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Research Article

Biological New Targets Prediction & ADME Pharmacokinetics Profiling of Newly Synthesized E / Z Isomers of Methyl 2-phenyl-2-(2-phenylhydrazono) Acetate Derivatives

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Abstract

Objective: In order to predict the pharmacokinetic properties, and new potential biological targets, biological targets prediction, and absorption, distribution, metabolism and excretion (ADME) profiling of newly synthesized Entgegen / Zusammen (E / Z isomers) of Methyl 2-phenyl-2-(2-phenylhydrazono) acetate derivatives were carried out.

Methods: The prediction of new biological targets, pharmacokinetic properties, membrane permeability, and bioavailability radar properties were carried out by using Swiss Targets Prediction and Swiss ADME tools, respectively.

Results: All the eight screened compounds possessed excellent drug-likeness criteria and passed successfully from Pan-assay interference compounds filter. Additionally, all screened compounds fell within the acceptable range in the bioavailability radar, showing excellent descriptors with a slight exceeding of insaturation properties. Compounds displayed elevated permeability across the Blood Brain Barrier, while compounds exhibited highest Human Intestinal Absorption according to the Egan Egg model. Moreover, the screened compounds also exhibited good pharmacokinetic properties. All the compounds exhibited activity against various enzymes, such as lyase, kinase, protease, and Family AG protein-coupled receptor.

Conclusion: This conducted study smartly reveals that *in-silico* based studies were considered to provide robustness towards a rational drug design and development approach; therefore, in this way, it helps for further investigation of drug design and drug discovery steps.

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Keywords: Swiss targets prediction, Swiss ADME, BOILED-Egg, pharmacokinetics properties, blood brain barrier, human intestinal absorption, methyl 2-phenyl-2-(2-phenylhydrazono) acetate E / Z isomers

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1 INTRODUCTION

Designing, discovering and developing of new drugs have perennially posed significant challenges for scientists and researchers over several decades. The complexity of human genome and the increased number of proteins production has rendered the searching for drug candidates a formidable task. It is quite difficult for identifying druglike candidates which binds accurately within the targeted active groove of a protein while exhibits minimizing adverse effects on the body[1]. Numerous drugs fail or show insignificant responses at various experimental stages of drug were design and discovery because of wrongly identified targeted binding sites of the receptor. Accurately mapping the binding site of the target is considered to be the most crucial step to evaluate the bioactivity for drug design[2,3].

A targeted macromolecule usually assumes a protein structure with proper-defined chemical properties, which undergoes various of conformational changes, in order to form best fit low energy specific binding interactive poses either with small organic molecules or with large peptide compounds which are administered for the diagnosis and treatment of various diseases[4].

The insightful information of large protein families like enzymes, receptors, membrane proteins, ion channels, etc., several druglike candidates have been screened and identified, data sourced from easily accessible public databases such as, Uniprot, ChEMBL ZINC, PubChem etc. The data pertaining to the multitude of drug-like candidates from these databases is automatically retrieved[5,6].

According to previous study, each drug candidate may have up to six potential biological targets. Identifying all of these targets is a quite tough and time-consuming process, because the new drug requirements are increasing day by day as the various types of infections are growing faster, stronger, and causing drug resistance[7,8]. To cope up with all these challenges, now a day's researchers are focusing on computational based predictive tools for drug designing and development process. By using different *in-silico* based techniques, the Drug-Protein Interactions or Protein-Protein Interactions can be estimated, which plays a critical contribution in various biological processes; for this purpose, selection of the most appropriate biological target is an important task from which it's easier to select the most suitable chemical ligand and convert it into a drug molecule. Computational-based predictions are quite helpful to narrow down a large number of potential targets space; researchers have screened a number of small organic molecules and developed structure-based approaches for new targets prediction[9,10]. In this regard, different software's have been introduced, one of which is Swiss Targets Prediction. It is a freely accessible online search engine dealing with a wide range of potential binding targets by using the High Throughput Screening method[11].

Swiss targets prediction works through inverse docking mechanism, in which molecular targets prediction is carried out with the identification of those proteins whose ligands are already known and structurally similar with respect to the provided query molecule. Swiss targets prediction consist of some distinguish features which may include 2 dimensional (2D), Finger Printing (FP2) and 3 dimensional (3D) similarity search methods for the known active ligands[12-18]. The modified version can produce the results by the help of three different biological species, including (Homosapiens, Rattus norvegicus and Musmusculus). It also builds up a user map of the predictions between various species or within the organism, which based on target receptor homology[19].

The combination of 2D and 3D similarity search methods are significantly helpful to increase the accuracy of targets prediction efficiently, specifically for new query molecules, which do not relate to any earlier well studied chemical library[20]. The Swiss Targets Prediction software work engine extensively dealing about the calculation of similarity search between the submitted queries of molecules with the data-base of known actives in an appropriately defined manner. The quantification of similarity search consist of two folds. First it consists of the computing by pair wise comparison of 1D vector properties, which describe about molecular structural properties.

The second is 2D similarity search which is quantified through the Tanimoto coefficient between the FP2 vectors

for both the query and the screened molecules, However the 3D similarity is quantified through the calculation of Manhattan distance between the electro shape vectors (ES5D) of 20 conformers for both the query and the screened molecules. While, through the combination of various similarity measures, the capacity for screening and prediction is significantly improved, specifically for drug like candidates The basic principle is that two similar molecules are represented by analogous vectors, which represents through quantified similarity score value near to 1. A combined score value higher than 0.5 predicts that the molecules are likely to share a common target receptor. The current optimized version of Swiss targets prediction consisting of new exciting features with more than a 30% faster rate in comparison with the old version[21-26].

The pharmacokinetics absorption, distribution, metabolism, and excretion (ADME) properties. also relate to P-glycoprotein, as it contributes for predicting whether the drug molecule is able to reach the affected target site (or it does not reach to the site and ultimately eliminates from the cell with any function). Cytochrome P450 (CYP450) is considered as one of the essential complex protein system located in hepatocytes, involved in drug metabolism and metabolites excretion. It is estimated that 50% to 90% of drug molecules are either the inhibitor or substrate of five major isoforms of CYP450 complex protein (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), and drug-drug interaction (DDI) is the result of inhibition of any of these isoenzymes[27-30]. Therefore, the rational approach of using *in-silico* based techniques is to predict the new biological targets of novel compounds and to profile up their pharmacokinetics as well as membrane permeability properties prediction and bioavailability radar mapping.

In this way through computational based drug designing and drug discovery approach, we can save time, chemicals, and manpower. It is ultimately cost effective too; we synthesized 8 compounds with its Entgegen / Zusammen (E / Z isomers)[31] (Table 1), and conducted its ADME profiling to check drug ability criteria and Absorption, Distribution, Metabolism and Excretion properties, furthermore to find out their biological targets prediction properties for further evaluation (Figure 1).

2 MATERIAL AND METHODS

2.1 Swiss Targets Prediction

Targets prediction of newly synthesized products[23] was performed through Swiss Targets Prediction tools. Molecules' structures in (smi) format were imported in the panel box and submitted to predict the new biological targets by selecting the organism (homosapiens) humans.

2.2 Swiss ADME Profilling

Pharmacokinetics studies of newly synthesized products were performed by using Swiss ADME tools. The Swiss ADME website can be accessible freely by following the link www.swissadme.ch/index.php[31]

2.3 Experimental Work

2.3.1 New Biological Targets Prediction by using SWISS Targets Prediction

Software Swiss targets prediction tool was used to predict new biological targets, compounds new query structure in (SMILES) format were uploaded., which highlights the red color button of 'predict targets'. By clicking on it, the computation process becomes start with the input of chemical structure through JChemWeb services (version 18.29.0), and Open babel (version 2.4.1), canonicalization, kekulization, and hydrogenation with pH 7.4 parameters applied on the (SMILES) format of molecules which is then translated both into (1) FP2 binary vectors, and (2) 20 conformers of each molecule which finally generate ES5D vectors. Validation of the input molecule through JChem structure checker was finally applied on the (2D and 3D) screening to search similar molecules among the compounds known to be already experimentally active against one or several of the 3068 available protein targets in the data base within few seconds. The results of the molecule target prediction are displayed on a single panel[32,33].

2.3.2 ADME Properties Profiling

In order to study the pharmacokinetics ADME properties of the molecules, all the compounds in (SMILES) format were imported from the specified directory on the drawing panel of Swiss ADME sketcher which highlighted "Run" red button; on clicking run button all the molecules sequentially submitted to calculate their pharmacokinetics, drug-likeness, physicochemical, medicinal chemistry properties, membrane permeability attributes and bioavailability radar, within few seconds, the results of all molecules were displayed on a single panel.

3 RESULTS AND DISCUSSION

All the newly synthesized E / Z isomers of compounds were subjected for new biological targets prediction. Geometrical isomers had same molecular formula but different physiological properties, for instance, Tomoxifen (Z) isomers is antioestrogenic whereas (E) isomer tamoxifen possess estrogen agonist activity. Drug isomerism opened up new era of drug designing, drug discovery and drug

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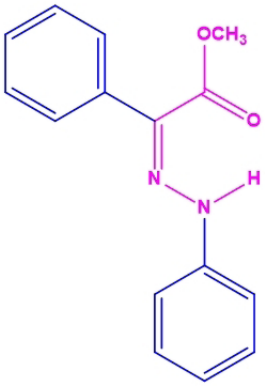
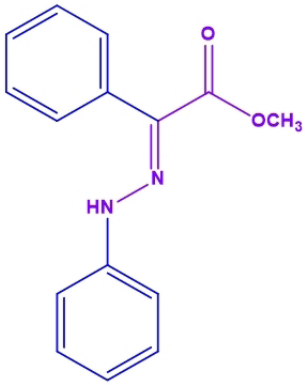
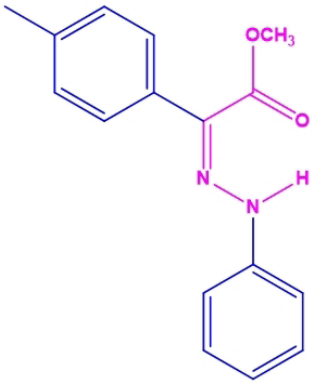
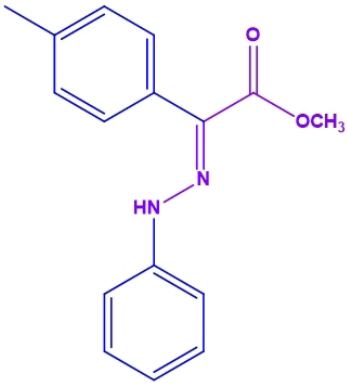
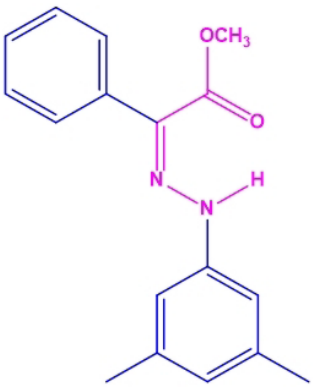
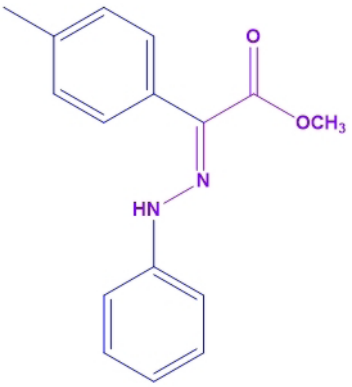
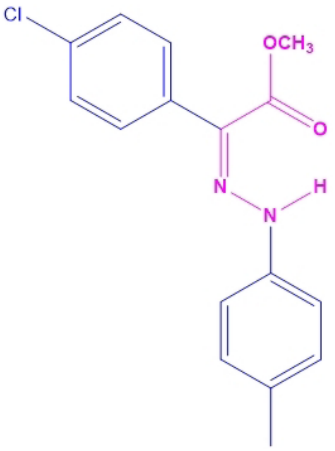
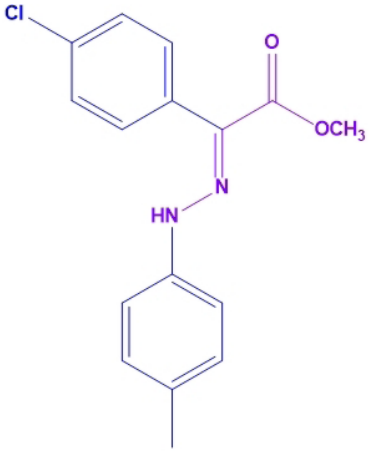
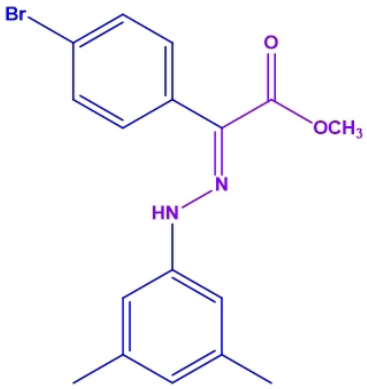
Table 1. All compounds isomers E/Z Isomers structures[32]

S.No	Z	E
1	 (Z)-methyl 2-phenyl-2-(2 phenylhydrazono) acetate	 (E)-methyl 2-phenyl-2-(2-phenylhydrazono) acetate
2	 (Z)-methyl 2-(2-phenylhydrazono)-2-p-tolylacetate	 (E)-methyl 2-(2-phenylhydrazono)-2-p-tolylacetate
3	 (Z)-methyl 2-(2-(3,5-dimethylphenyl)hydrazono)-2-phenylacetate	 (E)-methyl 2-(2-(3,5-dimethylphenyl)hydrazono)-2-phenylacetate
4	 (Z)-methyl 2-(4-chlorophenyl)-2-(2-p-tolylhydrazono) acetate	 (E)-methyl 2-(4-chlorophenyl)-2-(2-p-tolylhydrazono) acetate

5



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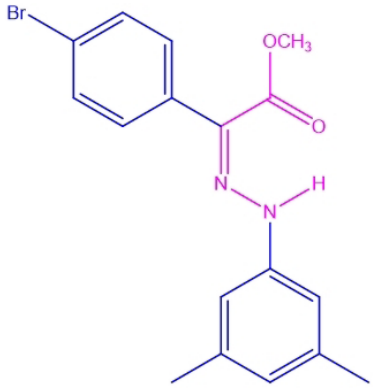
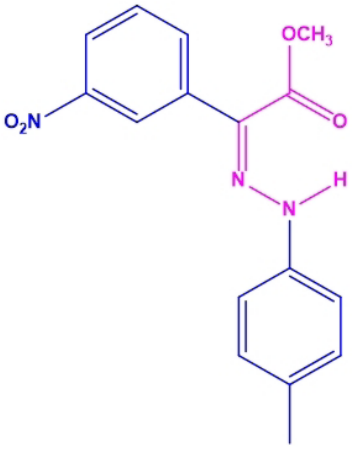
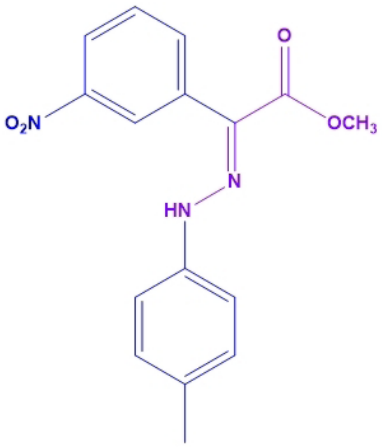


(E)-methyl 2-(4-bromophenyl)-2-(2-(3,5-dimethylphenyl) hydrazono) acetate

6

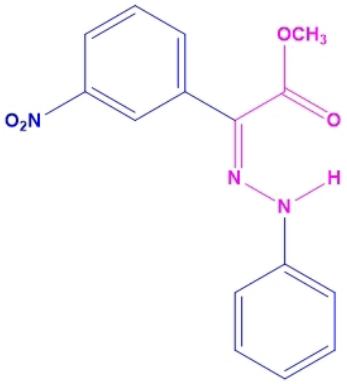


(Z)-methyl 2-(3-nitrophenyl)-2-(2-p-tolylhydrazono) acetate

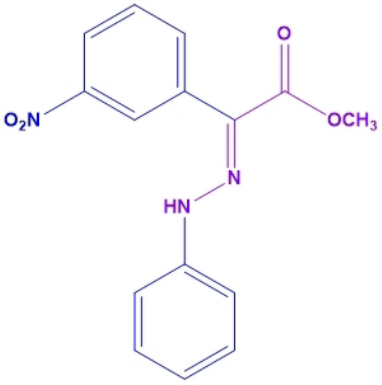


(E)-methyl 2-(3-nitrophenyl)-2-(2-p-tolylhydrazono) acetate

7

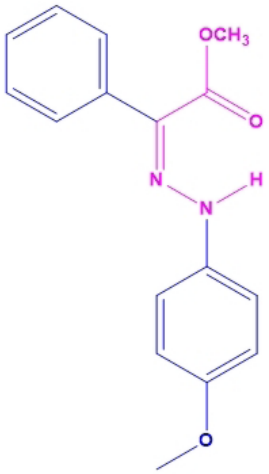


(Z)-methyl 2-(3-nitrophenyl)-2-(2-phenylhydrazono) acetate

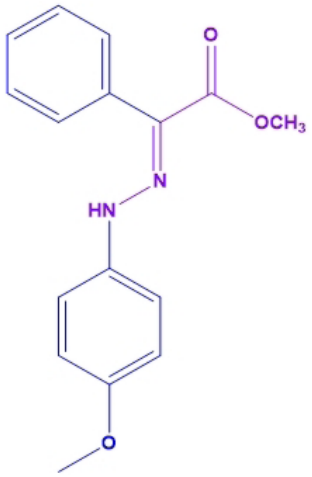


(E)-methyl 2-(3-nitrophenyl)-2-(2-phenylhydrazono) acetate

8



(Z)-methyl 2-(2-(4 methoxyphenyl)hydrazono)-2-phenylacetate



(E)-methyl 2-(2-(4-methoxyphenyl)hydrazono)-2-phenylacetate

https://doi.org/10.53964/jmbdd.2024001

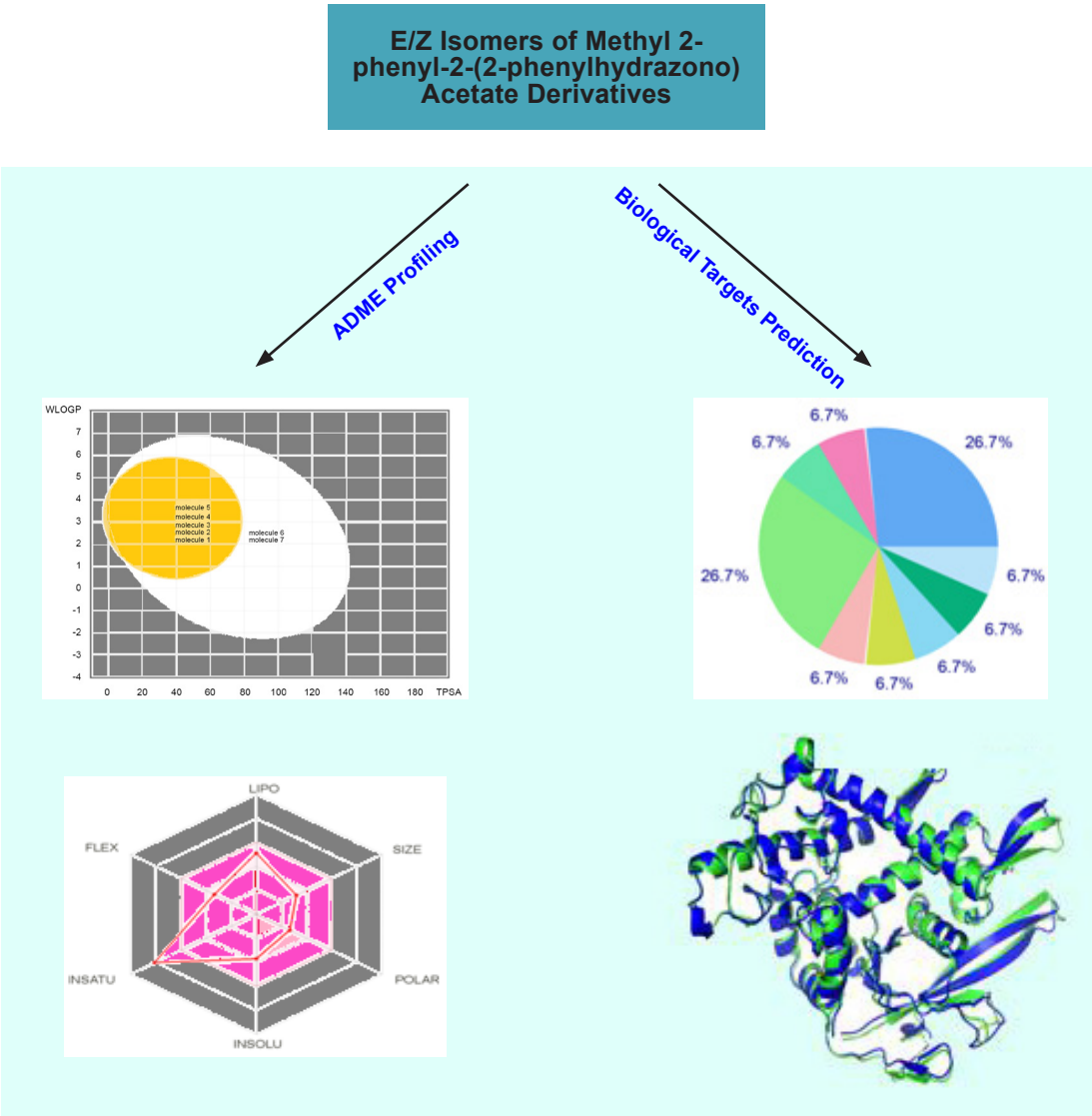


Figure 1. Demonstrating about the graphical depiction of ADME profiling, including membrane permeability, bioavailability radar, and new biological targets prediction of newly synthesized E/Z Isomers of Methyl 2-phenyl-2-(2-phenylhydrazono) acetate derivatives.

development. Current effective knowledge about the isomerism, played a significant role in the development of safer and potentially more effective drug alternatives, both for new and existing drugs. In the case of our screened E / Z isomers, they showed potential activity with varying frequencies against different target classes, for instance enzyme inhibitors, AG protein-coupled receptors, lyases, kinases, phosphodiesterases and protease enzyme inhibitors (Table 2).

3.1 Mapping of Bioavailability Radar of Newly Synthesized Products

Bioavailability radar display mapping of drugs provided a significant way to observe the drug-likeness (six descriptive properties) at a glance. These six descriptors, including: Lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), insaturation (INSATU), and flexibility (FLEX) represented the optimal range of every descriptor property. Those molecules existed within the pink region of radar were considered to possess good bioavailability property in the body (Table 3).

3.2 Brain or IntestinaL EstimateD permeation (Egan BOILED-Egg)

BOILED-Egg method was considered to be an accurate predictive model which was working efficiently by computing the lipophilicity and polarity behavior of small organic molecules. It was a plot b/w WLOGP and Total Polar Surface Area (TPSA), The compounds which existed in the egg yellow (egg yolk) region possesses blood-brain-barrier (BBB) permeation properties, while those compounds which exist in the egg white region possess high human intestinal absorption properties[25] (Figure 2).

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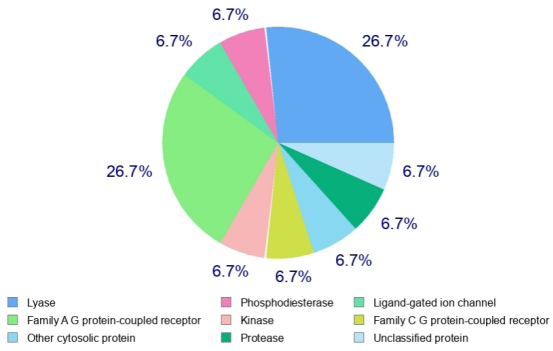
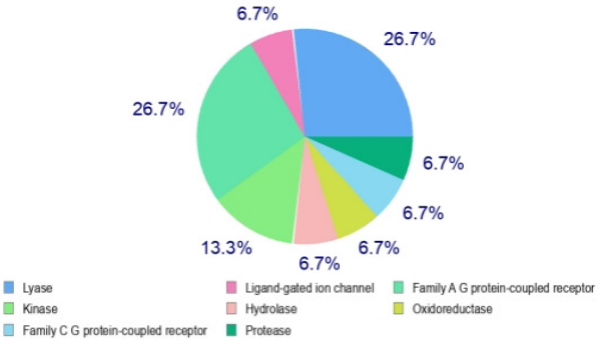
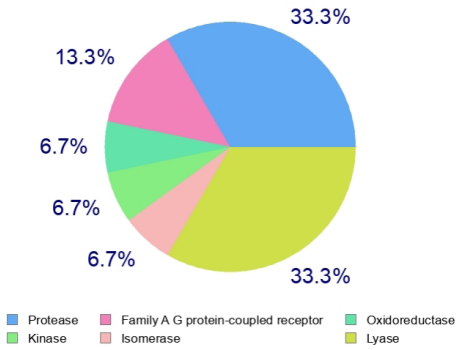
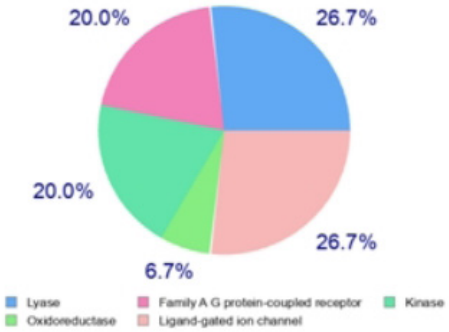
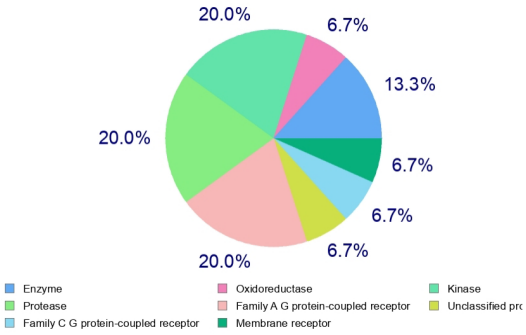
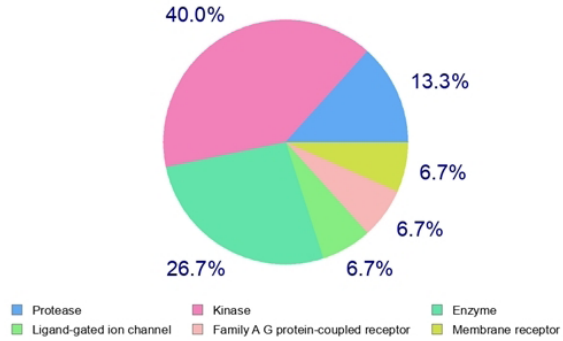
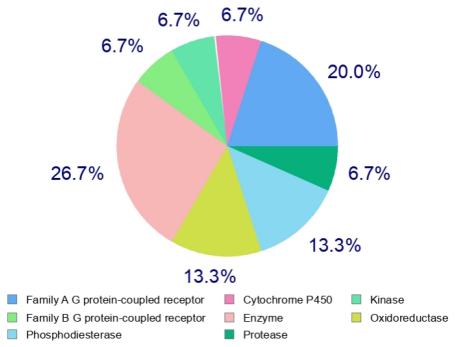
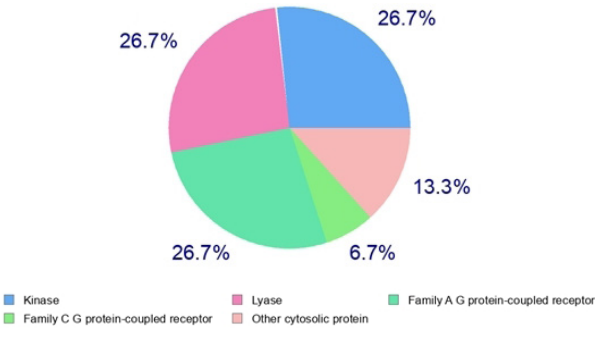
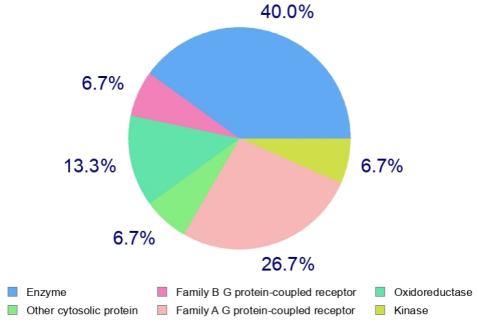
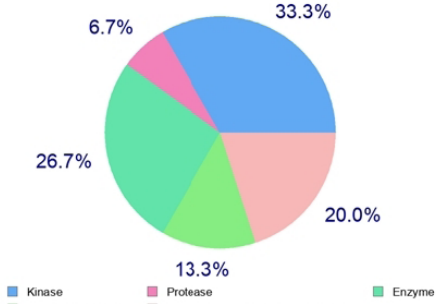
Table 2. Biological Targets Prediction of E/Z Isomers

S.No	Predicted Biological Activities of Z isomers	Predicted Biological Activities of E isomers
1		
2		
3		
4		
5		

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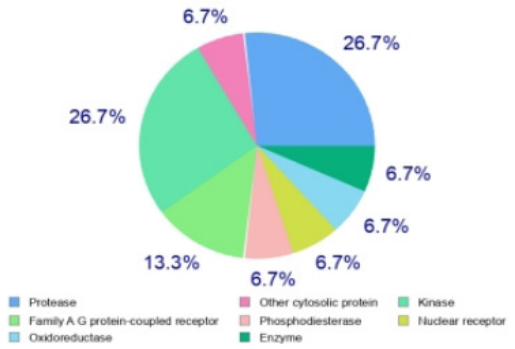

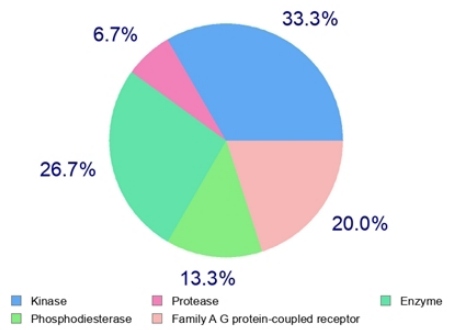

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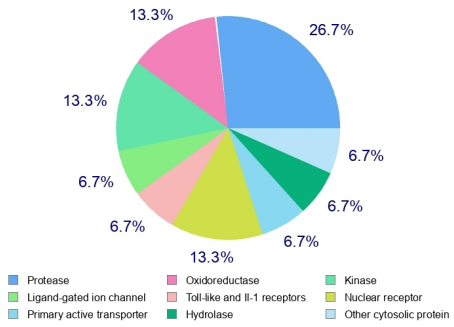

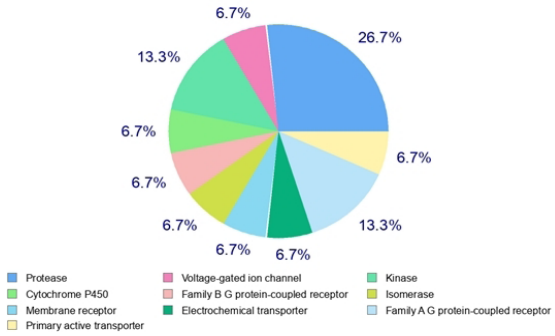

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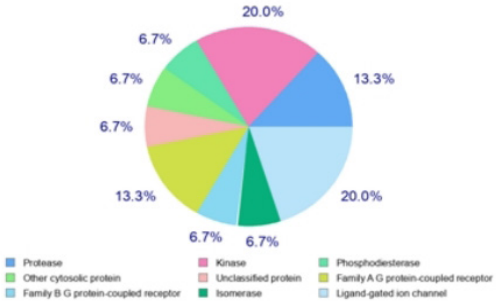
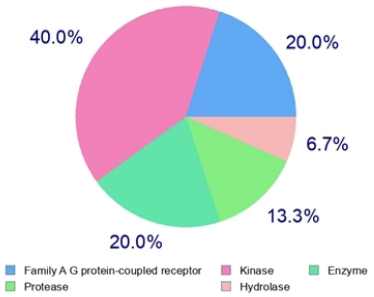




Notes: Table 2 Compounds 1Z, 1E, 4E, are predicted to be lyase inhibitor predominantly; Compounds 2Z, 3Z, 6Z, 7Z, 7E are predicted to be protease inhibitors, Compounds 3E,5E,6E, 8Z & 8E are predicted to be kinase inhibitors, Compounds 5Z, 6Z are family AG protein coupled receptor compound 4Z enzyme inhibitor and 6E is predicted to be phosphodiesterase inhibitor predominantly with highest percentage.

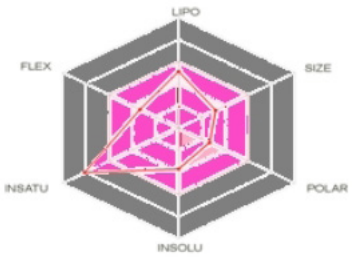
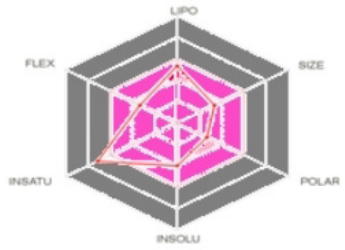
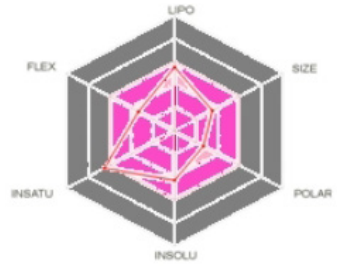
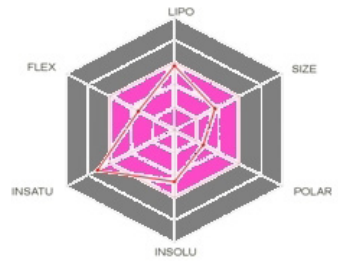
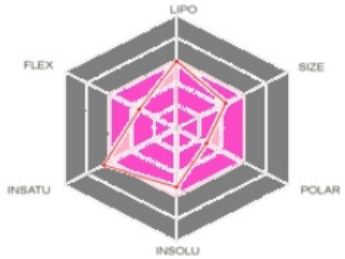
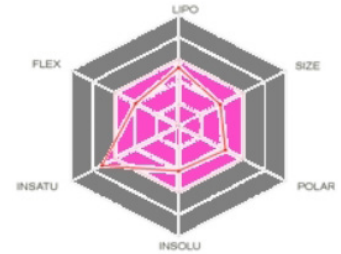
3.3 ADME Profiling by Using Swiss ADME Tools

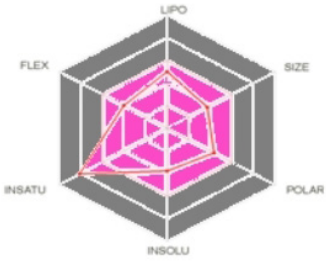
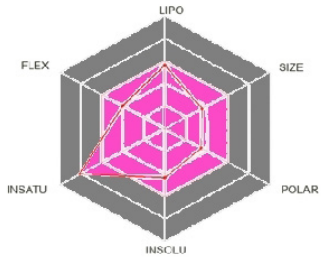
Profiling of Pharmacokinetic properties of newly synthesized compounds were computed against P-gp and isozymes of CYP450 through Swiss ADME tools. This efficiently predicted compounds which acted as a substrate or inhibitor of p-gp, and various CYP450 isozymes. In this design study, all the screened compounds were found not as a substrate of P-gp, while all the compounds showed inhibition against CYP1A2 & CYP2C19, three compounds showed no inhibition of CYP2C9, while four compounds showed inhibition of CYP2C9, however none of the compound showed inhibition of CYP2D6 & CYP3A4, isozymes were found to be an inhibitor of an isozyme of CYP450. Therefore, no possibility of DDI was predicted. However, all compounds showed high GI absorption and good BBB permeability except compound # 6-7 (no BBB permeation) (Table 4).

3.4 Lipinski ROF Drug Ability Criteria

Drug like properties of a molecule deals with various physicochemical descriptors as examined by Lipinski et al. For instance, molecular weight (MW) should not be greater than 500 a.m.u, the number of hydrogen bond donor (HBD) has to be less than 5, the number of hydrogen bond acceptor (HBA) should be less than 10, the octanol / water coefficient (log P) should be less than 5, the number of rotatable bonds should not exceed than 9, count of specific atom types, and total polar surface area have to be within the range (TPSA, 20-130 A^2) due to the presence of polar atoms specifically nitrogen "**N**" and sulphur "**S**" in the compounds. In our screened compounds, all the compounds successfully followed the ROF descriptors and showed an acceptable value of (TPSA, 20-130 A^2) (Table 5).

Table 3. Bioavailability Radar profiling

S.No	Bioavailability Radar	LIPO	SIZE	POLAR	INSOLU	INSATU	FLEX
1		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
2		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
3		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying at the border line	Lying in pink zone
4		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
5		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying at the border line	Lying in pink zone
6		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone

7		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone
8		Lying in pink zone	Lying in pink zone	Lying in pink zone	Lying in pink zone	Slightly exceeding the pink zone	Lying in pink zone

Notes: Table 3: All the compounds are showing excellent bioavailability radar properties for the descriptors (LIPO, SIZE, POLAR, INSOLU & FLEX,) while Compounds 1-2, 4, 6-8 are showing slight increase of INSATU descriptor.

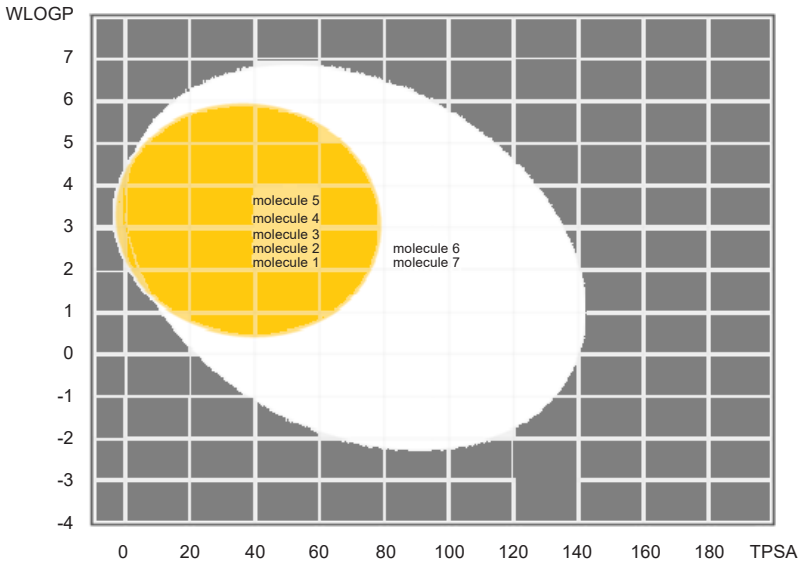


Figure 2. Molecules 1-5 and 8 are lying in egg yellow region so predicted to show BBB permeation while Molecules 6-7 are lying within egg white region so predicted to show GI permeation.

Table 4. ADME Profiling

S.No	GI Absorption	BBB Permeate	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
1	High	Yes	No	Yes	Yes	No	No	No
2	High	Yes	No	Yes	Yes	No	No	No
3	High	Yes	No	Yes	Yes	No	No	No
4	High	Yes	No	Yes	Yes	Yes	No	No
5	High	Yes	No	Yes	Yes	Yes	No	No
6	High	No	No	Yes	Yes	Yes	No	No
7	High	No	No	Yes	Yes	Yes	No	No
8	High	Yes	No	Yes	Yes	No	No	No

Notes: Table 4: Depicting pharmacokinetics and membrane permeability properties of all compounds, all the compounds showed high GI absorption, compounds (1-5 & 8) showed BBB permeation , while compounds (6&7) didn't show BBB permeation, none of the compounds founds to be Pgp substrate, all the compounds showed CYP1A2 isozyme inhibitors, none of the compounds showed CYP2D6 isozyme & CCYP3A4 isozyme Inhibitor, while compounds (4-7) showed CYP2C9 isozyme inhibition , and compounds (1-3 &8) showed no inhibition against CYP2C9 isozyme.

Table 5. Drugability Criteria

S.No	Mol. Formula	Mol.wt g/mol	Num. Rotatable Bonds	Num. HBA	Num. HBD	Log Po/w (iLOGP)	TPSA A^2
1	$C_{15}H_{14}N_2O_2$	254.28	5	3	1	2.45	50.69
2	$C_{16}H_{16}N_2O_2$	268.31	5	3	1	2.8	50.69
3	$C_{17}H_{18}N_2O_2$	282.34	5	3	1	2.96	50.69
4	$C_{16}H_{15}ClN_2O_2$	302.76	5	3	1	3.01	50.69
5	$C_{17}H_{17}BrN_2O_2$	361.23	5	3	1	3.31	50.69
6	$C_{16}H_{15}N_3O_4$	313.31	6	5	1	88.61	96.51
7	$C_{15}H_{13}N_3O_4$	299.28	6	5	1	83.64	96.51
8	C16H16N2O3	284.31	6	4	1	2.89	59.92

Notes: All the compounds are successfully following the drug ability criteria of ROF descriptors and showed an acceptable value of TPSA.

4 CONCLUSION

In conclusion, the results of this study smartly reveals that *in-silico* based studies were considered to provide robustness towards a rational drug design and development approach. Therefore, in this way, they assisted in creating ease in the further steps of drug design and drug discovery, saving time, chemicals, and manpower. Consequently, they facilitate the *in vitro* evaluation process.

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Conflicts of Interest

The authors declared no conflict of interest.

Author Contribution

Yousuf M conducted all computational based on ADME, pharmacokinetics profiling, bioavailability radar, membrane permeability study, new biological targets prediction study. Maharramov AM conducted synthesis of molecules. Shikhaliyev NG provided all lab facilities for the synthesis of molecules. Babazade AA provided chemicals for synthesis. Atakishiyeva GT helped in the synthesis of molecules. Zeynalli NR participated in spectral data characterization. Babayeva GV helped in data analysis. Ahmad I participated in the write up.

Abbreviation List

2D, 2 dimensional
3D, 3 dimensional
ADME, Absorption, distribution, metabolism and excretion
BBB, Blood brain barrier
BOILED-Egg, Brain or intestinal estimated
CYP450, Cytochrome P450
DDI, Drug-drug interaction
E / Z isomers, Entgegen / Zusammen
ES5D, Electro shape 5 dimensional
FLEX, Flexibility
FP2, Finger print
HBA, Hydrogen bond acceptor
HBD, Hydrogen bond donor
INSATU, Insaturation
LIPO, Lipophilicity
NSOLU, Insolubility
POLAR, Polarity
TPSA, Total polar surface area

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