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Synthesis, vibrational spectroscopic investigations, molecular docking, antibacterial studies and molecular dynamics study of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

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Abstract

Antimicrobial active 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole (NATPB) was synthesized and observed IR, Raman bands are compared with the theoretically predicted wave numbers. In the IR spectrum the NH stretching wave number splits into a doublet with a noted difference and is red shifted from the computed value, which indicates the weakening of NH bond resulting in proton transfer to the neighboring oxygen atom. The HOMO-LUMO plots reveal the charge transfer in the molecular system through the conjugated paths. The electrophilic and nucleophilic reactive sites are identified from the MEP plot. Mapping of average local ionization energy (ALIE) values to the electron density surface served us as a tool for prediction of molecule sites possibly prone to electrophilic attacks. Other important reactive centres of the title molecule were detected by calculations of Fukui functions. Calculations of bond dissociation energies (BDE) for

hydrogen abstraction were used in order to assess whether the NATPB molecules is prone to autoxidation mechanism or not, while BDE of the remaining single acyclic bonds were used in order to determine the weakest bond. Interaction properties with water were investigated by molecular dynamics (MD) simulations and calculations of radial distribution functions (RDFs). The compound possessed broad spectrum activity against all of the tested Gram-positive and Gram-negative bacteria and yeasts, their minimum inhibitory concentrations (MICs) ranging between 32 - 128 µg/ml. The compound exhibited significant antibacterial activity (32 µg/ml) against an antibiotic resistant *E. faecalis* isolate, at same potency with the compared standard drugs vancomycin and gentamycin sulfate. The molecular docking studies show that the compound might exhibit inhibitory activity against CDK inhibitors.

Keywords: DFT; benzoxazole; ALIE; RDF; BDE; Docking.

1. Introduction

Benzoxazole contains a phenyl ring fused to an oxazole ring and this moiety has found a number of practical applications and various biological activities and wide therapeutical properties. Benzoxazole derivatives possess antibiotic [1], antibacterial [2], antifungal [3,4] antitumor [5,6] anti-inflammatory [7], antiulcer [8] and anti-tubercular [9] activities.

Organic molecules that are candidates for pharmaceutical formulations are synthesized to be highly stable in aquatic surrounding. Unfortunately natural environmental conditions are not suitable for their degradation in water [10-12] and this has already led to their presence and accumulation in all types of waters all over the world [13]. Reactive and stability properties of molecules dictate the fate of the pharmaceutical in the environment.

In general to improve the degradation techniques, forced degradation studies are performed on the organic molecules that are candidates to be active components in pharmaceuticals [14]. In this regard the advanced oxidation processes are of great importance [13,15, 16]. However, these types of studies are very demanding from the aspect of needed resources, thus the molecular modeling principles are used for rationalization and optimization of such experiments. There are certain correlations between quantities that are readily calculated by DFT calculations and MD simulations from one side and the physicochemical properties of target molecules from the other. A fine example is employment of DFT calculations of bond dissociation energies (BDE) that can be used for the prediction of molecule sites where autoxidation mechanism might occur. Also, the influence of water and possible hydrolysis of investigated molecules can be assessed by molecular dynamics (MD) simulations and calculations of radial distribution functions.

Taking into account the potential importance of the title molecule from the pharmaceutical aspect, we have applied DFT calculations and MD simulations in order to predict some important reactive properties. Obtained results are valuable for the future degradation studies of the title compound.

2. Experimental details

2.1 Materials and methods

The chemicals and solvents were purchased from Sigma-Aldrich (Munich, Germany) and Fisher Scientific (Pittsburgh, PA, USA); they were used without purification. Silica gel HF₂₅₄ chromatoplates (0.3 mm) were used for thin layer chromatography, and the mobile phase was chloroform/methanol (10:0.5). Melting point was recorded on a Stuart Scientific SMP 1 instrument (Bibby Scientific Limited, Staffordshire, UK) and is uncorrected. NMR spectra were recorded on a Varian Mercury 400 MHz NMR spectrometer (Palo Alto, CA, USA). Trimethylsilane (TMS) was used as an internal standard. The mass spectra was recorded on a Waters ZQ Micromass LC-MS spectrometer (Milford, MA, USA) using the ESI(+) method.

The FT-IR (Fig. 1) and FT-Raman spectra (Fig. 2) were recorded using KBr pellets on a DR/Jasco FT-IR 6300 spectrometer and on a Bruker RFS 100/s, Germany, with excitation wavelength 1064 nm.

Materials used in the microbiology study were; Mueller Hinton agar (MHA) (Merck, Darmstadt, Germany), Mueller Hinton broth (MHB) (Merck), Sabouraud dextrose agar (SDA) (Merck), RPMI-1640 medium with L-glutamine (Sigma-Aldrich), 3-[N-morpholino]-propane-sulfonic acid (MOPS) (Sigma-Aldrich), 96-well micro plates (BD, Franklin Lakes, NJ, USA), ampicillin (Mustafa Nevzat Pharmaceuticals, Istanbul, Turkey), gentamycin sulfate (Paninkret Chem.-Pharm., Pinneberg, Germany), ofloxacin (Zhejiang Huangyan East Asia Chemical Co. Ltd., Huangyan, Zhejiang, China), vancomycin (Mayne Pharma, Salisbury South, SA, Australia), meropenem (Astra Zeneca, Istanbul, Turkey), fluconazole (Sigma-Aldrich), amphotericin B (Riedel de Haen, Seelze, Germany), isoniazid (Sigma-Aldrich), ethambutol (Sigma-Aldrich), DMSO (Riedel de Haen).

Microorganisms used in the assay were; *Klebsiella pneumoniae* clinical isolate (extended beta lactamase spectrum (ESBL)), *Escherichia coli* isolate (ESBL), *Enterococcus faecalis* isolate (resistant to vancomycin (VRE)), and *Staphylococcus aureus* isolate (resistant to methicilline (MRSA)), *K. pneumoniae* RSKK 574, *E. coli* ATCC 25922, *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, *Candida albicans* ATCC 10231, *Candida krusei* ATCC 6258, *Mycobacterium tuberculosis* H37RV ATCC 27294 and a clinical isolate of *M.*

tuberculosis. Reference strains and clinical isolates were provided by Gazi University, Faculty of Pharmacy, Department of Pharmaceutical Microbiology, Culture Collection, Ankara, Turkey and Gazi University Hospital Microbiology Laboratory, Ankara, Turkey, respectively.

2.2 Chemistry

General procedure for the preparation of 5-[(4-nitrophenyl)acetamido]-2-(4-tertbutylphenyl)benzoxazole

Firstly, 5-amino-2-(4-tert-butylphenyl)-benzoxazole was synthesized by heating 0.02 mol 2,4-diaminophenol·2.HCl with 0.02mol 4-tert-butylbenzoic acid in 25 g polyphosphoric acid (PPA) and stirring for 3-4 h. At the end of the reaction period, the residue was poured in to an ice/water mixture and the solution was neutralized with 10% NaOH. The resulting precipitate was filtered, washed with distilled water, dissolved in boiling ethanol with 0.2 g charcoal, and filtered off. Then distilled water was added to the filtrate slowly in order to stimulate crystallization. The crude compound **3** was obtained by filtering and drying the crystalline material [17]. Then, 4-nitrophenylacetic acid (0.5 mmol) and thionylchloride (1.5 ml) were refluxed in benzene (5 ml) at 80°C for 3h. Excess thionylchloride was removed *in vacuo*. The 4-nitrophenylacetic acid chloride (**5**) was dissolved in ether (10 ml) and this solution added during 1 h to a stirred, ice-cold mixture of 5-amino-2-[4-tert-butylphenyl]benzoxazole (**3**) (0.5mmol), sodiumbicarbonate (0.5 mmol), diethylether (10 ml) and water (10 ml). The mixture was kept stirred overnight at room temperature and filtered. The precipitate was washed with water, 2M HCl and water, respectively and finally with ether to give compound. The product was re-crystallized from ethanol-water as needles which are dried *in vacuo*. (Scheme 1).

2.3 Microbiological assays

For microbiological assays, standard powders of ampicillin, meropenem, gentamycin sulfate, ofloxacin, vancomycin, fluconazole, amphotericin B, isoniazid, and ethambutol were dissolved in appropriate solvents recommended by Clinical and Laboratory Standards Institute (CLSI) guidelines [18, 19]. Stock solutions of the test compounds were prepared in DMSO. Bacterial susceptibility testing was performed according to the guidelines of CLSI M100-S18 [19]. MHB was added to each well of the micro plates. The bacterial suspensions used for inoculation were prepared at 10^6 CFU/ml by diluting fresh cultures at McFarl and 0.5 density. Suspensions of the bacteria at 10^6 CFU/ml were inoculated to the two-fold diluted solution of the compounds. A 10- μ l bacterium inoculum was added to each well of the micro plates. There were 10^5 CFU/ml bacteria in the wells after inoculations. Micro plates were

incubated at 37°C overnight. Fungal susceptibility testing was performed according to the guidelines of CLSI M27-A3 [18]. RPMI-1640 medium with L-glutamine buffered to pH 7 with MOPS was added to each well of the micro plates. The colonies were suspended in sterile saline, and the resulting suspension was adjusted to McFarland 0.5 density. A working suspension was prepared by appropriate dilution of the stock suspension. A 10- μ l bacterium inoculum was added to each well of the micro plates resulting in 10^3 CFU/ml yeasts in the wells. Micro plates were incubated at 35 °C for 24-48 hours.

After incubation, the lowest concentration of the compounds that completely inhibited macroscopic growth was determined and reported as minimum inhibitory concentration (MIC). All solvents and diluents, pure microorganisms, and pure media were used in control wells. All experiments were done in three parallel series. The data on the antimicrobial activity of the compounds and the control drugs as MIC (μ g/ml) values are given in Table 1. The synthesized compounds were found to possess MIC values between 32 - 128 μ g/ml for some *Mycobacterium tuberculosis*, Gram-negative, Gram-positive bacteria and their isolates and some fungi. The compound exhibited significant antibacterial activity (32 μ g/ml) against an antibiotic resistant *E. faecalis* isolate, at same potency with the compared standard drugs vancomycin and gentamycin sulfate. Moreover, the synthesized compound exhibited the same antifungal activity against *C. krusei* with MIC values of 64 μ g/ml with the tested reference drug fluconazole.

3. Computational Details

Molecular geometries and vibrational wavenumbers of the title compound were computed using B3LYP/6-311++G(d,p) (5D, 7F) [20]. The theoretically obtained wavenumbers are scaled by using the scaling factor 0.9613 [21] for better agreement with the experimental results and vibrational assignments are done with help of potential energy distribution [22] and GaussView software [23]. The NMR chemical shifts were calculated within the gauge-independent atomic orbital approach applying the same method used for geometry optimization. NBO, MEP and frontier molecular orbital analysis were achieved using B3LYP/6-311++G(d,p) (5D, 7F) basis set. The natural bond orbital (NBO) calculations were performed using NBO 3.1 program [24] as implemented in the Gaussian09 package at the DFT/B3LYP level. The optimized geometrical (Fig.3) parameters are given in table 2.

Jaguar 9.0 [25] and Desmond [26-29] programs, as implemented in Schrödinger Materials Science Suite 2015-4, have been used for DFT calculations and MD simulations, respectively, in order to gain additional insight into the local reactivity properties of the NATPB molecule. With Jaguar ALIE, Fukui functions and BDE have been obtained using

the B3LYP exchange-correlation functional [30], with 6-311++G(d,p), 6-31++G(d,p) and 6-311G(d,p) basis sets, respectively. Based on the work of Johnson et al. [31, 32], which is implemented in Jaguar program, noncovalent interactions have been investigated. MD simulations have been performed with OPLS 2005 force field [33] and within NPT ensemble class. The system was modeled by placing one NATPB molecule into the cubic box with approximately 3000 water molecules and the simulation time was set to 10 ns. Cut off radius was set to 12 Å, temperature to 300 K, while pressure was set to 1.0325 bar. Solvent was treated within the simple point charge (SPC) model [34]. In all cases when Jaguar and Desmond were used, input and output files were manipulated by Maestro graphical user interface application for Schrödinger Materials Science Suite 2015-4.

4. Results and Discussion

In the following discussion, the rings, C₁-C₂-C₄-C₈-C₆-C₃, C₁₁-N₂₂-C₁₃-C₁₂-O₂₁, C₁₂-C₁₃-C₁₅-C₁₈-C₁₆-C₁₄, and C₃₀-C₃₂-C₃₆-C₃₉-C₃₅-C₃₁ are designated as PhI, PhII, PhIII and PhIV, respectively.

4.1 Geometrical parameters

The Phenyl ring C-C bond lengths of the title compound are, 1.4092-1.3876 Å for PhI, 1.4107-1.3811 Å for PhIII and 1.4018-1.3887 Å for PhIV rings which are in agreement with reported literature [35]. In the present case, the C-N bonds lengths are, C₁₁-N₂₂ = 1.2990 Å, C₁₃-N₂₂ = 1.3894 Å, C₁₈-N₂₃ = 1.4188 Å, C₂₅-N₂₃ = 1.3705 Å and C₃₉-N₄₀ (nitro) = 1.4777 Å. The C-O bond length of the title compound is, C=O = 1.2186 Å and the reported values are 1.2235 Å [36] and 1.2253 Å [36]. The C-O bond lengths of the title compound are, C₁₁-O₂₁ = 1.3794 Å and C₁₂-O₂₁ = 1.3713 Å while the reported values for a similar derivative are 1.3871 Å and 1.3653 Å [37].

For the nitro group of the title compound, the N-O bond lengths are N₄₀-O₄₁ = 1.2248 Å, N₄₀-O₄₂ = 1.2254 Å, the C-C-N bond angle is 117.7° and O-N-O bond angle is 124.6° while the reported values are 1.2236, 1.2257 Å (N-O) and 117.3, 117.7° (CNO) [35].

At the position C₁, the bond angles are, C₂-C₁-C₃ = 117.1°, C₂-C₁-C₄₃ = 122.9° and C₃-C₁-C₄₃ = 120.9° and the differences in the angles are due to the interaction between the methyl groups and the ring PhI. The interactions between the phenyl rings, PhI and PhII are revealed for the bond angles at C₈ and C₁₁ positions, which are respectively, C₄-C₈-C₆ = 118.7°, C₄-C₈-C₁₁ = 119.7°, C₆-C₈-C₁₁ = 121.6° and O₂₁-C₁₁-N₂₂ = 114.7°, O₂₁-C₁₁-C₈ = 117.4°, N₂₂-C₁₁-C₈ = 127.9°. The bond angles around C₁₈ position are, C₁₅-C₁₈-C₁₆ = 121.2°, C₁₅-C₁₈-N₂₃ = 116.5° and C₁₆-C₁₈-N₂₃ = 122.3° and this asymmetry in angles is due to the interaction between the ring PhIII and the NH group. The interaction between the carbonyl

with group with the neighbouring moieties, NH and CH₂ is given by the bond angles at the position C₂₅ and these angles are, N₂₃-C₂₅-C₂₇ = 114.3°, N₂₃-C₂₅-O₂₆ = 124.7°, and C₂₇-C₂₅-O₂₆ = 121.0°. At C₃₉ position, the angle C₃₅-C₃₉-C₃₆ is increased by 1.8°, C₃₅-C₃₉-N₄₀ is decreased by 0.8° and C₃₆-C₃₉-N₄₀ is decreased by 1.0° from 120° and this is due to the interaction between the nitro group and H_{37,38}.

4.2 IR and Raman spectra

The vibrational assignments of the title compound are given in Table 3. For the title compound, the carbonyl stretching mode is assigned at 1672 cm⁻¹ in the IR spectrum, 1680 cm⁻¹ in the Raman spectrum, 1677 cm⁻¹ theoretically while the C-O stretching modes are at 1175, 904 cm⁻¹ theoretically and according to literature, the C=O stretching modes are assigned in the range 1850-1550 cm⁻¹ [38] and the C-O-C stretching modes are in the range 1200-900 cm⁻¹ [39, 40]. For the C=O mode at 1677 cm⁻¹ the IR intensity is 259.89 with bands in the IR spectrum and with a PED of 75% and for the C-O modes at 1175 and 904 cm⁻¹, the PEDs are 43 and 47% with low IR intensities and no bands in the IR spectrum. Sebastian et al. reported the carbonyl stretching mode at 1694 cm⁻¹ (IR) 1696 cm⁻¹ (Raman) and at 1699 cm⁻¹ (DFT) [35]. For a similar derivative, the C-O-C stretching modes are reported at 1173, 890 cm⁻¹ in the IR spectrum, 1174, 888 cm⁻¹ in the Raman spectrum, 1172, 893 cm⁻¹ theoretically by Parveen et al. [37].

NO₂ stretching vibrations are expected in the regions 1565-1505 and 1375-1305 cm⁻¹ according to literature [41] and for the title compound, these modes are assigned at 1514 cm⁻¹ in the IR spectrum, 1512 cm⁻¹ in the Raman spectrum and 1515, 1315 cm⁻¹ theoretically with high IR intensities and PEDs 75 and 55% [41]. Sebastian et al. [35] reported NO₂ stretching modes at 1566, 1345 cm⁻¹ in the IR spectrum, 1565, 1345 cm⁻¹ in the Raman spectrum and 1568, 1342 cm⁻¹ theoretically. The deformation modes of NO₂ are expected in the regions at 850 ± 60, 740 ± 50 and 540 ± 70 cm⁻¹ according to literature [41] and in the present case, bands observed at 842, 705, 468 cm⁻¹ (IR), 702, 598, 460 cm⁻¹ (Raman) and 840, 703, 602, 465 cm⁻¹ (DFT) are assigned as NO₂ deformation modes. The PEDs of these deformation modes are in the range 33-47% with low values of IR intensity and Raman activities. NO₂ deformation modes are reported at 811, 724, 526 cm⁻¹ (IR), 810, 730, 530 cm⁻¹ (Raman) and 808, 726, 528 cm⁻¹ (DFT) [35].

According to literature, the NH stretching vibration is expected in the range 3500-3300 cm⁻¹ and the NH bending modes around 1500 and 1250 cm⁻¹ [42, 43] and in the present case, these modes are assigned at 3480, 3260 cm⁻¹ (IR), 3480 cm⁻¹ (Raman), 3485 cm⁻¹ (DFT) (stretching), 1500 cm⁻¹ (Raman), 1506, 1214 cm⁻¹ (DFT) (bending). These modes have PEDs

of 100, 49 and 30%. These modes are reported at 3462, 3324 cm^{-1} (IR), 3450 cm^{-1} (Raman), 3400 cm^{-1} (DFT) (stretching), 1508, 1219 cm^{-1} (DFT) [35]. The NH stretching wavenumber has two values in the IR spectrum with a difference of 220 cm^{-1} and is red shifted by 225 cm^{-1} from the computed value, which indicates the weakening of NH bond resulting in proton transfer to the neighbouring oxygen atom. Mary et al. reported values of NH modes at 1587, 1250, 650 cm^{-1} (IR), 1580, 1277, 652 cm^{-1} (DFT) [44]. In the present case, the NH out-of-plane mode is assigned at 522 cm^{-1} theoretically [41-43].

The CN stretching modes are expected in the region 1100-1300 cm^{-1} [39] and in the present case the bands at 1230, 1142 cm^{-1} in the IR spectrum, 1230, 1143 cm^{-1} in the Raman spectrum, 1255, 1232, 1139 cm^{-1} theoretically are assigned as these modes which are in agreement with literature [45]. Aromatic nitro compounds show a C-N stretching vibration near [39] 870 cm^{-1} . The band at 900 cm^{-1} theoretically is assigned as the C-N stretching mode of nitro group attached with the phenyl ring of the title compound. In the present case all the C-N stretching modes have PEDs around 40%. The C-N stretching modes are reported at 1258, 1245, 1103, 897 cm^{-1} (DFT) [46], 1215 cm^{-1} (DFT) [47]. The C=N stretching mode of the title compound is observed at 1526 cm^{-1} in the Raman spectrum and at 1525 cm^{-1} theoretically as expected [39].

The methyl stretching modes of the title compound are observed at 2964, 2902 cm^{-1} in the IR spectrum, 2982, 2963, 2916, 2901 cm^{-1} in the Raman spectrum and in the range 2979-2905 cm^{-1} theoretically as expected [41, 42]. The bending modes of the methyl groups are observed at 1427, 1340 cm^{-1} in the IR spectrum, 1451, 1428, 1342, 1321, 1085, 1007, 891 cm^{-1} in the Raman and in the range 1463-890 cm^{-1} theoretically [41, 42].

The CC_3 stretching modes are expected in the ranges 1295-1175 cm^{-1} and 890-710 cm^{-1} [41, 42] and in the present case these modes are assigned at 806 cm^{-1} in the IR spectrum, 1236, 808 cm^{-1} in the Raman spectrum and at 1234, 1173, 805 cm^{-1} theoretically with PEDs around 44-49%. Joseph et al. reported the CC_3 stretching modes at 1244, 907 cm^{-1} in the IR spectrum, 1247 cm^{-1} in Raman spectrum and at 1286, 1249, 906 cm^{-1} theoretically [48]. Joseph et al. reported the CC_3 stretching modes at 1244, 907 cm^{-1} in the IR spectrum, 1247 cm^{-1} in Raman spectrum and at 1286, 1249, 906 cm^{-1} theoretically [48]. The deformation modes of the CC_3 group are expected in the regions, 435 ± 85 , 335 ± 80 and 300 ± 80 cm^{-1} (total five modes, two asymmetric, one symmetric and two rocking) and for the title compound, these deformation modes are assigned at 446, 395, 341, 320 and 279 cm^{-1} theoretically and the reported values are 496, 326, 313, 290, 219 cm^{-1} theoretically [48]. The

CC₃ deformation modes have PEDs less than 50% except for the mode at 320 cm⁻¹ has a high PED of 60%.

The CH₂ modes of the title compound are observed at 1265 cm⁻¹ in the IR spectrum, 2965, 2932, 1419, 1264 cm⁻¹ in the Raman spectrum experimentally and the PED analysis gives these modes at 2966, 2929 cm⁻¹ (stretching) and 1434, 1422, 1263, 1214 cm⁻¹ (deformation modes) which are in agreement with the literature [41, 42].

The phenyl CH stretching modes of the title compound are assigned at 3082 cm⁻¹ (IR), 3077 cm⁻¹ (Raman), 3085, 3076, 3068, 3052 cm⁻¹ (DFT) for PhI, 3115 cm⁻¹ (IR) 3122 cm⁻¹ (Raman), 3121, 3077, 3052 cm⁻¹ (DFT) for PhIII and 3044 cm⁻¹ (IR), 3097, 3077, 3030 cm⁻¹ (Raman), 3098, 3098, 3076, 3049 cm⁻¹ (DFT) for PhIV rings as expected [41]. In the present case, the phenyl ring CC stretching modes are assigned at 1550, 1473 cm⁻¹ (IR), 1550, 1470, 1385 cm⁻¹ (Raman), 1588, 1545, 1473, 1383, 1280 cm⁻¹ (DFT), for PhI, 1601, 1402 cm⁻¹ (IR), 1321 cm⁻¹ (Raman), 1599 1583, 1437, 1396, 1323 cm⁻¹ (DFT) for PhIII and 1575 cm⁻¹ (Raman), 1580, 1573, 1464, 1391, 1306 cm⁻¹ (DFT) for PhIV as expected [41]. Tri-substituted phenyl rings have three wavenumber intervals for the ring breathing mode: 500-660, 1050-1100 and 600-750 cm⁻¹ for light substituent, heavy substituent and mixed substituent according to literature [49]. For the title compound, the ring breathing mode of tri-substituted benzene ring is assigned at 1101 cm⁻¹ theoretically with a PED of 46%. The ring breathing mode of tri-substituted phenyl rings are reported at 1110, 1129 cm⁻¹ [50] and at 1109 cm⁻¹ in the IR spectrum, 1100 cm⁻¹ theoretically 1109 cm⁻¹ (IR), 1100 cm⁻¹ (DFT) [51].

The ring breathing mode of para-substituted phenyl rings with entirely different substituent are expected in the range 780-880 cm⁻¹ according to literature [49] and in the present case, this is confirmed by the bands at 815 cm⁻¹ and 781 cm⁻¹ by PED analysis and the PED values are 47 and 52%. The phenyl ring breathing mode of para-substituted phenyl rings was reported at 795 cm⁻¹ [52], at 873 cm⁻¹ in the IR spectrum and at 861 cm⁻¹ theoretically [53] and at 753 cm⁻¹ in IR spectrum, 793, 759 cm⁻¹ theoretically [54].

The in-plane and out-of-plane CH bending vibrations of phenyl rings are expected above and below 1000 cm⁻¹ [41] and for the title compound, these modes are assigned at 1292, 1185 cm⁻¹ (IR), 1293 cm⁻¹ (Raman), 1295, 1178, 1163, 1078 cm⁻¹ (DFT) for PhI, 1105, 1142 cm⁻¹ (IR), 1105, 1143 cm⁻¹ (Raman), 1258, 1139, 1103 cm⁻¹ (DFT) for PhIII, 1170, 1068 cm⁻¹ (IR), 1068 cm⁻¹ (Raman), 1288, 1168, 1158, 1074 cm⁻¹ (DFT) for PhIV (in-plane CH deformation modes) and at 952 cm⁻¹ (IR), 954, 944, 829, 819 cm⁻¹ (DFT) for PhI, 930 cm⁻¹ (IR), 930 cm⁻¹ (Raman), 928, 823, 801 cm⁻¹ (DFT) for PhIII, 970, 842 cm⁻¹ (IR), 970 cm⁻¹ (Raman), 965, 956, 840, 818 cm⁻¹ (DFT) for PhIV (out-of-plane deformation modes).

4.3 NMR spectra

GIAO ^1H - and ^{13}C -NMR chemical shifts with respect to trimethylsilane were calculated using the DFT/B3LYP method (Table 4). The predicted chemical shifts of aromatic protons of the title compound are in the range 7.851-8.872 for PhI, 7.0809-9.1635 for PhIII and 7.6067-8.7193 for PhIV. The experimental shifts are 7.62-7.65 for PhI, 7.53-8.14 for PhIII and 8.10-8.24 for PhIV. For the tert-butyl group, the proton shifts are in the range, 1.6335-2.7547 (predicted), 1.33 (experimental) while in methylene group the shifts are 4.2892, 3.3271 (predicted), 3.89 (experimental). The hydrogen atom of amide group in this compound appears at a higher chemical shift of 6.5392 ppm theoretically, while the experimental shift is 10.49. We noted that, δ_{calc} of the NH protons strongly deviate from the experimental data due to the high polarity of these bonds.

For organic molecules, the range for ^{13}C NMR chemical shift is usually greater than 100 ppm [55]. For the carbonyl group, the carbon atom has a low lying excited state involving the movement of electrons from the oxygen lone pair to anti-bonding π orbital that generates a paramagnetic current [56] and this $n \rightarrow \pi^*$ transition produces a large shift to a higher frequency and hence the carbonyl carbon signals have a weaker intensity and appear in the range, 150-220 ppm [58, 58]. Thus it easy to recognize the carbonyl absorptions from the other resonances and for the title compound carbonyl shift is 162.738. The aromatic carbons give resonance in overlapped areas of NMR spectrum with chemical shift values from 100 to 150 ppm [59] and in the present case, the chemical shifts of the aromatic carbon atoms are, 125.4344-153.0048 PhI, 108.5366-147.2081 for PhIII and 124.2802-148.02324 for PhIV. The chemical shifts of the other carbon atoms are 53.1382 (C27), 163.456 (C11), 44.009 (C43), 38.7995 (C44), 38.7946 (C48) and 35.2413 (C52).

4.4 Nonlinear Optical properties

For the title compound, the polarizability is 5.5574×10^{-23} esu and the first and second hyperpolarizabilities are 211.26×10^{-30} and -85.049×10^{-37} esu. The first hyperpolarizability of the title compound is 1625 times that of the standard NLO material urea [60] and the reported first and second hyperpolarizability of a similar derivative are 31.139×10^{-30} and -22.127×10^{-37} esu [61]. The high values of hyperpolarizability may be due to the electron cloud transfer from donor to acceptor which makes the system highly polarized and the charge transfer.

4.5 Frontier Molecular Orbital

The intra molecular charge transfer between donor and acceptor groups through the conjugated paths can be explained by frontier molecular orbital analysis [62]. In the present case the HOMO and LUMO energies are -8.168 and -5.280 eV, respectively. The ionization

energy $I = -E_{\text{HOMO}} = 8.168$ eV and electron affinity $A = -E_{\text{LUMO}} = 5.280$ eV and energy gap = 2.888 eV. The global chemical descriptors are given as hardness $\eta = (I-A)/2$, chemical potential $\mu = -(I+A)/2$ and electronegativity index $\omega = \mu^2/2\eta$ [63, 64]. In the present case η , μ and ω are 1.444, -6.724 and 15.66 eV respectively. In the HOMO-LUMO plot (Fig. 4), the HOMO is localized over the acetamido group, benzoxazole, trisubstituted phenyl ring and the phenyl ring attached with the tert-butyl group, while the LUMO is over the tert-butyl phenyl, ring, butyl group, benzoxazole ring and trisubstituted phenyl ring and there is a charge transfer in the molecular system through the conjugated paths.

4.6 Molecular Electrostatic Potential

Molecular electrostatic potential of the title compound is calculated to predict the reactive sites of electrophilic and nucleophilic attacks. In the MEP map red represents most negative region, blue represents most positive region and green represents zero potential. The negative, red and yellow regions in the MEP plot were related to electrophilic reactivity and positive, blue region to nucleophilic reactivity. From the MEP plot (Fig. 5) it is clear that the nitro group, carbonyl oxygen atom and nitrogen atom in the benzoxazole ring are the most negative regions and nitrogen atom in the NH moiety is the most positive region.

4.7 ALIE surface, Fukui functions and non-covalent interactions

Determination of molecule sites prone to electrophilic attacks is of great importance for the overall understanding of the reactivity of some molecule. In this regards very frequently MEP surfaces are employed, while ALIE surfaces provide even more useful results concerning this. Namely, ALIE was introduced by Sjöberg et al. [65, 66] to indicate molecule areas where electrons are least tightly bound. It is defined as a sum of orbital energies weighted by the orbital densities:

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

where $\rho_i(\vec{r})$ represents the electronic density of the i -th molecular orbital at the point $\vec{r}$, ϵ_i represents the orbital energy and $\rho(\vec{r})$ is the total electronic density function. In this work ALIE values were visualized by their mapping to the electron density surface, Fig.6

Results concerning the ALIE surface of NATPB molecule indicate that two benzene rings and nitrogen atom N22 are possibly prone to electrophilic attacks. Namely, at these locations the red colour indicates molecule sites where electrons are least tightly bound and where they are most easily removed. On the other side the blue colour indicates molecule locations where electrons are most tightly bound and the most important locations from this

aspect are in the near vicinity of one benzene ring, oxygen atom O42 and hydrogen atom H24. Fig.6 also has visualized two intra-molecular non-covalent interactions involving atoms H20, H33 and O26.

In the same time it is also useful to track the changes of molecule's electron density with the addition or removal of charge. This can be done by the calculations of Fukui functions and in such way one is able to detect possible important reactive properties when molecule acts as electrophile or nucleophile. In Jaguar program a finite difference approximation is used for the calculations of Fukui functions according to the following equations:

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

$$f^- = \frac{(\rho^{N-\delta}(r) - \rho^N(r))}{\delta}, \quad (3)$$

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 [67].

In this case also, the values of Fukui functions have been mapped to the electron density surface and the results are presented in Fig.7. Concerning the Fukui f^+ function, purple colour in Fig.7a is designating molecule areas where electron density increased after the addition of charge. It can be seen that when molecule acts as an electrophile electron density increases in the near vicinity of NO₂ designating this part of the molecule as an important reactive centre. On the other side concerning the Fukui f^- function red colour in Fig.7b is designating molecule areas where electron density decreases after the removal of charge, thus it can be concluded that when molecule acts as a nucleophile electron density decreases in the near vicinity of carbon atom C27.

4.8 Natural Bond Orbital Analysis

The strong inter molecular hyper conjugative interactions (Tables 5 and 6) in the molecular system are listed below: C₁₁-N₂₂ from O₂₁ of $n_2(O_{21}) \rightarrow \pi^*(C_{11}-N_{22})$ which increases the electron density as, 0.31245e that weakens the respective bonds C₁₁-N₂₂ leading to stabilization of 34.63 kJ/mol; C₂₅-O₂₆ from N₂₃ of $n_1(N_{23}) \rightarrow \pi^*(C_{25}-O_{26})$ which increases the electron density as, 0.28955e that weakens the respective bonds C₂₅-O₂₆ leading to stabilization of 63.10 kJ/mol; N₂₃-C₂₅ from O₂₆ of $n_2(O_{26}) \rightarrow \sigma^*(N_{23}-C_{25})$ which increases the electron density as, 0.07566e that weakens the respective bonds N₂₃-C₂₅ leading to stabilization of 26.23 kJ/mol; N₄₀-O₄₁ from O₄₂ of $n_3(O_{42}) \rightarrow \pi^*(N_{40}-O_{41})$ which increases the electron density as, 0.62292e that weakens the respective bonds N₄₀-O₄₁ leading to stabilization of 164.96 kJ/mol; N₄₀-O₄₂ from O₄₂ of $n_2(O_{41}) \rightarrow \sigma^*(N_{40}-O_{42})$ which increases

the electron density as, 0.05655e which weakens respective bond N₄₀-O₄₂ leading to stabilization of 19.44kJ/mol. The important bonding in terms of the natural hybrid orbital are, n₂(O₂₁), n₂(O₂₆), n₂(O₄₁) and n₃(O₄₂) with higher energies, -0.33848, -0.25665, -0.28803, -0.27160a.u, considerable p-characters (100%), and low occupation numbers, 1.73156, 1.85607, 1.89690, 1.44578; while the orbital, n₁(O₂₁), n₁(O₂₆), n₁(O₄₁), n₁(O₄₂) occupy lower energies, -0.59151, -0.68247, -0.79162, -0.79187a.u, with p-characters, 62.33, 42.08, 25.55, 25.53% and high occupation number, 1.96933, 1.97337, 1.98105, 1.98102. Thus, a very close to pure p-type lone pair orbital participates in the electron donation to the $\pi^*(C_{11}-N_{22})$ orbital for n₂(O₂₁) $\rightarrow\pi^*(C_{11}-N_{22})$, $\sigma^*(N_{23}-C_{25})$ orbital for n₂(O₂₆) $\rightarrow\sigma^*(N_{23}-C_{25})$, $\sigma^*(N_{40}-O_{42})$ orbital for n₂(O₄₁) $\rightarrow\sigma^*(N_{40}-O_{42})$, $\pi^*(N_{40}-O_{41})$ orbital for n₃(O₄₂) $\rightarrow\pi^*(N_{40}-O_{41})$, $\pi^*(C_{25}-O_{26})$ orbital for n₁(n₂₃) $\rightarrow\pi^*(C_{25}-O_{26})$.

4.9 Reactive and degradation properties based on autoxidation and hydrolysis

Local reactivity properties of important biologically active molecules can be investigated and in such a way forced degradation experiments can be significantly rationalized [68] by using DFT calculations and MD simulations. Concerning the DFT calculations, if the BDE for hydrogen abstraction has appropriate value then it can be a candidate for the starting point in the case of autoxidation mechanism. In this regard it is important to mention that all peroxy radicals have similar BDE values (87–92 kcal/mol) and it can be approximated that they are independent on the chemical surrounding [69, 70].

On the other side the study of Wright et al. [71] indicated that the possibility for autoxidation mechanism is the highest if the BDE values for the hydrogen abstraction are in the interval of 75 to 85kcal/mol. Therefore, in order to investigate the possibility for autoxidation of NATPB molecule we have calculated BDE values for hydrogen abstraction. Also, BDE values of the remaining single acyclic bonds have been calculated to determine the weakest bonds and therefore possible locations where degradation process could start, Fig.8.

According to the results presented in Fig.8 there is one BDE value for hydrogen abstraction which could be considered as interesting for the autoxidation mechanism. Namely, the BDE value for the abstraction of hydrogen atom H28, denoted with number 7, is equal to ~88 kcal/mol. Of the remaining single acyclic bonds the lowest BDE values have been obtained for the ones denoted with numbers 14 and 15. These results indicate that the mentioned bonds are the weakest and that degradation process could start by detaching of part of the molecule with benzene ring and NO₂ group from one side, while from the other side degradation could start by detaching of the methyl group. The fact that the lowest BDE value for hydrogen

abstraction is very close to the weakest bond is very important, since it indicates that oxidation could have important role in the degradation of the NATPB molecule.

Atoms of NATPB molecule with relatively significant interactions with water molecules have been determined by calculations of RDF after MD simulations. RDF, $g(r)$, gives the probability of finding a particle in the distance r from another particle [72] and representative $g(r)$ curves are provided in Fig.9.

RDF results presented in Fig.9 indicate that five carbon and three non-carbon atoms of NATPB molecule have relatively pronounced interactions with water molecules. Of carbon atoms the most important is the carbon atom C43, with maximal $g(r)$ value of around 1.6 and with peak distance located at around 4.75 Å. The peak distance of carbon atom C30 is located in similar location as in the case of C43, but its maximal $g(r)$ value is much lower, around 1.2. Carbon atoms C6 and C25 have significantly lower maximal $g(r)$ values than C43, but their peak distances are located at much shorter distances, around 3.5 Å. Of non-carbon atoms the RDF that indicates the most pronounced interactions with water molecules is the RDF of hydrogen atom H24 with maximal $g(r)$ value of around 0.9, but located at distance lower than 2 Å. Oxygen atom O26 has similar maximal $g(r)$ value, but its located at distance somewhat higher than 3.5 Å. Nitrogen atom N40 also has the highest maximal $g(r)$ value of non-carbon atoms, located at distance of around 4 Å. RDF results related to atom O26 indicate that autoxidation and hydrolysis mechanisms could compete, since the mentioned atom is close to the hydrogen atoms for which abstraction BDE values are the lowest. In the same time O26 is practically adjacent bond to the weakest bond according to the BDE results, meaning that hydrolysis could be important for the degradation properties of this molecule. In the same time, beside Fukui functions RDFs also indicate the importance of NO₂ group for the general reactivity of NATPB molecule, as in Fig.9 it can be seen that nitrogen atom N40 has pronounced interactions with water.

4.10 Molecular docking

Benzoxazoles are the structural isosteres of natural nucleotides and interact easily with the biopolymers that they constitute an important class of heterocyclic compounds with antimicrobial, antitubercular, antiviral and antitumor [73] activity. Kumar et al. report the activity of UK-1 (structurally unique bis(benzoxazole) natural product isolated from a strain of *Streptomyces*) against a wide range of human cancer cell lines [74]. UK-1 displays a wide spectrum of potent anticancer activity²¹ against leukemia, lymphoma and certain solid tumour-derived cell lines [75]. Thus we simulate the title compound with CDK inhibitor as anti-cancer. High resolution crystal structure of CDK inhibitors as anti-cancer was obtained

from the protein data bank website (PDB ID: 2XMY) and all molecular docking calculations were performed on Auto Dock-Vina software [76] and as reported in literature [52, 61]. The ligand binds well at the active site was analyzed for detailed interactions (Figs. 10 and 11) in Discovery Studio Visualizer 4.0 software [77]. The interactions obtained are: Amino acid Lys88 forms π -cation, π -sigma and π -alkyl interaction with benzoxazole ring. Lys129, Lys88 shows H-bond interaction with NO₂, C=O group respectively. Asp92 forms π -cation interaction with phenyl ring and Ala95 forms alkyl interaction with CH₃ group. The docked ligand forms a stable complex with CDK inhibitors and gives a binding affinity value of -8.3kcal/mol (table 7) and the compound might exhibit inhibitory activity against CDK inhibitors.

5. Conclusions

The FT-IR and FT-Raman studies of the title compound in the ground state were reported experimentally and theoretically. Potential energy distribution of normal modes of vibrations was done using GAR2PED program. The theoretically predicted geometrical parameters are in agreement with that of similar derivatives. The title compound exhibited significant antibacterial activity against an antibiotic resistant *E. faecalis* isolate and antifungal activity against *C. krusei*. The first hyperpolarizability of the title compound is very much greater than that of the standard NLO material urea and the high values of hyperpolarizability may be due to the electron cloud transfer from donor to acceptor which makes the system highly polarized and the charge transfer. MEP studies reveals that the nitro group, carbonyl oxygen atom and nitrogen atom in the benzoxazole ring are the most negative regions and nitrogen atom in the NH moiety is the most positive region. Two benzene rings and nitrogen atom N22 have been recognized as possible molecule sites prone to electrophilic attacks. Additionally, according to the Fukui functions NO₂ group has been also recognized as possibly important reactivity centre. Analysis of non-covalent interactions indicated that two such interactions occurred within the NATPB molecule. BDE values indicate that there is one hydrogen atom for whose abstraction less than 92 kcal/mol is necessary. In the same time autoxidation mechanism could compete with hydrolysis, as in the close vicinity of the mentioned hydrogen atom is oxygen atom O26 with significant interactions with water molecule. The title compound forms stable complex with CDK inhibitors and exhibit inhibitory activity against CDK inhibitors.

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Figure captions

Fig.1 FT-IR spectrum of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.2 FT-Raman spectrum of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.3 Optimized geometry of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.4 HOMO-LUMO plots of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.5 MEP plot of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.6 ALIE surface of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole molecule

Fig.7 Fukui functions a) f^+ and b) f^- of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole molecule, Purple colour is positive colour, while red colour is the negative one

Fig.8 BDEs of all single acyclic bonds of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole molecule

Fig.9 RDFs of atoms of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole with pronounced interactions with: a) carbon atoms and b) non-carbon atoms

Fig.10 Schematic for the docked conformation of active site of title compound at CDK inhibitors

Fig.11 The docked protocol reproduced the co-crystallized conformation with H-bond (green), p-cation (brown), p-sigma (violet), alkyl (pink) and H-bond receptor surface shown

ACCEPTED MANUSCRIPT

Table 1

Antimicrobial and antitubercular activity (MIC $\mu\text{g/ml}$) of synthesized compound **6** and the standard drugs

	<u>Microorganism^a</u>											
	E.c.	E.c.*	K.p.	K.p.*	S.a.	S.a.*	E.f.	E.f.*	C.a.	C.k.	M.t.	M.t.*
-												
Compound	64	32	64	64	128	128	64	32	64	64	32	32
Vancomycin	n.d. ^b	n.d.	n.d.	n.d.	1	1	1	32	n.d.	n.d.	n.d.	n.d.
Gentamycin												
sulfate	1	1024	0.5	256	0.125	32	4	32	n.d.	n.d.	n.d.	n.d.
Meropenem	0.0625	<0.0625	0.03	<0.0625	0.125	-	2	0.5	n.d.	n.d.	n.d.	n.d.
Ofloxacin	<-.625	64	0.125	0.5	0.125	0.25	1	4	n.d.	n.d.	n.d.	n.d.
Ampicillin	2	>2048	2	>2048	0.5	>2048	1	0.5	n.d.	n.d.	n.d.	n.d.
Amphotericin B	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.25	2	n.d.	n.d.
Fluconazole	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1	64	n.d.	n.d.
Isoniazid	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<0.25	<0.25
Ethambutol	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	2	2

^aE.c., *Escherichia coli* ATCC 25922; E.c.*, *Escherichia coli* isolate (ESBL); K.p., *Klebsiella pneumoniae* RSKK 574; K.p.*, *Klebsiella pneumoniae* isolate (ESBL); S.a., *Staphylococcus aureus* ATCC 29213; S.a.*, *Staphylococcus aureus* isolate (MRSA); E.f., *Enterococcus faecalis* ATCC 29212; E.f.*: *Enterococcus faecalis* isolate (VRE); C.a., *Candida albicans* ATCC 10231; C.k., *Candida krusei* ATCC 6258; M.t., *Mycobacterium tuberculosis* H37RV ATCC 27294; M.t.*, *Mycobacterium tuberculosis* isolate.

^bn.d., not determined (microbiological assays were not performed due to following reasons: antibacterial drugs were not assayed against fungi and *M. tuberculosis*; antifungal drugs were not assayed against bacteria and *M. tuberculosis*; antitubercular drugs were not assayed against bacteria and fungi; Gram-negative bacteria employed in the study are naturally resistant to vancomycin).

Table 2

Geometrical parameters of the title compoundBond lengths (Å)

C1-C2	1.4015	C1-C3	1.4042	C1-C43	1.5376
C2-C4	1.3905	C2-H5	1.0817	C3-C6	1.3876
C3-H7	1.0836	C4-C8	1.3991	C4-H9	1.083
C6-C8	1.402	C6-H10	1.0828	C8-C11	1.4565
C11-O21	1.3794	C11-N22	1.299	C12-C13	1.3983
C12-C14	1.3811	C12-O21	1.3713	C13-C15	1.3914
C13-N22	1.3894	C14-C16	1.3951	C14-H17	1.0824
C15-C18	1.3998	C15-H19	1.0845	C16-C18	1.4107
C16-H20	1.0784	C18-N23	1.4188	N23-H24	1.0083
N23-C25	1.3705	C25-O26	1.2186	C25-C27	1.5365
C27-H28	1.0936	C27-H29	1.0925	C27-C30	1.5154
C30-C31	1.4018	C30-C32	1.3993	C31-H33	1.0827
C31-C35	1.3887	C32-H34	1.0846	C32-C36	1.3907
C35-H37	1.0813	C35-C39	1.392	C36-H38	1.0812
C36-C39	1.3897	C39-N40	1.4777	N40-O41	1.2248
N40-O42	1.2254	C43-C44	1.5469	C43-C48	1.5472
C43-C52	1.5396	C44-H45	1.0924	C44-H46	1.0942
C44-H47	1.0934	C48-H49	1.0942	C48-H50	1.0924
C48-H51	1.0935	C52-H53	1.0932	C52-H54	1.0934
C52-H55	1.0934				

Bond angles (°)

C2-C1-C3	117.1	C2-C1-C43	122.9	C3-C1-C43	120.0
C1-C2-C4	121.7	C1-C2-H5	120.2	C4-C2-H5	118.1
C1-C3-C6	121.9	C1-C3-H7	119.9	C6-C3-H7	118.2
C2-C4-C8	120.4	C2-C4-H9	120.4	C8-C4-H9	119.1
C3-C6-C8	120.2	C3-C6-H10	120.0	C8-C6-H10	119.8
C4-C8-C6	118.7	C4-C8-C11	119.7	C6-C8-C11	121.6 \
C8-C11-O21	117.4	C8-C11-N22	127.9	O21-C11-N22	114.7

C13-C12-C14	123.2	C13-C12-O21	107.4	C14-C12-O21	129.4
C12-C13-C15	120.0	C12-C13-N22	108.8	C15-C13-N22	131.2
C12-C14-C16	116.9	C12-C14-H17	122.2	C16-C14-H17	120.9
C13-C15-C18	117.8	C13-C15-H19	120.5	C18-C15-H19	121.7
C14-C16-C18	120.9	C14-C16-H20	120.2	C18-C16-H20	119.0
C15-C18-C16	121.2	C15-C18-N23	116.5	C16-C18-N23	122.3
C11-O21-C12	104.3	C11-N22-C13	104.8	C18-N23-H24	114.5
C18-N23-C25	129.5	H24-N23-C25	116.0	N23-C25-O26	124.7
N23-C25-C27	114.3	O26-C25-C27	121.0	C25-C27-H28	105.8
C25-C27-H29	111.7	C25-C27-C30	112.2	H28-C27-H29	107.4
H28-C27-C30	109.7	H29-C27-C30	109.8	C27-C30-C31	120.6
C27-C30-C32	120.4	C31-C30-C32	119.0	C30-C31-H33	119.4
C30-C31-C35	120.7	H33-C31-C35	119.9	C30-C32-H34	119.9
C30-C32-C36	121.1	H34-C32-C36	119.1	C31-C35-H37	121.5
C31-C35-C39	118.9	H37-C35-C39	119.7	C32-C36-H38	121.7
C32-C36-C39	118.6	H38-C36-C39	119.8	C35-C39-C36	121.8
C35-C39-N40	119.2	C36-C39-N40	119.0	C39-N40-O41	117.7
C39-N40-O42	117.7	O41-N40-O42	124.6	C1-C43-C44	109.4
C1-C43-C48	109.3	C1-C43-C52	112.4	C44-C43-C48	109.4
C44-C43-C52	108.1	C48-C43-C52	108.2	C43-C44-H45	112.0
C43-C44-H46	110.1	C43-C44-H47	110.9	H45-C44-H46	107.7
H45-C44-H47	107.8	H46-C44-H47	108.1	C43-C48-H49	110.2
C43-C48-H50	111.9	C43-C48-H51	110.9	H49-C48-H50	107.8
H49-C48-H51	108.1	H50-C48-H51	107.8	C43-C52-H53	109.5
C43-C52-H54	112.0	C43-C52-H55	111.9	H53-C52-H54	107.5
H53-C52-H55	107.5	H54-C52-H55	108.3		

Dihedral angles (°)

C3-C1-C2-C4	-0.0	C3-C1-C2-H5	179.9	C43-C1-C2-C4	179.9
C43-C1-C2-H5	-0.2	C2-C1-C3-C6	-0.1	C2-C1-C3-H7	179.9
C43-C1-C3-C6	-180.0	C43-C1-C3-H7	0.0	C2-C1-C43-C44	120.8
C2-C1-C43-C48	-119.4	C2-C1-C43-C52	0.7	C3-C1-C43-C44	-59.3

C3-C1-C43-C48	60.5	C3-C1-C43-C52	-179.4	C1-C2-C4-C8	0.1
C1-C2-C4-H9	-180.1	H5-C2-C4-C8	-179.9	H5-C2-C4-H9	0.1
C1-C3-C6-C8	0.1	C1-C3-C6-H10	-179.9	H7-C3-C6-C8	-179.9
H7-C3-C6-H10	0.1	C2-C4-C8-C6	-0.0	C2-C4-C8-C11	180.0
H9-C4-C8-C6	-180.0	H9-C4-C8-C11	0.0	C3-C6-C8-C4	-0.1
C3-C6-C8-C11	179.9	H10-C6-C8-C4	180.0	H10-C6-C8-C11	-0.0
C4-C8-C11-O21	-178.8	C4-C8-C11-N22	1.1	C6-C8-C11-O21	1.2
C6-C8-C11-N22	-178.8	C8-C11-O21-C12	179.9	N22-C11-O21-C12	-0.0
\C8-C11-N22-C13	-180.0	O21-C11-N22-C13	-0.0	C14-C12-C13-C15	-0.0
C14-C12-C13-N22	179.9	O21-C12-C13-C15	-180.0	O21-C12-C13-N22	-0.0
C13-C12-C14-C16	0.1	C13-C12-C14-H17	-179.9	O21-C12-C14-C16	-180.0
O21-C12-C14-H17	-0.0	C13-C12-O21-C11	0.0	C14-C12-O21-C11	-179.9
C12-C13-C15-C18	-0.1	C12-C13-C15-H19	179.9	N22-C13-C15-C18	-180.0
N22-C13-C15-H19	0.0	C12-C13-N22-C11	0.0	C15-C13-N22-C11	179.9
C12-C14-C16-C18	-0.1	C12-C14-C16-H20	-179.8	H17-C14-C16-C18	180.0
H17-C14-C16-H20	0.2	C13-C15-C18-C16	0.1	C13-C15-C18-N23	-179.6
H19-C15-C18-C16	-179.9	H19-C15-C18-N23	0.4	C14-C16-C18-C15	-0.1
C14-C16-C18-N23	179.6	H20-C16-C18-C15	179.7	H20-C16-C18-N23	-0.6
C15-C18-N23-H24	3.4	C15-C18-N23-C25	-176.2	C16-C18-N23-H24	-176.3
C16-C18-N23-C25	4.1	C18-N23-C25-O26	-0.1	C18-N23-C25-C27	-179.8
H24-N23-C25-O26	-179.7	H24-N23-C25-C27	0.6	N23-C25-C27-H28	-129.9
N23-C25-C27-H29	-13.3	N23-C25-C27-C30	110.5	O26-C25-C27-H28	50.4
O26-C25-C27-H29	167.0	O26-C25-C27-C30	-69.2	C25-C27-C30-C31	62.8
C25-C27-C30-C32	-117.3	H28-C27-C30-C31	-54.6	H28-C27-C30-C32	125.4
H29-C27-C30-C31	-172.4	H29-C27-C30-C32	7.6	C27-C30-C31-H33	-1.0
\C27-C30-C31-C35	-180.0	C32-C30-C31-H33	179.1	C32-C30-C31-C35	0.1
C27-C30-C32-H34	-0.3	C27-C30-C32-C36	-179.9	C31-C30-C32-H34	179.7
C31-C30-C32-C36	0.0	C30-C31-C35-H37	180.0	C30-C31-C35-C39	-0.1
H33-C31-C35-H37	1.0	H33-C31-C35-C39	-179.1	C30-C32-C36-H38	179.9
C30-C32-C36-C39	-0.0	H34-C32-C36-H38	0.2	H34-C32-C36-C39	-179.7
C31-C35-C39-C36	0.1	C31-C35-C39-N40	-179.8	H37-C35-C39-C36	-180.0

H37-C35-C39-N40	0.1	C32-C36-C39-C35	-0.0	C32-C36-C39-N40	179.8
H38-C36-C39-C35	-179.9	H38-C36-C39-N40	-0.1	C35-C39-N40-O41	0.4
C35-C39-N40-O42	-179.6	C36-C39-N40-O41	-179.5	C36-C39-N40-O42	0.5
C1-C43-C44-H45	60.2	C1-C43-C44-H46	-179.9	C1-C43-C44-H47	-60.3
C48-C43-C44-H45	-59.4	C48-C43-C44-H46	60.4	C48-C43-C44-H47	-180.0
C52-C43-C44-H45	-177.1	C52-C43-C44-H46	-57.2	C52-C43-C44-H47	62.4
C1-C43-C48-H49	-179.9	C1-C43-C48-H50	-60.1	C1-C43-C48-H51	60.4
C44-C43-C48-H49	-60.0	C44-C43-C48-H50	59.7	C44-C43-C48-H51	-179.8
C52-C43-C48-H49	57.4	C52-C43-C48-H50	177.3	C52-C43-C48-H51	-62.2
C1-C43-C52-H53	180.0	C1-C43-C52-H54	-60.9	C1-C43-C52-H55	60.9
C44-C43-C52-H53	59.1	C44-C43-C52-H54	178.2	C44-C43-C52-H55	-59.9
<u>C48-C43-C52-H53</u>	<u>-59.2</u>	<u>C48-C43-C52-H54</u>	<u>59.8</u>	<u>C48-C43-C52-H55</u>	<u>-178.3</u>

Table 3

Calculated scaled wave numbers, observed IR, Raman bands and assignments

B3LYP/6-311++G(d,p) (5D, 7F)			IR	Raman	Assignments ^a
$\nu(\text{cm}^{-1})$	IRI	RA	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3485	17.92	150.56	3480	3480	$\nu\text{NH}(100)$
			3260		
3121	18.74	85.29	3115	3122	$\nu\text{CHIII}(98)$
3098	2.66	113.02	-	3097	$\nu\text{CHIV}(95)$
3098	1.95	56.26	-	3097	$\nu\text{CHIV}(93)$
3085	6.93	126.18	3082	-	$\nu\text{CHI}(99)$
3077	2.21	98.72	-	-	$\nu\text{CHIII}(97)$
3076	4.23	51.36	-	3077	$\nu\text{CHI}(98)$
3076	0.23	43.73	-	3077	$\nu\text{CHIV}(99)$
3068	1.18	35.96	-	-	$\nu\text{CHI}(99)$
3052	13.62	82.63	-	-	$\nu\text{CHI}(98)$
3052	9.53	61.27	-	-	$\nu\text{CHIII}(99)$
3049	9.30	65.22	3044	3030	$\nu\text{CHIV}(97)$
2979	37.80	62.92	-	2982	$\nu\text{CH}_3(93)$
2976	25.91	48.46	-	-	$\nu\text{CH}_3(88)$
2973	110.32	383.22	-	-	$\nu\text{CH}_3(97)$
2971	18.41	26.61	-	-	$\nu\text{CH}_3(91)$
2970	11.05	61.15	-	-	$\nu\text{CH}_3(99)$
2966	4.61	38.12	2965	-	$\nu\text{CH}_2(99)$
2965	4.00	29.13	2964	2963	$\nu\text{CH}_3(92)$
2929	13.02	197.00	-	2932	$\nu\text{CH}_2(99)$
2912	35.95	596.37	-	2916	$\nu\text{CH}_3(92)$
2905	26.00	16.37	2902	2901	$\nu\text{CH}_3(98)$
2905	27.84	22.41	2902	2901	$\nu\text{CH}_3(81)$
1677	259.89	78.25	1672	1680	$\nu\text{C=O}(75)$
1699	10.73	1080.24	1601	1610	$\nu\text{PhIII}(45), \nu\text{PhI}(19)$
1588	65.96	2992.32	-	-	$\nu\text{PhIII}(29), \nu\text{PhI}(43)$

1583	7.52	130.94	-	-	ν PhI(23), ν PhIII(40)
1580	58.87	3.01	-	-	ν PhIV(54), ν NO ₂ (16), δ NH(21)
1573	30.27	342.58	-	1575	ν PhIV(57), δ CHIV(24)
1545	75.74	1355.93	1550	1550	ν C=N(16), ν PhI(46)
1525	24.98	2460.76	-	1526	ν C=N(45), ν PhI(28)
1515	220.13	17.38	1514	1512	ν NO ₂ (75)
1506	511.84	224.08	-	1500	δ NH(49), ν CN(22)
1473	133.66	188.00	1473	1470	ν C=N(14), δ CHI(13), ν PhI(46)
1464	33.85	1.97	-	-	δ CHIV(17), ν PhIV(45)
1463	1.87	0.15	-	-	δ CH ₃ (86)
1452	8.22	10.33	-	1451	δ CH ₃ (96)
1447	14.15	14.32	-	-	δ CH ₃ (87)
1437	66.03	158.71	-	-	ν PhIII(40), δ CHIII(18)
1434	9.99	25.80	-	-	δ CH ₂ (97)
1431	0.12	8.30	-	-	δ CH ₃ (93)
1426	0.08	1.19	1427	1428	δ CH ₃ (94)
1422	8.33	24.08	-	1419	δ CH ₂ (91)
1396	148.95	273.04	1402	-	ν PhIII(42), δ CHIII(20)
1391	2.30	36.89	-	-	ν PhIV(49), δ CHIV(18)
1383	70.96	173.87	-	1385	ν PhI(48), δ CHI(25)
1376	3.83	5.68	-	-	δ CH ₃ (95)
1346	7.66	0.03	-	1342	δ CH ₃ (99)
1343	8.49	0.03	1340	-	δ CH ₃ (94)
1323	111.77	729.08	-	1321	ν PhIII(40), δ CH ₃ (24)
1315	573.95	338.10	-	-	ν NO ₂ (55), ν CN(14)
1306	33.70	35.04	-	-	ν PhIV(80)
1295	6.49	559.02	1292	1293	δ CHI(45), ν PhI(17)
1288	10.29	30.07	-	-	δ CHIV(59), δ CH ₂ (12)
1280	1.19	191.01	-	-	ν PhI(47), δ CHI(21)
1263	44.10	64.90	1265	1264	δ CH ₂ (50), ν PhIII(27)
1258	11.82	254.10	-	-	δ CHIII(47), ν PhIII(21), ν CN(17)

1255	12.42	765.03	-	-	ν PhI(24), ν CN(44), δ CHIII(12)
1234	33.17	50.24	-	1236	ν CC ₃ (46), δ CH ₃ (22)
1232	106.38	1131.35	1230	1230	ν CN(34), δ CHIII(19), ν PhIII(30)
1214	68.88	19.41	-	-	δ CH ₂ (42), δ NH(30)
1178	3.36	7.94	1185	-	δ CH ₃ (13), ν CC(21), δ CHI(41)
1175	4.87	8.96	-	-	ν CO(43), δ CHI(11), δ CH ₃ (14)
1173	3.12	11.99	-	-	ν CC ₃ (49), δ CH ₃ (28)
1168	7.82	33.14	-	1170	ν CC(16), δ CHIV(47), ν PhIV(14)
1163	39.84	468.47	-	-	ν CO(16), δ CHI(54)
1158	2.84	2.90	-	-	δ CHIV(68), ν PhIV(24)
1139	142.58	121.09	1142	1143	ν CN(35), δ CHIII(39), δ CH ₂ (14)
1103	5.13	51.82	1105	1105	δ CHIII(44), ν PhIII(10)
1101	13.34	7.25	-	-	δ CHI(27), ν PhIII(46)
1096	12.19	7.19	-	-	δ CH ₂ (10), ν PhIV(12), δ CHIV(28)
1087	37.31	128.94	-	1085	ν PhI(26), ν CC(11), δ CH ₃ (46)
1078	83.35	109.67	-	-	δ CHI(45), δ CH ₂ (14), ν PhIV(10), ν CN(14)
1074	18.78	55.76	1068	1068	ν CN(19), δ CHIV(46), ν PhIV(24)
1028	40.50	34.96	1022	1024	ν CO(20), ν PhI(29), ν PhIV(21)
1006	0.09	1.57	-	1007	δ CH ₃ (75)
1001	10.94	7.17	-	-	δ CH ₃ (70)
994	8.59	4.76	-	-	δ PhIV(55), ν PhIV(31)
990	37.24	22.59	-	-	δ PhI(59), ν PhI(19)
965	0.30	0.33	970	970	γ CHIV(78), τ PhIV(11)
956	3.08	10.96	-	-	γ CHIV(78)
954	0.07	0.07	-	952	γ CHI(91)
947	2.71	4.79	946	-	γ CHIV(28), τ PhIV(14), τ PhI(27)
944	0.12	0.58	946	-	γ CHI(69), τ PhI(17)
928	0.37	0.92	930	930	γ CHIII(88)
924	0.14	0.02	-	-	δ CH ₃ (94)
919	35.13	73.06	-	916	δ CH ₂ (24), ν CC(14), δ PhIII(17)

904	11.35	228.00	-	-	$\delta\text{PhIII}(38)$, $\nu\text{CO}(47)$
903	0.48	9.74	-	-	$\nu\text{CC}_3(23)$, $\delta\text{CH}_3(42)$
900	3.36	9.96	-	-	$\delta\text{CH}_2(16)$, $\delta\text{PhIII}(16)$, $\nu\text{CN}(42)$
890	1.48	8.62	-	891	$\nu\text{CC}(49)$, $\delta\text{CH}_3(40)$
852	16.83	6.15	-	855	$\gamma\text{CHIV}(30)$, $\tau\text{PhIV}(10)$, $\tau\text{PhI}(22)$
840	51.12	22.62	842	-	$\delta\text{NO}_2(38)$, $\gamma\text{CHIV}(44)$
829	13.59	2.07	-	-	$\gamma\text{CHI}(36)$, $\tau\text{PhI}(10)$, $\tau\text{PhIII}(33)$
823	53.95	0.17	-	-	$\gamma\text{CHIII}(72)$, $\tau\text{PhIII}(13)$
819	2.10	0.10	-	-	$\gamma\text{CHI}(92)$
818	1.30	1.07	-	-	$\gamma\text{CHIV}(77)$
815	3.90	4.07	-	-	$\nu\text{PhI}(47)$, $\tau\text{PhIV}(18)$, $\delta\text{PhIV}(15)$
805	13.41	2.76	806	808	$\nu\text{CC}_3(44)$, $\delta\text{NO}_2(16)$, $\gamma\text{CHIV}(23)$
801	22.78	0.13	-	-	$\gamma\text{CHIII}(78)$
798	20.20	2.93	796	795	$\delta\text{NO}_2(20)$, $\gamma\text{CHIV}(23)$, $\delta\text{PhIV}(13)$, $\delta\text{PhII}(12)$
781	9.36	23.81	-	778	$\nu\text{PhIV}(52)$, $\delta\text{PhIII}(10)$
745	12.37	3.51	752	750	$\tau\text{PhIV}(22)$, $\delta\text{PhIV}(21)$, $\delta\text{PhII}(20)$
738	1.33	3.62	-	736	$\tau\text{PhI}(50)$, $\gamma\text{CC}(33)$
719	0.07	0.16	722	721	$\tau\text{PhIII}(49)$, $\tau\text{PhII}(27)$
715	2.47	34.66	-	-	$\delta\text{PhI}(35)$, $\delta\text{PhIII}(10)$, $\nu\text{CC}(18)$
703	25.73	3.76	705	702	$\gamma\text{NO}_2(47)$, $\tau\text{PhIV}(22)$
693	14.43	0.50	691	-	$\tau\text{PhII}(27)$, $\tau\text{PhI}(25)$, $\gamma\text{CC}(18)$, $\tau\text{PhIII}(10)$
671	7.71	1.57	-	674	$\tau\text{PhIV}(60)$, $\gamma\text{CN}(10)$, $\gamma\text{CC}(10)$
666	2.54	4.82	663	663	$\delta\text{PhII}(21)$, $\delta\text{PhIV}(13)$, $\tau\text{PhIV}(12)$, $\gamma\text{C=O}(11)$
627	0.41	8.41	627	633	$\delta\text{PhI}(79)$
620	1.41	5.70	-	-	$\delta\text{PhIV}(79)$
610	3.42	0.63	611	609	$\gamma\text{CN}(40)$, $\tau\text{PhIII}(38)$, $\tau\text{PhII}(13)$
602	0.63	2.85	-	598	$\delta\text{PhIII}(27)$, $\delta\text{NO}_2(43)$
581	2.89	0.30	583	-	$\gamma\text{C=O}(26)$, $\delta\text{PhIV}(20)$, $\delta\text{PhIII}(22)$

560	16.42	14.57	557	560	$\delta\text{C}=\text{O}(23)$, $\delta\text{PhII}(30)$, $\tau\text{PhI}(37)$
539	19.72	0.09	-	543	$\tau\text{PhI}(35)$, $\gamma\text{CC}(38)$
528	1.44	2.14	528	-	$\delta\text{PhIII}(31)$, $\delta\text{CC}(29)$, $\delta\text{CC}_3(11)$
522	30.59	7.00	-	-	$\gamma\text{NH}(30)$, $\tau\text{C}=\text{O}(18)$, $\delta\text{PhIII}(10)$
513	8.33	1.56	-	-	$\delta\text{CN}(61)$, $\gamma\text{NH}(10)$
507	28.48	2.93	-	509	$\delta\text{CN}(12)$, $\delta\text{C}=\text{O}(11)$, $\delta\text{PhIII}(10)$, $\gamma\text{NH}(10)$
465	4.70	0.87	468	460	$\tau\text{PhIV}(29)$, $\gamma\text{NO}_2(33)$, $\gamma\text{CC}(20)$
446	0.77	0.54	443	444	$\delta\text{CC}_3(47)$, $\delta\text{CC}(22)$
425	1.25	1.24	425	422	$\tau\text{PhIII}(33)$, $\tau\text{PhII}(41)$
414	1.27	0.26	-	412	$\tau\text{PhIII}(42)$, $\gamma\text{CN}(22)$
404	0.05	0.30	-	-	$\tau\text{PhIV}(83)$
398	0.01	0.06	-	-	$\delta\text{PhI}(81)$
395	0.02	3.09	-	393	$\delta\text{CC}_3(42)$, $\delta\text{PhI}(22)$
378	1.46	1.86	-	-	$\delta\text{CN}(25)$, $\delta\text{PhIV}(21)$
372	2.06	0.11	-	-	$\delta\text{CC}_3(19)$, $\tau\text{RII}(20)$, $\tau\text{RI}(10)$
357	8.84	1.41	-	-	$\delta\text{PhIV}(15)$, $\delta\text{CC}_3(15)$, $\tau\text{PhIV}(29)$
341	0.44	0.56	-	341	$\delta\text{CC}_3(39)$, $\delta\text{CC}(22)$, $\delta\text{CN}(15)$
328	2.34	2.13	-	-	$\delta\text{CC}(30)$, $\delta\text{CN}(10)$, $\tau\text{CH}_3(22)$
320	0.47	2.04	-	319	$\delta\text{CC}_3(60)$
316	1.63	0.78	-	-	$\delta\text{CC}(11)$, $\gamma\text{CN}(11)$, $\delta\text{CN}(15)$, $\tau\text{PhIV}(19)$
313	0.11	0.24	-	308	$\tau\text{CH}_3(84)$
279	0.02	0.11	-	283	$\tau\text{PhIII}(25)$, $\tau\text{PhI}(15)$, $\delta\text{CC}_3(29)$
274	2.24	1.63	-	-	$\delta\text{CC}_3(12)$, $\delta\text{CN}(28)$, $\tau\text{CH}_3(24)$
269	1.79	0.54	-	265	$\tau\text{CH}_3(64)$
253	4.02	3.33	-	255	$\gamma\text{CN}(23)$, $\delta\text{PhI}(20)$
231	0.03	0.86	-	231	$\tau\text{CH}_3(69)$, $\tau\text{PhIII}(11)$
217	4.03	1.13	-	-	$\delta\text{CN}(15)$, $\tau\text{RIII}(23)$, $\tau\text{CH}_3(24)$
213	3.69	0.38	-	-	$\tau\text{PhIII}(28)$, $\delta\text{CN}(12)$, $\tau\text{CH}_3(14)$
194	0.34	0.79	-	192	$\delta\text{CC}(30)$, $\delta\text{CN}(17)$, $\tau\text{PhII}(21)$

182	0.53	2.15	-	-	$\delta\text{CC}_3(18)$, $\gamma\text{CC}(20)$, $\tau\text{PhII}(19)$
171	1.16	1.28	-	-	$\delta\text{PhI}(21)$, $\tau\text{PhIII}(24)$, $\gamma\text{CC}(10)$
120	5.29	0.50	-	-	$\delta\text{CN}(46)$, $\delta\text{CC}(24)$
115	1.40	1.07	-	112	$\delta\text{CH}_2(22)$, $\tau\text{PhIV}(12)$, $\tau\text{PhI}(21)$, $\tau\text{PhII}(14)$
95	1.44	0.31	-	92	$\tau\text{PhI}(18)$, $\tau\text{PhII}(16)$, $\tau\text{NH}(10)$, $\gamma\text{CC}(13)$
65	4.53	0.97	-	66	$\tau\text{PhIV}(23)$, $\gamma\text{CC}(18)$, $\tau\text{CC}_3(12)$, $\tau\text{CC}(11)$
59	0.93	0.63	-	-	$\tau\text{CC}_3(25)$, $\tau\text{CC}(20)$
51	1.02	0.31	-	-	$\tau\text{CN}(40)$, $\tau\text{CC}_3(18)$, $\tau\text{CC}(11)$
48	0.38	1.45	-	-	$\tau\text{CC}_3(41)$, $\gamma\text{CC}(14)$
44	3.08	0.49	-	-	$\tau\text{NH}(23)$, $\delta\text{CC}(19)$, $\tau\text{CH}_2(10)$
36	0.08	2.20	-	-	$\tau\text{CC}(36)$, $\tau\text{CC}_3(28)$
24	0.31	7.15	-	-	$\tau\text{CC}(54)$, $\tau\text{CN}(12)$
20	0.11	1.60	-	-	$\tau\text{CH}_2(24)$, $\tau\text{CC}(16)$, $\gamma\text{CC}(17)$
18	0.42	4.51	-	-	$\tau\text{NH}(30)$, $\tau\text{CC}_3(12)$, $\delta\text{CH}_2(11)$, $\tau\text{C}=\text{O}(10)$
5	0.42	4.42	-	-	$\tau\text{CH}_2(45)$, $\tau\text{C}=\text{O}(10)$

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; PhI-C₁-C₂-C₄-C₈-C₆-C₃; PhII-C₁₁-N₂₂-C₁₃-C₁₂-O₂₁; PhIII-C₁₂-C₁₃-C₁₅-C₁₈-C₁₆-C₁₄,; PhIV-C₃₀-C₃₂-C₃₆-C₃₉-C₃₅-C₃₁.

Table 4

The predicted ^{13}C NMR isotropic chemical shifts (with respect to TMS, all values in ppm)

Atom	σ_{TMS}	B3LYP/6-31G(d) (6D, 7F) σ_{calc}	$\delta_{\text{calc.}} (\sigma_{\text{TMS}} - \sigma_{\text{calc.}})$
C1	196.852	43.8472	153.0048
C2	196.852	71.1689	125.6831
C3	196.852	69.1003	127.7517
C4	196.852	67.1025	129.7495
C6	196.852	68.9472	127.9048
C8	196.852	71.4176	125.4344
C11	196.852	33.396	163.456
C12	196.852	49.6439	147.2081
C13	196.852	53.7099	143.1421
C14	196.852	85.2191	111.6329
C15	196.852	88.3154	108.5366
C16	196.852	80.3121	116.5399
C18	196.852	60.3556	136.4964
C25	196.852	34.1139	162.7381
C27	196.852	143.7138	53.1382
C30	196.852	54.037	142.815
C31	196.852	66.514	130.338
C32	196.852	67.5381	129.3139
C35	196.852	71.9798	124.8722
C36	196.852	72.5718	124.2802
C39	196.852	48.8288	148.0232
C43	196.852	152.843	44.009
C44	196.852	158.0525	38.7995
C48	196.852	158.0574	38.7946
C52	196.852	161.6107	35.2413

The predicted ^1H NMR isotropic chemical shifts (with respect to TMS, all values in ppm)

Atom	σ_{TMS}	B3LYP/6-31G(d) (6D, 7F) σ_{calc}	$\delta_{\text{calc.}} (\sigma_{\text{TMS}} - \sigma_{\text{calc.}})$	Experimental
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H5	32.7711	24.9201	7.851	7.62
H7	32.7711	24.7457	8.0254	7.64
H9	32.7711	23.8991	8.872	7.66
H10	32.7711	24.2268	8.5443	7.65
H17	32.7711	25.0788	7.6923	7.73
H19	32.7711	25.6902	7.0809	8.14
H20	32.7711	23.6076	9.1635	7.53
H24	32.7711	26.2319	6.5392	10.49
H28	32.7711	28.4819	4.2892	3.89
H29	32.7711	29.444	3.3271	3.89
H33	32.7711	24.0518	8.7193	8.10
H34	32.7711	25.1644	7.6067	8.12
H37	32.7711	24.0609	8.7102	8.24
H38	32.7711	24.1559	8.6152	8.22
H45	32.7711	30.6317	2.1394	1.33
H46	32.7711	31.0204	1.7507	1.33
H47	32.7711	31.0224	1.7487	1.33
H49	32.7711	31.0025	1.7686	1.33
H50	32.7711	30.6561	2.115	1.33
H51	32.7711	30.0164	2.7547	1.33
H53	32.7711	31.1376	1.6335	1.33
H54	32.7711	30.6253	2.1458	1.33
H55	32.7711	30.6545	2.1166	1.33

Table 5

Second order perturbation theory analysis of Fock matrix in NBO basis corresponding to the intra-molecular bonds of the title compound

Donor(i)	Type	ED/e	Acceptor(j)	Type	ED/e	E(2) ^a	E(j) ^a -E(i) ^b	F(i,j) ^c
C11-O21	σ	1.98891	C4-C8	σ^*	0.02188	1.58	1.47	0.043
-	-	-	C12-C14	σ^*	0.02149	5.01	1.48	0.077
C11-N22	σ	1.98572	C6-C8	σ^*	0.02229	1.43	1.44	0.040
-	-	-	C8-C11	σ^*	0.03523	2.80	1.36	0.055
-	-	-	C13-C15	σ^*	0.02175	5.98	1.45	0.083
-	-	-	C13-N22	σ^*	0.01932	1.01	1.33	0.033
-	π	1.86221	C4-C8	π^*	0.38284	7.08	0.36	0.048
-	-	-	C12-C13	π^*	0.46317	16.55	0.34	0.074
C12-C13	σ	1.97526	C8-C11	σ^*	0.03523	1.45	1.19	0.037
-	-	-	C12-C14	σ^*	0.02149	4.49	1.28	0.068
-	-	-	C13-C15	σ^*	0.02175	3.76	1.28	0.062
-	π	1.59893	C11-N22	π^*	0.31245	10.49	0.27	0.049
-	-	-	C14-C16	π^*	0.33871	20.06	0.29	0.069
-	-	-	C15-C18	π^*	0.38939	18.62	0.28	0.065
C15-C18	π	1.69521	C12-C13	π^*	0.46317	20.31	0.29	0.071
C25-O26	π	1.99099	C27-C30	σ^*	0.02142	1.10	0.77	0.026
C25-C27	σ	1.97057	C18-N23	σ^*	0.02927	4.52	1.05	0.061
-	-	-	C30-C32	σ^*	0.02203	1.12	1.20	0.033
-	-	-	C30-C32	π^*	0.33847	2.24	0.66	0.037
N23-C25	σ	1.99007	C15-C18	σ^*	0.01664	1.31	1.41	0.038
-	-	-	C18-N23	σ^*	0.02927	1.91	1.25	0.044
C39-N40	σ	1.98964	C31-C35	σ^*	0.01467	1.49	1.38	0.041
-	-	-	C32-C36	σ^*	0.01462	1.53	1.37	0.041
N40-O41	π	1.98640	C36-C39	π^*	0.37809	4.21	0.46	0.043
-	-	-	N40-O41	π^*	0.62292	7.43	0.32	0.052
LPO21	σ	1.96933	C11-N22	σ^*	0.01746	5.00	1.16	0.068
-	-	-	C12-C13	σ	0.04115	3.59	1.13	0.057

LPO21	π	1.73156	C11-N22	π^*	0.31245	34.63	0.35	0.099
-	-	-	C12-C13	π^*	0.46317	23.55	0.36	0.087
LPN22	σ	1.91195	C11-O21	σ^*	0.06175	14.15	0.69	0.089
-	-	-	C12-C13	σ^*	0.04115	6.16	0.91	0.068
LPN23	σ	1.66240	C15-C18	π^*	0.38939	30.43	0.29	0.086
-	-	-	C25-O26	π^*	0.28955	63.10	0.28	0.120
LPO26	σ	1.97337	N23-C25	σ^*	0.07566	2.15	1.14	0.045
-	-	-	C25-C27	σ^*	0.06795	1.98	1.03	0.041
LPO26	π	1.85607	N23-C25	σ^*	0.07566	26.23	0.71	0.124
-	-	-	C25-C27	σ^*	0.06795	21.19	0.61	0.103
LPO41	σ	1.98105	C39-N40	σ^*	0.10773	4.25	1.07	0.062
-	-	-	N40-O42	σ^*	0.05655	2.48	1.22	0.050
LPO41	π	1.89690	C39-N40	σ^*	0.10773	13.28	0.56	0.077
-	-	-	N40-O42	σ^*	0.05655	19.44	0.72	0.107
LP042	σ	1.98107	C39-N40	σ^*	0.10773	4.25	1.07	0.062
-	-	-	N40-O41	σ^*	0.05623	2.47	1.22	0.049
LPO42	π	-	C39-N40	σ^*	0.10773	13.24	0.56	0.077
-	-	1.89710	N40-O41	σ^*	0.05623	19.37	0.72	0.106
LPO42	n	1.44578	N40-O41	π^*	0.62292	164.96	0.15	0.141

^aE(2) means energy difference of hyper-conjugative interactions (stabilization energy in kJ/mol)

^bEnergy difference (a.u.) between donor and acceptor i and j NBO orbitals

^cF(i,j) is the Fock matrix elements (a.u.) between i and j NBO orbitals

Table 6

NBO results showing the formation of Lewis and non-Lewis orbital

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ C11-N22	1.98572	41.13	58.87	0.6413(sp ^{1.80})C+	35.68	64.32
-	-0.8692	-	-	0.7673(sp ^{1.74})N	36.57	63.43
σ C12-C13	1.97526	49.96	50.04	0.7068(sp ^{1.85})C+	35.12	64.88
-	-0.69912	-	-	0.7074(sp ^{2.09})C	32.30	67.70
π C11-N22	1.86221	40.06	59.94	0.6329(sp ^{1.00})C+	0.00	100.0
-	-0.32210	-	-	0.7742(sp ^{1.00})N	0.00	100.0
π C12-C13	1.59893	50.71	49.29	0.7121(sp ^{1.00})C+	0.00	100.0
-	-0.26334	-	-	0.7021(sp ^{1.00})C	0.00	100.0
σ C11-O21	1.98891	30.75	69.25	0.5546(sp ^{2.99})C+	25.07	74.92
-	-0.89517	-	-	0.8321(sp ^{2.26})O	30.64	69.36
σ C12-C13	1.97526	49.96	50.04	0.7068(sp ^{1.85})C+	35.12	64.88
-	-0.69912	-	-	0.7074(sp ^{2.09})C	32.30	67.70
π C15-C18	1.69521	50.95	49.05	0.7138(sp ^{1.00})C+	0.00	100.0
-	-0.26276	-	-	0.7003(sp ^{1.00})C	0.00	100.0
π C25-O26	1.99099	30.14	69.86	0.5490(sp ^{99.99})C+	0.12	99.89
-	-0.3787	-	-	0.8358(sp ^{102.02})O	0.16	99.85
σ N23-C25	1.99007	63.35	36.65	0.7959(sp ^{1.69})N+	37.15	62.85
-	-0.84588	-	-	0.6054(sp ^{2.11})C	32.08	67.92
σ C25-C27	1.97057	47.94	52.06	0.6924(sp ^{1.83})C+	35.32	64.68
-	-0.63948	-	-	0.7215(sp ^{2.97})C	25.20	74.80
σ C39-N40	1.98964	37.75	62.25	0.6144(sp ^{3.12})C+	24.22	75.78
-	-0.80714	-	-	0.7890(sp ^{1.78})N	35.98	64.02
σ N40-O41	1.99585	48.47	51.53	0.6962(sp ^{2.12})N+	31.97	68.03
-	-1.09100	-	-	0.7179(sp ^{2.91})O	25.56	74.44
π N40-O41	1.98640	39.89	60.11	0.6316(sp ^{1.00})N+	0.00	100.0
-	-0.45027	-	-	0.7753(sp ^{1.00})O	0.00	100.0
n1O21	1.96933	-	-	sp ^{1.65}	37.67	62.33
-	-0.59151	-	-	-	-	-
n2O21	1.73156	-	-	sp ^{1.00}	0.00	100.0

-	-0.33848	-	-	-	-	-
n1N22	1.91195	-	-	sp ^{2.12}	32.13	67.87
-	-0.36966	-	-	-	-	-
n1N23	1.66240	-	-	sp ^{1.00}	0.00	100.0
-	-0.27325	-	-	-	-	-
n1O26	1.97337	-	-	sp ^{0.73}	57.92	42.08
-	-0.68247	-	-	-	-	-
n2O26	1.85607	-	-	sp ^{1.00}	0.00	100.0
-	-0.25665	-	-	-	-	-
n1O41	1.98105	-	-	sp ^{0.34}	74.45	25.55
-	-0.79162	-	-	-	-	-
n2O41	1.89690	-	-	sp ^{99.99}	0.10	99.90
-	-0.28803	-	-	-	-	-
n1O42	1.98102	-	-	sp ^{0.34}	74.48	25.53
-	-0.79187	-	-	-	-	-
n2O42	1.89710	-	-	sp ^{99.99}	0.10	99.90
-	-0.28820	-	-	-	-	-
n3O42	1.44578	-	-	sp ^{1.00}	0.00	100.0
-	-0.27160	-	-	-	-	-

^aED/e in a.u

Table 7

The binding affinity values of different poses of the title compound predicted by Autodock Vina.

<u>Mode</u>	<u>Affinity (kcal/mol)</u>	<u>Distance from best mode (Å)</u>	
		<u>RMSD l.b.</u>	<u>RMSD u.b.</u>
-	-		
1	-8.3	0.000	0.000
2	-7.7	5.683	13.904
3	-7.5	3.065	4.847
4	-7.4	18.551	20.182
5	-7.2	6.379	12.809
6	-7.2	20.626	22.377
7	-7.2	20.510	22.079
8	-7.2	19.079	20.210
9	-7.1	6.817	13.517

Fig.1 FT-IR spectrum of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.2 FT-Raman spectrum of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.3 Optimized geometry of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

Fig.4 HOMO-LUMO plots of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl) benzoxazole

Fig.5 MEP plot of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole

206.60 ALIE [kcal/mol] 354.88

Fig.6 ALIE surface of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole molecule

Fig.7 Fukui functions a) f^+ and b) f^- of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl) benzoxazole molecule, Purple colour is positive colour, while red colour is the negative one

Bond	BDE [kcal/mol]
1	115.65
2	118.73
3	119.41
4	120.92
5	118.10
6	99.10
7	88.15
8	118.98
9	121.44
10	107.26
11	126.90
12	91.79
13	81.22
14	68.81
15	68.83
16	89.05
17	95.50
18	72.48

Fig.8 BDEs of all single acyclic bonds of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl) benzoxazole molecule

Fig.9 RDFs of atoms of 5-[(4-nitrophenyl)acetamido]-2-(4-tert-butylphenyl)benzoxazole with pronounced interactions with: a) carbon atoms and b) non-carbon atoms

Fig.10 Schematic for the docked conformation of active site of title compound at CDK inhibitors

Fig.11 The docked protocol reproduced the co-crystallized conformation with H-bond (green), p-cation (brown), p-sigma (violet), alkyl (pink) and H-bond receptor surface shown

Scheme 1. Synthesis of compound 6

Highlights

- * IR and Raman spectra were measured
- * Exhibits significant antibacterial activity
- * ALI, BDE, RDF have been discussed in detail
- * Exhibits inhibitory activity against CDK inhibitors