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RESEARCH ARTICLE

ADMET ANALYSIS OF TRIAZOLE DERIVATIVE: A THEORETICAL INVESTIGATION TOWARDS ITS EVALUATION AS A DRUG CANDIDATE

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Abstract

The present work explores the potency of the 3-Ethoxy-5-phenyl-1H-1,2,4-triazole compound using in-silico experimental techniques. The compound was subjected to ADMET analysis to understand how well the compound can be used as drug. Further the ADMET analysis revealed that the compound showed excellent pharmacokinetic properties with all the values were found to be well within the limits. Further various properties of the compound were evaluated and the boiled egg model analysis revealed that the compound good gastrointestinal absorption property. The toxicity value of the compound were also evaluated.

Introduction:-

The heterocyclic compounds are well documented as fascinating skeletons having very good ability to interact with the targets and disrupt the biological pathways associated with the cancer progression [1-7]. Hence, further the addition of the various other functional groups to these compound enables the compound to have diverse chemical and biological applications. Further, these thiazole derivatives are extensively known in medicinal industry as anti obesity [8], antitubercular [9], antidiabetic [10], anticancer [11-13], antimicrobial [14-15] and antioxidant agents [16].

The Rufinmide (anticonvulsant), TSAO (anti-HIV), Cefatrizine (antibiotic), Tazobactam (antibacterial), and CAI (anticancer) are some of the FDA approved drugs bearing 1,2,3-triazole moiety, this emphasizes the medicinal properties of these derivatives [17-20]. The triazoles are used in the control of variety of fungal diseases in fruits, vegetables, legumes and grain crops, both as pre- and postharvest applications.

The study of the physicochemical, pharmacokinetic properties of the compounds has been emerged as one of the crucial stages in drug discovery process. This process looks for the compounds suitable for the drug-like traits which can be further involved in the structure-property relationship. This process will help in the selection of the particular compounds and nominated for the further drug advancement. In recent years lots of effort are going on towards the development of the structures in vitro computational of properties which will help us in the understanding of the absorption, distribution, metabolism, excretion, and toxicity (ADMET) behaviour.

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The ADMET analysis will help in the minimization of the probability of last-stage attrition of drug development procedure and to optimize the screening and trials by grazing the important candidates only.

As large number of the triazole derivatives have been structurally characterized, the need for the exploration of the biological properties of the compounds is essential.Hence in this research work we are performing the ADMET study of the 2-Ethoxy-5-phenyl-1H-1,2,4-triazole which was synthesized and it structural analysis was reported by Ali M. Hebishyet.al in 2019[21].

ADMET analysis

The understanding of the behaviour of the triazole derivative with the human body is crucial in proceeding towards the development of the drug. Hence, to explore the pharmacokinetic properties such as absorption, distribution, metabolism, excretion and toxicity of the compound ADMET analysis was carried out [22, 23]. Further, other properties of the compound such as hydrophilicity, hydrophobicity, solvent accessible surface area, number of rotatable bonds, donor-hydrogen bonds, acceptor-hydrogen bonds, blood brain barrier permeability (BBB), Caco-2 cell permeability, human intestinal absorption (HIA), skin permeability, cytochrome P4502D6 binding (CYP2D6), hepatotoxicity and plasma protein binding (PPB) were explored which plays a major role in the drug development.

Results and Discussions:-

Physicochemical and ADMET properties

The exploration of the physicochemical and ADMET properties of the compound using computational techniques will helps to save lot of resources and it is much more economical as it will prevent the failure of the compound to be drug in the later state or in showing side effects once it has been approved as drug.

Several physicochemical properties such as, molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), number of rotatable bonds (RB) and partition co-efficient (Log P) for the PPTT molecule is analysed and it is observed that all the properties lie in the satisfactory range. In addition, follow Lipinski's rule of five (Ro5), Jorgensen's Ro3, Ghose filter, Vebers's, Egan's, and Muegge's rules for oral bioavailable drugs. Compared drug-likeness predictions with their bioavailability scores and toxicity profiles are provided in Table 2 and 3.

Moreover, it is found that the compound under study is in optimal range for physicochemical and ADMET properties. The compound is found to be a substrate of P-glycoprotein (PGP+) the corresponding dot is red colour in Figure 5. The dot in the white region of egg are for compounds that are more passively absorbed through the gastro intestinal tract. The six descriptors such as LIPO, lipophilicity; SIZE, molecular weight; POLAR, polarity; INSOLU, insolubility; INSATU, unsaturation; FLEX, flexibility, show us that the compound exist within the pink region of radar are considered to possess good bioavailability property in the body. In general, the compound under investigation is showing excellent bioavailability radar properties (Figure 5).

The human oral availability and the BBB (blood, brain barrier penetration ability) of the compound is found to be 0.700 and 0.8250 respectively. Further the compound is very well absorbed human intestine (99.0%). The oral rat acute toxicity for the compound is found to be 1.542 log(1/(mol/kg)) and the biodegradation value of the compound is found to be 0.55. The compound inhibited all cytochrome P450 isomers as a regulator for the drug metabolism, such as CYP2C9, CYP1A2, CYP2C19, except CYP2D6 and CYP3A4. The overall score suggests a favourable pharmacokinetics to be accepted as a drug molecule.

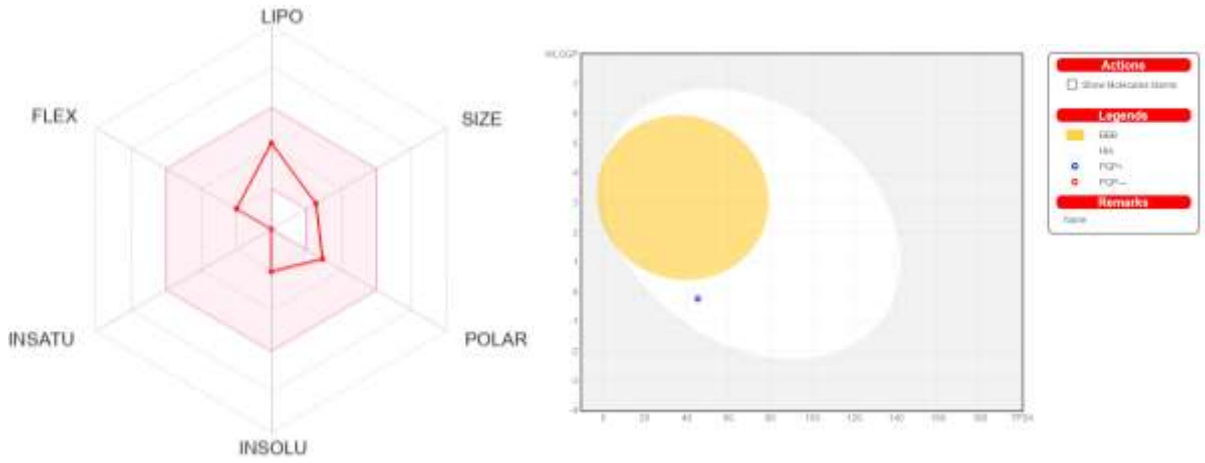

Figure 5:- Bioavailability radar of the compound under study for prediction of GI absorption and brain penetration (left), BOILED-Egg model (right).

Table 2:- Comparison of the physicochemical properties of the compound.

	MW	**HBD**	**HBA**	**RB**	**log p**	**Surface area Å^2**
Compound under investigation	199.29	3	4	3	1.19	45.32

Table 3:- ADMET profiles of the synthesized compound (as obtained from ADMET server).

ADMET properties	**Compound under investigation**
Human oral bioavailability	0.7000
BBB permeability (log BB)	0.8250
Subcellular localization	0.7758
Caco2 permeability (log P_{app} in 10^{-6} cm/s)	0.6782
Intestinal absorption (Human)	0.9901
Water solubility (log s)	-2.405
P-glycoprotein substrate	0.8831
P-glycoprotein substrate inhibitor	0.9336
Thyroid receptor binding	0.6291
Nephrotoxicity	0.5190
CYP1A2 inhibitor	0.6395
CYP2C9 inhibitor	0.7738
CYP2C19 inhibitor	0.6827
CYP2D6 inhibitor	0.7561
CYP3A4 inhibitor	0.9896
CYP2D6 substrate	0.8652
CYP3A4 substrate	0.5978
Oral rat acute toxicity log(1/(mol/kg))	1.542
Plasma protein binding	0.449
Biodegradation	0.5500

Conclusion:-

In this research work, the reported 3-Ethoxy-5-phenyl-1H-1,2,4-triazolemoleucle is subjected to theoretical evaluation of the pharmacokinetic properties of the compound to validate the use of the compound as drug.

The ADMET and boiled egg analysis was performed and the ADMET analysis revealed that the compound possess appropriate pharmacokinetic features as the compound adheres to all the Lipink's rule of five. The boiled egg model analysis revealed that the compound is more likely to have the partial gastrointestinal penetration ability. The compound showed good bioavailability radar properties with all the properties found to be well within the acceptable clinical limits. The overall conclusion of the work is that the compound is having very good pharmacokinetic properties and it is well suitable for the oral administration as drug (as evaluated by the computational analysis). Hence, further in vivo and in vitro studies will help us to further evaluate the efficacy of the compound, allowing us to design novel compounds having enhanced biological activities.

Declaration of author conflict statement
The authors have no conflict of interest.

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