



RESEARCH ARTICLE

Developing potential drugs for insomnia through computational analysis

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Abstract

Introduction: Insomnia is a condition that affects the quality of life of an individual. It is associated with a lack of sleep or interrupted sleep. If not managed, insomnia may end up causing conditions such as obesity, heart conditions, hypertension, and mental disorders. Lack of sleep is also associated with an increased risk of Alzheimer's disease. There is, therefore, a need to develop a drug that manages insomnia with desirable clinical outcomes

Methods: The canonical smiles of Zolpidem, Suvorexant, Ramelteon, and Triazolam were obtained from PubChem. The study used the online tool SwissSimilarity to identify structural analogs for Zolpidem, Suvorexant, Ramelteon, and Triazolam. The canonical smiles were copied to PubChem Sketcher were converted to a 2- dimensional (2D) format. The Avogadro was used to optimize the ligands. The respective receptors were obtained from the Protein Data Bank. Chimera was used to prepare the receptor and the docking, using AutoDock Vina. SwissADME and Protox server was used in the determination of the pharmacokinetics and toxicity profiles, respectively.

Results: Docking scores, pharmacokinetics, and toxicity profiles of the analogs were recorded. Nine structural analogs from the ZINC database (ZINC000004222622, ZINC000003981996, ZINC000003825731, ZINC000000000903, ZINC000039247014, ZINC000010152022, ZINC000000347721, ZINC000065743121, ZINC000022054496) were found to have a better docking score, blood brain barrier permeability, Lipinski's violations, synthesizability index, gastrointestinal tract absorption, p-glycoprotein substrate metabolism LD50 compared to the parent drug molecules. All the nine molecules had good synthesizability index, gastrointestinal absorption and zero

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Lipinski violations indicating good oral availability.

Conclusions: Ramelteon analogs ZINC000004222622, ZINC000003981996, and ZINC000003825731, Triazolam drug-like molecules, ZINC000000000903, ZINC000039247014, ZINC000010152022, and ZINC000000347721 and Zolpidem drug-like molecules ZINC000065743121 and ZINC000022054496 were identified as the best compound bases on the pharmacokinetic binding to the respective receptors and toxicity profiles.

Keywords

Insomnia , Computational analysis , MTR – Melatonin Receptor , CYP450 - Cytochrome P450, GABA - Gamma-Aminobutyric Acid , FDA- Food and Drug Administration CNS -Central Nervous System.



This article is included in the **Bioinformatics** gateway.

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Introduction

Sleep is considered an essential component of both physical and mental health. Sleep is especially important in the development of the immune system restoration, regulation of emotions, support of cognitive function in human learning, and brain recuperation processes.¹ It is recommended that adults sleep for about seven to eight hours a day while in infants, sleeping hours may be increased up to between 14 and 17 hours a day.² Sleep deprivation, is associated with physical and mental disorders that may eventually lead to conditions such as weight gain, heart disease, and diabetes.³ Lack of sleep has also been associated with suicidal ideation.^{2,3} Sleep also helps with the clearance of toxic materials from the brain through the glymphatic system.⁴ This system works 20 folds during sleep than when an individual is awake. Alzheimer's is believed to be caused by toxic materials such as amyloid and tau proteins.⁴ Lack of adequate sleep is considered a risk factor for Alzheimer's disease.⁴

Insomnia is a condition in which an individual complains of a lack of sleep. These individuals have difficulty in the initiation and maintenance of sleep.⁵ Insomnia is a condition that affects an individual's psychological, physical, biological, and social well-being.⁶ About one-third of the adult population presents with a symptom of insomnia.⁷ It is more prevalent in women compared to men.⁸ Individuals who are prone to conditions such as anxiety and those taking certain medication such as antiretrovirals may be disposed of this condition.⁸ Insomnia can lead to conditions such as depression, coronary heart disease, hypertension, diabetes, and severe migraine.⁸ Insomnia has also been indicated as a major cause of atrial fibrillation in postmenopausal women.⁹

Insomnia can be broadly classified into chronic and acute insomnia.⁷ Acute insomnia is short-term, it can be caused by factors such as a change in environment or even stress related and may only last for days.⁷ On the other hand, chronic insomnia is described as the lack of sleep for more than three weeks.⁷ In chronic insomnia, may predispose an individual to psychiatric disorders such as anxiety and depression.¹⁰ Symptoms may differ from children to adults with adults more likely to experience more problems related to problem maintaining sleep than problem associated to starting sleep.

Environmental factors such as exposure to stressors such as light, poor quality of air, and noise are common causes of insomnia.¹¹ In the world of industrialization, people are migrating from rural areas to cities or towns for employment and personal reasons.¹² With every country aiming to become industrialized, sound air and light pollution would be a common manifestation.¹² The extremities of weather conditions may cause serious sleep-related disorders. This may be a result of interference with the normal rhythm that controls the sleep cycle.¹³ The current management of insomnia is based on nonpharmacological and pharmacological interventions. These therapies may be limited based on the tolerance, side effects and the suitability of the given drug for the patient.¹⁴

Prescription drugs such as antidepressants, stimulants, bronchodilators such as theophylline, steroids, diuretics¹⁵ and some antiretroviral such as efavirenz,¹⁶ may present with insomnia as a side effect. The regimen may be designed for twice or three times daily. The patient may need to take the medication every eight hours or 12 hours respectively within a 24-hour interval which may end up interfering with sleep patterns.¹⁵ Short acting benzodiazepines and hypnotics are also associated with rebound insomnia as a result of chronic use of the drugs.¹⁷

Pharmacological treatment of insomnia is aimed at improving the quality of sleep. Currently, the European sleep research society has approved guidelines that are used in the treatment of insomnia.¹⁸ The classes of drugs in the treatment of insomnia include melatonin receptor agonists, benzodiazepine receptor agonists, anti-depressants and some first-generation antihistamines.¹⁸

Benzodiazepine receptor agonists work by binding to the gamma-aminobutyric acid (GABA) receptor. The drugs act as positive allosteric modulators increasing the inward flow of chloride ions. This causes depression of the central nervous system causing sleep.¹⁹ The GABBA receptor agonists include both benzodiazepines and the non-benzodiazepines, such as the Z-compounds; Zolpidem and Zaleplon. Quazepam is an The Food and Drug Administration (FDA)-approved benzodiazepine used in the treatment of chronic insomnia. Triazolam, Flurazepam, and Temazepam have been indicated in the treatment of sleep-onset insomnia. Temazepam is the most prescribed drug for insomnia.^{20,21} Benzodiazepines are common for abuse. For example, Flurazepam has been used in crime for stupefying people.¹⁹ These drugs are also associated with tolerance and these drugs are not advised to be given to patients during pregnancy.¹⁹

Zolpidem has been associated with increased orthostatic hypotension in hospitalized patients, confusion, dizziness, suicidal ideation, rebound insomnia, and daytime sedation.²² It has been categorized in class C. Women in pregnancy are at risk of getting children with a low weight if they take Zolpidem during pregnancy.^{22,23}

Zaleplon is available as intravenous and oral preparations. Has the same side effects as zolpidem but has high incidences of hallucination and hypersensitivity^{22,23} The dose should also be decreased in the elderly because of their slow metabolism.²³

Antihistamine drugs are also another group of drugs used in the treatment of insomnia. The commonly used drugs include diphenylamine, doxylamine, and chlorpheniramine. They work by H1 receptor antagonism.²⁰ Their application utilizes the side effect associated with first generations of antihistamines which is sedation. Although they are usually sold over the counter, these drugs are characterized by rapid tolerance and possible anticholinergic side effects such as urinary retention dry mouth, confusion, and constipation which may become worse as the dose is increased to obtain the desired effects.²³ Their rapid availability over the counter commonly allows misuse. They are not preferred as first line treatment because they are contraindicated in patients with concurrent medical conditions glaucoma, asthma, and bladder obstruction.²⁴

Melatonin receptor agonists are drugs that work by the activation of the melatonin receptors M1 and M2. Melatonin regulates the sleep-wake cycle and at the same time reproduction activities and growth that commonly happens during sleep.²⁵ The common drugs that have been used include Ramelteon and Melatonin. Others include Tasimelteon and agomelatine. Melatonin is rarely used because of the short duration of action.²⁴

Ramelteon binds to MTR1 and MTR2, this causes a reduction sleep-onset latency, slightly improve sleep efficiency and increase total sleep time.^{24,26} Although ramelteon has been described as not tending to cause tolerance and rebound insomnia, clinical trials did prove that ramelteon dosage at 8 milligrams may cause, retropharyngeal pain, depression galactorrhea, decreased libido, upper respiratory tract infections and exacerbated insomnia. This drug is also expensive and hence not readily available.²⁶

Orexin receptor antagonist suvorexant approved in the year 2014, and was first marketed for insomnia.²⁰ Orexin receptor antagonists influence patient wakefulness and sleep. The antagonism of this receptor is associated with decreased wakefulness.²⁰ Although the medication does not need adjustment in patients with renal and hepatic insufficiencies, the drug is a category c medication. The adverse effects are limited as compared to other drugs used for insomnia but the drug is comparatively costly.²⁷

Doxepin is a tricyclic anti-depressant. It has been approved for the treatment of insomnia based on its activity on the H1 receptor is associated improvement of sleep latency.²⁰ It is a category C drug, with wide metabolism by the CYP2D6 and CYP2C19 enzymes. This property makes the administration of the drug hard with drugs that are inhibitors or inducers of those enzymes. Patients on doxepin may also experience allergic reactions.²⁸

Drug development involves analyzing vast libraries of compounds for their capacity to bind to a target protein. Preclinical testing, clinical trials, and identifying possible drug candidates are all steps in drug discovery and development.²⁹ Virtual screening is a computational technique used in drug development to find prospective therapeutic candidates. Ligand-based virtual screening is a subset of virtual screening that looks for novel ligands with similar binding properties using the 3D structure of an existing ligand.^{30,31} This technique has been used in the discovery of drugs that are currently or being studied in use in conditions such as COVID-19, cancer, and Alzheimer's disease.^{4,32} There is a gap in drug development through virtual screening in the development of insomnia drugs.³³

This study works in line with the currently ongoing research for a drug that is most effective in the treatment of insomnia. Zolpidem, suvorexant, ramelteon, and triazolam are analyzed. The aim is to get a drug that can be given to patients in such a way the patient could continue their current medications and at the same time have a good sleep hence, the drug should have very few interactions with the drugs in concurrent use. The drugs should be effective in the lowest concentration given to patients suffering from insomnia. This means the drugs should then have a better docking score compared to the current drugs used. The drugs should also have minimal side effects. The drug should also be effective in insomnia related to environmental changes. It should also be able to treat the condition completely and treat the patient with the fewest doses possible. The drug should also be safe to use during pregnancy. In general, we aim at getting a drug with better pharmacokinetics pharmacodynamics, and pharmacogenomics compared to the current drugs in use.

Methods

Retrieving the drug models

The canonical smiles of Suvorexant, Ramelteon, Zolpidem and Triazolam were individually searched and copied from PubChem online library (RRID:SCR_004284). The Canonical smiles obtained were pasted into the SwissSimilarity search bar. The class of drugs was set as commercial. The combined, Zinc-Drug like was selected with combines 2D and

3D. This was used as a query to generate similar molecular structures from the ZINC database through ligand based virtual screening. The red search button of the page was clicked to allow the query to begin, which took a few minutes to generate the final results. The generated results were downloaded and saved as an excel file.

Retrieving and preparation of the retrieving the protein models

The receptors were obtained from the [protein data bank](#) GABA-A receptor, Orexin receptor, and melatonin receptor were individually searched on [protein data bank](#) (RRID:SCR_012820) search bar and downloaded using the 'Download file' option available on the Protein Data Bank. The receptors were saved in the project directory. The receptors were "Cleaned" by removing all non-standard compounds by clicking on the "Select" option on chimera, then selecting all non-standard compounds, and finally deleting using the 'Actions' option on chimera software (RRID: SCR_004097).

Ligand preparation

The first 20 canonical smiles of each parent drug compound, were pasted in the search bar at [PubChem Sketcher](#) and enter button clicked to allow the generation of a to a 2D molecular structure. The generated structure was saved as "All files" format by clicking the export button present in [PubChem Sketcher](#) to the Project folder in the desktop. [PubChem Sketcher](#) was refreshed before the next canonical smile was inserted for the next query.

The Avogadro software (RRID: SCR_011958) was opened. The software was used to open the 2D files which were generated from the project folder in the Desktop. The 2D structures of the analogs and the drug compounds were converted to 3D structures automatically, by opening them individually, and clicking "yes" on the prompt by Avogadro to generate a 3D model of the 2D structure that was being opened. The 3D generated structure was optimized by clicking the auto optimization option provided in Avogadro. The settings were set to MMF94s force field, and fixed atoms movable, on the Algorithm settings. The start button was clicked and the structure was allowed to form the most stable conformation. The most stable conformation was determined when the Auto optimization energy became constant. The resulting structure was saved as a.mol file to be used in the next step in chimera.

The optimized ligands were then opened and minimized (to add charges and hydrogen) using the Chimera software. This was done by clicking tools, then structure editing, using the steric only settings and then Gasteiger as the other residues, in the setting section. The resulting minimized structure was saved in the project folder to for the next process of docking

Docking

The minimized ligands and the cleaned receptor were opened simultaneously in Chimera. The docking process was initiated where the ligands were docked with their respective receptors using the chimera software, embedded with AutoDock Vina (RRID: SCR_011958). The docked compounds with better docking scores than the parent compounds were afterwards analyzed using the Biovia Discovery studio (RRID: SCR_01565) to determine the interaction between the receptor and the ligand using the 2D and 3D models of the complexes.

Determination of the pharmacokinetic properties

The canonical smiles of compound found to have a better docking score than the parent compounds were pasted on [SwissADME](#) online tool search box and queried to determine possible pharmacokinetic properties. The results were saved as an excel file. The results contained parameters such as Blood brain barrier permeability, the Lipinski's violations, Gastrointestinal tract absorption, p-glycoprotein substrate, metabolism and synthesizability index which were used in the study.

Determination of the toxicity profile

The [Protox](#) online tool was used to predict the toxicities of the compounds. The canonical smiles of the parent drug compounds and the analogues were pasted individually on the search bar in the Protox server and queried for the toxicity profiles prediction. The parameters that were analyzed included the individual toxicities based on the LD50 were automatically generated with the [Protox](#) which was directly obtained from the search results.

Data presentation

Tables of the specific analogues ([Table 1](#), [Table 2](#), [Table 3](#) and [Table 4](#)) were recorded showing various data obtained. The data include the docking scores, the pharmacokinetic profile, and the toxicities profile.

Table 1. Suvorexant and its analogs pharmacodynamic and toxicity data.

Compound	Docking scores	LD50 (mg/kg)	Blood brain barrier permeant	Gastrointestinal absorption	P-glycoprotein substrate	Metabolism	Lipinski violations	Synthetic accessibility
Suvorexant	-9.2	1000	No	High	No	CYP (2C19,2C9, 2C19)	0	3.97
ZINC000049036447	-10.6	1190	No	High	No	CYP (2C9, 2C19,3A4)	0	3.97
ZINC000095079930	-10.0	1190	No	High	No	CYP (2C9, 2C19 2D6,3A4)	0	3.97
ZINC000253476142	-9.8	1190	No	High	No	CYP (2C9, 2C19,3A4)	0	3.96
ZINC000206774725	-9.3	1190	Yes	High	No	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.34
ZINC000206770769	-9.6	1000	No	High	No	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.44
ZINC000206774070	-9.8	1000	Yes	High	Yes	CYP (2C9, 2C19 2D6,3A4)	0	3.51
ZINC000206774330;	-9.3	1190	Yes	High	No	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.46
ZINC000253409176	-9.8	1190	No	High	No	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.95
ZINC000253409179	-9.7	1190	No	High	No	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.95
ZINC000206774469	-3.8	1190	Yes	High	Yes	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.63
ZINC000253409181	-9.9	1190	Yes	High	No	CYP (1A2,2C9, 2C19 2D6,3A4)	0	3.36
ZINC000253409181	-9.5	1190	No	High	No	CYP (2C9, 2C19 2D6,3A4)	0	3.95

Table 2. Ramelteon and its analogs pharmacodynamic and toxicity data.

compound	Docking scores	LD 50 (mg/kg)	Gastrointestinal absorption	Blood brain barrier permeant	P-glycoprotein substrate	Metabolism	Lipinski violations	Synthetic accessibility
Ramelteon	-7.8	1000	High	Yes	Yes	CYP(2C19,2D6)	0	2.91
ZINC00000007031	-8.5	1190	HIGH	Yes	Yes	CYP(2C19 2D6)	0	2.91
ZINC000003960339	-8.8	860	HIFH	Yes	Yes	CYP(2D6)	0	2.81
ZINC000003981996	-7.9	860	HIGH	Yes	Yes	CYP(2D6)	0	2.96
ZINC000003825731	-8.5	860	HIGH	Yes	No	CYP(2D6)	0	2.45
ZINC0000068741265	-8.7	1190	HIGH	Yes	No	CYP (1A2,2C9, 2C19 2D6)	0	2.02
ZINC0000068741252	-8.5	1190	HIGH	Yes	Yes	CYP (1A2,2C9, 2C19 2D6)	0	2.18
ZINC0000068741294	-8.0	860	HIGH	Yes	Yes	CYP(2D6)	0	2.58
ZINC000225596222	-8.3	860	HIGH	Yes	Yes	CYP (2C9, 2C19,2D6)	0	2.68
ZINC000225596523	-8.6	860	HIGH	Yes	No	CYP (2C19 2D6)	0	3.36
ZINC000004222632	-8.5	860	HIGH	Yes	No	CYP (2C9, 2D6,3A4)	0	3.36
ZINC000225596253	-9.1	860	High	Yes	No	2C19,2D6	0	2.68
ZINC000225600895	-8.3	2000	High	Yes	No	CYP(1A2,2C19,2D6)	0	2.65
ZINC000004222622	-8.7	860	High	Yes	No	CYP(2D6)	0	3.28

Table 3. Triazolam and its analogs pharmacodynamic and toxicity data.

Compound	Docking scores	LD 50 (mg/kg)	Gastrointestinal absorption	Blood brain barrier permeant	P-glycoprotein substrate	Metabolism	Lipinski violations	Synthetic accessibility
Triazolam	-8.1	695	High	Yes	Yes	CYP (1A2,2C9, 2C19)	0	3.37
ZINC000000002212	-8.5	1080	High	Yes	Yes	CYP (1A2,2C9, 2C19)	0	3.37
ZINC0000000346674	-8.4	1080	High	Yes	Yes	CYP (1A2,3A4)	0	3.25
ZINC0000000000903	-8.8	1080	High	Yes	Yes	CYP (1A2)	0	3.33
ZINC0000039247014	-8.8	1080	High	Yes	Yes	CYP (1A2,2C9,3A4)	0	3.43
ZINC0000010152022	-8.2	1080	High	Yes	Yes	CYP (1A2, 2C19)	0	3.24
ZINC0000000347721	-8.8	1080	High	Yes	Yes	CYP (1A2,2C9)	0	3.46
ZINC0000079424448	-8.2	1000	High	Yes	Yes	CYP (1A2,3A4)	0	3.33
ZINC0000000702142	-8.3	1000	High	No	Yes	CYP (3A4)	0	3.61
ZINC0000039247035	-8.5	1000	High	Yes	Yes	CYP (1A2,3A4)	0	3.31

Table 4. Zolpidem analysis data.

compound	Docking scores	LD 50 (mg/kg)	Blood brain barrier permeability	P-glycoprotein substrate	Gastrointestinal absorption	Metabolism	Lipinski violations	Synthetic accessibility
Zolpidem	-8.1	695	yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.93
ZINC000000003876	-8.7	1000	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.93
ZINC0000067665462	-8.1	1000	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.92
ZINC0000065743121	-8.3	1000	Yes	No	High	CYP (1A2,2C9, 2C19,3A4)	0	2.9
ZINC0000041288365	-8.7	1000	Yes	Yes	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.71
ZINC000013801078	-8.9	1000	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.78
ZINC0000041292591	-8.9	695	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.78
ZINC000022054496	-8.1	1190	Yes	No	High	CYP (1A2,2C9, 2C19,3A4)	0	2.62
ZINC000071853335	-8.0	695	Yes	No	High	CYP (1A2,, 2C19 2D6,)	0	2.46
ZINC0000041282761	-8.0	695	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.45
ZINC0000063832471	-8.6	695	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.75
ZINC0000064675847	-8.6	695	Yes	No	High	CYP (1A2,2C9, 2C19 2D6,3A4)	0	2.85
ZINC000426519011	-8.8	695	Yes	Yes	High	CYP (1A2, 2C19 2D6,3A4)	0	2.5

Results and discussion

Suvorexant and its analogues

Suvorexant interacts with the orexin receptor through van der Waal forces hydrogen bonds, carbon-sulfur, Pi-sulfur, Pi-Pi alkyl, alkyl, and Pi alkyl (Figure 1). The increase in interaction forces between the receptor and the drug molecule increases the duration of activity of the drug in the receptor hence the activity of the drug and decreasing the concentration of the drugs needed to provide therapeutic effects.⁴

Docking scores, pharmacokinetic and toxicity profiles of 20 compounds similar to suvorexant were analyzed. From the 20 molecules, 12 compounds (Table 1) showed better docking scores compared to the parent drug. All the molecules showed higher Gastrointestinal absorption indicating that the molecules can easily be administered orally.³⁴ The parent molecule had a poor penetration to the central nervous system (CNS) which is their site of action. five molecules showed higher CNS bioavailability as compared to the parent compound. They include ZINC000206774725, ZINC000206774070, ZINC000206774330, ZINC000206774469 and ZINC000253409181.

Suvorexant

ZINC000206774070 and ZINC000206774469 have good CNS penetration ability but those molecules are good substrates of P-glycoprotein. P-glycoprotein is a transporter that decreases the absorption of a drug by pumping the molecule back into the lumen. As a substrate of P-glycoprotein, the drug concentration may not be enough to cause the desired therapeutic effects.³¹

All the molecules do not have any Lipinski violation. A molecule that violates Lipinski's rule of five indicates its limited bioavailability and oral absorption, these substances may need to be administered *via* other methods. In drug development, the rule is often applied.³⁵

ZINC000206774725, ZINC000206774330, and ZINC000253409181 are not a substrate of P-glycoprotein (Table 3). These molecules on the other hand have a greater Cytochrome P450 (CYP) enzyme interaction compared to the parent molecule. They all interact with CYP 1A2,2C9, 2C19 2D6,3A4 as an inhibitor. These enzymes are essential in the metabolism of many drugs.³⁶ Inhibition of those molecules may cause a serious interaction with other drugs which are administered to the patient. The molecules can all be synthesized. They all have a synthesizability index of above 3.2.

LD50 was used in the estimation of the molecule's toxicity profile. This is a dose that is necessary to kill 50% of the population or test subjects. As a result, a higher LD50 value implies that a drug is less dangerous since a larger dose is required to kill half of the population or test subjects.³⁷ ZINC000206774725, ZINC000206774330, and ZINC000253409181 have a higher LD50 compared to the parent compound; suvorexant indicating that the molecules are safer compared to the parent molecule.

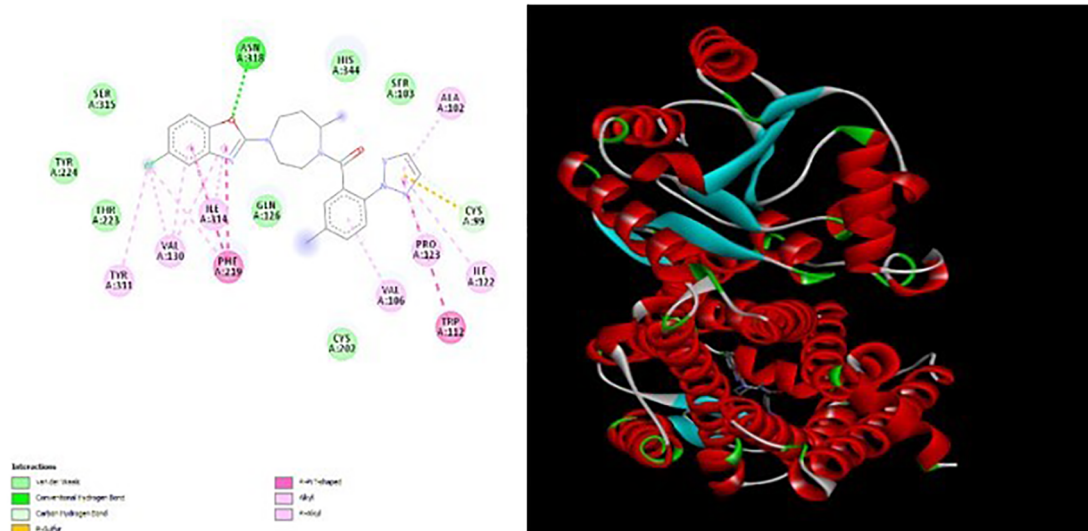


Figure 1. Suvorexant interaction with and orexin receptor.

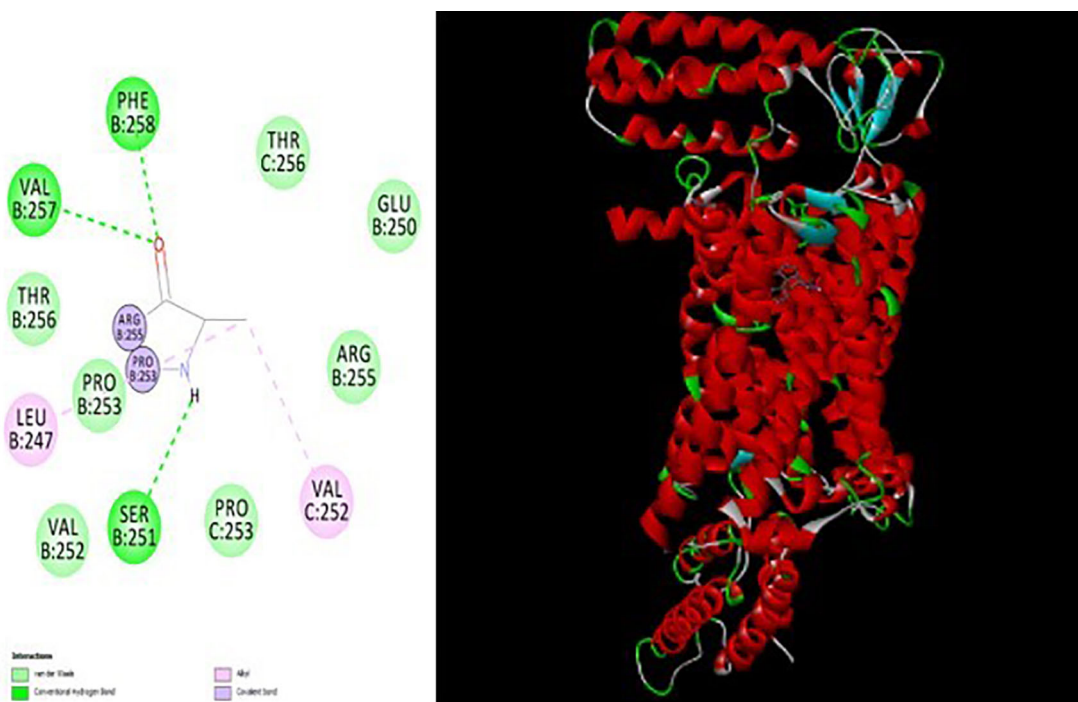


Figure 2. Ramelteon interaction with melatonin receptor type 1B.

Ramelteon and its analogues

Docking scores, pharmacokinetic and toxicity profiles of Ramelteon interacts with the melatonin receptor by the van der Waal forces hydrogen bonds, alkyl, and Pi alkyl (Figure 2). Van der Waal forces are the weakest involved in the interaction while the hydrogen bonds are the strongest forces involved.³⁵

Ramelteon

20 molecules similar to Ramelteon were analyzed. Thirteen compounds showed better docking scores compared to the parent molecule Ramelteon (Table 2). Out of the 13 compounds, two compounds had better pharmacokinetic properties compared to the parent compound. The two compounds ZINC000003825731, and ZINC000004222622 (Table 2) were affecting metabolism by affecting only the CYP2D6 enzyme compared to the parent compound affected which inhibits two enzymes CYP 2D6 and CYP 2C19.

Inhibition of the CYP enzymes may cause increased cases of drug-drug interactions associated with a particular drug. The parent drug interacts with more cytochrome enzymes compared to the ZINC000003825731, and ZINC000004222622 which only interact with one enzyme.

Ramelteon is a substrate for p-glycoprotein and hence may lead to the reduction of the concentration of the drugs in the CNS. P-glycoproteins proteins work to reduce the concentration thus reducing intracellular drug accumulation leading to treatment failure or increased concentration of the drugs used. The two molecules show fewer interactions with this protein which may improve the bioavailability after administration and at the same time decrease dose of administration of the drug and better clinical performance.

The molecules also have good oral bioavailability. They also pass and also cross the blood-brain barrier where they can execute their function.

They are both synthesizable. The synthesizability of ZINC000003825731 is 2.91 and ZINC000004222622 is 3.28 compared to that of 2.91 of Ramelteon. The synthesizability index of a molecule indicates how easy a drug is to be synthesized.

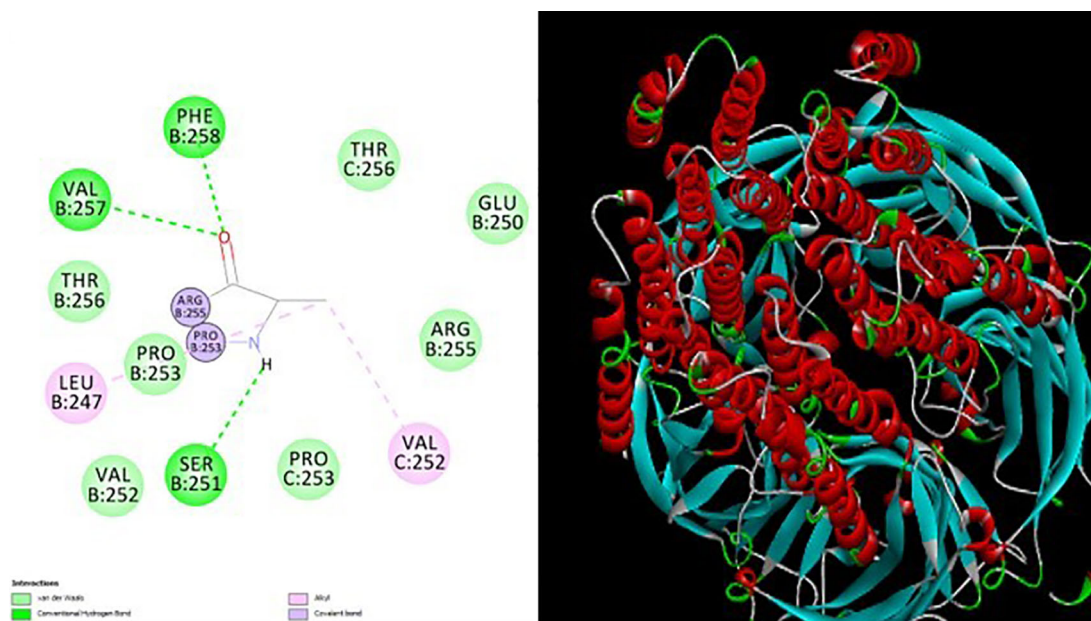


Figure 3. Triazolam receptor interaction and GABA A receptor.

Triazolam and its analogues

Triazolam interacts with the GABA A receptor through van der Waals forces (Figure 3). These are forces that attract neutral molecules to one another in gases solids and liquids. The binding may be weaker than that of other forms of interactions, such as hydrogen bonding or electrostatic interactions. This may reduce the drug's potency and at the same time increase the drug selectivity.³⁷

Triazolam had a docking score of -8.1 (Table 3). Nine molecules had a better docking score compared to triazolam. Of the nine molecules, only one molecule, ZINC000000702142, has poor penetration to the CNS this indicates that the molecule may not be able to reach the site of action. All the molecules have good oral bioavailability. All the molecules are substrates of the P-glycoprotein. This indicated that the molecules have less bioavailability.³⁴

Triazolam

ZINC000000000903, ZINC000010152022, and ZINC000000347721 do not interact with the CYP 3A4. The CYP3A4 enzyme is involved in the metabolism of the majority of drugs³⁶ including Statins, Calcium channel blockers, Benzodiazepines, Macrolide Antibiotics, Antidepressants, Antipsychotics, Immunosuppressants, and Opioids. This makes it a potential for interaction with any drugs hence the need to be careful during co-administration. ZINC000000000903 interacts with only one enzyme CYP 1A2. This molecule has then very few interactions as compared to the other molecules.³⁶ These molecules studies have a higher LD50; ZINC000000000903(1080 mg/kg), ZINC000010152022(1080 mg/kg), ZINC000000347721(1080 mg/kg) compared to triazolam (695 mg/kg) (Table 3).

Zolpidem and its analogs

Zolpidem interacts with the GABA A receptor through hydrogen bonds and van der Waal forces (Figure 4). This provides a stronger receptor drug-receptor complex as compared to triazolam. interactions with, arginine, serine, methionine, and leucine at positions 5 1, and 3, and two interactions between proline and arginine at locations 49 and 50 and 6 and 7 respectively.

Zolpidem has a docking score of -8.0. 10 molecules had a better docking score compared to the parent molecule (Table 4). Of the 10 molecules ZINC000041288365 and ZINC000426519011 are substrates of P-glycoprotein transporters indicating that the rest of the molecules have a good oral bioavailability. ZINC000065743121 and ZINC000022054496 have very little interaction with CYP 2D6 molecule but interact with CYP 1A2,2C9, 2C19, and 3A4. The rest of the molecules interact with CYP 1A2,2C9, 2C19 2D6, and 3A4 as inhibitors. This increases the range of drugs the molecules can interact with during the administration.

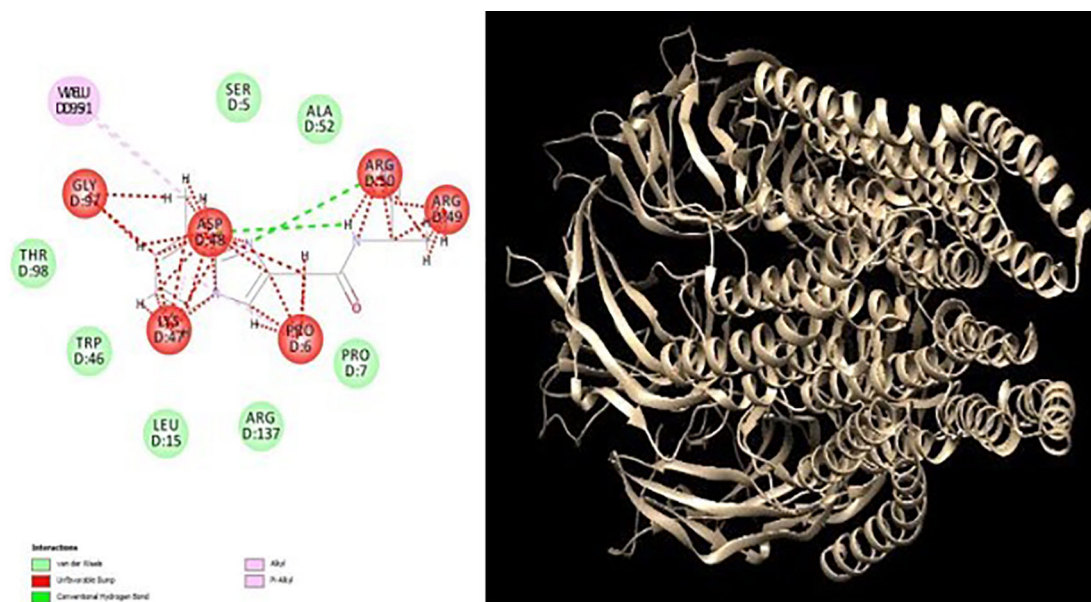


Figure 4. Zolpidem receptor interaction and GABA A receptor.

Zolpidem

Zolpidem has an LD50 of 695 mg/kg. ZINC000022054496 has the highest LD50 value of 1190 mg/kg. ZINC000065743121 has an LD50 of 1000 mg/kg, which is better than the parent molecule. The two molecules can be given at high concentrations compared to zolpidem without the patient experiencing serious adverse effects.³⁸ GI absorption of the drugs of all the molecules is good indicating they can be issued orally. The molecules have no Lipinski violations with a synthesizability index of above 2.5. This is an indication that the drug molecules can be synthesized.

Conclusions

The study identifies nine molecules from the Zinc database that have better docking scores pharmacokinetic and toxicity profiles compared to the parent compounds. Ramelteon analogs ZINC000004222622, ZINC000003981996, and ZINC000003825731 are potential drugs for development. They have good pharmacokinetic and toxicity profiles. The drugs interact with either their MT1 and MT2 receptors better compared to the parent molecule. These molecules are also synthesizable. Suvorexant analogs have a better docking score compared to the parent compound but the pharmacokinetic profiles are not better than the parent molecule. Triazolam drug-like molecules, ZINC000000000903, ZINC000039247014, ZINC000010152022, and ZINC000000347721 have better pharmacokinetic profiles compared to the parent compound. They show better binding to the GABA-A receptor compared to the GABA-A receptor suggesting better activity. These compounds are all synthesizable and with good GI bioavailability suggesting that the molecules can be taken orally.³¹ Zolpidem drug-like molecules ZINC000065743121 and ZINC000022054496 show better pharmacokinetic and toxicity profiles compared to the parent compound. All the molecules are synthesizable.

In-vitro studies should be conducted for the 9 molecules, ZINC000003981996, ZINC000003825731, ZINC000004222622, ZINC000000000903, ZINC000039247014, ZINC000010152022, ZINC000065743121, and ZINC000022054496 to ensure to determine their activity in the human subject. The molecules should undergo *in vivo* structure-activity relationship analysis for optimization before testing in their respective receptor.

Source data

The canonical smiles of the Parent compounds (Ramelteon, Zolpidem, Suvorexant and Triazolam) were obtained from [PubChem](#)

Structural analogues of the Parent compounds were obtained from [SwissSimilarity](#)

The pharmacokinetic profiles of the structural analogues and the Parent compounds were obtained from [SwissADME](#)

Protein Receptors of the parent drugs compounds and their analogues were obtained from the [Protein data bank](#)

Toxicity profile of the parent compounds and their structural analogues were obtained from the [Protox](#) server

Underlying data

Figshare: Developing potential drugs for *insomnia* through computational analysis: <https://doi.org/10.6084/m9.figshare.23674614>.³⁹

This project contains the following underlying data

- Pharmacokinetic of Ramelteon and its analogues.csv
- Canonical smiles of results for Suvorexant analogues.csv
- Pharmacokinetic of Suvorexant and its analogues.csv
- Canonical smiles of triazolam analogues.csv
- Pharmacokinetic of Triazolam and its analogues.csv
- Pharmacokinetic of Zolpidem and its analogues.csv
- Canonical Smiles for Zolpidem analogues.csv

Extended data

Figshare: Developing potential drugs for *insomnia* through computational analysis: <https://doi.org/10.6084/m9.figshare.23674614>.³⁹

- Figures.docx
- Results Summary.docx
- Pharmacokinetic Properties.docx
- Docking Scores.docx
- Toxicity Profiles.docx

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

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Authors of the presented manuscript computationally evaluated the potential activity of structural analogs of marketed anti-insomnia compounds against different sleep-associated biotargets. The manuscript is good however, several comments should be addressed:

1. A table/figure with all chemical structures of the investigated 20 compounds should be presented.
2. A brief introduction for the target surface topology, secondary protein structures, and pocket/binding site is recommended to allow readers to track the differential binding interaction and affinity of compounds towards the designated target.
3. Authors should elaborate more on the docking analysis. There is a need for explicit discussion regarding the residue-wise interactions between each compound and the target. Authors should mention the Hydrogen bond angles as well as their distances, since the strength of hydrogen bonding is based on both parameters in a way to ensure the adequacy of optimum hydrogen bonding. Moreover, the authors should mention the adopted distance criteria to determine the H-bond and Hydrophobic interactions.
4. Binding energies should be also calculated through mm-GBSA calculations using free on-line platform (HawkDock or similar). This would provide a true affinity index for ligand-target affinity. Additionally, this would allow efficient exploration for the nature of compound-target interactions where energy contribution terms (van der Waals, electrostatic, SASA solvation, polar solvation energies) could be estimated and then authors would identify which being most dominant through the MD simulation runs.
5. Authors should elaborate more on the docking figures. The 2D representation within Figures 2 and 3 are similar!!!! and the compound is not in its full structure. The 3D representations add nothing to the docking discussion, they only represent the target in cartoon structure without zooming in to the pocket/binding site highlighting the main compound-protein residue interactions as well as the compound predicted 3D orientation and conformation within the space.
6. Throughout a discussion section, authors should highlight the takeaway messages that would be adopted in future lead optimization and development based on the molecular docking and ADME analysis. Prospective/recommended structure modifications to improve

the ligand's binding and interactions, as well as pharmacokinetics should be provided within the discussion and conclusion sections.

7. Finally, concerning the conclusion, authors are advised to elaborate more on the future of this work? Will you test more related drugs? Will you broaden the scope to other targets? What are the study limitations and what approaches could be conducted to further address them?

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Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Drug discovery, drug development, molecular modelling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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