Drug and Chemical Toxicology

ISSN: 0148-0545 (Print) 1525-6014 (Online) Journal homepage: www.tandfonline.com/journals/idct20

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To cite this article: Verda Çoban, Nevin Çankaya & Serap Yalçın Azarkan (2024) New oxomethacrylate and acetamide: synthesis, characterization, and their computational approaches: molecular docking, molecular dynamics, and ADME analyses, Drug and Chemical Toxicology, 47:6, 1175-1184, DOI: 10.1080/01480545.2024.2349651

To link to this article: https://doi.org/10.1080/01480545.2024.2349651

DRUG AND CHEMICAL TOXICOLOGY
2024, VOL. 47, NO. 6, 1175–1184
https://doi.org/10.1080/01480545.2024.2349651

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RESEARCH ARTICLE

New oxomethacrylate and acetamide: synthesis, characterization, and their computational approaches: molecular docking, molecular dynamics, and ADME analyses

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ABSTRACT

The compounds 2-chloro-N-(3-methoxyphenyl)acetamide (m-acetamide) and 2-(3-methoxyphenylamino)-2-oxoethyl methacrylate (3MPAEMA) were synthesized in this study for the first time in the literature. FTIR, ^{1}H, and ^{13}C NMR spectroscopic techniques were used to characterize it. Subsequently, computational techniques were used to assess various ADME factors, such as drug-likeness properties, bioavailability score, and adherence to Lipinski's rule. Finally, molecular docking experiments were conducted with the human topoisomerase α2 (TOP2A) protein to verify and validate the reliability and stability of the docking procedure. The results of the docking scores, which quantify binding affinity, indicated that these derivatives exhibited a stronger affinity for TOP2A.

ARTICLE HISTORY
Received 16 January 2024
Revised 28 March 2024
Accepted 25 April 2024

KEYWORDS
Synthesis; characterization; molecular docking; ADME; drug-likeness

Introduction

Cancer represents a complex disease with various contributing factors, making its onset and progression intricate processes. A significant challenge in developing anticancer drugs lies in overcoming multidrug resistance and preventing relapse. Traditional chemotherapeutic agents typically act directly on the DNA of cells, whereas modern anticancer drugs focus on molecular-targeted therapies, such as targeting proteins with abnormal expression within cancer cells. Over the past few years, numerous promising drug targets have emerged for more effective cancer treatment. To develop novel drugs with heightened efficacy, researchers have designed new compounds. The quantity of these new drug candidates is steadily increasing and is expected to continue rising. In recent times, computer-based studies have gained significance in discovering active pharmaceutical ingredients, offering both cost-effectiveness and expedited processes in the discovery of new drugs (Bourzikat et al., 2022; Kumar et al., 2017).

Molecular docking is the method of computationally structure-based drug creation that has gained the most traction. This is the recommended method when the 3D structure of the protein target is known. The popularity of docking molecules has greatly increased because of the expansion of computing resources and availability, as well as the number and accessibility of protein and small molecule structures (Stanzione et al., 2021).

Understanding and predicting the identification of molecules from an energetic (forecasting binding affinity) and structural (identifying probable binding modes) perspective are the main goals of molecular docking. The original goal of molecular docking was to create a reaction between a tiny particle (a ligand) and a specific macromolecule (a protein). However, the demand for protein–protein docking, nucleic acid (DNA and RNA)–ligand docking, and nucleic acid–protein–ligand docking has increased over the past 10 years (Li et al., 2010). We will concentrate on protein–ligand docking in this paper.

Numerous uses for molecular docking exist in the drug development process, such as helping X-ray and cryo-EM crystallography fit substrates and inhibitors to electron densities, lead improvement, virtualize lead detection, and binding theories to aid in determining the outcome of mutagenesis experiments. Docking has been researched and enhanced for many years because of its tremendous success in structure-based medication creation. More than 60 distinct docking technologies have been created in academic and industrial environments in the past 20 years (Pagadala et al., 2017; Wang et al., 2016). We actively used the Autodock Vina software program in this study.

A DNA topoisomerase with the ability to regulate and modify the topological states of DNA during transcription is encoded by the gene topoisomerase α2 (TOP2A) (Fernandez-Ranvier et al., 2008). Chromatid segregation and chromosomal condensation are mechanisms by which TOP2A is active (Dawany et al., 2011). In numerous human malignancies, TOP2A is a marker of proliferation, severe illness, and treatment tolerance (Coss et al., 2009; Desmedt et al., 2011;

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Malhotra et al., 2011). Using several drugs with TOP2A inhibitory properties for cancer therapy to target, TOP2A, such as anthracycline drugs, is of great interest (Bedard et al., 2009; Song et al., 2011; Wang et al., 2010). DNA relaxation, a crucial stage in DNA replication, relies significantly on the action of DNA topoisomerases. Consequently, these enzymes become significant focal points for cancer medications. Compounds that inhibit DNA topoisomerases bind to the temporary enzyme–DNA complexes, impeding DNA replication. Numerous inhibitors targeting both topoisomerase I and II are utilized in pharmaceuticals. Particularly, topoisomerase II stands out as a pivotal target in the endeavor to craft anticancer treatments (Jadhav and Karuppayil, 2017).

In this study, we synthesized 2-chloro-N-(3-methoxyphenyl) acetamide (m-acetamide) and 2-(3-methoxyphenylamino)-2-oxoethyl methacrylate (3MPAEMA) for the first time. In our previous studies, we proved that molecules with a structure similar to the substances we synthesized in this article have biological properties and we conducted *in silico* studies (Çankaya et al., 2021, 2022, 2023; Tanış et al., 2019). In this study, molecular docking studies of m-acetamide, which has Cl and OCH_3 groups in its structure, and 3MPAEMA, which has functional groups (amide, ester, and OCH_3), were performed with TOP2A. The potential of newly synthesized ligands as inhibitors of TOP2A was investigated.

Experimental

Materials

For the synthesis of m-acetamide, 3-methoxy aniline, triethylamine (Et_3N), and chloroacetylchloride (Aldrich®) were used. For the synthesis of 3MPAEMA, sodium methacrylate, tebac (triethylbenzylammonium chloride), and NaI (Aldrich®) were used. Pure 1,4-dioxane and acetone were preferred as the solution mediums.

Instrumental measurements

A PerkinElmer Spectrum Two (UATR) IR spectrometer was used to obtain the FTIR spectra of each sample. We performed ^1H and ^{13}C NMR investigations with a Bruker TopSpin Ultra Shield at 400 MHz using $CDCl_3$-d_6 and DMSO-d_6 as solvents.

Synthesis of 2-chloro-N-(3-methoxyphenyl)acetamide (m-acetamide) and 2-(3-methoxyphenylamino)-2-oxoethyl methacrylate

Pure acetone was used to dissolve 3-methoxy aniline (1 mmol) and Et_3N (1.1 mmol), which were both incorporated into the solution together with chloroacetyl chloride (1.1 mmol) at a temperature between 0 and 5 °C. To remove the salt that developed and precipitated in the icy water, the dark brown solution underwent filtration (Çankaya et al., 2021, 2023). Figure 1 depicts the reaction diagram for the synthesized m-acetamide.

To create 3MPAEMA, m-acetamide (1 mmol), sodium methacrylate (1.1 mmol), hydroquinone (which inhibits polymerization), and Tebac-NaI (a phase-transfer agent) were all used. The reaction, which used 1,4-dioxane as the solvent, was completed with reflux after 48 h. Hydroquinone was removed from the solution by washing with a base solution after the excess solvent was removed through filtering (Çankaya et al.,

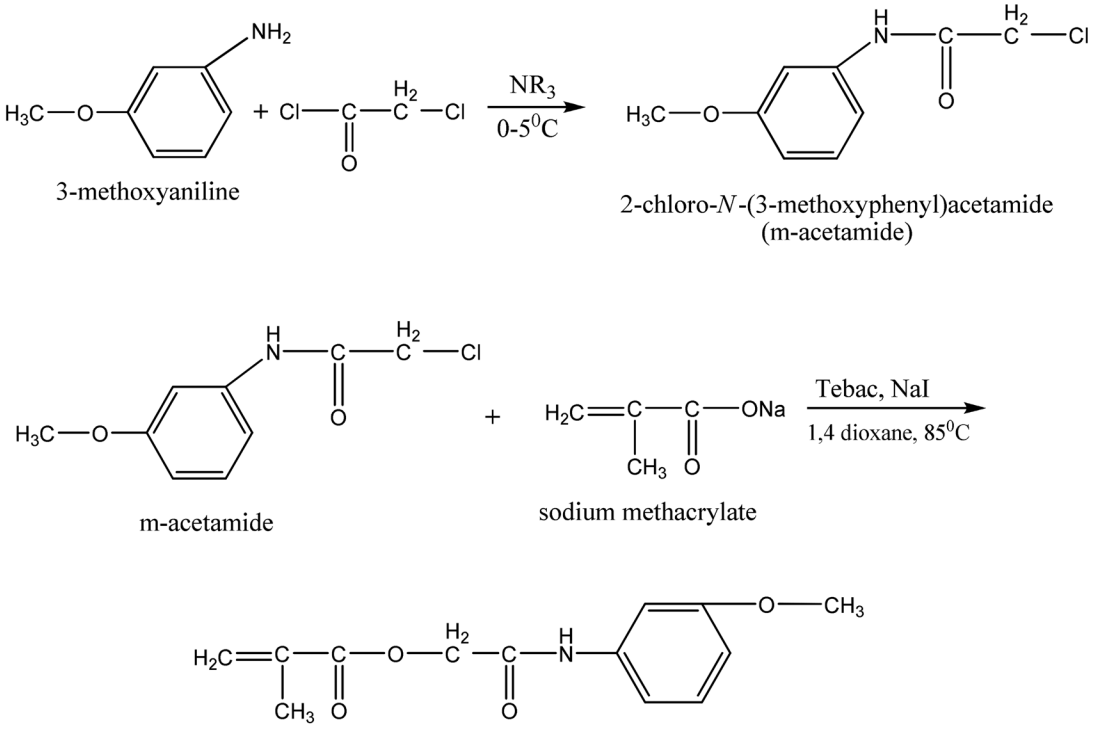

Figure 1. Synthesis scheme of m-acetamide and 3MPAEMA.

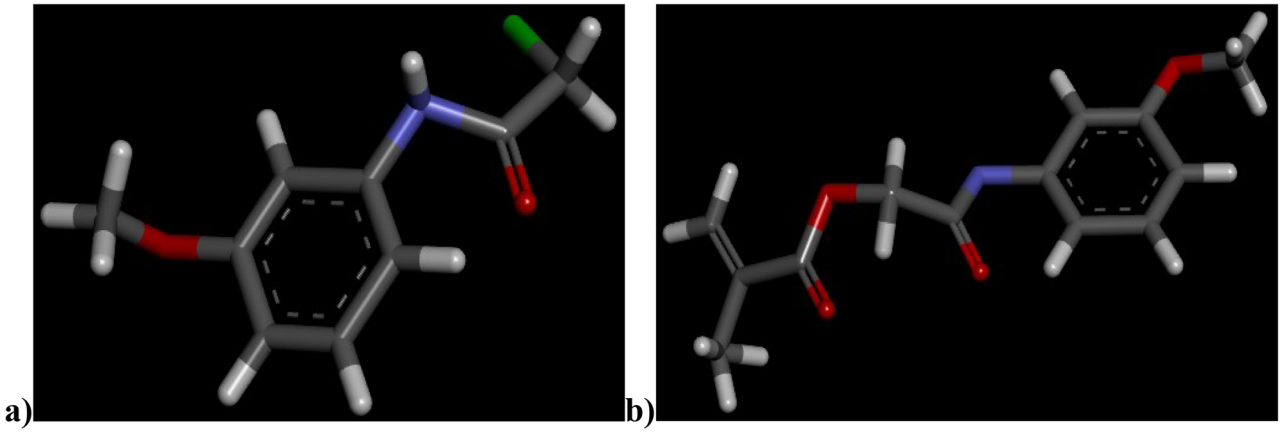

Figure 2. 3D structure of (a) m-acetamide and (b) 3MPAEMA.

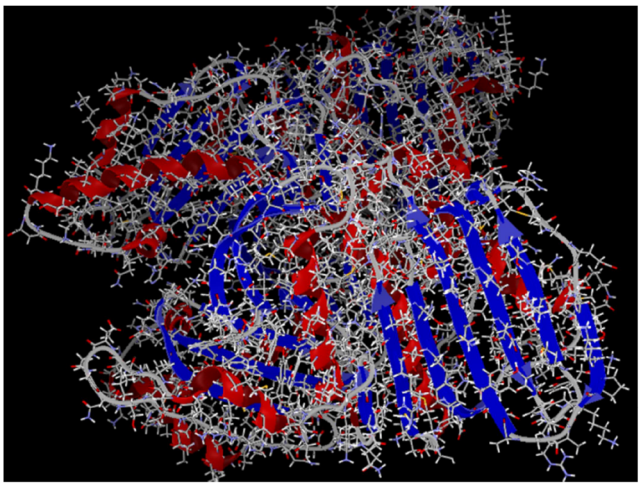

Figure 3. 3D structure of TOP2A.

2021, 2023; Tanış et al., 2019). The synthesis of the 3MPAEMA monomer is shown in Figure 1.

Molecular docking studies

The molecular docking computations were performed using Autodock Vina software (Çankaya et al., 2022; Trott and Olson, 2010). Water molecules and protein cofactors were excluded to clearly analyze the protein–ligand interaction. The structure and 3D theoretical model of the TOP2A protein can be accessed free of charge from the RCSB Protein Data Bank (https://www.rcsb.org/; PDB code: 1zxm). All proteins and ligands were validated before performing *in silico* calculations. Proteins and ligands visualized using BIOVIA Discovery Studio Visualizer Client 2017R2 (https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/). In Figure 2, the 3D structure of m-acetamide and 3MPAEMA is shown. Figure 3 shows the 3D structure of TOP2A.

Drug similarity and ADME prediction

An online tool called SwissADME (http://www.sib.swiss; http://www.swissadme.ch/index.php) was used to calculate the pharmacokinetics and similarities of drug candidates (Daina et al., 2017; Zoete et al., 2016). These toxicity estimations were also applied to the Lipinski, Ghose, and Veber bioavailability guidelines and scores (Ghose et al., 1999; Lipinski et al., 1997; Veber et al., 2002).

We evaluated the effectiveness of MM/PB(GB)SA in identifying the proper binding sites for ligands, including those obtained from Schrodinger and the Amber package (Wang, Sun, et al., 2019; Wang, Zhang, et al., 2019; http://cadd.zju.edu.cn/farppi). The CABSflex2 program was used to run the dynamic simulation. To examine the level of stability, a 50-ns simulation of MD was run (Jamroz, Kolinski, et al., 2013a; Jamroz, Orozco, et al., 2013b; Jamroz et al., 2014; http://212.87.3.12/CABSflex2).

Results and discussion

The m-acetamide and 3MPAEMA elemental analysis values were within 0.3% of the theoretical data generated for the suggested formulas.

Characterization of m-acetamide

The FTIR, ^{1}H, and ^{13}C NMR spectra of m-acetamide are shown in Figures 4–6. FTIR (cm^{-1}, characteristic bands): 787 (C–Cl stretching), 1603 (C=C stretching on aromatic ring), 1661 (C=O amide stretching), 2959 (C–H aliphatic stretching), and 3293 (N–H stretching).

The ^{1}H NMR spectrum of m-acetamide shows the following peaks: at 8.0 ppm for N–H, 7.8, 7.5, 7.0, and 6.9 ppm for aromatic ring protons, 4.3 ppm for CH_2-Cl, 3.9 ppm for O-CH_3, and 7.3 ppm for $CDCl_3$ protons.

The ^{13}C NMR spectrum of m-acetamide shows the following peaks: at 165.1 ppm for C=O, 161.3 ppm for Ar(C)=OCH_3, 140.2 ppm for Ar(C)=NH, 130.5, 117.2, 111.1, and 110.0 ppm for ring carbons, 55.81 ppm for CH_3–O, 43.0 ppm for CH_2–Cl, and 77.1 ppm for $CDCl_3$ carbons.

Characterization of 2-(3-methoxyphenylamino)-2-oxoethyl methacrylate

The FTIR, ^{1}H, and ^{13}C NMR spectra of 3MPAEMA are shown in Figures 7–9. FTIR (cm^{-1}, the most characteristic bands): 1636 (C=C olefinic stretch), 1668 (C=O amide stretch), 1723 (C=O

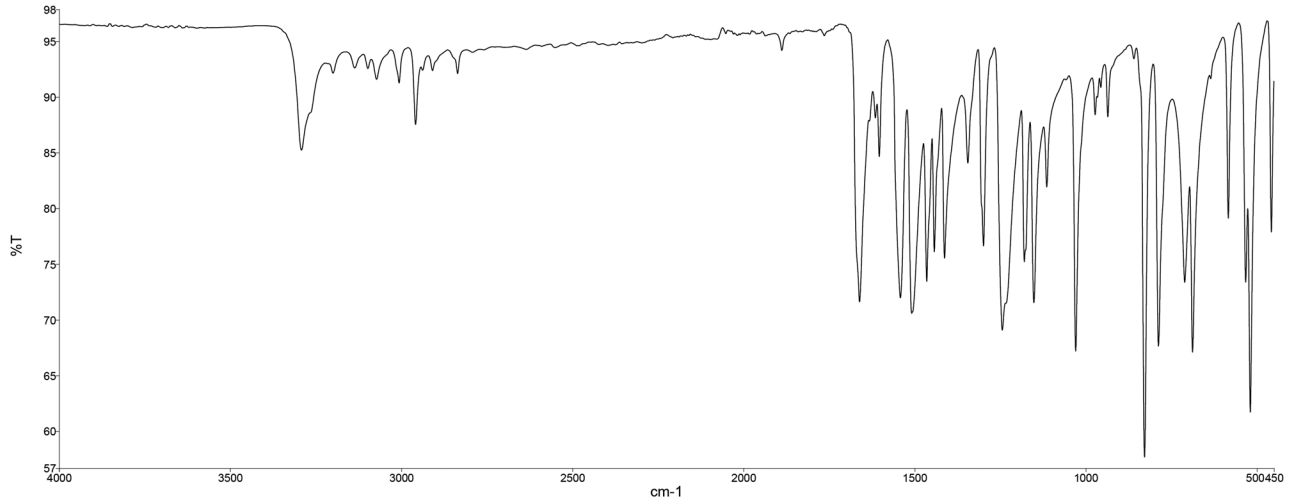

Figure 4. FTIR spectrum of m-acetamide.

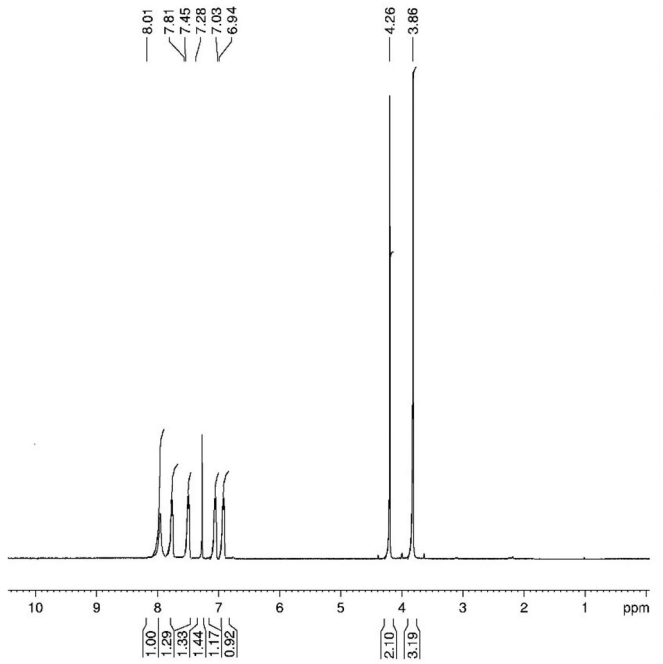

Figure 5. ^{1}H NMR spectrum of m-acetamide.

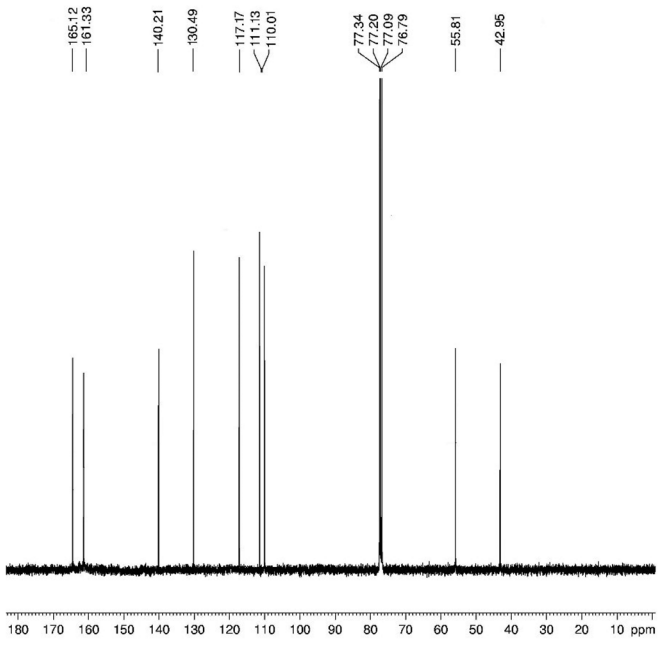

Figure 6. ^{13}C NMR spectrum of m-acetamide.

ester stretch), 3261 (N–H stretching), 1606 (C=C stretch on aromatic ring), 2937 (C–H aliphatic stretching), 1245 (C–O–C symmetric stretching), and 1511 (C–O–C asymmetric stretching).

The ^{1}H NMR spectrum of 3MPAEMA shows the following peaks: at 8.6 ppm for Ar(CH)–NH, 8.1 ppm for N–H, 7.5, 6.5, and 6.3 ppm for aromatic ring protons, 5.6 and 5.3 ppm for $=CH_2$ olefinic protons, 4.4 for ppm O-CH_2, 3.8 ppm for O-CH_3, 2.0 ppm for C-CH_3, and 3.5 and 2.5 ppm for DMSO-H_2O-d_6 and DMSO-d_6 protons, respectively.

^{13}C NMR spectrum of 3MPAEMA shows the following peaks: at 170.0 ppm for O"C–NH, 167.2 ppm for O"C–O, at 161.1 ppm for Ar(C)-OCH_3, 140.3 ppm Ar(C)-NH, 138.3 ppm C-CH_3, 124.4 ppm for $=CH_2$olefinic, 130.3, 116.2, 110.2, and 110.1 ppm for ring carbons, 65.7 ppm for O=C-CH_2-O, 56.2 ppm O-CH_3, 19.3 ppm for C-CH_3, 39.7 ppm for DMSO-d_6 carbons.

ADME, drug-likeness, and docking studies

M-acetamide and 3MPAEMA have been identified as being consistent with Lipinski's, Veber's, or Ghose's rules, depending on the drug-likeness assessment. Drug-likeness and ADME analyses of m-acetamide and 3MPAEMA are shown in Figures 10 and 11.

The molecular docking outcomes from our investigation revealed robust interactions between TOP2A and both m-acetamide and 3MPAEMA. The binding affinity was assessed using a scoring function based on the Lamarckian genetic algorithm. Both m-acetamide and 3-MPAEMA exhibited substantial binding affinities to the TOP2A protein, with energy values of −6.5 kcal/mol (H bound: 2) and −7.6 kcal/mol (H bound: 1), respectively (as depicted in Figures 12 and 13).

The stability of molecule interactions is evaluated using various molecular dynamics aspects. Furthermore, molecular dynamics is a prominent tool for scrutinizing molecular

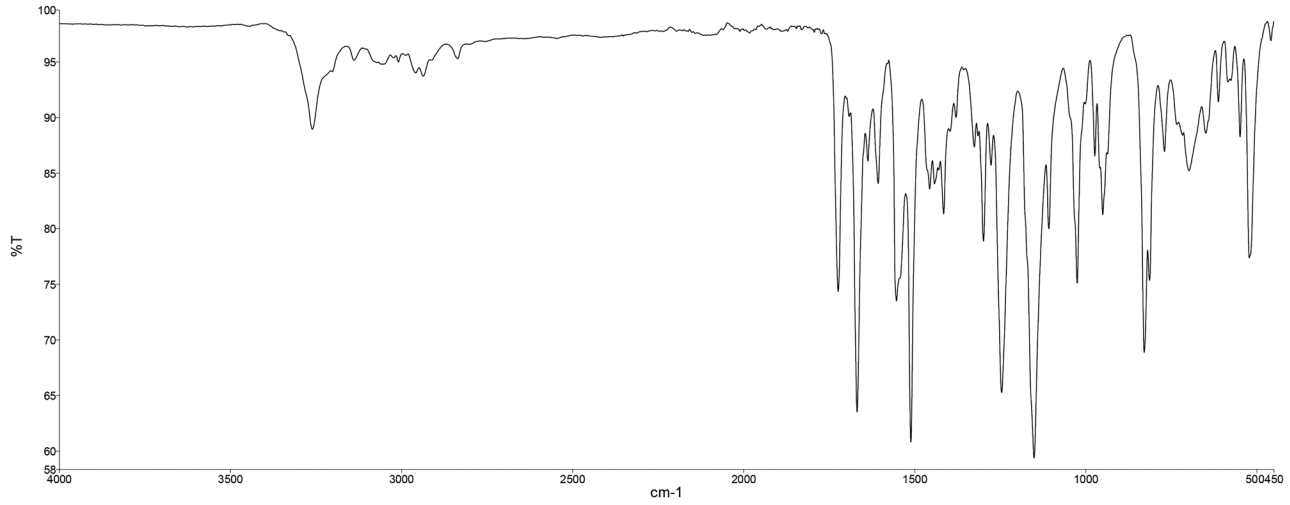

Figure 7. FTIR spectrum of 3MPAEMA.

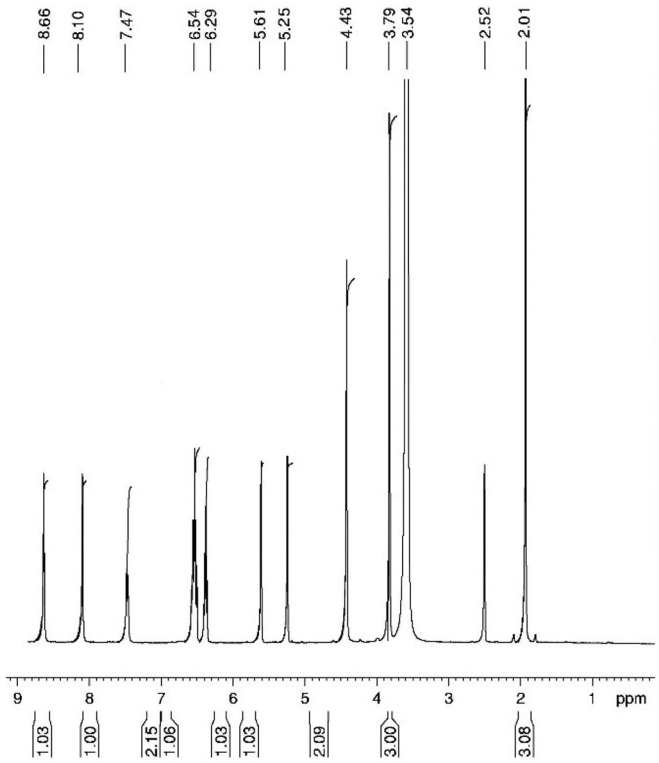

Figure 8. [1]H NMR spectrum of 3MPAEMA.

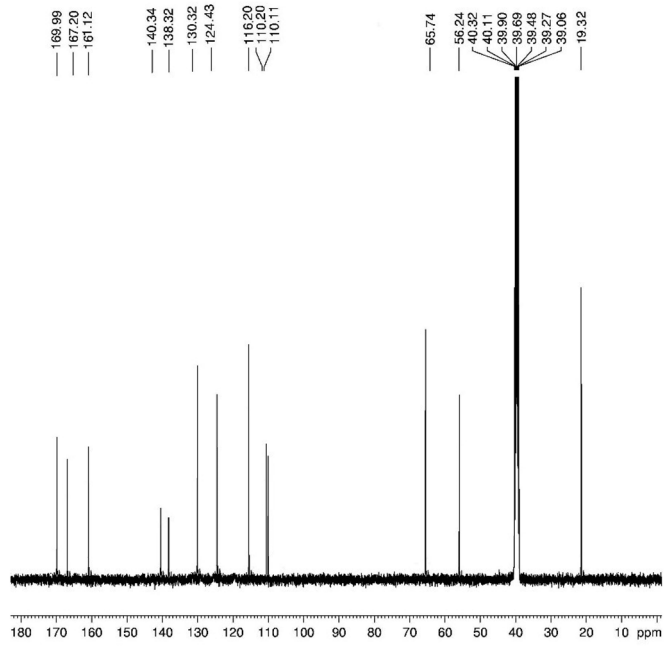

Figure 9. [13]C NMR spectrum of 3MPAEMA.

interactions and their stability. In this study, after conducting molecular dynamics simulations, root mean square fluctuation (RMSF) principles were used to compute values for the protein–ligand complex.

Figures 14 and 15 showcase RMSF values and demonstrate the duration of amino acid residues' involvement with the protein backbone interface, providing insight into the amino acid framework participating in the interaction. RMSF evaluates local variances along the protein chain. It is expected that RMSF values are higher in terminal regions compared to intermediate regions, indicating increased fluctuations at these sites. Conversely, RMSF values for intermediate regions are lower than those for terminal regions due to the rigid structure of the alpha-helix and beta-strand (Fatriansyah et al., 2022).

The Schrödinger suite and Amber program were used to compute the binding free energy of ligands using the MM/PB(GB)SA approach (http://cadddu.cn/farppi).

The input files were created using AutoDock Tools. The force field parameters were configured as GAFF2 for the ligand and ff14SB for the receptor, while the rescoring procedure was established as PB3 (with radii set as parse, $\gamma = 0.00542$, $\beta = 0.9200$). The AM1-BCC method was employed to compute the partial charges of the ligands using the antechamber module of Amber.

MM-PB(GB)SA analysis stands as a significant and widely used technique for screening drug candidates due to its simplicity and the favorable balance between speed and accuracy in providing information. Figures 16 and 17 show the outcome of the MM/PB(GB)SA graph of the ligands. In our investigation,

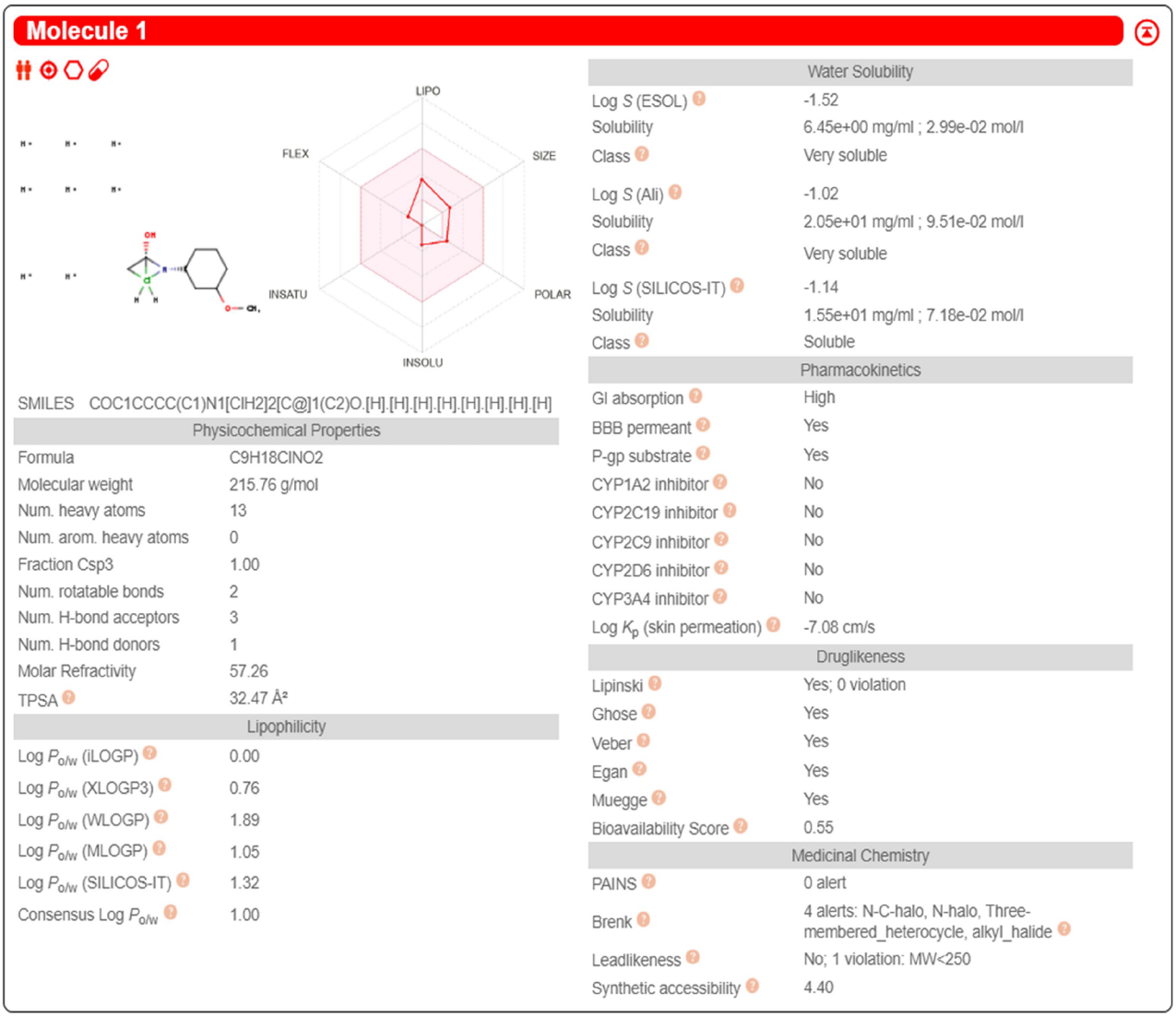

Figure 10. Drug-likeness and ADME analyses of m-acetamide.

we determined the highest and lowest binding free energies for m-acetamide and 3MPAEMA, respectively. Specifically, the binding free energies of m-acetamide and 3MPAEMA with TOP2A were computed as −28.4 and −29.8 kcal/mol, respectively.

Conclusions

By conducting a two-step reaction using 2-chloro-N-(3-methoxyphenyl)acetamide (m-acetamide), 2-(3-methoxyphenylamino)-2-oxoethyl methacrylate was produced. FTIR, ^{1}H, and ^{13}C NMR spectroscopy were used to characterize both compounds. Furthermore, m-acetamide and 3MPAEMA successfully met Lipinski's rule criteria, achieving a high bioavailability score. In molecular docking and dynamic analyses, it has been shown that 3MPAEMA exhibits promise as an anticancer agent targeting TOP2A, displaying a high level of activity. This study conducted molecular docking investigations of m-acetamide and 3MPAEMA, which possesses various functional groups, with TOP2A. The research aimed to assess the potential of these newly synthesized ligands as inhibitors of TOP2A. This new molecules can be showed on topoisomerase as a critical target in the development of anticancer therapies.

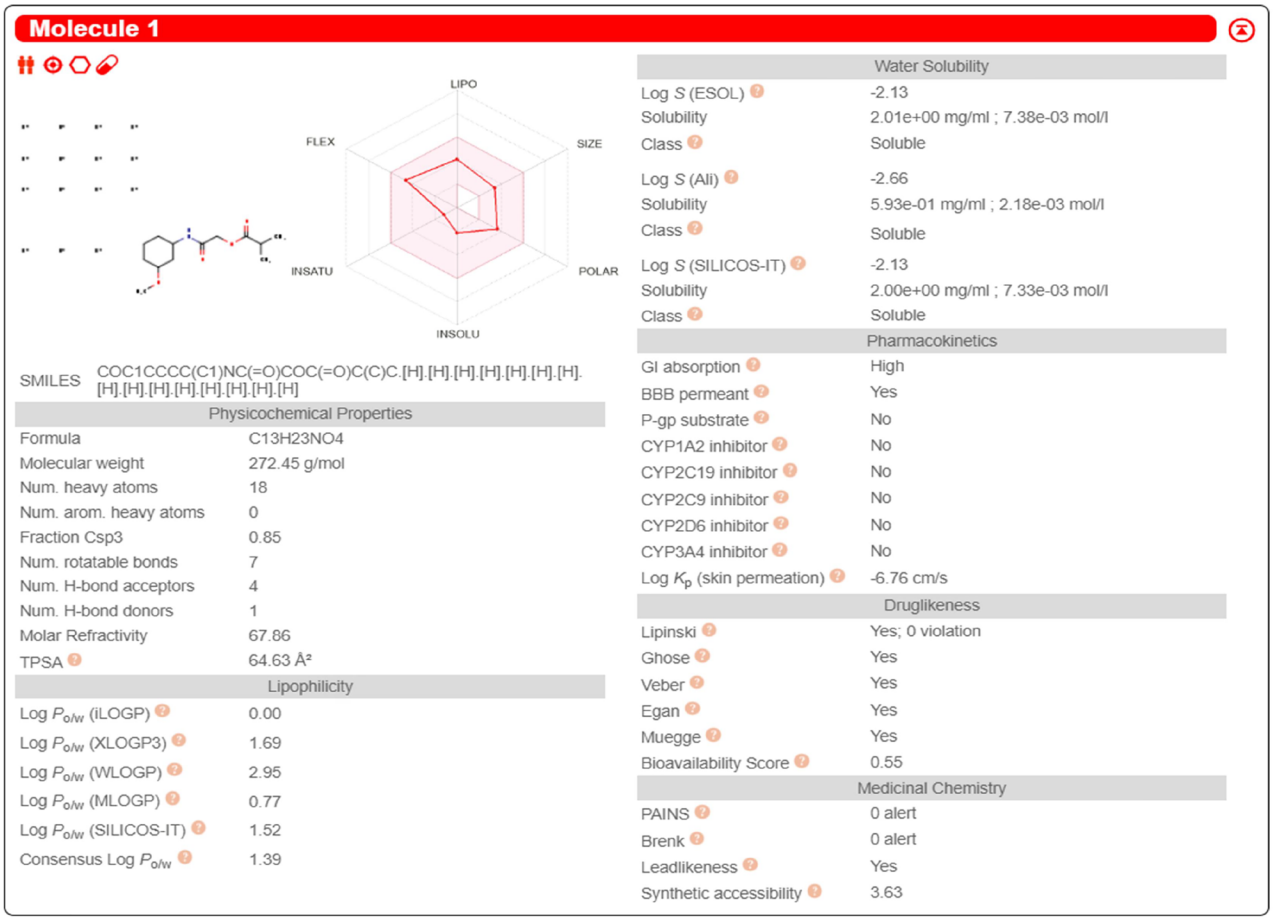

Figure 11. Drug-likeness and ADME analyses of 3MPAEMA.

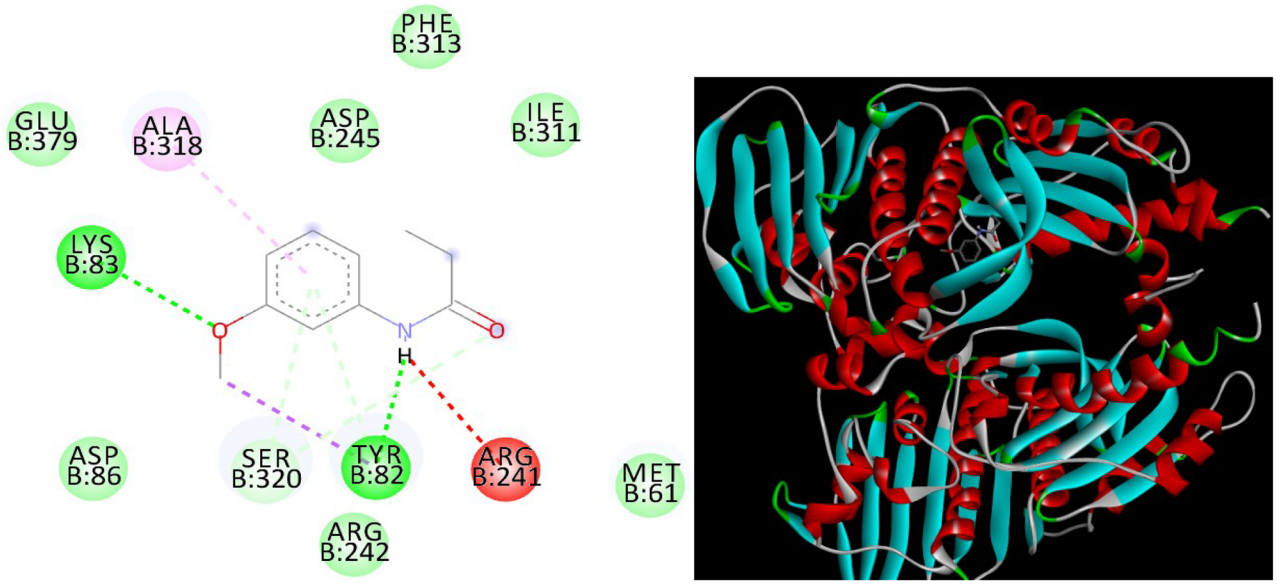

Figure 12. Interaction between the TOP2A protein and the m-acetamide ligand.

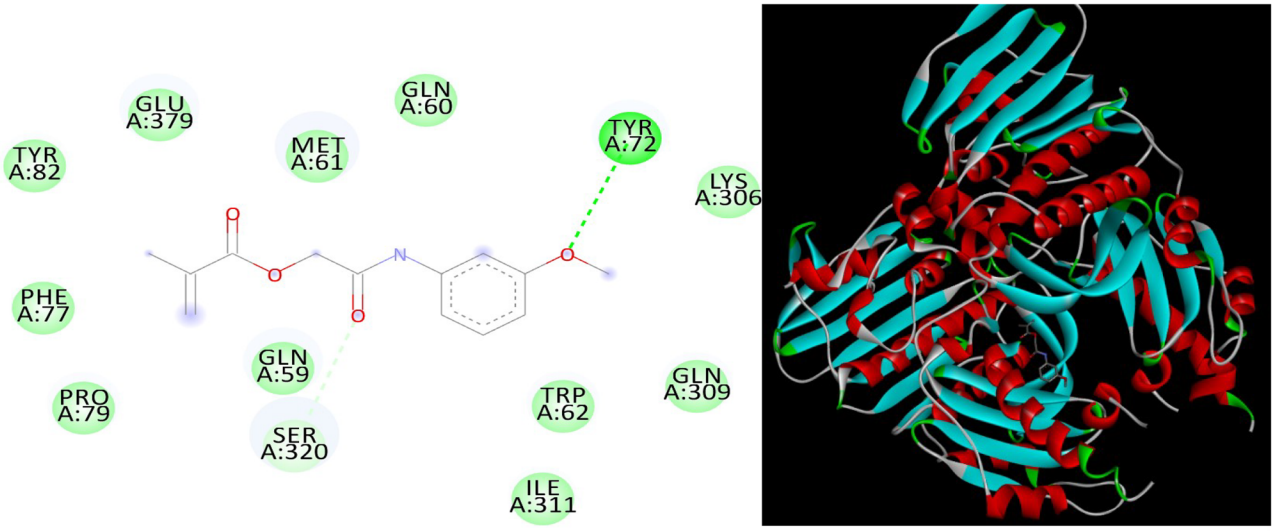

Figure 13. Interaction between the TOP2A protein and the 3MPAEMA ligand.

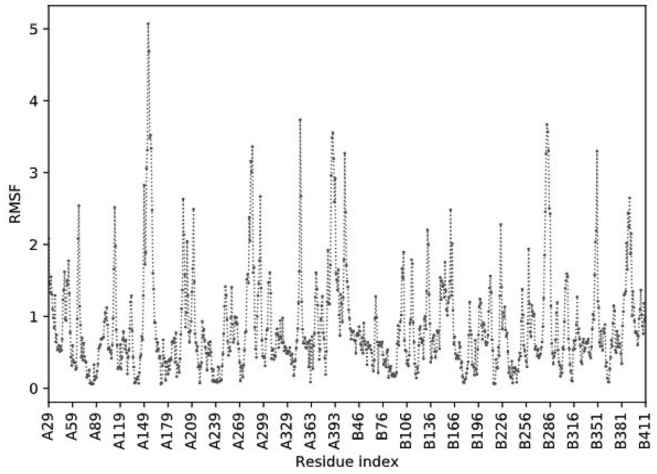

Figure 14. RMSF graph of TOP2A and m-acetamide.

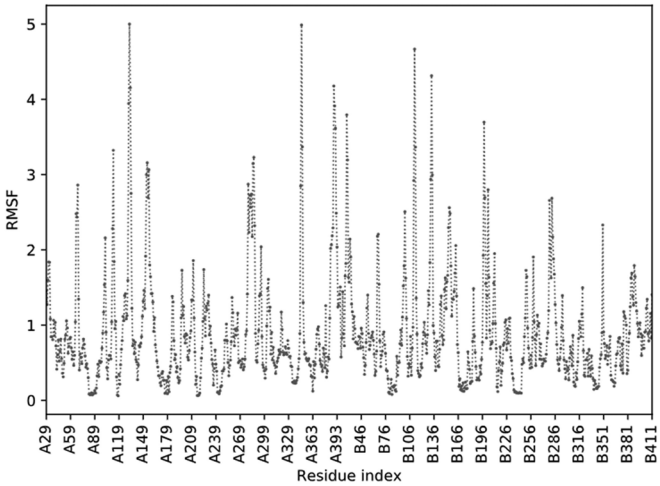

Figure 15. RMSF graph of TOP2A and 3MPAEMA.

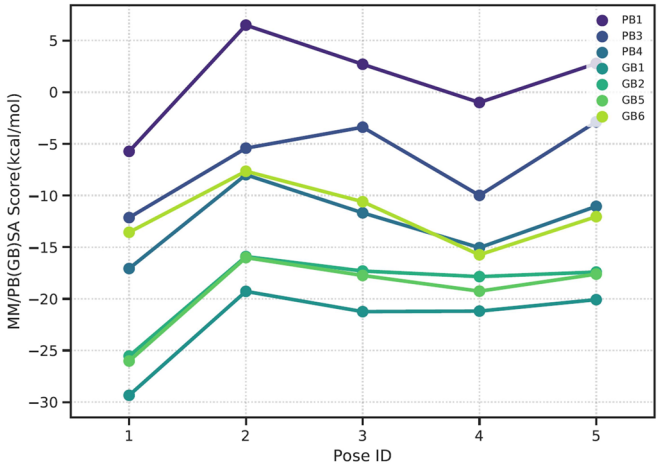

Figure 16. Binding free energy graph of m-acetamide and TOP2A.

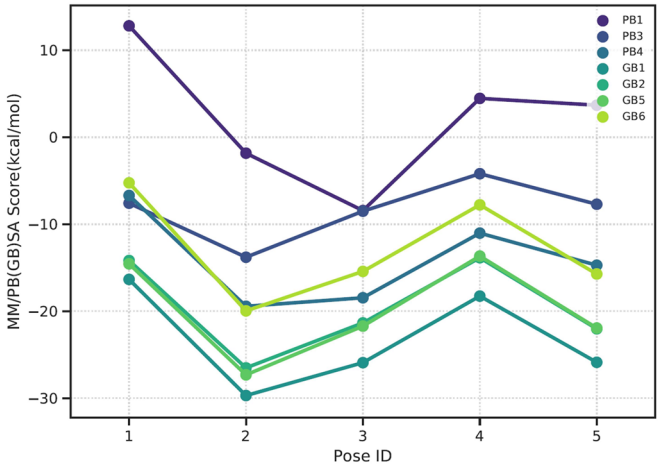

Figure 17. Binding free energy graph of 3MPAEMA and TOP2A.

Acknowledgements

This study was created from V. Çoban's master's thesis and we thank the Graduate Education Institute. The authors would like to thank The Research Foundation of Usak University (BAP) for financial support of this work. Project no: 2024/TP006.

Author contributions

VÇ: investigation; writing – original draft; methodology; validation; writing – review and editing. NÇ: investigation; software; formal analysis, writing – review and editing. SYA: writing – original draft; methodology; validation.

Ethics statement

This study did not include any humans or animals; therefore, we did not apply for ethical approval or register for clinical trials.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

There was no source of funding involved in this study.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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