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INVESTIGATION OF ANTI-DEPRESSANT POTENTIAL OF 2-(4-METHYL PIPERAZIN-1-YL) ACETOHYDRAZIDE-SYNTHESIS, DFT AND DOCKING STUDY

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ABSTRACT: 2-(4-methyl piperazin-1-yl) acetohydrazide was synthesized. The combined practice of IR, 1H NMR, and mass spectrometry established the structure of the synthesized compound. Geometry optimization was performed using DFT at the B3LYP level, employing the basis set 6-31G (d, p). For the optimized structure, surfaces were created to study excited state properties such as electrostatic potential mapped density, highest occupied molecular orbital, lowest unoccupied molecular orbital, ionization energy, and electron affinity. Electric dipole moment, bond length, and angles were computed using the same basis set for the optimized structure. ADMET prediction revealed that the compound possesses the ability to cross the blood-brain barrier and is non-toxic. Further Molecular docking studies with Human Monoamine Oxidase A were carried out to predict the mono-amine inhibitory potential of the compound. The compound revealed better energy scores than the standard. The synthesized compound was evaluated from all aspects concerning essential structural features as well as interaction patterns against selected receptors to be an effective antidepressant. This study would provide an excellent platform to further explore the acetohydrazide derivative toward designing and developing potent and target-specific drug candidates with enhanced binding affinities as an antidepressant.

INTRODUCTION: Nitrogen-based heterocyclic compounds play a crucial role in modern drug design and the development of pharmacologically active molecules. These compounds have a broad spectrum of pharmacological, physiological, and biological activities [1]. Nitrogen heterocycles are a privileged scaffold in the pharmaceutical industry [2-6]. Approximately 75% of FDA-approved small drug molecules contain a nitrogen heterocycle [7]. Nitrogen-containing heterocycles exhibit various bioactivities such as anticancer, anti-HIV, antimalarial, anti-tubercular, anti-microbial, and diabetic activities [8-19].

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The N-heterocyclic skeletons are frequently drawing the attention of chemists due to their distinct structural features, marginal toxicity, and high affinity toward various biological targets. Acetohydrazide is an important intermediate in organic synthesis. Recently Juan Chen *et al.* established the dual role of acetohydrazide as a directing group for the catalytic C(sp^3)–H activation process and as a protecting group for the CHO functional group in the palladium-catalyzed aldehyde-directed acetoxylation of C(sp^3)–H bonds [20].

Piperazine or Cyclizines are dinitrogen moieties, that are considered an indivisible component of a plethora of drugs. Piperazine is a versatile scaffold with diverse biological activities [21-26]. The introduction of piperazine moiety can escalate the bioactivity and can upgrade the therapeutic potential of the compound. Depression is the most

common psychiatric disorder reported worldwide. Approximately 280 million people in the world have depression (https://www.who.int/news-room/fact-sheets/detail/depression). Depression is referent to a mood or emotional state that causes persistent feelings of sadness, irritability, restlessness, anxiety, hopelessness, and decreased energy. Monoamine oxidase inhibitors (MAOIs) are a separate class from other antidepressants that are responsible for blocking the monoamine oxidase enzyme. Monoamine oxidase A (MAO-A) regulates levels of all 3 major monoamines (serotonin, norepinephrine, and dopamine) in the brain; therefore it is the most focused antidepressant target [27].

In the present investigation, 2-(4-methyl piperazin-1-yl) acetohydrazide (PZAH) was synthesized and various electronic properties, chemical reactivity, and site selectivity of the synthesized derivative were explored based on global reactivity descriptors obtained using the DFT/B3LYP method with 6-31G(d,p) basis set. Also, molecular docking simulation was employed to study the binding interactions between the receptor and PZAH compound as MAO-A inhibitors. The results obtained in this study could provide a rational template for further structural modifications for the development of potential MAO-A inhibitors as novel antidepressant agents.

MATERIALS AND METHODS: All reagents were purchased from SD fine chemicals and were used without further purification. Compound PZAH was synthesized by our earlier published method with slight modification [21]. Ethyl (4-methyl piperazin-1-yl) acetate (0.01mol) and hydrazine hydrate (98%) (0.01 mol) were refluxed in 10 ml ethanol for 12 h. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mass was cooled and kept in the refrigerator overnight. The precipitate formed was filtered off, washed with methanol, and dried.

Yield 75%; m.p.178–182 ˚C, IR (KBr) cm^{-1}: 3066.42 (-CONH), 2844.16 (C-H str.), 1687.35 (C=O); ^{1}H-NMR (DMSO) δppm: 1.061 (t, 4H, piperazine proton), 1.238 (s, 3H, N-CH_3 piperazine), 2.507 (dd, 4H, piperazine proton), 3.47 (broad singlet, 2H, -NH_2), 8.167 (s,1H, CONH); EI-MS: 172.13 (M^+); Anal Calcd for $C_7H_{16}N_4O$:C, 48.82; H, 9.36; N, 32.53; O, 9.29; Found: C, 48.81; H,9.32; N, 32.52; O, 9.32.

The structure of the PZAH derivative was drawn and constructed using ACD lab Chem sketch software **Fig. 1** and represents electron density clouds of the PZAH compound. The entire set of calculations was performed at the density functional theory (DFT) level using the GAUSSIAN 09W program package [28]. The optimized structural parameters were calculated using Density Functional Theory (DFT) using a 6-31G (d, p) basis set [29]. Surfaces were created to visualize the excited state properties such as Highest Occupied Molecular orbital (HOMO), Lowest Unoccupied Molecular Orbitals (LUMO), and electrostatic potentials (ESP) mapped density surface.

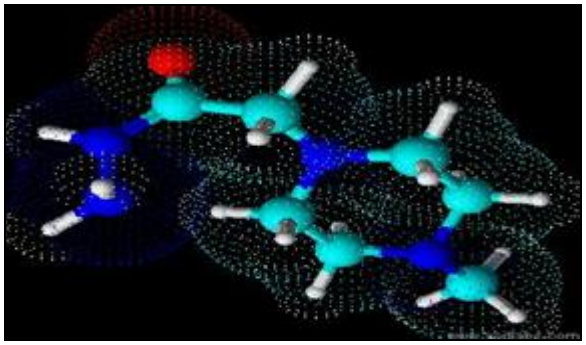

FIG. 1: ELECTRON DENSITY CLOUDS OF THE PZAH COMPOUND

RESULT AND DISCUSSION:

Molecular Geometry: The optimized molecular structure for PZAH in the ground state was computed by the B3LYP using the 6-31G (d, p) basis set in the gas phase with default tight convergence criteria. The analysis of molecular geometry has a significant role in determining the structure-activity relationship. Molecular geometry can be described by the positions of atoms in space, evoking bond lengths of two joined atoms, bond angles of three connected atoms, and torsion angles (dihedral angles) of three consecutive bonds. The optimization of PZAH was achieved by energy minimization, using DFT at the B3LYP level, employing the basis set 6-31G (d, p). The value of the total energy for the title compound is found to be -560. 2672 a.u. The optimized structure parameters of molecules calculated by using DFT – B3LYP levels with the 6-31G (d, p) basis set such

as bond lengths and bond angles of the PZAH derivative have been listed in **Table 1.**

TABLE 1: OPTIMIZED GEOMETRIC PARAMETERS OF PZAH DERIVATIVE

Bond Length (A°)		Bond Angles (°)	
C3C5	1.345	S4C3S2	113.686
N4C7	1.194	N4C2C1	117.836
C2N4	1.340	C7N4C2	171.177
C2C1	1.370	C1N11N12	173.673
C1N3	1.440	N11C1N3	116.369
C1N11	1.374	C6C5C8	158.836
N11N12	1.122	N3C5C8	59.892
N3C5	1.492	C8C9O10	169.109
C5C6	1.311	C5N3C8	57.880
C5C8	1.428	C5C8N3	62.226
N3C8	1.459	C5C8C9	141.47
C8C9	1.323	C1N3C5	118.887
C9O10	1.166	C2C1N11	112.338
		N3C5C6	141.194

Molecular Electrostatic Potential (MESP) Map: Molecular electrostatic potential (MESP) mapping is very useful to visualize variably charged regions of a molecule. It gives significant information about the charge distributions of molecules and charge-dependent properties of the molecules. The relative polarity of the molecule, partial charges, electronegativity, site of chemical reactivity, hydrogen bonding, and structure-activity relationship are some of the important parameters that can be well understood by investigating the molecular electrostatic potential map. The positive electrostatic potential corresponds to the repulsion of the proton by atomic nuclei in regions where low electron density exists and the nuclear charge is incompletely shielded (blue color on the ESP surface). In contrast, the negative electrostatic potential corresponds to an attraction of the proton by the concentrated electron density in the molecule (red color on the ESP surface).

Electrostatic potential increases in red < orange < yellow <green < blue. Electrostatic potential-mapped electron density surface showed the areas of the molecule that would be susceptible to nucleophilic and electrophilic attack. The electrostatic potential mapped on the total electron density surface of compound PZAH is illustrated in **Fig. 2.**

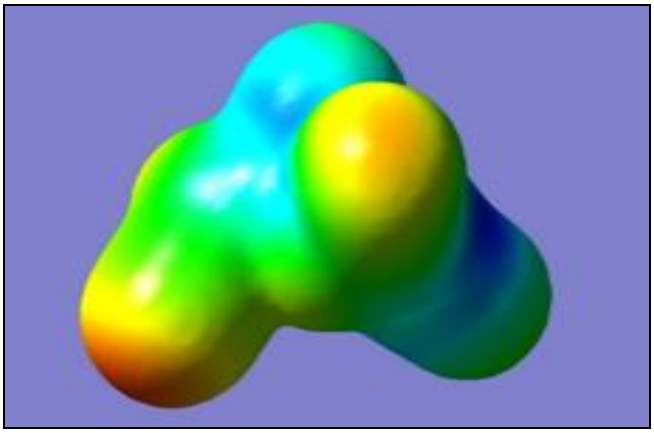

FIG. 2: THE MOLECULAR ELECTROSTATIC POTENTIAL SURFACE OF THE PZAH DERIVATIVE

Global Reactivity Descriptors: The hybrid functional B3LYP was used for the calculation of the electronic properties of the molecule such as electronic states, energy gap, ionization potentials, electron affinity, hardness, chemical potential, softness, and electronegativity. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are very important quantum chemical parameters in determining molecular reactivity. The frontier molecular orbital has a significant role in the optical and electric properties and quantum chemistry [29]. The quantum chemical descriptors of the PZAH derivative, such as the energy of the highest occupied molecular orbital (E_{HOMO}), the energy of the lowest unoccupied molecular orbital (E_{LUMO}), energy gap (ΔEgap), ionization energy (I), electron affinity (A) hardness (η), chemical potential (μ), softness (S), electronegativity (χ) and electrophilicity index (ω) were computed through Koopman's theorem[30] and are presented in **Table 2**. The energy gap ($E = E_{LUMO} - E_{HOMO}$) is an important parameter as a function of the stability of the compound. The energy of HOMO and LUMO are found to be negative, whereas the HOMO-LUMO energy gap has a positive value, reflecting

the titled compound's stability. The frontier molecular orbitals i.e. Highest energy-occupied molecular orbital (HOMO) and the lowest unoccupied (LUMO) molecular orbital of the PZAH derivative, have been illustrated in **Fig. 3.**

TABLE 2: QUANTUM CHEMICAL DESCRIPTORS OF PZAH DERIVATIVE

Para-meters	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔEgap (eV)	I (eV)	A (eV)	η (eV)	μ (eV)	X (eV)	S (eV)	ω (eV)
	-6.557	-4.234	2.323	6.557	4.234	1.1615	-5.3955	5.3955	0.4304	12.53

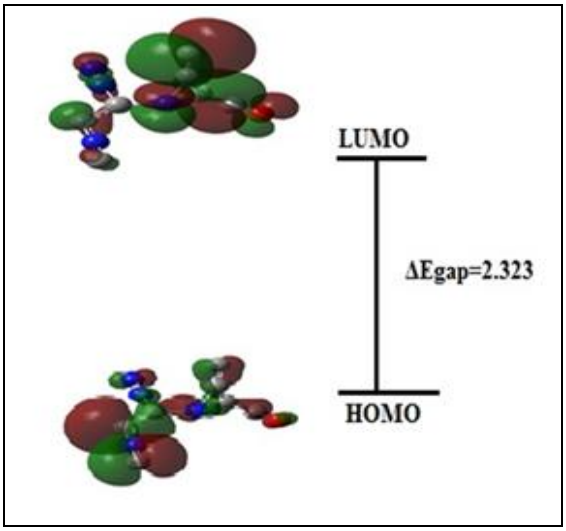

FIG. 3: HIGHEST OCCUPIED MOLECULAR ORBITALS AND LOWEST UNOCCUPIED MOLECULAR ORBITALS OF THE PZAH DERIVATIVE

Molecular Docking: Molecular docking was performed using the Autodock 4.2 software[31]. The crystal structure of three different antidepressant targets, Human Monoamine Oxidase A (PDB ID: 2Z5Y, 2BXR, 2Z5X) were fetched from the protein data bank (http://www.rcsb.org/pdb). The structure of the target protein and the ligand was regularized and optimized. In the protein, the presence of water molecules was removed and polar hydrogen was added. The root of the ligand molecule is detected and torsions were selected. All torsions of the ligand were allowed to rotate and checked for the selected residues. Phenelzine, a monoamine oxidase-inhibiting antidepressant was selected as the standard drug for the docking study. Blind docking was done to determine the preferential binding of the ligand. The docking was carried out using Lamarckian Genetic Algorithm (LGA) parameters for all the conformers in the binding site of the target protein. The docked compound was assigned a score according to its fit into the binding pocket. The results were evaluated based on the binding compatibility i.e. binding energy in kcal/mol and inhibition constant. From a total of 10 docking modes represented by cluster analysis, the lowest energy docking mode was selected from the docking simulation. The binding energy of the PZAH compound was found in the range of -6.36 Kcal/mole to -6.58 Kcal/mole (Table 3). The docking results revealed that the PZAH compound has a better docking score than the standard drug Phenelzine, predicting their good antidepressant potential against the selected protein target. ADMET properties were predicted using the admetSAR tool, and the calculated ADMET parameters are presented in **Table 4**. The results revealed that the PZAH compound is non-toxic and non-carcinogenic.

TABLE 3: DOCKING SIMULATIONS OF ANTIDEPRESSANT ACTIVITY OF THE COMPOUND PZAH

Target	2Z5Y		2BXR		2Z5X	
	Docking Score Kcal/mole	Inhibition Constant (Ki) (μM)	Docking Score Kcal/mole	Inhibition Constant (Ki) (μM)	Docking Score Kcal/mole	Inhibition Constant (Ki) (μM)
Compound	-6.58	14.94	-6.37	21.35	-6.36	21.62
SD	-5.80	55.98	-5.99	40.87	-5.80	55.77

TABLE 4: PREDICTION OF ADMET PROFILE OF THE TITLE COMPOUND

Compd.	Blood-Brain Barrier (BBB)	Human Intestinal Absorption (HIA)	Caco-2 Permeability	CYP Inhibitory Promiscuity	AMES toxicity	Carcinogenicity	Rat Acute Toxicity LD_{50} mol/Kg
PZAH	BBB+	HIA+	Caco2-	Low	Non-toxic	Non- Carcinogenic	2.4469
SD	BBB+	HIA+	Caco2+	Low	toxic	Carcinogenic	2.6507

CONCLUSION: In summary, 2-(4-methyl piperazin-1-yl) acetohydrazide derivative was synthesized and characterized. The molecular characteristics and structure parameters were examined to probe the chemical behavior of the compound. The Quantum chemical parameters such as E_{HOMO}, E_{LUMO}, energy gap (ΔE), electrostatic potential, and global reactivity descriptors were computed using density functional theory calculations within B3LYP/6-31G (d, p) basis set. The binding interactions of the PZAH derivative with Monoamine Oxidase A were carried out to investigate binding affinity, structural compatibility, and inhibitory predictions as an antidepressant. The compound revealed better energy scores than the standard and interacted with all the key amino acid residues. The synthesized PZAH was evaluated from all aspects for essential structural features and interaction patterns against selected receptors to be an effective antidepressant. This study would provide an excellent platform to further explore PZAH derivatives toward designing and developing potent and target-specific drug candidates with enhanced binding affinities as an antidepressant.

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