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Synthesis, Spectroscopic Characterizations and *In Silico* ADMET Analysis of a New Indolin-2-one-Based Schiff Base Compound

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Yeni Bir İndolin-2-on Temelli Schiff Bazı Bileşiğin Sentezi, Spektroskopik Karakterizasyonları ve *In Silico* ADMET Analizi

ABSTRACT

In this study, a new indolin-2-one-based Schiff base bearing a propargyl substituent was successfully synthesized. The compound was thoroughly characterized by a combination of spectroscopic techniques including FT-IR, ^{1}H-NMR,^{13}C-NMR and UV-Vis spectrometry, which confirmed the target molecular framework. Mass spectrometry analysis further validated the molecular composition, supporting the successful preparation of the target compound. *In silico* pharmacokinetic and ADMET analyses were performed to evaluate the drug-likeness properties of the synthesized compound. The results demonstrated high gastrointestinal absorption and bioavailability score of 0.55, with no predicted violations of Lipinski's rule of five. Furthermore, the compound exhibited favorable synthetic accessibility and low toxicity risks. The presence of a propargyl group, which is a versatile pharmacophoric motif, suggests additional opportunities for further structural modifications to enhance biological activity and molecular interactions. These findings highlight the potential of the obtained compound as promising scaffold for future drug development and bioactivity optimization.

Keywords: Indolin-2-one, hydrazone, propargyl ether, Schiff base, ADMET

ÖZ

Bu çalışmada yeni bir propargil sübstitüenti taşıyan indolin-2-on temelli Schiff bazı başarıyla sentezlenmiştir. Bileşik, FT-IR, ^{1}H-NMR, ^{13}C-NMR ve UV-Vis spektroskopisi dâhil olmak üzere çeşitli spektroskopik tekniklerle kapsamlı biçimde karakterize edilmiş ve hedef molekülün yapısı doğrulanmıştır. Kütle spektrometrisi analizi hedef bileşiğin başarılı bir şekilde hazırlandığını desteklemiştir. Sentezlenen bileşiğin ilaç-benzeri özelliklerini değerlendirmek amacıyla *In silico* farmakokinetik ve ADMET analizleri gerçekleştirilmiştir. Sonuçlar, bileşiğin yüksek gastrointestinal emilim ve iyi biyoyararlanım gösterdiğini ve Lipinski'nin beş kuralına uymayan herhangi bir durum olmadığını ortaya koymuştur. Ayrıca, bileşik uygun sentezlenebilirlik ve düşük toksisite riski profilleri sergilemiştir. Çok yönlü bir farmakoforik motif olan propargil grubunun varlığı, biyolojik aktiviteyi ve moleküler etkileşimleri artırmak amacıyla ek yapısal modifikasyonlara olanak sağlamaktadır. Bu bulgular, elde edilen bileşiğin gelecekteki ilaç geliştirme çalışmaları ve biyolojik aktivite optimizasyonu için umut verici bir potansiyele sahip olduğunu göstermektedir.

Anahtar Kelimeler : İndolin-2-one, hidrazon, propargil eter, Schiff bazı, ADMET

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INTRODUCTION

Indolin-2-one derivatives are widely recognized in medicinal chemistry owing to their structural diversity and broad spectrum of biological activities, including anticancer[1], antimicrobial[2] and antiviral activity.[3] The isatin framework, in particular, serves as a versatile pharmacophore that can be readily functionalized to yield novel bioactive scaffolds. Schiff bases derived from isatin or related indolin-2-one cores represent an important class of compounds, as the incorporation of the hydrazone linkage introduces additional hydrogen-bonding capacity and enhances molecular interactions with biomacromolecules.[4,5]

The biological potential of such scaffolds can be further optimized through strategic substitution. Among various substituents, propargyl groups have gained increasing interest due to their dual role as pharmacophoric units and synthetic handles for derivatization. Propargyl moieties not only contribute to improved molecular recognition but also serve as reactive sites in click chemistry, enabling the development of functionalized derivatives with expanded biological profiles.[6,7] The integration of propargyl functionalities into indolin-2-one-based Schiff bases may therefore provide access to promising candidates for drug discovery.[8,9]

A survey of related indolin-2-one hydrazones shows that substitution patterns typically feature either an ortho-hydroxy/para-methoxy array[10,11] or a para-O-propargyl group without an ortho-OH.[9] To the best of our knowledge, the 2-OH/4-O-propargyl combination present in the title compound has not been reported for this class. This positional pairing is chemically meaningful: the o-OH engages in a six-membered O–H···N intramolecular hydrogen bond that preorganizes the hydrazone[12], while the p-O-propargyl extends conjugation and provides a click-ready handle for rapid derivatization.[13,14] The resulting electronic and steric synergy is expected to modulate biomacromolecular recognition and ADME-relevant properties, motivating our design.

Our group has previously reported the synthesis of 1,2,3-triazole-containing molecules prepared *via* Cu(I)-catalyzed azide-alkyne cycloaddition, highlighting their strong DNA/protein binding affinities and promising anticancer activities.[15,16] These studies demonstrated the importance of incorporating propargyl group into molecules as synthetic precursors and pharmacologically relevant motifs. Building on this experience, the current work focuses on the design of a new indolin-2-one-based Schiff base incorporating a propargyl substituent.

In silico approaches such as ADMET (absorption, distribution, metabolism, excretion and toxicity) prediction have become indispensable in modern drug discovery for evaluating the pharmacokinetic and safety profiles of new chemical entities before experimental biological studies.[17,18] By combining experimental synthesis and spectroscopic characterization with computational modeling, a more comprehensive assessment of drug-likeness can be achieved.[19, 20]

In this study, we report the synthesis, structural elucidation and computational ADMET evaluation of a new indolin-2-one-derived Schiff base functionalized with a propargyl group, with the aim of exploring its potential as a new drug-like scaffold.

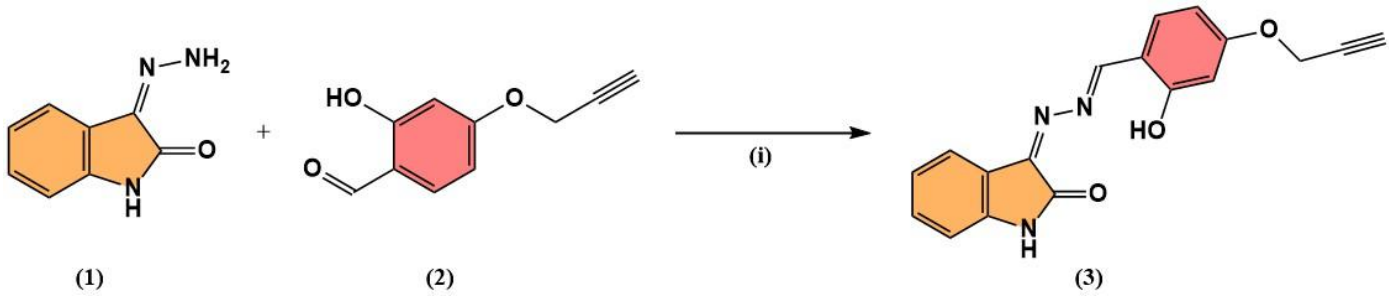
METHODS

Materials and Measurements

All reagents were purchased from Merck/Sigma and used as received. Elemental analyses (C, H, N) were carried out using a LECO 932 CHNS analyzer. NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal reference. IR spectra were acquired in the 4000-400 cm^{-1} range on a Thermo Scientific Nicolet iS10 FT-IR spectrometer using the attenuated total reflectance (ATR) technique. Electronic absorption spectra were measured on a PG Instruments T80+ UV-Vis spectrophotometer. Positive-ion MALDI-TOF mass spectra were obtained in DIT matrix with a Bruker Microflex LT instrument (Karlsruhe, Germany) in linear mode, using a nitrogen laser and averaging 50 laser shots. The precursor compounds (Z)-3-hydrazineylideneindolin-2-one (**1**) and 2-hydroxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2**) were synthesized according to previously reported methods.[21,22]

Synthesis and Characterization

The compound (**3**) was synthesized according to the previously reported method in literature.[21] Briefly, a solution of 3-hydrazineylideneindolin-2-one (**1**) (10 mmol) in methanol (2 mL) was added to a solution of 2-hydroxy-4-(prop-2-yn-1-yloxy)benzaldehyde (**2**) (10 mmol) in dichloromethane (10 mL). The mixture was heated at reflux for 72 h in the presence of ca. acetic acid (AcOH). The product that precipitated from the reaction medium was collected by filtration, washed with methanol and dried at room temperature to afford compound (**3**) as an orange/red solid (71%; m.p. 244-246 °C; Scheme 1).



Scheme 1. Synthesis of compound (**3**). (i) DCM/MeOH, 72 h, reflux, ca. AcOH

(Z)-3-(((E)-2-hydroxy-4-(prop-2-yn-1-yloxy)benzylidene)hydrazineylidene)indolin-2-one (3): Yield: 71%. m.p.: 244-246 °C. UV-Vis (DMF, nm) λ_{max}: 265, 392. FT-IR (ATR, ν, cm^{-1}): 3247, 3154, 2113, 1704 (C=O), 1614 (C=N), 1273. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H, OH), 10.97 (s, 1H, NH), 9.01 (s, 1H, CH), 7.62 (m, 2H, ArH), 7.44 (t, *J* = 7.8 Hz, 1H, ArH), 7.08 (t, *J* = 7.6 Hz, 1H, ArH), 6.91 (d, *J* = 7.8 Hz, 1H, ArH), 6.64 (m, 2H, ArH), 4.91 (d, *J* = 2.4 Hz, 2H, CH_2), 3.67 (d, *J* = 2.7 Hz, 1H, CH). ^{13}C-NMR (101 MHz, DMSO-d_6) δ 167.7, 162.8, 162.7, 159.8, 150.4, 144.7, 135.3, 134.0, 122.7, 120.4, 112.3, 111.2, 108.5, 102.6, 79.2, 79.1, 56.3. MALDI-TOF-MS (*m/z*): calculated for $C_{18}H_{13}N_3O_3$=319.096, found=318.643 $[M]^{\bullet+}$. Anal. calcd. for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found C, 67.70; H, 4.12; N, 13.16.

In Silico Studies

Parameters such as absorption, distribution, metabolism, excretion (ADME) define the essential characteristics a drug molecule should possess. The various ADME properties including TPSA, MW, no. of rotatable bonds/hydrogen bond donors/hydrogen bond acceptors, Log P, Log S, compatibility to Lipinski rule, GI absorption, BBB permeant, skin permeant, bioavailability, predicted LD_{50} were calculated using the SwissADME and Protox 3.0 online servers.[23,24]

RESULTS AND DISCUSSION

UV-Visible Spectroscopy

The electronic absorption spectra of the compound (**3**) were recorded in DMF solution over the wavelength range of 200-600 nm at room temperature (Figure 1). The compound exhibited characteristic π-π* and n-π* electronic transitions at 265 nm and 392 nm, respectively, corresponding to the transitions within the conjugated aromatic system and the lone pair electron excitation of the azomethine (C=N) group.[25]

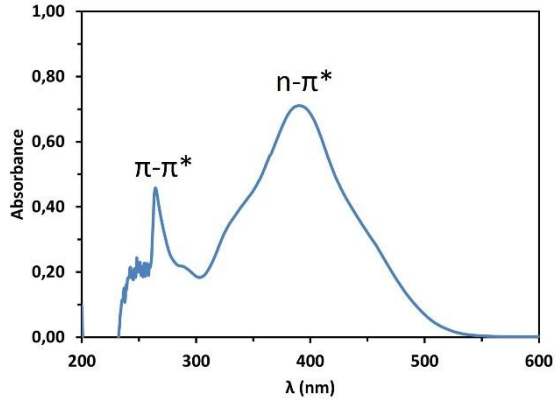


Figure 1. UV-Vis spectra of compound (**3**)

Infrared Spectroscopy

The FT-IR spectrum (Figure 2a) of compound (**3**) displayed characteristic absorption bands corresponding to its main functional groups. A broad band at 3247 cm^{-1} was assigned to the O-H stretching vibration of the phenolic hydroxyl group, overlapping with the N-H stretching of the indolin-2-one moiety.[4] The weak absorption at 3154 cm^{-1} is attributed to the ≡C-H stretching of the terminal propargyl group, additionally, a medium band at 2113 cm^{-1} is consistent with the C≡C stretching of this unit.[26] A strong band at 1704 cm^{-1} corresponds to the C=O stretching vibration of the isatin carbonyl group, while the band at 1614 cm^{-1} is assigned to the C=N stretching vibration of the azomethine (imine) linkage. Additionally, the absorption observed at 1273 cm^{-1} is attributed to C-O stretching vibrations of the phenolic group.[27, 28] These results confirm the presence of the hydroxyl, imine, carbonyl, indolinone N-H and terminal propargyl functionalities in the molecular structure of compound (**3**), consistent with the target Schiff base framework.

Nuclear Magnetic Resonance Spectroscopy

The ^{1}H-NMR spectrum (Figure 2b) of compound (**3**) exhibited characteristic signals in agreement with the target structure. A singlet at 12.32 ppm was assigned to the

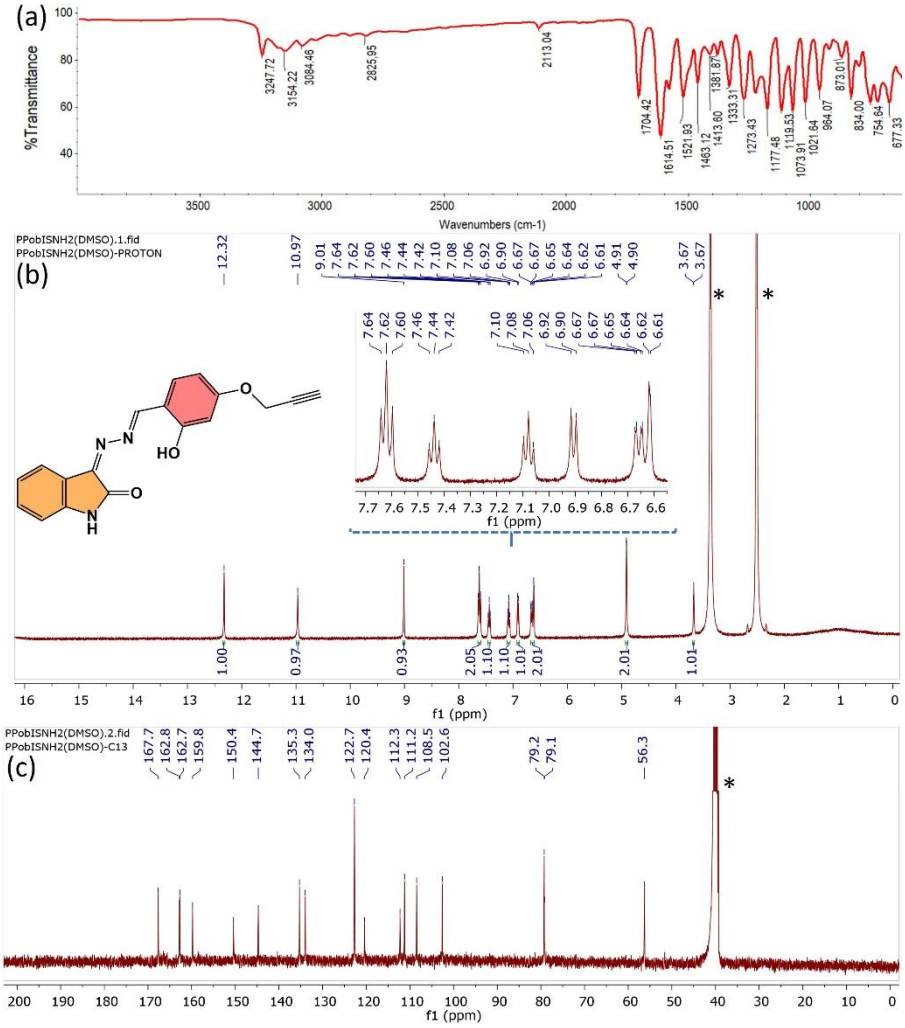


Figure 2. (a) FTIR, (b) ^{1}H-NMR and (c) ^{13}C-NMR spectra of compound (**3**). *Solvent peaks.

phenolic -OH proton, while another singlet at 10.97 ppm corresponded to the indolin-2-one -NH proton.[29, 30] The imine (-CH=N-) proton resonated as a singlet at 9.01 ppm.[31] The aromatic region showed multiple signals between 7.62-6.62 ppm, corresponding to the aromatic protons of both the indolinone and benzylidene rings. The methylene group adjacent to the oxygen of the propargyl substituent appeared as a doublet at 4.91 ppm, while the acetylenic -CH proton of the terminal propargyl moiety was observed as a doublet at 3.67 ppm.[22]

The ^{13}C-NMR spectrum (Figure 2c) of compound (**3**) showed resonances consistent with the target molecular structure. The indolin-2-one carbonyl carbon appeared at 167.7 ppm, while the azomethine (C=N) carbon resonated at 159.8 ppm.[32] Additional downfield signals at 162.8 and 162.7 ppm were attributed to aromatic carbons bearing hydroxyl and imine substituents. Signals at 150.4, 144.7, 135.3 and 134.0 ppm correspond to quaternary aromatic carbons of the indolinone and benzylidene rings. The aromatic CH carbons were observed at 122.7, 120.4, 112.3, 111.2 and 108.5 ppm, together with a signal at 102.6 ppm, confirming the presence of multiple substituted aromatic environments.

Characteristic resonances for the propargyl substituent were identified at 79.2 and 79.1 ppm (sp carbons of the C≡C unit) and 56.3 ppm (O-CH_2 adjacent to oxygen).[33] These assignments clearly indicate the presence of the propargyl moiety within the molecule. Overall, the ^{1}H-NMR and ^{13}C-NMR data are in full agreement with the target structure of compound (**3**).

Mass Spectral Analysis

The MALDI-TOF spectrum (Figure 3) of compound (**3**) exhibits a dominant peak at *m/z* 318.843, assigned to the radical cation $[M]^{\bullet+}$ of the compound (**3**). The observed value is in good agreement with the calculated monoisotopic mass for the neutral molecule $C_{18}H_{13}N_3O_3$: *m/z* (calcd.) 319.096; *m/z* (found) 318.643.

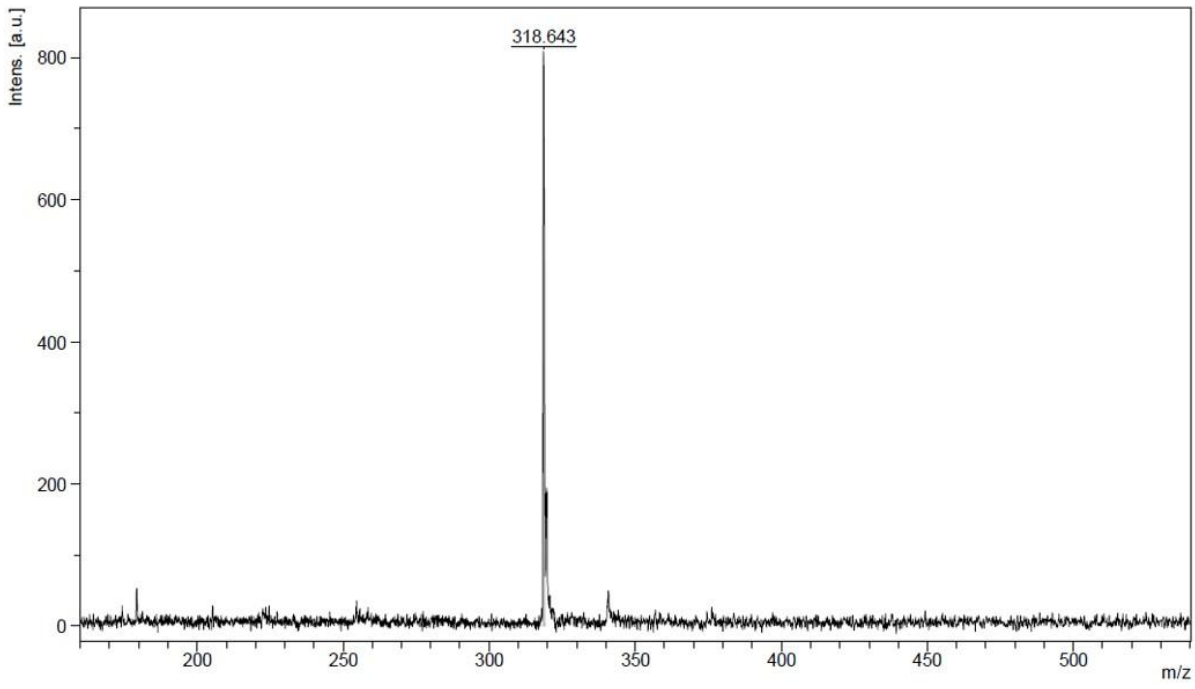


Figure 3. MALDI-TOF-MS spectra of compound (**3**)

ADMET Studies

In silico profiling (SwissADME) indicates that the compound (**3)** satisfies the key oral drug-likeness rules (Table 1, Figure 4). Computational analysis predicts high gastrointestinal absorption, no blood-brain barrier permeation (non-permeant) and no P-gp substrate behavior, which is favorable for minimizing efflux-related liabilities in the gut.[34] CYP inhibition is predicted for CYP1A2, CYP2C9 and CYP3A4, whereas CYP2C19 and CYP2D6 are not predicted to be inhibited; these results warrant attention in future optimization and DDI (drug-drug interaction) risk assessment.[35] Predicted skin permeation is low (logK_p = -6.57 cm/s), consistent with the polarity of the scaffold.[36]

From a medicinal-chemistry perspective, the molecule is lead-like and synthetically tractable (synthetic accessibility score 2.89) and complies with multiple drug-likeness filters (Lipinski,[37] Ghose,[38] Veber,[39] Egan,[40] Muegge[41]). Predicted aqueous solubility ranges from soluble to moderately soluble depending on the model: log*S* (ESOL) = -3.41 (soluble)[42], log*S* (Ali) = -3.75 (soluble)[43] and log*S* (SILICOS-IT) = -5.17 (moderately soluble).

Together with the moderate lipophilicity, these values suggest that standard enabling formulations or salt formation could readily secure adequate exposure if required.

Table 1. Pharmacokinetic properties of the compound (**3**)

	Compound (**3**)
Molecular weight (g/mol)	319.31
Number Heavy atoms	24
Rotatable bonds	4
H-Bond acceptors	5
H-Bond donors	2
Molar refractivity	94.69
TPSA (Å²)	83.28
Log $P_{o/w\ (consensus)}$	2.30
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	Yes
Log K_p (cm/s)	-6.57
Lipinski	Yes (0 violation)
Bioavailability Score	0.55
Synthetic accessibility	2.89
LD_{50} (mg/kg)	2100
Toxicity class	5

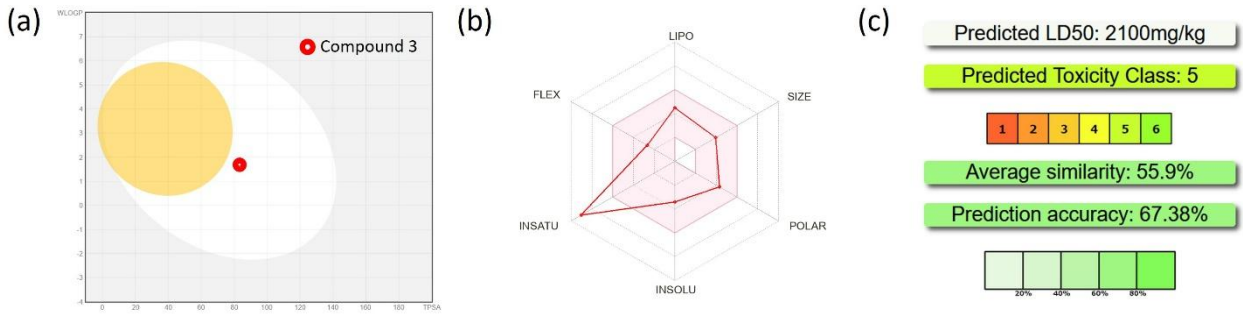


Figure 4. *In silico* ADME and toxicity summary for compound (**3**). (a) BOILED-Egg plot, (b) Bioavailability Radar, (c) ProTox 3.0 acute oral toxicity, predicted LD_{50} ≈ 2100 mg/kg (Class 5).

The compound (**3**) shows low acute oral toxicity with a predicted LD_{50}=2100 mg kg^{-1} (toxicity class 5) according to Protox 3.0. Overall, the profile indicates acceptable acute safety at the screening level, with several moderate-probability liabilities that should be experimentally verified.

Overall, the balance of polarity and lipophilicity, the high GI absorption and compliance with multiple drug-likeness filters indicate that this propargyl-functionalized indolin-2-one hydrazone constitutes a promising, chemically accessible starting point for further optimization, provided the predicted CYP inhibition and alerting motifs are managed experimentally.

CONCLUSIONS

In this work, a new indolin-2-one-based Schiff base compound incorporating a propargyl functionality was successfully synthesized and comprehensively characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry, UV-Vis spectrometry and elemental analysis. The spectroscopic data confirmed the formation of the hydrazone linkage and highlighted the presence of characteristic hydroxyl and propargyl groups, which play a key role in defining the structural and electronic properties of the compound (**3**).

In silico ADMET evaluations revealed that the compound (**3**) exhibits favorable drug-likeness features, including high gastrointestinal absorption and full compliance with Lipinski's rule of five. The predicted toxicity risks further support the potential of compound (**3**) as a promising drug-like candidate. The presence of the propargyl group may allow additional derivatization strategies, offering opportunities to expand its pharmacological scope.

Overall, the integration of experimental and computational approaches provided valuable insights into both the structural features and pharmacokinetic behavior of the synthesized Schiff base compound. These findings suggest that indolin-2-one-based hydrazone derivatives bearing propargyl substituents represent attractive scaffolds for future studies aimed at the development of bioactive agents with improved therapeutic potential. In future work, we will experimentally validate these predictions through standardized *in-vitro* cytotoxicity and antimicrobial panels, accompanied by mechanistic assays (e.g., apoptosis/ROS and target engagement), to establish a robust biological profile for the compound.

Etik Komite Onayı: Gerekmiyor.
Hasta Onamı: Gerekmiyor.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir, Tasarım, Denetleme, Kaynaklar, Veri Toplanması ve/veya İşlemesi, Analiz ve/ veya Yorum, Literatür Taraması, Yazıyı Yazan, Eleştirel İnceleme: Tolga Göktürk
Çıkar Çatışması: Yazar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazar, bu çalışma için finansal destek almadığını beyan etmiştir.
Yapay Zeka Kullanımı: Yapay zekâ destekli araçlar (ChatGPT, OpenAI) yalnızca yazım, imla ve noktalama denetimi gibi temel dil kontrolü amacıyla kullanılmıştır. Bilimsel içerik, yorum, veri analizi veya sonuç üretimi için herhangi bir yapay zekâ aracı kullanılmamıştır. Tüm bilimsel içerik tamamen yazarlara ait olup, yapılan düzenlemeler yazarlar tarafından gözden geçirilip doğrulanmıştır.

Ethics Committee Approval: Not necessary.
Informed Consent: Not necessary.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept, Design, Supervision, Resources, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Search, Writing Manuscript, Critical Review: Tolga Göktürk
Conflict of Interest: The author has no conflicts of interest to declare.
Financial Disclosure: The author declared that this study has received no financial support.
Use of Artificial Intelligence: AI-assisted tools (ChatGPT, OpenAI) were used only for basic checks of grammar, spelling and punctuation. No AI tool was used to generate scientific content, interpretations, data analyses or conclusions. All scientific content is entirely the work of the authors, who reviewed and verified all edits.

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