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IN SILICO APPROACHES FOR ANTIDEPRESSANT ACTIVITY OF NOVEL PYRAZOLE DERIVATIVE

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Abstract
Although pyrazole compounds have demonstrated an extensive variety of biological functions, nothing is known regarding their potential to operate as antidepressants. The objective of this work is to improve our understanding of these derivatives' intermolecular interactions by doing molecular docking studies at the human monoamine oxidase protein enzyme's active site. This study is primarily concerned with the synthesis, characterisation, pharmacokinetic evaluation, and molecular docking analyses of a new antidepressant that is intended to function as a monoamine oxidase inhibitor (MOA). Conventional heating was employed in the synthesis of six novel pyrazole derivatives. Pharmacokinetic predictions and molecular docking experiments were performed on these produced drugs. To assess their possible antidepressant effect, docking investigations were carried out using AutoDock Vina 1.2.3, focusing on the human MOA-A and MOA-B (PDB IDs: 2Z5X and 2XFN, respectively. SwissADME software was used for pharmacokinetic predictions, while PreADMET software was utilized for toxicity profiling. When compared to active medications, the outcomes of the docking investigations and pharmacokinetic estimates demonstrated encouraging antidepressant effects. The agreement found in the docking, SwissADME, and toxicity data points to bright futures for the creation of antidepressant drugs that work through the use of these six pyrazole derivatives.
Keywords: Carbaldehydes; Pyrazole; MOA; Binding affinity; Docking

1. Introduction

One of the most widespread neurological conditions is depression[i] It is brought on by a variety of genetic, environmental, social, and psychological variables[ii]. A reuptake mechanism[iii-v] and monoamine oxidase (MAOs) remove amines from the synaptic cleft, preserving the homeostasis of serotonin (5-HT), noradrenalin (NE), and dopamine (DA) in the brain[vi-vii]. Only a small portion of depression symptoms can currently be relieved by antidepressant medications, and adverse effects are frequent. As a result, there has been a lot of curiosity lately in the creation of antidepressants that are both safer and more effective[viii]. Mammals, plants, prokaryotic and eukaryotic microorganisms, and plants all include monoamine oxidases (MAOs), which are enzymes that catalyze the oxidative conversion of amines to aldehydes. Aminoxidases containing copper(II) (EC, 1.4.3.6) and aminoxidases containing flavin (EC,

1.4.3.4) are the two groups into which they fall in[ix] Semicarbazide inhibits the former aminoxidases, which had copper(II) 2,4,5-trihydroxyphenylalanine quinone as a cofactor (TPQ-Cu)[x]. The later aminoxidases have two isoforms, MAO-A and MAO-B, that vary in their susceptibility to inhibitors and substrate selectivity. They also include flavin adenine dinucleotide (FAD) as a cofactor. While MAO-B preferentially deaminates â-phenylethylamine and benzylamine and is selectively inhibited by Ldeprenil, MAO-A preferentially deaminates serotonin and norepinephrine and is selectively inhibited by clorgyline[xi]. MAO-A and MAO-B often use dopamine, tyramine, and tryptamine as substrates. Seventy percent of the amino acid similarity is shared by the two MAO isoforms, which are made up of 527 and 520 amino acids, respectively[xii]. The FAD cofactor is covalently attached to a cysteine residue in the active site of both isoforms[xiii]. Two distinct methods for the catalytic mechanism of MAOs have been proposed: one radical process that uses the iminium cation as an intermediary, and the other polar nucleophilic mechanism[xiv]. An excessive rise in MAO activity also causes an excessive production of harmful metabolites including ammonia and hydrogen peroxide, which are linked to tissue degeneration and oxidative stress[xv]. Two categories of MAO inhibitors—reversible and irreversible—can be studied. The use of nonselective and irreversible MAO inhibitors in clinical settings, such as hydrazine, cyclopropylamine, propargylamine, and allylamine derivatives, is restricted[xvi] because of the possibility of the "cheese effect," which is an abrupt increase in blood pressure and cerebral hemorrhage caused by excessive tyramine accumulation associated with excessive consumption of aged cheese. In order to allow the cleavage of the enzyme-inhibitor complex and restore the enzyme's activity, studies have concentrated on selective and reversible inhibitors with various chemical structures that function through non-covalent interactions[xvii]. Many substances have been shown to specifically and reversibly block MAO isoenzymes. While safinamide and lazabemide reversibly inhibit MAO-B, oxixatone, moclobemide, and brofaromine reversibly inhibit MAOA[xviii-xix.] Lazabemide was never put on the market[xx], and in clinical studies, more than 1% of participants had side symptoms such nausea, vertigo, insomnia, and low blood pressure when taking safinamide[xxi]. Thus, it is still crucial to find new selective reversible MAO inhibitors today. Since MAOs play a significant role in the metabolism of monoamine neurotransmitters, MAO inhibitors (MAOI) are being researched as potential treatments for a number of neurological and psychiatric conditions. MAO-B inhibitors are used as a coadjuvant in the treatment of Alzheimer's disease and Parkinson's disease[xxii-xxiii.] MAO-A inhibitors have been prescribed as anxiety and depression medications[xxiv]. Monoamine oxidase inhibitory characteristics of 1,3,5-triphenylpyrazolines have been reported, which are independent of their tranquilizing, muscle relaxant, psychoanaleptic, or anticonvulsant effects[xxv-xxvii]. The discovery of medications with diverse effects has been a new strategy in the treatment of AD, as the illness is caused by numerous factors[xviii]. MAO-B inhibitors with a variety of pharmacological effects appear to be good options to address this issue[xxix]. There is an urgent need to create new and better drug designs with the goal of reducing side effects because of the documented drawbacks and restrictions connected to current drugs. The goal of ongoing pharmacological research and improvements is to solve these issues by developing drugs that can minimize side effects while still providing therapeutic advantages, The ultimate goal is to maximize the safety and effectiveness profiles of medications, so offering better alternatives for therapy to those suffering from depression and anxiety. The purpose of this work was to use a molecular docking strategy with MAO-A and MAO-B (PDB ID: 2Z5X and 2XFN, respectively) to virtually screen six (06) substituted carbaldehyde molecules. The goal was to find a potential lead molecule that could be used as a template to create new hypothetical molecules with better binding affinities and molecular

residual interactions with the receptor. Additionally, the compounds' druglikeness and absorption, distribution, metabolism, and excretion (ADME) were assessed in silico.[xxx-xxxii]

2. Experimental

The chemicals employed in this research study were sourced from commercial suppliers, which included Merck and Sigma-Aldrich. These chemicals were utilized in their as-received state, without undergoing any additional purification procedures. Additionally, various solvents, such as methanol, ethanol, dimethylformamide (DMF), n-hexane, and ethyl acetate, were utilized throughout the study. The preparation process involved the use of 3-Chlorophenylhydrazine, 3-Methylphenylhydrazine, 2,4-dimethylphenylhydrazine, 4-Hydroxy acetophenone, 4-Aminoacetophenone, and phosphorousoxichloride. For the analysis of chemical samples, FT-IR spectra were obtained using a Perkin Elmer Spectrum BXw FT-IR Spectrometer, which covered the spectral range from 400 to 4000 cm-1. NMR spectra were collected using an Agilent 400 MR instrument, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. DMSO-D6 served as the solvent, and TMS was used as the internal standard. Mass spectra were recorded using a Waters LC-MS 8040 Model Spectrometer. To monitor reaction progress and assess product purity, TLC plates, specifically Merck Silica Gel 60 F254 plates, were employed.

2.1. General Method for the preparation of Hydrazone (AA-1 to AA-6)

The reaction was initiated by dissolving a mixture consisting of 10 mmol of various substituted acetophenones, substituted phenylhydrazine, and 1 ml of glacial acetic acid (used as a catalyst) in 20 mL of methanol. This solution was stirred for 4-5 hours at a temperature of 60°C to facilitate the progress of the reaction. To confirm the completion of the reaction, thin-layer chromatography (TLC) was conducted, providing visual confirmation. Once it was ascertained that the reaction had reached completion, ice was added to the reaction mixture, causing a precipitate to develop. The resulting hydrazone intermediates, labeled as AA-1 to AA-6, were isolated from the mixture through filtration. Subsequently, the filtrate was subjected to a washing step with water to remove any impurities present. These intermediates were then transferred to the next step in the process without undergoing any further recrystallization.

2.2. General method for the preparation of carbaldehydes containing pyrazole (BB-1 to BB-6)

In the subsequent step, a hydrazone compound (AA-1 to AA-6, 4 mmol) was introduced into the Vilsmeier-Haack reagent. The Vilsmeier-Haack reagent was prepared by the gradual addition of 3 mL of POCl3 to 15 mL of DMF (dimethylformamide) that had been pre-chilled on ice. This resultant mixture was stirred for 4-6 hours at a temperature of 70°C, allowing the reaction to proceed. To confirm the completion of the reaction, thin-layer chromatography (TLC) was conducted. Once it was verified that the reaction had concluded, the mixture was poured into crushed ice to facilitate cooling and induce precipitation of the reaction products. To neutralize the mixture and attain a neutral pH, a bicarbonate solution was added, stabilizing the reaction mixture. The crude product was subsequently separated from the mixture, possibly through filtration or other suitable separation methods. For further purification of the product, it underwent crystallization using ethanol.

1-(3-chlorophenyl)-3-(4-hydroxyphenyl)-1H-pyrazole-4-carbaldehyde(BB1)

Yield: 75%, Orange, mp 196-200ºC; Rf 0.42 (Ethyl Acetate : n-Hexane 1:4); IR (KBr, cm1): 3308 (OH), 1678 (-C=O), 1598 (C=N); 1H NMR (DMSO-D6,ppm): δ 9.95 (s, 1H, Ar-CHO), 9.83 (s, 1H, Ar-OH), 9.30 (s, 1H,- N-CH); 13C (DMSO-D6,ppm): 184.4(1C, -CHO), 158.5(1C, Ar-OH), 152.9(1C, C=N), 130.0(1C, C-N)); EI-MS: m/z [M+H]+ 298.0

3-(4-aminophenyl)-1-(3-chlorophenyl)-1H-pyrazole-4-carbaldehyde(BB2)

Yield: 59 %; Orange , mp 215-219 ºC; Rf 0.50 (Ethyl Acetate : n-Hexane 1:4); IR (KBr, cm-1): 3381 (-NH2), 1683 (C=O), 1596 (C=N); 1H NMR (DMSO-D6, ppm): δ 9.96 (s, 1H, Ar-

CHO), 6.90 (d, 2H, Ar-NH2), 9.29 (s, 1H,- N-CH); 13C NMR (DMSO-D6 , ppm) 184.5(1C, -CHO), 158.4(1C, C=N),152.9 (1C, C-NH2)MS: m/z [M+H]+ 298.05

1-(3-chlorophenyl)-3-(3,4-dimethoxyphenyl)-1H-pyrazole-4-carbaldehyde(BB3)

Yield: 64%; Orange, mp 128-132ºC; Rf 0.47 (Ethyl Acetate : n-Hexane 1:4); IR (KBr, cm-1): 3334 (-OH), 1661 (C=O), 1588 (C=N); 1H NMR (DMSO-D6, ppm): δ 9.95 (s, 1H, Ar-CHO), 9.78 (s, 1H, Ar-OH), 9.27 (s, 1H,- N-CH); 2.41 (s,3H Ar-CH3); 13C NMR (DMSO-D6,ppm): 184.4(1C, -CHO), 158.3(1C, Ar-OH), 152.7(1C, C=N), 130.0(1C, C-N), 20.8(1C, -CH3) EI-MS: m/z [M+H]+ 342.77

3-(4-hydroxyphenyl)-1-(3-methylphenyl)-1H-pyrazole-4-carbaldehyde(BB4)

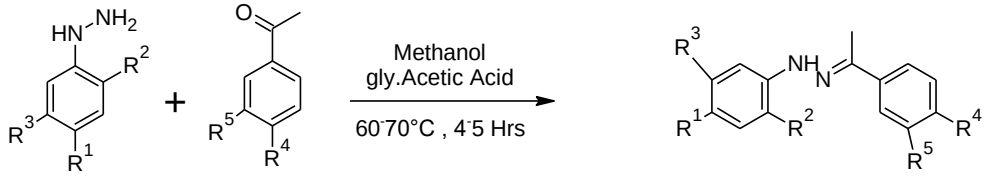
Yield: 72 %; Buff White , mp 152-155ºC; Rf 0.32 (Ethyl Acetate : n-Hexane 1:4); IR (KBr, cm-1): 3413 (NH2), 1674 (C=O), 1596 (C=N); 2918 (-CH3); 1H NMR (DMSO-D6, ppm): δ 9.98 (s, 1H, Ar-CHO), 8.00 (d, 2H, Ar-NH2), 9.32 (s, 1H,- N-CH); 2.42 (s,3H Ar-CH3); 13C NMR (DMSO-D6,ppm): 184.5(1C, -CHO),153.4(1C,$ArNH_2$),152.9(1C,C=N),159.7(1C,C-N) EI-MS: m/z [M-H]+ 278.30

3-(4-aminophenyl)-1-(3-methylphenyl)-1H-pyrazole-4-carbaldehyde(BB5)

Yield: 68 %; Buff White , mp 210-214ºC; Rf 0.46 (Ethyl Acetate : n-Hexane 1:4); IR (KBr, cm-1): 3325 (-OH), 1684(C=O), 1593(C=N); 2923(-CH3); 1H NMR (DMSO-D6, ppm): δ 10.00 (s, 1H, Ar-CHO), 8.19 (s, 1H, Ar-OH), 9.27 ; 2.41 (d,6H Ar-CH3); 13C (DMSO-D6,ppm): 184.9(1C, -CHO), 158.3(1C, Ar-OH), 130.7(1C, C=N),154.5(1C,C-N),20.95(1C,Ar-CH3) 17.82(1C, Ar-CH3) EI-MS: m/z [M+H]+ 277.32

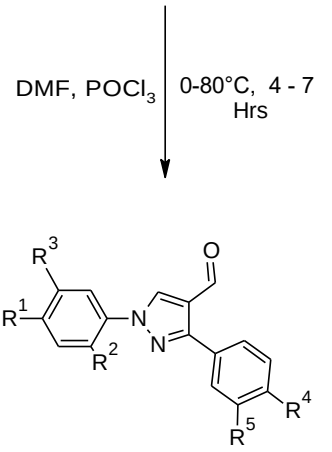
1-(2,4-dimethylphenyl)-3-(4-hydroxyphenyl)-1H-pyrazole-4-carbaldehyde(BB6)

Yield: 65 %; Orange, mp 185-189ºC; Rf 0.29 (Ethyl Acetate : n-Hexane 1:4); IR (KBr, cm-1): 1103 (-OCH3), 1677(C=O), 1597 (C=N); 1H NMR (DMSO-D6, ppm): δ 9.98 (s, 1H, Ar-CHO), 3.84 (s, 6H, Ar-OCH3), 9.33 (s, 1H,- N-CH); 13C (DMSO-D6,ppm): 184.4(1C, -CHO), 152.9(1C, C-OCH3),149.7(1C,C-N), 55.44(6C, -OCH3) EI-MS: m/z [M+H]+ 392.33



AA-1 to AA-6

	R1	R2	R3	R4	R5
B1	-H	-H	-Cl	-OH	-H
B2	-H	-H	-Cl	$-NH_2$	-H
B3	-H	-H	-Cl	$-OCH_3$	$-OCH_3$
B4	-H	-H	$-CH_3$	-OH	-H
B5	-H	-H	$-CH_3$	$-NH_2$	-H
B6	$-CH_3$	$-CH_3$	-H	-OH	-H



BB-1 to BB-6

Figure 1 Reaction Scheme

2.3. Molecular docking methodology

Molecular docking serves as a valuable tool for comprehending the interactions between a ligand and its receptor.[xxxiii-xxxiv] In this study, molecular docking was executed with AutoDock Vina 1.2.3. The Human Monoamine Oxidase A with Harmine and Human Monoamine Oxidase B with 2-(2-Benzofuranyl)-2-imidazoline crystal structures, which were retrieved from the Protein Data Bank, served as the foundation for this study.(PDB ID: 2Z5X and 2XFN respectively)[xxx-xxxvi]. The objective was to gain insights into the intricate interactions between the synthesized compound (ligand) and the enzyme's active site.

To initiate this process, the synthesized compound was constructed using ChemDraw 11.0, and its 2D structure was subsequently converted into a 3D structure with the assistance of Avogadro software.[xxxvii] The energy of all 3D structures was minimized, and the resulting structures were saved as PDB files. In preparation for the docking study, the protein file underwent necessary adjustments, including the removal of water molecules, addition of polar hydrogens, and the elimination of other bound ligands.

For this specific study, the selection of the binding site was based on the amino acid residues known to interact with the crystal structure of Human Monoamine Oxidase A and Human Monoamine Oxidase B as retrieved from the Protein Data Bank. This selection was deemed the most accurate and reliable region, given that it was established through experimental crystallographic data.[xxxviii] The docking protocol for the synthesized compound was executed as outlined in Table III, employing AutoDock Vina software with adherence to standard operating procedures.

2.4. Drug-likeness and pharmacokinetic (ADME) prediction

We employed the Swiss-ADME software, accessible at http://www.swissadme.ch, as an online tool to evaluate the drug-likeness and pharmacokinetic characteristics of the proposed derivatives. The prediction of drug-likeness for these compounds was based on Lipinski's Rule of 5, a set of guidelines established to define the suitability of new molecular entities for potential drug development. According to these rules, compounds exceeding specific thresholds—more than 5 H-bond donors, more than 10 H-bond acceptors, a molecular weight surpassing 500, and a log P (iLog P) greater than 5—tend to have less favorable pharmacological properties. Additionally, parameters such as a topological polar surface area (TPSA) below 140 Å2 and a high number of rotatable bonds (nRotb) are indicative of poor absorption. Furthermore, the Swiss-ADME software was instrumental in determining various pharmacokinetic properties, including molar refractivity (MR), skin permeability (log Kp), ability to penetrate the blood-brain barrier (BBB), status as a substrate for permeability glycoprotein (Pgp), gastrointestinal (GI) absorption, and interactions with cytochrome P450 (CYP450) enzymes, such as CYP1A2, CYP2C9, and CYP2C19. This comprehensive analysis allowed us to gain valuable insights into the potential drug-like properties and pharmacokinetics of the compounds under investigation.

2.5. Toxicity profile

Numerous open-source software applications may be utilized to forecast the in silico toxicity of compounds, we used the PreADMET software for in silico toxicity prediction of both paroxetine and the designed analogs.[xxxix] Our selection criteria included molecules with equivalent or enhanced toxicity profiles when compared to the commercial drug.[xl]

3. Result and Discussion

3.1. Chemistry

According to Scheme 1, the title compounds were synthesized. The compound AA1 - AA6 were obtained by condensation of Substituted Phenyl hydrazine and substituted Aromatic Ketone. Compound AA1-AA6 were further treated with Vilsmerheack reagent to afford

compound BB1-BB6. The formation of all the synthesized compounds were ascertained by IR, 1HNMR, 13CNMR and ESI-MS spectral data.

3.2. Docking Study

To comprehend the interactions between ligands and receptors, we conducted a detailed analysis involving the most potent compound (BB6). This compound was strategically docked within the active site of the with Human Monoamine Oxidase A's crystal structure with harmine and Human Monoamine Oxidase B with 2-(2-Benzofuranyl)-2-imidazoline. According to the docking data, BB6 generated binding energy values that were advantageous for both enzymes. MAO-Aand MAO-B showed the largest results, with −9.93 and −10.36 kcal·mol^{-1} respectively(Table-1). Notably, the benzene ring with primary amine group displayed a robust Pi-alkyl interaction with the amino acid VAL101 . The stability of this complex was further reinforced through notable interactions: a strong hydrogen bond formed between the carbaldehyde group (-CHO) and ASN117,TPR116 as well as primary amine group with GLU327,THR169. The synthesized compounds showed promising docking results, with compound BB2 exhibiting the most potent interactions within the active site. Notable interactions included Pi-alkyl interactions and hydrogen bonding with key amino acid residues. The docking results indicated that the synthesized compounds have potential antidepressant activity. The interactions observed between the ligands and the receptor provided insights into their binding mechanisms.

No	Sample code	Docking Affinity (kcal/ mol)-MOA-A	Docking Affinity (kcal/ mol) MOA-B
1	Isocarboxazid	-9.166	-9.035
2	Parnate	-6.594	-6.907
3	Phenelzine	-6.704	-6.822
4	Selegiline	-7.708	-7.206
5	BB1	-8.131	-9.884
6	BB2	-8.270	-8.612
7	BB3	-7.916	-9.616
8	BB4	-9.904	-8.832
9	BB5	-9.833	-8.443
10	BB6	-9.936	-10.362

Table 1-Binding Affinity for control drugs and all ligand

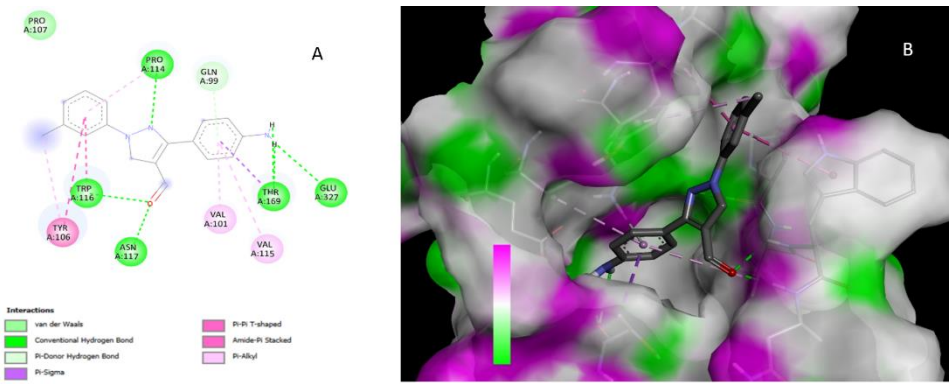


Figure 2 (A) 2D docking pose of BB2 with MOA-A (B) 3D docking pose of BB2 with MOA-A

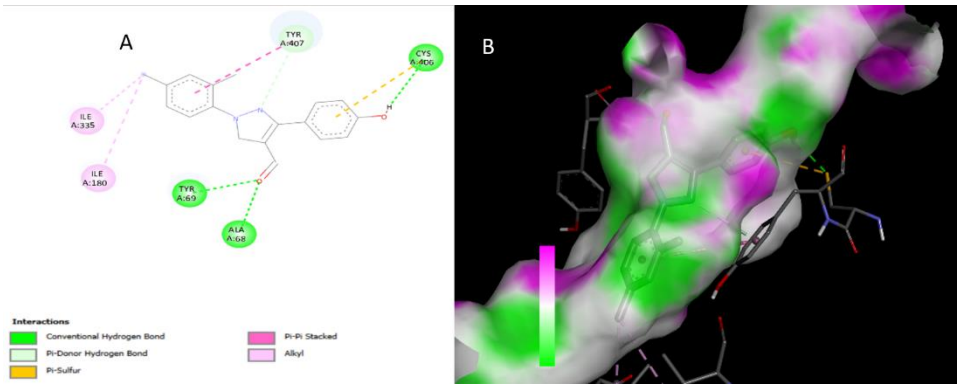


Figure 3 (A) 2D docking pose of BB6 with MOA-A (B) 3D docking pose of BB6 with MOA-A

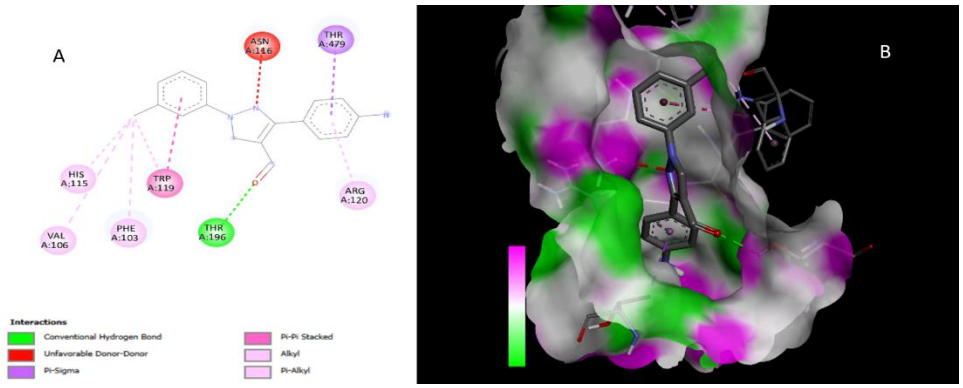


Figure 4 (A) 2D docking pose of BB2 with MOA-B (B) 3D docking pose of BB2 with MOA-B

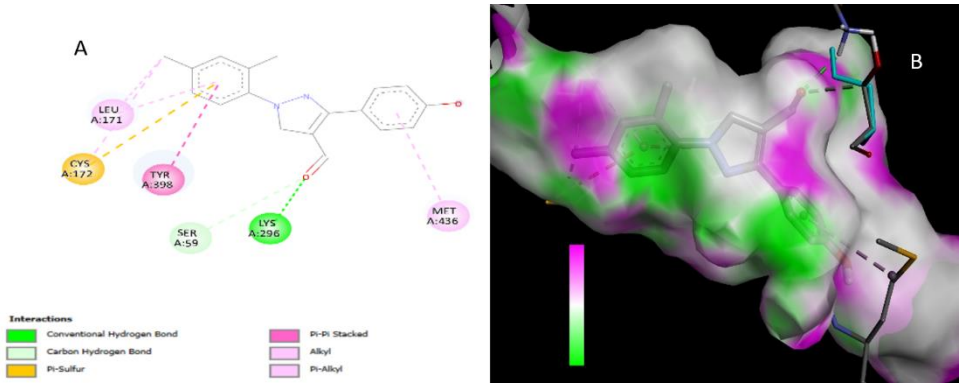


Figure 5 5 (A) 2D docking pose of BB6 with MOA-B (B) 3D docking pose of BB6 with MOA-B

3.3 Swiss ADME

All the compound are blood-brain barrier (BBB) Permeable which is necessary for showing activity for Antidepressant According to the aforementioned study, our chemical BB2 is less hazardous based on all logP values, and its TPSA value of 53.35 Å2 indicates very minimal toxicity throughout the drug-design process. All compounds that are positive indicators of our molecule likewise have a Lipinski violation of zero. The chemical may be readily accessible in the body, as shown by the bioavailability score of 0.55. Ultimately, the anticipated medical investigation makes it abundantly evident that the molecule itself exhibits lead resemblance, a certain sign of drug likeness.(Table 2).

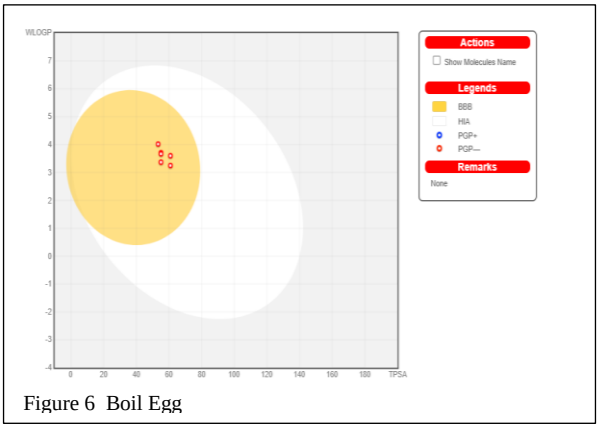


Figure 6 Boil Egg

Molecule	nHBA	nHBD	TPSA	iLOGP	WLOGP	GI	BBB	Pgp	nLV	BS	SA
BB1	3	1	55.12	2.35	3.71	High	Yes	No	0	0.55	2.39
BB2	2	1	60.91	2.36	3.6	High	Yes	No	0	0.55	2.43
BB3	4	0	53.35	3.2	4.02	High	Yes	No	0	0.55	2.72
BB4	3	1	55.12	2.41	3.37	High	Yes	No	0	0.55	2.41
BB5	2	1	60.91	2.39	3.25	High	Yes	No	0	0.55	2.46
BB6	3	1	55.12	2.59	3.67	High	Yes	No	0	0.55	2.56

Table 2 ADME prediction data
nHBA: number of hydrogen bond acceptor, nHBD: number of hydrogen bond donor ,TPSA: topological polar surface area ,WLOGP: water partition coefcient, GI: gastrointestinal absorption, BBB: blood–brain barrier permeant, Pgp: P-glycoprotein substrate, nLV: number of Lipinski violation, BS: Bioavailability Score , SA: synthetic accessibility

3.3. Toxicity profile

Compound	TOXICITY		
	Carcinogenicity in mice	Carcinogenicity in rats	Ames Test
BB1	Negative	Negative	Mutagenic
BB2	Negative	Negative	Mutagenic
BB3	Negative	Negative	Mutagenic
BB4	Negative	Positive	Mutagenic
BB5	Negative	Positive	Mutagenic
BB6	Negative	Positive	Mutagenic

Table 3 PreADMET Toxicity data for ligand

Parent compound was evaluated in PreADMET by examining two carcinogenicity assays in rodents and a mutagenicity assay in S. typhimurium (Ames Test) (Table 3). Results show that

three of the candidates were positive for at least one of the two carcinogenicity assays (BB4,BB5 and BB6) and three were negative on both (BB1,BB2 and BB3). Based on these results, candidates BB1, BB2 and BB3 presented a safer toxicity profile than BB4,BB5 and BB6 (Table 3). Although both compounds had similar binding affinity.

4. Conclusion

In this study, we conducted a comprehensive structural analysis of six newly synthesized compounds, denoted as BB1-BB6, all of which featured carbaldehydes with various substituents. Structural confirmation was achieved through a battery of analytical techniques, including Infrared Spectroscopy (IR), Proton Nuclear Magnetic Resonance (1H-NMR), Carbon-13 Nuclear Magnetic Resonance (13C-NMR), and Electrospray Ionization Mass Spectrometry (ESI-MS). Subsequently, we utilized advanced In Silico methodologies to evaluate the antidepressant potential of these compounds, employing molecular docking to assess their interactions with relevant receptors. Our findings unveiled intriguing insights into the antidepressant activity of these compounds, with particular emphasis on those bearing phenyl and substituted phenyl rings. Notably, the compound featuring a primary hydroxy substituent (BB6) exhibited the highest level of antidepressant activity. We also identified several compounds that outperformed the standard drug Isocarboxazid in terms of their antidepressant properties. Our future research endeavors will delve into exploring further substitutions on the benzyl ring and investigating the impact of varying spacer/linker lengths. These promising results suggest that our novel pyrazole derivatives may hold great potential as candidates for the development of new antidepressant agents.

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