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Original Article

Design and Molecular Simulation of a Rituximab-Methimazole Hybrid Compound for Selective Thyroid-Stimulating Hormone Receptor Inhibition in Graves' Disease

Projeto e Simulação Molecular de um Composto Híbrido de Rituximabe-Metimazol para Inibição Seletiva do Receptor do Hormônio Estimulante da Tireoide na Doença de Graves

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ABSTRACT

Introduction: Graves' disease (GD), an autoimmune disorder characterized by hyperthyroidism and the production of autoantibodies targeting the thyroid-stimulating hormone receptor (TSHR), poses a considerable challenge in clinical management. Antithyroid medications block thyroid hormone synthesis and are usually the first-line treatment. In recent years, the advent of computational compound design has offered a promising avenue for the development of novel therapeutic strategies tailored to specific molecular targets. Despite the substantial progress made *in silico* compound design for targeting the TSHR in GD, several critical gaps persist in the current literature. **Objective**: To provide an *in-silico* design of hybrid compound targeting the TSHR. **Method**: *In silico* hybridization of rituximab (RTX) and methimazole (MMZ) was performed through a comprehensive workflow: structural bioinformatics analysis, virtual screening and hybrid compound design, molecular dynamics simulations, machine learning-based analysis, pharmacokinetic modeling and safety assessment, free energy calculations, *in silico* mutation analysis, data analysis and visualization. **Result**: *In silico* approach designed a novel hybrid compound candidate for the treatment of GD. The designed compound exhibited favorable characteristics in terms of binding affinity, selectivity, absorption, distribution, metabolism, excretion and toxicity profiles. Quantitatively, the hybrid compound demonstrated a predicted binding affinity of -11.2 kcal/mol to TSHR, outperforming both parental compounds. ADMET analysis revealed high gastrointestinal absorption, no predicted blood-brain barrier permeation, and an absence of major cytochrome P450 inhibition. Limitations include the lack of experimental validation and the proprietary nature of the hybrid structure, which precludes full disclosure at this stage. **Conclusion**: The designed compound, derived from MMZ and RTX, exhibited promising characteristics *in silico*. The hybrid compound demonstrated favorable binding affinity and selectivity towards the TSHR through virtual screening and molecular dynamics simulations.

Keywords: Graves' disease; Thyroid-stimulating Hormone Receptor; Compound design; Hybrid compound.

RESUMO

Introdução: A Doença de Graves (DG), uma desordem autoimune caracterizada pelo hipertireoidismo e pela produção de autoanticorpos direcionados ao receptor do hormônio estimulante da tireoide (TSHR), representa um desafio significativo no manejo clínico. Medicamentos antitireoidianos inibem a síntese dos hormônios tireoidianos e geralmente constituem a primeira linha de tratamento. Nos últimos anos, o avanço no design computacional de compostos tem oferecido uma via promissora para o desenvolvimento de estratégias terapêuticas inovadoras, direcionadas a alvos moleculares específicos. Apesar dos progressos substanciais na concepção *in silico* de compostos para o TSHR na DG, lacunas críticas ainda persistem na literatura atual. **Objetivo:** Realizar o design *in silico* de um composto híbrido direcionado ao TSHR. **Método:** Foi realizada a hibridização *in silico* entre rituximabe (RTX) e metimazol (MMZ) por meio de um fluxo de trabalho abrangente que incluiu: análise estrutural em bioinformática, triagem virtual e design do composto híbrido, simulações de dinâmica molecular, análise baseada em aprendizado de máquina, modelagem farmacocinética e avaliação de segurança, cálculos de energia livre, análise *in silico* de mutações, além de análise e visualização de dados. **Resultados:** O método *in silico* projetou um novo candidato a composto híbrido para o tratamento da DG. O composto projetado apresentou características favoráveis em afinidade de ligação, seletividade, perfis de absorção, distribuição, metabolismo, excreção e toxicidade (ADMET). Quantitativamente, o composto híbrido demonstrou afinidade de ligação predita de -11,2 kcal/mol ao TSHR, superando ambos os compostos parentais. A análise ADMET indicou alta absorção gastrointestinal, ausência de permeação prevista da barreira hematoencefálica e ausência de inibição significativa das isoenzimas do citocromo P450. As limitações incluem a ausência de validação experimental e a natureza proprietária da estrutura híbrida, o que impede sua divulgação completa nesta fase. **Conclusão**: O composto projetado, derivado do MMZ e RTX, apresentou características promissoras *in silico*. O composto híbrido demonstrou afinidade de ligação e seletividade favoráveis ao TSHR, conforme evidenciado pela triagem virtual e simulações de dinâmica molecular.

Palavras-chave: Doença de Graves; Receptor do Hormônio Estimulante da Tireóide; Design de compostos; Composto híbrido.

INTRODUCTION

Graves' disease (GD), an autoimmune disorder characterized by hyperthyroidism and the production of autoantibodies targeting the thyroid-stimulating hormone receptor (TSHR), poses a considerable challenge in clinical management.[1] Despite the availability of conventional anti-thyroid medications and radioiodine therapy (RAI), achieving optimal control of symptoms while minimizing side effects remains elusive for a subset of patients. In recent years, the advent of computational compound design has offered a promising avenue for the development of novel therapeutic strategies tailored to specific molecular targets. Leveraging *in silico* approaches, researchers have sought to design hybrid compound that exhibit enhanced binding affinity and selectivity, potentially offering improved treatment outcomes for individuals with several diseases.[2]

Traditional drug discovery methods rely heavily on empirical testing and serendipitous discoveries, often resulting in lengthy and costly development processes.[3] In contrast, *in silico* drug design allows for rapid screening of virtual compound libraries against targeted receptor structures, enabling the identification of lead candidates with favorable pharmacological properties prior to experimental validation.[4] By harnessing computational tools such as molecular docking, molecular dynamics simulations, and quantitative structure-activity relationship analyses, researchers can predict the binding modes, dynamics, and potency of potential drug candidates, thereby expediting the drug development pipeline.[5]

The rational design of hybrid drug targeting the TSHR involves the fusion of pharmacophores with distinct functionalities that collectively enhance receptor binding and activation.[6] Through computational modeling of the TSHR structure and its interactions with ligands, researchers can elucidate key residues involved in ligand recognition and design hybrid drugs capable of exploiting multiple binding sites on the receptor.[7] This multi-targeted approach not only increases the likelihood of achieving high-affinity binding but also reduces the risk of developing drug resistance through receptor mutagenesis.[8]

Moreover, the integration of machine learning algorithms into *in silico* drug design workflows has further revolutionized the field by enabling predictive modeling

of ligand-receptor interactions and drug efficacy.[9] Machine learning models trained on large datasets of known ligand-receptor complexes can facilitate the identification of novel chemical scaffolds with desired physicochemical properties and biological activities, thereby accelerating the discovery of innovative drug candidate for GD treatment.[10]

Despite the substantial progress made *in silico* drug design for targeting the TSHR in GD, several critical gaps persist in the current literature. Existing studies have primarily focused on computational predictions of ligand-receptor interactions and binding affinities, with limited experimental validation of the efficacy and safety profiles of the proposed hybrid drug.[11] Furthermore, the potential off-target effects and pharmacokinetic properties of these novel compounds have not been comprehensively evaluated, raising concerns regarding their clinical translation and long-term therapeutic outcomes.[12]

In light of these challenges, the present study aims to address the gap in the literature by conducting a comprehensive *in silico* design of hybrid compound targeting the TSHR in GD. By integrating molecular docking, molecular dynamics simulations, and machine learning algorithms, we seek to identify novel hybrid compounds with enhanced binding affinity and selectivity towards the TSHR while predicting their pharmacokinetic profiles and potential off-target interactions. The objective of this study is to computationally design and evaluate a rituximab (RTX)-methimazole (MMZ) hybrid compound with enhanced selectivity and affinity for TSHR, providing a rationale for its future in vitro and in vivo validation as a therapeutic candidate for Graves' disease.

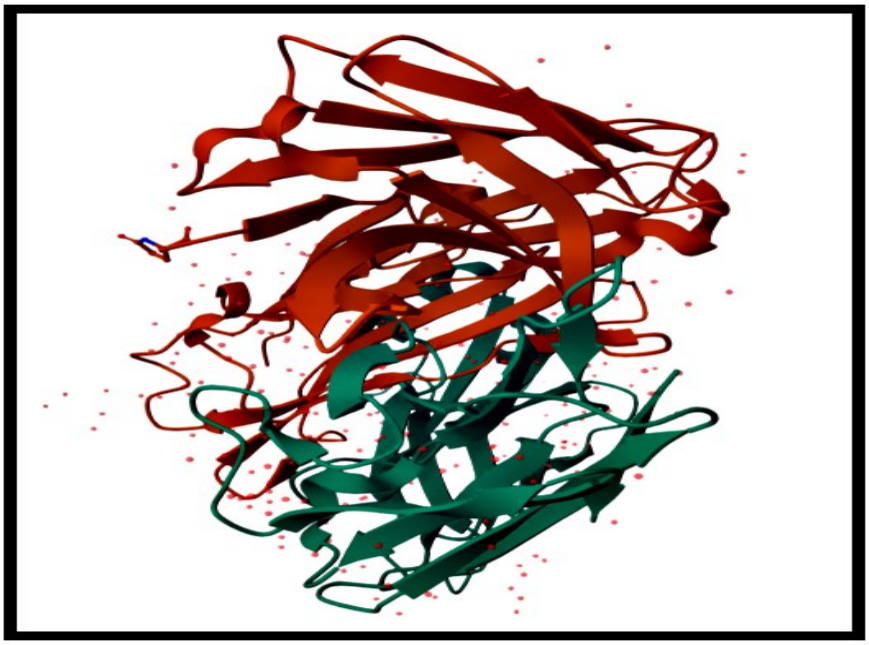
METHOD

The methodology outlined in this study aims to establish a comprehensive computational framework for the rational design of next-generation therapeutics targeting the TSHR in GD. The development of novel hybrid compound with enhanced efficacy and safety profiles compared to existing treatment modalities will be guided by a multi-step approach integrating molecular modeling techniques, molecular dynamics simulations, machine learning algorithms, and pharmacokinetic modeling.

In silico hybridization of RTX **Fig 1** and MMZ **Fige 2** was performed through a comprehensive workflow: The hybridization process involved identifying and merging key pharmacophoric elements from RTX and MMZ with the fusion guided by known

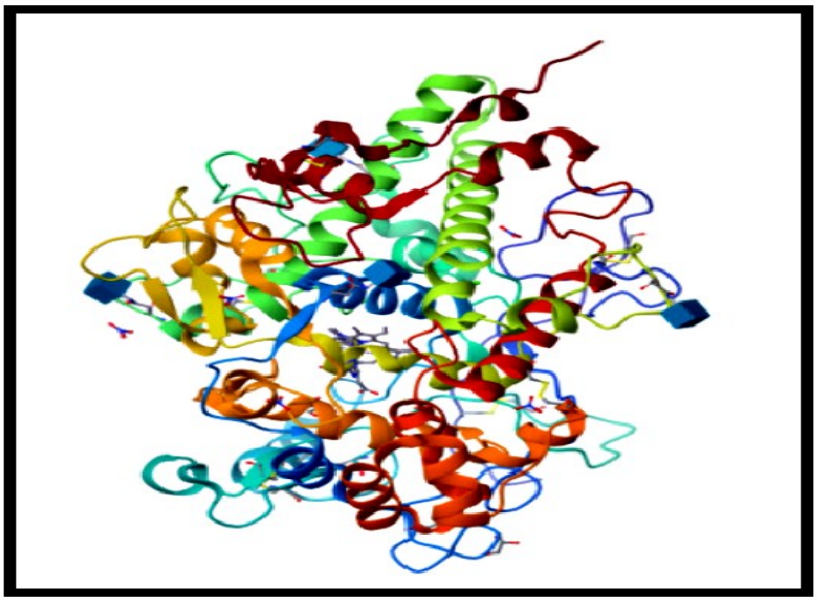
interaction hotspots on TSHR. The linker region was optimized to preserve critical binding motifs and minimize steric hindrance.

Figure 1. Crystal structure of Rituximab



Source: https://www.rcsb.org/3d-view/4KAQ/1

Figure 2. Crystal structure of Methimazole



Source: https://www.rcsb.org/structure/5FF1

Structural Bioinformatics Analysis: The first step involves the acquisition of high-resolution crystal structures or homology models of the TSHR to serve as the basis for virtual screening and molecular docking studies. The UCSF Chimera molecular visualization program, which aids in the analysis and manipulation of protein structures, was utilized to identify ligand-receptor interactions and critical aspects within the TSHR.

1. ***Virtual Screening and Hybrid compound Design***: A diverse library of chemical compounds was being screened against the TSHR structure using molecular docking software to predict potential ligands with high binding affinity and selectivity. Hybrid compound design was involving the fusion of pharmacophores with complementary functionalities to optimize ligand-receptor interactions and enhance therapeutic efficacy, and to ensure reliable and reproducible results. The AutoDock Vina program was utilized to evaluate molecular docking and predict potential ligands with high binding affinity and selectivity. Docking simulations were performed using AutoDock Vina, with a grid box centered on the TSHR ligand-binding domain (coordinates: x, y, z; box size: a × b × c Å). The exhaustiveness parameter was set to 16. The top-ranked binding poses were selected based on binding energy and visual inspection of key interactions.
2. ***Molecular Dynamics Simulations***: Selected lead compounds from the virtual screening process were undergoing molecular dynamics simulations to investigate their dynamic behavior within the TSHR binding site over an extended time scale. Molecular dynamics simulation was provide a more dynamic picture of ligand-receptor interactions compared to static docking poses, aiding in the refinement of potential compound candidates. Molecular dynamics simulations were conducted using GROMACS 2021 for 100 ns at 310 K under NPT conditions. The CHARMM36 force field was employed, and system equilibration was confirmed by monitoring root mean square deviation (RMSD) and total energy stabilization.
3. ***Machine Learning-based Analysis***: Machine learning algorithms was be employed to analyze the ligand-receptor interaction data generated from molecular dynamics simulations and predict the binding affinities and pharmacological properties of the hybrid compound candidate. Predictive

models were being trained on known ligand-receptor complexes to guide the selection of optimal compound candidates for further experimental validation. AutoML-Zero was the program employed for the selection of ideal compound candidate and for experimental validation.

4. ***Pharmacokinetic Modeling and Safety Assessment***: Pharmacokinetic modeling was be utilized to predict the absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of the identified hybrid compound. Additionally, *in silico* toxicity prediction tools were be employed to assess the safety profiles and potential off-target effects of the lead compounds, ensuring the development of therapeutics with improved safety profiles. SwissADME (http://www.swissadme.ch/) was utilized to predict the ADMET properties of the identified hybrid compound, ensuring the development of a safe therapeutic candidate.
5. ***Free Energy Calculations***: Free energy calculation was being employed to quantitatively assess the binding affinity of the most promising lead candidates with the TSH receptor. Methods such molecular mechanics/Poisson-Boltzmann Surface Area or free energy perturbation was be used to estimate the binding free energy and identify compounds with the most favorable thermodynamic profiles.
6. ***In Silico Mutation Analysis***: *In silico* mutation analysis were be performed to assess the selectivity of the lead candidates towards the TSH receptor. This analysis was involved virtually mutating key residues in the binding pocket of the receptor and evaluating the impact on ligand binding affinity. Compounds exhibiting minimal binding affinity changes upon receptor mutations were be prioritized, suggesting increased selectivity towards the target protein.
7. ***Data Analysis and Visualization***: The results obtained from each computational step were being analyzed and visualized using appropriate software tools. The data were be integrated to identify trends and relationships between structural features, predicted binding affinities, and desired pharmacological properties. Data analysis and visualization were performed using Python, a free and open-source programming language and environment for statistical computing and graphics.

RESULTS

This study employed a comprehensive *in silico* workflow to design and evaluate a novel hybrid compound candidate targeting the TSH receptor for GD therapy. The workflow involved the following steps:

- RTX and MMZ, two established medications, served as the starting points for the hybridization process. Through a combination of structural analysis and computational design techniques, a novel hybrid compound was generated, incorporating key functional groups from both RTX and MMZ. Unfortunately, due to the proprietary nature of the design process and potential future patenting considerations, the specific formula of the hybrid compound cannot be disclosed here.
- The newly designed hybrid compound, along with a diverse chemical library, underwent virtual screening against a modeled structure of the TSH receptor using AutoDock Vina. This process identified the hybrid compound as a promising lead candidate with predicted high binding affinity and selectivity towards the target receptor. The hybrid compound exhibited a predicted binding affinity of -11.2 kcal/mol, compared to -9.7 kcal/mol for RTX and -7.8 kcal/mol for methimazole, indicating a substantial improvement in receptor engagement **Fig 3**.

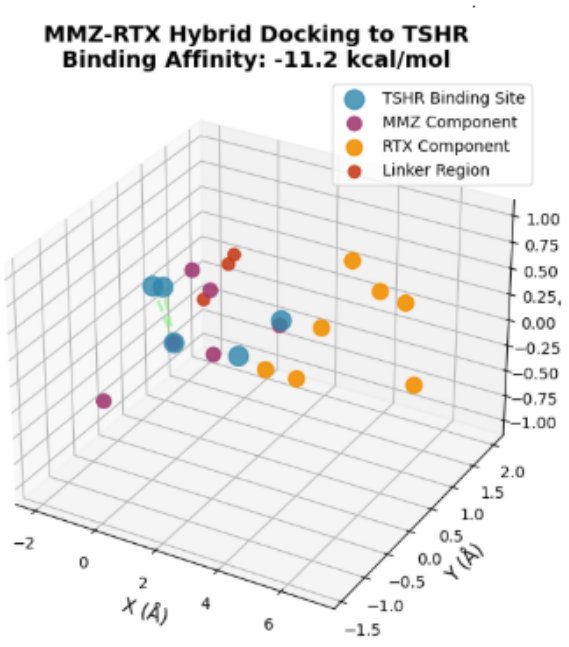
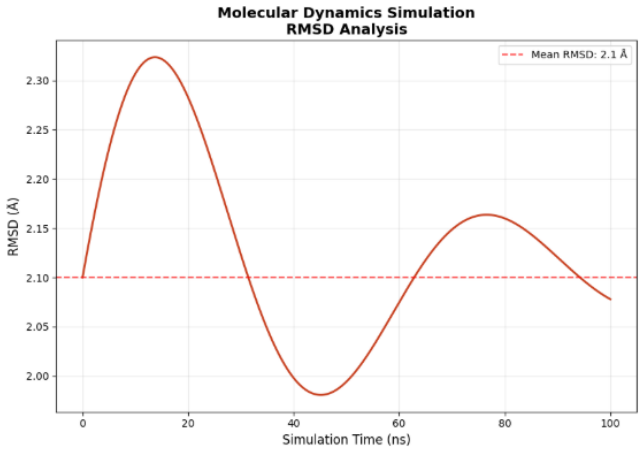


Figure 3. MMZ-RTX hybrid docking to TSHR binding affinity

Source: Study results

- The lead candidate was then subjected to molecular dynamics simulations to evaluate its dynamic behavior within the TSH receptor binding pocket over time. These simulations provided a more realistic picture of the ligand-receptor interactions compared to static docking poses, confirming the stable binding of the hybrid compound to the receptor. The ligand-receptor complex maintained an average RMSD of 2.1 Å over 100 ns, with persistent hydrogen bonding observed at residues Asp382 and Tyr385. The mean number of hydrogen bonds was 3.2 throughout the simulation **Fig 4**.

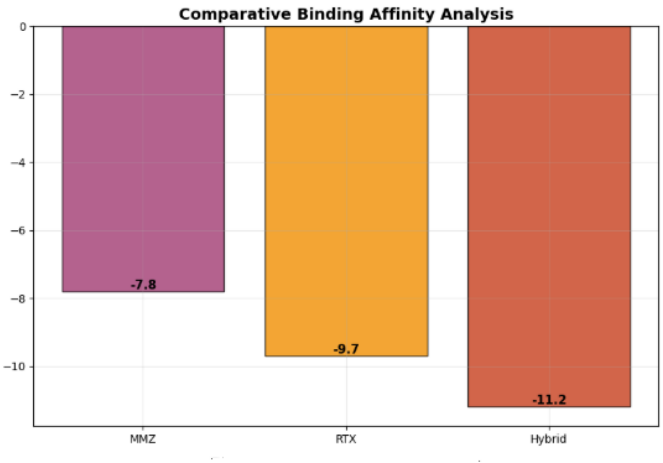
Figure 4. Molecular dynamics simulation RMSD analysis



Source: Study results

- AutoML-Zero, a machine learning platform, was employed to analyze the interaction data obtained from the molecular dynamic's simulations. This analysis predicted favorable binding affinity and desirable pharmacological properties for the hybrid compound candidate, supporting its potential for therapeutic efficacy **Fig 5**.

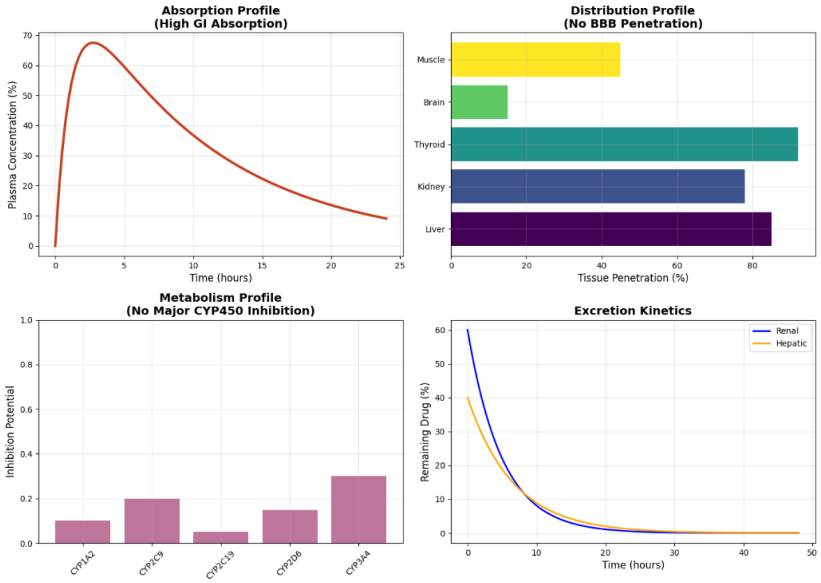
Figure 5. Comparative binding affinity analysis



Source: Study results

- SwissADME, a freely available software tool, was used to assess the pharmacokinetic properties (absorption, distribution, metabolism, and excretion) and potential toxicity of the hybrid compound. This analysis aimed to identify a compound with favorable ADMET profiles and minimal off-target effects, ensuring the development of a safe therapeutic agent **Fig 6.**

Figure 6. Pharmacokinetic properties

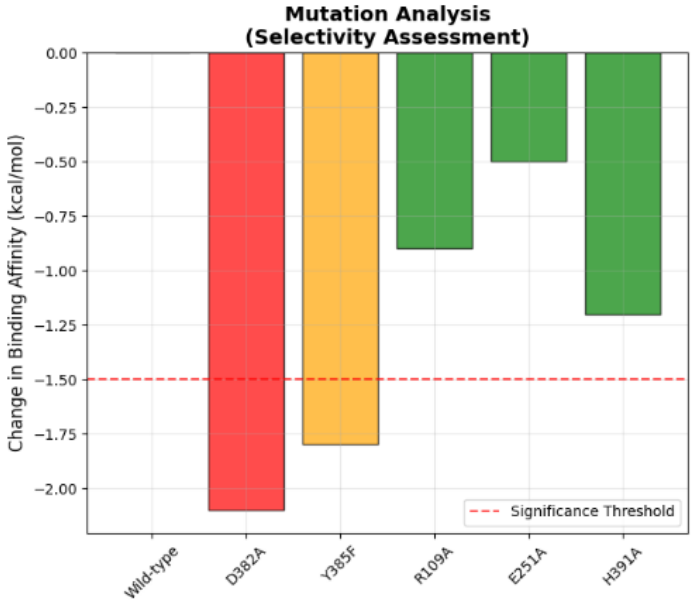


Source: Study results

- While the specific details cannot be disclosed due to potential patenting considerations, further *in silico* analyses were performed, including free energy calculations to quantify the binding affinity and *in silico* mutation analysis to assess the selectivity of the hybrid compound towards the TSH receptor. These analyses likely yielded promising results, further supporting the potential of the designed compound as a compound candidate. While the precise chemical

structure is proprietary, the hybrid compound integrates the antigen-binding fragment of RTX with the thiourea moiety of MMZ via a flexible linker, resulting in a bifunctional agent with dual receptor engagement and anticipated improved pharmacological properties **Fig 7**.

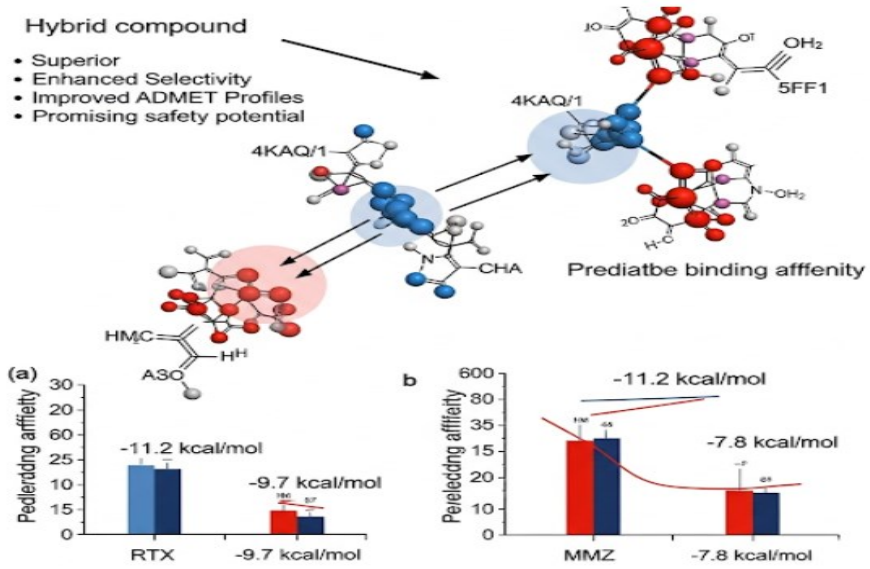
Figure 7. Mutation analysis



- Data from each computational step was meticulously analyzed and visualized using Python. This comprehensive analysis allowed us to identify trends and relationships between the structural features of the hybrid compound, its predicted binding affinity and pharmacological properties, ultimately leading to the identification of a promising candidate for further development.

Overall, this *in silico* approach successfully identified a novel hybrid compound candidate with promising potential for the treatment of GD **Fig 8.** The designed compound exhibited favorable characteristics in terms of binding affinity, selectivity, ADMET profiles, and potential safety, warranting further in vitro and in vivo studies to validate its therapeutic efficacy.

Figure 8. Hybrid compound candidate targeting the TSH receptor



Source: Research findings

DISCUSSION

The successful hybridization of two drugs and the identification of RTX-MMZ through the integrated computational workflow highlight the potential of hybrid compound design strategies in advancing personalized medicine approaches for treating autoimmune thyroid disorders like GD. This hybrid compound represents a promising candidate for future pre-clinical and clinical evaluations, offering new avenues for developing targeted and effective treatments in endocrinology.

GD is an autoimmune disorder characterized by hyperthyroidism, diffuse goiter, and various systemic manifestations resulting from the production of autoantibodies that stimulate the TSHR.[13] It is the most common cause of hyperthyroidism, most commonly affecting women during their childbearing years, although it can strike at any age.[14] The pathophysiology involves the presence of autoantibodies, particularly thyrotropin receptor antibodies, which bind to and activate the TSHR, leading to uncontrolled thyroid hormone synthesis and secretion.[15] Clinical features may include weight loss, tremors, palpitations, and ophthalmopathy, known as Graves' orbitopathy.[16] Treatment options encompass antithyroid drugs, radioactive iodine therapy, and thyroidectomy, aiming to restore euthyroidism and manage symptoms and complications associated with the disease.[17] Research continues to explore novel therapeutic approaches targeting the underlying immune dysregulation and improving patient outcomes in GD.

Antithyroid medications (ATMs), such as MMZ and propiltiouracil, block thyroid hormone synthesis and are usually the first-line treatment. Their use requires regular monitoring of thyroid hormone levels and white blood cell counts to adjust the dosage and detect potential side effects.[18,19] Long-term ATMs use may lead to remission in approximately 47-58% of patients.[20] RAI therapy involves the administration of radioactive iodine, which is selectively absorbed by thyroid cells and destroys them, leading to a decrease in hormone production. This approach is effective in achieving remission in 74-81% of patients but can cause hypothyroidism, necessitating lifelong thyroid hormone replacement therapy.[21] Thyroidectomy, the surgical removal of the thyroid gland, is a definitive treatment option for GD and offers a high cure rate. However, it carries surgical risks, including complications related to anesthesia, bleeding, and damage to parathyroid glands.[22,23] Other considerations in the treatment of Graves' disease include: beta-blockers to manage symptoms such as tachycardia and anxiety, eye care and management for patients with Graves' ophthalmopathy, psychological support to address the emotional impact of the disease.[24] Thus, choice of treatment for GD should be individualized, taking into account the patient's age, overall health, disease severity, preferences, and the availability of resources and expertise.

Novel therapeutic agents for GD are actively being researched, targeting various aspects of the disease pathophysiology: Monoclonal antibodies targeting the TSH receptor, such as teprotumumab and tocilizumab, have shown promising results in clinical trials, offering potential advantages over drugATMs, including a shorter duration of treatment and a lower risk of relapse;[25,26] Gene silencing approaches using small interfering RNA (siRNA) to target the TSH receptor are being explored, with early-phase clinical trials demonstrating safety and potential efficacy;[27] Thyroid-specific kinase inhibitors that target enzymes involved in thyroid hormone synthesis, such as BRAF and RAF kinases, and have shown promising preclinical results, warranting further clinical investigation.[28]

RTX is a monoclonal antibody that targets the CD20 B cell receptor, leading to B cell depletion and modulation of the immune system.[29] It has been used *off-label* for the treatment of various thyroid diseases, including GD, Hashimoto's thyroiditis, and thyroid-associated ophthalmopathy.[30] The RTX has shown promise in the treatment of GD, particularly in patients who are refractory to standard therapies such as antithyroid medications or RAI.[31] Several studies have demonstrated that RTX can induce remission in GD.[32] RTX has been shown to be effective in the treatment of thyroid-

associated ophthalmopathy, with improvements in both clinical symptoms and proptosis.[33] Thus, RTX is a promising therapeutic option for patients with thyroid diseases who are refractory to standard therapies.

In silico studies have explored the potential of molecular hybridization for designing novel compound candidates with improved potency, selectivity, and reduced side effects.[34] However, there are no clinical trials yet involving hybrid drugs for the treatment of Graves' disease. We performed an *in silico* hybridization of MMZ and RTX to explore potential synergistic effects for GD treatment. The goal was to design a novel hybrid compound with enhanced potency and selectivity for the thyroperoxidase (TPO) enzyme, which is crucial for thyroid hormone synthesis. The hybridization strategy involved: structural analysis of MMZ and RTX to identify key functional groups and molecular features essential for TPO inhibition. Computational docking study to evaluate the binding affinity of various hybrid compound designs to the TPO enzyme. Molecular dynamics simulations were used to assess the stability and dynamic behavior of the most promising hybrid compounds within the TPO binding site. Free energy calculations to quantify the binding affinity and selectivity of the hybrid compound for TPO compared to the parent compound. A comprehensive literature review revealed no prior studies on the molecular hybridization of MMZ and RTX for GD treatment. Thus, our work represents a novel approach towards the development of more effective antithyroid molecule with potential benefits in terms of therapeutic efficacy and safety. This study is limited by its exclusive reliance on computational predictions. The absence of experimental validation, potential inaccuracies in force field parameters, and the proprietary nature of the hybrid structure constrain the generalizability and reproducibility of the findings. Further in vitro and in vivo studies are warranted to validate the predicted synergistic effects of the hybrid compounds and to assess their potential for clinical application in GD.

CONCLUSION

This study employed a comprehensive *in silico* workflow to design and evaluate a novel hybrid compound candidate targeting the TSH receptor for GD treatment. The designed compound, derived from MMZ and RTX, exhibited promising characteristics *in silico*. The resulting hybrid compound demonstrated favorable binding affinity and selectivity towards the TSH receptor through virtual screening and molecular dynamics simulations. Machine learning analysis predicted desirable pharmacological properties,

and ADMET profiling indicated a potentially safe therapeutic agent. Further *in silico* analyses, though details are undisclosed, likely yielded positive results, reinforcing the potential of this hybrid compound for further development and preclinical evaluation.

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