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Theoretical Investigation on Biological Activity of Phenacetin and Its Derivatives via DFT and Docking Approach

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

The actions of Phenacetin (N-(4-Ethoxyphenyl) acetamide) on the sensory tracts of the spinal cord has exposed its biological importance. It has been observed to be a non-opioid analgesic. The derivatives of Phenacetin were calculated using quantum chemical calculation and the descriptors (EHOMO, ELUMO, Band gap, LogP, Polar Surface Area (PSA), polarizability, HBA, HBD) that described the anti-pain activity of the studied compounds were obtained. In this work, several derivatives of phenacetin were studied with the use of density functional theory and its inhibiting effect on pain cell line (PDB ID: 5bqh) was observed through docking study. Compounds PA1 and PA5 were studied to inhibit more effectively than phenacetin, paracetamol and other studied derivatives.

Keywords: Phenacetine; DFT; docking; paracetamol.

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1. INTRODUCTION

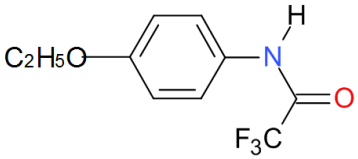
Phenacetin as one of the active components of analgesic has gained a wide recognition in several countries. Phenacetin (N-(4-Ethoxyphenyl) acetamide) is a non-opioid analgesic and antipyretic. It is also known as acetophenetidin, N-acetyl-p-phenetidine, aceto-4-phenetidine, acetophenetidine and p-ethoxyacetanilide. It was first synthesized in 1878 by Harmon Northrop Morse [1] and was used principally as an analgesic, for the treatment of fever and related complications [2,3]. The analgesic effects were observed owing to its activities on the sensory tracts of the spinal cord.

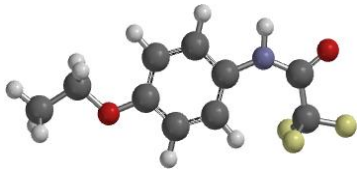
Phenacetin has a depressant action on the heart, where it acts as a negative inotrope i.e. weaken the force of muscular contractions [4]. The antipyretic effect was observed by its action on the brain via a decrease in the temperature set point [5]. It is also used to treat rheumatoid arthritis (sub-acute type) and intercostals neuralgia. However, the long-term and chronic consumption of phenacetin led to several toxicological complications ranging from nephrotoxicity to carcinogenicity [6]. The carcinogenicity is observed in the urinary tract and renal pelvis (transitional-cell carcinoma) [7,8]. As a result of these severe complications, phenacetin and drugs containing phenacetin were withdrawn from the market by the order of U.S. Food and Drug Administration in 1983 [9]. Due to its low cost, phenacetin is used for research into the physical and refractive properties of crystals.

The biological activity and the pharmaceutical properties of drugs are strongly dependent on their structure. The structural formulas and some physicochemical properties of phenacetin compounds have been known for decades. Detailed investigations of their crystal forms, however, were started in recent years [10]. A study of the molecular properties and molecular docking modelling of both compounds can be used to understand the differences in their biological activities.

In this work, seven molecules were subjected to calculation by using quantum chemical method (QCM) through density functional theory (DFT) method which were further used for docking studies. Thus, the aim of this work is to use quantum chemical method to calculate molecular parameters that defines the biological activities of the compounds under study as well as to identify the relationship that is existing between drug-like molecules and the receptor.

PA1





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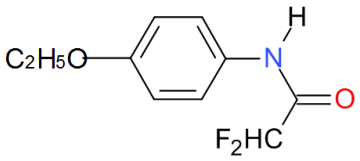
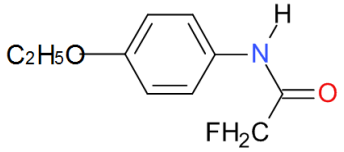
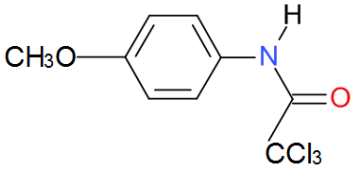
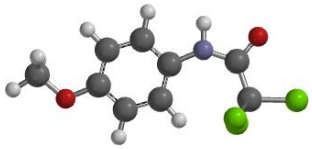


PA3



PA4





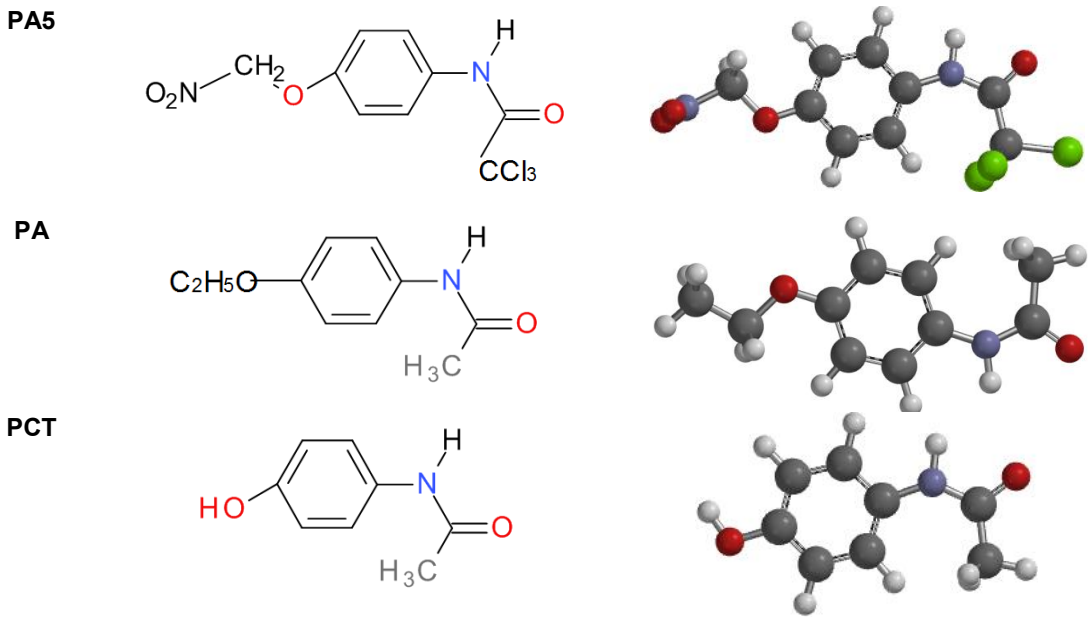


Fig. 1. Schematic and optimized structures of the studied compounds

2. MATERIALS AND METHODS

2.1 Quantum Chemical Calculation

Quantum chemical calculations were carried out on seven molecular compounds with three-parameter B3LYP density functional, i.e. Becke's gradient exchange correction [11] and the Lee, Yang, Parr correlation functional [12]. Therefore, the molecular compounds used in this work were calculated using B3LYP/6-31G* as basis set and the molecular descriptors (E_{HOMO}, E_{LUMO}, dipole moment (DM), molecular weight, hydrophobicity (log P), and polar surface area (PSA)) which described the bioactivity of the seven optimized molecular compounds were obtained. All quantum chemical calculations were performed by Spartan 14 program [13].

2.2 Docking Study

The studied receptor (PDB ID: 5qbh) [14] was downloaded from protein data bank and was subjected to treatment (i.e. removal of any water molecules, ligands etc.) that may be downloaded together with the enzyme and converted the receptor to the format (PDB) that will be accepted by the next software to be used using Discovery studio 4.1. Then, the AutoDock Tool 1.5.6 was used to locate the binding site of the receptor under study and it was used to convert both the ligand and the receptor to PDBQT which is the acceptable format for AutoDock Vina that will perform the docking. In this work, various conformations of the calculated ligand would be obtained with different binding energy. Therefore, the ligand with lowest binding energy is assumed to be stable and have the ability to inhibit the studied enzyme. Edupymol version 1.7.4.4 was finally used as post-dock analysis and inhibition constant (K_i) was also calculated using equation 1.

$$K_i = e^{\frac{-\Delta G}{RT}} \quad \text{---------- (1)}$$

3. RESULTS AND DISCUSSION

In this work, several molecular descriptors which describe the cytotoxicity of Phenacetine were obtained. The descriptors obtained were E_{HOMO}, E_{LUMO}, dipole moment (DM), molecular weight, hydrophobicity (log P), and polar surface area (PSA) (Table 1).

The theory of frontier molecular orbital give a detailed importance of HOMO and LUMO energies. They played a vital role in the determination of biological activity and general reactivity of molecular compounds [15-20]. The calculated E_{HOMO} for PA-PCT are -5.51eV, -5.69eV, -5.65eV, -5.57eV, -5.69eV, -5.88eV and -5.48eV as well as E_{LUMO} value is -0.24eV for PA, 1.10eV for PA1, -0.96eV for PA2, -0.55eV for PA3, -1.54eV for PA4, -2.69eV for PA5 and -0.23

for PCT. As shown in Table 1, PCT show highest ability to release more electron to the neighbouring compounds as well as PA5 possess more propensity to accept electron from the compounds that have the ability to release it. This could be due to nitro-group and CCl_3 that were attached as substituents. Therefore, both PCT and PA5 have biological importance.

The lower energy band gap of any molecular compounds bring about easier excitation and higher reactivity [21-24]. The calculated band gap are 5.27eV, 4.59eV, 4.69eV, 5.02eV, 4.15eV, 3.19eV and 5.25eV for PA-PCT respectively. The nitro-group and CCl_3 have an intense effect on the compound and this brought about lower band gap. Therefore, as shown in Table 1, PA5 have more tendency to react with proteins than other studied compounds. The calculated band gap could be arranged in the following order:

PA<PCT<PA3<PA2<PA1<PA4<PA5.

Moreover, the values obtained for Dipole moment were not arbitrarily large and as revealed in Table 1, PA5 proved /showed to be good as anti-pain drug. Also, the calculated log p which helps to probe into biological activity of studied compounds were shown in Table 1.

Also, in order to further established the effectiveness of the studied compounds, Lipinski's rule was considered where the drug-like molecules must possess the following: Hydrogen Bond Donor of drug-like molecule ≤ 5, Molecular Weight value of the ligand ≤ 500, Hydrogen Bond Acceptor of ligand ≤ 10 and Partition coefficient (Log P) value ≤ 5 [22]. Thus, all the studied compounds as shown in Table 1 agreed well with Lipinski's rule. More so, polar surface area (PSA) reveal the ability of a compound to be orally active if it is not more than $120A^2$, therefore, all the compounds used in this work can all be used orally [23,24]. All the studied compounds were good as pain-relieving agent, however, PA5 prove more efficient than other studied compounds in this work.

3.1 Docking Studies

Identification of pharmacophore with ability to interrelate with receptor which is a function of binding affinity defines docking study. As reported by Ritchie et al., 2008, the spontaneity of binding link between the drug-like compounds and the receptor could be enhanced by lowering of binding affinity [25]. Therefore, it was shown in Table 2 that PA1 and PA5 inhibited pain cell line (PDB ID: 5bqh) than both phenacetin, paracetamol, and other derivatives of phenacetin compound. The residues involved are LEU-83, PHE-87, PHE-16, SER-20 for PA1, LEU-83, SER-20, PHE-16, PHE-87 for PA2, SER-20, PHE-87, LEU-83, PHE-16 for PA3, SER-20,LEU-83, PRO-136 for PA4, PRO-136, PHE-87, GLY-86 for PA5, PHE-16, PHE-87, LEU-83, SER-20 for PA and SER-20, PHE-16, PHE-87 for PCT.

Table 1. The calculated molecular descriptors obtained for PCT and PA derivatives

	E_{HOMO} (eV)	E_{LUMO} (eV)	BG (eV)	DM (Debye)	MW	LOGP	OVALITY	PSA ($Å^2$)	POL	HBD	HBA
PA	-5.51	-0.24	5.27	4.80	179.219	1.15	1.35	31.604	55.99	1	3
PA1	-5.69	-1.10	4.59	6.16	233.189	2.30	1.37	31.409	57.31	1	3
PA2	-5.65	-0.96	4.69	4.09	215.199	1.71	1.36	31.629	56.90	1	3
PA3	-5.57	-0.55	5.02	4.50	197.209	1.16	1.36	31.610	56.43	1	3
PA4	-5.69	-1.54	4.15	5.98	268.527	2.71	1.38	30.896	58.21	1	3
PA5	-5.88	-2.69	3.19	3.47	313.524	-0.38	1.45	72.113	60.25	0	0
PCT	-5.48	-0.23	5.25	4.37	151.165	0.55	1.27	44.562	52.87	2	3

Note: PA = Phenacetin, PCT= Paracetamol

Table 2. Calculated binding affinity, inhibition constant and residues involved

Comp.	Affinity kcal/mol	K_i	Residue Involve in the interaction
PA1	-5.5	1.08×10^4	LEU-83, PHE-87, PHE-16, SER-20
PA2	-5.4	9.13×10^3	LEU-83, SER-20, PHE-16, PHE-87
PA3	-5.2	6.51×10^3	SER-20, PHE-87, LEU-83, PHE-16
PA4	-5.4	9.13×10^3	SER-20,LEU-83, PRO-136
PA5	-5.5	1.08×10^4	PRO-136, PHE-87, GLY-86
PA	-5.3	7.71×10^3	PHE-16, PHE-87, LEU-83, SER-20
PCT	-4.8	3.31×10^3	SER-20, PHE-16, PHE-87

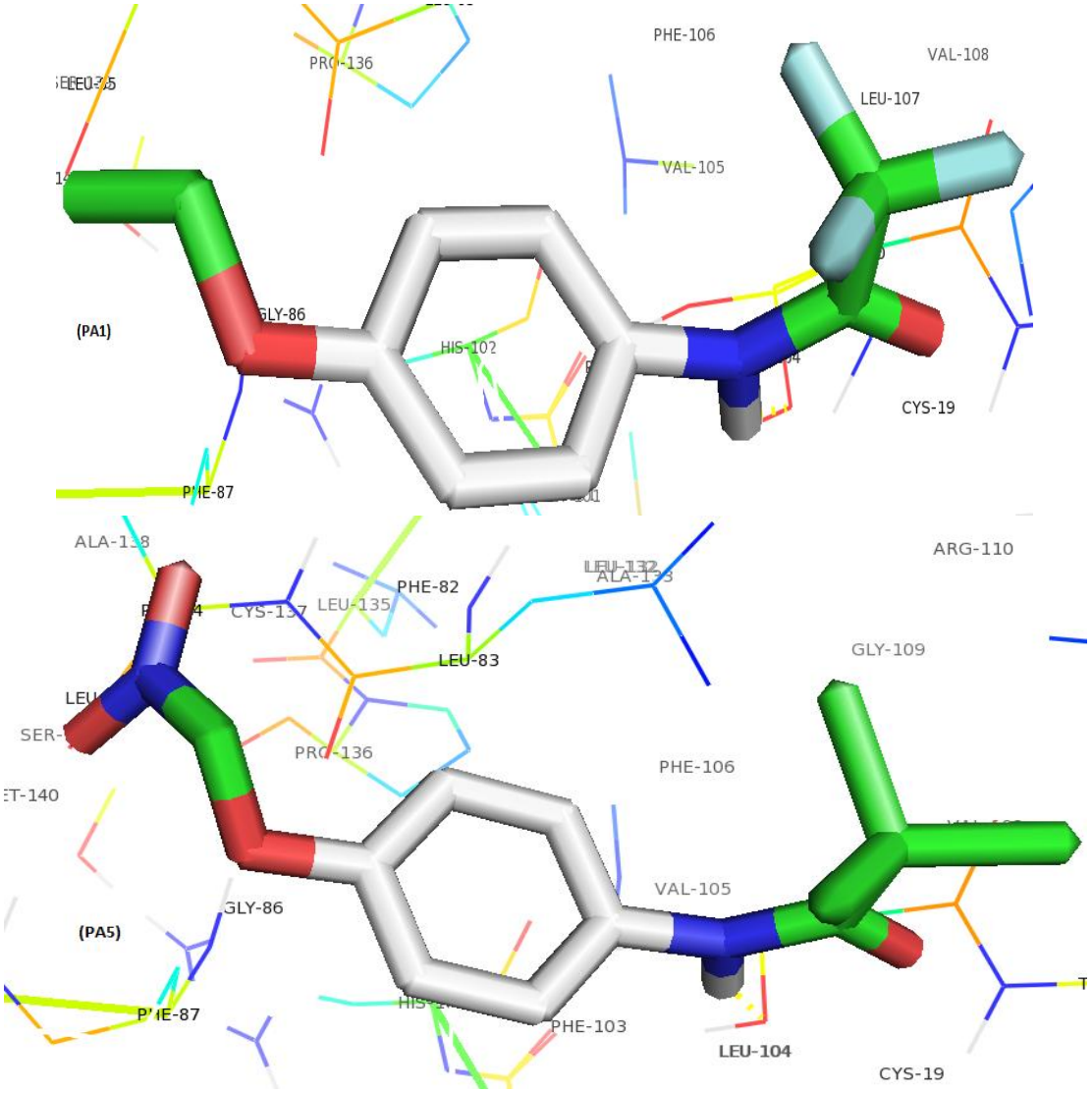


Fig. 2. Molecular binding interaction between PA1 and PA5 with 5bqh

Also, the calculated inhibition constant as shown in Table 2 revealed that the lowest binding affinity have the highest inhibition constant (K_i). Therefore, it was well confirmed that PA1 and PA5 possess the ability to inhibit well than paracetamol and other derivatives of phenacetin. The interaction for PA1 and PA5 were shown in Fig. 2.

4. CONCLUSION

Bioactivity of 7 sets of Phenacetine derivatives were studied by observing the calculated electronic descriptors using density functional theory method via 6-31G* as basis set. The obtained calculated descriptors proved that the studied compounds were drug-like molecules. The derivative of Phenacetin (PA5) possess excellence drug-like ability than other derivatives of phenacetine and paracetamol when compared together. Also, the binding affinity between the study compounds and pain cell line (PDB ID: 5bqh) were examined via docking study and both PA1 and PA5 with the same value for binding affinity inhibited more efficiently than other studied compounds.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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