Anti-Fungal Activities Of 2,4-Dintrophenyl Hydrazones Derivatives: Dft And Docking Approaches

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Abstract: In this work, a set of seven hydrazone derivatives were worked on using quantum chemical method and many molecular descriptors were obtained so as to probe in to their biological activities. Also, docking study was carried out on the studied compounds against the *C. albicans* cell line (receptor) 1q42 in order to obtain binding energy as well as to observe the interaction between them. The studied compounds were compared with Clotrimazole as standard drug. The order of binding energy of each molecule with the receptor is **AB7<AB1<AB5<AB6=AB4<AB3<AB2**. **AB7** was observed to inhibit better than the Clotrimazole that was used as standard.

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Introduction

The high rate of reports on complications encountered in diagnosing and treating multiple drug resistant (MDR) infections pose a threat to global health care (Coates, et al., 2002). In recent years, the mutilation caused by fungi infections has greatly increased (Eliopoulos, et al., 2002 and Subhedar, et al., 2017). Also, the rate of mortality and morbidity due to resistance to antifungal agent is on the high side and this has caused a major concern to medical world (Gao-Feng et al., 2017). In addition, several plant diseases are primarily caused by fungi infection and this has led to decrease in farming products worldwide which consequently affect negatively the food security in the entire world (Savary, et al., 2006).

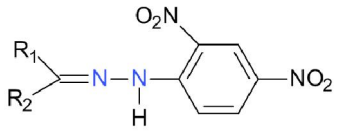
C. albicans, which is also known as yeast infection is a commensal in human beings. It is the basis for many disturbing diseases than other type of fungus (Elizabeth, et al., 2009). *C. albicans* is a yeast which is diploid in nature with two pairs of 8 genetic material. Several scientists have reported about *C. albicans* infection of the vaginal and oral mucosa meanwhile, few information is available on skin invasion (Andreas, et al., 2017).

Hydrazone and its analogues have several biological activities and also possess the capacity to form complexes (Ghazy et al., 2007, Kabil et al., 1999, Khalifa et al., 1995, Jackson et al., 1990, Abdelkarim et al., 2015, Sridhar et al., 2001). Over the years, their importance as anti-leprosy, antimicrobials, anti-tuberculosis, anti-tumor and anti-hypertensive have drawn the attention of many scientists (Joseph et al., 2016).

The positive impact made by quantum chemical method in the science world help it sustainability among scientists, especially in the determination of structure, explanation of molecular reactivity and explication of chemical structures (Kraka, et al., 2000). Density functional theory (DFT) as a tool offers additional useful basis for creating a new set of reasons justifying calculation in many areas of chemical processes (Cohen, 1996; Sanderson, 1952; Awad, 2004; Parr et al., 1984; Pearson, 1963) and has been widely accepted by researchers due to its relative accuracy (Oyebamiji, et al., 2016).

For several years, docking as a way of determining the relationship between the drug-like molecules and the receptor has been widely acknowledged. This is a function of its capacity to basically select vast set of molecules and scoring, together with revealing the steps involved in inhibition of targeted binding site by drug-like molecules (Cherfils, et al., 1993; Kuntz, et al., 1994). So, the calculated interactions from docking could be conveyed in a dock score form (Sharma, et al., 2011).

Seven molecular compounds (fig. 1) were worked on using quantum chemical method (QCM) via density functional theory (DFT) method including docking studies. The objective of this work is to use quantum chemical method for the calculation of descriptors which define the biological activities of the compounds under study as well as to detect the relationship between both the molecules (ligand) and the receptor.



	R_1	R_2
AB1	H	H
AB2	CH3	CH_3
AB3	Ph	H
AB4	Ph	CH_3
AB5	Ph	Ph
AB6	Ph	CF_3
AB7	Ph	CPh_2

Fig. 1. The schematic structures of hydrazone derivatives

Computational details

Quantum Chemical Methods

The density functional theory methods give more details for understanding many chemical models used in various areas of Chemistry. The parameters on which density functional theory is based are Becke's gradients exchange correction (Becke, 1993) and the Lee, Yang, Parr correlation functional (*i.e.* B3LYP) (Lee, et al., 1988). In addition, the exactness of density functional theory methods is a function of the selected basis set. In this work, 6-31+G* basis set was used for the optimization of the studied compounds. The optimizations of the compounds were accomplished using quantum chemical software Spartan' 14 by wave function Inc (Spartan '14). Likewise, the optimized drug-like molecules were used for docking study for the calculation of binding energy from the interaction between the molecular compounds and the *C. albicans* cell line (PDB ID: 1q42) (Claire, et al., 2003).

3.0 Results and Discussion

3.1 *Molecular Descriptors*

Table 1 shows the values of basic important descriptors E_{HOMO}, E_{LUMO}, dipole moment (DM), molecular weight, hydrophobicity (log P), volume, (V), area polar surface area (PSA) and average of muliken charges on all heteroatoms in the compound obtained through B3LYP/6 - 31+G* level of theory (Table 1).

According to frontier molecular orbital theory, E_{HOMO} and E_{LUMO} play very important role in determining the cytotoxicity of molecular compounds (Mu, et al., 2015; Mu, et al., 2016; Oyebamiji, et al., 2017) and general bioactivity of molecules (Kraka, et al., 2000; Cohen, 1996; Sanderson, et al., 1952). **AB2** has the highest value of E_{HOMO} and have the greatest ability to give electrons to adjoining compounds while **AB6** and **AB7** compounds that have the lowest values of E_{LUMO} have the highest affinity of receive electron from compounds with higher values of E_{HOMO}.

Band-gap ($E_{LUMO} - E_{HOMO}$) is a significant descriptor that tells more about the reactivity of the drug-like molecule towards the receptor. According to Oyebamiji *et al*., 2017, the lower the band gap, the better the reactivity of the drug-like molecules toward the receptor (Oyebamiji, et al., 2016). Thus, given the values of calculated band gap shown in Table 1, **AB2** is expected to have a better interaction with the receptor than other compounds. The order of energy band gap is **AB6> AB7 > AB3 > AB1 > AB5 > AB4 > AB2**.

Table 1. Calculated molecular descriptors of the studied compounds

	HOMO	LUMO	BG	DM	CH	CP	GN	H	LOG P	OVA	PSA	POL	HBD	HBA
AB1	-4.49	-4.11	0.38	6.42	0.19	-4.3	48.65	-0.65	-0.57	1.37	99.38	56.35	3	8
AB2	-4.47	-4.12	0.35	7.22	0.175	-4.29	52.70	-0.69	0.32	1.43	98.13	59.3	3	8
AB3	-4.52	-4.13	0.39	7.31	0.195	-4.32	47.96	-0.67	1.9	1.46	97.48	63.14	3	8
AB4	-4.51	-4.15	0.36	7.53	0.18	-4.33	52.08	-0.67	1.46	1.49	97.48	64.61	3	8
AB5	-4.54	-4.17	0.37	7.21	0.185	-4.35	51.25	-0.62	3.36	1.55	96.83	69.92	3	8
AB6	-4.62	-4.18	0.44	7.58	0.22	-4.4	44.0o	-0.92	2.61	1.52	97.78	65.77	3	8
AB7	-4.58	-4.18	0.4	6.84	0.2	-4.38	47.96	-0.62	5.06	1.66	96.75	78.25	3	8

Key: BG: Band gap, CH: Chemical hardness, Cp: Chemical potential, GN: global nucleophilicity, OVA: ovality, POL: polarizability, HBD: hydrogen bond donor, HBA: hydrogen bond acceptor.

Lipophilicity, log P, helps to probe into the biological activity of the drug-like molecule. Abass et al., 2011 reported the details of the application lipophilicity (log P) which is the sharing of molecular compounds between non-aqueous and aqueous phase (Abass, et al., 2011). The calculated log P values given in Table 1 showed that except for compound **AB7,** all the other studied compounds in this work are efficient in term of lipophilicity since the calculated log P values are not greater than 5 (Meanwell, 2011).

Dipole moment plays a crucial role in increasing the efficiency of the ligands. All the compounds (**AB1-AB7**) appear to be suitable in terms of dipole moment values because all the values obtained for dipole moment are not arbitrarily large [Table 1]. Polar surface area should not be larger than $120A^2$ for

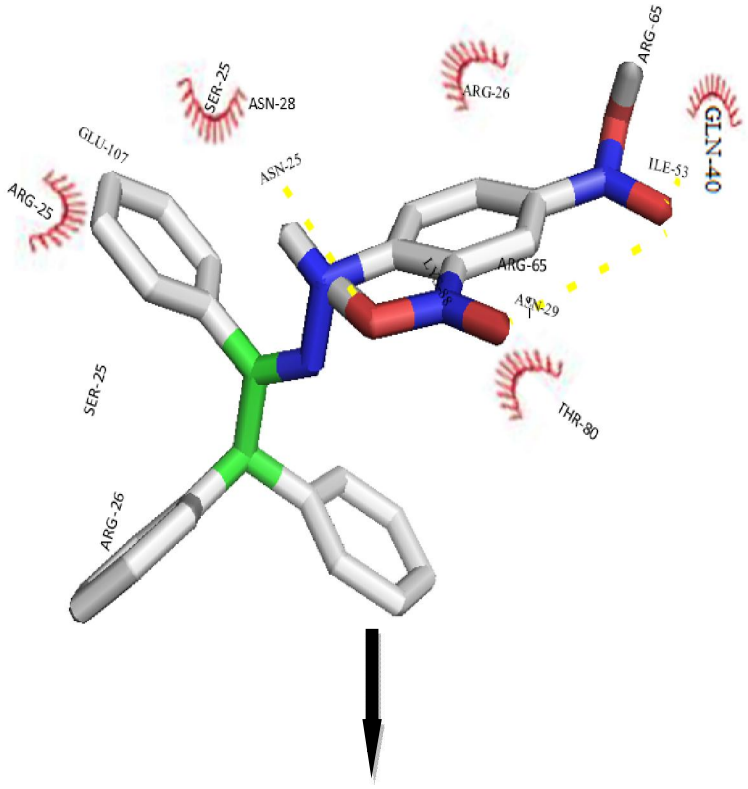
drug that are orally active and are carried by trans-cellular route (van de Waterbeemd, et al., 1998; Kelder et al., 1999). Thus, all the molecular compounds under study appear to be orally active. All other descriptors like ovality, HBA and HBD are calculated and shown in Table 1.

Docking and scoring

Clotrimazole and all the studied compounds (**AB1**-**AB7**) were docked against *C. albicans* cell line (PDB ID: 1q42) (Claire, et al., 2003) and values of the binding energy were calculated as well as other interactions like hydrogen bond and are displayed in Table 2. The receptor was downloaded from protein data bank (www.rcsb.org) and several softwares (Discovery studio, Autodock tool, Autodock vina and Pymol as the post-dock software) were used on it. Nine (9) conformations each was observed for individual interaction and the best conformation is presumed to be the conformation with lowest binding energy in each docking. Thus, **AB7** with the lowest binding energy has the greatest ability to hinder the receptor (1q42) as presented in Table 2. As observed in this research, **AB7** has higher ability to inhibit *C. albicans* than the Clotrimazole (Standard) and this could be attributed to the replacement of Hydrogen in **AB1** with phenyl and triphenyl methyl groups at R_1 and R_2 respectively. Similarly, the hydrogen bonds and hydrogen bond distances observed in the studied interaction are shown in Table 2. Also, the binding mode of **AB7** (with the utmost binding energy) in the active site of 1q42 is displayed in Figure 2.

Table 2: Interactions between Ligands and receptor (1q42)

	Affinity (Binding energy) (kcal/mol)	H-Bond Between Amino Acid and Drug	Distance
AB1	-7.3	(i) ILE-53, LIG:H (ii) PHE-103, LIG: N	(i) 2.8 (ii) 3.5
AB2	-5.0	(i) HIS-83, LIG:O (ii) ASP-21, LIG:O (iii) ASP-21, LIG: O (iv) LEU-23, LIG: O	(i) 3.1 (ii) 2.8 (iii) 2.8 (iv) 2.6
AB3	-6.4	(i) HIS-83, LIG: O (ii) HIS-83, LIG:O (iii) ASP-21, LIG:O (iv) ASP-21, LIG:O (v) LEU-23, LIG:O	(i) 2.7 (ii) 2.7 (iii) 2.8 (iv) 2.8 (v) 2.5
AB4	-6.6	(i) HIS-83, LIG: O (ii) HIS-83, LIG:O (iii) ASP-21, LIG:O (iv) ASP-21, LIG:O (v) LEU-23, LIG:O	(i) 2.7 (ii) 2.7 (iii) 2.8 (iv) 2.9 (v) 2.4
AB5	-7.0	(i) HIS-83, LIG: H (ii) HIS-83, LIG:O (iii) ILE-53, LIG:H	(i) 2.3 (ii) 2.1 (iii) 2.9
AB6	-6.6	(i) HIS-83, LIG: O (ii) HIS-83, LIG:O (iii) ASP-21, LIG:O (iv) ASP-21, LIG:H (v) LEU-23, LIG:O	(ii) 3.1 (ii) 2.8 (iii) 2.8 (iv) 2.8 (v) 2.7
AB7	-7.8	(i) ASN-55, LIG: O (ii) ASN-55, LIG: O (iii) ILE-53, LIG: O	(i) 2.1 (ii) 3.3 (iii) 3.0
CLO	-7.2		



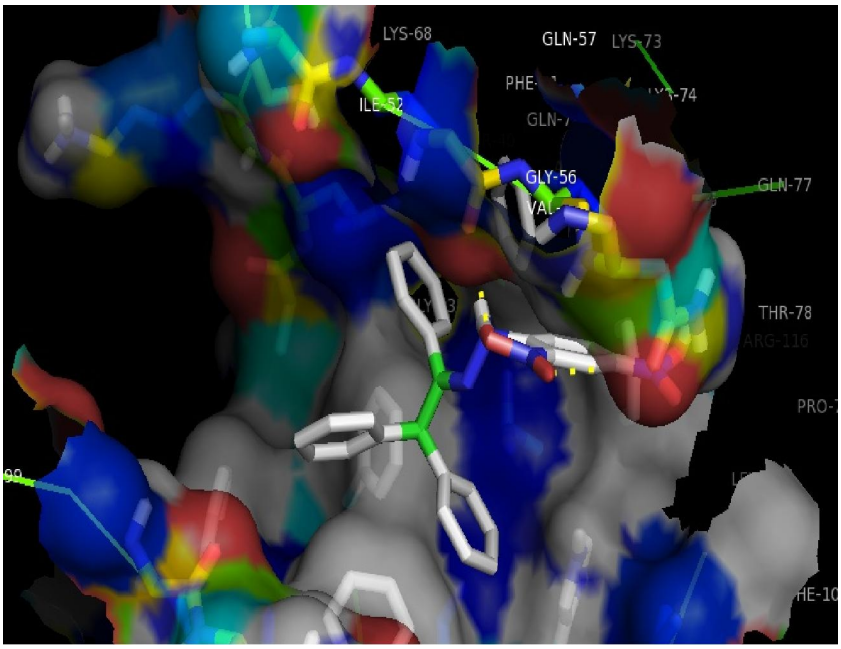


Figure 2: Binding interaction of compound **AB7** with 1q42

Conclusion

The electronic properties of hydrazones (**AB1-AB7**) have been calculated using density functional theory at B3LYP/6-31+G*. The calculated electronic descriptors obtained from the drug-like molecules revealed their anti-fungal activity. In addition, the docking studies showed that the compound, **AB7** inhibited the receptor more than Clotrimazole (standard) and other compounds under study.

Reference

1 Coates A, Hu Y, Bax R, Page C. The future challenges facing the development of new antimicrobial drugs. Nat. Rev. Drug. Discov. 2002; 1: 895–910.

2 Eliopoulos GM, Perea S, Patterson TF. Antifungi resistance in pathogenic fungi. Clin Infect Dis. 2002; 35: 1073.

3 Subhedar DD, Shaikh MH, Shingate BB, Nawale L, Sarkar D, Khedkar VM, Kalam Khan FA, Sangshett JN. Quinolidene-rhodanine conjugates: Facile synthesis and biological evaluation. Eur. J. Med. Chem. 2017; 125: 385.

4 Gao-Feng Z, Jing L, Darshini N, Shubhavathi T, Vivek HK, Abdullah MA, Hadi MM, Rakesh KP, Mallesha N, Hua-Li Q. Synthesis, SAR and molecular docking studies of benzo [d] thiazolehydrazones as potential antibacterial and antifungal agents. Bioorganic & Medicinal Chem. Lett. 2017;27:3148–3155.

5 Savary S, Teng PS, Willocquet L, Nutter FW Jr. Quantification and modeling of crop losses: A review of purposes. Annu. Rev. Phytopathol. 2006; 44:89−112.

6 Elizabeth MJ. Rare and Emerging *Candida* Species. Current Fungal Infection Reports. 2009; 3: 152-159.

7 Andreas K, Anke B-K, Steffen R. Interaction of Candida Species with the Skin. Microorganisms. 2017; 5(32):1-12.

8 Ghazy SE, Rakha TH, El-Kady EH, El-Asmy AA. Use of some hydrazine derivatives for the separation of mercury (II) from aqueous solutions by flotation techniques. Ind. J. Chem. Tech-nol. 2007; 7: 178-182.

9 Kabil MM, Akl MA, Khalifa ME. Selective flotation-spectrophotometric procedure forvthe trace analysis of palladium (II) in different matrices. Anal. Sci. (Jpn). 1999; 15: 433-438.

10 Khalifa ME. Extractive separation and spectrophotometric micro determination of palladium (II) with 2-hydroxy-imino-3-(2-hydrazonopyridyl) butane. Anal. Fr. 1995; 23: 453-466.

11 Jackson SH, Shepherd AM, Ludden TM, Janieson MJ, Woodworth J, Rogers D, Ludden LK, Muir KT. Effect of food on oral availability of apresoline and controlled release hydralazine in hypertensive patients. J. Cardiovasc. Pharmacol. 1990; 16(4): 624-628.

12 Abdelkarim AT. Spectroscopic characterization of novel Cu (II) mixed ligand complexes involving tridentate hydrazine ligand and some amino acids as antibacterial and antioxidant

agents. International Journal of Pharma Sciences. 2015; 5(1): 839-851.
13 Sridhar SK, Saravanan M, Ramesh A. Synthesis and antibacterial screening of hydrazones, Schiff and Mannich bases of isatin derivatives. Eur. J. Med. Chem. 2001; 36(6-8): 615-25.
14 Joseph NY, Peter FA, Kennedy DN, Romanus NN, Oswald NN. Synthesis, Spectroscopic Studies and Antimicrobial Activity of Novel Aromatic hydrazones Derived from 1-Hydralazinophthalazine. American Chemical Science Journal. 2016; 14(3): 1-10, Article no. ACSJ.26059.
15 Kraka E, Cremer D. Computer Design of Anticancer Drugs. A New Enediyne Warhead. J. Am. Chem. Soc. 2000; 122: 8245.
16 Cohen MH. In Topics in Current Chemistry, Nalewajski RF, Ed.; Springer-Verlag: Heidelberg, Germany. 1996; 183: 143.
17 Sanderson RT. Camoquin Relatives. J. Am. Chem. Soc. 1952; 74: 272.
18 Awad MK. Semiempirical investigation of the inhibition efficiency of thiourea derivatives as corrosion inhibitors. J. Electroanal. Chem. 2004; 567: 219.
19 Parr RG, Yang W. Density functional approach to the frontier-electron theory of chemical reactivity. J. Am. Chem. Soc. 1984; 106: 4049.
20 Pearson RG. Hard and Soft Acids and Bases. J. Am. Chem. Soc. 1963; 85: 3533.
21 Oyebamiji KA, Semire B. Studies of 1, 4-Dihydropyridine Derivatives for Anti-Breast Cancer (MCF-7) Activities: Combinations of DFT-QSAR and Docking Methods. New York Science Journal. 2016; 9(6).
22 Cherfils J, Janin J. Protein docking algorithms: simulating molecular recognition. Curr. Opin. Struct. Biol. 1993; 3: 265-269.
23 Kuntz ID, Meng EC, Shoichet BK. Structure-Based Molecular Design. Acc. Chem. Res. 1994; 27: 117-123.
24 Sharma V, Wakode SR, Lather V, Mathur R, Fernandes MX. Structure based rational drug design of selective phosphodiesterase-4 ligands as anti-inflammatory molecules. Bull Pharm. Res. 2011; 1(2): 33 - 40.
25 Becke AD. Density functional thermochemistry. III. The role of exact exchange. J. of phy Chem. 1993; 98: 5648 – 5652.
26 Lee C, Yang W, Parr RG. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B. 1988; 37: 785.
27 Spartan 14, Wavefunction, INC, Irvine CA 92612, USA.
28 Claire S, Paul F, Corinne R, Klaus-Jo¨rg R, Jacques W, Denis P, Yves B. Structural Insights into A Dual Role Of Mtr2 For Yeast Nuclear Export, The Journal Of Biological Chemistry. 2003; 278(48): 48395–48403.
29 Mu J-X, Yang M-Y, Sun Z-H, Tan C-X, Weng J-Q, Wu H-K, Liu X-H. Synthesis, Crystal Structure and DFT Studies of 8-chloro-3-((3-chlorobenzyl) thio)-[1,2,4] triazolo [4,3-a] pyridine. Crystals. 2015; 5(4): 491-500. [DOI: 10.3390/cryst5040491].
30 Mu J-X, Zhai Z-W, Yang M-Y, Sun Z-H, Wu H-K, Liu X-H. Synthesis, Crystal Structure, DFT Study and Antifungal Activity of 4-(5-((4-Bromobenzyl) thio)-4-Phenyl-4H-1,2,4-Triazol-3-yl) pyridine. Crystals. 2016; 6: 4. [DOI: 10.3390/cryst6010004].
31 Oyebamiji AK, Semire B. Studies of 2-[5-(aryloxymethyl)-1, 3, 4-oxadiazol-2-ylsulfanyl] acetic acid derivatives for antibacterial activities via dft, qsar and docking approaches. Bulletin of Pharmaceutical Research. 2017; 7(3): 148.
32 Oyebamiji AK, Semire B. Dft-Qsar Model and Docking Studies Of Antiliver Cancer (Hepg-2) Activities Of 1, 4-Diydropyridine Based Derivatives. Cancer Biology. 2016; 6(2).
33 Abass K, Reponen P, Mattila S, Pelkonen O. Metabolism of α-thujone in human hepatic preparations in vitro. Xenobiotica. 2011; 41(2): 101-11. [DOI: 10.3109/00498254.2010.528066].
34 Meanwell, N. A. (2011). Synopsis of some recent tactical application of bioisosteres in drug design. J. Med. Chem. 54(8), 2529-91. [DOI: 10.1021/jm1013693].
35 van de Waterbeemd H, Camenisch G, Folkers G, Chretien JR, Raevsky OA. Estimation of blood-brain barrier crossing of drugs using molecular size and shape, and H-bonding descriptors. J. Drug Target. 1998; 6(2):151-165. [DOI:10.3109/10611869808997889].
36 Kelder J, Grootenhuis PD, Bayada DM, Delbressine LP, Ploemen JP. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. Pharm. Res. 1999; 16(10): 1514-9. [DOI:10.1023/a:1015040217741].