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RESEARCH ARTICLE

DFT Studies and Quantum Chemical Calculations of Benzoyl Thiourea Derivatives Linked to Morpholine and Piperidine for the Evaluation of Antifungal Activity

Rameshwar K. Dongare[1], Shaukatali N. Inamdar[2] and Radhakrishnan M. Tigote[3,*]

[1]*Department of Chemistry, Ahmednagar College, Ahmednagar, 414001, India;* [2]*Department of Chemistry, Dattatray Govindrao Walse Patil College, Pargaon Tarfe Awsari, Pune 412406, India;* [3]*Department of Chemistry, Dr. B. A. M. University sub-Campus, Osmanabad, 413501, India*

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Abstract: ***Background*:** Benzoyl thiourea derivatives linked to morpholine and piperidine have been reported to possess good antifungal activity.

***Objective*:** The aim of the study was to find the correlations between the quantum chemical calculations and the antifungal activity of the benzoyl thiourea derivatives linked to morpholine and piperidine.

***Methods*:** Optimization of six compounds BTP 1-3 and BTM 4-6 was carried out with DFT using B3LYP method utilizing 6-31G(d,p) basis set. The structural parameters of the compounds as molecular geometry, bond lengths, bond angles, atomic charges and HOMO-LUMO energy gap have been investigated and compared with the reported experimental results.

***Results*:** A good correlation between the quantum chemical calculations and the antifungal activity of the benzoyl thiourea derivatives linked to morpholine and piperidine was found.

***Conclusion*:** The DFT study of benzoyl thiourea derivatives linked to morpholine and piperidine conducted with respect to their Quantum chemical parameters for evaluation of their antifungal activity showed good correlations between the antifungal activity and the quantum chemical parameters.

Keywords: DFT, HOMO-LUMO, benzoyl thiourea derivatives, morpholine, piperidine, antifungal activity.

1. INTRODUCTION

The pyridine, morpholine and thiourea exhibit broad biological activities, including antibacterial and antifungal effects [1-9]. Diaryl thioureas present significant antifungal activity against the plant pathogens *Pyriculariaoryzae* and *Drechslera oryzae* [10]. Acyl thioureas are well known for their superior pesticidal, fungicidal, antiviral and plant growth regulating activities [11].

On the other hand, sulfur-linked 1,2,4-triazoles represent an important group of sulphur compounds that are promising for use in lead compound discovery, especially thione-substituted 1,2,4-triazole ring. Thus far, many bioactive sulphur-linked 1,2,4-triazoles have been reported, such as having antibacterial activity, antitumor activity, anti-HIV activity, and fungicidal activity area; some pyridine derivatives can prevent the activites of *Ralstonia solanacearum*, *Cercospora beticola sacc.*, and *Colletotrichum orbiculare* [12-15].

The introduction of fluorine at a strategic position of a molecule is a powerful and versatile tool for the development of organic molecules possessing potential biological activities by changing the steric and electronic parameters [16-22]. The

*Address correspondence to this author at the Department of Chemistry, Dr. B. A. M. University sub-Campus, Osmanabad, 413501, India; E-mail: rmtigote.chemobad@bamu.ac.in

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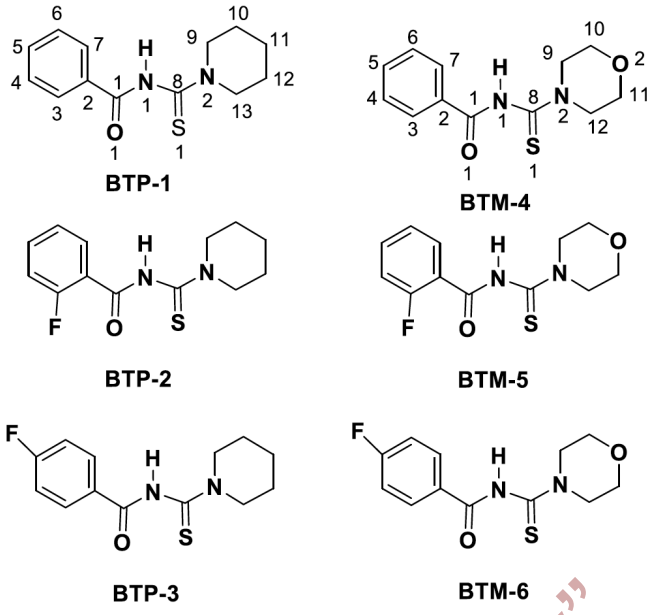

Fig. (1). Structures of benzoyl thiourea piperidine derivatives (BTP1, BTP2 and BTP3) and benzoyl thiourea morpholine derivatives (BTM4, BTM5 and BTM6).

inclusion of fluorine into organic molecules can increase lipophilicity, and thus, enhance the rate of cell penetration and transport of a drug to an active site [23]. Fluorinated thioureas constitute a novel class of potent influenza virus neuraminidase inhibitors [24]. The theoretical calculation of the benzoyl thiourea derivatives and their complexes with Cobalt was reported by Yang *et al.* to explain their antibacterial activities [25]. Later, C. Li *et al.* reported the antifungal activities of the Fluorine-containing thioureido complexes with Nickel(II) [26].

Here, we have used the ligands from these studies to evaluate the correlation between their activity and theoretical results. In this paper, six compounds with benzoyl thiourea derivatives linked to piperidine (BTP 1, BTP 2 and BTP 3) and benzoyl thiourea derivatives linked to morpholine (BTM 4, BTM 5 and BTM 6) were optimized using DFT/B3LYP method. The structures of studied compounds are shown in Fig. (**1**). The effect of fluorine substitution, frontier orbital energy and structure-activity relationship on the antifungal activities was explored.

2. RESULTS AND DISCUSSION

The obtained results are discussed as follows:

2.1. Comparison of DFT Structural Parameters with Experimental Values

The DFT calculations were carried out with B3LYP/6-31G (*d,p*) method in the GAMESS package [27-31]. Fig. (**2**) depicts the optimized structures of BTP 1-3 and BTM 4-6. The geometry parameters, viz. calculated bond distances, and bond angles of compounds BTP2, BTP3 and BTM6, are shown in Table **1**. In general, good agreement between the calculated and experimental bond lengths and bond angles [26] has been observed.

2.2. Frontier Orbital Energy Analysis

According to the frontier molecular orbital theory, HOMO and LUMO are the most important factors that affect the bioactivity. HOMO has the ability to provide electrons, while LUMO expresses the ability of the compound to accept electrons [32, 33].

The energies of HOMO -2 to LUMO +2 orbitals for the compounds BTP 1-3 and BTM 4-6 are given in Fig. (**3**) and Table **2**.

The quantum chemical parameters [34] were calculated as described by Cakmak *et al*. [35]. According to Janak's theorem, Ionization potential (IP) and Electron affinity (EA) can be obtained

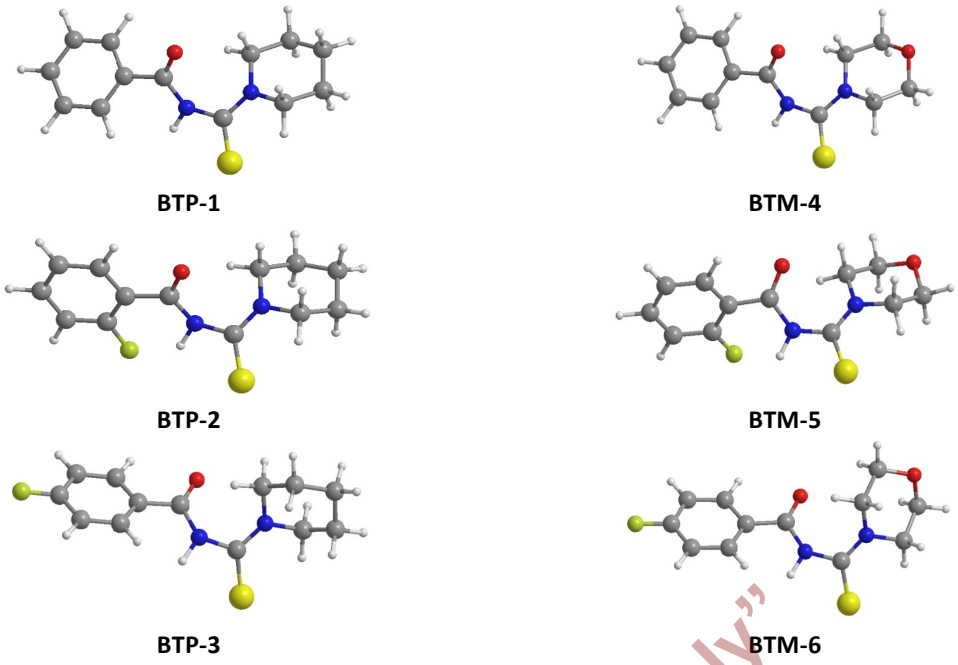

Fig. (2). B3LYP/6-31G (*d*,*p*) optimized structures of BTP 1-3, BTM 4-6.

Table 1. Comparative selected structure parameters of the compounds BTP2, BTP3 and BTM6.

Distances (Å) / Angles (^{0})	BTP 1	BTP 2		BTP 3		BTM 4	BTM 5	BTM 6	
	DFT	Expt.	DFT	Expt.	DFT	DFT	DFT	Expt.	DFT
S1-C8	1.685	1.673	1.683	1.668	1.681	1.681	1.683	1.679	1.682
O1-C1	1.222	1.213	1.223	1.233	1.221	1.221	1.222	1.219	1.223
N1-C1	1.397	1.378	1.390	1.358	1.403	1.403	1.399	1.392	1.399
N1-C8	1.417	1.413	1.417	1.434	1.417	1.417	1.415	1.397	1.417
N2-C8	1.344	1.414	1.346	1.314	1.346	1.346	1.346	1.330	1.346
S1-C8-N1	126.155	125.634	125.954	127.287	126.164	126.164	126.016	124.036	125.642
S1-C8-N2	117.086	117.506	117.105	117.920	117.105	117.105	117.356	118.950	117.105

using HOMO and LUMO energies by utilizing "Eq. (1)" [36].

$$IP = -E_{HOMO}, EA = -E_{LUMO} \quad (1)$$

Hardness (η) is the distortion of chemical species or in opposition to electron cloud polarization, and can be calculated by "Eq. (2)" [37]. To understand the chemical behaviour of molecules, the concepts of hardness and softness are used. The molecules with large energy gap are termed as hard, while the molecules with small energy gap are considered soft. Hence, hard molecules tend to be less polarizable than soft molecules.

$$\eta = (IP - EA)/2 \quad (2)$$

Reciprocal of global hardness provides softness (σ) value of the molecules, and is calculated using "Eq. (3)" [38].

$$\sigma = 1 / \eta \quad (3)$$

Electronegativity (χ) measures the tendency of the molecule for attracting an electron, which can be calculated by "Eq. (4)".

$$\chi = -(E_{HOMO} + E_{LUMO})/2 \quad (4)$$

Smaller ΔE implies higher chemical reactivity and lower kinetic stability for the investigated molecules [36].

Table 2. Energy levels (eV) of MOs for compounds BTP 1-3, BTM 4-6 calculated in their ground state in the gas phase.

Compound	HOMO-2	HOMO-1	HOMO	LUMO	LUMO+1	LUMO+2
BTP 1	-6.99	-5.85	-5.50	-1.36	-0.47	-0.31
BTP 2	-7.11	-5.77	-5.41	-1.57	-0.39	-0.36
BTP 3	-7.01	-5.84	-5.53	-1.50	-0.69	-0.35
BTM 4	-6.93	-5.98	-5.65	-1.46	-0.60	-0.40
BTM 5	-7.00	-5.90	-5.57	-1.67	-0.51	-0.46
BTM 6	-7.07	-6.00	-5.72	-1.65	-0.78	-0.51

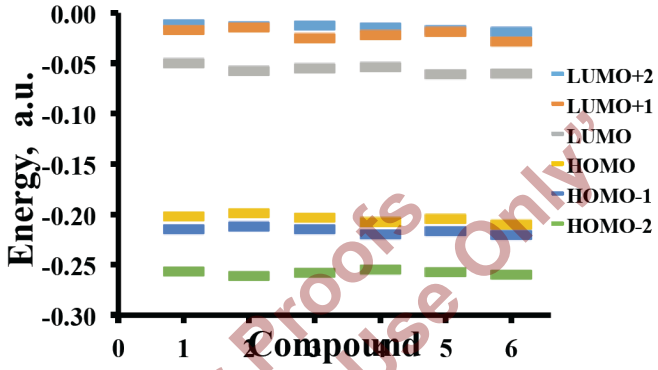

Fig. (3). Energy levels of MO diagrams for compounds BTP 1-3, BTM 4-6 calculated in their ground state in the gas phase structures.

Table 3. Quantum chemical parameters of compounds BTP 1-3 and BTM 4-6 calculated at B3LYP/6-31G (d,p).

	E_{HOMO} (eV)	E_{LUMO} (eV)	IP	EA	η	σ	χ	Log P	MIC Values*
BTP 1	-5.497	-1.358	5.497	1.358	2.069	0.483	3.427	3.636	31
BTP 2	-5.412	-1.570	5.412	1.570	1.921	0.521	3.491	3.337	27.5
BTP 3	-5.529	-1.499	5.529	1.499	2.015	0.496	3.514	3.115	20.5
BTM 4	-5.646	-1.461	5.646	1.461	2.093	0.478	3.554	2.504	2.5
BTM 5	-5.567	-1.668	5.567	1.668	1.950	0.513	3.618	2.205	31
BTM 6	-5.722	-1.652	5.722	1.652	2.035	0.491	3.687	1.982	8.0

* Antifungal activity against *Botrytis cinerea* [26].

The quantum chemical parameters of compounds BTP 1-3 and BTM 4-6 were calculated using the above equations. Thus, obtained values of IP, EA, hardness, softness, and electronegativity associated with HOMO and LUMO energies are formulated in Fig. (**4**) and Table **3**. For the BTP compounds, the sequence of the antifungal activity is BTP 1 < BTP 2 < BTP 3. This antifungal activity sequence is identical to the calculated sequence of electronegativity (χ). For the BTM compounds, the sequence of antifungal activity is BTM 5 < BTP 6 < BTP 4. For these BTM compounds, a direct correlation of antifungal activity has been observed with E_{LUMO}, EA, hardness (η) and softness (σ).

In SAR analyses, the most commonly used molecular descriptor is log P. It is a quantitative de-

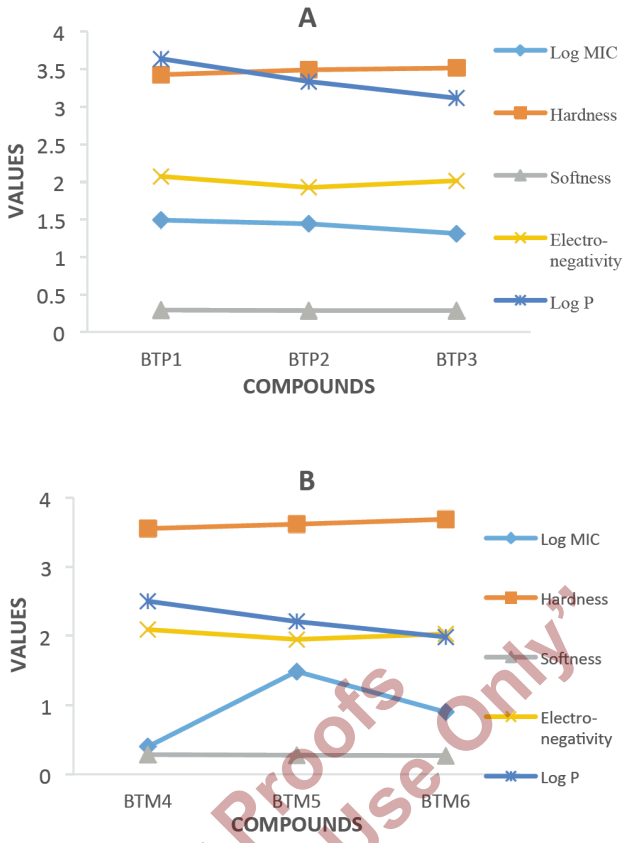

Fig. (4). Quantum chemical parameters of (**A**) BTP 1-3 and (**B**) BTM 4-6 calculated by DFT.

Table 4. Mulliken atomic charges for selected atoms of compounds BTP 1-3 and BTM 4-6 using DFT.

Atom	BTP 1	BTP 2	BTP 3	BTM 4	BTM 5	BTM 6
S1	-0.287	-0.279	-0.283	-0.279	-0.271	-0.272
F1	-	-0.293	-0.287	-	-0.293	-0.286
O1	-0.496	-0.502	-0.492	-0.494	-0.500	-0.498
O2	-	-	-	-0.477	-0.477	-0.483
N1	-0.551	-0.576	-0.560	-0.551	-0.573	-0.385
N2	-0.364	-0.366	-0.370	-0.380	-0.380	-0.558
C1	0.543	0.579	0.544	0.541	0.578	0.551
C8	0.283	0.288	0.291	0.284	0.285	0.291

scriptor of lipophilicity, which is one of the important factors influencing pharmacokinetic properties. Lipophilicity influences the penetration of bioactive molecules across non-polar cell membranes. The partition coefficient, which is obtained from distribution studies of the compound between an immiscible polar and non-polar solvent pair, is usually used to determine this property. Log P can be used to predict a drug's inhibitory activity. From the Log P calculations, BTP3, BTM4 and BTM6 have been observed to be less lipophilic in nature. Lower values of Log P are indicative of stronger antifungal activity.

2.3. Mulliken Atomic Charges

The calculated Mulliken atomic charges for selected atoms are shown in Table **4**. Two atoms C1

and C8 are the most positively charged ones, which can interact with the negatively charged part of the receptor easily. The negative charges are mainly located on atoms N1, N2, S1, F1, and O1, so they can interact easily with the positive part of the receptor. C1 is the most positive and N1 the most negative; therefore, C1-N1 bond polarity plays a key role in the atomic charge. DFT study evaluates a common set of electronic characteristics responsible for antifungal activity. Quantum chemical parameters of the compounds were observed to very well correlate with the antifungal activity of the compounds. Furthermore, lower values of Log p have been indicative of a stronger antifungal activity of the compounds.

CONCLUSION

The DFT study of benzoyl thiourea derivatives linked to morpholine and piperidine was conducted for evaluation of their antifungal activity. All the six compounds BTP 1-3 and BTM 4-6 were optimized with DFT, and various parameters were evaluated. Mulliken charge analysis results were found consistent with the antifungal activity. The presence of morpholine group and fluorine at para position enhanced the antifungal activity, as confirmed from the DFT study. In general, a good agreement between the calculated and experimental bond lengths and bond angles has been observed. For the BTP compounds, the antifungal activity sequence was found similar to that of calculated electronegativity. For the BTM compounds, a direct correlation of antifungal activity with E_{LUMO}, EA, hardness and softness, was observed.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the study are available within the article.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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