Chemical reactivity, molecular electrostatic potential and in-silico analysis on benzimidazole fungicide benomyl

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ABSTRACT

We are reporting theoretical concepts and biological activity of benomyl using different techniques. The molecular orbital contributions are studied by using Total Density of States (TDOS) analysis. The chemical reactivity of the molecule have been determined with the help of global reactivity descriptors. Molecular electrostatic potential is calculated by the density functional method and predicts the most reactive part in the molecule. In-silico molecular analysis is conducted for Benomyl compound.

1. Introduction

Fungicides play an important role in modern agriculture through the control of fungal diseases to achieve high productivity [1]. The use of fungicides in agriculture, to protect from soil-borne pathogens, is a common practice. Benomyl is an agricultural and horticultural systemic fungicide. Benomyl [methyl 1-(butyl carbamoyl) benzimidazol-2-yl carbamate] is a systemic fungicide introduced in 1968 by Dupont [2]. Dong-Jae Kim et al. [3] reported the benomyl induction of brain aromatase and toxic effects in the zebra fish embryo. Effect of the fungicide benomyl on spore germination and hyphal length of the arbuscular mycorrhizal fungus glomus Mosseae was explained by Chiocchio et al. [4]. DFT and Raman Scattering Studies of Benzimidazole was explained by Wang et al. [5]. G.P. Sheeja Mol et al. [6] discussed the Spectroscopic investigation, fungicidal activity, and molecular dynamics simulation on benzimidazol-2-yl carbamate derivatives. The Fungicide Benomyl (Methyl 1 -(Butylcarbamoyl)-2-benzimidazolecarbamate) Causes Testicular Dysfunction by Inducing the Sloughing of Germ Cells and Occlusion of Efferent Ductules was interpreted by Rex et al. [7]. Randal et al. [8] elucidated the Benomyl: A broad spectrum fungicide for use in plant cell and protoplast culture. The kinetics and mechanisms of conversion of methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate (benomyl) to methyl 2-benzimidazolecarbamate (MBC) were

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clarified by Calmon et al. [9]. Nachmias et al. [10] explained the decreased permeability as a mechanism of resistance to methyl benzimidazol-2-yl carbamate (MBC) in Sporobolomyces roseus. Sensitivity to the pesticide benomyl was explained by Van ketel [11]. The determination of some benzimidazole fungicides in tomato by high performance liquid chromatography was explained by Hamdan [12]. Marc et al. [13] elucidated the cloning and characterization of the gene for β-tubulin from a benomyl resistant mutant of Neurospora Crassa and its use as a dominant selectable. Benomyl, Nocodazole, Carbendazim and Thiabendazole are structurally related benzimidazole derivatives that inhibit microtubule assembly in vivo and in vitro reported by Katherine Jung et al. [14]. Jun ghee lim et al. [15] explained the role of the benomyl metabolite carbendazim in benomyl-induced testicular toxicity. Bollen et al. [16] interpreted the specificity of the in-vitro and in vivo antifungal activity of benomyl. The use of benomyl to control infection by vesicular-arbuscular mycorrhizal fungi clarified by Fitter et al. [17].

The literature review reveals that there is no detailed study on total density of states (TDOS) analysis, Molecular electrostatic potential, and In-silico analysis of benomyl. The present work involves the Total density of States (TDOS) analysis, Molecular Electrostatic Potential (MESP) and In-silico analysis of benzimidazole fungicide Benomyl. To the best of our knowledge no detailed in-silico analysis of the compound was performed.

2. Computational details

Gaussian 09 software program package is used for theoretical calculation [18]. The quantum chemical calculations are performed by applying Density Functional Theory [19, 20] method with the three parameter hybrid functional (B3) for the exchange part and the Lee-Yang-Par (LYP) correlation function with 6-311G (d,p) basis set [21, 22]. The TDOS spectrum is prepared by using the Gauss sum 2.2 program [23]. The docking studies are performed using the molecular docking software, Auto dock 4.2 [24] and visualization done by Discovery Studio 4.1 [25].

3. Results and discussion

3.1. Total density of states (TDOS) analysis

The optimized molecular structure of Benomyl is shown in Figure 1. The Total density of states of Benomyl and its structurally related compounds are shown in Supplementary Figs.1(1)-1(19). They provide a pictorial representation of molecular orbital composition and their contributions to chemical bonding. The global reactivity descriptors of Benomyl and its structurally related 19 compounds are measured. The Total Density of States (TDOS) of Benomyl is shown in Figure 2.

3.2. Chemical reactivity

3.2.1. Global reactivity descriptors

The global chemical reactivity descriptors like ionization potential(A), electron affinity (I), electron negativity (χ), chemical potential (μ), electrophilicity index(ω), Hardness(η) and softness(S) were based on HOMO-LUMO energy values. They were calculated and listed in Table 1. These chemical descriptors were defined by Koopman’s theorem [26] expressed by the relations

\[ I = -E_{\mathrm{HOMO}} \]  
\[ A = -E_{\mathrm{LUMO}} \]
The HOMO-LUMO energy gap is an important parameter that estimates the chemical stability, reactivity, and electron conductivity \[27, 28\]. The lowest value of HOMO-LUMO energy gap indicates the highest reactivity. In Benomyl, the energy gap is found to be 5.039\,eV. The HOMO (Highest Occupied Molecular Orbital) energy indicates the susceptibility of the molecule towards the attack by an electrophile and LUMO (Lowest Unoccupied Molecular Orbital) energy represents the susceptibility of the molecule towards the attack by a nucleophile \[29\]. The pictorial illustration of Frontier Molecular Orbital (FMO) is plotted in Figure 3. The electrophilicity index(\(\omega\)) for the title compound found to be 2.08 which suggests that this compound to be a good electrophile compared to other 19 related structures.

3.3. Molecular electrostatic potential (MESP)

Molecular electrostatic potential is an important descriptor to evaluate the active sites of electrophilic and nucleophilic region of the compound for the study of biological identification process. The blue colour represents the positive potential of the compound. The green colour indicates the zero potential and the red indicates the negative potential \[26\]. As can be seen from the molecular electrostatic potential map of the title compound, negative

| Compound Chemical formula | \(E_{\text{HOMO}}\) (eV) | \(E_{\text{LUMO}}\) (eV) | \(E_{\text{HOMO}}-E_{\text{LUMO}}\) (eV) | \(E_{\text{HOMO}}-1\) (eV) | \(E_{\text{LUMO}}-1\) (eV) | \(E_{\text{HOMO}}-1-E_{\text{LUMO}}-1\) (eV) | I | A | \(\chi\) | \(\mu\) | \(\eta\) | S | \(\omega\) |
|--------------------------|--------------------------|--------------------------|-----------------------------|--------------------------|--------------------------|-----------------------------|---|---|---|---|---|---|---|
| C\(_9\)H\(_9\)N\(_3\)O\(_2\) | -5.638 | -0.443 | 5.195 | -6.019 | 0.550 | 6.570 | 5.638 | 0.443 | 3.040 | -3.040 | 2.597 | 0.385 | 1.78 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -5.609 | -0.496 | 5.113 | -5.906 | 0.615 | 6.521 | 5.609 | 0.496 | 3.052 | -3.052 | 2.556 | 0.391 | 1.82 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -5.535 | 0.422 | 5.957 | -5.906 | 0.541 | 6.447 | 5.535 | 0.422 | 2.556 | -2.556 | 2.978 | 0.335 | 1.09 |
| C\(_4\)H\(_8\)N\(_2\)O \(_2\) | -5.757 | -0.348 | 5.409 | -5.906 | 0.615 | 6.595 | 5.757 | 0.348 | 3.053 | -3.053 | 2.704 | 0.369 | 1.72 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -5.943 | -0.366 | 5.577 | -6.173 | 0.703 | 6.875 | 5.943 | 0.366 | 3.155 | -3.155 | 2.788 | 0.358 | 1.78 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -5.867 | -0.443 | 5.424 | -6.096 | 0.779 | 6.875 | 5.867 | 0.443 | 3.155 | -3.155 | 2.712 | 0.368 | 1.84 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -6.128 | -0.570 | 5.557 | -6.350 | 1.051 | 7.005 | 6.128 | 0.570 | 3.349 | -3.349 | 2.741 | 0.365 | 1.83 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -5.906 | -0.274 | 5.631 | -6.054 | 0.764 | 6.818 | 5.906 | 0.274 | 3.164 | -3.164 | 2.741 | 0.365 | 1.83 |
| C\(_9\)H\(_9\)N\(_3\)O \(_2\) | -5.867 | -0.443 | 5.424 | -6.096 | 0.779 | 6.875 | 5.867 | 0.443 | 3.155 | -3.155 | 2.712 | 0.368 | 1.84 |

\(\eta = \frac{(I-A)}{2}\) \hspace{1cm} (3)

\(\sigma = \frac{1}{\eta}\) \hspace{1cm} (4)

\(\mu = -\frac{(I+A)}{2}\) \hspace{1cm} (5)

\(\chi = \frac{(I+A)}{2}\) \hspace{1cm} (6)

The HOMO-LUMO energy gap is an important parameter that estimates the chemical stability, reactivity, and electron conductivity \[27, 28\]. The lowest value of HOMO-LUMO energy gap indicates the highest reactivity. In Benomyl, the energy gap is found to be 5.039\,eV. The HOMO (Highest Occupied Molecular Orbital) energy indicates the susceptibility of the molecule towards the attack by an electrophile and LUMO (Lowest Unoccupied Molecular Orbital) energy represents the susceptibility of the molecule towards the attack by a nucleophile \[29\]. The pictorial illustration of Frontier Molecular Orbital (FMO) is plotted in Figure 3. The electrophilicity index(\(\omega\)) for the title compound found to be 2.08 which suggests that this compound to be a good electrophile compared to other 19 related structures.
regions are mainly localized over the carbonyl groups. The maximum positive regions are localized over the benzimidazole region and the negative potentials are over the electronegative atoms.

### 3.4. In-silico analysis

Benzimidazoles are a group of molecules which have shown potential for applications in a variety of pharmacological targets. Biologically active benzimidazoles involved in fungicidal, anthelminthics, antiviral, anticancer, antimycobacterial, anticonvulsant, antipsychotic and anti-diabetic activities [30]. Molecular docking is a computational technique that tries to predict the binding composites from multi-dimensional images of the macro molecule (protein) noncovalent bonding and a small molecule (ligand) [31]. A molecular docking study has been carried out for Benomyl with the help of Auto dock 4.2 software. Molecular docking helps to identify the ligand-protein interactions and the biological activity of benomyl. The different biological activity studies are carried out on benomyl compound and are described below.

#### 3.4.1. Fungicidal activity

For identifying fungicidal activity of benomyl, β-tubulin synthesis [32] type of pdb is selected. Molecular docking is performed for the different receptors (PDB ID-1KTK, 1LOX) and ligand. In the present investigation 1KTK target protein exhibits lowest binding energy due to the influence of the bounded residue ASP171:HN, which leads to the possibility of strong intra molecular hydrogen bonding. The target protein 1KTK shows hydrogen bonding interaction energy -6.348 kcal/mol corresponding bond distance is 1.980 Å.

#### 3.4.2. Anthelminthics activity

Anthelminthics are a group of antiparasitic drugs that expel parasitic worms. The precise mode of action of benzimidazole active compound on the parasite is unknown, but it may inhibit the helmint-specific enzyme fumarate reductase [33]. Molecular docking is performed for two different receptors 5GLG and 5MST. The 5MST target protein has two hydrogen bond interaction. The bounded residues are TRP440:HE1 and ASP429:OD2. The bounded residue TRP440:HE1 possess N–H⋯O hydrogen bonding shows the bond distance 2.405 Å and having hydrogen

#### Table 2. Molecular docking results of benzimidazole bioactive compound Benomyl with different target proteins.

| Biological activity | PDB-ID | Estimated inhibition constant (µM) | Reference RMSD(Å) |
|---------------------|--------|------------------------------------|-------------------|
| Antifungal          | 1KTK   | 23.63                              | 29.73             |
|                     | 1LOX   | 103.55                             | 41.14             |
| Anthelminthic       | 5MST   | 8.38                               | 16.29             |
|                     | 5GLG   | 101.20                             | 28.09             |
| Antiviral           | 5D2L   | 45.93                              | 58.71             |
|                     | 5D2N   | 23.61                              | 49.98             |
| Anticancer          | 5EQH   | 53.25                              | 38.24             |
|                     | 5EQG   | 30.67                              | 645.17            |
| Antimycobacterial   | 2CCA   | 7.43                               | 101.73            |
|                     | 4KBJ   | 49.42                              | 132.69            |
| Anticonvulsant      | 4ATQ   | 7.49                               | 102.79            |
|                     | 4ATP   | 5.29                               | 102.01            |
| Antipsychotic       | 6B98   | 6.35                               | 27.53             |
|                     | 6B97   | 3.65                               | 32.46             |
| Antidiabetic        | 5V4W   | 1.96                               | 31.05             |
|                     | 4NO7   | 4.31                               | 21.06             |
| Human binding protein FKBP12 | 3H9R | 58.24                              | 162.86            |
|                     | 2RSE   | 2.072                              | 6.05              |
bond energy -3.256 kcal/mol. The bounded residue ASP429:OD2 exhibits the N25-H26′′′-O interaction with H–O distance 2.251 Å and energy value -3.578 kcal/mol. The 5GLG target protein exhibits two intra molecular hydrogen bonding interaction. The bounded residues are SER79:HN and SER482:HG. The bounded residue SER79:HN leads to N–N hyper… conjugative interaction, the H-bond energy value is -3.166 kcal/mol and corresponding bond distance is 2.216 Å. The H-bond interaction energy shows that benomyl is less anthelmintics activity.

3.4.3. Antiviral activity

Benzimidazole and their derivatives exhibit antiviral activity via interaction with different enzymes in the viruses such as human cytomegalovirus (HCMV), human herpes simplex virus (HSV-1), human immune deficiency virus (HIV) and hepatitis B and C virus [32]. The proteins 5D2L and 5D2N are the two different receptors used for this activity. The protein 5D2L possess highest binding energy with benomyl. In benomyl, the bounded residue HIS70:HD1 possess the interaction energy -0.770 kcal/mol and corresponding bond distance is 2.218 Å. In 5D2N receptor the bounded residues exhibit two hydrogen bonds and is correlated to SER2 residue with H-bond energy values -1.790 kcal/mol and -2.713 kcal/mol.

3.4.4. Anticancer activity

The Topoisomerase 1 inhibitors constitute a novel family of antitumor agents. Molecular docking is performed for the different receptors (PDB ID-5EQH and 5EQG). The bounded residues for 5EQH protein are GLN283:HE2 and GLN282:OE1, which exhibits the bond distances 2.180 Å and 2.094 Å and H-bond energies are -2.587 kcal/mol and -0.450 kcal/mol.

3.4.5. Antimycobacterial activity

The receptors used for antimycobacterial activity are 2CCA and 4KBJ. In the present investigation, 2CCA target protein bounded residue H1S70:HE2 with bond distance 1.913 Å and H-bond energy is -3.447 kcal/mol. The target protein 4KBJ exhibits bounded residue is ASP103:OD2, the bond distance 1.992 Å and hydrogen bonding energy is -1.565 kcal/mol. We observed that there is no significant antimycobacterial activity with Benomyl.

3.4.6. Anticonvulsant activity

Anticonvulsant are a diverse group of pharmacological agents used in the treatment of epileptic seizures. The compound inhibits GABA transaminase for selecting different receptors [32]. The different receptors 4ATQ and 4ATP are required for biological activity calculations. In the present study, 4ATQ target protein bounded residue GLY319:HN with bond distance 2.201 Å and H-bond energy is -3.118 kcal/mol. The weak H-bond energy leads to the less anticonvulsant activity of Benomyl.

3.4.7. Antipsychotic activity

For the antipsychotic activity study, compound is surfaced out as the potent PDE10A (phospho distresses) inhibition with reduced CYP1A2 inhibitory because of the influence of benzimidazole ring [32]. The 6898 and 6897 are the two different receptors used for antipsychotic activity study. The bounded residues for 6898 protein are HIS700:HE2 and GLU727:OE2, which exhibits the bond distances 1.092 Å and 2.012 Å and H-bond energies are 0.0169 kcal/mol and -0.3109 kcal/mol. The weak H-bond energy leads to the less antipsychotic activity of Benomyl.

3.4.8. Antidiabetic activity

Molecular docking study has been performed on glucokinase activators to analyze the antidiabetic activity. The highest hydrogen bond energy values for 5V4W receptors are -3.195 kcal/mol, -3.906 kcal/mol and -1.416 kcal/mol. The bounded residues exhibit HN–O interaction due to the influence of hydrogen bonding.

3.4.9. Human binding protein FKBP12

Molecular docking is performed for human binding protein to identify the low toxic effect and lowest influence of human being as reported in Table 2 and Table S1. The target protein 3H9R exhibits the highest H-bond energy. The bounded residues are GLY191:HN and GLY328:HN, corresponding bond distances are 2.101 Å and 2.174 Å respectively. The highest hydrogen bonding energy shows that the human binding protein has less effect due to benomyl. The target protein 2RSE which creates the bounded residue TYR983: OH. The bond distance is 1.928 Å and corresponding H-bond energy is -0.0503 kcal/mol. The highest hydrogen bonding energy exhibits the less toxicity effect in human (see Table 2).

From above investigation we conclude that, benomyl possess highly fungicidal activity due to the influence of benzimidazole bioactive group. The hydrogen bonding interaction and it’s bounded residues are listed in Table S1 and these images are shown in Supplementary Figs. 2(a)-2(p). As shown in supplementary table S1 the auto dock binding energy, inhibition constant (µM), and Reference RMSD (Å) are obtained. The top ranked cluster for benomyl is plotted in Figures 5(a)-5(b).

4. Conclusion

The lowest value of HOMO-LUMO energy gap indicates the highest reactivity of Benomyl. In Benomyl, the energy gap is found to be 5.039 eV. The highest value of electrophilicity index (ω = 2.08) describes the biological activity of Benomyl. The protein receptor 1KTK target protein has the lowest binding energy and possesses highest potential affinity into the binding site of the compound. The maximum positive regions are localized over the benzimidazole region. As can be seen from the Molecular electrostatic potential map, regions having the negative potentials are over the electronegative atoms. In-silico analysis has shown that benomyl is an effective fungicide while comparing with other activities.

Figure 5. (a)-(b) Top ranked cluster for Benomyl- 1KTK, 1LOX target protein.
From above investigation we conclude that, benomyl possess highly fungicidal activity due to the influence of benzimidazole bioactive group.

**Declarations**

**Author contribution statement**

G.P. Sheeja Mol: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

D. ArulRhas: Analyzed and interpreted the data.

I. Hubert Joe: Contributed reagents, materials, analysis tools or data.

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**Data availability statement**

The data that has been used is confidential.

**Declaration of interests statement**

The authors declare no conflict of interest.

**Additional information**

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**References**

[1] C. Shu-kang, A.E. Clive, S. Scott, Effects of the fungicide benomyl, captan and chlorothalonil on soil microbial activity and nitrogen dynamics in laboratory incubations, Soil bio. and bio. chem 33 (2001) 1971–1980.

[2] C.D. Leen, Benzimidazole fungicides : mechanism of action and biological impact, Annual rev. phyto path. 24 (1986) 43-65.

[3] E. Viviana, V. Nadia, M. Alicial, M. Ana, A.O. Junan, G. Alicia, Effect of the fungicide benomyl on spore germination and hypha length of the arbuscular mycorrhizal fungus glomus mosseae, Inter. microbiology 3 (2000) 173-175.

[4] Xiao-bin, W. Wang, L. Rui-mei, Z. Mu-hua, L. Lu-ling, Lei, DFT and Raman scattering studies of benzimidazole, Spectro. Spectr. Anal. 35 (2015) 1562–1566.

[5] G.P. Sheeja Mol, D. Arul Rhas, J. Hubert Joe, S. Balachandran, A. Ronaldo, G. Jesby, Spectroscopic investigation, fungicidal activity and molecular dynamics simulation on benzimidazol-2-yl carbamate derivatives, J. Mol. Struct. 1176 (2019) 226–237.

[6] A.H. Riz, B.J. Moore, F. Janet, L. Ralf, Ahmed wadadaut,A. the fungicide benomyl (methyl 1- (Butylcarbamoyl)-2- benzimidazolecarbamate) Causes testicular dysfunction by inducing the slashing of Germ cells and occlusion of efferent Ductules, Fund. Appl. Toxi. 17 (1991) 733–745.

[7] M.H. Randal, M.W. Jack, D.P. Jack, Benomyl: A broad spectrum fungicide for use in plant cell and protoplast culture, Plant Cell Rep. 4 (1985) 129–132.

[8] J.P. Calmon, D.R. Sayag, Kinetics and mechanisms of conversion of methyl 1- (butylcarbamoyl)-2-benzimidazolecarbamate (benomyl) to methyl 2-benzimidazo- lecarbamate (MBC). J. Agric. Food Chem. 24 (2) (1976) 311–314.

[9] J.K. Dong, H.S. Seung, W.B. Min, Y.L. Hui, Y.-R. Na, H.P. Sung, K.L. Hyun, Characteristics of the in-vitro and in vivo antifungal activity of benomyl, Neth. J. Plant Pathol. 76 (1970) 299–312.

[10] J.O. Marc, B.P. Elena, Y. Charles, Cloning and characterization of the gene for β-tubulin from a benomyl-resistant mutant of neuro spora crassa and its use as a dominant selectable Marker, Mol.Cell.Bio. 6 (1986) 2452-2461.

[11] W.G. Van Ketel, Sensitive to the pesticide benomyl, Contact Dermatitis 2 (5) (1976) 290–291.

[12] G.P. Hamdan, Determination of some benzimidazole fungicides in tomato pure by high performance liquid chromatography with sample Q polymer SCX solid phase extraction, Arab. J. Chem. 4 (2011) 115–117.

[13] J.G. Randal, M.W. Jack, Aromatic alterations in the β-tubulin gene of Aspergillus nidulans that confer benomyl resistance, Cell.Mol. Cyto.Skel. 22 (1992) 170–174.

[14] L. Jung hee, G.M. Marion, The role of the benzimidazole carbendazim in benomyl-induced testicular toxicity, Tox.App. Pharm. 142 (1997) 401–410.

[15] G.J. Bollen, A. Fuchs, On the specificity of the in-vitro and in vivo antifungal activity of benomyl, Neth. J. Plant Pathol. 76 (1970) 299–312.

[16] A.H. Fitter, R. Nichols, The use of benomyl to control infection by vesicular-arbuscular mycorrhizal fungi, New Phyto. 110 (1988) 201–206.

[17] M.J. Frisch, G.W. Schlegel, Gaussian 09W Program, Gaussian Inc., Wallingford, CT, 2009.

[18] A.J. Camargo, H.B. Napolitano, J.Z. Schpector, Theoretical investigation of the intramolecular hydrogen bond formation, non-linear optic properties, and electronic absorption spectra of the 8-hydroxyquinoline, J.Mol.Struct.:Theochem 816 (1) (2007) 145–151.

[19] G.P. Sheeja Mol, D. Arul Rhas, I. Hubert Joe, S. Balachandran, A. Ronaldo, G. Jesby, Structural activity (monomer and dimer), spectroscopic analysis, chemical reactivity, fungicidal activity and molecular dynamics simulation of phenyl benzamide fungicides : a combined experimental and theoretical approach, J. Mol. Struct. 1193 (2019) 24–44.

[20] A.D. Becker, Density functional thermo chemistry. Ill. The role of exact exchange, J. Chem. Phys. 98 (1993) 5648–5652.

[21] A.D. Becker, Density-functional exchange-energy approximation with correct asymptotic behavior, Phys. Rev. 38 (1988) 3098–3100.

[22] N.M. O Boyle, A.L. Tenderholt, L.M. Langner, Software news and updates ccell: a library for package-independent computational chemistry algorithms, J. Comput. Chem. 29 (5) (2008) 839–845.

[23] G.M. Morris, R. Huey, W. Lindstron, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.L. Olson, Software news and updates AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility, J. Comput. Chem. 16 (2009) 2785–2791.

[24] S. Deigo, Cailf, Discovery Studio Modeling Environment, Accelry Software Release 4.0, USA, 2013.

[25] G.P. Sheeja Mol, D. Arul Rhas, I. Hubert Joe, S. Balachandran, A. Ronaldo, G. Jesby, Structural activity, fungicidal activity and molecular dynamics simulation of certain triphenyl methyl imidazole derivatives by experimental and computational spectroscopic investigations, Spectr.acta partA mol.bio. sp. 212 (2019) 105–120.

[26] W. Guerra, H. Lgaz, S. Kansiz, J.T. Mague, N. Dege, M. Anzar, R. Marzouki, J. Taoofik, Ill-MinChung, F. Youse, Raml, Synthesis of a novel phenytin derivative: crystal structure, Hirshfeld surface analysis and DFT calculations, J. Mol. Str. 1205 (2020), 127630.

[27] R.G. Parr, L. Scnepalay, S. Liu, Electrophilicity index, J. Am. Chem. Soc. 121 (1999) 1922–1924.

[28] D. Necmi, G. Halil, E. Onur, A. Gökhan, A. Tügcan, S. Muthu, Y. Sert, Quantum computational, spectroscopic investigations on N-(2-(2-chloro-4,5-dicyanophenyl) amino)ethyl)-1- methylbenzenesulfonamide by DFT/TD-DFT with different solvents, molecular docking and drug-likeness analyses, Colloids Surf. A Physicochem. Eng. Asp. 638 (2022), 126311.

[29] M.R. Albayati, K. Sevg, D. Necmi, K. Savas, M. Riadah, L. Hassane, S. Rachid, H. Isamat, M.A. Majed, Ill-Min C, Synthesis, crystal structure, Hirshfeld surface analysis and DFT calculations of 2-[(2,3-dimethylphenyl) amino]-N-(E)- thiophen-2-ylmethylidenbenzohydrazide, J. Mol. Str. 1205 (2020), 127654.

[30] Shanmunagapriy,N, Balachandran, V. Revath, B. Narayana, B. Vinutha, V. Sivan, Vanasundari, K, Sivakumar, G, Quantum Chemical Calculation, Performance of Selective Antimicrobial.

[31] Y. Geeta, G. Swastika, Structure activity relationship (SAR) study of benzimidazole scaffold for different biological activities: a mini review, European. J. Med. Chem. 97 (2015) 419–443.

[32] A. Dustin, P. Nader, M.B. Walter, J.K. Jacob, C.N. Sean, K.Q. Tiffani, F.B. Ray, K. Sol, A.H. Grant, E.B. Carls, R. Scott, Conformation of the cellular targets of benomyl and rapamycin using next-generation sequencing of resistant mutant in S.cerevisiae , Mol. Biolyst. 10 (12) (2014) 3179–3187.