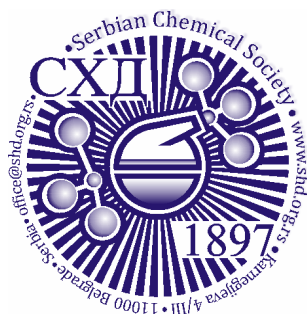




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Theoretical study of molecular structure, reactivity, and molecular docking of almotriptan and its metabolite

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Abstract: In this work, we performed a computational study of almotriptan, *N,N*-dimethyl-2-[5-((pyrrolidin-1-ylsulfonyl)methyl)-1*H*-indol-3-yl]ethanamine (denoted as Almo-I), and its metabolite, 4-(((3-(2-(dimethylamino)ethyl)-1*H*-indol-5-yl)methyl)sulfonamido)butanoic acid (denoted as Almo-II). Both species were examined at the X / DGDZVP level of theory (X = B3LYP, M06, M06L and ω B97XD). The reactive sites were identified through evaluation of the Fukui function using frozen-core and finite-difference approaches. For Almo-I, the sites most susceptible to nucleophilic attack are mainly located on the indole ring, whereas those prone to electrophilic attack are associated with the pyrrole double-bond region. The highest susceptibility toward radical attack was found at atoms C12, C13 and C14. In the case of Almo-II, the regions susceptible to nucleophilic attack shift from the indole ring toward the sulfonamide group, while the susceptibility to electrophilic and radical attack remains essentially unchanged. In addition, molecular docking studies showed favorable predicted interactions of Almo-I and Almo-II with the 5-HT_{1B} receptor, with docking scores of -38.07 and -33.47 kJ mol⁻¹, respectively. Almo-I interacted mainly with Tyr218 and Phe331 through hydrogen-bond, π - π , and van der Waals interactions, whereas Almo-II interacted with Arg236, Arg310, and Lys314 through hydrogen-bond and π -cation interactions. The more favorable docking score and binding orientation of Almo-I are consistent with its placement within the previously reported binding site. These findings contribute to a better understanding of the molecular and reactivity characteristics of almotriptan and its metabolite and may provide useful insights into its mechanism of action and drug-receptor recognition relevant to its therapeutic activity.

Keywords: triptanes; electronic structure; Fukui function; migraine; 5-HT_{1B}.

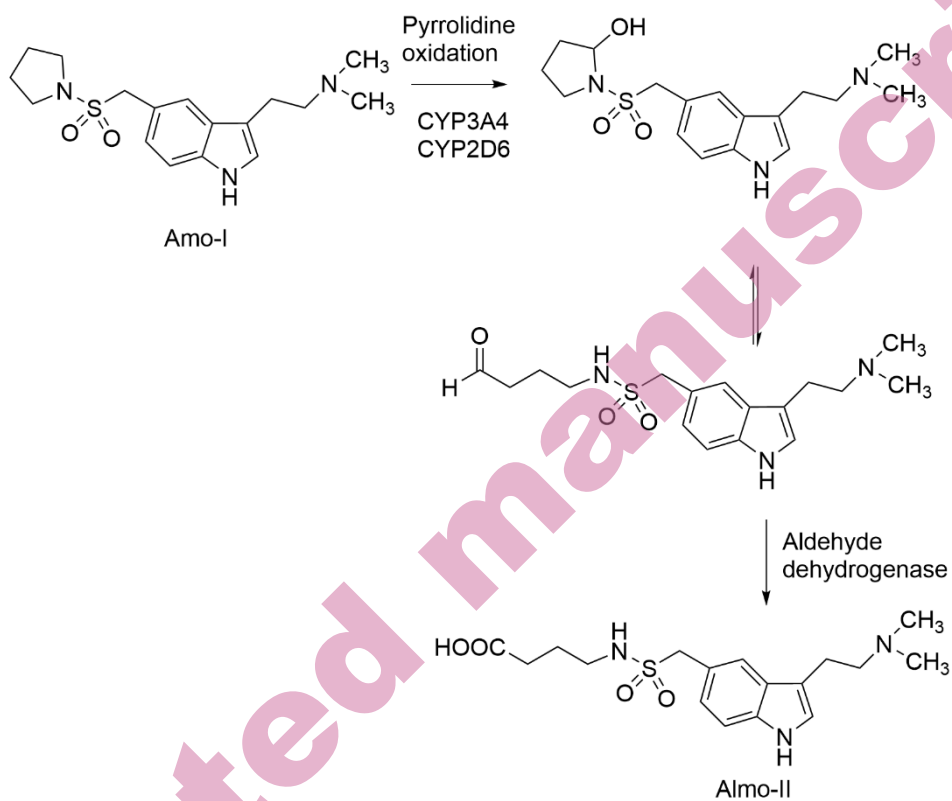
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INTRODUCTION

Migraine is a neurological disorder characterized by recurrent headache attacks of varying intensity, often accompanied by nausea, photophobia, phonophobia, and, in some cases, aura.¹ The underlying mechanism involves the release of neuropeptides such as calcitonin gene-related peptide (CGRP) and substance P within the trigeminovascular system, leading to neurogenic inflammation.¹ Pharmacological evidence supports the use of compounds that act as agonists of serotonin (5-hydroxytryptamine) receptors, particularly 5-HT_{1B/1D}, which are located in the cranial circulation and define the molecular basis for antimigraine drug action.² Key residues within the binding pocket include Asp129, Ile130, Cys133, Tyr208, Thr209, Ser212, Ala216, Trp327, Phe330, Phe331, Ser334, Asp352, Thr355, and Tyr359.³ Among these agents, almotriptan, *N,N*-dimethyl-2-[5-((pyrrolidin-1-ylsulfonyl)methyl)-1*H*-indol-3-yl]ethanamine, is a second-generation antimigraine drug with selectivity toward 5-HT_{1B} and 5-HT_{1D} receptors. It exhibits moderate binding affinity, which accounts for its clinical efficacy and reduced incidence of off-target effects,⁴ as well as a sustained pain-free response in both adolescents and adults at comparable doses.⁵ The drug shows high aqueous solubility and an oral bioavailability of approximately 20 %, primarily due to extensive hepatic metabolism.⁶ Metabolic studies have identified renal biotransformation pathways, where the major metabolite corresponds to a γ -aminobutyric acid derivative (Almo-II). This metabolite is formed through reactions catalyzed by monoamine oxidase (MAO-A) and cytochrome P450 isoenzymes (CYP3A4 and CYP2D6).⁷ From a reactivity perspective, almotriptan has been reported to be labile under hydrolytic (acidic, basic, and neutral), oxidative, and photolytic stress conditions, as demonstrated by reversed-phase UHPLC analyses.⁸ Computational studies on structurally related triptans, such as frovatriptan and naratriptan, have evaluated chemical reactivity using global descriptors, including molecular hardness derived from HOMO–LUMO energy gaps, electrostatic potential maps, and molecular docking approaches.^{9,10} Furthermore, molecular dynamics and nuclear magnetic resonance studies of sumatriptan have demonstrated that its protonation state influences its behavior and interactions with model lipid membranes under different conditions.¹¹ In this context, the present work examines the chemical reactivity and electronic properties of almotriptan and its metabolite using computational methods, with particular emphasis on the identification of reactive sites and their relationship to molecular stability and transformation pathways. Furthermore, molecular docking with the 5-HT_{1B} receptor was performed to relate reactivity patterns to binding interactions, providing a molecular-level interpretation of the drug's chemical behavior in connection with its therapeutic activity.

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Figure 1. Main metabolic pathways of almotriptan in humans.¹²

THEORY

Global reactivity parameters

Within the framework of Density Functional Theory (DFT), the global reactivity of molecular systems can be evaluated using a set of conceptual descriptors. These parameters provide an overall description of chemical reactivity, including the chemical potential (μ), which is associated with the tendency of electrons to escape from the system;¹³ the electronegativity (χ), which measures the ability of a system to attract electrons; the chemical hardness (η), which is related to molecular stability;^{14,15} and the electrophilicity index (ω), which quantifies the capacity of a species to accept electrons and allows classification of its nucleophilic or electrophilic character.^{16,17}

$$\mu = \left(\frac{\partial E}{\partial N} \right)_{v(r)} = -\frac{1}{2}(I + A) = \frac{1}{2}(\varepsilon_L + \varepsilon_H) = (\varepsilon_L - \varepsilon_H) \quad (1)$$

$$\chi = -\mu \quad (2)$$

$$\eta = \left(\frac{\partial \mu}{\partial N} \right)_{v(r)} = \left(\frac{\partial^2 E}{\partial N^2} \right)_{v(r)} = (I - A) = (\varepsilon_L - \varepsilon_H) \quad (3)$$

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

For Eqs. (1)–(4), the variables E , N , and $V(r)$ correspond to the total energy of the system, the number of electrons, and the external potential, respectively. These parameters can be estimated from the ionization potential (I) and the electron affinity (A). In this study I and A were obtained using both the Koopmans' theorem approximation, based on the frontier orbital energies, $I = -\varepsilon_H$ and $A = -\varepsilon_L$ ¹³, and the Δ SCF approach, based on total energy differences between the neutral and charged species, $I = E(N-1) - E(N)$ and $A = E(N) - E(N+1)$. The calculations for the charged species were performed using unrestricted DFT. Furthermore, the electrodonating (ω^-) and electroaccepting (ω^+) powers are defined as follows:¹⁸

$$\omega^- = \frac{(\mu^-)^2}{2\eta} = \frac{\left(-\frac{1}{4}(3I+A)\right)^2}{2(I-A)} = \frac{\left(-\frac{1}{4}(3\varepsilon_L+\varepsilon_H)\right)^2}{2(\varepsilon_L-\varepsilon_H)} \quad (5)$$

$$\omega^+ = \frac{(\mu^+)^2}{2\eta} = \frac{\left(-\frac{1}{4}(I+3A)\right)^2}{2(I-A)} = \frac{\left(-\frac{1}{4}(\varepsilon_L+3\varepsilon_H)\right)^2}{2(\varepsilon_L-\varepsilon_H)} \quad (6)$$

Local reactivity parameters

On the other hand, specific reactive sites in a molecular system can be identified using Density Functional Theory. In this context, the Fukui function ($f(r)$) is widely used to describe changes in electron density with respect to variations in the number of electrons,^{19,20} and is defined as follows:²¹

$$f(r) = \left(\frac{\partial \rho(r)}{\partial N}\right)_{v(r)} = \left(\frac{\partial \mu(r)}{\partial v}\right) \quad (7)$$

Three different approaches are commonly employed, namely the frozen-core (FC),²¹ finite-difference (FD),²¹ and atomic charge²² methods, which provide relevant information for the analysis of local reactivity in molecular systems. Within the FC approximation of the Fukui function, the descriptors for nucleophilic and electrophilic attacks are given by Eqs. (8) and (9), respectively:

$$f^-(r) = \varphi_H^*(r)\varphi_H(r) = \rho_H(r) \quad (8)$$

$$f^+(r) = \varphi_L^*(r)\varphi_L(r) = \rho_L(r) \quad (9)$$

Furthermore, within the FD approximation, the Fukui function allows the identification of preferred sites for electrophilic, nucleophilic, and radical attacks, as defined by Eqs. (10), (11), and (12), respectively:

$$f^-(r) = \rho_N(r) - \rho_{N-1}(r) \quad (10)$$

$$f^+(r) = \rho_{N+1}(r) - \rho_N(r) \quad (11)$$

$$f^0(r) = \frac{1}{2}[\rho_{N+1}(r) - \rho_{N-1}(r)] \quad (12)$$

where $\rho_{N+1}(r)$, $\rho_N(r)$ y $\rho_{N-1}(r)$ represent the electron density of the anionic, neutral, and cationic species, respectively. Additionally, the condensed Fukui function enables the evaluation of specific atomic sites using atomic charges, as defined in Eqs. (13), (14), and (15).

$$f_j^-(r) = q_{j(N-1)} - q_{j(N)} \quad (13)$$

$$f_j^+(r) = q_{j(N)} - q_{j(N+1)} \quad (14)$$

$$f_j^0(r) = \frac{1}{2} [q_{j(N-1)} - q_{j(N+1)}] \quad (15)$$

Non-covalent interaction index

The non-covalent interaction (NCI) index was used to characterize weak non-covalent interactions based on the electron density and reduced density gradient. The NCI index is defined as follows:³⁸

$$s(r) = \frac{1}{2(3\pi^2)^{\frac{1}{3}}} \frac{|\nabla\rho(r)|}{\rho(r)^{\frac{4}{3}}} \quad (16)$$

EXPERIMENTAL

Prior to geometry optimization, a conformational analysis of almotriptan and its metabolite was performed using molecular mechanics with the MM++ force field. Subsequently, the most stable conformers were fully optimized in the aqueous phase at the B3LYP/DGDZVP level of theory²³ (with additional calculations carried out using B3LYP,^{24,25} M06,²⁶ M06L,²⁷ and ω B97XD²⁸ functionals). Solvent effects were accounted for using the polarizable continuum model (PCM),²⁹ with water as the solvent for both geometry optimizations and single-point calculations. To confirm the nature of the stationary points, vibrational frequency calculations were carried out, ensuring that all optimized structures correspond to minima on the potential energy surface. The optimized neutral structures of Almo-I and Almo-II were used as reference geometries for the Fukui function analysis. The Fukui functions were evaluated using the finite-difference (FD) approach by considering the neutral species with N electrons, the corresponding cationic species with $N-1$ electrons, and the anionic species with $N+1$ electrons. Single-point calculations were performed for the three electronic states using the optimized neutral geometries, without further geometry optimization of the charged species. Hirshfeld atomic charges obtained for each state were used to calculate the condensed Fukui functions with the B3LYP, M06, M06-L, and ω B97XD functionals. All quantum chemical calculations were performed using the software Gaussian 09,³⁰ and the resulting structures were analyzed with GaussView V.3.09,³¹ ArgusLab,³² Gabedit,³³ and Multiwfn.³⁴ Molecular docking studies were conducted using the DockThor platform.³⁵ The three-dimensional structure of the 5-HT_{1B} receptor in complex with the agonist methiothepin was obtained from the Protein Data Bank (PDB code: 5V54). Prior to docking, the protein structure was cleaned, and the neutral forms of Almo-I and Almo-II, previously optimized using DFT calculations, were used as ligands. Although almotriptan can exist in protonated form under physiological conditions, previous computational studies of triptan drugs have shown that different protonation states may exhibit distinct molecular behavior depending on the environment.¹¹ The same docking protocol and parameters were applied to both compounds. The docking search space was defined by a grid box centered at (-17.12, -4.34, 27.14) Å, with dimensions of 40 × 40 × 40 Å and a grid spacing of 0.42 Å. Flexible docking was performed using a genetic algorithm with 1,000,000 evaluations, a population size of 750, and 24 runs, using the same initial random seed (-1985) for both ligands. The resulting ligand–receptor complexes were evaluated based on their predicted docking scores and interaction patterns. Visualization of the ligand-receptor complexes was performed using UCSF Chimera³⁶ and Discovery Studio Visualizer 2019.³⁷

RESULTS AND DISCUSSION

Geometry optimization

The conformational analysis enabled the identification of the lowest-energy structures of Almo-I and Almo-II. These structures were subsequently optimized without constraints at the X/DGDZVP level of theory²⁵ (X = B3LYP,^{24,25} M06,²⁶ M06L,²⁷ and ω B97XD²⁸) for both species in the aqueous phase (Fig. 2). Vibrational analysis at the same level of theory confirmed the stability of the optimized structures, as no imaginary frequencies were observed, indicating that true minima on the potential energy surface were obtained. The Cartesian coordinates of the optimized Almo-I and Almo-II structures are provided in Tables S1 and S2, respectively, while the theoretical IR spectra calculated at the B3LYP / DGDZVP level of theory in the aqueous phase are presented in Fig. S1 of the Supplementary Material.

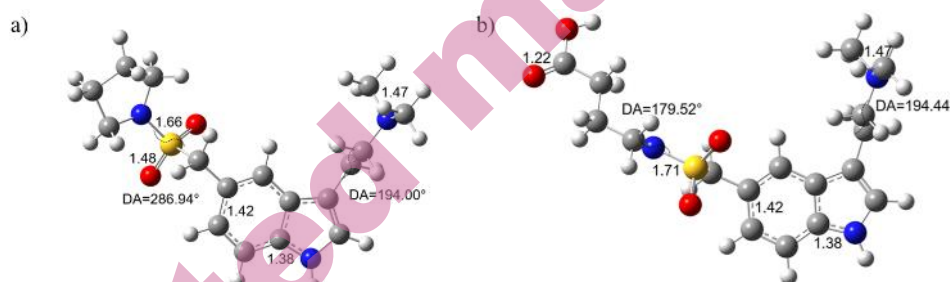


Figure 2. Structures of almotriptan and its metabolite: (a) Almo-I and (b) Almo-II, optimized at the B3LYP / DGDZVP level of theory in the aqueous phase using the PCM solvation model. Bond distances are given in Å; DA = dihedral angle.

Figure 3 shows the different orientations adopted by the functional groups in both structures, which can be attributed to the presence of noncovalent interactions. This behavior was confirmed through noncovalent interaction (NCI) analysis, based on the isosurface $s(r)$ defined by Eq. (16).³⁸ Figure S-2 in the Supplementary Material presents the NCI plots for Almo-I and Almo-II. It is observed that, in regions of low electron density, the reduced density gradient exhibits high positive values, whereas in regions of higher electron density, it approaches values close to zero, in agreement with previous reports.³⁸

Global reactivity parameters

The global reactivity descriptors of Almo-I and Almo-II were calculated using Eqs. (1)–(6). The results are summarized in Table 1. The HOMO and LUMO distributions of Almo-I and Almo-II are shown in Fig. S4. The corresponding frontier orbital energies were used to evaluate the global reactivity parameters presented in Table 1. It is observed that the values associated with electron-donating ability (chemical potential) and chemical hardness are higher for Almo-I

than for Almo-II, indicating that the parent drug exhibits a greater tendency to donate electrons and higher intrinsic stability than its metabolite. In contrast, the increase in the electroaccepting power (ω^+) for Almo-II suggests that the metabolic process leads to a species with lower electrophilic toxicity.

Table 1. Global reactivity parameters of Almo-I and Almo-II evaluated at the X / DGDZVP level of theory (X = B3LYP,^{24,25} M06,²⁶ M06L,²⁷ and ω B97XD²⁸) in the aqueous phase using Eqs. (1)–(6). The values in parentheses were calculated using Koopmans' theorem.

Procedure	I / eV	A / eV	μ / eV	η / eV	χ / eV	ω / eV	ω^+ / eV	ω^- / eV
Almo-I								
B3LYP	5.66 (5.77)	1.00 (0.85)	-3.33 (-3.31)	4.67 (4.92)	3.33 (3.31)	1.19 (1.11)	0.50 (0.44)	2.17 (2.09)
M06	5.76 (6.07)	1.03 (0.67)	-3.40 (-3.37)	4.73 (5.40)	3.40 (3.37)	1.22 (1.05)	0.52 (0.38)	2.22 (2.06)
M06L	5.46 (5.11)	0.94 (1.27)	-3.20 (-3.19)	4.53 (3.84)	3.20 (3.19)	1.13 (1.33)	0.47 (0.65)	2.07 (2.24)
ω B97XD	5.87 (7.71)	0.91 (-0.99)	-3.39 (-3.36)	4.96 (8.70)	3.39 (3.36)	1.16 (0.65)	0.47 (0.08)	2.16 (1.76)
Almo-II								
B3LYP	5.71 (5.82)	4.36 (0.93)	-5.04 (-3.37)	1.35 (4.88)	5.04 (3.37)	9.43 (1.16)	8.21 (0.47)	10.73 (2.16)
M06	5.81 (6.11)	4.50 (0.74)	-5.15 (-3.42)	1.31 (5.38)	5.15 (3.42)	10.17 (1.09)	8.92 (0.40)	11.50 (2.12)
M06L	5.52 (5.18)	4.29 (1.37)	-4.90 (-3.28)	1.23 (3.81)	4.90 (3.28)	9.75 (1.41)	8.57 (0.71)	11.02 (2.35)
ω B97XD	5.91 (7.75)	4.44 (-0.93)	-5.18 (-3.41)	1.46 (8.68)	5.18 (3.41)	9.16 (0.67)	7.92 (0.09)	10.50 (1.79)

Local reactivity parameters

Figures 3 and S-5 (Supplementary material) show the Fukui function analysis for Almo-I and Almo-II, respectively, using the FD approximation defined by Eqs. (10)–(12). The atom numbering schemes used for Almo-I and Almo-II throughout the Fukui function analysis are provided in Fig. S-15 (Supplementary material). For Almo-I, the sites most susceptible to nucleophilic attack, identified from f^+ , are located at atoms C7, C11, and C14, primarily within the indole ring. This behavior can be attributed to polarization of the conjugated π -system toward these atoms, induced by the substituents present in the molecule (Figure 3a). In contrast, the sites most prone to electrophilic attack, determined from f^- , are located at atoms C6, C7, and N2, in the region of the pyrrole double bond, which is consistent with the characteristic reactivity of π -bonds (Figure 3b). Additionally, radical susceptibility, evaluated using f^0 , is highest at atoms C12, C13, and C14. For the

metabolite Almo-II, the sites most susceptible to nucleophilic attack shift from the indole ring toward the sulfonamide group, specifically to atoms O17, O18, and S16, which can be associated with the formation of contributing resonance structures that modulate the electron density in this region (Figure S-5a). The sites susceptible to electrophilic attack are located at atoms C6, N7, N2, and N8, again in the region of the conjugated pyrrole system (Figure S-5b). Finally, the most reactive sites toward radical attack correspond to atoms C12, C13, and C14, in agreement with those identified for Almo-I. These results indicate that metabolic transformation alters the distribution of nucleophilic reactivity, while preserving the electrophilic and radical reactive regions, which may influence interactions with the 5-HT_{1B} receptor if such interactions involve these reactive regions. These findings provide insights into the local electronic characteristics of Almo-I and Almo-II, which may aid in the interpretation of their intermolecular interactions.

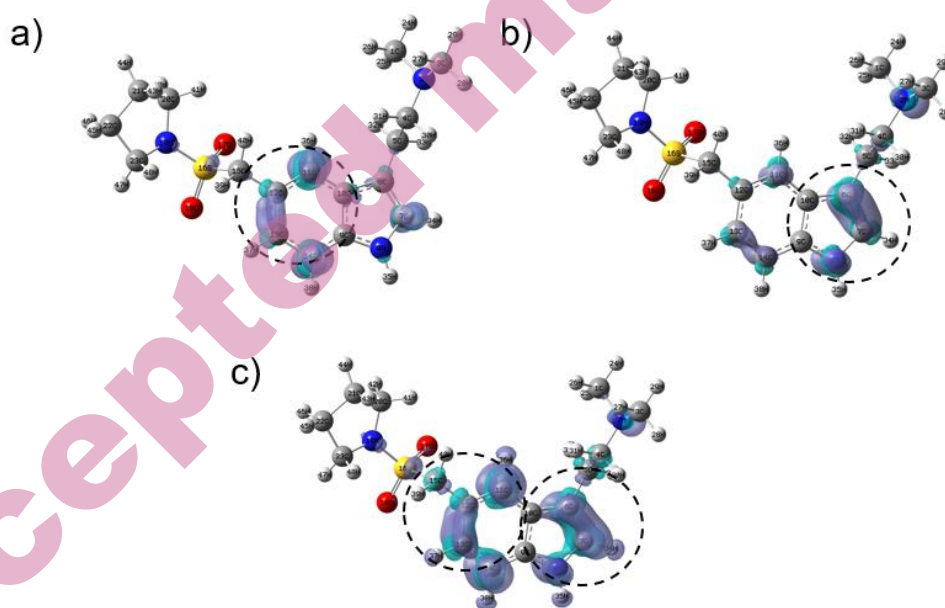


Figure 3. Fukui function isosurfaces for Almo-I, calculated according to Eqs. (10)–(12) at the B3LYP / DGDZVP level of theory using the PCM solvation model. The isosurfaces correspond to: (a) nucleophilic, (b) electrophilic, and (c) radical attacks. In all cases, the isosurfaces were generated at $0.004 \text{ e} \cdot \text{bohr}^{-3}$, and the dashed line highlights the most reactive regions of the molecule.

Furthermore, local reactivity can be analyzed using the condensed Fukui function, calculated at the X / DGDZVP level of theory (X = B3LYP,^{24,25} M06,²⁶ M06L,²⁷ and ω B97XD²⁸) in the aqueous phase from Eqs. (13)–(15), which enables identification of the site-specific distribution of reactive centers. Figures 4 and S6–

S11(Supplementary material) present the values obtained for the three types of attacks evaluated for Almo-I and Almo-II. Figures S-6–S-8 show the condensed Fukui function values for nucleophilic, electrophilic, and free-radical attacks, respectively, for Almo-I, whereas Figs. S-9–S-11 present the corresponding results for Almo-II. As shown in Figure 4, Almo-I exhibits the highest susceptibility to nucleophilic attack at atoms C7, N8, C11, C12, and C13. The reactive sites identified using this approach are consistent with those obtained from electron density analysis.

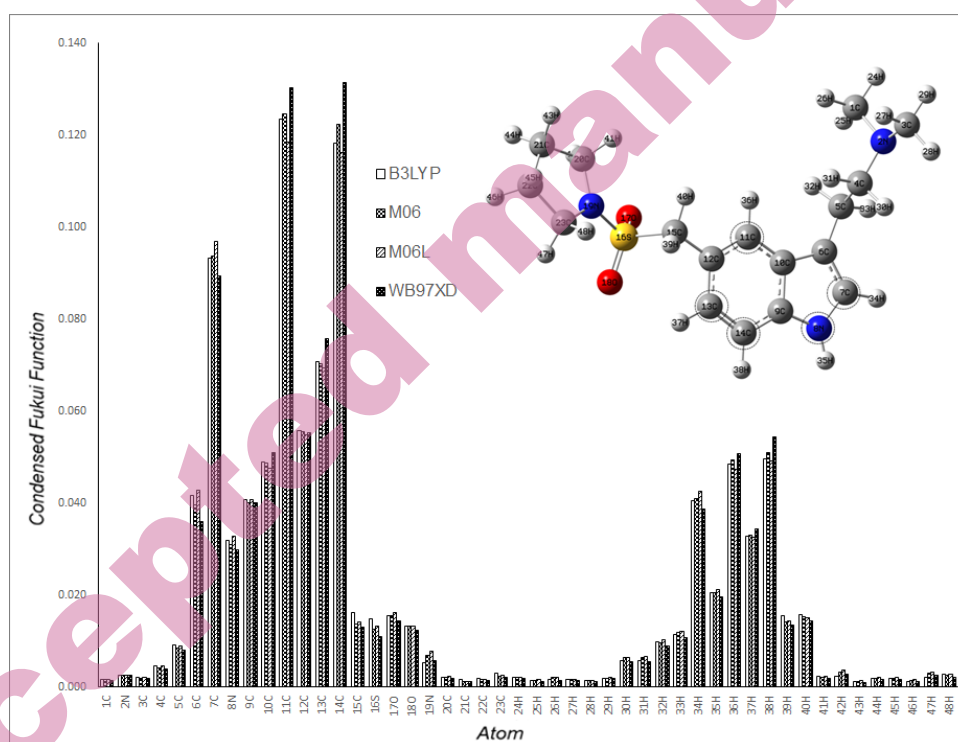


Figure 4. Condensed Fukui function values for nucleophilic attack on Almo-I, calculated at the X / DGDZVP level of theory (X = B3LYP,^{24,25} M06,²⁶ M06L,²⁷ and ωB97XD²⁸) in the aqueous phase using Hirshfeld population analysis and Eqs. (13)–(15).

To analyze the electronic distribution, the molecular electrostatic potential (MEP) maps for Almo-I and its metabolite Almo-II are shown in Figure S-12. In these representations, regions of negative potential (colored in red) are associated with higher electron density compared to other site of the molecule, whereas regions of positive potential (colored in blue) indicate a relative electron deficiency. For Almo-I, the oxygen atoms exhibit the most negative potential values, indicating a higher electron density localized around these sites. In contrast,

nitrogen atoms display more positive potential values, reflecting a relative deficiency. These electrostatic features provide complementary information on the distribution of electron-rich and electron-deficient regions in both molecules, which may influence their intermolecular interactions. To evaluate their intrinsic molecular properties, Almo-I and Almo-II were considered in their neutral forms. The potential interactions of almotriptan and its metabolite with the 5-HT_{1B} receptor, were subsequently investigated by molecular docking. The predicted binding poses and docking scores were used to characterize the ligand–receptor interactions. Figure S-13 shows the predicted binding modes of Almo-I and Almo-II within the 5-HT_{1B} receptor. Almo-I exhibited a docking score of $-38.07 \text{ kJ}\cdot\text{mol}^{-1}$, with the corresponding pose shown in Fig. S-13a. Several residues contributed to the predicted ligand–receptor contacts, with Tyr218 and Phe331 showing prominent interactions. The 2D interaction map indicated a hydrogen-bond contact between Almo-I and Tyr218 involving one of the sulfone oxygen atoms. Tyr218 also showed a π – π interaction with the benzene ring of the indole moiety. Phe331 contributed van der Waals contacts with Almo-I and has previously been identified as part of the 5-HT_{1B} receptor binding region³ (Fig. S-14a). For Almo-II, a docking score of $-33.47 \text{ kJ}\cdot\text{mol}^{-1}$ was obtained, with the predicted binding mode shown in Fig. S-13b. Arg236 and Arg310 formed hydrogen-bond contacts with Almo-II, whereas Lys314 was involved in two hydrogen-bond interactions with the sulfone oxygen atoms and two π -cation interactions with the benzene and pyrrole rings of the indole moiety (Fig. S-14b). These contacts may contribute to the predicted ligand–receptor association. The docking results are consistent with the electrostatic features identified for both molecules. Electron-rich regions associated with the sulfone groups participate in hydrogen-bond interactions with Tyr218 in Almo-I and Lys314 in Almo-II, whereas the indole aromatic system contributes to π – π and π -cation interactions, respectively. From a biothermodynamic perspective, ligand–receptor recognition can be described in terms of the energetic contributions associated with complex formation and stabilization. Binding affinity is therefore an important parameter for characterizing the energetic favorability of ligand–receptor association.^{39,40} In the present study, both compounds showed favorable predicted docking scores, with values of -38.07 and $-33.47 \text{ kJ}\cdot\text{mol}^{-1}$ for Almo-I and Almo-II, respectively. The more negative score predicted for Almo-I indicates a more favorable docking score under the applied computational protocol. In addition, the predicted pose places Almo-I closer to the reported receptor specificity pocket than Almo-II, suggesting differences in their predicted binding modes.

CONCLUSION

In the present work, the reactivity of almotriptan (Almo-I) and its metabolite (Almo-II) was analyzed in the aqueous phase. The calculated global reactivity

descriptors indicate that the metabolic process induces an electronic redistribution, reflected in an increase in the electroaccepting power (ω^+), suggesting a change in the reactivity profile associated with a reduced toxicological impact. Regarding the molecular docking analysis, both Almo-I and Almo-II showed favorable predicted interactions with the 5-HT_{1B} receptor. Almo-I exhibited a more favorable docking score and a binding orientation positioned deeper within the reported specificity pocket, with Tyr218 and Phe331 among the most relevant interacting residues. Almo-II also displayed several non-covalent interactions with the receptor, particularly involving Arg236, Arg310, and Lys314. These findings suggest that both compounds can form favorable interactions within the predicted receptor binding region, while their distinct interaction patterns may reflect the influence of structural differences on receptor recognition.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/13920>, or from the corresponding author on request.

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ИЗВОД

ТЕОРИЈСКО ПРОУЧАВАЊЕ МОЛЕКУЛСКЕ СТРУКТУРЕ, РЕАКТИВНОСТИ И МОЛЕКУЛСКОГ ДОКИНГА АЛМОТРИПТАНА И ЊЕГОВОГ МЕТАБОЛИТА

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У овом раду представљено је рачунарско проучавање алмотриптана, *N,N*-диметил-2-[5-((пиролидин-1-илсулфонил)метил)-1*H*-индол-3-ил]етанамина (означеног као Almo-I), и његовог метаболита, 4-(((3-(2-(диметиламино)етил)-1*H*-индол-5-ил)метил)сулфонамидо)бутанске киселине (означене као Almo-II). Обе молекулске врсте испитане су на X/DGDZVP нивоу теорије ($X = B3LYP, M06, M06L$ и $\omega B97XD$). Реактивна места идентификована су одређивањем Фукуијевих функција применом приступа замрзнутог језгра и метода коначних разлика. Код Almo-I, места најподложнија нуклеофилном нападу углавном су локализована на индолском прстену, док су места подложна електрофилном нападу повезана са регионом двоструке везе у пиролском прстену. Највећа подложност радикалском нападу утврђена је на атомима C12, C13 и C14. У случају Almo-II, региони подложни нуклеофилном нападу померају се са индолског прстена ка сулфонамидној групи, док подложност електрофилном и радикалском нападу

остаје суштински непромењена. Поред тога, резултати молекулског докинга предвиђају повољне интеракције Almo-I и Almo-II са 5-HT_{1B} рецептором, при чему су добијене вредности докинг-скора износили –38,07 и –33,47 kJ mol⁻¹, редом. Almo-I преваходно остварује интеракције са аминокиселинским остацима Tyr218 и Phe331 посредством водоничних веза, π-π интеракција и Ван дер Валсових интеракција, док Almo-II интерагује са остацима Arg236, Arg310 и Lys314 посредством водоничних веза и π-катионских интеракција. Повољнија вредност докинг-скора и оријентација везивања Almo-I у складу су са његовим позиционирањем у претходно идентификованом месту везивања. Добијени резултати доприносе бољем разумевању молекулских и реактивних карактеристика алмотриптана и његовог метаболита и могу пружити корисне увиде у механизам њиховог дејства и препознавање лека од стране рецептора, што је од значаја за његову терапијску активност.

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