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ORIGINAL ARTICLES

COMPUTATIONAL ANALYSIS OF 3-MONOSUBSTITUTED ISATIN DERIVATIVES FOR PHYSICOCHEMICAL PROPERTIES AND DRUG-LIKENESS

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ABSTRACT

Isatin and its derivatives have garnered significant interest in medicinal chemistry due to their diverse pharmacological activities, including anticancer, antiviral, and antimicrobial effects. This study investigates five 3-monosubstituted isatin derivatives—IA, I4AM, I2AP, I3AP, and I4AP—using the SwissADME platform to evaluate their drug-like properties. The derivatives were analyzed for molecular weight, lipophilicity, water solubility, and adherence to drug-likeness criteria, including Lipinski's Rule of Five and other established filters. The derivatives exhibited favorable molecular weights and topological polar surface areas, suggesting good membrane permeability. Lipophilicity assessments indicated moderate values, beneficial for absorption and distribution, while water solubility predictions varied across models, emphasizing the need for experimental validation. All compounds complied with multiple drug-likeness rules, with bioavailability scores suggesting moderate oral potential. This comprehensive *in silico* analysis highlights the potential of these isatin derivatives as promising drug candidates. Future studies should focus on synthesizing these compounds and validating their pharmacokinetic and therapeutic profiles in biological systems.

Keywords: *isatin, lipophilicity, water solubility, SwissADME, drug discovery, pharmacokinetics*

INTRODUCTION

Drug discovery and development are pivotal processes in the pharmaceutical industry, aiming to identify new therapeutic agents with optimal efficacy and safety profiles (1,2). The advent of computational tools has revolutionized these processes by enabling the *in silico* prediction of drug-like properties, which significantly streamlines the initial stages of drug design (3,4).

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Isatin derivatives have garnered considerable interest in medicinal chemistry due to their diverse pharmacological activities, including anticancer (5–7), antiviral (8), and antimicrobial (9,10), among others (11–16). In particular, monosubstituted isatins have shown promise as lead compounds in various therapeutic areas. This study focuses on the evaluation of five 3-monosubstituted isatin derivatives—IA (isatin substituted with aniline), I4AM (isatin substituted with 4-aminomorpholine), I2AP (isatin substituted with 2-aminopyridine), I3AP (isatin substituted with 3-aminopyridine), and I4AP (isatin substituted with 4-aminopyridine)—using computational prediction (4). The 2D structures of the isatin derivatives are presented in Fig. 1.

AIM

This research aims to perform an *in silico* evaluation of the five 3-monosubstituted isatin derivatives to assess their potential as drug candidates. The

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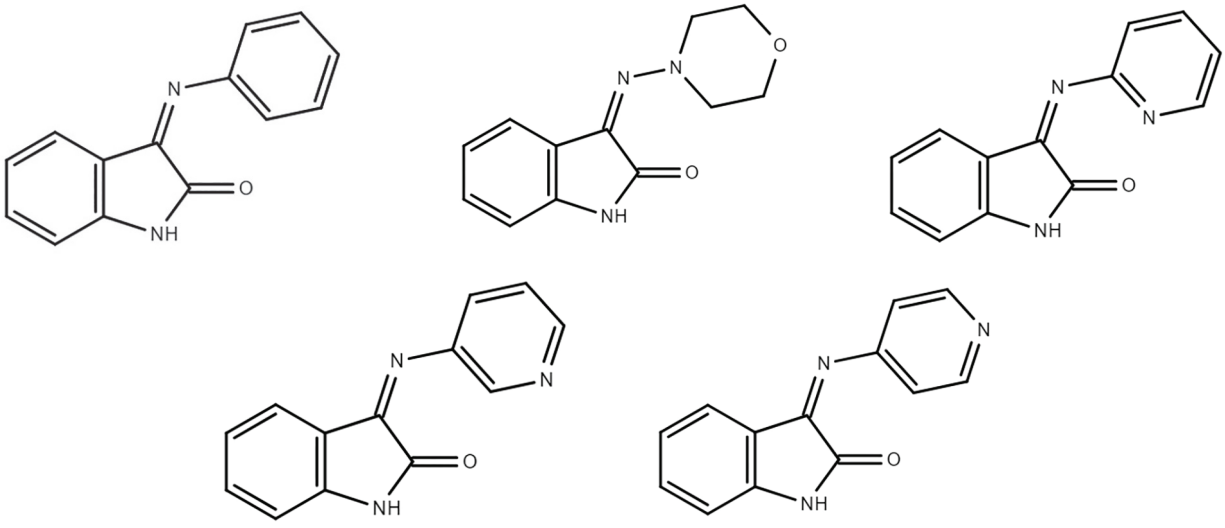


Fig. 1. 2D chemical structure of (a) IA (isatin substituted with aniline), (b) I4AM (isatin substituted with 4-aminomorpholine), (c) I2AP (isatin substituted with 2-aminopyridine), (d) I3AP (isatin substituted with 3-aminopyridine), and (e) I4AP (isatin substituted with 4-aminopyridine).

study will focus on key physicochemical properties and drug-likeness criteria.

MATERIALS AND METHODS

The SwissADME online platform (http://www.swissadme.ch/index.php#top) was utilized to predict the physicochemical properties and drug-likeness of the five 3-monosubstituted isatin derivatives: IA, I4AM, I2AP, I3AP, and I4AP (4). The computed physicochemical properties included molecular weight, lipophilicity (Log $P_{o/w}$), water solubility (Log S), and other relevant descriptors.

Drug-likeness was evaluated using several established criteria: Lipinski's Rule of Five (17,18), the Ghose filter (19), Veber rules (20), Egan rules (21), and Muegge rules (22). These assessments provided insights into the compounds' potential as drug candidates by evaluating their adherence to key criteria associated with oral bioavailability, pharmacokinetics, and drug safety.

RESULTS AND DISCUSSION

Physicochemical Properties

In this study, we evaluated the synthetic accessibility (SA) of the isatin derivatives. The SA scores for these compounds are as follows: IA (2.42), I4AM (2.56), I2AP (2.55), I3AP (2.47), and I4AP (2.36). These scores are predicted on a scale from 1 (very easy) to 10 (very difficult), based on 1024 fragmental contributions (FP2) modulated by size and complexity penalties. According to SwissADME (4), the model was trained on a dataset of 12 782 590 molecules and tested on 40 external molecules, achieving a coefficient of determination (R^2) value of 0.94. This value indicates a strong correlation between the observed and predicted synthetic accessibility scores, reflecting the model's high reliability.

The SA scores indicate that all the examined isatin derivatives have relatively low to moderate synthetic complexity, suggesting they can be synthesized with relative ease.

The predicted physicochemical properties of the five derivatives, presented in Table 1, provide key insights into their potential as drug candidates. All compounds have molecular weights within a favorable range (222.24 to 231.25 g/mol) for oral drug candidates, generally targeting weights under 500 g/mol. The TPSA values, ranging from 41.46 to 54.35 Å², suggest good cell membrane permeability, which is advantageous for oral bioavailability since TPSA values below 140 Å² are typically associated with good permeability.

The lipophilicity of these derivatives, while not explicitly detailed in the provided results, indicates moderate lipophilicity from previous data. This balance between hydrophilic and lipophilic proper-

Table 1. Predicted physicochemical properties of IA, I4AM, I2AP, I3AP, and I4AP by SwissADME software.

Physicochemical Properties	IA	I4AM	I2AP	I3AP	I4AP
Formula	$C_{14}H_{10}N_2O$	$C_{12}H_{13}N_3O_2$	$C_{13}H_9N_3O$	$C_{13}H_9N_3O$	$C_{13}H_9N_3O$
Molecular weight	222.24 g/mol	231.25 g/mol	223.23 g/mol	223.23 g/mol	223.23 g/mol
Num. heavy atoms	17	17	17	17	17
Num. arom. heavy atoms	12	6	12	12	12
Fraction Csp3	0.00	0.33	0.00	0.00	0.00
Num. rotatable bonds	1	1	1	1	1
Num. H-bond acceptors	2	3	3	3	3
Num. H-bond donors	1	1	1	1	1
Molar Refractivity	70.46	70.43	68.26	68.26	68.26
TPSA	41.46 Å²	53.93 Å²	54.35 Å²	54.35 Å²	54.35 Å²

ties supports favorable absorption and distribution profiles. Furthermore, the derivatives exhibit a balanced hydrogen bonding potential, with one hydrogen bond donor and two to three hydrogen bond acceptors. This balance helps maintain solubility and permeability, which are factors contributing to drug-likeness.

Overall, according to the physicochemical analysis it is suggested that the five 3-monosubstituted isatin derivatives possess favorable attributes for drug development. They exhibit appropriate molecular weights, TPSA values indicative of good permeability, balanced hydrogen bonding characteristics, and are synthetically accessible. Future work should involve synthesizing these compounds and experimentally validating their predicted properties.

Lipophilicity

Lipophilicity is an important parameter in drug development as it influences absorption, distribution, metabolism, and excretion (ADME) properties (23). The lipophilicity of was evaluated using several log P (partition coefficient) prediction models: iLOGP (4), XLOGP3 (24), WLOGP (25), MLOGP (17,26,27), and SILICOS-IT, with a consensus log P value calculated for a comprehensive understanding. Results are presented in Table 2.

Table 2. Predicted lipophilicity of IA, I4AM, I2AP, I3AP, and I4AP by SwissADME software.

Lipophilicity	IA	I4AM	I2AP	I3AP	I4AP
Log $P_{o/w}$ (iLOGP) (4)	1.71	1.83	1.36	1.53	1.59
Log $P_{o/w}$ (XLOGP3) (24)	2.67	1.08	1.82	1.48	1.48
Log $P_{o/w}$ (WLOGP) (25)	2.19	-0.28	1.58	1.58	1.58
Log $P_{o/w}$ (MLOGP) (17,26,27)	1.93	0.49	1.62	0.81	0.81
Log $P_{o/w}$ (SILICOS-IT)	3.27	1.66	2.72	2.72	2.72
Consensus Log $P_{o/w}$	2.35	0.96	1.82	1.63	1.64

For IA, the consensus log P value was 2.35, indicating moderate lipophilicity. The individual log P values from the models varied, with the iLOGP at 1.71 and the SILICOS-IT at 3.27. This range suggests that IA has a balanced hydrophilic and lipophilic profile, which is favorable for oral bioavailability.

I4AM displayed a consensus log P value of 0.96, showing lower lipophilicity compared to IA. The log P values varied significantly, with iLOGP at 1.83 and WLOGP at -0.28. The lower lipophilicity of I4AM suggests it may have better solubility in aqueous environments, which can be beneficial for certain pharmacokinetic properties but might require consideration for membrane permeability.

The consensus log P for I2AP was 1.82, indicating moderate lipophilicity. The log P values from

the models ranged from 1.36 (iLOGP) to 2.72 (SILICOS-IT). This profile suggests that I2AP, like IA, has a good balance between hydrophilicity and lipophilicity, potentially supporting favorable ADME characteristics.

I3AP had a consensus log P value of 1.63. The individual log P values were relatively consistent, ranging from 1.48 (XLOGP3) to 2.72 (SILICOS-IT). The moderate lipophilicity of I3AP indicates it should have good membrane permeability while maintaining reasonable solubility.

Similarly, I4AP also showed a consensus log P value of 1.64, with individual values spanning from 1.48 (XLOGP3) to 2.72 (SILICOS-IT). This indicates a moderate lipophilicity similar to I2AP and I3AP, suggesting good overall drug-likeness in terms of balance between solubility and permeability.

Water Solubility

Water solubility is a critical factor influencing a drug's absorption and bioavailability. The solubility was predicted using multiple models: ESOL (28), Ali (29), and SILICOS-IT, providing a comprehensive view of their solubility profiles. Results are presented in Table 3.

For IA, the water solubility results were mixed. According to the ESOL and Ali models, IA is classified as soluble, with solubility values of 9.78×10^{-02} mg/mL (4.40×10^{-04} mol/L) and 1.43×10^{-01} mg/ml (6.42×10^{-04} mol/L), respectively. However, the SILICOS-IT model classified it as moderately soluble, with a significantly lower solubility of 7.96×10^{-04} mg/mL (3.58×10^{-06} mol/L). This variation highlights the need for cautious interpretation, though the overall solubility is favorable for drug development.

I4AM demonstrated excellent water solubility. The ESOL model indicated that it was soluble (1.64 mg/mL, 7.09×10^{-03} mol/L), and the Ali model classified it as very soluble (3.63 mg/mL, 1.57×10^{-02} mol/L). The SILICOS-IT model also supported good solubility with a value of 1.77×10^{-01} mg/mL (7.67×10^{-04} mol/L). These consistent results across models suggest that I4AM has high water solubility, which is advantageous for oral administration and bioavailability.

For I2AP, the water solubility was generally favorable. The ESOL and Ali models classified it as soluble, with solubility values of 3.32×10^{-01} mg/mL (1.49×10^{-03} mol/L) and 5.86×10^{-01} mg/mL (2.62×10^{-03} mol/L), respectively. However, the SILICOS-IT model again predicted lower solubility, classifying it as moderately soluble (1.88×10^{-03} mg/mL, 8.43×10^{-06} mol/L). Despite this, the overall solubility profile supports its potential for further drug development.

I3AP exhibited similar solubility characteristics to I2AP. The ESOL and Ali models classified it as soluble, with values of 5.44×10^{-01} mg/mL (2.44×10^{-03}

Table 3. Predicted water solubility of IA, I4AM, I2AP, I3AP, and I4AP by SwissADME software.

Water Solubility	IA	I4AM	I2AP	I3AP	I4AP
Log S (ESOL) (28)	-3.36	-2.15	-2.83	-2.61	-2.61
Solubility	9.78e-02 mg/mL; 4.40e-04 mol/L	1.64e+00 mg/mL; 7.09e-03 mol/L	3.32e-01 mg/mL; 1.49e-03 mol/L	5.44e-01 mg/mL; 2.44e-03 mol/L	5.44e-01 mg/mL; 2.44e-03 mol/L
Class	Soluble	Soluble	Soluble	Soluble	Soluble
Log S (Ali) (29)	-3.19	-1.80	-2.58	-2.23	-2.23
Solubility	1.43e-01 mg/mL; 6.42e-04 mol/L	3.63e+00 mg/mL; 1.57e-02 mol/L	5.86e-01 mg/mL; 2.62e-03 mol/L	1.32e+00 mg/mL; 5.91e-03 mol/L	1.32e+00 mg/mL; 5.91e-03 mol/L
Class	Soluble	Very soluble	Soluble	Soluble	Soluble
Log S (SILICOS-IT)	-5.45	-3.12	-5.07	-5.07	-5.07
Solubility	7.96e-04 mg/mL; 3.58e-06 mol/L	1.77e-01 mg/mL; 7.67e-04 mol/L	1.88e-03 mg/mL; 8.43e-06 mol/L	1.88e-03 mg/mL; 8.43e-06 mol/L	1.88e-03 mg/mL; 8.43e-06 mol/L
Class	Moderately soluble	Soluble	Moderately soluble	Moderately soluble	Moderately soluble

mol/L) and 1.32 mg/mL (5.91×10^{-03} mol/L), respectively. The SILICOS-IT model, however, indicated moderate solubility (1.88×10^{-03} mg/mL, 8.43×10^{-06} mol/L). The general trend of high solubility according to ESOL and Ali models suggests good solubility for I3AP, beneficial for its oral bioavailability.

I4AP showed water solubility results consistent with those of I3AP. It was classified as soluble by the ESOL (5.44×10^{-01} mg/mL, 2.44×10^{-03} mol/L) and Ali models (1.32 mg/mL, 5.91×10^{-03} mol/L), whereas the SILICOS-IT model classified it as moderately soluble (1.88×10^{-03} mg/mL, 8.43×10^{-06} mol/L). The generally high solubility predicted by ESOL and Ali models supports its consideration for further drug development.

The water solubility predictions for these derivatives highlight a consistent pattern where the ESOL and Ali models generally agree on classifying the compounds as soluble, whereas the SILICOS-IT model tends to predict lower solubility, often placing the compounds in the moderately soluble category. This variation underscores the importance of experimental validation to confirm the computational predictions.

High solubility is significant for oral drugs as it enhances their absorption and bioavailability. The favorable solubility profiles of I4AM, I2AP, I3AP, and I4AP, particularly in the ESOL and Ali models, suggest they have good potential for further development. However, the discrepancies with the SILICOS-IT predictions indicate that additional work might be necessary to optimize their formulations to ensure consistent solubility across different environments.

Drug-Likeness

The drug-likeness was evaluated by applying several well-established rules: Lipinski's Rule of Five, Ghose filter, Veber rules, Egan rules, and Muegge filter. Additionally, the bioavailability scores of the compounds were calculated. Drug-likeness is a relevant factor in predicting the potential success of a compound as a drug candidate, as it encompasses various criteria related to the compound's pharmacokinetics and bioavailability.

All five isatin derivatives exhibited no violations of Lipinski's Rule of Five and complied with other drug-likeness filters, including the Ghose filter, Veber rules, Egan rules, and Muegge filter. The uniform bioavailability score of 0.55 across all derivatives indicates a moderate potential for oral bioavailability, which is an encouraging sign for their development as oral drug candidates.

The comprehensive adherence to multiple drug-likeness rules suggests that these isatin derivatives possess favorable pharmacokinetic and bioavailability properties. This favorable profile underscores the potential of these compounds to progress in the drug development pipeline. Future studies should focus on experimental validation of these *in silico* predictions, assessing the actual bioavailability, pharmacokinetics, and therapeutic efficacy of these derivatives in biological systems.

CONCLUSION

The comprehensive analysis of physicochemical properties, lipophilicity, water solubility, and drug-likeness indicates that the five 3-monosubstituted isatin derivatives possess favorable attributes for drug development. These *in silico* predictions provide a strong foundation for further experimental validation. Future studies should focus on synthesizing these compounds and assessing their bioavailability, pharmacokinetics, and therapeutic efficacy in biological systems to confirm their potential as drug candidates.

In conclusion, the five 3-monosubstituted isatin derivatives show promising characteristics that align with the key criteria for drug development. This study lays the groundwork for their advancement in the drug development pipeline, with a particular emphasis on experimental validation to confirm their predicted properties and therapeutic potential.

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