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Graphical abstract:

Title of the paper: Synthesis, XRD Crystal Structure, Spectroscopic Characterization, Local Reactive Properties using DFT and Molecular Dynamics Simulations and Molecular Docking Study of *(E)*-1-(4-bromophenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one.

In this work, a new chalcone derivative, *(E)*-1-(4-bromophenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one is synthesized and structurally characterized by single crystal XRD, FT-IR, ^1H and ^{13}C NMR. The IR spectrum was recorded and interpreted in details with the aid of Density Functional Theory (DFT) calculations and Potential Energy Distribution (PED) analysis. In order to investigate local reactivity properties of the title molecule, we have conducted DFT calculations of average local ionization energy surface and Fukui functions which were mapped to the electron density surface. In order to predict the open air stability and possible degradation properties, within DFT approach, we have also calculated bond dissociation energies. To determine which atoms of title molecule have pronounced interactions with water molecules, we have calculated radial distribution functions obtained after molecular dynamics simulations. In order to understand how the title molecule inhibits and hence increases the catalytic efficiency of MOA-B enzyme, molecular docking study was performed to fit the title compound into the binding site of MOA-B enzyme.

Synthesis, XRD Crystal Structure, Spectroscopic Characterization, Local Reactive Properties using DFT and Molecular Dynamics Simulations and Molecular Docking Study of *(E)-1-(4-bromophenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one*.

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Abstract

In the present study, the title compound named as *(E)-1-(4-bromophenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one* was synthesized and structurally characterized by single-crystal X-ray diffraction. The FT-IR spectrum was recorded and interpreted in details with the aid of Density Functional Theory (DFT) calculations and Potential Energy Distribution (PED) analysis. Average local ionization energies (ALIE) and Fukui functions have been used as quantum-molecular descriptors to locate the molecule sites that could be of importance from the aspect of reactivity. Degradation properties have been assessed by calculations of bond dissociation energies (BDE) for hydrogen abstraction and the rest of the single acyclic bonds, while molecular dynamics (MD) simulations were used in order to calculate radial distribution functions and determine the atoms with significant interactions with water. In order to understand how the title molecule inhibits and hence increases the catalytic efficiency of MOA-B enzyme, molecular docking study was performed to fit the title compound into the binding site of MOA-B enzyme.

Keywords: DFT; Chalcones; XRD; FT-IR; Molecular Dynamics; Molecular Docking.

1. Introduction

Organic synthesis has become a fast growing branch of chemical synthesis. Researches in this area concentrate more on fields like pharmaceuticals and agriculture from where humans derive direct benefit. Chalcones have become a centre of attraction in recent researches in organic synthesis [1, 2]. They are abundant in edible plants from ferns to higher herbs and are widely been recognized as the precursor of flavonoids and isoflavonoids. Chalcones (1,3-diphenyl-2-propen-1-one) are α , β -unsaturated ketones acquired by condensing an aromatic aldehyde with an aryl methane in the presence of a base. The significant features of chalcone derivatives are often attributed to α , β -unsaturated moiety. Introduction of different substituents into the two aryl rings may result in useful structure-activity relationship. Chalcones and their substituted derivatives demonstrate broad spectrum of biological activities like anti-inflammatory [3], antibacterial [4], anti-cancerous [5], anti malarial [6], anti leishmanial [7], antiviral [8] and anti-tuberculosis [9]. According to several researchers, the size as well as the hydrophobicity of substituents in the ring A of chalcones determines the *in vitro* antimalarial activity against human malarial parasite, *P. falciparum* [10]. Antifungal activity of chalcones against a group of dermatophytic fungi was reported by Boeck *et al.* [11], and their studies showed that the presence of electron-withdrawing groups in the para-position on ring B, increase their fungal activity, while the substitution of electron-donating groups make them weak antifungal agent. In a study reported by Jantan *et al.* [12], a series of chalcone derivatives were investigated for anti-inflammatory related activities and the study revealed that selected chalcones were potential inhibitors of secretory phospholipase A_2 , cyclooxygenases and lipoxygenase.

The rapid development in organofluorine chemistry during the past decades highlights the importance of trifluoromethyl group in the medicinal industry [13, 14]. The introduction of fluorine atom can modify physical and biological properties along with chemical reactivity of organic compounds. Its ability to enhance the transportation quality of a molecule by increasing the lipophilicity has been used conveniently in chemistry [15, 16]. Apart from this, the strength and durability of the C–F bond compared to the C–H bond (116 and 100 kcal/mol respectively) ceases undesirable metabolic transformations [17]. Trifluoromethyl moiety is one of the most popular fluorine containing functional groups present in drug molecules. It exerts significant changes in the acidity of neighbouring centres. Effect of trifluoromethyl on bioactive molecules widens the prospect of organofluorine chemistry in Pharmacology [18]. Antidepressants like Prozac (fluoxetine) [19] and Luvox (fluvoxamine) [20], contain a para-phenyl trifluoromethyl group. Also, famous antiprotozoal drug, Lariam

(Mefloquine) has two trifluoromethyl groups, on each of the aromatic rings of a quinoline nucleus [21]. Kaynak *et al.* [22] reported the synthesis and crystal structures of three novel compounds containing a trifluoromethoxy group. Kooriyaden *et al.* [23] investigated the influence of trifluoromethyl groups in the crystal packing motif of the metalloporphyrins using Hirshfeld surface analysis. With the aim of developing new antimalarial drugs, Boechat *et al.* [24] have reported the design and synthesis of a series of trifluoromethyl-substituted benzenesulfonamide derivatives. A combined experimental and computational studies of (E)-2-(((4-bromo-2-(trifluoromethoxy)phenyl)imino)methyl)-4-nitrophenol was reported by Tamer *et al.* [25].

In view of the significant applications organofluorine derivatives, here we are reporting the crystal structure of a newly synthesized chalcone derivative containing a trifluoromethoxy group. The molecular structure and spectroscopic properties were investigated by single crystal XRD, infrared (IR), ^1H and ^{13}C NMR. In order to investigate local reactivity properties of the title molecule, we have conducted DFT calculations of average local ionization energy surface and Fukui functions, which were mapped to the electron density surface. In order to predict the open air stability and possible degradation properties, within DFT approach, we have also calculated bond dissociation energies. Radial distribution functions obtained after molecular dynamics simulations indicated us which atoms of the title molecule are having the most pronounced interactions with water molecules. In order to explore possible binding mode of the title compound towards MAO-B isoform of the enzyme, molecular docking study was performed to fit the compound into binding site of the enzyme, which consists of a substrate cavity extends from the covalently bound redox cofactor flavin adenine dinucleotide (FAD) to the entrance cavity and an aromatic cage.

2. Experimental

2.1. Synthesis and Crystal Growth

Synthesis of (E)-1-(4-bromophenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one

A mixture of 4-bromoacetophenone (1 mol) and 4-trifluoromethoxybenzaldehyde (1 mol) was dissolved in methanol (20 mL). Catalytic amount of NaOH was added to the solution drop-wise with vigorous stirring. The reaction mixture was stirred for about 5–6 hrs at room temperature. The resultant crude products were filtered, washed successively with distilled water and recrystallized from acetone to get the corresponding chalcone (Scheme 1). The single crystals of the compound (CCDC No.: 1013207) which is suitable for X-ray structural analysis as shown in **Fig.S1**, given as supplementary information. The FT-IR

spectrum was recorded in the 4000–400 cm^{-1} region with a PerkinElmer Spectrum GX Frontier Spectrophotometer using KBr pellet. ^1H and ^{13}C NMR spectra were recorded at 500 MHz, in DMSO- d_6 , on Bruker 500MHz Avance III spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) internal reference.

Scheme 1 The synthesis route of the compound

2.2. X-Ray crystallographic Analysis

X-ray analysis of a suitable single crystal was performed on Bruker SMART APEXII Duo CCD area-detector diffractometer using MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). Data collection was performed by the APEX2 software [26], whereas the cell refinement and data reduction were performed by the SAINT software [27]. The crystal structure was solved by Direct Method using the program SHELXTL [27] and was refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters by SHELXTL [27]. Absorption correction was applied to the final crystal data using the SADABS software [26]. All geometrical calculations were carried out using the program PLATON [28]. The molecular graphics were drawn using SHELXTL [27] and Mercury program [29]. Anisotropic thermal factors were assigned to all non-hydrogen atoms. In this compound, all the hydrogen atoms were positioned geometrically and were refined using a riding model, with isotropic displacement parameters set to 1.2 times the equivalent isotropic U values of

the parent carbon atoms. The crystallographic data and structure refinement parameters of the compound are shown in **Table 1**.

3. Computational Details

Vibrational frequency calculations of the title compound was carried out with Gaussian09 software package [30], using the three-parameter hybrid functional of Becke based on the correlation functional of Lee, Yang, and Parr (B3LYP) [31]. The 6-311++g(d,p) basis set was assigned to all atoms in the title molecule. We have used a scaling factor of 0.9613 for DFT method, since the B3LYP functional tends to overestimate the fundamental vibrational modes [32]. The assignments of wavenumbers were carried out using the potential energy distribution (PED) analysis with the help of GAR2PED software [33] and animation option of the Gaussview program [34].

In this work for DFT calculations of ALIE, Fukui functions and BDE we have employed Jaguar 9.0 program [35] as implemented in Schrödinger Materials Science Suite 2015-4. All these calculations have been performed on the lowest energy conformation obtained by the following procedure. Firstly all possible conformations of the title molecule (total of 10) were obtained by using the MacroModel 11.0 program [36] for molecular dynamics, also as implemented in Schrödinger Materials Science Suite 2015-4, using the OPLS 2005 force field. All obtained conformations were optimized at B3LYP/6-31g(d) level of theory and five of them with the lowest energies have been chosen for further more detailed optimization at B3LYP/6-31g(d,p) level of theory with increased integral accuracy and finer grid density, followed by the frequency calculations in order to assure that true ground states are located. Finally, the lowest energy conformation of these five has been chosen for further detailed calculations of ALIE, Fukui functions and BDE with B3LYP exchange-correlation functional [37] and 6-31g(d,p), 6-31+g(d,p) and 6-311g(d,p) basis sets, respectively. For the investigation of interactions of the title molecule with water by MD simulations, a Desmond program [38–41] was used. After trajectories have been obtained the radial distribution functions (RDFs) have been calculated, enabling us to determine which atoms have the most pronounced interactions with water molecules. System was modelled in such way that one title molecule was placed in a cubic box with ~3000 water molecules. These simulations were also performed with OPLS 2005 force field [42], within the isothermal–isobaric (NPT) ensemble class. Temperature was set to 300 K, while pressure was 1.01325 bar. Simulation time was 10 ns and cut off radius was set to 12 Å. System was relaxed in the beginning of simulation (meaning that for certain simulation time system was optimized within canonical (NVT) ensemble) for a 100 ps. Solvent was treated within the

simple point charge (SPC) model [43]. For the investigation of intramolecular noncovalent interactions the method of Johnson [44, 45] was employed, also as implemented in Jaguar 9.0 program.

4. Results and Discussion

4.1. Description of the Crystal Structure

The molecular structure of the compound is depicted in **Fig.1a**. The crystal structure crystallizes in orthorhombic crystal system with *Pbca* space group. The compound exists in *trans* configuration with respect to the C8=C9 double bond with bond distance of 1.343(2) Å (**Table 2**). The 4-bromobenzaldehyde moiety (Br1/O1/C1–C7) of the compound is found to be deviated from the 1-(trifluoromethoxy)-4-vinylbenzene planarity [F1–F3/O2/C8–C16] at the C7–C8 bond with the C6–C7–C8–C9 torsion angle being 164.63(16)°. The twisted structure of the compound is shown in **Fig.1b**. In addition, the dihedral angle formed between the terminal benzene rings (C1–C6 and C10–C15) is 47.40(8)°. All bond lengths and angles are within the normal ranges [46] and comparable with the previously reported structure of chalcones [47, 48]. The selected geometrical parameters are tabulated in **Table 2**.

In the crystal packing of the compound, the molecules are stabilized by intermolecular C1—H1A...Cg1 (symmetry code: 1/2-*x*, 1/2+*y*, *z*) and C12—H12A...Cg2 (symmetry code: 1/2-*x*, -1/2+*y*, *z*) interactions (**Table 3**), forming one-dimensional columns running along the *b*-axis (**Fig.2a**). Furthermore, the short Br1...F3 (symmetry code: *x*, 3/2-*y*, -1/2+*z*; contact distance: 3.287(15) Å) and F3...F2 (symmetry code: 1/2-*x*, 1/2+*y*, *z*; contact distance: 2.820 (2) Å) contacts (**Table 4**) are also observed (**Fig.2b**) which connect the columns into a two dimensional sheet parallel to the *bc*-plane. The short Br...F and F...F interactions observed in the compound are less than the sum of Van der Waals radii of Br (1.86 Å) and F (1.47 Å) atoms which are 3.33 Å and 2.94 Å, respectively [49]. The short C3–Br1...F3 contact angles is 142.96(6) while the C16–F3...F2 contact angle is 139.77(13)°. The presence of these Br...F and F...F contacts are due to the greater polarizability and high electronegativity of the bromine and fluorine atoms.

4.2. Optimized Geometry using Periodic DFT

We have also performed geometric optimization of the periodic system based on the title molecule. In the periodic case, density functional tight-binding (DFTB) method [50], as implemented in Amsterdam Density Functional Molecular Modeling Suite (ADF) 2016 [51-53], has been applied with QUASINANO2015 parameters set [54, 55]. The structural parameters of the optimized geometry have been obtained using the B3LYP method at the 6-

311++g(d,p) level. The optimized geometry of the title compound is given in **Fig.S2**, as supplementary information and the selected geometrical parameters are tabulated (**Table 2**).

4.3. IR Spectrum

Theoretical and Experimental FT-IR spectra of the title compound are presented in **Fig.3**. Observed and calculated vibrational modes with their tentative assignments are summarized in **Table 5**. In the following discussion the para-substituted phenyl rings are designated as PhI (C1–C2–C3–C4–C5–C6) and PhII (C10–C11–C12–C13–C14–C15).

The vibrations involving both aromatic and aliphatic C–H stretching give rise to bands above 3000 cm^{-1} , in the IR spectrum. In the present case, two C–H stretching modes of the vinylenic group were calculated at 3064 and 3027 cm^{-1} and observed at 3017 cm^{-1} in the IR spectrum. According to Panicker *et al.* [56], the bands at 3086 cm^{-1} (IR) and at $3089, 3050\text{ cm}^{-1}$ (DFT) are due to the stretching modes of the vinylenic group. The absorption region of in-plane and out-of-plane bending vibrations of vinylenic C–H are generally $1390\text{--}1140\text{ cm}^{-1}$ and $1000\text{--}675\text{ cm}^{-1}$, respectively [57]. For the title compound, in-plane and out-of-plane vinylenic C–H bendings were calculated at $1311, 1155, 983$ and 793 cm^{-1} and observed at 986 cm^{-1} in the IR spectrum. In the present case, bands calculated at $1092, 1088$ and 1040 cm^{-1} were assigned to the C–C stretching modes and these vibrations were observed at 1096 and 1033 cm^{-1} in the IR spectrum.

The carbonyl moiety in substituted chalcones absorbs IR strongly in the $1750\text{--}1600\text{ cm}^{-1}$ region [57]. The C=O stretching occurs at lower frequencies when conjugated to C=C. Clothup *et al.* [58] found that substituted chalcones absorb infrared radiation strongly around 1650 cm^{-1} , because of the C=O stretching vibrations. In the present case, the C=O stretching vibration was observed at 1657 cm^{-1} in the IR spectrum and assigned at 1652 cm^{-1} , theoretically, which are in well agreement with the reported values for substituted chalcones [47, 59]. For the majority of condensed-phase organic samples, C=C stretching band is observed around 1600 cm^{-1} due to the conjugation with the adjacent carbonyl group [60]. Recently, Praveen *et al.* [61] has examined C=C bands in substituted chalcones that are seen at 1578 cm^{-1} (IR) and 1588 cm^{-1} (DFT). The C=C stretching frequency of the title compound is estimated to be at 1574 cm^{-1} , which is only 5 cm^{-1} higher than the experimental value of 1569 cm^{-1} in the IR spectrum.

In the present discussion of IR spectrum, the assignments of the substituted phenyl ring vibrations were made by referring the case of benzene derivatives with 1,4-disubstitution by Roeges [57]. As per the reference [57], C–H stretching modes in the para-substituted benzenes can give rise to IR bands in the range $3105\text{--}3000\text{ cm}^{-1}$. For the title compound,

phenyl C–H stretching modes are assigned to bands in the range 3084–3059 cm^{-1} for PhI and 3101–3055 cm^{-1} for PhII and observed at 3081, 3056 cm^{-1} in the IR spectrum. The four in-plane C–H bending modes of 1,4-disubstituted benzene ring usually give rise to bands in the 1315–1015 cm^{-1} region, while IR bands correspond to out-of-plane C–H stretching modes are located in a lower region, at 995–720 cm^{-1} [57]. In the present case, in-plane bendings of phenyl C–H were assigned at 1192, 1176, 1098, 1000 cm^{-1} for PhI and 1268, 1182, 1139, 992 cm^{-1} for PhII and observed at 1181, 1134, 1006 cm^{-1} in the IR spectrum. In 1,4-disubstituted benzenes, the C–H out-of-plane deformations are usually observed between 995 and 720 cm^{-1} [57] and for the title compound these vibrations were assigned to bands in the range 960–799 cm^{-1} for PhI and 981–791 cm^{-1} for PhII. In the IR spectrum, these vibrations were observed at 981, 928, 820, 808 and 788 cm^{-1} . General IR and Raman regions for para-substituted benzenes include 1630–1280 cm^{-1} (ring stretching) and 810–680 cm^{-1} (ring breathing) [57]. For the title compound, these phenyl ring stretching vibrations are assigned to bands in the range 1557–1271 cm^{-1} for PhI and 1587–1290 cm^{-1} for PhII and observed at 1583, 1559, 1484, 1448, 1398, 1364 cm^{-1} in the IR spectrum. The ring breathing modes of the phenyl rings of the title compound were calculated to be 749 cm^{-1} for PhI and 726 cm^{-1} for PhII, and the corresponding experimental values were found to be 741 and 719 cm^{-1} . The ring breathing mode of 1,4 di-substituted benzene was reported in the IR spectrum at 785 cm^{-1} [62]. Kaur *et al.* [63], investigated the vibrational spectra of 4-methylbiphenyl-2-carbonitrile and parasubstituted phenyl ring stretching vibrations were assigned to the bands at 1614, 1560, 1504, 1379 cm^{-1} , while the ring breathing mode was found at 820 cm^{-1} in the IR spectrum.

In general, it has been found that no pure C–X stretching vibration band is observed for aromatic halogen compounds [64]. The C–X (X is a halogen atom like chlorine, bromine or iodine) stretching vibrations tend to interact with the phenyl ring vibrations, when a halogen is directly attached to a benzene ring [65]. The characteristic frequencies of C–Br stretching vibrations of 1,4-disubstituted benzene falls in the range 650–395 cm^{-1} in the IR spectrum [66]. The C–Br stretching was reported to be at 621 cm^{-1} theoretically [67]. Smith [68] suggested that the IR band in the region of 650–500 cm^{-1} is due to the C–Br stretching vibration. Xiao *et al.* [69] designated the band at 526 cm^{-1} to the C–Br stretching mode. In the present case, C–Br stretching vibration was assigned to the band at 616 cm^{-1} theoretically and observed at 617 cm^{-1} in the IR spectrum.

Roeges [57] suggested that the $-\text{CF}_3$ moiety adjacent to an oxygen atom absorbs IR strongly in the 1330–1155 cm^{-1} region, due to C–F stretching vibrations. In the present case,

the asymmetric and symmetric CF_3 stretching vibrations were assigned to bands calculated at 1302, 1204 and 1160 cm^{-1} , respectively. Joseph *et al.* [70] reported that the IR absorption of a pyrazine derivative at 1140 and 1026 cm^{-1} were due to vibrations involving $-\text{CF}_3$ stretching mode. In the present case, one of the $-\text{CF}_3$ stretching vibrations was observed at 1205 cm^{-1} in the IR spectrum. Symmetric and asymmetric deformation frequencies for $-\text{CF}_3$ group fall in the region of 720–645 cm^{-1} and 610–440 cm^{-1} , respectively. In the low frequency region, there are two characteristic IR bands in 470–260 cm^{-1} range, where these frequencies were assigned to $-\text{CF}_3$ rocking deformations [57]. In the IR spectrum of the title compound, the bands at 692 and 520 cm^{-1} were attributed to the asymmetric and symmetric in-plane $-\text{CF}_3$ deformation modes and DFT values for the above vibrational modes were calculated at 690, 583 and 520 cm^{-1} . Also for the title compound, the bands calculated at 420 and 365 cm^{-1} , were assigned to the rocking deformations of trifluoromethyl group. The vibrational analysis of 3-Hydroxy benzylidene trifluoride has been studied by Arivazhagan and Kamala [71] and found that the skeletal stretching vibration of CF_3 occur at 1197 cm^{-1} in the IR spectrum. Al-Omary *et al.* [72] investigated the vibrational spectra of a pyrimidine derivative and CF_3 stretching vibrations were assigned to bands at 1110, 1064 and 1048 cm^{-1} , while the deformation bands were found in the region of 638–316 cm^{-1} .

From the previous studies of vibrational spectra of various methoxy derivatives [73, 74], it has been found that the $\text{C}_{\text{aromatic}}-\text{O}$ vibration absorbs strongly around 1250 cm^{-1} and the $\text{C}_{\text{aliphatic}}-\text{O}$ absorption takes place in the neighbourhood of 1010 cm^{-1} . If the hydrogen atoms were replaced by fluorine atoms, one might expect that the frequency of the C–O vibrations would shifted to lower frequency values. Kulik *et al.* [75] investigated the infrared spectra of aryl trifluoromethyl ethers and $\text{C}_{\text{aromatic}}-\text{O}$ and $\text{C}_{\text{aliphatic}}-\text{O}$ vibrations were assigned to bands at 1262, 1267 cm^{-1} and 928, 924 cm^{-1} , respectively. In this study, they have reported that increase in both the frequencies of the C–O vibrations was mainly due to the increase in the electron-acceptor character of the substituent in the para position of the benzene ring relative to the $-\text{OCF}_3$ group. For the title molecule, the bands calculated at 1263 and 920 cm^{-1} , were assigned as $\text{C}_{\text{aromatic}}-\text{O}$ and $\text{C}_{\text{aliphatic}}-\text{O}$ stretching vibrations, respectively and in the IR spectrum, a strong band at 1264 cm^{-1} and a medium intensity band at 921 cm^{-1} , were allocated to these vibrations. Tamer *et al.* [25] reported the COC stretching of a trifluoromethoxy group to be located at 1237, 1186 and 776 cm^{-1} . According to the vibrational study given by Kulik *et al.* [75], the intense IR bands at $1262 \pm 5 \text{ cm}^{-1}$ ($\nu_{\text{C}_{\text{aromatic}}-\text{O}}$), $1178 \pm 10 \text{ cm}^{-1}$ ($\nu_{\text{C}-\text{F}}$), $1222 \pm 4 \text{ cm}^{-1}$ ($\nu_{\text{C}-\text{F}}$) and 925 cm^{-1} ($\nu_{\text{C}_{\text{aliphatic}}-\text{O}}$) can be used in analysis for determining the presence of an $-\text{OCF}_3$ group in the benzene ring.

4.4. ALIE surface, Fukui functions and non-covalent interactions

MEP surfaces are very useful quantum molecular descriptor for the detection of molecular sites prone to electrophilic and nucleophilic attacks. On the other side ALIE values were introduced by Sjöberg *et al.* [76, 77] for the investigation of reactive properties of aromatic molecules. For detection of molecule sites prone to electrophilic attacks ALIE is better than MEP, as it indicates the areas where electrons are least tightly bound and therefore where electrons are most easily removed. ALIE is defined as a sum of orbital energies weighted by the orbital densities:

$$I(r) = \sum_i \frac{\rho_i(\vec{r}) |\varepsilon_i|}{\rho(\vec{r})}, \text{ where } \rho_i(\vec{r}) \text{ represents the electronic density of the } i\text{-th molecular orbital}$$

at the point $\vec{r}$, ε_i represents the orbital energy and $\rho(\vec{r})$ is the total electronic density function. When ALIE values are mapped to the electron density surface, which is the case in this work, molecule sites where electrons are the most easily removed are clearly visualized, **Fig.4**. Results presented in **Fig.4** indicate high values of ALIE. Even the lowest ALIE value is higher than 250 kcal/mol, while the highest ALIE value is far above the 400 kcal/mol. Nevertheless, if electrophilic attacks are option for the title molecule then the possibility is the highest in the near vicinity of Br1 atom and in the near vicinity of carbon atom C8 (locations of red colour in **Fig.4**). On the other side it can be seen in **Fig.4** that the electrons are the most tightly bound in the near vicinity of fluorine atoms.

The analysis of electron density and its topology between non bonded atoms indicate that four distinct intramolecular noncovalent interactions occur for the title molecule, as shown in **Fig.5**. Two of the noncovalent interactions are formed between hydrogen atoms H5A, H8A and H11A, in the central part of the molecule, while the other two noncovalent interactions are formed between hydrogen atom H14A and fluorine atoms F1 and F3. According to the obtained results the strongest noncovalent interaction occurred between hydrogen atoms H5A and H8A, with corresponding strength of -0.012 electron/bohr³, while the adjacent noncovalent interaction, between H8A and H11A is the weakest, with corresponding strength of -0.009 electron/bohr³. Noncovalent interactions between hydrogen atom and fluorine atoms have the strength of -0.010 electron/bohr³. All detected noncovalent interactions favour the non-planar shape of the molecule.

Molecule sites that are possibly important from the aspect of reactivity can also be detected by the calculation of the Fukui functions. Fukui functions show where electron density increases or decreases when the charge is added or removed, respectively. This

quantum molecular descriptor can be calculated in the finite difference approximation, which is the case with Jaguar program, according to the following equations:

$$f^+ = \frac{(\rho^{N+\delta}(r) - \rho^N(r))}{\delta},$$

$$f^- = \frac{(\rho^{N-\delta}(r) - \rho^N(r))}{\delta},$$

where N represents the number of electrons in reference state of the molecule, while δ is fraction of electron which default value is set to be 0.01 [78]. In this work the values of Fukui functions have been mapped to the electron density surface, **Fig.6**, while there is also the possibility to present them as isosurfaces.

For the case of Fukui f^+ function purple colour indicates location where electron density increased after the addition of charge, while for the case of Fukui f^- function red colour indicates where electron density decreased after the removal of charge. Results presented in **Fig.6a** in the case of f^+ function show that purple colour is located in the near vicinity of carbon atom C7, indicating that here electron density increases when molecule acts as an electrophile. On the other side, in the case presented in **Fig.6b**, results show that red colour is located in the near vicinity of carbon atom C8, indicating that here electron density decreases when molecule acts as nucleophile.

4.5. Reactive properties based on autoxidation and hydrolysis

Molecule investigated in this work could potentially belong to the group of very stable molecules that enter the water and that could be potentially toxic for aquatic organisms. Therefore, it is also important to investigate to what extent these molecules are prone to autoxidation and degradation, in order to develop or improve the methods for their efficient and economic removal. While for these purposes advanced oxidation processes are seen as the efficient alternative to conventional water purification methods, forced degradation experiments are long, tedious and expensive [79, 80]. Principles of molecular modelling, DFT calculations and MD simulations could be very helpful for the initial assessment of degradation properties. In this regard calculation of BDEs for hydrogen abstraction could be particularly useful for the determination of molecule sites where autoxidation process could start, while BDEs of the remaining single acyclic bonds could classify bonds according to their strength.

For autoxidation process it is important to notice that formation of a radical of pharmaceutical substance happens with the formation of peroxy radical [81]. In case that formed peroxy radical can abstract hydrogen from another pharmaceutical molecule, reaction

can proceed. Nevertheless, hydrogen atoms can be abstracted only at certain positions, if the BDE of hydrogen abstraction is in proper interval. While all peroxy radicals have similar BDE values (87–92 kcal/mol), independent of chemical surrounding [81, 82], study of Wright *et al.* [83] shows that BDE for hydrogen abstraction in the interval of 75–85 kcal/mol indicates very high sensitivity of a molecule towards autoxidation. BDE values of all single acyclic bonds of the title molecule are presented in **Fig.7**. Results provided in **Fig.7** clearly indicate the great stability of the investigated molecule towards the mechanism of autoxidation. Namely, all BDE values for hydrogen abstraction are much higher than 92 kcal/mol, emphasizing its great stability in the open air or in the presence of oxygen. BDE values of the remaining single acyclic bonds show that the weakest bonds could possibly be the bonds denoted with number 7 and 10, indicating that the degradation process could start by detaching of bromine atom or trifluoromethyl group. This is in accordance with the results obtained by ALIE surfaces, since these units are characterized by the lowest and the highest ALIE values, respectively.

RDFs have been calculated in order to determine which atoms of the title molecule have pronounced interactions with water molecules. RDF, $g(r)$, is quantity that gives the probability of finding a particle in the distance r from another particle [84], and the RDFs of the atoms with pronounced interactions with water are presented in **Fig.S3**, which is given as supporting information. RDFs presented in **Fig.S3** indicate that the title molecule has practically six atoms which possibly have significant interactions with water molecules, as determined by the shape and profile of $g(r)$ curves. Four of them are carbon atoms C3, C6, C7 and C16, among which the most important is certainly the carbon atom C16 with maximal $g(r)$ value of around 1.4 and with peak distance at around 4 Å. Peak distances of C3 and C6 are around 4.5 Å, while their maximal $g(r)$ value ranges between 1.1 and 1.2. From the aspect of RDFs the most important atoms are Br1 and O1. While O1 has maximal $g(r)$ value at peak distance of around 5 Å, the most important RDF is calculated for bromine atom, which has maximal $g(r)$ value of around 1.4, which is located at distance of somewhat less than 3.5 Å.

4.6. Frontier Molecular Orbitals

For organic derivatives, the HOMO–LUMO gap is significant because they relate to specific movements of electrons and may be most important for single electron transfer. This is useful for a number of reactions, and has huge implications in organic semiconductors, the field where this gap is most important. It has been found that molecules with large HOMO–LUMO gap are generally stable and unreactive [85]. By calculating the HOMO–LUMO

energy gap, one can easily determine the excitation energy of an organic derivative at its ground state [86].

The energy levels of the frontier molecular orbitals were obtained at the TDDFT/B3LYP/6-311++G(d,p) level of theory. The electron density plots of the HOMO and LUMO for the title molecule is presented in **Fig.8**. As can be seen from **Fig.8**, LUMO is distributed over the entire molecular skeleton. LUMO is centred on the enone system and the substituted phenyl rings with small contribution from the bromine atom. Also note that the CF₃ group do not play any role in the LUMO. HOMO is more localized at the enone system and phenyl ring B, with substantial contributions from phenyl ring A and bromine atom and a small contribution from the trifluoromethyl group. The energy values of the highest occupied molecular orbital (E_{HOMO}) and lowest unoccupied molecular orbital (E_{LUMO}) of the title compound are about -6.886 eV and -2.828 eV, respectively. In the present case, calculated $E_{\text{HOMO}}-E_{\text{LUMO}}$ energy gap is found to be 4.058 eV. It has been observed from the calculated values that the E_{HOMO} , E_{LUMO} and HOMO–LUMO gap of the title molecule are comparable to the corresponding values for the unsubstituted chalcones and is in good agreement with the reported values for different substituted chalcones [87].

4.7. NMR Spectra

GIAO ^1H and ^{13}C chemical shift values with respect to trimethylsilane (TMS) were calculated at DFT/B3LYP/6-311++g(d,p) level of theory and compared to the corresponding experimental values. The ^1H NMR and ^{13}C NMR spectra are presented in **Fig.S4** and **Fig.S5**, which are given as supporting information.

For the title compound, ^1H NMR chemical shift values were observed in the range 8.11–7.44 ppm, while the DFT values were calculated at 8.44–7.45 ppm. Two doublets observed at 8.11 and 7.45 ppm in the ^1H NMR spectrum was assigned to vinylenic group hydrogens and corresponding values were calculated at 8.33 and 8.05 ppm. In the ^1H NMR spectrum, doublets and multiplets observed at 8.09 and in the range 7.43–7.97 ppm, were assigned to aromatic C–H groups, where as the corresponding theoretical values are in the range 8.12–7.45 ppm. The results are summarized in **Table 6**.

Signal observed at 188.2 ppm in the ^{13}C NMR spectrum was assigned to C7 atom of the carbonyl group and this was calculated at 192.9 ppm. The signals observed at 142.6 and 122.8 ppm were assigned to vinylenic carbon atoms and these were calculated at 152.2, 122.8 ppm. The signal at 130.6 ppm is attributed to the carbon atom in the trifluoromethyl group, which is supported by the calculated value 131.2 ppm. ^{13}C NMR spectrum of the title compound show signals in the range 138.5–125.0 ppm corresponds to aromatic carbons of

the phenyl rings. ^{13}C NMR chemical shift values corresponding to aromatic carbons were calculated in the range 160.6–119.5 ppm. The ^{13}C NMR chemical shifts values are summarized in **Table 7**. Comparing the experimental data with the theoretical ones indicates that the DFT values are much closer to experimental values.

4.8. Molecular docking studies

Monoamine oxidases (MAO), one of the most essential enzymes belong to the protein family of flavin-containing amine, catalyzes the deamination of monoamines to the corresponding aldehyde and ammonia using oxygen as an electron acceptor [88]. The catalyzing mechanism of MAO is mainly due to the presence of covalently bound redox cofactor flavin adenine dinucleotide (FAD) and hence these enzymes are known as flavoproteins. Based on which substrate they execute their catalytic activity, two isoforms of MAO have been identified: MAO-A and MAO-B [89]. MAO-B dysfunction has been linked to a number of neurological and psychological disorders including Parkinson's disease [90] and Alzheimer's disease [91]. A series of fluorinated methoxylated chalcones were synthesized and evaluated as potential inhibitors of MAO-B isoform by Mathew *et al.* [92]. In this work they have studied the effect and orientation of fluorine and the trifluoromethyl group in methoxylated chalcones using molecular docking studies. The hMAO-B binding site consists of a substrate cavity, which extends from FAD to the entrance cavity. In addition to the substrate cavity, defined by Leu171, Tyr126, Phe168, Ile198 and Ile199, there exists an aromatic cage characterized by the tyrosine residues Tyr 186, 189, 398, 435 and Phe 343, together with the FAD [89, 92]. Residues Ile 199 and Tyr 326 form a bottle neck along the whole binding site, by separating the active pockets.

In order to understand how the title molecule inhibits and hence increases the catalytic efficiency of MOA-B enzyme, molecular docking study was performed to fit the title compound into the binding site of MOA-B enzyme. High resolution crystal structure of MOA-B (PDB ID: 2BYB) was used as the receptor enzyme [93] and AutoDock4 software was used to perform all molecular docking simulations. For the calculations, water molecules were removed and polar hydrogen atoms were added to the receptor molecule. The active centre around the binding site of the receptor was defined by incorporating all amino acid residues within a radius of sphere 7 Å centred on the co-crystallized inhibitor FAD. In order to model the interaction pattern between receptor and ligand, Lamarckian Genetic Algorithm (LGA) available in Autodock was employed. Out of ten docked confirmations obtained, one which has lowest binding energy (-8.62 kcal/mol) was selected and analyzed for detailed interactions using Discovery Studio Visualizer4.0 software. The predicted binding mode of

the title compound showing significant inhibition and the amino acid residues which form hydrophobic interactions with the ligand were labelled in **Fig.9**.

In the present case, the docking studies of the title compound revealed that the bromine substituted phenyl ring of the title molecule is positioned between the benzene ring of Tyr435 and reface of FAD with a distance of 4.80 Å from the aromatic cage of FAD unit. From the **Fig.9**, it can be seen that these interactions are highly stabilized by the π - π stacking and π - π -T shaped interactions between the A-ring of the title compound and the FAD cofactor and Tyr435. The trifluoromethoxy group attached to the phenyl ring-B of the title compound was found to be located within the entrance cavity of the binding site defined by Ile199 and form a halogen bond with Ile199. Three amino acids Leu171, Cys172 and Tyr 326 located in the substrate cavity of the enzyme interacts with the phenyl ring-B of the title compound which were stabilized by π -sigma, π -sulphur and π - π -T shaped interactions, respectively. From the docking study, it can be concluded that the substitution with the groups like trifluoromethoxy and bromine, reduces the electron density of the chalcone system and hence expected to enhance the interactions of the inhibitor within the substrate cavity of MOA-B and also with the FAD cofactor, via hydrophobic and halogen interactions. The results from molecular docking study demonstrate that the title compound is a selective inhibitor of MAO-B enzyme with a competitive mode of inhibition.

5. Conclusion

A novel chalcone derivative, *(E)-1-(4-bromophenyl)-3-(4-(trifluoromethoxy)phenyl)prop-2-en-1-one*, is synthesized and characterized by X-ray diffraction, FT-IR and ^1H and ^{13}C NMR spectra. DFT calculations were performed to predict the structural geometry and vibrational frequencies. The recorded FT-IR spectrum was interpreted in details with the aid of Density Functional Theory (DFT) calculations and Potential Energy Distribution (PED) analysis. From the analysis of Fukui functions, near vicinity of carbon atom C7 has recognized as potentially important reactive centre. BDE values for hydrogen abstraction clearly indicate that title molecule is very stable in the open air and in the presence of oxygen, since all such BDE values are much higher than 92 kcal/mol. BDE values of the remaining single acyclic bonds indicate that degradation process could start with detaching of the Br atom and trifluoromethyl group. RDFs indicate several atoms with significant interactions with water molecules, among which the most important are bromine atom Br1 and carbon atom C16. The results from molecular docking study demonstrate that the title compound is a selective inhibitor of MAO-B enzyme with a competitive mode of inhibition.

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Figure Captions

Scheme1. Schematic representation of the synthesis route of the title compound.

Fig.1. (a) The molecular structure of the compound with 50% ellipsoids probability with atomic numbering scheme (b) The twisted structure of the compound.

Fig.2. (a) The molecules connected into columns by intermolecular C-H $\cdots\pi$ interactions (b) The Br $\cdots$ F and F $\cdots$ F contacts.

Fig.3. Experimental and Theoretical FT-IR spectra of the title compound.

Fig.4. ALIE surface of the title compound.

Fig.5. Intramolecular noncovalent interactions with corresponding strengths in electron/bohr³

Fig.6. Fukui functions of the title compound: a) Fukui f^+ and b) Fukui f^- function.

Fig.7. BDEs of all single acyclic bonds of title molecule – red colour presents BDE values,

Fig.8. The molecular orbitals and energies for the HOMO and LUMO of the title compound.

Fig.9. Ligand-Enzyme interactions, Halogen, π - π -T shaped and alkyl- π interactions are represented by light blue, violet and pink dotted lines, respectively.

Fig.S1. Single crystals of the compound.

Fig.S2. The theoretically optimized geometric structure of the title compound.

Fig.S3. Significant RDFs of the title molecule.

Fig.S4. ¹H NMR spectrum of the title compound.

Fig.S5. ¹³C NMR spectrum of the title compound.

Table 1. Crystallographic refinement data

Refinement Parameters	
CCDC deposition numbers	1013207
Molecular formula	C ₁₆ H ₁₀ BrF ₃ O ₂
Molecular weight	371.15
Crystal system	Orthorhombic
Space group	<i>Pbca</i>
<i>a</i> /Å	14.1194 (9)
<i>b</i> /Å	5.7630 (3)
<i>c</i> /Å	34.848 (2)
α /°	90.00
β /°	90.00
γ /°	90.00
<i>V</i> / Å ³	2835.6 (3)
<i>Z</i>	8
<i>D</i> _{calc} (g cm ⁻³)	1.739
Crystal Dimensions (mm)	0.89×0.11×0.06
μ /mm ⁻¹	2.94
Radiation λ (Å)	0.71073
<i>F</i> (000)	1472
<i>T</i> _{min} / <i>T</i> _{max}	0.180/0.846
Reflections measured	55278
Ranges/indices (<i>h</i> , <i>k</i> , <i>l</i>)	<i>h</i> = −19→19 <i>k</i> = −8→8 <i>l</i> = −49→49
θ limit (°)	1.9-30.2
Unique reflections	4177
Observed reflections (<i>I</i> > 2 σ (<i>I</i>))	3386
Parameters	199
<i>R</i> ₁ ^[a] , <i>wR</i> ₂ ^[b] [<i>I</i> ≥ 2 σ (<i>I</i>)]	0.032/0.078
Goodness of fit ^[c] on <i>F</i> ²	1.08
<i>R</i> _{int}	0.061
Largest diff. peak and hole, e/Å ⁻³	0.59 and −0.59

$w = 1/[\sigma^2(F_o^2) + (0.0345P)^2 + 1.8047P]$, where $P = (F_o^2 + 2F_c^2)/3$; [a] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, [b] $wR = \{w\Sigma(|F_o| - |F_c|)^2/\Sigma w|F_o|^2\}^{1/2}$, [c] $GOF = \{\Sigma w(|F_o| - |F_c|)^2/(n-p)\}^{1/2}$, where *n* is the number of reflections and *p* the total number of parameters refined.

Table 2. Selected Bond Lengths and Angles of the title compound

<u>Bond Lengths (Å)</u>	<u>XRD</u>	<u>DFT</u>
Br1–C3	1.891 (17)	1.9140
O1–C7	1.222 (2)	1.2238
C6–C7	1.499 (2)	1.5020
C7–C8	1.476 (2)	1.4836
C8–C9	1.343 (2)	1.3455
C9–C10	1.456 (2)	1.4598
<u>Bond Angles (°)</u>		
O1–C7–C6	119.65 (16)	119.79
O1–C7–C8	122.09 (16)	121.44
C6–C7–C8	118.26 (14)	118.77
C9–C8–C7	119.71 (15)	120.34
C8–C9–C10	127.16 (16)	127.88
<u>Dihedral Angles (°)</u>		
C1–C6–C7–O1	21.8 (2)	13.94
C5–C6–C7–O1	-156.45 (17)	-164.55
O1–C7–C8–C9	16.4 (3)	5.83
C6–C7–C8–C9	-164.63 (16)	-174.97
C7–C8–C9–C10	-174.68 (15)	-179.04
C8–C9–C10–C11	9.20(3)	3.03
C8–C9–C10–C15	-174.15 (17)	-177.13

Table 3. Hydrogen bond metric of the compound

Bond D—H···A	Bond length, (Å)			Angle D—H···A, (°)
	D—H	H···A	D···A	
C1—H1A···Cg1 ⁽ⁱ⁾	0.93	2.95	3.5060(18)	120
C12—H12A···Cg2 ⁽ⁱⁱ⁾	0.93	2.81	3.5022(19)	132

Symmetry code: ⁽ⁱ⁾1/2-*x*, 1/2+*y*, *z*; ⁽ⁱⁱ⁾1/2-*x*, -1/2+*y*, *z*.

Cg1 = Centroid of phenyl (C1-C6); Cg2 = Centroid of phenyl (C10-C15).

Table 4. Halogen...Halogen [$I...J$ = F or Br] Interactions.

$X—I\cdots J$	Bond length, $I—J$, (Å)	Angle, $X—I\cdots J$, (°)
C3—Br1 $\cdots$ F3 ⁽ⁱⁱⁱ⁾	3.2870(15)	142.96(6)
C16—F3 $\cdots$ F2 ^(iv)	2.820(2)	139.77(13)

Symmetry code: ⁽ⁱⁱⁱ⁾ $x, 3/2-y, -1/2+z$; ^(iv) $1/2-x, 1/2+y, z$.

Van der Waals radii (Å) : F=1.47 ; Br=1.86.

Table 5. Vibrational Frequency Assignments of the title compound with experimental and DFT methods.

Theoretical		Experimental	Assignments
DFT		IR	
ν (cm ⁻¹)	IR _I	ν (cm ⁻¹)	
3101	0.99	-	ν CHII(97)
3084	3.53	-	ν CHI(98)
3082	6.65	3081	ν CHI(98)
3080	1.90	-	ν CHII(98)
3074	4.38	-	ν CH(25), ν CHII(75)
3070	0.61	-	ν CHI(98)
3064	7.65	-	ν CH(66), ν CHI(29)
3059	0.51	-	ν CH(19), ν CHI(59), ν CHII(23)
3055	3.35	3056	ν CHII(96)
3027	0.44	3017	ν CH(98)
1652	166.77	1657	ν C=O(83), ν C=C(17)
1587	45.14	1583	ν C=C(16), ν PhII(64), ν C=O(12)
1574	416.70	1569	ν C=C(65), ν PhII(30)
1557	113.67	1559	ν PhI(63), δ CHI(13)
1552	117.67	-	ν PhII(61), δ CHII(12)
1536	17.27	-	ν PhI(67), δ PhI(12)
1480	137.66	1484	δ CHII(24), ν PhII(63)
1455	14.55	1448	δ CHI(22), ν PhI(68)
1399	40.30	1398	ν PhII(52), δ CHII(32)
1367	23.63	1364	ν PhI(52), γ CHI(24), δ PhI(12)
1311	64.04	-	δ CH(56), ν PhII(23), ν CC(17)
1302	11.36	-	δ CH(19), δ CHII(14), ν CF ₃ (66)
1290	47.06	-	ν PhII(78), δ CHII(19)
1271	15.64	-	ν PhI(85)
1268	0.05	-	δ CHII(75), δ CH(15)
1263	154.42	1264	ν COC(73), ν PhII(15), δ CH(10)
1204	1190.42	1205	ν COC(29), ν CF ₃ (63)
1192	177.89	-	ν PhII(16), ν COC(18), δ CHI(56)
1182	211.13	1181	ν PhII(17), ν COC(12), δ CHII(52)
1176	229.58	-	ν CC(20), δ CHI(57), δ CHII(12)
1160	49.56	-	δ CHII(10), ν COC(12), ν CF ₃ (72)
1155	77.20	-	δ CH(62), ν PhI(16)
1139	646.80	1134	ν COC(12), δ CF ₃ (8), δ CHII(56)
1098	20.01	-	δ PhI(13), δ CHI(70), ν PhII(25)
1092	369.99	1096	ν CC(70), δ CF ₃ (15)
1088	5.17	-	ν CC (56), ν PhI(29)
1040	83.10	1033	ν CC (63), ν CBr(16)
1000	120.74	1006	ν CC(16), ν PhI(15), δ CHI(65)
992	0.65	-	δ CHII(57), ν PhII(26)

983	82.74	986	$\delta\text{PhI}(17)$, $\gamma\text{CH}(69)$, $\tau\text{CC}(12)$
981	141.85	981	$\delta\text{PhI}(23)$, $\gamma\text{CHII}(60)$, $\tau\text{CC}(12)$
960	0.18	-	$\gamma\text{CHI}(82)$, $\tau\text{PhI}(16)$
939	0.89	-	$\gamma\text{CHII}(91)$, $\tau\text{PhII}(8)$
930	0.89	928	$\gamma\text{CHI}(76)$, $\tau\text{PhI}(14)$
920	48.33	921	$\nu\text{COC}(75)$, $\tau\text{PhII}(18)$
894	42.31	896	$\nu\text{CF}_3(47)$, $\nu\text{PhII}(18)$, $\delta\text{PhII}(19)$
869	0.39	871	$\delta\text{CC}(20)$, $\delta\text{C}=\text{C}(12)$, $\nu\text{PhII}(18)$, $\delta\text{C}=\text{O}(9)$
860	0.40	-	$\gamma\text{CH}(51)$, $\gamma\text{C}=\text{O}(13)$, $\tau\text{CC}(16)$, $\gamma\text{CH}(11)$
824	2.81	820	$\gamma\text{CHI}(71)$, $\gamma\text{CHII}(22)$
809	46.67	808	$\gamma\text{CHI}(19)$, $\gamma\text{CHII}(62)$, $\tau\text{PhII}(12)$
799	42.31	-	$\gamma\text{CHI}(58)$, $\gamma\text{CHII}(25)$
793	66.10	-	$\delta\text{PhII}(13)$, $\gamma\text{CH}(68)$, $\nu\text{CF}_3(11)$
791	19.08	788	$\gamma\text{CHII}(84)$
749	8.17	741	$\delta\text{PhII}(12)$, $\nu\text{PhI}(66)$, $\delta\text{COC}(21)$
726	6.92	719	$\tau\text{PhI}(24)$, $\nu\text{PhII}(59)$, $\delta\text{C}=\text{O}(14)$
690	0.26	692	$\tau\text{PhII}(21)$, $\delta\text{CF}_3(57)$, $\gamma\text{COC}(19)$
686	1.87	-	$\delta\text{PhI}(25)$, $\delta\text{C}=\text{O}(50)$, $\nu\text{CBr}(10)$, $\delta\text{PhII}(6)$
668	11.15	674	$\delta\text{CF}_3(39)$, $\delta\text{COC}(17)$, $\delta\text{PhI}(12)$
652	6.88	658	$\tau\text{PhI}(41)$, $\tau\text{PhII}(17)$, $\gamma\text{C}=\text{O}(12)$, $\nu\text{CBr}(6)$
616	2.56	617	$\nu\text{CBr}(52)$, $\tau\text{PhII}(17)$, $\tau\text{PhI}(21)$
615	0.03	612	$\delta\text{PhII}(69)$, $\delta\text{COC}(15)$
583	0.59	-	$\delta\text{CF}_3(65)$, $\delta\text{PhII}(27)$
582	1.81	-	$\delta\text{PhII}(21)$, $\delta\text{CF}_3(21)$, $\gamma\text{C}=\text{O}(52)$
520	6.00	520	$\delta\text{CC}(22)$, $\delta\text{C}=\text{C}(11)$, $\delta\text{CF}_3(58)$
500	19.26	502	$\gamma\text{COC}(31)$, $\tau\text{PhII}(27)$, $\gamma\text{CC}(17)$
494	6.80	-	$\delta\text{CF}_3(26)$, $\delta\text{CC}(18)$, $\gamma\text{COC}(16)$, $\delta\text{PhII}(11)$
461	4.33	472	$\tau\text{PhI}(26)$, $\gamma\text{CBr}(16)$, $\gamma\text{CC}(10)$, $\delta\text{CC}(16)$
450	12.80	455	$\tau\text{PhI}(33)$, $\gamma\text{CBr}(23)$, $\gamma\text{CC}(18)$, $\nu\text{CBr}(18)$
420	0.80	-	$\delta\text{CF}_3(72)$, $\gamma\text{CC}(16)$
402	0.03	408	$\tau\text{PhII}(79)$, $\gamma\text{CHII}(11)$
399	0.50	-	$\tau\text{PhI}(81)$
365	1.69	-	$\delta\text{CF}_3(61)$, $\nu\text{CBr}(10)$, $\delta\text{CC}(23)$
349	1.49	-	$\tau\text{PhII}(24)$, $\gamma\text{COC}(17)$, $\gamma\text{CC}(11)$, $\delta\text{CF}_3(11)$
339	29.15	-	$\delta\text{COC}(20)$, $\delta\text{CC}(21)$, $\delta\text{CF}_3(18)$, $\delta\text{C}=\text{O}(16)$
309	5.52	-	$\delta\text{COC}(37)$, $\delta\text{CC}(14)$, $\delta\text{CBr}(13)$
271	1.00	-	$\delta\text{CBr}(19)$, $\nu\text{CBr}(14)$, $\delta\text{PhI}(19)$, $\delta\text{CC}(17)$
246	0.75	-	$\gamma\text{CC}(27)$, $\gamma\text{CBr}(22)$, $\nu\text{CBr}(7)$, $\tau\text{PhI}(17)$
216	0.84	-	$\delta\text{CBr}(28)$, $\delta\text{CC}(29)$
188	0.09	-	$\tau\text{PhII}(33)$, $\tau\text{CF}_3(15)$, $\tau\text{CC}(20)$, $\gamma\text{COC}(16)$
172	2.37	-	$\delta\text{COC}(19)$, $\delta\text{CC}(24)$, $\delta\text{PhI}(8)$, $\delta\text{PhII}(19)$
141	1.39	-	$\delta\text{CBr}(18)$, $\delta\text{CC}(20)$, $\tau\text{CC}(14)$
113	0.23	-	$\delta\text{COC}(16)$, $\tau\text{CC}(35)$, $\tau\text{PhI}(18)$, $\delta\text{CC}(16)$
88	1.24	-	$\tau\text{CF}_3(42)$, $\tau\text{CC}(12)$, $\delta\text{COC}(16)$

83	1.40	-	τ CF3(22), τ CC(38), δ COC(19), δ CC(11)
69	1.57	-	τ PhI(29), τ CF3(25), τ CC(25), γ CC(12)
48	0.44	-	τ PhII(23), τ COC(22), τ CC(18), γ COC(12)
30	0.05	-	τ CC(38), τ COC(17), δ CC(19)
24	0.06	-	τ COC(26), τ CC(19), τ CF3(18), δ CC(17)
22	0.08	-	τ COC(43), τ CF3(30), τ CC(12)
11	0.08	-	τ COC(38), τ CF3(27), τ CC(19)

ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -twisting; Ph-phenyl ring; as-asymmetric; s-symmetric; IR_I-IR intensity; PED contribution is given in bracket in the assignment column.

Table 6. Experimental and theoretical ^1H NMR isotropic shifts (ppm) for the title compound.

Atom	Experimental (ppm) (DMSO)	Calculated DFT/B3LYP
H1A	7.97	8.44
H2A	7.77	7.88
H4A	7.44	7.83
H5A	7.79	8.26
H8A	7.45	8.05
H9A	8.11	8.33
H11A	7.94	8.42
H12A	8.09	7.45
H14A	8.10	7.50
H15A	7.76	7.86

Table 7. Experimental and theoretical ^{13}C NMR isotropic shifts (ppm) for the title compound.

Atom	Experimental (ppm) (DMSO)	Calculated DFT/B3LYP (ppm)
C1	127.4	136.5
C2	130.9	138.3
C3	136.3	154.3
C4	127.4	137.8
C5	130.9	135.9
C6	133.8	143.5
C7	188.2	192.9
C8	122.8	122.8
C9	142.6	152.2
C10	122.8	137.6
C11	131.8	133.8
C12	118.9	125.1
C13	149.6	160.6
C14	118.9	119.5
C15	131.8	142.3
C16	130.6	131.2

Fig.1. (a) The molecular structure of the compound with 50% ellipsoids probability with atomic numbering scheme
(b) The twisted structure of the compound.

Fig.3. Experimental and Theoretical FT-IR spectra of the title compound.

253.17 ALIE [kcal/mol] 425.54

Fig.4. ALIE surface of the title compound.

Fig.5. BDEs of all single acyclic bonds of title molecule – red colour presents BDE values

Fig.6. Fukui functions of the title compound: a) Fukui f^+ and b) Fukui f^- function.

Fig.7. Intramolecular noncovalent interactions with corresponding strengths in electron/bohr³

Fig.8. The molecular orbitals and energies for the HOMO and LUMO of the title compound.

Fig.9. Ligand-Enzyme interactions, Halogen, π - π -T shaped and alkyl- π interactions are represented by light blue, violet and pink dotted lines, respectively.

Highlights

- * A novel chalcone derivative is synthesized and characterized using XRD, FT-IR ^1H and ^{13}C NMR.
- * The recorded FT-IR spectrum was interpreted in details with the aid of DFT and PED analysis.
- * Local reactivity properties are investigated by ALIE surfaces and Fukui functions.
- * Bond dissociation energies are calculated in order to predict the open air stability and possible degradation properties
- * In order to understand how the title molecule inhibits and hence increases the catalytic efficiency of MOA-B enzyme, molecular docking study was performed.

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