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Raspberry ketone: an emerging molecule for treating depression and associated symptoms - molecular docking and pharmacokinetics studies

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***Abstract*---**After analyzing multiple pharmaceutical databases like ScienceDirect, PubMed, Google Scholar, and others, it was discovered that RK has yet to be linked to any anti-depressant action. The primary goal of this work was to use *in-silico* techniques to investigate

the anti-depressant capability of RK against three major targets (monoamine oxidases, MAOs; human serotonin transporter, SERT; and serotonin receptors, 5HTs). Moreover, prediction of drug-likeliness, bioavailability, and pharmacokinetics of RK has been done using online computational tools (SwissADME, SwissTargetPrediction, and SwissBioisostere). The*in silico* study indicated the emerging role of RK in the management of clinical depression. The pharmacokinetic studies, target prediction studies against 3 species, and biosisosteric-based studies also supported the possibilities of lead development. The study will open new avenues of application of this low-molecular-weight-ligand (LMWL) for the clinicians, chemists, and other scientific professionals in context to emerging depression challenges.

***Keywords*---**Depression, Raspberry ketone,*Insilico*, Molecular Docking, Pharmacokinetics, Bioisosteric

Introduction

Major depressive disorder (MDD) is a terrible disease that may be fatal in extreme circumstances. Spite of significant study, our understanding of the disease's pathogenesis, distinct analytical, and mechanisms involved is still restricted[1]. The monoamine hypotheses were formulated over than fifty years ago, solely on medical impacts and molecular mechanisms of antidepressant drugs, and recommend that depression pathophysiology is linked to deficits of the monoamine neurotransmitters serotonin (5-HT), dopamine (DA), and norepinephrine (NE)[2]. Nevertheless, it is clear that monoamine deficit only accounts for a portion of the pathogenesis, and other neurotransmitters such as acetylcholine, glutamate, and gamma-amino butyric acid (GABA) have even been linked to the pathogenesis of despair. Monoamine insufficiency might be a result rather than a causation of the illness[3]. Despite the availability of several antidepressant medications, effective treatment of MDD continues to be a challenge. Antidepressants include selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI), as well as older tricyclic antidepressants (TCA) and a bevvy of alternative medications[4]. Unfortunately, unwanted side symptoms and a prolonged commencement of activity are prevalent. Additionally, notwithstanding optimal care, involving treatments of numerous medicines either with or without concomitant psychotherapy, roughly half of depressed people gain complete recovery. As a result, new techniques to obtaining more powerful, cheaper, and quicker antidepressants are urgently needed[5].

The principal fragrance chemical of red raspberries is raspberry ketone (RK), a natural phenolic compound (Figure 1). RK is found in raspberries, cranberries, and blackberries, among other fruits. Coumaroyl-CoA is used to research has looked it. It may be obtained from the fruit, with 1–4 mg per kilogramme of raspberries. RK is commercially produced via a number of processes based on chemical precursors because to its limited natural availability. RK is a fruity odorant that is occasionally used in perfumery, cosmetics, and as a food ingredient. It's among the most costly natural flavoring ingredients on the market. The natural substance may be expensive, costing up to $20,000 per kilogram[6].

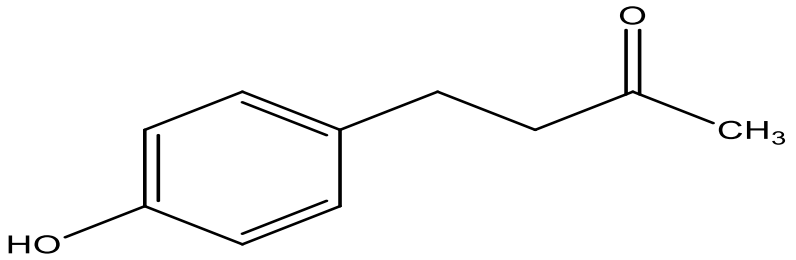


Figure 1. Structure of Raspberry Ketone.

Synthetic RK is less expensive, with various estimates from several dollars per pound to a quarter of the natural product's price. Despite the fact that weight-loss foods containing this chemical are advertised, there really is no clinical proof supporting this effect in people. The protracted efficacy of RK supplementation is unknown, particularly since human testing has been limited[7]. There are some worries regarding its safety since it is structurally linked to the stimulant synephrine. Cardiotoxic effects, as well as impacts on reproduction and development, are predicted by toxicological models. In addition, many nutritional products containing raspberry ketones include additional chemicals, such as caffeine, which may have harmful consequences. For tiny amounts that used flavour foods, the US Food and Drug Administration categorized RK as generally recognised as safe (GRAS)[8].

After analyzing multiple pharmaceutical databases like as ScienceDirect, PubMed, Google Scholar, and others, it was discovered that RK has yet to be linked to any anti-depressant action. The primary goal of this work was to use *in-silico* techniques to investigate the anti-depressant capability of RK against three major targets (monoamine oxidases, MAOs; human serotonin transporter, SERT; and serotonin receptors, 5HTs). Moreover, prediction of drug-likeliness, bioavailability and pharmacokinetic of RK have been done using online computational tools (SwissADME, SwissTargetPrediction, and SwissBioisostere).

Method

Preparation of Ligand

The structures were created using the Schrodinger Software suite 2021-2's 2D-sketcher module. For docking analysis, the Maestro environment version 12.8 was employed. The stereoisomers of these ligands were created using the LigPrep programme. Using the Epik ionizer, a maximum of four poses with correct protonation states were created for each ligand at a target pH of 7.0. The OPLS 2005 force field was utilized to construct tautomerized, desalted ligands while keeping the input files' requisite chiralities, resulting in an optimized low energy 3D ligand[9].

Preparation of Protein

The monoamine oxidase (MAO) targets; MAO-A (Crystal Structure of Human Monoamine Oxidase A with Harmine; PDB ID: 2Z5X), MAO-B (Crystal Structure of Human Monoamine Oxidase B; PDB ID: 1GOS); Human serotonin transporter (Cryo-EM structure of the wild-type human serotonin transporter complexed with paroxetine and 8B6 Fab; PDB ID: 6VRH); and Serotonin receptor (5HT) targets; $5HT_{1A}$ (Crystal structure of Aripiprazole-bound serotonin 1A (5-HT1A) receptor-Gi protein complex; PDB ID: 7E2Z), $5HT_{1B}$ (Crystal structure of 5-HT1B receptor in complex with methiothepin; PDB ID: 5V54), $5HT_{1D}$ (Crystal structure of Serotonin 1D (5-HT1D) receptor-Gi protein complex; PDB ID: 7E32), $5HT_{2C}$ (Crystal structure of 5-HT2C in complex with ritanserin; PDB ID: 6BQH), Peroxisome proliferator-activated receptor (PPAR)-α (Human PPAR alpha ligand binding domain in complex with a synthetic agonist APHM13; PDB ID:3VI8) and Cannabinoid Receptor (CB)-1(Crystal structure of the human CB1 in complex with agonist AM841; PDB ID:5XR8)was obtained from the RCSB Protein Data Bank. The protein structures were created using Maestro 9.1's Protein Preparation Wizard. The pre-processed and inspected structures were taken when developing the biological target. To get the right shape, the disulfide bonds, bond ordering, and formal charges were assigned using the Protein Preparation Wizard module of the Schrodinger Maestro 9.1. Co-factors, metal ions, water molecules in crystal formations beyond a distance of 5 A°, and the hetero group were all removed. The "impref utility" tool was used to optimize hydrogen atoms by keeping all heavy atoms in their original positions, while the "H-bond assignment" tool was used to optimize the hydrogen-bonding network. Molecular docking was used to define the receptor grids for the protein structure, allowing a variety of ligand poses to bind at the anticipated active site. Grids were built and placed at the ligand's centroid in such a way that they covered the whole ligand in a cubic box of defined measurement with the following characteristics: 1.00 Van der Waals scale factor and 0.25 charge cut off. The docking was done in XP mode, and only the energy-minimized postures were scored, which was expressed as a Glide score. The best-docked posture with the lowest Glide score value for each ligand was considered after the highest-scoring ligands were docked[10].

Induced-Fit Molecular Docking (IFD)

The structure-based drug design process is restarted after the target protein's structure is understood. The stiff receptor was docked with the low-energy ligands, and the fit into the active site was evaluated, as well as the predicted binding mechanism. In receptor-based computational techniques, the ligand interacting with the macromolecule protein (receptor) was represented using a molecular docking methodology. With low energy levels, IFD predicted that the ligand would have a good contact with the target. The method facilitates in the finding of low-free-energy conformations as well as the complete removal of steric conflicts. With 0.7 Van der Waals scaling for the receptor and 0.5 Van der Waals scaling for the ligand, side chains were eliminated, and a 0.18 RMSD value cut off, the maximum number of poses for each ligand remained at 20. The chemicals were ranked based on the information obtained, and a selection was tested for biological activity experimentally. The Glide Score was determined for each ligand[11].

Pharmacokinetics, Bioavailability, and Drug-likeliness studies

The SwissADME online tool was utilized to perform a pharmacokinetics prediction study, namely ADME, bioavailability, and ligand drug-likeness. The method calculates bioavailability radar based on six physicochemical properties: lipophilicity, size, polarity, insolubility, flexibility, and insaturation to determine drug-likeness. In the BOILED-Egg model inside the tool, ADME qualities such as passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) penetration, as well as substrate or non-substrate of the permeability glycoprotein (P-gp), were discovered positive or negative. 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 To forecast drug-likeness, the Lipinski (Pfizer) filter was utilized, which was the first rule-of-five to be incorporated in a tool. Based on many physicochemical properties, the bioavailability radar was utilized to predict oral bioavailability. The ranges of each parameter was mentioned as LIPO = lipophilicity as -0.7 < XLOGP3 < +5.0; SIZE = size as molecular weight 150gm/mol < MV < 500gm/mol; POLAR = polarity as 20Å² < TPSA (topological polar surface area) < 130Å²; 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[12].

Drug Target Identifications

SwissTargetPrediction is an online service that predicts the targets of bioactive small molecules. This website allows users to predict the targets of a small molecule. It uses a combination of 2D and 3D similarity measures to compare the query molecule to a library of 280,000 compounds active on more than 2000 targets in five different species. Understanding the molecular mechanisms behind bioactivity and predicting potential side effects or cross-reactivity necessitates identifying bioactive small molecule targets. Predictions have been produced in three different organisms (models), and mapping predictions by homology within and between species is doable for close paralogs and orthologs. RK inhibitory targets have been identified in the human (*Homo sapiens*), rat (*Rattus norvegicus*), and mouse (*Mus musculus*) models. Only the Top-15 molecular targets have been presented in the study and other molecular targets were neglected[13].

Core scaffold-based bioisosteric search

The SwissBioisostere database offers data on molecular replacements and how well they function in biochemical tests. Its purpose is to provide researchers working on drug development projects suggestions for bioisosteric alterations to their existing lead molecule, as well as access to data on specific chemical replacements. Bioisosteric substitutions of RK's core scaffold (benzene) were used to generate pyridine, pyrimidine, and 1,3,5-triazine. The factors that impact the biological goal and related activities were considered, and the resulting data was analyzed[14].

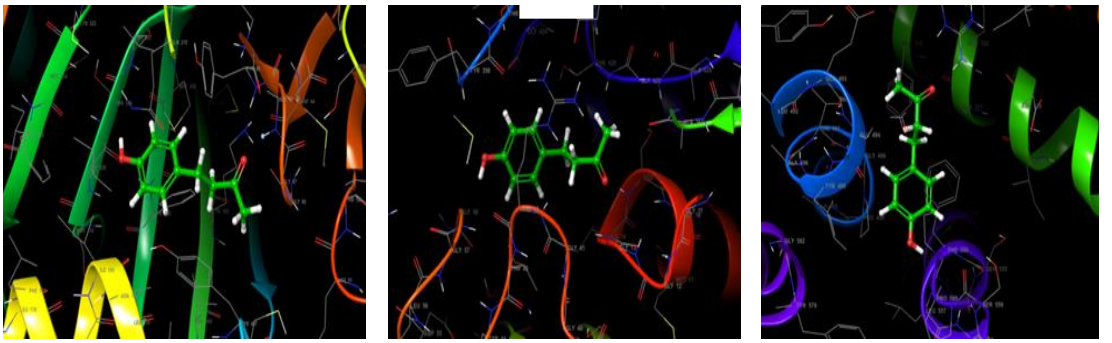
Results

Docking interaction analysis

The compound (RK) demonstrated interaction with one of the most antidepressant targets, monoamine oxide (MAO). The compound presented docking score of -7.206 Kcal/mol (against MAO_A) throughALA68, TYR69 amino acid residues (apart from PHE352 non-hydrogen interactions) and -5.650 Kcal/mol (against MAO_B) through SER15 residue, respectively. The compound also presented interaction with human serotonin transporter (SERT), one of the prominent antidepressant targets through ARG104, PHE556 amino acid residues with binding energy of -5.783 Kcal/mol (Figure 2). Also, the compound demonstrated interactions with all four serotonin receptors ($5HT_{1A}$, $5HT_{1B}$, $5HT_{1D}$, AND $5HT_{2C}$) through GLN408 and THR134 amino acid residues (along with several non-hydrogen interactions like GLY358, PHE331, TRP327, PHE328, and TRP324) with binding energy in the range -4.684 Kcal/mol to -7.463 Kcal/mol (Table 1).This LMWL presented a notable docking score of -6.315 Kcal/mol against PPAR-α throughTYR314, SER280 amino acid residues by forming hydrogen bonds.Similarly, against the cannabinoid receptor-1 (CB_1), this small molecule demonstrated inhibitory perspective with moderate docking score of -4.984 Kcal/mol by forming hydrogen bond with amino acid residue TYR405 as well as π-π stacking through TRP403 residue.

Overall, it was observed from the docking score as well as the docking poses that RK has immense perspectives to act as anti-depressant activity by promisingly inhibiting the molecular targets like MAO_A, $5HT_{1B}$, $5HT_{2C}$, and PPAR-α.

a. b. c.



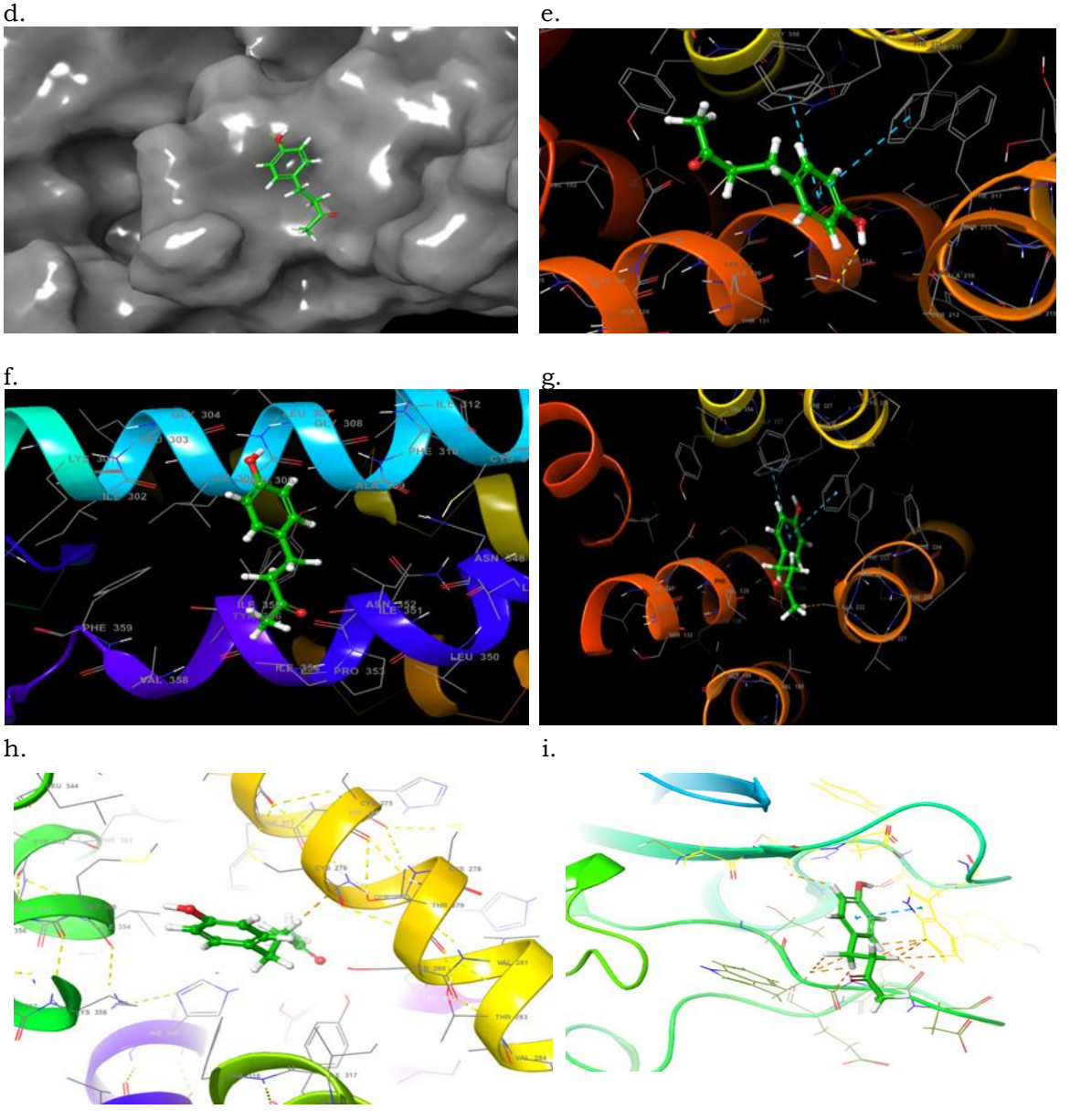


Figure 2. Docking poses of Raspberry ketone: [A] MAO_A, [B] MAO_B, [C] SERT, [D] $5HT_{1A}$, [E] $5HT_{1B}$, [F]$5HT_{1D}$, [G] $5HT_{2C}$, [H] PPAR-α, and [I] CB_1.

Table 1
Molecular docking studies.

Protein	Specific protein	Binding Energy (kcal/mol)	No. of H Bonds	Interacting amino acid residues	Non-hydrogen interactions
Monoamine oxidase (MAO)	MAO_A	-7.206	2	ALA68, TYR69	PHE352
	MAO_B	-5.650	1	SER15	-
Human serotonin transporter (SERT)	SERT	-5.783	2	ARG104, PHE556	PHE556
Serotonin (5HT)	$5HT_{1A}$	-4.747	1	GLN408	-
	$5HT_{1B}$	-6.665	-	-	GLY358, PHE331
	$5HT_{1D}$	-4.684	1	THR134	PHE331, TRP327
	$5HT_{2C}$	-7.463	-	-	PHE328, TRP324
Peroxisome Proliferator Activated Receptor (PPAR)	PPAR-α	-6.315	2	TYR314, SER280	-
Cannabinoid Receptor (CB)	CB-1	-4.984	1	TYR405	TRP403

In silico Pharmacokinetics, Bioavailability, and Drug-likeliness studies

Table 2 describes the predictive values for pharmacokinetics, bioavailability, and drug-likeness data on RK. The compound had a high rate of GIT absorption. The LogP value suggested good blood-brain permeability, whereas a greater negative value indicated decreased skin permeation. Except for CYP1A2 inhibitors, the compound did not show to be a p-glycoprotein substrate or a substrate for CYP2C19, CYP2C9, CYP2D6, or CYP3A4. A modest bioavailability score was achieved for the prediction of bioavailability and drug-likeness (satisfying the Lipinski's rule of 5). RK was found to have very high water solubility.

Table 2
Pharmacokinetics, bioavailability, and drug-likeness properties of Raspberry ketone.

Properties	Data
Physicochemical Properties	
Formula	$C_{10}H_{12}O_2$
Molecular weight	164.20 g/mol

Number of heavy atoms	12
Number of aromatic heavy atoms	6
Fraction Csp3	0.30
Number of rotatable bonds	3
Number of H-bond acceptors	2
Number of H-bond donors	1
Molar Refractivity	48.05
TPSA	37.30 A^2
Lipophilicity	
Log Po/w (iLOGP)	1.72
Log Po/w (XLOGP3)	1.48
Log Po/w (WLOGP)	1.91
Log Po/w (MLOGP)	1.74
Log Po/w (SILICOS-IT)	2.36
Consensus Log Po/w	1.84
Water Solubility	
Log S (ESOL)	-1.96
Solubility	1.79e+00 mg/ml ; 1.09e-02 mol/l
Class	Very soluble
Log S (Ali)	-1.87
Solubility	2.21e+00 mg/ml ; 1.35e-02 mol/l
Class	Very soluble
Log S (SILICOS-IT)	-2.96
Solubility	1.81e-01 mg/ml ; 1.10e-03 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log Kp (skin permeation)	-6.25 cm/s
Drug-likeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: MW<200
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert

Lead-likeness	No; 1 violation: MW<250
Synthetic accessibility	1.02

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp3 as 0.30, FLEX as per number of rotable bond 1, INSOLU Logs (ESOL) as -1.96 (soluble), SIZE as molecular weight (g/mol) of 164.20 g/mol, POLAR as TPSA (Å²) 37.30, and LIPO as XLOGP3 value of 1.48 (Figure 3).

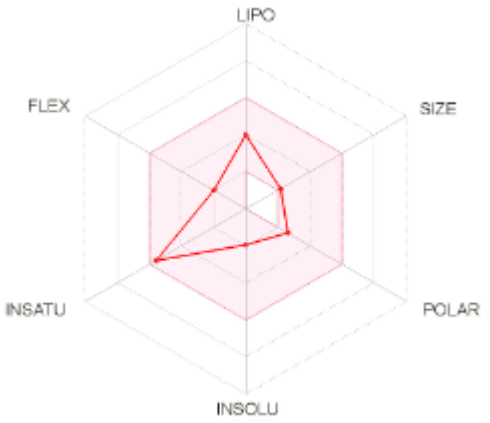


Figure 3. Bioavailability radar plot.

In the BOILED-Egg model (Figure 4), it was discovered that RK has the capacity to penetrate the blood-brain barrier and has a high gastrointestinal absorption penetration power. In the predicted model, the molecule was discovered to be PGP negative as a non-substrate. The Brain OrIntestinaLEstimateD permeation method (BOILED-Egg) has previously been suggested as a reliable predictive model, which aids in the computational prediction of small molecule lipophilicity and polarity. According to the bioavailability radar and the BOILED-Egg depiction, RK might be a good medication candidate. Furthermore, *in vitro* and *in vivo* functional and pharmacological assays should be used to confirm these prognostic findings for the treatment of depression.

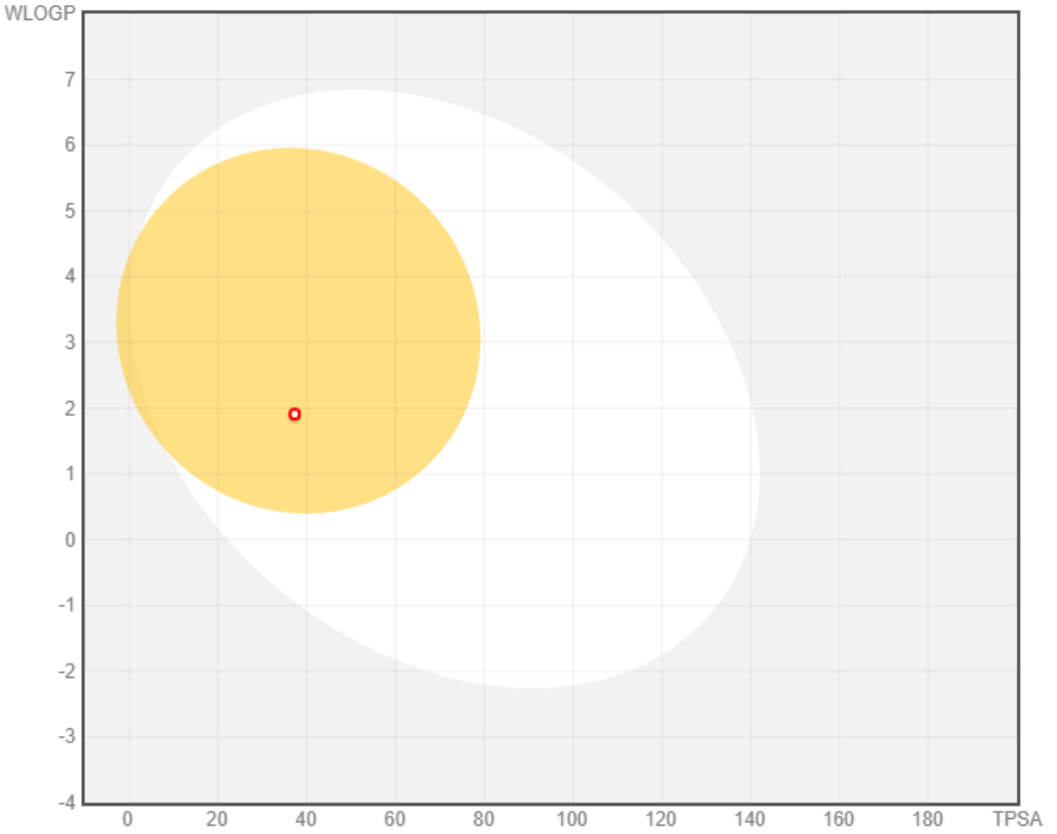


Figure 4. BOILED-Egg representation.

Drug Target Identifications

As the study is focused on drug repurposing, it remains crucial to determine the plausible therapeutic targets against which RK can inhibit them with micromolar concentrations, ideally.The human (*Homo sapiens*) (Figure 5A), rat (*Rattus norvegicus*) (Figure 5B), and mouse (*Mus musculus*) (Figure 5C) models revealed the inhibitory perspectives of RK against several targets like nuclear receptor, hydrolase, enzyme, oxidoreductase, Family A G protein-coupled receptor, transferase, ligand-gated ion channel, lyase, cytochrome P_{450}, electrochemical transporter, other cytosolic protein, secreted protein, etc. The predicted results strongly supported the basis of repurposing this small molecule for possible applications against clinical depression by revealing the possibilities of drug interactions with multiple targets (specifically enzymes and receptors). The prediction holds true for choosing 5HT-receptors and MAO-enzymes.

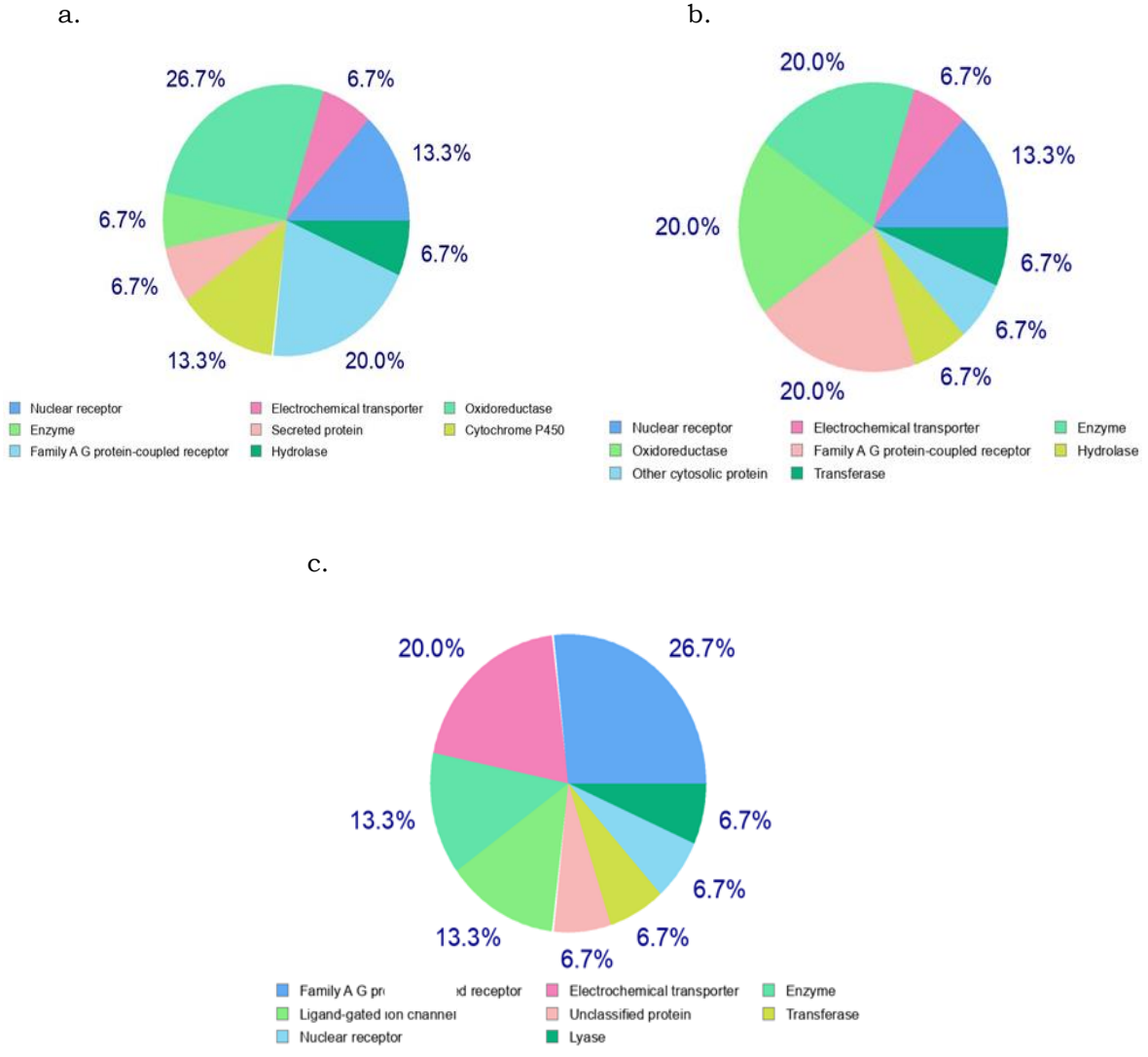


Figure 5. Drug Target Identifications: [A] *Homo sapiens*, [B]*Rattus norvegicus*, and [C] *Mus musculus*.

Bioisosteric studies

The bioisosteric study of the core scaffold successfully revealed several imperative data. The strategy of selectively replacing the central scaffold (benzene) of RK withpyridine, pyrimidine,and 1,3,5-triazine was taken into account for determining the target interaction perspective and structure-activity relationship(s) (Figure 5). It was observed from the obtained result that the number of interacting targets escalated when the benzene scaffold was replaced, in the following order: pyridine (32) >pyrimidine (12) >1,3,5-triazine (1). Whenthe

benzene scaffold was replaced with pyridine scaffold, the biological activity increases when aromatic ring is replaced at attachment point, whereas the activity remains similar when the aliphatic ring is replaced at attachment point (Figure 6A). Whenthe benzene scaffold was replaced with pyrimidine, the activity decreases when aromatic ring is replaced at attachment point, whereas the activity increases when the aliphatic ring is replaced at attachment point (Figure 6B). When the benzene scaffold was replaced with 1,3,5-triazine, the activity remains unchanged when aromatic ring and aliphatic linker are replaced at attachment points (Figure 6C). The changes in log P-value (lipophilicity), tPSA, and molecular weight and its influence were found to be negligible to influential under all the three conditions.

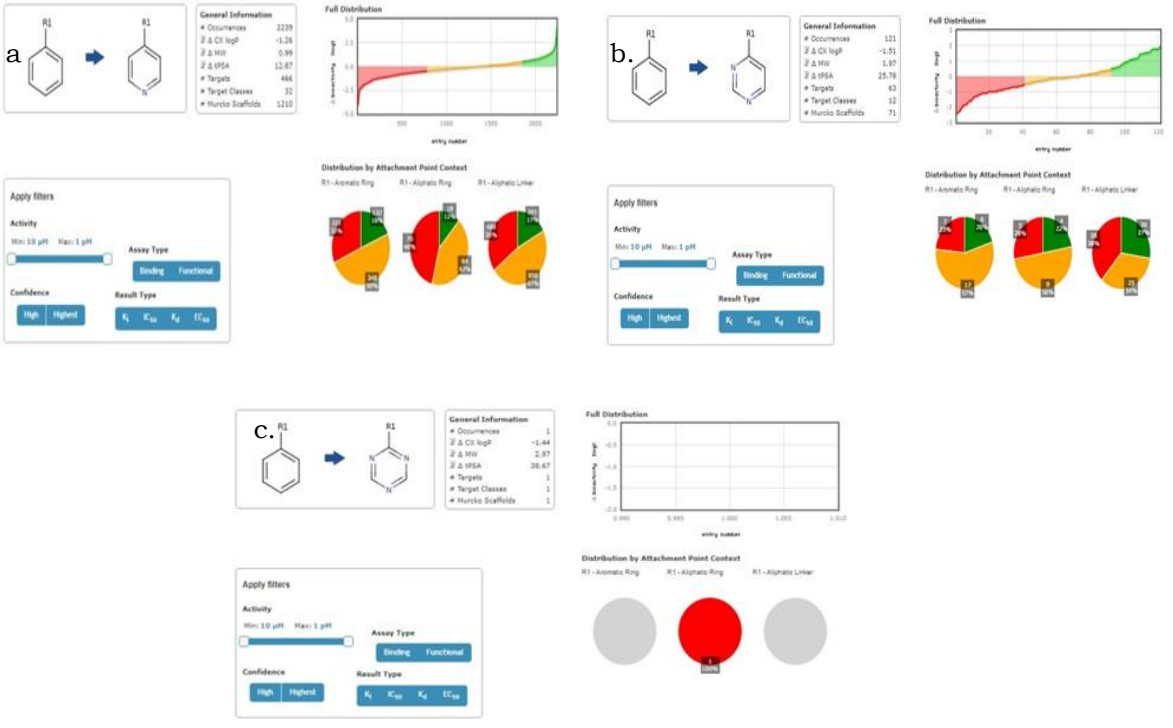


Figure 6. Bioisosteric replacement of benzene group with heterocyclic groups: [A] Pyridine, [B]Pyrimidine, and [C] 1,3,5-triazine

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