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MOLECULAR DOCKING STUDIES OF FEW 2, 3, 5-SUBSTITUTED INDOLE DERIVATIVES FOR GLUCOKINASE ACTIVATION

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ABSTRACT

Diabetes is a major global health issue, affecting public health and economic development. While some countries have seen a drop in new cases, diabetes has become more common in many other places[1-3]. In 2017, the International Diabetes Federation (IDF) estimated that 451 million adults had diabetes, and this number could rise to 693 million by 2045 without effective prevention. Both type 1 and type 2 diabetes are also increasing among children and teens, with over one million under 20 now having type 1 diabetes[4]. The prevalence of both type 1 and type 2 diabetes among children and adolescents has also increased, and the estimates of children and adolescents below age 20 with Type 1 Diabetes now exceed one million[5]. Glucokinase (GK or hexokinase IV) as the glucose sensor plays a pivotal role in glucose homeostasis[1]. Glucokinase (GK) is important for managing blood sugar levels. In the pancreas, it helps control insulin release, and in the liver, it helps store sugar and clear it from the blood after eating. Roche's early success in activating GK suggested it could be a new treatment for type 2 diabetes, leading to a lot of interest in GK activators (GKAs). However, research on how GKAs work has been limited. Early failures in developing GKAs have led researchers to revisit basic questions about GK activation to find long-term benefits for type 2 diabetes patients[3].

KEYWORDS

Diabetes, Glucokinase, Hexokinase, Glucose homeostasis, Activator-glucokinase complex and Glucokinase activator.

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INTRODUCTON

Diabetes is one of the top 10 global causes of death. Along with heart disease, cancer, and lung disease, it accounts for over 80% of early deaths from noncommunicable diseases (NCDs)[6].

People with diabetes have a 2-3 times higher risk of dying from any cause[7]. Diabetes is linked to higher death rates from infections, heart disease, stroke, kidney disease, liver disease, and cancer[8,9]. Despite

improvements in public health and longer life spans, diabetes is the second largest factor reducing global health-adjusted life expectancy[10].

The global impact of diabetes has grown a lot in recent decades and will keep rising. The Global Burden of Disease study (GBD) uses various data sources, like hospital records and death certificates, to estimate diabetes rates, deaths, and disability-adjusted life years (DALYs) worldwide[11].

DALYs measure total health loss by combining years lost to early death and years lived with disability. This data helps the Global Burden of Disease study (GBD) track diabetes' impact over time and plan health services. The study looks at trends in diabetes by type, year, socioeconomic status, and risk factors to help prevent and control non-communicable diseases (NCDs) by 2025[12-13]. A study found that people with hypertension and diabetes are more likely to have severe COVID-19, posing a new challenge for health professionals worldwide[14].

Diabetes Mellitus in summary

Diabetes was first noted by the Egyptians for causing weight loss and frequent urination. The Greek physician Aertaeus named it Diabetes mellitus, meaning "to pass through" (diabetes) and "honey" (mellitus) due to the sweetness of the urine. Diabetes is a major cause of long-term illness and early death, killing more people annually than HIV-AIDS, with nearly one death every 10 seconds. Industrialization and rising obesity have turned diabetes into a global epidemic. Measuring its prevalence is tough because data collection methods vary and many cases (about 50%) go undiagnosed. Changes in life expectancy and healthcare have contributed to the rise in diabetes, especially in urban areas. This will increase healthcare burdens worldwide, as diabetes leads to both short-term and long-term complications and early death.

Novel and emerging diabetes mellitus drug therapies (GKA) for treating type 2 diabetes patients

Glucokinase (GK or hexokinase IV) is crucial for maintaining blood sugar balance as it acts as a glucose sensor [15]. In pancreatic β-cells, glucokinase (GK) helps control insulin release based on blood sugar levels. In the liver, it aids in storing glycogen and clearing glucose after meals. It also helps regulate glucagon secretion from pancreatic α-cells. Since insulin secretion is impaired in Type 2 Diabetes (T2D), it was thought that drugs activating GK could boost insulin release. In the 1990s, developing GK activators (GKAs) for T2D was a new idea. Roche's early success showed that GK activation could be a new treatment for T2D, sparking interest in GKAs. However, research on how GKAs work has been limited. Early failures led researchers to revisit basic questions about GK activation for long-term benefits in T2D. The recent success of Dorzagliatin in Chinese T2D patients has renewed hope for GK as a T2D treatment, showing promise for repairing defects in the pancreas and liver. Pharmacological activation of GK is expected to be highly effective for treating T2D and possibly Type 1 Diabetes (T1D). Early results with GKAs support this potential.

METHODS AND MATERIAL

Co-Crystallization of the Human Glucokinase enzyme

The RCSB Protein Data Bank entry 1V4S (https://www.rcsb.org/structure/1V4S) features the computational structure of Human Glucokinase (GK). This protein was bound at its allosteric site by 5-(1-Methyl-1H-imidazol-2-yl-thio)-2-amino-4-fluoro-N-(thiazol-2-yl) benzamide, ATP and Mg++. The protein was devoid of its native ligand, refined and prepared for docking studies using Discovery Studio Visualizer 2019.

Approximately 700-800 protein structures, co-crystallized with Mg++ ion, ATP, and various ligands (such as RO-28-1675, Piragliatin, or other GKAs), were downloaded from the RCSB-PDB site. These structures, representing the metallo-enzyme with kinase activity, GK, were analyzed using the Ramachandran Plot. This analysis provided comprehensive insights into the suitability of amino acid residue orientations in the computed protein co-crystallized structures, aiding in the selection of one for docking studies. Consequently, co-crystals of 5-(1-methyl-1H-imidazol-2-ylthio)-2-amino-4-fluoro-N-(thiazol-2-yl) benzamide of GK

were obtained from the PDB site. The structures of the designed ligands were created using the ChemSketch freeware module from ACD Labs and are represented by the Markush formula in Table 1 listed in the Results and discussion section.

Docking studies

In the CADD software, the selected structures, used as ligands along with the standard RO-28-1675, were docked into the allosteric site of the enzyme's crystal structure to examine their interactions. This was done to identify the designed structures with suitable binding interactions for further studies. A grid with a 5 Å radius was set around the amino acids forming the enzyme's allosteric site. The structures were docked with a Root Mean Square Deviation (RMSD) tolerance of 2.0. Binding energies (G scores) were obtained, selecting the value with the lowest RMSD. For each docking study, the three interaction poses with the lowest G scores were considered for final selection. The docking studies were conducted using the protein interaction suite of Autodock 1.5.6 for 250 ligands. The results were then imported into Discovery Studio for visualization. Some ligands showed acceptable G-scores (-7.0127 to -7.1323), close to the G-score of the standard ligand, RO-28-1675 (-8.9124). Figure No.1 of the results and discussion section illustrates the docked pose of GK bound to one of the designed molecules in its allosteric cavity.

Screening through Molecular Docking

Figure No.2 of the results and discussion section shows a comprehensive view of all ligands actively docked in the allosteric site of the GK enzyme. The figure illustrates the ligand positioned within the allosteric site of the GK enzyme. The images were generated using the PyRx virtual screening tool. All the designed derivatives were docked, and only those showing expected interactions with the amino acid residues TYR215, TYR210, ARG63 and MET205 were selected. These chosen ligands were then evaluated for compliance with Lipinski's Rule of Five to optimize the study further.

Structures of the designed ligands that shows good docking score

Table No.2 of the results and discussion section presents the results of applying Lipinski's Rule of Five.

SWISS ADME Study

Free online software tools such as SwissADME, Schrodinger 2020, AutoDOCK (ver. 1.5.7) and Discovery Studio 2021 were used to assist in ADME and docking studies, examining the interaction between ligands and the selected protein structure. The toxicity of the designed structures was assessed by analyzing the SMILES formulas of quinazoline derivatives. This step helped eliminate potential toxicity concerns that could arise if these structures were synthesized in the laboratory. Parameters such as aqueous solubility (Log S), membrane permeability (Log Kp), synthetic accessibility scores (SA), percentage absorption, probable pharmacokinetics, and drug-likeness properties of the designed molecules were evaluated. According to Lipinski's Rule of Five, these parameters help summarize the molecular properties of the designed structures, aiming to develop them as potential drug candidates with predicted therapeutic, pharmacokinetic, and toxicity profiles. The rule suggests considering molecules with molecular weights $\leq$ 500, hydrogen bond donors $\leq$ 5, hydrogen bond acceptors $\leq$ 10, and rotatable bonds $\leq$ 10 for further studies. Consequently, significant drug-like molecules were shortlisted and further studied. The data obtained from SwissADME studies, including the amino acid residues interacting with the docked ligands, their types of interactions, and the number of hydrogen bonds formed, are presented in Table No.2. Followed by the 2D and 3D poses of docked ligands in Table No.3.

RESULTS AND DISCUSSION

Certain 2, 3, 5-trisubstituted indole derivatives were designed as ligands to interact with the amino acid residues located allosterically in GK enzyme and keep it in its active mode. These are tabulated below and are the structures that were docked with R, R1 and R_2 groups listed in the Table No.1.

Out of a total of 232 designed ligands and studied for ADME properties, seven were selected for performing docking analysis and based on favorable interactions 4 ligands were promoted to wet-lab synthesis.

Table No.1: R, R1 and R2 groups of the pharmacophore that has been synthesized

S.No	Compound Code	R	R1	R2	HBD	HBA	PKa
1	Ai	2-methyl-1, 3-thiazol-5-yl) carbamoyl	-H	$-CH_2COOH$	3	6	5.32
2	Aiii	2-methyl-1, 3-thiazol-5-yl) carbamoyl	$-NHCOCH_3$	-H	3	3	2.43
3	Aiv	2-methyl-1, 3-thiazol-5-yl) carbamoyl	-NHCOCH3	$-CH_2COOH$	5	7	2.19
4	Avi	2-methyl-1, 3-thiazol-5-yl) amino	$-NHCOCH_3$	-H	3	6	1.62
5	Aix	2-methyl-1, 3-thiazol-5-yl) amino	$-CH_2COOH$	-H	3	8	1.15
6	Axii	2-methyl-1, 3-thiazol-5-yl) amino	-OH	$-CH_2CH_2CH_3$	2	6	1.31
7	Axiv	2-methyl-1, 3-thiazol-5-yl) amino	H	-H	3	2	2.27

Table No.2: The results of the application of Lipinski Rule of Five

S.No	Code	pKa	Mol. Wt.	HBD	HBA	Lipinski	BBM
1	Ia	Log Po/w (iLOGP) 1.93 Log Po/w (XLOGP3) 2.69 Log Po/w (WLOGP) 3.01 Log Po/w (MLOGP) 0.74 Log Po/w (SILICOS-IT) 3.77 Consensus Log Po/w 2.43	287.34g/mol	3	3	Yes	No
2	Ib	Log Po/w (iLOGP) 1.11 Log Po/w (XLOGP3) 1.11 Log Po/w (WLOGP) 1.01 Log Po/w (MLOGP) 0.21 Log Po/w (SILICOS-IT) 3.77 Consensus Log Po/w 5.32	301.36g/mol	3	6	Yes	No
3	Ic	Log Po/w (iLOGP) 0. 16 Log Po/w (XLOGP3) 1.67 Log Po/w (WLOGP) 1.09 Log Po/w (MLOGP) 0.18 Log Po/w (SILICOS-IT 1.08 Consensus Log Po/w 1.31	315.391g/mol	2	6	Yes	yes
4	Id	Log Po/w (iLOGP) 1.66 Log Po/w (XLOGP3) 0.43 Log Po/w (WLOGP) 1.21 Log Po/w (MLOGP) 0.61 Log Po/w (SILICOS-IT) 2. 41 Consensus Log Po/w 1.62	329.41g/mol	3	6	Yes	No
5	IIa	Log Po/w (iLOGP) 1.84	286.35g/mol	3	2	Yes	No

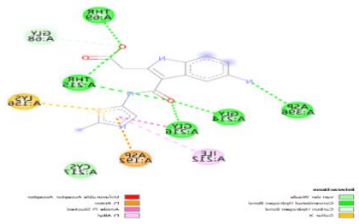
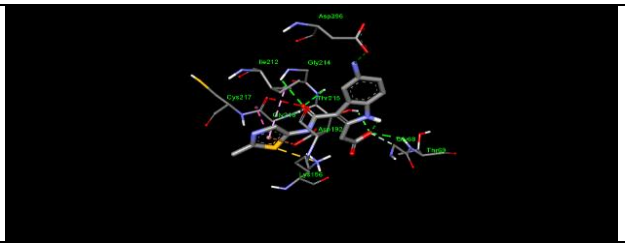
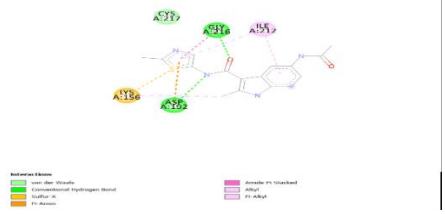
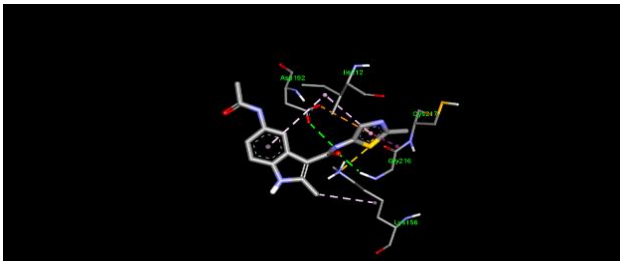
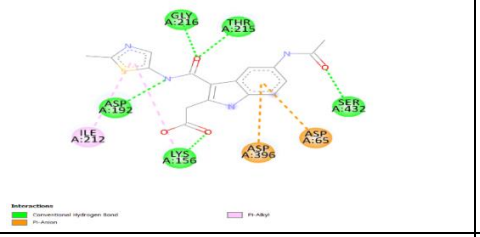
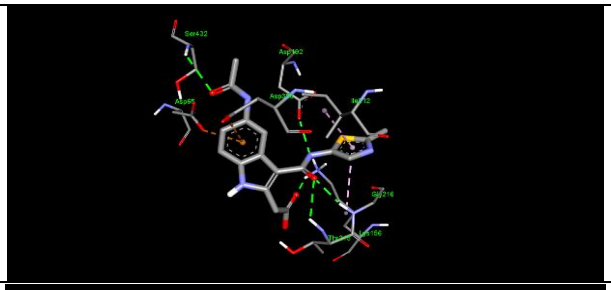
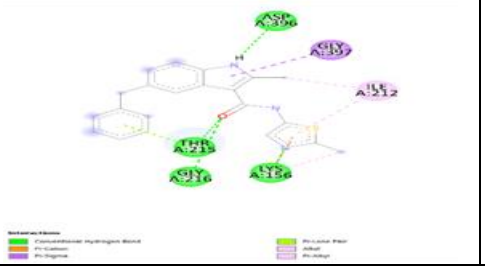
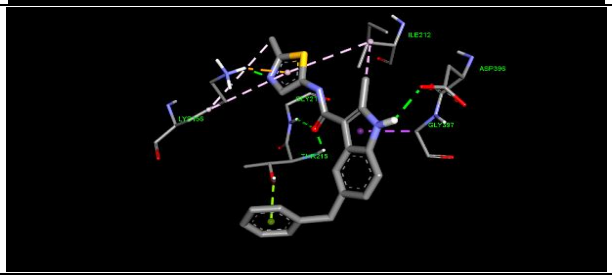
		Log Po/w (XLOGP3) 2.37 Log Po/w (WLOGP) 2.89 Log Po/w (MLOGP) 0.74 Log Po/w (SILICOS-IT) 3.53 Consensus Log Po/w 2.27					
6	IIb	Log Po/w (iLOGP) 1.22 Log Po/w (XLOGP3) 2.27 Log Po/w (WLOGP) 2.80 Log Po/w (MLOGP) 0.40 Log Po/w (SILICOS-IT) 3.43 Consensus Log Po/w 2.19	300.38g/mol	5	7	Yes	No
7	IIc	Log Po/w (iLOGP) 1.11 Log Po/w (XLOGP3) 1.11 Log Po/w (MLOGP) 0.18 Log Po/w (SILICOS-IT) 1.08 Consensus Log Po/w 1.15	314.40	3	8	Yes	Yes
8	IId	Log Po/w (iLOGP) 1.66 Log Po/w (WLOGP) 2.89 Log Po/w (MLOGP) 0.40 Log Po/w (SILICOS-IT) 3.43 Consensus Log Po/w 2.19	328.4	3	6	Yes	Yes
9	IIIa	Log Po/w (iLOGP) 0.71 Log Po/w (XLOGP3) 1.47 Log Po/w (WLOGP) 2.21 Log Po/w (MLOGP) 0.12 Log Po/w (SILICOS-IT) 2.84 Consensus Log Po/w 1.47	330.36g/mol	4	4	Yes	No
10	IIIb	Log Po/w (iLOGP) 0.877 Log Po/w (XLOGP3) 3.14 Log Po/w (WLOGP) 3.10 Log Po/w (MLOGP) 0.66 Log Po/w (SILICOS-IT) 3.45 Consensus Log Po/w 2.67	344.38g/mol	5	7	Yes	No
11	IIIc	Log Po/w (iLOGP) 0.81 Log Po/w (XLOGP3) 2.54 Log Po/w (WLOGP) 3.77 Log Po/w (MLOGP) 0.45 Log Po/w (SILICOS-IT) 6.23 Consensus Log Po/w 3.87	358.41g/mol	7	8	Yes	No
12	IIId	Log Po/w (iLOGP) 0.81 Log Po/w (XLOGP3) 2.54 Log Po/w (WLOGP) 3.77 Log Po/w (MLOGP) 0.45 Log Po/w (SILICOS-IT) 4.56 Consensus Log Po/w 2.67	373.45g/mol	8	8	Yes	No
13	IVa	Log $P_{o/w}$ (iLOGP) 2.25 Log $P_{o/w}$ (XLOGP3) 2.23	328.39g/mol	3	3	YES	No

		Log $P_{o/w}$ (WLOGP) 3.07 Log $P_{o/w}$ (MLOGP) 0.77 Log $P_{o/w}$ (SILICOS-IT) 3.89 Consensus Log $P_{o/w}$ 2.44					
14	Va	Log Po/w (iLOGP) 0.99 Log Po/w (XLOGP3) 1.32 Log Po/w (WLOGP) 2.39 Log Po/w (MLOGP) 0.16 Log Po/w (SILICOS-IT) 3.23 Consensus Log Po/w 1.62	372.40g/mol	5	4	YES	No
15	VIa	Log Po/w (iLOGP) 2.97 Log Po/w (XLOGP3) 4.97 Log Po/w (WLOGP) 4.89 Log Po/w (MLOGP) 2.75 Log Po/w (SILICOS-IT) 6.21 Consensus Log Po/w 4.36	361.46g/mol	2	2	YES	No
16	VIIa	Log Po/w (iLOGP) 2.45 Log Po/w (XLOGP3) 4.07 Log Po/w (WLOGP) 4.21 Log Po/w (MLOGP) 2.07 Log Po/w (SILICOS-IT) 5.53 Consensus Log Po/w 3.67	405.47g/mol	3	4	YES	No
17	VIIIa	Log Po/w (iLOGP) 2.53 Log Po/w (XLOGP3) 3.68 Log Po/w (WLOGP) 3.96 Log Po/w (MLOGP) 1.83 Log Po/w (SILICOS-IT) 4.88 Consensus Log Po/w 3.38	05.78g/mol	2	2	YES	No
18	XIa	Log Po/w (iLOGP) 1.55 Log Po/w (XLOGP3) 2.77 Log Po/w (WLOGP) 3.27 Log Po/w (MLOGP) 1.17 Log Po/w (SILICOS-IT) 4.20 Consensus Log Po/w 2.59	349.79g/mol	3	4	YES	No
19	Xa	Log Po/w (iLOGP) 2.34 Log Po/w (XLOGP3) 3.15 Log Po/w (WLOGP) 3.86 Log Po/w (MLOGP) 1.70 Log Po/w (SILICOS-IT) 4.67 Consensus Log Po/w 3.14	289.33g/mol	2	3	Yes	No
20	XIa	Log Po/w (iLOGP) 1.23 Log Po/w (XLOGP3) 2.25 Log Po/w (WLOGP) 3.18 Log Po/w (MLOGP) 1.05 Log Po/w (SILICOS-IT) 3.98 Consensus Log Po/w 2.34	333.34g/mol	3	5	Yes	No
21	XIIa	Log Po/w (iLOGP) 2.28	339.34g/mol	2	5	Yes	No

		Log Po/w (XLOGP3) 3.93 Log Po/w (WLOGP) 5.47 Log Po/w (MLOGP) 2.20 Log Po/w (SILICOS-IT) 5.30 Consensus Log Po/w 3.84					
22	XIIIa	Log Po/w (iLOGP) 1.63 Log Po/w (XLOGP3) 3.03 Log Po/w (WLOGP) 4.79 Log Po/w (MLOGP) 1.54 Log Po/w (SILICOS-IT) 4.64 Consensus Log Po/w 3.13	383.34g/mol	3	7	Yes	No

PKa= Partition Coefficient; Mol. Wt= Molecular Weight; HBD= Hydrogen Bond Doner; HBA= Hydrogen Bond Acceptor; Lipinski= Lipinski Rule followed; BBM= Blood Brain Membrane

Table No.3: 2D and 3D poses of docked ligands that shows good results of docking and ADME

S.No	Compound Code	2D Structure	3D Structure
1	i4		
2	i5		
3	i6		
4	i7		

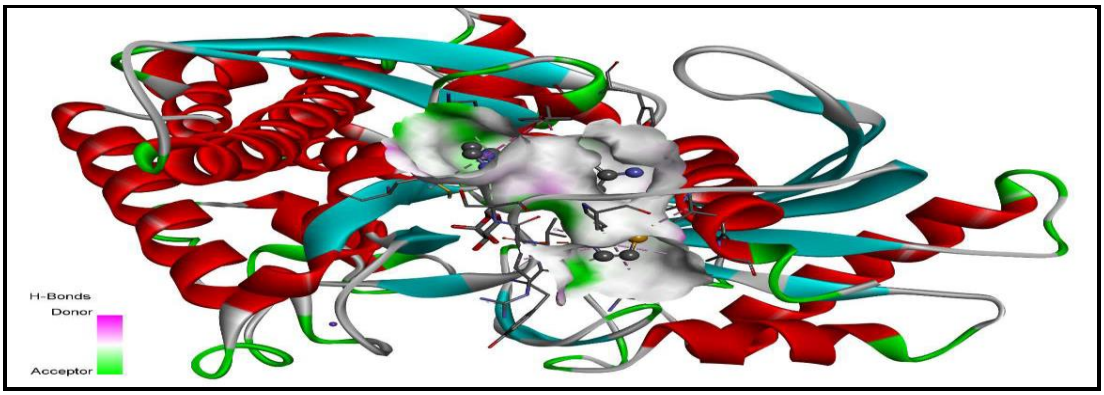


Figure No.1: Dock pose of GK bound to one of the designed molecules in its allosteric cavity

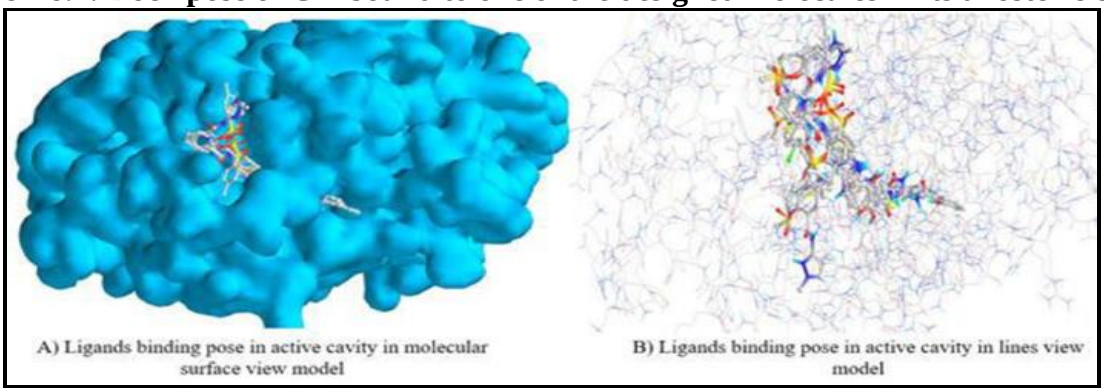


Figure No.2: Combined view of all ligands actively docked in the allosteric site of the GK enzyme

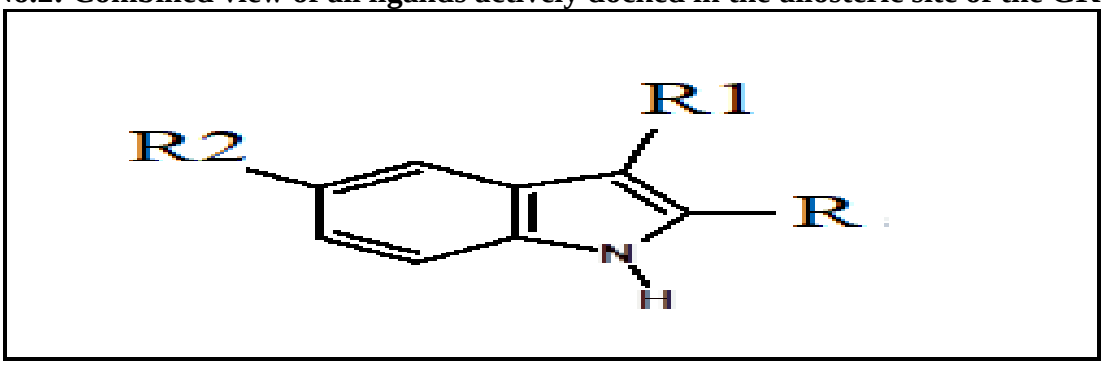


Figure No.3: Probable Pharmacophore

CONCLUSION

It is quite evident from the results given above that the ligands with substitution of more than one carbon-long chain would confer hydrophobic properties, thereby resulting in less polar molecules that would always have more hydrophobic interactions. Moreover, they would cross the blood brain barrier. Hence, structures of ligands with methyl substitution on the second position of the heterocyclic ring could be preferred for synthesizing in the wet-lab.

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AUTHOR CONTRIBUTION

Abdulrahman summed up the literature and drafted the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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