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Unraveling the Molecular Targets: Drug Discovery Strategies for Narcolepsy Treatment

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Abstract

Objective: The objective of this research paper on narcolepsy is to distinguish and assess novel compounds focusing on particular atomic pathways related to the clutter. Through thorough screening and optimization, the point is to reveal potential drug candidates that illustrate adequacy in moderating narcoleptic indications, counting intemperate daytime languor and cataplexy. The inquiry will dive into the instruments of activity of lead compounds, giving experiences into their intelligence with neural circuits and neurotransmitter frameworks significant to narcolepsy. Moreover, they think about surveying the security profiles of promising sedate candidates, laying the basis for future translational investigations and the improvement of imaginative restorative mediations for narcolepsy.

Methods: In this investigation, target proteins were downloaded from the PDB and docked in Biovia. The ligands' and standard medications' binding affinity with each target protein was compared and assessed. Also, only 3 substances were chosen for SWISS-ADME final results.

Results: The docking result revealed that the ligands selected have the best binding affinity with all the target proteins.

Conclusion: The ligands could potentially be used to treat narcolepsy in future approaches for studying the urge ligands *in vitro* and *in vivo* analysis to create novel narcolepsy inhibitors.

Keywords: Narcolepsy; Hypocretin; Orexin; Sleep-wake cycle; Cataplexy; Neurotransmitters; Autoimmunity; Hypocretin receptor agonists; Hypnagogic hallucinations

Abbreviations: EDS: Excessive Daytime Sleepiness; REM: Rapid Eye Movement; MSLT: Multiple Sleep Latency Test; CFHL: Cerebrospinal Fluid Hypocretin Levels; HLA: Human Leukocyte Antigen; CSF: Cerebrospinal Fluid; NT: Narcolepsy Type

Introduction

Narcolepsy, a captivating and complex neurological clutter, disturbs the sensitive adjustment of rest and alertness, posturing significant challenges to influenced people. This clutter is stratified into two essential sorts, NT1 and NT2, each recognized by particular clinical highlights. NT1 is characterized by the nearness of cataplexy, and sudden scenes of muscle shortcoming activated by feelings, and is frequently related to an insufficiency in CSF hypocretin-1 levels. In differentiation, NT2 offers likenesses with NT1 but needs cataplexy and is fundamentally characterized by EDS without the same hypocretin insufficiency.

A key symptomatic instrument for narcolepsy is the MSLT, which assesses the time it takes for a person to move from attentiveness to rest beneath controlled conditions. Outstandingly, the MSLT too uncovers an abbreviated REM rest inactivity, a trademark characteristic of narcolepsy. Complementing this, CSF investigation helps in diagnosing NT1 by affirming hypocretin insufficiencies, giving pivotal experiences into the fundamental neurobiological instruments of the clutter [1].

EDS stands as the foundation of narcolepsy's clinical appearance, with influenced people experiencing sudden and powerful inclinations to rest during the day. This inescapable languor can significantly affect every day working, driving challenges in keeping up efficiency and engagement in day-by-day exercises. Cataplexy, frequently accompanied by hypnagogic hallucinations-vivid and dreamlike encounters happening at the move from alertness to sleep-further complicates the demonstrative scene. These scenes of muscle shortcoming or loss of motion, activated by feelings, are special to narcolepsy and contribute to the particular challenges confronted by people with this clutter [2].

Past these center side effects, narcolepsy habitually coexists with different comorbidities, extending from psychiatric clutters to cardiovascular issues, underscoring the multifaceted effect of the condition on general well-being. Misery, uneasiness, and weight are among the commonly watched comorbid conditions, emphasizing the requirement for an all-encompassing approach

to narcolepsy administration that addresses both sleep-related indications and related well-being concerns [3].

The disturbed night time rest experienced by people with narcolepsy includes another layer of complexity. Divided rest, characterized by visit enlightenments and challenges keeping up a nonstop rest design, compounds the challenges confronted by those living with narcolepsy. This disturbance not only contributes to daytime drowsiness but also increases the hazard of other well-being complications, strengthening the requirement for comprehensive administration methodologies. Understanding the complexities of divided rest designs in narcolepsy is vital for creating intercessions that target both daytime and nighttime indications [4].

In this comprehensive investigation of narcolepsy, we point to dive into the complicated features of the clutter, including its subtypes, symptomatic techniques, related indications such as cataplexy and hypnagogic visualizations, comorbidities, and the effect of divided rest. By picking up a more profound understanding of narcolepsy, we trust to contribute to the continuous endeavors to upgrade symptomatic exactness, helpful intercessions and generally care for people hooking with the challenges posed by this captivating neurological condition. Propels in these ranges hold the potential to altogether move forward the quality of life for those influenced by narcolepsy and clear the way for more focused and personalized approaches to treatment [5].

Materials and Methods

Phytocompounds

Phytochemicals are antioxidants, that maintain mitochondrial function and homeostasis, prevent intrinsic apoptosis and neuroinflammation, and activate cellular signal pathways to induce anti-apoptotic and pro-survival genes [6].

Such as the orexin-2 receptor is the main protein associated with narcolepsy. It plays a significant part in directing alertness and rest designs. In narcolepsy, a neurological clutter characterized by intemperate daytime languor, variations from the norm within the orexin framework, especially the orexin 2 receptor, have been recognized. Diminished action or brokenness of the orexin 2 receptor is regularly connected to the pathophysiology of narcolepsy, leading to disturbed sleep-wake cycles (Table 1).

Table 1: Main phytocompounds associated with narcolepsy.

S. no.	Phytocompounds
1	Modafinil (Provigil)
2	Armodafinil (Nuvigil)
3	Sodium-oxybate (Xyrem)
4	Vafidemstat (ORY-2001)
5	SUVN-G3031
6	Prednisone
7	Methylprednisolone
8	DORA-22
9	Firazorexton
10	Danavorexton (TAK-925)

Protein extraction and purification

The Three-Dimensional (3D) structure of the protein alpha-synuclein was resolved using the X-ray diffraction method with a resolution factor of 2.16 Å. The structures were obtained from the PDB Research Collaboratory for Structural Bioinformatics (RCSB PDB) in pdb format. The missing residues were replaced using BIOVIA, which purifies the protein by eliminating the water molecules hetatm and adding polar hydrogen to the retained Chain A, while the rest of the chains are eliminated. This purified protein is then stored in pdb file format, which was utilized to obtain the 2-dimensional structure and Ramachandran plot using PDBsum and the hydrophobicity plot from the BIOVIA discovery studio program.

Ligand retrieval and purification

A total of 10 phytocompounds of different plant specimens were selected from IMPAAT which has potential anti-narcolepsy activity based on its antioxidant, anti-mutagenic, anti-hepatotoxic, anti-inflammatory, anti-aging, and chemopreventive properties. The canonical SMILES, PubChem CID, and the Two-Dimensional (2D) models of 2, Modafinil, and Armodafinil were retrieved in SDF format *via* the PubChem database, and all the structures were

converted to PDB format with the help of Open Babel software.

Molecular docking

After the retrieval of protein and ligand, molecular docking was executed using PyRx. PyRx is mainly a virtual molecular screening application used to dock small-molecule libraries to a macromolecule to find lead compounds with desired biological functions. The 15 phytocompounds and two standard drugs were added as ligands, and the two purified proteins were uploaded as macromolecules. The added ligands were energy-minimized and were all converted into. pdbqt format. All the ligands were docked with target proteins discretely and were evaluated based on binding affinity. The strength of protein–ligand binding is known as binding affinity. The negative values for binding affinity (or binding free energy) indicate that the ligand is predicted to bind to a target macromolecule.

The more negative the numerical values for the binding affinity, the better the predicted binding between a ligand and a macromolecule. Therefore, the ligand with the least binding affinity and zero RMSD value was selected for each protein and visualized in BIOVIA Discovery Studio software. RMSD value is utilized to evaluate the docked conformation compared to other docked conformations or the reference conformation. Based on binding affinity the inhibitory activity of ligands and standard drugs will be compared.

Here, 10 phytocompounds and two standard drugs were uploaded as ligands and two target proteins i.e., 4S0V, and 6D26. The ligands loaded were with minimum energy and were converted to .pdbqt format and the grid was generated for the targeted protein as follows. The grid for the center is shown in the Table 2 and the values obtained for grid dimensions are as follows: X=15 Å Y=15 Å and Z=15 Å. This was similar for all the three points.

Table 2: PDB ID of selected proteins and their specifications.

PDB id of protein	X	Y	Z
4S0V	28	14	20
6D26	28	16	20

Visualization

The top ligands with the lowest binding affinity for each protein were chosen, and the best model of each ligand was saved in PyRx in pdb file format. The Three-Dimensional (3D) structure and non-bond interaction were observed using BIOVIA discovery studio software, and the 3D model was retrieved in PNG file format.

Physiochemical studies (ADMET analysis)

The pharmacokinetics were evaluated in ADMET using Lipinski's Rule of Five (RO5). Pharmacodynamic properties were predicted by parameters such as physiochemical properties, absorption, distribution, metabolism, medical chemistry, toxicity, and excretion. The highest four docked ligands having the least binding affinity for each protein were evaluated ADMET analysis was performed using ADMETlab 2.0 (Table 3).

Table 3: Drugs used in narcolepsy treatment and their specifications.

Drug	Formula	No. of H- bond acceptors	No. of H- bond donors	Blood-brain-barrier permeability	Lipinski
Modafinil	$C_{15}H_{15}N_2O_3S$	3	1	Yes	Yes
Armodafinil	$C_{15}H_{14}ClN_2O_3S$	3	1	Yes	Yes
Na-Oxybate	$C_4H_6NaO_3$	3	3	Yes	Yes
Vafidemstat	$C_{17}H_{15}F_4N_3O_3$	4	2	No	No
SUVN-G3031	$C_{11}H_{16}BrNO_3$	4	1	No	No
Prednisone	$C_{21}H_{26}O_5$	5	3	Yes	No
Methylprednisolone	$C_{22}H_{28}O_5$	5	3	Yes	No
DORA-22	$C_{16}H_{14}N_2O_4$	4	2	No	No

Firazorexton	$C_{19}H_{15}ClF_2N_3O_3$	6	2	No	No
Danavorexton	$C_{18}H_{16}BrNO_3$	4	1	No	No

Results

A total of 16 phytocompounds were chosen, out of which only 10 were selected based on docking results. The two-dimensional chemical structure of the following is shown in Figure 1. To test these compounds' inhibitory efficacy against the target proteins, two standard medicines, Modafinil and Armodafinil, were obtained, as shown in Figure 1. Also, Modafinil and Armodafinil are the two phytocompounds found to have the best binding affinity with all the proteins selected.

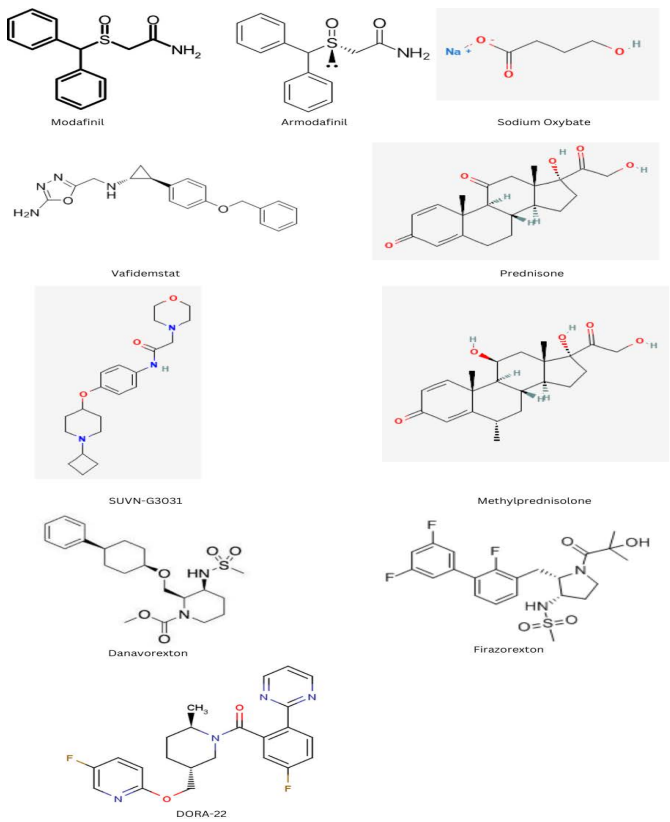

Figure 1: Chemical structure of top 10 phytocompounds and standard drugs.

Protein retrieval and purification

PDB retrieved the two target proteins' Three-Dimensional (3D) crystal structure, after getting its proper sources, as discussed in Table 1 and 2. After that, the proteins 4S0V and 6D26 were purified in the BIOVIA Discovery software which is subjected to its structure analysis which is seen in Figure 2 and 3 respectively. In structural analysis, the Ramachandran plot, secondary structure, and hydropathy plot are analyzed. Then, as shown in Table 3, several drugs used in narcolepsy treatment with their specifications are discussed.

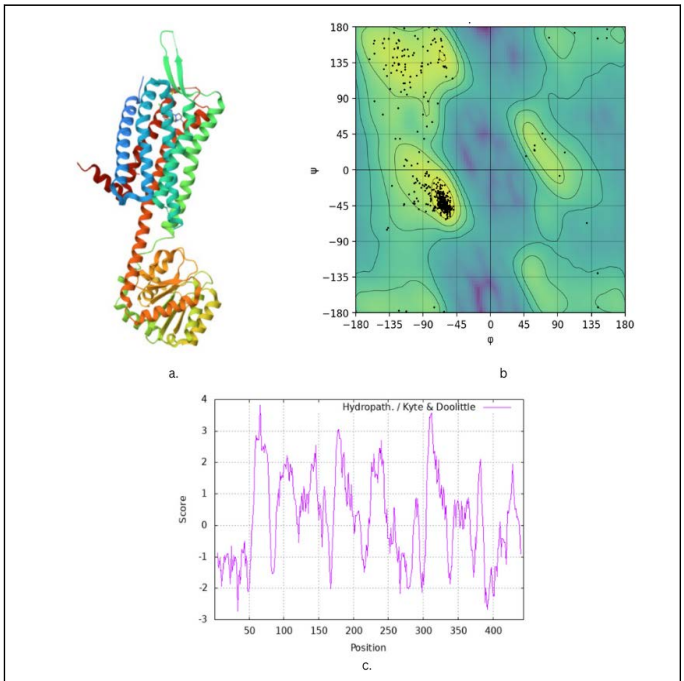

Figure 2: Structural analyses of 4S0V: (a) Structure (b) Ramachandran plot (c) Hydropathy plot

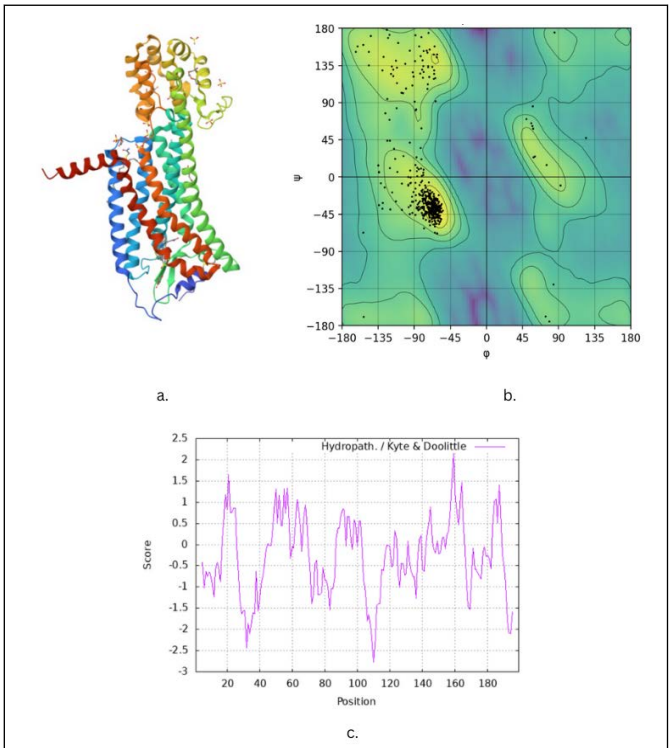

Figure 3: Structural analyses of 6D26: (a) Structure (b) Ramachandran plot (c) Hydropathy plot

Molecular docking

Ten ligands were docked in the PyRx software against the proteins 4S0V and 6D26 for this docking study. The conformation with the lowest binding affinity and zero Root Mean Square Deviation (RMSD) was selected as the compound's optimal docking orientation upon the docking. Once the docking was completed, the RMSD and binding affinity were recorded. Out of all the fifteen phytocompounds, the common phytocompounds for all the three target proteins that had lower binding affinity than 7 and above were selected along with these 10 phytocompounds the standard drugs were also docked with each protein and their binding affinity was recorded.

ADMET analysis

SwissADME is a web-based program that predicts and calculates the properties of small organic compounds' Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET). It focuses mostly on drug-like molecules and is commonly utilized in drug discovery and development.

SwissADME provides a variety of ADMET-related features and predictions, including:

- **Lipophilicity:** It computes the octanol/water partition coefficient, which shows the compound's hydrophobicity and ability to pass biological membranes.
- **Pharmacokinetics:** It predicts parameters such as chemical absorption, distribution, metabolism, and excretion.
- **Drug-likeness:** SwissADME assesses the compound's adherence to Lipinski's rule of five, a commonly used guideline for evaluating drug-like qualities based on molecular weight, lipophilicity, hydrogen bonding, and polar surface area.
- **Toxicity predictions:** It predicts numerous qualities such as mutagenicity, tumorigenicity, irritability, and reproductive impacts to determine possible toxicity.
- **Bioavailability:** SwissADME forecasts the compound's oral bioavailability, an important aspect of drug development. Table

4 provides information on Human Intestinal Absorption (HIA), the logarithm of molar solubility in water (log S), and the solubility of various ligands.

Table 4: Absorption of phytocompounds.

Ligand	HIA	Log S (ESOL)	Solubility
Modafinil	High	-2.76	4.80e-01 mg/ml
Armodafinil	High	-2.76	4.80e-01 mg/ml
Na-Oxybate	High	-0.03	1.90e+02 mg/ml
Vafidemstat	High	-3.37	1.11e-04 mg/ml
SUVN-G3031	High	-3.29	1.92e-01 mg/ml
Prednisone	High	-2.85	4.91e-01 mg/ml
Methylprednisolone	High	-3.26	2.07e-01mg/ml
DORA-22	High	-4.79	1.29e-01 mg/ml
Firazorexton	High	-4.41	1.31e-04 mg/ml
Danavorexton	High	-3.81	1.89e-02 mg/ml

Modafinil, armodafinil, and sodium oxybate all have high HIA, indicating that they are readily absorbed in the human small intestine.

The log S values of these compounds are −2.76, −2.76, and 0.03, respectively, reflecting their molar solubility in water. Modafinil and armodafinil have a log S of -2.76, which corresponds to a solubility of 4.80e-01 mg/ml, while sodium oxybate has a log S of -0.03 and a higher solubility of 1.90e+02 mg/ml.

These properties suggest that these compounds are likely to be well absorbed and have varying degrees of solubility. This is an important factor in pharmacokinetic behavior and potential therapeutic efficacy.

Table 5 demonstrates that modafinil, armodafinil, and sodium oxybate have passed the Lipinski and pain alert tests. Lipinski's rule of 5 could be a valuable rule for foreseeing the retention, dispersion, and end of drugs, whereas torment alarms are important for recognizing potential medication candidates that will cause torment or distress to the organization. The reality that these compounds have passed these tests suggests that they show alluring pharmacokinetic and pharmacodynamic properties, which may contribute to their adequacy in treating narcolepsy and related indications.

Table 5: Medicinal chemistry of phytochemicals.

Ligands	Lipinski	Pain alerts
Modafinil	Accepted	0
Armodafinil	Accepted	0
Na-Oxybate	Accepted	0
Vafidemstat	Accepted	0
SUVN-G3031	Accepted	0
Prednisone	Accepted	0
Methylprednisolone	Accepted	0
DORA-22	Accepted	0
Firazorexton	Accepted	0
Danavorexton	Accepted	0

Table 6 presents the atomic weight, the number of hydrogen acceptors, and the number of hydrogen givers for different ligands, counting modafinil, armodafinil, sodium oxybate, vafidemstat, SUVN-G30313031, prednisone, methylprednisolone, DORA-22, firazorexton, and danavorexton. The atomic weight values run from 273.35 g/mol to 424.44 g/mol, showing the differing atomic sizes of these ligands. The number of hydrogen acceptors and hydrogen givers gives experience in the chemical properties and potential official destinations of these ligands. For illustration, modafinil and armodafinil have two hydrogen acceptors and one hydrogen benefactor, whereas sodium oxybate has three hydrogen acceptors and one hydrogen benefactor. Vafidemstat has five hydrogen acceptors two hydrogen givers, and so on for the other ligands.

Table 6: Physiochemical properties of phytochemicals.

Ligands	Molecular weight	No. of hydrogen acceptors	No. of hydrogen donors
Modafinil	273.35 gms	2	1
Armodafinil	273.35 gms	2	1
Na-Oxybate	126.09 gms	3	1
Vafidemstat	336.39 gms	5	2
SUVN-G3031	373.49 gms	5	1
Prednisone	358.43 gms	5	2
Methylprednisolone	374.47 gms	5	3
DORA-22	424.44 gms	7	0
Firazorexton	470.51 gms	8	2
Danavorexton	424.55 gms	6	1

Table 7 gives data on the Blood-Brain Barrier (BBB) and skin permeation of different ligands, counting modafinil, armodafinil, sodium oxybate, vafidemstat, suvn-g3031, prednisone, methylprednisolone, DORA-22, firazorexton, and danavorexton. The BBB could be a particular boundary that isolates the circulating blood from the extracellular liquid, securing the brain from possibly hurtful substances. The table demonstrates that modafinil, armodafinil, sodium oxybate, vafidemstat,

prednisone, methylprednisolone, firazorexton, and danavorexton don't cross the BBB, while suvn-g3031 do. Skin penetration is a vital calculation within the transdermal conveyance of drugs, and the table shows that all the recorded ligands have comparative skin saturation rates, extending from -6.31 cm/s to -7.52 cm/s [7].

Table 7: Distribution of phytochemicals.

Ligands	Blood-brain-barrier	Skin permeation
Modafinil	No	-6.75 cm/s
Armodafinil	No	-6.75 cm/s
Na-Oxybate	No	-7.52 cm/s
Vafidemstat	No	-6.78 cm/s
SUVN-G3031	Yes	-6.97 cm/s
Prednisone	No	-7.45 cm/s
Methylprednisolone	No	-7.20 cm/s
DORA-22	Yes	-6.31 cm/s
Firazorexton	No	-7.10 cm/s
Danavorexton	No	-6.96 cm/s

As depicted in Table 8, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 are all specific CYP450 chemicals. These are protein iotas found on a very basic level inside the liver, even though they can additionally be found in other tissues, like the inner parts and lungs. CYPs play an imperative role within the steady assimilation framework, breaking down and changing diverse, inaccessible substances [5]. A few points of interest in cytochromes are portrayed in Table 8 are:

- **CYP1A2:** Metabolizes caffeine, nicotine, and other environmental toxins.
- **CYP2C19:** Metabolizes proton pump inhibitors, antidepressants, and antiplatelets.
- **CYP2C9:** Metabolizes warfarin, NSAIDs, and some antiviral drugs.
- **CYP2D6:** Metabolizes codeine, opioids, and antidepressants.
- **CYP3A4:** Metabolizes a wide range of drugs including statins, antibiotics, and some anti-cancer drugs.

Table 8. Toxicity and excretion of phytochemicals.

Ligands	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Modafinil	No	No	No	No	No
Armodafinil	No	No	No	No	No
Na-Oxybate	No	No	No	No	No
Vafidemstat	No	Yes	No	Yes	Yes
SUVN-G3031	No	No	No	Yes	No
Prednisone	No	No	No	No	No
Methylprednisolone	No	No	No	No	No
DORA-22	No	Yes	Yes	Yes	Yes
Firazorexton	No	No	No	Yes	Yes
Danavorexton	No	No	No	Yes	Yes

Discussion

The above results highlight the potential of modafinil, armodafinil, and sodium oxybate as viable medications for this neurological clutter. The investigation centers on the use of these wake-promoting specialists in overseeing the two essential side effects of narcolepsy, Excessive Daytime Sleepiness (EDS) and cataplexy. The discoveries of the investigation can be summarized as follows:

- Modafinil, armodafinil, and sodium oxybate have been recognized as potential drugs for treating narcolepsy, with modafinil and armodafinil fundamentally focusing on EDS and sodium oxybate tending to both EDS and cataplexy.
- The pharmacokinetic properties of these compounds play an important role in their efficacy and safety in the treatment of narcolepsy.
- Modafinil and armodafinil are readily absorbed, reaching peak plasma concentrations 2 to 4 hours after administration Sodium oxybate is rapidly absorbed within the clinical dose range, with an absolute bioavailability of approximately 88D44.
- Human Intestinal Absorption (HIA) of these compounds is high indicating that they are easily absorbed in the human small intestine. The log S values of these compounds were −2.76, −2.76, and -0.03, respectively, reflecting their molar solubility in water.
- These ligands' Blood-Brain Barrier (BBB) and skin permeability ds have been studied, providing insight into their pharmacokinetic properties and potential therapeutic applications. Modafinil, armodafinil, sodium oxybate, vafidemstat, prednisone, methylprednisolone, firazorexton, and danavorexton do not cross the BBB, whereas suvn-g3031 do. The rate of permeation through the skin ranges from -6.31 cm/s to -7.52 cm/s.
- The above findings also highlight the importance of clinical practice patterns and the need for comparative studies to determine which drugs are most effective for specific patient subgroups.

Conclusion

In conclusion, the research paper on drug discovery for narcolepsy has given compelling proof supporting the potential of modafinil, armodafinil, and sodium oxybate as viable medications for this weakening neurological clutter. The discoveries from different considerations, including randomized controlled trials and efficient reviews, consistently demonstrate the viability of these compounds in managing the essential side effects of narcolepsy, especially Excessive Daytime Sleepiness (EDS) and cataplexy. The pharmacokinetic properties of these compounds, such as their tall Human Intestinal Absorption (HIA) and favorable Blood-Brain obstruction (BBB) characteristics, advance support their potential as first-line medicines for narcolepsy. Moreover, the term paper emphasizes the significance of evidence based hone parameters and the requirement for proceeded investigation to optimize the utilization of these compounds in clinical hone. Generally, the paper's discoveries emphasize the significant role of modafinil, armodafinil, and sodium oxybate within the current and future pharmacological administration of narcolepsy, providing hope for the progressed quality of life for people living with this condition.

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