Targeting Dyrk1A with Benzothiazoles: Molecular Docking, ADMET Profiling

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Abstract

The benzothiazole analogues are found to interact with ATP-binding pocket-Dyrk1A through molecular docking. We found that BTZ-AC exhibits highest binding affinity as compare to all the analogues having docking score -9.28 from among the analogues. This substantial binding strength should perhaps be traced back to the acid group, as this is polar and can through hydrogen bonding and other polar interactions with amino acid residues. The overall ADMET analysis of all five compounds also indicates that each compound has a unique ADMET profile which may affect its therapeutic value. With similar features, moderate toxicity, and good bioavailability, BTZ and BTZ-M meet drug-likeness criteria, making them promising candidates for further optimization. The discovery of the present work opens a scope to design more benzothiazole analogues selective for tyrosine-phosphorylation-regulated kinase 1A enzyme.

Keyword: Benzothaizole, ATP, Dyrk1A, Molecular Docking, ADMET.

1. Introduction

Benzothiazoles are the most versatile and important heterocyclic compounds which has received high attention due to their diverse biological activities and applications in pharmaceutical industry.[1,2] Molecules containing these heterocyclic scaffolds such as their natural products and synthetic analogues demonstrated valuable pharmacological and biological properties like antiviral, antidiabetic, antiseptic, antitumor activities etc.[3, 4] Apart from its biological and pharmaceutical effects, compounds bearing benzothiazole scaffolds have an abundance of fields in the material science. Our research groups explored the diverse field of benzothiazole-scaffolds in recent past.[5-7] However, paradoxically increasing interest has been obtained for the development of benzothiazole derivatives showing a wide spectrum of biological activities such as anticancer and neuroprotective effects.[8] Out of these, the most investigated area of research for benzothiazole derivatives is their selective inhibition on Protein Kinase Dyrk1A (Dual-specificity tyrosine-phosphorylation-regulated kinase 1A) by targeting its ATP-binding pocket.[9, 10] Dyrk1A is a well-known serine/threonine kinase that is involved in various cellular processes such as cell cycle regulation, transcription, and neurodevelopment.[12, 13] Due to its known involvement in several diseases, including cancer and a variety of neurological disorders such as Alzheimer disease and Down syndrome, it has become an attractive target for therapeutic intervention.[14]

The ATP-binding pocket is important for the binding of ATP (adenosine triphosphate) and the transfer of phosphate groups to target substrates, defining an important module within signal transduction pathways. Benzothiazoles inhibit the binding of ATP to Dyrk1A and therefore act as a potent inhibitor that prevents downstream targets from being phosphorylated, interrupting pathways associated with cell growth and proliferation. Structural modifications usually allow benzothiazole derivatives to bind strongly with Dyrk1A ATP pocket and specifically may exert feature of off-target effects which triggers adverse side effect profile.[15]

The selective inhibition of Dyrk1A afforded by benzothiazole suggests potential for drug-like analogue modifications to further strengthen these properties and spurs interest in such scaffolds as candidates within drug discovery efforts. In the current investigation we have taken four Benzothiazole based compounds along with the parent moiety for analysis. Through molecular docking, we try to investigate the binding pattern of these compounds targeted to the enzyme. Besides, we have also screened the ADMET properties of five benzothiazoles in the present study. This study can help medicinal chemist to develop new benzothiazole based analogues for drug development in future.

2. Experimental procedure

Molecular Docking

We used AutoDock, a highly regarded non-commercial docking programme,[16] for our molecular docking experiment with the drugs BTZ, DM-BTZ, BTZ-M, BTZ-P and BTZ-AC with ATP-Binding Pocket of Protein Kinase Dyrk1A (PDB ID.5A4Q).[17] To further improve the thermodynamic stability of the ligand linked to the enzyme, we used a stochastic Lamarckian evolutionary algorithm for docking approach while concurrently minimising its scoring function. The Graphical User Interface programme AutoDock Tools (ADT) was used to perform intermediary tasks, such as creating grid boxes and pdbqt files for enzyme and ligand preparation. We have manually added the polar hydrogens, Kollman charges to the targeted enzyme. The initial files of targeted enzyme and compounds were saved in PDBQT format. AutoGrid was used for the preparation of the grid map using a grid boxwas and the dimensions were set to $50 \times 50 \times 50$ xyz points with a spacing of 0.275 Å. The docked structures that were acquired were examined using Biovia Discovery Studio.[18, 19] The labelled nucleotides, also known as the interacting residues, were in intimate contact with all three analogues. The presence of any potential interactions, such as H-bonding or other potential van der Waal interactions, in each docked complex was examined.

ADMET calculation

ADMET properties of all five compounds BTZ, DM-BTZ, BTZ-M, BTZ-P and BTZ-AC were calculated through ADMETlab 2.0 platform (https://admetmesh.scbdd.com/service/screening/index).[20] The chemical structures of all five compounds were uploaded in SMIlLES format to get all the data.

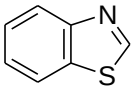
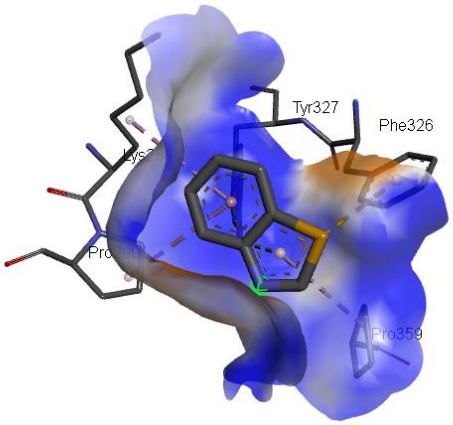
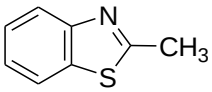
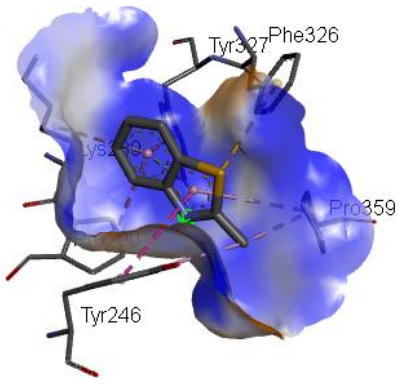
3. Result and Discussion

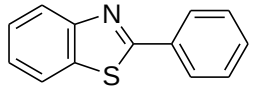
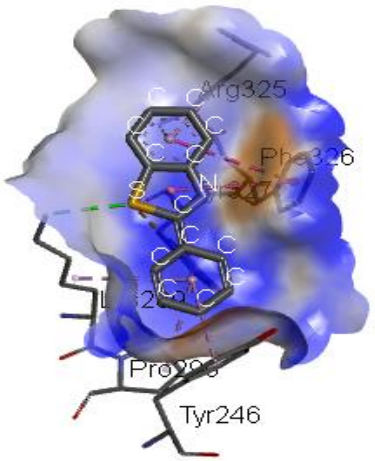
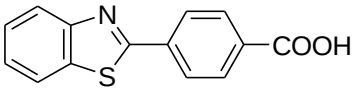
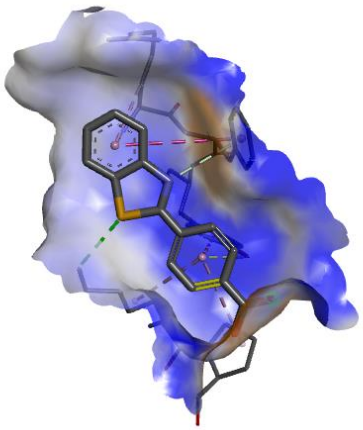
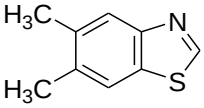
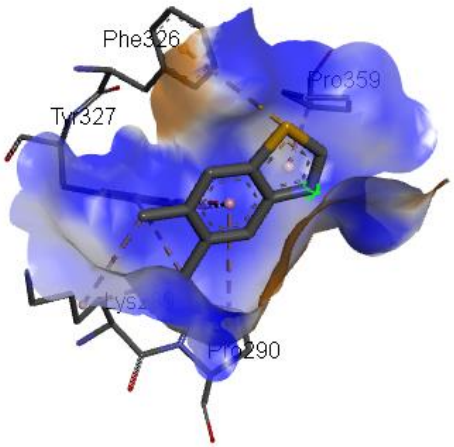
Binding analysis through Molecular Docking

The docking study of Benzothiazole (BTZ) analogues with ATP-Binding Pocket of Protein Kinase Dyrk1A enzyme provides insights into the binding interactions of various substituted BTZ compounds, shedding light on their potential effectiveness as enzyme inhibitors. The molecular docking scores, which reflect the binding affinities of these compounds with the enzyme, reveal that specific substitutions can significantly impact the stability and strength of binding. Each substitution interacts differently with the enzyme's active site amino acids, underscoring the structure-activity relationship of these analogues.

BTZ, the simplest form of Benzothiazole without any substitutions, interacts with five amino acids in the ATP-Binding Pocket of Protein Kinase Dyrk1A enzyme: Tyr327, Lys289, Pro290, Pro359, and Phe326 (Table 1). These interactions primarily involve aromatic and basic polar contacts, indicating that BTZ may form pi-cation interactions with residues such as Tyr327 and Lys289. However, BTZ has the least negative docking score (-7.13) among the compounds, suggesting relatively weaker binding to the enzyme compared to the other analogues. The lack of additional substituents means it cannot capitalize on hydrophobic or polar modifications that often enhance binding affinity. This limitation in interaction points could be a reason why BTZ shows relatively lower affinity for the enzyme's active site.

Table 1: Molecular Docking data with Protein Kinase Dyrk1A

Compound Entry with Interactive amino acids	Docking Score	Docked Structure with ATP-Binding Pocket of Protein Kinase Dyrk1A
 Compound name: **BTZ** Interactive amino acids: Tyr327, Lys289, Pro290, Pro359, Phe326	-7.13	
 Compound name: **BTZ-M** Interactive amino acids: Pro359, Phe326, Tyr327, Lys289, Pro290, Tyr246	-7.64	

 Compound name: **BTZ-P** Interactive amino acids: Arg325, Phe326, Tyr327, Lys289, Pro290, Tyr246	-8.16	
 Compound name: **BTZ-AC** Interactive amino acids: Arg325, Phe326, Tyr327, Lys289, Pro290	-9.28	
 Compound name: **DM-BTZ** Interactive amino acids: Pro359, Phe326, Tyr327, Pro290, Lys289	-7.45	

Arg: Arginine, Tyr: Tyrosine, Lys: Lysine, Pro: Proline, Phe: Phenyl alanine

The subclass BTZ-M had a methyl group as substitution to have a small improvement in binding with regard to docking score of -7.64. As a hydrophobic substituent, methylation improves non-polar interactions between BTZ-M and residues such as Pro359 and Phe326 (Table 1), making BTZ-M more competitive in stabilizing its binding state through

hydrophobic interactions. Additionally, previously not observed interaction with Tyr246 in unsubstituted BTZ may suggest that the methyl group rotates BTZ-M into position to make more favorable pi-stacking interactions. Finally, these changes to the binding profile of the molecule indicate that even a small hydrophobic group such as methyl can increase binding by helping stabilize additional interactions in the enzyme active site. In summary, lower binding affinity of BTZ with respect to BTZ-M confirms electrostatic nature of the interactions involved in molecular docking.

The presence of a phenyl group in BTZ-P makes it more aromatic and hydrophobic, leading to a lower docking score of -8.16 (see Table 1). The phenyl provides a large degree of pi-cation and pi-stacking potential, as can be seen with Arg325 and Phe326 respectively. In addition to Tyr327 and Tyr246, these residues help capture stabilization contacts through aromatic interactions, this may aid in increasing the binding affinity. The capacity of the phenyl ring to create these interactions indicates that there is a possibility for higher binding stability because aromatic interactions are known to stabilize bound compounds in an enzyme active site. The observed higher binding affinity of BTZ-P is appreciated as the presence of more aromatic substituents enhance docking scores due to stronger multi-point interactions with essential residues making it a favorable potential inhibitor.

BTZ-AC shows the level of binding attachment with a score of -9.28 suggesting a significant level of affinity. This strong binding connection is likely due, to the presence of the acid group, which's polar and has the ability to create hydrogen bonds and other polar interactions with amino acid residues. BTZ-AC interacts with Arg325 and Lys289 two residues and those are ideal for engaging in polar interactions. The electron withdrawing characteristics of the acid group might enhance the molecules ability to interact by facilitating hydrogen bonding, with polar residues in the active site as well. Not interacting with Tyr246 in BTZ-M and BTZ P indicates that BTZ-AC prioritizes hydrogen bonding over stacking. Despite this preference for hydrogen bonding over interactions, in BTZ-AC its stronger binding capability suggests that introducing substitutions can significantly improve binding stability when hydrogen bonding or ionic interactions are essential. This close connection makes BTZ-AC a contender, for inhibiting enzymes since it demonstrates a level of effectiveness, in binding within the enzymes active area.

DM-BTZ, with two methyl groups has a score of -7.45 which's slightly better than that of BTZ without substitutions. The intention, behind adding the methyl group was to enhance hydrophobic interactions; however it might have also caused steric-hindrance leading to suboptimal binding in the enzymes active site. The absence of this interaction suggests that the additional methyl group might limit the compound’s ability to engage in pi-stacking interactions.

In the present docking analysis, the impact of the substitutions on binding preference is described by the differences in the corresponding docking scores and changes in the interacting amino acid residues. Hydrophobic contacts are favored by hydrophobic substituent such as methyl and phenyl groups in BTZ-M and BTZ-P, and thus provide better binding affinities. In the case of BTZ-AC, additional polar groups enhance binding by interacting with potential hydrogen bonding residues yielding to the highest level of binding affinity. However, steric-effects, such as those observed in cases where DM-BTZ has di-methyl substitution, lead to steric hindrance, albeit enhancing hydrophobicity, lowers binding efficiency.

In conclusion, the presented work indicates that the choice of polar and aromatic substitutions in the formula of BTZ analogues will make them more effective inhibitors of ATP-Binding Pocket of Protein Kinase Dyrk1A due to increased binding affinity.

ADMET Property calculations

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) calculations are essential in drug development to predict a compound's pharmacokinetic and safety profiles. These calculations help assess how well a drug is absorbed in the body, its distribution across tissues, metabolic stability, clearance rate, and potential toxicity risks. ADMET predictions aid in identifying compounds with favorable pharmacological profiles, reducing the chances of late-stage failures. They also help optimize dosage forms and delivery methods. By screening for ADMET properties early, researchers can select compounds more likely to be effective and safe, streamlining drug discovery and development processes.

Table 2: ADMET profiling data

Properties	**BTZ**	**BTZ-M**	**BTZ-P**	**DM-BTZ**	**BTZ-AC**
LogS	-1.538	-2.182	-5.119	-3.416	-4.015
LogD	1.651	2.216	3.963	2.804	3.161
LogP	1.99	2.288	4.061	3.213	3.96
Pgp-inh	0.001	0.001	0.013	0.004	0.002
Pgp-sub	0	0.004	0.009	0.004	0.001
F(20%)	0.866	0.276	0.993	0.911	0.058
F(30%)	0.701	0.651	0.925	0.956	0.375
Caco-2	-4.278	-4.339	-4.579	-4.521	-4.612
BBB	0.535	0.945	0.49	0.693	0.16
PPB	80.46%	64.81%	98.04%	88.74%	97.94%
Fu	17.36%	13.65%	1.71%	11.25%	1.57%
CYP1A2-inh	0.991	0.988	0.992	0.982	0.569
CYP1A2-sub	0.852	0.92	0.268	0.94	0.09
CYP2C19-inh	0.507	0.838	0.844	0.539	0.194
CYP2C19-sub	0.524	0.425	0.067	0.585	0.051
CYP2C9-inh	0.09	0.34	0.659	0.083	0.267
CYP2C9-sub	0.5	0.646	0.464	0.534	0.074
CYP2D6-inh	0.856	0.069	0.133	0.643	0.079
CYP2D6-sub	0.668	0.701	0.185	0.904	0.068
CYP3A4-inh	0.053	0.058	0.116	0.106	0.039
CYP3A4-sub	0.36	0.476	0.208	0.489	0.099
CL	9.523	6.432	5.851	9.694	1.227
$T_{1/2}$ (Half Life)	0.593	0.267	0.128	0.337	0.461
hERG	0.023	0.008	0.048	0.017	0.105
H-HT	0.074	0.036	0.133	0.272	0.878
DILI	0.87	0.644	0.781	0.732	0.982

Ames	0.435	0.181	0.692	0.668	0.011
ROA	0.145	0.099	0.108	0.028	0.19
FDAMDD	0.029	0.02	0.032	0.52	0.009
SkinSen	0.353	0.347	0.162	0.15	0.067
Carcinogenicity	0.293	0.868	0.765	0.582	0.13
EC	0.711	0.883	0.048	0.598	0.004
EI	0.991	0.992	0.988	0.989	0.83
Respiratory	0.919	0.444	0.302	0.866	0.559
BCF	0.696	1.544	2.228	1.199	0.638
IGC_{50}	2.989	3.188	4.087	3.494	2.956
LC_{50}	3.326	3.879	4.51	3.967	4.059
$LC_{50}DM$	3.468	4.235	5.073	4.305	4.007
NR-AR	0.09	0.065	0.782	0.076	0.864
NR-AR-LBD	0.008	0.005	0.818	0.032	0.748
SR-ARE	0.509	0.082	0.921	0.48	0.909
SR-p53	0.071	0.022	0.505	0.468	0.764
Molecular Weight	135.01	149.03	211.05	163.05	255.04
Volume	131.475	148.771	218.785	166.067	251.025
Density	1.027	1.002	0.965	0.982	1.016
nHA	1	1	1	1	3
nHD	0	0	0	0	1
TPSA	12.89	12.89	12.89	12.89	50.19
nRot	0	0	1	0	2
nRing	2	2	3	2	3
MaxRing	9	9	9	9	9
nHet	2	2	2	2	4
nRig	10	10	16	10	17
Flex	0	0	0.062	0	0.118
nStereo	0	0	0	0	0
Non-Biodegradable	0	0	0	0	0
Non-Genotoxic_Carcinogenicity	0	0	0	0	0
SureChEMBL	0	0	0	0	0
LD_{50}_oral	0	0	0	0	0
Skin_Sensitization	0	1	1	0	1
Acute_Aquatic_Toxicity	0	0	0	0	0
Toxicophores	2	2	2	2	2
Genotoxic_Carcinogenicity_Mutagenicity	0	0	0	0	0
MCE-18	8	9	13	10	15
Natural Product-likeness	-1.927	-2.403	-1.957	-1.768	-1.595
Lipinski	Accepted	Accepted	Accepted	Accepted	Accepted
Pfizer	Accepted	Accepted	Rejected	Rejected	Rejected

The ADMET properties of BTZ, BTZ-M, BTZ-P, DM-BTZ, and BTZ-AC, owing to their solitary tenor in individual solubility, permeability, metabolic interaction, bioavailability, toxicity, and drug-likeness, are markers of drug potential. This helps in discrimination of each individual property and conducive for therapeutic purpose. Solubility and Lipophilicity are two crucial determinants for oral absorption and bioavailability. Within this dataset, BTZ has moderate solubility (LogS -1.538) and lipophilicity (LogP 1.99), suggesting a level of balance between the two properties where important for potentially successful oral delivery (Table 2). Solubility and lipophilicity profiles, designed to favor oral administration, seem to be most appropriate for BTZ and BTZ-M, whereas BTZ-P and BTZ-AC could require solubilization strategies to increase bioavailability.

The five compounds possess low permeability values, which indicate limits to passive diffusion across cell membranes. Highly expressed efflux transporter Pgp can pump drugs out of the cells before they can impart effective action. BTZ, BTZ-M had low interactions with Pgp (Pgp-inh 0.001, Pgp-sub 0) suggesting that these compounds would not be expelled by cells through this route, helping maintain the drug concentrations intra-cellularly. The expression of Pgp was able to pump out the compound limiting the therapeutic efficacy of the compound especially in tissue where Pgp is highly expressed. Low Pgp interaction values for DM-BTZ and BTZ-AC support a lower likelihood of efflux-mediated limitations and potentially improved intracellular retention.

Bioavailability and BBB Penetration are important for the amount of drug that is exposed to systemic circulation and whether it penetrates the CNS. BTZ exhibits F(20%) 0.866 and BBB penetration score of 0.535, indicative of relatively high bioavailability and moderate BBB permeability suggesting systemic use, but possibly limited access to CNS. BTZ-M displays a known moderate degree of bioavailability (F(20%) = 0.276) and the highest score for BBB penetration (BBB score = 0.945) conducive to CNS application. Of those, BTZ-P (sparing systemically effective however BB- and CNS-targeted due to high bioavailability [F(20%) 0.993] and low BBB score (0.49) respectively) proved to be the most promising compound (Table 2). DM-BTZ is also shown to have favorable bioavailability [F(20%) 0.911] and moderate BBB penetrability (0.693) and is therefore suggested to be useful for both systemic and CNS applications. BTZ-AC is the least bioavailable (F(20%) = 0.058) and has a low BBB score (0.16), which provides limited potential for BTZ-AC to be explored as a systemic or CNS xactogon in the absence of formulation changes. Conclusion: Of all compounds studied, BTZ, BTZ-M, and BTZ-P appear to have the most favorable bioavailability profiles, highlighting BTZ-M as the optimal candidate for targeted CNS delivery.

Distribution and Plasma Protein Binding (PPB) values tell us about how well the compounds distribute across the body and how much bind to the plasma proteins. PPB influences the time course of activity of the drug: highly bound drugs have long duration of action, but lower free drug at the site of action. BTZ has moderate PPB (PPB, 80.46%) balancing bound and free drug for effective action. BTZ-M has a lower in vivo PPB (64.81%) enabling increased availability of the free drug and possibly increasing its rapid therapeutic effect (Table 2). On the other hand, BTZ-P shows the highest PPB (98.04%) which might prolong its action but simultaneously limit the amount of free drug available for the immediate therapeutic effect.

DM-BTZ shows a relatively strong PPB (88.74%), producing a compromise suited to both rapid and sustained action. Similar to BTZ-P, BTZ-AC has high PPB (97, 94%), which may limit free drug availability for rapid action but may contribute to a long-lasting effect as well.
Information obtained from Metabolism (CYP Enzyme Interactions) is essential to potential drug-drug interaction (DDI) prediction. Cytochrome P450 (CYP) interactions can influence drug metabolism and have discoordinate implications for drug safety and efficacy. BTZ exhibited weak inhibition against the various isoforms of CYPs with the potential for drug-drug interactions (DDIs), due to the weak inhibition for several CYPs. The unavailability of CYP interaction with BTZ-M predicts a reduced risk of metabolic drug interactions, a possible advantage for the safety profile of BTZ-M. In vitro, BTZ-P displays intermediate inhibition for CYP1A2 and CYP2C9 and thus may affect concomitant medications metabolized by these enzymes. DM-BTZ is like BTZ with a lesser CYP inhibition and caution is still needed to avoid possible interaction between DM-BTZ and other drugs. BTZ-AC has minimal interaction with CYP, thus decreasing the chances of predictably drug interaction and ensuring good combination with other drugs.
Clearance (CL) and Half-life ($T_{1/2}$) data provide valuable insights into dosing requirements. Drugs that have higher clearance rates and shorter half-lives typically need to be administered more frequently to maintain therapeutic levels. For instance, BTZ has a high clearance rate of 9.523 and a short half-life of 0.593, which may require it to be given often. Similarly, BTZ-M has a clearance of 6.432 and an even shorter half-life of 0.267, suggesting that it too may need frequent dosing. BTZ-AC, with the lowest clearance of 1.227 and a moderate half-life of 0.461, may allow for less frequent dosing, which could be advantageous in a therapeutic context.
BTZ-M has the lowest toxicity indicators, suggesting it has a safer profile compared to the others. BTZ-P, however, presents a high mutagenic risk in the Ames test (0.692), which raises concerns about potential carcinogenicity and could hinder its development (Table 2). DM-BTZ shows moderate toxicity risks across the markers, indicating possible cardiac and liver toxicity that needs further investigation. BTZ-AC exhibits higher risks for cardiac toxicity (hERG), liver toxicity (DILI), and mutagenicity, necessitating careful consideration of adverse effects during its development.
Drug-likeness and Filter Compliance provide an initial assessment of each compound's potential as a drug based on the Lipinski, Pfizer, and GSK filters. All five compounds satisfy Lipinski’s criteria, indicating they are generally suitable for oral bioavailability. However, their compliance with the Pfizer and GSK filters differs. BTZ and BTZ-M pass all filters, suggesting a lower risk of toxicity and supporting their development potential. BTZ-P meets Lipinski’s criteria but does not pass the Pfizer filter, raising concerns about possible toxicity that could hinder its development.

In summary, each compound exhibits distinct ADMET properties that have implications for their therapeutic use. BTZ and BTZ-M are notable for their balanced bioavailability, moderate toxicity, and adherence to drug-likeness filters, making them strong candidates for further development. BTZ-M also shows significant potential for targeting the CNS due to its high BBB penetration. Although BTZ-P has high bioavailability, it presents considerable toxicity risks, especially regarding mutagenicity, which could restrict its application.

DM-BTZ and BTZ-AC encounter challenges due to high toxicity risks and limited bioavailability, making them less attractive without additional modifications. Further research, including *in vivo* testing, will be crucial to validate these findings and enhance each compound's suitability for therapeutic development.

4. Conclusion

Substitution of benzothiazole analogs reveals its potency as a selective ATP-binding inhibitor in Dyrk1A, especially with the BTZ-AC because of the polar acid group's contribution. ADMET profiling reveals that each compound has unique pharmacokinetic and toxicity characteristics. However, among the congeners, BTZ and BTZ-M demonstrate a favorable balance of bioavailability, toxicity scores, and drug-likeness properties. These data explain the further research of benzothiazole derivatives as drugs for the diseases caused by the dysfunction of Dyrk1A, to develop the selective and effective therapeutic strategies.

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Competing Interest

The Author declares no conflict of interest.

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