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Computational evaluation of leflunomide and ticagrelor combination targeting the A2A receptor for the management of rheumatoid arthritis

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Abstract: **Background**: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint damage and inflammation, which leads to a reduction in patients' quality of life. Traditional therapies are inadequate to eradicate these illnesses. Therefore, cutting-edge therapeutic approaches are required to eradicate these challenges and improve patients' lives. **Objectives**: In the current research work, computational analysis of ticagrelor, a purinergic P2Y G protein-coupled receptor antagonist (P2Y12) that increases extracellular adenosine by blocking equilibrative nucleoside transporter-1 (ENT-1), combined with leflunomide, a traditional disease-modifying anti-rheumatic drug (DMARD), was investigated. Additionally, the study hypothesizes that increased levels of adenosine may activate anti-inflammatory adenosine receptor (A2A) and enhance leflunomide's immunomodulatory effects. **Methods**: Molecular docking was performed using the Python Prescription (PyRx) tool, which integrates with AutoDock Vina and AutoDock 4, providing an optimal balance between computational speed and flexibility. **Results**: Molecular docking demonstrates strong affinities to A2AR Leflunomide -8.7Kcal/mol; and Ticagrelor -8.0 Kcal/mol. Both compounds showed low toxicity according to Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) profiling using Swiss-ADME and ADMETSAR. **Conclusion**: Based on initial *in-silico* findings, the combination of leflunomide and ticagrelor appears to be a promising treatment approach for RA, which warrants further experimental confirmation.

Keywords: Arthritis; Autoimmune disorder; Inflammation; Pain; Receptor

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INTRODUCTION

The main symptoms of Rheumatoid Arthritis (RA) are persistent inflammation of synovial tissues, which eventually leads to joint destruction and other systemic problems that impair general health and a person's quality of life (McInnes and Schett, 2017; Smolen *et al*., 2016). This disease, which is more common in women and particularly affects those between the ages of 30 and 60, affects between 0.5 and 1% of people globally. This condition is caused by a complex interplay among environmental and genetic factors and immune system disruption. The complex pathophysiology of RA is still emphasized in recent reviews, which also show how innate and adaptive immunity interact to cause persistent synovial inflammation.

The activation of macrophages, Beta (β) cells, T cells and other immune cells is the primary factor influencing the development of RA. This process leads to an excessive generation of pro-inflammatory cytokines, interleukin-1 β, tumor necrosis factor alpha and interleukin-6 (McInnes and Schett, 2017; Smolen *et al*., 2018). These cytokines promote inflammation that facilitates synovial hyperplasia (SH), angiogenesis and ultimately results in joint damage (Smolen and Aletaha, 2015).

The primary objective of current approaches, which involve corticosteroids, conventional disease-modifying antirheumatic drugs (csDMARDs), non-steroidal anti-inflammatory drugs (NSAIDs) and biological agents, is to minimize inflammation and prevent further damage to the body. Leflunomide's ability to modify the immune system and reduce cell growth makes it a primary disease-modifying anti-rheumatic drug used in the treatment of RA (Van de Corput *et al*., 1999). Combination or adjunctive medications are essential since a single medication over a long time often results in lower effectiveness and potential liver toxicity (Moulis *et al*., 2015).

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Adenosine plays a crucial role in regulating inflammatory responses and maintaining immune balance. One of the four adenosine receptor subtypes (A2A), A2AR, has become a prominent mediator of anti-inflammatory responses. In particular, recent studies on the microenvironment of RA emphasize the therapeutic potential of modifying the adenosinergic pathway. When activated, the production of anti-inflammatory cytokines such as interleukin-10 increases, the release of pro-inflammatory cytokines decreases and the activity of neutrophils and macrophages decreases. Disruption in adenosine signaling has been associated with the development of several autoimmune disorders, including multiple sclerosis, psoriasis and RA (Antonioli *et al*., 2019).

Ticagrelor, which was approved by the Food and Drug Administration (FDA) as a Purinergic receptor P2Y, G-protein coupled, 12 (P2Y12) receptor antagonist used to prevent blood clots, also works by enhancing the amount of adenosine outside cells. It does this by inhibiting equilibrative nucleoside transporter 1 (ENT-1). When Adenosine levels increase, the A2AR signaling pathways become active, resulting in additional anti-inflammatory effects in addition to their role in reducing platelet activity (Boncler *et al*., 2024).

Leflunomide and ticagrelor work together by targeting immune system regulation and inflammation. This combination is hypothesized to offer a dual-pathway attack on RA pathology: Leflunomide directly suppresses immune cell proliferation and cytokine production, while ticagrelor indirectly promotes the activation of the anti-inflammatory A2AR pathway via adenosine elevation, potentially leading to enhanced efficacy and reduced side effects through dose optimization (Antonioli *et al*., 2019). According to recent pharmacological research (Zhang *et al*., 2021), targeting multiple immune regulatory mechanisms has yielded better results than single-drug therapy, especially in cases with complex immunopathology such as RA. Therefore, examining this combination using computational methods provides a solid basis for preclinical validation. To address the intricate immunopathology of RA, multi-target interventions are becoming more and more popular in modern therapeutic approaches.

In-silico techniques, which allow for accurate and economical predictive modeling of molecular interactions, pharmacokinetics and safety profiles, have revolutionized the early phases of drug development (Daina *et al*., 2017). Molecular docking was used in biological systems to evaluate structural stability and possible ligand-receptor interactions.

Using computational modeling, this study assesses the potential synergistic interactions between ticagrelor and leflunomide via A2AR. While the pharmacokinetic criteria and compliance with Lipinski's rule of five were verified through ADMET profiling and drug likelihood assessment via SwissADME, their binding energies were evaluated using molecular docking analysis (Daina *et al*., 2017; Lionta *et al*., 2014). By modifying inflammatory and immunological responses via A2AR pathways, the research findings aim to provide a theoretical foundation for developing dual-target treatments for RA.

MATERIALS AND METHODS

Material

Python Prescription (PyRx), Chemical Drawing software (ChemDraw software), Python and Molecular Graphics (PyMol), Swiss Institute of Bioinformatics Absorption, Distribution, Metabolism and Excretion (SwissADME) and Absorption, Distribution, Metabolism, Excretion and Toxicity Structure-Activity Relationship database, version 2.0. (admetSAR 2.0).

Method

Selection of a molecular docking tool

PyRx was selected as the primary molecular docking tool because it combines AutoDock Vina and AutoDock 4 tools, providing a good trade-off between computational speed and flexibility (Khalaf *et al*., 2025). Its user-friendly interface makes handling ligands and receptors simple, which streamlines the process of creating and evaluating docking simulations. PyRx uses computational resources effectively and reliably generates accurate predictions of protein-ligand interactions. To validate the docking protocol, the native co-crystallized ligand was extracted and re-docked into the binding site. The root mean square deviation (RMSD) between the docked pose and the original crystallographic pose was calculated to be less than 2.0 A, confirming the reliability of the method. The grid box dimensions were set to 25x25x25 A points with a spacing of 1.0 A, centered on the active site and exhaustiveness was set to 8 (Khalaf *et al*., 2025).

Ligand selection and preparation

The ChemDraw software provided 3D structures of ticagrelor and Leflunomide. An important factor in converting ligands into Protein Data Bank Partial Charge Torsion (PDBQT) format was the Active Directory (AD) tools. The ligands were significantly affected in several ways by this process. It improved rotatable bonds, added Gasteiger charges and verified that the molecular structure was correct. A brief energy reduction was performed on each ligand structure in preparation for docking. Making the structure stable and improving docking predictions were the goals of this step (Kowsalya and Shanmugasundaram, 2022).

Protein target retrieval and preparation

It retrieves the A2A adenosine receptor 3D structure from the Protein Data Bank (PDB). This structure has a resolution of 2.25 Angstroms and PDB ID 7PX4.

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Table 1: Ticagrelor and leflunomide docking results with A2A receptor.

Target protein	Ligand	Binding affinity (kcal/mol)	No. of H-Bonds	Key interacting residues
A2A Receptor	Leflunomide	–8.7	3	Glu194, Ala106, Ile105
A2A Receptor	Ticagrelor	–8.0	5	Glu194, Asp195, Tyr392, Phe193, Ile91

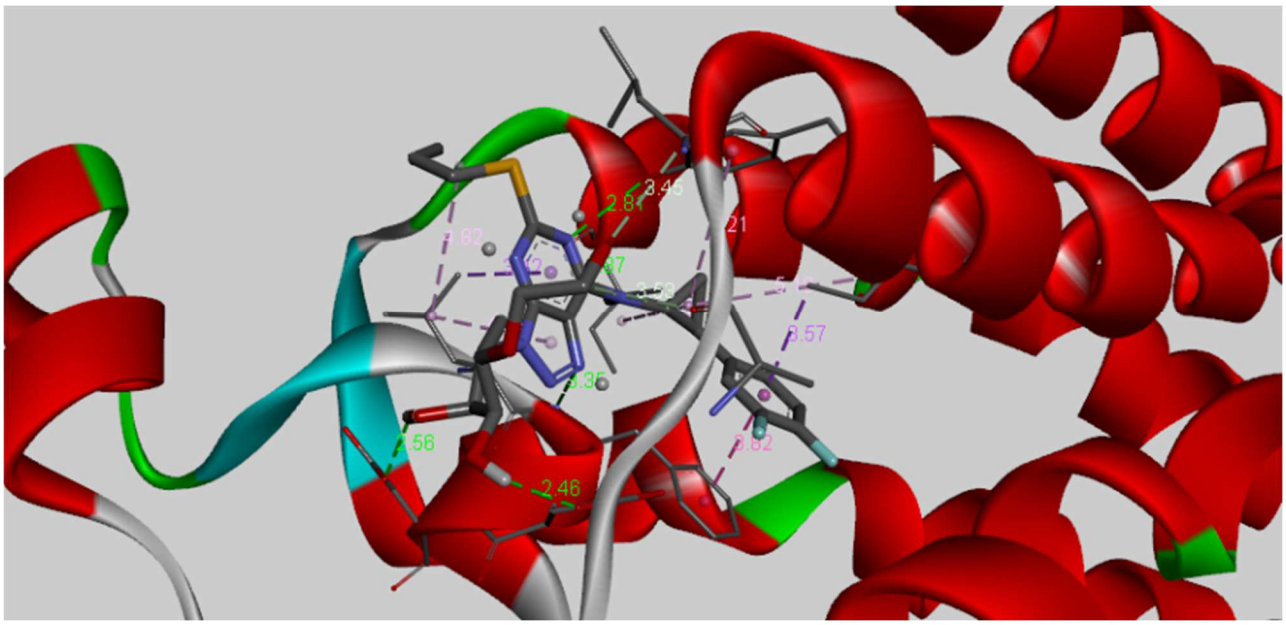

Fig. 1: 3D interaction view of A2A receptor with ticagrelor

The protein is preprocessed using a Python-powered molecular graphics system (PyMol). Co-crystallized ligands, additional heteroatoms and crystallographic water molecules were eliminated in this stage. Following the addition of H atoms (polar), AutoDock Tools (ADT) were used to assign Kollman charges. Because of these preparations, the receptor was prepared for docking.

Pharmacokinetic and drug-likeness evaluation

The pharmacokinetic behavior and drug-like characteristics of ticagrelor and Leflunomide were evaluated with the aid of SwissADME and admetSAR 2.0 (Yang *et al*., 2019). The assessment factors included molecular weight, gastrointestinal (GI) absorption, lipophilicity, Hydrogen (H) -Bond donors (HBD), H-Bond acceptors (HBA), inhibitory profile of CYP450, topological polar surface area and anticipated toxicity class (LD50).

RESULTS

Molecular docking analysis

To evaluate the binding affinities of ticagrelor and leflunomide for A2AR, Molecular Docking simulations were performed using AutoDock Vina integrated into PyRx. Important residues, H-Bond interactions and binding affinities are among the docking data shown in table 1.

By forming many stabilized H-Bonds with residues Glu194, Ala106 and Ile105, Leflunomide demonstrated a binding affinity of -8.7 Kcal/Mol with A2A receptor, which is considered a high binding affinity. In addition, ticagrelor demonstrated a significant affinity with residues Glu194, Asp195, Tyr392, Phe193 and Ile91. The binding interactions were visualized and are depicted in Fig. 1 (Ticagrelor 3D), Fig. 2 (Ticagrelor 2D), Fig. 3 (Leflunomide 3D) and Fig. 4 (Leflunomide 2D).

Visualization of docked complexes

Detailed information about the interaction geometry of both ligands was obtained by visualizing them in Discovery Studio Visualizer. Leflunomide and ticagrelor formed stable receptor ligand complexes via hydrogen bonding, hydrophobic interactions and Pie (π) π stacking, as demonstrated by the 3D and 2D interaction maps. The observed orientations suggested thermodynamic stability and favorable chemical complementarity, indicating that both molecules were well-fitted into the receptor's binding cavity.

Pharmacokinetic and drug-likeness assessment

Both medications meet the main requirements for oral drug likeness according to veber's criteria and Lipinski's Rule of Five, according to pharmacokinetic profiling conducted using SwissADME.

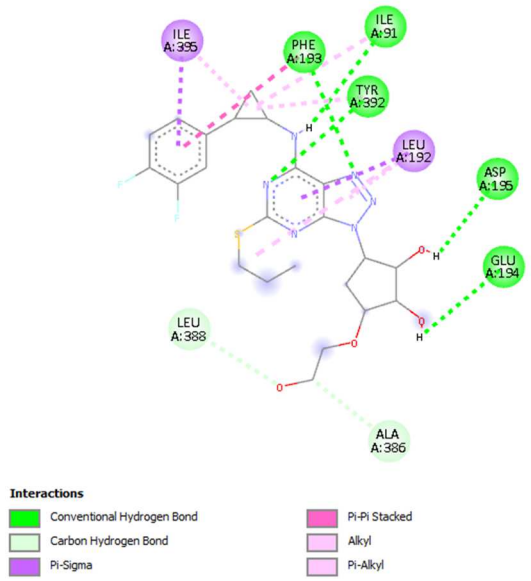

Fig. 2: 2D interaction diagram of A2A receptor with ticagrelor showing 5 H-bonds

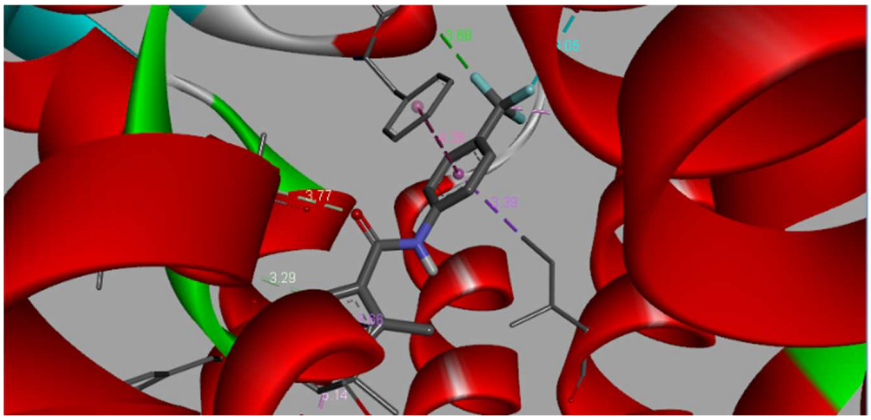

Fig. 3: 3D interaction of A2A receptor with leflunomide

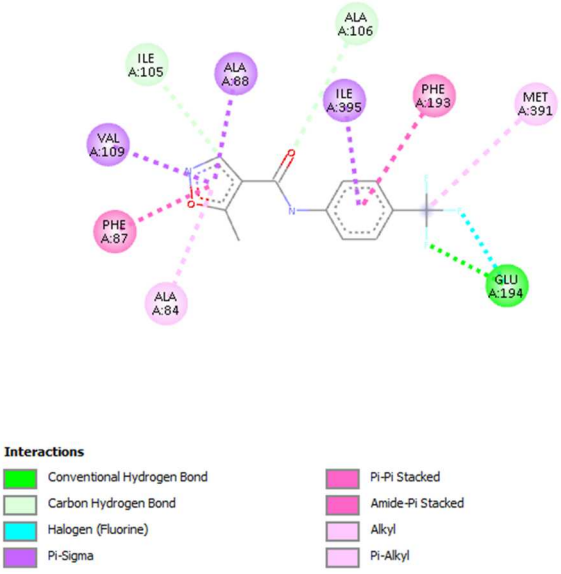

Fig. 4: 2D interaction diagram of A2A receptor with leflunomide showing 3 H-bonds

Table 2: Predicted pharmacokinetic and drug-likeness parameters (SwissADME).

Parameter	Leflunomide	Ticagrelor	Optimal range
Molecular weight (Da)	270.2	522.6	< 500
Log P	2.35	3.91	–0.4 to +5.6
H-Bond donors	1	4	≤ 5
H-Bond acceptors	6	10	≤ 10
TPSA (A²)	55.13	113.5	< 140
Lipinski violations	0	1 (MW > 500)	≤ 1
GI absorption (%)	High	Low	—
Blood brain barrier (BBB) permeability (cm/s)	Yes	No	—
CYP inhibition	Moderate (CYP450)	Mild (CYP450)	—
Bioavailability score	0.55	0.55	> 0.3

Table 3: Toxicity predictions from AdmetSAR 2.0.

Ligand	LD_{50} (mg/kg)	Toxicity class	Toxicity type
Leflunomide	1190	IV	Acute (Low)
Ticagrelor	1900	IV	Acute (Low)

Table 2 summarizes the anticipated parameters. Both compounds' pharmacokinetic and physicochemical characteristics were good. A summary of these parameters is provided in Table 2. Ticagrelor demonstrated reduced blood-brain barrier permeability, most likely as a result of P-glycoprotein-mediated efflux, which limits excessive central nervous system (CNS) exposure, but leflunomide showed greater gastric absorption and blood-brain barrier (BBB) permeability (Begley, 2004).

Toxicity and ADMET prediction

Both compounds have minimal acute toxicity and are non-mutagenic, according to toxicity and ADMET predictions made by admetSAR 2.0. According to the globally harmonized system (GHS) criteria, leflunomide and ticagrelor were classified as Class IV (low toxicity) with estimated Lethal Dose, 50% (LD_{50}) values of 1190 mg/kg and 1900 mg/kg, respectively. Neither compound was predicted to be carcinogenic or hepatotoxic by computational predictions from admetSAR 2.0. It is crucial to remember that these *in-silico* predictions are only preliminary and do not take precedence over established clinical safety profiles, such as the risk of hepatotoxicity associated with Leflunomide. The detailed toxicity predictions are shown in Table 3.

DISCUSSION

The current research work suggested that both leflunomide and ticagrelor have strong binding affinities for their respective molecular targets. The results of these computational studies provide preliminary support for a possible synergistic effect, whereby the two drugs may work together to modulate inflammatory pathways implicated in various diseases, such as RA. The binding affinity between leflunomide and dihydroorotate dehydrogenase (DHODH) is enhanced, consistent with its known mechanism of action as a DMARD: it suppresses de novo pyrimidine synthesis, thereby inhibiting lymphocyte proliferation and reducing inflammation (Zhang *et al*., 2021). On the other hand, the P2Y12 receptor antagonist effect of ticagrelor is most commonly reported in antiplatelet therapy. However, new evidence suggests that ticagrelor can also exert anti-inflammatory effects independent of platelet inhibition and possibly mediated by adenosine metabolism (Boncler *et al*., 2024). The positive binding affinities observed in the current study support this emerging hypothesis, providing molecular grounds to postulate that ticagrelor may have therapeutic effects beyond cardiovascular effects. The next line of research needs to support these *in-silico* findings with *in-vitro* and *in-vivo* models to verify the proposed synergistic anti-inflammatory effect and to define the exact clinical implications for RA treatment. The main ligand of leflunomide is DHODH. Although leflunomide primarily acts by inhibiting DHODH, a docking study revealed a potential interaction between leflunomide and the A2AR. This stabilizing interaction, typified by hydrogen bonds with key residues in the active site, suggests a potential secondary immunomodulatory mechanism that warrants further examination. The positive orientation and strong hydrogen-bonding interactions suggest that leflunomide could interact with A2AR in a form distinct from its canonical inhibition of DHODH.

These results are consistent with the existing literature, which suggests that leflunomide suppresses cytokine secretion and T-cell growth, fundamental processes that contribute to immune damage in RA (Zhang *et al*., 2021). If the A2AR signals are validated biologically, they may further explain immunomodulatory effects independent of inhibition of pyrimidine synthesis.

The primary pharmacological actions of ticagrelor are inhibition of the P2Y12 receptor and the ENT-1 protein, which elevates extracellular adenosine concentrations; these actions underlie the antiplatelet activity of ticagrelor. However, current *in-silico* docking results indicate that ticagrelor also exhibits high binding affinity for the A2A receptor. Provided that this interaction is empirically confirmed, it may indicate something extra, direct, that ticagrelor stabilizes adenosine-mediated anti-inflammatory signaling. This finding is consistent with recent evidence that ticagrelor can exhibit anti-inflammatory properties in the absence of platelet-inhibitory activity (Boncler *et al*., 2024). Despite the positive binding energies, it is worth noting that established A2AR ligands were not used as positive controls in this preliminary screening and additional experiments are needed. Ticagrelor primarily exerts its pharmacological effect by blocking the P2Y12 receptor and the ENT1 transporter, thereby increasing extracellular adenosine levels. It has a well-characterized mechanism of action as an antiplatelet agent. Docking experiments indicate that ticagrelor fits the essential amino acid locations (glutamic acid (Glu194) and aspartic acid (Asp195) in a pattern that is consistent with its previously known capability to act as an ENT -1 inhibitor. The compound also increases extracellular adenosine levels, activates A2AR and therefore stimulates anti-inflammatory and vasodilatory effects by inhibiting adenosine reuptake.

Notably, the *in-silico* docking studies show that ticagrelor, too, has a strong binding affinity with the A2AR itself. The docking pose indicates that ticagrelor can bind the receptor ligand-binding cavity, possibly stabilizing the active form. If it is proven biologically, there would be an additional mechanism whereby ticagrelor would further enhance adenosine-mediated anti-inflammatory signaling, thereby increasing adenosine levels against platelet aggregation (Bonello *et al*., 2014).

Pharmacokinetic and ADMET analyses also supported the favorable drug-like properties and safety profiles of both agents. Leflunomide has a molecular weight and lipophilicity that comply with the rule of five as proposed by Lipinski, making it susceptible to oral absorption. Ticagrelor, therefore, exhibits favorable pharmacokinetics, including slight CYP450 enzyme inhibition, despite its increased molecular weight.

Both compounds were found to have low toxicity, with a low mutagenic risk score. However, these *in-silico* predictions should be viewed with a grain of salt, as they may not accurately reflect toxic responses observed in the clinical setting, e.g., leflunomide-induced hepatotoxicity or the tendency to bleed with ticagrelor.

Remarkably, neither agent had appreciable potential to cross the BBB. The present observation supports the literature indicating that systemic drugs have limited penetration into the CNS and that efflux transporters, e.g., P-glycoprotein, act as barriers. Subsequently, the risk of CNS adverse effects is reduced, thereby supporting the safety profiles of the two drugs during prolonged administration.

These results support the hypothesis that leflunomide and ticagrelor, when used together, can produce a synergistic therapeutic effect: ticagrelor can increase anti-inflammatory effects through adenosine signaling and leflunomide acts as an immunomodulator, thereby inhibiting inflammation. This combination may therefore be a more effective way to control inflammatory responses. Duality can minimize the risk of side effects with high doses of monotherapy, which can increase the effect of therapy and provide a new approach to treating rheumatoid arthritis.

Even though ADMET predictions are supported by an optimal safety profile calculated using a computer, these observations should be placed within the framework of existing clinical pharmacology. Leflunomide is linked to hepatotoxicity and ticagrelor has a high risk of bleeding, as this is an antiplatelet drug. These risks are to be mitigated by careful selection and patient monitoring in the proposed combination therapy.

However, the possibility of synergistic interactions can also allow the use of lower doses of each agent, thus avoiding dose-related adverse effects. This hypothesis needs to be rigorously tested through comprehensive preclinical and clinical studies.

CONCLUSION

The initial evaluation suggests that ticagrelor and leflunomide are potential candidates for a new combinatorial therapeutic agent for RA. In pharmacokinetic and ADMET analyses, they were found to be safe and suitable for oral delivery and in molecular docking analyses, they exhibited the strongest binding affinities and prolonged receptor-ligand interactions. The immunomodulatory effects of leflunomide and the adenosine-enhancing effects of ticagrelor may be used to boost the therapeutic efficacy of addressing immune imbalance and inflammatory processes in parallel. Such a double approach illustrates the ongoing progressive trend toward precision combination therapies in the management of RA.

These findings are the result of *in-silico* studies, which provide a solid theoretical foundation for further testing in *in-vitro* and *in-vivo* experiments. Long-term safety, dose optimization and pharmacodynamic synergism are potential areas for future study, as these variables can enable the development of innovative multi-target regimens for managing autoimmune diseases.

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Authors' contributions
M.Z: Conceptualization; M.Q.K and W.S: Methodology; Z.A., A.K., A.K. and S.A: Final drafting; H.M.A and M.I.S: Review and editing.

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Data availability statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical approval
Not applicable

Conflict of interest
The authors declare no conflict of interest.

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