

COMPARATIVE HIRSHFELD SURFACE, SWISSADME, AND MOLECULAR DOCKING ANALYSIS OF A-(N-BENZOXAZOLIN-2-ONE)ACETIC ACID AND B-(N-BENZOXAZOLIN-2-ONE)PROPIONIC ACID

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Annotatsiya

Ushbu ishda α -(N-benzoksazolin-2-on)sirka kislotasi va β -(N-benzoksazolin-2-on)propion kislotasining molekulalararo ta'sirlari, farmakokinetik profili hamda oqsil bilan bog'lanish xususiyatlari zamonaviy kompyuter yondashuvlari asosida qiyosiy tahlil qilindi. Intellectual in silico screening vositalari sifatida Hirshfeld sirt tahlili, SwissADME bashorati va molekulyar docking usullari qo'llanildi. Natijalar qo'shimcha $-\text{CH}_2-$ guruhining kiritilishi $\text{H}\cdots\text{O}/\text{O}\cdots\text{H}$ kontaktlari ulushini kamaytirib, $\text{H}\cdots\text{H}$ o'zaro ta'sirlari hissasini oshirishini ko'rsatdi. Har ikkala birikma maqbul farmakokinetik xossalarga ega ekani aniqlandi, bunda β -hosila biroz yuqoriroq lipofilik va yaxshiroq docking skori bilan tavsiflandi. Olingan natijalar kompyuter yordamidagi tezkor screening usullari struktura-xossa va ligand-oqsil o'zaro ta'sirlarini baholashda samarali yondashuv ekanini ko'rsatadi.

Kalit so'zlar: benzoxazolinone, Hirshfeld surface analysis, SwissADME, molecular docking, in silico screening, intermolecular interactions, pharmacokinetic properties.

Аннотация

В данной работе проведён сравнительный анализ межмолекулярных взаимодействий, фармакокинетического профиля и связывания с белком α -(N-бензоксазолин-2-он)уксусной кислоты и β -(N-бензоксазолин-2-он)пропионовой кислоты с использованием современных компьютерных подходов. В качестве интеллектуальных in silico screening инструментов применены анализ поверхности Хиршфельда, прогноз SwissADME и молекулярный докинг. Результаты показали, что введение дополнительной группы $-\text{CH}_2-$ снижает вклад контактов $\text{H}\cdots\text{O}/\text{O}\cdots\text{H}$ и увеличивает долю $\text{H}\cdots\text{H}$ взаимодействий. Установлено, что оба соединения обладают благоприятными фармакокинетическими свойствами, при этом β -производное характеризуется несколько большей липофильностью и лучшим docking score. Полученные данные показывают, что методы быстрого компьютерного screening являются эффективным подходом для оценки взаимосвязи структура-свойство и взаимодействий лиганд-белок.

Ключевые слова: benzoxazolinone, анализ поверхности Хиршфельда, SwissADME, молекулярный докинг, in silico screening, межмолекулярные взаимодействия, фармакокинетические свойства.

Abstract

This work presents a comparative analysis of the intermolecular interactions, pharmacokinetic profile, and protein-binding behavior of α -(N-benzoxazolin-2-one)acetic acid and β -(N-benzoxazolin-2-one)propionic acid using modern computer-based approaches. Hirshfeld surface analysis, SwissADME prediction, and molecular docking were applied as intelligent in silico screening tools. The results showed that the introduction of an additional $-\text{CH}_2-$ group decreases the contribution of $\text{H}\cdots\text{O}/\text{O}\cdots\text{H}$ contacts and increases the proportion of $\text{H}\cdots\text{H}$ interactions. Both compounds were found to possess favorable pharmacokinetic properties, while the β -derivative exhibited slightly higher lipophilicity and a better docking score. The obtained results demonstrate that rapid computer-aided screening methods are effective tools for evaluating structure–property relationships and ligand–protein interactions.

Keywords: benzoxazolinone, Hirshfeld surface analysis, SwissADME, molecular docking, in silico screening, intermolecular interactions, pharmacokinetic properties.

Introduction

Artificial intelligence and computer-aided modeling are increasingly used in applied sciences as efficient tools for data analysis, virtual screening, and predictive evaluation of chemical and biological systems. In chemical research, these approaches reduce time, cost, and experimental workload by enabling the preliminary assessment of compounds before labor-intensive laboratory studies. Although Hirshfeld surface analysis, SwissADME prediction, and molecular docking are not strictly artificial intelligence methods, they represent related in silico tools that support rapid screening and informed decision-making in molecular research.

Benzoxazolinone derivatives are attractive model compounds because their physicochemical properties and potential biological activity are highly sensitive to minor structural modifications. Benzoxazolinones are naturally occurring heterocyclic compounds widely found in plants, especially in the Poaceae family, where they act as phytoalexins and allelochemicals [1,2]. Their structure is based on the 1,3-benzoxazol-2-one scaffold, while N-substitution plays an important role in tuning physicochemical and biological properties [3,4]. Related systems, including benzoxazinones and benzoxazolinones, have attracted considerable attention because of their antimicrobial, antifungal, anticancer, and anti-inflammatory activities [3,5,6]. Synthetic derivatives often show enhanced biological activity compared with natural analogues, making them promising scaffolds for the design of new bioactive compounds [5,7,8].

Previous studies have shown that α -(N-benzoxazolin-2-one)acetic acid can crystallize in different hydrate, solvate, salt, and polymorphic forms, indicating that small structural changes strongly influence intermolecular organization [9–12]. This makes structurally related derivatives suitable systems for comparative supramolecular investigation.

Hirshfeld surface analysis is a well-established method for visualizing and quantifying intermolecular interactions in molecular crystals [13–15]. In the present study, this approach was combined with SwissADME prediction and molecular docking in order to compare two structurally related benzoxazolinone derivatives and to evaluate how methylene spacer length affects intermolecular interactions, physicochemical characteristics, and predicted protein–ligand binding.

Aim and Methods of the Study

The aim of this study was to evaluate the effect of methylene spacer length on the intermolecular interactions, pharmacokinetic properties, and predicted protein–ligand binding of α -(N-benzoxazolin-2-one)acetic acid (I) and β -(N-benzoxazolin-2-one)propionic acid (II).

The crystal structures of I and II were taken from previously reported X-ray diffraction data [9–11]. Hirshfeld surface analysis was performed in CrystalExplorer 21.5 [15], with surfaces mapped over d_{norm} to quantify the main intermolecular contacts.

Physicochemical and pharmacokinetic properties were predicted using the SwissADME web tool [16], including molecular weight, TPSA, LogP, gastrointestinal absorption, blood–brain barrier permeation, CYP450 inhibition, and drug-likeness.

Protein–ligand interaction analysis was carried out using the *Escherichia coli* protein structure 1KZN [17]. Cavity detection and docking calculations were performed with CB-Dock2 to identify binding pockets, docking scores, and key contact residues. All calculations were carried out with default software parameters, and the results were compared to assess the effect of the additional –CH₂– group.

Results and discussion

Hirshfeld surface analysis showed that the intermolecular organization of both compounds is primarily governed by H $\cdots$ O/O $\cdots$ H contacts, highlighting the dominant role of hydrogen bonding in their supramolecular arrangement. For α -(N-benzoxazolin-2-one)acetic acid, these contacts account for 47.2%, whereas for β -(N-benzoxazolin-2-one)propionic acid their contribution decreases to 43.9%. Conversely, the proportion of H $\cdots$ H contacts rises from 22.2% to 29.3%, indicating that elongation of the side chain increases the importance of nonpolar and dispersion interactions. These differences are clearly reflected in the Hirshfeld surfaces shown in Fig. 1 and in the percentage contributions of intermolecular contacts presented in Fig. 2.

Changes are also observed in the geometric characteristics of the Hirshfeld surface. With the addition of one –CH₂– group, the surface volume increases from 207.01 to 227.85 Å³, and the surface

area from 202.90 to 225.15 Å². In parallel, globularity decreases from 0.834 to 0.801, while asphericity increases from 0.115 to 0.186. These data indicate that the β -derivative possesses a larger, less compact, and more anisotropic molecular surface.

SwissADME analysis revealed that both compounds have favorable pharmacokinetic profiles. They have the same topological polar surface area, show high gastrointestinal absorption, do not penetrate the blood–brain barrier, and satisfy Lipinski's rule of five. The β -derivative displays slightly higher lipophilicity, with consensus LogP increasing from 0.83 to 1.03, and also contains more rotatable bonds, indicating somewhat greater conformational flexibility.

Docking analysis against the 1KZN protein demonstrated that both ligands bind in the same predicted cavity. The docking scores were –6.3 kcal/mol for the α -derivative and –6.5 kcal/mol for the β -derivative. This suggests that the β -compound has a slightly stronger predicted affinity, possibly due to improved accommodation of the elongated side chain within the protein cavity.

Overall, the results show that the addition of a single methylene group causes a consistent redistribution of intermolecular contacts, modifies surface geometry, and slightly improves the predicted binding efficiency. In other words, even one extra –CH₂– can quietly rearrange the whole molecular “social life”.

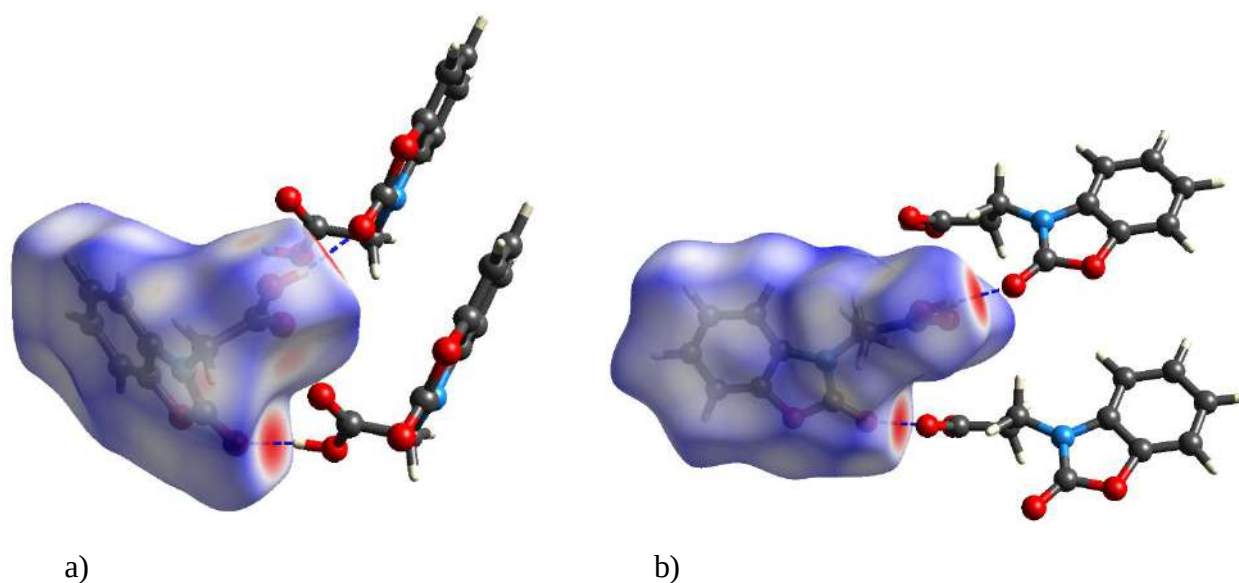


Figure 1. Hirshfeld surfaces of I (a) and II (b) mapped over d_{norm} , highlighting the intermolecular O—H...O hydrogen bonds corresponding to H...O/O...H contacts.

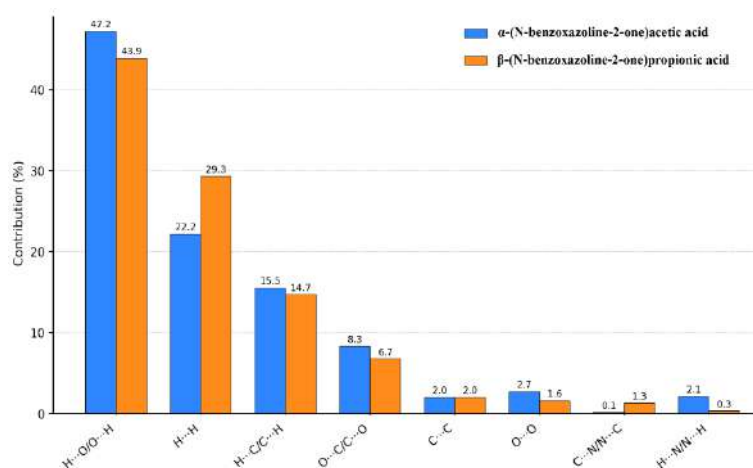


Figure 2. Percentage contributions of intermolecular contacts to the Hirshfeld surfaces of α -(N-benzoxazoline-2-one)acetic acid and β -(N-benzoxazoline-2-one)propionic acid.

Conclusion

The study demonstrates that modern intelligent computational approaches are effective tools for comparative analysis of structurally related benzoxazolinone derivatives. Hirshfeld surface analysis showed that extension of the side chain from the α - to the β -derivative decreases the contribution of hydrogen-bond-driven $\text{H}\cdots\text{O}/\text{O}\cdots\text{H}$ contacts and increases the role of $\text{H}\cdots\text{H}$ interactions. SwissADME prediction confirmed that both compounds retain favorable drug-like properties. Molecular docking indicated a slightly better binding score for β -(N-benzoxazolin-2-one)propionic acid. Thus, the additional $-\text{CH}_2-$ group significantly affects crystal packing, molecular surface characteristics, and predicted ligand–protein interaction, making the β -derivative a somewhat more promising compound for further investigation.

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