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Synthesis of Pyridine-Based Imine Compounds and Molecular Docking Studies Against Dopamine D2 Receptors

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ABSTRACT

In this study, new pyridine-based imine compounds (8-10) were synthesized and docking studies of these compounds against D2 Dopamine receptor (6CM4) were performed. The structures of these compounds, which were synthesized using the microwave method, were determined by 1H-NMR, 13C-NMR and elemental analysis techniques. The binding energy values vary range from -6.79 to -7.07 kcal/mol with D2 Dopamine Receptor/PDB: 6MC4. Compound 10 (-7.07 kcal mol^{-1}) showed better binding energy than 9 (-6.95 kcal mol^{-1}) and 8 (-6.79 kcal/mol).

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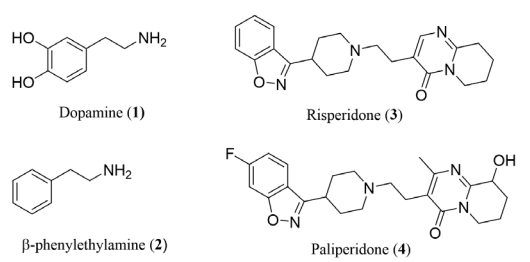
Keywords:
β-Phenylethylamine, Dopamine, Imine, D2 receptor, Molecular docking

INTRODUCTION

Dopamine (3,4-dihydroxyphenethylamine) (**1**) is a derivative of *β*-phenylethylamine (**2**) (1). This compound, which contains an amine functional group, is produced in the human body and plays a role in the functioning of the central nervous system, cardiovascular system and hormonal systems (2,3). Dopamine (1) is also a monoamine hormone, and it activates D1, D2, D3, D4 and D5 dopamine receptors in the brain and provides interneuron communication (4). In the human body, dopamine deficiency causes various diseases such as Parkinson's and Alzheimer's, and its excess causes schizophrenia (5). In addition, depending on the amount of dopamine in the body, diseases such as attention deficit, hyperactivity and restless legs syndrome can be seen (6). Drugs with dopamine-like activity (7) or inhibitors of monoamine oxidase enzymes (MAO) are used in the treatment of such diseases that occur due to the amount of dopamine (8). It has been reported that drugs to increase dopamine levels (9) to reduce the effects of Parkinson's disease and to block D2 receptors in schizophrenia (10) are used for treatment purposes. The dopamine D2 receptor antagonist risperidone (3) and paliperidone (4) a new generation antipsychiatric drugs are frequently used to treat psychotic symptoms (11, 12) (Scheme 1).

Similar to dopamine (1), *β*-phenylethylamine (2) also acts as a neuromodulator or neurotransmitter in the mammalian central nervous system (13,14). In addition, *β*-phenylethylamine (2) derivative compounds have pharmacological properties such as neuropsychiatric, antidepressant, stimulant, bronchodilator and decongestant (6, 15).

When the structure of existing drugs is examined, it has been reported that most of them contain amine functional groups with important biological activities



Scheme 1. Some psychotic active molecules

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(1,16). Imines are compounds that are synthesized through compounds containing amine groups and have a wide range of biological activity properties such as antibacterial, antifungal, antimalarial, antituberculosis, antiviral, anti-inflammatory, antidiabetic, antipyretic, and enzyme inhibition (17,18).

The process of researching pharmaceutical products and introducing them to human use is long and costly. Drug developers can detect candidate molecules in a short time with computerized molecular docking applications to reduce time and cost. Also, side effects of potential molecules can be detected by molecular docking method (19). Molecular docking studies are a computational method used to detect protein-ligand interactions in structure-based drug designs and to investigate the effectiveness of molecules against diseases to find treatments for diseases (20). In molecular docking studies, two molecules are used that are expected to form a stable complex when bound together. D2 receptors are abundant in Parkinson's and schizophrenia patients, thus most neuroleptic drugs aim to block D2 receptors. For this purpose, antipsychiatric drugs such as risperidone (3), which is a dopamine D2 receptor antagonist and paliperidone (4) are used (11, 12, 21). A detailed representation of the target of the D2 Dopamine receptor bound to the Risperidone structure is shown in Figure 1.

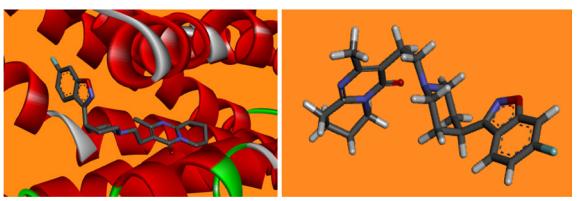


Figure 1. 3D-Structure of the D2 Dopamine Receptor (D2DR) bound to the Risperidone (green sticks) (PDB ID- 6CM4).

As is known, imine compounds are biologically active molecules (22). In this study, synthesis of new pyridine-based imine compounds and docking studies of synthesized imine compounds against D2 Dopamine receptor were performed. The pyridine-based imine compounds in the study were synthesized for the first time by microwave method (23,24) considering green chemistry purposes. The structures of the compounds were determined by ^{1}H, ^{13}C-NMR and elemental analysis techniques. The potential of the synthesized compounds for use as drugs in the treatment of the aforementioned diseases was determined by their affinity for D2 receptors. For this purpose, Molecular Docking (MD) studies were performed.

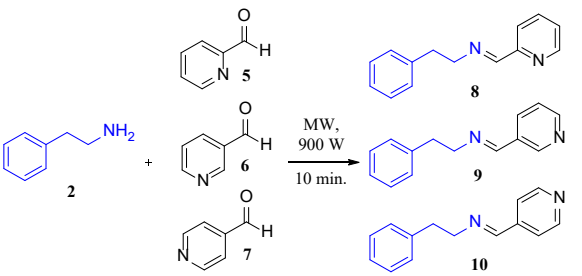
MATERIAL AND METHODS

Chemistry

All chemicals were purchased commercially from Sigma-Aldrich. Thin layer chromatography was used to monitor reactions (TLC). ^{1}H NMR and ^{13}C NMR spectra were recorded with Varian spectrometer (400 and 100 MHz). The reactions were carried out with a microwave oven (Vestel MD 20 DB model, 900 W). On a Leco CHNS-932 instrument, elemental analysis was carried out.

General Synthesis of new pyridine-based imines (8-10)

General procedure: The synthesis method of the compounds (8-10) within the scope of the study is given in Scheme 2 and synthesized according to the literature (23, 24). All reactions were carried out in an open system in a 5 mL glass flask under 900 W microwave radiation in solvent and catalyst-free conditions. β-phenylethylamine (2) (1 mmol) was reacted with different aldehyde compounds, picolinaldehyde (5) (1 mmol), nicotinaldehyde (6) (1 mmol) and isonicotinaldehyde (7) (1 mmol). The progress of the reactions was monitored by thin layer chromatography (TLC). It was seen that the reactions were completed within 10 minutes for all aromatic derivatives. ^{1}H NMR, ^{13}C NMR, FT-IR and elemental analyses of the obtained materials were performed. According to the results of the analysis, it was determined that there was only one compound in each reaction. Thus, new imine compounds (8-10) were obtained without any purification process.



Scheme 2. The synthesis of pyridine-based imine compounds (8-10)

Molecular Docking studies

Virtual screening of imines against the D2 Dopamine Receptor (PDB: 6CM4) was performed using AutoDock Tools 1.5.7. Avagadro was used to reduce the energies of the compounds and the structures of the compounds were determined. Figure 2 shows the pdb forms of the ligands. All compounds are then converted to AutoDock ligand format (PDBQT).

The molecular structure of D2DR with risperidone (PDB ID 6CM4) was obtained from the protein data bank (PDB) (http://www.rscb.org). The receptors are prepared for docking with AutoDock Tools 1.5.7 (25).

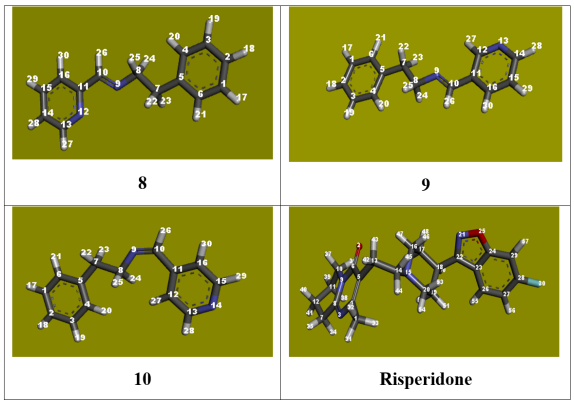


Figure 2. Avagadro-optimized structures of compound 8-10

The preparation of proteins and ligands was done using MGLTools. Water molecules removed, polar hydrogen charges added, torsional angles confirmed, and Kollman charges added. The active sites of the proteins were identified in order to more effectively complete the docking process. Therefore the grid parameters were selected as 60*60*60 Å, x, y, z dimensions, 0.553 Å space and 9.92, 5.84, -9.58 x, y, z centres for D2 Dopamine Receptor /PDB: 6CM4.

Molecular docking was carried out using the Lamarckian Genetic Algorithm (LA) technique. The auto dock calculation technique was used to determine pole contacts, Van der Waals forces, and interactions with other non-covalent proteins and linked ligands. As a result of the research, it was seen that the docking method was successful or sufficient both in determining the active site of the receptor and in determining the ligand conformation. 3D structures of molecules were obtained by drawing 2D structures of the molecules. The molecules were converted to PDB format by minimizing energy with the AVAGADRO program. AutoDock tools 1.5.7 were used to transform ligand and protein molecules into easily readable file formats (pdbqt). BioVia Discovery Studio Software was used to analyze the output files after converting them to protein-ligand complexes (http://www.3dsbiovia.com/). In Table 1 and Fig. 3-6, the molecular docking scores for each structure were sorted in kcal/mol.

RESULTS

Chemistry

(E)-N-phenethyl-1-(pyridin-2-yl)methanimine (8): It was obtained in %95 yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 3.8 Hz, 1H), 8.33 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.42 – 7.14 (m, 5H), 3.95 (td, *J* = 7.8, 1.3 Hz, 2H), 3.07 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.36, 154.47, 149.48, 139.70, 136.60, 128.96, 128.41, 126.22, 124.74, 121.28, 62.96, 37.33. Elemental Analysis: Calcd C, 79.97; H, 6.71; N, 13.32, Found C, 79.91; H, 6.77; N, 13.36.

(E)-N-phenethyl-1-(pyridin-3-yl)methanimine (9) : It was obtained in %96 yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, *J* = 1.8 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.16 (s, 1H), 8.07 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.45 – 7.10 (m, 6H), 3.89 (td, *J* = 7.4, 1.2 Hz, 2H), 3.02 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.61, 151.43, 150.15, 139.64, 134.44, 131.69, 129.04, 128.40, 126.24, 123.68, 63.32, 37.32. Elemental Analysis: Calcd C, 79.97; H, 6.71; N, 13.32, Found C, 79.94; H, 6.74; N, 13.28

(E)-N-phenethyl-1-(pyridin-4-yl)methanimine(10) : It was obtained in %96 yield. ^{1}H NMR (400 MHz, $CDCl^3$) δ 8.68 – 8.62 (m, 2H), 8.06 (s, 1H), 7.54 – 7.48 (m, 2H), 7.26 (t, *J* = 7.4 Hz, 2H), 7.21 – 7.14 (m, 3H), 3.87 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl^3$) δ 159.78, 150.60, 143.07, 139.69, 129.24, 128.63, 126.50, 122.09, 63.44, 37.35. Elemental Analysis: Calcd C, 79.97; H, 6.71; N, 13.32, Found C, 79.94; H, 6.74; N, 13.28.

Results of the Molecular Docking studies

Molecular docking experiments were performed to understand the interactions between the synthesized compounds and the structure of the D2 Dopamine Receptor attached to the Drug Risperidone (PDB ID: 6CM4). The structure of the D2 dopamine receptor bound to the drug risperidone was studied using molecular docking techniques to better understand the interactions between various compounds.

In this work, the compounds' docking scores and their interactions with the residues in the enzyme's active site were determined. It was calculated that the compounds 8, 9

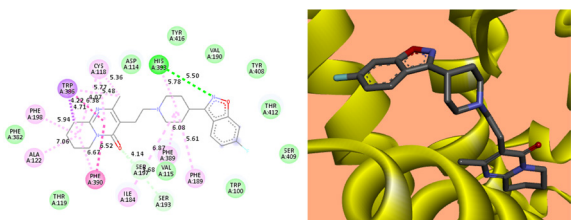


Figure 3. 2D and 3D interaction maps of compound 8 inside the 6MC4 active site.

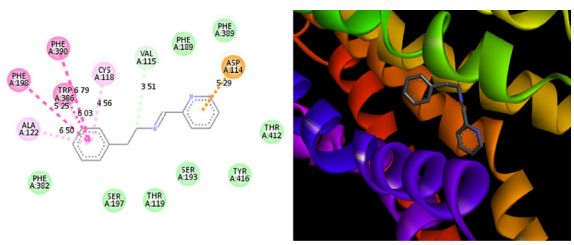


Figure 4. 2D and 3D interaction maps of compound 9 inside the 6MC4 active site.

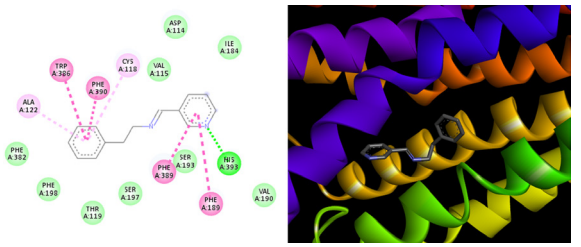


Figure 5. 2D and 3D interaction maps of compound 10 inside 6CM4 active site.

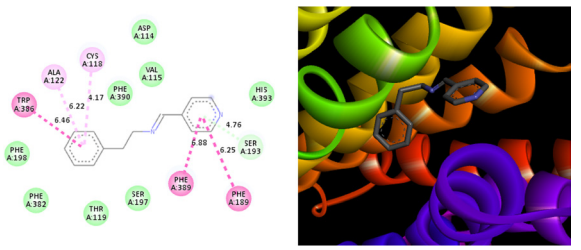


Figure 6. 2D and 3D interaction maps of compound 10 inside 6CM4 active site.

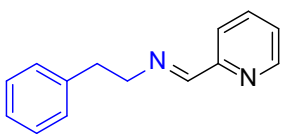
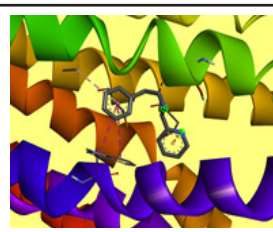
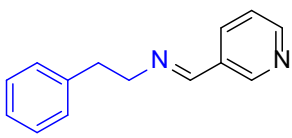
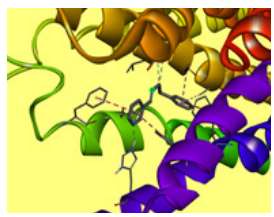
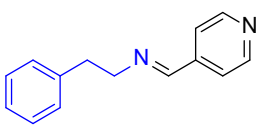
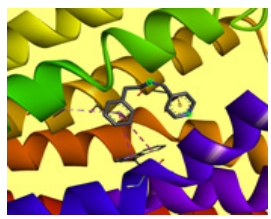
and 10 interact with D2 Dopamine Receptor /PDB: 6MC4 with energies of -6.79, -6.95, -7.07 kcal/mol, respectively. The entire docking pose made is given in Figure 3-6. It was found that compound 10 (-7.07 kcal mol^{-1}) which showed better binding energy than 9 (-6.95 kcal mol-1) and 8 (-6.79 kcal/mol) (Figure 3).

Compound 8 showed π-anion (π-sulphur) bond was observed between ASP114 residue with the 5.29 Å bond length (Fig. 4). π-alkyl interactions were observed between ALA122 (6.50 Å), CYS118 (4.56 Å) residues. The π-π T-shaped interactions were observed between PHE390, TRP386 and PHE198 residues and the centre of the phenyl ring with 6.79 Å, 6.03 Å and 5.25 Å bond lengths, respectively. Additionally, C-H bond interactions were observed between VAL115 (3.51 Å), and Wander Waals interactions were observed between PHE382, SER197, THR119, SER193 TYR416, THR412, PHE 389, and PHE 189.

Compound 9, as seen in Fig. 4, a conventional hydrogen bond was observed between N13 and HIS393 residues with the 5.66 Å bond length. The π- alkyl interaction was found in ALA122, CYS118 residue and the centre of the phenyl ring with 6.65 Å and 4.12 Å bond lengths. Additionally, π-π T-shaped interactions were observed between TRP386, PHE389, PHE189, and PHE390 residues and the centre of the phenyl ring with 5.95 Å, 6.40 Å, 6.41 Å and 7.06 Å bond lengths, respectively. Also, Wander Waals interactions were observed between PHE382, PHE198, THR119, SER197, SER193, VAL190, ILE184, ASP114, and VAL115.

Compound 10, As seen from Fig. 5, π-Donor hydrogen bond was observed between SER193 residue and phenyl ring with the 4.76 Å bond length. The π-alkyl interactions were observed between CYS118, ALA122 residues and the centre of the phenyl ring with 4.17 Å and 6.22 Å bond lengths. Additionally, π-π T-shaped interactions were observed betwe-

Table 1. Docking scores of the tested compounds 8-10 with D2DR (6CM4)

	2D structures of ligands	Residual interaction between compounds and D2 Dopamine receptor	Docking score (Kcal/Mol)
1			-6.79
2			-6.95
3			-7.07

en PHE389, PHE189, and TRP386 residues and the centre of the phenyl ring with 6.88 Å, 6.25 Å and 6.46 Å bond lengths, respectively. Also, Wander Waals interactions were observed between HIS393, SER197, THR119, PHE382, PHE198, PHE390, and VAL115.

CONCLUSION

In this study, new pyridine-based imine compounds were synthesized using microwave method. The structures of the compounds were determined by ^{1}H-NMR, ^{13}C-NMR and elemental analysis techniques. Then, docking studies of imine compounds against D2 Dopamine receptor (6CM4) were performed. Compound 10 (-7.07 kcal mol^{-1}) was found to show better binding energy than Compound 9 (-6.95 kcal mol^{-1}) and Compound 8 (-6.79 kcal mol^{-1}).

CONFLICT OF INTEREST

The author declares no conflict of interest.

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