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Supramolecular architecture of 5-bromo-7-methoxy-1-methyl-1*H*-benzoimidazole.3H₂O: Synthesis, spectroscopic investigations, DFT computation, MD simulations and Docking studies

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Abstract

Crystal and molecular structure of newly synthesized compound 5-bromo-7-methoxy-1-methyl-1*H*-benzoimidazole (BMMBI) has been authenticated by single crystal X-ray diffraction, FT-IR, FT-Raman, ¹H-NMR, ¹³C-NMR and UV-Visible spectroscopic techniques; compile both experimental and theoretical results which are performed by DFT/B3LYP/6-311++G(d,p) method at ground state in gas phase. Visualize nature and type of intermolecular interactions and crucial role of these interactions in supra-molecular architecture has been investigated by use of a set of graphical tools 3D-Hirshfeld surfaces and 2D-fingerprint plots analysis. The title compound stabilized by strong intermolecular

hydrogen bonds N...H-O and O...H-O, which are envisaged by dark red spots on d_{norm} mapped surfaces and weak Br...Br contacts envisaged by red spot on d_{norm} mapped surface. The detailed fundamental vibrational assignments of wavenumbers were aid by with help of Potential Energy distribution (PED) analysis by using GAR2PED program and shows good agreement with experimental values. Besides frontier orbitals analysis, global reactivity descriptors, natural bond orbitals and Mullikan charges analysis were performed by same basic set at ground state in gas phase. Potential reactive sites of the title compound have been identified by ALIE, Fukui functions and MEP, which are mapped to the electron density surfaces. Stability of BMMBI have been investigated from autoxidation process and pronounced interaction with water (hydrolysis) by using bond dissociation energies (BDE) and radial distribution functions (RDF), respectively after MD simulations. In order to identify molecule's most important reactive spots we have used a combination of DFT calculations and MD simulations. Reactivity study encompassed calculations of a set of quantities such as: HOMO-LUMO gap, MEP and ALIE surfaces, Fukui functions, bond dissociation energies and radial distribution functions. To confirm the potential of title molecule in the area of pharmaceuticals, we have also calculated a series of drug likeness parameters. Possibly important biological activity of BMMBI molecule was also confirmed by molecular docking study.

Keywords: Benzoimidazole; Supra-molecular architecture; BDE; RDF; molecular docking.

1. Introduction

Benzimidazole is a fused heterocyclic compound formed by the merger of benzene and imidazole, occupied a remarkable place among various heterocycles by virtue of their greater use in medicinal chemistry, drug discovery, structurally related to purine bases and is found in a variety of natural products, such as vitamin B12. Benzimidazole nucleus is termed “master key” as it is an important core in many bioactive compounds, key building block prevalently present of numerous compounds DNA intercalator [1], anticancer [2], cytotoxic, antitumor [3], Hv1 proton channel inhibitor [4], agonist neurotransmitter serotonin receptors, antiulcer [5], antifungal [6], analgesic and anti-amoebic [7]. At the same time, owing to the coordination ability of azoles, the benzimidazole chelating ligands have been extensively studied in the modelling biological systems [8]. In addition, these compounds have been used as organic ligands [9], liquid crystals [10], OLED's [11], chemo sensing [12] and in corrosion science [13]. Sundaraganesan et al. [14] have been investigated the vibrational spectra and DFT studies of benzimidazole. Miranda et al. [15] reported bis-(1*H*-Benzimidazol-2-yl)-methanone: new preparation method, crystal structure, and vibrational spectroscopy and DFT

calculations. Sudha et al. [16] investigated molecular structure, vibrational spectroscopic, first-order hyperpolarizability and HOMO, LUMO studies of 2-aminobenzimidazole. Most recently, Sundaraganesan et al. [17] carried out investigation of FT-IR, FT-Raman, dispersive Raman, NMR spectroscopic studies and NBO analysis of 2-Bromo-1*H*-Benzimidazol by density functional method. To our knowledge, crystal structural analysis, computational studies, MD simulations have no testimony till now. In this present study, we report synthesis, supra-molecular architecture of BMMBI along with detailed spectral investigation by FT-IR, FT-Raman and NMR, correlate these results with computational results and they shows good agreement. New molecular structures with great potential to be practically applied in the area of materials science, medicine, pharmacology are being proposed every day. An inexpensive and widely used tool for investigation of these structures is based on computational molecular modelling, mostly on DFT calculations and MD simulations. Thanks to these approaches various important reactive properties can be obtained for molecular structures that haven't been synthesized yet [18, 19]. Beside determination of molecule's "hot spots", the strength of molecular modelling lies in the fact that various spectra can be simulated with very high precision, if the proper levels of theory are used. This helps not only for characterization of compounds, but also to the structure confirmation of new and not synthesized molecules. In this particular work we have simulated IR and NMR spectral information in order to determine specificities of this newly synthesized molecule. Beside spectral investigation of the title molecule, in this work we have applied DFT calculations in order to determine global and local reactive properties [20]. Reactive properties predicted by this study were used in order to draw certain conclusions about the degradation properties of BMMBI molecule, because, as other pharmaceutical molecules, it could end up in various water resources [21]. Thanks to the fact that pharmaceutical molecules are highly stable and that natural conditions and conventional degradation pathways are not efficient enough for their removal, great attention of the scientific community is focused to the solving of this problem [21-23], especially by means of advanced oxidation processes [22, 24-28]. For these tasks computational molecular modelling turned out to be particularly useful [29-32].

2. Material and methods

2.1. General remarks

The reagents and solvents used for synthesis were of Analar grade and used without further purification. The synthesis was carried out under anaerobic condition (oxygen free inert atmosphere). ^1H -NMR and ^{13}C -NMR spectra were recorded on Bucker 400MHz

spectrometer operating at room temperature in DMSO-*d*₆ as solvent. The chemical shifts values (δ) are reported in parts per million (ppm) using TMS as an internal standard. FT-IR spectrum (Fig.S1-supporting material) was recorded in the range 4000-400 cm⁻¹ region with an ATR module ALPHA-T Bruker FT-IR spectrophotometer. FT-Raman spectrum (Fig.S2-supporting material) of the solid compound was recorded on a Bruker RFS 100/s (Germany) using 1064 nm line of Nd:YAG laser as excitation wavelength 1064nm in the region 4000-0 cm⁻¹.

2.2. Synthesis of 5-bromo-7-methoxy-1-methyl-1H-benzimidazole (BMMBI)

Take a mixture of 4-bromo-6-methoxy-N1-methylbenzene-1,2-diamine (800 mg, 3.461 mmol), trimethylorthoformate (417.6 μ L, 3.80 mmol) and para-toluene sulfonic acid (catalytic amount) in toluene (13 mL) and then the reaction mixture was refluxed for 2 hours at 105°C. Reaction was monitor by TLC. After, completion of reaction by TLC, the crude products purified by column chromatography to give 5-bromo-7-methoxy-1-methyl-1H-benzimidazole as beige solid (amount 820 mg, yield 78.8%) [33]. (Scheme-1 supporting information-Fig.S3).

2.3. X-ray crystallography

A colourless, needle shaped single crystal of the title compound, with dimensions of 0.5 mm $\times$ 0.4 mm $\times$ 0.3 mm was selected and mounted on a Bruker APEX-II CCD diffractometer with monochromated MoK α radiation (λ = 0.71073 Å) at 273(2) K. The data was processed with SAINT and corrected for absorption using SADABS [34]. The crystal structure solved by direct method using the program SHELXL [35] and was refined by full-matrix least squares technique on F² using anisotropic displacement parameters for all non-hydrogen atoms.

2.4. Computational details

The optimized geometry of title compound have been obtained by performing DFT calculations at B3LYP/6-311++G(d,p) using Gaussian09 software [36] with X-ray crystallography Cartesian coordinates as the starting geometry without any structural constraints were applied. The optimized geometry parameters were used for calculation of vibrational wavenumbers, isotropic chemical shifts, electronic properties and surface/counter studies. The assignments of the calculated wavenumbers are assisted by the animation option of GAUSSVIEW program, which gives a visual presentation of the vibrational modes [37] and the potential energy distribution values were calculated with the help of GAR2PED software package [38].

Two main programs of the Schrödinger Materials Science Suite 2017-1 (SMSS), Jaguar 9.4 [39] and Desmond [40-43], have been used as well for DFT calculations and MD simulations, respectively. B3LYP exchange-correlation functional [44] with 6-311++G(d,p), 6-31+G(d,p), and 6-311G(d,p) basis sets for obtaining ALIE, Fukui functions and BDEs, have been used respectively. For MD simulation an OPLS 3 force field [40, 45-47] was used. MD parameters also include: simulation time set to 10 ns, temperature set to 300 K, pressure set to 1.0325 bar, and cut off radius set to 12 Å, within isothermal–isobaric (NPT) ensemble class. Solvent was treated by simple point charge (SPC) model [48] was used. For MD simulation one BMMBI molecule was placed into the cubic box with ~3000 water molecules. Noncovalent interactions have been detected also by Jaguar program, relying to the method of Johnson et al. [49, 50] Maestro GUI [51] was used in the cases of activities with Schrödinger Materials Science Suite 2017-1. In order to investigate the charge transfer due to the excitation, a Multiwfn [52-55] program was used. Electron density variation and $C_{+/-}$ functions were visualized with the VMD program [56-62]. A Tachyon [63] ray tracing library, as implemented in VMD, was used for the rendering of figures.

2.5. Hirshfeld surface and finger print surface analysis

Hirshfeld surfaces [64] and the allied 2D fingerprint plots [65] are unique for any crystal structure, which are proposed as an effective way to discern intermolecular interactions between molecules that are responsible for the molecular arrangement in the crystalline state and the nature of packing of molecules in their solid-state are calculated by using Crystal Explorer [66] and which accepts a structure input file in the CIF format. The Hirshfeld surface fingerprint plots were generated using two distances, d_e , the distance from the point to the nearest nucleus exterior to the surface, and d_i , the distance to the nearest nucleus interior to the surface. Graphical plots of the molecular Hirshfeld surfaces mapped with a fixed colour scheme red-white-blue, where red highlights shorter contacts which is denoted as d_{norm} values with negative sign, white is used for contacts around the vdW separation represented as d_{norm} equal to zero and blue is for longer contacts which is denoted as d_{norm} values with positive sign.

3. Results and discussion

3.1. Crystal structural analysis

The title compound crystallizes in triclinic *P*-1 with $a = 7.147(5)$ Å, $b = 9.327(6)$ Å, $c = 18.214(11)$ Å, $V = 1147.4(13)$ Å³ and $Z = 4$. The crystallographic data and structure refinement parameters are summarized in Table S1 (supporting material) and geometric parameters for hydrogen bonds and other intermolecular contacts (Å, °) operating in the

crystal structure of BMMBI in Table S2 (supporting material). The ORTEP diagram of the molecule is shown in Fig.S4 (supporting material). The compound crystallizes with two independent molecules (A and B) in the asymmetric unit in addition to the three water molecules. The benzimidazole rings of both the molecules A and B are planar, the root mean squared deviations of two rings being 0.008 Å in molecule A and 0.005 Å in B. The crystal structure analysis revealed that, in the crystal, the water molecules self assemble to form ribbons along (100) with alternating tetrameric and hexameric clusters (Fig.S5a-supporting material) of water molecules. The hexameric cluster comprises of three water molecules (O1, O2 and O3) linked by six O-H...O hydrogen bonds (Table S2), while the O1 and O2 water molecules form an additional tetrameric cluster, the two adjacent alternating clusters being fused with O1 and O2 water molecules common to both. Two A molecules of the compound are linked into the O3 water molecules of the hexameric cluster via O-H...N hydrogen bonds (Table S2), while two B molecules are linked into the O2 water molecules of the tetrameric cluster (Fig.S5b-supporting material). Thus, in the absence of any direct structure directing interactions between the molecules, the self assembly of water molecules which in turn links with the molecules A and B is very crucial in deciding the supra-molecular architecture (Fig.S5b). The A molecules are further interconnected via short Br...Br contacts (3.592(3) Å) along the crystallographic b axis forming a two dimensional architecture (Fig.S5c). Several $\pi_{\text{aryl}} \cdots \pi_{\text{aryl}}$ interactions are also observed in the crystal structure which give additional stability to the crystal structure (Fig.S5d, Table S2).

3.2. Geometrical parameters

The optimized geometrical parameters with XRD data are given in Table S3 (supporting material) and atom labelling is given in Fig.1. In the present case the experimental C-C bond lengths are in the range of 1.4104-1.3785 Å and the calculated C-C bond lengths are in the range of 1.4057-1.3727 Å and the literature data for similar derivatives are, 1.389-1.413 Å [14] and 1.391-1.416 Å [16]. For the title compound, the C-Br bond length is 1.9237 Å (DFT) and 1.9055 Å (XRD) which is in agreement with literature [67]. For the title compound, the bond length C21-N9 = 1.3081/1.3277 Å (DFT/XRD) shows double bond character, while, the bond lengths (DFT/XRD), C11-N9 = 1.3831/1.3866 Å, C10-N16 = 1.3855/1.3816 Å, C21-N16 = 1.3729/1.3397 Å, C1-N6 = 1.4567/1.4627 Å are less than the normal single C-N bond length of about 1.48 Å [68] and the corresponding reported values of C-N bond lengths of similar derivatives are, 1.3211 Å, 1.3855 Å, 1.3853 Å, 1.4071 Å, 1.4596 Å [68]. At C17 position, the bond angles (/DFTXRD) are C19-C17-C6 = 123.5/123.7°, C19-C17-Br5 = 119.1/119.2° and C6-C17-Br5 = 117.3/117.1° and the asymmetry in angles is due

to the electronegative bromine atom. The influence of the methoxy group and methyl group are revealed from the bond angles (DFT/XRD) around C18 ($C6-C18-C10 = 117.4/117.9^\circ$, $C6-C18-O8 = 125.2/124.8^\circ$, $C10-C18-O8 = (17.4/117.3^\circ)$ and N16 ($C1-N16-C10 = 128.4/128.3^\circ$, $C1-N16-C21 = 126.1/125.2^\circ$, $C10-N16-C21 = 105.6/106.5^\circ$). The interactions between the two rings is evident from the bond angles (DFT/XRD) at C10 and C11, which are respectively, $C11-C10-C18 = 121.1/121.7^\circ$, $C11-C10-N16 = 105.5/104.9^\circ$, $C18-C10-N16 = 132.9/133.4^\circ$ and $N9-C11-C10 = 110.0/110.5^\circ$, $N9-C11-C19 = 129.0/128.8^\circ$, $C10-C11-C19 = 121.0/120.7^\circ$.

3.3 Hirshfeld surface analysis

The Hirshfeld surfaces of title compound (Fig.S6-supporting material) mapped over d_{norm} range of (A), shape index (B) and curvedness (C) -0.678 to $1.611 \text{ \AA}$, 1.0 to $1.0 \text{ \AA}$ and -4.0 to $0.4 \text{ \AA}$. The information present in Table S2 is summarized effectively, the large deep red spots visible on the d_{norm} mapped surfaces indicative of hydrogen bonding contacts and light red spot on the surface indicates weaker and longer contact other than hydrogen bonds. The title compound predominantly exhibits two strong intermolecular hydrogen bonds, one is N---H-O (which is denoted as a and b on d_{norm}) while another is O---H-O (which is denoted as c, d, e, f, g, h, i and j on d_{norm} mapped surface), due to the self-assembly of water molecules and former one is H-atom of water link with the nitrogen of imidazole ring (Fig.S6). The appearance of two distinct spikes of almost equal lengths in the 2D fingerprint plots of title compound, which is due to the dominant imidazole/water molecule interactions. The O---H-O (10.8%) and N---H-O (8.4%) intermolecular interactions appear as two distinct spikes of almost equal lengths in the 2D fingerprint plots labelled as A and B, respectively. The H---O/O---H interactions are represented by a spike in the lower left (donor) and upper right (acceptor) area of the fingerprint plot (mark as A), indicating that H-atom of water interacting with O-atom of water and as well as O-atom of water interacting with H-atom of water leads to the self-assembly of water molecules. The H---N/ N---H interactions are represented by a spike in the upper left (donor) and lower right (acceptor) area of the fingerprint plot (mark as B), indicating that H-atom of water interacting with N-atom of imidazole ring and as well as N-atom of imidazole ring interacting with H-atom of water (Fig.S7-supporting material). The wings marked with black circles in Fig.S7 represent the $H\cdots Br$ interactions and the sharpness of central spike marked with red circles in Fig.S7 is due to $H\cdots H$ contacts title compound. The relative contribution of the different interactions to the Hirshfeld surface was calculated for title compound. It is evident that the H---H contacts can account for about 48.9% of the Hirshfeld surface area; The remaining contribution was mostly due to H---O

10.8%, H---N 8.4%, H---Br 17.9%, C---C 4.2% and C---H 3.0% interactions, with only minor contribution from C---N, C---O, N---N and Br---Br (maximum 5.8%).

3.4. IR and Raman Spectra

The rings C10-C11-C19-C17-C6-C18 and N16-C21-N9-C11-C10 are designated as PhI and PhII in the following discussion and the vibrational assignments are presented in Table 1. In the present case, for the title compound, the phenyl CH stretching modes are assigned at 3078 cm^{-1} in the Raman spectrum and at $3103, 3095\text{ cm}^{-1}$ theoretically [69]. For the title compound, the phenyl ring C-C stretching modes are assigned at $1584, 1542, 1423, 1331, 1248\text{ cm}^{-1}$ (IR), $1584, 1549, 1441, 1249\text{ cm}^{-1}$ (Raman), in the range $1586\text{--}1251\text{ cm}^{-1}$ (DFT) with PEDs in the range 62–42%. The PED analysis gives ring breathing mode of PhI at 1052 cm^{-1} as expected [69,70] with a PED of 47% and low IR activity. According to literature [71], the ring breathing mode of a poly-substituted phenyl ring is assigned at 1025 cm^{-1} in IR, 1027 cm^{-1} in Raman and 1032 cm^{-1} theoretically. The CH in-plane deformation modes of PhI are assigned at $1185, 1073\text{ cm}^{-1}$ (IR), $1192, 1079\text{ cm}^{-1}$ (Raman) and the theoretical values are at 1190 cm^{-1} and 1079 cm^{-1} as expected [69]. The out-of-plane C-H modes are assigned at 830 cm^{-1} and 783 cm^{-1} (DFT) for PhI. According to literature, the C-O-C stretching modes are expected in the range $1200\text{--}850\text{ cm}^{-1}$ [69] and for the title compound, the C-O-C vibrations are assigned at 1103 and 959 cm^{-1} theoretically with PEDs 48 and 61%. Experimentally bands are observed at 955 cm^{-1} in the IR spectrum and at $1107, 960\text{ cm}^{-1}$ in the Raman spectrum. In the present case, the methyl CH_3 stretching modes are observed at $3050, 3002, 2954, 2925, 2895\text{ cm}^{-1}$ in the IR spectrum, $3054, 3002, 2958, 2931, 2902\text{ cm}^{-1}$ in the Raman spectrum and in the range $3016\text{--}2897\text{ cm}^{-1}$ theoretically [69]. The methyl CH_3 deformation modes of the title compound are observed at $1456, 1437, 1423, 1408, 1372, 1163, 1125\text{ cm}^{-1}$ (IR), $1444, 1410, 1360, 1027\text{ cm}^{-1}$ (Raman) and in the range $1458\text{--}1025\text{ cm}^{-1}$ theoretically [69]. The C-N stretching modes of the title compound are assigned at $1287, 1073\text{ cm}^{-1}$ in IR spectrum, $1288, 1079, 1027\text{ cm}^{-1}$ in Raman spectrum and at $1328, 1295, 1079, 1025\text{ cm}^{-1}$ (DFT) which are in agreement with literature [69]. The C=N stretching mode is observed at 1475 cm^{-1} in IR, 1475 cm^{-1} in Raman and at 1468 cm^{-1} theoretically [69]. The CN stretching modes have PEDs ranging from 35 to 55% with moderate IR intensities and Raman activities. Bromine compounds [69] absorb strongly in the region of $635 \pm 85\text{ cm}^{-1}$ due to C-Br stretching vibration and in the present case, band at 618 cm^{-1} (IR), 620 cm^{-1} (Raman) and 620 cm^{-1} (DFT) is as assigned as this mode.

3.5. Frontier molecular orbital analysis

HOMO means the ability of the molecule to donate an electron and is directly related to ionization potential, while LUMO means the ability to accept an electron and is directly

related to electron affinity, the energy gap between FMO's calculated by DFT/B3LYP/6-311++G(d,p) method and the pictorial representation shown in Fig.S8 (supporting material). HOMO (MO 60) of π nature is delocalized the entire molecule and LUMO (MO 61) also π -nature, delocalized full molecule except methyl groups, bromine atom. The energy gap between HOMO and LUMO molecular orbitals plays very crucial role in determining properties such as chemical behaviour (reactivity, kinetic stability), spectroscopic properties (optical, electronic, vibrational), the theoretical reactivity indices defined by Par and Pearson [72] (ionization potential (I), electron affinity (A), chemical potential (μ), electronegativity (χ) global hardness (η), global softness (ν) and global electrophilicity index (ω)) and biological activity. The E_{HOMO} and E_{LUMO} energy value, their difference ($\Delta E = E_{\text{HOMO}} - E_{\text{LUMO}}$) along with the global reactivity indices are given in Table S4 (supporting material) and the results indicates that the chemical potential of the title compound is negative and it means that the compound is stable.

3.6. Molecular Electrostatic Potential

The molecular electrostatic potential (MEP) is an effective tool to predict physiochemical property relationship, study of biological recognition processes and hydrogen bonding interactions. The MEP surfaces of title compound are generated from optimized geometry by DFT/B3LYP/6-311++G(d,p) method and mapped a rainbow colour scheme with red (representing the electron rich region) while blue (represents electron poor region). The molecular electrostatic potentials are mapped over in the range between -6.424 a.u. (deepest red) through 0 (white) to 6.424 a.u. (deepest blue) (Fig.S9-supporting material). From the MEP plot (Fig.S9), the negative region (red) localized over imidazole nitrogen (C=N) groups are possible sites for electrophilic attack and the positive region (blue) is covers all hydrogen atoms, as possible sites for nucleophilic attack. Also, the pictorial representation electrostatic potential mapped over the d_{norm} surface of the neighbouring molecules shown in Fig.S10 (supporting material) neatly indicates that the electrode potential on the hydrogen bond donors and acceptors in the neighbouring molecules are complementary to one another (red spots close to H-bond acceptors and blue spots close to H-acceptors) thus providing further evidence to the formation O-H...O hydrogen bonds by self assemble of water molecules leads to formation of alternating tetrameric and hexameric clusters and N...H-O hydrogen bonds by interaction of water molecules with nitrogen atom of imidazole ring.

3.7. ALIE surfaces, Fukui functions and non-covalent interactions

In order to locate molecule's "hot spots" from the aspect of sensitivity towards electrophilic attacks, besides using the MEP surfaces, it is also possible to employ the concept of ALIE

surfaces, Fig.2. This descriptor is defined as a sum of orbital energies weighted by the orbital densities [73, 74]. The following equation is valid in the case of ALIE surfaces according to the following equation:

$$I(r) = \sum_i \frac{\rho_i(\vec{r}) |\varepsilon_i|}{\rho(\vec{r})}, \quad (1)$$

$\rho_i(\vec{r})$ is electronic density of the i -th molecular orbital at the point $\vec{r}$, ε_i is orbital energy, while $\rho(\vec{r})$ is total electronic density function [75, 76]. Representative ALIE surface is provided in Fig.2.

ALIE surface of the BMMBI molecule indicate three molecule hot spots possibly sensitive towards the act of electrophilic attacks. These molecule sites where electrons are least tightly bound can be seen in the near vicinities of bromine atom Br5 and nitrogen atom N9, characterized by the ALIE values of 190 kcal/mol. Fig.2 also indicates that only one intra-molecular noncovalent bond is formed, between the oxygen atom O8 and carbon atom C1, with corresponding strength of -0.008 electron/bohr³. Further detection of molecule's hot spots has been performed by mapping of the Fukui functions to the electron density surface. In the case of Fukui functions in the finite difference approach, the following equations are valid:

$$f^+ = \frac{(\rho^{N+\delta}(r) - \rho^N(r))}{\delta}, \quad (2)$$

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

where N is number of electrons in reference state of the molecule, while δ is the fraction of electron which default value is set to be 0.01 [77]. In general, Fukui functions serve to track the changes of electron density as a consequence of charge addition or removal. If the charge is added then the locations where electron density increased (coloured by purple colour in Fig.3a), indicate electrophilic parts of the molecule, while the whole Fukui function is regarded as f^+ function. Similarly, if the charge is removed then the locations where electron density decreased (coloured by the red colour), indicate nucleophilic parts of molecule, while the whole Fukui functions is regarded as f^- function. Fukui functions mapped to the electron density surface in the case of BMMBI molecule are presented in Fig.3. According to the position of purple colour in the case of Fukui f^+ function represented in Fig.3a, it can be concluded that near vicinities of atoms C21 and H22 are of electrophilic character. This is in very good agreement with the results related to ALIE surface, according to which its adjacent

nitrogen atom has the lowest ALIE values. Thus, the five member ring of the BMMBI molecule could be sensitive towards electrophilic attacks. According to the Fig.3b, it can be seen that certain portions of red coloured surface are located around methyl groups, designating them as nucleophilic in case of the charge removal.

3.8. Nonlinear optical properties

Nonlinear optical (NLO) effect arise from the interactions of electromagnetic fields in various media to produce new fields altered in phase, frequency, amplitude or other propagation characteristics from the incident fields. NLO properties like the dipole moment, polarizability, first and second order hyperpolarizabilities are calculated using B3LYP/6-311++G(d) (5D, 7F). The total molecular dipole moment of the title compound is 5.8031 Debye, polarizability is 2.1686×10^{-23} esu, and the first and second order hyperpolarizabilities are 1.5286×10^{-30} and -7.03×10^{-37} esu. Here, the first hyperpolarizability of the title compound is 11.76 times that of the standard NLO material urea [77]. The larger component of second order hyperpolarizability is associated with the larger ground state polarization which leads to strong electronic coupling between the ground and the low lying excited state. The NLO properties are also related to the energy gap between HOMO and LUMO. The energy gap of the investigated compound is 4.332 eV which is lower than that of urea (6.7 eV) [77]. Therefore, the investigated molecule is considered good candidate for nonlinear optical applications.

3.9. Natural bonding orbital analysis

Natural bond orbital (NBO) calculations were performed using NBO 3.1 program [78] as executed in the Gaussian09 package at the DFT/B3LYP/6-311++G(d,p) method in order to understand various second-order interactions presented in Tables S5 and S6 (supporting material). The important inter-molecular hyper-conjugative interactions are: N9-C21 from N16 of $n1(N16) \rightarrow \pi^*(N9-C21)$, C10-C11 from N16 of $n1(N16) \rightarrow \pi^*(C10-C11)$ and C6-C18 from O8 of $n2(O8) \rightarrow \pi^*(C6-C18)$, with electron densities, 0.34171, 0.47308, 0.38200 e and stabilization energies, 47.61, 32.84, 29.08 kJ/mol. Almost 100% p-character was observed in π -bonding orbitals of N9-C21 (99.82), C10-C11 (99.97), C6-C18 (99.95) and the lone pairs of $n1N16(99.99)$ and $n2O18(99.96)$.

3.10. Mulliken atomic charges

The calculation and analysis of Mulliken atomic charges plays crucial role in the application of quantum mechanical calculations to the molecular systems [79]. The Mulliken atomic charges of title compound calculated in gaseous phase by using DFT/B3LYP/6-311++G(d,p) basic set are given in Table S7(supporting material). From the Table S7, all

nitrogen atoms have negative charge and all hydrogen have positive charge. It is worthy to mention that the C21(0.389) atom shows positive sign, it is due to substitution highly electronegative atoms like nitrogen. In imidazole ring azonitrogen (C=N) shows more negative charge when comparative other nitrogen, it may suggest the formation of intermolecular hydrogen bond with water molecules in solid state.

3.12. ^1H and ^{13}C NMR chemical shift analysis

After performing geometry optimization of title compound (BMMBI), then SCF GIAO Magnetic shielding (^1H and ^{13}C) calculations has been made by using DFT/B3LYP/6-311++G(d,p) method. The experimental ^1H and ^{13}C NMR spectra are given in Figs.S11 and S12 (supporting information). The experimental and calculated chemical shift values in ppm relative to TMS of title compound are given in Table S8 (supporting material). The signals of the proton spectra were observed in two regions; the first one is around 6.92-8.08/6.55-7.62 and second is one around 3.93-3.97/3.82-3.83 experimental/theoretical chemical shift values (in ppm), respectively. The first group is due to the protons in the aromatic region (imidazole proton (H22) 7.41/7.30, benzene ring protons (H20, H7) 8.08/7.62, 6.92/6.55, the second group is due to methyl group on O (H13, H14, H15) and N(H2, H3, H4) 3.93/3.83 and 3.97/3.82 (experimental/theoretical), respectively. The experimentally and theoretically calculated chemical shift values of ^{13}C -NMR for aromatic carbons were observed in the range 107.08-147.79/108.68-154.63. The experimentally/calculated chemical shift value of C18, C11 and C21 are also found significantly high due to the impact of electronegative oxygen atom and nitrogen atom, are observed at 147.79/153.03, 145.69/154.63 and 146.17/147.29 (experimental/theoretical), respectively. The upfield signal observed at 33.46 and 56.28 ppm and calculated at 34.75 and 55.14 ppm was assigned to methyl carbon on nitrogen and oxygen at C1 and C12. According to these results, the theoretical chemical shifts are in compliance with the experimental findings.

3.12. Reactive properties based on autoxidation and hydrolysis

Computational molecular modelling based on the DFT calculations and MD simulations is very important for the environmental studies [80-83], especially when it comes to the oxidation reactions, which are essential for the degradation and removal of the pharmaceutical pollutants from water resources [84-86]. In order to evaluate sensitivity of molecule towards the autoxidation mechanism, calculations of bond dissociation energies for hydrogen abstraction (H-BDE) could be particularly useful. Fig.4 contains bond dissociation energies for all single acyclic bonds of BMMBI molecule. According to the results in Fig.4, BMMBI molecule cannot be regarded as a molecule sensitive to autoxidation mechanism,

since there are no H-BDE values ranging from 70 to 85 kcal/mol [29, 87-89]. H-BDE values in the range between 85 and 90 kcal/mol [88] are also not present, thus it can be stated that BMMBI is highly stable in the open air or in the presence of oxygen. This also emphasizes the fact that its stability is high and that degradation of this molecule could be hardly initiated by natural conditions. On the other side, the lowest bond dissociation energy (~ 57 kcal/mol) was calculated for the bond denoted with number 8, indicating that degradation pathway could start by detachment of the methyl group. Stability of BMMBI molecule in water was also evaluated, by means of MD simulation and by calculation of radial distribution functions (RDF). RDF, $g(r)$, are useful indicators of the probability for finding a particle in the distance r from another particle [90]. Significant RDFs of the BMMBI molecule's atoms have been presented in Fig.5. According to the distance of the maximal $g(r)$ values, the most important atoms are oxygen atom O8 and nitrogen atom N9, located at around 2.7 Å. Also, RDFs of these atoms are characterized by two solvation spheres. The highest maximal $g(r)$ values have been calculated for bromine Br5 and carbon atoms C1 and C12. However, distances of their maximal $g(r)$ values are located at more than 3.5 Å. Nitrogen atom N16 also has significantly high maximal $g(r)$ value, however, it is located at distance of more than 4.5 Å, indicating not so significant interactions with water molecules. In general, the lack of hydrogen atoms with significant RDFs indicates high stability of BMMBI molecule in water.

3.13. Drug likeness

In order to initially assess to what extent BMMBI molecule could be considered as orally active, we have calculated a set of parameters recommended by Lipinski, Table 2 [91, 92]. Firstly, it can be seen in Table 2 that AlogP parameter has very competitive value of 2.24. Perspective drug candidate molecules should have less than 5 and 10 HBD and HBA, respectively, which is definitely fulfilled by BMMBI molecule. The mass criterion under 500 is also fulfilled by far in the case of BMMBI. According to the work of Ghose et al. [93], molar refractivity should take values between 40 and 130, while number of atoms should be in the range between 20 and 70. These conditions also go in favour of BMMBI molecule. PSA shouldn't take values above 140 Å^2 , which is easily accomplished by the BMMBI molecule, due to its size. Veber et al. [94] has also commented that a good oral bioavailability is reflected by less than 10 rotatable bonds, which is also true for BMMBI molecule. Along with Lipinski's rule of five, Congreeve et al. [95] introduced the "rule of three". By Congreeve's hardened criteria, logP value shouldn't take values above 3, molecule mass shouldn't take values above 300, while HBD, HBA and number of rotatable bonds must not take values above 3. Drug likeness parameters provided in Table 2 clearly indicate that

BMMBI molecule fulfils conditions of Congreeve's rule of three, thanks to which title molecule could be considered as lead compound for new drugs.

3.14. TDDFT calculations and UV spectra

In this work we have used TD-DFT calculations in order to simulate UV spectra and to investigate the charge transfer within the BMMBI molecule, arising from the lowest energy excitation. UV spectrum of the BMMBI molecule has been presented in Fig.S13 (supporting material), while information regarding the first ten excitations have been provided in Table S9 (supporting material). According to the results provided in Fig.S13 there is only one pronounced absorption peak located at wavelength of 196 nm. Results provided in Table S9 indicate that two most important excitations from the aspect of light absorption are excitations 6 and 7, with corresponding oscillator strengths of 0.9 and 0.3, respectively. Due to the size and structure of BMMBI molecule it can be concluded that the most important part of the molecule, with respect to UV absorption, is benzene ring, which is also confirmed by visualization of natural transition orbitals (NTO), Fig.S14 (supporting material). Results presented in Fig.S14 indicate that hole and particle of NTO 1 match to the frontier molecular orbitals, indicating that the lowest energy excitation is principally depending on the HOMO to LUMO transition. In order to further identify the nature of the lowest energy excitation we will refer to the analysis of C functions, Fig.S15 (supporting material), according to the procedure incorporated within the Multiwfn program. Classifications of the excitations can be done by measuring the distance between the barycenters of C_+ and C_- functions, provided in Fig.S15. Green coloured surface in the Fig.S15 corresponds to the C_+ function, while blue coloured surface corresponds to the C_- function. This distance is also called CT length and besides this quantity it is also useful to measure the Δr parameter, whose value also indicates the type of the excitation. Appropriate definitions on CT length and Δr parameter can be found can be found in papers [96, 97]. Visualization presented in Fig.S15 indicates that in the case of the first excitation of the BMMBI molecule, CT length has the value of 0.91 Å, while Δr parameter has the value of just 0.673 Å. These results indicate that the first excitation is of the local excitation (LE) type, localized within benzene ring.

3.15. Molecular docking

PASS [98] is an online tool to predict the biological activity spectrum of a compound. PASS analysis of the compounds predicts the title ligands to be Antineurotic agents with P_a score of 0.68. To further establish their Antineurotic activity, we decided to carry out molecular docking studies of the compound against human acetylcholinesterase [PDB ID: 5HF5]. The PDB structure 5HF5 [99] was selected for docking as the reported structure has

been established from X-ray Crystallographic data with a good resolution of 2.15 Å. Further the enzyme has an attached co-crystallized inhibitor so has a well defined binding site which could be targeted. All docking calculations were performed on AutoDock-Vina software [100]. The 3D crystal structure of PfDHFR-TS was obtained from Protein Data Bank. Before docking the ligands, the protein was prepared by removing co-crystallized waters, ligands and co-factors. The AutoDockTools graphical user interface was used to calculate Geisterger charges, add polar hydrogen and partial charges using Kollman united charges. The active site of the enzyme was defined to include residues of the active site within the grid size of 50 x 50 x 50 Å. The ligand was prepared for docking by minimizing its energy at B3LYP/6-311++G(d,p)(5D, 7F) level of theory. The most popular algorithm, Lamarckian Genetic Algorithm (LGA) available in Autodock was employed for docking. The docking protocol was tested by docking the co-crystallized inhibitor onto the enzyme catalytic site which showed perfect synergy with the co crystallised ligand with RMSD close to zero. Amongst the docked conformations the best scored conformation predicted by AutoDock scoring function was visualized in DSV, LigPlot and Pymol softwares for ligand–protein interactions. The molecule binds at the catalytic site of the substrate by weak non-covalent interactions (Fig.6). Amino acid SER125, ASP74, TYR337, GLY121, TRP86 and TYR124 are the main interacting residues. TRP86 forms H-bond with N atom of the title molecule (Fig.S16-supporting material). TYR124 forms a strong π - π interaction (Fig.S17-supporting material). Docking scores of -6.2 kcal/mol is predicted for the title compound. These results reveal that the ligands bind at the active site of the macromolecule and could restrict or block the functioning of Acetylcholinesterase, thereby acting as antineurotic agents.

4. Conclusion

A novel bezimidazole derivative was synthesized and characterized by XRD, FT-IR, CT-Raman and NMR spectra and MD simulations and DFT calculations were used to predict stability and reactive properties. The predicted geometrical parameters were in good agreement with the experimental geometrical parameters. The theoretically predicted wavenumbers are in agreement with the experimentally observed wavenumbers. From the MEP plot the negative region localized over imidazole nitrogen groups are possible sites for electrophilic attack and the positive region is covers all hydrogen atoms, as possible sites for nucleophilic attack. The first hyperpolarisability of the title compound is 11.76 times that of the standard NLO material urea. ALIE surface and Fukui functions indicate that five member ring could be sensitive towards the electrophilic attacks. According to the distribution of ALIE values on electron density surface, near vicinity of bromine atom could also be

sensitive towards the electrophilic attacks. BMMBI molecule is highly stable, when it comes to the sensitivity towards the autoxidation mechanism, as all H-BDE values are much higher than 90 kcal/mol. MD simulations and RDFs of significant atoms indicate that title molecule is highly stable in water as well. Drug likeness parameters indicate that BMMBI molecule could be considered as one of the lead compounds for the development of new drugs. Study of the first excitation within the BMMBI molecule indicates that the charge transfer is of LE type. Molecular docking studies reveal that the ligands bind at the active site of the macromolecule and could restrict or block the functioning of Acetylcholinesterase, thereby acting as anti-neurotic agents.

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Supplementary Material

The cif file of the title compound have been assigned CCDC number 1478268 and can be obtained free of cost on application to CCDC 12 Union Road, Cambridge CB21 EZ, UK. (Fax: (+44) 1223 336-033; e-mail: data_request@ccdc.cam.ac.uk).

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Figure captions

Fig.1 Optimized geometry of 5-bromo-7-methoxy-1-methyl-1H-benzimidazole

Fig.2 ALIE surface of the BMMBI molecule

Fig.3 Fukui functions a) f^+ and b) f^- of the BMMBI molecule

Fig.4 Bond dissociation energies of all single acyclic bonds of BMMBI molecule

Fig.5 RDFs of atoms of BMMBI molecule with significant interactions with water molecules

Fig.6 Surface representation of the binding of title compound with 5hf5 shows that it binds at the active site

Table captions

Table 1. Calculated scaled wave numbers, observed IR, Raman bands and assignments of 5-bromo-7-methoxy-1-methyl-1*H*-benzoimidazole(BMMBI).

Table 2 Drug likeness parameters of 5-bromo-7-methoxy-1-methyl-1*H*-benzoimidazole molecule

Table 1

Vibrational assignments of title compound

B3LYP/ B3LYP/6-311++G(d,p)			IR	Raman	Assignments ^a
$\nu(\text{cm}^{-1})$	IR_I	R_A	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3103	2.22	50.65	-	-	$\nu\text{CHI}(99)$
3100	1.75	129.83	3103	3098	$\nu\text{CH}(99)$
3095	0.27	75.38	-	3078	$\nu\text{CHI}(99)$
3016	18.09	108.65	3050	3054	$\nu\text{CH}_3(90)$
3011	9.87	70.24	-	-	$\nu\text{CH}_3(99)$
2997	12.12	64.22	3002	3002	$\nu\text{CH}_3(99)$
2956	29.32	52.66	2954	2958	$\nu\text{CH}_3(100)$
2933	44.41	207.08	2925	2931	$\nu\text{CH}_3(99)$
2897	49.57	162.42	2895	2902	$\nu\text{CH}_3(99)$
1586	63.46	2.50	1584	1584	$\nu\text{PhI}(50)$, $\nu\text{CN}(10)$
1546	120.87	44.12	1542	1549	$\nu\text{PhI}(62)$, $\delta\text{CH}(14)$
1468	80.25	31.22	1475	1475	$\nu\text{CN}(52)$, $\delta\text{CH}(17)$
1458	36.98	13.88	1456	-	$\delta\text{CH}_3(88)$
1450	16.98	10.46	-	-	$\delta\text{CH}_3(54)$, $\nu\text{PhI}(11)$
1446	96.52	4.92	-	1444	$\delta\text{CH}_3(37)$, $\nu\text{PhI}(42)$
1435	9.22	11.75	1437	-	$\delta\text{CH}_3(92)$
1424	11.00	12.17	1423	-	$\delta\text{CH}_3(100)$
1422	11.84	9.45	1423	-	$\nu\text{PhI}(50)$, $\delta\text{CH}_3(19)$
1409	47.05	4.38	1408	1410	$\delta\text{CH}_3(68)$
1379	38.46	22.36	1372	1360	$\delta\text{CH}_3(48)$, $\nu\text{CN}(16)$, $\nu\text{PhI}(17)$
1333	17.05	43.16	1331	-	$\nu\text{PhI}(61)$, $\delta\text{CHI}(10)$
1328	14.26	29.81	-	-	$\nu\text{CN}(55)$, $\delta\text{CHI}(11)$, $\nu\text{PhI}(10)$
1295	26.77	73.75	1287	1288	$\nu\text{CN}(35)$, $\nu\text{CN}(11)$, $\nu\text{PhI}(22)$
1251	146.71	10.72	1248	1249	$\nu\text{CO}(19)$, $\nu\text{CN}(17)$, $\nu\text{PhI}(49)$
1213	25.14	5.10	1213	1214	$\delta\text{CH}(35)$, $\nu\text{CO}(11)$, $\delta\text{CHI}(17)$, $\nu\text{CN}(10)$
1190	12.13	3.10	1185	1192	$\delta\text{CHI}(45)$, $\delta\text{CH}(14)$, $\nu\text{CN}(10)$
1162	4.02	3.36	1163	-	$\delta\text{CH}_3(75)$
1124	0.85	2.34	1125	-	$\delta\text{CH}_3(94)$

1103	164.11	2.59	-	1107	ν CO(48), ν CN(18)
1102	0.11	0.79	-	-	δ CH ₃ (96)
1079	9.15	7.45	1073	1079	ν CN(42), δ CHI(38)
1052	0.74	22.05	-	-	ν PhI(47), δ CHI(16)
1025	16.29	3.19	-	1027	δ CH ₃ (40), ν CN(35)
959	8.02	1.92	955	960	ν CO(61), ν CN(10)
836	38.31	7.16	833	838	δ PhI(47), δ PhII(18)
830	20.22	0.47	-	-	γ CHI(63), γ CH(18), τ PhI(10)
820	0.55	0.26	-	818	γ CH(65), γ CHI(18), τ PhII(12)
783	28.57	0.47	781	782	γ CHI(69), τ PhI(14), γ CO(10)
756	73.31	0.39	753	750	ν CBr(11), δ PhII(30), δ PhI(10)
731	1.26	0.04	735	-	τ PhI(43), τ PhII(33), γ CO(11)
689	3.60	12.88	690	687	δ CO(26), δ PhII(39)
621	4.04	8.04	625	-	δ PhII(36), δ CO(10), δ PhI(18)
620	10.39	0.59	618	620	τ PhII(23), τ PhI(10) ν CBr(39)
561	0.10	0.16	-	565	τ PhII(20), τ PhI(42)
547	8.52	0.58	-	538	τ PhI(36), γ CO(25), γ CBr(20), τ PhII(11)
502	3.61	1.98	-	505	δ PhI(50), δ CN(13)
495	3.64	1.13	-	-	δ PhI(48), δ CO(15)
366	0.21	8.03	-	362	δ CO(36), δ CN(22)
330	0.30	0.14	-	331	τ PhII(39), τ PhI(24), γ CBr(11), γ CN(10)
322	0.72	0.10	-	-	δ CN(30), δ CO(34), δ CBr(15)
255	0.28	0.03	-	252	τ CO(59), τ PhI(18), γ CBr(10)
237	1.53	8.35	-	-	δ PhI(37), δ CN(11)
223	0.01	0.07	-	-	τ PhII(28), τ PhI(30), γ CN(14), τ CO(16)
196	0.02	1.80	-	202	τ CO(27), τ PhI(39), γ CN(18)
179	3.33	0.10	-	-	δ CO(24), δ CBr(15), δ CN(15), δ PhI(10)
146	1.86	1.12	-	152	γ CBr(23), γ CN(13), τ CH ₃ (12), τ CO(12)
141	0.96	1.37	-	139	δ CBr(56), δ CO(32)

89	0.99	0.07	-	-	$\tau\text{CH}_3(51)$, $\tau\text{PhII}(10)$, $\gamma\text{CN}(10)$
82	3.83	0.45	-	-	$\tau\text{CO}(70)$, $\tau\text{CH}_3(12)$, $\gamma\text{CN}(10)$
59	1.06	0.87	-	-	$\gamma\text{CN}(39)$, $\tau\text{CH}_3(21)$, $\tau\text{PhI}(18)$, $\tau\text{CO}(10)$

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; PhI-C10-C11-C19-C17-C6-C18; PhII-N16-C21-N9-C11-C10.

Table 2Table 2 Drug likeness parameters of 5-bromo-7-methoxy-1-methyl-1H-benzimidazole molecule

<u>Descriptor</u>	<u>Value</u>
Hydrogen Bond Donor (HBD)	0
Hydrogen Bond Acceptor (HBA)	2
Mass	241.09
AlogP	2.24
Polar surface area (PSA) [$\text{\AA}^2$]	27.05
Molar refractivity	52.77
Number of atoms	22
<u>Number of rotatable bonds</u>	<u>1</u>

Fig.1 Optimized geometry of 5-bromo-7-methoxy-1-methyl-1H-benzimidazole

190.03 ALIE [kcal/mol] 355.50

Fig.2 ALIE surface of the BMMBI molecule

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Fig.4 Bond dissociation energies of all single acyclic bonds of BMMBI molecule

Fig.5 RDFs of atoms of BMMBI molecule with significant interactions with water molecules

Fig.6 Surface representation of the binding of title compound with 5hf5 shows that it binds at the active site

Highlights

- A novel benzoimidazole derivate is synthesized and characterized by XRD
- The FT-IR and FT-Raman spectra were interpreted
- Local reactivity properties are investigated
- Possible degradation properties are predicted
- Molecular docking study is also done