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Spectroscopic characterization of 8-hydroxy-5-nitroquinoline and 5-chloro-8-hydroxy quinoline and investigation of its reactive properties by DFT calculations and molecular dynamics simulations

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Abstract

Combined spectroscopic and computational study of two 8-hydroxyquinoline derivatives, 8-hydroxy-5-nitroquinoline (8H5NQ) and 5-chloro-8-hydroxyquinoline (5CL8HQ) has been performed in order to perform detailed characterization and evaluation of their reactive properties. Spectroscopic characterization of 8-hydroxyquinoline derivatives has been performed by means of IR and FT-Raman techniques, while computational study has been performed by set of DFT calculations and MD simulations in order to address global and local reactive properties. Spectroscopic properties have also been obtained with DFT calculations as well, and the obtained results have been mutually compared. The calculated values of dipole moment, polarizability, first and second order hyperpolarizability values indicate that the title compounds exhibit NLO behaviour and hence may be considered for further development of NLO materials. NBO analysis is made to study the stability of the molecular systems arising from hyper conjugative interactions and charge delocalization. The docked ligands form stable complexes with dehydrogenase inhibitor which gives binding affinity value of -6.2kcal/mol for 5CL8HQ and -5.8kcal/mol for 8H5NQ and the docking results suggest that the compounds might exhibit inhibitory activity against ACP reductase.

Keywords: DFT; ALIE; RDF; BDE; Molecular docking.

1. Introduction

Quinoline derivatives have wide applications such as optical switches in nonlinear optics, live saving drugs, sensors in electrochemistry and in the field of inorganic chemistry [1, 2]. Chloroquinoline derivatives exhibit antileishmanial activity [3] and antimalarial activity [4-7]. Hydroxyquinoline derivatives are commonly used for chelating metal cations and are highly fluorescent [8-11], and used for quantification of metal ions. The importance of computational molecular modelling lies in the fact that it can be employed efficiently for the prediction of various reactive properties of organic molecules such as the ones investigated in this study [12-16]. Among many properties, certain set of quantities calculated by DFT calculations and MD simulations can be used in order to address degradation properties of organic molecules, which is of great importance taking into account the necessity to constantly improve degradation procedures [17-20]. Modern degradation procedures are based on the advanced oxidation processes, thanks to which organic molecules such as 5CL8HQ and 8H5NQ can be efficiently removed from different types of water [21-23].

2. Experimental details

Fine samples of the title compounds were obtained from Sigma Aldrich chemical company, USA and used without any further purification for spectral measurements. The FT-IR spectrum (Fig.1) of the title compound was recorded in the region 4000-400 cm^{-1} using Perkin-Elmer spectrum RX1 spectrometer equipped with Helium-Neon laser source, potassium bromide beam splitter and LiTaO₃ detector. The sample was prepared by pressing the title compound with KBr into pellet form. The FT-Raman spectrum (Fig.2) of the title compound was recorded in 4000-0 cm^{-1} with a Nocolet model 950 FT-Raman spectrometer at 4 cm^{-1} spectral resolution using the 1064 nm line of a Nd:YAG laser for excitation at a 200 mW output power.

3. Computational details

Calculations of the wavenumbers, polarizability values, frontier molecular orbital analysis were carried out with Gaussian 09 program [24] using the B3LYP/6-311++G(d)(5D,7F) quantum chemical calculation method. A scaling factor of 0.9613 is used to scale the theoretically obtained wavenumbers [25] and the assignments of the vibrational wavenumbers are done by using GaussView [26] and GAR2PED software [27]. Combination of DFT calculations and MD simulations with Schrödinger Materials Science Suite 2017-3(SMSS) has been undertaken in order to address the most important reactive properties of these two 8-hydroxyquinoline derivatives. By using Jaguar 9.6 [28] program for DFT calculations and Desmond [29-32] program for MD simulations, we have evaluated a set of global and local reactive properties. For DFT calculations a B3LYP exchange-correlation functional [33] was employed, with 6-311++G(d,p), 6-31+G(d,p) and 6-311G(d,p) basis sets, for calculations of ALIE, Fukui functions and BDEs, respectively. For MD simulations with Desmond program, an OPLS3 [29, 34-36] force field was employed with simulation time of 10 ns. Other parameters of MD simulation included temperature of 300 K, pressure of 1.0325 bar and cut off radius of 10 Å. The whole system was considered as isothermal-isobaric (NPT) ensemble class, with simple point charge (SPC) model [37] used for modelling of the solvent. MD system was prepared by placing of one molecule into the cubic box with approximately 2000 water molecules. All calculations and simulations by Jaguar and Desmond programs have been prepared and analyzed with Maestro GUI [38].

4. Results and discussion

4.1. IR and Raman spectra

The observed IR, Raman bands, theoretical scaled wavenumbers and assignments of the vibrational modes of 8H5NQ and 5CL8HQ are presented in table 1. In the following discussion, the rings in the optimized geometries of the title molecules (Fig.3) C1-C2-C3-C4-C5-C6 and C4-C5-C10-C9-C8-N7 are designated as PhI and PhII, respectively.

Although structures studied in this work are not significantly complex to yield many conformations, in general it is important to mention that selection of conformations is crucial [39]. In these regards, a method based on the optimal wavelet signal compression algorithm has been developed recently for selection of conformations obtained by MD simulations [40]. In poly substituted benzenes, [41] the aromatic CH stretching modes absorb between 3000 and 3120 cm^{-1} and for the title compounds, the bands at 3102, 3081 (PhI) and 3134, 3070, 3040 cm^{-1} (PhII) (DFT) are assigned the CH stretching vibrations of 8H5NQ and 3091, 3075 cm^{-1} (PhI) and 3086, 3068, 3049 cm^{-1} (PhII) (DFT) for 5CL8HQ [42]. These modes are observed at 3099, 3093, 3070, 3065, 3030 cm^{-1} in the Raman spectrum and 3125, 3069 cm^{-1} in the IR spectrum, experimentally. The CC phenyl stretching modes are assigned at 1604, 1546, 1442, 1376, 1327 cm^{-1} for PhI, 1571, 1546, 1485, 1353, 1238 cm^{-1} for PhII (8H5NQ) and at 1606, 1532, 1442, 1393, 1325 cm^{-1} for PhI, 1559, 1532, 1470, 1325, 1240 cm^{-1} for PhII (5CL8HQ) [43] theoretically. Experimentally these modes are observed at 1615, 1376, 1322 cm^{-1} (PhI), 1572, 1480, 1349 cm^{-1} (PhII) cm^{-1} in the IR spectrum, 1615, 1442, 1375, 1323 cm^{-1} (PhI), 1573, 1481, 1242 cm^{-1} (PhII) in the Raman spectrum for 8H5NQ and at 1599, 1392 cm^{-1} (PhI), 1565, 1467 cm^{-1} (PhII) cm^{-1} in the IR spectrum, 1395 cm^{-1} (PhI), 1564, 1468, 1244 cm^{-1} (PhII) in the Raman spectrum for 5CL8HQ. The ring breathing mode

of poly substituted phenyl rings is reported at 1006 cm^{-1} (IR) and at 998 cm^{-1} (DFT) [44] and at 1003 cm^{-1} (DFT) [42]. In the present case the ring breathing mode of phenyl rings of 8H5NQ and 5CL8HQ are assigned theoretically at 1027 and 1016 cm^{-1} . The C-H deformation (in-plane) of the phenyl ring are assigned at 1162 cm^{-1} (IR), 1164 cm^{-1} (Raman), $1137, 1169\text{ cm}^{-1}$ (DFT) for PhI, $1137, 1118, 1027\text{ cm}^{-1}$ (DFT) for PhII (8H5NQ) and at 1196 cm^{-1} (IR), 1175 cm^{-1} (Raman) $1193, 1173\text{ cm}^{-1}$ (DFT) for PhI, $1223, 1147\text{ cm}^{-1}$ (IR), $1244, 1219, 1150\text{ cm}^{-1}$ (Raman), $1240, 1225, 1146\text{ cm}^{-1}$ (DFT) for PhII (5CL8HQ) as expected in literature [43]. The γCH bending modes of the phenyl rings are assigned at $834, 790\text{ cm}^{-1}$ (IR), $977, 931, 790\text{ cm}^{-1}$ (Raman), $971, 941, 929, 826, 787\text{ cm}^{-1}$ (DFT) for 8H5NQ and at $982, 945, 803\text{ cm}^{-1}$ (IR), $983, 944, 735\text{ cm}^{-1}$ (Raman), $985, 943, 836, 806, 749\text{ cm}^{-1}$ (DFT) for 5CL8HQ [43].

Quinoline ring stretching modes are reported at: 1563 cm^{-1} (IR), 1560 cm^{-1} (Raman) and 1568 cm^{-1} (DFT) (C=C stretching); 1500 cm^{-1} (Raman) and 1527 cm^{-1} (DFT) (C=N stretching); 1281 cm^{-1} (IR), 1285 cm^{-1} (Raman) and 1285 cm^{-1} (DFT) (C-N stretching); 1476 cm^{-1} (IR), 1205 cm^{-1} (Raman), 1204 and 1474 cm^{-1} (DFT) (C-C stretching) [45]. Sureshkumar et al. [46] reported the ring PhII modes at $3115, 3076, 3025\text{ cm}^{-1}$ (IR), $3109, 3077\text{ cm}^{-1}$ (Raman), $3107, 3078, 3044\text{ cm}^{-1}$ (DFT) (CH stretching modes), 1571 cm^{-1} (DFT) (C=C stretching), 1055 cm^{-1} (IR), 908 cm^{-1} (Raman), $1052, 915\text{ cm}^{-1}$ (C-C stretching), 1233 cm^{-1} (IR), 1260 cm^{-1} (Raman), $1255, 1237\text{ cm}^{-1}$ (DFT) (C-N stretching), $1372, 1130\text{ cm}^{-1}$ (IR), $1372, 1130\text{ cm}^{-1}$ (Raman), $1368, 1349, 1127\text{ cm}^{-1}$ (DFT) (in-plane CH deformation modes) and at $972, 779\text{ cm}^{-1}$ (IR), $977, 782\text{ cm}^{-1}$ (Raman), $970, 935, 781\text{ cm}^{-1}$ (DFT) (out-of-plane CH deformation modes).

The in-plane OH bending mode is expected in the range $1350\text{--}1480\text{ cm}^{-1}$ [43] and the bands at 1403 cm^{-1} (IR), 1402 cm^{-1} (Raman), 1405 cm^{-1} (DFT) and 1372 cm^{-1} (IR), 1374 cm^{-1} (Raman), 1378 cm^{-1} (DFT) are assigned as the OH in-plane deformation modes for 8H5NQ and 5CL8HQ. The C-O stretching mode is assigned theoretically at 1264 cm^{-1} and 1225 cm^{-1} for 8H5NQ and 5CL8HQ [47, 48]. The out-of-plane OH deformation is expected in the range $730\text{--}570\text{ cm}^{-1}$ [43] and in the present case this mode is assigned at 653 and 598 cm^{-1} (DFT) for 8H5NQ and 5CL8HQ, respectively.

The stretching modes of NO_2 group are assigned at $1508, 1293\text{ cm}^{-1}$ (IR), $1502, 1292\text{ cm}^{-1}$ (Raman) and $1505, 1294\text{ cm}^{-1}$ (DFT) [43] and the reported values are [49] at $1566, 1345\text{ cm}^{-1}$ (IR), $1565, 1345\text{ cm}^{-1}$ (Raman) and $1568, 1342\text{ cm}^{-1}$ (DFT). In the present case, bands at 820 cm^{-1} (IR), 822 cm^{-1} (Raman) and $823, 786, 588\text{ cm}^{-1}$ (DFT) are assigned as NO_2 deformation vibrations which are expected in regions at $850 \pm 60, 740 \pm 50$ and $540 \pm 70\text{ cm}^{-1}$ [43] and reported values are at $811, 724, 526\text{ cm}^{-1}$ (IR), $810, 730, 530\text{ cm}^{-1}$ (Raman) and $808, 726, 528\text{ cm}^{-1}$ (DFT) [49]. For the title compound, 5CL8HQ, C-Cl stretching mode is assigned at 628 cm^{-1} as expected [50]. The reported values of C-Cl stretching modes are 670 cm^{-1} (IR), 663 cm^{-1} (Raman) and 665 cm^{-1} (DFT) [51].

4.2. Nonlinear optical properties

Nonlinear optics gives the effect of electromagnetic fields in various materials to produce new fields, altered in wavenumber and other properties of the molecular systems [52, 53]. The calculated polarizability of 8H5NQ and 5CL8HQ are 2.035×10^{-23} and 1.845×10^{-23} esu. The dipole moments of 8H5NQ and 5CL8HQ are respectively, 4.139 and 2.187 Debye. The first order hyperpolarizabilities are 9.773×10^{-30} and 79.914×10^{-30} esu for 8H5NQ and 5CL8HQ which are comparable with the reported values of similar derivatives [45] and these values are 75.18 and 614.72 times that of the standard NLO material urea [54]. The reported values of first hyperpolarizability of similar derivatives are 5.37×10^{-30} [45] and 16.9×10^{-30} [55]. The theoretically predicted second order hyperpolarizabilities are -5.556×10^{-37} esu for 8H5NQ and -4.892×10^{-37} esu for 5CL8HQ and the reported values are -28.33×10^{-37} esu [45], -21.14×10^{-37} esu [56]. Hence the title compounds and its derivatives are good objects for further studies of nonlinear optical properties. The calculated C-N distances ($1.3159, 1.3555, 1.4662\text{ \AA}$ for 8H5NQ and $1.3707, 1.4245\text{ \AA}$ for 5CL8HQ) in the molecular

structures of the title compounds are in between a single and double bond character of C-N bond and hence, the calculated data suggests an extended π -electron delocalization of the quinoline moiety, which were responsible for the nonlinearity of the molecules [57].

4.3. Frontier molecular orbital analysis

Concerning the frontier molecular orbitals of molecules studied in this work, HOMO and LUMO plots of 8H5NQ and 5CL8HQ molecules are shown in Fig.4 and the delocalization of molecular orbitals show the charge transfer in the molecular systems. Using information on the energies of HOMO and LUMO, useful and frequently used quantum-molecular descriptors such as the ionization energy and electron affinity can be calculated according to the following simple relations: $I = -E_{\text{HOMO}}$, $A = -E_{\text{LUMO}}$, $\eta = (-E_{\text{HOMO}} + E_{\text{LUMO}})/2$ and $\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2$ [58]. Parr et al. [59] proposed the global electrophilicity power of a ligand as $\omega = \mu^2/2\eta$. For the title compounds, energy difference between HOMO and LUMO, HOMO-LUMO gap, are equal to 2.95 eV for 8H5NQ and 2.52 eV for 5CL8HQ. Ionization potential, I , and electron affinity, A , are calculated to be 8.35 eV, 5.4 eV and 7.72, 5.20 eV for 8H5NQ and 5CL8HQ, respectively. The values of HOMO-LUMO gap and global hardness ($\eta = 1.48$ for 8H5NQ and 1.26 eV for 5CL8HQ) are almost the same as in the case of other similar derivatives that we have previously investigated [45, 56]. Although the stability parameters of these derivatives are practically the same, there are significant differences in the values of chemical potential and global electrophilicity. Also, the calculated electrophilicity of the 8H5NQ and 5CL8HQ molecules are 15.99 and 16.56 eV, which is significantly lower than the value of electrophilicity of derivative in the work of Rajeev et al. [45,56], with the values of 28.29 and 24.40 eV, meaning that the title molecules are much more stable. While analysis of reactive properties based on frontier molecular orbitals has certain limitations [60], it remains frequently utilized technique in computational molecular modelling. Beside HOMO and LUMO orbitals, it is also important to mention concept of frontier effective-for-reaction molecular orbital (FERMO), which allows understanding of reactions that are not driven by HOMO and LUMO [60]. Another set of useful descriptors is based on charge transfer, which was coupled with FERMO concept by La Porta et al. [61] to yield novel reactivity index capable to describe thermodynamic properties of certain reactions. For the purpose of understanding reactivity and influence of substitutions to fundamental physical and chemical properties, it is also useful to mention that principal component analysis can be applied [62].

4.4. Natural bond orbital analysis

Using NBO 3.1 program [63] the NBO calculations were performed at the DFT level to understand the various second order interactions in the title compounds. For 8H5NQ, the strong intra-molecular hyper-conjugative interactions are: C_3-C_4 from N_{13} of $n_1(N_{13}) \rightarrow \sigma^*(C_3-C_4)$, C_4-C_5 from O_{14} of $n_1(O_{14}) \rightarrow \sigma^*(C_4-C_5)$, C_5-C_6 from O_{14} of $n_2(O_{14}) \rightarrow \pi^*(C_5-C_6)$ and $n_3(O_{14}) \rightarrow \sigma^*(C_5-C_6)$, $N_{18}-O_{20}$ from O_{19} of $n_2(O_{19}) \rightarrow \sigma^*(N_{18}-O_{20})$ and $n_3(O_{19}) \rightarrow \pi^*(N_{18}-O_{20})$ and $N_{18}-O_{19}$ from O_{20} of $n_2(O_{20}) \rightarrow \sigma^*(N_{18}-O_{19})$ with electron densities, 0.038, 0.043, 0.322, 0.023, 0.056, 0.647, 0.057e and stabilization energies, 10.64, 7.14, 38.03, 5.60, 19.64, 156.03, and 19.14 kJ/mol. The natural hybrid orbitals with higher energies, and low occupation numbers are $n_2(O_{14})$, $n_2(O_{19})$ and $n_2(O_{20})$ with energies, -0.33152, -0.29074, -0.28535 a.u, p-characters, 100.00, 99.54, 99.94% and occupation numbers, 1.81482, 1.90103 and 1.89160 whereas the orbitals with lower energies and high occupation numbers are, $n_1(O_{14})$, $n_1(O_{19})$ and $n_1(O_{20})$ with energies, -0.599, -0.789, -0.791 a.u and p-characters, 57.59, 25.65, 25.33% and occupation numbers, 1.976, 1.978 and 1.981. Thus, a very close to pure p-type lone pair orbital participates in the electron donation to the $\sigma^*(C_3-C_4)$ orbital for $n_1(N_{13}) \rightarrow \sigma^*(C_3-C_4)$, $\sigma^*(C_4-C_5)$ orbital for $n_1(O_{14}) \rightarrow \sigma^*(C_4-C_5)$, $\pi^*(C_5-C_6)$ orbital for $n_2(O_{14}) \rightarrow \pi^*(C_5-C_6)$, $\sigma^*(C_5-C_6)$ orbital for $n_3(O_{14}) \rightarrow \sigma^*(C_5-C_6)$, $\sigma^*(N_{18}-O_{20})$ orbital for $n_2(O_{19}) \rightarrow \sigma^*(N_{18}-O_{20})$, $\pi^*(N_{18}-O_{20})$ orbital for $n_3(O_{19}) \rightarrow \pi^*(N_{18}-O_{20})$ and $\sigma^*(N_{18}-O_{19})$ orbital for $n_2(O_{20}) \rightarrow \sigma^*(N_{18}-O_{19})$ interaction in the compound.

For 5CL8HQ, the strong intra-molecular hyper-conjugative interactions are: C₅-N₁₅ from C₄ of n₁(C₄)→π*(C₅-N₁₅), C₃-C₄ from N₁₅ of n₁(N₁₅)→σ*(C₃-C₄), C₈-C₁₂ from Cl₁₆ of n₃(Cl₁₆)→π*(C₈-C₁₂), C₄-C₉ from O₁₇ of n₁(O₁₇)→σ*(C₄-C₉) and C₉-C₁₁ from O₁₇ of n₂(O₁₇)→π*(C₉-C₁₁) with electron densities, 0.317, 0.041, 0.326, 0.041, 0.319e and stabilization energies, 62.08, 9.64, 9.26, 6.25 and 32.28kJ/mol. The natural hybrid orbital with high energy and low occupation number is n₂(O₁₇) with energy -0.311a.u, p-character 100% and occupation number 1.851 whereas the orbital with lower energy and high occupation number is n₁(O₁₇) with energy -0.570 a.u and p-character 55.24% and occupation number 1.978. Thus, a very close to pure p-type lone pair orbital participates in the electron donation to the π*(C₅-N₁₅) orbital for n₁(C₄)→π*(C₅-N₁₅), σ*(C₃-C₄) orbital for n₁(N₁₅)→σ*(C₃-C₄), π*(C₈-C₁₂) orbital for n₃(Cl₁₆)→π*(C₈-C₁₂), σ*(C₄-C₉) orbital for n₁(O₁₇)→σ*(C₄-C₉), π*(C₉-C₁₁) orbital for n₂(O₁₇)→π*(C₉-C₁₁) interaction in the compound. The results are tabulated in tables 2 and 3.

4.5. ALIE surface, Fukui functions and noncovalent interactions

Molecular electrostatic potential (MEP) is very useful quantum-molecular descriptor for detection of reactive molecular areas [17, 64]. This descriptor is frequently employed in order to detect molecular sites that are possibly prone to electrophilic or nucleophilic attacks. Very convenient illustration of the reactive sites determined by MEP descriptor is obtained by mapping of MEP values to the electron density surface, which has been done in the case of this work as well (Fig.5). However, in order to obtain clearer picture on sites that could be prone to electrophilic attacks, we have also calculated and visualized average local ionization energies (ALIE) in the same manner as in the case of MEP. Considering the definition of ALIE descriptor, according to which it represents the energy required to remove an electron from the certain area of molecule, it can be stated that ALIE is a little bit more appropriate quantum-molecular descriptor than MEP, when it comes to determination of molecule sites prone to electrophilic attacks. ALIE values mapped to the electron density surface indicate molecule sites characterized by the least tightly bonded electrons, which are easiest for removal from molecule [65-68]. ALIE surfaces of the investigated molecules have also been presented in Fig.5. Concerning the MEP surfaces it can be seen in Fig.5 that much higher magnitudes of MEP values have been calculated in the case of 5CL8HQ molecule, indicating its higher reactivity comparing with 8H5NQ molecule. Similar conclusion can be drawn for ALIE descriptor, as much lower values (more than 30 kcal/mol) have been also calculated in the case of 5CL8HQ, indicating that much lower energy is required for the removal of electrons comparing to 8H5NQ. According to the MEP surfaces, the lowest values of the MEP in the case of 5CL8HQ molecule have been calculated in the molecular area between oxygen and nitrogen atom, with corresponding MEP values of 46kcal/mol, which indicates that this molecule area could be prone to electrophilic attacks. On the other side, the highest MEP values in the case of 5CL8HQ molecule have been calculated in the near vicinity of hydrogen atom belonging to OH group, thanks to which this molecular area could be prone to nucleophilic attacks. On the other side, the lowest ALIE values in the case of 5CL8HQ molecule are located more in the near vicinity of nitrogen atom, indicating that sensitivity of 5CL8HQ molecule towards electrophilic attacks is higher in the near vicinity of nitrogen rather than oxygen atom. While MEP and ALIE surfaces in the case of 5CL8HQ molecule are relatively similar in terms of identification of molecule's sites sensitive towards electrophilic attacks, they significantly differ in the case of 8H5NQ molecule. Namely, MEP surface of 8H5NQ recognizes near vicinity of oxygen atoms as possibly sensitive towards electrophilic attacks, while ALIE surface of 8H5NQ again recognizes near vicinity of nitrogen atom and two locations above rings as sensitive towards electrophilic attacks. Lowest ALIE values are also located in the near vicinity of oxygen atoms of NO₂ group, but to much lower extent in comparison with 5CL8HQ molecule.

Investigation of electron density between atoms of 5CL8HQ and 8H5NQ molecules revealed that two very strong intra-molecular non-covalent interactions formed in the case of 8H5NQ

molecule (Fig.6), comparing to the 5CL8HQ molecule in which case intra-molecular non-covalent interactions didn't form at all.

Aside of MEP and ALIE surfaces, electrophilic and nucleophilic properties of 5CL8HQ and 8H5NQ molecules have been addressed by Fukui functions in finite difference approximation according to equations:

$$f^+ = \frac{(\rho^{N+\delta}(r) - \rho^N(r))}{\delta}, \quad (1)$$

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

where N stands for the number of electrons in reference state of the molecule, while δ stands for the fraction of electron which default value is set to be 0.01 [69]. Same as in the cases of MEP and ALIE surfaces, the values of Fukui functions have been mapped to the electron density surface and the following illustrative Fig.7 has been obtained. According to definitions provided in equations (1) and (2), in case of Fukui f^+ function, positive color (purple color) corresponds to the areas where electron density increased after the addition of overall charge. This means that in case of 5CL8HQ electron density increased in the near vicinity of hydrogen atom of OH group as a consequence of charge addition, marking this molecule area as electrophilic. In the case of 8H5NQ molecule purple color is located in the near vicinity of carbon atom C5, marking this location as electrophilic after the charge addition. On the other side, in case of Fukui f^- function, negative color (red color) corresponds to the areas where electron density decreased after the removal of charge. Red color in case of 5CL8HQ molecule is located between carbon atoms C4 and C5, marking this location as nucleophilic. On the other side, red color in case of Fukui f^- function of 8H5NQ molecule is located in the area above carbon atom C5, marking it also as nucleophilic molecular area.

4.6. Reactive and degradation properties based on autoxidation and hydrolysis

DFT calculations also enable prediction of molecular sites that are possibly sensitive towards the autoxidation mechanism, which is of great importance for understanding of the degradation properties of organic molecules. This is especially important when it is taken into account that oxidation reactions are considered to be among the most important degradation pathways of pharmaceuticals and organic materials [70]. Sensitivity towards the autoxidation can be assessed by calculations of bond dissociation energies for hydrogen abstraction (H-BDE) [70-72]. H-BDE values for 5CL8HQ and 8H5NQ molecules are summarized in Fig.8, together with BDE values for the rest of single acyclic bonds. Sensitivity of molecules towards the autoxidation is reflected by H-BDE values ranging between 70 and 85 kcal/mol [73,74]. H-BDE values between 85 and 90 kcal/mol also might indicate sensitivity towards the autoxidation [74], however H-BDE values lower than 70 kcal/mol don't indicate sensitivity towards the autoxidation mechanism [12, 73, 75].

Results provided in Fig.8 show that there is one representative H-BDE value in the case of 5CL8HQ molecule, which indicates sensitivity towards the autoxidation mechanism. Namely, in the case of 5CL8HQ molecule, H-BDE value for the O-H bond is equal to 85.5kcal/mol. However, the presence of NO₂ group in the 8H5NQ molecule dramatically increases the H-BDE value of the aforementioned O-H bond to the value of almost 119kcal/mol, which clearly doesn't indicate sensitivity of 8H5NQ towards autoxidation mechanism. In the same time, BDE value for the detachment of NO₂ group in the case of 8H5NQ is much lower than the BDE value of detachment of chlorine atom in the case of 5CL8HQ.

Understanding the influence of water as solvent to the organic molecules such as 5CL8HQ and 8H5NQ is of particular importance in order to understand their stability in water. In this regard it is particularly useful to identify which atoms are having significant interactions with water molecules, which is readily obtained by calculations of radial distribution functions (RDF) after molecular dynamics simulations. RDFs for 5CL8HQ and 8H5NQ molecules

have been summarized in Fig.9. RDFs of 5CL8HQ and 8H5NQ are practically identical in terms of number of atoms with significant interactions with water and their $g(r)$ profiles. RDF results indicate that in cases of both 5CL8HQ and 8H5NQ molecules hydrogen atoms of OH group have the most important $g(r)$ profiles whose maximums are located at distances somewhat lower than 2 Å. The importance of OH group in terms of interactivity with water is also seen in the fact that oxygen atoms corresponding to OH group also have relatively significant $g(r)$ curves. Carbon atoms C8 of both molecules have relatively significant profiles. Chlorine atom of 5CL8HQ and nitrogen atom of 8H5NQ have practically the same $g(r)$ curves, characterized by maximal $g(r)$ values located at distances between 3.5 Å and 4 Å.

4.7. Molecular docking

PASS (Prediction of Activity Spectra) [76] predicts different types of activities of the molecules and the PASS analysis of the title compounds, 5CL8HQ and 8H5NQ, predicts activities given in the table 4; Amine dehydrogenase inhibitor with probability to be active (Pa) value of 0.907 for 5CL8HQ and 0.892 for 8H5NQ. Different literature suggest that quinolone derivatives [77, 78] and aminodehydrogenase [79] as antimalarial. Thus we have to design these two compounds are new antimalarial drugs because Malaria is one of the leading causes of severe infectious disease worldwide and the effective therapy to combat the illness is continually challenged by the emergence of drug resistance. High resolution crystal structure of dehydrogenase inhibitor was downloaded from the protein data bank website (PDB ID: 5TBO). All molecular docking calculations were performed on AutoDock-Vina software [80] and as reported in literature [81, 82]. The ligands bind at the active site of the substrate by weak non-covalent interactions. Amino acids Arg296, Asp235 and Lys193 form π -cation, π -anion and π -alkyl interaction with phenyl ring in both the compounds as detailed in Fig.10. The docked ligands form stable complexes with dehydrogenase inhibitor which gives binding affinity value of -6.2kcal/mol for 5CL8HQ and -5.8kcal/mol for 8H5NQ. These binding affinity values of different poses of ligands with same protein are tabulated in Table 5. These preliminary results suggest that the compounds might exhibit inhibitory activity against ACP reductase (Fig.11).

5. Conclusion

Theoretical and experimental studies on the title compounds are reported employing DFT level of theory, FT-IR and FT-Raman spectra. Using potential energy distribution all the wavenumbers are assigned and infrared intensities and Raman activities of the title compounds are reported. Using HOMO-LUMO energies reactivity parameters were reported. MEP and ALIE surfaces indicate significantly higher reactivity of 5CL8HQ, comparing to the 8H5NQ, thanks to the higher magnitudes of MEP values and lower minimal ALIE values. Regarding 5CL8HQ, both MEP and ALIE values indicate that molecule areas in the near vicinity of nitrogen atom are sensitive towards the electrophilic attacks. On the other side, in the case of 8H5NQ, MEP and ALIE surfaces indicate sensitivity of oxygen atoms towards the electrophilic attacks, while ALIE surface additionally recognizes two sites above rings of 8H5NQ as possibly prone to electrophilic attacks. Fukui f^+ function indicate that hydrogen atom of OH group in the case of 5CL8HQ and carbon atom C5 of 8H5NQ have electrophilic characters, while Fukui f^- function indicates that area between C4 and C5 in the case of 5CL8HQ and area in the vicinity of carbon atom C5 of 8H5NQ could have nucleophilic character. According to calculated H-BDE values, 5CL8HQ molecule is significantly sensitive towards the autoxidation mechanism, thanks to the H-BDE value of 85kcal/mol in the case of OH bond. Contrary to 5CL8HQ, OH bond of the 8H5NQ molecule is characterized by the H-BDE value of almost 119kcal/mol, indicating great stability towards the autoxidation mechanism. According to the RDFs, in cases of both molecules, hydrogen atoms of OH groups are having the strongest interactions with water molecules. PASS analysis predicts activity for amine dehydrogenase inhibitor and the docking studies suggest that the title compounds might exhibit inhibitory activity against ACP reductase.

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Figure captions

Fig.1 FT-IR spectra of a)5CL8HQ and b)8H5NQ

Fig.2 FT-Raman spectra of a)5CL8HQ and b)8H5NQ

Fig.3 Optimized geometries of a)5CL8HQ and b)8H5NQ

- Fig.4 HOMO-LUMO plots of a)5CL8HQ and b)8H5NQ
- Fig.5 Representative MEP and ALIE surfaces of a)5CL8HQ and b)8H5NQ molecules
- Fig.6 Intramolecular noncovalent interactions of 8H5NQ in electron/bohr³
- Fig.7 Furkui functions with corresponding maximal and minimal values of a)5CL8HQ and b)8H5NQ molecules
- Fig.8 H-BDE values of a)5CL8HQ and b)8H5NQ
- Fig.9 Significant RDF's of a)5CL8HQ and b)8H5NQ
- Fig.10 The docked ligands a)8H5NQ and b)5CL8HQ interactions with the amino acids of the receptor dehydrogenase inhibitor
- Fig.11 The ligands, a)8H5NQ and b)5CL8HQ at the active site of the receptor

Highlights

- * IR and Raman spectra were measured
- * Studied NLO behavior, MEP and NBO analysis
- * ALI, BDE, RDF have been discussed in detail
- * Molecular docking studies have been reported.

Raman Intensity

a) 5CL8HQ

b) 8H5NQ

Wavenumber (cm⁻¹)

a)

b)

HOMO

LUMO

a)

b)

MEP

ALIE

a)

-46.05 MEP [kcal/mol] 55.85

188.37 ALIE [kcal/mol] 378.81

b)

-34.02 MEP [kcal/mol] 34.72

220.72 ALIE [kcal/mol] 385.42

f^+ f^-

a)

4×10^{-5} 520×10^{-5} 5×10^{-5} 29×10^{-5}

b)

8×10^{-5} 59×10^{-5} -40×10^{-5} 48×10^{-5}

a)

b)

a) 8H5NQ :

b) 5CL8HQ

a)8H5NQ

b)5CL8HQ

Table 1

Calculated scaled wavenumbers, observed IR, Raman bands and assignments

8H5NQ

B3LYP/6-311++G(d) (5D, 7F)			IR	Raman	Assignments ^a
$\nu(\text{cm}^{-1})$	IR_I	R_A	$\nu(\text{cm}^{-1})$	$\nu(\text{cm}^{-1})$	-
3425	118.62	108.82	3426	-	$\nu\text{OH}(100)$
3134	4.73	55.69	3125	-	$\nu\text{CHII}(98)$
3102	2.53	97.99	-	3099	$\nu\text{CHI}(99)$
3081	3.00	119.10	-	-	$\nu\text{CHI}(99)$
3070	13.77	201.63	-	3070	$\nu\text{CHII}(98)$
3040	17.26	135.77	-	-	$\nu\text{CHII}(99)$
1604	46.73	13.90	1615	1615	$\nu\text{PhI}(51)$, $\delta\text{CHII}(21)$
1571	18.67	13.41	1572	1573	$\nu\text{PhII}(50)$, $\delta\text{CHII}(14)$
1546	64.10	132.75	-	-	$\nu\text{PhI}(44)$, $\nu\text{PhII}(45)$
1505	203.90	18.94	1508	1502	$\nu\text{NO}_2(73)$, $\delta\text{CN}(14)$
1485	217.00	13.28	1480	1481	$\nu\text{PhI}(19)$, $\nu\text{PhII}(44)$, $\delta\text{CHII}(10)$
1442	64.94	12.86	-	1442	$\nu\text{PhI}(42)$, $\nu\text{PhII}(15)$, $\delta\text{CHII}(15)$
1405	59.02	82.49	1403	1402	$\delta\text{OH}(41)$, $\delta\text{CHII}(15)$, $\nu\text{PhI}(16)$
1376	52.05	11.64	1376	1375	$\delta\text{CHII}(21)$, $\nu\text{PhI}(44)$
1353	13.62	11.57	1349	-	$\nu\text{PhII}(42)$, $\delta\text{CHII}(22)$
1327	17.48	94.25	1322	1323	$\nu\text{PhI}(47)$, $\nu\text{PhII}(20)$
1294	348.28	347.30	1293	1292	$\nu\text{NO}_2(52)$, $\nu\text{CN}(13)$
1264	419.68	136.16	-	-	$\nu\text{CO}(35)$, $\delta\text{OH}(12)$, $\nu\text{NO}_2(10)$
1238	0.96	6.05	-	1242	$\nu\text{PhI}(15)$, $\nu\text{PhII}(44)$, $\delta\text{CHII}(16)$
1197	154.20	17.12	1197	1201	$\delta\text{OH}(19)$, $\nu\text{PhI}(20)$, $\nu\text{PhII}(17)$, $\delta\text{CHII}(10)$
1169	39.85	31.29	1162	1164	$\delta\text{CHI}(55)$, $\nu\text{PhI}(12)$, $\nu\text{PhII}(11)$, $\delta\text{CHII}(10)$
1137	22.55	15.66	-	-	$\delta\text{CHI}(16)$, $\delta\text{CHII}(49)$
1118	29.84	33.67	-	-	$\nu\text{PhI}(21)$, $\delta\text{CHI}(13)$, $\delta\text{CHII}(42)$
1058	13.53	5.35	1060	1055	$\nu\text{PhII}(18)$, $\delta\text{CHI}(11)$
1027	0.84	13.76	-	-	$\nu\text{PhI}(45)$, $\delta\text{CHII}(43)$
971	0.57	0.53	-	977	$\gamma\text{CHII}(86)$

967	22.02	9.33	-	961	ν CN(38), δ PhII(16), δ PhI(12)
941	2.34	0.83	-	-	γ CHI(83)
929	0.04	0.10	-	931	γ CHII(87)
826	26.57	0.23	834	-	γ CHI(68), γ CO(10)
823	23.74	3.71	820	822	δ NO ₂ (32), δ PhII(25), γ CHI(10)
787	31.76	3.89	790	790	γ CHII(70)
786	11.98	6.88	-	-	δ PhI(25), δ NO ₂ (39), δ PhII(15)
755	9.31	0.37	750	760	τ PhII(39), τ PhI(32), γ CO(11)
710	16.22	22.04	715	-	γ CN(27), δ PhI(16), δ PhII(10)
704	13.06	9.64	-	-	γ CN(64), δ PhII(11)
653	126.12	1.23	-	650	τ OH(88)
633	1.93	1.39	635	-	δ PhII(43), δ PhI(19)
625	9.82	0.34	-	-	γ CO(28), τ PhII(25), τ PhI(27)
588	21.83	3.27	-	-	δ NO ₂ (34), δ CO(12)
553	2.38	2.74	-	558	δ PhII(18), τ PhI(40), δ CO(11)
545	1.44	6.92	-	542	τ PhI(31), δ PhII(13)
481	0.31	8.28	-	483	δ PhI(50), δ PhII(18)
453	0.43	0.42	-	455	τ PhI(47), τ PhII(28)
407	1.87	2.88	-	410	τ PhII(45), τ PhI(19)
398	4.16	6.47	-	-	δ CN(28), τ PhII(17)
334	2.10	1.64	-	-	δ PhI(45), τ PhII(23)
306	2.16	0.72	-	-	γ CN(29), τ PhI(24), τ PhII(12)
284	2.92	1.35	-	290	δ CO(42), δ PhI(13), δ PhII(11)
226	4.85	0.79	-	-	δ CN(81)
180	1.64	0.46	-	-	τ PhI(46), γ CN(18), τ PhII(16), γ CO(10)
140	0.09	0.60	-	142	τ PhI(55), τ PhII(28)
88	4.28	1.17	-	83	τ PhI(51), γ CN(14), τ PhII(11)
31	0.42	0.98	-	-	τ CN(69)

5CL8HQ

B3LYP/6-311++G(d) (5D, 7F) IR Raman Assignments^a

$\nu(\text{cm}^{-1})$ IR_I R_A $\nu(\text{cm}^{-1})$ $\nu(\text{cm}^{-1})$ -

3490	86.07	77.76	-	3465	ν OH(100)
3091	2.93	203.70	-	3093	ν CHI(99)
3086	9.91	141.69	-	-	ν CHII(97)
3075	3.30	60.91	-	-	ν CHI(99)
3068	14.04	149.21	3069	3065	ν CHII(100)
3049	11.27	103.24	-	3030	ν CHII(97)
1606	7.98	7.84	1599	-	ν PhI(50), δ CHI(22)
1559	18.62	4.14	1565	1564	ν PhII(53), δ CHII(20)
1532	5.43	58.86	-	-	ν PhI(42), ν PhII(41)
1470	66.00	2.20	1467	1468	ν PhII(49), δ CHII(16), ν PhI(19)
1442	76.11	7.52	-	-	δ CHII(12), ν PhI(48), δ CHI(19)
1393	23.13	132.45	1392	1395	ν PhI(43), δ CHII(17), δ OH(15)
1378	32.03	5.68	1372	1374	δ OH(38), δ CHI(22), ν PhI(18)
1343	35.14	8.76	-	1345	ν PhI(27), δ CHII(19), ν PhII(15)
1325	34.26	104.40	-	-	ν PhI(41), ν PhII(43)
1240	51.07	3.87	-	1244	ν PhII(43), δ CHII(40)
1225	55.02	6.60	1223	1219	ν CO(38), δ CHII(42)
1193	4.22	4.16	1196	-	δ CHI(42), ν PhI(11), ν PhII(10)
1173	225.79	11.95	-	1175	δ CHI(45), ν PhI(20), ν CO(10)
1146	3.05	2.00	1147	1150	δ CHII(41), δ CHI(12), ν PhII(12)
1099	1.09	13.13	-	-	ν PhI(30), δ PhII(16), δ CHI(12), ν PhII(13)
1046	12.00	4.46	1042	1044	δ CHI(16), ν PhII(20), ν CO(12)
1016	11.08	11.54	-	-	ν PhI(51), δ PhII(12)
985	0.38	0.67	982	983	γ CHII(89)
943	0.16	1.43	945	944	γ CHI(55), γ CHII(33)
933	0.01	0.21	-	-	ν PhII(33), γ CHI(15), γ CHII(14)
905	46.54	4.23	-	-	δ PhII(22), δ PhI(29)
836	35.93	0.47	-	-	γ CHI(82)
807	2.11	2.42	810	808	δ PhI(31), δ PhII(38), ν PhI(11)
806	57.15	0.29	803	-	γ CHII(76)
749	10.79	0.25	-	735	γ CHII(62), τ PhII(10)

698	26.39	22.64	-	689	δ PhII(26), ν CO(12), ν PhI(18), ν PhII(13)
628	13.89	1.34	-	-	δ PhII(14), δ PhI(12), ν CCl(34)
624	20.52	0.63	626	-	τ PhI(43), τ PhII(16), γ CO(15), γ CCl(10)
609	45.16	0.12	-	-	γ CO(22), τ PhI(24), τ OH(15), τ PhII(15)
598	81.01	1.65	-	-	τ OH(48), τ PhI(12), γ CO(12), γ CCl(10)
554	4.96	8.72	558	-	δ PhII(43), δ CO(24)
510	27.19	12.67	515	515	δ CCl(20), δ PhII(18), δ CO(14), δ PhI(11)
485	0.06	6.84	481	487	δ PhI(55), δ PhII(19)
468	0.04	0.07	-	463	τ PhI(52), τ PhII(34)
424	1.97	1.62	-	422	τ PhII(67)
346	3.81	11.72	-	345	δ PhI(34), τ PhII(25)
339	0.08	0.68	-	-	γ CCl(31), γ CO(20), τ PhI(15), τ PhII(17)
269	5.05	0.82	-	-	δ CO(54), δ CCl(10)
200	2.23	4.39	-	-	δ CCl(75), τ PhII(10)
185	3.26	0.34	-	-	τ PhII(59), γ CCl(17), γ CO(11)
148	0.04	0.65	-	151	τ PhI(54), τ PhII(34)
109	1.47	1.89	-	-	τ PhI(60), γ CCl(14), τ PhII(11)

^a ν -stretching; δ -in-plane deformation; γ -out-of-plane deformation; τ -torsion; IR_I-IR intensity in KM/Mole; R_A-Raman activity in Å⁴/AMU; potential energy distribution(%) is given in brackets in the assignment column; PhI-C1-C2-C3-C4-C5-C6 ring; PhII-C4-C5-C10-C9-C8-N7 ring.

Table 2

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

8H5NQ

Donor	Type	ED/e	Acceptor	Type	ED/e	E(2) ^a	E(j)-E(i) ^b	F(i,j) ^c
C5-C4	σ	1.968	C6-C5	σ^*	0.029	3.03	1.22	0.054
-	-	-	C6-N12	σ^*	0.101	4.58	0.99	0.061
-	-	-	C5-C10	σ^*	0.022	2.51	1.23	0.050
-	-	-	C4-C3	σ^*	0.043	2.93	1.20	0.053
-	-	-	C4-N7	σ^*	0.021	1.78	1.20	0.041
-	-	-	C3-O11	σ^*	0.018	2.39	1.08	0.046
C4-C3	σ	1.976	C5-C4	σ^*	0.038	2.53	1.22	0.050
-	-	-	C5-C10	σ^*	0.022	2.10	1.23	0.045
-	-	-	C4-C3	σ^*	0.043	1.46	1.20	0.037
-	-	-	C3-C2	σ^*	0.023	2.95	1.28	0.055
-	-	-	C8-N7	σ^*	0.014	3.18	1.26	0.057
C8-C9	σ	1.986	C10-C9	σ^*	0.015	2.18	1.30	0.048
-	-	-	C8-N7	σ^*	0.014	1.30	1.27	0.036
C3-C2	σ	1.978	C1-C2	σ^*	0.014	2.36	1.30	0.049
-	-	-	C4-C3	σ^*	0.043	2.87	1.23	0.053
-	-	-	C4-N7	σ^*	0.021	2.20	1.23	0.046
C3-C2	π	1.649	C1-C6	π^*	0.340	26.37	0.29	0.078
-	-	-	C5-C4	π^*	0.451	15.04	0.28	0.060
-	-	-	C3-C2	π^*	0.322	1.71	0.29	0.020
C6-N12	σ	1.989	C1-C2	σ^*	0.014	1.93	1.37	0.046
-	-	-	C5-C4	σ^*	0.038	1.45	1.38	0.039
N12-O14	π	1.988	C1-C6	π^*	0.340	2.97	0.46	0.036
-	-	-	N12-O14	π^*	0.647	8.00	0.32	0.055
LPN7	σ	1.904	C5-C4	σ^*	0.038	10.64	0.88	0.088
-	-	-	C4-C3	σ^*	0.043	2.37	0.86	0.041
-	-	-	C8-C9	σ^*	0.026	9.25	0.90	0.083
LPO11	σ	1.976	C4-C3	σ^*	0.043	7.14	1.09	0.079

-	π	1.815	C3-C2	π^*	0.322	38.03	0.34	0.106
-	n	1.535	C4-C3	σ^*	0.043	1.59	0.97	0.039
-	-	-	C3-C2	σ^*	0.023	5.60	1.05	0.077
LPO13	σ	1.978	C6-N12	σ^*	0.101	4.84	1.08	0.066
-	-	-	N12-O14	σ^*	0.056	1.83	1.22	0.042
-	π	1.901	C6-N12	σ^*	0.101	11.48	0.58	0.073
-	-	-	N12-O14	σ^*	0.056	19.64	0.72	0.107
-	n	1.468	N12-O14	π^*	0.647	156.03	0.15	0.138
LPO14	σ	1.981	C6-N12	σ^*	0.101	4.40	1.08	0.063
-	-	-	N12-O13	σ^*	0.057	2.23	1.21	0.047
-	π	1.892	C6-N12	σ^*	0.101	13.45	0.57	0.078
-	-	-	N12-O13	σ^*	0.057	19.14	0.71	0.105

5CL8HQ

C8-N7	σ	1.988	C8-C9	σ^*	0.26	1.29	1.38	0.038
-	-	-	C4-C3	σ^*	0.041	2.57	1.38	0.054
-	-	-	C4-N7	σ^*	0.022	1.15	1.32	0.035
-	π	1.795	C9-C10	π^*	0.229	11.97	0.33	0.057
C3-C2	σ	1.977	C4-C3	σ^*	0.041	3.87	1.25	0.062
-	-	-	C4-N7	σ^*	0.022	2.59	1.19	0.049
-	-	-	C1-C2	σ^*	0.015	2.38	1.27	0.049
-	π	1.694	C6-C1	π^*	0.326	22.00	0.28	0.070
C8-C9	σ	1.986	C9-C10	σ^*	0.014	2.49	1.29	0.051
-	-	-	C8-N7	σ^*	0.013	1.22	1.23	0.035
C5-C4	σ	1.961	C5-C10	σ^*	0.024	2.98	1.22	0.054
-	-	-	C5-C6	σ^*	0.034	3.96	1.22	0.062
-	-	-	C4-C3	σ^*	0.041	3.61	1.22	0.059
-	-	-	C4-N7	σ^*	0.022	1.66	1.16	0.039
-	-	-	C6-C112	σ^*	0.041	4.99	0.77	0.055
-	-	-	C3-O11	σ^*	0.021	2.67	1.01	0.047
C6-C1	σ	1.982	C5-C10	σ^*	0.024	3.13	1.27	0.056
-	-	-	C5-C6	σ^*	0.034	4.42	1.27	0.067
-	-	-	C1-C2	σ^*	0.015	2.58	1.29	0.052

-	π	1.764	C3-C2	π^*	0.319	13.66	0.30	0.059
C1-C2	σ	1.965	C6-C1	σ^*	0.021	3.35	1.27	0.058
-	-	-	C6-Cl12	σ^*	0.041	5.59	0.76	0.058
-	-	-	C3-C2	σ^*	0.021	2.47	1.28	0.050
-	-	-	C3-O11	σ^*	0.021	4.62	1.00	0.061
C4-C3	σ	1.975	C5-C10	σ^*	0.024	2.13	1.23	0.046
-	-	-	C5-C4	σ^*	0.041	3.25	1.23	0.057
-	-	-	C4-N7	σ^*	0.022	2.13	1.17	0.045
-	-	-	C8-N7	σ^*	0.022	2.79	1.23	0.053
-	-	-	C2-C3	σ^*	0.021	3.89	1.30	0.064
LPC4	σ	1.019	C8-N7	π^*	0.317	62.08	0.12	0.094
-	-	-	C2-C3	π^*	0.319	56.89	0.15	0.102
LPN7	σ	1.911	C8-C9	σ^*	0.026	8.71	0.87	0.079
-	-	-	C5-C4	σ^*	0.041	9.64	0.87	0.082
LPCL12	n	1.951	C6-C1	π^*	0.326	9.26	0.32	0.053
-	-	-	C1-C2	σ^*	0.015	6.39	0.78	0.063
LPO11	σ	1.978	C4-C3	σ^*	0.041	6.25	1.08	0.074
-	π	1.851	C3-C2	π^*	0.319	32.28	0.32	0.096

^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 3

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

8H5NQ

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ C5-C4	1.968	50.63	49.37	0.7116(sp ^{2.18})C+	31.42	68.58
-	-0.709	-	-	0.7026(sp ^{1.69})C	37.11	62.89
σ C4-C3	1.976	50.78	49.22	0.7126(sp ^{2.04})C+	32.85	67.15
-	-0.712	-	-	0.7016(sp ^{1.84})C	35.15	64.85
σ C8-C9	1.986	49.29	50.71	0.7021(sp ^{1.64})C+	37.81	62.19
-	-0.720	-	-	0.7121(sp ^{1.96})C	33.72	66.27
σ C2-C3	1.978	50.56	49.44	0.7111(sp ^{1.58})C+	38.77	61.23
-	-0.739	-	-	0.7031(sp ^{1.91})C	34.32	65.68
π C2-C3	1.649	44.33	55.67	0.6658(sp ^{1.00})C+	0.00	100.0
-	-0.280	-	-	0.7461(sp ^{1.00})C	0.00	100.0
σ C6-N12	1.989	37.88	62.12	0.6155(sp ^{2.97})C+	25.18	74.82
-	-0.816	-	-	0.7881(sp ^{1.74})C	36.51	63.49
π N12-O14	1.988	39.28	60.72	0.6267(sp ^{1.00})C+	0.00	100.0
-	-0.447	-	-	0.7793(sp ^{1.00})N	0.00	100.0
σ LPN7	1.904	-	-	sp ^{2.69}	27.08	72.92
-	-0.372	-	-	-	-	-
σ LPO11	1.976	-	-	sp ^{1.36}	42.41	57.59
-	-0.599	-	-	-	-	-
π LPO11	1.815	-	-	sp ^{1.00}	0.00	100.0
-	-0.330	-	-	-	-	-
nLPO11	1.535	-	-	sp ^{3.62}	21.63	78.37
-	-0.479	-	-	-	-	-
σ LPO13	1.978	-	-	sp ^{0.34}	74.35	25.65
-	-0.789	-	-	-	-	-
π LPO13	1.901	-	-	sp ^{99.99}	0.46	99.54
-	-0.291	-	-	-	-	-
nLPO13	1.468	-	-	sp ^{1.00}	0.00	100.0
-	-0.273	-	-	-	-	-
σ LPO14	1.981	-	-	sp ^{0.34}	74.66	25.33
-	-0.791	-	-	-	-	-

π LPO14	1.892	-	-	$sp^{99.99}$	0.06	99.94
-	-0.285	-	-	-	-	-

5CL8HQ

Bond(A-B)	ED/e ^a	EDA%	EDB%	NBO	s%	p%
σ C8-N7	1.988	39.82	60.18	0.6311($sp^{2.25}$)C+	30.79	69.21
-	-0.868	-	-	0.7757($sp^{1.64}$)N	37.92	62.08
π C8-N7	1.795	41.54	58.46	0.6445($sp^{1.00}$)C+	0.00	100.0
-	-0.325	-	-	0.7646($sp^{1.00}$)N	0.00	100.0
σ C2-C3	1.977	50.49	49.51	0.7106($sp^{1.55}$)C+	39.23	60.77
-	-0.736	-	-	0.7036($sp^{1.86}$)C	34.92	65.08
π C2-C3	1.694	47.30	52.70	0.6878($sp^{1.00}$)C+	0.00	100.0
-	-0.276	-	-	0.7259($sp^{1.00}$)C	0.00	100.0
σ C8-C9	1.986	50.74	49.26	0.7123($sp^{1.98}$)C+	33.60	66.40
-	-0.718	-	-	0.7018($sp^{1.66}$)C	37.57	62.43
σ C5-C4	1.961	50.79	49.21	0.7127($sp^{2.17}$)C+	31.59	68.41
-	-0.707	-	-	0.7015($sp^{1.75}$)C	36.37	63.63
σ C1-C6	1.982	50.67	49.33	0.7118($sp^{1.46}$) C+	40.60	59.40
-	-0.755	-	-	0.7024($sp^{1.83}$)C	35.36	64.64
π C1-C6	1.764	54.64	45.36	0.7392($sp^{1.00}$) C+	0.00	100.0
-	-0.288	-	-	0.6735($sp^{1.00}$)C	0.00	100.0
σ C1-C2	1.965	49.60	50.40	0.7043($sp^{1.90}$)C+	34.42	65.58
-	-0.698	-	-	0.7099($sp^{1.89}$)C	34.66	65.34
σ C4-C3	1.975	51.02	48.98	0.7143($sp^{1.92}$)C+	34.23	65.77
-	-0.717	-	-	0.6998($sp^{1.82}$)C	35.52	64.48
n1C4	1.019	-	-	$sp^{1.00}$	0.00	100.0
-	-0.140	-	-	-	-	-
n1N7	1.911	-	-	$sp^{2.59}$	27.83	72.17
-	-0.355	-	-	-	-	-
n3Cl12	1.951	-	-	$sp^{1.00}$	0.00	100.0
-	-0.319	-	-	-	-	-
n1O11	1.978	-	-	$sp^{1.23}$	44.76	55.24
-	-0.570	-	-	-	-	-
N2O11	1.851	-	-	$sp^{1.00}$	0.00	100.0
-	-0.311	-	-	-	-	-

^aED/e is expressed in a.u.

Table 4

PASS prediction for the activity spectrum of 8H5NQ and 5CL8HQ**8H5NQ**

<u>Pa</u>	<u>Pi</u>	<u>Activity</u>
0.957	0.002	Monodehydroascorbate reductase (NADH) inhibitor
0.955	0.002	Arylacetonitrilase inhibitor
0.943	0.001	Alcohol oxidase inhibitor
0.939	0.001	Rhamnulose-1-phosphate aldolase inhibitor
0.937	0.002	4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor
0.934	0.002	Dehydro-L-gulonate decarboxylase inhibitor
0.931	0.001	N-carbamoyl-L-amino-acid hydrolase inhibitor
0.928	0.001	Histidinol-phosphatase inhibitor
0.927	0.001	P-benzoquinone reductase (NADPH) inhibitor
0.924	0.001	Guanidinoacetase inhibitor
0.921	0.001	UGT2B12 substrate
0.921	0.002	Glutathione thiolesterase inhibitor
0.916	0.002	Benzoate 4-monooxygenase inhibitor
0.908	0.002	Corticosteroid side-chain-isomerase inhibitor
0.907	0.002	Catechol 2,3-dioxygenase inhibitor
0.904	0.002	Nitrilase inhibitor
0.901	0.001	Methylaspartate ammonia-lyase inhibitor
0.900	0.003	Alkane 1-monooxygenase inhibitor
0.895	0.002	4-Hydroxyproline epimerase inhibitor
0.891	0.002	(R)-6-hydroxynicotine oxidase inhibitor
0.892	0.003	Amine dehydrogenase inhibitor
0.888	0.003	Aldehyde dehydrogenase (pyrroloquinoline-quinone) inhibitor
0.888	0.005	Glucose oxidase inhibitor
0.882	0.002	Bothrolysin inhibitor
0.877	0.003	Arylalkylacylamidase inhibitor
0.871	0.002	Nitrite reductase [NAD(P)H] inhibitor
0.870	0.002	Hydroxylamine reductase (NADH) inhibitor
0.872	0.003	Glyceryl-ether monooxygenase inhibitor
0.872	0.004	Glucan endo-1,6-beta-glucosidase inhibitor
0.870	0.002	Cis-1,2-dihydro-1,2-dihydroxynaphthalene dehydrogenase inhibitor

0.870 0.003 Laccase inhibitor
 0.862 0.002 Nicotinamidase inhibitor

5CL8HQ

0.947 0.002 Antiseborrheic
 0.942 0.002 Dehydro-L-gulonate decarboxylase inhibitor
 0.930 0.002 Glutathione thiolesterase inhibitor
 0.925 0.001 Biphenyl-2,3-diol 1,2-dioxygenase inhibitor
 0.911 0.002 Alkane 1-monooxygenase inhibitor
 0.910 0.003 Glycosylphosphatidylinositol phospholipase D inhibitor
 0.907 0.002 Amine dehydrogenase inhibitor
 0.903 0.002 Corticosteroid side-chain-isomerase inhibitor
 0.894 0.001 Hydroxylamine oxidase inhibitor
 0.889 0.001 Nicotine dehydrogenase inhibitor
 0.890 0.003 2-Hydroxyquinoline 8-monooxygenase inhibitor
 0.885 0.002 Cis-1,2-dihydro-1,2-dihydroxynaphthalene dehydrogenase inhibitor
 0.883 0.003 Glyceryl-ether monooxygenase inhibitor
 0.883 0.004 Arylacetonitrilase inhibitor
 0.882 0.005 Glucose oxidase inhibitor
 0.879 0.002 UGT2B12 substrate
 0.879 0.003 Phthalate 4,5-dioxygenase inhibitor
 0.873 0.003 Nitrate reductase (cytochrome) inhibitor
 0.854 0.003 Indanol dehydrogenase inhibitor
 0.853 0.005 Monodehydroascorbate reductase (NADH) inhibitor
 0.850 0.003 Sulfite reductase inhibitor
 0.838 0.003 Rhamnulose-1-phosphate aldolase inhibitor
 0.835 0.003 Fructose 5-dehydrogenase inhibitor
0.835 0.004 Creatininase inhibitor

Table 5

The binding affinity values of different poses of the 8H5NQ predicted by AutodockVina.

Mode	Affinity (kcal/mol)	Distance from best mode (Å)	
-	-	RMSD l.b.	RMSD u.b.
1	-5.8	0.000	0.000
2	-5.7	11.888	12.219
3	-5.5	2.628	4.454
4	-5.2	3.276	4.518
5	-5.2	2.304	3.555
6	-5.1	16.028	17.135
7	-5.1	8.972	9.948
8	-5.0	2.638	3.952
9	-4.9	8.002	8.410

The binding affinity values of different poses of the 5CL8HQ predicted by AutodockVina.

Mode	Affinity (kcal/mol)	Distance from best mode (Å)	
-	-	RMSD l.b.	RMSD u.b.
1	-6.2	0.000	0.000
2	-5.9	10.819	11.957
3	-5.9	10.902	11.961
4	-5.8	21.483	22.203
5	-5.7	21.633	22.063
6	-5.4	21.350	21.620
7	-5.2	21.519	22.856
8	-5.2	21.546	22.446
9	-5.1	20.237	21.439