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OPTIMIZATION AND MOLECULAR DOCKING STUDIES ON 2,2,2-TRIPHENYLACETOPHENONE PHENYLHYDRAZONE AND ITS ANALOGUES AS ANTI-TUBERCULAR AGENT

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ABSTRACT: *Density functional theory with 6-31G* as basis set have been used to examine selected Phenylhydrazone of 2,2,2-triphenylacetophenone and two analogues. The electronic descriptors obtained from the optimization of studied compounds are reported. It was discovered that dipole moment correlated well with the scoring. Also, inhibiting ability of selected Phenylhydrazones were observed using docking studies.*

KEYWORDS: Phenylhydrazone**,** DFT, docking, *Mycobacterium tuberculosis*

INTRODUCTION

Tuberculosis, a serious threat to human health has been in existence for several years. Tuberculosis is caused by *Mycobacterium tuberculosis* (Shingate, et al., 2018; Kashyap, et al., 2018; Balcells, et al., 2018). According to the world health organization (WHO), over 1 million people were reported killed by this disease while the number of both men and women with tuberculosis was reported to be close to 10 million (WHO, 2016). Tuberculosis was categorized to be among the top ten leading cause of death by contagious infection (Zhang, 2004). In spite of the continuous and growing cure of this preventable disease, yet, its spreading rate among human beings is a cause for great concern (Bishai, et al., 1997).

Hydrazones are organic molecules with several biological properties like antituberculous, anti-HIV, anti-inflammatory, antimicrobial activity, analgesic, anticancer and anticonvulsant (Nataliya, et al., 2007; Rollas, et al., 2007; Chimenti, et al., 2007; Mao, et al., 2007; Andreani, et al., 2008; Noulsri, et al., 2009; Vicini, et al., 2006). Over the years, several scientists have used different phenylhydrazines for many purposes such as (i) for derivatization (ii) characterization of organic compounds that contain carbonyl (iii) for defence of the carbonyl groups in the synthesis of organic compounds and (iv) for investigating the revolution of hydrazone-enhydrazine tautomers in the synthesis of indole analogues (Barton, et al., 1996; Jiang, et al., 1997; Chomcheon, et al., 2006; Kereselidze, et al., 1999). However, there is no literature report on 2,2,2-triphenylacetophenone phenylhydrazone.

Therefore, this work is aimed at using quantum chemical calculations (density functional theory (DFT) method) for optimization and observing the anti-tubercular activities of synthesized 2,2,2-triphenylacetophenone phenylhydrazone and two other hydrazone derivatives as well as observing the interaction that occurs as each studied ligand inhibits the *Mycobacterium tuberculosis* cell line. The studied antitubercula agent are acetophenone

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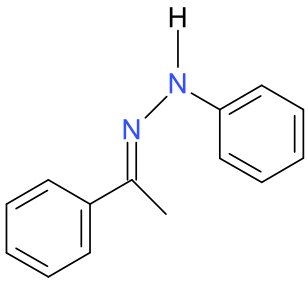
phenylhydrazone (**APPH**), benzophenone phenylhydrazone (**BPPH**) and 2,2,2-triphenyl phenylhdrazone (**TPPH**) (Figure 1).

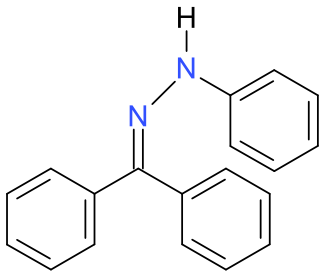
MATERIALS AND METHOD

Theoretical calculation

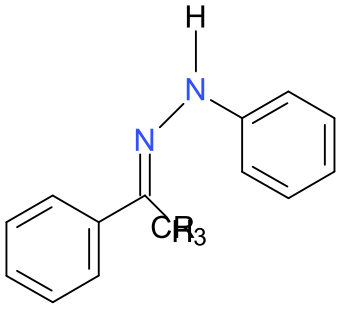
Quantum chemical calculations were carried out on the studied molecular structure of hydrazone derivatives (Figure 1) using Spartan 14 software package (Wim, et al., 2018; Derek, et al., 2018) on a computer with 1.70 GHz processor and 500 HDD. Molecular mechanics conformational distribution was used to obtain different conformers with diverse energies and the conformer with lowest energy which is assumed to be most stable was optimized via density function theory method with 6-31G* as the basis set. The optimized ligands were used for docking studies against *Mycobacterium tuberculosis* cell line (PDB ID: 2i1u) (Gareth, et al., 2006).



Acetophenone phenylhydrazone (**APPH**)



Benzophenone phenylhydrazone (**BPPH)**



2,2,2-triphenylacetophenone phenylhydrazone (**TPPH**) (R=C_6H_5)

Figure 1: Schematic structures of the studied compounds

RESULTS AND DISCUSSION

Optimization and Docking Studies

The molecular descriptors obtained from the optimized compounds using Spartan 14 are E_{HOMO} (eV), the E_{LUMO} (eV), band gap (eV), chemical hardness (η), global nucleophilicity, dipole moment (Debye), chemical potential, log P, molecular weight (amu), Ovality are given in Table 1.

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The three optimized molecular structures (Acetophenone phenylhydrazone **APPH**, Benzophenone phenylhydrazone **BPPH** and 2,2,2-triphenylacetophenone phenylhydrazone **TPPH**) served as ligands and the enzyme downloaded from Protein Data Bank (www.pdb.org) served as receptor. As reported by Pratik *et al*., 2018, binding mode and affinity of the active site of the enzyme could be predicted by molecular docking (Pratik, et al., 2018). Thus, the studied molecules which served as ligands were docked into the active gouge of the enzyme in order to inhibit the activities of the receptor. The scoring obtained from the docked complex were displayed in Table 2.

Furthermore, the role played by the calculated molecular descriptors in the relationship between the studied compounds and the receptor were examined and it was discovered that dipole moment correlated well with the binding affinity (R^2=0.9376) (Figure 2).

Table 1: Calculated molecular descriptors obtained by B3LYP/6-31G*

	E_{HOMO} (eV)	E_{LUMO} (eV)	BG (eV)	DM (Debye)	LOGP	MW	OVALITY	PSA (Å^2)	POL
APPH	-5.30	-0.85	4.45	3.57	3.28	210.280	1.39	18.418	59.75
BPPH	-5.32	-1.22	4.10	3.33	5.18	272.315	1.46	17.850	65.14
TPPH	-5.43	-0.78	4.65	3.37	8.87	438.574	1.61	16.318	79.96

Table 2: Binding affinity obtained from studied complexes

	Scoring (kcal/mol)
APPH	-4.90
BPPH	-5.40
TPPH	-5.20

As shown in Table 2, the calculated binding affinity ranged from -4.90 to -5.20 kcal/mol. This result showed that **BPPH** has a greatest ability to inhibit *Mycobacterium tuberculosis* cell line and this confirm the report made by Ritchie *et al*., 2008, that lower binding affinity improves spontaneity of binding relationship that take place between ligands and the receptor (Ritchie, et al., 2008). Figure 3 showed the interaction that occur between **BPPH** and 2i1u. Also, hydrophobic interactions and hydrogen bond were observed in the complex; PRO-91 of the receptor form coordination (Amide-Pi stacked and Pi-Alkyl) with benzene ring of benzophenone with the distance 4.81Å and 4.10 Å respectively. Also, ILE-84Å and ARG-94Å coordinated (Pi-Alkyl) with benzene ring of benzophenone with distance of 5.06Å and 4.80 Å respectively. More so, the hydrogen bond was formed between GLN-76 and N2 of **BPPH** with the distance of 2.82Å.

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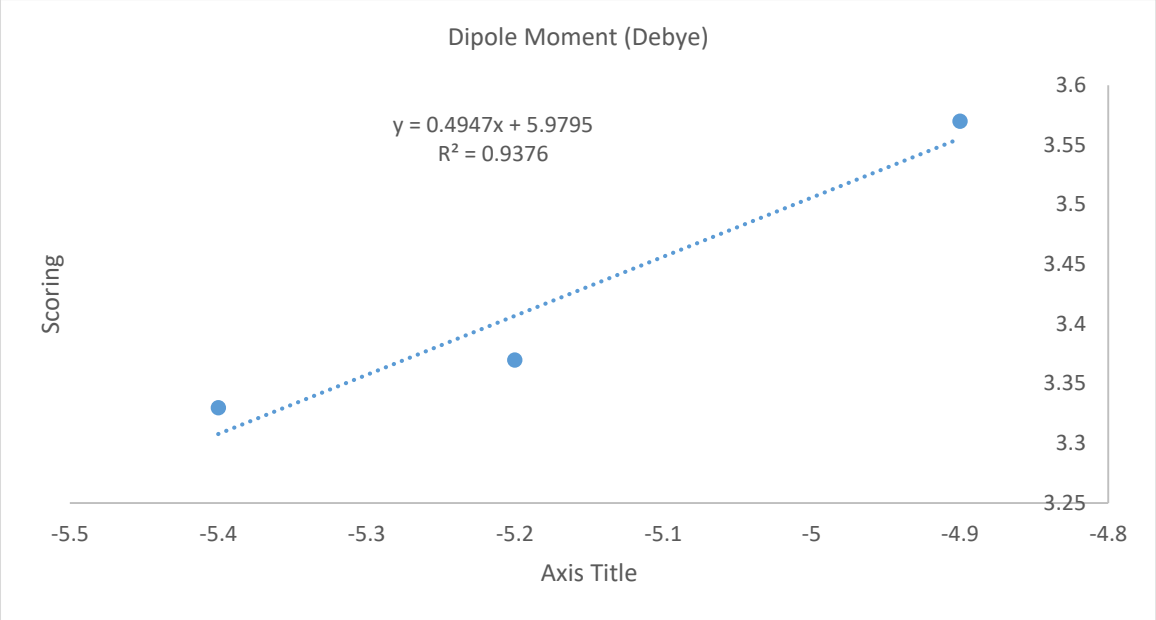

Figure 2: Correlation between Scoring and Dipole Moment

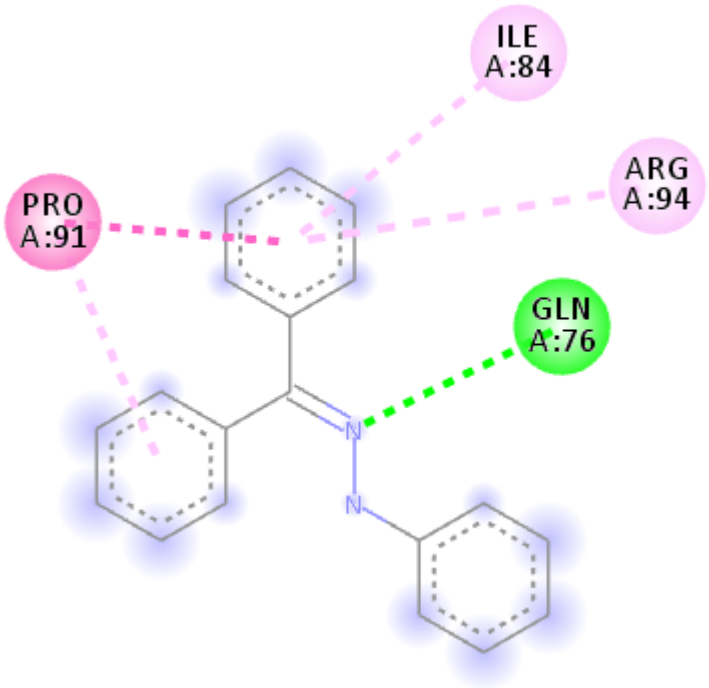

Figure 3: Binding interaction of **BPPH** with **2i1u**

CONCLUSION

Phenylhydrazone derivatives have been observed to be an active anti-microbial agent as reported by several scientist over the years. In this work, optimization of the studied

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compounds were observed and several descriptors like E_{HOMO} (eV), the E_{LUMO} (eV), band gap (eV), chemical hardness (η), global nucleophilicity, dipole moment (Debye), chemical potential, log P, molecular weight were calculated. Also, docking study was carried out on the Phenylhydrazone derivatives against *Mycobacterium tuberculosis* cell line (PDB ID: 2i1u) and **BPPH** inhibited the receptor more than **APPH** and **TPPH**. Dipole moment correlated well with the binding affinity than other descriptors calculated in this work.

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