RESEARCH ARTICLE

In-silico Evaluation of Tetramethyl-pyrazine: Treating Recurring Seizures

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Abstract

Epilepsy, a chronic neurological disorder characterized by recurrent seizures, remains a challenging condition to treat due to the limited availability of potent and safe molecules. This study explores Tetramethyl-pyrazine (TMP) as a potential scaffold for epilepsy treatment, leveraging its diverse pharmacological properties. Utilizing structure-based virtual screening, we identified 300 active ligands from a virtual chemical library of 4,427 compounds, narrowing down to the top 7 potential ligands based on binding energy, drug-likeness, non-covalent interactions, and toxicity. Our results revealed a compound (PubChem ID 227746) with high binding affinity to protein 4MS4 (GABA agonist), strong interactions within the active site, and favorable pharmacokinetic and toxicological properties, suggesting TMPz holds promise as an anti-epileptic agent.

Keywords: Epilepsy, Tetramethyl-pyrazine (TMP), Virtual Screening, Antiepileptic Agents.
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Introduction

One of the most prevalent brain disorders, epilepsy affects over 70 million people globally. It has many neurological, cognitive, and psychosocial repercussions and is characterized by a persistent propensity to produce ongoing epileptic seizures (1).

Although seizures are a common symptom of epilepsy, not everyone who has seizures also has epilepsy. Epileptic seizures may also occur after an acute central nervous system (CNS) like (structural, systemic, toxic, or metabolic). These events (acute symptomatic or provoked seizures) are intended as acute manifestations of the insult(2) and may not recure when the underlying cause has been removed, or the acute phase has elapsed(3).

According to the International League Against Epilepsy (ILAE), epilepsy is defined by any of the following conditions: first one is at least 2 unprovoked (or reflex) seizures occurring > 24 h apart; second one is one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years; and third and the last one is diagnosis of an epilepsy syndrome. However, the ILAE Epidemiology Commission recommends that epilepsy be defined as two or more unprovoked seizures that occur at least 24 hours apart to perform population-based studies(4).

Tetramethylpyrazine (TMP) demonstrates efficacy against focal seizures, as evidenced by its ability to inhibit the progression of seizures in hippocampal and corneal kindling models, both of which are models of focal epilepsy. In these models, TMP limited seizure progression and reduced after-discharge duration. Conversely, TMP did not show protective effects in models of generalized seizures, such as the maximal electroshock (MES) and pentylenetetrazole (PTZ)-induced seizure models, indicating a selective action against focal rather than generalized seizure types (5).

Mechanisms of Tetramethyl pyrazine in Neuroprotection:

By using the brain's natural tendency to regenerate itself, tetramethylpyrazine (TMP) shows great potential for promoting recovery from an ischemic stroke. Research has demonstrated that TMP can improve neurological function in animal models of stroke by restoring connections in the brain and increasing levels of a protein essential for nerve transmission (6). Furthermore, it seems to protect the brain by reducing harmful inflammation and increasing the production of a specific protective protein. On a deeper level, TMP has been observed to calm down overactive immune cells in the brain during inflammation and inhibit the production of damaging molecules, possibly through a specific molecular pathway. Interestingly, TMP's influence on the process of cellular clean-up, known as autophagy, might also contribute to its benefits, potentially lessening inflammation, improving cognitive functions like memory and learning in animal models, and even protecting nerve cells in lab settings through specific signaling pathways (7). In addition to these effects, TMP has shown antioxidant qualities and the capacity to cause autophagy and cell death in specific nerve cells. TMP's ability to reduce inflammatory

responses via a crucial signaling route makes it an especially appealing therapy option, which gives it an important role in prevention of inflammation that plays important role in stroke. Additionally, TMP seems to shield the delicate blood vessels in the brain from damage through another molecular pathway and can counteract the harmful effects of oxygen deprivation and reduced blood flow, common in various brain disorders, by influencing specific molecular mechanisms that regulate cellular stress and antioxidant defenses (8).

Material and Methods

Virtual Screening

To find possible bioactive compounds in this work, virtual screening was used as a computer method to forecast how those molecules will interact with a target protein. By carefully analyzing large chemical libraries using computer tools to evaluate the compounds' binding affinity and potential activity, virtual screening significantly minimizes the requirement for time-consuming experimental testing. Through virtual screening, about 4427 tetramethyl pyrazine compounds were evaluated for this purpose, and 300 promising candidates were selected. These 300 compounds were then subjected to Virtual screening and order to investigate their interactions with the target protein which are shown in (Figure 1). The seven top-performing compounds were chosen for additional examination based on the docking findings (Table 3).

Schrodinger software was used to screen 300 compounds in order to assess their binding affinities. The Y-axis displays the compounds' binding energies, while the X-axis displays the number of compounds; lower values indicate stronger interactions. Our study identified potential lead compounds for further investigation based on their binding strength and target selectivity.

Quantum Computational Studies

For over ten years, quantum computing techniques have proven crucial in studying the physicochemical properties of medicinal compounds. In this work, the electrical properties of tetramethyl pyrazine (TMPz) were investigated. Density Functional Theory (DFT) stability studies were used to examine the lowest unoccupied molecular orbitals (LUMO) and the highest occupied molecular orbitals (HOMO), which provided insight into significant electronic transitions and reactivity patterns. The HOMO-LUMO energy gap was calculated to be 4.71 eV using GaussView 6 software was used to view all of the results(9).

ADMET Analysis

Tetramethyl pyrazine's intestinal absorption and BBB penetration were evaluated using the Swiss ADME online program(10). Additionally, the pkCSM online platform(11) was used to examine its drug-likeness and provided quantitative information about its Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties. Swiss ADME & pkCSM both the softwares are used in ADMET Analysis.

Molecular Docking Analysis

Protein Selection

Based on Ramachandran plot of protein 4MS4 whose 3D structure is shown in (figure 2) analysis of this plot revealed that the protein's backbone dihedral angles (phi and psi) are largely located in favorable regions, reflecting a stable and well-folded structure. Its suitability for biological activity is shown by its structural stability. These findings provide potential pathways for identifying new treatment targets and motivate further research into the possible roles that 4MS4's structural characteristics may play in the molecular processes leading epilepsy.

Active site Detection

The SiteMap function in Schrödinger, which helps identify and assess possible binding sites, was used to determine the protein's active site. Molecular docking experiments were conducted to investigate the interaction and inhibitory potential of Tetramethylpyrazine against the GABA(agonist) receptor (PDB ID: 4MS4), which is linked to epilepsy. The 4MS4 protein structure was downloaded from the RCSB PDB database and converted into a protein.pdb file using Biovia Discovery Studio. The protein.pdbqt and ligand.pdbqt files

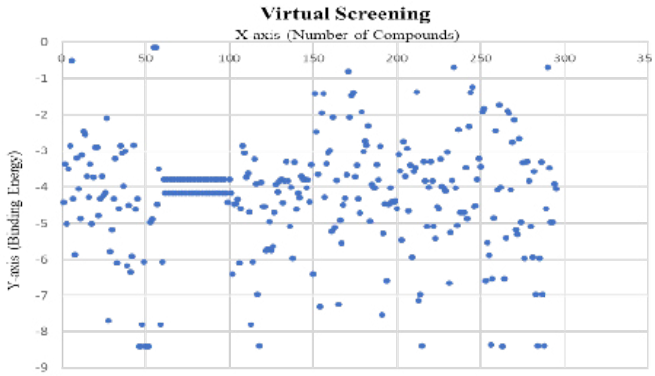


Figure 1: Virtual screening of 300 compounds

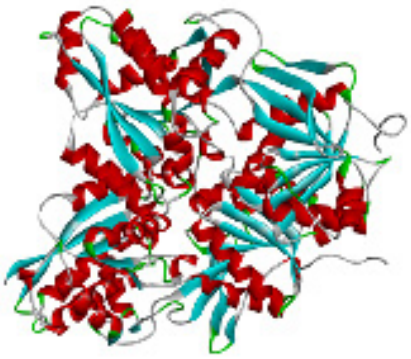


Figure 2: 4MS4 Protein

required for docking were generated using Autodock Tools (12). A three-dimensional grid box with a predetermined center and grid size was used for docking simulations using Autodock software. The docked protein-ligand complex and its two-dimensional interactions were visualized using Biovia Discovery Studio.

Designing of Ramachandran plot:

Obtaining the 4MS4 protein structure from the Protein Data Bank (PDB) is the primary step in making a Ramachandran plot. Then Biovia Discovery Studio starts. To load the protein structure that was downloaded, go to File, pick the file, and then click Open. Once the structure has loaded, create the Ramachandran plot by choosing Chart then choosing Ramachandran Plot in the program(13).

The Ramachandran plot of the 4MS4 protein which is shown in (figure 3) which provides crucial details on its structural stability, activity, and their suitability for functional applications. The majority of the residues (green dots) are found in the preferred (blue) and permitted (pink) regions, confirming the protein's well-folded and reliable structure, which is essential for maintaining its stability and functionality. Flexible residues like glycine, loops, or active site residues may be represented by a few outliers (red triangles) in prohibited areas. These residues often take on peculiar conformations that are essential for activity. As shown in figure 3, proteins with large percentages of residues in the preferred and permitted areas are often dependable for computational or experimental investigations, guaranteeing structural integrity. The 4MS4 protein's good structural quality suggests that it is likely to display appropriate biological activity, which makes it appropriate for more research or functional investigations. This plot supports the choice of the 4MS4 protein for study or applications.

Docking Simulation

Molecular docking (14)studies targeting the protein with PDB ID 4MS4, which corresponds to the GABA(B) receptor(15)—a G-protein-coupled receptor crucial for inhibitory neurotransmission in the brain—were used to evaluate 300 interesting candidates. This investigation indicated their potential in the treatment of epilepsy. Neuronal excitability and synaptic transmission are regulated by the GABA(B) receptor, which is necessary to reduce excessive neuronal activity. By regulating the amount of excitatory to inhibitory brain impulses, this receptor helps to avoid the abnormal neuronal activity associated with epileptic seizures. Therefore, targeting the GABA(B) receptor is one potential therapeutic approach for the treatment of epilepsy.

Results and Discussion

Quantum Stability Studies

The stability and electrical characteristics of Tetramethylpyrazine were investigated using simulations of the Density Functional Theory (DFT) (16). Important details on the stability and electrical transitions of the molecule were revealed by calculating the energy difference between the Lowest Unoccupied Molecular Orbital (LUMO) and the Highest Occupied Molecular Orbital (HOMO) (17). The LUMO and HOMO energies were determined to be -0.04344 and -0.21636 a.u., respectively. The formula for the calculated energy difference is:

Egap = LUMO – HOMO = (–0.04344) – (–0.21636) =0.17292 Hartree.

The energy gap is around 4.71 eV in electronvolts (eV). This substantial HOMO-LUMO gap suggests significant molecular

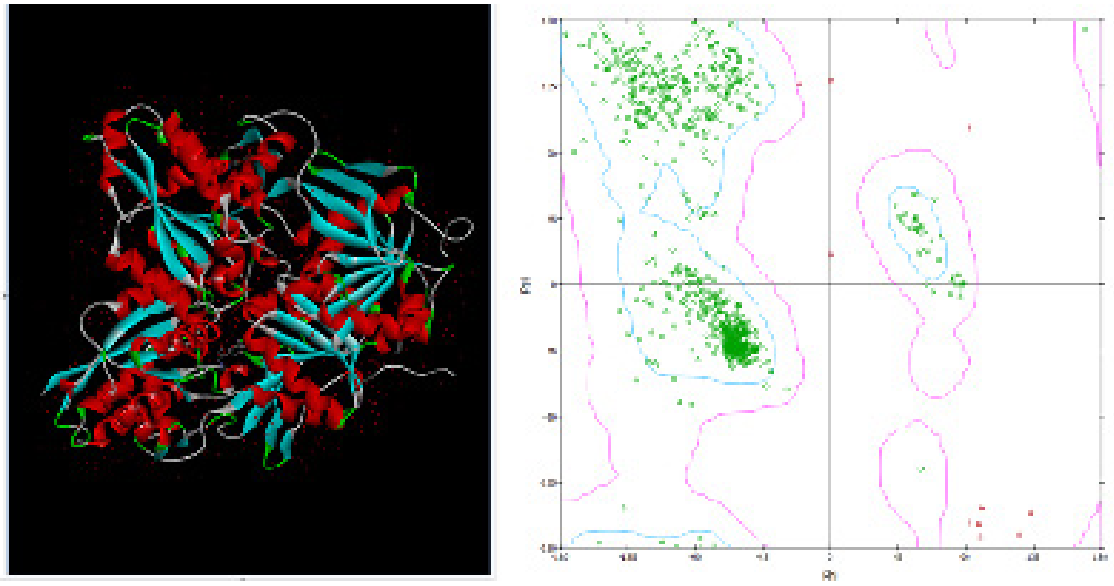


Figure 3: Ramachandran Plot of 4MS4 protein

Table 1: *In-Silico* Pharmacokinetic Profiling Outcomes of TMP Analogues

Property	*Model name*	*Compound*	*Predicted value*
Absorption	Water absorption	TMP1	-0.27
		TMP2	-0.384
		TMP3	-2.647
		TMP4	-2.66
		TMP5	-2.005
		TMP6	-1.425
		TMP7	-2.324
	Caco2 Permeability	TMP1	1.162
		TMP2	1.455
		TMP3	1.185
		TMP4	0.752
		TMP5	1.384
		TMP6	1.063
		TMP7	1.272
	Intestinal absorption (human)	TMP1	98.468
		TMP2	99.721
		TMP3	100
		TMP4	99.851
		TMP5	94.21
		TMP6	83.181
		TMP7	96.128
	Log P	TMP1	0.18708
		TMP2	0.94868
		TMP3	0.50532
		TMP4	-0.4445
		TMP5	0.7112
		TMP6	-2.0816
		TMP7	1.55692
	Mol Wt.	TMP1	168.196
		TMP2	152.197
		TMP3	194.238
		TMP4	236.251
		TMP5	154.277
		TMP6	212.273
		TMP7	205.261
	Rotatable bonds	TMP1	0
		TMP2	0
		TMP3	0
		TMP4	1
		TMP5	0
		TMP6	0
		TMP7	0
	Acceptor	TMP1	2
		TMP2	2
		TMP3	4
		TMP4	5
		TMP5	0
		TMP6	2
		TMP7	3
	Donor	TMP1	0
		TMP2	0
		TMP3	1
		TMP4	1
		TMP5	1
		TMP6	1
		TMP7	1
	Surface area	TMP1	71.247
		TMP2	66.289
		TMP3	82.694
		TMP4	98.826
		TMP5	69.772
		TMP6	89.615
		TMP7	89.306
Distribution	VDss (hum)	TMP1	0.403
		TMP2	0.207
		TMP3	0.002
		TMP4	-0.84
		TMP5	0.712
		TMP6	0.265
		TMP7	-0.067
	Fractional unbounded	TMP1	0.892
		TMP2	0.764
		TMP3	0.702
		TMP4	0.786
		TMP5	0.587
		TMP6	0.908
		TMP7	0.604
	BBB Permeability	TMP1	-0.25
		TMP2	-0.208
		TMP3	-0.251
		TMP4	-0.311
		TMP5	0.2
		TMP6	-0.099
		TMP7	-0.226
	CNS Permeability	TMP1	-2.808

Property	*Model name*	*Compound*	*Predicted value*
		TMP2	-2.887
		TMP3	-2.949
		TMP4	-3.005
		TMP5	-1.686
		TMP6	-3.539
		TMP7	-3.374
Excretion	Total clearance	TMP1	0.518
		TMP2	0.563
		TMP3	0.217
		TMP4	0.237
		TMP5	1.083
		TMP6	0.971
		TMP7	0.175
Toxicity	Max tolerated dose	TMP1	0.436
		TMP2	0.593
		TMP3	0.091
		TMP4	0.933
		TMP5	0.315
		TMP6	0.533
		TMP7	0.646
	Oral rat acute tox (LD50) [mol/Kg]	TMP1	2.567
		TMP2	2.405
		TMP3	2.326
		TMP4	2.202
		TMP5	2.06
		TMP6	1.65
		TMP7	2.587
	Oral rat chr. Tox (LOAEL) [log mg/kg _bw/day]	TMP1	0.689
		TMP2	1.247
		TMP3	0.731
		TMP4	0.834
		TMP5	1.104
		TMP6	1.532
		TMP7	0.922
	T.Pyriformis toxicity (log ug/L)	TMP1	0.426
		TMP2	-0.215
		TMP3	0.377
		TMP4	0.251
		TMP5	0.524
		TMP6	-0.239
		TMP7	0.524
	Minnow toxicity	TMP1	2.877
		TMP2	2.348
		TMP3	2.679
		TMP4	3.043
		TMP5	1.666
		TMP6	4.008
		TMP7	2.342

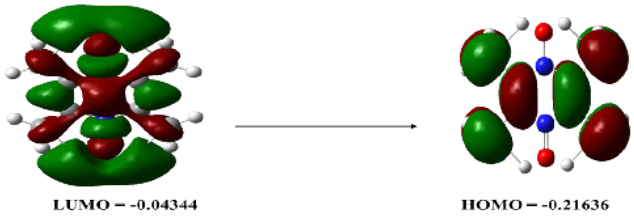


Figure 4: The molecular orbital distribution with an energy level

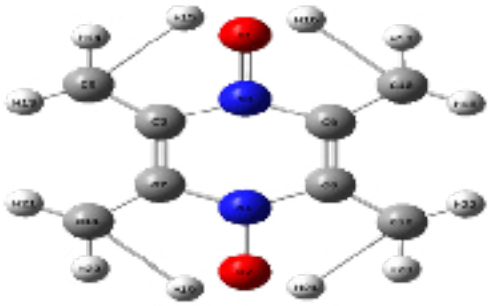


Figure 5: Optimized molecular structures of Tetramethyl-pyrazine

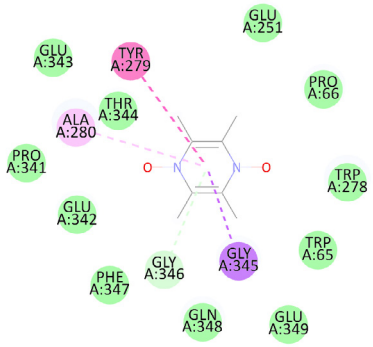
stability and a reduced tendency for electronic excitation under normal conditions (18). The Egap magnitude, which denotes a stable electronic structure, supports the chemical adaptability of Tetramethylpyrazine.

An energy gap of 4.71 eV indicates a major difference between the HOMO and LUMO energy levels, which significantly affects the compound's electrical and optical properties. Since electrons need a significant amount of energy to go from the HOMO to the LUMO, a large energy gap denotes both strong stability and low reactivity, which minimizes the possibility that the molecule would engage in chemical or redox activities. Moreover, it implies limited electrical conductivity since the molecule is more likely to function as an insulator than a conductor or semiconductor. Additionally, the huge energy gap corresponds to UV absorption rather than visible light since the required excitation energy coincides with shorter wavelengths.

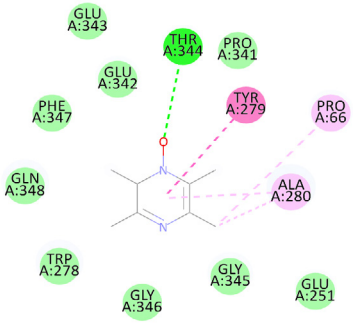
Molecular Orbitals and Visualization

The HOMO and LUMO distributions were shown to help visualize the electrical structure of the molecule. The HOMO, which had an electron density mostly concentrated around

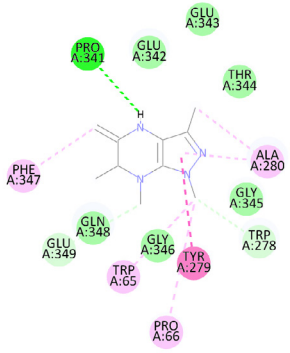
Table 2: 2D Interactions of TMPz Derivatives



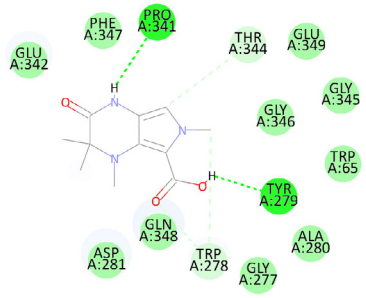
TMP1



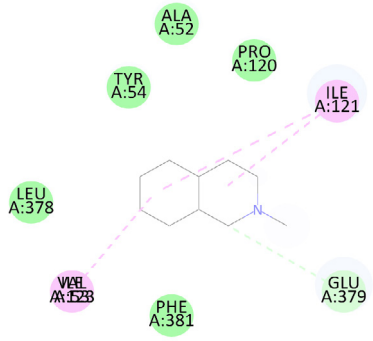
TMP2



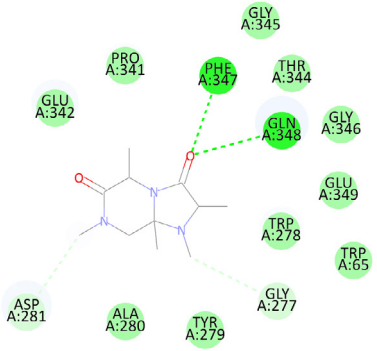
TMP3



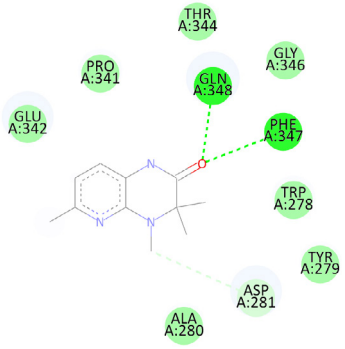
TMP4



TMP5



TMP6

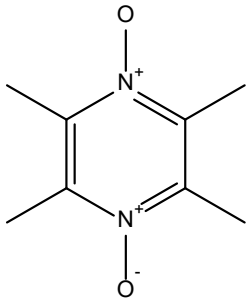
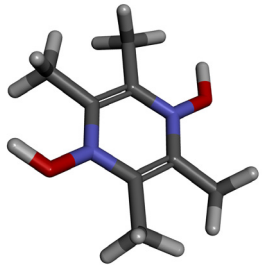
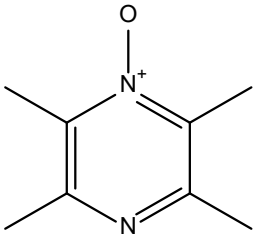
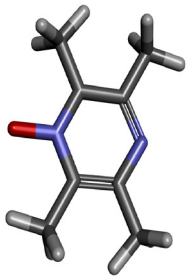
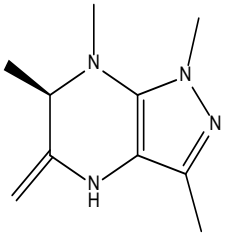
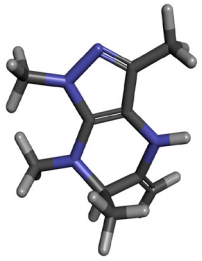
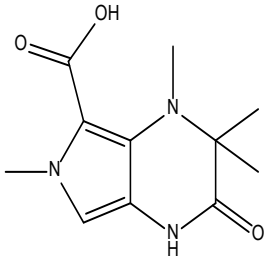
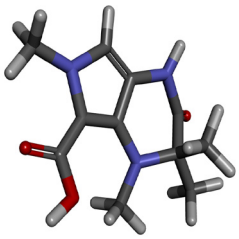
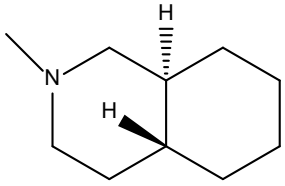
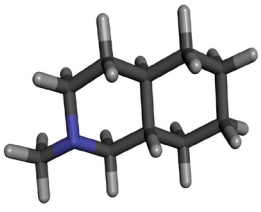


TMP7

Interactions

- van der Waals
- Pi-Donor Hydrogen Bond
- Pi-Sigma
- Amide-Pi Stacked
- Pi-Alkyl

Table 3: Structures of TMPz Derivatives

S. No.	Compound name	*2D structure*	*3D structure*
1	TMP1	 2,3,5,6-tetramethylpyrazine 1,4-dioxide	
2	TMP2	 2,3,5,6-tetramethylpyrazine 1-oxide	
3	TMP3	 (*R*)-1,3,6,7-tetramethyl-5-methylene-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyrazine	
4	TMP4	 3,3,4,6-tetramethyl-2-oxo-2,3,4,6-tetrahydro-1*H*-pyrrolo[3,4-*b*]pyrazine-5-carboxylic acid	
5	TMP5	 (4a*R*,8a*S*)-2-methyldecahydroisoquinoline	

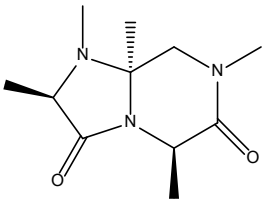
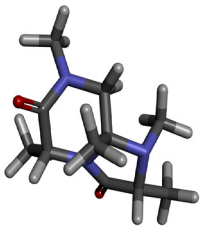
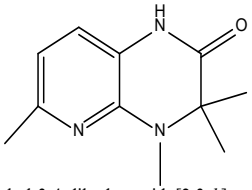
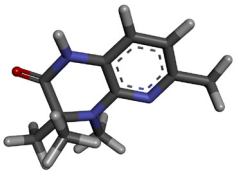
6	TMP6	 (2*R*,5*R*,8a*R*)-1,2,5,7,8a-pentamethyltetrahydroimidazo[1,2-*a*]pyrazine-3,6(2*H*,5*H*)-dione	
7	TMP7	 3,3,4,6-tetramethyl-3,4-dihydropyrido[2,3-*b*]pyrazin-2(1*H*)-one	

Table 4: Molecular docking results of 7 major compounds

S No.	*Compounds*	*Binding Energy (Kcal/mol)*
1.	TMP1	-8.14
2.	TMP2	-8
3.	TMP3	-7.813
4.	TMP4	-7.312
5.	TMP5	-7.242
6.	TMP6	-7.135
7.	TMP7	-7.11
8.	Sodium Valproate	-6

the pyrazine ring with significant delocalization throughout the molecular structure, indicating strong conjugation within the system.

The LUMO, on the other hand, showed a more dispersed electron density, with notable contributions near the methyl groups and heteroatoms. The stability of the molecule's boundary molecular orbitals is supported by the π-conjugated structure, which is highlighted in these graphical depictions.

Implications of the Energy Gap

The HOMO-LUMO value (19), which is shown in (figure 4) and the calculated gap of 4.71 eV correlates with values often seen in stable aromatic heterocyclic systems. Tetramethylpyrazine is positioned as a viable choice for applications requiring chemically stable or long-lasting compounds since a larger gap often signals less reactivity and better stability. The discovered orbital patterns further indicate the role of the pyrazine core in maintaining the electrical stability of the molecule and the Optimized molecular structures of Tetramethyl-pyrazine is shown in (figure 5).

ADMET Results

The SwissADME (20) and pkCSM (21) online predictive models were used to evaluate the drug-likeness of tetramethylpyrazine compounds. Properties including toxicity, distribution, excretion, metabolism, and absorption were also assessed using the pkCSM program. The table below provides a summary of the analysis' findings. TMP1 exhibited remarkable absorption in the human intestine (Table 1). Furthermore, the ADMET study found no toxicity or hepatotoxicity in the chemical, suggesting a high safety profile for potential epilepsy treatment.

Molecular Docking Results:

According to the molecular docking data, seven of the 300 compounds analyzed had the highest binding energies, indicating that they interacted significantly with the target protein 4MS4 whicch is GABA (B) receptor (22). These compound's excellent docking sites and binding affinities suggest that they could be useful inhibitors. The table below displays the binding energy values of these top 7 molecules, which were noticeably lower than those of the other compounds (Table 2 and 4). This implies that there is a greater chance of stable complexes forming between these chemicals and the protein. These results highlight the seven compounds' promising therapeutic potential and suggest further investigation into them as potential treatments for epilepsy (23)(24).

Conclusion

Using modern computational techniques, we demonstrate in this study the potential of Tetramethylpyrazine derivatives as alternatives to anti-epileptic drugs. Seven compounds with a high affinity for the GABA(B) receptor were identified via the use of molecular docking and virtual screening (PDB ID: 4MS4). With a binding energy of -8.14 kcal/mol for TMP1, the best compound demonstrated a robust receptor engagement via non-bonding forces. The electronic stability of the compounds with a HOMO-LUMO energy gap of 4.71 eV was validated by simulations using Density Functional Theory. According to the ADMET research,

their moderate lipophilicity, low toxicological profile, excellent absorption, and limited blood-brain barrier penetration further supported their potential as drug candidates. This method, which blends pharmacokinetic assessment, quantum chemical analysis, and virtual screening, gives sufficient evidence of these medications' potential to treat epilepsy. Further research is required to verify their efficacy and safety, which will aid in the creation of novel epilepsy therapies.

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