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Research Article

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Comprehensive *In Silico* Exploration of Some Novel Tetrazole Molecules

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ABSTRACT

Background: Tetrazole is a nitrogen-rich, five-membered heterocyclic ring structure that has emerged as a significant pharmacophore in medicinal chemistry. Owing to its bioisosterism with carboxylic acids, superior metabolic stability, and ability to form stable complexes, tetrazole derivatives have gained substantial attention in drug discovery. However, existing literature reveals a considerable research vacuum surrounding the pharmacokinetics, pharmacodynamics, and toxicity profiles of tetrazole derivatives, largely due to synthetic limitations and underexplored substitution patterns.

Aim: To perform a comprehensive *in silico* exploration of novel tetrazole molecules with potential anti-inflammatory properties.

Methods: A range of computational techniques was employed to assess tetrazole derivatives. Molecular docking was conducted against an anti-inflammatory target to evaluate binding affinity and interaction profiles. *In silico* target identification tools were utilized to predict off-target interactions. ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling, IC_{50} and LD_{50} estimations, and organ-specific toxicity predictions (including hepatotoxicity, neurotoxicity, and nephrotoxicity) were carried out. Bioisosteric replacement studies and metabolic pathway predictions were also performed to explore the chemical space and metabolite activity of the compounds.

Results: Initial *in silico* studies revealed promising docking scores and pharmacokinetic profiles for selected tetrazole derivatives. The compounds demonstrated favorable ADMET parameters, low predicted toxicity, and potential for bioisosteric optimization. Metabolite prediction studies indicated structurally stable and pharmacologically relevant metabolites.

Conclusion: This study highlights the untapped therapeutic potential of novel tetrazole derivatives and supports their further investigation through *in silico* and experimental approaches for anti-inflammatory drug development.

Keywords: Tetrazole, *in silico*, molecular docking, ADMET, anti-inflammatory, toxicity, pharmacokinetics, bioisostere.

INTRODUCTION

Tetrazole is a five membered heterocyclic compound and one of the important pharmacophore in the field of medicinal chemistry. It consists of four nitrogen and one carbon atom along with a hydrogen atom in the ring. Tetrazole is having electron rich planar structure. Unsubstituted tetrazole is the simplest form having molecular formula CN_4H_2. This simplest tetrazole is crystalline solid having white to pale yellow color with characteristic odor.[1] This simplest tetrazole contains 80% nitrogen of its molecular weight; which is the largest among the stable unsubstituted heterocyclic compounds. In this context, tetrazole exceeds tetrazine and superior to other heterocyclic nitrogen rich systems except some which are practically not exist in the free form like pentazoles and pentazines.[2] Though tetrazoles are having high number of nitrogen atoms in five member heterocyclic class compounds, they exhibits relatively stable properties in presence of heat, micro-irradiation and many chemical reagents like oxidizing agents, alkylating agents, various acids and bases. Tetrazoles are also known as tetrazolic acid which contains N-H bond. In the crystal form, tetrazole exists as 1H tautomer and in solution form, it co-exists as 1H and 2H tautomers.[3] In solution form, tetrazole tautomarises very rapidly and hence individual tautomer cannot be detected even at low temperature. It is also known that in solution form, 1H tautomer is dominant and in gaseous phase, 2H tautomer of tetrazole is dominant over the other one. The polarity of solvent plays vital role in the relative proportion of respective tautomer. Higher polarity of the solvent leads

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to higher proportion of the 1H tautomer. However, two tautomeric forms can be differentiated by dipole moments. The dipole moment for 1H tetrazole is 5.63D while for 2H form, dipole moment is 2.19D.[4]

Due to having the highest numbers of nitrogen atoms in the five member heterocyclic ring, tetrazole possesses high values of basicity and acidity. Presence of free N-H bond makes tetrazole an acidic molecule. Both, the aliphatic and aromatic tetrazole derivatives have pKa value very similar to the corresponding carboxylic acid (4.5-4.9 vs. 4.2-4.4, respectively) because tetrazole structural motif has ability to stabilize the negative charge by delocalization of electrons.[5] Tetrazole also possesses very high complex formation properties owing to the large numbers of nitrogen atoms in the ring. They can produce considerably stable metal and molecular complexes due to high electron availability in the tetrazole ring. In addition to this, tetrazole rings behaves as deactivating moiety due to having strong electron withdrawing inductive effect. Tetrazole heterocyclic ring is very similar to carboxylic acid and regarded as bioisostere of carboxylic acids. Though tetrazoles are bioisostere of carboxylic acids, they are comparatively more stable than the carboxylic acid group during metabolism and expect to have more half life time during biological interactions. Due to unique structural ring having high number of nitrogen, tetrazoles possess wide variety of chemical, thermo chemical properties and show multiple reactivities.[6]

Tetrazoles also find applications in the field of material sciences and in the information recording systems. Decomposition of tetrazole can release high energy along with release of nitrogen gas. Due to these special properties of tetrazole, they are also used in the field of propellant and explosives and air bag of automobiles.[7] Many researchers have conducted extensive research work on the tetrazole compounds to develop tetrazoles as bioisosteres, metabolically more stable surrogate of the respective carboxylic acids. Many important transformations make the tetrazole a versatile compound. It is less appreciated, but due to enormous potentials, tetrazole en route to other substituted tetrazole compounds and especially to other 5-membered ring heterocyclic via Huisgen rearrangement.[8]

The aim of the present study is a comprehensive *in silico* exploration of some novel tetrazole molecules. The primary objectives include performing molecular docking studies of tetrazole molecules against an anti-inflammatory target, conducting *in silico* target identification studies, and evaluating pharmacokinetic profiles using computational tools. Additionally, the study aims to determine *in silico* IC_{50} and LD_{50} values, estimate toxicity profiles (including hepatotoxicity, neurotoxicity, and nephrotoxicity), conduct bioisosteric replacement studies, and explore the metabolism patterns and potential activity of resulting metabolites. The rationale behind this study is based on a detailed literature survey of reputed scientific databases such as PubMed and Scopus, which revealed that limited data is available on tetrazole molecules due to restricted substitution patterns, low popularity, and synthetic challenges. These gaps indicate a significant research vacuum in understanding the pharmacodynamic, pharmacokinetic, toxicity, metabolic, and molecular targeting aspects of tetrazole derivatives. Therefore, this study proposes to bridge these gaps through a systematic computational investigation, leveraging freely available bioinformatics and cheminformatics tools.

MATERIALS AND METHODS

Pharmacokinetics, Bioavailability, and Drug-likeliness studies

The SwissADME online tool will be used to conduct a prediction research of pharmacokinetics, namely ADME, bioavailability, and drug-likeness of ligands. To identify drug-likeness, the technology estimates bioavailability radar based on six physicochemical properties: lipophilicity, size, polarity, insolubility, flexibility, and insaturation. The ADME properties, such as passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation, as well as substrate or non-substrate of the permeability glycoprotein (P-gp) will be detected positive or negative in the BOILED-Egg model within the tool. The lipophilicity estimation (Log p/w) parameters such as iLOGP on free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model, XLOGP3 is an atomistic method with corrective factors and a knowledge-based library, WLOGP is an implementation of a purely atomistic method, and MLOGP is an archetype of topological method rely. The Lipinski (Pfizer) filter, which will be the first rule-of-five to be implemented in a tool, will be used to predict drug-likeness. The bioavailability radar will be used to predict oral bioavailability based on several physicochemical characteristics. The ranges of each parameter will be mentioned as LIPO = lipophilicity as $-0.7 < XLOGP3 < +5.0$; SIZE = size as molecular weight $150gm/mol < MV < 500gm/mol$; POLAR = polarity as $20Å^2 < TPSA$ (topological polar surface area) $< 130Å^2$; INSOLU = insoluble in water by log S scale $0 < Logs (ESOL) < 6$; INSATU = insaturation or saturation as per fraction of carbons in the sp^3 hybridization $0.3 <$ Fraction $Csp3 < 1$ and FLEX = flexibility as per rotatable bonds $0 <$ Number ofrotatable bonds < 9.[9]

Drug Target Identifications

Swiss Target Prediction is a web service for bioactive small molecule target prediction. This website enables to anticipate a tiny molecule's targets. It compares the query

molecule to a library of 280,000 molecules active on more than 2000 targets in five distinct species using a mix of 2D and 3D similarity metrics. Understanding the molecular processes behind bioactivity and anticipating possible side effects or cross-reactivity requires mapping the targets of bioactive small compounds. Predictions have been made in three distinct organisms (models), and for near paralogs and orthologs, mapping predictions by homology within and across species is possible. The human (*Homo sapiens*), rat (*Rattus norvegicus*), and mouse (*Mus musculus*) models have all been shown to have credible inhibitory targets for the molecules.[10]

RESULTS AND DISCUSSION

Pharmacokinetics, Bioavailability, and Drug-likeliness studies

Table 1 describes the predictive values for pharmacokinetics, bioavailability and drug-likeness data on novel Tetrazole derivative. The molecule-1 showed high absorption rate. Good blood-brain permeability was obtained based on LogP value while low negative value indicated less skin permeation. In case of metabolism, the molecule did not prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically inhibits CYP1A2 and CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score was obtained. Poor water soluble characteristics were obtained for the novel Tetrazole derivative. The molecule-2 showed high absorption rate. Good blood-brain permeability was obtained based on LogP value while moderate negative value indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically inhibits CYP2D6 isoform. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55) was obtained. Poor to moderate water soluble characteristics were obtained for this novel Tetrazole derivative. The molecule-3 showed low absorption rate. Poor blood-brain permeability was obtained based on LogP value while low negative value indicated less skin permeation. In case of metabolism, the molecule did prove to be a p-glycoprotein substrate. It acts as CYP_{450} inhibitors and specifically inhibits CYP2C19 and CYP2D6 isoforms. For the prediction of bioavailability and drug-likeness, a moderate bioavailability score (0.55) was obtained. Poor water soluble characteristics were obtained for the novel Tetrazole derivative.

Table 1: Pharmacokinetics and physicochemical properties of novel Tetrazole derivatives.

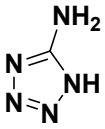
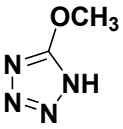
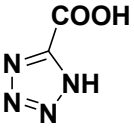
PROPERTIES	Compound-1	Compound-2	Compound-3
Structure			
Physicochemical Properties			
Formula	CH_3N_5	$C_2H_4N_4O$	$C_2H_2N_4O_2$
Molecular weight (g/mol)	85.07	100.08	114.02
Number of heavy atoms	26	27	26
Number of aromatic heavy atoms	12	12	12
Fraction Csp^3	0.48	0.50	0.50
Number of rotatable bonds	7	8	7
Number of H-bond acceptors	2	2	1
Number of H-bond donors	2	1	1
Molar Refractivity	111.71	116.18	114.65
TPSA (A^2)	35.05	24.50	15.27
SMILES	NC1=NN=NN1	COC1=NN=NN1	O=C(C1=NN=NN1)O
Lipophilicity			
Log Po/w (Ilogp)	3.67	4.42	4.40
Log Po/w ($XLOGP_3$)	5.99	6.32	6.71
Log Po/w (WLOGP)	5.53	5.84	6.14
Log Po/w (MLOGP)	4.05	4.26	4.87
Log Po/w (SILICOS-IT)	4.65	5.20	5.66

Table 1: ***(Continued)***

PROPERTIES	Compound-1	Compound-2	Compound-3
Consensus Log Po/w	4.78	5.21	5.56
Water Solubility			
Log S (ESOL)	-5.68	-5.90	-6.12
Solubility	7.39e-04 mg/ml ; 2.09e-06 mol/l	4.67e-04 mg/ml ; 1.27e-06 mol/l	2.66e-04 mg/ml ; 7.58e-07 mol/l
Class	Moderate Soluble	Moderate Soluble	Poorly Soluble
Log S (Ali)	-6.51	-6.62	-6.83
Solubility	1.08e-04 mg/ml ; 3.07e-07 mol/l	8.71e-05 mg/ml ; 2.38e-07 mol/l	5.13e-05 mg/ml ; 1.46e-07 mol/l
Class	Poorly Soluble	Poorly Soluble	Poorly Soluble
Log S (SILICOS-IT)	-6.83	-7.53	-7.80
Solubility	5.17e-05 mg/ml ; 1.47e-07 mol/l	1.09e-05 mg/ml ; 2.97e-08 mol/l	5.58e-06 mg/ml ; 1.59e-08 mol/l
Class	Poorly Soluble	Poorly Soluble	Poorly Soluble
Pharmacokinetics			
GI absorption	High (93.747%)	High (94.736%)	Low (83.636%)
BBB permeant	Yes (-0.942)	Yes (-0.168)	No
CNS permeability	-2.159	-2.337	-2.281
P-gp substrate	No	Yes	Yes
Caco2 permeability	0.421	1.131	0.943
CYP1A2 inhibitor	Yes	No	No
CYP2C19 inhibitor	No	No	Yes
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	Yes	Yes	Yes
CYP3A4 inhibitor	No	No	No
Log Kp (skin permeation) (cm/s)	-4.20	-4.05	-3.67
Total clearance (log ml/min/kg)	-0.317	-0.106	-0.462
Renal OCT2 substrate	No	No	No
Toxicity			
Minnow toxicity (log mM)	-1.583	-1.013	-1.083
T. pyriformis toxicity (log ug/L)	0.295	1.099	1.259
Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	2.349	2.577	2.667
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	1.17	1.287	1.374
Max. tolerated dose (human) (log mg/kg/day)	0.321	0.787	0.344
Hepatotoxicity	No	No	No
Skin Sensitisation	No	No	No
AMES toxicity	No	No	No

Table 1: ***(Continued)***

PROPERTIES	Compound-1	Compound-2	Compound-3
Drug-likeness			
Lipinski	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15
Ghose	Yes	No; 1 violation: WLOGP>5.6	No; 1 violation: WLOGP>5.6
Veber	Yes	Yes	Yes
Egan	Yes	Yes	No; 1 violation: WLOGP>5.88
Muegge	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55	0.55	0.55
Medicinal Chemistry			
PAINS	0 alert	0 alert	0 alert
Brenk	1 alert: hydroquinone	0 alert	0 alert
Lead-likeness	No; 2 violations: MW>350, XLOGP3>3.5	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.19	3.30	3.28

Bioavailability Radar Plot

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.48, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -5.68 (insoluble), SIZE as molecular weight (g/mol) of 329.04, POLAR as TPSA (Å²) 35.05, and LIPO as XLOGP3 value of 5.99 (**Figure 1A**). The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.50, FLEX as per number of rotable bond 8, INSOLU Logs (ESOL) as -5.90 (insoluble), SIZE as molecular weight (g/mol) of 366.54, POLAR as TPSA (Å²) 24.50, and LIPO as XLOGP3 value of 6.32 (**Figure 1B**). The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.50, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -6.12 (insoluble), SIZE as molecular weight (g/mol) of 350.54, POLAR as TPSA (Å²) 15.27, and LIPO as XLOGP3 value of 6.71 (**Figure 1C**).

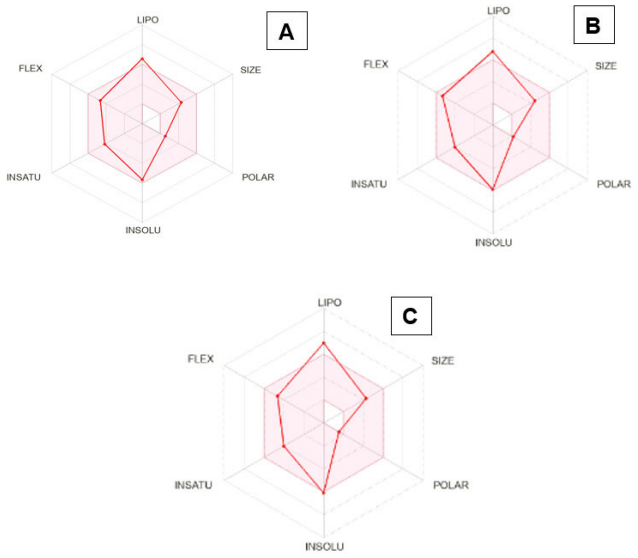


Figure 1: Bioavailability Radar Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

Boiled Egg Plot

In case of BOILED-Egg model (**Figure 2**), the Brain OrIntestinaLEstimateD permeation method (BOILED-Egg) has already been proposed as an accurate predictive model, which helps by computational prediction of the lipophilicity and polarity of small molecules. In overall predictive results, novel Tetrazole derivative can be suitable drug candidate as per bioavailability radar and BOILED-Egg representation.

It was observed in the predictions that compound-1 (**Figure 2A**) was a PGP positive non-substrate. PGP positive non-substrate molecules are compounds that interact with P-glycoprotein but are not themselves transported by it. These molecules can influence PGP activity in several ways, such as inhibiting or activating its transport function, altering its expression levels, or modulating its conformation. Unlike

substrates that are actively pumped out of cells by PGP, non-substrate molecules bind to PGP and affect its function without being expelled. It was obtained that novel Tetrazole derivative, compound-2 (**Figure 2B**) has limited capability of blood-brain barrier penetration as well as it also showed low gastrointestinal absorption. The molecule was found to be PGP positive as non-substrate in predictive model. PGP positive non-substrate behaviour was observed in the predictions for compound-3 (**Figure 2C**). PGP positive non-substrate molecules represent a significant area of interest in pharmacology and drug development. By modulating the function and expression of P-glycoprotein, these molecules offer potential strategies for overcoming multidrug resistance, optimizing drug pharmacokinetics, and enhancing therapeutic efficacy. Ongoing research continues to explore and develop new PGP inhibitors and modulators, aiming to address the challenges posed by drug resistance and improve patient outcomes across various medical conditions.

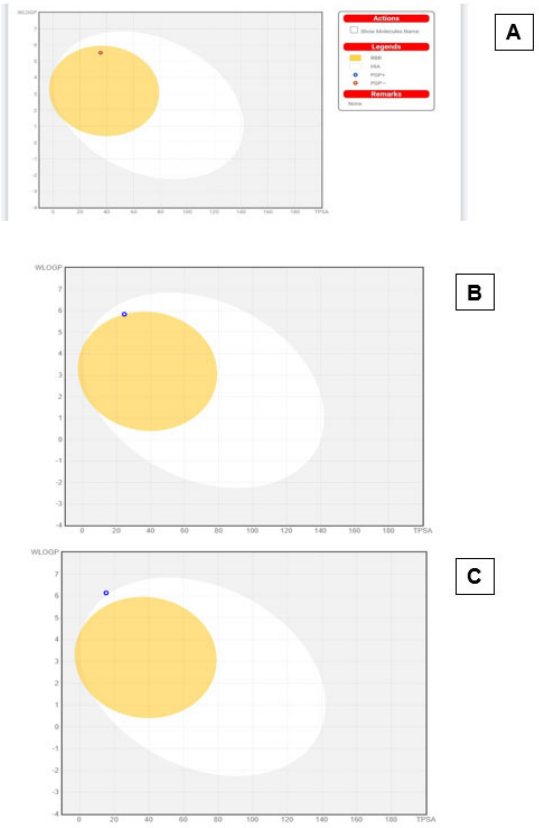


Figure 2: Boiled Egg Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

Drug Target Identifications

As the study is focused on drug repurposing, it remains crucial to determine the plausible therapeutic targets against which Compound-1 can inhibit them with micromolar concentrations, ideally. The human (*Homo sapiens*), rat (*Rattus norvegicus*), and mouse (*Mus musculus*) models revealed the inhibitory perspectives of compound-1 against several targets like hydrolase, enzyme, oxidoreductase, Family A G protein-coupled receptor, transferase, voltage-gated ion channel, primary active transporter, ligand-gated ion channel, etc.. The predicted results strongly supported the basis of semi-synthesized natural product for possible applications against inflammation by revealing the possibilities of drug interactions with multiple targets.

As the study is focused on determining the interacting profile of Compound-2 against therapeutic targets that have immense pharmacological perspectives, it remains crucial to exactly quantify the plausible therapeutic targets against which Compound-2 can inhibit them with micromolar concentrations, ideally. The human (*Homo sapiens*) model revealed the inhibitory perspectives of Compound-2 against the targets such as Family A G protein-coupled receptor (33.3%), Kinase (26.7%), Electrochemical transporter (13.3%), Protease (20%), and Hydrolase (6.7%). The mouse (*Mus musculus*) model revealed the inhibitory perspectives of Compound-2 against the targets such as Family A G protein-coupled receptor (53.3%), Kinase (6.7%), Electrochemical transporter (6.7%), Unclassified protein (6.7%), Protease (20%), and Enzymes (6.7%). The rat (*Rattus norvegicus*) model revealed the inhibitory perspectives of Compound-2 against the targets such as Family A G protein-coupled receptor (33.3%), Ligand-gated ion channel (20%), Voltage-gated ion channel (6.7%), Electrochemical transporter (6.7%), Enzyme (6.7%), Kinase (6.7%), and Hydrolase (6.7%). The procured predicted results strongly supported the basis of interaction of this small molecule for possible applications against colorectal cancer by revealing the possibilities of interactions with multiple targets (majorly with Family A G protein-coupled receptor).

As the study is focused on determining the interacting profile of Compound-3 against therapeutic targets that have immense pharmacological perspectives, it remains crucial to exactly quantify the plausible therapeutic targets against which Compound-3 can inhibit them with micromolar concentrations, ideally. The human (*Homo sapiens*) model revealed the inhibitory perspectives of Compound-3 against the targets such as Family A G protein-coupled receptor (40%), secreted proteins (20%), other cytosolic protein (20%), enzymes (13.3%), and kinase (6.7%). The mouse (*Mus musculus*) model revealed the inhibitory perspectives of Compound-3 against the targets such as Family A G protein-coupled receptor (40%), kinase (6.7%), enzymes (6.7%), nuclear receptor (6.7%), transcription factor (6.7%), unclassified protein (6.7%), electrochemical transporter (6.7%), and other cytosolic protein (6.7%). The rat (*Rattus norvegicus*) model revealed the inhibitory perspectives of Compound-3 against the targets such as Family A G protein-coupled receptor (40%), enzymes (13.3%), voltage-gated ion channel (6.7%), ligand-gated ion channel (6.7%), kinase

(6.7%), nuclear receptor (6.7%), and unclassified protein (6.7%). The procured predicted results strongly supported the basis of interaction of this small molecule for possible applications against inflammatory targets by revealing the possibilities of interactions with multiple targets (majorly with Family A G protein-coupled receptor).

CONCLUSION

The present *in silico* investigation of novel tetrazole molecules provides valuable insights into their potential as promising anti-inflammatory agents. Through comprehensive computational analyses—including molecular docking, target prediction, pharmacokinetic profiling, toxicity assessment, IC_{50} and LD_{50} estimation, and metabolism studies—it was observed that several tetrazole derivatives exhibit favorable drug-like properties with significant binding affinities toward selected inflammatory targets. Moreover, bioisosteric replacement studies further enhanced the pharmacological profiles and metabolic stability of these molecules. The limited availability of data in existing literature regarding substituted tetrazoles, primarily due to synthetic challenges and under-exploration, underscores the relevance of this study in bridging current knowledge gaps. Overall, the findings support the rationale that tetrazole scaffolds hold immense potential in rational drug design and warrant further experimental validation through *in vitro* and *in vivo* studies to establish their efficacy and safety in a biological system.

CONFLICT OF INTEREST

None declared.

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