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RESEARCH ARTICLE
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MOLECULAR DESIGN OF PYRROLIDINE DERIVATIVES WITH GABA–ERGIC ACTIVITIES

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Abstract
In this study, a one-pot method for synthesizing N-substitute pyrrolidine derivatives from 1,4-butanediol and R-amine as antiepileptic drugs was established. More than 90% derivative yield was achieved over a Cu and Ni-modified ZSM-5 catalyst under optimum reaction conditions. In the current study, the AutoDock 1.5.6 for Docking program was utilized to perform molecular docking research on suggested derivatives of proteins from the protein data bank. protein binding affinity research with the 4COF (GABA) receptor pyrrolidine derivatives As a result, the role of gamma-aminobutyric acid (GABA) transmission in the control of convulsive epileptic seizures is examined through the lens of medications that enhance GABA transmission in the brain. The greatest binding affinity for 4COF was found in the N-substituted pyrrolidine derivative (2-(pyrrolidine1-yl)ethan-1-amine), with a value of -3.7 kcal/mol. Other results (in kcal/mol) are as follows: 1-propyl-H-pyrrolidine (-3.4), 1-butyl-1H-pyrrolidine (-3.6), 2-(1H-pyrrolidine-yl)ethan-1-ol (-3.6), and 1H-pyrrolidine-1 carbonitrile (-3.2).

Keywords: Pyrrolidine, Synthesis, Molecular Docking, GABAergic.

INTRODUCTION

Synthesizing derivatives of pyrrolidine can involve various chemical reactions and methods. Pyrrolidine is a five-membered heterocyclic compound containing a nitrogen atom and is commonly found in alkaloids and pharmaceuticals.[1,2] To synthesize derivatives of pyrrolidine, you can modify the substituents attached to the pyrrolidine ring, which can result in a wide range of compounds with different properties and functionalities.

Pyrrolidine derivatives such as levetiracetam and brivaracetam have been thoroughly studied and are licensed for the treatment of epilepsy. The neurological condition epilepsy is characterized by recurring and spontaneous seizures. Seizures are produced by aberrant electrical activity in the brain, which disrupts normal brain function for a brief period of time. These drugs have been used in clinical practice and have demonstrated success in managing seizures in various kinds of epilepsy. Antiepileptic drugs (AEDs) are medications used to treat epilepsy and prevent or reduce the

occurrence of seizures. The mechanisms of action for different AEDs can vary, but some common mechanisms include.[3,4]

***Increasing GABAergic inhibition*:** GABA is an inhibitory neurotransmitter that helps regulate neuronal excitability.

***Blocking voltage-gated sodium channels*:** By preventing sodium influx, they reduce the incidence of seizures by preventing fast depolarization of neurons and the propagation of aberrant electrical activity.

***Calcium channel modulation*:** AEDs such as ethosuximide and gabapentin may act on calcium channels, namely T-type calcium channels in thalamic neurons. This modulation aids in the management of irregular rhythmic firing and absence seizures.

Docking study

A docking research is a computer approach used in drug development and molecular biology. It is also known as molecular docking or protein-ligand docking. It entails anticipating a ligand's preferred orientation and conformation when it binds to a given target protein (receptor). The purpose of docking research is to comprehend the binding interactions between the ligand and the receptor and to forecast the binding affinity or intensity of the relationship. Advances in computational research have enabled in silico approaches to give epochal advantages to both regulatory needs and the pharmaceutical business in terms of safety profile analysis.

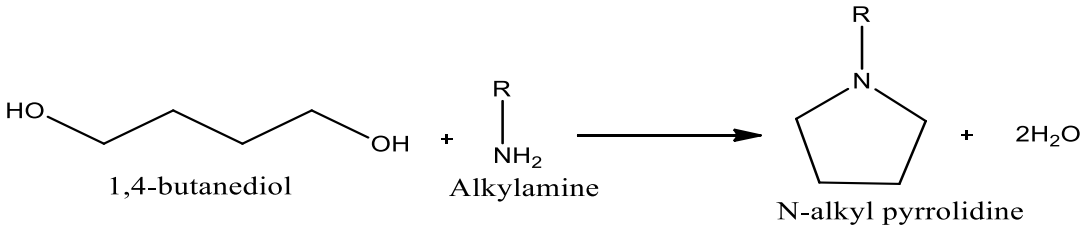
The docking software AutoDock 1.5.6 for Docking was used to conduct a molecular docking examination of proposed derivatives with protein from the protein data bank.the pyrrolidine derivatives of the protein binding affinity research using the 4COF(GABA) receptor. The significance of gamma-aminobutyric acid (GABA) transmission in the regulation of convulsive epileptic seizures is examined in light of the activities of medicines that enhance GABA transmission in the brain. In specifically, the effects of muscimol, a directly acting GABAA receptor agonist, are compared to the effects of gamma-vinyl GABA (GVG, vigabatrin), a GABA-elevating drug, in animal models of convulsive seizures.[5]

Evidence suggests that increasing GABA transmission is anticonvulsant in some areas of the brain, while blocking GABA transmission is anticonvulsant in others. Furthermore, due to a very low degree of endogenous GABA transmission in certain locations, the actions of muscimol and GVG are unique from one another. Direct activation of postsynaptic GABA receptors (through direct receptor agonists) bypasses normal synaptic transmission pathways and can result in aberrant neurological symptoms, whereas increasing presynaptic GABA availability avoids these difficulties.

GVG increases presynaptic GABA reserves, which may subsequently be used physiologically; this may explain why anticonvulsant dosages of GVG have a low incidence of CNS-related side effects. It is advised that in future pharmacological development for seizure disorders, more emphasis be placed on methods of increasing endogenous GABA availability.[6,7]

EXPERIMENTAL

General Procedure for the Synthesis



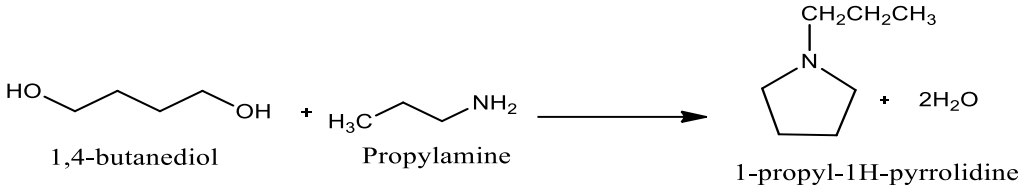
Scheme 1 Synthesis of pyrrolidine derivatives

A green, efficient, and occasional-value process for the one-pot synthesis of N-substitute pyrrolidine from 1,4-butanediol (BDO) and alkyl amine was devised in this work. Over a Cu and Ni modified ZSM-5 catalyst, more than 90% yield of pyrrolidine derivatives was achieved under optimum reaction conditions.[8] The catalyst may be reused for several cycles while maintaining remarkable catalytic overall performance and the scale-up operation validated the competence of industrial software. Meanwhile, it was discovered that the H2 atmosphere, the high dispersion of metallic oxides, and the synergistic action of Cu and Ni species on ZSM-5 all contributed to the excellent catalytic performance.[9,10]

A possible mechanism based entirely on a borrowing-hydrogen process was also presented. As a result, the cutting-edge synthesis technique has grown very capable of being put into practice. Because product yield was dependent on the working circumstances at the time, the catalysts, temperature, ratio of reactants, and solvent might all be critical considerations.[11,12]

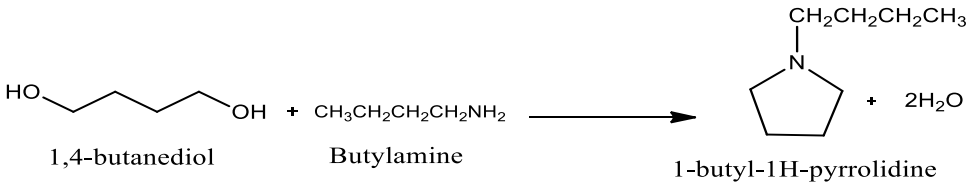
Synthesis the pyrrolidine derivatives

1. 1-propyl-1H-pyrrolidine



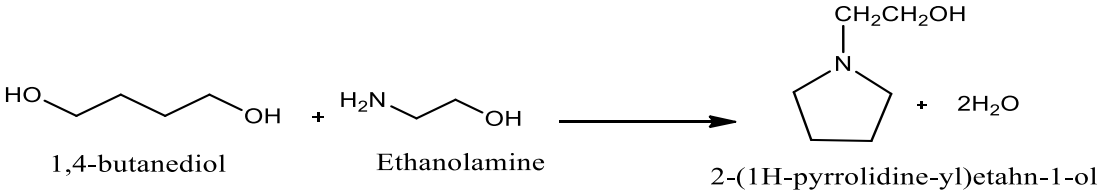
Scheme 2 Synthesis of 1-propyl-1H-pyrrolidine from 1,4-butanediol & propylamine

2. 1-butyl-1H-pyrrolidine



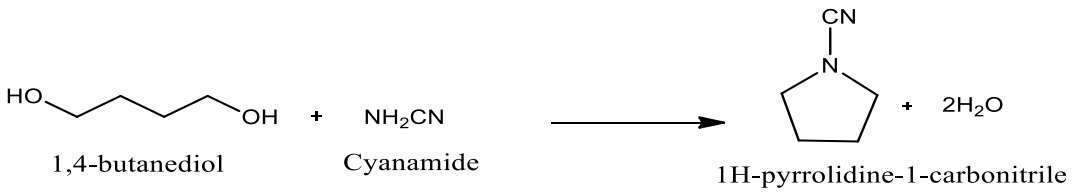
Scheme 3 Synthesis of 1-butyl-1H-pyrrolidine from 1,4-butanediol & butylamine

3. 2-(1H-pyrrol-yl)ethan-1-ol



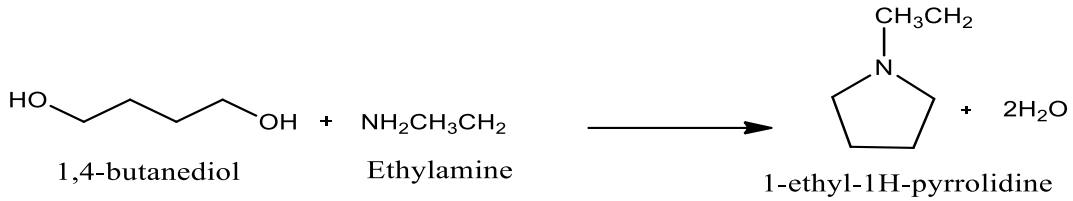
Scheme 4 Synthesis of 2-(1H-pyrrolidine-yl)ethan-1-ol from 1,4-butanediol & ethanolamine

4. 1H-pyrrolidine-1-carbonitrile



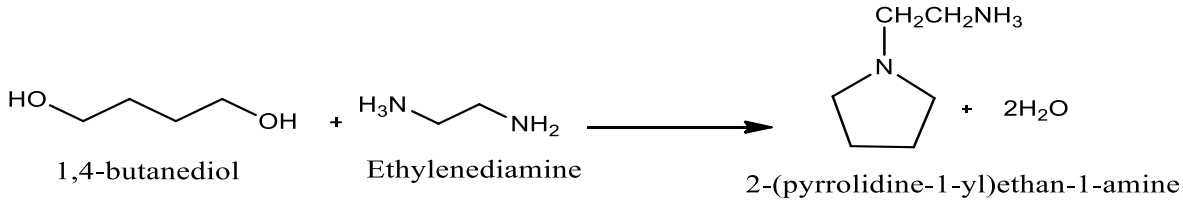
Scheme 5 Synthesis of 1H-pyrrolidine-1-carbonitrile from 1,4-butanediol & cyanamide

5. 1-ethyl-1H-pyrrolidine



Scheme 6 Synthesis of 1-ethyl-1H-pyrrolidine from 1,4-butanediol & ethylamine

6. 2-(pyrrolidine-1-yl)ethan-1-amine



Scheme 7 Synthesis of 2-(pyrrolidine-1-yl)ethan-1-amine from 1,4-butanediol &ethylenediamine

Catalytic reactions were carried out in a stainless steel autoclave with a magnetic stirrer of 100 mL capacity. Regularly, 1,4-butandiol (0.05 mol), alkylamine (0.1 mol, 40% aqueous solution), and catalyst (0.45 g) were loaded into the autoclave, which was then filled with H2 at 1 MPa pressure. The reactor was heated to 300 °C and magnetically swirled continuously during the reaction.[13,14,15]

MOLECULAR DOCKING STUDIES

Ligand Preparation

ChemDraw Ultra 19.0 was used to create a 2D molecular structure of synthesized ligands (My1-6), which was then transferred to a 3D (.pdb) format for energy optimization. The energy-efficient compounds were loaded into Auto Dock 4.2 for further molecular docking. The ligand's .pdb file is also stored in.pdbqt format, making it dockable. Because the precise center and radius of the binding sphere were uncertain, the target grid box was selected to encompass the majority of the protein structure. It was originally planned to look for adequate binding sphere parameters in the literature, but this was abandoned to avoid settling for local minima.[16]

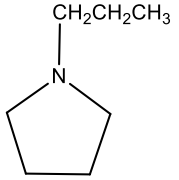
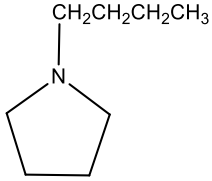
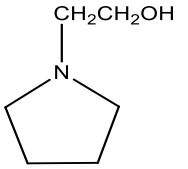
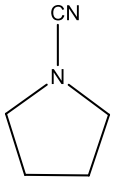
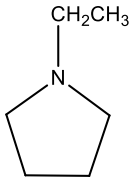
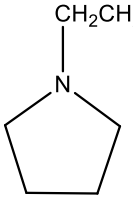
The basic idea was to allow the Auto Dock Vina to discover the most energetically promising active site cavity for the ligand (My1-My6) binding poses onto the receptor. Docking was accomplished using Vina's default algorithm. The protein is kept rigid for molecular docking studies, while the ligands are flexible. A set number of docking runs were performed at random. To obtain the docking results using AutoDock Vina, various commands were conducted on the DOS and Windows platforms. All parameters were recorded, and the lowest binding energy values were used to pick the optimal chemical. Several docking experiments were done to minimize the local minima difficulties, and then the best lead compound was chosen.[17,18]

Protein Preparation

Following a thorough review of the literature, pyrrolidine docking on GABA receptor (PDB ID 2eg7) was chosen as the target protein for the current docking study.[19,20] The protein complexed structure (three-dimensional) was retrieved from the protein data bank with a resolution of 2.0 Ao (https://www.rcsb.org/structure/2EG7). The protein crystal structure is refined using the Accelrys Discovery Studio 3.5 software. The program is used to remove water molecules as well as a complexed ligand that is bonded to them. Before docking, Auto dock tools (ADT) 1.5.6 was used to introduce polar water and Gasteiger charges to the protein structure.[21] Using the binding site tools,

the protein binding sphere (26.85, 40.56, 73.05) was chosen. The protein.pdb file is subsequently stored as.pdbqt. The protein .pdb file is then saved to .pdbqt format which is ready for docking study.[22,23,24]

Table:1 Binding affinity of pyrrolidine derivatives with GABAergic receptor (4COF)

S.NO.	Derivatives	With GABA (4COF) Docking
1.	 1-propyl-1H-pyrrolidine (MY-1)	-3.4
2.	 1-butyl-1H-pyrrolidine (MY-2)	-3.6
3.	 2-(1H-pyrrolidine-1yl)ethan-1-ol (MY-3)	-3.6
4.	 1H-pyrrolidine-1-carbonitrile (MY-4)	-3.4
5.	 1-ethyl-1H-pyrrolidine (MY-5)	-3.2
6.	 2-(pyrrolidine-1-yl)ethan-1-amine (MY-6)	-3.7

RESULTS AND DISCUSSION

To conduct a docking investigation, pyrrolidine derivatives complexed with 4COF GABA receptor were chosen as the target protein. This receptor is a valuable target for the development of new anticonvulsants. The AutoDock Vina docks synthesized products. The obtained results (Fig.1&4) and table 1 demonstrate that all of the synthesized compounds (My1-6) had good binding affinity (-3.7 to

-3.2) and co crystallized ligand efficiency (-4.9). My1, My2, My3, My4, My5, and My6 had binding affinity values of -3.4, -3.6, -3.6, -3.4, -3.2, -3.7, kcal/mol, respectively. The binding energy estimates demonstrated that the majority of the compounds had a high affinity for the 4COF GABA receptor. The graphic depicts the findings of all ways of molecular docking.

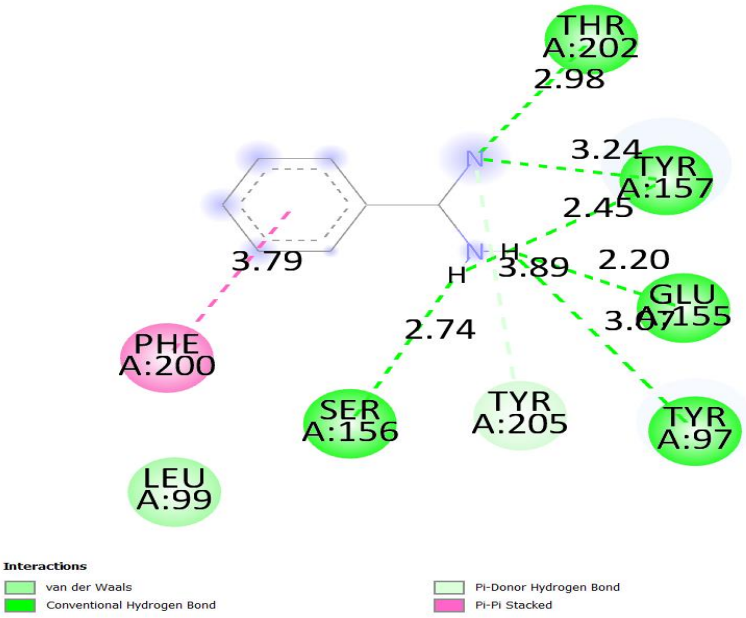


Figure:12D structure of 4COF GABA receptor

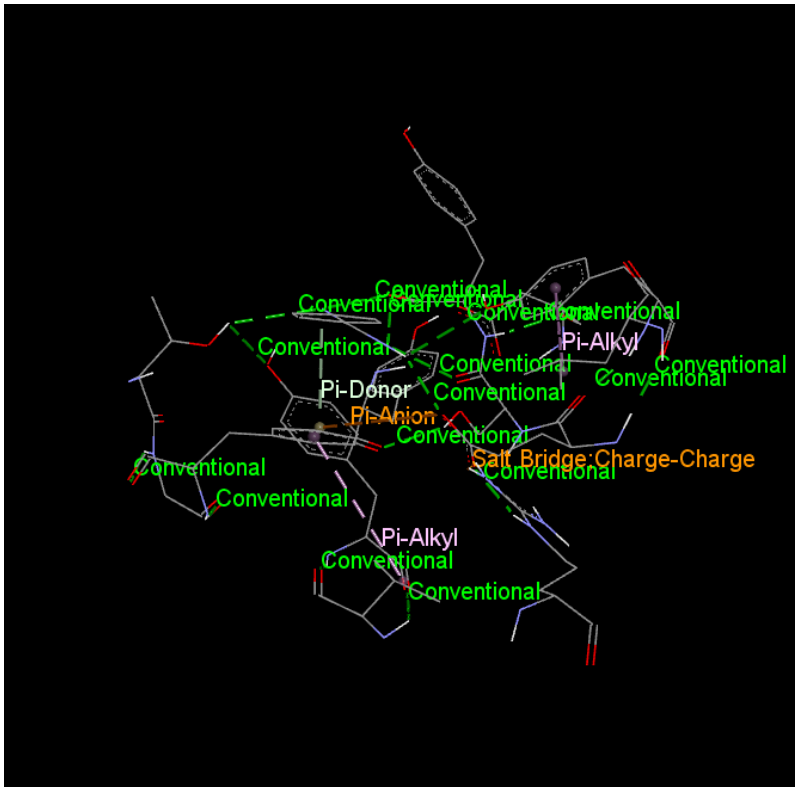


Figure: 23D structure of 4COF GABA receptor

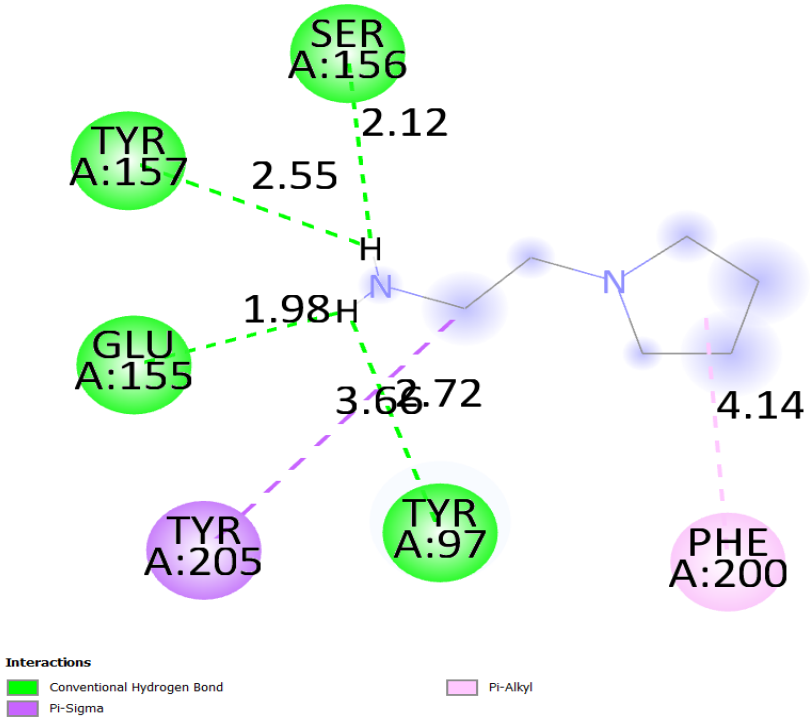


Figure: 32D structure of 2-(pyrrolidine1-yl)ethan-1-amine

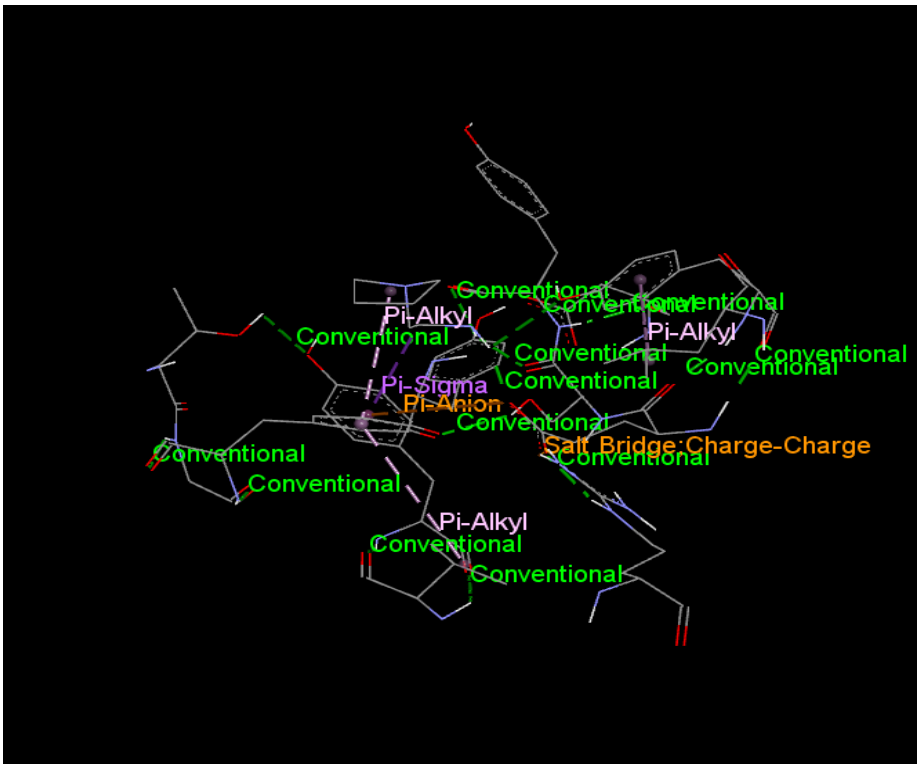


Figure: 43D structure of 2-(pyrrolidine1-yl)ethan-1-amine

CONCLUSION

The Discovery studio 2023 program and AutoDock vina energy scoring were utilized in this investigation, and there are many scoring functions. The pyrrolidine derivatives have the highest affinity for the 4COF GABA receptor. In trials with six active compounds, it also demonstrated high affinity values. We are interested in the protein binding rates that emerge from the docking investigation. Because the affinity value achieved in the ligand-protein docking study is low, given

the low IC50 value and high protein binding rate, we may conclude that the stronger the bond they form, the better the connection.

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CONFLICT OF INTREST
No conflict of interest

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