




IN SILICO DRUG EVALUATION AND DRUG RESEARCH OF BIOACTIVE MOLECULE METHYL 4-BROMO-2- FLUOROBENZOATE

*BİYOAKTİF MOLEKÜL METİL 4-BROMO-2-FLOROBENZOAT'IN İN SİLİKO İLAÇ
DEĞERLENDİRMESİ VE ARAŞTIRMASI*

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ABSTRACT

Objective: *The biochemical analysis plays an important role in pharmaceutical chemistry. Fungal infections are the most common infectious disease worldwide. The result of this research study can be very useful for the pharmacy and drug discovery process.*

Material and Method: *The experimental UV-Vis absorption is recorded with DMSO as solvent in SAIF IIT (Sophisticated Analytical Instrument Facility, Indian Institute of Technology, Chennai, India). Biologically active sites are reviewed by Gauss software via MEP. Toxic predictions are completed with the Preadme online tool. Protein-Ligand interaction was studied by Autodock tools 4.2.6.*

Result and Discussion: *Methyl 4-bromo-2-fluorobenzoate (MBF) molecule is structurally stable. Hydrogen binding sites of MBF molecule are found around carbonyl group. The HOMO/LUMO energy values are -6.509 eV and -4.305 eV, respectively. Stabilization energy (3.63 kcal/mol) was calculated as O4=C11 atoms. Toxicity parameters are calculated. Overall results shows stabilized MBF molecule is intoxic and suitable for drug nature of fungal diseases.*

Keywords: *DFT, drug likeness, molecular docking, NBO, toxicity*

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ÖZ

Amaç: *Biyokimyasal analiz farmasötik kimyada önemli bir rol oynar. Mantar enfeksiyonları dünya çapında en yaygın bulaşıcı hastalıktır. Bu araştırma çalışmasının sonucu, eczacılık ve ilaç keşif süreci için çok faydalı olabilir.*

Gereç ve Yöntem: *DeneySEL UV-Vis absorpsiyonu çözücü olarak DMSO kullanılarak SAIF IIT'de (Gelişmiş Analitik Cihaz Tesisi, Hindistan Teknoloji Enstitüsü, Chennai, Hindistan) kaydedildi. Biyolojik olarak aktif bölgeler, Gauss yazılımı tarafından MEP aracılığıyla incelendi. Toksikite tahminlemesi Preadme çevrimiçi aracı ile tamamlandı. Protein-Ligand etkileşimi Autodock 4.2.6 programıyla incelendi.*

Sonuç ve Tartışma: *Metil 4-bromo-2-florobenzoat (MBF) molekülü yapısal olarak kararlıdır. MBF molekülünün hidrojen bağlanma yerleri karbonil grubu çevresinde bulunur. HOMO/LUMO enerji değerleri, sırasıyla -4,305 eV ve -6.509 eV'dir. Stabilizasyon enerjisi (3.63 kcal/mol) O4 = C11 atomları olarak hesaplandı. Toksikite parametreleri hesaplandı. MBF molekülü ile mantar proteini arasında iki hidrojen bağı oluştu. Genel sonuçlar, stabilize edilmiş MBF molekülünün zehirli olmadığını ve mantar hastalıkları için ilaç olarak uygun olduğunu göstermektedir.*

Anahtar Kelimeler: *DFT, ilaç benzerliği, moleküler yerleştirme, NBO, toksisite*

INTRODUCTION

Benzoates and their halogenated derivatives represent an interesting class of biologically active compounds [1-3]. The title molecule, methyl 4-bromo-2-fluorobenzoate (MBF) is a halogenated benzoate derivative. Halogenated benzoate derivatives have drawn much attention because of their medicinal activities, such as antimicrobial [4] and anticancer [5]. In addition, benzyloxy-benzaldehyde derivatives were tested against the HL-60 cell line for anticancer activity [6]. Due to wide range of pharmaceutical application benzoate derivative attracts the attention of researchers. Quantum chemical computations have been proved to cost effective tool for structural exploration of any biologically active compounds. The quantum chemical calculations of methyl 2,5-dichlorobenzoate has been proposed in the literature [7]. Bacterial degradation properties are reported earlier in the literature and plant fungal diseases are studied on related fluorobenzoate derivative [8, 9]. Sodium benzoate and benzoate derivatives were studied earlier on biological activity mainly, fungal activity [10, 11]. From a thorough literature survey, *In silico* structure stable properties, pharmaceutical evaluations and biological behaviour of methyl 4-bromo-2-fluorobenzoate have been not reported so far.

In this present work, we report on optimized structure properties, chemical bond with stabilization [12] energy of bioactive headline compound. Band gap energies from molecular orbitals were calculated [13]. Pharmaceutical investigations like Drug likeness, Toxic and ADME properties, and Biochemical properties have explored. The electronic absorption spectrum of MBF has also been estimated using TD-DFT process. Furthermore, biologically active sites are identified from the electrostatic potential of MBF molecule [14], frontier molecular properties were investigated using theoretical calculations. Antifungal activity of MBF was studied by molecular docking method.

MATERIAL AND METHOD

Experimental details

The pure sample of MBF [methyl 4-bromo-2-fluorobenzoate] was obtained from the Sigma-Aldrich company, India with 99% of purity. UV-visible absorption spectrum of the sample was recorded in the range from 200 to 700 nm using a Perkin Elmer Lambda 35 spectrophotometer with 1 nm resolution.

Computational details

All the calculations were carried out using the Gaussian'09 program package [15]. All Druglikeness and toxic prediction was completed by PreAdme [16]. Docked protein was downloaded from RSCB [17]. The computation of the atomic charges was done by Kollman and Gasteiger method after the polar hydrogen was attached. The active with the Lamarckian Genetic Algorithm (LGA) being used to carry site of the protein was defined with 126 Å x 126 Å x 126 Å grid size, out the process [18]. The docking calculations were carried out using the AutoDock 4.2 program software [19]. Protein-ligand interaction was visualized with PyMol [20].

RESULT AND DISCUSSION

Stabilized geometry

Geometrical parameters explains bond properties [21], the optimized stable structure of headline compound is shown in Figure1. Stabilized global minimum energy is -3133.0601Hartree. The title molecule has three substituents, namely fluorine, bromine and methyl carboxylate (-CO₂CH₃) group, which are attached with benzene ring. In the present work, the bond length 1.910, 1.339, 1.355, 1.439, 1.206, 1.401, 1.404Å of Br1-C10, F2-C6, O3-C11, O3-C12, O4-C11, C5-C6, C5-C7. The highest bond length is predicted between as Br1-C10 with the value of 1.910Å. The torsion angles are 179.9° for (C6-C5-C11-O3), 0.0° for (C7-C5-C11-O3) and 179.9° for (C5-C11-O3-C12). This conjugative charge transfer enhances the bioactivity of the MBF molecule. All the optimized structural parameters of MBF compound is given in Table.1.

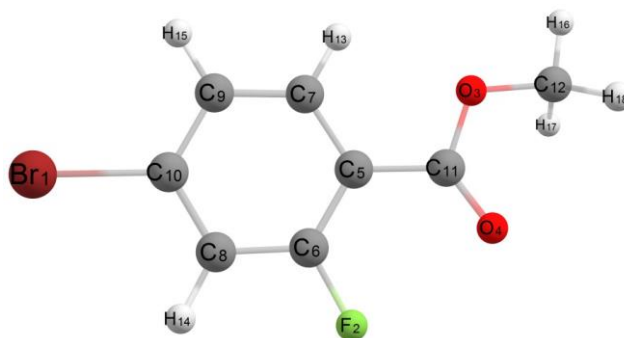


Figure 1. Stabilized geometrical structure of MBF molecule.

Table 1. Stabilized geometrical parameters of MBF compound.

Bond length	Value (Å)	Bond angle	Value (°)
	Calc.		Calc.
Br1-C10	1.910	C6-C5-C11	121.71
F2-C6	1.339	C7-C5-C11	121.33
O3-C11	1.355	C6-C5-C7	116.96
O3-C12	1.439	C5-C6-C8	122.40
O4-C11	1.206	C8-C10-C9	121.26
C5-C6	1.401	C7-C9-C10	118.79
C5-C7	1.404	C5-C11-O3	111.20
C6-C8	1.389	C11-O3-C12	115.63
C8-C10	1.389		
C10-C9	1.393	Torsional angle	
C9-C7	1.388	C6-C5-C11-O4	0.00
C7-H13	1.081	C6-C5-C11-O3	179.99
C9-H14	1.081	C5-C11-O3-C12	179.99
C8-H15	1.081	C6-C5-C7-C9	0.00
C12-H16	1.088	C5-C7-C9-C10	0.00
C12-H17	1.091	C10-C8-C6-C5	0.00
C12-H18	1.091		

Natural bond orbital analysis

The Donor-acceptor interactions are important parameter study the lone pair electrons of chemical or biochemical structures [22]. The predicted parameters of donor acceptor interactions theoretically are $\pi(\text{C-C})$, $\pi(\text{O-C})$ and $\pi^*(\text{C-C})$ orbitals as a function in this intramolecular charge transfer causes the stabilization in the molecular system and it is responsible for responsible for bioactivity. This interactions are identified from the overlap of the orbitals of $\pi(\text{O4-C11})$ to $\pi^*(\text{C5-C6})$, $\pi(\text{C5-C6})$ to $\pi^*(\text{C8-C10})$ and $\pi(\text{C8-C10})$ to $\pi^*(\text{C7-C9})$. The energy values of these interactions are shown in Table 2.

Table 2. Calculated stabilization energy between bonds by NBO method.

Donor-i		Acceptor-j		E(2) ^a kcal/mol	E(j)-E(i) ^b (a.u.)	F(i,j) ^c (a.u.)
Bonds	(Occupancy)	Bonds	(Occupancy)			
n1(O3)	1.96360	$\sigma^*(\text{C12-H16})$	0.00907	2.31	0.96	0.042
		$\sigma^*(\text{C12-H17})$	0.01329	4.60	0.72	0.054
		$\sigma^*(\text{C12-H18})$	0.01340	4.78	0.72	0.055
		$\sigma^*(\text{C7-H113})$	0.01156	2.78	2.07	0.070
n2(O4)	1.85367	$\sigma^*(\text{C5-C11})$	0.05584	14.95	0.72	0.094
$\pi(\text{O4=C11})$	1.98078	$\pi^*(\text{C5-C6})$	0.41107	3.63	0.39	0.037
$\pi(\text{C5-C6})$	1.63072	$\pi^*(\text{C7-C9})$	0.30312	21.18	0.30	0.072
		$\pi^*(\text{C8-C10})$	0.39699	19.25	0.28	0.066
$\pi(\text{C7-C9})$	1.66006	$\pi^*(\text{C5-C6})$	0.41107	19.03	0.27	0.065
		$\pi^*(\text{C8-C10})$	0.39699	22.79	0.26	0.070
$\pi(\text{C8-C10})$	1.68638	$\pi^*(\text{C5-C6})$	0.41107	20.42	0.29	0.070
		$\pi^*(\text{C7-C9})$	0.30312	17.22	0.30	0.064

^a E (2) hyperconjugative interactions energy.

^b Donor and acceptor differences (i)-(j) NBO orbitals.

^c F i,j Fock matrix element (i)-(j) NBO orbitals.

The lone pair interactions LP(1) carboxylate O3 to antibondings $\sigma^*(C7-H13)$ with stabilization energy 2.78 kcal/mol. This transfer of charge confirms the existence of C7-H13...O3 intramolecular hydrogen bonding.

Electronic properties

The FMO theory is important in defining the reactivity, bioactivity, and electronic properties of organic compounds. The HOMO energy represents to the being able to donate an electron [23, 24]. The HOMO-LUMO plots MBF is shown in Figure 2. The HOMO/LUMO energy values are -6.509eV along-4.305eV, respectively. The lowering energy gap authenticates the charge transfer within the MBF molecule. The bioactivity of MBF was verified by the discovery difference in energy value 2.204eV. The lower band gap energy of MBF compound is comparable with the bioactive materials. From the HOMO-LUMO energy values the global chemical reactivity descriptors such as electronegativity (χ), global hardness (η), global softness (S) and electrophilicity index (ω) of MBF are 0.1459, 0.1301, 0.5203 and -0.0818, respectively.

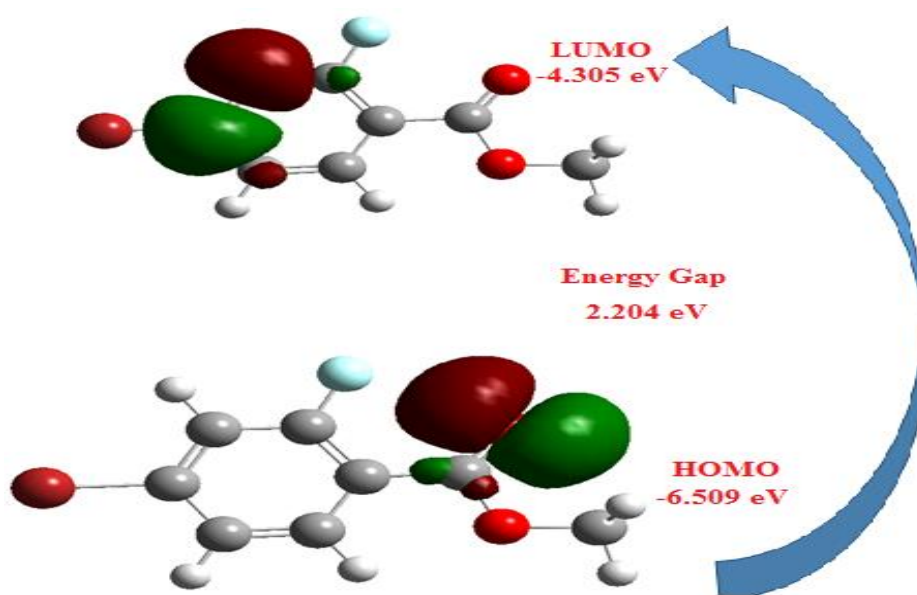
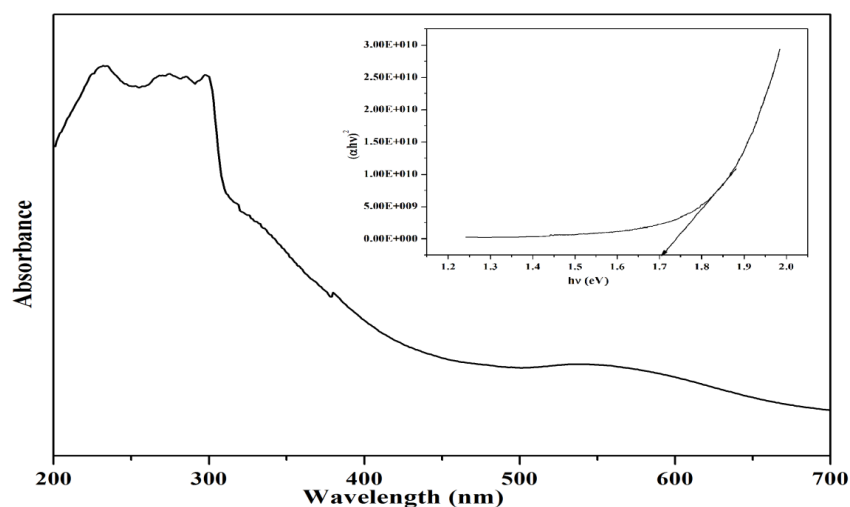


Figure 2. HOMO-LUMO orbitals of MBF molecule with bandgap energy.

The UV-Vis absorption spectrum recorded by using DMSO solvent and compared with the computed spectrum of MBF by same level theory. Predicted parameters like, excitation energies, absorption maxima are shown in Table 3. The compared UV-visible absorption spectrum of MBF compound is shown in Figure 3. The band gap value is 1.707eV calculated using Tauc's plot method [25], the measured UV-vis spectrum agrees well with the simulated HOMO-LUMO energy difference 2.204eV.

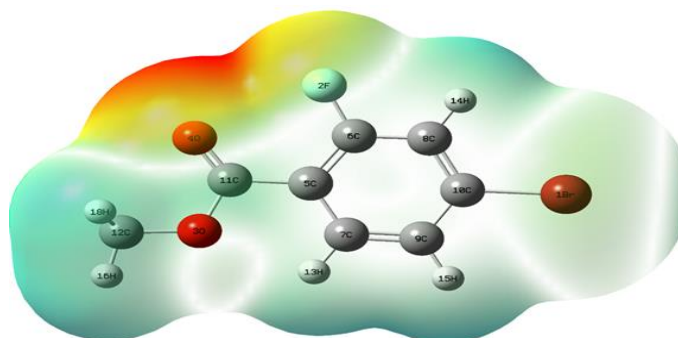
Table 3. Absorption wavelength and excitation energies of MBF molecule.

Wavelength(nm) inDMSO		Energy (eV)	Oscillator-strength (f)	Transition (assignments)
Theoretical	Experimental			
262	297	4.7362	0.1618	H-1->LUMO (36%), HOMO->LUMO (47%), HOMO->L+1 (12%) H-1->L+1 (3%)
256	271	4.8347	0.0001	H-2->LUMO (96%) H-2->L+6 (3%)
251	233	4.9313	0.3725	H-1->LUMO (42%), HOMO->LUMO (48%) HOMO->L+1 (8%)

**Figure 3.** UV-Vis spectrum of MBF molecule.

MEP analysis

MEP surface analysis provides information on a molecule's chemical reactivity and its uses allows limit to predict the electrophilic and nucleophilic attacks of any chemical compound [26, 27]. The MEP surface is shown in Figure 4 with electron density range of $-5.552e^{-2}$ (red) to $5.552e^{-2}$ (blue). The electrophilic sites are predicted on the surface of carbonyl group in MPF compound. Atom O4 in carbonyl is expected to have more bioactivity with the molecule due its electrophility.

**Figure 4.** MEP surface of MBF molecule.

ADME

Absorption, Distribution, Metabolism and Excretion properties of a chemical structure are important parameters in pharmaceutical research [28]. Solute permeability (Blood Brain Barrier) value is 1.91742, while the buffer solubility is 11218. The Caco2 is 20.4652, CYP 2C19, CYP 2C9 are an inhibitor, HIA n value is 98.447181, MDCK is 0.277822, Plasma protein binding is 70.38, pure water solubility is 552.998, Skin permeability is -1.98533, SK logD value is 1.40496, and SKlogP value is 2.65296. The Plasma protein binding value is within the limit for the headline compound, which also has a reputed role in therapeutic uses and recommendations pharmacokinetics drug metabolism [29].

Drug likeness properties

In drug discovery process the drug likeness properties has effective role in the production of active drugs [30]. By comparing the values reported with parameters, HIA value between 70 and 100% shows good human intestinal absorption and for this molecule it is 96.91%. Caco-2 and MDCK cell permeability are two predicted parameters for oral absorption of drugs. The computed Caco-2 cell permeability value is 21.803 nm/s and MDCK cell permeability value is 0.5697 nm/s respectively. The inhibited P-glyco protein value for the molecule shows that the inhibitor and the protein were responsible for the pharmacokinetic properties of the drug. The analysis of pure water solubility is 2370.34 mg/L. The cytochrome protein indicates that the molecule is inhibitor of 2C19, 2C9 and 3A4 which reduces the capability of the drug and pharmacological effects of the drug [9]. In present the different types of rules are implemented to study violations of the headline compound. The Lead-like has suitable of its binding affinity is greater than 0.1microM and it has zero violations, MDDR like rule shows the nondrug-like nature, because of no rings, no rigid bonds, no rotatable bonds, while the important rule of five shown that hydrogen bond donors and hydrogen bond acceptors are less than five in headline molecule, molecular mass is less than 500, which shows that the Lipinski rule has no violations and this molecule is suitable for drug discovery procedure. Moreover the WDI like rule is out of 90% cutoff. Overall, the of MBF structure druglikeness properties shows as a suitable compound for drug discovery procedure.

Toxicity

Toxic prediction plays crucial role in drug discovery process and it is important parameters to identify the intoxic nature of various chemical compounds [31]. For the MPF compound algae at value is 0.051268, Ames test is as usual mutagen and the important carcino mouse is negative and the carcino rat is positive. The daphnia at value is 0.195, while the hERG is at low risk inhibition stage. The medaka at and minnow at values are 0.0526 and 0.028, respectively. All the above values are compared with the resultant parameters of reported literature. All the predicted toxic parameters values show the in toxic nature in the compound.

Ramachandran plot

Statistical distributions of amino acids in protein crystal structure can be studied from Ramachandra plot. In present study the Pass online bio activity predictor [32, 33] is used to find the inhibition activity of the MBF compound. The protein 4FPR is chosen study the PL interaction and it is subjected to find the quality of protein. Most of the amino acids are fall within the allowed region of 4FPR crystal structure. This shows the crystal structure of protein is stable in nature. The allowed regions of 4FPR protein residues are shown in Figure 5.

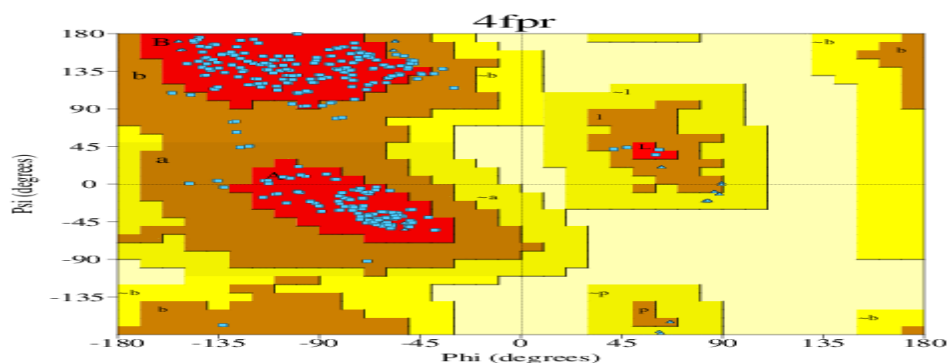


Figure 5. 2D Ramachandra plot for fungal protein structure (4FPR).

Molecular docking study

Molecular docking plays prominent role in drug design for treating of many diseases [34, 35]. In this process, we have explored the binding of a molecule with protein and thus effectively act as a drug and so docking has a great importance in the field of drug discovery. In present case, MBF compound is subjected to dock with the 4FPR fungal protein. Fungal disease is an infectious disease across the world. Piperazine derivative was investigated and reported for fungal activity with -4.73 kcal/mol binding with single hydrogen bond interaction [36]. The MBF ligand forms two hydrogen bonds the chosen protein structure. Hydrogen bond interacted image is shown in Figure 6.

The atom O4 forms the bonds with the distance of 2.0 Å and 1.8 Å with the residues SER'28, and GLU'130, respectively. The binding energy -5.00kcal/mol is recorded as highest binding energy in this PL interaction. Hence, this MBF compound is predicted as potential drug candidate for fungal disease and bioactivity of the headline compound is confirmed.

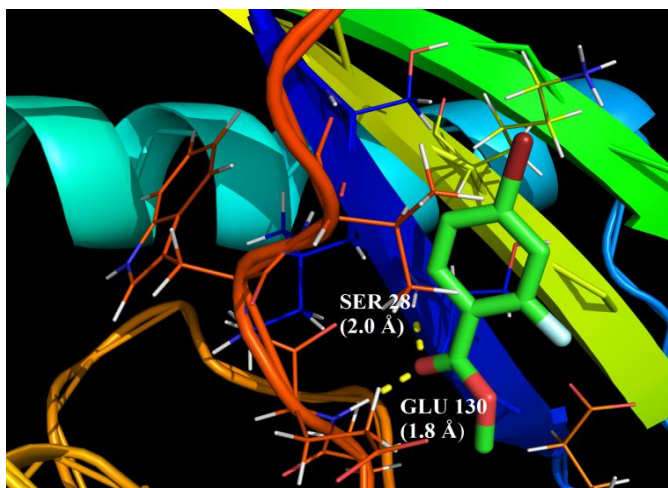


Figure 6. Hydrogen bond interacted image of MBF ligand with receptor fungal protein 4FPR.

In this study we investigated, structural properties (bond length between each atoms) of methyl 4-bromo-2-fluorobenzoate by optimizing the structure using DFT tools. The bioactive conformation revealed the existence of C-H \cdots O hydrogen bonding in between halo-benzene hydrogen and carboxylate oxygen, which confirmed through NBO study. Calculated band gap energy (1.707 eV) from absorption spectra is compared with the band gap energy of HOMO-LUMO and which comparable with biologically active molecules. Different parameters like Solute permeability (Blood Brain Barrier) value are 1.91742, while the buffer solubility is 11218 of MBF compound is calculated from ADME properties. In drug likeness predictions, the Lipinski rule of five has no violation and the all the rules are suitable on the headline compound for drug nature. Carcino mouse is negative, which shows intoxic nature of MPF compound. Molecular docking result corroborates this result with -5.00 kcal/mol binding energy. Hence the MPF compound and docked protein is structurally stable and form hydrogen bond between each other. So, we predict MPF compound might be a potential anti fungal drug candidate for fungal disease.

AUTHOR CONTRIBUTIONS

Conception: *M.M.J., F.B.A.*; Design: *M.M.J., F.B.A.*; Supervision: *T.P., S.M.*; Resources: *T.P., S.M.*; Materials: *T.P., S.M.*; Data collection and/or processing: *M.M.J., F.B.A.*; Analysis and/or interpretation: *M.M.J.*; Literature search: *M.M.J.*; Writing manuscript: *M.M.J., F.B.A.*; Critical review: *M.M.J., T.P.*; Other: *M.M.J., F.B.A.*

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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