Int. J. Pharm. Investigation, 2022; 12(4) : 418-422

Original Article

In silico Toxicity Prediction on Novel Antiobesity Drug Using Cheminformatics Approaches

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ABSTRACT

Background: Obesity is a major problem that many individuals suffer presently. Using *in silico* Tools and Servers, we propose to build a novel chemical drug and validate its oral toxicity effect. Our strategy entails first picking an existing anti-obesity drug *2-methyl-1-phenylpropan-2-amine* as well as an agent which is then coupled with the existing drug *lithium; bis(trimethylsilyl)* utilizing cheminformatics software and tools. **Materials and Methods:** Pharmacokinetic studies of the compounds were analyzed to show Lipinski's rules via *in silico* methods of Molinspiration. The drug likeness calculations were also carried out in Molinspiration analyses. Some toxicity risk parameters were quantified using ProTox II. The results will be thoroughly examined, including calculations of the intended compound's molecular characteristics and bioactivity. **Results:** The calculations obtained through Molinspiration show that it has a good drug likeness score with the LogP value of 2.34 and TPSA valued at 26.02. The toxicity prediction was done with the help of the website ProTox II, the website was used to examine toxicology in organisms, organs, cells, and genes, as well as molecular mechanisms of toxicity. The drug compound according to the projected LD_{50} values, it is non-toxic and safe for various organs and pathways. The mechanism of toxicity of the compound was obtained as class III. The drug has good Lipophilicity and acceptable ADMET properties; The projected developed drug compound demonstrates that the intended molecule has no hazardous effect. Advanced molecular imaging technologies will be used to visualise the structures in 3D. **Conclusion:** *In silico* study indicates that the proposed chemical compounds had no negative effects and has the potential to be used as an obesity therapy agent. This medicine can also be utilised to conduct more docking research on human protein targets associated with obesity.

Keywords: Drug designing, Oral toxicity, 3D structure prediction.

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DOI: 10.5530/ijpi.2022.4.72

INTRODUCTION

Obesity, a severe public health issue with a high prevalence, is associated with increased mortality and morbidity, including an increased risk of type 2 diabetes and cardiovascular disease, physical limitations, sleep apnea, and a lower quality of life. Around 30% of the global population is overweight or obese. According to projections, the prevalence of extreme obesity would reach 11% per cent in 2030, more than doubling the current rate. Obese patients should adhere to current treatment guidelines, which include lifestyle adjustments, increased physical activity, and calorie restriction. If these therapies fail, medication may be used. Over the years, many drugs have been used to treat obesity. However, the majority of anti-obesity medications that were approved and sold have now been removed due to substantial side effects.[1] Anti-obesity medications affect many targets in the central nervous system or peripheral tissues, improving regulatory and metabolic abnormalities that contribute to obesity development. Pharmacotherapy, as a key component of an aggressive obesity intervention strategy, could be utilised to avoid bariatric surgery in moderately to severely obese people who have been diagnosed with obesity.[2] Computational predictions provide numerous benefits in the drug development process. Exploring whether existing medications could be used to treat ailments other than those for which they were originally intended is one technique to avoid the time-consuming drug discovery process.[3] The increasing digitalization of data, which may be obtained from a wide range of sources ranging from clinical pharmacology to cheminformatics-driven databases, has altered biomedical discovery. Publicly available resources such as biological, physicochemical, and clinical data can be merged to build a comprehensive map of signalling pathways and pharmacological modes of action associated with drug candidates. Recent improvements in computer-aided data mining have facilitated studies of 'big data' techniques, as well as the discovery of new indications for already approved medications has hastened. Attempts to minimize pharmaceutical Research and development timeframes are frequently associated with increased risk. Drug repositioning, on the other hand, provides a way out of this quandary.[4] Drug repositioning is a topic of great interest in the international drug development community (i.e. identifying second or additional therapeutic indications for established pharmaceuticals).[5] This technique, which has already produced several intriguing candidates, has the ability to increase the drug development process and reach previously unreached patient populations, such as those suffering from uncommon diseases.[6]

The Food and Drug Administration (FDA) has approved *2-methyl-1-phenylpropan-2-amine* as an appetite suppressant for the treatment of obesity. It has already been approved for short-term usage of less than 12 weeks to combat obesity by suppressing appetite or limiting fat absorption decreases appetite by raising epinephrine secretion in the hypothalamus.[7] *2-methyl-1-phenylpropan-2-amine* has been proven to considerably reduce body weight and improve cardiovascular and metabolic markers such as blood pressure, cholesterol, and HbA_{1C}.[8] Lithium is a basic light metal that, due to its strong intrinsic reactivity, is only employed as a lithium salt. Despite its basic structure, *lithium;*

bis (trimethylsilyl) azanide has a wide range of biological effects. It also has a great therapeutic impact in the prevention of manic depression and is being studied for its potential function in reducing violent and self-mutilating behavior.[9] It also helps treat manic depression (similar to mania, but less severe)bipolar disorder, in which the mood swings of a person fall between feeling very high (mania) and very low (depression) frequently when other medications have failed to help depression.[10] The combination of diverse *in silico* drug-discovery methodologies, has resulted in numerous examples of effective medication repositioning.[4] Although lifestyle changes remain the cornerstone of obesity care, pharmacologic medications may be a useful adjunct for patients with co-morbidities who do not react effectively to diet and exercise.[7]

MATERIALS AND METHODS

Compound Selection

A vast array of online resources for biological data and information is offered by the National Center for Biotechnology Information (NCBI). PubChem is a public database for chemical structures and the outcomes of biological tests. One of the largest collections of freely accessible chemical information may is on PubChem.[11] The target compound, (*2-methyl-1-phenylpropan-2-amine*) was selected using NCBI-PubChem[12] chemical compound database to apply to chemical repurposing techniques.

Drug designing and validation: According to Lipinski's rule of five, an orally active drug should typically have no more than five hydrogen bond donors (OH and NH groups), no more than ten hydrogen bond acceptors (notably N and O), a molecular weight under 500 g/mol, a partition coefficient log P of no more than five, and no more than four violations. Using a software programme called Molinspiration a Physicochemical Properties Calculator, the physical and chemical properties of the two medicinal compounds were examined (www. molinspiration.com). Partition coefficient (log P), molecular weight, number of heavy atoms, number of hydrogen donors, number of hydrogen acceptors, and number of violations are the properties that are calculated.[13] The drug compound, (*2-methyl-1-phenylpropan-2-amine*) was combined with (*lithium;bis(trimethylsilyl)azanide*) using Molinspiration.[14] The canonical SMILES of the drug compound was converted into 3D structure using Online SMILES Translator and Structure File Generator in PDB 3D form. The analysis's final output was shown visually was viewed with the help of Discovery Studio Software.[15]

Oral toxicity studies: The predicted de novo drug was validated using *in silico* Oral Toxicity Study software ProTox II. According to Drwal., *et al.* parameters such rat oral acute toxicity with a special focus on median lethal dosage (LD_{50}) as mg/Kg, organ toxicity, particularly Hepatotoxicity, Immunotoxicity, and genetic toxicity, an *in-silico* analysis was carried out. Cytotoxicity, Mutagenicity, and Carcinogenicity outcomes, as well as nuclear receptor signaling Stress response pathways (such as AhR, AR, AR-LBD, ER, ER-LBD.[16]

RESULTS

SMILES format of *2-methyl-1-phenylpropan-2-amine and lithium;bis (trimethylsilyl) azanide* were obtained from NCBI PubChem, and the resulting structure's molecular characteristics and bioactivity were validated using Molinspiration software. In this *in silico* work, the predicted chemical compounds were completely validated using Molinspiration for finding out the structural drug affinity scores. The chemical compounds were examined to see if they satisfied the drug-likeness requirements. Drug similarity features Lipinski's rule of 5 and Molinspiration were used to validate values such as the number of hydrogen acceptors 10, number of hydrogen donors 5, molecular weight 500 Da, and partition coefficient log $P > 5$. Lipophilicity (LogP value) and polar surface area are two important factors in predicting oral bioavailability of pharmaceutical drugs (TPSA value).[13] Drug likeness score of the novel structure shows Molecular weight as149.24g/mol as shown in Table 1, and the calculated LogP value is 2.34 which is an acceptable range for a good drug. The predicted value of our drug compound is 26.02 which shows it has a good TPSA score as shown in Table 3. It also has zero violations. The predicted drug compound follows all of Lipinski's rule of five as seen in Figure 1.

Based on chemical similarities to dangerous chemicals and trained machine learning models, the acute toxicity class and several endpoints are determined for an input substance. ProTox-II envisions itself as a completely free computational platform. Toxicologists, regulatory agencies, computational chemists, and medicinal chemists can use this platform to predict toxicity *in silico.*[17] ProTox web server provides a simple interface, and the only prerequisite is the 2D structure of the molecule whose toxicity is to be predicted.[16] The evaluation is used to predict oral toxicity of 2D similarities and the recognition of dangerous fragments. In addition to the predicted LD_{50} in mg/kg, the input component is classified into a hazard class ranging from I to VI using the worldwide harmonised method of chemical labelling classification.[18] The accuracy of prediction generated from cross-validation findings is also provided.

According to Drwal., *et al.*[16] Class I is death after swallowing ($LD_{50} \leq 5$); Class II is death after swallowing ($5<LD_{50}\leq 50$); Class III is toxic after swallowing ($50<LD_{50}\leq 300$); Class IV is harmful after swallowing ($300<LD_{50}\leq 2000$); Class V is potentially harmful after swallowing ($2000<LD_{50}\leq 5000$); and Class VI is non-toxic ($LD_{50}>5000$).

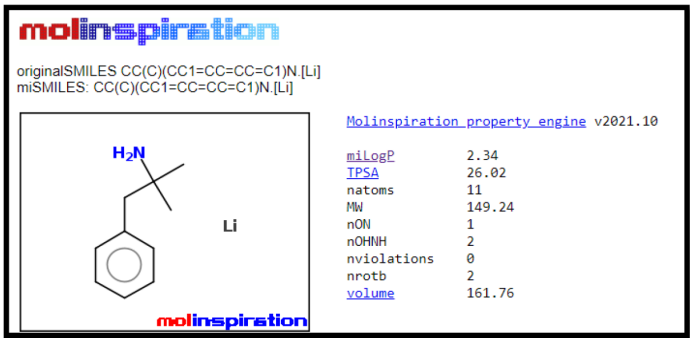


Figure 1: Molinspiration Interface – The software analyses the function and impact of substituents on bioactivity and highlight negative structural factors in actual drug design: such as LogP value, TPSA (Total Polar Surface Area) and Molecular Weight.

Table 1: Molecular structure, compound CID and molecular weight of the selected drug.

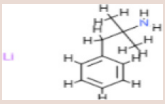
IUPAC name	Molecular structure	Molecular Weight
(3Z,5Z,7Z)-1,1-Dimethyl-3,5,7-octatrienylamine		149.24g/mol,

Table 2: Prediction of oral acute toxicity, class, average similarity and prediction accuracy.

Predicted LD_{50}:	Predicted Toxicity	Average similarity:	Prediction accuracy:
160mg/kg	Class: 3	96.43%	72.9%

Table 3: ADMET/physicochemical properties measured for the drug compound.

Name	CC(C)(CC1=CC=CC=C1)N.[Li]
Molweight	157.18
Number of hydrogen bond acceptors	18
Number of hydrogen bond donors	2
Number of atoms	28
Number of bonds	27
Number of rotable bonds	2
Molecular refractivity	49.69
Topological Polar Surface Area	26.02
Octanol/water partition coefficient (log P)	2.78

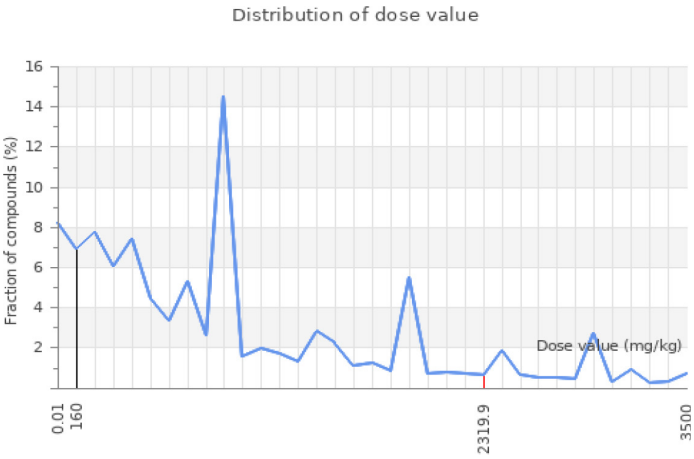


Figure 2: Oral toxicity prediction - Graphical presentation of the predicted dose value of the drug compound the above graph highlights that the designed compound is devoid of toxic effects. It also shows the daily dosage value of the drug.

Figure 2 The above Picture shows the Predicted Toxicity class of the Drug and also its prediction accuracy with the already existing drugs.

The ProTox-II server showed that the two compounds are predicted to have LD_{50} values ranging from LD_{50}: 160mg/kg and the graphical accuracy of prediction 72.9%% as shown in Figure 2. Class 3 is the predicted toxicity of the drug compound as shown in Table 2.

The predictions of organ toxicity with special reference to hepatotoxicity were examined, and liver toxicity was found to be inactive with a probability score of 0.95. Toxicity endpoints of carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity are inactive, with likelihood scores of 0.71, 0.99, 0.89, and 0.73, respectively. Several factors, including AhR, AR, AR-LBD, Aro, ER, ER-LBD, and PPAR-Gamma, were predicted inactive for Tox21- Nuclear receptor signaling pathways, with likelihood scores of 0.97, 0.99,0.99,0.88,0.98,0.96. Tox21-stress response pathway characteristics such as nrf2/ARE, HSE, MMP, p53, and ATAD5 were predicted and are inactive for examined substances with probability values of 0.88,0.88,0.93,0.97, and 0.08. The probability scores are all predicted under 1 score indicating that the drug would not induce any toxic effect in human beings and is safe to be administered.

Table 4: Prediction of Organ toxicity, Toxicity endpoints, Tox21 - Nuclear receptor signaling pathways, Tox 21 - Stress response pathways.

Toxicity Model Report				
Classification	Target	Shorthand	Prediction	Probability
Organ toxicity	Hepatotoxicity	Dili	Inactive	0.95
Toxicity end points	Carcinogenicity	carcino	Inactive	0.71
Toxicity endpoints	Immunotoxicity	Immuno	Inactive	0.99
Toxicity endpoints	Mutagenicity	mutagen	Inactive	0.89
Toxicity endpoints	Cytotoxicity	Cyto	Inactive	0.73
Tox21-Nuclear receptor signalling pathways	Aryl hydrocarbon Receptor (AhR)	nr_ahr	Inactive	0.97
Tox21-Nuclear receptor signalling pathways	Androgen Receptor (AR)	nr_ar	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Androgen Receptor Ligand Binding Domain (AR-LBD)	nr_ar_lbd	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Aromatase	nr_ aromatase	Inactive	0.99
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Alpha (ER)	nr_er	Inactive	0.88
Tox21-Nuclear receptor signalling pathways	Estrogen Receptor Ligand Binding Domain (ER-LBD)	nr_er_lbd	Inactive	0.98
Tox21-Nuclear receptor signalling pathways	Peroxisome Proliferator-Activated Receptor Gamma (PPAR-Gamma)	nr_ppar_ gamma	Inactive	0.96
Tox21-Stress response pathways	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	sr_are	Inactive	0.88
Tox21-Stress response pathways	Heat shock factor response element (HSE)	sr_hse	Inactive	0.88
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	sr_mmp	Inactive	0.93
Tox21-Stress response pathways	Phosphoprotein (Tumor Suppressor) p53	sr_p53	Inactive	0.97
Tox21-Stress response pathways	ATPase family AAA domain-containing protein 5 (ATAD5)	sr_atad5	Inactive	0.98

DISCUSSION

To acquire parameters such as Mi LogP, TPSA, and drug similarity, web-based programme called Molinspiration was employed. Mi LogP is calculated using Molinspiration's methodology as a total of fragment-based contributions and corrective factors. The log P parameter is used to determine cell membrane permeability. TPSA is connected to the compound's hydrogen bonding potential.[19] Lipophilicity (c LogP

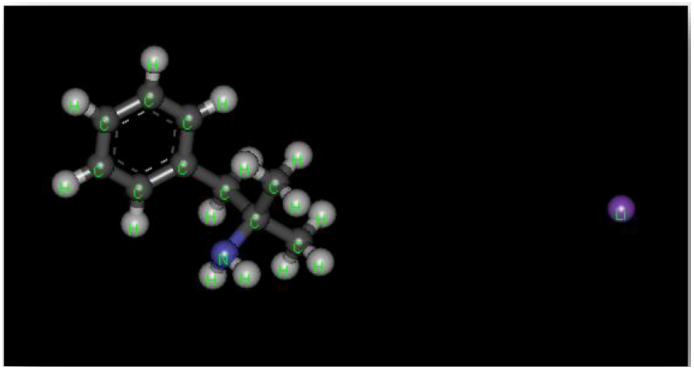


Figure 3: The designed compounds 2-methyl-1-phenylpropan-2-amine) and (lithium;bis(trimethylsilyl)azanide as visualized using Discovery studio software.Grey represents Carbon, White represents Hydrogen and Blur represents Nitrogen.

value) and polar surface area (TPSA value) are two key parameters for predicting drug molecules per oral bioavailability. The Log *P* value of 2.34 and TPSA value of 26.02 shows that our drug has good parameter scores.

Numerous weight-loss drugs have been created, and a few of them have been approved for the treatment of obesity. Several techniques to preventing and treating the rising prevalence of obesity and related disorders have been explored. One such strategy is the use of appetite suppressing medicines, which are often used in many nations to reduce energy intake.[20] Phentermine hydrochloride (2-methyl-1-phenylpropan-2-amine) is a sympathomimetic amine that was licensed for short-term obesity therapy by the US Food and Drug Administration (FDA) in 1959 at a dose range of up to 37.5 mg/day. 2-methyl-1-phenylpropan-2-amine increases hypothalamic norepinephrine release while having no effect on serotonin.[21] It has a significant history of weight loss effectiveness, but with a clinically moderate effect. As with most obesity medications, the clinical response to 2-methyl-1-phenylpropan-2-amine can be extremely variable, ranging from very mild to profound, with associated favourable effects on obesity-related co morbidities such as blood pressure, glycemic and lipid profiles.[22] lithium;bis(trimethylsilyl) Azanide has anti-stress characteristics and is widely considered to be the most successful augmentation medicine in the treatment of resistant depression. Its anti-suicidal properties are extensively documented in various studies.[23] The suggested obesity treatment strategy is lifestyle modification, which includes reducing calorie intake and increasing physical exercise. However, the results of such an approach have been poor.

The physiochemical qualities of existing small organic pharmaceuticals or therapeutic prospects have been frequently utilised to screen compounds with undesirable qualities, notably those with poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, should be avoided.[24] Druglikeness scores can be used to remove compounds that are expected to fail in clinical trials ahead of time, which is significant for increasing success rates and lowering the economic expenses of medication development[25] Our drug combination of 2-methyl-1-phenylpropan-2-amine and lithium;bis(trimethylsilyl) azanide shows good Drug likeness score with zero number of violations as projected by Lipinski's rule of five in molinspiration (Figure 1). The designed drug belongs to toxicity class 3 i.e., they are slightly toxic. Study by Kouj., *et al.* shows that lithium;bis(trimethylsilyl)azanide toxicity is essentially classified as acute (e.g., induced by overdosing), acute-on-chronic (e.g., when a patient with nephrogenic diabetes insipidus due to chronic lithium toxicity) and chronic toxicity. lithium;bis(trimethylsilyl) azanide toxicity can be avoided by properly evaluating serum lithium concentrations, the importance of doing appropriate therapeutic medication monitoring has been highlighted physicians who prescribe lithium should monitor serum lithium concentrations.[26] Animals were involved in toxicity studies for the first time in 1920, when J. W. Trevan proposed using the 50 percent lethal dosage (LD_{50}) test to establish the lethal dose of specific drugs.[27] The LD_{50} value was predicted to be 160mg/kg. In the screening toxicological report, the prediction is shown. Toxicity endpoints of carcinogenicity, immunotoxicity, mutagenicity, cytotoxicity, and Tox21 - Nuclear receptor signaling pathways, Tox 21 - Stress response pathways endpoints were revealed to be inactive (Table 4) which demonstrates that the combination of 2-methyl-1-phenylpropan-2-amine and lithium;bis(trimethylsilyl)azanide produced good toxicity report showing no harm to the Organs or causing mutations. The probability scores are all predicted under 1 score indicating that the drug would not induce any toxic effect in human beings and is safe to be administered.

Hence the predicted chemical structure has augmented efficiency to inhibit the obesity protein target and give good results with less toxicity. The oral toxicity prediction performed during our study elucidated that the predicted denovo compound is eligible for treating human targets. The current study detects a limited number of dangerous or less toxic substances, which can be validated in an experimental study by additional research. The 3D structure of the two drugs can be seen as visualized by Discovery studio software in Figure 3.

CONCLUSION

Increasing the efficiency of the existing drug using Chemical Re-purposing Techniques is a current trend in the field of Cheminformatics. Our study showed that the efficiency of the existing molecule, *2-methyl-1-phenylpropan-2-amine* increased when combined with *lithium;bis(trimethylsilyl)azanide*. The designed drug, when checked with advanced *in silico* Toxicity protocols, showed eligibility for an efficient drug. Drug-likeness and ADMET investigations validated the potential biological identified compounds and raised interest in developing them as good candidates. The synergistic effect was seen on the two drug compounds. ProTox II web server enables faster screening of a huge number of chemicals and per compound within a minute, without incurring financial costs or requiring animal testing. This study suggests additional experimental analysis to confirm the current prediction. Hence, we finally conclude that the predicted chemical compound is a potential therapeutic agent for various Obesity disorders.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Article History: Submission Date : 09-06-2022; Revised Date : 02-07-2022; Acceptance Date : 12-08-2022.
Cite this article: Zashumo KJ, Mathivanan V, Grace H, Leelavathi D. *In silico* Toxicity Prediction on Novel Antiobesity Drug Using Cheminformatics Approaches. Int. J. Pharm. Investigation. 2022;12(4):418-22.