Journal of Neonatal Surgery
ISSN (Online): 2226 -0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Synthesis, Characterization and Computational Studies Of (Z)-3-((5-Chloropyridin-2-Yl) Imino)-1-(Oxiran-2-Ylmethyl) Indolin-2-One

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Cite this paper as: Deepanjali Shukla, Iqbal Azad, Mohd Arsh Khan, Ziaul Husain, Abdul Rahman Khan, Firoj Hassan, (2025) Synthesis, Characterization and Computational Studies Of (Z)-3-((5-Chloropyridin-2-Yl) Imino)-1-(Oxiran-2-Ylmethyl) Indolin-2-One. *Journal of Neonatal Surgery*, 14 (32s), 535-545.

ABSTRACT

Heterocyclic scaffolds, particularly those derived from isatin, have arisen as promising choices for the generation of new druglike candidates because of their structural flexibility and potent biological activity. This study describes the synthesis and characterization of a new *N*-substituted indolin-2-one derivative. The synthesized compound was structurally confirmed using FT-IR, ^{1}*H*-NMR, and ESI-MS. The compound was synthesized *via* a one-pot reaction, and it is obtained in 80% yield. Furthermore, a thorough *in-silico* analysis was also performed by using ADMETlab 3.0, admetSAR3, and SwissADME. Its physicochemical, pharmacokinetic, and toxicity profiles were compared to the reference. The synthesized indolin-2-one derivative showed positive absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, improved drug likeness, and promising safety as well as efficacy markers, including low expected toxicity and high oral bioavailability. These results show that the synthesized indolin-2-one derivative shows a promising potential as a druglike candidate.

Keywords: *Indolin-2-one derivative; Heterocyclic compounds; Drug-likeness, ADMET profiling*.

1. INTRODUCTION

Defined as ring structures with at least one atom other than carbon, such as nitrogen, oxygen, or sulfur, heterocyclic compounds are among the most productive and important kinds of organic links [1]. Their distinctive electronic and chemical properties have made heterocyclic compounds excellent skeletons in medicinal chemistry, pharmacology, and agrochemical fields. Heterocyclic compounds are present in numerous natural goods, synthetic chemicals, and pharmaceuticals because of their defined structural variety and range of biological activities, including antimicrobial properties, etc. One example of a heterocyclic compound is isatin (1H-indole-2,3-dione), a commonly available one that could be easily synthesized [2]. Isatin is appealing because of its versatility in derivatization and bioconjugation for drug activity as well as the reactive carbonyl sites at positions 2 and 3. First seen in *Indigofera tinctoria*, isatin is an endogenous substance as well as a tryptophan metabolic product found in several mammalian systems [3]. This feature highlights the ability of isatin as a synthetic core for drug design. It has several beneficial pharmacological properties, including anticonvulsant [4-5], antiviral [6], anti-tubercular [7-8], anti-cancer [9-10], and particularly antibacterial activity [11-13].

Substitution at the nitrogen (N1) atom and/or the addition of various functional groups at C5, C6, or C7 of the benzene ring can radically alter the biological activity of isatin. Recent breakthroughs have shown that *N*-substituted isatin derivatives are vital analogs having greater antibacterial activity because of better membrane permeability, higher lipophilicity, and different target-intracellular interactions [14]. Alkyl, aryl, acyl, or heteroaromatic substituents could modify the steric characteristics and electronic distribution around a pharmacophore for isatin, therefore changing binding affinity to intracellular targets and microorganisms. Recent developments in medicinal chemistry have supported the idea that the design of *N*-substituted isatin scaffolds could generate potent inhibitors of microbial DNA gyrase, topoisomerase IV, and bacteria in general, therefore driving the ongoing examination of these possible new-generation topical antibacterial agents [15].

Isatin Schiff bases, formed from the condensation of the isatin carbonyl group and primary amines, which have azomethine functional groups (-CH=N-), constitute a significant class of isatin entities in isatin chemistry development [16-17]. These Schiff bases are known for their capacity to chelate with metal ions and raise biological activity by means of oxidative stress, enzyme inhibition, and DNA intercalation [18]. These compounds' imine bond is vital for increasing electron dispersion, which boosts their antibacterial activity. Their ability to disrupt cell wall synthesis, protein function, or nucleic acid metabolism accounts for their excessive activity against a range of Gram-positive and Gram-negative bacteria.[19].

Combining other bioactive heterocycles such as thiazoles, quinolines, or triazoles helps to design hybrid molecules known to have known synergistic action, therefore sometimes further enhancing the antibacterial efficacy of isatin-inspired compounds. Particularly, metal complexes of isatin Schiff bases with transition metal ions (e.g., copper, cobalt, and zinc) possess more efficacious antimicrobial properties than the isatin itself [20]. Responses associated with redox characteristics, membrane permeability, and reactive oxygen species (ROS) activity often increased antimicrobial potentials. Many of the isatin-based molecules have been found to be good scaffolds, so the search for new scaffolds is driven by the growing resistance of pathogenic bacteria to current antibiotics [21-22].

According to the above literature report, changing substitutions and molecular alterations might influence the drug-likeness and biological activity [23]. Therefore, the aim of this study is to design, synthesize, and characterize an indolin-2-one derivative to explore its drug-likeness and *in-silico* biological activity potentials.

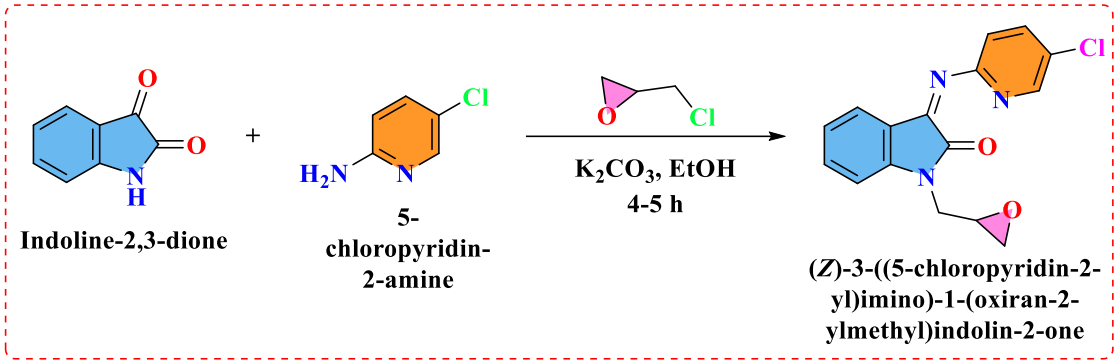
2. MATERIALS AND METHODS

2.1. Materials

Sigma-Aldrich, USA sourced all reagents and solvents of top quality without carrying out additional refinement steps used in this study. TLC was examined on silica gel G using glass plates coated with 100-400 mesh silica gel (GF254), and iodine vapor was used to identify dots. A Bruker Avance spectrometer was used to record ^{1}H-NMR (400 MHz). A PerkinElmer Nicolet 6700 FTIR (Fourier transform infrared spectroscopy) spectrometer operating in the frequency range of 400-4000 cm^{-1} was used using potassium bromide pellets. Positive mode electro-spray ionization (ESI) resulted in mass spectra using an ESI Micromass ZMD 2000 mass spectrometer.

2.2. Methods (General synthesis of indolin-2-one derivative)

In a dry round-bottom flask, equimolar amounts of K_2CO_3, indoline-2,3-dione, epichlorohydin, and 5-chloropyridin-2-amine were dissolved in EtOH and stirred for about 4-5 hours at room temperature. Completion of the reaction was monitored by using TLC plates with n-hexane and ethyl acetate in a 7:3 ratio mixture solvent. The precipitate of indolin-2-one derivative was formed after pouring the reaction mixture into distilled water and washing it thoroughly (**Scheme 1**).



Scheme 1. General synthesis of indolin-2-one derivative

2.2.1. *In-silico* methodology (absorption, distribution, metabolism, excretion, and toxicity (ADMET) and drug-likeness and properties)

In-silico evaluations of the indoline-2-one derivative were performed in comparison to the reference (Sunitinib) using openly available web tool ADMETlab 3.0 (scbdd.com) and admetSAR3

(https://lmmd.ecust.edu.cn/admetsar3/predict.php). Drug-likeness and ADMET properties of the synthesized compound have been calculated using several parameters which confirm the drug-likeness behaviour of the indoline-2-one derivative. ChemDraw Professional v15.1, Molinspiration Engine v2022.08 and SwissADME (http://www.swissadme.ch) were employed to analyse molecular properties, BOILED-Egg and bioactivity radar view in this study.

3. RESULTS

3.1. Chemistry

Synthesis of *N*-substituted indoline-2-one derivative has been performed using a one-pot reaction method under ambient temperature. All the reactants and solvent were used in equimolar quantities and resulted in an 80 % yield of the product. C=N bond was prepared along with *N*-substitution in the isatin molecule. This method provides a comparably potential reaction according to the various methods reported previously. This method provides a convenient and efficient approach to synthesize such hybrid compounds.

3.2. Characterization of indoline-2-one derivative

Orange solid, Yield = 80%, $R_{f\,(product)}$ = 0.71 in 7: 3 hexane/ethyl acetate, ^1H *N*MR (400 MHz, $CDCl_3$, ppm) δ_H: 2.27 (2H, d, J = 7.8 Hz), 2.49 (1H, m), 3.41 (2H, d, J = 5.1 Hz), 7.44 (1H, dd, J = 7.7, 8.6 Hz, Aromatic-H (isatin)), 7.46 (1H, dd, J = 8.6, 7.5 Hz, Aromatic-H (isatin), 7.05 (1H, dd, J = 7.8, 7.5 Hz, Aromatic-H (isatin)), 7.57 (1H, dd, J = 7.8, 1.4 Hz), 7.44 (1H, d, J = 8.3 Hz, Aromatic-H (pyridine ring)), 7.88 (1H, d, J = 8.3 Hz, Aromatic-H (pyridine ring)), 7.89 (1H, s, Aromatic-H (pyridine ring)), FT-IR (KBr) vmax (cm^{-1}): 3048 (C-H; epoxy), 945 (C-O; epoxy), 1331 (C=N; aromatic-pyridine ring), 1672 (C=N; imine), 1732 (C=O; isatin ring), 1124 (C-Cl), ESI-MS : m/z calcd for $C_{16}H_{12}ClN_3O_2$; 312.74 $[M+H]^+$, found 312.20

3.3. *In silico* evaluations

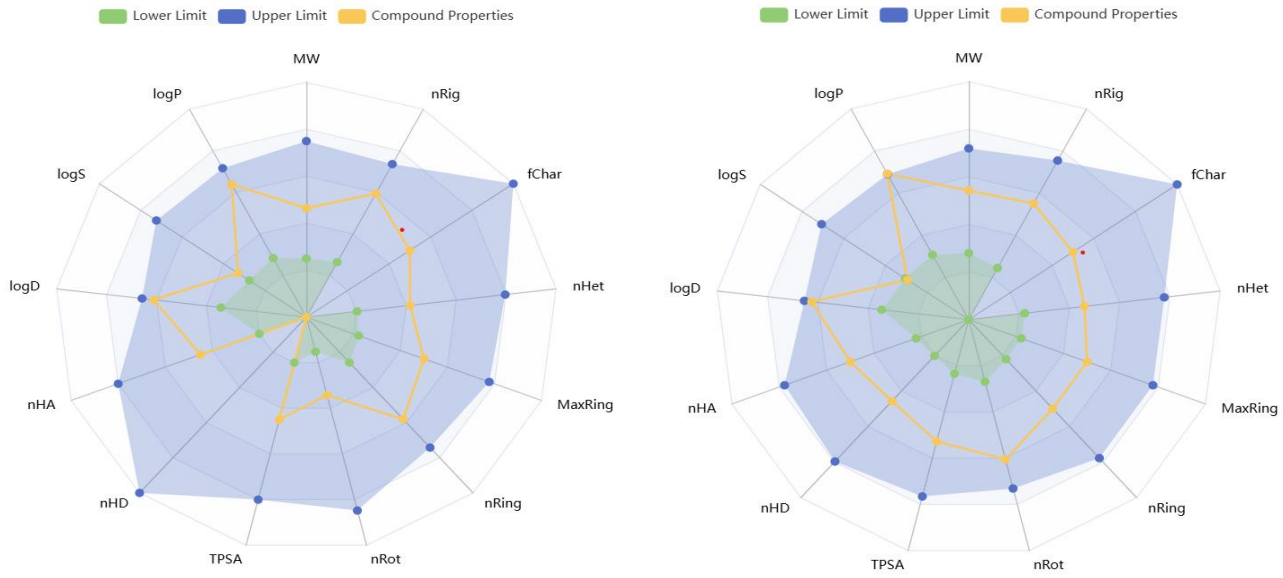
3.3.1. Drug likeness properties

Physicochemical characteristics of the synthesized indolin-2-one derivative as well as the reference were determined using the freely accessible online web tool ADMETlab 3.0. Aspects including molecular weight, volume, density, number of hydrogen acceptors (nHA), number of hydrogen donors (nHD), number of rotatable bonds (nRot), number of rings (nRing), max ring, number of heteroatoms (nHet), flexibility, stereo centres, topological polar surface area (TPSA), logarithm of aqueous solubility (logS), logarithm of the partition coefficient (logP), acid dissociation constant (pKa-acid), basic dissociation constant (pKa-base), melting point, and boiling point were assessed [24] (**Table 1** and **Figure 1**).

Table 1. Relative physiochemical properties of indoline-2-one derivative and reference

Parameter	Indoline-2-one derivative	Sunitinib
Molecular Weight (MW)	313.06	398.21
Volume	295.757	409.942
Density	1.059	0.971
Number of hydrogen acceptors (nHA)	5.0	6.0
Number of hydrogen donors (nHD)	0.0	3.0
Number of rotatable bonds (nRot)	3.0	8.0
Number of rings (nRing)	4.0	3.0
MaxRing	9.0	9.0
Number of heteroatoms (nHet)	6.0	7.0
Flexibility	0.143	0.444
Stereo Centers	1.0	0.0
Topological Polar Surface Area (TPSA)	58.09	77.23
Logarithm of aqueous solubility (logS)	-3.451	-4.12
Logarithm of the partition coefficient (logP)	2.465	3.018
Acid dissociation constant (pka-Acid)	6.77	10.001
Basic dissociation constant (pka-Base)	5.281	7.238

Melting point	91.259	177.363
Boiling point	250.66	325.763



Indoline-2-one derivative **Sunitinib**

Figure 1. Radar view for relative physiochemical properties of indoline-2-one derivative and reference

3.3.2. ADMET evaluations

ADMETlab3 was used to evaluate the absorption profiles of the indoline-2-one derivative and the reference (**Table 2-9** and **Figure 2**). Factors including Caco-2 permeability, MDCK permeability, PAMPA, Pgp inhibitor, Pgp substrate, and HIA were evaluated. The distribution parameters of the synthesized compound include PPB, VDss, BBB, OATP1B1 inhibitor, OATP1B3 inhibitor, BCRP inhibitor, MRP1 inhibitor, and BSEP inhibitor, as well as the reference. The inhibitor and substrate specificities of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP2B6, CYP2C8, and HLM stability were also assessed. Assessment was done on the toxicity indicators of the synthesized compound in combination with the reference. The variables considered included hERG blockers, carcinogenicity, hERG blockers, skin sensitisation, DILI, AMES toxicity, rat oral acute toxicity, eye corrosion, eye irritation, drug-induced nephrotoxicity, respiratory, human hepatotoxicity, drug-induced neurotoxicity, ototoxicity, haematotoxicity, genotoxicity, RPMI-8226 immunotoxicity, RPMI-8226 immunotoxicity, A549 cytotoxicity, Hek293 cytotoxicity, BCF, IGC50, LC50DM and LC50FM. The Tox21 pathway parameters for the synthesized compound were established with the respected reference. The study covered such parameters as AhR, AR, AR-LBD, Aromatase, ER, ER-LBD, PPAR-gamma, ARE, ATAD5, HSE, MMP, and p53. Toxicophore rules of the synthesized compound in combination with the reference were evaluated. The standard parameters include the aquatic toxicity rule, genotoxic, carcinogenicity and mutagenicity rules, non-genotoxic carcinogenicity rule, skin sensitisation rule, acute toxicity rule, non-biodegradable sureChEMBL rule and FAF-Drugs4 rule. The medicinal properties of the indoline-2-one derivative together with the reference were evaluated using ADMETlab. QED, SAscore, GASA, Fsp3, MCE-18, NPscore, Lipinski rule, Pfizer rule, GSK rule, GoldenTriangle, PAINS, BMS rule, Chelating rule, blue fluorescence, and green fluorescence were among the factors considered. The indoline-2-one derivative and reference were also evaluated on cosmetic risk assessment standards. Considered were factors like skin sensitisation, acute dermal toxicity, photoallergy, phototoxicity, photoinduced toxicity, skin irritation, skin corrosion, eye irritability, and eye corrosion [25].

Table 2. Relative Absorption profile of indoline-2-one derivative and reference

Parameter	**Indoline-2-one derivative**	**Sunitinib**
Humancolon carcinoma cell line (Caco-2 Permeability)	-4.328	-5.566
Madin-Darby Canine Kidney cells (MDCK Permeability)	0.0	0.0

Parralel Artificial membrane permeability (PAMPA)	---	---
P-glycoprotein inhibitor (Pgp inhibitor)	+++	+++
P-glycoprotein substrate (Pgp substrate)	---	---
HumanIntestinal Absorption (HIA)	---	---
F20%	---	---
F30%	---	---
F50%	---	---

Symbols indicate the following values ranges: 0-0. 1 (---), 0. 1-0. 3 (--), 0. 3-0. 5 (-), 0. 5-0. 7 (+), 0. 7-0. 9 (++), and 0. 9-1. 0 (+++).

Table 3. Relative Distribution profile of indoline-2-one derivative and reference

Parameter	**Indoline-2-one derivative**	**Sunitinib**
PlasmaProteinBinding (PPB)	98.0%	87.0%
Volumn of Distribution at steady state (VDss)	0.785	3.297
Blood-Brain Barrier (BBB)	---	---
OATP1B1 inhibitor	-	-
OATP1B3 inhibitor	+++	--
BCRP inhibitor	---	---
MRP1 inhibitor	---	--
BSEP inhibitor	+++	+++

Table 4. Relative Metabolism profile of indoline-2-one derivative and reference

Parameter	**Indoline-2-one derivative**	**Sunitinib**
CYP1A2 inhibitor	+++	-
CYP1A2 substrate	+++	--
CYP2C19 inhibitor	+++	---
CYP2C19 substrate	---	-
CYP2C9 inhibitor	+++	---
CYP2C9 substrate	-	---
CYP2D6 inhibitor	---	---
CYP2D6 substrate	---	---
CYP3A4 inhibitor	+++	---
CYP3A4 substrate	+++	+
CYP2B6 inhibitor	--	---
CYP2B6 substrate		---
CYP2C8 inhibitor		---
HLM Stability		---

Table 5. Relative Toxicity profile of indoline-2-one derivative and reference

Parameter	Indoline-2-one derivative	Sunitinib
Human ether-a-go-go related gene (hERG Blockers)	0.103	0.888
Human ether-a-go-go related gene (hERG Blockers (10um))	0.394	0.868
Drug-Induced Liver Injury (DILI)	0.999	0.96
AMES Toxicity	0.997	0.933
Rat Oral Acute Toxicity	0.4	0.88
Skin Sensitization	0.999	0.999
Carcinogenicity	0.98	0.658
Eye Corrosion	0.066	0.0
Eye Irritation	0.98	0.006
Respiratory	0.338	0.992
Human Hepatotoxicity	0.994	0.993
Drug-induced Nephrotoxicity	0.918	0.994
Drug-induced Neurotoxicity	0.991	0.986
Ototoxicity	0.077	0.92
Hematotoxicity	0.406	0.966
Genotoxicity	1.0	1.0
RPMI-8226 Immunitoxicity	0.079	0.191
A549 Cytotoxicity	0.038	0.421
Hek293 Cytotoxicity	0.782	0.858
Bioconcentration Factor (BCF)	1.339	1.051
50% inhibition growth concentration (IGC50)	3.944	3.462
LC50DM	5.102	4.996
LC50FM	4.727	4.409

Table 6. Relative Toxicity profiles (TOX21 Pathway) of indoline-2-one derivative and reference

Parameter	Indoline-2-one derivative	Sunitinib
Aryl Hydrocarbon Receptor (AhR)	++	---
Androgen Receptor (AR)	---	---
Androgen Receptor Ligand Binding Domain (AR-LBD)	---	---
Aromatase	-	---
Estrogen Receptor (ER)	-	-
Estrogen Receptor Ligand Binding Domain (ER-LBD)	---	---

Peroxisome Proliferator-Activated Receptor Gamma (PPAR-gamma)	---	---
Antioxidant Response Element (ARE)	+++	+
ATPase Family AAA Domain-Containing Protein 5 (ATAD5)	+	---
Heat Shock Element (HSE)	+	---

Table 7. Relative Toxicophore rules of indoline-2-one derivative and reference

Parameter	**Indoline-2-one derivative**	**Sunitinib**
Aquatic Toxicity Rule	3	4
Genotoxic Carcinogenicity Mutagenicity Rule	6	1
NonGenotoxic Carcinogenicity Rule	1	1
Skin Sensitization Rule	2	5
Acute Toxicity Rule	0	0
NonBiodegradable	4	2
SureChEMBL Rule	2	0
FAF-Drugs4 Rule	3	3

Table 8. Relative various drug likeness medicinal parametres of indoline-2-one derivative and reference

Parameter	**Indoline-2-one derivative**	**Sunitinib**
QED	0.818	0.626
SAscore	Easy	Easy
GASA	Easy	Easy
Fsp^3	0.188	0.364
MCE-18	64.211	40.0
NPscore	-1.204	-1.208
Lipinski Rule	Accepted	Accepted
Pfizer Rule	Accepted	Accepted
GSK Rule	Accepted	Accepted
GoldenTriangle	Accepted	Accepted
PAINS	0	0
Alarm_NMR Rule	1	1
BMS Rule	1	0
Chelating Rule	0	0
Colloidal aggregators	0.145	0.347
FLuc inhibitors	0.416	0.525

Blue fluorescence	0.428	0.37
Green fluorescence	0.466	0.596
Reactive compounds	0.016	0.001
Promiscuous compounds	0.003	0.91

Table 9. Relative Cosmetic risk parametres of indoline-2-one derivative and reference

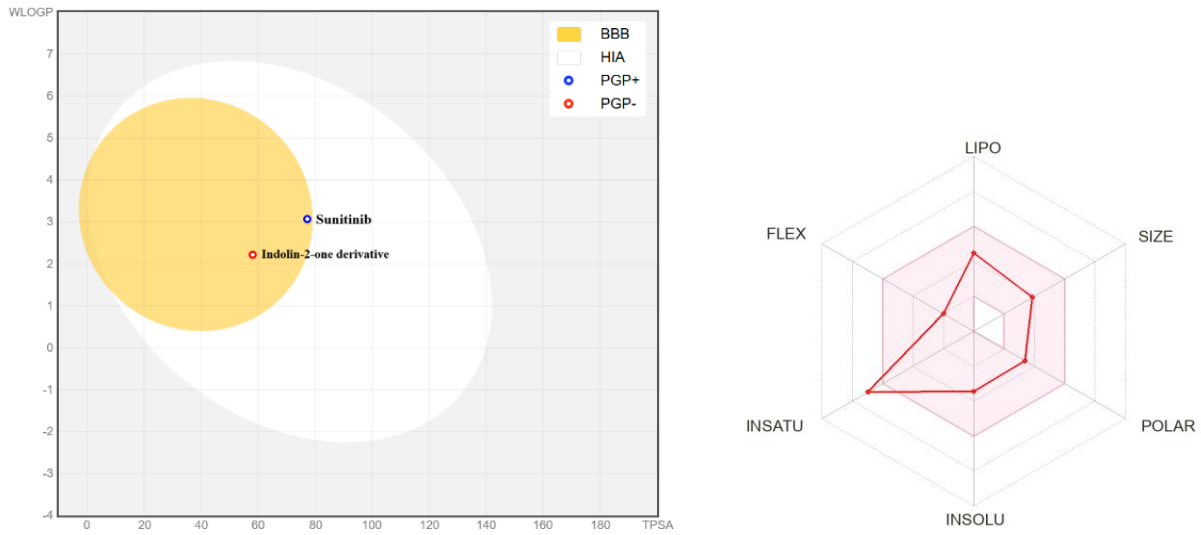
Parameter	**Indoline-2-one derivative**	**Sunitinib**
Eye corrosion	0	0
Eye irritation	1	0
Skin corrosion	0	0
Skin irritation	0	0
Skin sensitisation	0	0
Acute dermal toxicity	0	1
Photoinduced toxicity	1	1
Phototoxicity	1	1
Photoallergy	1	1

Indoline-2-one derivative **Sunitinib**

Figure 2. Radar view for relative cosmetic risk parameters of indoline-2-one derivative and reference

3.3.3. Brain Or Intestinal Estimated (BOILED-Egg) and Bioactivity Radar (Bar) Analysis

Using the BOILED-Egg system, the permeability and absorption characteristics of the produced hybrids were calculated in connection to the blood-brain barrier and intestinal tract. The BOILED-Egg model shown indicates that the white area indicates the field where the gastrointestinal tract absorbs the chemical, and the yellow spot (yolk area) suggests that the compounds can easily traverse the blood-brain barrier. While Indoline-2-one derivative and the reference have passed through the BBB, the model in this study features synthesized compound and the reference, both of which are shown to be well absorbed through the GI tract [26] (**Figure 3**).



(a) **(b)**

Figure 3. (a) BOILED–Egg plot and (b) bioactivity radar plot of the indoline-2-one derivative and reference

4. DISCUSSION

In this study, we used FT-IR, ^{1}H-NMR, and ESI-MS primarily to figure out the structure of synthesized indoline-2-one derivative. During the characterization of the indoline-2-one derivative, it was found that IR frequencies were observed at 996 cm^{-1}, which corresponds to C-O of the epoxy group connected to the isatin moiety, whereas a 3046 cm^{-1} stretching frequency was observed for C-H present in the epoxy group. The IR stretching frequency of the aromatic C=O group present in the isatin moiety was observed at 1732 cm^{-1}. On the other hand, the stretching frequency of aromatic C=N, present in the pyridine ring, was observed at 1331 cm^{-1}, whereas C=N (imine) showed IR stretching at 1672 cm^{-1}, which confirms the characterization of the synthesized compound in the basis of FT-IR spectroscopy. Additionally, *in silico* studies showed that bioavailability and drug-likeness scores along with the calculation of molecular descriptors of indoline-2-one derivatives have matched the measures required and given comparable values as the reference. ADMET profiles of the synthesized compound have passed all the ADMET barriers to prove that the synthesized indoline-2-one derivative is showing drug-like properties. The synthesized indoline-2-one derivative has potential Caco-2 permeability (-4.328). Both compounds act as P-glycoprotein inhibitors without becoming substrates and show similar MDCK permeability and P-glycoprotein interaction profiles.

Regarding distribution, synthesized indoline-2-one derivative demonstrates potential plasma protein binding (98.0%). Therefore, suggesting less free drug availability but perhaps longer circulating times. Still, its volume of distribution (VDss, 0.785) is showing less tissue permeability. Indoline-2-one derivative also has a lower free drug percentage (Fu) (1.6% vs. 11.3%). The indoline-2-one derivative shows potential inhibition of OATP1B3 and BSEP transporters, possibly impacting hepatic uptake and bile acid transport, respectively. The metabolism profile also indicates that the synthesized compound is a CYP1A2 substrate and a CYP3A4 substrate with general inhibition of several main CYP450 enzymes, including CYP1A2, CYP2C19, CYP2C9, and CYP3A4. Along with indicating a metabolically active profile, this polypharmacology points to potential drug-drug interactions. In contrast, the reference exhibits minimal inhibitory potential and is a poor substrate for CYP3A4, resulting in a more straightforward metabolic interaction profile.

Toxicity profiling emphasises the lower cardiotoxicity potential of indoline-2-one derivative (hERG block) and the lower system-wide toxic effects over several measures. Indoline-2-one derivative has a lower predicted rat oral acute toxicity. Implying a more secure acute toxicity profile and less risk for nephrotoxicity, neurotoxicity, and haematotoxicity. The synthesized compound has potential scores for genotoxicity, DILI, and AMES toxicity. The compound has much lower cytotoxicity against RPMI-8226 and A549 cell lines, driving a potential therapeutic index. TOX21 pathway mapping suggests that indoline-2-one derivatives trigger theARE and AhR pathways. Therefore, oxidation stress reactions or xenobiotic metabolism are possible. Indoline-2-one derivative needs to be investigated more, as it has several toxicophore indicators (e.g., genotoxicity and skin sensitisation traits). Even though indoline-2-one derivatives have more alerts than references.

Synthesized indoline-2-one derivatives have potential drug-likeness according to drug-likeness and medicinal chemistry profiles, with a higher quantitative estimate of drug-likeness (QED = 0.818). Furthermore, it has a lower PAINS value, as well as minor structural liabilities (e.g., reactive or promiscuous moieties). Its synthetic accessibility (SAscore and GASA: "Easy") further supports its development potential. Its low Fsp3 value (0.188) might suggest potential connected to planar structure that should be optimised for improved pharmacokinetics and reduced off-target effects. Dermal and photo-

induced toxicity profiles of indoline-2-one derivatives and references are quite similar. Therefore, controlled use suggests acceptable cosmetic safety. Although it has a higher risk of eye irritation in terms of cosmetic risk assessment.

5. CONCLUSIONS

The current study successfully synthesized and characterized a novel indoline-2-one derivative. The synthetic method was efficient, and user-friendly. Extensive *in silico* ADMET analyses indicated that the indoline-2-one derivative displays potential drug-likeness and bioactivity metrics as reference. Significantly, the compound showed low toxicity risks, potential metabolic stability, and efficient absorption and distribution characteristics, which bolster its potential for additional biological assessment. These results highlight the promise of rationally designed indoline-2-one derivative as potential scaffolds for the development of drug-like candidates. Forthcoming studies aimed at assessing the *in vitro* and *in vivo* biological activity effectiveness of the synthesized indoline-2-one derivative.

Author Contributions: D.S. (synthesis and writing the original manuscript), I.A. (writing the original manuscript and proof reading), M.A.K. (technical support and ADMET calculations), Z.H. (making schemes and literature survey), F.H. (supervision and writing manuscript). All authors have read and agreed to the published version of the manuscript.

Funding: NA

Institutional Review Board Statement: NA

Informed Consent Statement: NA

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgments: The authors are also grateful to Integral University, Lucknow, India's R & D division, for giving manuscript communication number (IU/R&D/2025-MCN0003706) and the facilities to carry out research work.

Conflicts of Interest: The authors declare no competing interests.

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