-like or pharmacological properties which could make them orally bioavailable [11, 13].

Likewise, the predicted ADMET properties for some selected compounds were presented in Table 3. From

Table 1 Types of interactions and amino acid residues between the target protein and some designed inhibitors

S/N	Binding affinity (kcal/mol)	Hydrogen bonding and amino acid residues with bond length (Å)	Hydrophobic interactions and amino acid residues	Other interactions and amino acid residues
39b	-10.5	ARG52 (2.38665) ARG52 (2.46439)	PHE319, PHE319 ILE116, ALA117, ALA117 ILE116, ILE483, PHE43, PHE325, ALA117, VAL120	ASP475 (Electrostatic)
39c	-10.2	ARG52 (2.28487) ARG52 (2.36122)	PHE319, PHE319, PHE325, ALA48, ALA117, VAL120	ASP46 (Electrostatic) PHE325 (Halogen)
39f	-10	ARG52 (2.42665) ARG52 (2.30477)	PHE319, PHE319, ALA117 ALA428, VAL327, ALA48, ARG52, ALA117, VAL120	–
39g	-10.7	ARG52(2.39222) ARG52 (2.52234)	PHE319, PHE319, THR315, GLN316, ALA117, ALA117 ALA428, VAL327, ILE116, PHE325, ALA117, VAL120	ASP475 (Electrostatic)
39m	-10.6	ARG52 (2.40652) ARG52 (2.45719)	PHE319, PHE319, PHE325 ALA117, ALA479, LE483, VAL327, PHE319, PHE325 ALA117, VAL120	ASP475 (Electrostatic)
Lumateperone (Referenced drug)	-9.7	PHE319 (3.52353)	PHE319, PHE325, ALA48 ARG52, PHE319, PHE319, ALA117, VAL120	PHE325 (Halogen)

Fig. 3 Panels **a** and **b** are 2D and 3D interactions of the compounds 39g and 39m between the target protein while panel **c** is the docking pose of compound 39g showing hydrogen bonding and hydrophobic interactions between the protein

ADMET predictions, the computed parameters for absorption properties revealed to be within the threshold values (%Human Intestinal absorption > 30%, Caco2 permeability > 0.90, and Skin Permeability logKp > -2.5) and all the selected compounds including the referenced drug were found to be P-glycoprotein II inhibitors. This implies that all the selected compounds possessed excellent pharmacological properties with good human intestinal absorption [23, 17]. Similarly, the predicted permeability values for both blood-brain barrier (BBB) and central nervous system (CNS) and other predicted properties (metabolic and excretion) suggested that all the selected compounds (Table 3) have good therapeutic potentials as

inhibitors of dopamine transporter [17]. A compound with BBB value of logBB greater than 0.3 is considered as highly absorbing to the central nervous system (CNS) [24, 17]. Luckily enough, all the selected compounds including the referenced drug have computed BBB value of logBB greater than 0.3 as reported in the table. Furthermore, the pharmacokinetic assessment of Cytochrome P450 inhibitions showed that all the selected compounds are non-inhibitors of CYP2C19, CYP2C9, and CYP3A4 but as inhibitors of CYP2D6 enzyme including the referenced drug.

In like manner, human intestinal absorption (HIA), the brain penetration, and medicinal properties for all

Table 2 Predicted physicochemical parameters of the designed inhibitors and a referenced drug (Lumateperone)

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	AlogP	WLOGP	Lipinski violations
39a	C20H21N4	317.41	3	1	2	47.26	1.94	1.03	0
39b	C20H19Cl2N4	386.3	3	1	2	47.26	3.25	2.34	0
39c	C20H20FN4	335.4	3	2	2	47.26	2.08	1.59	0
39d	C21H20F3N4	385.41	4	4	2	47.26	2.96	3.2	0
39e	C20H20N5O2	362.41	4	3	2	93.08	1.85	0.94	0
39f	C21H23N4	331.43	3	1	2	47.26	2.25	1.34	0
39g	C22H25N4	345.46	3	1	2	47.26	2.56	1.65	0
39h	C20H21N4O3	365.41	3	4	5	107.95	1.06	0.15	0
39i	C20H21N4O	333.41	3	2	3	67.49	1.65	0.74	0
39j	C21H23N4O	347.43	4	2	2	56.49	1.95	1.04	0
39k	C21H29N4	337.48	3	2	2	47.26	2.32	1.41	0
39l	C21H21N4O2	361.42	4	3	3	84.56	1.64	0.73	0
39m	C22H25N4	345.46	3	1	2	47.26	2.64	1.73	0
Lumateperone (referenced drug)	C24H28FN3O	393.5	5	3	0	26.79	3.92	3.19	0

the designed compounds and the standard drug (Lumateperone) were demonstrated by the BOILED Egg diagram as shown in Fig. 4 using Swiss ADME online software. The white region of the diagram (Fig. 4a) represents a region of the highest likelihood of being absorbed by the human gastrointestinal system while the yellow part (yolk) depicts the region of the highest probability to the brain penetration [25]. The diagram (Fig. 4a) revealed that most of the designed compounds

including the standard drug (Lumateperone) reside within the yellow region (yolk). This is suggesting that all designed compounds possessed a high probability to be absorbed by the human gastrointestinal tract and permeate into the brain to reach the target enzyme [13, 26]. Figure 4b represents oral bioavailability radar chart for the designed compound 39g which relied on the 6 important physicochemical properties as displayed on the chart. All the designed compounds and the

Table 3 Predicted ADME/pharmacokinetics properties of some designed inhibitors

		Some selected designed inhibitors					Referenced drug
Properties	Parameters	39b	39c	39f	39g	39m	Lumateperone
Absorption	Water solubility	− 3.761	− 3.362	− 3.386	− 3.483	− 3.363	− 4.03
	Caco2 permeability	0.999	1.25	1.013	1.011	1.02	1.175
	Intestinal absorption (% Absorbed)	92.854	94.5	95.056	94.854	94.608	93.538
	Skin Permeability	− 2.747	− 2.751	− 2.748	− 2.748	− 2.741	− 2.59
	P-glycoprotein II inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
Distribution	VDss (human)	0.912	0.726	0.902	0.935	0.915	1.404
	Fraction unbound (human)	0.241	0.251	0.238	0.225	0.237	0.071
	BBB permeability(log BB)	0.339	0.337	0.357	0.37	0.43	0.676
	CNS permeability	− 1.451	− 1.446	− 1.42	− 1.406	− 1.444	− 1.423
Metabolism	CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes	No
	CYP2C19 inhibitor	No	No	No	No	No	No
	CYP2C9 inhibitor	No	No	No	No	No	No
	CYP2D6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes
	CYP3A4 inhibitor	No	No	No	No	No	Yes
Excretion	Total clearance	1.084	1.297	1.35	1.427	1.275	1.095
	Renal OCT2 substrate	Yes	Yes	Yes	Yes	Yes	Yes

standard drug proved to exhibit a good physiochemical profile because their predicted parameters lied within the limit [14].

Predicting bioactivity score, in silico toxicology, and medicinal chemistry properties of some designed inhibitors of dopamine transporter

Bioactivity, toxicity, and medicinal chemistry properties of some designed compounds were further investigated using the online based web tools [18, 17]. Table 4 represents predicted bioactivity scores and medicinal chemistry properties while Table 5 shows the in silico toxicity profiles of some designed compounds. The bioactivity scores of G protein-coupled receptor (GPCR) ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, and enzyme inhibitor were evaluated for the selected compounds. A compound is considered to be more bioactive if the predicted value is greater than 0.00

(> 0), moderate active if the value lies between -0.5 and 0.00 while a compound is assumed to be non-active if the predicted value is less than -0.5 [27]. Remarkably, all the selected compounds including the referenced drug are very active to G protein-coupled receptor (GPCR) ligand because the predicted bioactive values are greater than 0.00 as reported in Table 4. Similarly, the predicted PAINS alerts (pan assay interference) and synthetic accessibility for medicinal chemistry properties were also examined. The results (Table 4) revealed that only two of the selected (39b and 39c) including the referenced drug have no alert (PAINS alert = 0) while the remaining compounds (39f, 39g, and 39m) displayed alerts of one (PAINS alert = 1). Thus, compounds 39b and 39c possessed no attributes that would provide false positive biological assays for the compounds [14]. Also, a synthetic accessibility or complexity score of 1–4 indicates easy, 4–7 medium, and 8–10 hard/difficult to

Table 4 Predicted bioactivity scores and medicinal chemistry of some designed inhibitors

		Predicted variables of some newly designed inhibitors					Referenced drug
Predicted properties	Predicted Parameters	39b	39c	39f	39g	39m	Lumateperone
Bioactivity score	GPCR ligand	0.24	0.25	0.2	0.19	0.21	0.32
	Ion channel modulator	0.21	0.2	0.14	0.12	0.16	-0.01
	Kinase inhibitor	0.18	0.23	0.15	0.16	0.1	-0.11
	Nuclear receptor ligand	0.02	0.06	0.01	0.02	0.04	-0.06
	Enzyme inhibitor	0.11	0.15	0.11	0.09	0.1	-0.08
Drug likeness	Lipinski violations	0	0	0	0	0	0
Medicinal chemistry	PAINS alerts	0	0	1	1	1	0
	Synthetic accessibility	2.67	2.55	2.64	2.77	3.16	3.92

Table 5 In silico toxicity profiles of some designed inhibitors

	Some newly designed inhibitors					Referenced drug
Toxicity properties	39b	39c	39f	39g	39m	Lumateperone
AMES toxicity	Yes	Yes	Yes	Yes	No	Yes
hERG I inhibitor	No	No	No	No	No	No
Carcinogenicity	No	No	No	No	No	No
Hepatotoxicity	No	Yes	Yes	Yes	No	Yes
Skin sensitization	No	No	No	No	No	No

synthesize [14, 15]. Interestingly, the synthetic accessibility scores for all the selected compounds and the referenced drug lied within the range of easy (i.e., 1–4) with their predicted values range from 2.55 to 3.92; this is a good indication that all the selected compounds would be very easy to synthesis in the laboratory [28].

In silico toxicity prediction of some selected inhibitors of dopamine transporter

Investigation and determination of intolerable toxicity properties of a drug candidate are extremely important prior to a drug candidate moves into clinical trials phase [14, 29]. The investigated toxicity properties of some selected compounds (Table 5) revealed that none of the compounds including the referenced drug is carcinogens with no toxicity tendency toward human ether-a-go-go related gene (hERG I) inhibitor or skin sensitization. Conversely, all the selected inhibitors including the referenced drug exhibited AMES toxicity except compound (39m) and also only compounds 39b and 39m that are not hepatotoxic (Table 5). Hence, the investigated toxicity profiles showed that most of the selected compounds would be safe with compound 39m to be safer as potential drug candidates.

Conclusion

In this current study, *in silico* drug design approach was employed to design 13 new inhibitors of dopamine transporter by selecting the molecule with serial number 39 from our previous work as the template compound because it exhibits good pharmacological attributes. Molecular docking simulation was performed to examine the binding modes and the amino acids residues responsible for the biochemical interaction at the active site of the protein target (receptor) of PDB code 4m48 and the ligands (designed inhibitors). The result of molecular docking revealed excellent biochemical interactions between the receptor and the designed inhibitors with major interactions that involved hydrogen bonding and hydrophobic interactions. Also, some of the designed inhibitors exhibited superior binding affinities range from -10.0 to -10.7 kcal/mol compared to the referenced drug (Lumateperone) with a binding affinity of -9.7

kcal/mol. To evaluate the drug-like profiles and pharmacological properties of the designed inhibitors, *in silico* pharmacokinetics properties and ADMET predictions were investigated. The computed physicochemical parameters showed that none of the designed inhibitors including the referenced drug violate Lipinski's rule of five, which means that all the designed inhibitors would be orally bioavailable and pharmacological active as potential drug candidates. Similarly, the ADMET properties of some designed inhibitors revealed that the selected inhibitors exhibit good absorption, distribution, metabolism, excretion properties, and none of the selected inhibitors is neither carcinogens nor toxic toward human ether-a-go-go related gene (hERG I) inhibitor or skin sensitization. Likewise, the BOILED-Egg graphics unveils all the designed inhibitors demonstrate a high probability to be absorbed by the human gastrointestinal tract and could easily permeate into the brain. The predicted bioactive parameters suggested that all the selected inhibitors would be very active as drug candidates. Furthermore, the synthetic accessibility scores for all the selected inhibitors and the referenced drug lied within the range of easy (i.e. between 1–4) because their predicted values lied between 2.55 to 3.92; thus, most of the designed inhibitors would be very easy to synthesize in the laboratory. Following these results, the designed inhibitors could be developed and optimized as novel therapeutic agents for the treatment of schizophrenia-related cognitive impairments and other neuropsychiatric disorders. However, further experimental investigations and clinical evaluations are recommended to examine the mechanisms of their actions and other pharmacological effects.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s43094-021-00198-3>.

Additional file 1: Supplementary Table DS2. 2D structures, molecular docking results and some physicochemical parameters of the designed inhibitors. **Supplementary Table SD1.**

Abbreviations

ADHD: Attention deficit hyperactivity disorder; BBB: Blood-brain barrier; CNS: Central nervous system; 2D: Two-dimensional structures; 3D: Three-dimensional structures; DA: Dopamine; DAT: Dopamine transporter; DFT: Density functional theory; GPCR: Group protein-coupled receptor; PDB: Protein data bank; ADMET: Absorption, distribution, metabolism, excretion, and toxicity; hERG: Human ether-a-go-go related gene; HIA: Human intestinal absorption; RO5: Rule of five; PAINS: Pan assay interference; SBDD: Structure-based drug design

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Authors' contributions

AU and OSB conceived, analyzed and interpreted the results. GAS, SU, and OSB performed the computational study and wrote the paper. All authors have read and approved the manuscript.

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