ORIGINAL PAPER

INTERACTION OF PARACETAMOL, PROPYPHENAZONE AND THEIR COMPLEXES WITH CYCLOOXYGENASE ISOFORMS: A MOLECULAR DOCKING APPROACH

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Abstract. *The paracetamol–propyphenazone combination is one of the classic analgesic formulations used for the treatment of acute pain of mild to moderate intensity. By combining the antipyretic and analgesic properties of paracetamol with the rapid analgesic and anti-inflammatory effects of propyphenazone, this association provides an enhanced therapeutic response, characterized by a fast onset of action and effective symptom relief. It is frequently used in the management of tension-type headaches, migraines, and other forms of acute pain, being appreciated for its relatively favorable tolerability profile. The main objective of this study is to determine whether the interactions between paracetamol, propyphenazone, and cyclooxygenase enzymes are influenced by the combination of these two drugs. This was achieved using the HEX 8.0 docking program. Binding energy was used as a measure to assess the strength of the interactions. Our analysis shows that the strongest interaction with COX-2 was observed for the propyphenazone–paracetamol complex, indicating that when propyphenazone is assigned as the receptor and paracetamol as the ligand, the resulting complex achieves optimal accommodation within the COX-2 active site. These findings highlight the importance of understanding drug–drug interactions. Therefore, a solid comprehension of these dynamics is essential to ensure the efficacy of therapeutic combinations.*

Keywords: *paracetamol; propyphenazone; cyclooxygenase 1; cyclooxygenase 2; molecular docking.*

1. INTRODUCTION

Pain and fever are among the most frequent complaints in general practice, and their effective management often requires agents that combine analgesic and antipyretic properties. Paracetamol is widely used due to its good tolerability and central mechanism of analgesia, while propyphenazone offers a more rapid onset, though with a shorter duration. The

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combination of paracetamol and propyphenazone aims to merge their complementary pharmacodynamic profiles, potentially enhancing efficacy and onset of relief [1–3].

Paracetamol (also known as acetaminophen) is an analgesic and antipyretic drug that exerts its effect primarily through central inhibition of prostaglandin synthesis. Its primary mechanism of action is believed to involve central inhibition of cyclooxygenase (COX) enzymes, particularly under low-peroxide conditions, which distinguishes it from classical nonsteroidal anti-inflammatory drugs (NSAIDs) [4–6].

Its lack of significant peripheral anti-inflammatory activity makes it relatively gentle on the gastrointestinal tract compared to classical NSAIDs [7–9].

Propyphenazone, a pyrazolone derivative, exerts analgesic, antipyretic, and mild anti-inflammatory effects through reversible inhibition of both COX-1 and COX-2. Compared with paracetamol, propyphenazone acts more like a conventional NSAID, showing consistent peripheral prostaglandin inhibition. This difference accounts for its modest anti-inflammatory activity as well as typical NSAID-related risks, including gastrointestinal irritation [10,11].

Although both drugs interact with COX enzymes, the inhibition achieved by paracetamol is strongly influenced by peroxide tone, which limits its effect in inflamed peripheral tissues but allows significant central activity [8,12].

Propyphenazone does not share this limitation. The combination of paracetamol and propyphenazone is used clinically because the two agents provide complementary mechanisms of action [13].

When used together in combination preparations, pharmacokinetic and pharmacodynamic interactions have been described. Thus, paracetamol can increase the plasma concentration and prolong the elimination half-life of propyphenazone. The result is a potentially enhanced and prolonged analgesic/antipyretic effect compared to either agent alone [14].

The clinical rationale for combining paracetamol and propyphenazone (often also with minor amounts of a stimulant such as caffeine) is to provide a more rapid onset of analgesia, while benefiting from the longer duration and tolerability of paracetamol. Indeed, fixed-dose combinations containing propyphenazone, paracetamol (and sometimes caffeine) are widely used for the management of various pains: headaches (including tension and migraine), toothache, dysmenorrhea, musculoskeletal pain, pain associated with colds/flu, and fever. Moreover, the combination has been directly compared with paracetamol alone, aspirin, NSAIDs (e.g., ibuprofen), and placebo. A pooled analysis of eight clinical studies assessing a fixed-dose combination (propyphenazone 150 mg/paracetamol 250 mg/caffeine 50 mg) concluded that the combination achieved faster onset of pain relief: more patients reported “pain gone or partly gone” at 30 and 60 minutes compared with paracetamol alone, aspirin, or placebo. The difference with ibuprofen became significant at 60 minutes. These findings support the view that the paracetamol–propyphenazone combination offers a synergistic or at least additive effect on analgesia and antipyresis, with a favorable onset profile [14].

Cyclooxygenases (COXs) are key enzymes in the biosynthesis of prostanoids - prostaglandins and thromboxanes - which play essential roles in inflammation, hemostasis, and various physiological processes. These enzymes catalyze the conversion of arachidonic acid into prostaglandin H_2 (PGH_2), a precursor for multiple downstream lipid mediators. Two major isoforms have been characterized: COX-1 and COX-2, encoded by distinct genes and exhibiting differential patterns of expression, regulation, and physiological function [15–17].

COX-1 is constitutively expressed in most tissues and is considered a “housekeeping” enzyme that maintains homeostatic functions such as gastric mucosal protection, platelet aggregation, and renal blood flow. Its activity ensures the continuous production of prostanoids required for normal cellular function. In contrast, COX-2 is generally inducible, expressed at low basal levels but upregulated in response to pro-inflammatory cytokines,

growth factors, and mitogens. This inducible expression makes COX-2 a central mediator of inflammation, pain, and fever. Nevertheless, COX-2 also contributes to physiological processes including ovulation, embryonic implantation, and regulation of renal function [18,19].

Structurally, COX enzymes are membrane-bound homodimers associated with the endoplasmic reticulum and nuclear membrane. Each monomer contains a cyclooxygenase active site and a peroxidase site. NSAIDs exert their therapeutic effects primarily through inhibition of COX activity. Traditional NSAIDs inhibit both COX-1 and COX-2, often leading to gastrointestinal side effects associated with COX-1 suppression. The development of selective COX-2 inhibitors (coxibs) aimed to minimize such adverse effects while maintaining anti-inflammatory efficacy. However, concerns regarding cardiovascular risks associated with selective COX-2 inhibition have led to increased scrutiny of this drug class [20].

Beyond their role in pharmacology, cyclooxygenases have significant implications in pathology. Overexpression of COX-2 has been linked to tumorigenesis through its influence on angiogenesis, inhibition of apoptosis, and enhancement of cell proliferation [20,21].

Cyclooxygenases are central to the regulation of diverse physiological and pathological processes. Their dual role in maintaining homeostasis and mediating inflammation underscores the importance of understanding their biochemical properties and regulatory mechanisms. Continued research into COX function and inhibition holds promise for improving therapeutic strategies targeting inflammation, pain, and cancer [22].

2. MATERIALS AND METHODS

2.1. MATERIALS

A computational chemistry approach was employed to examine the structural characteristics of paracetamol and propyphenazone. Initial molecular modeling and geometry optimization were carried out using the HyperChem software package [23], which enabled the generation of energy-minimized three-dimensional conformations and the analysis of relevant electronic parameters for both compounds. These optimized molecular structures served as the basis for subsequent docking studies.

To explore potential intermolecular interactions, the binding affinities and spatial orientations of paracetamol and propyphenazone were assessed using the Hex docking program [24]. Hex allows for the evaluation of shape complementarity, electrostatic interactions, and potential steric constraints that may influence complex formation [24,25].

For the biological component of the study, the three-dimensional crystal structures of the receptor targets were retrieved from the Protein Data Bank (PDB) [26,27]. Only structures exhibiting high crystallographic resolution and complete active-site information were selected, ensuring reliable docking results. Before simulations, the receptor files were preprocessed by removing water molecules, adding missing hydrogen atoms, and optimizing protonation states where required.

2.2. METHODS

The methodological workflow consisted of two major stages: intermolecular complex construction and receptor docking simulations. First, it was examined whether the order of molecular docking - that is, assigning one compound as the ligand and the other as the receptor - had any significant effect on complex formation and stability. Using Hex 8.0.0, paracetamol and propyphenazone were docked against each other in both orientations. In each scenario, one molecule was designated as the ligand (mobile docking partner), while the other served as the receptor (stationary partner). This bidirectional analysis allowed us to identify potential differences in interaction geometry, binding strength, and predicted stability that might arise from docking asymmetry.

Following the generation of these intermolecular complexes, a second stage of simulations was conducted. The optimized structures of paracetamol, propyphenazone, and their pre-docked complexes were each subjected to protein–ligand docking against the selected biological receptor targets. These simulations aimed to determine whether the paracetamol–propyphenazone complex exhibits distinct binding behavior compared to the individual molecules alone.

Docking parameters were standardized across all simulations to ensure comparability. Search algorithms within Hex were configured to include both shape-only and electrostatic scoring modes, and multiple solutions were generated for each simulation to evaluate binding pose consistency. The best scoring poses were then analyzed in terms of binding energy, orientation within the active site, intermolecular hydrogen bonds, hydrophobic contacts, and potential steric hindrance.

This two-step methodological approach - first modeling drug–drug interactions and subsequently examining their interactions with a target receptor - provides a comprehensive view of how combination analgesics may behave at a molecular level, offering insight into potential synergistic or competitive binding mechanisms [28–33].

3. RESULTS AND DISCUSSION

After completing the modeling procedure, the compounds (Table 1) were assembled into complexes using the Hex 8.0.0 program. The primary goal of this investigation is to evaluate how the binding sequence of these two compounds within a complex influences their interaction (Table 2).

Table 1. Chemical structure of the studied compounds.

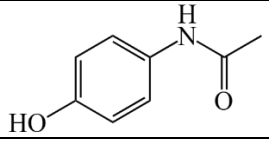
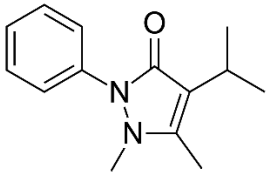
Compound	Structure
Paracetamol	
Propyphenazone	

Table 2. Docking order and docking energies for the drugs paracetamol and propyphenazone

Receptor	Ligand	Energy [kcal/mol]
Paracetamol	Propyphenazone	-116.11
Propyphenazone	Paracetamol	-115.65

In the next phase of our study, we present the results derived from the molecular docking simulations conducted between the generated complexes and the selected receptor structures obtained from the Protein Data Bank (PDB). Specifically, we employed PDB entry 3N8V, which corresponds to cyclooxygenase-1 (COX-1), and PDB entry 5W58, representing cyclooxygenase-2 (COX-2). These enzymes play central roles in prostaglandin synthesis and are key pharmacological targets for many analgesic and anti-inflammatory agents. Through these docking analyses, we sought to characterize the three-dimensional orientation, binding affinities, and interaction networks formed between each ligand or ligand complex and its respective protein target. This includes assessing hydrogen bonding patterns, hydrophobic interactions, steric complementarity, and the spatial arrangement of key active-site residues. Such structural insights allow us to infer potential pharmacodynamic implications at the COX enzymes. These findings contribute to a more comprehensive understanding of the molecular determinants governing the activity and selectivity of the investigated compounds [29].

The binding energy values obtained from the docking simulations provide important insights into the relative affinity of paracetamol, propyphenazone, and their intermolecular complexes toward the COX-1 enzyme. As shown in Table 3, all tested configurations demonstrated negative binding energies, indicating thermodynamically favorable interactions with the COX-1 active site. However, the magnitude of these energies reveals clear differences in binding strength and potential biological relevance.

Table 3. Values of binding energy with COX-1

Complex/Compound	Energy [kcal/mol]
Paracetamol - Propyphenazone	-303.18
Propyphenazone - Paracetamol	-282.1
Propyphenazone	-218.74
Paracetamol	-183.03

The paracetamol–propyphenazone complex exhibited the most favorable binding energy (–303.18 kcal/mol), suggesting a substantially stronger interaction with COX-1 than either compound alone. This enhanced affinity may arise from complementary structural features of the two molecules when assembled as a complex, allowing them to occupy the active site more efficiently than the individual ligands.

Reversing the docking order (propyphenazone–paracetamol complex) yielded a slightly less favorable, but still significantly strong binding energy (–282.10 kcal/mol). The difference between the two complex orientations suggests that the spatial arrangement and initial positioning of the molecules influence the resulting interaction geometry within the active site. Nevertheless, both complex configurations exceed the individual drugs, highlighting the robustness of the combined ligand approach.

Among the single-molecule dockings, propyphenazone displayed a stronger binding energy (–218.74 kcal/mol) compared to paracetamol (–183.03 kcal/mol). This fits well with the known properties of propiphenazone, which typically exhibits greater potency as an analgesic and better affinity for cyclooxygenase isoforms, with much stronger side effects than paracetamol. Paracetamol, although active at COX enzymes, generally exhibits weaker binding and relies more heavily on central mechanisms of action; its adverse reactions, especially at the digestive level, are not common. The binding-energy data therefore reflect the intrinsic differences between the two molecules in their interaction with COX-1.

The interaction patterns of the four tested configurations with the COX-1 active site reveal notable differences in binding orientation and residue engagement (Fig. 1).

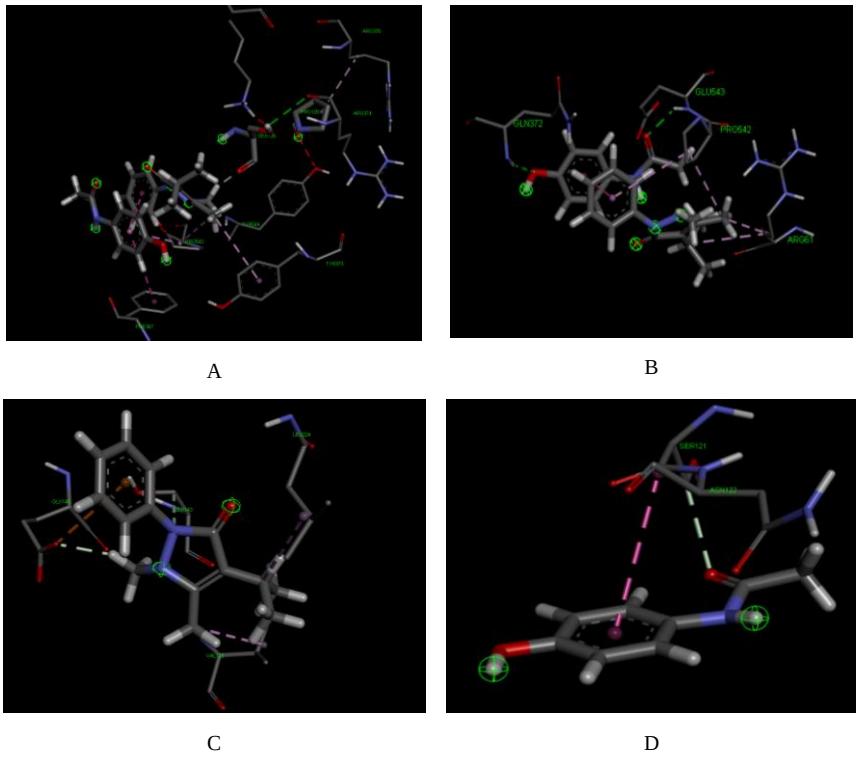


Figure 1. High-resolution 3D docking images of the COX-1 receptor with A paracetamol–propyphenazone, B propyphenazone–paracetamol, C propyphenazone, and D paracetamol. These representations illustrate the spatial orientation of each ligand within the COX-1 active site, highlighting the key amino acids involved in binding [31].

The paracetamol–propyphenazone complex (A) demonstrates a cooperative binding profile, positioning both molecules within the catalytic groove and engaging residues commonly associated with NSAID interactions, suggesting potential synergistic stabilization. Conversely, the propyphenazone–paracetamol configuration (B) exhibits a slightly altered orientation, with shifts in contact points that may influence overall binding strength and steric compatibility within the active site.

When evaluated independently, propyphenazone alone (C) shows strong affinity for the hydrophobic portion of the COX-1 pocket, consistent with its known activity. Its interactions are dominated by contacts with key residues involved in substrate access. In contrast, paracetamol alone (D) binds more superficially, forming fewer stabilizing interactions and exhibiting lower occupancy of the catalytic channel, in agreement with its weaker intrinsic COX-1 inhibition.

Collectively, these findings suggest that the combined presence of paracetamol and propyphenazone may modify spatial orientation within the COX-1 binding site compared to individual compounds.

Taken together, these results demonstrate that the formation of paracetamol–propyphenazone complexes markedly enhances the predicted binding affinity toward COX-1. The higher binding energies of the complexes suggest improved stability within the active site and possibly more efficient inhibition of the enzyme. These findings support the broader concept that drug–drug interactions at the molecular level may influence pharmacodynamics, contributing to therapeutic effects and adverse reactions.

The docking results obtained for COX-2 further clarify the interaction patterns of paracetamol, propyphenazone, and their complexes, revealing trends that are broadly

consistent with those observed for COX-1. All docking configurations yielded negative binding energies, confirming favorable interactions with the COX-2 active site (Table 4); however, the magnitude of these values highlights meaningful differences in affinity and potential inhibitory capacity.

Table 4. Values of binding energy with COX-2

Complex/Compound	Energy [kcal/mol]
Propyphenazone – Paracetamol	-290.8
Paracetamol - Propyphenazone	-283.52
Propyphenazone	-234.74
Paracetamol	-186.51

The strongest interaction was observed for the propyphenazone–paracetamol complex (–290.80 kcal/mol). This result indicates that when propyphenazone is assigned as the receptor and paracetamol as the ligand, the resulting complex achieves optimal accommodation within the COX-2 active site. The binding energy closely approximates that of the highest-affinity COX-1 complex, suggesting that such intermolecular assemblies may consistently enhance inhibitory potential across both cyclooxygenase isoforms.

The reverse docking orientation, paracetamol–propyphenazone, produced a slightly less favorable but still notably strong binding energy (–283.52 kcal/mol). As with COX-1, the modest difference between the two complex configurations demonstrates that docking directionality influences the final binding pose, likely due to changes in how the two molecules orient relative to one another before entering the enzyme's active pocket. Nonetheless, both complexes exhibit substantially greater affinity than the individual molecules, reinforcing the conclusion that paracetamol–propyphenazone association enhances COX-2 binding, potentially providing a molecular explanation for the improved analgesic performance often observed in combination formulations.

For the single-compound dockings, propyphenazone again displayed a stronger interaction with COX-2 (–234.74 kcal/mol) compared to paracetamol (–186.51 kcal/mol). This pattern mirrors the trend seen with COX-1 and is consistent with the known pharmacological profile of propyphenazone as a more potent cyclooxygenase inhibitor relative to paracetamol. The comparatively weak binding energy of paracetamol reflects its limited direct inhibitory activity on COX isoforms and supports the broader understanding that its major analgesic effects involve additional central mechanisms [12].

The observed increase in binding strength supports the hypothesis that intermolecular association between paracetamol and propyphenazone could contribute to synergistic pharmacological effects, particularly in analgesic and antipyretic actions.

Overall, the binding-energy results for COX-2 demonstrate that complex formation between paracetamol and propyphenazone yields a substantial enhancement in predicted affinity, surpassing the binding capacities of either drug alone. The magnitude of improvement is considerable, suggesting that coordinated binding through complex formation may facilitate a more stable and energetically favorable interaction with the enzyme's active site. These findings offer a molecular rationale for the enhanced therapeutic performance of propyphenazone–paracetamol combination formulations and highlight the potential importance of drug–drug interactions at the structural level in modulating COX-2 inhibition.

The docking analysis of the four configurations with COX-2 highlights distinct differences in binding behavior compared to COX-1, reflecting the broader and more flexible architecture of the COX-2 active site (Fig. 2).

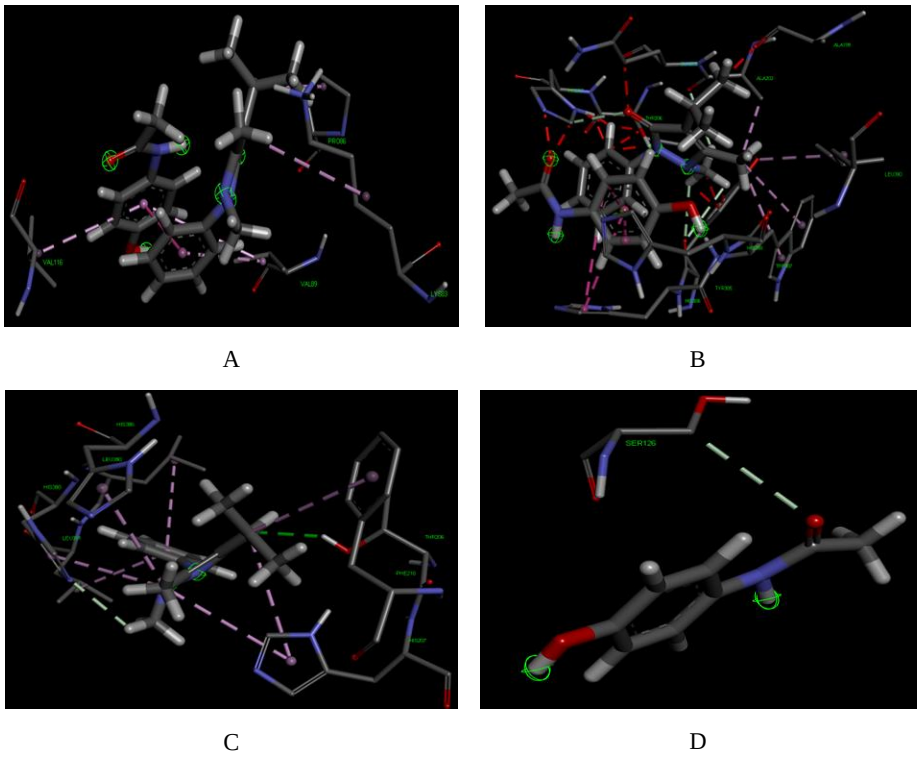


Figure 2. High-resolution 3D docking images of the COX-2 receptor with A propyphenazone–paracetamol, B paracetamol–propyphenazone, C propyphenazone, and D paracetamol. These representations illustrate the spatial orientation of each ligand within the COX-2 active site and highlight the key amino acids involved in binding [31].

The propyphenazone–paracetamol complex (A) adopts a stable orientation within the catalytic pocket, engaging both hydrophobic regions and polar residues characteristic of COX-2 selectivity. This suggests a complementary fit in which the two molecules contribute cooperatively to binding stabilization.

The paracetamol–propyphenazone orientation (B) shows a similar interaction pattern but with a noticeable shift in spatial alignment, which alters the distribution of contact points. These differences may influence the affinity and overall binding efficiency of the complex, indicating that the sequence of docking or ligand positioning plays a role in optimizing interactions within the COX-2 environment.

When evaluated individually, propyphenazone (C) shows substantial affinity for the COX-2 channel, occupying deeper regions of the pocket and forming stabilizing interactions consistent with its anti-inflammatory properties. Meanwhile, paracetamol (D) binds less extensively, interacting primarily with surface residues and demonstrating a comparatively weaker anchoring within COX-2, aligning with its modest inhibitory capabilities.

Overall, the results suggest that the combined presence of propyphenazone and paracetamol enhances molecular accommodation within the COX-2 active site relative to each compound alone. This cooperative behavior may contribute to the improved analgesic and anti-inflammatory effects observed clinically for this drug combination.

Considering the binding energies for both isoforms, it can be observed that the propyphenazone–paracetamol complex exhibits weaker binding to COX-1, suggesting a lower likelihood of COX-1-related adverse effects. In contrast, its noticeably stronger binding to COX-2 indicated a potentially enhanced therapeutic response related to the inhibition of this isoform. Taken together, these findings suggest that the propyphenazone–paracetamol complex may offer a more therapeutically favorable profile by maximizing efficacy while minimizing undesired side effects.

4. CONCLUSIONS

The association of paracetamol and propyphenazone in a single pharmaceutical formulation rests on a sound pharmacological rationale: combining the centrally mediated, longer-acting analgesic/antipyretic effect of paracetamol with the rapid-onset, stronger analgesic effect of propyphenazone. Clinical data support that such combinations (often with caffeine) provide faster and more effective relief of acute pain than paracetamol alone, aspirin, or placebo.

In clinical practice, the paracetamol–propyphenazone combination may be justified primarily for short-term treatment of acute pain or fever, when rapid relief is desired.

This study provides an integrated computational assessment of the interactions between paracetamol, propyphenazone, and their intermolecular complexes with their pharmacological targets. By combining molecular modeling with systematic docking simulations, we demonstrate that the formation of a paracetamol–propyphenazone complex substantially enhances predicted binding affinities compared to the individual compounds.

For COX-2, the primary enzymatic target involved in analgesic and antipyretic mechanisms, the ligand complexes yielded significantly more favorable binding energies than either drug alone. This suggests that the intermolecular association of the two molecules may facilitate a more stable and energetically advantageous fit within the active site. Such structural complementarity provides a plausible molecular basis for the synergistic or additive pharmacological effects often reported for paracetamol–propyphenazone combination therapies.

Moreover, the docking results for individual ligands reinforce known pharmacological distinctions: propyphenazone exhibited stronger intrinsic binding to both COX isoforms, while paracetamol showed comparatively weaker affinities, aligning with their established profiles of COX inhibition. The fact that the complexes surpass both in predicted affinity underscores the potential functional relevance of drug–drug interactions at the molecular level.

Overall, the findings highlight that drug–drug molecular interactions can meaningfully influence binding behavior at therapeutic targets, potentially affecting efficacy and safety profiles. The enhanced docking performance of the paracetamol–propyphenazone complexes suggests that such interactions may contribute to the clinical effectiveness of combination formulations. Future studies, particularly involving molecular dynamics, experimental binding assays, and pharmacokinetic evaluation, are warranted to validate these computational predictions and further elucidate their therapeutic implications.

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