Methoxylated Quinoline-Chalcones with Potential Pesticidal Activity: From Synthesis to Supramolecular Framework

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In this work, the molecular properties of the (E)-3-(4-nitrobenzylidene)-2-(4-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1H)-one were studied, both in a solid and isolated state. The effect of changing the substituent groups –OCH₃ and –Cl in the phenyl portion was verified, where the structural and electronic properties were compared. The density functional theory was employed using the hybrid exchange-correlation functional with long-range correction M06-2X, combined with the polarized and diffuse basis set 6-311++G(d,p), in the gas phase. The electronic structure was also analyzed by frontier molecular orbitals and molecular electrostatic potential maps, where information about its chemical reactivity was obtained. Also, the supramolecular arrangement was analyzed by Hirshfeld surface (HS), 2D fingerprint plots, and quantum theory of atoms in molecules (QTAIM). The natural bond orbitals (NBO) calculations were carried out to analyze the stability and hyperconjugation energy. Finally, molecular docking was carried out to investigate the affinities of the quinoline-chalcone with a bacterial protein (Agrobacterium pathogens) and an ecdysone receptor-potential pesticidal activity. The results encourage further in vitro and in vivo analyses of the two kinds of organisms investigated.

Keywords: quinoline-chalcones, X-ray diffraction, Hirshfeld surface, density functional theory

Introduction

Hybrid compounds between quinolines and chalcones are widely studied due to their biological potential.1-5 Characterized by its heterocyclic nitrogenous nature and formed by the union of a benzene ring and a pyrimidine, quinoline,6 when associated with a chalcone chain, the α,β-unsaturated ketone aromatic system,7 can exhibit diverse biological effects,1-5 ranging from antibiotics,8 cytotoxics,9 antimalarials,9 antioxidants,4 anti-inflammatoryst,10 anticancer,11 and even as pesticides.12,13 Moreover, it displays interest from the scientific community due to its potential as a substrate for new bioactive compounds through specific chemical changes.14

The quinoline-chalcone pesticidal effect has shown to be promising due to their natural origin, as they are used to control weeds,15 insects,16 and microorganisms10 harmful to agriculture, especially in more sensitive crops such as fruits and vegetables. Playing a fundamental role in agricultural production, pesticide use is unquestionable regarding efficiency and food needs. However, it is toxicity and environmental pollution still need attention from researchers.17 Therefore, a new biodegradable compound with a lower environmental impact is essential for society regarding environmental protection and sustainability.

In this work, the quinoline-chalcone (E)-3-(4-nitrobenzylidene)-2-(4-methoxyphenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1H)-one (CNP-OM) was analyzed and compared to a similar compound (E)-3-(4-nitrobenzylidene)-2-(4-chlorophenyl)-2,3-dihydro-1-(phenylsulfonyl)-quinolin-4(1H)-one (CNP-CL). The effect of the para-substituent groups –OCH₃ and –Cl on the phenyl portion was described on a structural and electronic basis. For this, theoretical calculations based on density functional theory (DFT) were carried out. Then, the intermolecular

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interaction patterns of both compounds were verified by Hirshfeld surfaces (HS) and 2D fingerprint plots, quantum theory of atoms in molecules (QTAIM), and natural bond orbitals (NBO) to evaluate their respective natures and stabilities in the supramolecular arrangement. Molecular docking was carried out to investigate the affinities of CNP-OM with a bacterial protein (periplasmic binding protein, present in Agrobacterium pathogens) and an ecdysone receptor in Bemisia tabaci (insecticide potential).

**Experimental**

**General procedures**

Nuclear magnetic resonance (NMR) spectra were collected using a Bruker Avance III 500 spectrometer (Rheinstetten, Germany) operating at 11.75 T. The spectrometer observed $^1$H at a frequency of 500.13 MHz and $^{13}$C at 125.76 MHz. A 5 mm inverse-detection three-channel (1H, 2H, 13C, and XBB) probe and a 5 mm broadband observe (BBO) probe were utilized for the measurements. The samples, weighing approximately 10 mg, were dissolved in 600 μL of deuterated chloroform (CDCl$_3$), with tetramethylsilane (TMS) serving as the internal standard. Signal assignments were accomplished through correlation spectroscopy (COSY), heteronuclear multiple bond correlation (HMBC), and heteronuclear single quantum correlation (HSQC) experiments.

The purity of the compounds was determined based on the $^1$H spectra by analyzing the proportion of areas between the assigned peaks corresponding to the structure of the compound and the total area encompassing all peaks attributed to the studied material. The melting points were determined using a melting point apparatus (Karl Kolb, Frankfurt a.M., Germany) by placing the solid sample on glass coverslips and subjecting it to heating.

**Synthesis and crystallization**

The synthesis of the CNP-OM$^{18,19}$ was undertaken using precursor I$^{19}$ (1.0 mmol) and 4-nitro-benzaldehyde (2.0 mmol) (Scheme 1). Both were dissolved in 15 mL of basic ethanol (56.1 mg of potassium hydroxide dissolved) and reacted (at 25 °C) for 48 h. The solution was filtered, and the precipitate was rinsed with 15 mL of ethanol. The precipitate was dissolved in dichloromethane (10 mL), and this solution was extracted with water. The organic phase was allowed to evaporate slowly, yielding a yellow crystalline solid product with 97.8% purity.

Pale yellow crystalline solid, yield 47.5%, purity of 98.4%, mp 166-167 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 3.74 (s, 3 $^1$H), 6.57 (s, 1 $^1$H), 6.78-6.81 (m, 2 $^1$H), 7.10-7.13 (m, 2 $^1$H), 7.19-7.23 (m, 2 $^1$H), 7.28-7.33 (m, 2 $^1$H), 7.37-7.40 (m, 2 $^1$H), 7.49 (t, J 1.23, 7.48 Hz, 1 $^1$H), 7.53 (s, 1 $^1$H), 7.55 (ddd, J 1.65, 7.38, 8.18 Hz, 1 $^1$H), 7.71 (dd, J 0.80, 8.15 Hz, 1 $^1$H), 7.89 (dd, J 1.58, 7.83 Hz, 1 $^1$H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 55.2, 59.6, 114.3, 127.2, 127.3, 127.9, 128.3, 128.4, 128.7, 128.8, 128.9, 129.4, 131.2, 131.3, 132.1, 132.2, 133.4, 136.4, 137.5, 138.6, 138.9, 152.6, 182.7; IR (KBr) 1671 (m), 1605 (m), 1476 (w), 1355 (s), 1304 (m), 1253 (m) (Figure S1, Supplementary Information section); HRMS calcd. for C$_{29}$H$_{23}$ClNO$_4$S: 516.1036, found: 516.0902.

The first step of this reaction is the intramolecular addition of the nitrogen of the sulfonamide group to the β carbon of precursor I, followed by the reaction of the β carbonyl of the quinolinone formed to the aldehyde employing Claisen-Schmidt condensation, yielding the desired compounds. The CNP-OM obtained is a yellow crystalline solid with 74.1% purity. To get a single crystal for an X-ray diffraction study, a sample of the compounds was further purified by recrystallization by dissolving them in dichloromethane and exposing them to ethyl ether vapor.

**X-ray diffraction analysis**

The single crystal X-ray diffraction measurements were performed in a Bruker APEX II CCD Mo Kα radiation diffractometer (λ = 0.71073 Å), at a temperature of 120 K. The programs ShelXT$^{20}$ and SHELXL$^{21}$ were used to solve (direct method) and refine the structure carried out with Olex2 platform.$^{22}$ All hydrogen atoms were placed in calculated positions and refined with fixed individual displacement parameters [U iso (H) = 1.2Ueq or 1.5Ueq] using the riding model. CNP-OM molecular structure was verified and compared to the CNP-CL structure, also synthesized in our group.$^{13}$ Compound structures were
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deposited at Cambridge Crystallographic Data Centre (CCDC) under codes 2241212 (CNP-OM) and 1981002 (CNP-CL).

Molecular modeling

Theoretical calculations were carried out by DFT\textsuperscript{23,24} (implemented in the Gaussian16\textsuperscript{25} software package) using the hybrid exchange and correlation functional with long-range correction, M06-2X,\textsuperscript{26} combined with the basis set 6-311++G(d,p), in the gas phase. The geometric parameters obtained were compared to the experimental ones. The substituent groups –OCH\textsubscript{3} and –Cl of the aromatic B ring (Figure 1) are considered electron-withdrawing. Their molecular configurations were analyzed using electron density distributions from solid-state conformations. Frontier molecular orbitals\textsuperscript{27} (the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO)) were obtained, and quinoline-chalcone chemical reactivity indices were determined. Molecular electrostatic potential maps\textsuperscript{28} (MEP) contributed to analyzing global electrophilicity through their electronic isodensity surfaces. The electrostatic potential V(\(r\))\textsuperscript{29} at the point \(r\) is defined as equation 1.

\[
V(\mathbf{r}) = \sum_{\alpha} \frac{Z_{\alpha}}{|\mathbf{r}_{\alpha} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}'
\]

where \(Z_{\alpha}\) is the charge of nuclei \(\alpha\) at point \(\mathbf{r}_{\alpha}\) and \(\rho(\mathbf{r}')\) is the charge density at the point \(\mathbf{r}'\).\textsuperscript{28} Furthermore, from the MEP map, it is possible to predict the possible regions where intermolecular interactions occur.

Supramolecular arrangement

In supramolecular chemistry, it is possible to understand the geometric parameters formed in crystalline structures by analyzing the intermolecular interactions between molecules (or ions), regardless of the structural nature of the molecular systems.\textsuperscript{30,31} The supramolecular arrangements of the quinoline-chalcones were evaluated by HS\textsuperscript{32} and 2D fingerprint plots,\textsuperscript{33} implemented in the CrystalExplorer software,\textsuperscript{34,35} providing information about the intermolecular interaction patterns by color mapping, in addition to describing the surface-specific properties. The HS is a computational approach used to analyze and visualize the electron density distribution based on Hirshfeld partitioning, which divides the electron density of a crystal into individual atomic contributions. Once the molecular electron density is calculated using quantum mechanical methods (DFT or Hartree-Fock), it is partitioned by assigning respective electron densities to each atom in the solid-state structure.\textsuperscript{36}

\[
W(\mathbf{r}) = \frac{\rho_{\text{molecule}}(\mathbf{r})}{\rho_{\text{crystal}}(\mathbf{r})}
\]

where \(\rho_{\text{molecule}}(\mathbf{r})\) and \(\rho_{\text{crystal}}(\mathbf{r})\) are the electron densities at point \(\mathbf{r}\) inside the molecule and the crystal, respectively.

Once the partitioning is complete, the HS is constructed by plotting the molecular surface in three dimensions, where the surface points represent equal HS values. These color-coded surface points provide information about the nature and strength of intermolecular interactions. The HS fingerprint provides a detailed distribution of interatomic contacts, revealing the relative contributions of different atoms to the overall crystal packing.\textsuperscript{33,37}

Furthermore, QTAIM\textsuperscript{38,39} calculations showed these interactions’ characteristics through the topological parameters analysis. The inputs were constructed from the crystallographic data at the M06-2X/6-311++G(d,p) level of theory, in which the atomic coordinates were kept fixed during the calculations, and the topological parameters were obtained using the Multiwfn program.\textsuperscript{40} Then, NBO\textsuperscript{41,42} calculations were carried out to determine the stability of interactions by the hyperconjugation energy,\textsuperscript{43} estimated by the second-order perturbation formula, equation 3.

\[
E^{(2)}_{j\alpha*} = -n_{\alpha} \left\langle \sigma_j \vert F^2 \vert \sigma^*_{\alpha} \right\rangle = -n_{\alpha} \frac{F_j^2}{\epsilon_{\alpha} - \epsilon_j}
\]

where \(\left\langle \sigma_j \vert F \vert \sigma^*_{\alpha} \right\rangle^2\) or \(F_j^2\) is the Fock matrix element between the NBO i, and j; \(\epsilon_{\alpha}\) is the energy of the antibonding orbital \(\sigma^*\); \(\epsilon_j\) is the energy of the bonding orbital \(\sigma\); \(n_{\alpha}\) stands for the population occupation of the \(\sigma^*\) donor orbital.

Molecular docking

The molecular interactions of CNP-OM used to inhibit targets were studied by GOLD Suite 5.7.0\textsuperscript{44} (Mark Thompson and Planaria Software LLC). The optimized structure was docked at the active site of two targets: PBP, present in Agrobacterium tumefaciens,\textsuperscript{45} and ecdysone receptor, present in Bemisia tabaci.\textsuperscript{46} The coordinates of these proteins were extracted from the crystal structures found in the RCSB Protein Databank (PDB) under the PDB IDs 5ORG and 1Z5X, respectively. The 2D interaction maps were produced using the PoseView Interface.\textsuperscript{58-50} PyMOL Molecular Graphics System 2.0\textsuperscript{51} software was employed to build 3D images. Redocking was carried out using the structures in which the target protein and its ligands were co-crystallized. Default values were employed for all other parameters, and arrangements were submitted to 10 genetic algorithm runs using the CHEMPLP fitness function.
Results and Discussion

Molecular modeling analysis

The CNP-OM carbonic chain consists of five nuclei, four of which are aromatic (A, B, D, and E) and one pyrimidine (C), so that the chalcone scaffold comprises rings B and D. The nuclei B and C are condensed in the form of quinoline, and a sulfonyl group, –(SO₂)–, connects the A ring to the quinoline through a bond with the quinolinic nitrogen atom. The E ring is also connected to the quinoline portion by the bond with the chiral carbon atom, C₁. In the para position, there is a methoxy substituent group, –OCH₃. Figure 1 shows the CNP-OM molecular structure. The S enantiomer was used for the molecular modeling analysis. The CNP-OM crystallized on monoclinic crystal system C2/c, with the following crystallographic parameters: a = 22.469(2) Å, b = 15.387(2) Å, c = 15.4935(18) Å, α = 90°, β = 108.456(3)°, γ = 90° and V = 5081.07 Å³. The substitution of the –OCH₃ group by the –Cl group in CNP-CL is bulky, the C–Cl bond is 21.1% larger than the C–group on the benzene ring. Since the Cl atom represents the theoretical and experimental geometric parameters, respectively. The

![Figure 1. CNP-OM quinoline-chalcone molecule.](image)

The molecular geometries of the compounds do not show significant differences, despite the different substituent groups. For bond lengths, it was observed that the C₁–C₁₇–C₁₈ angle is greater in the CNP-OM, around 1.52%, and the N₁–S–C₂₃, C₁₉=C₁₀–C₁₁, C₁₅–C₁₄–N₂, C₁₀–C₁₆–C₂₁, and C₁–C₁₇–C₂₂ angles are smaller, respectively, 1.82, 1.35, 1.22, 1.41, and 1.21%, compared to the CNP-CL. In Figure 2, it is possible to observe that the geometric parameters are homogeneous. The A, B, D, and E rings are plane in both compounds. The C₁ and N₁ atoms are in the same plane of the B ring; however, the carbonyls of the chalcone chains are 12.76° out of this plane in CNP-OM and 16.66° in CNP-CL, a difference of ca. 30%. Furthermore, rings B and D are at 47.49° in CNP-OM and 26.44° in CNP-CL, while rings B and E are almost perpendicular (81.77° in CNP-OM and 73.17° in CNP-CL). Finally, the S atom of the sulfonyl group is 7.08° out of the plane of the A ring in CNP-OM, while it is 2.88° in CNP-CL.

The theoretical geometric parameters were compared to the experimental data through the mean absolute deviation percentage (MADP), equation 4.

\[
\text{MADP} = \frac{100}{n} \sum_{i=1}^{n} \frac{\chi_{\text{DFT}} - \chi_{\text{XRD}}}{\chi_{\text{XRD}}} \tag{4}
\]

where \( \chi_{\text{DFT}} \) and \( \chi_{\text{XRD}} \) represent the theoretical and experimental geometric parameters, respectively. The
results showed that the theory level used could well describe the quinoline-chalcone molecular structures. MADP values for bond lengths were 0.718% in CNP-OM, with Pearson’s correlation coefficient, $R^2 = 0.9936$, and 0.645% in CNP-CL, with $R^2 = 0.9967$. Figure 3 shows the graphs for the theoretical geometric parameters compared.

**Figure 2.** Scatter plots comparing experimental values of bond lengths (a) and bond angles (b) in CNP-OM and CNP-CL quinoline-chalcones.

**Figure 3.** Scatter plots comparing experimental and theoretical values of the bond lengths (a) and (b), and bond angles (c) and (d) in CNP-OM and CNP-CL quinoline-chalcones.
to the experimental ones. In the case of bond angles, the MADP values were 0.680% (R² = 0.9229) for CNP-OM and 0.588% (R² = 0.9780) for CNP-CL.

The data showed that the dihedral angles undergo minor changes in the CNP-OM molecule, depending on the molecular environment; moreover, the superposition of the CNP-OM structure in the crystal and isolated form showed that the –OCH₃ group can rotate in different environments (Figure 4a). On the other hand, in the CNP-CL molecule, the torsional variation is greater when compared to the settings described above; however, the values of their dihedrals changed in a non-significant way compared to the experimental data (Figure 4b).

The electron density function ρ(r) is very useful in modeling the chemical behavior of molecules, and from the results of the CNP-OM and CNP-CL quinoline-chalcone electronic structures, it was possible to predict some important information about the kinetic stability and chemical reactivity. According to Pearson’s Principle, compounds that exhibit an acidic character have low LUMO energies, while compounds with a basic character have high HOMO energies. Thus, it is expected that the electron-withdrawing effect of the –OCH₃ group gives the CNP-OM molecule a more basic character than CNP-CL, even with the electron-withdrawing group –Cl.

The isosurfaces of the localized FMOs (HOMO and LUMO) obtained for the compounds are shown in Figure 5, and their energy values are shown in Table 2. From the results, the HOMO energy in CNP-OM is about 2.2% higher, and the LUMO energy is about 2.6% lower compared to CNP-CL. In CNP-OM, HOMO is located at the C₁₇–C₁₈ bond and has a bonding π character. This orbital has an occupancy of 1.67e, formed by the contribution of 54.28% of the p orbital of C₁₇ and 45.72% of the p orbital of C₁₈, perpendicular to the plane of the benzene ring. Due to the slightly higher HOMO value, CNP-OM has a slightly higher basic character. The HOMO of CNP-CL is also a bonding π orbital with occupancy 1.62e, located in the C₇–C₈ bond and formed by the contribution of 48.51% of the p orbital of C₇ and 51.49% of the p orbital of C₈. On the other hand, the lower LUMO energy value in CNP-CL

![Figure 4](image_url)  
**Figure 4.** CNP-OM (a) and CNP-CL (b) overlapping molecular structures, where molecules with C atoms in light gray correspond to the crystal and molecules with C atoms in dark gray correspond to theoretical calculations.

![Figure 5](image_url)  
**Figure 5.** HOMO and LUMO plots for (a) CNP-OM and (b) CNP-CL obtained at M06-2X/6-311++G(d,p) level of theory.
Table 2. Reactivity indices for CNP-OM and CNP-CL compounds obtained at M06-2X/6-311++G(d,p) level of theory

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>CNP-OM / (kcal mol⁻¹)</th>
<th>CNP-CL / (kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{HOMO}}$</td>
<td>−189.143</td>
<td>−193.351</td>
</tr>
<tr>
<td>$E_{\text{LUMO}}$</td>
<td>−70.610</td>
<td>−72.492</td>
</tr>
<tr>
<td>$\Delta E_{\text{hl}}$</td>
<td>118.533</td>
<td>120.859</td>
</tr>
<tr>
<td>Ionization energy (I)</td>
<td>189.143</td>
<td>193.351</td>
</tr>
<tr>
<td>Electronic affinity (A)</td>
<td>70.610</td>
<td>72.492</td>
</tr>
<tr>
<td>Electronegativity ($\chi$)</td>
<td>129.877</td>
<td>132.921</td>
</tr>
<tr>
<td>Chemical potential ($\mu$)</td>
<td>−129.877</td>
<td>−132.921</td>
</tr>
<tr>
<td>Chemical hardness ($\eta$)</td>
<td>118.533</td>
<td>120.859</td>
</tr>
<tr>
<td>Electrophilicity index ($\omega$)</td>
<td>71.153</td>
<td>73.094</td>
</tr>
</tbody>
</table>

*The energy gap is the difference between the HOMO and LUMO energies, $\Delta E_{\text{hl}} = E_{\text{LUMO}} - E_{\text{HOMO}}$.

out for several organic molecules, which determined the regions of

The local electrophilicity can be obtained from the Fukui function, which determines the regions of nucleophilic ($f^+$, equation 8), electrophilic ($f^-$, equation 9), or radical attacks ($f^0$, equation 10).

$$f^+ = \left[ \frac{\partial p(r)}{\partial N} \right]_0$$

$$f^- = \left[ \frac{\partial p(r)}{\partial N} \right]_0$$

$$f^0 = \left[ \frac{\partial p(r)}{\partial N} \right]_0$$

The MEP maps of CNP-OM and CNP-CL (Figure 6) revealed that the regions over the oxygen atoms (in red) contain a high charge density, configuring the nucleophilic regions of the molecules. Evaluating the isosurfaces obtained for the $f^+$ function (Figure 7), we noticed that the O atoms present in the –NO₂, –(CO)–, and –(SO₂)– groups can carry nucleophilic attacks during chemical processes, including the O₃ atom of the –OCH₃ group of the CNP-OM. In addition to these regions, we observed that the –OCH₃ substituent group in CNP-OM makes C₁₈ and C₂₁ (or C₁₉ and C₂₂) atoms susceptible to attacks of this nature, while the –Cl substituent group in CNP-CL alters the nucleophilic attack regions to atoms C₁₉ and C₂₀ (or C₂₀ and C₂₁). The quinoline N atom is susceptible to this type of attack, which is more pronounced in the CNP-CL structure. Finally, the unsaturated C₁₀ atom of the chalcone bridge of the chlorinated compound is susceptible to this type of attack.

Electrophilic attacks, according to the $f^-$ function iso-surfaces, can occur on the C₂₀ atom of the –OCH₃ group in CNP-OM. As the –CH₃ group is an electron-donating group and the O₂ atom is very electronegative, C₂₅ acquires a partial positive charge, making the charge density in its region low and susceptible to electrophilic attacks. The blue color in the MEP map shows that this is an electrophilic region. In the region of the –Cl substituent group, in CNP-CL, we observed that this type of attack does not occur. Electrophilic attacks can occur on C₄, C₅, C₆, and C₇ atoms in the quinoline portion. Compared with the LUMO in both compounds described above, the results
Figure 6. MEP surface at $\rho(r) = 4.0 \times 10^{-4}$ electrons/Bohr contour of the total SCF electronic density for (a) CNP-OM and (b) CNP-CL at the M06-2X/6-311++G(d,p) level of theory.

Figure 7. Isosurfaces of the $f^+$, $f^-$, and $f^0$ functions indicating the nucleophilic, electrophilic, and radical attack regions, respectively, for CNP-OM and CNP-CL molecules, obtained with isodensity 0.5.
indicate the same trend since they are regions formed by orbitals that tend to capture electrons. In the nitrobenzene ring, the C₁₀ (or C₁₁) and C₁₁ atoms are also susceptible to electrophilic attacks since −NO₂ is an electron-attracting group, causing the minimization of the charge density on these atoms and making them electrophilic. Finally, in the A ring, the carbon atoms in the meta-position can undergo electrophilic attacks. However, in CNP-CL, the ortho-opposite position is also susceptible to this attack.

According to the isosurfaces of the \( p^+ \) function, it is possible to observe that radical attacks are common throughout the chalcone core in both compounds, mainly on C₁₀ and O₃ atoms. Furthermore, the O₁³ and O₈ atoms of the −NO₂ group and the C₁₁ atom of the D ring can also suffer this attack. However, changing the substituent group modified the E ring and quinoline radical attack regions in the molecules. In the case of CNP-OM, the C₃₀, C₁₉ (or C₁₇), and C₁₅ atoms, as well as the O₂ atom of the −OCH₃ group, are susceptible to attacks of this nature. In CNP-CL, it was observed that the sites of radical attacks were on the C₇, C₉, and C₉ atoms of the B ring and the N₁ atom of the quinoline.

Supramolecular arrangement

The comparison of the CNP-OM and CNP-CL supramolecular arrangements showed that −OCH₃ and −Cl cause different intermolecular interaction patterns in the respective crystals. Initially, an interaction between the E ring and the −NO₂ group (C₁₀-H₂₀⋯O₂) was observed in compounds whose distances between the H atom and the acceptor atom differed by only 0.5%, while the D−H⋯A angles differed by 20.3%. This difference is related to the fact that, in CNP-OM, the O ether atom also participates in the formation of dimer 1, represented by the HS in Figure 8a. In contrast, the Cl atom in CNP-CL does not carry out other interactions in addition to the mentioned above. The quinoline portion of both compounds forms dimers: in CNP-OM, by the C₈−H₂₇⋯O₂ interaction (dimer 3), while in CNP-CL, by the C₁₅−H₁₅⋯O₅ interaction (dimer 3). In addition to the formation of this dimer, two other chain interactions were observed in CNP-OM through contacts between the B ring and the −NO₂ group (C₁₀−H₂₀⋯O₂) and contacts between the quinoline-ketone group and the D ring (C₁₅−H₁₅⋯O₅). The A ring also participates in the formation of dimers in the compounds so that, in CNP-CL, this portion of the molecule forms a dimer through contacts with the −NO₂ group by the intermolecular interactions C₂₈−H⋯O₅ and C₂₆−H⋯O₅; also, ring A participates in the interaction C₂₈−H⋯O₅. On the other hand, in CNP-OM, we observed only the formation of dimer 2 (Figure 8b) by the interaction C₂₈−H₂₈⋯O₅.

There are three independent dimers of CNP-OM in the supramolecular arrangement: dimer 1 (Figure 8a) with C₁₂−H₁₁⋯O₁ and C₁₅−H₁₅⋯O₁ interactions (2.591 and 2.653 Å, respectively) described by R₂(22) 6,66, dimer 2 (Figure 8b) with C₁₆−H₃₂⋯O₁ (2.589 Å) interaction described by R₂(10); dimer 3 (Figure 8c) with C₇−H₂⋯O₅ interaction described by R₂(10). In addition, other intermolecular interactions were observed in the CNP-OM: C₉−H₂⋯O₅, at 2.366 Å, described by C(13) (Figure 8d), C₁₀−H₁₅⋯O₂, at 2.511 Å, described by (13) (Figure 8e), and C₁₅−H₁₅⋯O₅, at 2.586 Å, described by C(8) (Figure 8f). Furthermore, through the shape index 32 (Figure 9), there are two \( \pi \cdots \pi \) stacking interactions in the CNP-OM supramolecular arrangement. The first occurs in dimer 1 due to the contact between the E rings (Figure 9a) at 4.324 Å, while the second occurs due to the contact between the D rings (Figure 9b) at 3.616 Å.

Similarly, three dimers constructed in the CNP-CL supramolecular arrangement were observed.3 Dimer 1 (Figure 10a) is formed by the contacts between the O₁ and O₂ atoms of the sulfonyl group with the D ring, whose interactions C₁₂−H⋯O₁ and C₁₅−H⋯O₂ have lengths of 2.528 and 2.441 Å, respectively. This dimer is described by R₂(18) and (20). Described by R₂(28) and R₂(30), dimer 2 (Figure 10b) is formed by contacts of the O₂ and O₄ atoms of the −NO₂ group with the A ring of the compound at 2.591 and 2.673 Å, observed by C₁₅−H⋯O₂ and C₂₅−H⋯O₁ interactions. In dimer 3 (Figure 10c) C₁₂−H⋯O₁ interactions are observed, carried out by contacts between the O₁ atom of the quinoline-ketone group and the A ring at 2.655 Å. In this case, the dimer can be described by R₂(20). Only the C₁₅−H⋯O₁ interaction participates in chain contacts (Figure 10d) in the supramolecular arrangement of CNP-CL, described by C(13). Finally, we observed C−H⋯π interactions (Figure 11) in the CNP-CL supramolecular arrangement.

2D fingerprint analysis33 (Figure 12) showed that 31.8% of the HS of the quinoline-chalcone corresponds to O⋯H contacts, 13.4% to C⋯H contacts, 42.8% to H⋯H contacts, and only 4.9% to C⋯C contacts. The latter is related to the π⋯π stacked contacts observed in dimer 1. The analysis of the 2D fingerprint plots of both compounds showed that replacing the Cl group by −OCH₃ increased the area of O⋯H and H⋯H type contacts by 26.2 and 25.9% on the HS of CNP-OM, respectively. Likewise, C⋯C contacts increased by almost 2.5 times. However, the number of C⋯H contacts is about 19.8% lower in CNP-OM. Figure 12c shows the CNP-OM fingerprint plot, and the column plot compares the contents of each contact over the HS areas in both quinoline-chalcones.

According to QTAIM,34 the observable properties of a chemical system are contained in its electron density,
Figure 8. The HS $d_{min}$ map showing the interactions observed in the CNP-OM molecular packing.

Figure 9. Shape index surface showing the $\pi-\pi$ stacking interactions establishing the CNP-OM crystal packing.
ρ(r), so that the gradient vector of ρ, \( \nabla \rho(r) \), defines the bond paths (BP), starting from atomic nuclei (attractors). This way, points between two attractors are called bond critical points (BCP). The Laplacian electron density determines the location of a BCP (\( \nabla^2 \rho \)), which describes the electron concentration in the BP. In shared interactions, as in a covalent bond, electrons are accumulated in the BCP, resulting in \( \nabla^2 \rho < 0 \); on the other hand, in closed-shell interactions, as in partially covalent bonds, hydrogen bonds, or van der Waals interactions, the attractors support all the charge and \( \nabla^2 \rho > 0 \). After this brief description of the method and the topological parameters obtained (Table 2),

Figure 10. The HS \( d_{\text{max}} \) map shows the interactions observed in the CNP-CL molecular packing.

Figure 11. Shape index surface showing the C–H–π interactions establishing the CNP-CL crystal packing.

Figure 12. (a) 2D fingerprint plots of the nearest external distance (\( d_e \)) versus the nearest internal distance (\( d_i \)) for CNP-OM, and (b) the regions corresponding to O–H, C–H, C–C, and H–H contacts. The colors represent the number of points that share the same \( d_i, d_e \) coordinate (light blue: many; dark blue: few). (c) Graph of the percentages of each contact on the HS in the quinoline-chalcones CNP-OM (blue) and CNP-CL (red).
we observe that the electron density is very low ($\rho < 0.1$) between two attractors that form the intermolecular interaction in both quinoline-chalcones. Furthermore, the $V^2\rho > 0$ values indicate that electrons are depleted in the BCP, configuring closed-shell interactions.

By the virial theorem (equation 11), in atomic units, and by the equation 12, it was shown that the energetic topological parameters are related to $V^2\rho$, where $hv(r)$ corresponds to the electron density energy, $G(r)$ to the kinetic energy density, and $v(r)$ the potential energy density.

$$\frac{1}{4}V^2\rho(r) = 2G(r) + v(r)$$

$$h(r) = G(r) + v(r)$$

For H bonds, it was shown that the intensity of the interaction is powered for values of $V^2\rho < 0$ and $h < 0$, strong for values of $V^2\rho > 0$ and $h < 0$ and weak or moderate for values of $V^2\rho > 0$ and $h > 0$. In the case of interactions in the supramolecular arrangement of the quinoline-chalcones CNP-OM and CNP-CL, by analogy, the interactions are weak H-bonds. Furthermore, the values found for the ratio $\lvert v / G \rvert$ showed that the potential energy density is smaller than the kinetic energy density, indicating that the internuclear electronic flux is small between the attractors, resulting in weak interactions. Molecular graphs of supramolecular arrangements are shown in Figure 13, and only the BPs and the respective BCPs for the interactions are presented in Table 3.

The NBO analysis$^{31,42}$ showed that the H-bonds in both quinoline-chalcones are weakly stabilized by the hyperconjugation$^{43}$ of the donor orbitals (Lewis type) with the acceptor orbitals (non-Lewis type). Interactions in the supramolecular arrangement of CNP-OM occur by hyperconjugation of lone pairs of oxygen atoms or by bonding orbitals with antibonding $\sigma^*$ or $\pi^*$ orbitals. In CNP-CL, hyperconjugations occur between lone pairs of O with antibonding $\rho^*$ or $\pi^*$ orbitals, except for the $C_{5H}^–H^–O_3$ interaction. For example, dimmer 1, present in the supramolecular arrangement of CNP-OM, is formed by the H-bonds $C_{11}^–H^–O_3$ and $C_{13}^–H^–O_3$. The $C_{11}^–H^–O_4$ interaction is stabilized by the hyperconjugations $\eta_1(O_1) \rightarrow \sigma^*(C_{11}^–C_{12}^*)$ and $\eta_2(O_1) \rightarrow \sigma^*(C_{12}^–H^–)$, with $E^H$ values equal to 0.16 and 0.11 kcal mol$^{-1}$, respectively. In this case, the $\eta_1(O_1)$ orbital is a $sp^3$ hybrid that has an occupancy of 1.97$e$, hyperconjugated with the antibonding orbital of $C_{11}^–C_{12}^*$, formed by the contribution of 49.35% of the $sp^3$ hybrid orbital of $C_{11}$ and 50.65% of the $sp^3$ hybrid orbital of $C_{12}$, presenting an occupancy of 0.03$e$. The $\eta_2(O_1)$ orbital is a $p$ orbital with occupancy 1.87$e$ and is hyperconjugated with the $\sigma^*$ antibonding orbital of the $C_{12}^–H$ bond, formed by the contribution of 40.22% of the $sp^3$ hybrid orbital of $C_{12}$ atom with 59.78% of the orbital of H. However, the $C_{11}^–H^–O_4$ interaction is stabilized only by the $\eta_1(O_4) \rightarrow \sigma^*(C_{14}^–C_{13}^*)$

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<th>Interaction</th>
<th>H–A / Å</th>
<th>D – H–A / degree</th>
<th>$\rho_{BCP}^*$ / a.u.</th>
<th>$V^2\rho_{BCP}^*$ / a.u.</th>
<th>$G(r)^*$ / a.u.</th>
<th>$v(r)^*$ / a.u.</th>
<th>$h(r)^*$ / a.u.</th>
<th>$G(r)$</th>
<th>$\nabla^2G(r)$</th>
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<td><strong>CNP-CL</strong></td>
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<td>154.97</td>
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</table>

$^a$Total electronic density on BCP; $^b$Laplacian of electron density on BCP; $^c$Lagrangian kinct energy; $^d$potential energy density; $^e$total energy density. $^f$reference 13.
Figure 13. Molecular graphs of some BP of the intermolecular interactions in the supramolecular arrangements of the (a) CNP-OM and (b) CNP-CL quinoline-chalcones.
hyperconjugation, where the \( \sigma^* \) antibonding orbital is formed by 49.28% of the \( sp^{1.63} \) hybrid of the C14 atom and by 50.72% of the \( sp^{1.88} \) hybrid of the C13 atom, with occupancy 0.02e.

In the case of CNP-CL, the C13–H⋯O1 and C12–H⋯O2 interactions present in dimer 1 are formed by hyperconjugation of the lone pairs of the O1 atom with the antibonding \( \sigma^* \) orbitals of the C13–H and C12–C14 bonds, and the O2 lone pairs with the antibonding \( \sigma^* \) orbitals of the C13–H and C12–C14 bonds. For the formation of the C13–H⋯O1 bond, the hyperconjugations \( \eta_1(O_1) \rightarrow \sigma^*(C13–H) \) and \( \eta_1(O_1) \rightarrow \sigma^*(C11–C12) \) occur, where the values of \( E^{(2)} \) are 0.16 and 0.07 kcal mol\(^{-1}\), respectively. In this case, \( \eta_1(O_1) \) is formed by an \( O_1 \) \( sp^{0.40} \) hybrid orbital with occupancy 1.98e (this hybrid orbital has 71.26% s character versus only 28.73% p character); the antibonding \( \sigma^* \) orbital of C13–H is formed by the contribution of 40.00% of the \( sp^{2.19} \) hybrid orbital of C13 and 60.00% of the s orbital of H. The C13–C12 antibonding \( \sigma^* \) orbital is formed by 50.67% of the C13 \( sp^{1.88} \) hybrid orbital and 49.33% of the C12 \( sp^{1.88} \) hybrid orbital. The hyperconjugations \( \eta_2(O_2) \rightarrow \sigma^*(C12–H) \) and \( (O_2) \rightarrow \sigma^*(C11–C13) \) also occur, where the \( E^{(2)} \) values are 0.09 and 0.09 kcal mol\(^{-1}\), respectively, contributing even less to the stabilization of the H-bond for the dimer. Here, the \( \eta_2(O_2) \) lone pair is a pure p orbital with occupancy 1.83e. Finally, we observe the hyperconjugation \( \eta_3(O_1) \rightarrow \sigma^*(C11–H) \) for the formation of the interaction, where the \( E^{(2)} \) value is 0.11 kcal mol\(^{-1}\), and the lone pair is also a p orbital with occupancy 1.80e. The C13–H⋯O2 interaction is formed by the hyperconjugations \( \eta_1(O_2) \rightarrow \sigma^*(C13–H), \) \( (O_2) \rightarrow \sigma^*(C11–C13) \) and \( \eta_3(O_2) \rightarrow \sigma^*(C11–H) \), which contributes more to the stabilization of the H-bond in the dimer with \( E^{(2)} \) values equal to 0.13, 0.56, and 0.23 kcal mol\(^{-1}\), respectively. The lone pairs are formed by the O2 \( sp^{0.39} \) hybrid orbital (\( \eta_1 \)) and by the O2 pure p orbitals (\( \eta_2 \) and \( \eta_3 \)). The occupancies obtained for these orbitals are 1.98e, 1.82e, and 1.78e. The antibonding \( \sigma^* \) orbital of C13–H is formed by 39.33% of the \( sp^{2.05} \) hybrid orbital of C13 and 60.67% of the s orbital of H. Hyperconjugation of the lone pair (O2) with the antibonding \( \sigma^* \) orbital of the C12–C11 bond was also observed: \( \eta_3(O_2) \rightarrow \sigma^*(C12–C11) \), with \( E^{(2)} = 0.09 \) kcal mol\(^{-1}\).

In Tables S1 and S2 (SI section), we present the hyperconjugations of the other interactions mentioned in Table 2. In addition to these, we observed weak hyperconjugation between the bonding \( \pi \) orbitals of the C20–C28 bond and the antibonding \( \pi^* \) orbital of the C30–C32 bond, where the \( E^{(2)} \) value is 0.09 kcal mol\(^{-1}\). This hyperconjugation justifies, in another way, the formation of the \( \pi \cdots \pi \) stacked interaction observed by the shape index of Figure 9. In this hyperconjugation, the \( \pi \) orbital has an occupancy of 1.67e, being formed by 46.10% of the \( sp^{1.00} \) hybrid orbital of C20 and by 53.90% of the \( sp^{1.00} \) hybrid orbital of C19, while the \( \pi^* \) orbital has an occupancy of 0.30e and is formed by 48.42% of the \( sp^{1.00} \) hybrid orbital of the C21 and 51.58% of the \( sp^{1.00} \) hybrid orbital of C22.

The C28–H and C24–H bonds present in ring A are equivalent and interact with O atoms from different environments: O1=S in CNP-OM and O3=N in CNP-CL. Different quantities of hyperconjugation have been identified in both cases; whereas two occur in the first quinoline-chalcone, twice as many occur in CNP-CL. The sum of the stabilizing energies of these hyperconjugations gives stability to the interaction, which is approximately 1.3 times larger in CNP-CL. Likewise, the C12–H bonds of the D ring interact with the O3 ether atom in CNP-OM and with O2 of the sulfonyl group in CNP-CL. While the sum of the \( E^{(2)} \) values obtained from the two hyperconjugations in CNP-OM are contrasted to the sum of the \( E^{(2)} \) values produced by the five hyperconjugations found in CNP-CL, the latter compound has almost twice the stability. The same happens in the case of the interactions of the C11–H bonds with O4 (in CNP-OM) and O5 (in CNP-CL); however, hyperconjugations provide about 6.7 times more stability in CNP-CL. Finally, the interactions C19=H⋯O6 (in CNP-OM) and C119–H⋯O5 (in CNP-CL) are in the same environment, and, in this case, CNP-OM performs two hyperconjugations, resulting in an \( E^{(2)} \) value about 1.3 times greater than the single hyperconjugation observed in CNP-OM.

**Molecular docking**

The molecular docking method helps predict the interactions between small molecules and active sites in proteins at the atomic level so that the behavior of these structures at the binding site of the proteins can be elucidated as biochemical mechanisms.\(^\text{69}\) Before docking analysis the octopine was redocking with the PBP, and RMDS (root mean square deviation) values (10 poses) were less than 1.0 Å. Docking analysis has shown that the CNP-OM appears to fit well in the binding site of the PBP (Figures 14a and 14b). A \( \pi \) stacking with TYR33A (distance \( = 3.5 \) Å) seems to play an essential role in the conformation of this chemical structure with the binding of the PBP. These results suggest that this compound could inhibit the *Agrobacterium tumefaciens*, which consists in an organism that transfers a T-DNA from the tumor-inducing plasmid into the plant cells.\(^\text{70}\) *A. tumefaciens* is considered one of the most important plant pathogens, producing characteristic crown galls on numerous dicotyledonous plants.\(^\text{71}\)
The docking analysis also suggested that the CNP-OM could interact with the active site of the ecdysone receptor. A π stacking with PHE285E seems to play an essential role in the conformation of this chemical structure with the binding (Figures 14c and 14d) of the target (distance = 3.3 Å). The ecdysone receptor is a hormone-dependent transcription factor. One reinforced hydrogen bond with CYS394 was the more intense interaction between the CNP-OM and the protein’s binding site (distance = 3.0 Å). The ecdysone receptor is a hormone-dependent transcription factor that regulates the development and reproduction of arthropods. This receptor is an important environmentally friendly target of other compounds (bisacylhydrazine insecticides), effective against Lepidoptera order. The transcription factor is absent from mammals and is thus potentially useful as a safe insecticide target with more selective activity.

Thus, based on the results obtained in the two molecular docking analyses, the CNP-OM potential as a candidate substance to be applied to control pathogens and insects in agriculture is verified. In addition, the results obtained corroborate analyzes previously carried out by Vaz et al., in which computational analyses presented similar targets for a structure similar to the one used in this work.

**Conclusions**

Although CNP-OM and CNP-CL crystallized in different environments, no significant changes were observed in their molecular geometries, not even in their reactivity. The chemical descriptors showed that the CNP-OM molecule is slightly more reactive and more basic than CNP-CL. Such functional groups also did not change the nature of intermolecular interactions, in which the short-range contacts showed low intensity since the regions between the nuclear attractors have low charge density; that is, the electrons are depleted in the internuclear regions, so these are closed-shell interactions. Thus, the low ρ values, combined with the ∇²ρ > 0 and h > 0 values, lead to the conclusion that they are van der Waals interactions. However, the different substituted para groups on the
benzene ring resulted in different patterns of interactions in the supramolecular arrangement of the crystals. The docking studies of the CNP-OM quinoline-chalcone have shown potential pesticidal agent for its interaction and binding to amino acids in the ec dysone receptor and periplasmatic binding protein active sites. These possible activities raise a perspective on the economic interest of testing this molecule in vitro and in vivo models.

Supplementary Information

Crystallographic data (excluding structure factors) for the structures in this work were deposited in the Cambridge Crystallographic Data Centre as supplementary publication number codes 2241212 (CNP-OM) and 1981002 (CNP-CL). Copies of the data can be obtained, free of charge, via https://www.ccdc.cam.ac.uk/structures/.

Supplementary information from NBO analyses of the CNP-OM and CNP-CL quinoline-chalcone structures is found in Tables S1 and S2, as well as the CNP-OM infrared spectrum (Figure S1) and is freely available at http://jbcs.sbq.org.br as a PDF file.

Acknowledgments

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Author Contributions

Antônio S. N. Aguiar was responsible for the conceptualization, data curation, investigation, methodology, project administration, resources, writing-original draft, review and editing; João P. M. Rodrigues for the investigation, resources, writing-original draft, review and editing; Leonardo L. Borges for the data curation, methodology, resources, validation, writing-original draft, review and editing; Wesley F. Vaz for the formal analysis, investigation, resources, writing-original draft, review and editing; Giulio D. C. d’Oliveira for the conceptualization, investigation, resources, and writing-original draft; Caridad N. Perez for the conceptualization, data curation, formal analysis, investigation, methodology, resources, validation, writing-original draft, review and editing; Hamilton B. Napolitano for the conceptualization, data curation, formal analysis, methodology, project administration, supervision, validation, visualization, and writing-review and editing.

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