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Original Article

New 4-Aminophenazone derivatives: synthesis, design, and docking analysis as selective COMT inhibitors

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Received: 08 June 2025; **Revised:** 22 September 2025; **Accepted:** 07 October 2025

ABSTRACT

Different compounds of 4-amino antipyrine (4-Aminophenazone) were synthesized through two lines: the first line was through the reaction of the raw material with phenacyl bromide derivatives, which are three derivatives with the presence of triethylamine as a catalyst, and the second line was through the reaction of the starting material with two derivatives of benzoyl chloride one of the compound Pre-factory (B1). The results were analyzed through FTIR, HNMR, and ^{13}CNMR, and molecular docking was performed, and the results were confirmed. The results showed that the compounds act as inhibitors of the COMT enzyme, but to a lesser extent than the basic substance, tolcapone. This work involved molecular docking of synthesized molecules with the COMT enzyme, yielding favorable ratings in comparison to the co-crystal ligand and tolcapone. The molecule exhibiting the highest docking score was chosen for molecular dynamics (MD) simulation utilizing the GROMACS program. The simulation results were evaluated using several parameters, including RMSD, SASA, RMSF, and Rg. The RMSD study demonstrated consistent ligand binding throughout the simulation duration. The SASA results indicated uniform solvent accessibility, whereas the RMSF emphasized areas of flexibility within the protein. The Rg values indicated the overall compactness and stability of the protein-ligand complex. The results indicate that the synthesized chemical demonstrates significant binding stability and interaction with the COMT enzyme, necessitating additional research for possible therapeutic uses.

Keywords: 4-Aminophenazone, Molecular docking, Molecular dynamics, COMT enzyme

Introduction

Antipyrine (1, 5-dimethyl-2-phenylpyrazole-3-one) is a chemical entity characterized by a pyrazolone structure, comprising a five-membered ring containing two nitrogen atoms and a ketone functional group. The nomenclature "antipyrine" was first coined by Ludwig Knorr in the late 18th century. This compound was recognized as the inaugural synthetic analgesic and maintained its status as the most prevalent medication until the advent of aspirin in the early 20th century [1, 2]. Numerous compounds derived from antipyrine have been developed through careful derivatization, including isopropyl antipyrine L2, aminopyrine L3, Ramifenazone L4, and Dipyrone L5, which are extensively utilized globally as anti-inflammatory and analgesic medications [3-6]. **Figure 1**.

Aminoantipyrine (Ampyrone) is a derivative of antipyrine featuring an amino group at the C-4 position, exhibiting numerous biological activities [7]. **Figure 2** shows that 4-aminoantipyrine, with its reactive amino group, is a promising amphoteric substrate for Schiff base formation due to its free amine and cyclic ketone [8]. Numerous derivatives have been synthesized through reactions involving aldehydes or ketone compounds to produce Schiff bases, or by condensation with acyl

Access this article online	
Website: www.japer.in	**E-ISSN:** 2249-3379

How to cite this article: Yaseen YS, Tawfeeq MF, Hamdoon YS, Mahmood AAR. New 4-Aminophenazone derivatives: synthesis, design, and docking analysis as selective COMT inhibitors. J Adv Pharm Educ Res. 2025;15(4):22-31. https://doi.org/10.51847/f7Txs6CkSy

or alkyl halides [9, 10]. Moreover, the reactivity of cyclic ketones has been harnessed to generate compounds with various amine derivatives, resulting in products exhibiting notable ligation properties. These derivatives have further been utilized as ligands in the development of versatile transition metal complexes for prospective biological applications, encompassing anti-inflammatory agents [11, 12]. Their functions span a range of biological activities, including anticonvulsant [13], cytotoxic [14], superoxide dismutase [2, 6, 15], and antidiabetic effects [16], as well as acting as non-steroidal anti-inflammatory drugs, non-narcotic analgesics, anti-rheumatic agents, peripheral nervous system medications, prostaglandin-endoperoxide synthase inhibitors, antipyretics, and marine xenobiotic metabolites. Additionally, they serve as reagents in biochemical reactions that yield peroxides or phenols [17, 18]. Ampyrone stimulates liver microsomes and is biochemically associated with antipyrine [19, 20]. It is also used for measuring extracellular water and is classified as a primary amino compound and a pyrazolone [21-23].as shown in **Figure 1**.

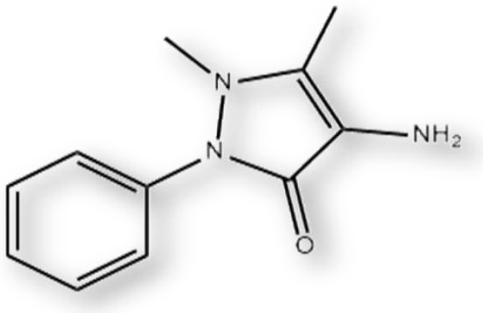


Figure 1. 4-aminoantipyrine

COMT (catechol-O-methyltransferase) inhibitors are medications used alongside carbidopa-levodopa and tolcapone to alleviate the symptoms of Parkinson's disease (PD). Carbidopa-levodopa combined with tolcapone represents the most effective treatment for PD's motor symptoms. Nevertheless, patients may notice diminished effects from the medication over time. COMT inhibitors help prolong the efficacy of carbidopa-levodopa therapy, enabling the use of lower doses of the latter [24-26]. Incorporating a COMT inhibitor reduces the breakdown of levodopa and tolcapone in the body, facilitating a greater amount to reach the brain and enhancing its therapeutic effects [27-29], as illustrated in **Figure 2**.

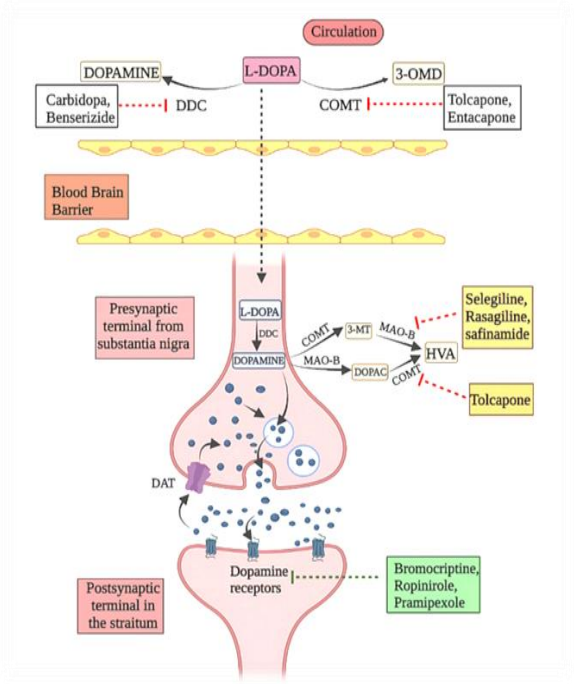


Figure 2. Mechanism of action of COMT Inhibitors

Experimental part

Materials and Methods

The materials were procured from Sigma-Aldrich and included 4-Aminoantipyrine. Infrared spectra were recorded utilizing the Shimadzu Specac GS 10800-R IR Affinity-1 Spectrometer (v = cm^{-1}). For the compounds synthesized, proton nuclear magnetic resonance (^1H NMR) spectra were obtained with an AVANCE-III 300 MHz Nano Bay FT-NMR spectrometer, employing tetramethylsilane (TMS) as the internal reference standard. The chemical shifts were reported in delta (δ, ppm), with DMSO-d6 serving as the solvent [15, 30].

Chemical synthesis

General method for synthesis of 4-aminoantipyrine derivatives (A1, A2 & A3).

In a 150 mL flask, combine 4-aminoantipyrine (0.0024 mol, 0.5 g) with 10 mL of ethanol and introduce trimethylamine (0.0024 mol, 0.3 mL). Agitate the mixture for 15 minutes. In a separate vessel, dissolve 2,4'-dibromoacetophenone (0.0007 mol, 0.66 g), 2-bromo-4'-chloroacetophenone (0.0007 mol, 0.6 g), and 2-bromo-4-nitroacetophenone (0.0007 mol, 0.58 g) in dimethyl sulfoxide. Incorporate this solution into the initial mixture and continue stirring for 15 hours at ambient temperature. Subsequently, filter the product and recrystallize the resultant precipitate using 70% ethanol.

4-((2-(4-bromophenyl)-2-oxoethyl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one

(A1)

Orange powder, yield (70%), melting point = (220-224 ^{o}C), Rf = 0.62,

ATR-FTIR (υ, cm-1): 3251 (NH) stretching of secondary amide, 1657 (C=O) stretching of carbonyl, 1582, 1539, 1491 Ar (C=C) stretching,11227 (C-N) stretching, 708 (Ar-p-Br substitution).

1H-NMR (300 MHz, DMSO-d6, δ = ppm): 9.23 (t, 1H, NH), 8.13-7.37 (m, 9H, Ar-H), 3.35 (d, 2H, CH2), 2.43 (s, 3H, N-CH3), 1.23 (s, 3H, C-CH3).

13C-NMR (75 MHz, DMSO-d6, δ = ppm): 10.20, 34.94, 114.07, 126.86, 128.68, 128.83, 129.86, 132.32, 134.02, 135.28, 138.01, 149.04, 153.06, 158.28, 191.22.

4-((2-(4-chlorophenyl)-2-oxoethyl)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (A2)

Yellow powder, yield (65%), melting point = (237-240 ^{o}C), Rf = 0.66,

ATR-FTIR (υ, cm-1): 3260 (NH) stretching of secondary amide, 1657 (C=O) stretching of carbonyl, 1586, 1546, 1456 Ar (C=C) stretching, 1326 (C-N) stretching, 841 (Ar-p-Cl substitution).

1 H-NMR300MHz,DMSOd6,δ=ppm): 9.22(t,1H, NH), 8.04-7.37(m,9H, Ar-H),3.57(d,2H,CH2), 2.42(s,3H, N-CH3), 1.23(s,3H, C-CH3).

^{13}CNMR(75MHz,DMSOd6,δ=ppm):10.21,34.94,114.06,126.85,127.18,128.68,129.86,131.76,133.42,134,135.60,148.96,153.04,158.25,191.12

1,5-dimethyl-4-((2-(4-nitrophenyl)-2-oxoethyl)amino)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one(A3)

yellow powder, yield (60%), m.p = (206-2210 ^{o}C), Rf = 0.68,

ATR-FTIR (υ, cm-1): 3314 (NH) stretching of secondary amide, 1661 (C=O) stretching of carbonyl, 1598, 1546, 1469 aromatic (C=C) stretching, 1318 (C-N) stretching, symmetric NO2 at 1546 and asymmetric at 1358 cm-1

1 H-NMR 300MHz, DMSO-d6, δ=ppm): 9.23 (t, 1H, NH), 8.39-7.38 (m, 9H, Ar-H), 3.36 (d, 2H, CH2), 2.45 (s, 3H, N-CH3), 1.23 (s, 3H, C-CH3).

13C NMR (75MHz, DMSO-d6, δ=ppm): 10.19, 34.89, 114.03, 123.64, 127.04, 128.83, 129.89, 131.75, 133.89, 142.02, 148.31, 149.75, 152.93, 158.09, 191.39

General method for synthesis of 4-Aminoantipyrine derivatives (B1, B2)

In a solution comprising 4-aminoantipyrine (0.0024 mol, 0.5 g) dissolved in 10 mL of ethanol, trimethylamine (0.0024 mol, 0.3 mL) was introduced and agitated for a duration of 15 minutes in a 150 mL flask. Subsequently, p-hydroxybenzoyl chloride (0.0024 mol, 0.376 g) and benzoyl chloride (0.0024 mol, 0.336 g) were incorporated after initially dissolving p-hydroxybenzoyl chloride in several drops of dimethyl sulfoxide, and the mixture was stirred for 15 hours at ambient temperature. The resultant solid was subjected to filtration and recrystallization utilizing 70% ethanol.

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)benzamide (B1)

Bright yellow powder, yield (70%), melting point = (192-196 ^{o}C), Rf = 0.60,

ATR-FTIR (ν, cm-1): 3251 (NH) stretching of secondary amide, 1687 cm-1 (C=O) stretching of carbonyl, 1601, 1583, 1453 aromatic (C=C) stretching, 1292 (C-N) stretching.

1H-NMR (300 MHz, DMSO-d6, δ=ppm): 9.30 (t, 1H, NH), 8.40-7.29 (m, 9H, Ar-H), 3.39 (s, 1H, OH), 2.80 (s, 3H, N-CH3), 1.52 (s, 3H, C-CH3).

13C-NMR (75 MHz, DMSO-d6, δ=ppm): 10.20, 34.90, 114.03, 123.64, 127.44, 128.83, 129.89, 131.75, 133.89, 142.02, 148.31, 149.75, 158.09.

N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-4-hydroxybenzamide (B2)

Vibrant orange powder, yield (70%), melting point = (201-203 ^{o}C), Rf = 0.68,

ATR-FTIR (ν, cm-1): 3251 (NH) stretching of secondary amide, 1696 (C=O) stretching of carbonyl, 1594 (C=N) stretching, 1637, 1594, 1495 aromatic (C=C) stretching, 1332 (C-N) stretching, 694 (aromatic p-Bromine substitution).

1 H-NMR300MHz,DMSOd6,δ=ppm): 9.23(t,1H,NH), 8.40-7.39(m,9H,Ar-H), 2.77(s,3H, N-CH3), 1.50 (s,3H, C-CH3).

^{13}CNMR(75MHz,DMSOd6,δ=ppm):12.5,34.9,122.8,123.9,128.8,129.2,103.4,132.1,133.2,133.7,133.9,160.7,166.2,

Molecular induced fit (flexible) docking study

Molecular docking analysis was conducted on the catechol-O-methyltransferase (COMT) protein (4XUC) [31, 32], which was resolved through X-ray crystallography at a resolution of 1.80 Å. Chain A, comprising 218 amino acids, contains a binding site for a co-crystal ligand (43G). Prior to docking chain A, water molecules were eliminated and hydrogen atoms were incorporated; the AMBER10 force field was employed to minimize energy [33-35]. The binding site is constituted by specific amino acid residues, and the docking process was executed utilizing MOE 2022 software. The SMILE representations of the compounds under investigation were produced with Chem-Bio Draw Ultra 13.0, and three-dimensional models were developed in MOE 2022. These three-dimensional structures underwent protonation and energy minimization to achieve a root-mean-square deviation of 0.1 Å. Numerous methodologies for the validation of scoring functions and docking software are available, including the selection of poses, which re-dock compounds in known conformations. The software's efficiency was evident in docking the co-crystallized ligand (NO2) with this protein, yielding a good RMSD Dock of 0.78 Å with MOE, indicating its effectiveness for our new ligand [9, 36, 37].

Molecular dynamics simulation

Molecular dynamics (MD) simulations were performed on the highest-ranking complexes. of the molecular docking score. The

purpose of MDS was to suggest a mechanism of action for the synthesized compound. The system was prepared using the TIP3P water model and simulated using GROMACS 2023.0 on Linux 22.4. The following setup includes Ligand and Protein Modeling. Ligand topologies were generated using the SwissParam server [6]. The protein was modeled using the CHARMM27 force field. System Preparation: A salt concentration of 0.15 mol/L was added to ensure system neutrality. Energy minimization was performed using the steepest descent method for 50,000 steps [38]. Equilibration phases for NVT (constant number of particles, volume, and temperature) and NPT (constant pressure and temperature) were conducted at 300 K and 1 atm. V-rescale thermostat and Parrinello-Rahman barostat were employed to maintain temperature and pressure stability. The 100-nanosecond production run was conducted at 300. The following metrics were calculated to assess system stability and interactions: Root Mean Square Deviation (RMSD), RMSF, Radius of Gyration (ROG), and SASA. Plots for these analyses were generated using Xmgrace software and the matplotlib library [5, 29, 39-41].

Results and Discussion

Chemistry [42, 43]

The synthesis of compounds (A1, A2, A3 and B1, B2) is show in the **Figure 3**.

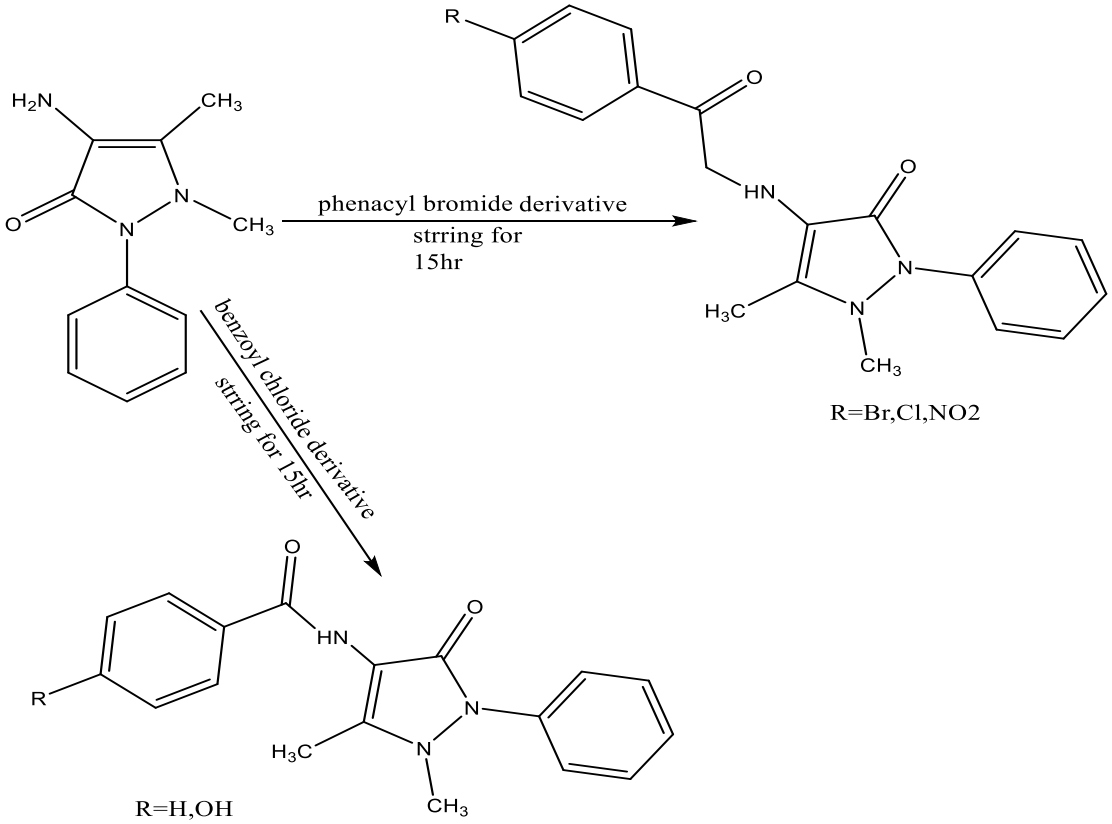


Figure 3. synthesis of titled compounds (A1, A2, A3, and B1, B2)

The synthesis of compounds (A1, A2, A3)

In the first interaction resulted three compounds (A1, A2, and A3) were produced. As a result of 4-aminoantipyrin interacts with Phenacyl Bromide shown in the **Figure 4**.

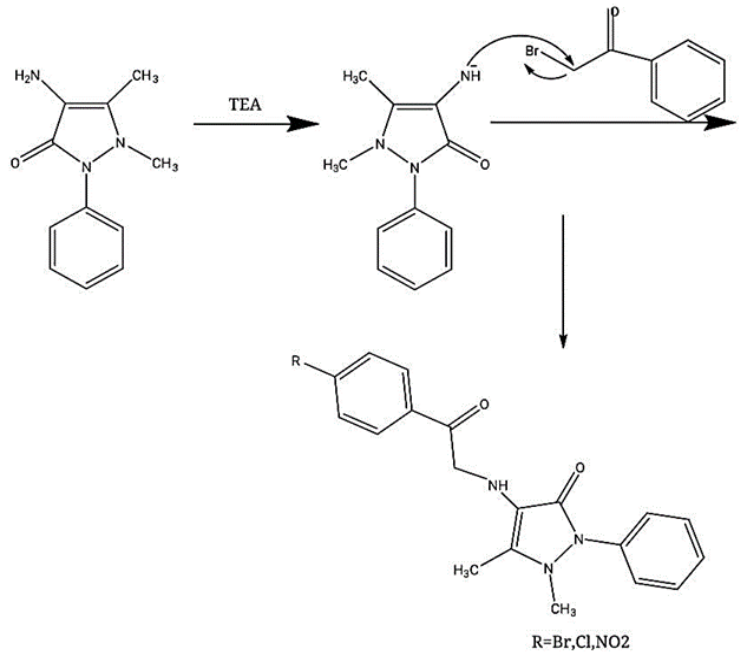


Figure 4. The mechanism of compounds (A1, A2, and A3)

The synthesis of compounds (B1, B2)

In the second interaction resulted in two compounds (B1, B2). This is a result of 4-amino antipyrin's interaction with benzoyl chloride, as shown in **Figure 5**.

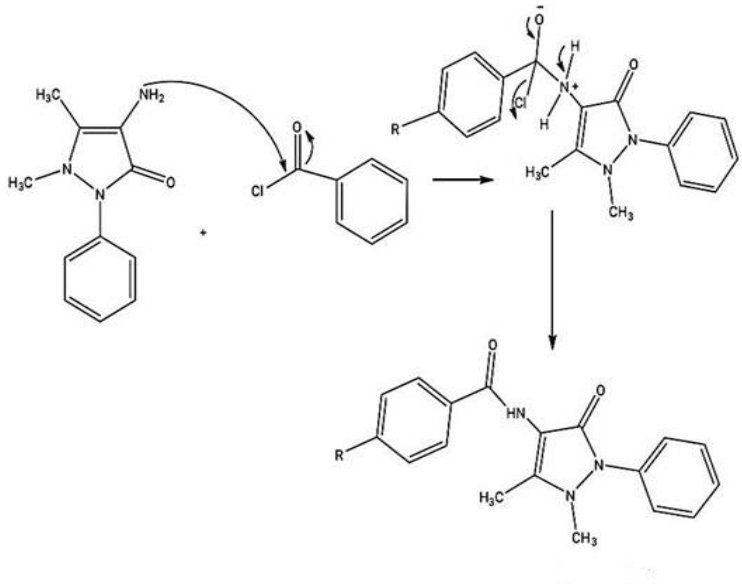


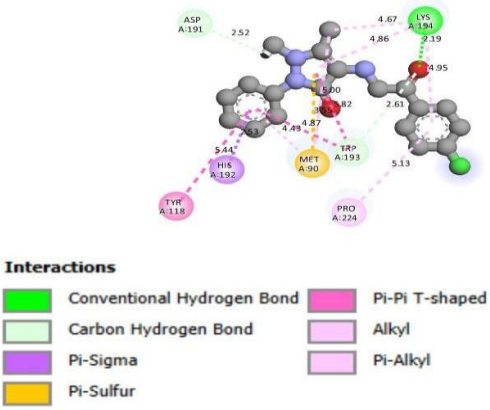
Figure 5. The mechanism of compounds (B1, B2)

Molecular docking analysis

The molecular docking employed the MOE software to ascertain the most substantial binding site in catechol-O-methyltransferase (COMT) through the SITE FINDER module . The ligand and the interacting amino acids were maintained in a flexible state to accommodate the induced fit during the flexible docking procedure. Each molecule exhibited five unique interactions with the protein. The docking scores corresponding to the optimal conformation within the active pocket were documented, alongside the binding site, as detailed in **Table 1**. This data predicted the recommended binding mode and affinity of the compounds tested, represented as binding free energy (ΔG). The ligand-protein interaction is shown in the COMT binding site in **Figure 6** and **Table 1**, providing insights into the binding mode, affinity, orientation of each pose, and binding free energy (ΔG) for the compounds assessed [44].

Table 1 shows the (DG) kcal/mol of compounds against the COMT enzyme

Compound	Docking Score Kcal/mole
Co crystal	-5.78
tolcapon	-6.09
Compound A1	-6.67
Compound A2	-6.85
Compound A3	-6.61



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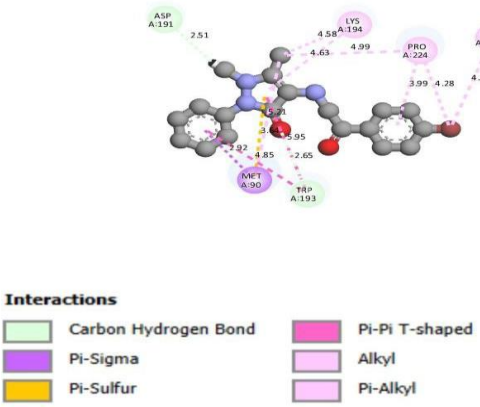

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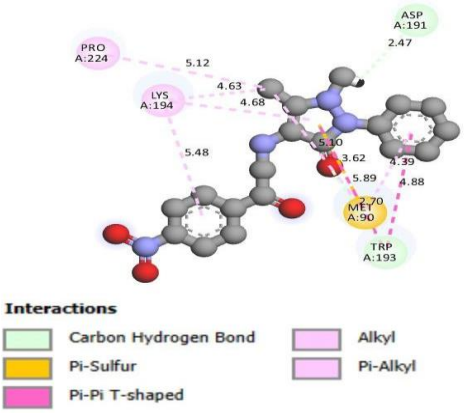

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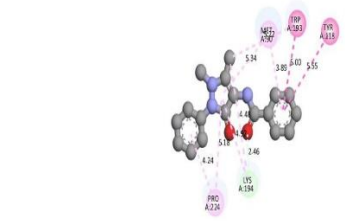

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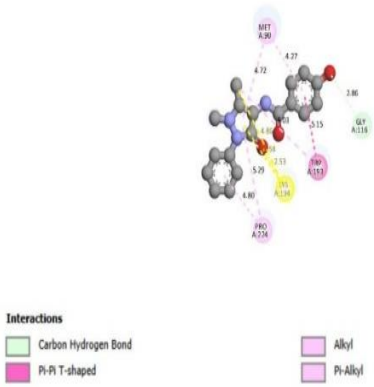

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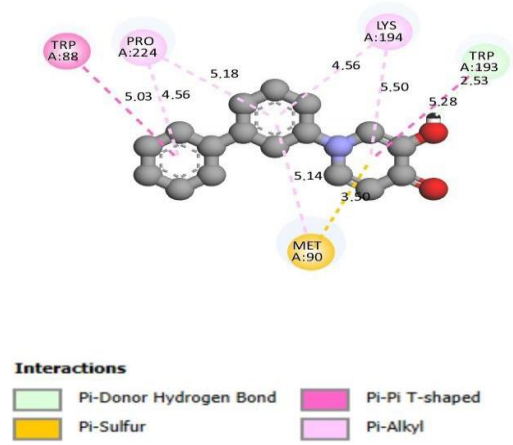

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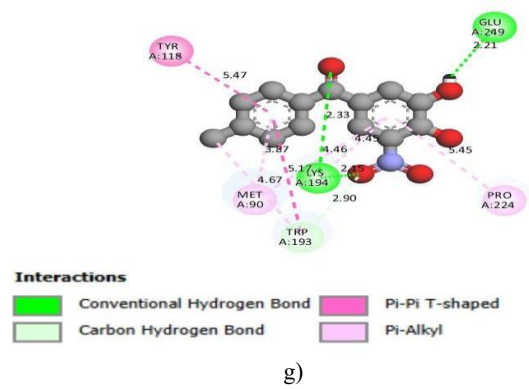


g)

Figure 6. Candidate compound (A1,A2,A3,B1,B2 ,co crystal and tolcapone) docked in COMT ENZYME

RMSD: root mean square deviation

RMSD is a key measure in the analysis of the stability of trajectories in molecular dynamics simulations. Plotting the RMSD along the x-axis as a function of time was done [20, 45, 46]. The variations in the backbone atoms of the protein (green), ligand (blue), and complex for the protein and ligand (red) are examined to examine the stability complex system under investigation during the simulation. The RMSD complex of ligand and backbone (green color) is regarded as stable after 5 ns despite some fluctuations in RMSD. This may result from the thermal energy of molecules that vibrate and rearrange themselves continuously; perhaps the system is not quite balanced. As the system enters its stable state, the RMSD may exhibit more variations during this early phase; the simulation's force field may impact how accurately atoms interact and are positioned, as shown in **Figure 7** [47-50].

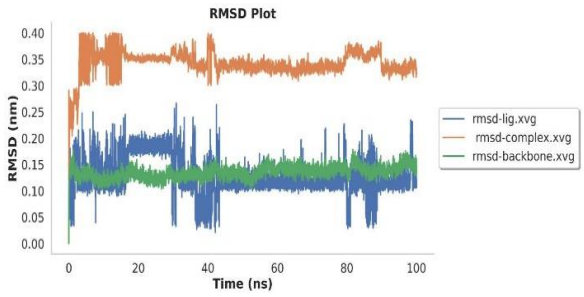


Figure 7. The RMSD of compound A2/COMT complex for 100 ns.

Solvent accessible surface area

It is a crucial concept in computational chemistry and biomolecular modeling. It represents the area of a molecule's surface that is accessible to solvent molecules (typically water) in a given conformation. This surface area plays a significant role in various biological processes, influencing molecular interactions, protein folding, and drug design strategies. Our SASA plot values against time, showcasing the evolution of the solvent-accessible surface area of a molecule during an MD simulation [51]. The SASA values stability over time, indicating dynamic changes in the molecule's solvent accessibility, as shown in **Figure 8**.

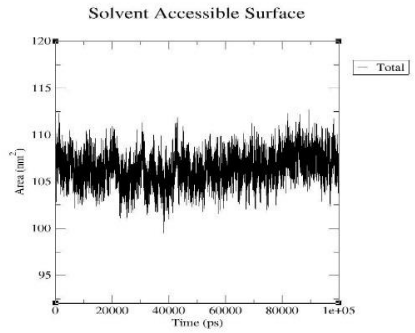


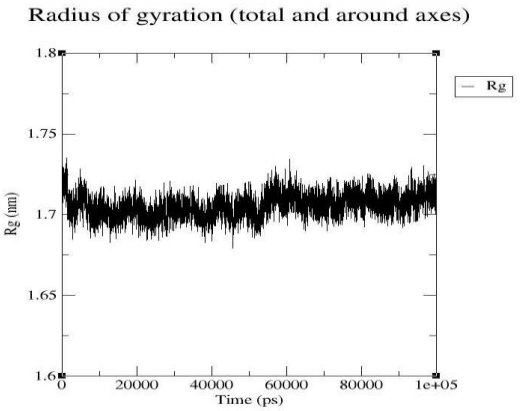
Figure 8. solvent accessible surface area of compound A2/COMT complex for 100 ns.

Root mean square fluctuation

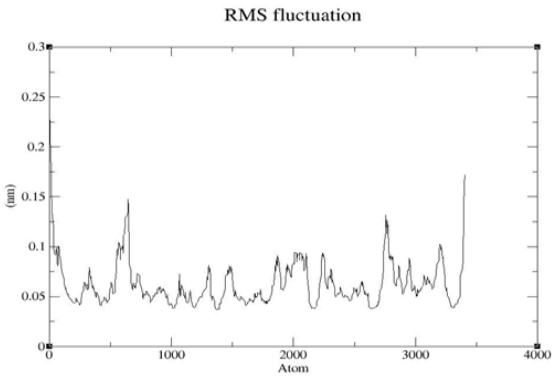
RMSF (Root Mean Square Fluctuation) quantifies the average displacement of atomic coordinates from their mean positions within molecular dynamics simulations [52-56]. This metric serves as an indicator of the flexibility and dynamic behavior of protein architectures. Elevated RMSF values are indicative of increased flexibility, whereas diminished values reflect structural rigidity [57-63]. The accompanying figure presents a comparative RMSF graph of the complexes, emphasizing the active site residues delineated in red, produced using 'gmx rmsf.' As illustrated in **Figure 9**.

Radius of gyration

The Rg values show that the molecule's structure is comparatively stable, with no discernible changes in its general shape over time, fluctuating within a range of 1.7 nm The minute changes in Rg may be due to heat oscillations or small conformational changes in the molecule, as shown in **Figure 9**.



a)



b)

Figure 9. The RMSD and Radius of gyration of compound A2/COMT complex for 100 ns

Conclusion

The novel compounds (A1, A2, A3, B1, and B2) were synthesized and validated through spectroscopic methods such as FTIR, HNMR, and 13CNMR. These compounds were also developed and evaluated for their binding affinity to the active

site of the COMT enzyme using molecular docking studies. The results of binding energy indicate that all of the compounds show approximately comparable binding energy to the reference drug, tolcapone. The new compounds can be synthesized as a new selective COMT inhibitor [64, 65]. Molecular docking and subsequent molecular dynamics simulations provided valuable insights into the interaction between the synthesized compound and the COMT enzyme. The RMSD plot showed that the ligand maintained a stable conformation during the simulation, indicating a strong binding affinity. SASA analysis confirmed that solvent accessibility remained constant, indicating that there are no significant structural changes that would hinder ligand binding. Examination of the protein by RMSF reveals general stability, with only some limited areas of flexibility observed that do not significantly affect ligand binding. This demonstrates the ability of the ligand to stabilize the protein and enhance its function as a potential inhibitor. Finally, Rg analysis revealed that the protein-ligand complex maintained a stable and compact structure over time. Overall, these results demonstrate that the synthesized compound exhibits a stable and positive interaction with the COMT enzyme, comparable to known inhibitors such as tolcapone. This mixture has potential as a candidate for further development and optimization in the treatment of conditions in which COMT inhibition is beneficial. Future research should focus on experimental confirmation and further optimization of the pharmacokinetic properties of the drug to increase its therapeutic potential.

Acknowledgments: The authors are grateful to the Department of Pharmaceutical Chemistry, College of Pharmacy, University of Tikrit, Iraq, for supporting the current work.

Conflict of interest: None

Financial support: None

Ethics statement: None

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