



Predicting toxicity of triazole fungicide: A molecular-based insight into triadimefon and triadimenol

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ARTICLE INFO

Keywords:

Triazoles
Fungicides, DFT, supramolecular arrangement
Toxicity prediction

ABSTRACT

Background: Triazole fungicides, such as triadimefon (TF) and its stereoisomeric metabolite, triadimenol (TN), remain cornerstone agrochemicals. However, their stereochemistry may affect shape reactivity, intermolecular recognition, and ecotoxicity in different ways, with potential impacts on non-target species. **Objective:** This study employs computational methods to describe structural and electronic descriptors, quantify supramolecular interactions, and predict toxicological endpoints *in silico* for TF and its individual stereoisomer, TN. **Methods:** Density functional theory calculations were employed to optimize the molecular geometries and calculate reactivity descriptors at the M06-2×/6-311++G(d,p) level of theory. The intermolecular interactions were compared using Hirshfeld surface analysis, quantum theory of atoms in molecules, and natural bond orbital analysis. Chemical reactivity descriptors were calculated to assess reactive sites. Pharmacophore modeling was performed to verify the potential of the six isomers to interact with the lanosterol 14 α -demethylase target. Toxicity was predicted using computational models available online. **Results:** Differences were found between the electronic properties and intermolecular interactions of TF and TN, due to the presence of –OH or –CO– functional groups. These variations influence the molecular electrostatic potential, reactivity descriptors, and interaction energies, affecting their biological behavior. The results of the pharmacophore modeling suggest that only the 1R-TF, 1S,2R-TN, and 1S,2S-TN isomers demonstrated potential for interaction with the lanosterol 14 α -demethylase target. Toxicity predictions revealed that some triadimenol stereoisomers exhibit a greater potential for adverse effects on non-target organisms when compared to TF. **Conclusion:** The findings highlight the crucial role of stereochemistry in modulating the chemical behavior and toxicity of triazole fungicides. Additionally, the use of *in silico* methods proves effective in predicting the ecotoxicological profiles of such compounds and supports the development of safer and more sustainable agrochemical practices.

1. Introduction

In modern agriculture, pesticides are key tools that safeguard yield and quality by suppressing insect pests, plant diseases, and weeds [1]. However, due to their inherent bioactive nature designed to eliminate various species, these compounds are toxic [2]. Among the different classes, triazole fungicides stand out for their systemic efficacy, broad spectrum of action, and favorable physicochemical properties [3,4]. Since their introduction in the 1970s, triazole fungicides have become indispensable tools for managing fungal diseases worldwide. Owing to

their broad-spectrum activity, high efficacy, rapid onset of action, long-lasting effects, and strong absorption and systemic translocation, these compounds are extensively employed in crops such as wheat, corn, fruits, vegetables, and ornamental plants to control rusts, powdery mildews, and to regulate plant growth [5–7].

Triazoles represent a significant class of heterocyclic compounds due to their broad spectrum of biological activities. Their core structure consists of a five-membered heterocycle containing three nitrogen atoms, which can occur in two distinct isomeric forms depending on the position of the nitrogen atoms: 1,2,3-triazoles and 1,2,4-triazoles [8].

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<https://doi.org/10.1016/j.rechem.2026.103268>

Received 28 November 2025; Accepted 25 March 2026

Available online 31 March 2026

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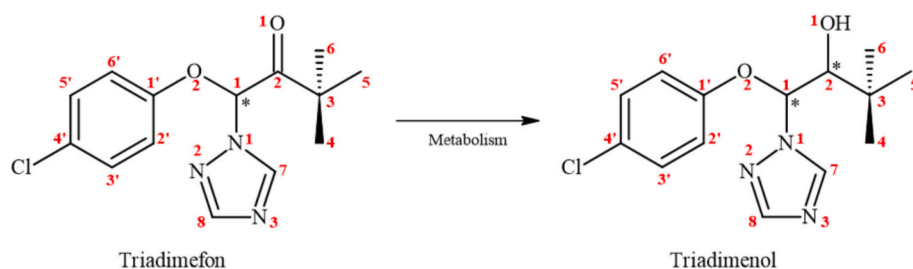


Fig. 1. Structural formulas of Triadimefon and its metabolite Triadimenol, with numbering schemes. The asterisk (*) indicates the chiral carbon present in their chemical structures.

Derivatives of 1,2,3-triazoles have demonstrated outstanding pharmacological properties, including potent antibacterial [9–12], anticancer [12,13], and antitumor [14,15] activities, making them valuable in medicinal chemistry. On the other hand, 1,2,4-triazole derivatives are extensively employed in agriculture as fungicidal agents [5–7], primarily due to their high efficacy and selectivity against a wide range of phytopathogenic fungi. 1,2,4-triazole fungicides present electronic stability and high affinity for lanosterol 14 α -demethylase (CYP51), the target enzyme responsible for ergosterol biosynthesis. Their mechanism of action involves inhibition of this cytochrome P450 monooxygenase, which catalyzes the demethylation of lanosterol – a crucial step in the formation of fungal cell membranes [16].

Among them, triadimefon (TF), triadimenol (TN), diniconazole, hexaconazole, myclobutanil, and tebuconazole – exhibit chirality due to one or more stereocenters, influencing their biological activity and environmental behavior [17]. TF [1-(4-chlorophenoxy)-1-(1,2,4-triazol-1-yl)-3,3-dimethylbutan-2-one] contains a single chiral center (*C₁) and exists as a pair of enantiomers *S*-(+) and *R*-(−) [18]. Its biotransformation leads to TN [1-(4-chlorophenoxy)-1-(1,2,4-triazol-1-yl)-3,3-dimethylbutan-2-ol], its major metabolite in plants, soils, and animals (Fig. 1). While TF contains a single chiral center, TN possesses two, giving rise to four stereoisomers – (1*R*,2*S*), (1*S*,2*R*), (1*R*,2*R*), and (1*S*,2*S*) – which are organized into two diastereomeric pairs: TN-A and TN-B [19,20]. These structural variations significantly affect physicochemical and toxicological properties. Notably, the 1*S*,2*R* stereoisomer exhibits up to 1000-fold greater fungicidal activity than its counterparts, and the A diastereomer is markedly more toxic to mammals based on oral LD₅₀ values in rats [21,22]. Such stereochemical asymmetry is essential for understanding the biological performance, toxicological profile, and environmental fate of these compounds.

Given the extensive agricultural use of TF and TN and the associated ecotoxicological concerns, this study elucidates their electronic and supramolecular characteristics through a comprehensive computational workflow. It was predicted that toxicological profiles using *in silico* models informed by intermolecular interaction patterns and reactivity descriptors, aiming to resolve stereoisomer-specific differences and anticipate potential impacts on non-target organisms. The findings are intended to inform safer and more rational use of these fungicides while supporting regulatory assessments that incorporate stereochemical considerations.

2. Computational procedures

2.1. Solid-state analysis

The crystallographic structures of TF and TN were obtained from the Cambridge Structural Database (CSD) [23], under the codes 1109431 [24] and 1108987 [25]. The selection considered the presence of functional groups associated with antifungal activity, such as triazoles [26]. The structural data of the compounds were obtained in crystallographic information file format and served as the basis for structural analyses, including geometry and supramolecular arrangement.

Molecular representations, tables, and figures were constructed with Mercury (version 3.8) [27] and GIMP [28] software. Additionally, Hirshfeld surfaces (HS) in the *d*_{norm} and *shape index* configurations, as well as their respective 2D fingerprint plots, were obtained using the Crystal Explorer (version 21.5) [29], allowing a more detailed evaluation of the interactions. The HS was carried out using the normalized contact distance function (*d*_{norm}),

$$d_{\text{norm}} = \frac{d_i - r_i^{\text{vdw}}}{r_i^{\text{vdw}}} + \frac{d_e - r_e^{\text{vdw}}}{r_e^{\text{vdw}}}, \quad (1)$$

which identifies regions of molecular contact by considering the internal (*d_i*) and external (*d_e*) distances to the surface, normalized by the corresponding van der Waals radii (*r*^{vdw}). The shape index was employed to identify interactions involving π systems [30]. The compounds TF and TN feature a chiral center at C₁, while TN possesses an additional chiral center at C₂ (Fig. 1), resulting in four distinct stereoisomers for TN. For discussion purposes, the *R* and enantiomer B1 (1*R*,2*R*) configurations were chosen, respectively.

Quantum theory of atoms in molecules (QTAIM) [31,32] was employed to determine the exact nature of the observed intermolecular interactions. At the same time, natural bond orbital (NBO) [33,34] analysis was used to evaluate their respective stabilities. These calculations were performed using density functional theory (DFT) [35,36], as implemented in the Gaussian 16 [37] software package. Input geometries were constructed based on the experimentally observed structures and optimized using the highly parameterized exchange–correlation functional M06-2 $\times$ [38] in combination with the diffuse and polarized Pople-style split-valence triple- ζ basis set 6-311++G(d, p). Previous studies have demonstrated that this functional provides reliable descriptions of medium-range electronic correlation effects and non-covalent interactions and is among the best-performing options for modeling the thermodynamics of chemical processes [39]. Frequency calculations were also carried out to ensure that the molecular systems corresponded to true *minima* on the potential energy surface.

The topological parameters analyzed by QTAIM included the electron density [$\rho(\mathbf{r})$], the Laplacian of $\rho(\mathbf{r})$ ($\nabla^2\rho$), the electron kinetic energy density [*G*($\mathbf{r}$)], the electron potential energy density [*v*($\mathbf{r}$)], and the total energy density [*h*($\mathbf{r}$)] [40,41]. These parameters were collected by the Multiwfn 3.5 [42] program. For the NBO analysis, hyperconjugative interactions between donor (Lewis-type) and acceptor (non-Lewis-type) orbitals [43] were examined using the second-order perturbation theory formula,

$$E_{i \rightarrow j}^{(2)} = -n_{\sigma} \frac{\langle \sigma_i | \hat{F} | \sigma_j^* \rangle}{\varepsilon_j^* - \varepsilon_i} = -n_{\sigma} \frac{F_{ij}^2}{\varepsilon_j^* - \varepsilon_i}, \quad (1)$$

where $\langle \sigma_i | \hat{F} | \sigma_j^* \rangle$ (or *F*_{ij}²) is the Fock matrix element between the *i* and *j* NBOs, ε_{σ^*} is the energy of the antibonding orbital σ^* , and ε_{σ} is the energy of the bonding orbital σ ; *n*_σ is the population occupation of the σ donor orbital.

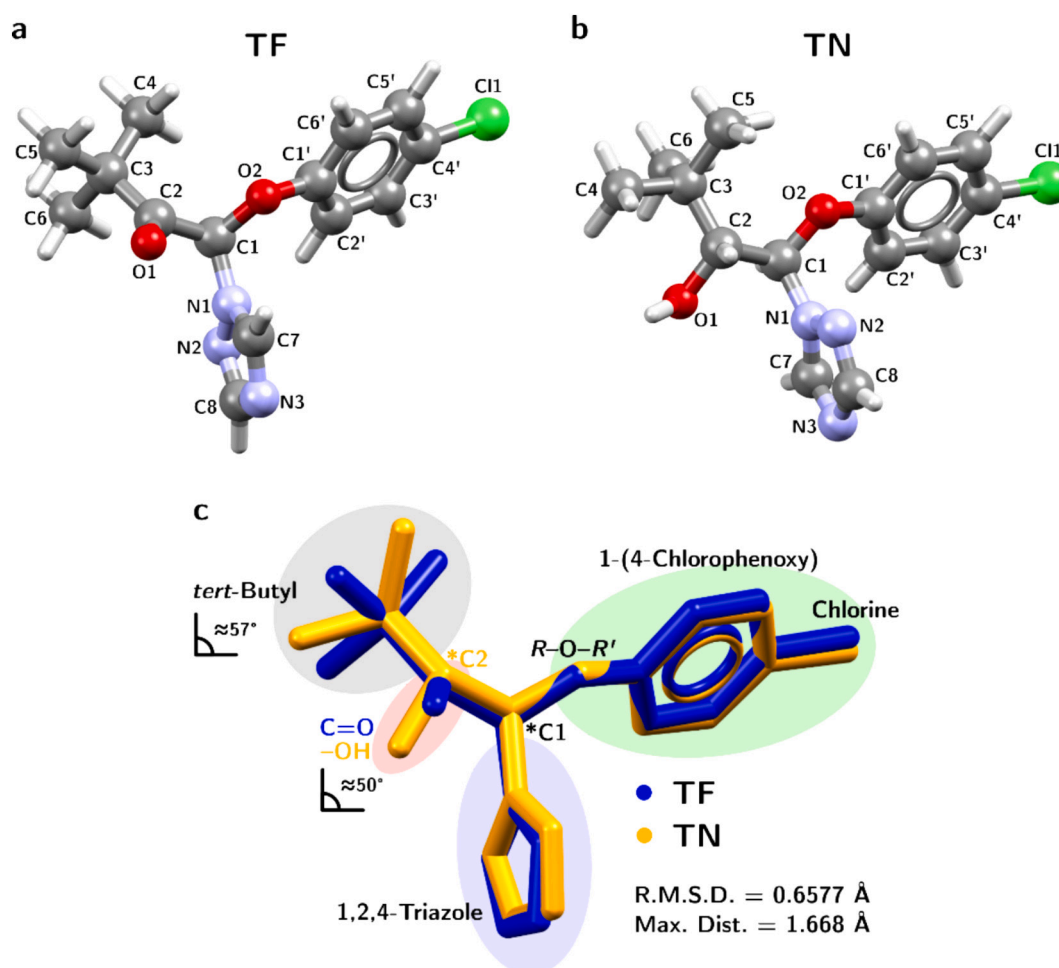


Fig. 2. Molecular structure of selected triazole fungicides, TF (a) and TN (b), and their numbering scheme for all non-hydrogen atoms. (c) Overlap of the compounds: TF (blue) and TN (orange), circles detach the chemical moieties in both molecules. RMSD of 0.6577 Å, and maximum distance of 1.668 Å. The superposition excludes hydrogen atoms and allows inversion to fit better. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. Molecular modeling study

The calculations were performed using the same level of theory. The TF and TN molecules were initially optimized following a conformational search based on a relaxed scan approach, aiming to identify the ground-state conformation. Subsequently, the energies of the frontier molecular orbitals [44] – the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) – were used to calculate chemical reactivity descriptors, including chemical hardness [45,46],

$$\eta = \frac{1}{2} \left(\frac{\partial^2 E}{\partial N^2} \right)_n = \frac{I - A}{2}, \quad (2)$$

which measures the resistance to deformation of the electron cloud during chemical processes; chemical potential [46],

$$\mu = \left(\frac{\partial E}{\partial N} \right)_n = -\frac{I+A}{2} = -\chi, \quad (3)$$

which is related to charge transfer from a species with a higher chemical potential (μ_{large}) to one with lower chemical potential (μ_{small}); and the global electrophilicity index [47],

$$\omega = \frac{\mu^2}{2\eta}. \quad (4)$$

which measures energy stabilization when the system acquires an electronic charge from the environment. In Eqs. (2) and (3), E is the energy of the system, N is the number of particles, v is the external potential, χ is the electronegativity, $I \approx -E_{\text{HOMO}}$ is the ionization potential, and $A \approx -E_{\text{LUMO}}$ is the electron affinity. The nucleophilic and electrophilic regions of the compound were evaluated using the molecular electrostatic potential (MEP) map [48,49], where the electrostatic potential, $V(\mathbf{r})$ [50], at point $\mathbf{r}$, is defined by

$$V(\mathbf{r}) = \sum_{\alpha} \frac{Z_{\alpha}}{|\mathbf{r}_{\alpha} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')}{|\mathbf{r}' - \mathbf{r}|} d\mathbf{r}', \quad (5)$$

where Z_α is the charge of nuclei α at point $\mathbf{r}_\alpha$ and $\rho(\mathbf{r}')$ is the charge density at the point $\mathbf{r}'$ [48]. Furthermore, through the Fukui function [51,52], defined by the equation,

$$f^0(\mathbf{r}) = \left[\frac{\partial \rho(\mathbf{r})}{\partial N} \right]_n^0, \quad (6)$$

it was possible to predict the local reactivity sites, so that the indices for the nucleophilic, electrophilic, and radical attacks were obtained.

2.3. Toxicity prediction and pharmacophore modeling

For the pharmacophore modeling of the different isomers of fungicides with lanosterol 14 α -demethylase (CYP51 family) target ligands,

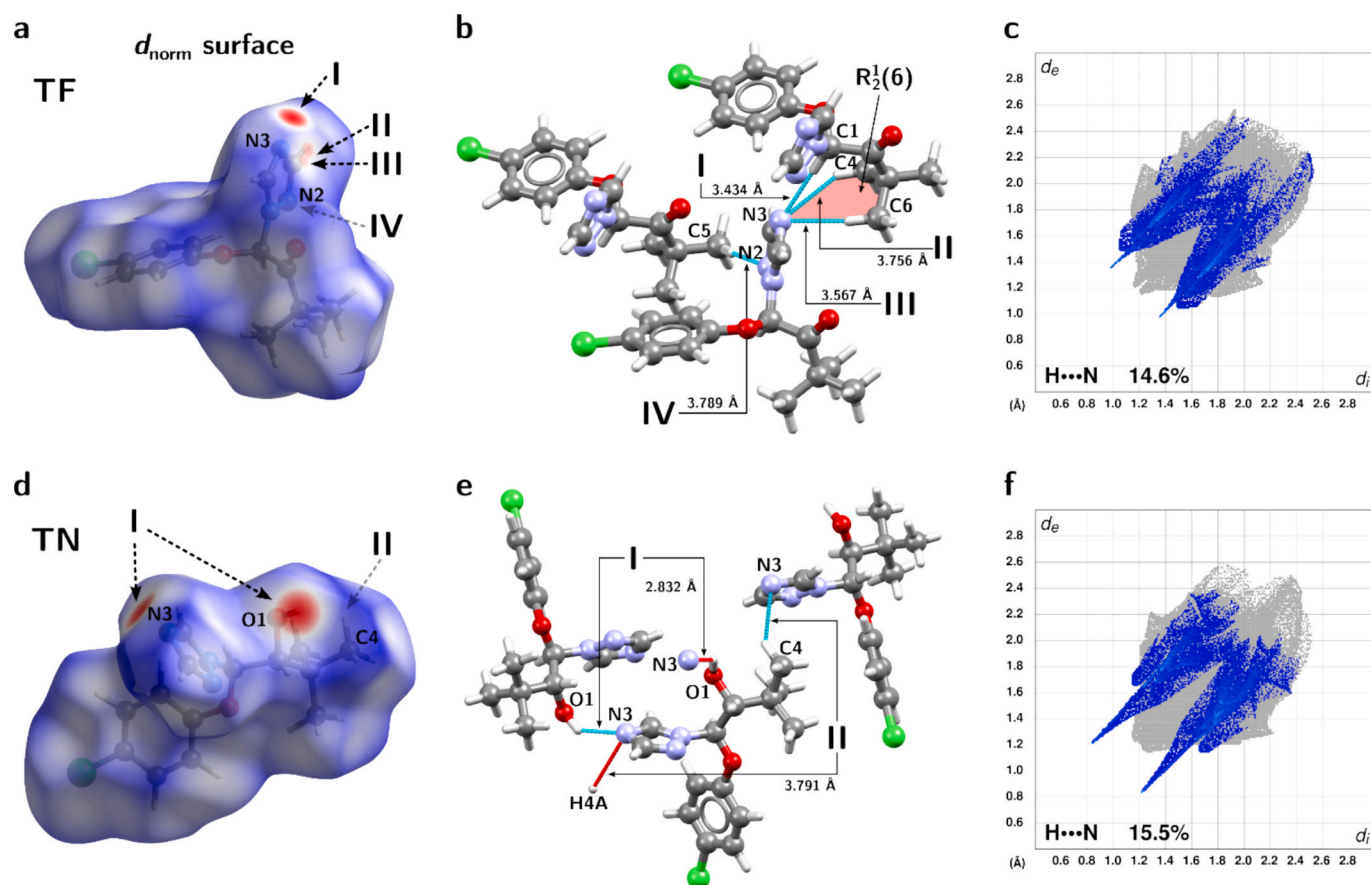


Fig. 3. HS with the d_{norm} property mapped and the detailed view of C-H...N and O-H...N interactions in the supramolecular arrangement of TF and TN. (a) d_{norm} surface mapped for TF. (b) Representation of C-H...N interactions I ($\text{C}_1 \cdots \text{N}_3$), II ($\text{C}_4 \cdots \text{N}_3$), III ($\text{C}_6 \cdots \text{N}_3$), and IV ($\text{C}_5 \cdots \text{N}_2$) with their donor-acceptor distances in TF. (c) The 2D *fingerprint* plot of the H...N, with 14.6% of the total contacts, was mapped for TF. (d) d_{norm} surface mapped for TN. (e) Representation of O-H...N interaction I ($\text{O}_1 \cdots \text{N}_3$), and C-H...N interaction II ($\text{C}_4 \cdots \text{N}_3$) with their donor-acceptor distances for TN. (f) The 2D *fingerprint* plot of the H...N with 15.5% of the total contacts was mapped for TN.

we employed LigandScout v4.5 [53] (<https://docs.inteligand.com/ligandscout>). LigandScout identified combinations of shared pharmacophoric features, including hydrogen-bond donors (HBDs), hydrogen-bond acceptors (HBAs), positively and negatively charged groups, hydrophobic (HyPho) regions, and aromatic rings (ARs) [53]. These unique pharmacophores were subsequently integrated into the alignment process to develop the shared feature pharmacophore (SFP) model. A literature review was conducted using the databases in Binding DB (<https://www.bindingdb.org/rwd/bind/index.jsp>) to identify compounds with lanosterol 14 α -demethylase antagonist activity. A total of five compounds with the lowest inhibitory concentration (IC_{50}) values were included in a dataset used to calculate the pharmacophore models.

To assess the pharmaceutical viability, a pharmacokinetic study was carried out to measure parameters related to absorption, distribution, metabolism, and excretion (ADME). This study utilized the SwissADME online (<http://www.swissadme.ch/>) tool for analysis [54,55]. The following platform was used to predict the toxicity of chemical studies. ProTox-3.0 - Prediction of TOXicity of chemicals [56] (<https://tox.charite.de/protox3/>), which applies all the toxicity parameters to the most promising component that is likely to be the source of biological activity.

The assessment of potential toxic effects was conducted through computational predictions, with cardiac toxicity evaluated using the Pred-Herg server [57,58] (<https://predherg.labmol.com.br/>) and cutaneous toxicity assessed employing the Pred-Skin server [59,60] (<https://predskin.labmol.com.br/>). The environmental toxicity assessment was conducted using the ADMETSAR [61,62] server (<https://lmmd.ecus>

t.edu.cn/admetSar2/). The analyses included assessments of *Tetrahymena pyriformis* toxicity, honeybee toxicity, fish toxicity, and biodegradation.

3. Results and discussion

3.1. Solid-state analysis

The TN and TF compounds crystallize in the monoclinic systems $\text{P}2_1/\text{c}$ and $\text{P}2_1/\text{n}$ space groups (Fig. 2), respectively, with one independent molecule in the asymmetric unit ($Z' = 1$) and four in the unit cell ($Z = 4$) (see Fig. S1 a and b). Both structures have a chlorine atom in the *para*-position of aromatic ring 1 and a triazole attached to carbon 1, which is also connected to ring 1 via an ether moiety (R-O-R). The main difference lies in the presence of a hydroxyl (OH) at C_2 in TN, while TF has a carbonyl ($\text{C}=\text{O}$) and the second chiral center at C_2 . Fig. 1a and b shows in detail the crystal structures and atomic numbering scheme through the illustration of the asymmetric unit. Overlaid compounds with root mean square deviation (RMSD) of 0.6577 Å and maximum distance of 1.668 Å, highlighting the angles formed between the *tert*-butyl groups of TF and TN in $\approx 57^\circ$, and at C_2 between the oxygen from hydroxyl ($-\text{OH}$) and carbonyl ($\text{C}=\text{O}$) in $\approx 50^\circ$ (Fig. 1c).

The supramolecular analysis of TF and TN using the full interaction maps tool [63] revealed predominantly weak interactions such as C-H...N, C-H...O, C-H...Cl, C-H... π and $\pi \cdots \pi$. Notably, O-H...N interactions were observed exclusively in TN, due to the presence of a hydroxyl group. The blue regions of the interaction maps highlight

Table 1

Geometries of the intermolecular interactions, distances are in angstrom (Å), and angles are in degrees (°), for TF and TN. Cg1 is the centroid of the phenyl ring, and Cg2 is the centroid of the triazole ring.

^(id) Interaction	D...H (Å)	H...A (Å)	D...A (Å)	∠(D—H...A) (°)	Symmetry Codes
Triadimefon					
⁽ⁱ⁾ C ₁ —H ₁ ...N ₃	1.080	2.354	3.434	178.80	$-\frac{1}{2}+x, \frac{3}{2}-y, \frac{1}{2}+z$
⁽ⁱⁱ⁾ C ₄ —H _{4C} ...N ₃	1.079	2.802	3.756	147.36	$\frac{1}{2}+x, \frac{3}{2}-y, \frac{1}{2}+z$
⁽ⁱⁱⁱ⁾ C ₆ —H _{6A} ...N ₃	1.081	2.563	3.567	154.08	$-\frac{1}{2}+x, \frac{3}{2}-y, -\frac{1}{2}+z$
^(iv) C ₅ —H _{5A} ...N ₂	1.080	2.710	3.789	176.40	$y, -\frac{1}{2}+z, -\frac{1}{2}+x, \frac{3}{2}-y$
^(v) C ₅ —H ₅ ...O ₁	1.081	2.810	3.602	130.09	$y, \frac{1}{2}+z, 1-x, 1-y, 1-z$
^(vi) C ₆ —H ₆ ...O ₂	1.079	2.823	3.903	179.06	$1-x, 1-y, 1-z$
^(vii) C ₄ —H _{4A} ...Cg ₁	1.080	2.855	3.912	166.15	$-1+x, y, z$
^(viii) C ₆ —H _{6C} ...Cg ₂	1.080	3.201	3.857	120.12	$1+x, y, z, -x, 2-y, 1-z$
^(ix) C ₄ —H _{4B} ...Cl ₁	1.080	3.275	3.672	102.96	$1-x, 2-y, 1-z$
^(x) C ₅ —H _{5C} ...Cl ₁	1.080	3.531	3.765	94.08	$1-x, 2-y, -z$
Triadimenol					
⁽ⁱ⁾ O ₁ —H _{1A} ...N ₃	1.047	1.996	2.832	134.66	$-x, \frac{1}{2}+y, \frac{1}{2}-z$
⁽ⁱⁱ⁾ C ₄ —H _{4A} ...N ₃	1.155	2.819	3.791	141.42	$x, \frac{1}{2}-y, \frac{1}{2}+z, -x, -\frac{1}{2}+y, \frac{1}{2}-z$
⁽ⁱⁱⁱ⁾ C ₈ —H ₈ ...O ₁	0.813	2.997	3.536	125.88	$\frac{1}{2}-z, x, \frac{1}{2}-y, -\frac{1}{2}+z$
^(iv) C ₃ —H ₃ ...O ₂	1.029	3.307	3.667	102.31	$\frac{1}{2}-z, x, \frac{1}{2}-y, -\frac{1}{2}+z$
^(v) C ₄ —H _{4C} ...Cg ₁	0.991	3.121	4.104	172.03	$-\frac{1}{2}+z, -x, \frac{1}{2}+y, \frac{1}{2}-z$
^(vi) C ₇ —H ₇ ...Cg ₂	0.958	3.004	3.678	128.60	$1-x, 1-y, 1-z$
^(vii) C ₅ —H _{5A} ...Cl ₁	1.024	3.085	3.843	131.66	$1-x, 1-y, 1-z$
^(viii) C ₆ —H _{6C} ...Cl ₁	0.954	3.354	4.016	128.29	$1-z$

where donors are expected to be followed by CSD data, the red regions indicate likely acceptor positions, the orange regions indicate likely positions of hydrophobic groups, and the brown regions indicate likely positions of $\pi\cdots\pi$ interactions. The maps were created using carbonyl/oxygen, methyl/carbon, aromatic CH/carbon, and uncharged (NH) nitrogen probes. Illustrated in Fig. S1c-d, the intermolecular interaction maps of both compounds TF and TN, respectively, show two high-probability areas near the nitrogen atoms of the triazole ring, and two slightly lower probability regions near the oxygen of the carbonyl in TF. The hydroxyl group in TN donates a hydrogen bond in this structure, with a high-probability area close to it. Conversely, the C—H groups in the triazole and phenyl rings have the potential to interact with H-bond acceptors, as indicated by the red regions in the structure. Despite a subtle difference, it can play an important role, since the presence of such areas can perform interactions with other molecules, likely influencing the physical-chemical properties of the molecule, such as solubility, affinity with cell membranes, and interactions with biomolecules.

Depicting the interactions, we have applied the graph set analysis

Table 2

Percentage contribution of contacts present in the Triadimefon and Triadimenol crystal structures.

Molecule	H...H	H...N	H...O	H...C	H...Cl	C...C	Others
TF	41.2	14.6	11.8	15.4	12.8	0.6	3.6
TN	46.4	15.5	4.8	16.1	13.3	1.0	2.9

[64], to identify the interaction motifs in supramolecular arrangement, combining with the HS analysis [30] also used in this study through the d_{norm} surface of the compounds TF (volume = 372.04 Å³, area = 330.42 Å²) and TN (volume = 367.77 Å³; area = 325.40 Å²) as illustrated in Fig. 3a and c, representing both, acceptor and donor regions of interactions. The red color indicates closer contacts, while the blue color indicates outlying contacts. TN and TF compounds exhibit similar patterns of intermolecular interactions, and their respective geometry parameters are given in Table 1. The 2D fingerprint plots [65] of intermolecular interactions were mapped within the range of 0.8–2.6 Å view of d_e vs d_i for TF and TN compounds. The total contribution for each type of contact is described in Table 2.

Detaching the H...N contacts in the d_{norm} HS (Fig. 3a and d), they occur mainly through C—H...N type of interactions, in TF with N₂ as acceptor the C₅—H_{5A}...N₂ with donor acceptor distance (D...A = 3.789 Å), while N₃ alone as acceptor show three other interactions due to the arrangement where it is positioned surrounded by the methyl from *tert*-butyl group, than we observed the interaction C₁—H₁...N₃ (D...A = 3.434 Å), and also the bifurcated by C₄—H_{4C}...N₃ (D...A = 3.756 Å) and C₆—H_{6A}...N₃ (D...A = 3.567 Å) resulting in the formation of a R₂¹(6) supramolecular motif, as detailed in Fig. 3b. Topological parameters from QTAIM [40] analysis indicate that electron density is depleted at the bond critical points (BCPs) of these interactions, with $\rho(r) < 0.1$ a.u. and $\nabla^2\rho > 0$, characterizing them as closed-shell interactions [41,66] with van der Waals nature [67,68] (See Table 3). Among these, C₁—H₁...N₃ exhibits the highest electron density at the internuclear region ($\rho(r) = 0.01268$ a.u.), representing the most stable intermolecular contact in TF, with a stabilization energy ($E_{i\rightarrow j}^{(2)}$) of 3.71 kcal/mol, as supported by the hyperconjugative interaction $\eta_1(\text{N}_3) \rightarrow \sigma^*(\text{C}_1\text{—H}_1)$ in the NBO analysis. The C₆—H_{6A}...N₃ interaction presents a relatively greater partially covalent character, as indicated by a $(|V|/G)$ ratio of 0.9; however, the corresponding hyperconjugation $\eta_1(\text{N}_3) \rightarrow \sigma^*(\text{C}_6\text{—H}_{6A})$ contributes minimally to the supramolecular stabilization, with an $E_{i\rightarrow j}^{(2)}$ value of only 0.20 kcal/mol.

TN forms a bifurcated interaction on N₃ as acceptor from two molecules via the C₄—H_{4A}...N₃ (D...A = 3.791 Å) and an O—H...N interaction (Fig. 3d and e). The 2D fingerprint plot of H...N contacts is used to quantify the relative contribution of these types of interactions (C—H...N and O—H...N), with 14.6% of total contacts mapped for TN and 15.5% for TF 15.5% (Fig. 3c and f). However, the O—H...N interaction is only present in TN through the O₁—H_{1A}...N₃, which among all interactions and contacts for both compounds is the shortest donor-acceptor distance (D...A = 2.832 Å), occurring between the oxygen (O₁) from hydroxyl group towards the lone pair on nitrogen (N₃) in 1,2,4-triazole ring at position 4 (Fig. 3e). QTAIM analysis characterizes the O₁—H_{1A}...N₃ interaction with topological parameters of $\rho(r) = 0.02195$ a.u., $\nabla^2\rho = 0.11416$ a.u., and $h(r) = 0.00237$ a.u., suggesting a medium-intensity hydrogen bond [41]. The binding energy (BE), calculated by equation [69],

$$BE \approx -223,08\rho(r) + 0,7423, \quad (7)$$

is 8.4 kcal/mol [70], strongly contributing to the stabilization of TN's supramolecular arrangement. The observed hyperconjugation corroborates this $\eta_1(\text{N}_3) \rightarrow \sigma^*(\text{O}_1\text{—H}_{1A})$, with $E_{i\rightarrow j}^{(2)} = 10.47$ kcal/mol. In contrast, the C₄—H_{4A}...N₃ interaction is weaker, with topological descriptors of $\rho(r) = 0.00527$ a.u., $\nabla^2\rho = 0.01651$ a.u., and $h(r) = 0.00048$ a.u.,

Table 3

Topological parameters from QTAIM for the intermolecular interactions within the supramolecular arrangement of the Triadimefon and Triadimenol fungicides, obtained at the M06-2×/6-311++G(d,p) level of theory.

^(id) Interaction	$\rho(r)^a$ (a.u.)	$\nabla^2\rho^b$ (a.u.)	$G(r)^c$ (a.u.)	$v(r)^d$ (a.u.)	$h(r)^e$ (a.u.)	$\frac{ v }{G}$	Interaction Type
Triadimefon							
^(I) C ₁ –H ₁ ...N ₃	0.01268	0.04872	0.01057	–0.00896	0.00161	0.8	van der Waals
^(II) C ₄ –H _{4C} ...N ₃	0.00536	0.01783	0.00404	–0.00363	0.00041	0.9	van der Waals
^(III) C ₆ –H _{6A} ...N ₃	0.00482	0.01480	0.00310	–0.00250	0.00060	0.8	van der Waals
^(IV) C ₅ –H _{5A} ...N ₂	0.00555	0.01884	0.00406	–0.00340	0.00065	0.8	van der Waals
^(V) C ₅ –H ₅ ...O ₁	0.00390	0.01614	0.00344	–0.00284	0.00060	0.8	van der Waals
^(VI) C ₆ –H ₆ ...O ₂	0.00378	0.01546	0.00334	–0.00281	0.00053	0.8	van der Waals
^(IX) C ₄ ...Cl ₁	0.00335	0.01399	0.00260	–0.00170	0.00090	0.7	van der Waals
^(X) C ₅ –H _{5C} ...Cl ₁	****	****	****	****	****	****	****
Triadimenol							
^(I) O ₁ –H _{1A} ...N ₃	0.02195	0.11416	0.02617	–0.02379	0.00237	0.9	H-Bond
^(II) C ₄ –H _{4A} ...N ₃	0.00527	0.01651	0.00365	–0.00317	0.00048	0.9	van der Waals
^(III) C ₈ –H ₈ ...O ₁	0.00296	0.01424	0.00284	–0.00212	0.00072	0.7	van der Waals
^(IV) C ₃ –H ₃ ...O ₂	****	****	****	****	****	****	****
^(VII) C ₅ –H _{5A} ...Cl ₁	0.00195	0.00681	0.00129	–0.00087	0.00042	0.7	van der Waals
^(VIII) C ₆ –H _{6C} ...Cl ₁	0.00437	0.01557	0.00311	–0.00232	0.00079	0.7	van der Waals

^aElectron Density; ^bLaplacian of ρ ; ^cKinetic Energy Density; ^dPotential Energy Density; ^eTotal Energy Density

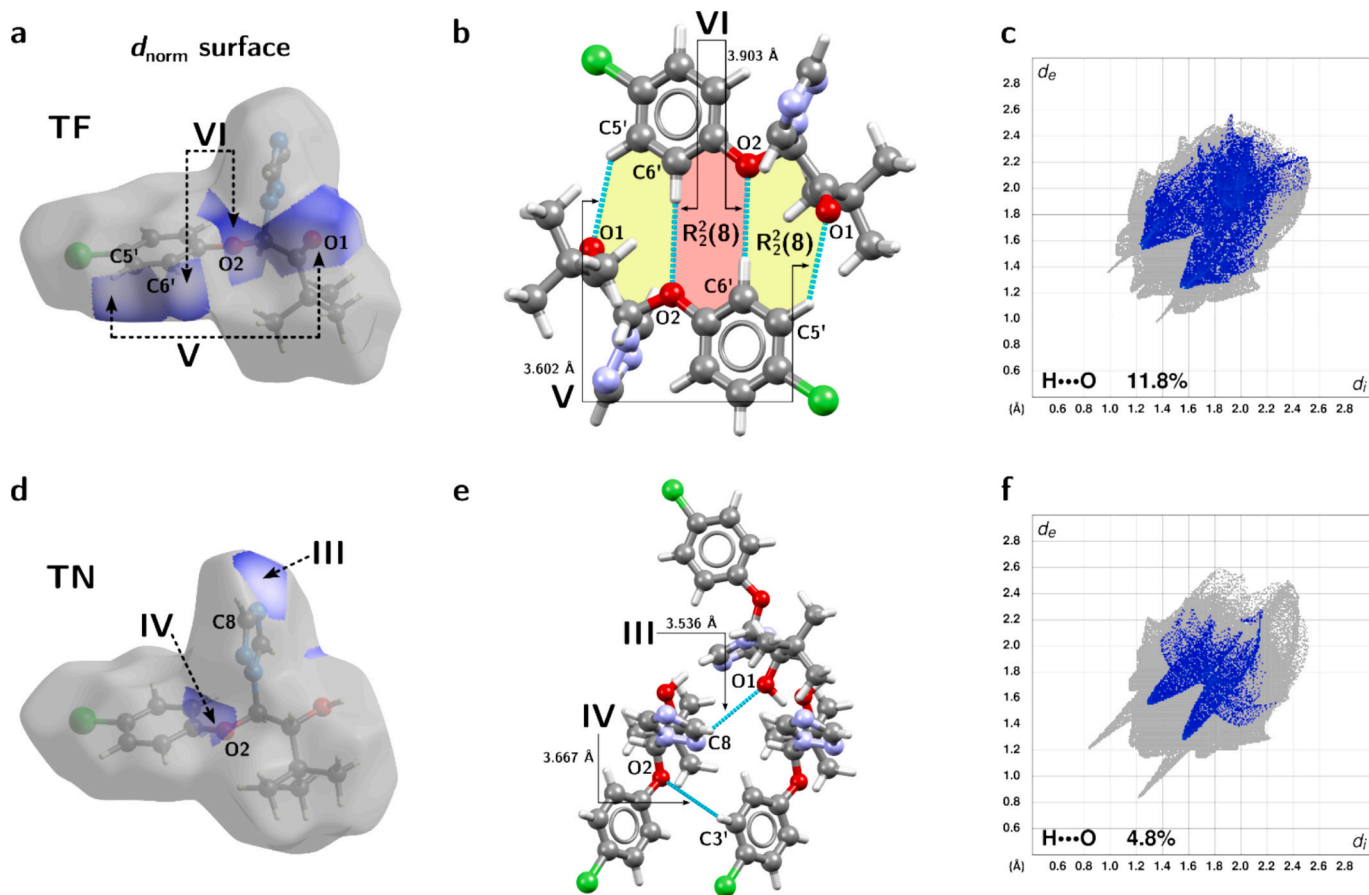


Fig. 4. HS with the d_{norm} property mapped and the detailed view of C—H...O interactions in the supramolecular arrangement of TF and TN. (a) d_{norm} surface mapped for TF. (b) Representation of interactions: V (C₅...O₁) and VI (C₆...O₂), with their donor-acceptor distances in TF forming a dimer with two parallel $R_2^2(8)$ supramolecular motifs. (c) The 2D fingerprint plot of the H...O, with 11.8% of the total contacts, was mapped for TF. (d) d_{norm} surface mapped for TN. (e) Representation of interactions: III (C₈...O₁) and IV (C₃...O₂) with their donor-acceptor distances in TN. (f) The 2D fingerprint plot of the H...O, with 4.8% of the total contacts, was mapped for TN.

indicative of a van der Waals character. The corresponding hyper-conjugation $\eta_1(N_3) \rightarrow \sigma^*(C_4-H_{4A})$ contributes minimally to stabilization,

with an $E_{i \rightarrow j}^{(2)}$ value of only 0.32 kcal/mol. Alongside the chirality, this interaction is likely to play an essential role for TN in the biological

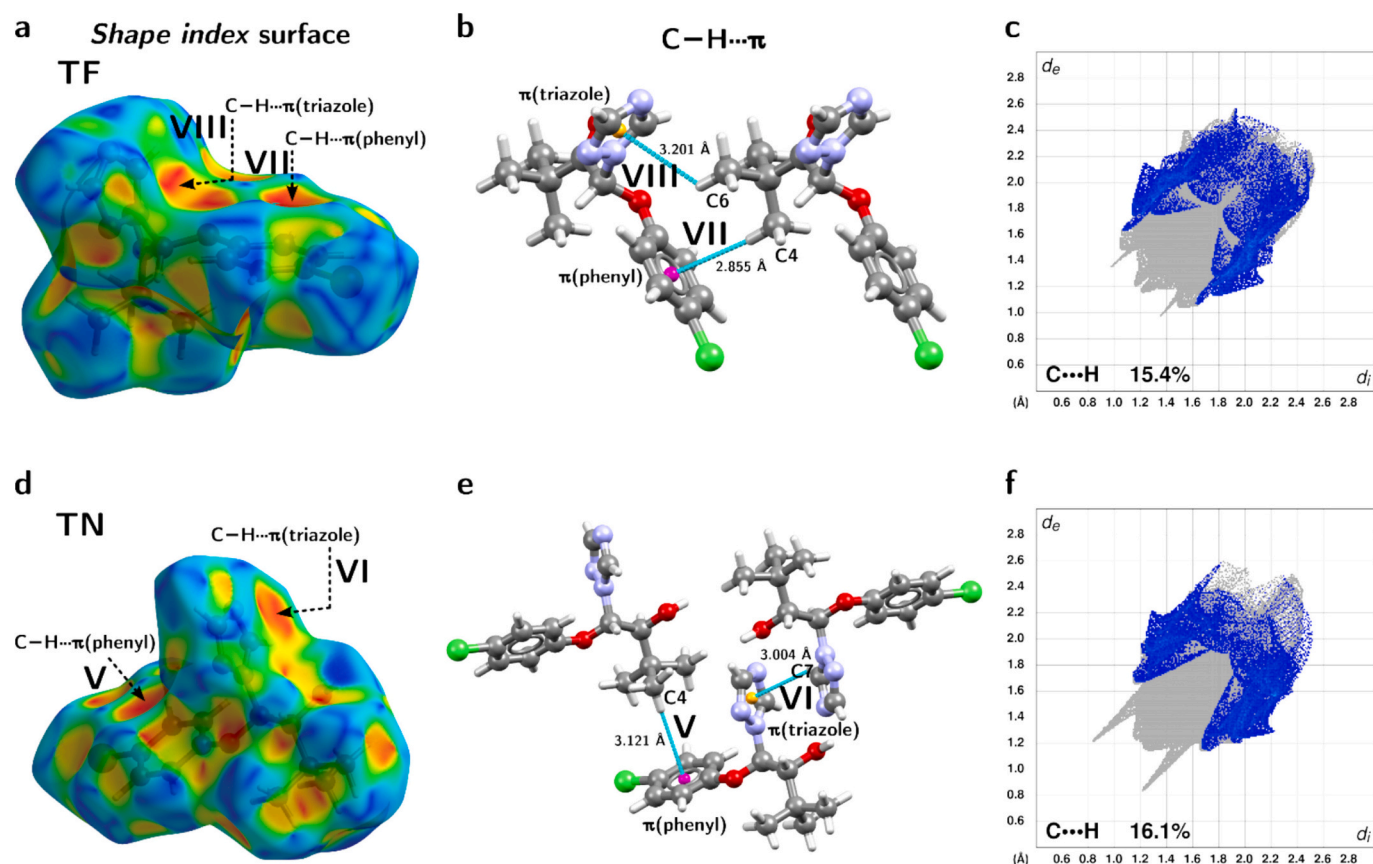


Fig. 5. HS with the *shape index* property mapped, highlighting the red concave regions where C-H... π interactions occur and the detailed view of these interactions in the supramolecular arrangement of TF and TN. (a) *shape index* surface mapped for TF. (b) Representation of C-H... π interactions VII [C₄-H_{4C}... π (phenyl)] and VIII [C₆-H_{6C}... π (triazole)], with their H... π (Cg) distances in TF. (c) The 2D *fingerprint* plot of the C...H with 15.4% of the total contacts was mapped for TF. (d) *shape index* surface mapped for TN. (e) Representation of interactions V [C₄-H_{4C}... π (phenyl)] and VI [C₇-H₇... π (triazole)] with their H... π (Cg) distances in TN. (f) The 2D *fingerprint* plot of the C...H with 16.1% of the total contacts was mapped for TN. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

environment, considering that it can result from TF by the enzymatic reduction of a carbonyl to an alcohol group in soils, plants, and fungi, forming this metabolite, which is also observed separately and with superior fungicidal activity than TF [71].

The C-H...O type of interactions was observed in both TF and TN, forming different patterns of arrangement, as illustrated in Fig. 4a. The d_{norm} surface of TF indicates the regions of H...O contacts located horizontally in the structure through the C-H groups in the phenyl ring towards the oxygens in carbonyl (O₁) and ether (O₂). Together, the interactions C₅-H₅...O₁ (3.602 Å) and C₆-H₆...O₂ (3.903 Å) form two parallel R₂²(8) supramolecular motifs resulting in a dimeric arrangement (see Fig. 4b), which corresponds to 11.8% of total contacts mapped for TF (Fig. 4c). The electron density at the bond critical points (BCPs) of these interactions is low, characterizing them as van der Waals interactions. Nevertheless, the C₆-H₆...O₂ interaction contributes more effectively to system stabilization, as indicated by the hyperconjugation $\eta_1(\text{O}_2) \rightarrow \sigma^*(\text{C}_6-\text{H}_6)$, with an $E_{i \rightarrow j}^{(2)}$ value of 0.31 kcal/mol. In TN the d_{norm} surface also indicates the region of H...O contact, but on C-H group at C₈ from triazole ring towards the oxygen of carbonyl (O₁) to establish the interactions C₈-H₈...O₁ (3.536 Å) and C₃-H₃...O₂ (3.667 Å) (Fig. 4d and 4e), corresponding to only 4.8% of total contacts (Fig. 4f). In both cases, these are long-range interactions with donor-acceptor distances from 3.5 to 3.9 Å. None of these interactions produce hyperconjugations between donor and acceptor orbitals, meaning that they do not contribute to the stabilization of the supramolecular arrangement of TN.

Furthermore, the QTAIM topology showed the formation of a bond

path (BP) only at C₈-H₈...O₁, whose parameters suggested a van der Waals character. However, distinct arrangements were observed through C-H...O interactions, reflecting a difference that is more than double in the percentage contribution of these contacts to TF in relation to TN. It is important to note that TF has oxygens only as H-bond acceptors, while TN has the hydroxyl group as a donor but is involved in an O-H...N interaction.

The occurrence of hydrophobic interactions involving systems such as methyl groups, phenyl rings, and triazole rings in both structures of TF and TN. These interactions are C-H... π and π ... π -stacking, occurring between methyl (C-H) groups that act as donors and the π (phenyl) and π (triazole) systems as acceptors. To represent the π -electron system, measurements were taken using their respective centroids (Cg). The C-H... π interactions were identified through the HS mapped with the *shape index* property, which display red concave regions over the phenyl and triazole rings, and corresponding blue convex regions over the C-H atoms (see Fig. 5a and d). TF presents the shortest and the longest C-H... π interactions, with distances between H... π (Cg), C₄-H_{4C}... π (phenyl) with 2.855 Å, and C₆-H_{6C}... π (triazole) with 3.201 Å, respectively (Fig. 5b). It corresponds to 15.4% of total contacts, as illustrated in Fig. 5c. For this type of interaction in TN intermediate distances were observed, while the opposite is noted for C₄-H_{4C}... π (phenyl) with 3.121 Å – longer, and for C₇-H₇... π (triazole) with 3.004 Å – shorter (Fig. 5e), corresponding to 16.1% of total contacts (Fig. 5f). These percentage contributions suggest that such interactions occur with similar frequency in both structures, despite the differences between the π systems, which play a relevant role in the

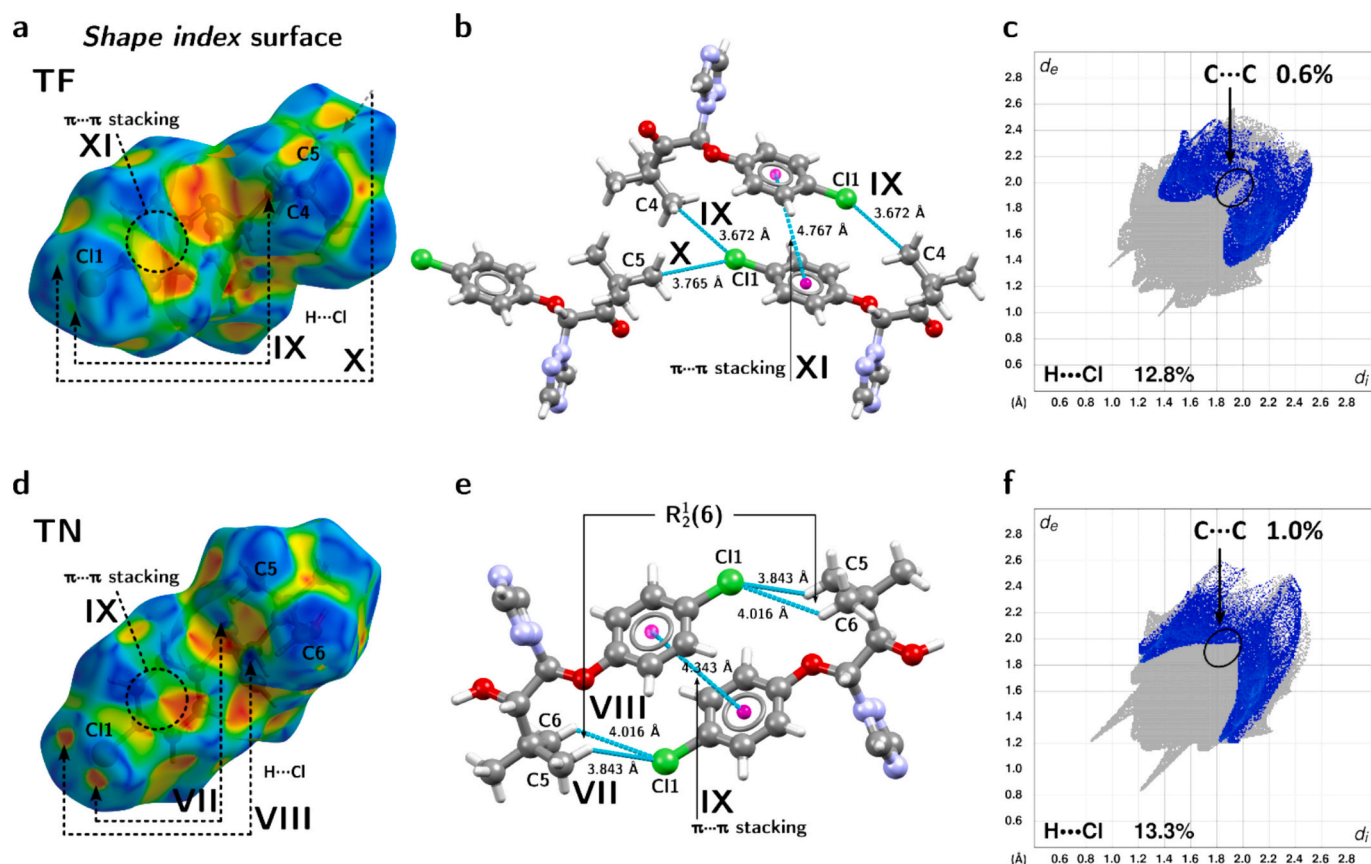


Fig. 6. HS with the *shape index* property mapped, highlighting the complementary patches (red and blue), where $\pi\cdots\pi$ interactions occur, also the blue convex and red concave patches for C—H $\cdots$ Cl interactions. A detailed view of C—H $\cdots$ Cl and $\pi\cdots\pi$ -stacking interactions in the supramolecular arrangement of TF and TN. (a) *shape index* surface mapped for TF. (b) Representation of C—H $\cdots$ Cl interactions: IX (C4 $\cdots$ Cl1) and X (C5 $\cdots$ Cl1), with their donor-acceptor distances in TF. Representation of $\pi\cdots\pi$ -stacking interaction XI, with the centroid distances (Cg-Cg) between phenyl rings. (c) The 2D *fingerprint* plot of the H $\cdots$ Cl with 12.8% and C $\cdots$ C with 0.6% of the total contacts was mapped for TF. (d) *shape index* surface mapped for TN. (e) Representation of the interactions VII (C5 $\cdots$ Cl1) and VIII (C6 $\cdots$ Cl1) with their donor-acceptor distances in TN. Representation of $\pi\cdots\pi$ -stacking interaction IX, with the centroid distances (Cg-Cg) between phenyl rings. (f) The 2D *fingerprint* plot of the H $\cdots$ Cl with 13.3% and C $\cdots$ C with 1.0% of the total contacts was mapped for TN. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

stability and organization of the crystal packing.

The $\pi\cdots\pi$ -stacking interactions were observed between centroids (Cg) from phenyl groups, it is highlighted in Fig. 6 and d through the shape index HS as two complementary triangular patches formed on the phenyl rings characteristic of $\pi\cdots\pi$ interactions [72], featuring a dimeric arrangement with centroid distances (Cg-Cg) of 4.767 Å in TF and 4.343 Å in TN (see Fig. 6b and e). The corresponding 2D *fingerprint* plot is characterized by the C $\cdots$ C contacts, centrally located in Fig. 6c and f, 0.6% in TF and 1.0% in TN of total contacts, respectively. These supramolecular assembly also include halogen-involved interactions, the weak C—H $\cdots$ Cl hydrogen bonds [73], in which the chlorine acts as an acceptor from the C—H from methyl group (CH₃) of the neighboring molecule, connecting two molecular units shorter in distance and angles in TF involving three molecules (Fig. 6b), includes the dimer with C4—H_{4B} $\cdots$ Cl1 (3.912 Å, 102.96°) and a side located C5—H_{5C} $\cdots$ Cl1 (3.765 Å, 94.08°), accounting 12.8% of total contacts (Fig. 6c). In the C4—H_{4B} $\cdots$ Cl1 interaction, no BP was detected connecting the Cl1 atom to H_{4B}; instead, the BP connects Cl1 to C4 (see C4 $\cdots$ Cl1 in Table 3). According to the topological parameters, this interaction exhibits van der Waals character. Similarly, for the C5—H_{5C} $\cdots$ Cl1 interaction, no BP was observed, indicating the absence of a direct interaction between these atoms. Whereas in TN, the assembly is also a dimer arrangement by bifurcated interactions in Cl1, C5—H_{5A} $\cdots$ Cl1 (3.843 Å, 131.36°) and C6—H_{6C} $\cdots$ Cl1 (3.843 Å, 131.36°), forming two R₂¹(6) supramolecular motifs (Fig. 6e), which sum to 13.3% of total contacts (Fig. 6f). The

QTAIM parameters revealed that the electron density at the BCP for the C5—H_{5A} $\cdots$ Cl1 interaction is very low. In contrast, the electron density in the internuclear region of the C6—H_{6C} $\cdots$ Cl1 interaction is approximately 2.2 times higher. However, NBO analysis indicated a stronger hyperconjugation between the donor and acceptor orbitals [η_3 (Cl1) $\rightarrow$ σ^* (C5—H_{5A})] in the former, with an $E_{i\rightarrow j}^{(2)}$ value of 0.13 kcal/mol, compared to 0.07 kcal/mol in the latter, by the hyperconjugation σ (C6—H_{6C}) $\rightarrow$ σ^* (C4—Cl1).

Halogen-involving interactions were also identified. In the TN structure, a C—H $\cdots$ Cl type interaction is observed, in which the chlorine atom acts as an acceptor towards a C—H group from a methyl group (CH₃) of a neighboring molecule, connecting two molecular units. This interaction occurs alongside a $\pi\cdots\pi$ interaction, characterized by a Cg $\cdots$ Cg distance of 4.343 Å, as illustrated in Fig. 6e. TF exhibits the same bonding pattern, with shorter distances for halogen-involving contacts and a longer distance for the $\pi\cdots\pi$ interaction (Fig. 6b).

3.2. Electronic structure analysis

The stereoisomers of each fungicidal were calculated and compared. The data indicated that the 1S-TF isomer exhibits slightly lower HOMO (E_H) and LUMO (E_L) energies (differences of 0.608 kcal/mol for E_H and 0.320 kcal/mol for E_L), suggesting a more pronounced oxidative character compared to the 1R-TF isomer (Fig. 7). The energy gap (ΔE_{H-L}) and chemical hardness (η) values suggest that the chemical reactivities

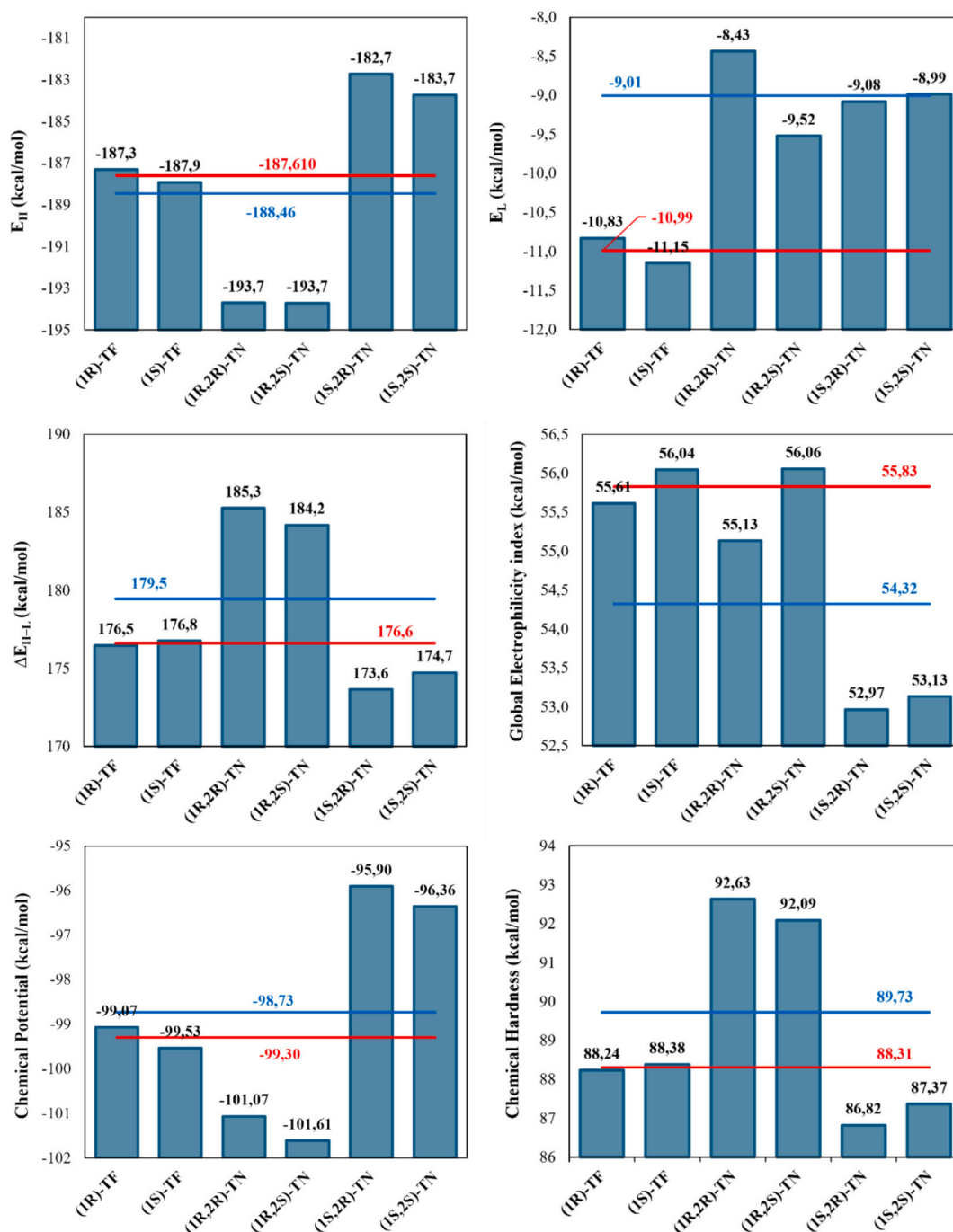


Fig. 7. escriptors of the stereoisomers of triadimefon and triadimenol, calculated at the M06-2×/6-311++G(d,p) level of theory. The columns represent each reactivity descriptor, while the red lines indicate the average values for triadimefon and the blue lines for triadimenol. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of these two isomers are similar, although slightly higher for 1S-TF. For TN, the results allowed the stereoisomers to be grouped into two categories: Group A (1R,2R-TN and 1R,2S-TN) and Group B (1S,2R-TN and 1S,2S-TN). Group A isomers were found to be less reductive in redox processes, as indicated by their low E_H and ionization energy (I) values and higher chemical potentials (μ). Conversely, Group B isomers showed greater electron-donating capacity, suggesting a higher potential for interactions with biomolecules. This may translate into stronger adverse effects on fungi, as supported by *in vitro* activity against *Basidiomycete* fungi [74]. Moreover, the Group B isomers were found to be more chemically reactive, which may influence their persistence both in fungal organisms and in the environment. It is noteworthy that, in *in*

vitro tests with *Aspergillus niger*, the 1R,2S-TN and 1S,2R-TN stereoisomers exhibited less prominent fungitoxic effects [75].

The electrophilicity index (ω) values of the stereoisomers ranged from 52 to 56 kcal/mol. According to the results reported by Domingo-Pérez [76,77], all these values classify the isomers as good electrophiles. The 1R-TF, 1S-TF, and Group A TN isomers exhibited similar ω values, with 1S-TF being the most electrophilic. The Group B TN isomers, in contrast, showed slightly lower electrophilicity. MEP maps of TF and TN stereoisomers are presented in Fig. 8 and show that the most electrophilic regions (dark blue) are located at the hydrogen atoms of carbons C₇ and C₈ of the triazole moiety, at the hydrogens of aromatic carbons, and in the acyclic regions of the molecules. Meanwhile, the triazolic N

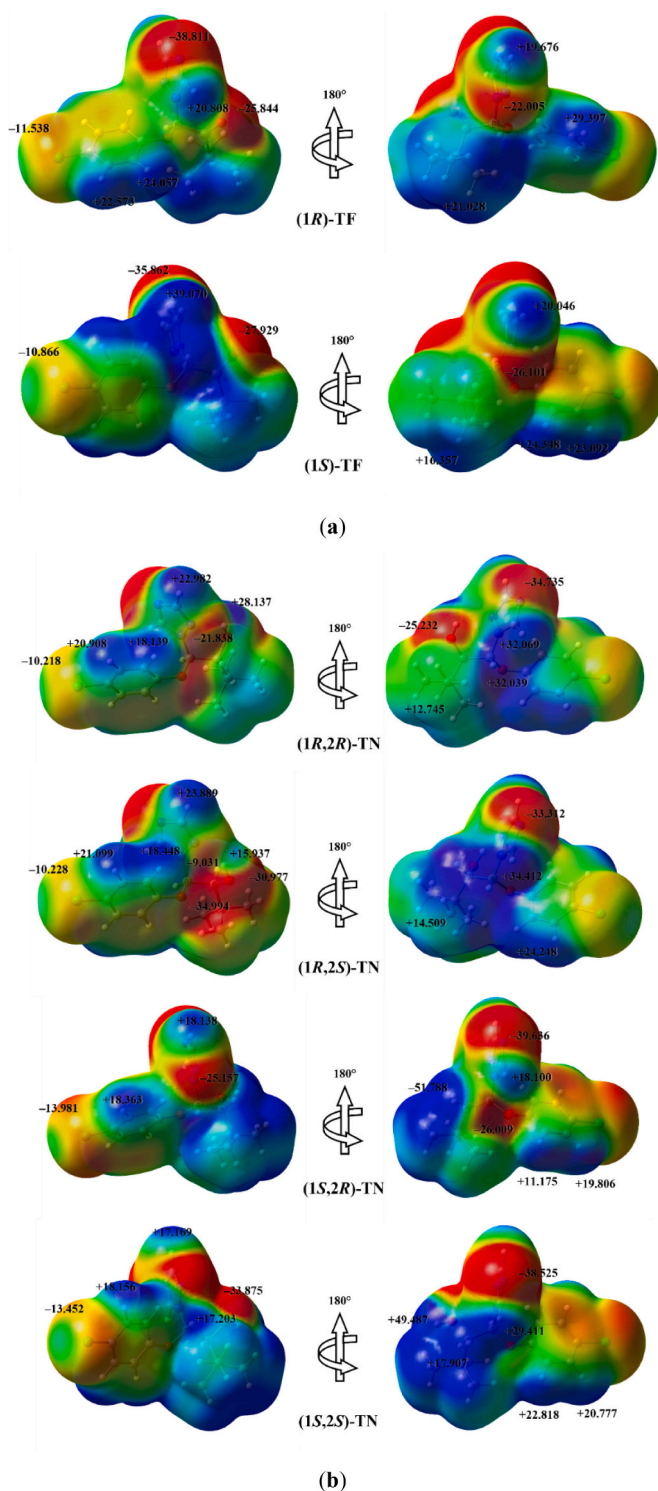


Fig. 8. Molecular electrostatic potential map at $\rho(r) = 4.0 \times 10^{-4}$ electrons/Bohr [3] contour of the total SCF electron density, highlighting regions of electrophilic and nucleophilic character to (a) Triadimefon and (b) Triadimenol. Calculations were performed at the M06-2 $\times$ /6-311++G(d,p) level of theory.

atoms and the O₁ oxygen atoms represent the main nucleophilic sites (in red) of the molecules. Overall, TF isomers tend to be more reactive than TN isomers (Fig. 7) and exhibit a more pronounced electrophilic character. These properties may help explain the lower environmental persistence of TF [78] and its less specific interactions with biological targets [79].

Moreover, the molecular polarity indices (MPI) of the fungicide stereoisomers exhibit distinct polarities, which may also account for their different biological effects. Overall, as shown in the graph in Fig. 9a, both compounds present similar polarity levels (10.65 kcal/mol for TF and 10.54 kcal/mol for TN). Individually, although 1R-TF and 1S-TF display comparable MPI values, the former stereoisomer shows a 6.54% higher polar surface area, as seen in the graph in Fig. 9b. For TN, an increase in MPI values was observed from Group A to Group B, corresponding to a proportional increase in the polar surface area of the isomers (Fig. 9b). The polar surface area of 1R,2R-TN is slightly smaller than that of benzene, comparatively. On average, the polar surface areas of TF stereoisomers and Group B TN isomers are approximately 17.7% and 24.2% higher, respectively, than the surface area of the benzene molecule.

Higher polar surface areas and molecular polarity indices (MPI) influence key physicochemical properties such as aqueous solubility, membrane permeability, and the affinity of molecules for lipophilic or hydrophilic biological compartments. As a result, the pharmacokinetic and toxicological behaviors of TF and TN—and of their stereoisomers—may vary in biological and environmental contexts. More polar stereoisomers tend to interact more readily with proteins, enzymes, and cellular membranes, potentially enhancing their biological effects [80]. In contrast, less polar stereoisomers may exhibit lower immediate bioavailability but greater environmental persistence, increasing the likelihood of bioaccumulation in non-target organisms. Molecular polarity also modulates the solubility of these fungicides in different media and their affinity for biological targets, contributing to the stabilization of intermolecular interactions and facilitating systemic distribution within fungal tissues as well as interactions with intracellular targets [81,82].

The reactivity descriptors obtained are essential for predicting the molecular behavior of these fungicides in biological systems. Scientific literature shows that the fungicidal efficacy of both compounds is highly dependent on the agricultural crop and the application method used. Studies conducted by Embrapa Trigo have shown that TN, when applied in seed treatment, provides efficient control of foliar diseases such as powdery mildew (*Blumeria graminis*) and leaf rust (*Puccinia triticina*) for up to 98 days after plant emergence. In addition, a significant increase in grain yield was observed, with productivity of 1815 kg/ha in plots treated with TN, compared to 1270 kg/ha in the untreated control [83].

On the other hand, TF has shown high efficacy when applied through the root system, particularly in the control of coffee rust (*Hemileia vastatrix*). Soil applications of TF have demonstrated significant systemic and protective effects, highlighting its suitability for perennial crops such as coffee. Thus, although both compounds exhibit consistent fungicidal properties, TN is more effective in seed treatment strategies, providing prolonged control of foliar phytopathogens. In contrast, TF is particularly effective in soil applications, making it more suitable for disease management in perennial crops. Therefore, the choice between these fungicides should take into account the application method, target crop, and the mechanisms of action most compatible with each agronomic context.

The Fukui index calculations revealed that the replacement of the carbonyl group (C=O) by a hydroxyl group (C—OH) between the compounds TF and TN induces significant changes in the electronic profile of their molecules. The C=O group is strongly electrophilic due to the high polarization of the carbonyl bond, in which the more electronegative oxygen atom attracts electron density, rendering the adjacent carbon (C₂) highly electron-deficient. As a result, this group withdraws electron density through both inductive and resonance effects, making the C₂ atom highly susceptible to nucleophilic attack (Fig. 10a). Furthermore, the electronic influence of the carbonyl group contributes to an increase in electron density over the C₄ atom in TF, rendering it more prone to interactions with electrophiles.

Fig. 10 In contrast, the C—OH group, although also an electron-withdrawing group via the inductive effect, acts as an electron donor

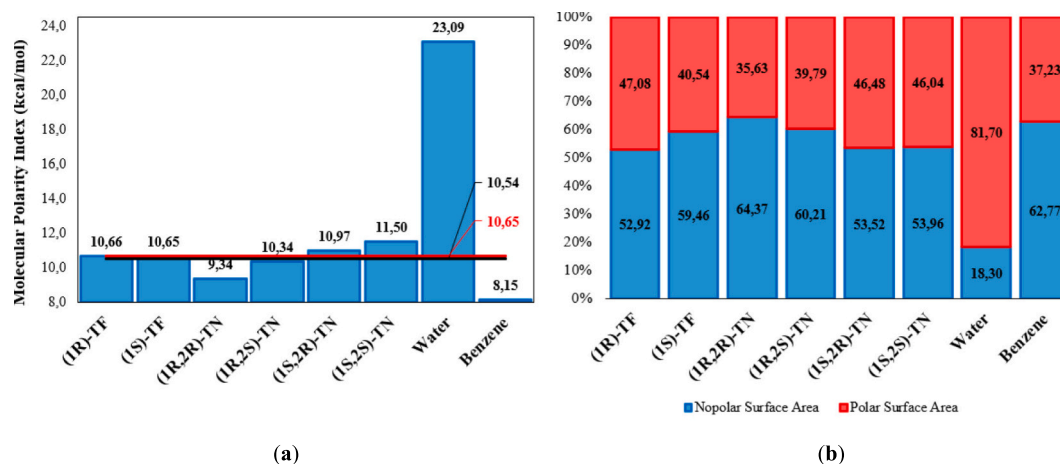


Fig. 9. Variation in the polarity of Triadimefon and Triadimenol fungicides. (a) Molecular polarity index (MPI) values and (b) polar and nonpolar surface area contributions of these compounds, both compared to those of water and benzene.

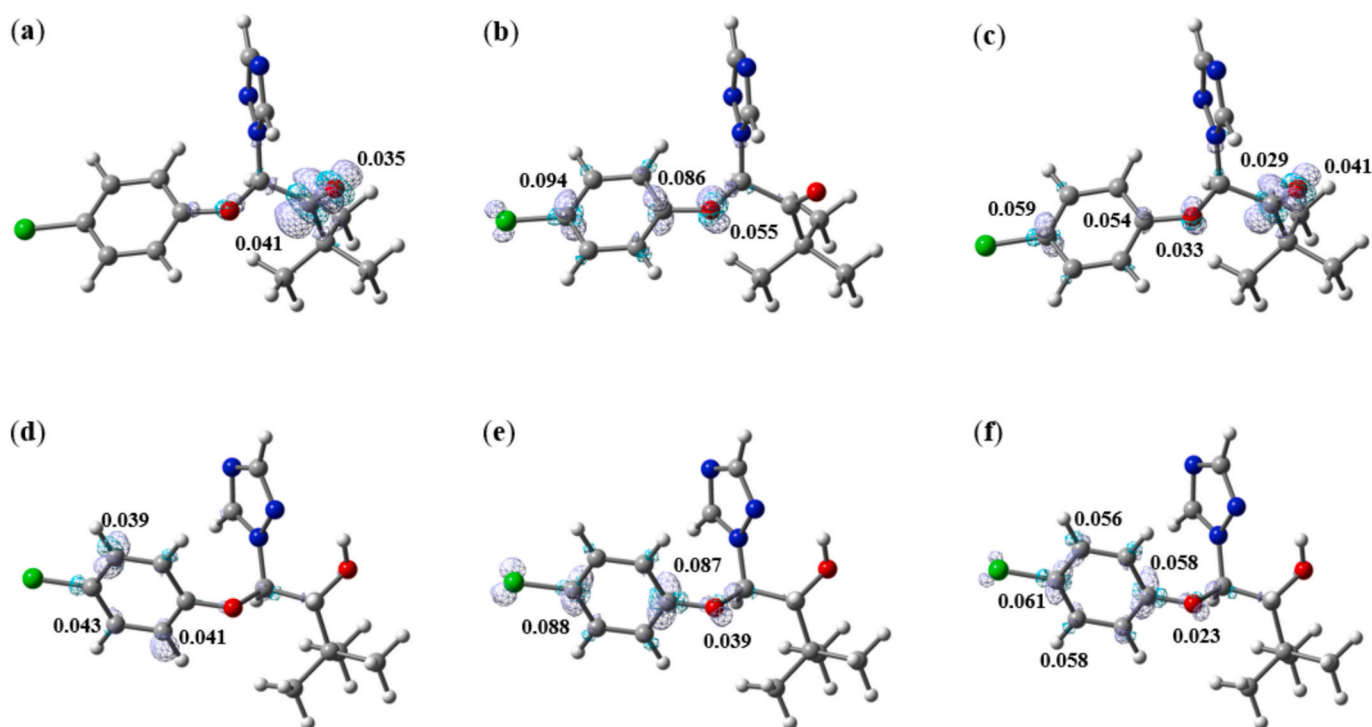


Fig. 10. Isosurfaces of Fukui function for nucleophilic attacks (a) and (d), electrophilic attacks (b) and (e), and radical attacks (c) and (f) for the fungicides Triadimefon (upper panel) and Triadimenol (lower panel).

through resonance, thereby reducing the electrophilic character of C₂ and making it less susceptible to nucleophilic attack. This shift promotes the aromatic ring as the preferred site for nucleophilic attack, with the C_{5'} atom emerging as the primary center, followed by C₆. Similar to TF, the C_{4'} atom in TN remains the leading site for electrophilic attack; however, the electronic effects induced by the C—OH group render it a less nucleophilic center.

3.3. Toxicity prediction and pharmacophore modeling

Pharmacophore analysis is an essential analysis for gaining insights into the molecular characteristics of lanosterol 14 α -demethylase ligands, which are critical for effective drug design. Each pharmacophore model emphasizes key features such as hydrogen bond acceptors (HBAs), hydrogen-bond donors (HBDs), aromatic rings (ARs), and

hydrophobic (HyPho) regions. These features are visually represented in Figs. 11, 12, and 13 as follows: the pharmacophore features are color-coded for hydrogen-bond acceptors (red), hydrogen-bond donors (green), hydrophobic (yellow), and aromatic rings (blue).

Of the six stereoisomers of TF and TN molecules, only three showed alignment with the five most potent lanosterol 14 α -demethylase inhibitor ligands. The stereoisomers that exhibited the spatial characteristics were 1R-TF, 1S,2R-TN and 1S,2S-TN. The 1R-TF isomer shared two hydrogen bond acceptor groups and one aromatic ring (Fig. 11). The 1S,2R-TN stereoisomer exhibited one hydrogen bond acceptor group, one donor group, and one hydrophobic group (Fig. 12). The 1S,2S-TN stereoisomer also displayed three pharmacophoric groups, with two hydrogen bond acceptor groups and one hydrophobic group. It is possible that these three structures would have a greater potential for interaction with the target, which could explain part of their fungicidal

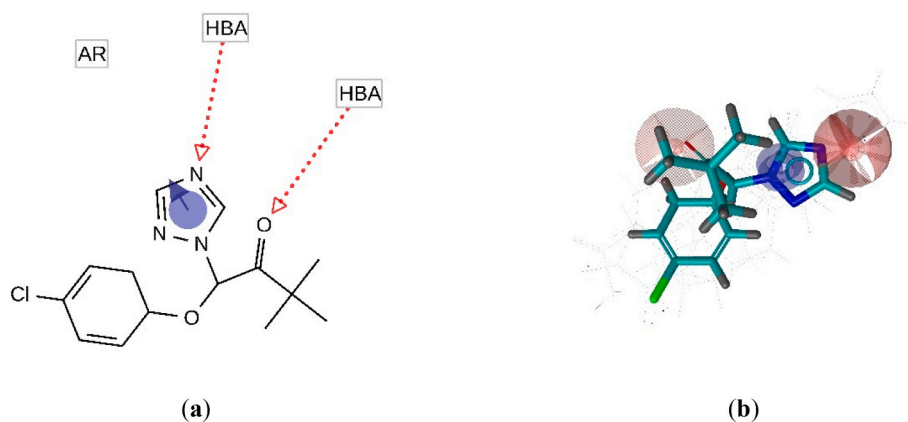


Fig. 11. Pharmacophore mapping analysis for 1R-TF for its potential interaction with the lanosterol 14 α -demethylase. (a) Individual pharmacophores of 1R-TF. Hydrogen bond acceptors (HBA) and aromatic rings interactions (AR). (b) Three-dimensional model of shared feature pharmacophore between 1R-TF and the lanosterol 14 α -demethylase ligands. The pharmacophore features are color-coded for hydrogen bond acceptors (red) and aromatic ring interactions (blue). The five compounds employed in this analysis were BDBM24656, BDBM25806, BDBM25807, BDBM25808, and BDBM25809 (color figure online). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

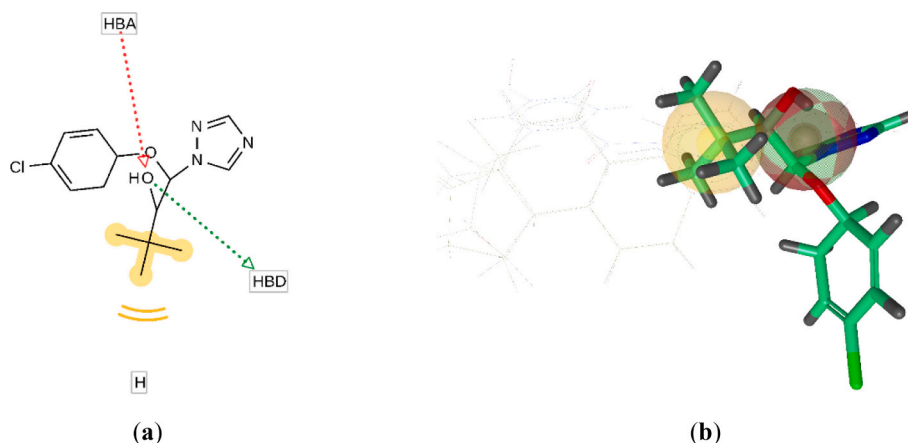


Fig. 12. Pharmacophore mapping analysis for 1S,2R-TN for its potential interaction with the lanosterol 14 α -demethylase. (a) Individual pharmacophores of 1S,2R-TN. Hydrogen bond acceptors (HBA) and aromatic rings interactions (AR). (b) Three-dimensional model of shared feature pharmacophore between 1S,2R-TN and the lanosterol 14 α -demethylase ligands. The pharmacophore features are color-coded for hydrogen bond acceptors (red) and aromatic ring interactions (blue). The five compounds employed in this analysis were BDBM24656, BDBM25806, BDBM25807, BDBM25808, and BDBM25809 (color figure online). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

effects.

The pharmacophore modeling study of triadimenol (TN) and triadimefon (TF) isomers provides crucial insights into the stereoselective interaction of these fungicides with the lanosterol 14 α -demethylase target [84]. The finding that only three out of six isomers – 1R-TF, 1S,2R-TN, and 1S,2S-TN – align with the most potent inhibitor ligands allows us to propose a definitive structure-activity relationship (SAR) and hypothesize their binding mode at the molecular level.

The development of effective antifungal agents is fraught with a unique and critical challenge: achieving selectivity. Unlike bacterial pathogens, fungi are eukaryotic organisms, sharing fundamental cellular machinery with their plant and animal hosts. This similarity means that a compound designed to inhibit a vital fungal process can easily disrupt equivalent pathways in the host, leading to detrimental toxic effects. In an agricultural context, this toxicity extends to the environment and human health through pesticide residues on food and ecosystem contamination [85]. Therefore, the pursuit of selectivity is not merely a desirable goal but a fundamental requirement for sustainable agrochemistry. It is within this framework that the pharmacophore alignment of specific isomers, such as 1R-TF, 1S,2R-TN and 1S,2S-TN, emerges as a powerful tool for designing safer and more targeted

fungicides.

Both antifungals showed high gastrointestinal absorption and blood-brain barrier permeability in the toxicokinetic prediction analyses. Furthermore, the studies indicate that both compounds could inhibit the cytochrome P450 2C19 (CYP2C19) enzyme. This suggests potential for drug-drug interactions with medications metabolized by CYP2C19. Some drugs that are substrates of this enzyme include Omeprazole, Citalopram, Voriconazole, and Diazepam. Consequently, the presence of these two antifungals could lead to increased bioavailability and a higher risk of toxicity for these substances [86].

In the toxicity analysis, the two compounds exhibited similar adverse effects, including hepatotoxicity, neurotoxicity, blood-brain barrier disruption, ecotoxicity, and aromatase inhibition. However, the LD₅₀ values for TF and TN were 363 mg/kg and 3250 mg/kg, respectively. This result suggests that TN is more toxic. The presence of a hydroxyl group instead of a carbonyl group in the TN molecule appears to influence this compound's toxicity primarily in a quantitative manner. Some studies have shown that triazole fungicides can cause liver toxicity [87], neurotoxicity [88], reproductive toxicity [89], and carcinogenic effects [90] in both *in vivo* and *in vitro* mouse models. This evidence suggests that the *in silico* analyses were suitable for predicting these effects in this

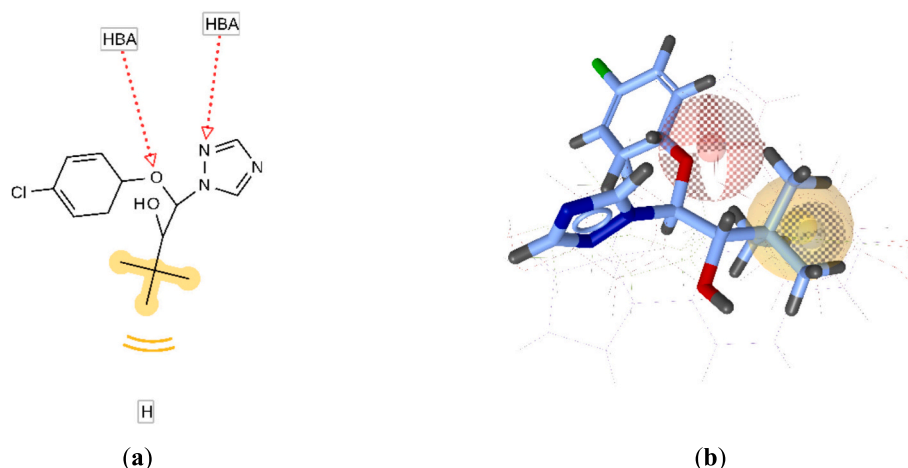


Fig. 13. Pharmacophore mapping analysis for 1S,2S-TN for its potential interaction with the lanosterol 14 α -demethylase. (a) Individual pharmacophores of 1S,2S-TN. Hydrogen bond acceptors (HBA) and aromatic rings interactions (AR). (b) Three-dimensional model of shared feature pharmacophore between 1S,2S-TN and the lanosterol 14 α -demethylase ligands. The pharmacophore features are color-coded for hydrogen bond acceptors (red) and aromatic ring interactions (blue). The five compounds employed in this analysis were BDBM24656, BDBM25806, BDBM25807, BDBM25808, and BDBM25809 (color figure online). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

kind of compound.

It was shown that TN causes significant changes in hematological parameters, and induces higher hepatotoxic and nephrotoxic effects in broilers, and the residues in the edible tissues could also bring problems to human health [91]. The analysis on the Pred-Herg server suggests that the two antifungals could present a moderate potential for heart block according to the multiclass prediction model. Regarding the prediction of cutaneous toxicity, TF showed potential for sensitizing dendritic cells and inducing the production of pro-inflammatory cytokines. The TN compound exhibited the same property, in addition to potential covalent interaction with skin proteins and increased proliferation of specific antigens in T cells. This suggests that contact with these compounds has the potential to cause toxicity when in contact with the skin. Through the ADMETSAR server, it was possible to corroborate the hypothesis of ecotoxicity previously indicated by PROTOX 3.0. The predictive analyses indicated high toxicity in fish, high toxicity in *Tetrahymena pyriformis*, low toxicity in bees, and non-biodegradability. Studies have shown that TF acts as a fungicide in crops by converting into TN [92], which has greater fungicidal activity than TF itself [93]. Therefore, improper or excessive use of TF or TN can lead to excessive residues in the environment and agricultural raw materials, exposing organisms to TN and adversely affecting human and animal health.

The structural and electronic differences, as well as the distinct supramolecular arrangements observed for TF and TN, provided a consistent rationale for the divergent toxicological profiles of these compounds, highlighting the value of integrated theoretical approaches in predicting toxicity. Differences in their solid-state intermolecular interaction patterns can decisively influence toxicodynamic behavior. The relatively weaker and more dissociable supramolecular structure of TF, due to the presence of nonclassical hydrogen bonds (C—H...O), can facilitate greater molecular mobility, faster dissolution, and reduced environmental persistence—factors that may reduce its overall bioaccumulation and toxicity. In contrast, the more robust and stable crystal lattice of TN, due to the presence of classical hydrogen bonds (O—H...N), can significantly modulate physicochemical properties such as solubility, release kinetics, and transport through biological membranes, while promoting stronger and more selective interactions with biomolecular targets. These characteristics are likely to result in greater environmental retention and more pronounced ecotoxicological impacts. Furthermore, the electronic redistribution associated with the replacement of the carbonyl group (C=O) in TF by a hydroxyl group (C—OH) in TN modifies the molecular reactivity landscape—altering

the nucleophilic and electrophilic centers and, consequently, the compounds' potential for biochemical interaction. Molecular polarity further refines this differentiation, such that the greater polarity of TF correlates with increased aqueous solubility and bioavailability, while the lower polarity of TN may increase its partitioning into lipophilic compartments, thus intensifying its toxicological potential.

4. Conclusion

This study presents a comprehensive theoretical analysis of TF and its stereoisomeric metabolite, TN, combining solid-state characteristics, molecular modeling, and *in silico* toxicity prediction tools. It was shown that replacing the carbonyl group in TF by the hydroxyl group in TN, together with stereochemical configuration, systematically shifts molecular electrostatic potential and reactivity indices, and remodels non-covalent recognition (e.g., stronger H-bond and π -contacts in selected TN stereoisomers as evidenced by Hirshfeld/QTAIM/NBO metrics). These variations are closely related to their differential behavior in biological systems and may explain the asymmetric toxicological effects observed experimentally.

The data further suggests that specific stereoisomers of triadimenol may pose greater ecotoxicological risks to non-target organisms. Taken together, these findings reinforce the importance of considering stereochemistry in environmental risk assessments of fungicides and support the application of computational approaches as efficient tools in predictive toxicology. Future work could integrate these predictions with experimental ecotoxicity assays to validate theoretical models and guide more sustainable pesticide use.

CRediT authorship contribution statement

Áureo B. Souza: Writing – review & editing, Writing – original draft, Visualization, Investigation. **Ronaldo G. Freitas Junior:** Writing – review & editing, Writing – original draft, Investigation. **Ana L.M. Monteiro:** Writing – review & editing, Writing – original draft, Investigation. **Leonardo R. de Almeida:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Lucas D. Dias:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Lucas B. Ribeiro de Carvalho:** Writing – original draft, Visualization, Investigation. **Hamilton B. Napolitano:** Writing – review & editing, Visualization, Formal analysis. **Leonardo L. Borges:** Writing – review & editing, Writing – original draft,

Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Antônio S.N. Aguiar:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by Fundação de Amparo à Pesquisa do Estado de Goiás (FAPEG) and Innovation, Development and Sustainability: Strengthening the University and the Productive Sector in the State of Goiás Agreement for research, development and innovation – PD&I 07/2020, notice 21/2024 – Public Call for Aid 2024 (Process: 202510267000600), notice 12/2023 CAPES/FAPEG – Research and Development Network of the Central-West Region, FAPEG/SES No. 18/2025 research support – Technological Innovations for Vector Control of Arboviruses, FAPEG notice 12/2025 – Support for Extension Projects of Institutions of Higher Education of the State of Goiás, Coordination for the Improvement of Higher Education Personnel (CAPES), and National Council for Scientific and Technological Development – CNPq (Productivity Grant/303307/2025-0; Inova Talentos Project (IEL/CNPq/Laboratório Teuto; Universal Call CNPq/MCTI No. 44/2024; Process: 404074/2025-1).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rechem.2026.103268>.

Data availability

Data will be made available on request.

References

- [1] M. Aliste, G. Pérez-Lucas, I. Garrido, J. Fenoll, S. Navarro, Risk assessment of 1,2,4-Triazole-typed fungicides for groundwater pollution using leaching potential indices, *Water Air Soil Pollut.* 232 (2021) 469.
- [2] D.L. Roman, D.I. Voiculescu, M. Filip, V. Ostafe, A. Isvoran, Effects of triazole fungicides on soil microbiota and on the activities of enzymes found in soil: a review, *Agriculture (Switzerland)* 11 (2021), <https://doi.org/10.3390/agriculture11090893>.
- [3] C.J.R. Klittich, Fungicide Mobility and the Influence of Physical Properties, 2014, pp. 95–109, <https://doi.org/10.1021/bk-2014-1171.ch005>.
- [4] N. Singh, Sorption behavior of triazole fungicides in indian soils and its correlation with soil properties, *J. Agric. Food Chem.* 50 (2002) 6434–6439.
- [5] V. Nagappan, S. Deresinski, Posaconazole: A Broad-Spectrum triazole antifungal agent, *Clin. Infect. Dis.* 45 (2007) 1610–1617.
- [6] C. Li, et al., Toxicity, bioactivity of triazole fungicide metconazole and its effect on mycotoxin production by fusarium verticillioides: new perspective from an enantiomeric level, *Sci. Total Environ.* 828 (2022) 154432.
- [7] G.R. Thompson, N.P. Wiederhold, Isavuconazole: a comprehensive review of spectrum of activity of a new triazole, *Mycopathologia* 170 (2010) 291–313.
- [8] B. Zhang, Comprehensive review on the anti-bacterial activity of 1,2,3-triazole hybrids, *Eur. J. Med. Chem.* 168 (2019) 357–372.
- [9] A. Ramírez-Villalva, et al., Synthesis and antifungal activity of novel oxazolidin-2-one-linked 1,2,3-triazole derivatives, *Medchemcomm* 8 (2017) 2258–2262.
- [10] K.N. Venugopala, et al., Crystallography, in silico studies, and in vitro antifungal studies of 2,4,5 trisubstituted 1,2,3-Triazole analogues, *Antibiotics* 9 (2020) 350.
- [11] N. Marepu, S. Yeturu, M. Pal, 1,2,3-Triazole fused with pyridine/pyrimidine as new template for antimicrobial agents: Regioselective synthesis and identification of potent n-heteroarenes, *Bioorg. Med. Chem. Lett.* 28 (2018) 3302–3306.
- [12] K. Ratnakar Reddy, et al., Synthesis of novel 1,2,3-triazole/isoxazole functionalized 2H-Chromene derivatives and their cytotoxic activity, *Bioorg. Med. Chem. Lett.* 24 (2014) 1661–1663.
- [13] A. Németh-Rieder, et al., Synthesis and in vitro anticancer evaluation of flavone—1,2,3-Triazole hybrids, *Molecules* 28 (2023) 626.
- [14] F.-C. Wang, et al., A 1,2,3-Triazole derivative of quinazoline exhibits antitumor activity by tethering RNF168 to SQSTM1/P62, *J. Med. Chem.* 65 (2022) 15028–15047.
- [15] P. Deng, et al., Synthesis and antitumor activity of erlotinib derivatives linked with 1,2,3-Triazole, *Front. Pharmacol.* 12 (2022).
- [16] B.C. Monk, et al., Fungal lanosterol 14 α -demethylase: a target for next-generation antifungal design, *Biochim. Biophys. Acta Proteins Proteomics* 1868 (2020) 140206.
- [17] N.C.P. Albuquerque, D.B. Carrão, M.D. Habenschus, A.R.M. de Oliveira, Metabolism studies of chiral pesticides: a critical review, *J. Pharm. Biomed. Anal.* 147 (2018) 89–109.
- [18] N. Kurihara, et al., Pesticides report 37: chirality in synthetic agrochemicals: bioactivity and safety consideration (technical report), *Pure Appl. Chem.* 69 (1997) 2007–2026.
- [19] Y. Li, et al., Chiral fungicide triadimefon and triadimenol: Stereoselective transformation in greenhouse crops and soil, and toxicity to daphnia magna, *J. Hazard. Mater.* 265 (2014) 115–123.
- [20] J.F. Kenneke, C.S. Mazur, S.E. Ritger, T.J. Sack, Mechanistic investigation of the noncytochrome P450-mediated metabolism of triadimefon to triadimenol in hepatic microsomes, *Chem. Res. Toxicol.* 21 (2008) 1997–2004.
- [21] J.F. Kenneke, et al., Integration of metabolomics and in vitro metabolism assays for investigating the stereoselective transformation of triadimefon in rainbow trout, *Chirality* 22 (2010) 183–192.
- [22] R.S. Burden, et al., Comparative activity of the enantiomers of triadimenol and paclobutrazol as inhibitors of fungal growth and plant sterol and gibberellin biosynthesis, *Pestic. Sci.* 21 (1987) 253–267.
- [23] Cambridge Crystallographic Data Centre, Inc, CCDC- The Cambridge Crystallographic Data Centre. Cambridge Structural Database (CSD). <https://www.ccdc.cam.ac.uk/>, 2023.
- [24] I.W. Nowell, P.E. Walker, N.H. Anderson, Structure of 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1,2,4-triazol-1-yl)-2-butanone, *Acta Crystallogr. B* 38 (1982) 1857–1859.
- [25] T. Spitzer, J. Kopf, G. Nickless, 1-(4-chlorophenoxy)-1-(1,2,4-triazol-1-yl)-3,3-dimethyl-butan-2-ol C₁₄H₁₈O₂N₃Cl, *Cryst. Struct. Commun.* 11 (1982) 315–320.
- [26] T. Huang, et al., A comprehensive review of 1,2,4-triazole fungicide toxicity in zebrafish (danio rerio): a mitochondrial and metabolic perspective, *Sci. Total Environ.* 809 (2022) 151177.
- [27] C.F. Macrae, et al., Mercury 4.0 : from visualization to analysis, design and prediction, *J. Appl. Crystallogr.* 53 (2020) 226–235.
- [28] The GIMP Development Team, GNU image manipulation program (GIMP), Preprint at, 2025.
- [29] P.R. Spackman, et al., CrystalExplorer: a program for hirshfeld surface analysis, visualization and quantitative analysis of molecular crystals, *J. Appl. Crystallogr.* 54 (2021) 1006–1011.
- [30] M.A. Spackman, D. Jayatilaka, Hirshfeld surface analysis, *CrystEngComm* 11 (2009) 19–32.
- [31] R.F.W. Bader, Atoms in molecules, *Acc. Chem. Res.* 18 (1985) 9–15.
- [32] R.F.W. Bader, Atoms in Molecules - a Quantum Theory, Clarendon Press Publication, Ontario, 1994.
- [33] F. Weinhold, C.R. Landis, Discovering Chemistry with Natural Bond Orbitals, John Wiley & Sons, Inc, USA, 2012.
- [34] F. Weinhold, C.R. Landis, Natural bond orbitals and extensions of localized bonding concepts, *Chem. Educ. Res. Pract.* 2 (2001) 91–104.
- [35] P. Hohenberg, W. Kohn, Inhomogeneous electron gas, *Phys. Rev.* 136 (1964) B864.
- [36] W. Kohn, L.J. Sham, Self-consistent equations including exchange and correlation effects, *Phys. Rev.* 140 (1965) A1133–A1138.
- [37] M.J. Frisch, et al., Gaussian 16, Revision C.01, Preprint at, 2016.
- [38] Y. Zhao, D.G. Truhlar, The m06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four m06-class functionals and 12 other functionals, *Theor. Chem. Accounts* 120 (2008) 215–241.
- [39] Y. Zhao, N.E. Schultz, D.G. Truhlar, Exchange-correlation functional with broad accuracy for metallic and nonmetallic compounds, kinetics, and noncovalent interactions, *J. Chem. Phys.* 123 (2005).
- [40] R.F.W. Bader, T.T. Nguyen-Dang, Y. Tal, A topological theory of molecular structure, *Rep. Prog. Phys.* 44 (1981) 893.
- [41] R.F.W. Bader, H. Essén, The characterization of atomic interactions, *J. Chem. Phys.* 80 (1983) 1943–1960.
- [42] T. Lu, F. Chen, Multiwfn: a multifunctional wavefunction analyzer, *J. Comput. Chem.* 33 (2012) 580–592.
- [43] I.V. Alabugin, K.M. Gilmore, P.W. Peterson, Hyperconjugation, *Wiley Interdiscip. Rev. Comput. Mol. Sci.* 1 (2011) 109–141.
- [44] G. Zhang, C.B. Musgrave, Comparison of DFT methods for molecular orbital eigenvalue calculations, *J. Phys. Chem. A* 111 (2007) 1554–1561.
- [45] R.G. Pearson, Chemical hardness and density functional theory, *J. Chem. Sci.* 117 (2005) 369–377.
- [46] R.G. Pearson, The electronic chemical potential and chemical hardness, *J. Mol. Struct. (THEOCHEM)* 255 (1992) 261–270.
- [47] R.G. Parr, L.V. Szentpály, S. Liu, Electrophilicity index, *J. Am. Chem. Soc.* 121 (1999) 1922–1924.
- [48] H. Weinstein, R. Osman, J.P. Green, S. Topiol, Electrostatic potentials as descriptors of molecular reactivity: The basis for some successful predictions of biological activity, in: *Chemical Applications of Atomic and Molecular Electrostatic*

- Potentials 309–334, Springer US, Boston, MA, 1981, https://doi.org/10.1007/978-1-4757-9634-6_14.
- [49] P. Sjöberg, P. Politzer, Use of the electrostatic potential at the molecular surface to interpret and predict nucleophilic processes, *J. Phys. Chem.* 94 (1990) 3959–3961.
- [50] J. Zhang, T. Lu, Efficient evaluation of electrostatic potential with computerized optimized code, *Phys. Chem. Chem. Phys.* 23 (2021) 20323–20328.
- [51] K. Fukui, Role of frontier orbitals in chemical reactions, *Science* 179 (218) (1982) 747–754.
- [52] Y. Li, J.N.S. Evans, The Fukui function: a key concept linking frontier molecular orbital theory and the hard-soft-Acid-Base principle, *J. Am. Chem. Soc.* 117 (1995) 7756–7759.
- [53] T. Langer, G. Wolber, Pharmacophore definition and 3D searches, *Drug Discov. Today Technol.* 1 (2004) 203–207.
- [54] A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Sci. Rep.* 7 (2017) 42717.
- [55] E.M. Salah, et al., Chemical composition and antifungal activity of *teucrium leucocladum* boiss. Essential oils growing in Egypt using two different techniques. *Futur, J. Pharm. Sci.* 10 (2024) 51.
- [56] P. Banerjee, E. Kemmler, M. Dunkel, R. Preissner, ProTox 3.0: a webserver for the prediction of toxicity of chemicals, *Nucleic Acids Res.* 52 (2024) W513–W520.
- [57] I.H. Sanches, R.C. Braga, V.M. Alves, C.H. Andrade, Enhancing hERG risk assessment with interpretable classificatory and regression models, *Chem. Res. Toxicol.* 37 (2024) 910–922.
- [58] R.C. Braga, et al., Pred-hERG: a novel web-accessible computational tool for predicting cardiac toxicity, *Mol Inform* 34 (2015) 698–701.
- [59] J.V.B. Borba, et al., Pred-skin: a web portal for accurate prediction of human skin sensitizers, *Chem. Res. Toxicol.* 34 (2021) 258–267.
- [60] V.M. Alves, et al., A perspective and a new integrated computational strategy for skin sensitization assessment, *ACS Sustain. Chem. Eng.* 6 (2018) 2845–2859.
- [61] H. Yang, et al., AdmetSAR 2.0: web-service for prediction and optimization of chemical ADMET properties, *Bioinformatics* 35 (2019) 1067–1069.
- [62] F. Cheng, et al., AdmetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties, *J. Chem. Inf. Model.* 52 (2012) 3099–3105.
- [63] P.A. Wood, et al., Evaluation of molecular crystal structures using full interaction maps, *CrystEngComm* 15 (2013) 65–72.
- [64] J. Bernstein, R.E. Davis, L. Shimoni, N.-L. Chang, Patterns in hydrogen bonding: functionality and graph set analysis in crystals, *Angew. Chem. Int. Ed. Eng.* 34 (1995) 1555–1573.
- [65] M.A. Spackman, J.J. McKinnon, Fingerprinting intermolecular interactions in molecular crystals, *CrystEngComm* 4 (2002) 378–392.
- [66] C.F. Matta, R.F.W. Bader, Atoms-in-molecules study of the genetically encoded amino acids. III. Bond and atomic properties and their correlations with experiment including mutation-induced changes in protein stability and genetic coding, *Proteins Struct. Funct. Genet.* 52 (2003) 360–399.
- [67] W. Nakanishi, S. Hayashi, K. Narahara, Atoms-in-molecules dual parameter analysis of weak to strong interactions: behaviors of electronic energy densities versus laplacian of electron densities at bond critical points, *J. Phys. Chem. A* 112 (2008) 13593–13599.
- [68] W. Nakanishi, S. Hayashi, K. Narahara, Polar coordinate representation of hb(rc) versus $(h/2/8m)V^2p/rc$ at BCP in AIM analysis: classification and evaluation of weak to strong interactions, *J. Phys. Chem. A* 113 (2009) 10050–10057.
- [69] S. Emamian, T. Lu, H. Kruse, H. Emamian, Exploring nature and predicting strength of hydrogen bonds: a correlation analysis between atoms-in-molecules descriptors, binding energies, and energy components of symmetry-adapted perturbation theory, *J. Comput. Chem.* 40 (2019) 2868–2881.
- [70] G. Gilli, P. Gilli, The Nature of the Hydrogen Bond: Outline of a Comprehensive Hydrogen Bond Theory vol. 23, Oxford University Press, 2009.
- [71] J. Li, et al., Tissue distribution and metabolism of triadimefon and triadimenol enantiomers in chinese lizards (*eremias argus*), *Ecotoxicol. Environ. Saf.* 142 (2017) 284–292.
- [72] J.J. McKinnon, M.A. Spackman, A.S. Mitchell, Novel tools for visualizing and exploring intermolecular interactions in molecular crystals, *Acta Crystallogr. Sect. B: Struct. Sci.* 60 (2004).
- [73] P. Panini, E. Boel, L. Van Meervelt, G. Van den Mooter, Solvatomorphism in Miconazole: The Role of Weak C—H...Cl Hydrogen Bonds and C—Cl...Cl—C Halogen Interactions in Similarities and Differences in the Crystal Packing, *Cryst. Growth Des.* 22 (2022) 2703–2724.
- [74] A.H.B. Deas, D.R. Clifford, Reductive and oxidative metabolism of triazolymethanes by two basidiomycete fungi, *Pestic. Biochem. Physiol.* 22 (1984) 276–284.
- [75] A.H.B. Deas, D.R. Clifford, Metabolism of the 1,2,4-triazolymethane fungicides, triadimefon, triadimenol, and diclobutrazol, by *aspergillus niger* (van tiegh.), *Pestic. Biochem. Physiol.* 17 (1982) 120–133.
- [76] L.R. Domingo, M.J. Aurell, P. Pérez, R. Contreras, Quantitative characterization of the global electrophilicity power of common diene/dienophile pairs in Diels–Alder reactions, *Tetrahedron* 58 (2002) 4417–4423.
- [77] P. Pérez, L.R. Domingo, M.J. Aurell, R. Contreras, Quantitative characterization of the global electrophilicity pattern of some reagents involved in 1,3-dipolar cycloaddition reactions, *Tetrahedron* 59 (2003) 3117–3125.
- [78] L. Hou, et al., Triadimefon in aquatic environments: occurrence, fate, toxicity, and ecological risk, *Environ. Sci. Eur.* 34 (2022) 12.
- [79] Y. Li, et al., Chiral fungicide triadimefon and triadimenol: Stereoselective transformation in greenhouse crops and soil, and toxicity to *daphnia magna*, *J. Hazard. Mater.* 265 (2014) 115–123.
- [80] P.P. Madeira, L.A. Ferreira, V.N. Uversky, B.Y. Zaslavsky, Polarity of Aqueous Solutions. *Liquids* 4 (2024) 107–116.
- [81] D.L. Roman, M.A. Matica, A. Ciorsac, B.V. Boros, A. Isvoran, The effects of the fungicide myclobutanil on soil enzyme activity, *Agriculture* 13 (2023) 1956.
- [82] Q.D. Walker, R.B. Mailman, Triadimefon and triadimenol: effects on monoamine uptake and release, *Toxicol. Appl. Pharmacol.* 139 (1996) 227–233.
- [83] E.C. Picinini, J.M.C. Fernandes, Efeito do tratamento de sementes com fungicida sobre o controle de doenças na parte aérea do trigo, *Fitopatol. Bras.* 28 (2003) 515–520.
- [84] B.C. Monk, et al., Architecture of a single membrane spanning cytochrome p450 suggests constraints that orient the catalytic domain relative to a bilayer, *Proc. Natl. Acad. Sci.* 111 (2014) 3865–3870.
- [85] N. Wang, Y. Liu, J. Li, L. Xu, X. Liang, Advances in selective bioactivity and toxicity of chiral triazole fungicides and their selective behavior in mammals, *Chirality* 37 (2025).
- [86] C. Ducker, J. Brockmöller, How precise is quantitative prediction of pharmacokinetic effects due to drug-drug interactions and genotype from in vitro data? A comprehensive analysis on the example CYP2D6 and CYP2C19 substrates, *Pharmacol. Ther.* 217 (2021) 107629.
- [87] H. Zhang, et al., Insights into the effects of difenoconazole on the livers in male mice at the biochemical and transcriptomic levels, *J. Hazard. Mater.* 422 (2022) 126933.
- [88] F. Drenzo, M. Broccia, E. Giavini, E. Menegola, Citral, an inhibitor of retinoic acid synthesis, attenuates the frequency and severity of branchial arch abnormalities induced by triazole-derivative fluconazole in rat embryos cultured in vitro, *Reprod. Toxicol.* 24 (2007) 326–332.
- [89] E. Menegola, M.L. Broccia, F. Di Renzo, V. Massa, E. Giavini, Study on the common teratogenic pathway elicited by the fungicides triazole-derivatives, *Toxicol. in Vitro* 19 (2005) 737–748.
- [90] K. Tamura, et al., Involvement of constitutive androstane receptor in liver hypertrophy and liver tumor development induced by triazole fungicides, *Food Chem. Toxicol.* 78 (2015) 86–95.
- [91] Y. Tang, et al., Toxicological risk assessment of triadimenol for human exposure, broiler health, and food safety, *Food Chem. Toxicol.* 194 (2024) 115071.
- [92] L. Hongwei, et al., Translocation and enrichment behavior of triadimefon and its metabolite triadimenol in rubber trees, *Chin. J. Pesti. Sci.* 25 (2023) 444–452.
- [93] H. Liang, et al., Stereoselective transformation of triadimefon to metabolite triadimenol in wheat and soil under field conditions, *J. Hazard. Mater.* 260 (2013) 929–936.