Molecular structure, chemical reactivity and molecular docking studies of 1,7,8,9-
tetrachloro-10,10-dimethoxy-4-[3-(4-benzylpiperazine-1-yl)propyl]-4-azatricyclo[5.2.1.0^{2,6}]
dec-8-ene-3, 5-dione.

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Abstract

1,7,8,9-tetrachloro-10,10-dimethoxy-4-[3-(4-benzylpiperazine-1-yl)propyl]-4-
azatricyclo[5.2.1.0^{2,6}] dec-8-ene-3, 5-dione (TCDBPAD) have been calculated theoretically to
obtain optimized geometry, vibrational frequencies and corresponding vibrational assignments.
Charge transfer within the molecule was evaluated using HOMO and LUMO analysis. By hyper-
conjugative interaction and charge delocalisation which can be analysed using NBO analysis, we
can understand about the stability of the molecule. By using DFT method Molecular electrostatic
potential (MEP) was calculated. First hyperpolarizability values are calculated in order to check
the non-linear optical activity. Using MD simulations, we have visualized the ALIE and Fukui functions. The degradation property of compound in presence of water was evaluated using RDF curves. By solubility parameter we have identified suitable excipient for the title compound. Molecular docking studies proved that the title compound can be used for the treatment of Cardiovascular and Cerebrovascular diseases.

**Keywords:** Azatricyclo, FT-IR, FT-Raman, DFT, ALIE, RDF, Solubility, Molecular docking.

1. Introduction

The Piperazines or cyclizines is a cyclic-organic compound that consists of a six membered ring containing two opposing nitrogen atoms. Piperazine exists as small alkaline deliquescent crystals and was introduced as a solvent for uric acid. Inside the body the drug is partly oxidized and partly eliminated unchanged. Outside the body, piperazine has an ability to dissolve uric acid and producing a soluble urate [1,2]. Piperazine derivatives used as nucleoside reverse transcriptase inhibitors for the treatment of HIV Virus [3]. Aryl piperazine derivatives exhibit a wide class of biological activities such as antiarrhythmic [4,5], anticancer [6,7], antiviral [8,9], antioxidative [10], and antibacterial [11]. Compounds of this type show high affinity for dopaminergic [12], α1-adrenergic [13], and serotonergic receptors [14,15]. A large class of aryl piperazine derivatives of 1,7,8,9-Tetrachloro-10,10-dimethoxy-4-azatricyclo [5.2.1.0²,6] dec-8-ene-3,5-dione were evaluated in vitro against agents of different virus classes, such as the single-stranded RNA+ viruses, Yellow Fever virus and Bovine viral diarrhoea virus, both belonging to the Flaviviridae, a HIV-1 (Retrovirus), and HBV (Hepadnavirus) [16]. Complexes of diarylpiperidin-4-one were found as the new variety of antimicrobial agents with activity against pathogenic bacterial species and fungal strains [17]. In order to analyse the effect of halogen substitution, in the parent molecule, the position of four chlorine atoms are replaced by bromine, and fluorine atoms respectively and which are designated as TCDBPAD, TCDBPAD Br and TCDBPAD F. The title compound was spectroscopically characterized by employing FT-IR and FT-Raman studies. To understand about the stability, hardness and other parameters we have calculated the HOMO-LUMO gap using DFT calculations. ALIE and Fukui functions were plotted against electron density to identify the sites of electrophilic attack. The degradation of
compound by hydrolysis was examined using the RDF curves [18]. To find out a suitable excipient we have calculated the solubility parameter by MD simulations. Thus the aim of our study was to find out the most prominent reactive sites, degradation property, suitable excipient and carrying out the docking studies.

2. Experimental Details

1,7,8,9-Tetrachloro-10,10-dimethoxy-4-azatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione (1) was synthesized (scheme 1) as previously described [19]. 1,7,8,9-Tetrachloro-4-(3-chloropropyl)-10,10-dimethoxy-4-azatricyclo[5.2.1.0^2,6]dec-8-ene-3,5-dione (2) was prepared as follows: A mixture of imide 1 (0.5 g, 0.00138 mol), 1-bromo-3-chloropropane (0.6 g, 0.00415 mol) and anhydrous K_2CO_3 (0.5 g, 0.0036 mol) in acetonitrile (50 mL) was refluxed for 8 h. The inorganic precipitate was filtered off, the solvent was evaporated [16]. The title compound, 1,7,8,9-tetrachloro-10,10-dimethoxy-4-[3-(4-benzylpiperazine-1-yl)propyl]-4-azatricyclo[5.2.1.0^2,6] dec-8-ene-3, 5-dione (3) was prepared as follows: A mixture of compound 2 (0.3 g, 0.0007 mol), 1-benzylpiperazine (0.21 g, 0.0013 mol), anhydrous K_2CO_3 (0.3 g, 0.0022 mol) and KI (0.2 g, 0.0012 mol) was dissolved in acetonitrile (50 mL) and refluxed for 30 h. The solvent was evaporated, then the residue was purified by column chromatography (eluent: CH_2Cl_2-CH_3OH, 95:5) [16]. Yield 75%, m.p. 245.5-246 °C. Anal. Calculated: 48.06% C, 4.71% H, 7.01% N Found: 48.03% C, 4.59% H, 6.80% N.

The FT-IR spectrum (Fig.1) was recorded using KBr pellets on a DR/Jasco FT-IR 6300 spectrometer. The FT-Raman spectrum (Fig. 2) was obtained on a Bruker RFS 100/s, Germany. For excitation of the spectrum the emission of Nd:YAG laser was used, excitation wavelength 1064 nm, maximal power 150 mW, measurement on solid sample.
Scheme 1: Pathway of compound synthesis

3. Computational Details

Calculations of the title compound were carried with using the Gaussian09 program [20] using the B3LYP/6-31G(d') basis set to predict the molecular structure and wavenumbers in the gaseous phase and a scaling factor of 0.9613 had to be used for obtaining a considerably better agreement with the experimental data [21]. The structural parameters corresponding to the optimized geometry of the title compound (Fig. 3) are given in Table 1. The assignments of the calculated wavenumbers are done using GAR2PED [22] and Gauss view software [23]. Jaguar 9.0 and Schrodinger materials science suite 2015-4 was used for the investigation of the reactivity of the compound [24]. DFT calculations with the Jaguar were carried out using B3LYP exchange correlation functional, with 6-311++G(d,p), 6-31+G(d,p), 6-311G(d,p) basis set for the calculations of ALIE, Fukui functions and BDEs, respectively. Desmond program was used for MD simulations which was performed by OPLS 2005 force field [25], with simulation time set to 10 ns. The pressure was set at 1.0325 bar while temperature was set to 300 K. Cut-off radius was set to 12 Å, while the modelled system was of isothermal-isobaric (NPT) ensemble class. For the solvent of SPC model [26] was used here.
4. Result and Discussion

4.1 Geometrical Parameters

No data is available regarding the X-ray crystallography of the molecule, to the best our knowledge. Moreover, the reported structural parameters of the parental molecule significantly correlate with our theoretical predictions attesting the authenticity of our results.

In the following discussion, the cyclohexene ring is designated as RI, the imido fragment ring is designated as RII, piperazine ring is designated as RIII, Phenyl ring is designated as RIV.

The bond angles of imido fragment of title compound give theoretically as C₁₆-N₁₅-C₁₃ = 114.0, O₁₈-C₁₃-N₁₅ = 124.6, O₁₈-C₁₃-C₄ = 127.4, N₁₅-C₁₃-C₄ = 107.9, C₁₃-C₄-C₅ = 105.0, C₁₃-C₄-H₁₀ = 107.3, C₅-C₄-H₁₀ = 114.2, C₁₆-C₅-H₁₂ = 107.6, C₄-C₅-H₁₂ = 114.1, O₁₇-C₁₆-N₁₅ = 124.7, O₁₇-C₁₆-C₅ = 127.3, N₁₅-C₁₆-C₅ = 107.9° respectively, whereas the reported values of similar derivatives are 114.7, 124.0, 128.5, 107.4, 105.8, 112.3, 113.8, 113.3, 113.1, 126.3, 129.2, 106.5° and 111.0, 126.1, 128.4, 105.5, 109.9, 115.0, 136.0, 118.0, 118.0, 123.7, 131.4, 104.9° [27]. Conley et al. [27] reported the dihedral angles, C₁₆-N₁₅-C₁₃-O₁₈ = 179.5, C₁₆-N₁₅-C₁₃-C₄ = 4.0, O₁₈-C₁₃-C₄-C₅ = 177.5, N₁₅-C₁₃-C₄-C₅ = 0.5, C₁₃-C₄-C₅-C₁₆ = 1.7, C₁₃-N₁₅-C₁₆-C₅ = 5.1, C₄-C₅-C₁₆-O₁₇ = 176.7, C₄-C₅-C₁₆-N₁₅ = 4.0° whereas for the title compound the corresponding values are 177.3, 6.7, 177.6, 1.7, 3.1, 8.8, 176.5 and 7.0° respectively. Pinho e Melo et al. [28] reported the bond lengths N₁₅-C₁₆ = 1.3654, N₁₅-C₁₃ = 1.4484 Å, bond angles C₁₆-N₁₅-C₁₃ = 116.8, C₁₆-N₁₅-C₁₉ = 121.6, C₁₃-N₁₅-C₁₉ = 121.6, C₅-C₁₆-N₁₅ = 121.9, N₁₅-C₁₃-C₄ = 107° which are in agreement with our calculated values. Lee and Swager [29] reported the bond lengths C₁₆-O₁₇ = 1.1954, C₁₃-O₁₈ = 1.2054, N₁₅-C₁₆ = 1.3776, C₁₃-N₁₅ = 1.3765 Å and the bond angles C₅-C₁₆-N₁₅ = 106.3, C₄-C₁₃-N₁₅ = 106.5°. The B3LYP calculations give the bond lengths within the imido fragment as C₁₆-O₁₇ = 1.2095, C₁₃-O₁₈ = 1.2077, N₁₅-C₁₆ = 1.3917, C₁₃-N₁₅ = 1.3933, C₁₃-C₄ = 1.5337, C₁₆-C₅ = 1.5373, C₅-C₄ = 1.5534 Å and bond angles C₅-C₁₆-N₁₅ = 107.9, C₄-C₁₃-N₁₅ = 107.9°. Conley et al. [27] reported the corresponding values as 1.2025, 1.3985, 1.2104, 1.4054, 1.4865, 1.5155, 1.555 Å and 1.1974, 1.3995, 1.2004, 1.3824, 1.4866, 1.4826, 1.3436 Å for different similar derivatives. The N₁₅-C₁₉ bond length (1.4617 Å) is longer than N₁₅-C₁₃ (1.3933 Å) and N₁₅-C₁₆ (1.3917 Å) bond lengths. This indicates, as expected, a delocalized p-
electron system along the imide part of the molecule (O18-C13-N15-C16-O17) as reported by Bartkowska et al. [30]. Berendsen et al. [26] reported the bond lengths, C13-O18 = 1.2032, N15-C13 = 1.3913, C13-C4 = 1.5193, C4-C5 = 1.5453, C16-O17 = 1.2073, N15-C16 = 1.3880 Å and the bond angles, N15-C19-C28 = 111.3, O18-C13-N15 = 124.3, O18-C13-C4 = 127.8, N15-C13-C4 = 107.8, O17-C16-N15 = 127.2, N15-C16-C5 = 107.0, C16-N15-C13 = 114.2, C16-N15-C19 = 123.8 and C13-N15-C19 = 121.7° whereas the corresponding values in the present case are 1.2077, 1.3933, 1.5337, 1.5534, 1.2095, 1.3917 Å and 113.0, 124.6, 127.4, 107.9, 124.7, 107.9, 114.0, 123.3, 122.4°. For the title compound the C4-H10, C5-H12 bond lengths are 1.0945, 1.0948 Å respectively, whereas reported values are 0.9600, 0.9601 Å [27]. The cyclohexene ring fragment is a sterically strained system. Presumably, this is the reason for elongation of skeletal CC bonds, C1-C2, C2-C3, C3-C4, C5-C6, and C6-C1. The CC bond lengths in the five member ring (C5-C16, C4-C13) are elongated to a lesser extent. These may be explained by change of the substitution pattern in the nitrogen containing five member rings as reported by Tarabara et al. [31]. The methoxy groups, O14-C11-H23, 24, 27 and O9-C8-H20, 21, 22 inclined almost equally with respect to the other parts of the six member ring. The bond angles C1-C6-C7, C5-C6-C7, C2-C3-C7, C4-C3-C7, C6-C1-C2 and C4-C3-C2 are respectively 99.5, 102.3, 99.6, 102.8, 107.9 and 104.7°. In addition, the declination of the five member ring from the cyclohexene ring are given by the angles C6-C5-C16 and C3-C4-C13 by 118.2 and 118.8° which are almost equal as reported in the literature [31]. The conjugation in the imido group is essentially disturbed; the torsion angles C13-N15-C16-C5, C16-N15-C13-C4 are 8.8, -6.7° and the C13-N15 and C16-N15 bond lengths are elongated to 1.3933, 1.3917 Å relative to the average value 1.3925 Å [32]. For the cyclohexene ring, Manohar et al. [33] reported the bond lengths C1-C2 = 1.3194, C1-C6 = 1.5174, C6-C5 = 1.5523, C6-C7 = 1.5484, C5-C4 = 1.5353, C4-C3 = 1.5543, C3-C7 = 1.5473, C3-C2 = 1.5144 Å and the corresponding bond lengths of the title compound are 1.3421, 1.5304, 1.5638, 1.5810, 1.5534, 1.5711, 1.5854, 1.5265 Å. The bond angles reported by Manohar et al. [33] are C3-C4-C5 = 102.9, C3-C2-C1 = 107.5, C3-C7-C6 = 92.4, C2-C3-C4 = 107.2, C6-C5-C4 = 103.1, C6-C1-C2 = 107.7, C5-C6-C1 = 106.8, C2-C3-C7 = 99.52, C4-C3-C7 = 101.1, C5-C6-C7 = 101.1, C1-C6-C7 = 99.4Å whereas the corresponding calculated (DFT) values of the title compound are 103.1, 107.3 91.4, 104.7, 103.1, 107.9, 105.7, 99.6, 102.8, 102.3, 99.5°. In the present case, the oxygen atoms O17 and O18 are equally inclined from the N15 atom given by the angles O17-C16-N15, O18-C13-N15 (124.6°) and from C4 and C5 atoms given by the angles O17-C16-C5, O18-C13-C4 (127.3°) as reported in the literature [34].
There are four types of CC bonds involved in the title compound, strained CC bonds of R1, RII, RIII, RIV, propyl group and of the carbon-carbon bridge. The CC bond lengths are in the range 1.5265-1.5711, 1.5337-1.5534 and 1.5340,1.5342 Å, in R1, RII, propyl group, 1.5854, 1.5810 Å in the carbon-carbon bridge and 1.5255 in benzyl fragment respectively. The CH bond lengths are calculated as Cα-Hα = 1.0945 and Cβ-Hβ = 1.0948 Å. The CH bond lengths are in the range 1.0950-1.1126 Å for the bridging CH2 groups, and for the CH3 groups, CH bond lengths are in the range of 1.0931-1.0957 Å. The optimized carbon-carbon bridge angles C3-C7-C6 = 91.4° is similar to the structures reported by Manohar et al. [33]. The propyl group is tilted from the RII, as is evident from torsion angles, C5-C16-N15-C19 (177.1°), C16-N15-C19-C28 (92.2°), C4-C13-N15-C19 (179.2°) and C13-N15-C19-C28 (81.5°). The double bonds C16-O17 and C13-O18 are conjugated with the p-system of the RII, with the torsion angles O17-C16-N15-C13, C16-N15-C13-C4 being 174.6, 6.7° and O18-C13-N15-C16, C13-N15-C16-C5 being 177.3, 8.8° respectively as reported by Kasyan et al. [35]. At N15 position, the bond angles C16-N15-C19 = 123.3, C13-N15-C19 = 122.4 and C16-N15-C13 = 114.0° and this asymmetry of angles reveal the steric repulsion of the atoms H26, H25 and O17, O18 [35]. For the piperazine ring, El-Emam et al. [36] reported the bond lengths N38-C40 = 1.4650, N38-C39 = 1.4630, C39-C46 = 1.5140, N47-C45 = 1.4580, N47-C46 = 1.4710, C40-C45 = 1.5110 Å and the corresponding bond lengths of the title compound are 1.4714, 1.4574, 1.5400, 1.4540, 1.4646, 1.5438 Å respectively. The DFT calculations give the bond angles within the piperazine ring N38-C39-C46 = 110.2, N38-C40-C45 = 111.6, N47-C45-C40 = 109.5, N47-C46-C39 = 110.8, C45-N47-C46 = 112.3°. El-Emam et al. [36] reported the corresponding values as 110.0, 109.7, 109.7, 110.0 and 110.0° for different similar derivatives. Gao et al. [37] reported the dihedral angles C40-N38-C39-C46 = 55.3, C45-N47-C46-C39 = 57.6, N38-C39-C46-N47 = 56.3, C46-N47-C45-C40 = 57.7, C39-N38-C40-C45 = 55.3, N47-C45-C40-N38 = 55.9° which in agreement with our calculated values.

4.2 IR and Raman Spectra

The calculated (scaled) wavenumbers observed IR, Raman bands and assignments are given in Table. 2. The assignments of the benzene ring vibrations are made by referring [38] the case of benzene derivatives with mono substitution as summarized by Roeges. According to Roeges, the CH stretching modes for mono substituted benzene are found in the region 3105-3000 cm⁻¹ [38].
For the title compound, the bands observed at 3069 cm⁻¹ in the IR spectrum and 3068, 3053 cm⁻¹ in the Raman spectrum are assigned as CH stretching mode of the phenyl ring. The calculated (DFT) values are at 3078, 3066, 3058, 3046 and 3044 cm⁻¹ [38]. The bands observed at 1621, 1477, 1438 and 1307 cm⁻¹ in the IR spectrum and at 1610 and 1573 cm⁻¹ in the Raman spectrum are assigned as νIV ring stretching modes. Theoretically these modes are assigned at 1598, 1579, 1479, 1437 and 1309 cm⁻¹. These vibrations are expected in the region 1620-1300 cm⁻¹ [38]. For the title compound, the ring breathing mode of phenyl ring is found at 979 cm⁻¹ theoretically [38]. The bands observed at 1140, 1065 cm⁻¹ in the IR spectrum and 1161, 1014 cm⁻¹ in the Raman spectrum are assigned as the in-plane bending vibrations of CH modes of phenyl ring. DFT calculations give these modes at 1164, 1161, 1140, 1068 and 1016 cm⁻¹. For the title compound, the bands at 921, 891, 828 cm⁻¹ in the IR spectrum and 930, 893, 824, 735 cm⁻¹ in the Raman spectrum are assigned as the out-of-plane CH deformations of the phenyl ring. The υCH bands are found theoretically at 950, 924, 893, 828 and 731 cm⁻¹. In aromatic methoxy compounds, υasCH₃ bands are expected in the region [38] 2985 ± 20 and 2955 ± 20 cm⁻¹ and the symmetrical stretching mode υsCH₃ is expected in the range 2845 ± 45 cm⁻¹ in which all the three CH bonds extend and contract in phase [38]. For the title compound, corresponding calculated wavenumbers are at 3048, 3035, 3034, 3019 cm⁻¹ as υsCH₃ and 2952, 2941 cm⁻¹ for υsCH₃ vibrations. Experimentally υasCH₃ band is assigned at 3030 cm⁻¹. With methyl esters the overlap of the regions in methyl asymmetrical deformations are active (1465 ± 10 and 1460 ± 15 cm⁻¹) and is quite strong, which leads to many coinciding wavenumbers [38]. This is obvious, not only for the asymmetric deformation, but also for the symmetric deformation [38] mostly displayed in the range 1450 ± 20 cm⁻¹. The intensity of these absorptions is only weak to moderate. The DFT calculations give the deformation modes of CH₃ at 1474, 1465, 1459, 1453, 1437, 1422 cm⁻¹ for the title compound. The bands observed at 1453, 1418 cm⁻¹ in the Raman spectrum are assigned as the deformation bands of the methyl group. The methyl rocking vibration [38] are expected at 1190 ± 45 cm⁻¹. The second methyl rock [38] absorb at 1150 ± 30 cm⁻¹. The bands at 1191, 1178, and 1133 cm⁻¹ theoretically were assigned as rocking modes of the methyl group. These modes are observed at 1178 cm⁻¹ in the IR spectrum. Methoxy groups attached to an aromatic ring give CO stretching modes in the range 1200-900 cm⁻¹ [39]. The DFT calculation gives CO stretching vibrations at 1167, 1143, 1091, 1031, 1005, 989, 970 and 947 cm⁻¹. The bands observed at 1087, 1004, 969, 943 cm⁻¹ in the IR spectrum and at 1088, 997,
973, 948 cm\(^{-1}\) in the Raman spectrum are assigned as \(\nu\)CO stretching vibrations. Renjith et al. [40] reported the asymmetric and symmetric \(\nu\)CO stretching vibrations in the range 1145, 1065 cm\(^{-1}\) and 961-947 cm\(^{-1}\). Castaneda et al. reported the methoxy vibrations at 1252, 1190, 1172, 1028 and 1011 cm\(^{-1}\) [41]. The C=O stretching frequency appears strongly in the IR spectrum in the range 1600-1700 cm\(^{-1}\) because of its large change in dipole moment. The carbonyl group vibrations give rise to characteristics bands in vibration spectra and its characteristic frequency used to study a wide range of compounds. The intensity of these bands can increase owing to conjugation or formation of hydrogen bonds [42,43]. The carbonyl band of cyclic imides is shifted to higher wavenumber if the ring is strained [43]. The carbonyl groups in the imide fragment give rise to bands [43,44] in the region of 1790-1720 cm\(^{-1}\). For the title compound, the C=O stretching bands are observed at 1766, 1698 cm\(^{-1}\) in the IR spectrum, 1788, 1727 cm\(^{-1}\) in the Raman spectrum and at 1786, 1728 cm\(^{-1}\) theoretically (DFT). The CC vibrations in RI and RII are calculated at 1135, 1100 and 1052 cm\(^{-1}\) theoretically and in between 1137-1054 cm\(^{-1}\) experimentally. Renjith et al. reported these values in between 1093-962 cm\(^{-1}\) theoretically, at 1011, 999, 964 cm\(^{-1}\) in the Raman spectrum [40]. The CN stretching modes are reported [45] in the range 1300-1100 cm\(^{-1}\). Silverstein et al. assigned CN stretching absorption in the region 1382-1266 cm\(^{-1}\) for aromatic amines [46]. In the present case, the \(\nu\)CN stretching modes to C\(_{13}\)-N\(_{15}\), C\(_{16}\)-N\(_{15}\), C\(_{19}\)-N\(_{15}\), C\(_{31}\)-N\(_{38}\) and C\(_{63}\)-N\(_{47}\) are observed at 1347, 1151, 1121 cm\(^{-1}\) in the IR spectrum 1340, 1121 cm\(^{-1}\) in the Raman spectrum and at 1348, 1339, 1144, 1127, 1107 cm\(^{-1}\) theoretically. Kasyan reported the \(\nu\)CN stretching in the region 1350-1100 cm\(^{-1}\) [47]. For bridging methylene groups, the CH\(_2\) (at C\(_{19}\), C\(_{28}\), C\(_{31}\), C\(_{63}\)) vibrations are observed in the region of 3000-2800, 1400-1200, 1150-875 and 850-600 cm\(^{-1}\) [48]. The vibrations of these CH\(_2\) groups (the asymmetric stretch \(\nu_a\)CH\(_2\), symmetric stretch \(\nu_s\)CH\(_2\), the scissoring vibration and wagging vibration) appear in the regions of 3005-2940, 2940-2870, 1480-1420 and 1380-1320 cm\(^{-1}\) respectively [38,39,49]. These bands are observed at 2989, 2954, 2781 cm\(^{-1}\) in the IR spectrum, 3016, 2988, 2961, 2792 cm\(^{-1}\) in the Raman spectrum and at 3018, 2991, 2962, 2953, 2947, 2930, 2910, 2782 cm\(^{-1}\) theoretically (DFT) for the title compound respectively. According to literature [46] scissoring mode of the CH\(_2\) group give rise to characteristic band near 1465 cm\(^{-1}\) in IR and Raman spectra. These modes are unambiguously correlated with the strong bands in the region of 1449-1376 cm\(^{-1}\) observed experimentally and theoretically these bands are assigned in between 1464-1378 cm\(^{-1}\). The twisting and rocking vibrations of the CH\(_2\) group appear in the
region [39] of 1280-1200 and 900-740 cm\(^{-1}\) respectively. These modes are also assigned (Table 2). For the title compound these deformation modes are observed in the range 1298-716 cm\(^{-1}\) theoretically and are observed at 1246, 845, 799, 746 cm\(^{-1}\) in the IR spectrum, 1297, 1280, 1252, 1235, 835, 754 cm\(^{-1}\) in the Raman spectrum. These modes are not pure, but contain significant contributions from other modes also. In the bridging methylene group (C\(_{19}\)-C\(_{28}\), C\(_{28}\)-C\(_{31}\) and C\(_{63}\)-C\(_{52}\)) CC stretching modes are found at 1169, 1035, 1009 cm\(^{-1}\) theoretically and at 1035, 1010 cm\(^{-1}\) in the IR spectrum. The CH stretching vibrations occur [39] above 2900 cm\(^{-1}\) and CH deformations absorb weakly in the region of 1350-1315 cm\(^{-1}\) in the infrared and more distinctive in Raman spectrum. For the title compound the DFT calculations give the υCH modes in RI at 2991 and 2983 cm\(^{-1}\). Kasyan et al. and Tarabara et al. reported the υCH modes at 3080 cm\(^{-1}\) and 3070-3050 cm\(^{-1}\) for similar derivatives [47,31]. Most of the bands are not pure, but contains significant contributions from other modes. The C=O stretching mode is expected in the region [48] 1667-1640 cm\(^{-1}\). For the title compound, the C=O stretching mode is assigned at 1595 cm\(^{-1}\) in the Raman spectrum and at 1597 cm\(^{-1}\) theoretically. For a series of propenoic acid esters, Felfoldi et al. reported the υC=O at 1625 cm\(^{-1}\) [49] theoretically. The deformation modes in RI are observed at 1270, 1261, 1226, 1192 (DFT), 1270, 1194 cm\(^{-1}\) (IR) and at 1265, 1194 cm\(^{-1}\) (Raman). The vibrations belonging to the bond between the ring and chlorine atoms are worth to discuss here since mixing of vibrations is possible due to the lowering of the molecular symmetry and the presence of heavy atoms on the periphery of the molecule [50-52]. Mooney assigned vibrations of CCl, CBr and CI in the wavenumber range of 1129-480 cm\(^{-1}\) [51,52]. The CCl stretching vibrations give generally strong bands in the region 710-505 cm\(^{-1}\). For simple organic chlorine compounds, CCl absorptions are in the region 750-700 cm\(^{-1}\). Sundaraganesan et al. reported CCl stretching at 704 (IR), 705 (Raman) and 715 cm\(^{-1}\) (DFT) and the deformation bands at 250 and 160 cm\(^{-1}\) [53]. The aliphatic CCl bands absorb [34] at 830-560 cm\(^{-1}\) and putting more than one chlorine on a carbon atom raises the CCl wavenumber. The CCl stretching mode is reported at around 738 cm\(^{-1}\) for dichloromethane and scissoring mode δCCl at around 284 cm\(^{-1}\) [54,39]. Pazdera et al. reported the CCl stretching mode at 890 cm\(^{-1}\) [55]. For 2-cyanophenylisocyanide dichloride, the CCl stretching mode is reported at 870 (IR), 877 cm\(^{-1}\) (Raman), and 882 cm\(^{-1}\) theoretically [56]. Arslan et al. reported the CCl stretching mode at 683 (experimental) and at 736, 711, 697 and 687 cm\(^{-1}\) theoretically [57]. The deformation bands of CCl are reported [56] at 441, 435 and 431 cm\(^{-1}\). For the title compound the bands at 668, 616 cm\(^{-1}\)
in Raman and 700, 657 and 610 (DFT) are assigned as CCl stretching modes. The asymmetric stretching CH\textsubscript{2} vibrations in the piperazine ring is reported in the range 3033-2966 cm\textsuperscript{-1}, while the symmetric vibrations lying in the range 2874-2834 cm\textsuperscript{-1} [36]. For the title compound, the bands observed at 2963, 2958, 2935, 2917, 2857, 2837, 2817, 2804 cm\textsuperscript{-1} (DFT) are assigned for CH\textsubscript{2} stretching modes. These bands are observed at 2878, 2837 cm\textsuperscript{-1} in the IR spectrum and 2959, 2832, 2817, 2805 cm\textsuperscript{-1} in the Raman spectrum. In a study on the determination of piperazine rings in ethylene amines, poly (ethyleneamine) and polyethylenimine by infrared spectrometry, Spell reported that the piperazine ring was found to be associated with sharp, well defined absorptions at 1345-1300 cm\textsuperscript{-1}, 1170-1125 cm\textsuperscript{-1}, 1025-1010 cm\textsuperscript{-1} and 940-915- cm\textsuperscript{-1} regions of the IR spectrum [58]. El-Emam et al. reported the vibrations of CH\textsubscript{2} groups in the piperazine ring (the asymmetric stretch $\nu_a$CH\textsubscript{2}, symmetric stretch $\nu_s$CH\textsubscript{2}, the scissoring vibration and wagging vibration) in the range 3033-2966, 2874-2834, 1457-1422 and 1379-1344 cm\textsuperscript{-1} respectively [36]. As stated by Spell, this is one of the most useful bands for detecting the presence of di-substituted piperazines [58]. The twisting and rocking vibrations of the CH\textsubscript{2} group appear in the region [39] of 1280-1200 and 900-740 cm\textsuperscript{-1} respectively. These modes are also assigned (Table 2). For the title compound the deformation modes are observed at in the range 1473-860 cm\textsuperscript{-1} theoretically, at 1402, 1378, 1229, 1212 cm\textsuperscript{-1}(IR) and at 1473, 1402, 1376, 1357, 1321, 1211, 1071, 1044, 860 cm\textsuperscript{-1}(Raman). These modes are not pure, but contain significant contributions from other modes also. El-Emam et al. reported the CN stretching vibrations in the region 1154-756 cm\textsuperscript{-1} [36]. For the title compound (C\textsubscript{40}-N\textsubscript{38}, C\textsubscript{39}-N\textsubscript{38}, C\textsubscript{45}-N\textsubscript{47}, C\textsubscript{46}-N\textsubscript{47}) CN stretching vibrations (in RIII) are found at 1188, 1116, 954, 804, 788, 764 cm\textsuperscript{-1} theoretically. Experimentally these modes are assigned at 805, 785, 778, 771 cm\textsuperscript{-1}. The shift in the wavenumber may be attributed to the bulky groups attached to the piperazine ring. The CC stretching vibrations for the title compound in RIII are observed at 986, 960, 895 cm\textsuperscript{-1} theoretically, and at 987 cm\textsuperscript{-1} experimentally. These vibrations in the piperazine ring were reported at 972, 903 cm\textsuperscript{-1} [36].

4.3 Frontier Molecular Orbital

Frontier molecular study is used to explain the chemical behaviour and stability of molecular system. The atomic orbital components of the frontier molecular orbital are shown in Fig. 4.
delocalization of HOMO and LUMO over the molecular system shows the charge transfer with in the molecular system. The HOMO-LUMO gap is found to be 3.144 eV. The chemical description can be evaluated by using HOMO-LUMO orbital energies, $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ as: ionisation energy $I = -E_{\text{HOMO}}$, electron affinity $A = -E_{\text{LUMO}}$, chemical hardness $\eta = (I-A)/2$, chemical potential $\mu = -(I+A)/2$ and electrophilicity index $\omega = \mu^2/2\eta$ [59]. For the title compound $I = 8.087$, $A = 4.943$, $\eta = 1.572$, $\mu = -6.515$, $\omega = 13.500$ eV (Table. 3). For the title compound, HOMO is delocalized over cyclohexene ring, partially over imido fragment while the LUMO is delocalized strongly over the phenyl ring and partially over the piperazine ring. For fluorine substitution HOMO is delocalized strongly over cyclohexene, piperazine rings and partially over the bridge CH$_2$ while LUMO is deeply over phenyl ring and N$_{47}$ atom of piperazine ring. For halogen bromine substitution HOMO is delocalized strongly over cyclohexene ring while LUMO is delocalized strongly over phenyl ring. The chemical potential decreases for halogen substitution in the order of bromine substitution $<$ fluorine substitution $<$ parent molecule. The electrophilicity index decreases for halogen substitution in the order fluorine substitution $<$ parent molecule $<$ bromine substitution.

4.4 Molecular Electrostatic Potential Map

Molecular electrostatic potential and electron density are associated to each other to find the reactive sites for electrophilic and nucleophilic sites [60,61]. For the parent molecule most electrophilic (red and yellow) regions of MEP map (Fig. 5) were related electrophilic reactivity while positive blue regions to nucleophilic reactivity. For the parent molecule the electrophilic regions are deeply over N$_{38}$ atom of piperazine ring, slightly over the phenyl ring, marginally over the carbon atoms of cyclohexene ring, slightly over oxygen atoms of imido fragment. The nucleophilic region (blue) is deeply over the hydrogen atoms in the phenyl ring and strongly over methoxy group of cyclohexene ring and deeply over the chlorine atoms of parent molecule.

For fluorine substitution electrophilic region is deeply over the N$_{38}$ atom in the piperazine ring, very slightly over carbon atoms in the phenyl ring (C$_{55}$, C$_{59}$). The electrophilic region of carbon atoms in the cyclohexene ring is slightly greater than parent molecule. The nucleophilic region of fluorine substitution is deeply over fluorine atoms and CH$_2$ groups of propyl part of the molecule. The other part of nucleophilic region of TCDBPAD fluorine is almost same as that of
parent molecule. For halogen substitution bromine atom, the electrophilic region is strongly over the N_{38} atom in the piperazine ring, slightly over carbon atoms in the cyclohexene ring but greater than that of TCDBPAD fluorine. Nucleophilic region is maximum pronounced over the methoxy group, bromine atoms and phenyl ring. Electrophilic region of phenyl ring of parent molecule > TCDBPAD fluorine > TCDBPAD bromine. Nucleophilic region is same for halogen atoms in parent molecule and fluorine substitutions but greater than bromine substitutions. The electrophilic region in the piperazine ring is same for three halogen substitutions. The electrophilic region of cyclohexene ring is more pronounced in bromine substitution than parent molecule and fluorine substitutions.

### 4.5 Natural Bond Orbital Analysis

The NBO (Natural Bond Orbitals) calculations were executed using NBO 3.1 program [62]. The strong interactions are: LPN_{15}→C_{13}-O_{18}, LPN_{15}→C_{16}-O_{17}, LPO_{17}→C_{5}-C_{16}, LPO_{17}→N_{15}-C_{16}, LPO_{18}→C_{4}-C_{13}, LPO_{18}→C_{13}-N_{15}, LPCl_{35}→C_{2}-C_{3} and LPCl_{36}→C_{1}-C_{2} with energies, 50.47, 51.78, 20.16, 25.63, 20.01, 25.99, 14.68 and 14.97 kcal/mol. 100% p-character is found in lone pairs of O_{9}, O_{14}, N_{15}, O_{17}, O_{18}, Cl_{34}, Cl_{35}, Cl_{36} and Cl_{37} atoms. The significant results are tabulated in Tables 4 and 5.

### 4.6 First Hyperpolarizability

Organic molecules able to control photonic signals efficiently and are of importance in technologies such as optical communication, optical computing and dynamic image processing. The calculated first hyperpolarizability of the 1,7,8,9-Tetrachloro-10,10-dimethoxy-4-[3-(4-benzylpiperazin-1-yl)propyl]-4-azatricyclo[5.2.1.0^{2,6}] dec-8-ene-3,5-dione is 1.6690 X 10^{-30} esu which is 12.84 times that of the standard NLO material urea (0.13 x 10^{-30} esu) [63]. Which is comparable with the reported values of similar derivatives (11.77 times that of urea) [64]. From this value we can say that the title compound is an attractive object for future nonlinear studies. In the halogen substituted NLO study of the title compound showed that the hyperpolarizability increases to 2.4111 x 10^{-30} esu for fluorine substitution and 1.7503 x 10^{-30} esu for bromine substitution in the place of chlorine atoms in the title compound (Table 6).
4.7 ALIE surfaces and Fukui functions

The local reactivity and the energy required to remove an electron from a molecule are explained using the quantum molecular descriptor ALIE (Average local ionization energy) sjoberg et al. defined that ALIE consists sum of orbital energies [65]. According to this we can say that the sites with least values of ALIE are the most probable sites for an electrophilic attack [66]. The equation of ALIE is the sum of orbital energies weighted by the orbital density.

\[ I(r) = \sum_i \frac{\rho_i(\vec{r})e_i}{\rho(\vec{r})} \]

Where \( \rho_i(\vec{r}) \) denotes electronic density of the i-th molecular orbital at the point \( \vec{r} \), \( e_i \) denotes orbital energy and \( \rho(\vec{r}) \) denotes total electronic density function. We have mapped the ALIE values to the electron density surface in order to foresee the attacking sites of electrophiles. The ALIE figure is represented in Fig. 6. Here in this figure we can see that the two nitrogen atoms show the least ALIE values that is 167.81 kcal/mol, while the hydrogen atom shows the highest ALIE value 332.15 kcal/mol. Fukui functions are very useful in determining the local reactive sites in a molecule. The functional derivative of chemical potential with respect to external potential is termed as Fukui functions. This quantum molecular descriptor is interpreted as the derivative of electronic density with respect to the number of electrons [67-69]. In physical sense it is the change in electron density as a consequence of change in charge. These functions in Jaguar program are calculated with the help of finite difference approach, according to the following equations:

\[ f^+ = \left( \frac{\rho^{N+\delta}(r) - \rho^N(r)}{\delta} \right), \]
\[ f^- = \left( \frac{\rho^{N-\delta}(r) - \rho^N(r)}{\delta} \right), \]

where \( N \) stands for the number of electrons in reference state of the molecule, while \( \delta \) stands for the fraction of electron which default value is set to be 0.01 [69]. By plotting Fukui functions to
electron density surfaces we get all information’s about the important reactive centres [65,66]. The Fukui function plot is represented in Fig. 7. The colour coding in the plot is as follows, purple (positive) colour in Fukui function $f^+$ means the electron density has been increased by the addition of charges to the system while red (negative) color in Fukui function $f^-$ means the electron density has been diminished by the addition of charges. Electron density is increased in the near vicinity of carbon atoms C$_{28}$, C$_{31}$ and electron density is decreased near the O$_{18}$, O$_{17}$ atom.

4.8 Degradation properties based on autoxidation and hydrolysis

RDF is calculated to predict degradation properties based on autoxidation and hydrolysis mechanisms. To find the extend of hydrolysis we have calculated the RDF for the molecule. In Fig.8 RDFs of atoms with the most pronounced interactions with water molecules are presented. In RDF plot, $g(r)$ represents the probability of finding a particle in the distance $r$ from another particle [70]. Results provided in Fig.8 indicate that only five atoms of TCDBPAD molecule have relatively significant interactions with water molecules. These are oxygen and nitrogen atoms O$_9$, O$_{17}$, O$_{18}$, N$_{38}$ and N$_{47}$. Peak distance in all cases is located between 2.7 to 3 Å. According to the maximal $g(r)$ values the most important RDF is certainly for O$_{18}$ atom. In pharmaceutical industry stability of molecule near water sorroundings, relatively high peak and absence of hydrogen atoms in the peak is very much relevant.

4.9 Hildebrand solubility parameter - Identification of excipients

The emerging field in pharmaceutical is the production of new products and the identification of the active ingredient. To be considered for drug production there are certain parameters. Some of them are the solubility, stability and deliverability of the active ingredient. Modifications are done to the molecules which lack these parameters. Without any structural changes we can modify the molecule by intermixing them with the excipient. Wide range of excipients are identified over the time. Excipients can be identified using computational methods as well as experimental methods. Experimental identification is a laborious process, while computational methods are uncomplicated and effortless. Compatibility is the major property needed between
the active ingredient and the excipient. Hildebrand solubility parameter can be used to predict the compatible nature of excipient and the ingredient [71-73]. The solubility parameter of active component and that of the excipient must be same. The equation for the Hildebrand solubility parameter using MD calculations is given below

\[
\delta = \sqrt{\frac{\Delta H_v - RT}{V_m}}
\]

In this work, the solubility parameter has been calculated for the TCDBPAD molecule. Its value has been compared with the common excipient compounds polyvinylpyrrolidone polymer (PVP), maltose, and sorbitol. MD systems used to calculate this quantity consisted of 32 molecules placed in a cubic simulation box. Solubility parameters of all mentioned compounds have been summarized in Table. 7. As indicated by the results presented in Table. 7, TCDBPAD molecule has the highest compatibility with the PVP compound. In this particular case, the difference between corresponding values of solubility parameter is less than 0.5 MPa\(^{1/2}\), indicating very high compatibility. Solubility parameters of sorbitol and maltose is much higher than the solubility parameter of the TCDBPAD molecule. Therefore, the MD calculations suggest that it is reasonable to consider PVP as an excipient for TCDBPAD molecule.

4.10 Molecular Docking

Molecular docking tries to predict the structure of intermolecular complex formed between two or more constituent molecules. The final goal uses to be to predict the biological activity of a given ligand. Molecular docking was employed to recognize the active site of the receptor and acquire the best geometry of ligand-receptor complex. Based on the structure of the title compound, we find the activity of non-basic fXa inhibitors with excellent potency in anti-fXa and anticoagulant assays. Among the many enzymes in the coagulation cascade, factor fXa is one particularly attractive target [74]. Cardiovascular and cerebrovascular diseases, such as deep venous thrombosis (DVT), myocardial infarction (MI), pulmonary embolism (PE), and ischemic stroke, are now and may continue to be leading causes of morbidity and mortality around the world [74]. Factor Xa (PDB ID: 1wu1) was downloaded from the RCSB protein data bank website. Although thrombin is one of the adequate targets for anticoagulation, there are a few
reports in which direct factor Xa (fXa) inhibitors decrease the likelihood of bleeding tendency compared with direct thrombin inhibitors [75-77]. The structure of a large molecular fragment of factor Xa that lacks only a Gla domain has been solved by x-ray crystallography and refined at 2.2Å resolution of crystallographic R value of 0.168 [78]. Among several approaches to address the unmet needs, the inhibition of factor Xa (fXa) is known as one of the most popular. This is mainly because fXa inhibitors seemed to have a lower risk of bleeding than heparin and warfarin. The reason would be attributed to the inhibition position in the coagulation cascade. As is well-known, fXa catalyzes thrombin production and is situated at the confluence of the intrinsic and extrinsic pathways. Thus, fXa inhibitors do not block thrombin directly rather, they block the confluent position of the coagulation cascade [79]. Thus, we choose title compound as ligand and Factor Xa receptor as target for docking study. All molecular docking calculations were performed on AutoDock 4.2 [80] and AutoDock Vina software [81]. The original ligand as well as water molecules were removed from the crystal structure, and polar hydrogens and united atom Kollman charges were assigned for the receptor using the graphical user interface AutoDock Tools (ADT). The Lamarckian Genetic Algorithm (LGA) [82] was employed to calculate the energy between ligand and receptor. The compound docked the active site of receptors with the grid centre dimension 40×40×40. The conformations with the lowest binding energy is extracted and analysed for detailed interactions in Discovery Studio Visualizer 4.0 software. The ligand binds at the active site of the substrates by weak non-covalent interactions. The amino acids Gly216 forms H-bond with carbonyl group while Gln 192 has an H-bond with methoxy group. Glu97 having an H-bond with CH2 and electrostatic interactions are detailed in Fig. 9. The docked ligand forms a stable complex with Factor Xa receptor as depicted in Fig. 10 and the binding free energy value is −5.7 kcal/mol. tabulated in Table 8. The docked ligand embedded in the catalytic site of factor Xa (fXa) as shown in Fig. 11. These preliminary results suggest that the compound having inhibitory activity against the coagulation cascade. Thus the title compound can be developed as drug used for the treatment of Cardiovascular and Cerebrovascular diseases.
5. Conclusions

In the present study, the molecular structure and vibrational frequencies of 1,7,8,9-tetrachloro-10,10-dimethoxy-4-[3-(4-benzylpiperazine-1-yl) propyl]-4-azatricyclo [5.2.1.0^2,6] dec-8-ene-3,5-dione have been studied theoretically and experimentally. The calculated geometrical parameters of the title compound are in good agreement with experimental values. The small difference between experimental and calculated vibrational wavenumbers was that, the experimental results belong to solid phase and the theoretical calculations belong to gaseous phase. For the title compound HOMO is delocalized over cyclohexene ring and LUMO is delocalized at phenyl ring. HOMO-LUMO band gap of the title compound is found to be 3.144 eV and shows the stability of the molecule. From NBO analysis strong interactions are C_{13}-O_{18} from N_{15}, C_{16}-O_{17} from N_{15}, N_{15}-C_{16} from O_{17}, C_{5}-C_{16} from O_{17}, C_{13}-N_{15} from O_{18} and C_{4}-C_{13} from O_{18}. The MEP studies shows that the title compound and halogen substitution the electrophilic region is strongly over N_{38} of piperazine ring and nucleophilic region is maximum pronounced over the methoxy group. The compound is optically active because the calculated first hyperpolarizability of the compound is comparable with the standard compound. By DFT calculations we were able to calculate the ALIE values, beside benzene ring, hydrogen atoms are prone to electrophilic attacks. Thanks to the mapping of the Fukui function values to the electron density surface we have also determined that carbon atom C_{28}, C_{31} and oxygen atoms O_{18}, O_{17} are important reactive centres. The RDF peaks conclude that the compound is stable near moisture. The MD calculations of solubility parameter suggests that it is reasonable to consider PVP as an excipient for TCDBPAD molecule. The title compound can be developed as drug used for the treatment of Cardiovascular and Cerebrovascular diseases.

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Figure Caption

Fig 1 FT-IR
Fig 2 FT-Raman
Fig 3 Molecule
Fig 4 HOMO-LUMO
Fig 5 MEP
Fig 6 ALIE
Fig 7 Fukui
Fig 8 RDF
Fig 9 Docking
Fig 10 Docking
Fig 11 Docking
Table Caption

Table 1 Geometrical Parameters
Table 2 Frequency
Table 3 HOMO-LUMO
Table 4 NBO-1
Table 5 NBO-2
Table 6 NLO of Substitution
Table 7 Solubility parameter
Table 8 Docking

Graphical Abstract
Fig. 1. FT-IR spectrum of TCDBPAD
Fig. 2. FT-Raman spectrum of TCDBPAD
Fig. 3. Optimized geometry of TCDBPAD

Fig. 4. HOMO-LUMO plots of TCDBPAD with halogen substitutions
Fig. 5. MEP plots of TCDBPAD with halogen substitutions

Fig. 6. ALIE surface of TCDBPAD
Fig. 7. Fukui functions $f^+$ and $f^-$ of TCDBPAD

- $f^+ = -4.23 \times 10^{-5}$ to $3.74 \times 10^{-4}$
- $f^- = -7.5 \times 10^{-5}$ to $5.02 \times 10^{-4}$

Fig. 8. RDFs of TCDBPAD atoms with significant interactions with water molecules
Fig. 9. Ligand interactions TCDBPAD with the amino acids of factor Xa (fXa) inhibitor

Fig. 10. The docked ligand TCDBPAD at the active site of the receptor
Fig. 11. The docked ligand embedded in the catalytic site of factor Xa (fXa)

Tables

Table 1
Optimized geometrical parameters of TCDBPAD

| Bond length (Å) | Bond angle (°) | Dihedral angle (°) |
|-----------------|----------------|--------------------|
| C₁-C₂           | 1.3421         | C₂-C₁-C₆           | 107.9  |
| C₁-C₆           | 1.5304         | C₁-C₂-C₆           | 127.6  |
| C₁-Cl₃6         | 1.7185         | C₁-C₂-Cl₃6         | 124.2  |
| C₂-C₃           | 1.5265         | C₁-C₂-Cl₃6         | 107.3  |
| C₂-Cl₃5         | 1.7193         | C₁-C₂-Cl₃5         | 127.9  |
| C₃-C₄           | 1.5711         | C₁-C₆-C₅           | 105.7  |
| C₃-C₇           | 1.5854         | C₁-C₆-C₇           | 99.5   |
| C₃-Cl₃₄         | 1.7837         | C₁-C₆-Cl₃7         | 114.6  |
| C₄-C₅           | 1.5534         | C₁-C₂-Cl₃5         | 124.4  |
| C₄-H₁₀          | 1.0945         | C₁-C₂-C₃-Cl₃4      | 111.9  |
| C₄-C₁₃          | 1.5337         | C₁-C₂-C₃-Cl₃4      | 99.6   |
| C₅-C₆           | 1.5638         | C₁-C₂-C₃-Cl₃4      | 115.9  |
| C₅-H₁₂          | 1.0948         | C₁-C₂-C₃-Cl₃4      | 102.8  |
| C₅-C₁₆          | 1.5373         | C₁-C₂-C₃-Cl₃4      | 114.3  |
| C₆-C₇           | 1.5810         | C₁-C₂-C₃-Cl₃4      | 114.3  |
| C₆-Cl₃₇         | 1.7826         | C₁-C₂-C₃-Cl₃4      | 114.3  |
|      |       |       |       |       |       |
|------|-------|-------|-------|-------|-------|
| C7-O9 | 1.3823 | C7-C4-C11 | 118.8 | C2-C3-C4-C5 | -69.3 |
| C7-O14 | 1.3903 | C7-C3-Cl14 | 117.4 | C2-C3-C4-C13 | 175.2 |
| O8-C9 | 1.4342 | C3-C7-C6 | 91.4 | C7-C3-C4-C5 | 34.4 |
| C8-H20 | 1.0957 | C3-C7-O9 | 118.3 | C7-C5-C6-C13 | -81.1 |
| C8-H21 | 1.0953 | C3-C7-O14 | 107.8 | Cl34-C3-C4-C5 | 162.8 |
| C8-H22 | 1.0938 | C5-C4-H10 | 114.2 | Cl34-C3-C4-C10 | -75.7 |
| C11-O14 | 1.4421 | C3-C4-C13 | 105.0 | Cl34-C3-C4-C13 | 47.3 |
| C11-H23 | 1.0935 | C4-C5-C6 | 103.1 | C2-C3-C7-C6 | 52.6 |
| C11-H24 | 1.0949 | C4-C5-H12 | 114.1 | C2-C3-C7-O9 | -58.6 |
| C11-H27 | 1.0931 | C4-C5-C16 | 104.5 | C2-C5-C7-O14 | 171.0 |
| C13-N15 | 1.3933 | H10-C4-C13 | 107.3 | C4-C5-C7-C6 | -55.1 |
| C13-O18 | 1.2077 | C4-C13-N15 | 107.9 | C4-C5-C7-O9 | -166.3 |
| C16-N15 | 1.3917 | C4-C13-O18 | 127.4 | C4-C5-C7-O14 | 63.4 |
| C19-N15 | 1.4617 | C6-C5-H12 | 109.4 | Cl34-C3-C7-C6 | 178.5 |
| C16-O17 | 1.2095 | C6-C5-C16 | 118.2 | Cl34-C3-C7-O9 | 67.3 |
| C19-H25 | 1.0950 | C5-C6-C7 | 102.3 | Cl34-C3-C7-O14 | -63.0 |
| C19-H26 | 1.0959 | C5-C6-Cl17 | 115.9 | C5-C4-C5-C6 | 2.2 |
| C19-C28 | 1.5340 | H12-C5-C16 | 107.6 | C3-C4-C5-C16 | -122.0 |
| C28-H29 | 1.0966 | C5-C16-N15 | 107.9 | C13-C4-C5-C6 | 127.3 |
| C28-H30 | 1.0969 | C5-C16-O17 | 127.3 | C13-C4-C5-C16 | 3.1 |
| C28-C31 | 1.5342 | C7-C6-Cl37 | 116.6 | C3-C9-C13-N15 | 116.2 |
| C31-H32 | 1.0997 | C6-C7-O9 | 107.9 | C3-C4-C13-O18 | -67.9 |
| C31-H33 | 1.1126 | C6-C7-O14 | 116.5 | C5-C4-C13-N15 | 1.7 |
| C31-N38 | 1.4566 | O4-C7-O14 | 113.4 | C5-C4-C13-O18 | 177.6 |
| N38-C39 | 1.4574 | C7-O9-C8 | 118.2 | C4-C5-C6-C1 | 65.4 |
| C40-N38 | 1.4714 | C7-O14-C11 | 117.8 | C4-C5-C6-C7 | -38.3 |
| C39-H41 | 1.1096 | O3-C9-H20 | 110.7 | Cl16-C5-C6-C1 | -179.9 |
| C39-H43 | 1.0971 | O3-C8-H23 | 111.5 | Cl16-C5-C6-C7 | 76.3 |
| C39-C46 | 1.5400 | O4-C8-H22 | 105.6 | Cl16-C5-C6-Cl37 | -51.7 |
| C40-H42 | 1.1089 | H20-C8-H21 | 109.4 | C4-C5-C16-N15 | -7.0 |
| C40-H44 | 1.0979 | H20-C8-H22 | 109.6 | C4-C5-C16-O17 | 176.5 |
| C40-C45 | 1.5438 | H21-C8-H22 | 109.9 | C6-C5-C16-N15 | -120.8 |
| C45-N47 | 1.4540 | O14-C11-H23 | 110.9 | C6-C5-C16-O17 | 62.6 |
| Compound   | Bond Length (Å) | Bond Angle (°) | Bond Order | Description |
|------------|----------------|---------------|------------|-------------|
| **C₄₅-H₅₀** | 1.0977         |               |            |            |
| **C₄₅-H₅₁** | 1.1073         |               |            |            |
| **C₄₆-N₄₇** | 1.4646         |               |            |            |
| **C₄₆-H₄₈** | 1.1005         |               |            |            |
| **C₄₆-H₄₉** | 1.1055         |               |            |            |
| **N₄₇-C₆₃** | 1.4638         |               |            |            |
| **C₅₂-C₅₃** | 1.4032         |               |            |            |
| **C₅₂-C₅₄** | 1.4026         |               |            |            |
| **C₅₂-C₆₃** | 1.5255         |               |            |            |
| **C₅₃-C₅₅** | 1.3962         |               |            |            |
| **C₅₃-H₅₆** | 1.0893         |               |            |            |
| **C₅₄-C₅₇** | 1.3973         |               |            |            |
| **C₅₄-H₅₈** | 1.0895         |               |            |            |
| **C₅₅-C₅₉** | 1.3975         |               |            |            |
| **C₅₅-H₆₂** | 1.0885         |               |            |            |
| **C₅₇-C₅₉** | 1.3965         |               |            |            |
| **C₅₇-H₆₀** | 1.0884         |               |            |            |
| **C₅₉-H₆₁** | 1.0882         |               |            |            |
| **C₆₃-H₆₄** | 1.0998         |               |            |            |
| **C₆₃-H₆₅** | 1.0993         |               |            |            |
| **H₂₉-C₂₈-C₃₁** | 107.8          |               |            |            |
| **H₂₀-C₂₈-C₃₁** | 108.8          |               |            |            |
| **C₂₈-C₃₁-H₃₂** | 108.8          |               |            |            |
| **C₂₈-C₃₁-H₃₃** | 109.2          |               |            |            |
| **H₂₈-C₃₁-H₃₈** | 112.6          |               |            |            |
| **H₃₂-C₃₁-H₃₃** | 106.6          |               |            |            |
| **H₃₂-C₃₁-H₃₈** | 107.6          |               |            |            |
| **H₃₃-C₃₁-H₃₈** | 111.9          |               |            |            |
| **C₃₁-H₃₈-C₃₉** | 113.3          |               |            |            |
| **C₃₁-H₃₈-C₄₀** | 113.0          |               |            |            |
| **C₃₉-H₃₈-C₄₀** | 111.0          |               |            |            |
| **N₃₈-C₃₉-H₄₁** | 112.2          |               |            |            |
| **N₃₈-C₃₉-H₄₃** | 108.9          |               |            |            |
| Bond                  | Angle | Bond                  | Angle |
|-----------------------|-------|-----------------------|-------|
| N₃₈-C₃₉-C₄₆           | 110.2 | C₄₀-C₆₃-N₄₇-C₆₃      | −164.8|
| N₃₈-C₄₀-H₄₂           | 111.4 | C₄₀-C₅₂-N₄₇-C₆₃      | −159.9|
| N₃₈-C₄₀-H₄₄           | 108.6 | C₅₂-C₅₃-C₅₄-C₅₅      | 0.7   |
| N₃₈-C₄₀-C₴₅           | 111.6 | C₆₃-C₅₂-C₅₃-C₅₅      | −178.2|
| H₄₁-C₃₉-H₄₃           | 106.3 | C₅₃-C₅₂-C₅₄-C₅₇      | −0.7  |
| H₄₁-C₃₉-C₄₆           | 110.1 | C₆₃-C₅₂-C₅₄-C₅₇      | 178.2 |
| H₄₃-C₃₉-C₄₆           | 109.0 | C₅₂-C₅₄-C₅₅-C₅₉      | 0.2   |
| C₃₉-C₄₆-N₄₇           | 110.8 | C₅₃-C₅₅-C₅₉-C₅₇      | −0.3  |
| C₃₉-C₄₆-H₴₈           | 110.0 | C₅₄-C₅₇-C₅₉-C₅₅      | 0.3   |
| C₃₉-C₄₆-H₴₉           | 107.9 |
| H₴₂-C₄₀-H₄₄           | 107.2 |
| H₴₂-C₄₀-C₄₅           | 108.4 |
| H₴₄-C₄₀-C₴₅           | 109.5 |
| C₄₀-C₅₂-N₄₇           | 109.5 |
| C₄₀-C₅₂-H₵₀           | 108.8 |
| C₄₀-C₅₂-H₵₁           | 110.3 |
| N₄₇-C₅₂-H₵₀           | 108.8 |
| N₄₇-C₅₂-H₵₁           | 113.1 |
| C₅₂-N₄₇-C₄₆           | 112.3 |
| C₅₂-N₄₇-C₆₃           | 116.5 |
| H₵₀-C₅₂-H₵₁           | 106.2 |
| N₄₇-C₆₃-H₴₈           | 108.0 |
| N₄₇-C₆₃-H₴₉           | 112.6 |
| N₄₆-C₄₇-C₆₃           | 114.6 |
| H₴₈-C₄₆-H₴₉           | 107.4 |
| N₄₇-C₆₃-C₅₂           | 116.9 |
| N₄₇-C₆₃-H₶₄           | 107.0 |
| N₄₇-C₆₃-H₶₅           | 107.2 |
| C₅₃-C₅₂-C₅₄           | 118.2 |
| C₅₃-C₅₂-C₆₃           | 120.8 |
| C₅₂-C₅₃-C₅₅           | 121.0 |
| C₅₂-C₅₃-H₵₆           | 119.4 |
| C₅₄-C₵₂-C₶₃           | 121.0 |
### Table 2
Calculated Scaled wavenumbers, observed IR, Raman bands and vibrational assignments of TCDBPAD

| B3LYP/6-31(d') | IR ν(cm⁻¹) | Raman ν(cm⁻¹) | Assignments       |
|----------------|-----------|---------------|-------------------|
| ν(cm⁻¹) | IR₁ | RA | | | |
| 3078 | 23.96 | 310.05 | - | - | νCHIV(93) |
| 3066 | 40.52 | 47.84 | 3069 | 3068 | νCHIV(99) |
| 3058 | 8.36 | 103.41 | - | 3053 | νCHIV(99) |
| 3048 | 13.01 | 62.12 | - | - | νCH₃(99) |
| 3046 | 4.39 | 76.61 | - | - | νCHIV(95) |
| 3044 | 9.20 | 14.74 | - | - | νCHIV(98) |
| 3035 | 7.15 | 45.53 | - | - | νCH₃(99) |
|    |     |     |   |   |     |
|----|-----|-----|---|---|-----|
| 3034 | 21.89 | 73.57 | -  | 3030 | νCH₃(97) |
| 3019 | 19.57 | 26.71 | -  | 3016 | νCH₂(98) |
| 2991 | 7.27  | 32.67 | 2989 | 2988 | νCH₂(97) |
| 2962 | 41.70 | 12.00 | -  | 2961 | νCH₂(91) |
| 2958 | 58.22 | 85.08 | -  | 2959 | νCH₂III(82) |
| 2952 | 25.00 | 116.70| -  | 2954 | νCH₂(95) |
| 2941 | 31.86 | 80.31 | -  | 2943 | νCH₂(87) |
| 2935 | 28.31 | 54.94 | -  | 2936 | νCH₂(88) |
| 2917 | 50.99 | 64.85 | -  | 2919 | νCH₂(95) |
| 2910 | 32.61 | 86.16 | -  | 2912 | νCH₂(97) |
| 2857 | 75.87 | 121.35 | 2878 | - | νCH₂III(92) |
| 2837 | 104.79| 73.05 | 2837 | 2832 | νCH₂III(97) |
| 2817 | 32.46 | 28.02 | -  | 2817 | νCH₂III(98) |
| 2804 | 45.84 | 36.22 | -  | 2805 | νCH₂III(93) |
| 2782 | 56.58 | 46.66 | 2781 | 2792 | νCH₂(94) |
| 1786 | 36.63 | 16.33 | 1766 | 1788 | νC=O(82) |
| 1728 | 498.50| 0.30  | 1698 | 1727 | νC=O(83) |
| 1598 | 1.51  | 36.61 | 1621 | 1610 | νIV(62), δCHIV(12) |
| 1597 | 57.17 | 31.74 | -  | 1595 | νC=C(76) |
| 1579 | 0.87  | 9.16  | -  | 1573 | νIV(70) |
| 1493 | 4.49  | 6.75  | -  | -   | δCH₂III(53), δCH₂(29) |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
|   | δCH₃(83) |   |   |   |   |
| 1474 | 11.89 | 10.37 | - | - | δCH₂(83) |
| 1473 | 2.47 | 7.24 | - | 1473 | δCH₂III(79) |
| 1466 | 0.84 | 14.26 | - | - | δCH₂III(83) |
| 1465 | 14.85 | 2.64 | - | - | δCH₃(90) |
| 1464 | 5.67 | 14.78 | - | - | δCH₂(47), δCH₂III(44) |
| 1459 | 1.13 | 13.97 | - | - | δCH₃(83) |
| 1453 | 7.84 | 1.86 | - | 1453 | δCH₂(67), δCH₂(13) |
| 1450 | 4.08 | 18.84 | 1449 | - | δCH₂(70), δCH₃(11) |
| 1437 | 5.13 | 0.76 | 1438 | - | νIV(45), δCHIV(43) |
| 1437 | 1.45 | 3.58 | - | - | δCH₃(46), νIV(25) |
| 1432 | 10.05 | 15.88 | - | 1434 | δCH₂(89) |
| 1431 | 19.96 | 27.39 | - | - | δCH₂(88) |
| 1422 | 1.98 | 10.59 | - | 1418 | δCH₃(91) |
| 1396 | 2.30 | 3.66 | 1402 | 1402 | δCH₂III(51), δCH₂(25) |
| 1382 | 8.86 | 4.40 | - | - | δCH₂III(67) |
| 1378 | 12.28 | 1.45 | 1378 | 1376 | δCH₂(36), δCH₂III(35) |
| 1372 | 49.41 | 4.91 | - | - | δCH₂III(31), δCH₂(25) |
| 1357 | 91.58 | 4.26 | - | 1357 | δCH₂III(30), δCH₂(23) |
| 1348 | 210.27 | 6.10 | 1347 | - | νCNII(39), δCH₂(32) |
| 1339 | 98.34 | 8.44 | - | 1340 | νCNII(49), δCH₂(39) |
| 1331 | 38.55 | 13.16 | - | - | δCH₂(68) |
| 1327 | 24.43 | 0.65 | - | - | δCH₂III(61), δCN(18) |
| 1321 | 8.24 | 3.19 | - | 1321 | δCH₂III(30), δCN(20) |
| 1309 | 0.12 | 0.70 | 1307 | - | νIV(59), δCHIV(39) |
| 1298 | 11.36 | 6.96 | - | 1297 | δCH₂(48), δCH₂III(14) |
| 1287 | 12.69 | 10.74 | - | - | δCH₂(45), νIV(14) |
| 1280 | 9.84 | 5.58 | - | 1280 | δCH₂(48) |
| 1274 | 4.21 | 8.35 | - | - | δCH₂III(61) |
| 1270 | 1.08 | 3.42 | 1270 | - | δCHI(68) |
| 1261 | 12.84 | 5.56 | - | 1265 | δCHI(73) |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 1248 | 18.75 | 2.29 | 1246 | 1252 | δCH₂(37), δCH₂III(29) |
| 1236 | 17.49 | 7.87 | - | 1235 | δCH₂(44), δCH₂III(23) |
| 1229 | 7.58 | 10.86 | 1229 | - | δCH₂III(48) |
| 1226 | 1.52 | 2.95 | - | - | δCHI(76) |
| 1212 | 8.43 | 9.31 | 1212 | 1211 | δCH₂III(77) |
| 1192 | 23.15 | 2.46 | 1194 | 1194 | δCHI(34) |
| 1191 | 99.24 | 1.95 | - | - | δCH₃(52), νCO(23) |
| 1188 | 62.08 | 8.23 | - | - | νCNIII(25) |
| 1178 | 3.09 | 2.48 | 1178 | - | δCH₃(53), νCO(47) |
| 1169 | 21.40 | 20.92 | - | - | νCC(33), δIV(11) |
| 1167 | 119.31 | 6.12 | - | - | νCO(31), δCO(19) |
| 1164 | 3.91 | 5.74 | - | - | δCHIV(54) |
| 1161 | 9.41 | 7.51 | - | 1161 | δCHIV(27) |
| 1144 | 15.50 | 7.51 | 1151 | - | νCNIII(17) |
| 1143 | 15.92 | 3.68 | - | - | νCO(66) |
| 1140 | 0.11 | 4.72 | 1140 | - | δCHIV(78) |
| 1135 | 63.05 | 2.47 | - | 1137 | δI(46), δI(15), νCCI(12) |
| 1133 | 51.01 | 5.26 | - | - | δCH₃(62) |
| 1127 | 33.47 | 15.10 | 1121 | 1121 | νCNIII(26), δCH₂(13) |
| 1116 | 12.55 | 2.78 | - | - | νCNIII(30), νCCI(12) |
| 1107 | 34.56 | 2.59 | - | - | νCNII(28), δCH₂(13) |
| 1100 | 129.37 | 3.74 | 1100 | 1106 | δI(24), δCC(20), νCO(16) |
| 1091 | 87.04 | 6.05 | 1087 | 1088 | νCO(37), νI(17) |
| 1073 | 75.09 | 2.11 | - | 1071 | δCH₂III(39), νCNIII(20) |
| 1068 | 15.04 | 0.66 | 1065 | - | δCHIV(59), νI(36) |
| 1058 | 37.80 | 1.84 | - | - | δI(22), νI(20), νCCI(11) |
| 1052 | 25.18 | 5.33 | - | 1054 | νI(43), νCCI(18), νCN(14) |
| 1047 | 5.19 | 18.85 | - | 1044 | δCH₂III(60) |
| 1035 | 4.21 | 5.10 | 1035 | - | νCC(45), δCH₂(20) |
| 1031 | 7.75 | 5.57 | - | - | νCO(62), δCC(13), νI(11) |
| Frequency | Intensity | Energy | Mode | Frequency | Intensity | Energy | Mode |
|-----------|-----------|--------|------|-----------|-----------|--------|------|
| 1016      | 2.53      | 13.45  | -    | 1014      | δCHIV(42), νIV(27) |
| 1009      | 6.17      | 1.89   | 1010 | -         | νCC(41), νl(10)    |
| 1005      | 20.26     | 4.73   | 1004 | -         | νCO(28), νl(12)    |
| 989       | 15.15     | 3.72   | -    | 997       | νCO(46), νCCIII(17) |
| 986       | 15.20     | 9.07   | 987  | -         | νCCIII(22), νCO(21) |
| 979       | 1.50      | 25.76  | -    | -         | νIV(54), δIV(36)   |
| 970       | 19.63     | 5.12   | 969  | 973       | νCO(43), νl(35)    |
| 967       | 3.73      | 1.00   | -    | -         | νl(33)            |
| 960       | 2.75      | 1.85   | -    | -         | νCCIII(28), δCH2(20) |
| 954       | 10.21     | 1.66   | -    | -         | νCNIII(22), δCH2III(17) |
| 950       | 1.12      | 0.16   | -    | -         | γCHIV(84), τIV(14) |
| 947       | 25.49     | 3.53   | 943  | 948       | νCO(42), νl(21), νCCI(11) |
| 924       | 0.05      | 0.14   | 921  | 930       | γCHIV(92)         |
| 895       | 2.92      | 1.95   | -    | -         | νCCIII(30), γCHIV(21), δCN(23) |
| 893       | 2.36      | 0.61   | 891  | 893       | γCHIV(64)         |
| 890       | 12.25     | 4.69   | -    | -         | τI(14), νCCI(10), νl(10) |
| 881       | 7.68      | 4.77   | 872  | 887       | τI(21), νCCI(10)  |
| 860       | 7.48      | 0.35   | -    | 860       | δCH2III(64)      |
| 832       | 3.22      | 0.38   | 845  | 835       | δCH2(49)          |
| 828       | 0.01      | 4.64   | 828  | 824       | γCHIV(100)        |
| 819       | 49.53     | 1.52   | -    | -         | δI(12)            |
| 804       | 11.98     | 1.54   | -    | 805       | νCNIII(40)        |
| 797       | 3.76      | 9.48   | 799  | -         | δCH2(42), τIV(11) |
| 788       | 16.75     | 0.62   | 778  | 785       | νCNIII(42)        |
| 764       | 14.63     | 10.95  | -    | 771       | νCNIII(51)        |
| 747       | 36.05     | 0.87   | 746  | 754       | δCH2(35)          |
| 731       | 14.72     | 19.43  | -    | 735       | γCHIV(44), γIV(21) |
| 716       | 3.70      | 2.52   | -    | -         | δCH2(36)          |
| 713       | 4.53      | 4.70   | 713  | 711       | γC=O(17), τII(12) |
| 700       | 18.35     | 2.22   | -    | -         | νCO(18), νCCI(14) |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 690 | 30.46 | 2.72 | 684 | 687 | τIV(48), γCHIV(35) |
| 690 | 6.53  | 0.83 | -  | -  | τI(13) |
| 657 | 41.63 | 1.67 | -  | 668 | νCCl(43), δII(35) |
| 646 | 10.28 | 3.35 | -  | 648 | τIV(24), δIII(19) |
| 632 | 5.82  | 3.13 | 633 | 634 | δCO(24) |
| 610 | 0.06  | 4.06 | -  | 616 | νCCl(45), δIV(36) |
| 610 | 8.49  | 0.27 | -  | -  | δCCl(41) |
| 598 | 4.30  | 3.79 | 602 | 588 | δII(36), νCNII(11) |
| 578 | 6.39  | 2.46 | -  | 566 | δIV(18), τIV(12), δCH₂(11) |
| 545 | 0.08  | 1.38 | 547 | 546 | γCCl(29), τI(23), δC=O(11) |
| 526 | 18.93 | 4.85 | 527 | 524 | δCH₂(13) |
| 509 | 4.08  | 3.02 | -  | 505 | δIII(53) |
| 494 | 0.38  | 0.61 | 496 | 488 | νCC(17), γC=O(17) |
| 492 | 8.67  | 3.24 | 483 | -  | δIV(26), δIII(16) |
| 456 | 3.19  | 1.50 | 461 | 462 | τIV(34), γCC(15) |
| 444 | 9.01  | 0.41 | -  | 447 | δI(18), τIV(17) |
| 405 | 8.27  | 0.50 | 412 | -  | δIII(14), τIV(11), δCN(10) |
| 404 | 0.07  | 0.04 | -  | 403 | τIV(81) |
| 390 | 8.20  | 0.26 | 399 | 384 | δCN(23), δCC(10) |
| 377 | 7.29  | 3.95 | -  | -  | δCC(22), δC=O(16) |
| 366 | 9.96  | 6.82 | -  | 366 | νCCl(20) |
| 351 | 4.18  | 0.62 | -  | -  | γCN(33), δIII(15), τIII(13) |
| 346 | 1.06  | 1.88 | -  | 348 | νCCl(41), δI(22) |
| 340 | 3.12  | 4.89 | -  | -  | δCO(32), νCCl(31) |
| 332 | 6.71  | 1.94 | -  | -  | δCO(43) |
| 331 | 5.77  | 0.58 | -  | 331 | γCN(32), τIII(15), δIII(13) |
| 323 | 2.94  | 3.12 | -  | -  | δCO(21), γCN(15) |
| 312 | 8.12  | 3.49 | -  | 317 | δCO(24), γCN(10) |
| 283 | 2.75  | 3.46 | -  | 281 | δCN(30), δC=O(15) |
| 273 | 2.75  | 1.41 | -  | -  | δCN(26) |
|   |   |   |   |   |   |
|---|---|---|---|---|---|
| 265 | 3.51 | 2.99 | - | 267 | δCC(17), τII(14) |
| 259 | 2.43 | 2.03 | - | 254 | τIV(13), τIII(11) |
| 244 | 2.75 | 0.57 | - | 232 | δCN(20), δCC(17) |
| 218 | 3.96 | 0.58 | - | 219 | τIII(39), γCN(19) |
| 203 | 2.48 | 0.46 | - | - | τCO(36), τCH(3) |
| 197 | 0.14 | 0.78 | - | 196 | τCH(34), δCCI(14) |
| 187 | 2.24 | 0.37 | - | - | δCCI(28), τCO(21) |
| 184 | 0.79 | 1.13 | - | - | τIII(10), τII(10), τCO(10) |
| 172 | 0.09 | 2.48 | - | 171 | τIII(16), γCN(21) |
| 168 | 0.16 | 0.75 | - | - | τIII(36), δCCI(17) |
| 164 | 0.19 | 1.62 | - | - | δCCI(79) |
| 162 | 0.28 | 0.66 | - | - | δCCI(35), τCH(3) |
| 160 | 1.02 | 0.79 | - | - | τCO(35), δCCI(22) |
| 149 | 1.47 | 0.30 | - | 150 | τCO(44) |
| 146 | 2.05 | 1.00 | - | - | δCCI(22), δCC(16) |
| 133 | 0.96 | 0.94 | - | - | τCO(35) |
| 127 | 1.79 | 1.22 | - | 128 | δCC(17), τII(12) |
| 123 | 1.46 | 0.63 | - | - | τII(26), γCN(19), τCO(14) |
| 115 | 0.44 | 0.19 | - | - | τCH(33), τCN(33) |
| 107 | 1.60 | 0.47 | - | 110 | τIII(41), τII(24) |
| 94  | 1.68 | 0.42 | - | 89  | τCO(21) |
| 84  | 0.29 | 0.57 | - | 83  | τI(25), τCH(3) |
| 78  | 0.79 | 2.63 | - | - | τCO(17), τI(14) |
| 72  | 0.15 | 1.98 | - | - | γCCI(27), τCH(2) |
| 59  | 0.10 | 3.75 | - | 65  | τII(31), τI(22), τCC(13) |
| 54  | 0.11 | 1.32 | - | - | τII(20), γCCI(20) |
| 52  | 0.24 | 2.99 | - | - | τCC(28), τII(18), τI(14) |
| 39  | 0.11 | 0.79 | - | - | τCH(27), τCN(17) |
| 26  | 0.03 | 1.55 | - | - | τIII(70) |
| 21  | 0.08 | 0.94 | - | - | τCN(31), τCH(2) |
| ν         | δ         | γ         | τ         |
|-----------|-----------|-----------|-----------|
| stretching| in-plane  | out-of-plane | torsion   |
| deformation| deformation| deformation|          |

Table 3
Chemical descriptors of TCDBPAD with halogen substitutions

|        | HOMO     | LUMO     | I = −E\text{HOMO} | A = −E\text{LUMO} | ΔE     | η = (I−A)/2 | μ = −(I+A)/2 | ω = μ²/2η |
|--------|----------|----------|-------------------|-------------------|--------|-------------|-------------|-----------|
| TDBPAD | −8.087   | −4.943   | 8.087             | 4.943             | 3.144  | 1.572       | −6.515      | 13.500    |
| TDBPAD Br | −7.750   | −4.945   | 7.750             | 4.945             | 2.805  | 1.403       | −6.347      | 14.357    |
| TDBPAD F | −8.069   | −4.944   | 8.069             | 4.944             | 3.425  | 1.713       | −6.507      | 12.359    |

Table 4
NBO results showing the formation of Lewis and non-Lewis orbitals

| Bond(A-B) | ED/e^a | EDA% | EDB% | NBO | s% | p% |
|-----------|--------|------|------|-----|----|----|
| σC₁-C₂    | 1.97824| 49.97| 50.03| 0.7069(sp^{1.53}) | 39.53| 60.47|
| -         | −0.79537| - | - | +0.7074(sp^{1.52})C | 39.63| 60.37|
| πC₁-C₂    | 1.93817| 49.60| 50.40| 0.7043(sp^{99.99})C | 0.78 | 99.22|
| -         | −0.35716| - | - | +0.7099(sp^{99.99})C | 0.71 | 99.29|
| σC₁-C₆    | 1.95491| 49.52| 50.48| 0.7037(sp^{1.85})C | 35.04| 64.96|
| -         | −0.68814| - | - | +0.7105(sp^{2.64})C | 27.45| 72.55|
| σC₁-Cl₃₆  | 1.98385| 45.17| 54.83| 0.6721(sp^{3.13})C | 24.18| 75.82|
| -         | −0.75533| - | - | +0.7405(sp^{4.94})Cl | 16.83| 83.17|
| σC₂-C₃    | 1.95585| 49.62| 50.38| 0.7044(sp^{1.85})C | 35.06| 64.94|
| -         | −0.68912| - | - | +0.7098(sp^{2.67})C | 27.27| 72.73|
| σC₁-Cl₃₅  | 1.98368| 45.11| 54.89| 0.6716(sp^{3.14})C | 24.15| 75.85|
| -         | −0.75561| - | - | +0.7409(sp^{4.65})Cl | 16.82| 83.18|
| σC₃-C₄    | 1.95171| 50.86| 49.14| 0.7132(sp^{2.63})C | 27.54| 72.46|
| -         | −0.64730| - | - | +0.7010(sp^{2.76})C | 26.58| 73.42|
| Bond | Distance (Å) | Angle (°) | u (Å) | v (Å) | w (Å) | σC (°) | σN (°) |
|------|-------------|-----------|-------|-------|-------|--------|--------|
| σC₃-C₇ | 1.93894 | 52.00 | - | - | - | 0.72111(sp².70)C | +0.6928(sp².69)C |
| σC₃-Cl₁₃ | 1.97855 | 44.74 | - | - | - | 0.6689(sp².66)C | +0.7434(sp³.15)Cl |
| σC₄-C₅ | 1.94613 | 49.96 | - | - | - | 0.7068(sp².05)C | +0.7074(sp³.06)C |
| σC₄-C₁₃ | 1.96505 | 52.36 | - | - | - | 0.7236(sp².98)C | +0.6902(sp³.178)C |
| σC₅-C₆ | 1.95457 | 49.37 | - | - | - | 0.7026(sp².05)C | +0.7115(sp³.06)C |
| σC₅-C₁₆ | 1.96469 | 52.21 | - | - | - | 0.7225(sp³.05)C | +0.6913(sp³.178)C |
| σC₆-C₇ | 1.93690 | 51.96 | - | - | - | 0.7208(sp².72)C | +0.7115(sp³.06)C |
| σC₆-Cl₁₇ | 1.97833 | 44.94 | - | - | - | 0.7225(sp³.05)C | +0.6913(sp³.178)C |
| σC₇-O₉ | 1.98700 | 31.75 | - | - | - | 0.5635(sp³.30)C | +0.8261(sp².12)O |
| σC₇-O₁₄ | 1.98639 | 31.24 | - | - | - | 0.5589(sp³.45)C | +0.8292(sp².14)O |
| σC₈-O₉ | 1.98644 | 30.69 | - | - | - | 0.5540(sp³.14)C | +0.8325(sp³.97)O |
| σC₁₁-O₁₄ | 1.98578 | 30.16 | - | - | - | 0.5492(sp³.24)C | +0.8357(sp³.03)O |
| σC₁₃-N₁₅ | 1.98295 | 35.62 | 64.38 | - | - | 0.5968(sp².28)C | +0.8024(sp².05)N |
| σC₁₃-O₁₈ | 1.99057 | 33.96 | 66.04 | - | - | 0.5828(sp³.96)C | +0.8126(sp³.16)O |
| πC₁₃-O₁₈ | 1.98302 | 32.18 | 67.82 | - | - | 0.5672(sp².99)C | +0.8236(sp².99)O |
| σN₁₅-C₁₆ | 1.98320 | 64.28 | 35.72 | - | - | 0.8018(sp².02)N | +0.5976(sp².27)C |
| σN₁₅-C₁₉ | 1.98111 | 64.94 | 35.06 | - | - | 0.8059(sp³.96)N | +0.5976(sp².27)C |
| Bond          | σ  | C  | O  | C  | C  | O  | C  | C  | N  | C  | C  | N  | C  | C  | N  | C  | C  | N  | C  | C  | N  | C  | C  | N  |
|---------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| C_16-O_17     | -  | -  | -  | +0.5921(sp\(^3\)C | 21.77 | 78.23 |
| C_16-O_17     | 1.99064 | 33.94 | 66.06 | 0.5826(sp\(^2\)C | 33.28 | 66.72 |
| C_16-O_17     | -1.06019 | -  | -  | +0.8128(sp\(^1\)O | 37.62 | 62.38 |
| C_17-O_17     | 1.98338 | 31.96 | 68.04 | 0.5653(sp\(^9.99\)C | 0.41 | 99.59 |
| C_17-O_17     | -0.40345 | -  | -  | +0.8249(sp\(^9.99\)O | 0.63 | 99.37 |
| C_19-C_28     | 1.97279 | 51.12 | 48.88 | 0.7150(sp\(^2\)C | 29.59 | 70.41 |
| C_19-C_28     | -0.59967 | -  | -  | +0.6991(sp\(^2\)C | 26.27 | 73.73 |
| C_28-C_31     | 1.97392 | 50.19 | 49.81 | 0.7084(sp\(^2\)C | 27.47 | 72.53 |
| C_28-C_31     | -0.58756 | -  | -  | +0.7058(sp\(^2\)C | 28.23 | 71.77 |
| C_31-N_38     | 1.97944 | 39.01 | 60.99 | 0.6246(sp\(^3\)O | 24.86 | 75.14 |
| C_31-N_38     | -0.68825 | -  | -  | +0.7810(sp\(^2\)N | 30.20 | 69.80 |
| N_38-C_39     | 1.98175 | 61.09 | 38.91 | 0.7816(sp\(^2\)N | 29.69 | 70.31 |
| N_38-C_39     | -0.68402 | -  | -  | +0.6238(sp\(^3\)C | 24.30 | 75.70 |
| N_38-C_40     | 1.98249 | 61.20 | 38.80 | 0.7823(sp\(^2\)N | 28.87 | 71.13 |
| N_38-C_40     | -0.67074 | -  | -  | +0.6229(sp\(^3\)C | 23.96 | 76.04 |
| C_39-C_46     | 1.97836 | 50.24 | 49.76 | 0.7088(sp\(^2\)C | 27.87 | 72.13 |
| C_39-C_46     | -0.58690 | -  | -  | +0.7054(sp\(^2\)C | 27.98 | 72.02 |
| C_40-C_45     | 1.97839 | 49.82 | 50.18 | 0.7058(sp\(^2\)C | 28.26 | 71.74 |
| C_40-C_45     | -0.58765 | -  | -  | +0.7084(sp\(^2\)C | 27.88 | 72.12 |
| C_45-N_47     | 1.98384 | 38.98 | 61.02 | 0.6244(sp\(^3\)N | 24.23 | 75.77 |
| C_45-N_47     | -0.68989 | -  | -  | +0.7811(sp\(^2\)N | 30.59 | 69.41 |
| C_46-N_47     | 1.98279 | 38.63 | 61.37 | 0.6215(sp\(^3\)N | 23.98 | 76.02 |
| C_46-N_47     | -0.67605 | -  | -  | +0.7834(sp\(^3\)N | 29.85 | 70.15 |
| N_47-C_63     | 1.97644 | 61.02 | 38.98 | 0.7811(sp\(^2\)N | 30.52 | 69.48 |
| N_47-C_63     | -0.68315 | -  | -  | +0.6244(sp\(^3\)N | 24.08 | 75.92 |
| C_52-C_53     | 1.97418 | 50.03 | 49.97 | 0.7073(sp\(^1\)C | 34.19 | 65.81 |
| C_52-C_53     | -0.67898 | -  | -  | +0.7069(sp\(^1\)C | 36.20 | 63.80 |
| C_52-C_54     | 1.97438 | 50.06 | 49.94 | 0.7076(sp\(^1\)C | 34.34 | 65.66 |
| C_52-C_54     | -0.68015 | -  | -  | +0.7067(sp\(^1\)C | 36.27 | 63.73 |
| C_52-C_54     | 1.65132 | 49.48 | 50.52 | 0.7034(sp\(^9.99\)C | 0.01 | 99.99 |
| C_52-C_54     | -0.24136 | -  | -  | +0.7108(sp\(^9.99\)C | 0.00 | 100.00 |
| C_52-C_63     | 1.97587 | 50.93 | 49.07 | 0.7136(sp\(^2.18\)C | 31.46 | 68.54 |
| C_52-C_63     | -0.60545 | -  | -  | +0.7005(sp\(^2.36\)C | 29.77 | 70.23 |
| Bond       | σ       | σ'       | σ''      | σ'''     | σ''''    | σ''''''  | σ'''''''' | σ'''''''''' |
|------------|---------|---------|----------|----------|----------|----------|-----------|-------------|
| C_53-C_55  | 1.97948 | -0.68226| 50.31    | 49.69    | 0.7093(sp^{1.83})C | +0.7049(sp^{1.80})C | 35.31      | 64.69       |
| C_54-C_57  | 1.97936 | -0.68122| 50.29    | 49.71    | 0.7092(sp^{1.84})C | +0.7050(sp^{1.80})C | 35.22      | 64.78       |
| C_55-C_59  | 1.98096 | -0.68066| 50.06    | 49.94    | 0.7075(sp^{1.83})C | +0.7067(sp^{1.83})C | 35.34      | 64.66       |
| C_57-C_59  | 1.98105 | -0.68145| 50.06    | 49.94    | 0.7075(sp^{1.83})C | +0.7067(sp^{1.82})C | 35.38      | 64.62       |
| n_1O_9     | 1.95633 | -0.55802| -        | sp^{1.32} | -        | -        | 43.17      | 56.83       |
| n_2O_9     | 1.90856 | -0.32359| -        | sp^{99.99} | -        | -        | 0.24       | 99.76       |
| n_1O_14    | 1.95235 | -0.56939| -        | sp^{1.31} | -        | -        | 43.32      | 56.68       |
| n_2O_14    | 1.90829 | -0.32907| -        | sp^{1.00} | -        | -        | 0.00       | 100.00      |
| n_2N_15    | 1.58281 | -0.28576| -        | sp^{99.99} | -        | -        | 0.20       | 99.80       |
| n_1O_17    | 1.97276 | -0.69378| -        | sp^{0.62} | -        | -        | 61.76      | 38.24       |
| n_2O_17    | 1.86985 | -0.28049| -        | sp^{99.99} | -        | -        | 0.03       | 99.97       |
| n_1O_18    | 1.97322 | -0.69164| -        | sp^{0.62} | -        | -        | 61.81      | 38.19       |
| n_2O_18    | 1.86933 | -0.27815| -        | sp^{99.99} | -        | -        | 0.03       | 99.97       |
| n_1Cl_34   | 1.98558 | -0.96771| -        | sp^{0.19} | -        | -        | 83.74      | 16.26       |
| n_2Cl_34   | 1.96397 | -        | sp^{99.99} | -        | -        | -        | 0.02       | 99.98       |
|     | ED/e in a.u. |     |     |     |     |     |
|-----|-------------|-----|-----|-----|-----|-----|
| n_1Cl_{34} | 1.95935 | -0.32502 | - | - | sp^{1.00} | 0.00 | 100.00 |
| n_2Cl_{35} | 1.96514 | -0.34298 | - | - | sp^{99.99} | 0.38 | 99.62 |
| n_3Cl_{35} | 1.96474 | -0.34179 | - | - | sp^{99.99} | 0.44 | 99.56 |
| n_1Cl_{36} | 1.98623 | -0.95771 | - | - | sp^{0.21} | 82.73 | 17.27 |
| n_2Cl_{36} | 1.96375 | -0.31995 | - | - | sp^{99.99} | 0.14 | 99.86 |
| n_3Cl_{36} | 1.95864 | -0.32218 | - | - | sp^{1.00} | 0.00 | 100.00 |
| n_1N_{38} | 1.88515 | -0.23865 | - | - | sp^{7.90} | 11.24 | 88.76 |
| n_1N_{47} | 1.87222 | -0.22884 | - | - | Sp^{10.06} | 9.04 | 90.96 |

*a ED/e in a.u.*
Table 5
Second-order perturbation theory analysis of Fock matrix in NBO basis corresponding to the intramolecular bonds of TCDBPAD

| Donor(i) | Type | ED/e | Acceptor(j) | Type | ED/e | E(2) | E(j)-E(i) | F(i,j) |
|----------|------|------|-------------|------|------|------|-----------|--------|
| C_{52}-C_{54} | π | - | C_{53}-C_{55} | π* | 0.32725 | 20.57 | 0.28 | 0.068 |
| C_{52}-C_{54} | π | - | C_{57}-C_{59} | π* | 0.33212 | 22.42 | 0.28 | 0.071 |
| C_{53}-C_{55} | π | 1.66968 | C_{52}-C_{54} | π* | 0.34688 | 21.93 | 0.29 | 0.071 |
| C_{53}-C_{55} | π | - | C_{57}-C_{59} | π* | 0.33212 | 20.86 | 0.28 | 0.068 |
| C_{57}-C_{59} | π | 1.66603 | C_{52}-C_{54} | π* | 0.34688 | 20.35 | 0.29 | 0.068 |
| C_{57}-C_{59} | π | - | C_{53}-C_{55} | π* | 0.32725 | 21.54 | 0.28 | 0.070 |
| LPN_{15} | σ | 1.58281 | C_{13}-O_{18} | π* | 0.23191 | 50.47 | 0.26 | 0.108 |
| LPN_{15} | σ | - | C_{16}-O_{17} | π* | 0.24727 | 51.78 | 0.26 | 0.108 |
| LPO_{17} | π | 1.86985 | C_{5}-C_{16} | σ* | 0.07452 | 20.16 | 0.59 | 0.099 |
| LPO_{17} | π | - | N_{15}-C_{16} | σ* | 0.08987 | 25.63 | 0.63 | 0.115 |
| LPO_{18} | π | 1.86933 | C_{4}-C_{13} | σ* | 0.07415 | 20.01 | 0.60 | 0.099 |
| LPO_{18} | π | - | C_{13}-N_{15} | σ* | 0.09077 | 25.99 | 0.63 | 0.115 |
| LPC_{35} | n | - | C_{2}-C_{3} | σ* | 0.05851 | 14.68 | 0.33 | 0.064 |
| LPC_{36} | n | 1.91620 | C_{1}-C_{2} | π* | 0.19750 | 14.97 | 0.33 | 0.064 |

a E(2) means energy of hyperconjugative interactions (stabilization energy).
b Energy difference between donor and acceptor i and j NBO orbitals.
c F(i,j) is the Fock matrix element between i and j NBO orbitals.

Table 6
Polarizability values of TCDBPAD and halogen substitutions

|        | μ  | α × 10^{-23} esu | β × 10^{-30} esu | γ × 10^{-37} esu | MR = 1.333παN = 25.21 α |
|--------|----|-----------------|-----------------|-----------------|------------------------|
| TCDBPAD| -6.515 | 4.7836 | 1.6690 | -73.528 | 120.595 |
| TCDBPAD Br | -6.347 | 5.1027 | 1.7503 | -82.795 | 128.639 |
| TCDBPAD F | -6.507 | 4.1196 | 2.4111 | -61.574 | 103.855 |
Table 7

Values of solubility parameters $\delta$ [MPa$^{1/2}$] for studied molecules and the excipients

| Molecules  | $\delta$ [MPa$^{1/2}$] |
|------------|------------------------|
| TCDBPAD    | 19.104                 |
| PVP        | 18.515                 |
| Maltose    | 28.564                 |
| Sorbitol   | 32.425                 |

Table 8

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

| Mode | Affinity (kcal/mol) | Distance from best mode (Å) | RMSD l.b. | RMSD u.b. |
|------|---------------------|----------------------------|------------|-----------|
| 1    | −5.7                | 0.000                      | 0.000      |           |
| 2    | −5.6                | 4.557                      | 7.013      |           |
| 3    | −5.4                | 4.988                      | 6.946      |           |
| 4    | −5.2                | 3.252                      | 5.035      |           |
| 5    | −5.1                | 3.181                      | 5.055      |           |
| 6    | −5.1                | 2.128                      | 3.957      |           |
| 7    | −4.9                | 4.194                      | 6.630      |           |
| 8    | −4.9                | 19.743                     | 23.149     |           |
| 9    | −4.8                | 26.463                     | 29.416     |           |