

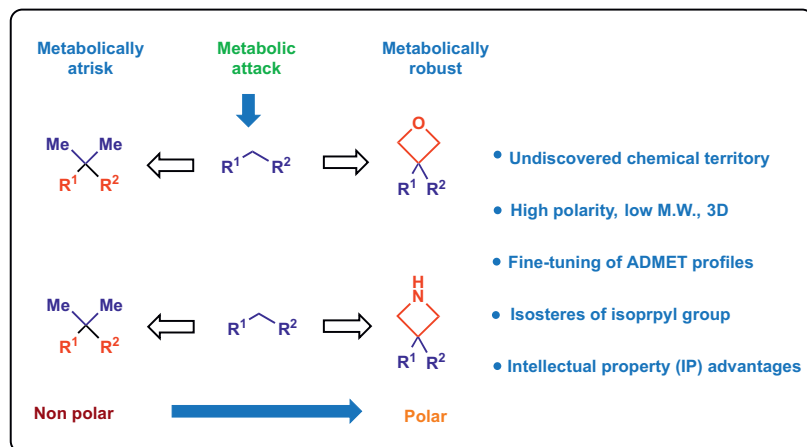
Letter

Exploration of Oxetanes and Azetidines in Structure-Based Drug Design

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GRAPHICAL ABSTRACT



ABSTRACT

Oxetane and azetidine motifs are widely used in medicinal chemistry to enhance various attributes such as hydrophilicity, metabolic stability, hydrophobicity, and conformational preference. These stable structures are present in numerous bioactive compounds, including FDA-validated therapeutic agents. This study aims to demonstrate the use of oxetane and azetidine ring systems as bioisosteric replacements for isopropyl groups in the development of novel lead candidates. The objective is to improve physicochemical and structural characteristics to facilitate effective molecular optimization, improve pharmacological activity, and simplify synthetic pathways. This can ultimately increase the chances of discovering medication that is more efficient and safer to use. We report the virtual screening of selected 14 approved drugs with a replacement of isopropyl to oxetane and azetidine group transformation, enabling optimization for receptor binding potential and absorption, distribution, metabolism, and excretion (ADME) properties. The results indicate that oxetane alectinib (−6.906 kcal/mol), azetidine procarbazine (−8.083 kcal/mol), azetidine erdafitinib (−7.677 kcal/mol), oxetane anastrozole (−7.454 kcal/mol), azetidine nateglinide (−6.686 kcal/mol), oxetane repaglinide (−7.831 kcal/mol), oxetane nilutamide (−9.649 kcal/mol), and oxetane proguanil (−8.555 kcal/mol) have excellent molecular affinity when compared to their parent molecule. This perspective aims to inspire medicinal chemists to explore the use of oxetane and azetidine moieties in the development of effective drug candidates.

Keywords Oxetane, Azetidine, Isopropyl group, Drugs, Binding potential, ADME properties

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Introduction

In medicinal chemistry, there is growing interest in the strategic incorporation of aliphatic four-membered ring systems such as oxetanes and azetidines.¹⁶ These ring systems are characterized by their favorable structural and physicochemical properties, making them efficient bioisosteric substitutions.¹⁵ Their incorporation has been shown to improve important drug-like properties, such as lipophilicity (LogP)²⁸ and aqueous solubility (LogS). Due to their reduced structural flexibility, these compounds may be less susceptible to oxidative metabolism by certain cytochrome P450 (CYP450) enzymes, as their conformational rigidity and electronic properties are less favorable for single-electron oxidation.^{36,46} Additionally, unlike planar aromatic rings, the presence of compact aliphatic ring systems increases the complete fraction of sp³-hybridized carbon, which can enhance solubility through nonplanar substituent vectors. These small rings, coupled with the ability to form explicit polar interactions, offer avenues for enhancing potency and selectivity by improving the protein–ligand interface and exploiting molecular preorganization to facilitate more efficient and specific target interactions. Oxetane rings adopt a conformationally rigid molecular scaffold with a slight puckering angle of approximately 8.7°, contributing to their defined three-dimensional geometry as strained cyclic ethers, making them metabolically more stable, and their lipophilicity neutral.^{6,7,9,15} Several drugs featuring oxetane as a functional group have been reported to progress through various stages of clinical development.⁵⁵ Azetidines are unique polar 4-membered rings that contain a basic nitrogen atom, making them distinct from their neutral small ring counterparts.^{20,32} According to a recent study, azetidines are used as bioisosteric replacements for piperidine, pyrrolidine, pyrazine, β -lactam, diazepane, piperazine, pyrrolidinone, and proline.^{5,8,17,19,33}

Additionally, oxetanes and azetidines have shown great potential as isosteric replacements for less desirable functional groups in drug design, such as lipo-neutral isopropyl and metabolically labile carbonyl functionalities.^{3,4,6,7,15,31,38,54} According to a recent screening of the Drug Bank version 5.0 database, there are 229 isopropyl-containing therapeutic compounds permitted for clinical use by the FDA and 100 isopropyl-containing compounds in clinical studies.⁵¹ Currently, 41 azetidine and 4 oxetane-containing compounds are US FDA-approved. Over the past two decades, there has been a significant increase in the exploration of oxetane and azetidine scaffolds within medicinal chemistry.⁴⁰ Numerous drug candidates incorporating these four-membered ring systems have advanced into various stages of clinical development.

A recent study reported that replacing the isopropyl group with azetidine and oxetane moieties can have a significant impact on PK/PD-related parameters.^{5–7} These rings can be considered functional groups and are used as preferred surrogates for other commonly used drug discovery functionalities. Introduction of steric bulk may lead to better fit of motifs in the receptor pockets, thereby blocking the active sites and enhancing intrinsic activity. These motifs also act to shield adjacent functional groups from chemical and metabolic degradation without substantially increasing lipophilicity.⁵³ Nevertheless, challenges

related to synthetic accessibility and chemical stability must be addressed.^{7,43,53} To explore the effect of replacing isopropyl groups with oxetane and azetidine, virtual screening (VS) was performed on 14 clinically approved drugs containing isopropyl molecules, including antineoplastic, antihyperglycemic drugs, and NSAIDs, using DrugBank version 5.0 database (<https://go.drugbank.com/>). This analysis will help develop more potent drugs with better binding modes.

It is widely recognized in medicinal chemistry that compounds with high molecular weight and elevated lipophilicity often exhibit poor oral druglike characteristics. Within a chemical series, higher cLogP values are frequently linked to increased microsomal clearance and pharmacological promiscuity, whereas very low lipophilicity is commonly associated with reduced cell permeability and suboptimal absorption.^{31,39} Numerous studies have explored the optimal scale of lipophilicity required to attain “drug-likeness,” as this attribute affects a variety of other molecular properties in addition to binding affinity.^{78,79} In fact, variations in lipophilicity within a series of designed molecules can reliably impact essential characteristics such as absorption, distribution, metabolism, and excretion (ADME). To achieve good bioavailability (*F*), a drug must have optimal solubility and permeability. The present study investigates the impact of bioisosteric substitution of an isopropyl group with oxetane and azetidine moieties. These ring systems serve as more polar analogues of the isopropyl group while maintaining a similar spatial orientation. This substitution led to a scaling down in lipophilicity (cLogP) and resulted in kinetic solubility values within an acceptable range. These findings support a designed approach to enhance solubility and achieve reasonable *in silico* ADME profiles.^{39,79}

Enhancing the ADME properties of lead compounds by fine-tuning the lipophilicity of analogues is a potent approach. Computational lipophilicity prediction followed by experimental measurement of synthesized analogues can yield promising results. Successful optimization of drug discovery programs requires identifying structural changes in leads that maintain or enhance potency while reducing lipophilicity. Unfortunately, there are few examples of oxetane- and azetidine-containing molecules in the literature due to their expensive and time-consuming preparation methods. This study focuses on molecular modification as a strategy to identify new classes of lead compounds with enhanced drug likeness and biological activity, reducing the need for extensive synthetic work and increasing the likelihood of discovering more effective and safer medications.

Results and Discussion

Molecular Docking

Molecular docking is a significant aspect of computer-aided drug discovery, as it enables the evaluation of the binding efficacy between selected molecules and the target of interest. Using Maestro (Schrödinger Release 2025-1: Maestro, build 12, Schrödinger, LLC, New York, NY, 2025) tool, the identified molecules from VS were docked with protein to assess their binding affinity and interaction. After analyzing the binding interaction and energy, we found that 7 modified isopropyl-containing drugs

(alectinib, procarbazine, eradafitinib, anastrozole, nateglinide, repaglinide, nelutamide, and proguanil) exhibited better binding energy and interaction with the receptor with a stable conformation. Notably, oxetane alectinib displayed a docking score of -6.906 kcal/mol, which is comparable to alectinib's binding energy (B.E) of -5.159 kcal/mol, indicating a 33.0% increase. Oxetane alectinib was observed to interact with the ALK tyrosine kinase receptor's active site (PDB ID:3AOX) through hydrogen bond interactions with MET1199(2.05 Å) and ASP1203(3.47 Å) and aromatic interactions with LEU1266, LEU1122, as well as hydrophobic interactions with LEU1196, VAL1180, VAL1130, ALA1148, LEU1198, and ALA1200, as shown in Table S1 and Figs. S1 and S2.

In this study, the azetidine procarbazine was docked with DNA; the resulting conformation with minimum energy clearly indicated that procarbazine interacts with DNA through multiple hydrogen bonding (Table S1; Figs. S1 and S2). The relative binding strength of the interaction between azetidine procarbazine and DNA was found to be -8.083 kcal/mol. Specifically, two hydrogen bonds were observed when azetidine procarbazine was docked to the DNA: one between the hydrogen of the azetidine ring and the 10th guanine of DNA chain A exhibiting a bond distance of 1.68 Å, and another between the hydrogen of the azetidine procarbazine and the 17th adenine of DNA chain B exhibiting a bond distance of 2.20 Å.

The molecular docking simulation studies on oxetane procarbazine found that it interacts with DNA through multiple hydrogen bonding, similar to procarbazine. The calculated relative binding free energy for this interaction was observed to be -6.522 kcal/mol. The molecular docking result also revealed that the compound with azetidine-modified procarbazine had better binding affinity compared to the standard procarbazine. Additionally, our computational studies indicated that both moieties provided increased structural stability.

The compound azetidine eradafitinib displayed four conventional hydrogen bonds at positions ALA(A)564 (2.26 Å), carbon-hydrogen bonds at positions ALA(A)640 (2.83 Å) and LEU(A)484 (2.54 Å). There is a double interaction with ASP(A) 641 and GLU(A)531, along with four interactions involving alkyl groups with LEU(A)630, VAL(A)492, ALA(A)512, and PHE(A)642 and four pi-alkyl interactions with ILE(A)545, LYS(A)514, VAL(A)561, and VAL(A)559 (Table S1, Fig. 1 and Fig. 2).

For oxetane anastrozole, the primary hydrogen bond forms with THR(A)310 (2.57 Å) and MET(A)374 (1.72 Å). There are three carbon-hydrogen bonds with ALA(A)306 (3.00 Å), VAL(A)373 (2.45 Å), and SER(A)478 (2.77 Å). Additionally, there is a single pi-alkyl interactions at ILE(A)133 and an alkyl interaction at CYS(A)437 (Table S1, Figs. S1 and S2).

In the case of azetidine nateglinide, it was identified that there were four conventional hydrogen bonds with ARG(B)1246 (2.37 Å), ASN (B)1245 (2.33 Å), SER(B)1238 (2.38 Å), as well as ARG(B)1300 (2.87 Å). An alkyl bond along ILE(B)381 and two pi-alkyl interactions with PHE(B)433 and TRP(B)430 (as depicted in the Figs. 2 and Fig. 3) were present. Similarly, in nateglinide, three conventional hydrogen bonds were formed with GLN(B) 374 (2.76 Å), ARG(B)1300 (5.55 Å), and ASN(B)1296 (2.04 Å), one alkyl interaction was observed with TYR(B)377, and two

pi-alkyl interactions were formed with ALA(B)380 and ILE(B)381 (Table S1, Figs. S1 and S2).

Moving on to oxetane repaglinide, it demonstrates conventional hydrogen-bond interactions with TYR(B)377(1.82 Å), ARG(B)1246 (1.95 Å), and ASN(B)1245(1.68 Å). It shows one pi-alkyl bond with ILE(B)381 (Table S1, Figs. S1 and S2).

Interestingly, the compound oxetane nelutamide displayed three conventional hydrogen bonds at positions ASN(A)705 (1.84 Å), GLN(A)711(2.65 Å), and MET(A)745 (2.75 Å) and carbon-hydrogen bonds at positions THR(A)877 (2.67 Å), GLY(A) 708 (3.41 Å), and LEU(A)704(2.53 Å). There is a single alkyl interaction with MET(A)780 (Table S1, Figs. S1 and S2).

Upon docking oxetane proguanil with the parasitic dihydrofolate reductase enzyme, it was identified that the docked conformation with minimum energy had a value of -8.555 kcal/mol. This conformation involved the formation of two hydrogen bonds with serine of chain A (SER83) at a bond distance of 1.94 Å and glutamic acid of chain A (GLU401) at a bond length of 1.83 Å. Additionally, there were two Pi-anion bonds with PHE402 and TRP36, Pi-Pi stacked with PHE84, and a single Pi-alkyl bond with ARG37. It is apparent that proguanil interacts with the parasitic dihydrofolate reductase enzyme through conventional hydrogen bonding with SER of chain A (2.00 Å) and ASP of chain A (2.45 Å) (Table S1, Figs. S1 and S2).

***In silico* ADME Analysis**

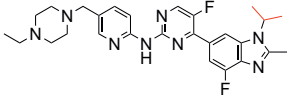
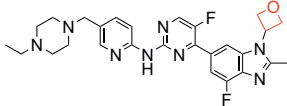
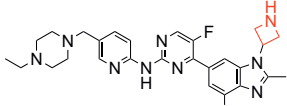
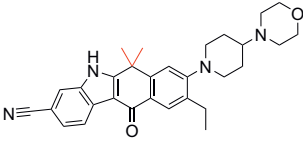
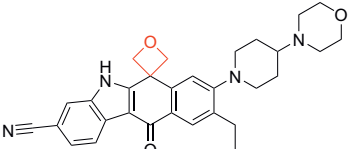
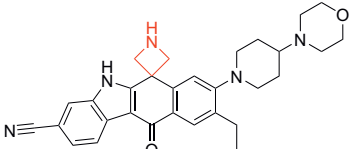
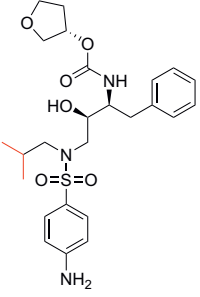
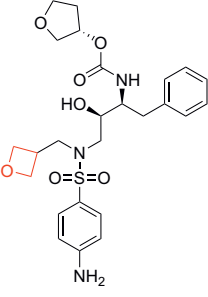
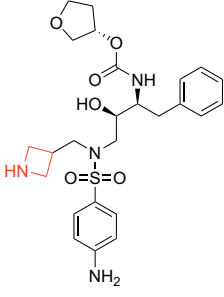
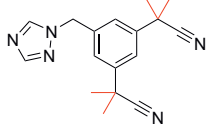
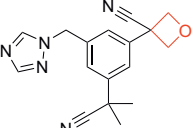
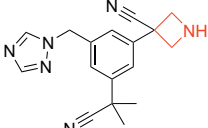
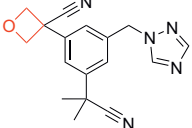
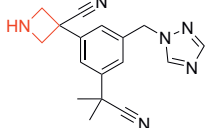
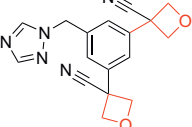
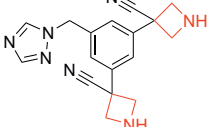
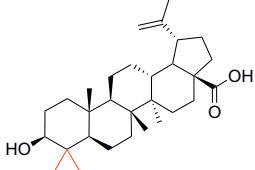
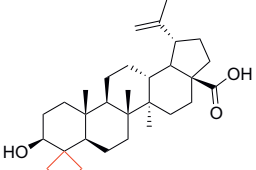
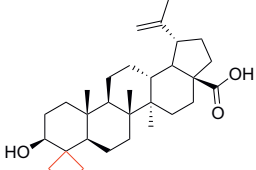
To achieve therapeutic efficacy, a drug must reach its biological target at an adequate concentration and maintain its bioactive form for the duration required to elicit the intended pharmacological response. The drug development process therefore necessitates early evaluation of ADME properties.²⁵ In this context, computational approaches serve as efficient and reliable alternatives to experimental methods.^{75,76} In the present study, the SwissADME online platform was employed to predict key pharmacokinetic parameters, physicochemical attributes, and drug-likeness. This tool integrates a suite of rapid and accurate predictive models, including proprietary algorithms such as iLOGP, the Bioavailability Radar, and the BOILED-Egg model.^{11,12}

Most of the modified azetidines and oxetane derivatives was found to be obeying Lipinski's rule of 5.⁷⁷ Drugs that have good bioavailability may have an enhanced therapeutic effect. In this study, all identified molecules showed improved solubility profiles after modification. Additionally, all molecules exhibited higher gastrointestinal absorption rates, which is a positive sign for oral drugs. The presence of rotatable bonds in a molecule, described as any single bond not attached to a terminal hydrogen atom, also plays a role in bioavailability, with a favorable range being observed for all molecules in this study.²¹ The selected molecules—oxetane alectinib, azetidine procarbazine, azetidine eradafitinib, oxetane anastrozole, azetidine nateglinide, oxetane repaglinide, oxetane nelutamide, and oxetane proguanil—showed acceptable ADME profiles and have the potential to be developed as therapeutic agents (see Table 2).

***In silico* Toxicity Evaluation**

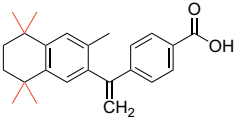
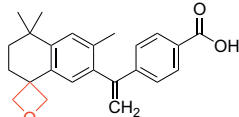
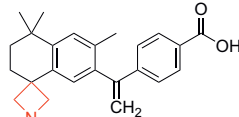
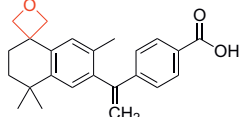
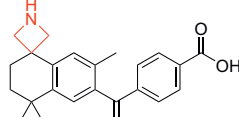
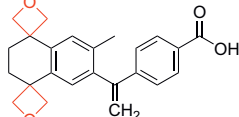
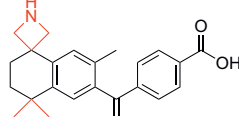
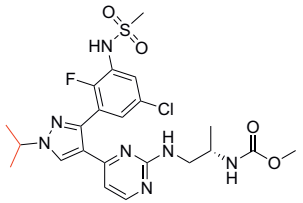
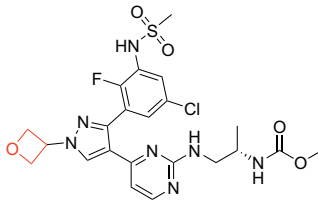
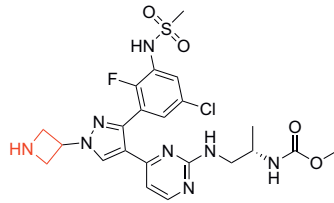
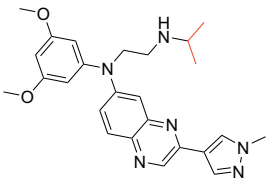
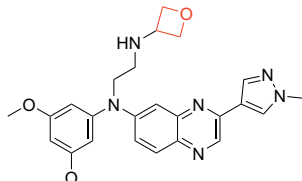
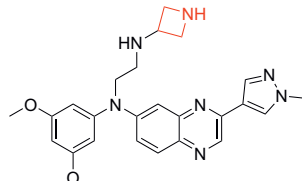
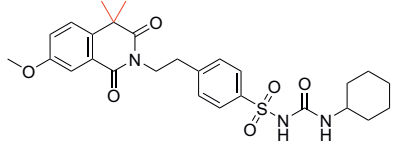
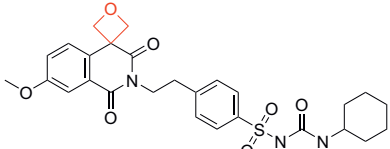
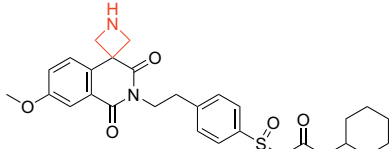
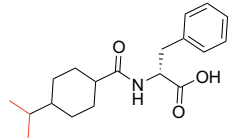
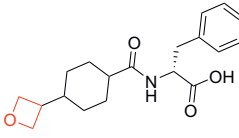
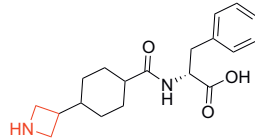
Computational toxicity prediction serves as a key determinant in the early phases of drug discovery by enabling the identification

Table 1 List of selected isopropyl-containing molecules.

Entry	Molecules	Oxetane-modified	Azetidine-modified
1	 <p>BE = -9.607 Abemaciclib^{80,81} Breast cancer, PDB ID: 5L2S⁹</p>	 <p>BE = -10.489</p>	 <p>BE = -10.363</p>
2	 <p>BE = -5.159 Alectinib Non-small cell lung cancer, PDB ID: 3AOX^{30,60}</p>	 <p>BE = -6.906</p>	 <p>BE = -5.811</p>
3	 <p>BE = -9.674 Amprenavir HIV infection, PDB ID: 1T7J⁴⁹</p>	 <p>BE = -8.361</p>	 <p>BE = -7.217</p>
4	 <p>BE = -6.138 Anastrozole Breast cancer, PDB ID: 3EQM⁵⁰</p>	 <p>BE = -5.876</p>	 <p>BE = -5.955</p>
		 <p>BE = -7.454</p>	 <p>BE = -6.529</p>
		 <p>BE = -7.101</p>	 <p>BE = -5.673</p>
5	 <p>BE = -6.467 Betulinic Acid Anti-inflammatory activity, PDB ID: 1KQU²²</p>	 <p>BE = -7.099</p>	 <p>BE = -6.483</p>

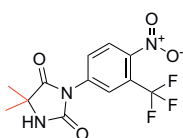
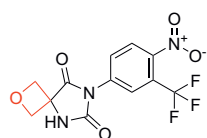
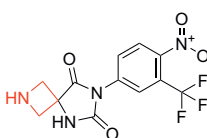
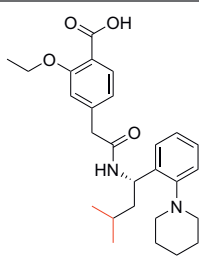
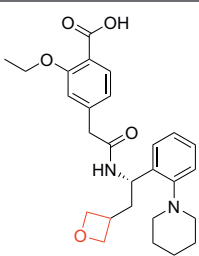
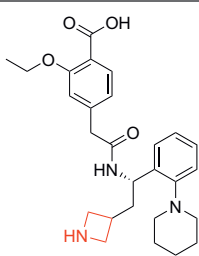
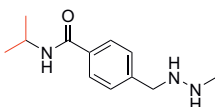
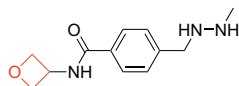
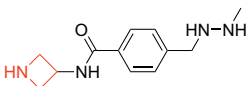
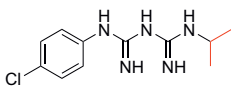
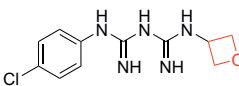
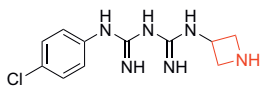
(Continued)

Table 1 (Continued)

Entry	Molecules	Oxetane-modified	Azetidine-modified
6	 <p>BE = -12.508BrexaroteneAntineoplastic, PDB ID:4K61⁶¹</p>	 <p>BE = -12.410</p>	 <p>BE = -10.682</p>
		 <p>BE = -12.642</p>	 <p>BE = -10.625</p>
		 <p>BE = -9.842</p>	 <p>BE = -10.082</p>
7	 <p>BE = -10.167Encorafenibkinase inhibitor, PDB ID:3IDP²⁰</p>	 <p>BE = -9.190</p>	 <p>BE = -10.554</p>
8	 <p>BE = -6.285ErdafitinibAnti-cancer, PDB ID:5EW8¹</p>	 <p>BE = -6.794</p>	 <p>BE = -7.677</p>
9	 <p>BE = -5.074GliquidoneDiabetes mellitus type 2, PDB ID:6JB1¹⁴</p>	 <p>BE = -5.491</p>	 <p>BE = -2.747</p>
10	 <p>BE = -5.495NateglinideNoninsulin dependent diabetes mellitus, PDB ID:6JB1^{13,23}</p>	 <p>BE = -5.785</p>	 <p>BE = -6.686</p>

(Continued)

Table 1 (Continued)

Entry	Molecules	Oxetane-modified	Azetidine-modified
11	 BE = -8.594 Nilutamide Prostate cancer, PDB ID :2AX6 ⁵²	 BE = -9.649	 BE = -6.908
12	 BE = -6.769 Repaglinide Antihyperglycemic, PDB ID:6JB1 ^{14,48}	 BE = -7.831	 BE = -4.515
13	 BE = -6.446 Procarbazine ³⁵ Anti neoplastic, PDB ID: 1BNA ²	 BE = -6.522	 BE = -8.083
14	 BE = -7.584 Proguanil ^{26,45} Antimalarial, PDB ID :8F4T ²⁹	 BE = -8.555	 BE = -8.361

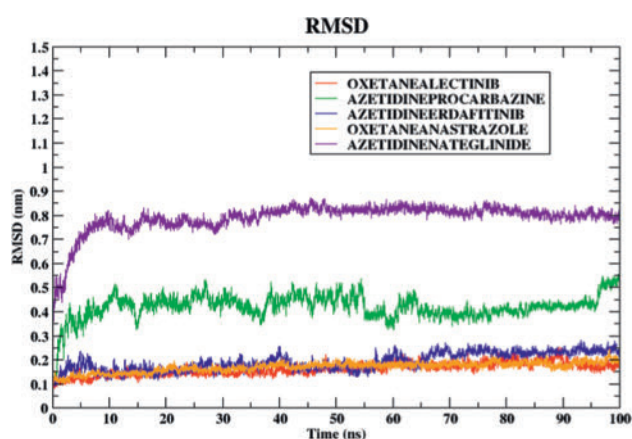


Fig. 1 RMSD analysis comparing the backbone stability of the protein and benchmark compounds (oxetane alectinib, azetidine procarbazine, azetidine erdafitinib, oxetane anastrozole, and azetidine nateglinide) and selected ligand-bound complexes over the simulation time.

of potential safety liabilities prior to experimental verification. Computational toxicity prediction methods have gained wide acceptance due to their speed, approachability, and reliable accuracy.²⁵

In the present study, six selected compounds underwent *in silico* toxicity profiling utilizing two open-access platforms: ProTox-II and the Toxicity Estimation Software Tool (TEST). The analysis focused on critical toxicity endpoints, including hepatotoxicity, cytotoxicity, immunotoxicity, acute toxicity, mutagenicity, the predicted median lethal dose (LD₅₀), and carcinogenicity (Table 3).

The results revealed that anastrozole falls under toxicity ranking 2, with a calculated LD₅₀ value of 50 mg/kg, indicating a high potential for toxicity when administered orally. whereas oxetane anastrozole was classified under the category of class 4.

The molecules alectinib, oxetane alectinib, procarbazine, azetidine procarbazine, erdafitinib, azetidine erdafitinib, repaglinide, oxetane repaglinide, proguanil, oxetane proguanil, nateglinide, oxetane nateglinide, nilutamide, and oxetane nilutamide fall

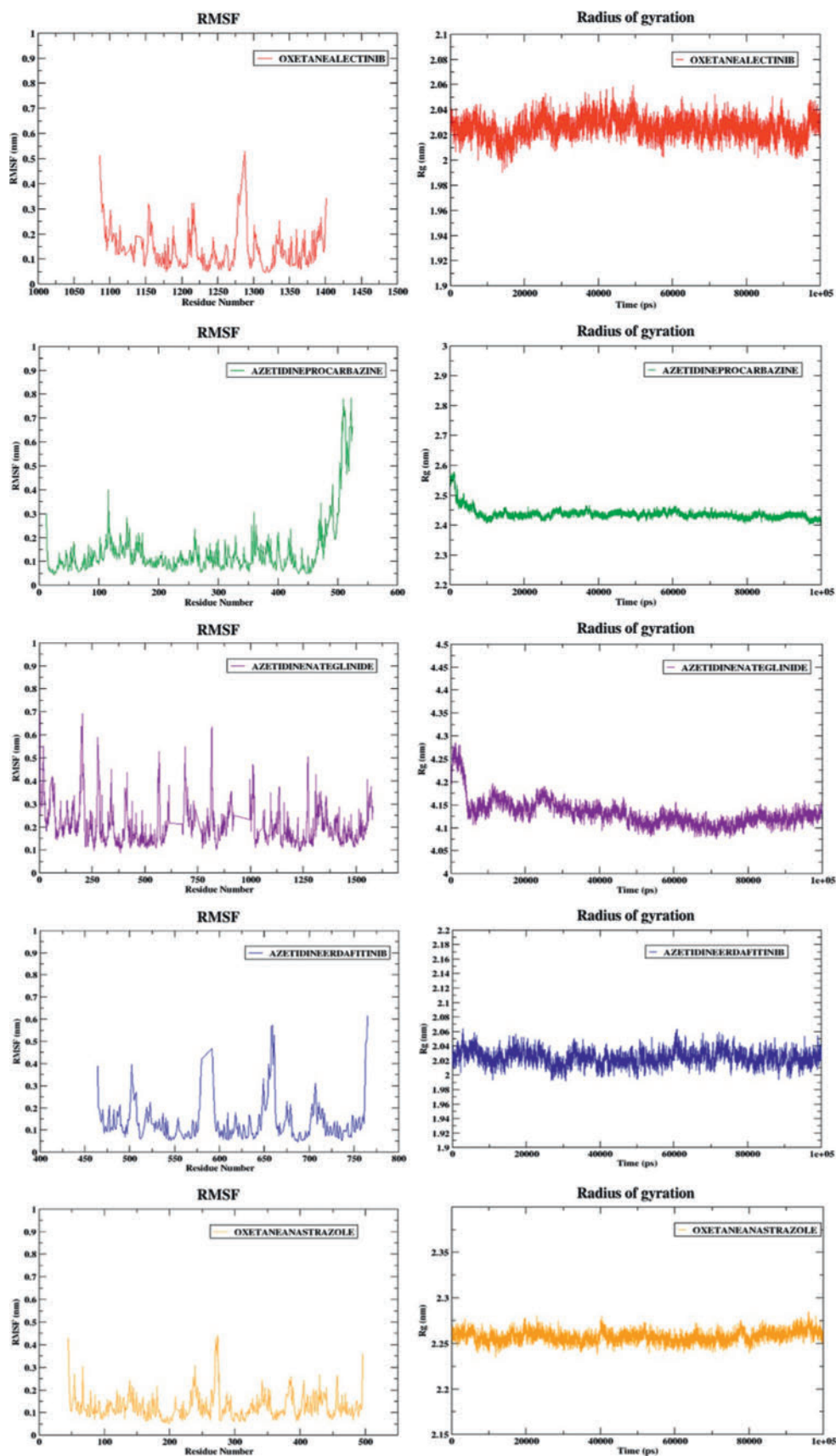


Fig. 2 Root mean square fluctuation (RMSF) and radius of gyration (R_g) plot illustrating compactness structural stability, structural stability, and residue-wise flexibility of the protein, benchmark compounds (oxetane alectinib, azetidine procarbazine, azetidine erdafitinib, oxetane anastrozole, and azetidine nateglinide), and ligand-bound complexes during MD simulation.

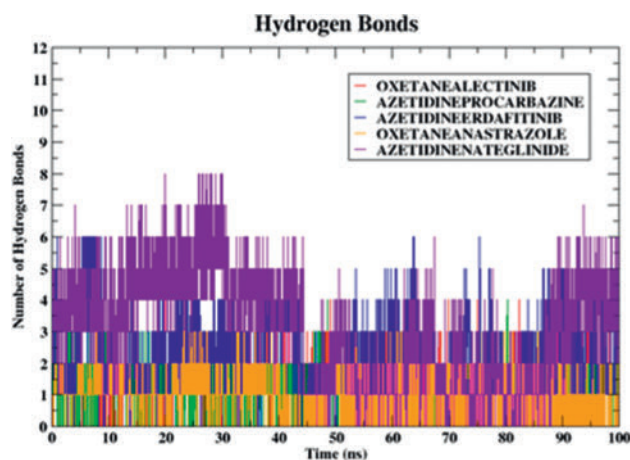


Fig. 3 Hydrogen bond analysis of oxetane alectinib, azetidine procabazine, azetidine erdafitinib, oxetane anastrozole, and azetidine nateglinide.

under toxicity class 4, with predicted LD₅₀ values ranging from 50 to 4000 mg/kg, suggesting a potential for toxic potential via the oral administration. In contrast, the remaining oxetane repaglinide was classified as class 5, indicating a low toxicity profile. In terms of mutagenic potential, oxetane alectinib, erdafitinib, azetidine-modified erdafitinib, nilutamide, and its oxetane

derivative were predicted to be mutagenic, whereas the other compounds were identified as nonmutagenic. Importantly, with the exception of nilutamide and its oxetane derivative, which exhibited signs of hepatotoxicity, all other compounds demonstrated nonhepatotoxic behavior, underscoring their overall favorable safety profiles for further development.

Molecular Dynamics Simulations and Binding Free Energy Calculations

To investigate the dynamic behavior and conformational stability of the docked protein–ligand complexes, molecular dynamics (MD) simulations were executed using GROMACS version 2019.4. Complexes identified through prior molecular docking studies were subjected to 100-nanosecond simulation trajectories, encompassing 50 million integration steps. Protein topology parameters were derived using the AMBER99SB force field, whereas ligand topologies were generated based on the General AMBER Force Field (GAFF), with partial atomic charges computed via the bond charge correction (BCC) method implemented through the ACPYPE tool.^{67,68} Each protein–ligand complex was positioned at the center of a cubic simulation box, maintaining a minimum distance of 10 Å from the box boundaries and subsequently solvated using the TIP3P water model.⁶⁹ To ensure electrostatic neutrality, appropriate counterions were introduced into the system. Energy minimization was carried out

Table 2 *In silico* ADME parameters of selected molecules.

Molecules	Molecular weight, g/mol	Rotatable bonds	H-bond acceptors	H-bond donors	Molar refractivity	Lipophilicity, Log P o/w	Water solubility, Logs (ESOL)	Pharmacokinetics, GI absorption	Drug likeness, Lipinski's rule
Alectinib	482.62	3	4	1	149.63	4.08	−6.25	High	Yes
Oxetane alectinib	496.60	3	5	1	148.60	3.85	−5.41	High	Yes
Procabazine	317.42	7	3	2	91.75	2.52	−4.10	High	Yes
Azetidine procabazine	330.42	7	4	3	96.35	2.57	−1.64	High	Yes
Erdafitinib	446.54	9	6	1	131.48	4.23	−4.48	High	Yes
Azetidine erdafitinib	459.54	9	7	2	136.08	3.80	−3.67	High	Yes
Anastrozole	293.37	4	4	0	83.81	2.25	−3.04	High	Yes
Oxetane anastrozole	307.35	4	5	0	82.78	2.06	−2.67	High	Yes
Nateglinide	317.42	7	3	2	91.75	2.52	−4.10	High	Yes
Azetidine nateglinide	331.41	7	4	2	90.72	2.21	−3.26	High	Yes
Repaglinide	452.59	11	4	2	135.45	3.81	−5.45	High	Yes
Oxetane repaglinide	466.57	11	5	2	134.42	3.46	−4.62	High	Yes
Nelutamide	317.22	3	7	1	77.26	1.86	−3.07	High	Yes
Oxetane nelutamide	331.20	3	8	1	76.23	1.39	−2.45	High	Yes
Proguanil	253.73	4	2	3	72.77	1.04	−2.37	High	Yes
Oxetane proguanil	267.71	6	3	5	71.74	1.70	−2.15	High	Yes

Table 3 *In silico* toxicity profiles of the selected molecules.

Molecules	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	LD ₅₀ (mg/kg)	Toxicity class
Alectinib	Inactive	Active	Active	Active	Inactive	2000	4
Oxetane alectinib	Inactive	Inactive	Active	Inactive	Inactive	2000	4
Procarbazine	Inactive	Active	Inactive	Inactive	Inactive	560	4
Azetidine procarbazine	Inactive	Active	Inactive	Inactive	Inactive	560	4
Erdaftinib	Inactive	Active	Active	Active	Inactive	800	4
Azetidine erdaftinib	Inactive	Active	Active	Active	Inactive	800	4
Anastrozole	Inactive	Inactive	Inactive	Inactive	Inactive	50	2
Oxetane anastrozole	Inactive	Active	Inactive	Inactive	Inactive	2000	4
Nateglinide	Inactive	Inactive	Inactive	Inactive	Inactive	800	4
Azetidine nateglinide	Inactive	Inactive	Inactive	Inactive	Inactive	800	4
Repaglinide	Inactive	Inactive	Inactive	Inactive	Inactive	1420	4
Oxetane repaglinide	Inactive	Inactive	Inactive	Inactive	Inactive	4000	5
Nilutamide	Active	Active	Active	Active	Inactive	625	4
Oxetane nilutamide	Active	Active	Active	Active	Inactive	625	4
Proguanil	Inactive	Inactive	Inactive	Inactive	Inactive	310	4
Oxetane proguanil	Inactive	Inactive	Inactive	Inactive	Inactive	310	4

employing the steepest descent algorithm under periodic boundary conditions.⁷⁰

The minimization parameters were set as follows: energy tolerance (emtol) of 1000 kJ/mol/nm, maximum number of steps (nsteps) of 50,000, and timestep value (emstep) of 0.01 nm. Long-range electrostatic interactions were evaluated using the Particle Mesh Ewald (PME) approach, which enables accurate calculation of coulombic forces in periodic systems.

Subsequent to energy optimization, the system was subjected to two phases of equilibration. The first phase involved a 100 ps NVT simulation set to maintain temperature setting at 300 K, followed by a 100 ps NPT ensemble to equilibrate the pressure at 1 bar. Temperature and pressure regulation during the simulation was achieved using the Berendsen thermostat and barostat, employing a coupling time constant of 1.0 ps. Constraints on all bonds, including those involving hydrogen atoms, were enforced using the LINCS algorithm. The production phase of the MD simulation was executed for a duration of 100 ns with a timestep of 2 fs.⁴⁸ System trajectory snapshots were recorded every 10 ps for downstream analysis.^{71,82}

The Molecular Mechanics/Poisson–Boltzmann Surface Area (MM/PBSA) method was employed to estimate the binding free energy associated with the interaction between protein and ligand complexes. Calculations were conducted utilizing the g_mmpbsa tool, which utilizes GROMACS trajectory data.^{72–74} The binding free energy ($\Delta G_{\text{binding}}$) was evaluated by combining force field-based modeling energies (van der Waals and electrostatic interactions) with solvation energies (polar and nonpolar contributions).

The binding free energy was computed by means of the following thermodynamic cycle:

$$\Delta G_{\text{binding}} = G_{\text{complex}} - (G_{\text{protein}} + G_{\text{ligand}})$$

where G_{complex} denotes the total free energy of the bound protein–ligand system, while G_{protein} and G_{ligand} relate to the free energies of the isolated protein and ligand, respectively.

Structural Dynamics and Stability of Protein–Ligand Complexes

To understand the dynamic and stability behavior of the protein–ligand systems, we analyzed key structural parameters obtained from 100 ns MD simulations. These include root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (R_g), and hydrogen bond formation. Together, these metrics provide a multidimensional view of how each ligand influences protein stability, flexibility, compactness, and interaction strength factors that are critically important in determining binding affinity and the potential efficacy of a drug candidate.²⁷

Root Mean Square Deviation (RMSD)

RMSD is a fundamental measure of how much a protein structure deviates from its initial conformation during a simulation.¹⁸ Lower RMSD values generally indicate that the complex remains close to its starting geometry, reflecting structural stability. In our study, the complexes formed with oxetane alectinib, oxetane anastrozole, and azetidine erdaftinib showed low and consistent RMSD values of 0.16, 0.17, and 0.19 nm, correspondingly. These results propose that these ligands bind in a stable manner without causing significant structural disruptions, which is often a desirable trait for lead drug candidates. Also, their average deviation from the initial structure was within the acceptable range of 2–3 Å, especially in the case of protein–ligand complex. In contrast, azetidine procarbazine exhibited a moderately higher RMSD of 0.42 nm, pointing toward increased flexibility or possible adjustments in the binding pocket. The highest RMSD was observed for azetidine nateglinide (0.79 nm), which initially underwent significant deviation before stabilizing, possibly indicating an induced-fit mechanism where the protein adjusts its conformation to better accommodate the ligand although the

graph (Fig. 1) remains conserved after 40 ns around 0.7 nm until the end of the simulation. Biologically, such an adaptation may suggest functional relevance but could also reflect potential instability depending on the binding site context.

Root Mean Square Fluctuation (RMSF)

RMSF measures the flexibility or fluctuation acquired by individual amino acid residues, monitored over the course of the simulation to assess their dynamic behavior and interactions, highlighting regions of local mobility. Proteins with stable ligand (Fig. 2) interactions typically show lower RMSF values, especially around the binding site. In our analysis, the complexes with oxetane alectinib, oxetane anastrozole, and azetidine erdafitinib demonstrated low average RMSF values of 0.14, 0.13, and 0.14 nm, correspondingly, indicating that these ligands contribute to stabilizing the protein backbone. Azetidine procarbazine showed slightly more variability (0.14 nm), suggesting local flexibility, which could be tolerated in loop or surface regions. However, azetidine nateglinide had the highest average RMSF of 0.21 nm, signifying greater residue-level movement. During analysis, all the protein–ligand complexes acquired an RMSF within an acceptable range. All the higher peaks of RMSF appeared at the N and C terminal or loop sites. None of the increased RMSFs appeared around the binding sites. While some flexibility may aid binding in allosteric or adaptable pockets, excessive fluctuations might compromise structural integrity, especially in the functionally critical domain (Fig. 2).

Radius of Gyration (R_g)

The radius of gyration (R_g) serves as an indicator of the protein's structural compactness and conformational stability. A stable R_g value throughout the simulation implies preservation of the protein's globular architecture. The R_g values for oxetane alectinib, oxetane anastrozole, and azetidine erdafitinib were 2.03, 2.26, and 2.02 nm, respectively, parameters typical of well-folded and compact proteins. Azetidine procarbazine showed a slightly more expanded structure with an R_g of 2.44 nm, potentially due to minor unfolding or flexible domain movement. The most striking observation was the R_g value of 4.13 nm for azetidine nateglinide, indicating a significantly expanded protein conformation, which gradually decreased over time. This pattern supports the hypothesis of a ligand-induced structural rearrangement, which may facilitate binding in flexible or partially disordered regions but could also signal destabilization of the global fold, an important consideration in therapeutic design (Fig. 2).

Hydrogen Bond Analysis

Hydrogen bonding is a critical determinant of both the specificity and stability of protein–ligand interactions, significantly contributing to molecular recognition and binding affinity (Fig. 3). Consistent hydrogen bonding throughout the simulation is often associated with favorable binding affinity and residence time. Among the complexes studied, azetidine nateglinide formed the highest average number of hydrogen bonds (3), suggesting a

robust interaction network that may contribute to strong affinity, even in the presence of higher structural flexibility. Azetidine erdafitinib followed with 2 hydrogen bonds, reflecting a balance between strong polar interactions and structural stability. Conversely, oxetane alectinib and azetidine procarbazine exhibited fewer hydrogen bonds (1 and 1, respectively), while oxetane anastrozole had the lowest count (1). These results suggest that while oxetane-based ligands may induce higher structural stability (as seen from RMSD and R_g data), azetidine-based compounds particularly nateglinide appear to compensate for their flexibility through stronger polar interactions. This difference in interaction profiles could be leveraged during lead optimization, depending on the intended therapeutic mechanism such as transient inhibition versus sustained receptor engagement.

Biological Significance and Implications for Drug Design

Together, these structural analyses offer valuable insights into how different ligand scaffolds influence the protein's dynamic behavior. Stable RMSD and R_g values suggest a ligand's ability to maintain the protein's structural integrity, which is often desirable for active site targeting and catalytic inhibition. On the other hand, ligands like azetidine nateglinide, which promote flexibility and extensive hydrogen bonding, may be better suited for allosteric modulation or dynamic binding pockets. These complementary interaction profiles underscore the importance of integrating multiple biophysical metrics in the rational design of small-molecule therapeutics (Table 4).

Binding Free Energy Evaluation Using MM-PBSA

To evaluate the thermodynamic feasibility of ligand binding, MM-PBSA calculations were performed utilizing the g_mmpbsa module on trajectories generated from 100 ns MD simulations. The binding free energy ($\Delta G_{\text{binding}}$) was estimated by integrating energy components including van der Waals interactions, electrostatic forces, polar solvation effects, and solvent-accessible surface area (SASA) contributions. These parameters offer valuable insights into the magnitude and characteristics of the noncovalent forces stabilizing the protein–ligand complexes. Among the selected compounds evaluated, oxetane alectinib demonstrated the most favorable binding energy (-73.401 ± 0.581

Table 4 Average values along with standard deviations of RMSD, R_g , and HB.

Compound	RMSD (nm)	R_g (nm)	RMSF (nm)	HB
Oxetane alectinib	0.16 ± 0.03	2.03 ± 0.01	0.14 ± 0.08	1
Azetidine procarbazine	0.42 ± 0.05	2.44 ± 0.02	0.14 ± 0.12	1
Azetidine erdafitinib	0.19 ± 0.04	2.02 ± 0.01	0.14 ± 0.09	2
Oxetane anastrozole	0.17 ± 0.02	2.26 ± 0.01	0.13 ± 0.06	1
Azetidine nateglinide	0.79 ± 0.06	4.13 ± 0.03	0.21 ± 0.09	3

kcal/mol), suggesting strong and stable association with the protein target.

This high binding affinity predominantly arose from substantial van der Waals (-52.409 ± 0.338 kcal/mol) and electrostatic (-87.378 ± 0.675 kcal/mol) interactions, partially balanced by an opposing polar solvation component ($+71.985 \pm 0.656$ kcal/mol). The nonpolar solvation energy, derived from SASA, contributed moderately to the stability of the complex (-5.632 ± 0.0284 kcal/mol), likely reflecting favorable hydrophobic packing within the binding site.

Azetidine procarbazine shows the least favorable binding profile, with a total $\Delta G_{\text{binding}}$ of -10.658 ± 0.239 kcal/mol. Whereas its van der Waals interactions were reasonable (-35.502 ± 0.200 kcal/mol), and weak electrostatic contributions (-2.005 ± 0.129 kcal/mol) and a large polar solvation energy ($+26.853 \pm 0.223$ kcal/mol) undermined its overall binding strength.

The complex with azetidine erdafitinib exhibited intermediate binding affinity (-26.501 ± 1.146 kcal/mol), with favorable van der Waals (-41.607 ± 1.636 kcal/mol) and electrostatic (-20.681 ± 1.217 kcal/mol) energies. However, its net interaction was reduced by polar solvation energy ($+39.985 \pm 1.979$ kcal/mol). A similar energetic profile was observed for oxetane anastrozole, whose binding energy (-20.343 ± 0.352 kcal/mol) was again shaped by strong noncovalent attractions counteracted by moderate desolvation energy.

Azetidine nateglinide, which exhibited robust hydrogen bonding during the simulation, showed a comparatively weak binding free energy (-6.625 ± 0.716 kcal/mol). Although it displayed a remarkably high electrostatic component (-60.020 ± 1.368 kcal/mol) and decent van der Waals interactions (-28.076 ± 0.707 kcal/mol), the complex suffered from a very large polar solvation energy ($+85.404 \pm 2.014$ kcal/mol), suggesting that the energetic cost of desolvating the ligand outweighed the favorable interactions within the protein binding pocket (Table 5).

Table 5 Results for binding free energy calculations using MM-PBSA of selected compounds.

Compound name	Binding energy (kcal/mol)	Vander Waal energy (kcal/mol)	Electrostatic energy (kcal/mol)	Polar Solvation energy (kcal/mol)	SASA energy (kcal/mol)
Oxetane alectinib	-73.401 ± 0.581	-52.409 ± 0.338	-87.378 ± 0.675	71.985 ± 0.656	-5.632 ± 0.0284
Azetidine procarbazine	-10.658 ± 0.239	-35.502 ± 0.200	-2.005 ± 0.129	26.853 ± 0.223	-4.007 ± 0.017
Azetidine erdafitinib	-26.501 ± 1.146	-41.607 ± 1.636	-20.681 ± 1.217	39.985 ± 1.979	-4.308 ± 0.167
Oxetane anastrozole	-20.343 ± 0.352	-39.222 ± 0.307	-8.100 ± 0.333	31.279 ± 0.344	-4.283 ± 0.021
Azetidine nateglinide	-6.625 ± 0.716	-28.076 ± 0.707	-60.020 ± 1.368	85.404 ± 2.014	-3.904 ± 0.061

Conclusion

Four-membered oxetane and azetidine rings have attracted considerable attention in medicinal chemistry owing to their distinct physicochemical characteristics, which can beneficially influence molecular behavior and drug-like properties. Our study builds on previous literature, which suggested that modifying these rings could enhance solubility properties of newly designed molecules. To optimize our efforts, we replaced the isopropyl moiety with two motifs, comparing the binding energy and ADME properties to the parent molecule. Our study found that the selected molecules, including oxetane alectinib, azetidine procarbazine, azetidine erdafitinib, oxetane anastrozole, azetidine nateglinide, oxetane repaglinide, oxetane nelutamide, and oxetane proguanil, exhibited excellent binding affinity toward the receptor. The highest-ranking compounds from each group were chosen for MD simulations and subsequent binding free energy evaluations to assess their stability and interaction profiles. Additionally, in-silico pharmacokinetic analysis of these molecules revealed acceptable physicochemical and drug-like properties. Notably, none of these molecules were previously reported according to the SciFinder search.

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Statements and additional information

Conflict of Interest The authors declare that they have no conflict of interest.

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Contributors' Statement Mohana Krishna Ramisetty: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft. Vikas Yadav: Formal analysis, Software, Visualization. Venkatasamy Kesavan: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing. Sundarababu Baskaran: Project administration, Writing - review & editing.

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References

- 1 Amir M, Qureshi MA, Javed S. J Biomol Struct Dyn 2021; 39: 3934–3947
- 2 Anwer R, Ahmad N, Al Qumaizi KI, Al Khamees OA, Al Shaqha WM, Fatma T. J Mol Recognit 2017; 30(1/6):e2599
- 3 Bachrach SM. J Org Chem 2008; 73: 2466–2468
- 4 Bauer MR, Di Fruscia P, Lucas SCC et al. RSC Med Chem 2021; 12: 448–471
- 5 Brandi A, Cicchi S, Cordero FM. Chem Rev 2008; 108: 3988–4035

- 6 Bull JA, Croft RA, Davis OA, Doran R, Morgan KF. *Chem Rev* 2016; 116: 12150–12233
- 7 Litskan O, Semenchenko S, Lynnyk D et al. *Org Chem Front* 2025; 12: 3775–3785
- 8 Candel FJ, Peñuelas M. *Drug Des Dev Ther* 2017; 11: 881–891
- 9 Albitz K, Tóth S, Csókás D. *Angew Chem Int Ed* 2025; 64: e202416441
- 10 Das T, Mukhopadhyay C. *J Biomol Struct Dyn* 2023; 41: 3368–3381
- 11 Delaney JS. *J Chem Inf Comput Sci* 2004; 44: 1000–1005
- 12 Delaney JS. *J Chem Inf Comput Sci* 2004; 44: 1000–1005
- 13 Dey S, Basak S, De A et al. *J Chromatogr Sci* 2020; 58: 309–322
- 14 Ding D, Wang M, Wu J-X, Kang Y, Chen L. *Cell Rep* 2019; 27: 1848–1857
- 15 Dubois MAJ, Croft RA, Ding Y et al. *RSC Med Chem* 2021; 12: 2045–2052
- 16 Dubois MAJ, Smith MA, White AJP et al. *Org Lett* 2020; 22: 5279–5283
- 17 Evans GB, Furneaux RH, Greatrex B, Murkin AS, Schramm VL, Tyler PC. *J Med Chem* 2008; 51: 948–956
- 18 Madhav H, Reddy GS. *RSC Med Chem* 2024; 15: 1022–1037
- 19 Ikee Y, Hashimoto K, Kamino M et al. *Chem Pharm Bull* 2008; 56: 346–356
- 20 Mughal H, Szostak M. *Org Biomol Chem* 2021; 19: 3274–3286
- 21 Johnson TW, Gallego RA, Edwards MP. *J Med Chem* 2018; 61: 6401–6420
- 22 Khan MF, Nahar N, Rashid RB, Chowdhury A, Rashid MA. *BMC Complement Altern Med* 2018; 18: 48
- 23 Kumari S, Maurya J, Ramamoorthy A, Sundarajan S, Lulu S, Arumugam M. *Int J Pharm Pharm Sci* 2014; 6: 66–69
- 24 Lonikar N, Choudhari P, Bhusnuare O. *J Biomol Struct Dyn* 2021; 39: 3515–3522
- 25 Venkatasamy KJ. *J Biomol Struct Dyn* 2023; 41: 14638–14650
- 26 Maetani M, Kato N, Jabor VAP et al. *ACS Med Chem Lett* 2017; 8: 438–442
- 27 Manish M, Mishra S, Anand A, Subbarao N. *Comput Biol Med* 2022; 150: 106125
- 28 Moriguchi I, Hirono S, Liu Q, Nakagome I, Matsushita Y. *Chem Pharm Bull* 1992; 40: 127–130
- 29 Mugumbate G, Abrahams KA, Cox JAG et al. *PLoS One* 2015; 10: 1–10
- 30 Ono F, Chiba S, Isaka Y et al. *Sci Rep* 2020; 10: 1–10
- 31 Jeffries B, Wang Z, Troup RI et al. *Beilstein J Org Chem* 2020; 16: 2141–2150
- 32 Leelavathi PT, Shankar M, Pasha TY, Ramesh B, Sekar M. *Pharm Res* 2023; 7: 000282
- 33 Parsy C, Alexandre FR, Brandt G et al. *Bioorg Med Chem Lett* 2014; 24: 4444–4449
- 34 Pastewska M, Bednarczyk-Cwynar B, Kovačević S et al. *J Chromatogr A* 2021; 1656: 462552
- 35 Pletsa V, Valavanis C, van Delft JH, Steenwinkel MJ, Kyrtopoulos SA. *Carcinogenesis* 1997; 18: 2191–2196
- 36 Raffa RB, Pergolizzi JV. *Pharmacol Pharm* 2019; 10: 465–473
- 37 Girdhar N, Yadav V, Kumari N, Subbarao N, Krishnamachari A. *Biomol Struct Dyn* 2024
- 38 Rogers-Evans M, Knust H, Plancher JM et al. *Chimia* 2014; 68: 492–499
- 39 Ryckmans T, Edwards MP, Horne VA et al. *Bioorg Med Chem Lett* 2009; 19: 4406–4409
- 40 Sachdeva H, Khaturia S, Saquib M et al. *Appl Biochem Biotechnol* 2022; 194: 6438–6467
- 41 Shaker B, Yu MS, Lee J, Lee Y, Jung C, Na D. *J Microbiol* 2020; 58: 235–244
- 42 Raturi A, Yadav V, Hoda N, Subbarao N, Chaudhry SA. *J Biomol Struct Dyn* 2023; 42: 585–611
- 43 Dubois MAJ, Smith MA, White AJP et al. *Org Lett* 2020; 22: 5279–5283
- 44 Shweta M, Rashmi D. *J Drug Delivery Ther* 2019; 9: 266–369
- 45 Skinner-Adams TS, Fisher GM, Riches AG et al. *Commun Biol* 2019; 2: 1–7
- 46 Stepan AF, Karki K, McDonald WS et al. *J Med Chem* 2011; 54: 7772–7783
- 47 Su M, Yang Q, Du Y et al. *J Chem Inf Model* 2019; 59: 895–913
- 48 Verma J, Subbarao N. *J Biomol Struct Dyn* 2022; 30: 127457
- 49 Surleraux DLNG, Tahri A, Verschuere WG et al. *J Med Chem* 2005; 48: 1813–1822
- 50 Suvannang N, Nantasenamat C, Isarankura-Na-Ayudhya C, Prachayasittikul V. *Molecules* 2011; 16: 3597–3617
- 51 Butler MS. *J Nat Prod* 2004; 67: 2141–2153
- 52 Tian X, He Y, Zhou J. *Front Pharmacol* 2015; 6: 57
- 53 Wuitschik G, Carreira EM, Wagner B et al. *J Med Chem* 2010; 53: 3227–3246
- 54 Zheng X, Gao L, Wang L et al. *J Med Chem* 2019; 62: 6315–6329
- 55 Zheng X, Liang C, Wang L et al. *J Med Chem* 2018; 61: 10228–10241
- 56 Daina A, Michielin O, Zoete V. *Sci Rep* 2017; 7: 42717
- 57 Sastry GM, Adzhigirey M, Day T, Annabhimoju R, Sherman W. *J Comput Aided Mol Des* 2013; 27: 221–234
- 58 Agrawal A, Chanana P. *J Biomol Struct Dyn* 2023; 20: 1201–1214
- 59 Chen P, Lee NV, Hu W et al. *Mol Cancer Ther* 2016; 15: 2273–2281
- 60 Sakamoto H, Tsukaguchi T, Hiroshima S et al. *Cancer Cell* 2011; 19: 679–690
- 61 Boerma LJ, Xia G, Qui C et al. *J Biol Chem* 2014; 289: 814–826
- 62 Raies AB, Bajic VB. *WIREs Comput Mol Sci* 2016; 6: 147–172
- 63 Banerjee P, Eckert AO, Schrey AK, Preissner R. *Nucleic Acids Res* 2018; 46: W257–W263
- 64 Martin TM, Harten P, Venkatapathy R, Das S, Young DM. *Toxicol Mech Methods* 2008; 18: 251–266
- 65 Banks JL, Beard HS, Cao Y et al. *J Comput Chem* 2005; 26: 1752–1780
- 66 Abraham MJ, Murtola T, Schulz R et al. *SoftwareX* 2015; 1–2: 19–25
- 67 Hornak V, Abel R, Okur A, Strockbine B, Roitberg A, Simmerling C. *Proteins: Struct, Funct, Bioinf* 2006; 65: 712–725
- 68 Sousa da Silva AW, Vranken WFA. *NPY*. Notes 2012; 5: 367
- 69 Mark P, Nilsson L. *J Phys Chem A* 2001; 105: 9954–9960
- 70 Mahoney MW, Jorgensen WL. *J Chem Phys* 2000; 112: 8910–8922
- 71 Kashif M, Subbarao N. *J Biomol Struct Dyn* 2023; 41: 13914–13922
- 72 Kollman PA, Massova I, Reyes C et al. *Acc Chem Res* 2000; 33: 889–897
- 73 Kumari R, Kumar R, Lynn A. *J Chem Inf Model* 2014; 54: 1951–1962
- 74 Richmond TJ. *J Mol Biol* 1984; 178: 63–89
- 75 Kirchmair J, Williamson MJ, Tyzack JD et al. *J Chem Inf Model* 2012; 52: 617–648
- 76 Wang Y, Xing J, Xu Y et al. *Quart Rev Biophys* 2015; 48: 488–515
- 77 Duchowicz PR, Talevi A, Bellera C, Bruno-Blanch LE, Castro EA. *Bioorg Med Chem* 2007; 15: 3711–3719
- 78 Leeson P, Springthorpe B. *Nat Rev Drug Discovery* 2007; 6: 881–890
- 79 Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. *Adv Drug Delivery Rev* 1997; 23: 3–25
- 80 Coates JT, Lindsley CW, McKinney D, Rhodes GR. *US Patent Application US 2010/0160340 A1* 2010
- 81 Chen S, Liu Z, Xu B, Gao Y. *WO 2017/114512 A1* 2017. <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2017114512>
- 82 Yadav V, Kashif M, Kamali Z, Gourinath S, Subbarao N. *Mol Inf* 2025; 44: 1–13